Hürthle Cell Tumors
Using Molecular Techniques to Define a Novel Classification System

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Background: Since ret/PTC gene rearrangements are specific to papillary thyroid carcinoma (PTC), the diagnosis of Hürthle cell PTC (HCPTC) has recently been expanded to include a subset of Hürthle cell tumors (HCTs) that may lack both papillary architecture and/or classic nuclear features but that harbor a ret/PTC gene rearrangement. We hypothesize that such HCPTCs behave in a fashion analogous to other papillary carcinomas, while Hürthle cell carcinomas (HCCs) behave similarly to follicular carcinomas.

Educational Objectives: At the conclusion of this article, participants should be able to discuss HCTs and to identify HCPTCs using molecular techniques.

Methods: A retrospective chart review was carried out on 56 patients with HCTs. All pathological specimens were analyzed for ret/PTC gene rearrangements. Hürthle cell adenoma (HCA) was defined as an HCT that did not exhibit capsular and/or vascular invasion and that lacked a ret/PTC gene rearrangement when evaluated by immunohistochemical and reverse transcription polymerase chain reaction analysis. An HCC was defined as an HCT with capsular and/or vascular invasion that lacked a ret/PTC gene rearrangement, and an HCPTC was defined as any HCT that harbored a ret/PTC gene rearrangement.

Results: The subclassification of the 56 HCTs was as follows: 21 HCAs, 15 HCCs, and 20 HCPTCs. No patients with HCA or HCC were ret/PTC positive. Five of the 6 patients with definite lymph node metastasis were in the HCPTC group, demonstrating that molecular analysis helps to explain biological behavior.

Conclusions: Hürthle cell neoplasms can now be classified using histopathological as well as molecular criteria. It appears that the new subclassification of malignant HCTs into follicular (HCC) and papillary (HCPTC) variants identifies 2 distinct biological groups.

PATIENTS AND METHODS

A retrospective chart review was carried out on 56 patients who had been diagnosed as having HCT between January 1993 and April 1999. The patients were referred by 4 surgeons at Mount Sinai Hospital, Toronto, Ontario. One surgical pathologist (S.L.A.) analyzed all pathology reports. The HCTs were classified as HCA, HCC, or HCPTC according to Cheung et al.13 An HCA was defined as an HCT that did not exhibit capsular and/or vascular invasion and that lacked a ret/PTC gene rearrangement when evaluated by immunohistochemical and reverse transcription polymerase chain reaction analysis. An HCC was defined as an HCT with capsular and/or vascular invasion that lacked a ret/PTC gene rearrangement when evaluated by immunohistochemical and reverse transcription polymerase chain reaction analysis. An HCPTC was defined as any tumor that harbored a ret/PTC gene rearrangement when evaluated by immunohistochemical and reverse transcription polymerase chain reaction analysis. An HCC was defined as any tumor that harbored a ret/PTC gene rearrangement when evaluated by immunohistochemical and reverse transcription polymerase chain reaction analysis. An HCPTC was defined as any tumor that harbored a ret/PTC gene rearrangement when evaluated by immunohistochemical and reverse transcription polymerase chain reaction analysis.

Data were collected for each patient with respect to age, sex, clinical presentation, result of fine-needle aspiration, extent of surgery, size of primary lesion, presence of extracapsular extension, presence of lymph node metastasis, and presence of distant metastasis. Data on whether the patients received radioactive iodine treatment and/or external beam radiation therapy, whether the tumor recurred after treatment, and whether the patients died of their disease were also recorded. Follow-up care ranged from 1 month to 106 months or death, with a mean follow-up duration of 30 months.

differentiated thyroid cancers,14-16 while others believe them to be very aggressive.17,18

The behavior of apparently benign HCTs is equally confusing.18 Several authors have reported tumors initially diagnosed as HCAs that later recurred or metastasized.17,18 Unfortunately, the inability to accurately predict the clinical behavior of HCTs has led some authors to advocate aggressive surgical treatment for all HCTs.17,19-22 Until the identification of the HCPTC, there was no adequate explanation as to why some HCTs developed lymph node metastasis, particularly in tumors that were morphologically classified as HCAs.

We hypothesize that HCCs behave in keeping with other follicular carcinomas with hematogenous spread and a more aggressive clinical course and that HCPTCs behave in a fashion analogous to other PTCs, with lymphatic spread and a more indolent clinical course.

RESULTS

The features of 56 HCTs are summarized in the Table. Of the 56 tumors, 15 (27%) were diagnosed as HCC, 20 (36%) were diagnosed as HCPTC, and 21 (38%) were diagnosed as HCA. There was a female predominance both overall (43 of the 56 tumors) and in each subgroup. The age of patients ranged from 26 to 89 years. The average age of the patients was higher in the HCC group (mean age, 63.4 years) than in the HCPTC group (mean age, 49.4 years) and the HCA group (mean age, 48.0 years). None of the patients had a history of exposure to radiation. The majority of patients presented with an asymptomatic nodule of the thyroid. Other presentations included multinodular goiters, symptomatic goiters (choke, dysphagia), thyroid mass on chest x-ray film, hypothyroidism, and a thyroglossal duct cyst.

