Value of Preoperative Ultrasonography in the Surgical Management of Initial and Reoperative Papillary Thyroid Cancer

John M. Stulak, MD; Clive S. Grant, MD; David R. Farley, MD; Geoffrey B. Thompson, MD; Jon A. van Heerden, MD; Ian D. Hay, MD; Carl C. Reading, MD; J. William Charboneau

Background: Cervical recurrences, predominantly in lymph nodes, occur in 14% to 30% of patients with papillary thyroid cancer (PTC). Postoperative surveillance for recurrent PTC increasingly includes thyrotropin-stimulated thyroglobulin and high-resolution ultrasonography (US). This combination commonly can detect recurrent disease as small as 5 mm.

Hypothesis: Preoperative US will increase detection and assessment of the extent of lymph node metastasis (LNM) in patients with PTC.

Design: Retrospective cohort study.

Setting: Tertiary care academic center.

Patients: From January 1, 1999, to December 31, 2004, a total of 770 patients were seen, 551 (381 female and 170 male; median age, 47 years; age range, 9-89 years) who underwent initial surgical management and 219 (154 female and 65 male; median age, 44 years; age range, 5-90 years) who underwent cervical reoperation for PTC. The US images were obtained preoperatively for 486 initial and 216 reoperative patients. Therapeutic radioactive iodine was administered to 151 (68.9%) of the reoperative patients before the subsequent operation (median dose, 5.6 x 10^9 Bq; range, 7.4 x 10^8-3.7 x 10^10 Bq).

Results: Ultrasonography identified nonpalpable lateral jugular LNMs in 70 (14.4%) of the patients undergoing initial exploration. Similarly, in reoperative patients, nonpalpable lateral LNMs were detected via US in 106 (64.2%), and 61 (28.2%) had LNMs detected in the central neck. Even when nodes were palpable preoperatively (37 [6.7%] of the initial and 56 [25.6%] of the reoperative patients), US assessment of the extent of LNM involvement altered the operation in 15 (40.5%) of the initial and 24 (42.9%) of the reoperative patients. The sensitivity, specificity, and positive predictive value for US were 83.5%, 97.7%, and 88.8% in initial patients, and 90.4%, 78.9%, and 93.9% in reoperative patients.

Conclusions: Overall, preoperative US detected nonpalpable LNMs in 231 (32.9%) of the 702 patients with PTC who underwent US, thereby altering the operative procedure performed. In addition, even in patients with palpable LNs, US helped to guide the extent of lymphadenectomy.

Arch Surg. 2006;141:489-496

For more than 2 decades, the most hotly contested surgical debate in the management of thyroid cancer was the extent of surgery: total vs near-total thyroidectomy vs unilateral lobectomy.1,2 Superseding this controversy since the turn of the 21st century has emerged the question of extent of associated lymph node dissection, particularly in papillary thyroid cancer (PTC), which represents nearly 90% of all thyroid cancers.

Formerly, lymph node metastases (LNMs) attracted less attention for several reasons. Large retrospective studies3-5 have consistently failed to identify LNMs as an important prognostic factor—they rarely either progressed to or even indicated an increased risk of death. Commonly quoted was an initial 30% frequency of LNMs,6 but if routine lateral jugular node dissection was performed, this figure soared to greater than 80%.7,8 Yet, such “prophylactic” dissection failed to enhance survival. Therefore, this led to the accepted standard of care stated by the American Thyroid Association: “A modified radical neck dissection is usually indicated for patients with clinically palpable extensive ipsilateral cervical adenopathy.”9(p2169) Similarly, according to a consensus statement by the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons, “surgeons should remove all enlarged lymph nodes in the central and lateral neck areas. Prophylactic lateral neck
of these recurrences could be discovered and treated to been identified in 30% to 40% of patients. Because most overall modus operandi, recurrent cervical LNMs have
tion, either preoperatively or intraoperatively. With this
guidelines as the mode of detection of LNMs was palpa-
side of the neck are benign.
metastasis in the midright jugular chain. The other slender-appearing nodes
papillary thyroid carcinoma in the right lobe but a nonpalpable lymph node
Figure 2. Ultrasonographic lymph node “map” demonstrating a palpable papillary thyroid cancer in the right lobe and lymph node metastases in compartments II, III, and IV.

