A keen instinct for drama and a mastery of expressive gesture are intensified by the subtle use of color and chiaroscuro in this example of Japanese art.

**Hürthle Cell Carcinoma**

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Total thyroidectomy with central neck lymph node dissection is the therapy of choice for patients with Hürthle cell carcinoma.

**Background:** Hürthle cell carcinoma represents approximately 3% of all differentiated thyroid cancers. The terminology is often confusing, and discrimination between Hürthle cell carcinoma and benign Hürthle cell tumors can be unclear. Thus, optimal treatment of patients with these diseases remains unsettled.

**Methods:** The authors reviewed published evidence on the presentation, biologic behavior, and treatment outcomes for this disease. In addition, they summarized their experience involving a series of 14 patients with Hürthle cell carcinoma.

**Results:** Hürthle cell carcinoma generally produces thyroglobulin and rarely takes up radioactive iodine. It is frequently bilateral or multifocal within the thyroid gland and often presents with local invasion. Hürthle cell carcinoma is associated with a high rate of locoregional recurrence and significant mortality.

**Conclusions:** The authors advocate total thyroidectomy with central neck dissection as the therapy of choice for patients with Hürthle cell carcinoma.

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**Introduction**

Hürthle cell carcinoma of the thyroid is a rare neoplasm comprising about 3% of all differentiated thyroid cancer. Discrimination of Hürthle cell carcinoma from benign Hürthle cell tumors, the natural history of Hürthle cell carcinoma and the optimal treatment of patients who have them, are unsettled issues in thyroid surgery. The terminology itself arose in confusion when Ewing in 1919 mistook the histologic appearance of these oxyphilic tumors and applied to them the name of the man who earlier had described the canine C cell.[1] Hürthle cell tumors appear to be of follicular rather than C cell origin and are also referred to as oxyphil tumors, oncocytomas, mitochondriomas or Askanazy cell tumors. The latter designation honors the description of the oxyphil cell by Askanazy in 1898.[2]

Evidence suggesting that Hürthle cells tumors arise from follicular cells includes histologic features, the frequent production by Hürthle cell carcinomas of thyroglobulin (Tg), and the presence in benign Hürthle cell tumors of an intact thyrotropin receptor adenylate cyclase signal transduction pathway.[3] Hürthle cell carcinomas do not appear to be variants of follicular cell carcinoma, however, as they express different oncogenes.[4]

**Presentation and Diagnosis**

The predominant presentation of Hürthle or oxyphilic cells in the thyroid is as a nonencapsulated hyperplastic island, termed Hürthle cell change or Hürthle cell hyperplasia, often noted incidentally in the setting of goiter or thyroiditis (Fig 1). Hürthle cell change is generally regarded to be a form of benign metaplasia rather than frank neoplasia. Solitary encapsulated tumors composed of Hürthle cells are neoplastic. Most are benign adenomas.

Absence in the past of uniform pathologic criteria for distinguishing adenoma from malignancy contributed to widely disparate reports of the prevalence of Hürthle cell carcinoma, ranging from 5%[5] to 56% of all Hürthle cell tumors.[6] In our experience, the breakdown of Hürthle cell tumors is approximately 80% benign Hürthle cell adenomas and 20% Hürthle cell carcinomas. Misclassification in older studies of some Hürthle cell carcinomas as benign Hürthle cell tumors, and vice versa, led to the perception that some histologically benign appearing Hürthle cell tumors are malignant.[7] In the past, some authors advocated the use of an “intermediate” category of malignancy based on “partial” angio or capsular invasion.[8] These reports ignited a lively debate over how much thyroid to remove in the surgical treatment of patients with Hürthle cell tumors.

Cytologic criteria cannot distinguish Hürthle cell adenoma from Hürthle cell carcinoma.[11-13] Aspiration biopsy cytology (ABC) may show only...
"Hürthle cell neoplasm," which will be Hürthle cell carcinoma in 15% to 20% of cases. Thyroid scanning will show a "cold" nodule except in the rare Hürthle cell carcinoma that takes up iodine.[14] Neither radionuclide scanning nor ultrasound can distinguish Hürthle cell adenomas from Hürthle cell carcinomas.

Fewer than 400 cases of Hürthle cell carcinoma have been reported in the literature over the past 75 years. From the more recent series employing reliable criteria for malignancy, a clinical picture of Hürthle cell carcinoma is beginning to emerge.[8,9,15–20] Hürthle cell carcinoma is a disease with peak incidence in the fifth to seventh decade. Women are predominantly affected by a ratio of 3:1, similar to the other thyroid tumors of follicular origin. Our recent series is unusual in its nearly 2:1 predominance of men.[20] The tumors present as a solitary or dominant mass within the thyroid gland and measure 4.0 to 5.0 cm on average by the time they are resected. Lymphadenopathy, vocal cord paralysis or distant metastases are unusual at presentation but may complicate recurrent disease. Hürthle cell tumors are almost always endocrinologically silent (though they may produce as yet unidentified hormonal factors) and patients are euthyroid unless thyroid hormone homeostasis is perturbed for another reason. Hürthle cell carcinomas usually produce Tg but rarely trap radioactive iodine.

