Prognostic Importance of Vascular Invasion in Papillary Thyroid Carcinoma

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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.

Approximately 75% of thyroid cancers in the United States are papillary carcinomas. Its peak incidence is in the fourth and fifth decades of life with a female preponderance. This multicentric disease is seen with bilateral foci in 20% to 30% of the cases. With appropriate therapy, 10-year survival rates exceed 90%. Several factors have been determined which identify tumors with more aggressive clinical behaviors. These factors, as noted by Mazzaferi and Jhiang, include male sex, older age at diagnosis, larger tumor size, capsular invasion, and regional and distant metastasis at diagnosis. In one study, distant metastasis reduced 10-year survival to 31%.

Papillary thyroid carcinoma tends to metastasize via the lymphatic system, with cervical metastasis occurring in 40% to 60% of the patients at diagnosis. Despite this high frequency, cervical nodal metastasis has been shown to be only a minor predictor of prognosis, affecting recurrence rather than mortality. Distant metastasis has been shown to portend a worse prognosis. Its presence implies hematogenous spread of tumor cells. Therefore, we hypothesized that the presence of vascular invasion, either intrathyroidal or extrathyroidal, would be associated with metastasis at the initial diagnosis and a higher incidence of tumor recurrence.

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 represents biopsy-proven abnormal tissue or a positive signal on radioiodine scan. The population of patients with either intrathyroidal (25 patients) or extrathyroidal (6 patients) vascular invasion noted was selected as the study group. These were then compared with the remaining 379 patients with documentation of no vascular invasion within the 2 registries. All metastasis reported reflects biopsy-proven abnormal tissue or findings of uptake on radioiodine scan.

Fisher exact test and Mantel-Haenszel χ² exact test were used to examine the association of distant metastasis at diagnosis with intrathyroidal and extrathyroidal vascular invasion, gross local invasion at surgery, nodule size, cervical metastasis, sex, and age. Fisher exact test was chosen because of the small number of affected patients. Local and distant recurrences also were examined in relation to intrathyroidal and extrathyroidal vascular invasion. A multivariate logistic regression was used to determine an independent relationship between intrathyroidal vascular invasion or extrathyroidal vascular invasion and distant metastasis. Multiple regression analysis was also used to examine the relation between vascular invasion and recurrence.

Distant recurrence rates in relation to the type of vascular invasion are given in Figure 2. Univariate analysis was next 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-

### 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 next 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 develop distant metastases compared to those without such invasion ($P = .02$). Patients with intrathyroidal vascular invasion also had a higher incidence of local recurrence ($P = .03$).
velop distant recurrence. These patients even tended to develop more local recurrence. Those tumors with intrathyroidal invasion seem to have more aggressive local behavior. Indeed, models of recurrence with vascular 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 clinical significance.

Because our overall sample size is small, a conservative statistical tool was used to verify our results. The Fisher exact test was chosen for its accuracy and validity with a small number of affected patients. Because of the standard reporting of the absence of vascular invasion, 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 metastasis is known to be associated with a poorer prognosis in papillary thyroid carcinoma.\(^1\)\(^\textsuperscript{17}\) Our data suggest that intrathyroidal vascular invasion is independently associated 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 carcinoma. These data indicate intrathyroidal vascular invasion suggests a worse prognosis. Therefore, we believe increased emphasis should be placed on reporting vascular invasion at the time of pathologic evaluation as more aggressive initial and subsequent therapy may be warranted.

Proper and expeditious surgical and medical therapy at the time of diagnosis remains the most important 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 information 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.

REFERENCES