Impact of Preoperative Ultrasonographic Staging of the Neck in Papillary Thyroid Carcinoma

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Objective: To determine the frequency of occult macroscopic metastasis detected by preoperative US evaluation of the neck in patients with PTC. Papillary thyroid carcinoma (PTC) is a malignancy with a high rate of lymph node metastasis. The findings of routine thyroid ultrasonography (US) and physical examination may underestimate metastatic disease. Thus, we propose that patients diagnosed as having PTC undergo preoperative US staging of the neck.

Design: This prospective study included 60 patients diagnosed as having PTC from January 1 through June 30, 2006. Patients had undergone previous thyroid US evaluation with no palpable adenopathy. Lymph nodes were deemed suspicious by US findings with a minor axis greater than 10 mm, a minor axis greater than 50% of the major axis, or hyperechogenicity with or without microcalcifications. Metastasis was confirmed by fine-needle aspiration biopsy or frozen section analysis. Patients with confirmed metastasis underwent a neck dissection. The location of adenopathy reported by US was correlated with the pathological report.

Results: The US evaluation identified 12 of 60 patients (20%) with adenopathy suggestive of metastasis. Metastasis was confirmed in 11 of 12 patients (92%). Metastasis was found in 1 of 48 patients who had a negative US finding. Overall, sensitivity, specificity, and positive and negative predictive values were 92%, 98%, 92%, and 98%, respectively. All neck levels with suspicious adenopathy detected by US evaluation, with 1 exception, were confirmed by pathological findings. Nine patients had additional neck levels involved with microscopic disease undetected by the US evaluation.

Conclusions: In patients with PTC, preoperative US evaluation of the neck is effective in detecting nonpalpable metastasis. Therefore, routine preoperative neck US evaluation is recommended to optimize primary surgical planning.

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Papillary thyroid carcinoma (PTC) is an endocrine neoplasm of increasing incidence that has a high frequency of lymphatic metastasis. Lymph node metastases have been reported to be as high as 80% if subclinical disease is considered.1-2 Metastatic spread of PTC to the neck has little if any effect on overall or disease-specific survival; however, the presence of lymph node metastasis is a clear prognostic factor affecting recurrence.3-4 Because cervical recurrence has been reported in up to 31% of cases, it is most likely that many patients have macroscopic metastases at the time of initial diagnosis that are not systematically detected by thyroid ultrasonography (US) and not eradicated by radioactive iodine therapy.

The management of neck metastasis for PTC has had different approaches ranging from “berry picking” in patients with palpable neck disease to bilateral modified radical neck dissection in all patients regardless of the nodal status of the neck.7-8 Berry picking has been discontinued given the high rate of neck recurrence and the morbidity associated with multiple surgeries, mostly recurrent laryngeal nerve paralysis and hypoparathyroidism. The radical approach is clearly unnecessary given the lack of evidence demonstrating that prophylactic neck dissection improves disease-specific or disease-free survival in patients without evidence of macroscopic disease.9 Therefore, the present recommendation includes the removal of all enlarged lymph nodes in the central and lateral compartments.10 In our institution, patients with proved metastatic disease undergo a central compartment dissection if disease is confined to level VI and a selective neck dissection of levels IIa, III, IV, Vb,
and VI if adenopathy is detected in the lateral compartment of the neck.

Metastatic PTC most frequently occurs in the central compartment or deep to the sternocleidomastoid muscle in levels III and IV. Detection of neck metastasis in these areas solely by palpation can be difficult and may miss a significant proportion of patients who have smaller macroscopic metastasis. Proper preoperative imaging of the neck by the introduction of improved high-definition US performed by highly specialized neck radiologists has allowed the detection and localization of small pathologic lymph nodes.13 Hence, careful US staging of the neck may identify patients who have nonpalpable adenopathy, thus avoiding reoperations associated with persistent or recurrent disease. The purposes of the present study were to determine the value of preoperative US staging of the neck in patients with an initial diagnosis of PTC and nonpalpable neck disease and to determine the effect of that staging in surgical management.

