Central Nodal Metastases in Papillary Thyroid Carcinoma Based on Tumor Histologic Type and Focality

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Objective: To determine the risk of nodal metastases to the central compartment from differentiated papillary thyroid carcinoma (PTC) relative to known prognostic variables.

Design: A 7-year single-institutional retrospective review.

Setting: Tertiary academic center.

Patients: A total of 115 patients undergoing central neck dissection (CND) for PTC or follicular variant PTC (FVPTC).

Main Outcome Measure: Number, location, and positivity of lymph nodes for malignant disease in the central compartment based on patient age, sex, extrathyroidal extension, and primary tumor size, histologic type, and focality.

Results: Eighty-seven percent of patients had PTC, and 13% had FVPTC. Bilateral (64%) or ipsilateral (36%) CND was performed in patients with PTC. Patients with FVPTC underwent only ipsilateral CND. There was no significant difference in the number of lymph nodes retrieved based on patient age or sex, histologic type of the primary tumor, size or focality, or surgeon or pathologist. Seventy-eight percent of patients with PTC had malignant lymph nodes in the ipsilateral (75%) or bilateral/contralateral (69%) central compartment. Ipsilateral nodal metastases directly correlated with tumor multifocality ($r=0.93; \quad P=0.001$) and size ($r=0.89; \quad P=0.001$). Bilateral nodal metastases directly correlated with tumor multifocality ($r=0.92; \quad P=0.001$) but was independent of size ($r=0.56; \quad P=0.001$). No malignant lymph nodes were identified in the central compartment of FVPTC.

Conclusions: Malignant central nodal metastases occur with high frequency in PTC but not in FVPTC. The risk of metastases correlated with the size and multifocality of the primary tumor. Additional studies are warranted to determine the extent of CND in patients with and without known multifocal disease and to determine the role of CND in patients with FVPTC.


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Differentiated thyroid carcinoma accounts for more than 90% of all thyroid cancers and is derived from thyroid follicular epithelial cells. Histologic types include papillary and follicular. Papillary thyroid carcinoma (PTC) is characterized by increased multifocal disease, frequent clinical nodal metastases (20%-50%), and an even higher rate of subclinical micrometastases (50%-90%).

Metastases from PTC usually occur in a stepwise fashion from the central to lateral neck compartments. Therefore, the central compartment lymph nodes are at greatest risk of metastases from PTC. While the effectiveness of “therapeutic” central neck compartment lymph node dissection (central neck dissection [CND]) is undisputed, there is no consensus on the role of elective CND in clinically node-negative patients with PTC. Proponents of CND propose that elective CND offers more accurate staging and may decrease the likelihood of locoregional recurrence that occurs in 10% to 15% of patients. Opponents of elective CND highlight the potential for increased morbidity secondary to risk of recurrent laryngeal nerve injury and hypoparathyroidism. The overall risk and benefits of elective CND must be determined on a patient-by-patient basis. Preoperative identification of patients with PTC at greatest risk of metastases to the central compartment would be valuable. Therefore, the purpose of this study was to determine the risk of nodal metastases to the central compartment from PTC relative to known prognostic variables.
PATIENTS

A 7-year, single-institution, retrospective review of patients treated for PTC at a high-volume academic thyroid center was performed. This retrospective review was approved by the institutional review board at Oregon Health & Science University (Portland). Inclusion criteria for the study were as follows: (1) pathologically confirmed PTC or follicular variant PTC (FVPTC), (2) preoperative ultrasonographic with or without computed tomographic (CT) imaging of thyroid and cervical lymph node basins, (3) CND (ipsilateral or bilateral) during planned total thyroidectomy (primary or completion), and (4) medical records and histologic data available for review. A total of 115 patients undergoing CND for PTC from January 1, 2000, through December 31, 2007, met inclusion criteria for participation.

PREOPERATIVE EVALUATION

Prior to surgery, each patient underwent a comprehensive head and neck examination including flexible fiberoptic laryngoscopy as well as ultrasonographic evaluation of the thyroid and cervical lymph node basins. A CT scan of the head and neck was also performed in patients with clinically indeterminate cervical lymphadenopathy. Fine-needle aspiration (FNA) of the primary tumor was performed routinely to investigate primary disease.

