Sentinel Node Navigation Surgery in Early-Stage Esophageal Cancer

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The sentinel node (SN) concept has revolutionized the surgical staging of both melanoma and breast cancer over the past two decades. However, the validity of the SN hypothesis has been controversial for esophageal cancer, because SN mapping for esophageal cancer is technically complicated, and the number of early-stage esophageal cancer is very limited. Nevertheless, previous studies nicely demonstrated that SN mapping may be feasible in patients with early-stage esophageal cancer. Transthoracic extended esophagectomy with three-field radical lymph node dissection has been recognized as a curative procedure for thoracic esophageal cancer in Japan. However, uniform application of this highly invasive procedure might increase the morbidity and markedly reduce the quality of life (QOL) after surgery. Although further accumulation of evidence based on multicenter clinical trials using a standard protocol is needed, SN mapping and SN navigation surgery would provide significant information to perform individualized selective lymphadenectomy which might reduce the morbidity and retain the patients’ QOL. In addition, technical innovation including the development of new tracers is expected to confirm the accuracy and reliability of SN mapping in esophageal cancer.

Keywords: esophageal cancer, sentinel node, radioisotope, micrometastasis

Introduction

Esophageal cancer has one of the highest malignant potentials of any tumor. The post-operative, 5-year survival rate of American Joint Committee on Cancer (AJCC) stage I esophageal cancer is about 90%, and decreases to 45% for stage II, 20% for stage III, and only 10% for stage IV patients.1 Lymph node metastasis has been recognized as one of the useful indicators for predicting the outcome of esophageal cancer. Lymph node metastasis is not a rare event in esophageal cancer, and the incidence of lymph node metastasis, even in pT1b tumors, reaches 45%.1 Other specific characteristics of esophageal cancer are multi-directional lymphatic flow from the primary lesion and wide-spread and random patterns of lymph node metastasis from cervical to abdominal areas. Actually, anatomical skip metastases to the second or third compartment of regional lymph nodes were found in 50%–60% of esophageal cancer.1 Based on these clinical observations, extended radical esophagectomy with three-field lymph node dissection has become recognized as a standard procedure in Japan, even for clinically node-negative cases.1,2 However, the esophagectomy with three-field lymph node dissection is one of the most invasive procedures in gastrointestinal (GI) surgeries even by thoracoscopic and laparoscopic approaches, as minimally invasive...
esophagectomy. A significant increase in morbidity and mortality after invasive procedures has been reported.\textsuperscript{3–5)} To eliminate the necessity of uniform application of highly invasive surgery, sentinel node (SN) mapping may play a significant role by obtaining individual information to permit adjustments and modifications of the surgical procedure for that specific patient.

The SN is defined as the lymph node(s) first receiving lymphatic drainage from the site of primary tumor.\textsuperscript{6)} The SN is thought to be the first possible site of micrometastasis along the route of lymphatic drainage from the primary lesion. The pathological status of the SN is considered to predict the status of all regional lymph nodes. If the SN is recognizable and negative for cancer metastasis, unnecessary radical lymph node dissection could be avoided. The SN hypothesis was advanced to specifically address those patients at high risk of having lymph node metastasis based on the characteristics of their primary tumors, but who had no evidence of clinically-detectable regional, metastatic disease.

Initially SN mapping and biopsy was applied to melanoma and breast cancer and was subsequently extended to many other solid tumors including GI cancers.\textsuperscript{6–10)} More efficient and accurate diagnosis of lymphatic spread and prognostic information could be obtained from a small number of lymph nodes, by intraoperative lymphatic mapping and sentinel lymphadenectomy. The SN concept has revolutionized the approach to the surgical staging of both melanoma and breast cancer, and these techniques can yield patients’ benefit by avoiding various complications due to unnecessary prophylactic radical lymph node dissection in cases with negative SN for cancer metastasis.\textsuperscript{6,7)}

SN mapping for esophageal cancer is relatively complicated compared to that for gastric cancer,\textsuperscript{10)} and the number of early-stage esophageal cancer is very limited in Western countries. However, SN might be seen as a great instrument for minimally invasive surgery which avoids unnecessary lymph node dissection, following diagnosis of nodal metastasis targeting SN.

**Sentinel Node Mapping Procedures in Esophageal Cancer**

To detect the SN in esophageal cancer, we prefer to perform a radio-guided method rather than the conventional blue dye method.\textsuperscript{10–12)} In our procedures, technetium-99m tin colloid solution is injected at four quadrants into the submucosal layer around the primary tumor using an endoscopic puncture needle the day before surgery. Preoperative lymphoscintigraphy is usually obtained 3 to 4 h after the tracer injection (Fig. 1). Distribution of SN was widely spread from cervical to abdominal areas.

