Survival and Prognosis in Hürthle Cell Carcinoma of the Thyroid Gland

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Objective: To determine factors that affect survival in patients with Hürthle cell carcinoma of the thyroid gland.

Methods: Data for all cases of Hürthle cell carcinoma that occurred between January 1, 1988, and December 31, 1998, were extracted from the Surveillance, Epidemiology, and End Results database. Clinical data regarding age, sex, tumor size, primary site extension, nodal involvement, and vital status were tabulated. Patients with distant metastases were excluded, and Kaplan-Meier survival analysis was conducted. Survival data for patients with Hürthle cell carcinoma were compared with data for a control group of patients with follicular cell carcinoma matched for age, sex, tumor size, and local disease extension. Cox multivariate regression analysis was conducted to determine the effect of predictor variables on overall survival in Hürthle cell carcinoma.

Results: We identified 555 cases of nonmetastatic Hürthle cell carcinoma (mean age at diagnosis, 55.9 years; women, 67.9%). The primary tumor was intrathyroidal in 83.8% of patients, whereas 11.2% had minor local extension. Mean tumor size was 3.5 cm. Mean, 5-year, and 10-year survival for Hürthle cell carcinoma was 109 months, 85.1%, and 71.1%, respectively. Mean survival for 411 matched patients with follicular cell carcinoma was 113 months, which was not statistically different from that of patients with Hürthle cell carcinoma (P = .47, log-rank test). On multivariate analysis, increasing age at diagnosis, male sex, and increasing tumor size were statistically significant predictors of poor survival; degree of primary site extension did not affect survival.

Conclusions: Overall survival for Hürthle cell carcinoma is similar to that of comparably staged follicular cell carcinoma. Increasing age, male sex, and increasing tumor size substantially diminish survival in patients with Hürthle cell carcinoma.


WELL-DIFFERENTIATED thyroid carcinomas are the most common endocrine malignancies.1 Hürthle cell carcinomas account for approximately 5% of well-differentiated thyroid carcinomas, and some debate has emerged regarding the classification of Hürthle cell carcinomas. Once thought to be a subset of follicular cell carcinomas, they most likely represent a distinct histologic tumor.2 As a group, Hürthle cell carcinomas are relatively rare malignancies.

Because of their relative rarity, only small single-institutional experiences with Hürthle cell carcinomas have been reported in the literature.3-6 As such, relatively little is known about the clinical and pathological behavior of Hürthle cell carcinoma. Some researchers have reported a very favorable clinical course for this tumor, whereas others have considered Hürthle cell carcinoma to be a relatively aggressive thyroid gland malignancy.7 Such controversy may be fueled by relatively small sample sizes, selection biases, and institutional treatment biases. This study was conducted to examine a large patient population with Hürthle cell carcinoma to better characterize this malignancy, determine survival variables, and identify factors that may affect prognosis.

METHODS

The Surveillance, Epidemiology, and End Results (SEER) database for January 1, 1973, to December 31, 1998, was examined.8 All cases of thyroid carcinoma occurring between January 1, 1988, and December 31, 1998, were extracted and imported into a statistical software package (SPSS version 10.0; SPSS Inc, Chicago, Ill). From the initial data extraction, only cases of Hürthle cell carcinoma were selected based on the International Classification of Diseases for Oncology; other histopathologic conditions were excluded. From extent of disease information, disease at the primary (thyroid) site was subclassified as delineated in Table 1. Cases with distant metastatic disease or unknown local extension were excluded from subsequent analysis. Lymph node involvement was classified as positive or negative based on data for histopathologic analysis of involved nodes. Survival time was imputed in months.
Table 1. Classification of Primary Site Extent of Disease for Hürthle Cell Carcinoma

<table>
<thead>
<tr>
<th>Degree of Local Extension</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathyroidal disease</td>
<td>Tumor does not extend outside the capsule of the thyroid gland; may be multifocal within the gland</td>
</tr>
<tr>
<td>Minor local extension</td>
<td>Tumor invades the soft and connective tissues of the thyroid gland, parathyroid glands, strap musculature, or recurrent laryngeal nerve</td>
</tr>
<tr>
<td>Major local extension</td>
<td>Tumor extends into the carotid sheath, sternocleidomastoid muscle, esophagus, or thyroid and cricoid cartilages</td>
</tr>
<tr>
<td>Extravisceral extension</td>
<td>Tumor invades the trachea, paraspinal musculature, or vertebral bone</td>
</tr>
</tbody>
</table>

