An Analysis of Factors Predicting Lateral Cervical Nodal Metastases in Papillary Carcinoma of the Thyroid

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Objective: To analyze the possible correlation between the location of the primary tumor within the thyroid gland and the patterns of central vs lateral compartment lymph node metastasis.

Design: Retrospective analysis of papillary thyroid carcinoma (PTC) treated in an academic university setting from July 1, 2004, through August 31, 2010.

Setting: Head and neck oncology clinic.

Patients: Those receiving surgical therapy for PTC at the University of Utah.

Main Outcome Measures: Tumor characteristics of patients with central vs lateral nodal metastatic disease in PTC.

Results: Two hundred one patients with PTC met inclusion criteria. There were 136 females (67.7%), and the mean age was 44.8 years. Histologic subtypes included 68 follicular variants of PTC, 111 conventional variants of PTC, and 22 patients with both follicular and conventional PTC variants. Metastatic nodal disease was confirmed histologically in 81 patients (40.3%): 42 with central nodal disease only (20.9%), 10 with lateral disease only (5.0%), and 29 with both central and lateral nodal disease (14.4%). Positive lateral compartment nodal metastasis correlated with distant metastases ($P < .01$), extrathyroid extension ($P < .05$), histologic subtype (conventional PTC greater than follicular variant PTC) ($P < .05$), and tumor location within the thyroid lobe ($P < .01$). Tumors involving the superior aspect of the thyroid lobe were more likely to be associated with metastasis to the lateral cervical lymph nodes ($P < .01$), and 76.9% of patients with lateral cervical lymph node disease had involvement of the superior aspect of the lobe. Thyroid microcarcinomas were not associated with lateral cervical compartments in this study.

Conclusions: The intrathyroidal location of PTC predicts the pattern of nodal spread. Therefore, patients with PTC involving the superior aspect of the lobe should undergo specific imaging evaluation of the lateral neck compartments to determine the need for lateral compartment neck dissection.


WELL-DIFFERENTIATED thyroid cancer is a common disorder with an increasing incidence.1 Regional metastases to the lymph nodes of the neck are common, affecting as many as 80% of those with well-differentiated thyroid cancer.2-5 Despite the high prevalence of nodal spread, papillary thyroid carcinoma (PTC) has an excellent prognosis. Thus, the impact of lymph node metastases on survival is controversial. Previously, nodal disease was not considered an important determinant in overall survival.6-8 However, in the past 2 decades, there has been growing recognition that lymph node metastases adversely affect survival, particularly in older patients with larger tumors and extrathyroidal extension.3,9,10 The impact of lymph node involvement on recurrence is less controversial. The presence of lymph node metastases significantly increases locoregional recurrence rates.3,5,7,12,13 Although the majority of lymph node metastases are within the central neck, approximately 15% occur in the lateral neck and can be detected by ultrasound.14 These metastatic sites respond to radioactive iodine in only 53% of patients older than 40 years.15 This makes surgery a critical modality in the treatment of the disease. If these lateral cervical neck metastases are detected preoperatively, a lateral neck dissection may improve outcomes.

Although most thyroid neoplasms undergo preoperative ultrasound evaluation, detailed examination of the lateral cervical chain lymph nodes is far from standardized. Prediction of those patients at increased risk for lateral cervical

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Lesions confined to the isthmus were treated as middle third lobe lesions. If the tumor extended into the inferior or superior aspects of the adjacent lobe, it would be categorized by all aspects that it involved. In cases of multifocal disease, the location of all tumor foci greater than 1.0 cm was recorded. Most microcarcinomas in multifocal disease were not classified according to location within the gland because of the inability to localize the lesion on imaging or pathologic evaluation. If lymph nodes were involved, they were classified as either central or lateral compartment disease. If patients were treated for a lymph node recurrence, the primary tumor characteristics were obtained from evaluation of the initial thyroidectomy that was performed, if available. Patients were excluded if the initial pathology or imaging reports were unavailable or inadequate.

Statistical evaluation was performed of factors that predicted central vs lateral compartment spread. Age and tumor size were compared using a Wilcoxon rank sum analysis. All other variables were compared using Pearson \( \chi^2 \) analysis.

## RESULTS

### PATIENT CHARACTERISTICS

Two hundred thirty-three patients diagnosed as having well-differentiated thyroid cancer were treated in the head and neck oncology clinic at the University of Utah from June 2004 through June 2010. Of those patients, 201 met criteria for inclusion in the study and included the following histologic subtypes: 111 conventional variants of PTC, 68 follicular variants of PTC, and 22 patients with both conventional and follicular variants identified within the pathologic specimen. The mean age of the study population was 44.8 years. One hundred thirty-nine (69.2%) were females. Overall patient and tumor characteristics can be found in **Table 1**.