Table. AJCC Staging for Initial and Reoperative Patients*

<table>
<thead>
<tr>
<th>AJCC Stage</th>
<th>Initial Patients</th>
<th>Reoperative Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>376 (68.2)</td>
<td>118 (53.9)</td>
</tr>
<tr>
<td>II</td>
<td>40 (7.3)</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>III</td>
<td>85 (15.4)</td>
<td>23 (10.5)</td>
</tr>
<tr>
<td>IV</td>
<td>50 (9.1)</td>
<td>74 (33.8)</td>
</tr>
<tr>
<td>Total</td>
<td>551 (100.0)</td>
<td>219 (100.0)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients.

Abbreviation: AJCC, American Joint Committee on Cancer.

Figure 1. Ultrasonographic lymph node “map” demonstrating the primary papillary thyroid cancer in the right lobe and lymph node metastases in compartments II, III, and IV.

From January 1, 1999, through December 31, 2004, 770 pa-
tients underwent thyroid surgery for PTC at our institution.
Surgery was performed in the initial setting in 551 patients and
in the reoperative setting in 219 patients. Medical records were
reviewed for patient demographics, preoperative clinical and
radiological evaluation results, operative procedure, and post-
operative follow-up.

Pathologic TNM stage (based on the American Joint Com-
mittee on Cancer staging system18) was determined by the his-
topathologic results from all operations based on extent of the
disease at the first operation performed at the Mayo Clinic
(Table). If no lymph nodes were removed, the node status was
considered N0.

Ultrasonography was performed with a high-resolution in-
strument (Sequoia; Acuson, Mountain View, Calif) equipped
with a high-frequency linear-array transducer of 7 to 13 MHz.
Each examination included the central (VI) compartment (the
space between the carotid arteries laterally, the thyroid carti-
lage superiorly, and the sternal notch or innominate artery in-
feriorly) and the lateral compartments (II-V) of the neck in the
initial and reoperative patients (Figures 1, 2, and 3). How-
ever, because we consider removal of the central compart-
ment nodes the responsibility of the surgeon during the initial
operation, and the thyroid often obscures these nodes in this
situation, we did not make any false-negative assessments by
US of the central compartment in these patients. Therefore,
we assessed the US accuracy of only the lateral compartment
nodes in the patients initially operated on, and the central and lateral
compartment nodes in the reoperative group, based on the
radiologist’s interpretation together with any US-directed fine-

Two significant technological advances have facili-
tated a major change in the clinical management of PTC.
The introduction and refinement of high-resolution cer-
talan ultrasonography (US) and recombinant human thy-
rotropin (Thyrogen) have enabled screening for and loca-
ization of microscopic recurrent LNMs in those with
PTC. The use of US has been embraced by some,12,13 but
Heller et al14(p1190) recently voiced significant skepti-
cism, “[if] we do ultrasonography on everybody, we would
do a lot of unnecessary neck dissections to avoid a small
number of possibly insignificant recurrences.” Just in
the past 5 years, recombinant human thyrotropin–
stimulated thyroglobulin measurements have been widely
recognized and enthusiastically advocated by endocri-
nologists and endocrine surgeons.15,16 Irrespective of the
threat of disease-related mortality, even slightly detect-
able postoperative levels of thyroglobulin often lead to
extensive radiological investigations, administration of
radiiodine, and/or a subsequent operation.17 The inev-
itable consequence forced by this intense postoperative
regimen is reconsideration of technologically enhanced
preoperative investigation and extent of intraoperative
lymphadenectomy. Therefore, we hypothesized that
the use of preoperative high-resolution US would im-
prove the detection and assessment of LNMs in those
with PTC.
needle aspiration (FNA), compared with the final histological features. The right and left lateral compartments were considered separately in patients initially operated on and those who underwent reoperation, and each side of the central compartment was considered separately in the patients who underwent reoperation. Level II (superior spinal accessory and superior jugular and jugulodigastric) compartment nodes were considered separately from compartments III (midjugular nodes), IV (inferior jugular and jugular-omohyoid nodes), and V (transverse cervical and supraclavicular nodes). In the absence of US FNA proof of LNMs, if the US report led to compartment dissection that would not normally have been performed during the usual operation (eg, lateral compartment in the initial operation), metastatic nodes would be counted as “true positive,” whereas benign nodes would be “false positive.” From the surgical perspective, in the initially operated on patients, a compartment VI dissection was defined either by specific notation in the operative note or when a minimum of 5 nodes were identified histologically. This typically encompassed supraclavicular, pretracheal, and bilateral tracheoesophageal groove lymph nodes. When LNMs were verified, lateral surgical dissection was considered adequate if compartments III and IV and at least the anterior portion of compartment V were included. The carotid and jugular vessels, the vagus, phrenic, spinal accessory, and the brachial plexus nerves were preserved unless involved by disease. In addition, most branches of the cervical plexus nerves could also be preserved. Even if more LNMs were identified histologically than anticipated by US within the specified compartments, these were still considered true-positive scans. A level II dissection was performed when indicated by US. In reoperative patients in whom a formal lateral compartment dissection had previously been performed, selective node dissection (limited to a single compartment) or “node picking” (selective removal of individual lymph nodes) was sometimes preferred to complete compartment resection. Ultrasonography was considered beneficial in patients with palpable nodes only if pathologic nonpalpable nodes were identified outside the scope of what would have been the normal dissection indicated by the palpable nodes. For example, palpable nodes in compartment III in the right lateral neck in a reoperative patient would indicate dissection of compartments III, IV, and V. If, however, additional nonpalpable pathologic nodes were identified in the right thyroid bed (compartment VI, right side) by US, these nodes would be dissected and the US considered beneficial. Cervical recurrences were considered nodal for either central or lateral LNMs. In contrast, true local recurrence was defined as tumor nodules within soft tissue with no evidence of associated lymph node tissue. 