Table 2. Clinical Features of 555 Patients With Hürthle Cell Carcinoma*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, No. (%)</th>
<th>Survival, Mean mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>178 (32.1)</td>
<td>98</td>
</tr>
<tr>
<td>F</td>
<td>377 (67.9)</td>
<td>114</td>
</tr>
<tr>
<td>Extent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrathyroidal</td>
<td>465 (83.8)</td>
<td>113</td>
</tr>
<tr>
<td>Minor local extension</td>
<td>62 (11.2)</td>
<td>93</td>
</tr>
<tr>
<td>Major local extension</td>
<td>20 (3.6)</td>
<td>79</td>
</tr>
<tr>
<td>Extravisceral spread</td>
<td>8 (1.4)</td>
<td>51</td>
</tr>
<tr>
<td>Cervical nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>15 (2.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Negative</td>
<td>88 (15.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Not sampled</td>
<td>452 (81.4)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*NA indicates not assessed owing to small sample size.

RESULTS

Among 20025 patients with thyroid cancer between January 1, 1988, and December 31, 1998, 602 cases of Hürthle cell carcinoma were identified (3.0% of all thyroid malignacies). Forty-seven patients had either distant metastases or incomplete information as to the extent of primary site disease and were thus excluded. For the 555 remaining patients, the mean age at diagnosis was 53.9 years, and there was a female preponderance (67.9%). Mean tumor size was 3.5 cm (95% confidence interval [CI], 3.3-3.9 cm). Lymph nodes were histopathologically assessed for 103 patients (18.6%). Among these, 15 patients had positive nodes (2.7% of all 555 cases). Five- and 10-year survival for the Hürthle cell carcinoma cohort was 85.1% and 71.1%, respectively. Mean survival time was 109 months (95% CI, 105-114 months). Table 2 lists the distribution of clinical variables for the Hürthle cell carcinoma cohort. Overall survival for the Hürthle cell carcinoma cohort is depicted in Figure 1.

Matching of Hürthle cell carcinoma cases to follicular cell carcinoma cases was achieved for 411 patients. Mean age at diagnosis was 53.6 years for the Hürthle cell carcinoma cohort and 53.5 years for the follicular cell carcinoma reference group. Similarly, mean follow-up for each group was 49.0 months. For the matched reference group of patients with follicular cell carcinoma, 5- and 10-year actuarial survival was 89.2% and 56.7%, respectively. Mean survival time was 113 months (95% CI, 109-118 months). Comparative survival curves for the Hürthle cell carcinoma cohort and the follicular cell carcinoma cohort are depicted in Figure 2. The slightly poorer survival for Hürthle cell carcinoma vs follicular cell carcinoma was not statistically significant (P=.47, log-rank test).

Kaplan-Meier survival curves according to sex and degree of local extension are depicted in Figure 3 and Figure 4, respectively. On univariate analysis, both male sex and increasing local extension resulted in poorer survival (P=.001 for both). The results of the Cox proportional hazards model are given in Table 3. Increasing age at diagnosis, male sex, and increasing tumor size were each statistically significantly associated with substantially poorer survival on multivariate analysis. Local extent was not a statistically significant predictor of survival on multivariate analysis.
COMMENT

Hürthle cell carcinomas account for approximately 5% of thyroid malignancies. They are relatively rare tumors, and, as such, relatively little is known on a large-scale basis about the long-term survival of patients with Hürthle cell carcinoma. Some researchers have reported a relatively benign course and prolonged survival, whereas others have found these tumors to behave aggressively and to confer poor expected survival. Perhaps stemming from these differences in experience, controversy has emerged as to the best treatment for Hürthle cell carcinoma. Some researchers recommend conservative management of these cancers, whereas others recommend aggressive management.

Some of the controversy in clinical management stems from the difficulties in pathological assessment of Hürthle cell tumors in general. Varying criteria have been used to separate adenoma from carcinoma, and many researchers have suggested varying morphologic criteria to distinguish benign from malignant Hürthle cell tumors. Recent molecular studies have suggested that Hürthle cell carcinomas have separate oncogenic features, making them a distinct pathological entity from Hürthle cell adenomas and follicular cell carcinomas. With recent advances in morphologic and molecular diagnoses, tumors diagnosed in the past several decades are more likely to be correctly classified as carcinomas. In a critical pathological appraisal by Stojadinovic et al., a review of 102 patients with Hürthle cell tumors treated in 50 years resulted in diagnostic revisions in 28% of cases. Even with experienced pathological evaluation, a fraction of Hürthle cell tumors will be classified as “indeterminate” or “of uncertain behavior” because of difficulties with assessment of malignancy in these lesions. Even DNA studies may not distinguish between benign and malignant Hürthle cell tumors. The effect of time on the understanding of Hürthle cell neoplasms must be considered when evaluating the literature.

