Prognostic Importance of Vascular Invasion in Papillary Thyroid Carcinoma

Richard E. Gardner, MD; R. Michael Tuttle, MD; Kenneth D. Burman, MD; Shinin Haddady, MD; Cynthia Truman, MD; Yvonne H. Sparling, MS; Leonard Wartofsky, MD; Roy B. Sessions, MD; Matthew D. Ringel, MD

Background: The prognostic importance of vascular invasion has not been extensively studied in patients with papillary thyroid cancer.

Objective: To determine whether the presence of vascular invasion in papillary thyroid carcinoma, even within the thyroid gland, is associated with more aggressive disease at diagnosis and a higher incidence of tumor recurrence.

Patients and Methods: We identified 410 patients who had been diagnosed with papillary thyroid cancer since 1986 who had a follow-up period of longer than 1 year (median follow-up, 5.5 years). Pathology reports were reviewed and patients were separated into 3 groups: no vascular invasion, intrathyroidal vascular invasion, and extrathyroidal vascular invasion.

Main Outcome Measures: Statistical comparison was performed by univariate and multivariate analysis.

Results: Patients with intrathyroidal vascular invasion were more likely to have distant metastasis at the time of diagnosis (26.1% vs 2.2%, \(P = .001\)). Similarly, patients with extrathyroidal vascular invasion had a higher incidence of distant metastases at diagnosis (40% vs 4.4%, \(P = .02\)). Patients with tumors identified to have intrathyroidal vascular invasion were more likely to develop distant recurrence (20% vs 3%, \(P = .002\)).

Conclusions: These associations were found to be independent by multiple regression analysis. Patient age, sex, palpable or fixed lymph nodes, radiation exposure, and race did not differ between the patient group with and those without vascular invasion. Preliminary analysis of our data suggests that the presence of vascular invasion in papillary thyroid carcinoma, even within the thyroid gland, is associated with more aggressive disease at diagnosis and with a higher incidence of tumor recurrence.

PATIENTS AND METHODS

We identified adults with a diagnosis of papillary thyroid cancer through use of the databases of the Walter Reed Army Medical Center Thyroid Registry and the Washington Hospital Center Cancer Registry, both in Washington, DC. These databases comprised patients treated consecutively since 1986. Patients with 1 year or less of follow-up were excluded from this study (median follow-up, 5.5 years; reference range, 1-13 years). Pathology reports were reviewed. The pathology departments of the institutions used routinely comment on the presence of vascular invasion. Patients were separated into the following 3 groups: those with no vascular invasion, those with intrathyroidal vascular invasion, and those with extrathyroidal vascular invasion. The association of vascular invasion and stage at diagnosis, as well as the development of recurrences, was assessed.

Physicians examined the medical records of patients with a diagnosis of papillary thyroid carcinoma seen at the participating institutions. The preoperative, operative, pathologic, and postoperative findings were entered into a central database, which included a total of 82 separate data points. Only those patients who underwent total thyroidectomy or completion thyroidectomy within 3 months of diagnosis were included in the study. All patients received postoperative radioiodine ablative therapy. Of the 547 persons in the 2 registries, a total of 410 patients were identified with papillary thyroid carcinoma. If there was no comment (positive or negative) regarding vascular invasion, the patient was excluded from this study. Metastasis reported represented biopsy-proven abnormal tissue or a positive signal on radioiodine scan. The population of patients with metastasis at diagnosis was defined as those patients who received postoperative radioiodine ablative therapy. Of the 547 persons in the 2 registries, a total of 410 patients were identified with papillary thyroid carcinoma. Patients lacking information regarding 2 specific characteristic included in the statistical analysis performed were excluded, thus the overall number of patients (affected and unaffected) is fewer than the number of persons initially identified in the database. Both numbers are included in the article, as is appropriate for a statistical database study.

DISTANT METASTASIS AT THE TIME OF DIAGNOSIS

Metastasis at diagnosis was defined as those patients who were seen within 3 months of diagnosis of their condition. Univariate analysis of all 410 patients in the study revealed that being male (P < .001), the presence of gross local invasion (P = .03), and cervical nodal metastasis (P = .04) predicted metastasis at the time of diagnosis (Table 2). These points are consistent with previous reports.1-7,9-11,13-19 Nodule size was recorded in accord with the Ohio State University staging system. The size of the nodule was not found to be statistically significant (P = .09), though a trend toward metastasis with increasing size was noted. Extrathyroidal and intrathyroidal vascular invasion were significant predictors of metastasis at diagnosis, with P values of .02 and less than .001, respectively (Figure 1). Multivariate analysis revealed an independent association between intrathyroidal and extrathyroidal vascular invasion and the presence of distant metastasis at the time of diagnosis (P < .001 and P = .003, respectively).

RECURRENCE

Distant recurrence rates in relation to the type of vascular invasion are given in Figure 2. Univariate analysis was used to compare intrathyroidal and extrathyroidal vascular invasion with recurrence (Table 3). Intrathyroidal vascular invasion was a predictor of distant recurrence (P = .002). The association between intrathyroidal vascular invasion and local recurrence was strong (Figure 3), but not statistically significant (P = .06). This association was independent per multivariate analysis (P = .04), which probably represents the elimination or a confounding variable during logistic regression. Ex-
trathyroidal vascular invasion was not found to be a significant predictor in either local or distant recurrence ($P = .34$ and $P = .23$, respectively), possibly related to the few patients involved. Multivariate analysis for the relation between intrathyroidal vascular invasion and any recurrence revealed a significant, independent relation ($P = .01$).

