Feasibility and Cost-effectiveness of Sentinel Lymph Node Radiolocalization in Stage N0 Head and Neck Cancer

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Objectives: To determine the feasibility of sentinel lymph node (SN) radiolocalization and to assess the cost-effectiveness of the SN navigation surgery strategy in patients with stage N0 squamous cell carcinoma (SCC) of the head and neck.

Patients: Eleven consecutive patients with stage N0 SCC of the head and neck.

Methods: Head and neck lymphoscintigraphy was performed 2 hours after the injection of technetium Tc 99m tin colloid or phytate. A handheld gamma probe was used to detect the SN before and directly after making a skin incision. Nodes were evaluated histopathologically for micrometastasis. To determine the expected cost savings, a decision tree sensitivity analysis was designed based on the 2 competing strategies: ipsilateral neck dissection vs SN navigation surgery. The costs referred to billed costs based on the Japanese national insurance reimbursement system.

Results: The sensitivity of SN navigation surgery in our series was 100% (11/11) on a patient-by-patient basis and 94% (17/18) on a node-by-node basis. Micrometastasis was found in 36% (4/11). Assuming the micrometastasis prevalence, sensitivity, and specificity of navigation surgery for detecting SN to be 30%, 90%, and 100%, respectively, the decision tree sensitivity analysis showed that introduction of SN navigation surgery in place of ipsilateral neck dissection would yield cost savings of $1218 (US) per stage N0 patient in Japan and avoid 7 surgical deaths per 1000 patients who are supposed to undergo neck dissection in the neck dissection strategy. Break-even point analysis for the SN navigation surgery strategy showed that the threshold value required more than 41 patients for the savings to begin to accrue.

Conclusion: Our results indicate that SN navigation surgery using radiolocalization is feasible and cost-effective, based on decision tree sensitivity analysis, in patients with stage N0 SCC of the head and neck.

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In patients with head and neck squamous cell carcinoma (SCC), neck lymph node status is the most important prognostic factor. Most patients with stage N0 head and neck cancer have no micrometastases or occult metastasis and are unnecessarily subjected to neck dissection, which is time-consuming, costly, and associated with morbidity. Several studies documented radiolocalization of the sentinel lymph node (SN), using scintigraphic mapping and gamma probe radiolocalization with biopsy, to be feasible in preoperative or intraoperative patients with stage N0 head and neck cancer, though subject numbers were limited in these studies.1,6

Navigation surgery, using radiolocalization of the SN and its biopsy, is based on the SN concept. This technique is quite new and the SN concept is, at present, somewhat theoretical. Its efficacy has not yet been fully proven. Cost, time spent, and morbidity could be reduced or eliminated if the SN concept proved to be valid, because SN navigation surgery would allow unnecessary elective neck dissection to be avoided in most clinically node-negative patients with head and neck cancer. This would not only spare patients the complications of neck dissection, but also reduce costs.

Focusing on the savings expected from introduction of this new technique in place of neck dissection, the cost-effectiveness of SN navigation surgery was assessed using decision tree and 1-way sensitivity analysis on the basis of a pooled analysis of individual level data from the different studies including ours.

The objectives were to determine the feasibility of SN radiolocalization and to assess the cost-effectiveness of the SN navigation surgery strategy in patients with stage N0 SCC of the head and neck.
PATIENTS

Eleven consecutive patients with stage N0 SCC of the head and neck were enrolled in this study (Table 1). Contrast computed tomography or magnetic resonance imaging and physical examination revealed no node metastasis. Informed consent was obtained from all participating patients. The institutional review board of National Defense Medical College, Tokorozawa, approved the protocol.