INITIALLY OPERATED ON PTC GROUP

Of the 551 patients in this group, 170 (30.9%) were male and 381 (69.1%) were female, with a median age at operation of 47 years (range, 9-89 years). Cervical lymph nodes were palpable by physical examination in 37 patients (6.7%). Preoperative US was performed in 486 patients (88.2%), and detected nonpalpable LNMs in the central compartment in 10 patients (2.1%) and in the lateral compartment in 70 patients (14.4%).

REOPERATIVE PTC GROUP

Of the 219 patients in this group, 65 (29.7%) were male and 154 (70.3%) were female, with a median age at operation of 44 years (range, 3-90 years). Cervical lymph nodes were palpable by physical examination in 56 patients (25.6%). Preoperative US was performed in 216 patients (98.6%), and detected nonpalpable cervical LNMs in the central compartment in 61 patients (28.2%) and in the lateral compartment in 106 patients (64.2%). A total of 131 patients (68.9%) had received radioactive iodine before the subsequent operation. The median number of doses received was 2 (range, 1-6), and the median dose was $5.6 \times 10^8$ Bq (range, $7.4 \times 10^5$-$3.7 \times 10^{10}$ Bq). Patients underwent a median of 2 (range, 1-6) prior cervical explorations, with a median of 1 each in the central (range, 1-5) and lateral (range, 1-5) neck compartments.

DATA ACQUISITION AND ANALYSIS

Demographic and other patient-related data were obtained from Mayo Clinic medical records. Follow-up information was obtained from subsequent clinic visits, written correspondence from local physicians, and mailed questionnaires to patients or families. Data are expressed as mean ± SEM. The Mayo Foundation institutional review board approved this study, and all patients or their families gave written informed consent.

INITIALLY OPERATED ON PTC GROUP

Initial operations were performed on a total of 551 patients: thyroidectomy was performed in 233 patients (42.3%), near-total thyroidectomy in 233 patients (42.3%), lobectomy in 83 patients (15.1%), isthmectomy in 1 patient (0.2%), and biopsy only in 1 patient (0.2%), for unresectable disease (percentages do not total 100 because of rounding). The size of tumor removed was $1.7 \pm 1.2$ cm, with 14.2% of tumors measuring 5 mm or smaller. The PTC was multicentric in 176 patients (31.9%) and bilateral in 128 patients (23.2%); 56 tumors (10.2%) had evidence of extrathyroidal invasion.

A full central compartment lymph node dissection was performed in 279 patients (50.6%) and node picking was performed in 120 patients (21.8%); no central compartment operation occurred in 132 patients (27.6%). In patients who underwent some form of central compart-
ment lymph node clearance, 44.9% had evidence of metastases, with an average of 2 positive lymph nodes of an average total of 7 removed.

A lateral compartment lymph node dissection was performed in 94 patients (17.1%), of whom a standard neck dissection of levels III, IV, and V was performed in 47 (50.0%); a level II dissection was added to levels III through V in 20 patients (21.3%), node picking in 20 patients (21.3%), and a select dissection in 7 patients (7.4%). Of these patients, 91.5% had LNMs, with an average of 5 positive lymph nodes of an average total of 22 removed.

Overall, for patients undergoing an initial operation for PTC, cervical LNMs were present in the central compartment in 179 (32.5%) and in the lateral compartment in 86 (15.6%). Preoperative US was helpful in guiding the extent of dissection in 15 (40.5%) of the 37 patients who had palpable cervical lymph nodes preoperatively.