Only 3 of the patients in the series did not undergo fine-needle aspiration biopsy as part of their workup. The most common result of cytological examination was “Hurthle cell lesion” (24/56), with “follicular neoplasm” (8/56) being the second most common reported finding. Only 1 patient had a cytology report of “carcinoma” that went on to a final diagnosis of HCC, whereas 7 patients had a cytology report of “papillary carcinoma” and went on to a final diagnosis of HCPTC. One HCA was mistakenly called carcinoma on cytological examination.

Of the 15 patients with the final diagnosis of HCC, 9 underwent total thyroidectomy and 7 underwent hemithyroidectomy, with the completion thyroideotomy at a later date. One patient underwent a comprehensive neck dissection for grossly positive neck disease. Of the 20 patients with the final diagnosis of HCPTC, 17 underwent total thyroideotomy and 3 underwent hemithyroidectomy, with the completion thyroideotomy at a later date. Three patients underwent neck dissection for grossly positive neck disease. Of the 21 patients with HCA, 19 underwent hemithyroidectomies as their only treatment. Two patients with HCA underwent total thyroideotomy because intraoperative frozen sections were reported as carcinoma.

The size of the primary lesion ranged from 1.0 to 10.6 cm in maximum diameter. This size was comparable across all 3 groups. The mean maximal diameters for the follicular, papillary, and adenoma groups were 4.0, 3.4, and 3.1 cm, respectively.

Three patients with a final diagnosis of HCC had extrathyroidal extension noted on their final pathology report. Seven patients with a final diagnosis of HCPTC had extrathyroidal extension noted on their final pathology report. No patients with a final diagnosis of HCA had extrathyroidal extension.

Only 1 patient with a final diagnosis of HCC was histologically positive for lymph node metastasis. Five patients with a final diagnosis of HCPTC were positive for lymph node metastasis histologically or on radioactive iodine body scan. No patients with a final diagnosis of HCA had lymph node metastasis. No patients in any group had distant metastasis during the follow-up period.

Radioactive iodine treatment was given to 14 of 15 patients with HCC patients and to 18 of 20 patients with HCPTC. No patients with HCA received radioactive iodine treatment. External beam radiation therapy was administered to 3 of 20 patients with HCPTC and gross local residual disease. No patients with HCC or HCA received external beam radiation therapy.

After surgical treatment, 2 patients with HCPTC had a recurrence of their disease. Both of these recurrences were in the form of lymph node metastases and were
treated with subsequent doses of radioactive iodine. There was only 1 death in the series. The patient, who had HCC in a thyroglossal duct cyst, died of carotid artery erosion.

## COMMENT

The Hürthle cell variant of papillary carcinoma has been described in the literature. It was diagnosed on the basis of papillary architecture. Recently, Cheung et al.\(^1\) established the molecular basis of HCPTC with the identification of ret/PTC gene rearrangements in a subset of HCTs. In the absence of papillary architecture, the diagnosis of a “follicular variant papillary carcinoma” with a Hürthle cell morphological appearance cannot rely on nuclear features, as the nuclear hyperchromasia that often accompanies Hürthle cell metaplasia may obscure the diagnostic nuclear features.

Being able to accurately divide malignant HCTs into follicular and papillary variants may account for the heterogeneity in clinical behavior that has caused major controversy in the past.\(^1,4,15\) One would expect HCPTCs to behave in keeping with other PTCs, with a tendency for lymph node metastasis and a more indolent clinical course; HCCs might account for the reports of more aggressive HCTs.

All the HCTs in our large series were analyzed for the presence of ret/PTC gene rearrangements. There was a definite predominance of lymph node metastasis in the group that was ret/PTC positive, with only 1 ret/PTC-negative tumor displaying lymph node metastasis. Since ret/PTC gene rearrangements are identified in only a percentage of papillary carcinomas, it may be that other markers of papillary carcinoma will identify this lesion as a PTC as well.

Recurrence of disease after treatment was uncommon in all groups. Recurrence occurred twice in the HCPTC group, and in both cases it was in the form of lymph node metastasis. The overall low recurrence and mortality rates in all groups may be a true reflection of the biological behavior of Hürthle cell cancers, but the duration of follow-up was too short in many cases to confirm this theory. The only death in the series happened in a patient with HCC arising in a thyroglossal duct cyst, an extremely rare occurrence.

Previous reports of aggressive behavior suggested that the diagnosis of HCA could not be trusted.\(^1,7,18\) The recognition of HCPTC identified a group of lesions that demonstrated no invasive behavior at the time of diagnosis but that harbored a ret/PTC gene rearrangement. These tumors have the potential to metastasize, explaining the occurrence of malignancy in patients with a histopathological diagnosis of adenoma. These data indicate the need for application of analysis for ret rearrangements as a diagnostic tool.

This series of HCTs suggests that being able to divide malignant HCTs into follicular and papillary groups does identify 2 biologically different groups, which may enable the clinician to predict which HCT will behave in a more aggressive fashion (as traditionally has been believed) and which will behave in a more indolent fashion, as many authors have more recently noted.

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REFERENCES