Hürthle Cell Carcinoma

73

Kenneth D. Burman and Leonard Wartofsky

Introduction

The Hürthle cell variant of follicular carcinoma is composed of large acidophilic, Askanazy, or oncocytic cells that are considered altered follicular cells [1–10]. For instance, Hürthle cells bind thyrotropin (TSH) and have TSH receptors, like other types of follicular thyroid cells [11, 12]. Similar to other follicular neoplasms, Hürthle cell carcinoma is more common in women than men, but the patients tend to be older than those with typical follicular thyroid carcinoma (FTC; see Chap. 70). Hürthle cells contain many mitochondria (which are the basis for the abundant, eosinophilic, and granular cytoplasm), frequently eccentric nuclei, and visible nucleoli. The Hürthle cell carcinoma variant of follicular carcinoma discussed here is to be distinguished from the variant of papillary thyroid cancer, "Hürthle cell papillary thyroid carcinoma," which also contains an abundance of oxyphilic cells [13]. The central genetic or environmental factors that allow a thyrocyte to differentiate into a Hürthle cell are unknown, and Hürthle cells may occur in a variety of thyroid disorders. Solitary thyroid nodules may have a predominance of Hürthle cells, to the exclusion of more typical thyrocytes, and these lesions are often highly cellular with minimal colloid. When such a lesion is aspirated for cytologic examination, the interpretation would likely be "suggestive of a Hürthle cell neoplasm," because as with follicular tumors, a definite diagnosis of benign or malignant would be difficult or impossible to make. Hürthle cell neoplasms may be benign or malignant, and the distinction is based on the demonstration of vascular or capsular invasion, metastatic capacity, and growth rate, similarly to other follicular neoplasms [7, 14, 15].

When patients with Hürthle cell carcinoma are stratified regarding low vs high risk, there does not appear to be a significantly worse prognosis than that for follicular carcinoma; see Chaps. 70 and 79 [16, 17]. In contrast to other follicular carcinomas, they have a higher rate of bilaterality or multi-centricity.

With the use of fine-needle aspiration (FNA) cytology, some solitary thyroid nodules may also have a more varied appearance, where Hürthle cells intermingle with thyrocytes, macrophages, and lymphocytes and have moderate amounts of colloid. In such circumstances, the cytology may be more difficult to interpret, and when insufficient Hürthle cells are present, the tumor is characterized as a Hürthle cell neoplasm. Furthermore, Hürthle cells may be found in the thyroid glands of patients with Hashimoto's thyroiditis and other benign thyroid disorders but usually in this circumstance, the Hürthle cells are scattered and are not the predominant cell type [7, 18]. In one study, age greater than 65 years and an elevated preoperative serum thyroglobulin level aided in the prediction of a follicular neoplasm being malignant [8].

The typical Hürthle cell neoplasm is composed mostly of these distinctive cells and is generally considered to be a variant of follicular carcinoma. Recognizing the malignant potential of a tumor depends on the evidence of aggressive behavior at its periphery [19–23]. Bizarre, large, and/or hyperchromatic nuclei may be a striking histological feature, and these are more common than in benign proliferations of oxyphilic cells.

Metastases to cervical lymph nodes are more frequent than with the usual follicular carcinoma, especially after the patient has undergone surgery. Notwithstanding the comments above, there are some studies that suggest oxyphilic

K.D. Burman, MD (✉)
Director, Divisions of Endocrinology, Washington Hospital Center and Georgetown University Hospital, 110 Irving Street, N.W. 2A-72, Washington, DC 20010, USA
e-mail: kenneth.d.burman@medstar.net

L. Wartofsky, MD, MACP
Department of Medicine, MedStar Washington Hospital Center, Georgetown University School of Medicine, 110 Irving Street, N.W., Washington, DC 20010-2975, USA
e-mail: leonard.wartofsky@medstar.net

L. Wartofsky, D. Van Nostrand (eds.), *Thyroid Cancer*, DOI 10.1007/978-1-4939-3314-3_73

follicular carcinomas are more aggressive than typical nonoxyphilic follicular carcinomas. Particularly, the presence of nondiploid cells in an oxyphilic carcinoma indicates a poorer prognosis than that with diploid nuclei [24]. Papillary carcinomas may also contain significant populations of these cells [13]. Whether they are more aggressive than a nonoxyphilic cancer with otherwise similar characteristics remains uncertain.