MATERIALS

Twenty-four hours before surgery, unfiltered technetium Tc 99m tin colloid (8 patients) or phytate (3 patients) was injected into the submucosa at 4 locations around the circumference of the primary tumor. Each injection volume was approximately 0.2 mL and the total dose used was less than 1.9 mCi (70 MBq). Head and neck lymphoscintigraphy was performed 2 hours after the injection in all 11 patients. Anterior and oblique planar images were obtained with a dual-head gamma camera (Millennium VG; General Electric Medical Systems, Milwaukee, Wis). During imaging, the primary injection site was lead shielded allowing the SN to be detected more easily. A Tc 99m flood field image phantom was also placed beneath the patient to facilitate body contour visualization and anatomic localization.

INTRAOPERATIVE IDENTIFICATION AND PROCESSING OF SPECIMENS

Lymphoscintigraphy was conducted to provide preoperative information on the general location and number of SNs, rather than specific anatomical localization. A handheld gamma probe (Navigator GPS; Auto Suture Japan, Inc, Tokyo) was used to detect the SN transcutaneously prior to and directly after making a skin incision. Removal of the primary tumor and neck dissection were performed, while SN was identified with the aid of the gamma probe.

The radioactivity of the entire resected node specimen was measured with an auto-well type scintillation counter. Nodes, including the SNs, were subsequently evaluated histopathologically for micrometastasis. Subserial sectioning was performed to detect lymph node micrometastasis.

DECISION TREE AND 1-WAY SENSITIVITY ANALYSIS

To determine the expected cost savings, a decision tree and 1-way sensitivity analysis was designed based on the 2 competing strategies: ipsilateral neck dissection vs SN navigation surgery (Figure 1). The baseline and range of all relevant variables used in the decision trees are shown in Table 2. The exact probability of each outcome in the decision tree was calculated according to the Bayesian theory.

The neck dissection strategy for patients with stage N0 SCC of the head and neck assumes that every patient undergoes elective neck dissection. The mortality incidence following neck dissection was assumed to be 1.0%. The SN navigation surgery strategy for patients with stage N0 SCC of the head and neck assumes that every patient first undergoes SN biopsy with lymphoscintigraphy and gamma probe radiolocalization. Then, the patient undergoes neck dissection when the biopsy result is positive for micrometastasis. A “wait-and-see” policy is followed when the biopsy result is negative for micrometastasis, and subsequent salvage neck dissection is performed only when clinical evidence of metastases emerges. False-positive cases are null based on the assumption that the success rate of SN biopsy is 100%. A hypothetical 1000-patient cohort study was performed.

COST AND DISCOUNT RATE

Present value is expressed as $PV = C/(1+r)^t$, where $PV$ is the present value, $C$ is the amount of money paid, $r$ is the risk-adjusted discount rate, and $t$ is the time period after which future money is to be paid. Future costs in our series were discounted 5%. The biological features of micrometastasis are unknown in detail. However, it is assumed that all patients with micrometastasis would have clinically positive nodes within 2 years following primary tumor resection.

The costs referred to billed costs based on the Japanese national insurance reimbursement system. Expected costs of the competing strategies were calculated by summing the products of the probabilities and values of the outcome of each strategy. A labor cost was calculated, including the salaries per hour for head and neck surgeons, anesthesiologists, and nurses because elimination of ipsilateral neck dissection shortens operative time by 3 hours. A labor cost of a pathologist and nuclear medicine specialist was calculated, since the SN technology would take more approximately 60 minutes for the diag-

