Sentinel Lymphadenectomy in Thyroid Malignant Neoplasms

Pond R. Kelemen, MD; Andre J. Van Herle, MD; Armando E. Giuliano, MD

**Background:** Lymph node metastases for well-differentiated thyroid cancer are associated with high recurrence rates. Surgical options consist of blind nodal sampling, “berry-picking” procedures, and modified radical neck dissections. Sentinel lymph node dissection (SLND) has been described by our institution for melanoma and breast cancer. We have investigated the feasibility of SLND for thyroid cancer.

**Design:** From August 1994 to October 1996 we investigated the technique of intraoperative lymphatic mapping and SLND in 17 patients undergoing surgical management of a suspicious thyroid nodule not accompanied by palpable cervical adenopathy.

**Setting:** Patients were referred from endocrinologists in community and academic practices. Procedures were performed in a community hospital.

**Patients:** There were 14 women and 3 men, ranging in age from 22 to 69 years (median, 48 years).

**Interventions:** At surgery, we exposed the thyroid lobe and used a tuberculin syringe to inject 0.1 to 0.8 mL of 1.0% isosulfan blue dye (mean, 0.5 mL) directly into the thyroid mass. Within seconds the blue dye passed along the lymphatics to the sentinel lymph node, which was then excised. Nodes were examined by routine processing and keratin immunohistochemical analysis to detect micrometastasis.

**Main Outcome Measures:** The feasibility of lymphatic mapping in determining primary drainage of suspicious thyroid nodules.

**Results:** Lymphatic mapping and SLND was followed by total thyroidectomy, except in 1 patient who underwent lobectomy for benign disease. Of the 17 nodules, 12 were ultimately diagnosed as thyroid carcinoma, 3 were follicular adenomas, and 2 were colloid nodules. Tumor sizes ranged from 0.8 to 4.0 cm. Lymphatic mapping was unsuccessful in 2 patients, whose lymphatics mapped to the retrosternum. All of the sentinel lymph nodes were paratracheal except in 2 women who also had jugular nodes that stained blue. Five (42%) of the 12 tumor nodules were associated with positive sentinel lymph nodes. Central neck dissections were performed in 5 patients; in 2 instances (17%), the sentinel node was the only tumor-bearing lymph node.

**Conclusions:** This is the first report of SLND for thyroid carcinoma. Our preliminary findings indicate that SLND can detect nonpalpable nodal metastasis with the same ease as in melanoma and breast cancer. The clinical significance of this technique in thyroid cancer remains to be determined.

Arch Surg. 1998;133:288-292

---

An estimated 16 100 cases of thyroid cancer will be diagnosed in 1997, and the overwhelming majority of these will be well-differentiated malignant neoplasms. The virulence of papillary and follicular carcinoma is low, with overall mortality rates ranging from 1.2% to 17%. No differences in survival have been seen, to our knowledge, between follicular and papillary cancers. These low death rates are attributed primarily to the biological characteristics of the disease and perhaps to the success of surgery and radioactive iodine therapy.

Stage for stage, risk of death is mostly related to age and sex. Cady and Rossi described a prognostic scoring system based on age, metastasis, extent, and size of tumor (AMES score). Age limits were defined as older than 40 years in men and older than 50 years in women. Extent of tumor indicated extracapsular tumor invasion and size limits were greater than 5.0 cm. Distant metastasis at the time of diagnosis was the greatest predictor of survival.

Most reports have shown that lymph node metastases are not associated with increased mortality as they are in other tu-

*From the John Wayne Cancer Institute at Saint John’s Health Center, Santa Monica (Drs Kelemen and Giuliano) and Section of Endocrinology, University of California, Los Angeles (Drs Van Herle and Giuliano), Los Angeles, Calif.*

This article is also available on our Web site: www.ama-assn.org/surgery.
PATIENTS AND METHODS

From August 1994 to October 1996, 17 patients underwent thyroidectomy with intraoperative lymphatic mapping and SLND. Inclusion criteria were at least 1 thyroid nodule suspicious for malignant neoplasm and no palpable evidence of cervical lymphadenopathy. Prior to our evaluation, most patients had undergone a diagnostic workup consisting of ultrasonography, technetium thyroid scan, and/or fine-needle aspiration biopsy at other institutions.