Follow-up information was obtained for 501 (90.9%) of the 552 patients, with an average of 2.5 years. Forty-seven patients (9.4%) had evidence of relapse of PTC. Cervical lymph node recurrences accounted for 44 (8.0%), distant in 7 (1.3%), and true local recurrence in 6 (1.1%). The median time to recurrence was 10 months (range, 1.5-75 months). Of the 47 patients with recurrent PTC, the reason for relapse was attributed to no preoperative US in 11 (23.4%), false-negative US in 12 (25.5%), recurrence in the operative field in 25 (53.2%), and disease virulence (evidence of distant metastases or true soft tissue local recurrence in a previously operated on field) in 13 (27.7%).

REOPERATIVE PTC GROUP

Of the 219 reoperative patients, 123 (56.2%) underwent a subsequent central compartment operation. A full central compartment lymph node dissection (left and right thyroid beds) was performed in 64 patients (52.0%), a right central node clearance in 20 (16.3%), a left central node clearance in 20 (16.3%), and node picking in 19 (15.4%). In patients who underwent some form of central compartment lymph node clearance, 79.7% had evidence of metastases, with an average of 3 positive lymph nodes of an average total of 6 removed.

A lateral compartment lymph node dissection was performed in 130 patients (59.4%). A standard neck dissection of levels III, IV, and V was performed in 30 patients (23.1%); a level II dissection was added to levels III through V in 31 patients (23.8%), node picking in 48 patients (36.9%), and a select dissection in 21 patients (16.2%). In these patients, 92.8% had LNMs, with an average of 4 positive lymph nodes of an average total of 16 removed.

Preoperative US was helpful in 24 (42.9%) of the 56 patients who had palpable cervical lymph nodes preoperatively.

VALUE OF PREOPERATIVE US

Initial PTC

When used before a first-time operation for PTC, US had a true-positive rate of 14.7%, a true-negative rate of 80.5%, a false-positive rate of 1.9%, and a false-negative rate of 2.9%. Furthermore, US displayed 83.5% sensitivity, 97.7% specificity, 88.8% positive predictive value, and overall 95.2% accuracy.

Reoperative PTC

When used before a subsequent operation for PTC, US had a true-positive rate of 56.7%, a true-negative rate of 13.8%, a false-positive rate of 3.7%, and a false-negative rate of 6.0%. Furthermore, US displayed 90.4% sensitivity, 78.9% specificity, 93.9% positive predictive value, and overall 87.9% accuracy.

COMMENT

For decades at the Mayo Clinic, standard surgical practice for the treatment of PTC included either near-total or total thyroidectomy, excision of palpably worrisome lymph nodes, and often subsequent treatment with radioactive iodine.1 The multicentric bilateral nature of the disease with lymphatic metastases was addressed surgically, and whatever small amount of uptake that was discovered by a postoperative iodine 131 scan, whether residual thyroid or LNMs, was presumably easily ablated by as little as an outpatient therapeutic dose of radioiodine. Disease mortality and surgical complications were rare—certainly by comparison with other solid tissue tumors. But disease recurred in 15% of these patients. With the introduction followed by the routine incorporation of US and serum thyroglobulin (often stimulated by recombinant human thyrotropin) into the postoperative evaluation of patients with PTC, macroscopic but non-palpable metastatic lymph nodes could be detected and proved with US FNA. This postoperative regimen has been vigorously advocated by the endocrinology leadership in the United States and has reached widespread adoption by the endocrinology community.6,15,17,19,20 In response to this, we increasingly adopted the routine use of preoperative US when the FNA of a thyroid nodule was either positive or suspicious for PTC, and in all patients with PTC who underwent reoperation.

From 1999 through 2004, 770 patients with PTC underwent surgical treatment at the Mayo Clinic. Ultrasonography was performed in 486 (88.2%) of those undergoing initial operation and in 216 (98.6%) of the reoperative patients. Of the 702 patients who underwent US, 231 (32.9%) had nonpalpable LNMs detected that directly altered the operative procedure. These were macroscopic nodes that clearly would have been detected by follow-up US and thyroglobulin measurements, and in our practice, would have led to a subsequent operation.