However, what does appear clear is that without specific attention to risk stratification, Hürthle cell malignancies will tend to have a worse prognosis than other follicular tumors in many [24–26], but not all, studies [27]. This may be partly because of their greater tendency to be locally invasive and propensity to concentrate radioiodine less avidly, thereby rendering them more difficult to manage with isotopic scanning and therapy [28, 29]. Yet, this is not universal, and some Hürthle cell cancers will trap iodine [30]). In a review of 89 cases of Hürthle cell carcinoma seen at the MD Anderson Cancer Center, Lopez-Penabad et al. [31] expressed a rather pessimistic assessment of the efficacy of currently available therapies for this variant of FTC. There was a 40 % cause-specific mortality over their long follow-up interval, with no improvement in mortality rates found over the past 50 years. Larger tumor size and more advanced age were negative prognostic indicators. Additionally, in the setting of metastatic disease, there was no further survival advantage seen with more extensive surgery, external radiation therapy, chemotherapy, or even radioactive iodine therapy. Mills et al. noted that the stage of disease, the existence of metastatic lesions, and the presence of cervical lymph node disease affected outcome in patients with Hürthle cell carcinoma [32].

Clinical Presentation

Hürthle cell carcinomas may represent about 3–5 % of all types of thyroid carcinomas. Most Hürthle cell carcinomas appear to be a more aggressive kind of follicular carcinoma, with more frequent recurrences, higher morbidity, and higher mortality [7, 14, 18, 24, 26, 31]. The tumors are frequently multifocal and bilateral.

Thompson and associates [14, 19, 20] suggested that it is difficult to differentiate benign from malignant Hürthle cell tumors. The implication of their studies is that even experienced pathologists may not be able to make a reliable distinction. Carcangiu and coworkers [33] and Grant and associates [22] support the concept that strict histological criteria and adequate sampling may be able to differentiate Hürthle cell carcinoma from adenoma in nearly all cases. Grant et al. [22] reviewed the world literature and observed that only 6 of 642 patients with apparent benign Hürthle cell adenomas were found to have a recurrence, thereby indicating that the tumor was a carcinoma, with an incidence of less than 1 %. Gosain and Clark [23] found no patients with Hürthle cell adenoma in whom recurrences were observed. Similarly, Bondeson and coworkers [24] studied 42 patients diagnosed with Hürthle cell adenoma over a 2–20-year period and found no recurrences.

The above reports help to support the contention that Hürthle cell adenomas can be accurately diagnosed and distinguished from carcinoma on histological examination by experienced pathologists. As with other follicular carcinomas, the major histological criteria that separate a Hürthle cell adenoma from a carcinoma are vascular and/or capsular invasion. However, subtleties do remain. For example, does the capsular invasion have to be completely through the capsule, or is invasion into, but not through, the capsule enough to make the diagnosis? It is also important to ensure that sufficient histologic sections were taken and examined. Notwithstanding these concerns, it is likely that experienced pathologists can reliably make this differential diagnosis.

The absence of radioiodine uptake by residual or metastatic follicular cancer renders management much more difficult, but not impossible. Typically, these tumors are less avid for radioactive iodine and therefore respond less often than the usual follicular carcinoma. Several groups are currently evaluating the thyroidal sodium iodide symporter (Na^+/I^- symporter function and expression in Hürthle cell carcinomas relative to FTC [11, 12, 18]. These studies are exploring methods for the management of follicular cancers that have lost their ability to either trap iodide (and be treatable with radioiodine) or to synthesize and release thyroglobulin. The ability of both normal and malignant thyroid cells to concentrate iodide is dependent on expression of the *NIS* gene [34–36]. The loss of this gene during tumor dedifferentiation can account for the tumor's failure to concentrate iodide. Gene therapy or redifferentiation therapy with retinoic acid, depsipeptide, and other agents had been thought to hold promise for the restoration of both radioiodine uptake for potential treatment and thyroglobulin production for monitoring recurrence [37–41]. However, further analysis of results with retinoic acid was less than optimistic [42].

It is reasonable to assume that one major reason why these tumors do not respond as well to therapy is because they do not concentrate radioiodine as well as usual follicular carcinomas. It may be appropriate to approach Hürthle cell carcinomas as if they were medullary carcinomas, i.e., with more aggressive diagnostic procedures and treatment [23, 43].

