HURTHLE CELL TUMORS OF THYROID GLAND
A CLINICOPATHOLOGIC STUDY AT
NATIONAL CANCER INSTITUTE

Thesis
Submitted by
Mahmoud Mohamed Ibrahim Sarhan
M.B, B.CH-Alexandria University
For partial fulfillment of Master Degree in
Surgical oncology
Supervised by
Dr.Gamal Amira
Professor of Surgical Oncology
National Cancer Institute
Cairo University
Dr.Ihab Samy
Lecturer of Surgical Oncology
National Cancer Institute
Cairo University
Dr.Neveen Tahoun
Assistant prof. of cancer pathology
National Cancer Institute
Cairo University
2015
ABSTRACT
Hurthle cell tumors of thyroid gland is a rare neoplasm, the gold standard from this thesis study is to evaluate the surgical management, detect patterns of failure and recurrence after surgery, chemotherapy or radiotherapy and finally to determine survival of patients.

**Keywords:** thyroid tumors, hurthle cell tumor, locoregional recurrence.

INTRODUCTION
Hurthle cell tumors (also referred to as oncocytic or oxyphilic tumors) represent about 3% of thyroid tumors. They are defined as encapsulated tumors consisting of at least 75% Hurthle cells and can be classified as benign Hurthle cell adenomas (HCA) or malignant, Hurthle cell carcinomas (HCC) on the basis of capsular or vascular invasion and the presence of metastases. *(Mills et al; 2008).*

Hurthle cell tumors are thyroid tumors composed exclusively or predominantly of Hurthle cells, a name considered to be a synonym for oxyphilic, eosinophilic, Askanazi or oncocytic cells. The designation Hurthle cells is referring to the thyroid and the designations oxyphilic and oncocytic cells, and oncocytoma, is referring to other organs (namely salivary gland, kidney and parathyroid). In the thyroid, Hurthle cells are not restricted to follicular cells and follicular cell-derived tumors. Indeed, some medullary thyroid carcinomas are composed of cells that are morphologically indistinguishable from Hurthle cells derived from the follicular cells. *(Maximo and Sobrinho-Simoes; 2000)*

Malignant Hurthle cell neoplasms account for approximately 5% of thyroid carcinomas and, in general, occur in patients slightly older than those with papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC). Despite their relatively uncommon nature, hurthle cell tumor enters diagnostic consideration frequently because hurthle cells are frequently seen on fine needle aspiration (FNA) from thyroid nodules. Patients with Hashimoto's disease or colloid nodules may demonstrate hurthle cells. It is the nodule that contains almost entirely Hurthle cells, however, that raises concern for HCT. If this is suggested on FNA, operation, which at minimum is a thyroid lobectomy, is appropriate to establish the nature of the tumor. *(Miller and Gauger; 2011)*
Hurthle cells of the thyroid are characterized by their large polygonal shape and their abundant granular eosinophilic cytoplasm. Cytologically, Hurthle cell carcinomas usually look identical to Hurthle cell adenomas. Due to this feature, cytological evaluation of (FNA) specimen is unable to distinguish between benign and malignant Hurthle cell neoplasms (HCN) of the thyroid. The only way to accurately distinguish between benign and malignant Hurthle cell neoplasms is on final pathology, when a careful inspection for capsular and vascular invasion is performed. (Sippel et al; 2008) Hurthle cell adenomas (neoplasms with no evidence of capsular or vascular invasion) certainly exist but, occasionally, a tumor that is otherwise histologically compatible with a Hurthle cell adenoma is found to be associated with lymph node or distant metastases. For these reasons and considering the perspective that Hurthle cell carcinoma (HCC) may behave more aggressively, many surgeons advocate total thyroidectomy for any Hurthle cell neoplasm. (Miller and Gauger; 2011) HCC is more prevalent in women than men and is more often associated with lymph node metastases and distant metastases than PTC and FTC in general. Although it is a differentiated thyroid carcinoma (DTC) likely of follicular cell origin, very few HCC tumors take up radioiodine (approximately 10 percent). For this reason, and taking into consideration the more aggressive nature of HCC, complete surgical resection is especially important in this disease. Therefore, total thyroidectomy is often combined with central compartment lymphadenectomy and perhaps modified radical neck dissection if lateral compartment lymph node involvement is evident. (Miller and Gauger; 2011) Tumor size correlates directly with malignant potential in patients with Hurthle cell neoplasms of the thyroid. Malignancy was not present in any tumors 2 cm or smaller and was present in all tumors larger than 6 cm. Because the risk of malignancy is greater than 50% in patients with a tumor larger than 4 cm, consideration should be given for an initial total thyroidectomy in these patients. (Sippel, et al; 2008) Advanced patient age and larger nodule size are two important factors that predict malignancy in patients with HCT. In patients with these and other known risk factors for HCC, total thyroidectomy should be considered. (Zhang et al; 2008) Recurrence among patients with Hurthle cell carcinoma is a grave sign. None of patients with HCC with recurrence were cured by treatment, and 70% have died of disease.
Radioactive iodine, the most useful nonsurgical therapy for recurrent well-differentiated thyroid carcinoma, is rarely useful in HCC, making recurrences harder to treat. However, it is used because they sometimes take it up and other options are limited. *(Sanders and Silverman; 1998)*