METHODS

In a prospective study performed from January 1 through June 30, 2006, 74 patients were referred to our institution for surgery with a diagnosis of PTC confirmed by fine-needle aspiration biopsy findings. Patients included did not have palpable disease on the physical examination findings and had only undergone a previous thyroid scan with no reliable information of the nodal status of the neck. Therefore, 14 patients with palpable neck adenopathy or with previous US information of neck lymph node status were excluded, leaving a study population of 60 patients. After thorough physical examination by a head and neck surgeon (H.E.G.), patients underwent comprehensive US evaluation of the neck of levels I through VI performed by 2 highly trained neck radiologists (F.C. and A.O.). The US evaluation was performed with a high-resolution instrument (Philips HD11 XE; Philips Medical Systems, Bothell, Washington) equipped with a high-frequency linear-array 5- to 12-MHz transducer. Lymph nodes were characterized by US findings as highly suggestive of metastasis with any of the following criteria: minor axis greater than 10 mm, minor axis greater than 50% of major axis, or hyperechoegenicity with or without microcalcifications.11 In the US report, the nodal status of each neck level was given separately, including level VI, which was specified as right or left. If no adenopathy suggestive of metastasis was detected by US, systematic careful exploration of the central compartment was performed. The presence of macroscopic metastasis was confirmed by the results of preoperative US-guided fine-needle aspiration biopsy or by intraoperative frozen section analysis. Therefore, we defined macroscopic metastatic disease as pathologically confirmed metastasis detected by US findings or by intraoperative central compartment exploration. For statistical analysis, patients with a negative US finding and negative results of central compartment exploration were considered to be without metastasis because the interest of this study was the assessment of macroscopic disease. If metastasis was detected in level VI, a paratracheal dissection was performed. If metastasis was detected in the lateral compartment of the neck, patients underwent a comprehensive dissection including levels Ila, III, IV, Vb, and VI with preservation of the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve. Removed neck levels were divided in the operating room by the same surgeon and sent separately to the pathologist so that the status of each node level reported by the US finding could be correlated with the pathological report. Medical information for all patients was recorded in a prospective database, including demographics, preoperative clinical evaluation findings, operative procedure, and pathological reports. All patients signed an informed consent form approved by the institutional ethics committee.

RESULTS

In this study, 60 consecutive patients with nonpalpable neck disease and no previous imaging information about nodal status underwent detailed preoperative US staging of the neck. The study population included 49 female patients (82%) and 11 male patients (18%); the median age at diagnosis was 40 (range, 10-83) years. The final pathological report confirmed PTC in all patients, including the usual type in 51 (85%) and the follicular variant in 9 (15%). The mean±SD size of the tumor removed was 10.0±7.6 mm, with a minimum of 5 mm and maximum of 36 mm. Papillary thyroid carcinoma was multicentric in 18 patients (30%) and showed evidence of extrathyroidal extension in 7 (12%).

The US staging of the neck detected adenopathy suggestive of metastasis in 12 of the 60 patients (20%), which was pathologically confirmed in 11 of the 12 (92%) (Figure). The patient with false-positive US findings reported as nonspecific reactive lymphadenitis associated with thyroiditis did not undergo lymph node dissection (positive predictive value, 92%) (Table 1). One false-negative case of metastasis was detected by careful exploration of the central compartment (negative predictive value, 98%). Overall, the sensitivity and specificity were 92% and 98%, respectively (Table 1).

The decision to extend the lymph node dissection relied on whether metastases were found in the central compartment only (paratracheal dissection) or in the lateral neck (comprehensive dissection). The US evaluation detected metastasis in the central compartment alone in 2 of 11 patients (18%), the central and lateral compartments in 6 (35%), and the lateral compartment alone in 3 (27%) (Table 2). Therefore, the operative procedure chosen on the basis of US findings determined that 2 of 11 patients (18%) underwent central dissection.
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the central compartment. In fact, some authors recom-
mend only US staging of the lateral neck given that the
purpose of this

<table>
<thead>
<tr>
<th>US Finding</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>11</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>48</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 1. Identification of Occult Metastasis by Ultrasonographic (US) Evaluation

Table 2. Ultrasonographic (US) Compartment Localization of Metastasis and Type of Neck Dissection Performed

<table>
<thead>
<tr>
<th>Neck compartment</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central compartment</td>
<td>2:11 (18)</td>
</tr>
<tr>
<td>Central and lateral compartment</td>
<td>6:11 (55)</td>
</tr>
<tr>
<td>Lateral compartment</td>
<td>3:11 (27)</td>
</tr>
<tr>
<td>Type of neck dissection</td>
<td></td>
</tr>
<tr>
<td>Central compartment</td>
<td>2:11 (18)</td>
</tr>
<tr>
<td>Comprehensive</td>
<td>9:11 (82)</td>
</tr>
</tbody>
</table>

(a) Includes patients with adenopathy suggestive of metastasis. (b) Data are expressed as the ratio of compartments with positive US findings to the total number of patients with positive US findings. (c) Data are expressed as the ratio of type of neck dissection to the total number of neck dissections.