### Treatment Approach

While many studies have questioned whether Hürthle cell neoplasms are malignant, few have addressed the treatment of patients with Hürthle cell carcinoma. The debate over how much thyroid to remove follows the controversy over differentiated thyroid carcinoma in general, with some authorities claiming that thyroid lobectomy is adequate in that papillary cancer, in particular, is a well-behaved lesion with little tendency to recur. Our position has been that total thyroidectomy is indicated for well-differentiated thyroid cancer over 1 cm in diameter, because even though the risk of recurrence may be low, the outcome of as many as one third of recurrences is fatal. As long as the operation is performed safely by an experienced endocrine surgeon, total thyroidectomy offers the advantages of removing all diseased gland (up to 85% of papillary thyroid cancers are multifocal or bilateral within the gland), facilitating thyroid scanning with lower doses of radioactive iodine (absence of thyroid gland concentrates uptake into residual or recurrent disease), improving radioablative uptake by metastases, and allowing postoperative surveillance with the measurement of serum Tg levels (in the absence of a thyroid gland, a high postoperative baseline Tg, or a rising Tg later on, is a sensitive marker for residual tumor or tumor recurrence, respectively).

The picture emerging of Hürthle cell carcinoma is that of an aggressive lesion, with a prognosis worse than papillary carcinoma of the thyroid.[20–22] In our series of 14 patients with Hürthle cell carcinoma, four patients have died.[20] Of five patients followed longer than 18 months, four (80%) had recurrence and three (60%) died of Hürthle cell carcinoma. Four of five recurrences were located in the neck, and two of the four deaths were due to locally recurrent disease. The other two deaths were the result of metastatic disease. In the literature, the overall cause-specific mortality rate is 111 patient deaths out of 364 cumulative cases of Hürthle cell carcinoma reported (30% death rate).

A number of factors argue for total thyroidectomy as the initial treatment of patients with Hürthle cell carcinoma, although the incidence of the disease is so low that a prospective, randomized study of treatment options probably will never be conducted. Several studies have confirmed that Hürthle cell carcinoma is multifocal in approximately 30% to 35% of cases[9,20,23]; fewer studies have examined resected glands for the presence of bilateral disease, but we found an incidence of almost 15%.[20] Any operation less than total thyroidectomy might leave behind foci of cancer. Hürthle cell carcinomas generally produce Tg, so removal of the entire gland increases the utility of this marker of recurrence. While the failure of most Hürthle cell carcinomas to take up radioactive iodine means that total thyroidectomy does not offer any advantage in increasing tumor uptake of the isotope, it does portend that thyroidectomy is the only treatment available, and that because radioactive iodine in ablative doses is usually ineffective for salvage, surgical treatment should be most aggressive at the outset.

We treat patients with Hürthle cell neoplasms in the same manner as patients with follicular neoplasms of the thyroid. We generally obtain an ABC as part of the preoperative workup. We generally do not obtain a preoperative thyroid scan in the evaluation of a patient with a Hürthle cell tumor as so few take up iodine. If indicators during surgery are strong that the Hürthle cell lesion is malignant (eg, gross appearance or frozen section demonstrating local invasion), we perform a total thyroidectomy with ipsilateral central neck lymphadenectomy. Malignancy can be diagnosed in the operating room by frozen section or gross criteria about half the time. If the frozen section appears benign and there are no other indicators of malignancy, we perform thyroid lobectomy and isthmusectomy. No further treatment is necessary if the permanent section confirms a benign histology. If the permanent section shows Hürthle cell carcinoma, we return the patient to the operating room for completion total thyroidectomy. While this algorithm results in two trips to the operating room for about 10% of all patients with Hürthle cell tumor (or 50% of patients with Hürthle cell carcinoma), it succeeds in bringing to the operating room only once that 10% of patients who have carcinoma treated by total thyroidectomy at the outset and that 80% of patients whose final diagnosis is Hürthle cell adenoma are adequately treated with lobectomy.

The completeness of the total thyroidectomy should be assessed by radioiodine scan three to four months after surgery. We ablate any thyroid remnant with 131I to eliminate all tissue at risk and to facilitate the use of Tg in surveillance for tumor recurrence. If the serum Tg does not fall to 3 ng/mL or lower after total thyroidectomy or rises during follow-up, residual or recurrent disease, respectively, should be suspected. Thyroid-stimulating hormone elevation occurring when the patient is hypothyroid during preparation for thyroid scanning may elicit rises in Tg that are not otherwise detectable, and this, therefore, is the optimal time to assay Tg in search of early recurrences. Tg elevations noted while the patient is euthyroid, on thyroid hormone replacement, are especially concerning for a larger burden of recurrent disease. Radioiodine scanning should be performed in the workup of possible recurrence to detect the small number of Hürthle cell carcinomas that take up the isotope and may be susceptible to ablation.[14] Recently, abnormal 99mTc-sestamibi accumulation by Hürthle cell carcinoma has been reported to be a sensitive marker of recurrence.[24] Unfortunately, sestamibi cannot be used for ablation.

### Follow-up

Most recurrences of Hürthle cell carcinoma are found in the neck, while the lung is the most common site of distant metastasis. Palpation of the neck may reveal recurrent disease, while chest x-ray may suggest metastasis. A computed tomography scan or magnetic resonance imaging of the neck, mediastinum, and chest are valuable adjuncts in diagnosis of recurrent disease.

Recurrent disease is treated surgically with good palliation and appreciable prolongation of life often resulting from local excision and neck dissection for recurrent disease or pulmonary wedge resection for lung metastasis.[20,25,26] External beam radiation may be considered for patients with unresectable disease but is not
Octreotide has also been employed without success in the treatment of recurrent carcinoma.[27] In our series, patients died of Hürthle cell carcinoma an average of 34 months after recurrence.[20]

References


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