Intra-operative SN (i.e. radiolabeled lymph nodes) sampling is performed using a handheld gamma-probe (GPS Navigator, Tyco Healthcare, Tokyo, Japan). Gamma-probing is also feasible in thoracoscopic or laparoscopic sampling of SN using the special gamma-detector, which is introducible from trocar ports (Fig. 2). SN located in the cervical area could be identified by percutaneous gamma-probing. In general, intra-operative SN sampling is subsequently followed by esophagectomy.
with extended regional lymph node dissection (at least D2 dissection on the Japanese Guidelines) at this moment.\textsuperscript{12} On the back table, the residual SN in the resected specimen is carefully investigated using the gamma-probe, and all SN are sent for intra-operative pathology examination. After lymph node dissection, the absence of SN in the mediastinum or abdominal cavity is carefully confirmed by gamma-probe from the incisional wound, or thorascopic or laparoscopic ports.

For abdominal esophageal cancer or adenocarcinoma of gastroesophageal (GE) junction, a dual tracer method of the radioactive tracer and blue dye (isosulfan blue or indocyanine green) is principally used for SN detection. The blue-dye is injected into the submucosal layer of the primary lesion endoscopically right after surgery began. Subsequently, the tracer passes through the afferent lymphatics, and blue-stained nodes are identified as the SN approximately 15 minutes after the injection.

We believe that dye-only-guided SN mapping, which was used in another study,\textsuperscript{13} is not so suitable for thoracic esophageal cancer because regional lymph nodes of the thoracic esophagus in the mediastinum are frequently pigmented by anthracosis. Furthermore, real-time observation of the lymphatic route using blue dye is impossible without operative mobilization of the esophagus; however, mobilization itself may interfere with active lymphatic flow from the primary lesion.

Endoscopic submucosal injection is considered a reasonable and feasible route of administration of radioactive tracer for SN mapping of esophageal cancer. The radioactive tracer, technetium-99m tin colloid, has a larger particle size (approximately 200 nm in diameter) than other tracers such as rhenium sulfide nanocolloid and blue dye, and may be useful to avoid excessive diffusion.\textsuperscript{14} The radioactive tracer injected using an endoscopy the day prior to surgery is known to migrate into the SN within 2h and is accumulated in the SN. The radioactivity generally lasts at least for 20h, and is sufficient for detection during the surgery, as previously described.\textsuperscript{15,16} In fact, our previous study for early gastric cancer demonstrated that the timing of tracer administration made no significant difference to the number of SN identified between patients with tracer injection 2h before surgery and patients with tracer administered 16h before surgery.\textsuperscript{16} For these reasons, we think that the radioactive tracer could be injected one day (within 16h) prior to surgery. Pre-operative lymphoscintigraphy is useful in predicting SN in unexpected sites distant from the primary lesion of esophageal cancer before surgery. Shine-through effect from the primary lesion may interfere with accurate sampling of SN by the gamma-probe. However, our previous results demonstrated that intra-operative SN sampling using gamma-probe was considerably accurate and useful for prediction of lymph node metastasis in esophageal cancer.\textsuperscript{12} Gamma-probing was feasible, even in thorascopic or laparoscopic sampling of SN.\textsuperscript{12}

**Results of Sentinel Node Biopsy for Esophageal Cancer**

There have been relatively less number of studies demonstrating the feasibility and validity of the SN concept in esophageal cancer,\textsuperscript{10,12,17-23} compared to those in gastric cancer (Table 1). Till date, however, a number of single institutional studies including us have demonstrated acceptable outcomes of SN mapping for early esophageal cancer. In particular, radio-guided method seems superior in terms of the SN detection rate and accuracy of determination of lymph node status to the conventional blue dye method (Table 1).

Other authors highlighted the importance of the type of radiocolloid in SN studies, which has important implications for surgical planning and SN study.\textsuperscript{17,19,22} Basically, the particle size of the radiocolloid is related to the time of tracer deposition in the lymph node; therefore, bigger size (tin colloid) would be longer time of deposition. This might represent methodological problems or incomparable results in SN mapping for esophageal cancer, which could interfere in accuracy rates. Kato et al.\textsuperscript{17} reported that lymphatic mapping with technetium-99m colloidal rhenium sulfide in 25 patients with esophageal cancer was useful to identify the lymphatic basin, and their results were mostly coincident with ours. Further studies will be required for appropriate selection of radioisotope tracers.