Of the 551 patients undergoing initial operation, 70 (12.7%) had nonpalpable nodes detected in the lateral compartment, whereas only 10 (1.8%) had similar nodes identified in the central compartment. Of the 37 (6.7%) with preoperatively palpable LNMs, US information directly altered the planned surgical procedure in 15 (40.5%). Soon after initiating preoperative US screening for PTC, it became clear that in patients with the thy-
roid still present, LNMs in the tracheoesophageal groove along the course of the recurrent laryngeal nerve were commonly obscured from US detection. As is apparent from our data that LNMs were found in 44.9% of patients undergoing central neck dissection, this needed to be a standard part of our initial operative treatment for PTC. Therefore, the crucial preoperative US assessment in these patients is directed to the lateral jugular lymph node compartments. Moreover, because level II nodes are infrequently involved and to dissect them requires significant extension of the neck dissection incision, we adopted levels III, IV, and the anterior portion of level V as our standard lateral compartment dissection. The dissection is extended to incorporate level II nodes when indicated. To rely on US so heavily as not only the threshold to proceed with lateral neck dissection but also the extent of dissection requires highly skilled, dedicated, and intellectually committed ultrasonographers. This skill is extremely operator dependent because distinguishing benign from malignant nodes by image criteria is vital. Nodes located outside the planned scope of the operation that are indeterminate but suspicious for disease require FNA. But for the 80% of patients without lateral LNMs, this judgment is usually made on image criteria only. Incorrect US interpretation occurred in only 4.8% of our initially operated on patients, but 11 patients may have avoided subsequent operation for LNMs detected by follow-up US had they undergone similar screening preoperatively.

Adequate preoperative imaging with precise anatomical localization has become virtually mandatory in the surgical management of reoperative PTC patients. Cervical US is more sensitive and precise than any other modality in our experience. That 167 (75%) of the reoperative patients had nonpalpable nodes discovered by US bears strong testimony to its value. In addition, in more than 40% of patients with palpable nodes, the operation was altered because of US findings. Scarring and altered anatomical features render US imaging more difficult, and 10% of these patients had incorrect interpretations. However, without clear compartment-oriented US mapping, the operative treatment in the remaining 90% would have been markedly compromised. The same scarring and altered anatomical features cause the operative risks of damage to healthy structures to increase with each subsequent operation. Recognizing that these LNMs may not alter the patient’s lifespan, balancing the risks of subsequent operation against the patient’s anxiety of tumor recurrence and the potential of tumor-related morbidity becomes more precarious. It is ironic, then, that critics of routine preoperative US and thorough central neck lymphadenectomy at the initial thyroidectomy procedure support subsequent operation for subsequently discovered enlarged lymph nodes.14 Admittedly, a full compartment VI dissection requires additional time and expertise because the tracheoesophageal nodes are always found adjacent to the recurrent laryngeal nerve. In almost all initially operated on PTC patients, however, these nodes are easily separated from the nerve and can be readily distinguished from the preserved parathyroid glands. In contrast, cervical reexploration can be considerably more demanding. Although locating the nerve is usually safely accomplished rather low in the neck, dissecting it to its insertion may be quite challenging in the area of prior thyroid dissection. Moreover, the parathyroid glands have often been relocated by the thyroid dissection, and are totally obscured by the resulting scar in most patients. The logical conclusion, therefore, would be to expend the additional time and effort to complete a thorough dissection at the initial operation, irrespective of tumor-related mortality expectations. Specifically, this should be done even in low-risk patients—young patients with a much increased likelihood of LNMs—who would be expected to benefit by this approach. However, it is our impression, based on hundreds of subsequent operations, that failure to excise these nodes reflects as much surgeon indifference as surgeon inexperience.

The defense that “nodes don’t matter” or that radioactive iodine can “mop up the nodes” is no longer tenable. Almost 70% of our reoperative patients with pathologically confirmed LNMs had undergone iodine 131 treatment. A substantial median dose of 5.6 × 10⁶ Bq had been administered, virtually always to the point that no further uptake was seen on radioiodine scan. The usual indicator for persistent disease in these 151 patients was an elevated thyroglobulin level. Many times the elevated thyroglobulin level was detected after a 5-day testing protocol including 2 doses of recombinant human thyrotropin. A thyrotropin-stimulated thyroglobulin level of 2 µg/L is considered the threshold for further imaging investigation for PTC.15 However, in one report,17 only 1 of 11 patients with thyroglobulin levels of 4 µg/L actually had disease identified. Clearly, the trend among endocrinologists is to pursue almost molecular levels of thyroglobulin as a marker for PTC recurrence. Our data demonstrate that even repeated doses of radioactive iodine are often ineffective at completely ablating such recurrences, necessitating surgical removal.