In most clinical circumstances, patients diagnosed with a Hürthle cell neoplasm by FNA should undergo surgery somewhat promptly. We recommend a near-total to total thyroidectomy by an experienced thyroid surgeon. It is important to discuss with the patient the alternative approaches of a near-total thyroidectomy compared to a lobectomy with isthmusectomy [44]. If only a lobectomy and isthmusectomy

are performed, and if the lesion is found to be cancerous, then a subsequent completion thyroidectomy must be performed. This completion thyroidectomy frequently causes mental and psychosocial distress to the patient, especially if the requirement for this procedure is not expected by the patient. However, only about 20 % of Hürthle cell neoplasms diagnosed by FNA are found to be malignant. If a total thyroidectomy is conducted initially, then in 80 % of cases, this procedure would be unnecessarily aggressive and exposes the patient to a higher risk of temporary and permanent hypocalcemia, along with recurrent laryngeal nerve paralysis.

The decision regarding which operation is needed for a patient with a solitary thyroid nodule and an FNA consistent with Hürthle cell neoplasm is difficult. A frozen-section interpretation is often problematic and therefore not helpful [45]. It is important to candidly discuss the advantages and disadvantages of each approach with the patient and family and arrive at a mutual decision. The initial operation should include an ipsilateral central node dissection. Obviously, the surgeon must be allowed to exercise judgment at the time of surgery about the precise operative procedures. It has been suggested [11] that a routine modified radical neck dissection be performed when the tumor is found in the central compartment or cervical nodes or, alternatively, a total thyroidectomy [44].

Because these tumors are somewhat less differentiated than most papillary thyroid cancers and FTCs, there is a reasonable chance that they can be detected by 18-fluorodeoxyglucose positron emission tomography (FDG-PET) when they do not concentrate radioiodine. Lowe et al. [46] found PET scanning to be useful to identify both local and metastatic disease, thereby facilitating disease management. Growth of Hürthle cell tumors has been described to reflect the net of proliferative vs apoptotic indices, and it may become feasible to exploit these characteristics to distinguish benign from malignant lesions [47].

McDonald and coworkers [48] reviewed 40 cases of Hürthle cell carcinoma, noting that this number represented 4 % of all thyroid cancers in their experience. Their median follow-up interval after thyroidectomy was 8.5 years. Vascular or capsular invasion was observed in 32 patients, extrathyroidal invasion in 11, and regional lymph node involvement in 2. One patient had distant metastases at presentation, and only nine patients received ^{131}I. Of 34 subjects analyzed, 5 died of thyroid cancer, 9 died of nonthyroidal causes, 4 were alive with existing disease, and 16 were alive without evidence of disease. At about an average of 4 years, nine patients had recurrences and five had distant disease. Recurrent disease was associated with mortality in half of these patients. Risk factors assessed at initial presentation were useful to help predict recurrence. Low-risk tumors did not recur (e.g., tumors less than 5-cm diameter, lack of distant metastases, men younger than 41 year, and women younger than 51 year). Tumor size and the presence of distant metastases were more important prognostic indicators than age in one recent series of patients [49].

Bhattacharyya [50] performed a retrospective review of the Surveillance, Epidemiology, and End Results (SEER) database for cases between 1973 and 1998, finding that 3 % of cases represented Hürthle cell carcinoma, and 555 of the patients (377 women, 178 men) were analyzed. Outcomes in 411 were compared to outcomes in 411 matched patients with follicular carcinoma; 5- and 10-year mortality rates were 15 % and 29 % vs 11 % and 45 %, respectively. The survival time was also not different, with an average of 109 months for Hürthle cell carcinoma and 113 months for follicular cancer. For the patients with Hürthle cell carcinoma, increased mortality was associated with larger tumor size and male gender, but not the presence of local invasion. In a small patient series, Lopez-Penabad et al. [31] observed the worst prognosis in older patients with larger tumors and local extension. Similar findings were reported by Kushchayeva et al. in a series of 33 patients [51].