All patients underwent total thyroidectomy immediately after lymphatic mapping and SLND, except 1 patient whose thyroid nodule was found to be benign by intraoperative frozen section and therefore had only a lobectomy. At the time of surgery, the thyroid gland was exposed with a standard transverse low-collar skin incision and lateral retraction of the strap muscles. Using a tuberculin syringe, 0.1 to 0.8 mL (average, 0.5 mL) of 1.0% isosulfan blue dye (Ben Venue Labs Inc, Bedford, Ohio) was injected into the thyroid nodule. Within seconds the blue dye was seen to pass through lymphatic channels toward the sentinel lymph node (Figure). Once identified, all nodes that were stained blue were excised and sent for frozen section and permanent pathologic evaluation. In addition to routine hematoxylin-eosin staining, the sections underwent immunohistochemical staining for cytokeratin to help identify micrometastasis.

In our study group there were 14 women and 3 men, with ages ranging from 22 to 69 years (median, 48 years). Nine thyroid masses were discovered by self-examination, 7 were found by clinical examination, and 1 was detected on chest x-ray film. Forty-one percent of the patients experienced dysphagia or odynophagia. The rest were asymptomatic except for a mass. Duration of goiters or symptoms ranged from a few weeks to 15 years. Three patients (17%) had thyroid tumors discovered 23, 30, and 45 years after radiation exposure. Family histories of goiter or thyroid cancer were noted in 35% of our patients.

Patients had clinically measurable thyroid nodules ranging from 1.0 to 3.0 cm. Ultrasonographic examination was performed in 9 patients; size determinations were concordant with clinical but not with pathologic measurements. Preoperative thyroid scans were performed in 3 patients and revealed “cold” nodules, only 1 of which eventually became malignant. Fifteen patients underwent fine-needle aspiration biopsy: 12 (80%) yielded accurate results, 1 specimen was incorrectly diagnosed as a follicular neoplasm instead of a follicular variant of papillary cancer, and 2 specimens were diagnosed as papillary cancers (1 just by the presence of psammoma bodies) but were benign on permanent sections. In these last 2 cases, the biopsies were performed at a referring tertiary medical center.

Pathologic review of the 17 thyroid nodules revealed 12 malignant tumors (11 papillary carcinomas, 1 follicular cancer) and 5 benign lesions. Of the 5 benign lesions, 3 were follicular adenomas and 2 were colloid nodules. Two microscopic foci of papillary cancer were found incidentally in the thyroid glands with the benign nodules. Tumor sizes ranged from 0.8 to 4.0 cm (mean, 2.0 cm) (Table). All of the papillary cancers were well differentiated and 3 were follicular variants. Fifty percent of the glands showed a background of Hashimoto thyroiditis.

Intraoperative lymphatic mapping located at least 1 sentinel lymph node in all but 2 patients, both of whom appeared to have lymphatic channels coursing beneath the clavicles. In these 2 cases, we elected not to deliver the nodes into the operative field. In the remaining 15 patients, SLND removed 1 to 5 lymph nodes (median, 2).
Analysis of frozen sections and then permanent sections was undertaken in the 12 SLND specimens from patients with malignant thyroid nodules. There was only 1 discrepancy in which the frozen section was negative but the permanent section contained a small metastatic focus. No micrometastases were identified by immunohistochemical analysis alone.