Table 1. Results of 11 Patients With Head and Neck Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Tumor Site</th>
<th>Clinical Stage</th>
<th>Scintigraphic Mapping</th>
<th>Gamma Probe</th>
<th>Pathological Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/69</td>
<td>RT</td>
<td>T2 No</td>
<td>I (SM)</td>
<td>I (SM)</td>
<td>−</td>
</tr>
<tr>
<td>2/M/69</td>
<td>FM</td>
<td>T2 No</td>
<td>III (MJ)</td>
<td>I (SM)</td>
<td>−</td>
</tr>
<tr>
<td>3/M/54</td>
<td>T</td>
<td>T2 No</td>
<td>I (SM, SM)</td>
<td>I (SM, SM)</td>
<td>+ SmMe</td>
</tr>
<tr>
<td>4/M/47</td>
<td>T</td>
<td>T2 No</td>
<td>III (MJ)</td>
<td>III (MJ)</td>
<td>−</td>
</tr>
<tr>
<td>5/M/51</td>
<td>FM</td>
<td>T2 No</td>
<td>I (SMe)</td>
<td>I (SMe)</td>
<td>−</td>
</tr>
<tr>
<td>6/M/42</td>
<td>T</td>
<td>T3 No</td>
<td>I, II (SM, UJ)</td>
<td>I, II (SM, UJ)</td>
<td>+ SM, UJ, RP</td>
</tr>
<tr>
<td>7/F/76</td>
<td>T</td>
<td>T2 No</td>
<td>I (SM)</td>
<td>I (SM)</td>
<td>+ SM</td>
</tr>
<tr>
<td>8/F/65</td>
<td>T</td>
<td>T2 No</td>
<td>I (SM)</td>
<td>I (SM)</td>
<td>−</td>
</tr>
<tr>
<td>9/M/66</td>
<td>L</td>
<td>T2 No</td>
<td>III (MJ)</td>
<td>III (MJ)</td>
<td>−</td>
</tr>
<tr>
<td>10/M/68</td>
<td>FM</td>
<td>T3 No</td>
<td>I, II, III (SM, UJ, MJ)</td>
<td>I, II, III (SM, UJ, MJ)</td>
<td>+ SM</td>
</tr>
<tr>
<td>11/M/57</td>
<td>T</td>
<td>T2 No</td>
<td>I, II, III (SM, UJ, MJ)</td>
<td>I, II, III (SM, UJ, MJ)</td>
<td>−</td>
</tr>
</tbody>
</table>

Abbreviations: FM, floor of mouth; L, larynx; MJ, midjugular nodes; RP, retropharyngeal nodes; RT, retromolar trigone; SM, submandibular nodes; SMe, submental nodes; SN, sentinel lymph node; T, tongue; UJ, upper jugular nodes; +, histologically proven micrometastasis; −, histologically negative micrometastasis.

*aLymph nodes were categorized by zones (I−VI).*
nosis and interpretation. Fixed costs were allocated to purchase of a gamma probe. Break-even point analysis was performed because profits begin to accrue once all costs have been covered. However, regulatory costs, disposable materials, overhead, and maintenance costs were not allocated in the present study since the cost increase due to the introduction of the SN technology would be small in the nuclear medicine department. The cost in US dollars was calculated at a yendollar conversion rate of 120 yen to $1.

POOLED ANALYSIS

We performed pooled analysis of individual level data from the different studies on SN navigation surgery using Tc 99m colloid. Based on the results of 74 cases in the literature, the sensitivity of SN radiolocalization for detecting micrometastasis was calculated on a patient-by-patient basis.

All SNs but one were accurately identified by gamma probe radiolocalization. In the patient with T3 N0 tongue cancer (No. 6, Table 1), one skip nodal metastasis was missed in the retropharyngeal node, which we failed to identify by either gamma probe radiolocalization or scintigraphic mapping. The sensitivity of SN navigation surgery in our series was 100% (11 of the 11 patients) on a patient-by-patient basis and 94% (17 of 18 nodes) on a node-by-node basis. Identification of SN by scintigraphic mapping correlated well with gamma probe radiolocalization in all but one case (No. 2, Table 1). Micrometastasis was found in 36% (4 of 11 patients) on a patient-by-patient basis. The sensitivity and the negative predictive value of SN navigation surgery for detecting micrometastasis, as calculated in the pooled analysis, were 93% and 98%, respectively (Table 1).

Figure 2 shows the 1-way sensitivity analysis for micrometastasis prevalence, ranging from 0% to 100% on the expected cost savings per patient for the SN navigation surgery strategy vs ipsilateral neck dissection strategy. The expected cost savings per patient in the SN navigation surgery strategy decreases as micrometastasis prevalence increases, because the number of neck dissections for micrometastasis increases. The break-even point requires less than 85% prevalence in order for the SN navigation surgery strategy to reduce costs per patient.

