**Hürthle Cell Tumors**

*Applying Molecular Markers to Define a New Management Algorithm*

Evelyn L. Maxwell, AB, MD, FRCSC; Carsten E. Palme, MBBS, FRACS; Jeremy Freeman, MD, FRCSC

**Objective:** To design a new management algorithm for all Hürthle cell tumors and variants based on histopathologic findings and the *ret/PTC* molecular marker.

**Design:** A retrospective medical record review.

**Setting:** A large tertiary care teaching center.

**Patients:** Forty-five consecutive cases of Hürthle cell carcinoma were gathered from a database of 661 patients with well-differentiated epithelial thyroid cancers compiled over 22 years. Data collected included patient information, tumor information, and treatment factors.

**Main Outcome Measures:** Outcome parameters included tumor and treatment variables, which were analyzed statistically using the χ² and t tests. Disease-free survival and disease-specific survival analyses were performed using Kaplan-Meier analysis.

**Results:** A female-male ratio of 3:1 was found, with a median patient age of 57 years. Twenty-three patients had American Joint Commission on Cancer stage II disease.

Treatment factors had no significant effect on disease recurrence or survival. More than half of the patients had histologically proved regional metastases. Vascular invasion significantly diminished disease-specific survival and disease-free interval.

**Conclusions:** We found a high incidence of Hürthle cell carcinoma with cervical metastasis. On the basis of findings of this study and our previous clinical and molecular findings, we propose a treatment algorithm that combines histologic examination and molecular assays for the *ret/PTC* gene rearrangements specific to papillary thyroid carcinoma. After permanent section analysis demonstrating Hürthle cell metaplasia, the algorithm mandates completion thyroidectomy in patients with *ret/PTC*-positive Hürthle cell tumors and clinical observation for *ret/PTC*-negative Hürthle cell adenomas. We recommend more aggressive treatment of *ret/PTC*-positive Hürthle cell lesions (or Hürthle cell papillary thyroid cancer), because of the higher incidence of regional metastatic disease.

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**A HÜRTHLE CELL TUMOR (HCT) is defined as a thyroid tumor composed of at least 75% Hürthle cells.**

The Hürthle cell is a large, thyroglobulin-producing cell thought to be related to follicular epithelium. The Hürthle cell, also known as the “oncocytic cell,” the “oxyphilic cell,” or the “Askanazy cell,” demonstrates abundant pink granular cytoplasm and is characterized by numerous mitochondria. Described initially in 1928 by Ewing, Hürthle cell carcinomas (HCCs) are rare tumors that account for approximately 6% of all well-differentiated thyroid cancers. Hürthle cell carcinoma is considered by the World Health Organization as a follicular thyroid cancer variant. Traditionally, HCTs have been classified as either benign Hürthle cell adenomas or malignant HCCs. On the basis of the classification of follicular thyroid tumors, HCCs have been differentiated from adenomas on the basis of presence of capsular invasion, vascular invasion, or metastatic lesions. However, papillary thyroid carcinomas (PTCs) composed of Hürthle cell variants of PTC have been described. These tumors show oncocytic cells organized in papillary architecture. In some cases, these HCTs show the nuclear features characteristic of PTC. In other cases, the typical nuclear features of PTC may be obscured by the nuclear hyperchromasia characteristic of Hürthle cell metaplasia.

Prediction of the clinical behavior of HCC is controversial. Some studies have shown that HCC is biologically aggressive, with disease-specific mortality attributable to distant metastases. It has been...
shown that survival is poorer compared with survival with papillary carcinoma, and, therefore, HCC should be managed aggressively. Others have suggested that HCC may be a low-grade tumor, less aggressive than follicular carcinoma, resulting in minimal morbidity and mortality. There have been reports of tumors initially diagnosed as benign Hurthle cell adenomas later recurring or metastasizing to regional lymph nodes. A higher incidence of metastasis to lymph nodes has been noted with HCT compared with follicular carcinoma. This observation has led some investigators to believe that HCTs have an indolent clinical course with lymphatic spread, analogous to the behavior of PTC. This controversy about the biological behavior of HCTs has led some authors to propose aggressive surgical management of all HCTs.