Cases with clinically apparent lymph node metastasis should be excluded from SN mapping because the purpose of this technique is to identify clinically undetectable lymph node involvement. Clinically T1 esophageal cancers were suitable targets of the SN mapping.\textsuperscript{10,11,23} On the other hand, clinically T3 or T4 tumors, in which original lymphatic drainage routes might be obstructed and altered, result in high incidence of false-negative cases. In previous reports, SN mapping failure cases were recognized more frequently in clinically T3/T4 cases than that in T1 cases.\textsuperscript{23} Therefore, clinically T3 or T4 tumors should be also excluded from the indication for SN mapping.
In our previous study, we have performed radio-guided SN mapping for clinically T1N0 or T2N0 esophageal cancer to verify the feasibility of the SN mapping.\(^2\) Our data indicates successful SN detection in 71 (95%) of 75 patients, and the diagnostic accuracy based on SN status was 94%. The SN mapping was successful even during thoracoscopic esophagectomy, along with conventional surgical procedures.\(^2\) The mean number of identified SN per case was 4.7, and not 1 or 2 in our study.\(^2\) Furthermore, previous reports indicated that SN in thoracic esophageal cancer were distributed from the cervical to the abdominal areas, especially in upper and middle thoracic esophageal cancers.\(^2\) These results may have been because of the complicated multidirectional lymphatic networks of the esophagus.

Also in our study, distribution of identified SN was widely spread from cervical to abdominal areas.\(^2\) In upper thoracic esophageal cancer, lymph nodes along the bilateral, recurrent laryngeal nerve chain (referred as station #106recR and #106recL in the Japanese Guidelines) were identified most frequently as SN. The SN was also frequently identified in the cervical area. Surprisingly, 25% of cases with upper thoracic esophageal cancer showed SN along the left gastric artery (station #7). Middle thoracic esophageal cancer had a wide distribution of SN with metastasis from cervical to abdominal areas.

The station #106rec, bifurcational and main bronchus lymph nodes (station #107 and #109), and middle thoracic paraesophageal lymph nodes (station #108) were all identified, most-frequently, as SN in middle thoracic esophageal cancer. However, more than 10% of the cases contain SN in the area along the lesser curvature of the stomach. Although the SN was mainly detected in the abdominal area in lower thoracic esophageal cancer, some cases revealed a SN in the upper mediastinum, such as #106rec and upper thoracic paraesophageal lymph nodes (station #105). In more than 85% of cases with thoracic esophageal cancer, at least one SN was found to be located in the second or third compartment of regional lymph nodes.\(^2\) In general, the stations which were frequently identified as SN tended to have a high incidence of metastasis pathologically.

Most of SN studies have shown that in the squamous cell carcinoma (SCC), the distribution of SN is randomizized (cervical, thoracic, and abdominal); however in the adenocarcinoma (AC), the distribution is relatively located in peri-esophageal tissue and abdominal area. Grothenhuis et al.\(^3\) found a high false-negative rate (15%) in the SN in the AC. However, perhaps it was related to dye-only-guided SN mapping in the study, and transhiatal operation, which had limited lymphadenectomy of supra-carinal lymph nodes and the fact that there was a high

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Year</th>
<th>Tracers</th>
<th>Tumor depth</th>
<th>Number of patients</th>
<th>SN detection rate (%)</th>
<th>Sensitivity (%)</th>
<th>Accuracy (%)</th>
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<tr>
<td>Kitagawa(^{10})</td>
<td>2000</td>
<td>RI ((^{99m})technetium tin colloid)</td>
<td>cT1-T3</td>
<td>27 SCC</td>
<td>25/27 (93)</td>
<td>14/16 (88)</td>
<td>23/25 (92)</td>
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<td>2003</td>
<td>RI ((^{99m})technetium rhenium sulfide)</td>
<td>pT1-T4</td>
<td>25 SCC</td>
<td>23/25 (92)</td>
<td>13/15 (87)</td>
<td>21/23 (91)</td>
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<td>pT1-T3</td>
<td>23</td>
<td>23/23 (100)</td>
<td>9/12 (75)</td>
<td>20/23 (87)</td>
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<td>Lamb(^{16})</td>
<td>2005</td>
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<td>N.D.</td>
<td>57 Adeno</td>
<td>57/57 (100)</td>
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<td>14/18 (78)</td>
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<td>cT1-T2</td>
<td>75 SCC+ Adeno</td>
<td>71/75 (95)</td>
<td>29/33 (88)</td>
<td>67/71 (94)</td>
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<td>pT1a-T3</td>
<td>16 SCC+ Adeno</td>
<td>14/16 (88)</td>
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<td>134 SCC+ Adeno</td>
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RI: radioisotope; N.D.: not determined; HSA: human serum albumin
number of T3 tumors (65%), which could supplied to low accuracy rate. On the other hand, Lamb et al.\textsuperscript{19} reported excellent results of SN mapping in 57 patients with AC. Burian et al.\textsuperscript{24} also demonstrated that SN mapping is feasible and reliable in patients with adenocarcinoma of GE junction. We think that the SN mapping and biopsy will also be adaptable and reliable to AC of the distal esophagus or GE junction.