Assuming the micrometastasis prevalence, sensitivity, and specificity of navigation surgery for detecting SN to be 30%, 90%, and 100%, respectively, the decision tree sensitivity analysis showed that introduction of the SN navigation surgery strategy in place of ipsilateral neck dissection strategy would yield cost savings of $1218 per stage N0 patient in Japan. In addition, the introduction would avoid 7 surgical deaths per 1000 patients who are supposed to undergo neck dissection in the neck dissection strategy (Figure 3).

Break-even point analysis for the SN navigation surgery strategy showed that the patient number requiring a break-even point increases as the prevalence of micrometastasis increases. The threshold value requires more than 41 patients for the savings to begin to accrue when the micrometastasis prevalence is 30% (Figure 4).

RESULTS

Table 2. Baseline of All Relevant Variables Used in the Decision Trees

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity of sentinel lymph node (SN) navigation surgery for micrometastasis, %</td>
<td>90</td>
</tr>
<tr>
<td>Specificity of SN navigation surgery for micrometastasis, %</td>
<td>100</td>
</tr>
<tr>
<td>Prevalence of neck micrometastasis, %</td>
<td>0-100</td>
</tr>
<tr>
<td>Success rate of SN biopsy, %</td>
<td>100</td>
</tr>
<tr>
<td>Mortality of SN biopsy, %</td>
<td>0</td>
</tr>
<tr>
<td>Mortality of neck dissection, %</td>
<td>1</td>
</tr>
<tr>
<td>Costs, yen (US $)</td>
<td></td>
</tr>
<tr>
<td>Lymphoscintigraphy</td>
<td>30 000 (250)</td>
</tr>
<tr>
<td>SN biopsy</td>
<td>12 000 (100)</td>
</tr>
<tr>
<td>Neck dissection, ipsilateral</td>
<td>124 000 (1033)</td>
</tr>
<tr>
<td>Labor (per hour)</td>
<td></td>
</tr>
<tr>
<td>Surgeon, anesthesiologist, pathologist, and nuclear medicine specialist</td>
<td>5800 (48)</td>
</tr>
<tr>
<td>Nurse</td>
<td>2180 (18)</td>
</tr>
<tr>
<td>Fixed cost, gamma probe</td>
<td>600 000 (50 000)</td>
</tr>
</tbody>
</table>

Early-stage head and neck cancer is surgically curable, but accurate preoperative staging is imperative for avoiding unnecessary neck dissection and thereby reducing medical costs.

Neck node metastatic rates of 14% for T1, 30% for T2, 48% for T3, and 76% for T4 head and neck cancer have been documented. In general, the risk of micrometastases is approximately 30% in patients with stage N0 head and neck SCC.11,12 Clinically, positive neck node metastasis are accurately diagnosed by a combination of morphological imaging studies and fine-needle aspiration cytology,12 with 95% sensitivity. However, micrometastases (cN0, pN1) can only be diagnosed with 50% sensitivity.13 Positron emission tomography with 18fluorodeoxyglucose (FDG-PET) appears to be a valuable imaging technique for the detection of cervical lymph node metastasis. However, false-negative errors in FDG-PET studies are ascribed to micrometastases.13-17 Detection of microscopic disease is beyond the scope of PET spatial resolu-
tion since micrometastasis is defined as a metastatic lesion measuring no more than 2 mm in greatest dimension. The presence of cervical metastasis cannot consistently be detected clinically, or even pathologically, by current routine clinical histopathological methods.

In our series, micrometastasis was found in 36% (4/11) on a patient-by-patient basis, indicating that SN navigation surgery would make neck dissection unnecessary in as many as 64% (7/11) of patients with stage N0 SCC. This raises the possibility of dramatically reducing the number of neck dissections performed in patients with stage N0 head and neck SCC. Furthermore, the SN navigation surgery technique is simple and easily performed, and would thus reduce morbidity and complications associated with neck dissection as well as costs in this patient group.