### TUMOR LOCATION WITHIN THE GLAND

Ninety-one tumors (45.3%) involved the superior aspect of the thyroid to some degree. This included 16 tumors that were limited to the superior aspect of the lobe, 12 lesions that involved both the middle and superior aspects of the lobe, and 60 lesions that involved the entire lobe. In addition, there were 3 patients who had multifocal disease that involved inferior and superior aspects of the lobe without involving the middle third of the lobe. There were 24 microcarcinomas in which the location was unable to be determined precisely. Overall, there were 102 multifocal lesions, of which 35 specimens contained only multiple foci of microcarcinomas (<1 cm). In addition, multiple tumor foci greater than 1 cm were found in 12 specimens and were classified according to the involvement of all lesions identified. The remaining 55 multifocal lesions included a single carcinoma greater than 1 cm accompanied by a single or by multiple microcarcinomas. **Table 1** contains a complete list of tumor locations.

### PATTERN OF LYMPH NODE INVOLVEMENT

Overall, metastatic lymph node involvement was confirmed in 81 of the 201 patients (40.3%). Of these 81 patients, nodal involvement was isolated to the central compartment in 42 patients (51.9%) and the lateral compartment...
in 10 (12.3%). Both compartments were involved in 29 of the 81 patients (35.8%).

**PREDICTORS OF LATERAL CERVICAL LYMPH NODE INVOLVEMENT**

Of the 201 study patients, lateral compartment metastasis occurred in 39 patients (19.4%), which included 29 patients who also had central compartment disease. These patients were significantly more likely to have extrathyroid extension ($P < .01$) and histological characteristics of a conventional variant of PTC ($P < .05$). The location of the primary tumor within the thyroid gland was also predictive. Of patients with lateral compartment involvement, 76.9% of the primary tumors involved the superior aspect of the thyroid lobe ($P < .01$). Of note, distant metastatic disease was also associated with lateral cervical lymph node metastases ($P < .01$). Table 2 provides a complete list of variables. For comparison, the same analysis was performed for central compartment lymphatic spread. It was similar in many categories, significantly correlating with tumor histologic variant ($P < .01$), extrathyroid extension ($P < .01$), and tumor location ($P < .01$). However, size was also predictive of central compartment lymph node metastasis ($P < .01$), which differed from risk factors for lateral compartment lymphatic spread. There was also an association of central compartment disease with distant metastases ($P < .05$). Table 3 contains the complete list of variables compared.

**COMMENT**

The importance of lymph node metastases has been underrecognized. Risk assessment systems such as AGES (age, grade, extent of disease, size), AMES (age, metastasis, extent of disease, size), and MACIS (metastasis, age at presentation, completeness of surgical resection, invasion [extrathyroidal], size) have not included nodal status as a prognostic factor for survival. In recent years, however, the importance of nodal status has emerged. Several studies have confirmed that nodal status influences the recurrence rate. For high-risk patients, this recurrence rate may be as high as 60%, requiring repeated surgical procedures. Surgery is often the best option for these patients, and approximately 10% of those with recurrent lymph node metastasis will die of their disease. In fact, multiple studies show that lymph node status affects survival. The importance of nodal status is further substantiated by the American Joint Committee on Cancer staging system, in which the presence of lymph node metastases is recognized as a prognostic factor for survival and increases the overall stage in patients older than 45 years. Thus, predicting the pattern of nodal spread is important to determine those at risk for lateral compartment disease. This determination allows for appropriate evaluation and tailored initial treatment.

The current study examines the importance of primary tumor location on the pattern of lymphatic spread. Tumors involving the superior aspect of the gland were 4.5 times more likely to have lateral compartment lymphatic spread compared with tumors that were limited to the middle and inferior aspect of the lobe. Qubain et al reported similar findings in Japan in 2002 in a cohort of 80 patients identifying increased lateral lymphatic spread in lesions involving the upper third of the gland. However, these patients were being evaluated for micrometastasis, and 60% of the tumors were confined to one-third of a lobe. Of these 48 patients, 6 had tumors confined to the upper third of the lobe, with 3 having micrometastasis. The current study consisted of a larger variety of tumor sizes and locations, and we evaluated factors that were associated with any lymph node spread, not just micrometastasis. Also, there are differences in surgical philosophies in the United States compared with Japan, because radioactive iodine is infrequently used for ablation in Japan. This leads to a more