We performed a retrospective review of our cases of HCC to identify tumor and management variables predictive of outcome and prognosis. We also integrated findings from 2 of our previously published studies and propose a new management algorithm for HCTs.

## METHODS

A database of 661 patients with well-differentiated epithelial thyroid cancers was compiled over 22 years at Mount Sinai Hospital, Toronto, Ontario. The use of the database was approved by the research ethics board. Forty-five patients with HCC were identified. Cases were defined as HCC on the basis of presence of typical histologic features and the presence of capsular or vascular invasion or distant metastases.

Information was collected retrospectively from patient medical records. Patient information included sex, age, exposure to ionizing irradiation, and family history of well-differentiated epithelial thyroid cancer. Tumor information included tumor size, multifocality, extracapsular spread, vascular invasion, American Joint Committee on Cancer (AJCC) stage, and regional lymph node metastases. Treatment factors included type of thyroidectomy, neck dissection (excluding diagnostic lymph node sampling), and administration of radioactive iodine treatment or external beam radiation. Outcome measures included complication rate, recurrence, and disease-specific survival. Tumor and treatment variables were analyzed statistically using the \( \chi^2 \) and \( t \) tests. Disease-free survival and disease-specific survival analyses were performed using Kaplan-Meier analysis. \( P \leq 0.05 \) was considered statistically significant for all tests.

## RESULTS

Of the 661 cases of well-differentiated epithelial thyroid carcinomas compiled, 45 patients with HCC (7%) were identified. A 3.1 ratio of female patients (34/45) to male patients (11/45) was found. Their median age was 57 years (range, 35-92 years). Few patients (3/45) had exposure to ionizing irradiation. One patient had an identifiable family history of well-differentiated thyroid cancer.

Most tumor variables did not influence recurrence or survival (Table 1). The median tumor size in our patients was 2.5 cm (range, 0.5-8.0 cm). One third of patients (15/45) had multifocal tumors. Nine patients had extracapsular tumor extension. Seven patients showed histologic evidence of vascular invasion. Twenty-five patients demonstrated regional lymph node metastases.

Twenty-three of 45 patients had AJCC stage II disease. Five patients had AJCC stage I disease, 16 patients had AJCC stage III disease, and 1 patient had AJCC stage IV disease. Of all tumor variables, vascular invasion and AJCC staging were found to significantly affect survival and recurrence and to negatively influence prognosis.

The vast majority of patients with HCC (41/45) underwent total thyroidectomy; use of subtotal thyroidectomy was limited (4/45). Twenty-two of 45 patients required surgical management of neck disease. Thirty-nine patients received at least 1 course of adjuvant therapy with radioactive iodine I 131. External beam radiation therapy was used infrequently (2/45). Statistical analysis of management and treatment variables had no significant effect on recurrence or survival (Table 2).

Most patients (40/45) were alive without disease at the time of the study. The median follow-up was 94 months (range, 2-261 months). Three patients were lost to follow-up. Three patients had recurrence of disease. Two patients died of thyroid carcinoma. Kaplan-Meier analysis demonstrated disease-specific survival of 96% at 5 years (Figure 1).

Vascular invasion was found to negatively influence recurrence and survival significantly. Kaplan-Meier analysis revealed that vascular invasion significantly diminished disease-specific survival to 87% at 5 years (\( P = .001 \); Figure 2) and significantly reduced the disease-free interval to 87% at 5 years (\( P = .02 \); Figure 3).

We found a complication rate of 13%, all due to hypoparathyroidism. There were no cases of recurrent laryngeal nerve injury.

## Table 1. Effect of Tumor Variables on Recurrence of Disease and on Survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median size, cm (range)</td>
<td>2.5 (0.5-8.0)</td>
</tr>
<tr>
<td>Extracapsular spread</td>
<td>9</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>7</td>
</tr>
<tr>
<td>Multifocal</td>
<td>15</td>
</tr>
<tr>
<td>Stage (AJCC), I/II/III/IV†‡</td>
<td>5/23/16/1</td>
</tr>
<tr>
<td>Regional metastases</td>
<td>25</td>
</tr>
</tbody>
</table>

Abbreviation: AJCC, American Joint Committee on Cancer.