Problems may also arise in diagnosis of Hürthle cell tumors by fine-needle aspiration (FNA). Several studies have shown that FNA can reliably identify Hürthle cell neoplasms among thyroid nodules, although this experience is not uniform. However, further classification of Hürthle cell neoplasms as benign or malignant based on FNA data alone can be difficult. Within the subset of Hürthle cell neoplasms, FNA exhibits poor sensitivity but relatively high specificity for the determination of malignancy. More advanced biological markers, although promising, have yet to demonstrate clinical utility in improving the diagnostic accuracy of FNA in Hürthle cell neoplasms. Thus, FNA cannot be used to exclude the possibility of malignancy in Hürthle cell neoplasms, and the same considerations applied to follicular cell neo-
plasms should also be applied to Hürthle cell neoplasms with respect to operative planning.18

Hürthle cell carcinomas tend to present at a larger size than Hürthle cell adenomas. In a recent review attempting to determine clinical factors that predicted Hürthle cell carcinoma rather than Hürthle cell adenoma, Chen et al13 found that Hürthle cell carcinomas exhibited a mean tumor size at presentation of 4.0 cm, whereas Hürthle cell adenomas had a mean tumor size of 2.4 cm at presentation. The mean tumor size of 3.5 cm reported herein is in keeping with several other studies of Hürthle cell carcinomas.8 For Hürthle cell tumors approaching 4 cm, total thyroidectomy may be considered at the outset given the elevated risk of identifying carcinoma in such large Hürthle cell nodules.5

The present data indicate that Hürthle cell cancers behave similarly to their follicular cell carcinoma counterparts. Indeed, Hürthle cell tumors share many clinicopathologic features with follicular cell carcinoma, including difficulties with determination of malignancy vs adenomatous change and assessment of locally invasive features. One of the clinical problems with Hürthle cell cancer is its propensity to metastasize distantly.19 This is in keeping with the propensity for lymphovascular invasion of follicular cell carcinomas, but Hürthle cell cancers may show an even greater tendency for distant metastasis.20 In a review of 59 patients with Hürthle cell carcinoma treated in 6 decades, Shaha et al19 reported a 33% rate of distant metastasis and a 21% rate of nodal metastasis. These and other studies suggest that Hürthle cell carcinoma is a somewhat more aggressive malignancy compared with follicular or papillary carcinoma of the thyroid.21

The SEER database has previously been used to analyze outcomes and survival data for carcinoma of the nasal cavity, major salivary gland malignancy, and other head and neck tumors.22-24 It is considered a gold standard database for tumor surveillance and survival analysis in the United States. The SEER database represents approximately 10% of the US patient population, capturing and tracking patients from diverse geographic regions within the United States.8 One of the major advantages of using the SEER database is the large sample size provided with which to conduct multivariate regression analysis. With a sufficiently large sample size, we were able to identify male sex, increasing tumor size, and increasing patient age as clinically significant predictors of poorer outcome in Hürthle cell carcinoma. Thus, patients with these features should be considered for more aggressive treatment, including total thyroidectomy. Because Hürthle cell carcinomas generally do not concentrate radioiodine, the initial surgical attempt at therapy has even greater importance.2,23

However, use of the SEER database has limitations. For example, analysis of the SEER database is limited to assessment of overall survival; disease-specific survival and locoregional recurrence cannot be assessed. However, given that most patients with terminal well-differentiated carcinoma of the thyroid die of distant disease rather than local recurrence, assessment of local-regional recurrence is likely to be less important.20 Although there are limitations to this type of database analysis, the considerable advantages of large sample size, geographically unbiased sampling, and extended follow-up make the SEER database advantageous for analysis of a relatively rare tumor such as Hürthle cell carcinoma.

In conclusion, although it is a distinct thyroid histologic tumor, Hürthle cell carcinoma clinically behaves similarly to follicular cell carcinoma. Based on risk factor analysis, Hürthle cell carcinoma should be treated aggressively with total thyroidectomy, especially in older patients, men, and those with large tumor size. Extrathyroidal extension of the primary tumor should not preclude aggressive management and does not substantially reduce survival.

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REFERENCES