American Journal of Otolaryngology and Head and Neck Surgery

Review Article
Published: 30 Aug, 2023

Thyroid Hurthle Cell Neoplasms: Review Article

Abdulhaleem M[1*] and Aldajani A[2,3]

[1]Department of Otolaryngology Head and Neck Surgery, Intermed Clinic, Jeddah, Saudi Arabia

[2]Department of Otolaryngology Head and Neck Surgery, Collage of Medicine, University of Jeddah, Jeddah, Saudi Arabia

[3]Department of Otolaryngology Head and Neck Surgery, McGill University Health Center, Canada

Abstract

Hurthle cell carcinoma is a rare type of Differentiated Thyroid Cancer (DTC), accounting for only 5% of all cases of DTC [1]. In 2017, the World Health Organization reclassified the Hurthle cell variant of follicular thyroid carcinoma as a distinct type, due to its different histopathological characteristics from follicular thyroid carcinoma. This reclassification was supported by recent discoveries in molecular characteristics through genetic sequencing tests. Despite these advances, the behavior of Hurthle cell carcinoma and adenoma remains unpredictable. In this paper, we present a short literature review of Hurthle cell neoplasms.

Keywords: Hurthle cell carcinoma; Hurthle cell neoplasms; Hurthle cell adenoma; Follicular carcinoma

Histopathology of Hurthle Cell Neoplasms

The histopathology of Hurthle cell neoplasms is still a topic of debate. While it was initially classified as a follicular variant due to its possible origin from follicular cells, some studies have suggested that it may originate from parafollicular cells, given its lymphatic metastasis capability, resistance to radioactive iodine, and different oncogene expression profile compared to follicular thyroid cancer. Hurthle cells are characterized by granular eosinophilic cytoplasm, which is attributed to the presence of numerous mitochondria, and nuclei with prominent nucleoli [2]. These cells can be present in various thyroid conditions, including benign thyroid nodules (Bethesda 2) as Hurthle cell metaplasia, as well as non-neoplastic conditions such as thyroiditis, and neoplastic conditions such as Hurthle cell adenoma and Hurthle cell carcinoma.

The diagnosis of a Hurthle cell neoplasm requires the observation of over 75% of oxyphilic cells.

Mitochondrial abnormalities can cause disruptions in energy production, resulting in defects that trigger compensatory mechanisms. These mechanisms promote mitochondrial proliferation, resulting in oncocytic cytoplasm and eventually Hurthle cell appearance. This progression is a gradual process rather than an abrupt occurrence. HCC can display necrosis, which can occur spontaneously or following fine-needle aspiration. This necrosis is believed to be a consequence of the observed mitochondrial abnormalities [3-5].

Hurthle Cell Adenoma

Hurthle cell adenoma, also known as thyroid eosinophilic adenoma, is a rare benign thyroid condition that can only be confirmed through postoperative histopathological findings. The diagnostic criteria for Hurthle cell adenoma include a thyroid tumor consisting entirely or predominantly (>75%) of follicular cells characterized by eosinophils and without any capsular or vascular invasion. Moreover, cytologically, a significant difference in all markers of proliferative activity has been reported between malignant and benign tumors. (HCC:HCA p<0.01)[6]. Hurthle cell adenoma can grow slowly for up to 10 years without causing any symptoms, and due to its good prognosis, subtotal thyroidectomy can be the optimal management without the need for any adjuvant therapy.

Hurthle Cell Carcinoma

Hurthle Cell Carcinoma (HCC) can be classified as minimally or widely invasive based on the extent of capsular and vascular invasion. Histologically, minimally invasive HCC preserves the encapsulation of the tumor with limited capsular invasion or less than four foci of vascular invasion, while widely invasive HCC is characterized by extensive capsular invasion and/or extra thyroidal extension and/or more than four foci of vascular invasion [7]. Clinically, HCC can present as a painless thyroid nodule or mass with euthyroid status, or it can present within a thyrotoxicosis condition as reported in the literature [8]. Additionally, male sex and advanced age are among the

OPEN ACCESS

Correspondence:
Mawaddah Abdulhaleem, Department of Otolaryngology Head and Neck Surgery, Intermed Clinic, Jeddah, Saudi Arabia

Received Date: *07 Aug 2023*
Accepted Date: *24 Aug 2023*
Published Date: *30 Aug 2023*

Citation:
Abdulhaleem M, Aldajani A. Thyroid Hurthle Cell Neoplasms: Review Article. Am J Otolaryngol Head Neck Surg. 2023; 6(5): 1243.

factors associated with malignancy in Hurthle cell tumors [9].