*Except for vascular invasion and stage, all \( P \) values were not significant.

†\( P = .20 \) for recurrence; \( P = .001 \) for survival.

‡\( P < .001 \) for both recurrence and survival.

## Table 2. Effect of Management and Treatment Variables on Disease Recurrence and on Survival in 45 Patients

<table>
<thead>
<tr>
<th>Treatment Variable</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thyroidectomy</td>
<td>41</td>
</tr>
<tr>
<td>Subtotal thyroidectomy</td>
<td>4</td>
</tr>
<tr>
<td>Neck surgery</td>
<td>22</td>
</tr>
<tr>
<td>Iodine I 131 therapy</td>
<td>39</td>
</tr>
<tr>
<td>External beam radiation therapy</td>
<td>2</td>
</tr>
<tr>
<td>Complication</td>
<td>6</td>
</tr>
</tbody>
</table>

*All \( P \) values were not significant.
This retrospective study was conducted in a patient cohort drawn from a single database at a single institution. All tumors were histologically confirmed to be composed of at least 75% Hürthle cells. We found a 7% incidence of HCC among all well-differentiated thyroid cancers. Review of the literature revealed a reported incidence of 0.4% to 10%.11 Female patients outnumbered male patients by a factor of 3. Hürthle cell carcinoma seems to be a disease of the more aged (median age, 57 years), although there was a vast age range (35-92 years). These findings are similar to those of other reports.11 Radiation exposure was not particularly common (7%), nor was a family history of well-differentiated thyroid cancer (2%).

The only tumor variables found to significantly affect recurrence and survival were evidence of vascular invasion and AJCC stage, with more advanced stage significantly reducing survival and increasing the risk for disease recurrence. Despite a wide range of tumor sizes in this study, tumor size did not influence survival or recurrence. In addition, evidence of extracapsular spread, multifocality, and regional metastases did not confer survival or recurrence disadvantage. This finding is somewhat different from that found in other studies.10,12

None of the treatment options had a significant effect on recurrence or disease-specific survival. The treatment of choice in 41 (91%) of our 45 patients was total thyroidectomy. In 22 (49%) patients neck dissection was required for management of regional disease. Thirty-nine patients (87%) received postoperative ablative radioactive iodine therapy. This intervention did not affect survival or recurrence. This has been found by other authors.11 Most HCCs are thought to concentrate radioactive iodine poorly.12 Rarely, patients (4%) who were poor surgical candidates or who required palliative therapy received external beam radiation.

There was a high incidence of regional cervical metastases. In addition, most patients experienced a favorable, disease-free outcome. The favorable outcome differs significantly from what would be expected for a follicular lesion, which is characterized by aggressive clinical behavior and a propensity for hematogenous spread. The high incidence of lymphatic spread and the relatively benign clinical course of HCC in this study are more in keeping with the clinical behavior of typical PTC.

PART 2

Hürthle cell variants of PTC have been described histopathologically on the basis of presence of oxyphilic cells arranged in a papillary architecture.6 A recent study published by our research group was among the first reports to support a molecular basis for a subset of HCTs.13 Cheung et al14 examined the expression of the ret/PTC gene rearrangement specific to PTC in 50 HCTs. The ret proto-oncogene, found on chromosome 10, is not normally expressed in thyroid epithelial cells. The rearrangement of the ret proto-oncogene to form the oncogenic ret/PTC product is specific to PTC.12 We found that
34 of 50 benign and malignant HCTs expressed the ret/PTC oncogene, irrespective of histologic structural organization. These findings suggest that a significant number of HCTs, including adenomas, were HCT variants of PTC. We suggest that a substantial number of malignant HCTs were missed when evaluation was based solely on histologic examination. We proposed a new subclassification system of HCTs (Hürthle cell adenomas, HCCs, Hürthle cell PTCs) based on a molecular marker rather than on histologic findings.\textsuperscript{14}