**COMMENT**

This study suggests that vascular invasion, be it extrathyroidal or intrathyroidal, is an indication of more aggressive disease in papillary thyroid carcinoma. Patients with extrathyroidal vascular invasion had a 40% incidence of distant metastases at diagnosis, compared with only 4% of those patients with a documented lack of vascular invasion ($P = .02$). Similarly, of the 23 patients with intrathyroidal vascular invasion, 6 (26.1%, $P < .001$) had distant metastases at diagnosis. Patients with intrathyroidal vascular invasive tumors were more likely to de-

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**Table 2. Univariate Risk Factors of Distant Metastasis at Diagnosis**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients With Metastasis, (No. of Patients With Metastasis/Total No. of Patients) $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of vascular invasion</td>
<td></td>
</tr>
<tr>
<td>Intrathyroidal</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (6/23) $&lt; .001^*$</td>
</tr>
<tr>
<td>No</td>
<td>3 (7/230)</td>
</tr>
<tr>
<td>Extrathyroidal</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40 (2/5) $P = .02^*$</td>
</tr>
<tr>
<td>No</td>
<td>4 (11/248)</td>
</tr>
<tr>
<td>Gross local invasion surgery</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (3/19) $P = .03^*$</td>
</tr>
<tr>
<td>No</td>
<td>3 (4/160)</td>
</tr>
<tr>
<td>Size of nodule, mm</td>
<td></td>
</tr>
<tr>
<td>$&lt; 1.5$</td>
<td>2 (2/116) $P = .09^+$</td>
</tr>
<tr>
<td>1.5-3.9</td>
<td>4 (5/117) $P = .001^*$</td>
</tr>
<tr>
<td>$\geq 4.0$</td>
<td>11 (2/19) $P = .04^*$</td>
</tr>
<tr>
<td>Cervical metastasis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (8/80) $P = .01^*$</td>
</tr>
<tr>
<td>No</td>
<td>4 (7/196)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>14 (12/83) $&lt; .001^*$</td>
</tr>
<tr>
<td>F</td>
<td>3 (7/214)</td>
</tr>
</tbody>
</table>

* Fisher exact test used to calculate $P$ value.

† Mantel-Haenszel $\chi^2$ exact test used to calculate $P$ value.

**Table 3. Univariate Risk Factors for Distant and Local Recurrence**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recurrence, % (No. of Patients With Metastasis/Total No. of Patients) $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of vascular invasion</td>
<td></td>
</tr>
<tr>
<td>Intrathyroidal</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (5/25) $P = .002^*$</td>
</tr>
<tr>
<td>No</td>
<td>3 (6/234)</td>
</tr>
<tr>
<td>Extrathyroidal</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (1/6) $P = .07^*$</td>
</tr>
<tr>
<td>No</td>
<td>4 (10/235)</td>
</tr>
<tr>
<td>Local recurrence</td>
<td></td>
</tr>
<tr>
<td>Type of vascular invasion</td>
<td></td>
</tr>
<tr>
<td>Intrathyroidal</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (4/25) $P = .34^*$</td>
</tr>
<tr>
<td>No</td>
<td>6 (13/235)</td>
</tr>
<tr>
<td>Extrathyroidal</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (1/6) $P = .34^*$</td>
</tr>
<tr>
<td>No</td>
<td>6 (16/254)</td>
</tr>
</tbody>
</table>

* Fisher exact test used to calculate $P$ value.

**Figure 1.** The percentage of patients with either extrathyroidal or intrathyroidal vascular invasion who were initially seen with distant metastasis within 3 months of diagnosis. Comparison is made to those patients with documentation of no such invasion.

**Figure 2.** The percentage of patients with either extrathyroidal or intrathyroidal vascular invasion who later developed distant recurrence. Comparison is made to those patients with documentation of no such invasion.

**Figure 3.** The percentage of patients with either extrathyroidal or intrathyroidal vascular invasion who later developed local recurrence. Comparison is made to those patients with documentation of no such invasion.
velop distant recurrence. These patients even tended to
develop more local recurrence. Those tumors with in-
trathyroidal invasion seem to have more aggressive lo-
cal behavior. Indeed, models of recurrence with vascu-
lar invasion and local invasion could not be generated
because these 2 characteristics varied too closely with one
another. Vascular invasion is an independent variable for
metastasis at the time of diagnosis and recurrence. We
believe these findings are novel and have potential clinic-
ical significance.

Because our overall sample size is small, a conser-
ватive statistical tool was used to verify our results. The
Fisher exact test was chosen for its accuracy and valid-
ity with a small number of affected patients. Because of
the standard reporting of the absence of vascular inva-
sion, we believe the potential effects of selection bias in
the population are small.

Vascular invasion has anecdotally been reported as
a negative predictor in papillary carcinoma. Distant me-
tastasis is known to be associated with a poorer progno-
sis in papillary thyroid carcinoma.1-17 Our data suggest
that intrathyroidal vascular invasion is independently as-
sociated with a higher rate of distant metastasis at the time
of diagnosis and is also independently associated with a
higher rate of recurrence in papillary thyroid carci-
noma. These data indicate intrathyroidal vascular inva-
sion suggests a worse prognosis. Therefore, we believe
increased emphasis should be placed on reporting vas-
cular invasion at the time of pathologic evaluation as more
aggressive initial and subsequent therapy may be warr-
anted.

Proper and expeditious surgical and medical
therapy at the time of diagnosis remains the most im-
portant factor in relation to disease-free survivability.
Those patients at greater risk of recurrence must be
identified for closer observation, and perhaps even
more aggressive therapy. Our data provide new infor-
mation relating to the poor prognostic features of intra-
thyroidal and extrathyroidal vascular invasion. Further
studies with a larger number of patients assessing this
issue are warranted. We hope that additional studies
will be performed and believe these will confirm our
findings.

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Reprints: Richard E. Gardner, MD, 6065 Joust Ln,
Alexandria, VA 22315.

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