In 1 (9%) of our 11 patients, SN visualization by scintigraphic mapping was discordant with SN detected by gamma probe radiolocalization, probably due to “shine-through” artifact. The role of routine preoperative scintigraphic mapping in SN navigation surgery is controversial. We believe that scintigraphic mapping is helpful in that it provides head and neck surgeons with a bird’s-eye view of all head and neck nodes. Furthermore, there is a high association between scintigraphic mapping and gamma probe radiolocalization. It is possible for unexpectedly missed nodal metastasis to be visualized by scintigraphic mapping, though this technique failed to visualize a missed nodal metastasis in our patient. Skip nodal metastasis can occur in a small portion of patients with stage N0 head and neck SCC. The higher tracer activity might be needed to facilitate detection of the deep neck nodes or skip nodal metastasis many hours after peritumor injection.

Sentinel node navigation surgery may be criticized for the following issue: the examination of intraoperative biopsy (frozen section analysis) of SN may underestimate the true incidence of micrometastasis. We did not perform the newer technologies such as immunohistochemistry and molecular analysis. Nonetheless, SN navigation surgery appears technically feasible considering the results of pooled analyses with high sensitivity and negative predictive value.
In the decision tree and 1-way sensitivity analysis, we adopted 90% sensitivity and 100% specificity for navigation surgery in detecting SN. These values are reasonable compared with the meta-analysis value calculated from our literature review. The 30% prevalence of micrometastasis is also consistent with previously reported values and our data. However, the prevalence of micrometastasis may have a major influence on the clinical setting and vary from T1 to T4. Therefore, sensitivity analyses to determine the influence of micrometastasis prevalence values were performed for the neck dissection strategy vs the SN navigation surgery strategy. This study illustrates the power of sensitivity analysis in proving a hypothesis when there is medical uncertainty.

Assuming the micrometastasis prevalence, sensitivity, and specificity of navigation surgery for detecting SN to be 30%, 90%, and 100%, respectively, our decision tree sensitivity analysis results indicate that introducing SN navigation surgery in Japan in place of neck dissection would result in savings of $1165 per stage N0 patient without loss of life expectancy. The cost-effectiveness could be proven over a wide range of micrometastasis prevalence values, with the break-even point of 85%. Our results might suggest that stage N0 patients with greater than 85% prevalence of micrometastasis are candidates for immediate neck dissection.

We assumed life expectancies of stage N0 patients under the “wait-and-see” policy and subsequent salvage neck dissection to be identical to those of stage N0 patients undergoing elective neck dissection. The management of patients with stage N0 SCC with micrometastases is controversial. There is reportedly no difference in survival between the neck dissection group and the “wait-and-see” group (treatment when metastasis manifests). On the other hand, Tankere et al. emphasized that the presence of occult metastases in the T4 N0 SCC group justifies routine neck dissection. The prognostic significance of micrometastasis is not yet fully understood, ie, will it evolve into manifest neck disease or remain indolent or silent for the patient’s remaining life? The indications for SN navigation surgery may thus be strictly limited to patients with T1 N0, T2 N0, and T3 N0 disease. The wait-and-see group will have to be placed on a regular recall schedule and be more judiciously followed up for the rest of their life.

The technique remains economically variable, differing among countries. The strategies, costs, and variables that have been described herein are unlikely to be applicable in other countries. Nonetheless, we believe that the technology would be cost-effective even in other countries. To determine how society’s resources are allocated within the scientific realm of medical economics, we recommend that cost-effectiveness of the SN navigation surgery strategy be assessed in each country for the management of patients with stage N0 SCC of the head and neck.

In conclusion, our results indicate SN navigation surgery using scintigraphic mapping and gamma probe radiolocalization to be logistically feasible and cost-effective, based on decision tree sensitivity analysis, in patients with stage N0 SCC of the head and neck.

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