Table 3. Neck Level Localization of Metastasis by US Finding

<table>
<thead>
<tr>
<th>Neck Level</th>
<th>Positive Pathological/Positive US Findings (%)</th>
<th>Positive Pathological/Negative US Findings (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ila</td>
<td>1/1 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>III</td>
<td>3/3 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>IVa</td>
<td>5/5 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>Vb</td>
<td>1/1 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>VI</td>
<td>8/9 (89)</td>
<td>1/9 (11)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable (corresponds to negative US findings at lateral neck levels that were not surgically explored); US, ultrasonography. (a) The percentage represents the percentage of nodes with positive pathological findings for macroscopic metastasis and positive US findings for that neck level. (b) The percentage represents the percentage of nodes with positive pathological findings for macroscopic metastasis and negative US findings for that neck level.

compartment dissection alone and 9 (82%) underwent a comprehensive dissection (Table 2).

The US evaluation detected adenopathy suggestive of metastasis most frequently in level VI, followed by levels IV and III (Table 3). All suspicious adenopathy reported by US findings in the different levels of the lateral neck were confirmed to have metastasis (Table 3), whereas the US evaluation of the central compartment correctly predicted macroscopic disease in 8 of 9 patients (89%) and missed 1 patient (false-negative rate, 11%). In the 9 patients undergoing a comprehensive dissection, additional microscopic disease was found in 9 more nodal basins (data not shown). In this series, there were no cases of permanent vocal cord paralysis or hypoparathyroidism in patients undergoing total thyroideotomy alone or with a neck dissection.

In routine endocrine practice, patients with a thyroid nodule frequently undergo US evaluation of the thyroid and receive a diagnosis that is based on fine-needle aspiration biopsy findings. If malignancy is confirmed, patients are usually referred to surgery with no further studies. Approximately 10% of these patients will have palpable neck adenopathy, and further evaluation in these patients will include a US study of the neck to de-
termin the extension of metastatic disease. However, the frequency of macroscopic metastasis in PTC is greater than 10%; therefore, staging the neck solely by means of physical examination will overlook a significant number of patients with nonpalpable macroscopic disease requiring lymph node dissection. For this reason, preoperative US evaluation of the neck has been recommended to identify patients with subclinical macroscopic neck metastasis.

This prospective study has shown that 20% of patients initially staged as having N0 disease at the initial diagnosis of PTC have nonpalpable adenopathy suggestive of metastasis detected by US evaluation. Pathological confirmation revealed that the US evaluation predicted metastasis in 92% of the cases, with a specificity of 98% and a sensitivity of 92%. These findings are consistent with previous studies that have reported a detection rate of 14% to 20% of nonpalpable metastasis in patients with thyroid cancer. Overall, US evaluation had a substantial effect in 11 of 60 patients (18%) of this series, who ultimately underwent more extensive surgery for small macroscopic metastasis. Moreover, 9 patients required a comprehensive neck dissection for lateral neck disease that had multiple macroscopic and microscopic neck level involvement. Therefore, in this study, preoperative US staging of the neck was effective in identifying patents with occult macroscopic disease requiring lymph node dissection.