In general, lymphadenectomy is still necessary at least for staging purposes even after neoadjuvant therapy such as neoadjuvant chemotherapy or chemoradiotherapy, and the distribution of nodal metastasis after neoadjuvant therapy could be useful information in planning the operative techniques. Therefore if we could use the SN to study the remained pathologic lymph nodes after neoadjuvant therapy, this could avoid extended lymphadenectomy, or using SN to establish a new pathologic staging disease. Thompson et al.\textsuperscript{21} didn’t find any difference between patients who received neoadjuvant therapy, as well did not have and increased difficulty in identifying SN in these patients. On the other hand, Uenosono et al.\textsuperscript{23} agreed that SN navigation surgery also is unacceptable for patients who have had neoadjuvant chemoradiotherapy.

Recently, some groups have reported on the utility of single-photon emission computed tomography/computed tomography (SPECT/CT) for SN mapping in various malignancies.\textsuperscript{25} They found that SPECT/CT for SN mapping brought precise localization with three-dimensional imaging. Application of SPECT/CT to SN mapping might improve detection and localization even in esophageal cancer. More recently, Yuasa et al.\textsuperscript{26} attempted the intraoperative indocyanine green fluorescence imaging for SN biopsy in early esophageal cancer. Moreover, they combined the fluorescence imaging with preoperative CT lymphography. Although further studies will be needed to verify the clinical relevance of these new methods, the technical innovation including the development of new tracers might improve the accuracy and reliability of SN mapping in esophageal cancer.

**Micrometastasis in Sentinel Nodes of Patients with Early Esophageal Cancer**

Despite recent improvements in positron emission tomography (PET)/CT imaging, several investigators have reported that PET/CT scan has limited sensitivity in detecting subclinical nodal metastasis, such as micrometastasis in esophageal cancer.\textsuperscript{27–30} On the other hand, many reports have indicated that immunohistochemical nodal micrometastasis is a significant prognostic indicator in patients with cN0 esophageal cancer.\textsuperscript{31–33} Although SN mapping in esophageal cancer is obviously more invasive than other imaging techniques, nodal micrometastasis in SN that may affect survival of the patient cannot be ignored. At present, SN biopsy is believed to detect micrometastasis more accurately and cost-effectively than other imaging procedures in patients with cN0 early esophageal cancer.\textsuperscript{34}

A number of reports have clearly demonstrated the underestimation of micrometastasis in regional lymph nodes by conventional pathological diagnosis using hematoxylin and eosin staining.\textsuperscript{35} However, intensive examinations, such as immunohistochemistry and reverse-transcriptase polymerase chain reaction (RT-PCR), are not practically feasible for all resected lymph nodes. More focused examinations of SNs may resolve this issue. Furthermore, it has been reported that immunohistochemistry, rather than hematoxylin and eosin staining, improves the sensitivity of SN biopsy for the prediction of lymph node metastasis in patients with esophageal cancer.\textsuperscript{23}

Recently we established highly sensitive real-time RT-PCR system to detect mRNA of cytokeratin (CK) 19, CK20, squamous cell carcinoma (SCC) and carcinoembryonic antigen (CEA). In a preliminary study, two of six cases with thoracic esophageal cancer with histopathology-negative but PCR-positive SN showed postoperative recurrence.\textsuperscript{36} However, the clinical impact of micrometastasis detected by RT-PCR in SN of patients with early esophageal cancer remains controversial. We need to accumulate sufficient data to assess the clinical significance of molecular micrometastasis in SN of patients with early esophageal cancer.