Because some Hürthle cell carcinomas were found to have *ret*/*PTC* gene rearrangements similar to papillary thyroid cancers [52], as well as a propensity to spread to local lymph nodes like papillary cancers, it may be that there can be subspecies of what we have presumed to be classic Hürthle cell carcinoma that represent variants of either follicular or papillary thyroid cancer [13]. Such differences might account for our difficulty in comparing individual reports in the literature with mortality and morbidity rates, of which some but not all support the view that Hürthle cell carcinoma is linked with a poorer prognosis than the usual FTC or papillary thyroid cancer.

Following appropriate surgery for Hürthle cell carcinoma, radioiodine scanning and therapy is recommended. Scan preparation would be routine and is usually performed about 6 weeks after surgery. Preparation by the use of levothyroxine withdrawal or stimulation by the use of rhTSH can be utilized. A diagnostic radioiodine scan is important before therapy to help determine the avidity of the remaining thyroid cells for radioiodine and to define the nature and extent of remaining thyroid tissue or disease. Assuming that there is visible uptake, the diagnostic scan is then followed by radioiodine therapy, usually with 100–150 mCi ^{131}I. A post-treatment scan is performed approx 7–10 day after treatment. (These protocols are detailed in Chaps. 11, 19, 33 and 34) rhTSH stimulation is not presently approved by the FDA for use in patients with metastatic thyroid cancer, although two recent studies have suggested it may be as effective as levothyroxine withdrawal [53, 54].

As described above, many Hürthle cell cancers will not trap radioiodine, and sometimes only as little as 10 % of Hürthle cell cancers will trap and respond to radioiodine. This number seems low in our experience and, of course, some-

what depends on the dose of ^{131}I used for scanning, the length of time that the patient did not receive thyroid hormone, the extent of TSH elevation, and possibly the assiduous adherence to a low-iodine diet. Based on published reports, it may be difficult to adequately assess these factors. Perhaps in some cases, lack of apparent iodine avidity by the tumor may not be an accurate representation of the tumor's true properties.

For surveillance over the subsequent 5 years after initial surgery and ablation, we recommend following the patient with physical examinations, thyroid function tests, and thyroglobulin monitoring about every 3–6 months for the first several years, and possibly every 4–6 months for the next several years if there has been no evidence of disease recurrence. Our approach of utilizing radioiodine scans is consistent with that of Besic et al. [30]. In the initial year or two of surveillance, levothyroxine therapy is used in a dosage designed to achieve suppressed TSH in most patients (0.1 μU/mL or lower), depending on the clinical context. Thyroglobulin levels are analyzed at the same time as thyroid function tests, and the thyroglobulin level during L-thyroxine suppression must be less than 2 ng/mL (according to the assay). rhTSH stimulation testing may be employed as outlined by a consensus group of thyroid cancer investigators [55] The latter follow-up would generally include a repeat whole-body ^{131}I scan in 1 year, then again 3–5 years later. Given the aggressive nature of this tumor, we may also obtain occasional radiographs of the chest. An imaging study of the neck, such as a magnetic resonance image or sonogram, is routinely performed, especially if the tumor is not iodine-avid, if the thyroglobulin level is increasing, or if palpable cervical abnormalities become manifest. In women, particularly those who are postmenopausal, suppressive doses of levothyroxine therapy should be accompanied by measures to prevent osteoporosis (daily oral ingestion of 1–1.5 g of calcium, 400 U of vitamin D, exercise against gravity, and the possible addition of a bisphosphonate as appropriate.

Other scanning agents may have reasonably good utility for the detection of Hürthle cell carcinoma. In a study comparing radioiodine and thallium scanning to that with $^{99mTc\text{-}MIBI}$, Yen et al. [56] reported a 100 % specificity and an 82 % sensitivity for ^{99m}Tc-MIBI in patients with Hürthle cell carcinoma. The utility of FDG-PET scanning has already been mentioned [46] and was also reported earlier [57] to have an 80 % specificity and a 92 % sensitivity for this tumor. The issue of which scanning agent to employ arises when serum thyroglobulin levels indicate residual or recurrent disease. Despite the proven value of PET scanning, because of its cost and lack of widespread availability, we believe that radioiodine scanning should be attempted first, followed by ^{99m}Tc-MIBI, before utilizing FDG-PET.