NECK DISSECTION

Central neck dissection was conducted by 1 of 3 surgeons (P.E.A., J.I.C., or N.D.G.) during the study period. The study period was selected to maximize homogeneity of the surgical technique such that 96% of CNDs were performed by a single surgeon (J.I.C.). Boundaries of the CND (level VI) were as described previously.21 Lymph nodes in this compartment included the pretracheal and paratracheal nodes, precricoid (Delphian) node, and the perithyroidal nodes, including the lymph nodes medial and lateral to the recurrent laryngeal nerves. The superior boundary was defined as the cricoid cartilage, the inferior boundary was the innominate artery, and the lateral boundaries were the common carotid arteries. Central neck dissection was performed as either an ipsilateral dissection (same side as the primary tumor) or bilateral. The pretracheal lymph nodes were included with the ipsilateral CND. In general, bilateral CND was considered for patients with preoperative or intraoperative evidence of ipsilateral central compartment adenopathy, contralateral central neck adenopathy, or bilateral disease in the thyroid. The rationale for the extent of dissection (ipsilateral vs bilateral) was not explicitly defined in the medical record for every case.

ANALYSIS OF CENTRAL LYMPH NODE SPECIMENS

After completion of CND, neck specimens were divided in the operating suite by the surgeon into ipsilateral and contralateral specimens. The ipsilateral paratracheal and pretracheal nodes were defined as “ipsilateral CND” and the contralateral paratracheal and pretracheal lymph nodes as the “contralateral CND.” The CND specimens were then accessioned by the pathologist with the primary thyroid tumor and processed routinely. The frequencies and patterns of CND metastases were analyzed with respect to patient characteristics (age, sex) and pathologic variables (tumor size, histologic type, primary tumor location [ipsilateral, contralateral], multifocality). For multiple primary lesions, the diameter of the largest dominant tumor was used in the analyses.

RESULTS

One hundred and fifteen CNDs for PTC were conducted from January 1, 2000, through December 31, 2007. Contents of the central compartments were reviewed by 1 of 7 pathologists. There was no significant difference in the number of lymph nodes retrieved based on surgeon or pathologist (P > .99 for both comparisons). Eighty-seven percent of patients (n=100) had conventional PTC, and 13% (n=15) had FVPTC. Bilateral CND was performed in 64% of patients with conventional PTC. Ipsilateral CND was performed in the remaining 36%. All patients with FVPTC underwent only ipsilateral CND. The number of lymph nodes removed in the CND ranged from 2 to 24 (mean [SD], 9.4 [4.6]) and was independent of histologic type (PTC vs FVPTC) or tumor size (data not shown). Among patients who underwent bilateral CND, there was a greater number of lymph nodes retrieved from the ipsilateral (12.1 [3.6]) vs contralateral (4.5 [2.1]) neck compartment (P < .03). This finding is consistent with the inclusion of pretracheal lymph nodes with the “ipsilateral CND.”

The influence of tumor histologic type on central nodal metastases is summarized in Table 1. Seventy-eight percent of patients with conventional PTC had malignant lymph nodes in either the ipsilateral (75%) or contralateral (69%) central compartments. Three percent of patients exhibited malignant lymph nodes in the contralateral central compartment without ipsilateral positive lymph nodes. All of the tumors within this subgroup exhibited multifocality. No malignant lymph nodes or multifocal tumors were identified in patients with FVPTC.

Clinicopathologic factors affecting central nodal metastases in patients with conventional PTC are summarized in Table 2. There was no significant difference between patients with central nodal metastases with respect to age (P = .65), sex (P = .73), tumor size (P = .35), extrathyroid extension (P = .48). The mean (SD) tumor size in patients with conventional PTC was 3.0 (1.7) cm

<p>| Table 1. Influence of Tumor Histologic Type on Central Nodal Metastases |
|--------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Patients, No.</th>
<th>Positive LN, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTC</td>
<td>100</td>
<td>78 (78)</td>
</tr>
<tr>
<td>FVPTC</td>
<td>15</td>
<td>0 (0)</td>
</tr>
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</table>

Abbreviations: FVPTC, follicular variant papillary thyroid carcinoma; LN, lymph node; PTC, conventional papillary thyroid carcinoma.
Patients with multifocal disease were significantly more likely to have central nodal metastases. Multifocality of the tumor was exhibited by 69% of patients with conventional PTC. Of these, 89% exhibited lymph node metastases to the central compartment compared with 55% of patients with unifocal disease (P < .03). Three percent of patients with multifocal tumors exhibited malignant lymph nodes in the contralateral central neck compartment without evidence of ipsilateral metastatic lymph nodes. Tumors not exhibiting multifocality tended to be larger (4.1 [1.9] cm) than tumors with multifocality (2.1 [0.7] cm). None of the tumors in patients with FVPTC exhibited multifocality.