Widely invasive HCC presents with local invasion of adjacent structures such as strap muscles, prevertebral fascia, trachea, and esophagus. From our observation and literature review, HCC tends to present in larger thyroid nodules, unlike papillary thyroid cancer, and is more aggressive with a worse prognosis compared to follicular cell carcinoma [10]. Widely invasive HCC can have non-avidity and resistance to radioactive iodine, which can mimic poorly differentiated thyroid carcinoma. Thankfully, the minimally invasive type of HCC is more common than the widely invasive type.

Metastasis in Hurthle Cell Carcinoma

Hurthle cell carcinoma may manifest with regional cervical lymph node metastases at the time of diagnosis. In comparison to follicular carcinoma, Hurthle cell carcinoma has a higher likelihood of regional lymph node metastases, which may require more aggressive management due to its elevated mortality rate and greater propensity to metastasize to distant sites. With regards to distant metastases, the 5-year mortality rate can reach up to 80%. However, some studies have suggested a more benign course of the disease with comparable survival rates to follicular carcinoma, when the tumor is treated aggressively.

Hurthle Cell Neoplasms and Molecular Characteristics

Hurthle cell neoplasms typically manifest as Bethesda category 3 or 4 on fine needle biopsy, and until recently, were managed with diagnostic hemi- or subtotal thyroidectomy. With molecular genetic advances, active surveillance is now used more frequently, avoiding unnecessary surgeries. However, no definitive point mutation has been associated with the incidence of Hurthle cell carcinoma. Unlike follicular thyroid cancers, HCC genetic analysis shows a low rate of RAS mutations and PAX8-PPARG fusions. Until the last decade, the genetic mechanism of developing HCC was not entirely clear. It was believed that chromosomal disturbances, in terms of chromosomal gains or losses, played a role in Hurthle cell tumorigenesis. In 2012, Corver et al. reported that Copy Number Alterations (CNAs) leading to genome haploidization are the genetic mechanism of HCC [11]. CNAs are considered driver alterations in thyroid carcinogenesis, defined as a section of DNA that presents variable copy numbers in comparison with a reference genome. Several genetic studies have supported that CNA is a hallmark of the HCC process. Recently, Doerfler et al. investigated whether CNAs are a hallmark of HCC specifically or Hurthle cell adenoma as well [12]. They concluded that CNAs could present in both conditions. Moreover, the presence of CNAs with other aggressive mutations, such as TERT mutation, suggests an aggressive malignant histology rather than a benign process. In addition to CNAs, Doerfler et al. identified RAS and EIF1AX mutations as common in both HCC and HCA in similar frequency [12]. Other studies reported a high prevalence of TP53 among widely invasive HCC compared to minimally invasive types [13]. Additionally, gene expression analysis can reveal differences between minimally invasive and widely invasive HCC. One of the significant differences observed was an enriched gene set related to beta-catenin (CTNNB1). In widely invasive HCC, beta-catenin plays a crucial role in the regulation of processes that govern vascular invasion [14].

Radiology is Hurthle Cell Neoplasms

Ultrasound is typically the first radiological method used for any thyroid condition, but preoperative diagnosis of HCC by US is almost impossible. However, certain features may suggest a malignant or aggressive condition. HCC typically presents as TIRADS 3, 4, or 5 in thyroid US. In 2008, Maizlin et al. attempted to distinguish HC neoplasms radiologically in ultrasound. They reviewed 15 proven cases of Hurthle cell neoplasms and found that the lesions varied from hypo- to hyper-echoic and from low to high vascularity, and no feature suggested Hurthle cell neoplasms by US at that time [15]. With advances in US technology, a review of 139 cases of HCNs found that size was the only suggestive feature of HCC, particularly when the size was above 3.35 cm [16]. In another study, it was found that malignant tumors displayed a higher probability of hypoechoic and hyperechoic nodules as opposed to benign tumors. Conversely, isoechogenicity was a more dependable indicator of benignity [17].

CT scan may be requested if local lymph node metastases are suspected, if the nodule is large and compression of adjacent structures is suggested, or if CT chest is suspected for metastases to the lung. The more aggressive the HCC, the larger it will appear in the CT scan, with a necrotic center and invasion of adjacent structures. In some advanced cases, it may mimic poorly differentiated or undifferentiated thyroid cancer.