**Future Application of Sentinel Node Mapping in Esophageal Cancer**

Transthoracic extended esophagectomy with three-field radical lymph node dissection has been recognized as a curative procedure for thoracic esophageal cancer in Japan.\textsuperscript{1,2} The esophagectomy with three-field lymphadenectomy may be a reasonable procedure on account of the wide SN distribution and unpredictable metastatic patterns.\textsuperscript{12,37} With regard to this point, the clinical application of SN mapping in esophageal cancer might be limited. However, uniform application of this highly invasive procedure might increase the morbidity and markedly reduce the quality of life (QOL) after surgery. SN
mapping would provide significant information to perform individualized selective lymphadenectomy that might reduce the morbidity without having a negative impact on the prognosis.38 For instance, if the SN was identified only in the mediastinum or abdominal area and all SN were pathologically negative in patients with cT1N0 middle or lower thoracic esophageal cancer, the cervical lymph node dissection would be unnecessary.12)

On the other hand, subtotal esophagectomy with two-field lymphadenectomy is widely performed in most countries. We think that the SN mapping will have relevance even for two-field lymphadenectomy, and provide significant information about the extent of intensive lymph node dissection.12) For instance, if the SN is pathologically positive for metastasis, the lymph node dissection of the SN basin should be performed carefully and intensively. In particular, if the SN is identified along the recurrent laryngeal nerves in the upper mediastinum and positive for metastasis, extended lymphadenectomy for upper mediastinum and/or additional cervical lymphadenectomy might be considered. The other benefit of SN mapping is that the absence of SN in the mediastinum or abdominal cavity can be carefully confirmed by gamma probe after lymph node dissection even for the two-field lymphadenectomy.

The SN mapping and biopsy will also be adaptable and reliable to adenocarcinomas of the distal esophagus or GE junction.12) We think that the SN mapping and biopsy for adenocarcinomas of the distal esophagus or GE junction is useful to adjust and modify the surgical procedures. For instance, if the SN was identified only in the abdominal area and pathologically negative in the case with cT1N0 adenocarcinoma of the distal esophagus, the patient would be treated with limited resection of distal esophagus by transhiatal approach without extensive mediastinal lymph node dissection.24,39) On the other hand, if the SN were positive for metastasis by intraoperative diagnosis, the patient should be treated with extended transthoracic lymphadenectomy.40) Prognostic benefit of modified lymphadenectomy based on SN concept should be considered carefully. At least, however, the new surgical procedure might reduce the morbidity and mortality without having a negative impact on the QOL for early-stage esophageal cancer patients with pathologically negative SN.

Metastatic status of regional lymph nodes is regarded as one of the most important prognostic factors in patients with esophageal cancer. Previous randomized trials showed that post-operative adjuvant chemotherapy with cisplatin and 5-FU for esophageal cancer had a significant preventive effect on relapse in patients with lymph node metastasis.41) Therefore, accurate and sensitive detection of micrometastasis assessed by SN mapping is very important clinically in aiding the performance of adequate adjuvant chemotherapy for cN0 esophageal cancer.

Recently, definitive chemoradiotherapy was reported as a promising strategy for patients with cT1N0M0 esophageal squamous cell carcinoma (ESCC).42) However, the design of radiation fields is still controversial because the use of larger fields containing regional lymph nodes is not only believed to be effective in controlling subclinical nodal metastasis but also believed to result in adverse effects during long-term follow-up.43) We are now performing concurrent chemoradiotherapy for patients with cT1N0M0 ESCC with minimized radiation fields which contain SN identified by lymphoscintigraphy in order to achieve local control of subclinical metastasis in SN (unpublished results). In addition, further investigations will clarify the feasibility and efficacy of novel esophagus-preserving treatments, such as endoscopic mucosal resection or endoscopic submucosal dissection in patients with cT1 ESCC patients having pathologically negative SN confirmed by thoracoscopic or laparoscopic SN biopsy.

Conclusion

The incidence of lymph node metastasis cannot be ignored in cN0 esophageal cancer. Therefore, the accuracy of SN mapping has to be indispensable for SN navigation surgery in esophageal cancer. Previous reports suggest that SN concept seems to be valid, and radio-guided SN mapping may be feasible in cT1N0 esophageal cancer. Further accumulation of evidence-based, multicentric clinical trials using standard protocols is required. Nevertheless, SN mapping and SN navigation surgery have proved to be promising strategies for less invasive, individualized surgery for early-stage esophageal cancer.

References