In this study, we aim to provide a complete clinicopathologic profile at National Cancer Institute (NCI) for HCT in the last 8 years. Also to evaluate the surgical management, detect patterns of failure and recurrence after surgery and finally to determine survival of patients.*Material and methods*

In a retrospective study collected data of patients who had preoperative evaluation and thyroidectomy from year 2005 till year 2011 regarding:

**1-clinical features:**

Age.

Sex.

Initial presentation.

T3, T4, Tsh.

TG.

Neck U/S.

Thyroid scan.

FNAC.

**2-surgical management:**

Lobectomy.

Hemithyroidectomy with or without neck dissection.

Total thyroidectomy with or without neck dissection.

**3-Pathologic features:**
Tumor size.

Histology (adenoma, minimally invasive or invasive cancer) & Percentage of hurthle cell component.

Capsular invasion.

Blood vessels invasion.

Extrathyroid extension.

Multifocality and foci of follicular or micropapillary carcinoma.

Neck node status.

4-follow up:

Postoperative complications (hypoparathyroidism or RLN injury).

Prognosis: local recurrence.

Locoregional recurrence.

Distant metastases by WBS.

Follow up for (24-96 months)

Exclusion criteria:

The following lesions were excluded from the work:

Papillary, follicular & anaplastic carcinoma.

Grave's disease or thyroiditis.

Cases in which the patient lost follow up.

Aim of the work

This study is aiming to provide a complete clinicopathologic profile at National Cancer Institute (NCI) for HCT in the last 8 years. Also to evaluate the surgical management, detect patterns of failure and recurrence after surgery and finally to determine survival of patients.
CHAPTER I
Thyroid Evaluation

A. Tests of thyroid function
A multitude of different tests are available to evaluate thyroid function. No single test is sufficient to assess thyroid function in all situations and the results must be interpreted in the context of the patient's clinical condition. TSH is the only test necessary in most patients with thyroid nodules that clinically appear to be euthyroid.

i. Serum Thyroid-Stimulating Hormone (TSH) (Normal 0.5–5 U/mL)
Serum TSH levels reflect the ability of the anterior pituitary to detect free T4 levels. There is an inverse relationship between the free T4 level and the logarithm of the TSH concentration—small changes in free T4 lead to a large shift in TSH levels. The ultrasensitive TSH assay has become the most sensitive and specific test for the diagnosis of hyper- and hypothyroidism and for optimizing T4 therapy.

ii. Serum Thyroglobulin
Thyroglobulin (Tg) is a prohormone of thyroxine (T4) and triiodothyronine (T3). It is synthesized only by thyroid follicular cells and released into serum along with the thyroid hormones. Given the cellular specificity of Tg, its detection in biopsy specimens provides proof of the thyroid origin of the tissue. In addition, measurements of serum Tg provide important information about the presence or absence of residual, recurrent, or metastatic disease in patients with differentiated thyroid cancer. (Spencer et al; 2005)