When the neck compartments were analyzed separately, US evaluation correctly predicted metastasis in the central compartment in 8 of 9 patients (89%), whereas central compartment exploration identified 1 additional false-negative case with macroscopic metastasis. Three other patients with level VI involvement had microscopic disease that was found after a comprehensive neck dissection performed in the patients with lateral disease. It is not surprising that patients with lateral disease detected by US results had microscopic disease in the central compartment. In fact, some authors recommend only US staging of the lateral neck given that the presence of the thyroid may obscure the visualization of the central compartment. However, the purpose of this
study was to detect macroscopic disease, which in the central compartment was achieved correctly in 89% of the cases. Given the high frequency of metastasis to the central compartment (50%-80%) and the increased morbidity associated with central compartment reexploration, the fact that level VI dissection was not routinely performed in all patients included in this series may be questionable.10,12,13 However, in our opinion, the clinical benefit of eradicating microscopic disease in all patients without macroscopic adenopathy has not been proven, even for the central compartment.14,15 Moreover, in many patients with microscopic disease, metastasis will never progress or will be effectively treated with radioactive iodine. Finally, although central compartment dissection can be safely performed by an experienced head and neck surgeon, caution should be taken in recommending this procedure to less experienced surgeons given the risk of severe permanent morbidity. Therefore, we systematically search for macroscopic diseases in the central compartment with US. If results of the US evaluation are negative, exploration of the central compartment is performed by carefully displacing the parathyroid glands laterally and opening the paratracheal fat, taking care not to damage the recurrent laryngeal nerve and inferior thyroid artery. With this approach, 1 patient was identified as having macroscopic metastasis that was not detected by US evaluation.

The US evaluation of the lateral compartment identified 9 of 60 patients (15%) as having macroscopic metastasis; these 9 underwent a comprehensive neck dissection. This finding is similar to those of 2 previous studies that reported a rate of 14% of nonpalpable disease in the lateral neck of patients with thyroid cancer.12,13 Because patients with proved macroscopic lateral neck metastasis have a high risk of neck involvement at multiple levels,16,17 the proper neck dissection should include levels IIa, III, IV, Vb, and VI. Although it seems contradictory to dissect microscopic and macroscopic disease in the lateral neck, evidence has shown that this subgroup of patients with macroscopic disease has a higher risk of recurrence.4,5,14 In our study, separate pathological evaluation of neck levels consistently revealed additional metastases that were not detected by US evaluation. The value of detailed US staging of the neck in PTC has been challenged. In a series of 508 patients who underwent neck dissection only in the presence of palpable disease, Wang et al18 reported a 3% rate of recurrence in the lateral neck, suggesting that US evaluation of the neck would have little additional benefit. In a discussion comment by Heller,19 preoperative US evaluation of the neck would induce the performance of many unnecessary neck dissections to avoid a small number of recurrences. This view seems reasonable because, to our knowledge, there is no available evidence that preoperative staging of the neck reduces neck recurrence in patients with PTC. However, to follow this treatment proposal, a concordant postoperative follow-up study would also have to be limited to physical examination; otherwise, many patients will be diagnosed as having persistent or recurrent disease.20 Given the widespread use of thyrotropin-stimulated thyroglobulin detection, an increasing number of patients with biochemical disease are undergoing thorough diagnostic workup, including high-definition US and positron emission tomography with computed tomography. This follow-up strategy has increased the number of patients undergoing radioactive iodine therapy or even surgery for small disease. Therefore, it is likely that detailed knowledge of the nodal status of the neck in the preoperative stage will allow for adequate removal of small macroscopic disease, avoiding extensive postoperative diagnostic workups and additional operations.

Our findings support the use of high-resolution US evaluation of the neck for the preoperative staging among patients with PTC. Such evaluation is very effective in identifying patients with small macroscopic metastasis and in orienting the extension of surgery. Nevertheless, the following critical questions are unanswered: (1) Does US staging of the neck reduce the rate of recurrence? and (2) Is the potential morbidity associated with more extensive and a greater number of surgeries based on US-detected metastasis outweighed by that observed in patients treated for recurrent disease?

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Author Contributions: Dr O’Brien had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fardella. Acquisition of data: Carrasco. Analysis and interpretation of data: H. E. González, Cruz, O’Brien, Goñi, León, Claire, Camus, Domínguez, Mosso, Arteaga, G. González, López, and Rodríguez. Drafting of the manuscript: H. E. González. Critical revision of the manuscript for important intellectual content: H. E. González, Cruz, O’Brien, Goñi, León, Claire, Camus, Domínguez, Mosso, Arteaga, G. González, López, Rodríguez, Carrasco, and Fardella. Study supervision: H. E. González, Cruz, O’Brien, Goñi, León, Claire, Camus, Domínguez, Mosso, Arteaga, G. González, López, Rodríguez, Carrasco, and Fardella.

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