The influence of tumor size and focality on ipsilateral and bilateral/contralateral central nodal metastases is summarized in the Figure. Nodal metastases to the central compartment were independent of tumor size for the entire cohort. However, a statistical difference in the rate of metastases was identified based on tumor size when stratifying by compartment location (ipsilateral vs bilateral/contralateral). Of the 75 patients with ipsilateral central nodal metastases, 24% had primary tumors smaller than 2 cm compared with 76% with primary tumors 2 cm or larger (P < .001). Of the 55 patients with bilateral/contralateral central nodal metastases, there was no significant difference between patients with primary tumors smaller than 2 cm or 2 cm or larger (47% vs 53%) (P = .17) (Figure, A). The impact of tumor focality on ipsilateral and bilateral/contralateral central nodal metastases was even more pronounced. For patients with ipsilateral central nodal metastases, 17% had unifocal primary tumors compared with 83% with multifocal primary tumors (P < .001). Similarly, for patients with bilateral/contralateral central nodal metastases, 2% had unifocal primary tumors compared with 98% with multifocal primary tumors (P < .001) (Figure, B). Lymph node metastases in the ipsilateral central neck compartment of patients with PTC directly correlated with both multifocality of tumor (r = 0.93; P = .001) and tumor size (r = 0.89; P = .001). Bilateral/contralateral central compartment nodal metastases directly correlated with multifocality of the tumor (r = 0.92; P = .001) but was independent of tumor size (r = 0.56; P = .001).

**Table 2. Clinicopathologic Factors Affecting Central Nodal Metastases**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No.</th>
<th>Positive LN, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>46</td>
<td>34 (74)</td>
<td>.65</td>
</tr>
<tr>
<td>≥45</td>
<td>54</td>
<td>44 (81)</td>
<td>.65</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>18 (75)</td>
<td>.73</td>
</tr>
<tr>
<td>Female</td>
<td>76</td>
<td>60 (79)</td>
<td>.73</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>25</td>
<td>21 (88)</td>
<td>.35</td>
</tr>
<tr>
<td>≥2</td>
<td>75</td>
<td>57 (76)</td>
<td>.35</td>
</tr>
<tr>
<td>Tumor focality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unifocal</td>
<td>31</td>
<td>17 (55)</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>Multifocal</td>
<td>69</td>
<td>61 (89)</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>Extrathyroid extension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54</td>
<td>41 (76)</td>
<td>.48</td>
</tr>
<tr>
<td>No</td>
<td>46</td>
<td>37 (80)</td>
<td>.48</td>
</tr>
</tbody>
</table>

Abbreviation: LN, lymph node.

Differentiated PTC has a high propensity to spread to regional lymph nodes. The reported incidence of clinically positive lymph nodes ranges from 20% to 50%. A higher proportion (80%-90%) of patients exhibit subclinical lymph node metastases (micrometastases) at the time of surgical intervention. Despite the high incidence, lymph node metastases are not considered prognostic for poor survival in patients with well-differentiated PTC. Therefore, treatment of the cervical lymph nodes in well-differentiated PTC remains controversial.