The previously quoted guidelines for lymphadenectomy in patients with PTC, published by endocrine and thyroid specialty organizations, actually remain accurate. However, palpation as the sole means of detection has been demonstrated by our data and by those from The University of Texas M. D. Anderson Cancer Center, Houston,12 to be woefully inadequate. Preoperative US has consistently identified nonpalpable LNMs in at least 15% of patients undergoing initial thyroidectomy and in 70% of reoperative patients. In nearly half of patients who have palpable nodes, the operation will be altered by information gleaned from preoperative US. Pivotal to this success are highly skilled ultrasonographers. They must be knowledgeable and experienced in distinguishing benign from suspicious or malignant nodes mostly based on image criteria alone, and devoted to the time-consuming effort of a careful examination. They must be able to perform US-directed FNA safely and accurately. In the initially operated on patient, their most important zones of interest are the entire lateral jugular chains bilaterally. In the reoperative patient, the right and left thyroid beds (compartment VI) must also be carefully examined. Anatomical precision in the dictated report is vital, and an accompanying “map” is beneficial. Of even greater importance by virtue of the associated risks is the surgeon’s responsibilities. A thorough compartment VI dissection in the initially operated on patient can be ac-
Although there is a decrease in the number of lymph node metastases in patients with papillary thyroid carcinoma, the risk of recurrence in the neck is substantial. Studies have shown that in about 20% to 30% of patients, cervical lymph node metastases occur only in about 20% to 30% of patients, and this is clinically significant. However, some lymph node metastases can grow and become clinically significant. In patients, up to 80% of patients with papillary thyroid carcinoma (PTC) will be found to have cervical node metastases. The rule of thumb is that you will find positive nodes in the central neck in two thirds of the patients, in the contralateral lateral neck in one third of the patients, and in the mediastinum in one third of the patients. In contrast, clinically significant cervical node recurrences occur only in about 20% to 30% of patients, and this risk can be lowered by radioactive iodine treatment. Thus, most lymph node metastases remain dormant and will not become clinically significant. Some, however, can grow and become clinically significant. The problem is, we do not know what will happen.

If we are finding more nodes by ultrasound, are we now doing more aggressive lymph node dissection than we need to? Is detecting and removing these ultrasound-positive nonpalpable nodes beneficial to the patient? The controversy regarding management of lymph nodes in PTC stems from the fact that not all cervical lymph node metastases are the same. We know from historical studies and from the Japanese experience that if we routinely dissect all compartments in the neck, about 80% of patients with PTC will be found to have cervical node metastases. The rule of thumb is that you will find positive nodes in the central neck in two thirds of the patients, in the ipsilateral lateral neck in two thirds of the patients, in the contralateral lateral neck in one third of the patients, and in the mediastinum in one third of the patients. This widespread lymph node involvement can even be found in the very-low-risk patients with micropapillary thyroid cancer. In contrast, clinically significant cervical node recurrences occur only in about 20% to 30% of patients, and this risk can be lowered by radioactive iodine treatment. Thus, most lymph node metastases remain dormant and will not become clinically significant. Some, however, can grow and become clinically significant. The problem is, we do not know what will happen to these ultrasound-positive nonpalpable lymph nodes if we leave them alone. We need to keep in mind that many of these patients may not develop clinically palpable or invasive disease and that neck dissection is not without morbidity.

DISCUSSION

Quan-Yang Duh, MD, San Francisco, Calif: The quantity of data and the quality of analysis are what we have come to expect from the Mayo Clinic. I agree with their conclusion that preoperative US is valuable and their recommendation that it should be done routinely. Having said that, I would like to discuss briefly why I am concerned that routine preoperative US may lead to more aggressive lymph node dissection than necessary. Then I will ask a few questions.

At UCSF [University of California, San Francisco], we also perform routine preoperative cervical ultrasound. Our main reason, however, is "if the endocrinologists are going to find them by ultrasound after the operation, we better find them before the operation." That is really the main reason.

Most endocrine surgeons would agree that clinically obvious large or palpable nodes should be resected. And most, I am sure, would also agree that very small lymph nodes, even if they harbor a few thyroid cancer cells, do not need to be resected. There is a third group of patients: those with ultrasound-positive nonpalpable lymph nodes. With the improving resolution of ultrasound and increasing body mass index of the population with thicker necks, more patients with PTC are falling into this intermediate group. In this study, 15% of those undergoing initial operation and 64% of those undergoing re-operation belong to this intermediate group with ultrasound-positive nonpalpable lymph nodes. These data are similar to what was found in the published M. D. Anderson series and in our own experience.

If we are finding more nodes by ultrasound, are we now doing more aggressive lymph node dissection than we need to? Is detecting and removing these ultrasound-positive nonpalpable nodes beneficial to the patient?
Perhaps we should give these ultrasound-positive nonpalpable lymph nodes a shorter name. I suggest that we call them “pythian nodes,” since we already have the “delphin nodes.” Pythia was the priestess of Delphi whose utterance was ambiguous and can be interpreted many ways. These nodes are like Pythia’s utterance: we hear it, but we may not truly understand what it really means.

