Hurthle Cell Lesions- A Retrospective Review of Final Surgical Pathology

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Abstract

Background: A cytology diagnosis of a Hurthle cell lesion does not provide information regarding the presence or absence of thyroid cancer. The risk of malignancy in Hurthle cell lesions varies in the literature, ranging from 4% to 69%. Objectives of this study are to determine what percent of Hurthle cell lesions are found to be malignant on final pathology and to determine if there are demographics, risk factors, or ultrasound characteristics that will preoperatively help predict malignancy.

Methods: A total of 99 consecutive patients had a cytology diagnosis of a Hurthle cell lesion. All fine needle aspirations were performed and interpreted at a single tertiary care referral hospital. Final surgical pathology as well as pre-operative variables including demographics, risk factors, and ultrasound characteristics were reviewed.

Results: Eighteen of 50 (36%) patients had thyroid cancer on final surgical pathology. None of the pre-operative variables were significantly associated with the final histopathological diagnosis on univariate analysis.

Conclusions: A thyroid lobectomy is an acceptable approach for the patient with a cytology diagnosed Hurthle cell lesion, proceeding with a completion thyroidectomy if cancer is seen on final surgical pathology.

Keywords: Hurthle cell; Lesions; Neoplasms; Risk factors; Cancer

Introduction

Contrary to the name, Max Askanazy first described the Hurthle cell in 1898 in patients with Graves' disease [1]. What we now call a "Hurthle cell" is very different from what Karl Hurthle described in 1894, in his paper entitled "Studies on the Secretory Activity of the Thyroid Gland", in which he studied the thyroids of dogs [2]. Karl Hurthle described "interfollicular cells" in the thyroids of dogs that were later determined by Roediger in 1975, to be calcitonin producing C-cells [3]. James Ewing coined the term "Hurthle Cell" while writing his textbook *Neoplastic Diseases* in 1919, in which he named the cell first coined by Askanazy as "Hurthle Cells" [4]. Today, a Hurthle cell is defined as an enlarged thyroid follicular cell characterized by a finely granular and deeply acidophilic cytoplasm; the nucleus is also enlarged and shows a predominant nucleolus [5]. Hurthle cells can be found in other non-neoplastic conditions of the thyroid gland including Hashimoto's thyroiditis, multinodular goiter, Graves' disease, and in patients who have been treated with radioactive iodine and systemic chemotherapy [6-12].

While a fine needle aspiration diagnosis of papillary thyroid carcinoma is highly specific for thyroid cancer, a cytology diagnosis of a Hurthle cell lesion does not provide information regarding the presence or absence of thyroid cancer. The aim of this retrospective review is [1] to determine what percent of Hurthle cell lesions are found to be malignant on final pathology and [2] determine if there are demographics, risk factors, or ultrasound characteristics that will help predict malignancy, so as to better counsel patients in regard to extent of surgery.

Material and Methods

All thyroid fine needle aspiration (FNA) results at Mount Sinai Hospital from 2007 to 2010 were reviewed by the Mount Sinai pathology department, including six pathologists. A total of 99 patients had a cytology diagnosis of a Hurthle cell lesion. A Hurthle cell lesion

was defined by our pathology department as an encapsulated lesion composed mainly of Hurthle cells with a predominance of greater than 75%. Twenty-one patients were excluded based on lack of follow-up. Data regarding patient demographics, risk factors, ultrasound characteristics, and final surgical pathology was retrospectively collected after receiving approval from the Research Ethics Board at Mt. Sinai Hospital. Data was compiled using MS Excel 2007. All statistical analyses were performed using Stata v8.2 (Stata Corp. Inc., College Station, Texas, USA). Chi-square analysis was utilized with a significance level set at p<0.05.