### Table 2. Risk Factors for Lateral Compartment Lymphatic Spread

<table>
<thead>
<tr>
<th>Variable</th>
<th>Absent (n = 162)</th>
<th>Present (n = 39)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>46 (37)</td>
<td>37 (63)</td>
<td>.03</td>
</tr>
<tr>
<td>Male sex</td>
<td>45 (28)</td>
<td>17 (44)</td>
<td>.06</td>
</tr>
<tr>
<td>Histologic feature</td>
<td></td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Conventional variant papillary thyroid carcinoma</td>
<td>83 (51)</td>
<td>28 (72)</td>
<td>.01</td>
</tr>
<tr>
<td>Follicular variant papillary thyroid carcinoma</td>
<td>62 (38)</td>
<td>6 (15)</td>
<td>.01</td>
</tr>
<tr>
<td>Both variants</td>
<td>17 (10)</td>
<td>5 (13)</td>
<td>.05</td>
</tr>
<tr>
<td>Multifocal tumor</td>
<td>79 (49)</td>
<td>23 (59)</td>
<td>.25</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>1.5 (1.5)</td>
<td>1.5 (1.5)</td>
<td>.20</td>
</tr>
<tr>
<td>Extrathyroid extension</td>
<td>30 (19)</td>
<td>14 (36)</td>
<td>.02</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>1 (1)</td>
<td>4 (10)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Tumor location, superior pole</td>
<td>61 (38)</td>
<td>30 (77)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

aData are given as number (percentage) unless otherwise indicated.

### Table 3. Risk Factors for Central Compartment Lymphatic Spread

<table>
<thead>
<tr>
<th>Variable</th>
<th>Absent (n = 126)</th>
<th>Present (n = 75)</th>
<th>$P$ Value</th>
</tr>
</thead>
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<tr>
<td>Age, mean, y</td>
<td>46 (37)</td>
<td>37 (63)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Male sex</td>
<td>34 (27)</td>
<td>28 (37)</td>
<td>.12</td>
</tr>
<tr>
<td>Histologic feature</td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Conventional variant papillary thyroid carcinoma</td>
<td>51 (40)</td>
<td>60 (80)</td>
<td>.12</td>
</tr>
<tr>
<td>Follicular variant papillary thyroid carcinoma</td>
<td>60 (48)</td>
<td>8 (11)</td>
<td>.01</td>
</tr>
<tr>
<td>Both variants</td>
<td>15 (12)</td>
<td>7 (9)</td>
<td>.76</td>
</tr>
<tr>
<td>Multifocal tumor</td>
<td>65 (52)</td>
<td>37 (49)</td>
<td>.01</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>1.2 (2.0)</td>
<td>1.2 (2.0)</td>
<td>&lt;.01</td>
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<tr>
<td>Extrathyroid extension</td>
<td>17 (13)</td>
<td>27 (36)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>0 (5)</td>
<td>5 (7)</td>
<td>.02</td>
</tr>
<tr>
<td>Tumor location, inferior pole</td>
<td>67 (53)</td>
<td>56 (75)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

aData are given as number (percentage) unless otherwise indicated.
aggressive surgical approach with frequent elective neck dissections in Japan. Micrometastases are generally believed to be of little importance in survival in the United States, especially with the use of radioactive iodine postoperatively. More important, however, both studies demonstrate the influence of primary tumor location on the pattern of lymph node metastasis. This influence is likely due to the pattern of lymphatic drainage that follows the venous drainage of the thyroid gland. Specifically, venous and lymphatic drainage patterns of the superior lobe of the thyroid gland course superiority with the superior thyroid vessels to the lateral compartment of the neck. The lateral cervical compartment is classically regarded as a second line of lymphatic drainage after the central compartment. However, depending on the location of the primary tumor, the first line of lymphatic drainage may be the lateral cervical compartment because skip lesions are recognized in multiple studies. In the past decade, several groups have studied the role of sentinel lymph node biopsy in thyroid cancer. Balasubramanian and Harrison performed a meta-analysis of the role of sentinel lymph node biopsy in the management of thyroid cancer, identifying sentinel lymph nodes in the lateral compartment in 22.5% of patients. Of these patients, 14.8% of the sentinel lymph nodes were only in the lateral compartment.