I have 3 questions: (1) Were there any complications related to the neck node dissection in these patients? Specifically, were there complications in the group of patients with these pythian nodes? (2) How do you interpret the oracle? How do you decide that a lymph node is clinically significant by ultrasound and requires a neck dissection? Do you have a size threshold? 1 cm, 5 mm, or any size if it looks abnormal? And when do you confirm your suspicion by FNA? Do you always do that? (3) Do you have any data to show that routine preoperative US has lowered your lymph node recurrence rate? Perhaps compared with your historical controls?

Dr Grant: I would agree entirely with the reason we started to obtain preoperative ultrasound was, like you, because when the endocrinologists started using it postoperatively. Specifically, postoperative ultrasound detected a small metastatic node in the lateral jugular chain in a young patient that I had not palpated intraoperatively. This led to reoperation and convinced me that I would initiate preoperative ultrasound to facilitate a 1-stage operation rather than facing other 2-stage procedures.

Regarding complications related to the neck node dissection in these patients, we are presently analyzing these data as part of a subsequent study specifically addressing the surgical and outcome details. However, at least in the initial operation, the frequency of permanent unintentional recurrent laryngeal nerve damage was 0.7% and permanent hypoparathyroidism was 0.6%. There is no question that our advice to routinely add central neck lymphadenectomy is more technically demanding. But I suspect that when the central neck is not dissected, it is less a matter of surgeon expertise or experience and more a matter of surgeon indifference.

You asked about distinguishing clinically significant lymph nodes by ultrasound, size criteria, and the use of FNA. We recognize that there are multiple phenotypic characteristics that are typical for metastatic papillary cancer, such as cystic degeneration, microcalcifications, rounded rather than elongated appearance, loss of the fatty hilum, heterogeneous texture, and increased blood flow. Most of the time, even when the nodes may have these characteristics that are very suspicious for metastasis, we advise ultrasound-directed FNA for confirmation.

We do not have any set size threshold. Lymph nodes as small as 4 to 5 mm in the lateral jugular chain have prompted us to extend the thyroidectomy procedure to include a modified radical neck dissection. As noted in the article, this involves compartments III, IV, and V, but not routinely level II. Unless the ultrasound demonstrates metastatic nodes in level II, we do not extend the incision and dissection to that level.

You asked has routine ultrasound lowered our recurrence rate. Again, that will be answered when we analyze the details of relapse. Presently, we know that in the initially operated group with a mean follow-up of 2.5 years, there is a 9% relapse rate. Of these, as might be expected, 8% are lymph node recurrences, whereas only one half of 1% each are true soft tissue recurrence and distant disease.

As part of our future analysis, we plan to look not only at type of recurrence but hopefully we will be able to determine specifically the value of ultrasound: was it performed, was it false negative, did the lymph node recurrence develop in the previously operated field, was the recurrence related to a “node-picking” procedure vs an “en bloc” node dissection, or was the recurrence more a reflection of increased virulence of the disease as evidenced by concurrent soft tissue recurrence or distant metastases?

Gary B. Talpos, MD, Detroit, Mich: Dr Joe Atty reported a 25% incidence of lymph node metastases associated with PTC 25 years ago. However, because they rarely impacted the patient’s prognosis, he stopped operating on them. It concerns me to think we are doing ultrasound examinations just to preempt the endocrinologists in their follow-up, but to no benefit to the patient.

My questions have to do with patient selection. Do you have any information on the TSH levels, specifically regarding TSH suppression postoperatively, on your patients? Do you monitor thyroglobulin? Are these higher-risk patients who could have been equally managed by increasing thyroxine suppression of the TSH?

Thank you for limiting this paper to PTC as opposed to including all thyroid cancer subgroups. But we know that not all papillary cancers are “created equal.” Are these the good-risk, less than 45-year-old, stage I patients with lymph node metastases? Or are there others with insular or tall-cell variants of papillary cancer that we know carry a higher risk and might justify reoperation?

Dr Grant: Relating to the selection of the patients, virtually all of these patients postoperatively have tightly monitored adequate TSH suppression.

Prototypic of our reoperative patients are those who are referred with a negative iodine 131 scan but elevated thyroglobulin, but the home physician has not found the location of the disease. Commonly, with the use of ultrasound, the nodes are identified and mapped, verified to be malignant by FNA, the patients undergo node dissection, and their thyroglobulin usually drops to undetectable levels. I cannot give you our data on thyroglobulin levels but we will be assessing that as part of the relapse analysis.