Results

Of the 78 patients who were retrospectively reviewed, 28 were observed by their surgeon and endocrinologist, while 50 underwent surgery. Thirty were treated with a thyroid lobectomy, and 20 were treated with a total thyroidectomy. Table 1 shows demographics, risk factors, and ultrasound characteristics of the 50 patients treated surgically. There were 44 (88%) women and 6 (12%) men. A total of 18 patients (36%) had cancer on final pathology, not including 10 incidentally discovered papillary microcarcinomas, depicted in Table 2. Fifteen of the women (34%) and three of the men (50%) had thyroid cancer on final pathology. Sixty-six percent (12 of 18) of patients with cancer were 45 years old or greater. Of patients with thyroid cancer,

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78% (14 of 18) of nodules on ultrasound were greater than or equal to 20 mm, 22% (four of 18) had stippled calcifications on ultrasound, and 22% (four of 18) had risk factors of either family history or prior radiation to the neck. Of patients with benign lesions, 75% (24 of 32)

Variable	Value	No. of patients	Percentage of patients in study
Age	<45	12	24
	45-59	17	34
	≥ 60	21	42
Sex	Male	6	12
	Female	44	88
Family history of thyroid cancer	Yes	5	10
	No	45	90
Radiation exposure to neck	Yes	3	6
	No	47	94
Nodule size	0-19 mm	12	24
	20-39 mm	35	70
	≥ 40 mm	3	6
Calcifications on US	Yes	10	20
	No	40	80

Table 1: Demographics, risk factors, and ultrasound characteristics of study patients.

Pathology	Type	No. of patients	Percentage of patients in study
Malignant	Papillary thyroid cancer	12	24
	Hurthle cell carcinoma	4	8
	Medullary thyroid cancer	1	2
	Anaplastic thyroid cancer	1	2
	Papillary microcarinoma	10	20
Benign	Hurthle cell adenoma, hyperplastic nodule	22	44

Table 2: Final pathology results of study patients.

of nodules on ultrasound were greater than or equal to 20 mm, 19% (six of 32) had stippled calcifications, and 13% (four of 32) had risk factors. There were ten patients with cancer on final pathology that were initially surgically treated with a thyroid lobectomy, eight of those going on to have a completion total thyroidectomy. None of the pre-operative variables were significantly associated with the final histopathological diagnosis on univariate analysis, as shown in Table 3.

Discussion

Hurthle cell lesions are uncommon, accounting for 4.5-10% of all thyroid neoplasms and up to 6% of all differentiated thyroid cancer [13,14]. A Hurthle cell lesion is defined as a hypercellular lesion with a predominance of Hurthle cells (>75%) and a paucity of colloid on cytological examination [11]. Fine needle aspiration is useful in identifying Hurthle cell lesions, as Zhang reported the true-positive and false-negative rates of FNA in their series as 89% and 11% respectively [15]. McIvor showed in 1993 that there is little value in using FNA to differentiate between a benign or malignant Hurthle cell lesion, as nuclear atypia and pleomorphism did not accurately distinguish between the two [16]. It is impossible to diagnose Hurthle cell carcinoma on FNA, as histologic identification of capsular or vascular invasion is required to diagnose carcinoma [17].

The risk of malignancy in Hurthle cell lesions varies in the literature, ranging from 4% to 69% [18,19]. An FNA result of a Hurthle cell lesion in our series has a malignancy rate of 36%, and this malignancy rate does not reflect the ten patients who were found to have papillary microcarcinomas on final pathology. One series of 140 Hurthle cell lesions reported a malignancy rate of 19%, which was similar to the rate of malignancy in 463 follicular neoplasms (17%) examined in the same study [20]. Hurthle cell carcinomas have been reported to be more aggressive than other well-differentiated thyroid cancers, with a higher incidence of metastases and lower survival rate [13,21,22]. Therefore, when counseling a patient pre-operatively, a surgeon needs to know what factors are predictive of malignancy in order to make a recommendation regarding the extent of surgery.

In a review of 279 patients with Hurthle cell lesions, Strazisar

Variable	Value	Final histopathology		Pearson chi2(1)	P-value
		Benign (n)	Malignant (n)		
Age less than or greater than 60	0-59	16	13		
	≥ 60	16	5	2.3353	0.126
Age less than or greater than 45	0-44	6	6		
	≥ 45	26	12	1.3432	0.246
Sex	Male	3	3		
	Female	29	15	0.5800	0.446
Radiation exposure to neck	No	31	16		
	Yes	1	2	1.3027	0.254
Family history of thyroid cancer	No	29	16		
	Yes	3	2	0.0386	0.844
Calcifications on US	No	26	14		
	Yes	6	4	0.0868	0.768
Size less than or greater than 2.0cm	0-19 mm	8	4		
	≥ 20 mm	24	14	0.0487	0.825

Table 3: Univariate statistical analysis of demographics, risk factors, and ultrasound characteristics of the study patients.

reported that a pre-operative serum Tg concentration over 1,000 ng/ml was an independent predictor of malignancy, with carcinoma present in 43% of patients with a Tg above 1,000 ng/ml and in only 21.5% of patients with a Tg less than 1,000 ng/ml. This review also found age to be predictive of carcinoma, as patients older than 65 had a relative risk of 2.3 for carcinoma compared to patients less than 65 years old [23]. Zhang found similar results as patients with malignancy in their study were more than a decade older (66 ± 6 years) than those with Hurthle cell adenomas (53 ± 2 years), which was statistically significant [15].