\section*{PART 3}

The observed clinical heterogeneity of HCCs may be attributed to the fact that they are a variety of biologically different tumor types, including follicular HCCs and papillary HCCs. Immunohistochemical and molecular tests may identify papillary HCC on the basis of the presence of the ret/PTC rearrangement, regardless of cellular patterns.\textsuperscript{15} We have observed that HCTs that express the ret proto-oncogene tend to behave pathologically like PTCs. In the study by Belchetz et al.,\textsuperscript{13} 56 HCTs were identified from a previously unpublished database. We found that the papillary HCTs that metastasized to regional lymph nodes were ret/PTC positive. These HCTs behaved like PTCs rather than follicular carcinomas, showing lymphatic metastases and an indolent clinical course. They did not show aggressive behavior or a propensity for hematogenous spread.\textsuperscript{13}

The identification of ret enables accurate categorization of malignant HCTs as follicular or papillary types. Moreover, the possibility of morphologically benign HCTs harboring the ret/PTC gene would explain the metastatic potential of these tumors. We suggest that ret-positive HCTs tend to spread to locoregional lymph nodes, similar to PTCs. We found that locoregional metastatic disease did not negatively influence survival or recurrence. The utility in screening HCTs for ret positivity lies in accurate categorization of HCTs and differentiation between papillary and follicular types. This differentiation enables improved prognostication, patient counseling, and planning of adjunctive treatments such as radioactive iodine ablation therapy or external beam radiation, depending on patient and tumor factors.

Figure 4 illustrates our proposed management approach for HCTs and is based on the presence or absence of the ret/PTC gene marker. We emphasize the useful role of the ret/PTC gene assay in determining subsequent management of Hürthle cell adenomas. To our knowledge, this approach has not been previously published in the literature. When an HCT is identified in a specimen obtained at fine-needle aspiration, we recommend a subtotal thyroidectomy with intraoperative frozen section analysis of the specimen. If frozen section analysis reveals HCC, a total thyroidectomy should be performed. If frozen section analysis reveals a papillary HCC, we recommend a management strategy based on that of typical PTC, including total thyroidectomy and appropriate lymphadenectomy. Should frozen section analysis identify an HCT without histologic evidence of malignancy, we recommend completion of the subtotal thyroidectomy and analysis of the permanent specimen sections. If permanent section analysis reveals a true HCC or a papillary HCC, a completion thyroidectomy should be done. When a Hürthle cell adenoma is identified at permanent section analysis, we suggest analysis for ret/PTC rearrangement using the polymerase chain reaction, as outlined in other studies.\textsuperscript{12,14} In ret/PTC-negative HCTs, clinical follow-up is adequate. However, ret/PTC-positive tumors should be managed as papillary thyroid lesions, and completion thyroidectomy and appropriate lymphadenectomy should be performed.

The role of adjunctive radioactive iodine treatment has not been included in the algorithm. Radioactive iodine
is an important component in the treatment of papillary, follicular, and Hurthle cell neoplasms. However, we suggest that the use of radioactive iodine therapy be determined on a patient-by-patient basis, weighing tumor and patient variables. We suggest that radioactive iodine therapy be considered in cases with patient or tumor factors traditionally considered unfavorable, such as large tumor size, advanced patient age, extracapsular invasion, vascular invasion, distant metastases, or incomplete surgical resection.

CONCLUSIONS

Hurthle cell tumors have caused substantial diagnostic and management controversy. They likely represent a heterogeneous group of tumors with a wide spectrum of clinical aggressiveness. Our study demonstrated HCCs with a high incidence of indolent clinical behavior and regional metastases. We theorize that immunohistochemical examination and polymerase chain reaction analysis of these tumors would likely demonstrate the papillary variant of HCC. Differentiating HCCs into different biological groups on the basis of the presence or absence of the ret/PTC rearrangement specific to PTC would enhance the diagnosis and treatment of these tumors and assist in patient counseling.

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Correspondence: Jeremy Freeman, MD, FRCSC, Department of Otolaryngology–Head and Neck Surgery, Mount Sinai Hospital, 600 University Ave, Room 401, Toronto, Ontario, Canada M5G 1X5 (j.freeman@utoronto.ca).

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REFERENCES