We pay attention to the thyroglobulin levels but do not routinely follow the intensive protocol that is suggested in the endocrinology literature. That protocol extends over 5 days, including 2 doses of synthetic human TSH (rh [recombinant human] TSH), followed by thyroglobulin measurement. If the level exceeds 2 µg/L, further efforts at either localization or therapeutic treatment such as I-131 are considered.

As suggested by both Drs Duh and Talpos, there is an apparent divergence of opinion and practice between ignoring the seemingly innocent microscopically involved lymph nodes on one hand and intensively seeking evidence of minimal recurrence on the other hand. As Dr Duh suggests, these are the pythian nodes. Because they represent macroscopic disease—albeit not necessarily palpable—and lead to recurrence sufficiently large enough to be detectable by both ultrasound imaging and thyroglobulin measurement, we endorse ultrasound imaging as our threshold.

I cannot give you figures on the frequency of tall-cell variant or insular subtypes of PTC. These are rare but virulent subtypes, and often when they recur, it is in the form of soft tissue recurrence or distant disease.

Samuel Snyder, MD, Temple, Tex: We also agree with the use and the benefit of preoperative ultrasound to evaluate these patients, particularly for nonpalpable disease in the lateral neck.

Who is doing the ultrasound on your patients? Our preference would be for the surgeon to look at these lymph nodes with ultrasound and guide the biopsy to prove metastatic disease. It is difficult to follow ultrasound when you have radiologists creating images, and it is so operator dependent on what image they take. It is not like CT [computed tomographic] scans. It is difficult sometimes to compare 1 series of ultrasounds to another.

How did you get false positives? I take it that these patients did not have biopsy-proven metastatic disease and surgery was...
done just on the morphologic characteristics seen on the ultrasound.

Lastly, how do you manage patients who show up with 1 lateral biopsy-proven metastatic lymph node, in compartment II, III, or IV?

Dr Grant: We rely on dedicated ultrasonographers who perform the ultrasounds. That does not mean that surgeons cannot do them. I think that decision is largely determined by the local practice. What is crucial is that whoever is doing it must be good. Really good. The communication between the ultrasonographer and the surgeon must be good, which we have enjoyed for more than 2 decades.

The false positives are exactly as you suggested—phenotypically convincing for malignancy but were not needle aspirated and proved to be benign histologically. Although this occurred only rarely, we have evolved to almost routinely utilizing ultrasound-directed FNA to avoid these false positives.

And the last question about single malignant lateral jugular lymph nodes, 1 per compartment. It is not at all unusual for the ultrasound to identify only 1 or 2 lymph nodes in 1 or 2 compartments. In an initial operation, this would be an indication for a compartment-directed en bloc dissection. Frequently, the number of metastatically involved nodes histologically has been more than indicated by ultrasound. We do not think this is a failing of ultrasound. They simply do not see them all. The situation is more complex in patients who have undergone prior neck dissection in the area that nodes are identified. Reoperation in this setting is often more difficult, carries increased risk, and is usually more conservative—either node picking or limited en bloc dissection.

Baiba J. Grube, MD, Galveston, Tex: One alternate approach would be to identify these tumor cells in the central neck or lateral neck with lymphatic mapping. The lymphatic mapping was initiated first for melanoma and for breast, but the experience of the John Wayne Cancer Institute has adapted this to thyroid disease. And it has been useful for at least the central neck and low lateral neck to identify the presence or absence, helping one decide whether central neck dissection is indicated or not. I wonder if you have had any experience with lymphatic mapping in your institution.

Dr Grant: We regularly use lymph node mapping for breast cancer and melanoma. We have not undertaken a study of lymphatic mapping in papillary cancer because nodes are so commonly positive. Once a single node is positive, we would proceed with en bloc dissection as previously indicated. I do not know of any data that would allow us to use mapping to discriminate any further information or limit the subsequent dissection. Additionally, because nodes are so commonly positive, and because there is very limited morbidity with these node dissections compared to axillary or groin dissections, at least in first-time operations, we have chosen the alternative to clear the central neck rather than do the lymphatic mapping.

---

**Announcement**

In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Surgery* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as [http://ClinicalTrials.gov](http://ClinicalTrials.gov)). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after March 1, 2005. For trials that began enrollment before this date, registration will be required by June 1, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004; 292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of *JAMA*. Also see the Instructions to Authors on our Web site: www.archsurg.com.