Although our results showed that age, nodule size and gender had no significant association with the final diagnosis of cancer on univariate analysis (Table 3), increased lesion size and male gender have been reported to be risk factors for malignancy in Hurthle cell lesions. In a review of 116 Hurthle cell tumors on final pathology, Dahl reported size as a strong predictive factor for malignancy. For neoplasms 4 cm or larger, 69% were malignant, whereas tumors less than 4 cm had a 34% malignancy rate.The same review also found a statistically significant difference in risk of carcinoma in men (67%) and women (36%) with Hurthle cell tumors [24]. Chen reviewed 57 patients with Hurthle cell lesions and reported that patients with tumors greater than 4cm were malignant 65% of the time. For lesions less than 1cm, the malignancy rate was 17%, and for lesions between 1-4 cm, the malignancy rate was 23% [25]. In a review of 57 patients, Sippel reported an overall malignancy rate of 21% with a 55% risk of malignancy in tumors greater than four centimeters and 13% risk of malignancy in tumors less than four centimeters [26]. Another review by Pisanu of 57 patients with Hurthle cell lesions reported an overall risk of malignancy of 49% with the mean tumor size being significantly greater for carcinomas than for adenomas (3.0 cm vs 1.8 cm) [27]. Zhang reviewed 55 patients with Hurthle cell lesions and found 16% to have carcinoma. Patients with malignancy were found to have significantly larger thyroid nodules (4.5 ± 0.7 cm vs. 2.5 ± 0.2 cm). The malignancy rate was 18% in lesions 2-4 cm and 44% in lesions greater than 4 cm. In their series, no tumors less than 2 cm (n=19) were malignant [15].

Further research must be done to enable surgeons and patients to make an informed decision about the extent of surgical resection for Hurthle cell lesions. Erickson at the Mayo Clinic in 2001 analyzed 29 Hurthle cell lesions by interphase fluorescence in situ hybridization and found that Hurthle cell caricinomas tended to have more chromosome losses than adenomas, with chromosome 22 being the most common loss identified [28]. Other research has shown that Ki67 (a marker of cell proliferation) and cyclin D1 (a cell cycle promoter) are upregulated in Hurthle cell carcinoma, while Bcl-2 is down-regulated in Hurthle cell carcinoma [29-31].

Once the decision is made to go to the operating room, the question of the utility of an intraoperative frozen section arises for the patient that opts for a thyroid lobectomy. In Dahl's series of 116 patients with Hurthle cell lesions, intraoperative frozen section was done on 111, and 9 of 49 (19%) patients with Hurthle cell carcinoma were diagnosed on frozen section [24]. In Udelsman's prospective study of follicular neoplasms, only 3.4% of the time did a frozen section diagnose malignancy [32]. Chen showed similar findings with a frozen section of a follicular neoplasm showing malignany only 5% of the time [33]. In general, routine frozen-section analysis in patients with follicular lesions is not necessary secondary to the poor sensitivity and significant cost.

In our series of patients, 36% were found to have thyroid cancer on final surgical pathology. The majority (67%) were papillary thyroid cancer. None of the pre-operative variables were significantly associated with the final histopathological diagnosis on univariate analysis in our study, whereas other retrospective studies have found age, sex, and size of lesion to be predictive factors for malignancy. This could be viewed as not contributing anything new to existing knowledge, but we view this as a valuable contrasting paper to the existing literature. Future research must be done to better predict for malignancy in Hurthle cell lesions. Until further conclusions are reached, a thyroid lobectomy is an acceptable approach for the patient with a cytology-diagnosed Hurthle cell lesion, proceeding with a completion total thyroidectomy if carcinoma is seen on final surgical pathology.

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