Tg is made by normal or abnormal thyroid tissue. It is normally not released into the circulation in large amounts but increases dramatically in destructive
processes of the thyroid gland, such as thyroiditis, or overactive states such as Graves' disease and toxic multinodular goiter. The most important use for serum Tg levels is in monitoring patients with differentiated thyroid cancer for recurrence, particularly after total thyroidectomy and RAI ablation. Elevated anti-Tg antibodies can interfere with the accuracy of serum Tg levels and should always be measured when interpreting Tg levels. *(Clark; 2010)* The functional sensitivity of most Tg assays had been about 0.9 ng/mL. However, several assays with functional sensitivities of 0.2 ng/mL or slightly lower have become commercially available. *(Schlumberger et al; 2007)* To further enhance the sensitivity of serum Tg in the detection of persistent/recurrent thyroid cancer, serum Tg levels are often measured during TSH stimulation (either thyroid hormone withdrawal or with recombinant human TSH [rhTSH] administration). When using the less sensitive assays (functional sensitivities of approximately 1 ng/mL), TSH stimulation will result in a previously undetectable serum Tg value becoming measurable in as many as 20 to 25 percent of patients. *(Mazzaferri et al; 2003)* Tg levels in patients who have undergone total thyroidectomy should be <2 ng/mL when the patient is taking T4, and <5 ng/mL when the patient is hypothyroid. A Tg level >2 ng/mL is highly suggestive of metastatic disease or persistent normal thyroid tissue, especially if it increases when TSH levels increase when hypothyroid during preparation for RAI scanning or after recombinant TSH. More recently, Tg measurements in FNAB aspirates have been shown to be useful in the detection of nodal metastatic disease. *(Cunha et al; 2007)*

The three major determinants of the serum Tg concentration are:
- The mass of thyroid tissue present (both normal and malignant thyroid cells)
- The presence of injury to the thyroid (eg: after fine needle aspiration, thyroidectomy or radioactive iodine therapy, or during thyroiditis)
• The degree of TSH receptor stimulation (eg: endogenous TSH, recombinant human TSH, serum HCG, TSH receptor antibodies associated with autoimmune thyroid disease). *(Spencer and Lopresti; 2008)*

**iii. Serum anti-Tg antibody**

Although the pathophysiologic importance of these antibodies after total thyroidectomy is unclear, their persistence for more than one year after thyroidectomy and radioiodine ablation probably indicates the presence of residual thyroid tissue, and possibly an increased risk of recurrence with serum anti-Tg antibody concentrations >100 U/mL. *(Chung et al; 2002)*

**B. Thyroid imaging**

❖ **Ultrasound**

Ultrasound (US) is often the first imaging modality used to investigate a thyroid mass in the euthyroid patient. US is advantageous because it is accessible, inexpensive, noninvasive, and avoids ionizing radiation. *(Nucera et al; 2009)*

Normal thyroid lobes show a homogenous echogenicity, whereas the echogenicity of the sternocleidomastoid and strap muscles (sternohyoid and sternothyroid) are lower. Posterolaterally, the thyroid is bordered by the sonolucent common carotid artery and internal jugular vein and medially by trachea. The esophagus with its echogenic mucosa can usually be seen behind and to the left of the trachea. Lymph nodes can be seen medial or lateral to the 8 major neck vessels; lymph nodes in the level VI (pretracheal) compartment are more difficult to see because of shadowing by the tracheal air column. *(Yousem and Scheff; 1996)*

---

**Figure 1:** Normal thyroid anatomy seen on transverse ultrasound images. In the left, Trachea is seen as a midline structure (TR), and carotid artery (C) and internal jugular vein (IJ) are seen bilaterally. In the right, the esophagus is seen on the left posteriorly. *(Nucera et al; 2009)*