Of the 12 primary thyroid carcinomas, 5 (42%) were associated with lymph node metastasis. None of the patients with incidental microscopic papillary tumors had metastasis. All of the excised sentinel lymph nodes were paratracheal except in 2 women who had additional jugular nodes that stained blue. In the 2 patients with jugular sentinel nodes, 1 had paratracheal and jugular lymph node metastasis, and the other had no metastasis. One patient had a negative sentinel lymph node with a micrometastasis in a non–blue-staining node discovered by immunohistochemical analysis. However, this lymph node was perithyroidal and removed with the thyroidectomy.

Central lymph node dissection was performed in 3 patients who had metastasis of the sentinel node diagnosed by frozen section. In 2 of these patients, the sentinel node was the only positive lymph node. In the other patient, the nonsentinel nodes as well as a jugular sentinel node had metastases. Subsequently, she underwent a modified radical neck dissection that revealed more cervical nodal disease. Two patients had suspicious nonsentinel palpable lymph nodes at surgery and therefore underwent central neck dissection. No metastases were found in these nodes. Intraoperative notes reported suspicious palpable adenopathy in 3 other cases, only 1 of which was found to have a lymph node metastasis. Intraoperative assessment of lymph nodes for metastasis was accurate in only 1 of the 5 cases that were believed to have suspicious nodes at the time of surgery.

Postoperatively, there were no permanent complications. One woman experienced temporary loss of voice projection. In all patients, postoperative calcium and parathy-

### Patients Who Underwent SLND* for Thyroid Cancer

<table>
<thead>
<tr>
<th>Patient/ Age, y/Sex</th>
<th>Tumor Size, cm</th>
<th>Tumor Type</th>
<th>Blue-Stained Nodes</th>
<th>Blue-Stained Node Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/31/F 2.0</td>
<td>Papillary, follicular variant</td>
<td>Paratracheal</td>
<td>0 of 2</td>
<td></td>
</tr>
<tr>
<td>2/45/F 2.0</td>
<td>Papillary</td>
<td>Paratracheal</td>
<td>1 of 2</td>
<td></td>
</tr>
<tr>
<td>3/58/F 2.0</td>
<td>Papillary</td>
<td>Paratracheal</td>
<td>0 of 2</td>
<td></td>
</tr>
<tr>
<td>4/69/M 0.8</td>
<td>Papillary, follicular variant</td>
<td>Paratracheal</td>
<td>1 of 1</td>
<td></td>
</tr>
<tr>
<td>5/44/F 0.8</td>
<td>Papillary</td>
<td>Paratracheal</td>
<td>0 of 2</td>
<td></td>
</tr>
<tr>
<td>6/50/F 1.0</td>
<td>Papillary</td>
<td>Paratracheal</td>
<td>0 of 1</td>
<td></td>
</tr>
<tr>
<td>7/22/F 4.0</td>
<td>Papillary</td>
<td>Paratracheal and jugular</td>
<td>2 of 2</td>
<td></td>
</tr>
<tr>
<td>8/42/F 3.0</td>
<td>Papillary</td>
<td>Paratracheal</td>
<td>1 of 2</td>
<td></td>
</tr>
<tr>
<td>9/67/M 2.5</td>
<td>Papillary, follicular variant</td>
<td>Paratracheal</td>
<td>0 of 3</td>
<td></td>
</tr>
<tr>
<td>10/42/F 1.5</td>
<td>Papillary</td>
<td>Paratracheal and jugular</td>
<td>0 of 2</td>
<td></td>
</tr>
<tr>
<td>11/51/F 1.5</td>
<td>Papillary</td>
<td>Paratracheal</td>
<td>1 of 1</td>
<td></td>
</tr>
<tr>
<td>12/48/F 2.7</td>
<td>Follicular</td>
<td>Paratracheal</td>
<td>0 of 5</td>
<td></td>
</tr>
</tbody>
</table>

*SLND indicates sentinel lymph node dissection.
roid hormone levels were within normal limits. None of the patients experienced problems from the blue dye. One patient underwent a modified radical neck dissection after the jugular sentinel node and central neck dissections revealed multiple positive lymph nodes. Radioactive uptake scans obtained postoperatively in 4 patients did not reveal cervical uptake. These patients included 3 with tumor-negative sentinel lymph nodes and 1 with a positive blue-stained node and negative results of central neck dissection.