In PET scan, Hurthle cell neoplasms can have very high FDG avidity [18]. In fact, 18F-FDG PET has excellent diagnostic accuracy in Hurthle cell thyroid cancer patients. It been suggested that all patients with Hurthle cell thyroid cancer should undergo 18F-FDG PET as part of their initial postoperative staging and periodically to screen for occult recurrence, particularly in patients with elevated serum thyroglobulin [19].

At present, radiological methods are unable to provide a definitive diagnosis for any Hurthle cell neoplasms. However, it is possible that this may change in the future with the help of technological advancements.

Management of Hurthle Cell Neoplasms

Surgery is the main treatment for Hurthle cell neoplasms, as with other differentiated thyroid carcinomas. The choice between total or subtotal thyroidectomy depends on tumor features and aggressiveness, and molecular testing can help determine the appropriate surgical option. Unlike other differentiated thyroid cancers, HC tumors do not take up RAI, making treatment of advanced cases challenging. However, RAI can improve survival in HCCs >2 cm, which should be considered in tumor board discussions. Adjuvant RAI can be offered after total thyroidectomy in cases with HCC >1 cm, vascular invasion, extra thyroidal extension, lymph node metastases, or elevated postoperative un stimulated thyroglobulin levels. Studies have shown that older age is associated with worse prognosis, and aggressive management may be warranted in older patients with HCC.

A prognostic nomogram has recently been published to assess cancer-specific survival in HCC, which could assist in making treatment decisions [20]. The study's findings suggest that age, sex, tumor size, summary stage, lymph node metastasis, and distant metastasis are independent prognostic factors that significantly influence HCC prognosis. Moreover, the nomogram has been designed to predict the probability of survival in HCC patients, which could help reduce unnecessary medical expenses and tests while identifying patients at high risk [20].

Prophylactic central Compartment Neck Dissection (CND) is an adopted procedure by some surgeons. In a recent German study of

51 HCC patients, 46 had prophylactic CND at the time of primary surgery, and 7 had lymph node recurrence despite the prophylactic CND. None of the patients had radiologic (28.5% cN0) or pathologic (71.4% pN0) lymph node involvement at the time of diagnosis [21]. The current German guidelines recommend total thyroidectomy and routine prophylactic central lymphadenectomy for Hurthle cell carcinoma, regardless of the primary tumor's vascular invasion status [22].

Metastatic progressive HCC can be treated with Lenvatinib and sorafenib, which have been approved by the FDA [23]. However, their effectiveness in treating HCC is limited, and there is a need for new therapeutic approaches that target specific targets. Immunotherapy has been used for advanced and metastatic HCC, and ongoing clinical trials include combination therapies with TKIs and mTOR inhibitors, TKIs and checkpoint inhibitors against PD1 (nivolumab) and CTLA4 (ipilimumab), and TKIs with anti-PD1 monoclonal antibody pembrolizumab [24-26]. The field of HCC therapy is constantly evolving, and recent findings may provide effective strategies to prolong the survival rate of patients with HCC.