Because of the high prevalence of small, clinically inapparent thyroid nodules
and the minimal aggressiveness of most thyroid cancers, US should be used as a screening test only if well-known risk factors are present. Sonographic examination should be ordered for all patients who have a history of familial thyroid cancer, multiple endocrine neoplasia type 2, or childhood head/neck history irradiation, even if the thyroid is normal by palpation. *(Hoos et al; 2002).*

Current methods of ultrasonography permit "real-time" identification of structures as small as 2 mm in diameter, thereby allowing the visualization of very small tumors of the thyroid and parathyroid glands. These methods also permit estimates of overall and regional blood flow to the thyroid. However, the results of thyroid ultrasonography do not correlate well with histopathologic findings.

9

At present, ultrasonography is considered useful in the following situations:
- To evaluate the anatomic features of thyroid nodules
- To assist in fine needle aspiration of thyroid nodules and cervical lymph nodes
- To monitor nodular thyroid disease
- To assist in the planning of thyroid cancer surgery
- To assist in the surveillance for recurrence in patients with thyroid cancer
- To assess for fetal goiter
- To screen for the presence of thyroid nodules in high risk groups (e.g., history of childhood radiation exposure *(Sipos; 2009)*

Table 1: Ultrasound features of thyroid cancer. *(Cappelli et al; 2007)*

**Ultrasonographic features that are associated with an increased risk of thyroid cancer**
- Hypoechoic
- Microcalcifications
- Central vascularity
- Irregular margins
- Incomplete halo
- Nodule is taller than wide
- Documented enlargement of a nodule
Ultrasonographic features that are associated with a low risk of thyroid cancer
Hyperechoic
Large, coarse calcifications (except medullary cancer)
Peripheral vascularity

Summary
Hurthle cell is derived from the epithelium of the thyroid follicle. It’s a polygonal cell, containing abundant granular cytoplasm because of excessive mitochondria and large nucleus with a prominent nucleolus. Hurthle cell tumors are considered a distinct type of thyroid tumors and generally are considered unusual types of tumors; they are more aggressive in the biological behavior. Malignant Hurthle cell neoplasms account for approximately 5% of thyroid carcinomas and, in general, occur in patients slightly older than those with papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC). Despite their relatively uncommon nature, hurthle cell tumor enters diagnostic consideration frequently because hurthle cells are frequently seen on fine needle aspiration (FNA) from thyroid nodules. If this is suggested on FNA, operation, which at minimum is a thyroid lobectomy, is appropriate to establish the nature of the tumor

Aim of the work: A clinic-pathological profile of HCT patients who were managed from Jan 2005 to Jan 2011 at National cancer Institute, to evaluate the surgical management, detect patterns of failure and recurrence after surgery and finally to determine survival of patients.

Patients and methods: A retrospective review of 20 patients with HCT who
were managed from Jan 2005 to Jan 2011 and were put under follow up till Jan 2013 at National cancer Institute, Cairo University

**Results:** In this study 20 patients were included, 14 females (70%) and 6 males (30%), with a female to male ratio of 2.3:1, The median age at diagnosis was 56 years (15-76). Final histopathology revealed eight patients was confirmed to have HCC representing (40%), three patients diagnosed as HCA (15%) whereas rest of patients (45%) had HCN. Tumor size range was (0.5 - 5 cm) with mean 2.4 cm. local and distant recurrence had the same percentage 5%, the disease free survival rate (DFS) was 77.8 % and The overall survival rate (OS) was 83.3 % in five years.

**Conclusion:** HCT represent a diagnostic challenge, best results in management could be reached when the diseased lobe is excised entirely, then it’s mandatory to do completion thyroidectomy if it revealed HCC, this is associated with central neck dissection in N0 neck and radical dissection if there are positive nodes. And finally HCT and specifically HCC were not found to display an aggressive behavior, unlike those reported by other authors when risk factors, including the extent of tumor invasion were taken into account, it has low mortality rate compared to other studies. The DFS and overall survival rates were acceptable.