This study presents a technique of intraoperative lymphatic mapping with SLND to assess occult lymph node metastasis in thyroid malignant neoplasms. Our experience confirms the findings of others' that surgical exploration and palpation is very inaccurate for predicting nodal disease. Lymphatic mapping was able to locate the sentinel lymph node in 88% of cases, a rate that compares favorably with rates reported for early trials of SLND in melanoma and breast cancer.17,20 The 2 failures were in patients who had lymphatic drainage toward the retrosternal-mediastinal area. In addition, 1 patient had a negative sentinel paratracheal lymph node but a positive nonsentinel perithyroidal lymph node that was adherent to the thyroid capsule and thus removed during thyroidectomy. This node could not be identified as a sentinel node because during this procedure the entire thyroid nodule turns blue (Figure).

In a study by Noguchi et al,19 of 68 patients with thyroid cancer who after elective neck dissection were found to have metastasis to only 1 lymph node, 78% of nodal metastases were found in the paratracheal region and 22% in the jugular chain. Our findings are similar, with 13% of sentinel nodes from the jugular region. All patients had paratracheal sentinel nodes. One might argue that a routine central neck dissection will diagnose most patients with nodal metastasis. However, Hamming et al20 showed that injury to the recurrent laryngeal nerve and parathyroid glands was greater in those patients undergoing central neck dissection than in those having only suspicious nodes excised. This is particularly true if dissection is undertaken after the development of a palpable metastasis, when exploration of a scarred neck would be hazardous. One of our patients had an occult metastasis in a jugular sentinel node and a subsequent modified neck dissection revealed multiple jugular and paratracheal metastases. A routine paratracheal node dissection or blind jugular sampling might have missed the jugular metastasis in our patient. In a series of 69 patients undergoing only central neck clearance, 20% of those with nodal metastasis subsequently required neck dissection for palpable disease.21

Nodal disease represents a marker for those who will die of their disease: 87% of patients in 1 report showed lymph node metastasis with synchronous or metachronous systemic disease.13 The mortality rate was the same in groups divided into those with greater or less than 5 metastatic lymph nodes.16 Distant metastasis is the true harbinger of poor survival, with almost all dying of their disease.21 In an autopsy review of 21 patients who died of metastatic well-differentiated thyroid cancer, 80% had locoregional disease at death, although only 14% died of locoregional disease.23 Death as a result of local disease resulted from airway compromise or perforation of the carotid artery. Samaan et al11 reported a mortality rate of 11% in 1599 patients. The most common cause of death was locoregional disease (38%) resulting from respiratory compromise.

Most clinical trials confirm that regional nodes are usually the first site of recurrence.13,22 It is estimated that the chance of nodal recurrence is 30% to 50% during 10 years.2 The overall recurrence rate has been documented at 20%, with most recurrences discovered within 24 months: 70% of sodium iodide I 131 scans detected tumor and 40% of clinically detected disease.22 Postoperative 131I scanning reveals clinically silent nodal metastasis in approximately 40% of patients with local recurrence.4 Several studies have shown that modified neck dissections have resulted in better local control.13,16 Patients with extensive nodal disease achieve better local control with more radical neck dissections vs simple excision of metastasis.24

Separating groups of patients into high- and low-risk groups may define patients who would benefit from lymph node dissection of occult metastasis. Using the AMES system, 1 series27 reported recurrence and death rates of 33% and 27% for high-risk patients vs 11% and 4% for low-risk patients, respectively. In addition, 70% of low-risk patients with recurrence or metastasis were cured with radioactive iodine, compared with a mere 10% in the high-risk group. Preemptive surgical excision of occult lymph node metastasis might be of advantage in high-risk patients, who have a greater chance of death and recurrence with a smaller chance of salvage with radioactive iodine. In addition is the possible transformation of well-differentiated tumors into the universally fatal anaplastic variety, which has been reported in 40% of patients who die of papillary cancer.23