As expected, extrathyroid extension correlated with both lateral compartment and central compartment lymphatic spread. Tumor size did not correlate with lateral compartment lymphatic spread of tumor. In contrast, size did correlate with central compartment lymphatic spread of disease. This may be due to the relatively small volume of thyroid making up the superior portion of the lobe. This thin area of the gland may lead to tumors reaching the thyroid capsule more quickly. This may lead to earlier lymphatic spread of tumor even with small-volume disease, making preoperative lymph node evaluation important. The American Thyroid Association and Taskforce recommends preoperative imaging with ultrasound for patients with thyroid cancer. Ultrasound has adequate specificity for detecting lateral lymph node disease, but sensitivity is often limited, especially for central compartment metastasis. Also, fine-needle aspirate can be obtained at the time of the ultrasound to evaluate the nodal status. For difficult cases, fine-needle aspirate washings can be sent for thyroglobulin levels to detect pathologic features. However, detection of macroscopic lymph node metastasis is likely more clinically relevant, especially in locations where radioactive iodine is frequently given to high-risk patients. In fact, Moreno et al. showed preoperative ultrasonography to be predictive of lateral neck disease-free survival in PTC. The presence of ultrasound-detected disease in the central and lateral compartments as well as the number of compartments involved influenced long-term disease-specific survival, with the presence of lateral neck disease decreasing the 10-year disease-specific survival from 98.3% to 66.9%. By use of this approach, their recurrence rates in the lateral neck were low at 0.3%. Many factors contribute to the effectiveness of preoperative ultrasonography, including device, technician, quality of needle aspirate, cytologic interpretation, and patient habitus. For successful preoperative evaluation, all of these factors need to be optimized and performed in a standardized fashion by an experienced ultrasonographer and cytologist. One concern regarding ultrasound evaluation is that it is extremely sensitive and may detect clinically insignificant disease. This is a difficult topic to address because there are limited data evaluating the specificity of ultrasound evaluation for determining nodal metastatic disease.

There are some limitations of the current study. The patient population included both primary neck dissections and secondary surgical procedures. This heterogeneity does not include the true incidence of lymph node disease at presentation. It is not possible to describe the true incidence of lateral nodal disease at presentation in patients treated in the United States because elective lateral neck dissections are not routinely performed. However, the current study does evaluate clinically relevant nodal disease that required surgery initially or secondarily and the relationship of tumor location on those patterns of lymph node spread. Another limitation is in regard to having multiple treating surgeons with different treatment philosophies. This could contribute to some patients having different treatments and in some cases having different patterns of lymph node dissection. However, in general, the nodal evaluations were similar. Specifically, for lateral compartment neck dissections, only patients with imaging and/or biopsy concerning for lateral compartment disease underwent lateral compartment neck dissection. There were no elective lateral neck dissections performed by any of the treating surgeons. There was greater variety in patients who underwent central compartment neck dissection, in terms of prophylactic vs therapeutic central compartment neck dissection. Last, the location of the primary tumor within the gland was determined by ultrasonography and/or pathology reports. Accurate identification of tumor location in this study is dependent on the accuracy of ultrasound and pathology reporting. Ultrasound evaluations were primarily performed by the senior author (D.A.) in a standardized fashion. This greatly improves the accuracy of identifying tumor location. There was limited imaging performed by outside institutions or through other ultrasonographers that might affect accurate tumor location. However, this was limited. Tumor locations were also identified from surgical specimens during gross evaluation. The glands were not oriented in a standardized fashion among all treating surgeons. However, there is a high priority on correct specimen orientation, with open communication between surgeon and pathology team. There were no major discrepancies in location of tumor between imaging and pathology reports. A prospective analysis would allow for more control over these factors and would allow further validation of these results.

In conclusion, lymph node status is important in terms of disease recurrence and overall survival. Lymph node spread to the lateral neck compartment can be predicted by identifying the location of the primary tumor within the thyroid gland. All patients with known PTC should undergo preoperative ultrasound evaluation for lymph node involvement. Patients with lesions involving the superior thyroid lobe should have the lateral com-
partment examined during ultrasonographic evaluation of the primary tumor and central compartment.

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Author Contributions: Drs Hunt and Buchmann 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: Hunt, Buchmann, and Abraham; Acquisition of data: Wang; Analysis and interpretation of data: Hunt, Buchmann, and Abraham; Drafting of the manuscript: Hunt, Buchmann, and Wang; Critical revision of the manuscript for important intellectual content: Buchmann and Abraham; Study supervision: Hunt.

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REFERENCES