References

1. Bhattacharyya N. Survival and prognosis in Hurthle cell carcinoma of the thyroid gland. Arch Otolaryngol Head Neck Surg. 2003;129(2):207-10.
2. Sobrinho-Simoes MA, Nesland JM, Holm R, Sambade MC, Johannessen JV. Hurthle cell and mitochondrion-rich papillary carcinomas of the thyroid gland: An ultra-structural and immunocytochemical study. Ultrastruct Pathol. 1985;8(2-3):131-42.
3. Muller-Hocker J. Immunoreactivity of p53, Ki-67, and Bcl-2 in oncocytic adenomas and carcinomas of the thyroid gland. Hum Pathol. 1999;30(8):926-33.
4. Maximo V, Sobrinho-Simoes M. Hurthle cell tumours of the thyroid. A review with emphasis on mitochondrial abnormalities with clinical relevance. Virchows Arch. 2000;437(2):107-15.
5. Maximo V, Lima J, Prazeres H, Soares P, Sobrinho-Simões M. The biology and the genetics of Hurthle cell tumors of the thyroid. Endocr Relat Cancer. 2012;19(4): R131-47.
6. Augustynowicz A, Dziecioł J, Machała MB, Dadan J, Puchalski Z, Sulkowski S. Assessment of proliferative activity of thyroid Hurthle cell tumors using PCNA, Ki-67 and AgNOR methods. Folia Histochem Cytobiol. 2004;42(3):165-8.
7. Ganly I, McFadden DG. Short review: Genomic alterations in Hurthle cell carcinoma. Thyroid. 2019;29(4):471-9.
8. Karanchi H, Hamilton DJ, Robbins RJ. Hurthle cell carcinoma of the thyroid presenting as thyrotoxicosis. Endocr Pract. 2012;18(1):e5-9.
9. Chindris AM, Casler JD, Bernet VJ, Rivera M, Thomas C, Kachergus JM, et al. Clinical and molecular features of Hurthle cell carcinoma of the thyroid. J Clin Endocrinol Metab. 2015;100(1):55-62.
10. Grani G, Lamartina L, Durante C, Filetti S, Cooper DS. Follicular thyroid cancer and Hurthle cell carcinoma: Challenges in diagnosis, treatment, and clinical management. Lancet Diabetes Endocrinol. 2018;6(6):500-14.
11. Corver WE, Ruano D, Weijers K, den Hartog WCE, Nieuwenhuizen MP, de Miranda N, et al. Genome haploidisation with chromosome 7 retention in oncocytic follicular thyroid carcinoma. PLoS One. 2012;7(6):e38287.
12. Doerfler WR, Nikitski AV, Morariu EM, Paul Ohori N, Chiosea SI, Landau MS, et al. Molecular alterations in Hurthle cell nodules and preoperative cancer risk. Endocr Relat Cancer. 2021;28(5):301-09.
13. Gopal RK, Kübler K, Calvo SE, Polak P, Livitz D, Rosebrock D, et al. Widespread chromosomal losses and mitochondrial DNA alterations as genetic drivers in Hurthle cell carcinoma. Cancer Cell. 2018;34(2): 242-55.
14. Ganly I, Filho JR, Eng S, Ghossein R, Morris LGT, Liang Y, et al. Genomic dissection of Hurthle cell carcinoma reveals a unique class of thyroid malignancy. J Clin Endocrinol Metab. 2013;98(5):E962-72.
15. Maizlin ZV, Wiseman SM, Vora P, Kirby JM, Mason AC, Filipenko D, et al. Hurthle cell neoplasms of the thyroid: Sonographic appearance and histologic characteristics. J Ultrasound Med. 2008;27(5):751-7.
16. Kim MJ, Shin JH, Hahn SY, Lyun Oh Y, Wook Kim S, Kim TH, et al. Ultrasonographic characteristics of Hurthle cell neoplasms: Prediction of malignancy. Ultrasonography. 2022;41(4):689-97.
17. Parikh PP, Allan BJ, Lew JI. Surgeon-performed ultrasound predictors of malignancy in patients with Hurthle cell neoplasms of the thyroid. J Surg Res. 2013;184(1):247-52.
18. Yu R, Auerbach MS. FDG-avid Hurthle cell thyroid adenoma. Clin Nucl Med. 2019;44(9):752-53.
19. Pryma DA, Schöder H, Gönen M, Robbins RJ, Larson SM, Yeung HWD. Diagnostic accuracy and prognostic value of 18F-FDG PET in Hurthle cell thyroid cancer patients. J Nucl Med. 2006;47(8):1260-6.
20. Shen C, Zhao Y, Qiu X, Peng Li, Ding Y, Wang W, et al. Development and validation of a prognostic nomogram for Hurthle cell thyroid carcinoma: A SEER-based study. Gland Surg. 2022;11(3):535-44.
21. Chiapponi C, Hartmann MJM, Schmidt M, Faust M, Bruns CJ, Schultheis AM, et al. Hurthle cell carcinoma: Single center analysis and considerations for surgical management based on the recent literature. Front Endocrinol (Lausanne). 2022;13:904986.
22. Dralle H, Musholt TJ, Schabram J, Steinmüller T, Frilling A, Simon D, et al. German association of endocrine surgeons practice guideline for the surgical management of malignant thyroid tumors. Langenbecks Arch Surg. 2013;398(3):347-75.
23. Schmidbauer B, Menhart K, Hellwig D, Grosse J. Differentiated thyroid cancer-treatment: State of the art. Int J Mol Sci. 2017;18(6):1292.
24. Sorafenib Tosylate with or without everolimus in treating patients with advanced, radioactive iodine refractory Hurthle cell thyroid cancer. April 4, 2022.
25. Testing the combination of cabozantinib, nivolumab, and ipilimumab (cabonivoipi) for advanced differentiated thyroid cancer. January 18, 2023.
26. Lenvatinib and pembrolizumab in differentiated thyroid cancers (DTC). February 14, 2023.