For those surgeons who prefer lobectomy for well-differentiated thyroid tumor, detection of nonpalpable nodal metastasis might identify those patients best served by total or near-total thyroidectomy. For patients with a tumor-positive sentinel lymph node, completion thyroidectomy would allow postoperative 131I scanning and the use of thyroglobulin levels to screen for signs of recurrence or metastasis. Clinically occult lymph node metastasis can be successfully treated with 131I in 74% of patients, with an overall survival rate of more than 90%,4,22,26 Clinically apparent nodal metastasis carries a worse prognosis, with only a 50% to 60% salvage rate.4,22

This technique has particular applicability to patients with medullary thyroid cancer. In this tumor there is also debate as to the use of elective node dissection vs observation. However, the incidence of nodal metastasis and the eventual clinical presentation of occult metastasis is high. A series of 36 patients27 revealed that aggressive management of palpable or radiographically identified adenopathy resulted in appreciably better survival. Again, the use of routine central neck dissection would be inexact because 78% of patients in this series had multiple levels of nodal involvement. Identification and surgical excision of any occult metastases is particularly important because this pernicious tumor does not take up radioactive iodine.

Our technique for assessment of lymph node status in thyroid malignant neoplasms was able to detect...
solitary occult metastasis as well as jugular disease with no morbidity. This confirms the potential usefulness of SLND in solid tumors other than melanoma and breast, for which it was originally described.17,18 Although the impact of SLND for well-differentiated thyroid cancer is not entirely clear at this time, it clearly has clinical utility for patients undergoing lobectomy or for those with medullary or Hurthle cell carcinomas that do not take up.13,14 It may have universal applicability in solid tumors.

Presented at the 50th Annual Symposium of the Society of Surgical Oncology, Chicago, Ill, March 22, 1997.

Reprints: Armando E. Giuliano, MD, John Wayne Cancer Institute, 2200 Santa Monica Blvd, Santa Monica, CA 90404.

REFERENCES


Invited Commentary

The report by Kelemen et al reflects an extension of an interesting and potentially valuable surgical concept that has undergone initial evaluation for melanoma and breast cancer and appropriately could be assessed in thyroid cancer. The authors are experts in the technique of sentinel lymph node biopsy.

Patients with differentiated thyroid cancer enjoy excellent survival overall, but there remains significant controversy regarding what prognostic influence lymph node metastases portend and the most effective method of selecting patients for whom lymphadenectomy would be recommended.

Preoperative and intraoperative palpation, 131I scan, magnetic resonance imaging, computed tomographic scan, and high-resolution ultrasonography are possible modalities to identify patients with metastatically involved nodes. When abnormal nodes are located, even though their influence on overall prognosis remains uncertain, they do require treatment, which often consists of surgical excision.

Of the 12 patients who proved to have thyroid cancer, none had suspicious palpable cervical adenopathy preoperatively—precisely the clinical situation in which an accurate means of detecting metastatic nodes would be most valuable. Moreover, a technique that would predict accurately which patients do not have metastatic nodes would be equally helpful. Sentinel nodes were identified in 5 patients; all nodes were paratracheal and 2 patients had lateral jugular sentinel nodes. Somewhat troubling were patients with both false-positive (1 patient with staining of both central and lateral sentinel nodes) and false-negative (1 patient with nonstained lateral jugular nodes) results.

Ideally, a similar study design with a larger cohort of patients would include a complete central neck lymph node dissection, including patients whose nodes did not stain blue. In this way, the usual statistical measures of sensitivity, specificity, positive and negative predictive values, and accuracy could be assessed. Nevertheless, this report serves as an interesting and stimulating concept aimed at enhancing surgical precision for cervical lymphadenopathy in differentiated thyroid cancer.

Clive S. Grant, MD
Rochester, Minn