The primary argument for performing CND in the treatment of well-differentiated PTC is to more accurately stage the patient’s tumor. More accurate staging allows for better risk stratification and the more rational application of levotyroxine suppression and adjuvant therapy (eg, iodine 131 ablation). The presence or absence of pathologic lymph nodes in neck dissection specimens has been shown to correlate to the incidence of disease recurrence. Elective CND may help prevent local recurrences in the central compartment where re-operation can be difficult. Therefore, proponents of CND argue that elective excision of central compartment lymph nodes may improve locoregional control and possibly reduce long-term morbidity. Opponents of elective CND contend that microscopic nodal disease can be treated with radioactive iodine and that more aggressive surgery offers no survival advantage. Some papillary thyroid cancers (approximately 25%), especially in the older patient population (those ≳45 years), concentrate radioactive iodine poorly. In these cases, radioactive iodine treatment may not adequately treat residual nodal micrometastases. Thus, it is likely that elective CND is most beneficial at the time of initial surgery for selected high-risk patients. Determining which patients are high-risk before surgery remains difficult.

In this study, we aimed to identify factors associated with central neck compartment nodal metastases as an initial step toward defining those patients most likely to benefit from elective CND. We found that the incidence of lymph node metastases to the central neck compartment to be similar to that reported in other studies. Malignant lymph nodes were found to occur with high frequency in patients with conventional PTC but not those with FVPTC. Additional studies are warranted to confirm whether elective CND can be avoided in patients with FVPTC.

We found that the overall incidence of central compartment nodal metastases seemed to be similar between patients with smaller multifocal tumors and patients with larger unifocal tumors. However, the rate of central nodal...
metastases was variable between the ipsilateral vs bilateral/contralateral compartments depending on tumor size and focality. The risk of metastases to the ipsilateral neck compartment in patients with conventional PTC correlated with size and multifocality of the primary tumor. By contrast, the likelihood of bilateral/contralateral neck metastases was increased by tumor multifocality independent of primary tumor size. The data suggest that patients with primary tumors larger than 2 cm and multifocal disease are most likely to have central compartment nodal metastases from PTC. A strategy of elective CND seems warranted for these patients and might argue for a role of preoperative imaging and biopsy to ascertain if multifocal disease is present to guide the decision regarding the extent of elective CND. Additional studies are warranted to determine if bilateral CND is indicated in patients with large unifocal tumors. Second, FNA was not performed on clinically indeterminate central neck nodes identified on preoperative imaging. Therefore, it was not possible to confirm in this retrospective review that the tumors of all patients were properly classified as clinically N0. Certainly, misclassified ipsilateral adenopathy could influence the presence or absence of disease in the contralateral central compartment.

The strength of this study is the large number of patients who were treated in a uniform manner by an experienced thyroid cancer team at a high-volume, academic center. This study does not define which patients would benefit most from CND. Rather, it is intended as a descriptive study to determine the risk of nodal metastases to the central neck compartment from PTC relative to known prognostic variables. None of the known prognostic variables for conventional PTC (age, sex, tumor size, extrathyroid extension) correlated with the presence of metastases to the central compartment. Only patients with multifocal disease were more likely to have micrometastases to the central compartment, including both the ipsilateral and contralateral compartments. This suggests a potential important biologic difference be-

Figure. Influence of focality and tumor size on ipsilateral and bilateral/contralateral central nodal metastases (CNM). Ipsilateral CNM in 75 patients (A), and bilateral/contralateral CNM in 55 patients (B), according to the focality of the primary tumor. Ipsilateral CNM in 75 patients (C) and bilateral/contralateral CNM in 55 patients (D), according to the size of the primary tumor. Numbers in parentheses refer to the number of patients with lymph nodes positive for papillary thyroid carcinoma.
tween unifocal and multifocal tumors. Interestingly, the risk of metastases to the ipsilateral neck compartment in patients with conventional PTC correlated with primary tumor size. Patients with unifocal tumors smaller than 2 cm were far less likely to have ipsilateral central compartment metastases than those patients with larger tumors. This information may be helpful for preoperative planning, particularly in low-risk patients.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Salter, Andersen, Cohen, Sauer, and Gross. Acquisition of data: Salter, Lester, and Sauer. Analysis and interpretation of data: Salter, Andersen, Cohen, Schuff, Shindo, Sauer, and Gross. Drafting of the manuscript: Salter. Critical revision of the manuscript for important intellectual content: Salter, Andersen, Cohen, Schuff, Lester, Shindo, Sauer, and Gross. Statistical analysis: Salter. Obtained funding: Salter. Administrative, technical, and material support: Salter and Sauer. Study supervision: Salter, Andersen, Cohen, Shindo, and Gross. Clinical input: Lester.

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REFERENCES