Hürthle cell cancer is discussed further in Chaps. 55, 56, and 57. These and other follicular cancers that do not concentrate radioiodine may be treated with chemotherapy (see Chaps. 64 and 99), external radiation therapy [58–61]; see Chaps. 63, 78, 88 and 101, or redifferentiation therapy with retinoic acid or other agents could be attempted [37–39, 62]. However, although external radiation therapy may cause apparent tumor regression and provide palliation and reduced recurrence rate, even in Hürthle cell carcinoma [63], the effect may be transitory with little improvement in survival rate [64].

Recent advances in molecular analysis of thyroid FNA samples and thyroid histopathology samples hold promise of improved ability to predict the presence of thyroid cancer as well as its potential aggressiveness [3, 65–67].

References

1. Mete O, Asa SL. Oncocytes, oxyphils, Hurthle, and Askanazy cells: morphological and molecular features of oncocytic thyroid nodules. Endocr Pathol. 2010;21(1):16–24.
2. Parameswaran R, Brooks S, Sadler GP. Molecular pathogenesis of follicular cell derived thyroid cancers. Int J Surg. 2010;8(3):186–93.
3. Vriens MR, et al. MicroRNA expression profiling is a potential diagnostic tool for thyroid cancer. Cancer. 2012;118:3426–3432.
4. Umbricht CB, et al. Telomerase activity: a marker to distinguish follicular thyroid adenoma from carcinoma. Cancer Res. 1997;57(11):2144–7.
5. Cochand-Priollet B, et al. The Bethesda terminology for reporting thyroid cytopathology: from theory to practice in Europe. Acta Cytol. 2011;55(6):507–11.
6. Watson RG, et al. Invasive Hurthle cell carcinoma of the thyroid: natural history and management. Mayo Clin Proc. 1984;59(12):851–5.
7. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov Y, Pacini F, Randolph G, Sawka A, Shepard D, Sosa J, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Available online at Thyroid 25: DOI:10.1089/thy.2015.0020; print version in Thyroid 26:1–133, 2016.
8. Strazisar B, et al. Predictive factors of carcinoma in 279 patients with Hurthle cell neoplasm of the thyroid gland. J Surg Oncol. 2010;101(7):582–6.
9. Guerrero MA, et al. Age and tumor size predicts lymph node involvement in Hurthle cell carcinoma. J Cancer. 2010;1:23–6.
10. Troncone G, et al. Accumulation of p27(kip1) is associated with cyclin D3 overexpression in the oxyphilic (Hurthle cell) variant of follicular thyroid carcinoma. J Clin Pathol. 2007;60(4):377–81.
11. Soh EY, Clark OH. Surgical considerations and approach to thyroid cancer. Endocrinol Metab Clin North Am. 1996;25(1):115–39.
12. Cooper DS, Schneyer CR. Follicular and Hurthle cell carcinoma of the thyroid. Endocrinol Metab Clin North Am. 1990;19(3):577–91.
13. Beckner ME, Heffess CS, Oertel JE. Oxyphilic papillary thyroid carcinomas. Am J Clin Pathol. 1995;103(3):280–7.
14. Gundry SR, et al. Total thyroidectomy for Hurthle cell neoplasm of the thyroid. Arch Surg. 1983;118(5):529–32.
15. Cannon J. The significance of hurthle cells in thyroid disease. Oncologist. 2011;16(10):1380–7.
16. Kutun S, et al. The predicting factors for clinical outcomes in patients with Hurthle cell carcinoma: how we do it. Clin Otolaryngol. 2011;36(1):73–7.
17. Kushchayeva Y, et al. Comparison of clinical characteristics at diagnosis and during follow-up in 118 patients with Hurthle cell or follicular thyroid cancer. Am J Surg. 2008;195(4):457–62.
18. Azadian A, et al. Management considerations in Hurthle cell carcinoma. Surgery. 1995;118(4):711–4. discussion 714–5.

19. Thompson NW, et al. Hurthle cell lesions of the thyroid gland. Surg Gynecol Obstet. 1974;139(4):555–60.
20. McLeod MK, Thompson NW. Hurthle cell neoplasms of the thyroid. Otolaryngol Clin North Am. 1990;23(3):441–52.
21. Carangiu M. Hurthle cell carcinoma: clinic-pathologic and biological aspects. Tumori. 2003;89:529–32.
22. Grant CS, et al. Benign Hurthle cell tumors of the thyroid: a diagnosis to be trusted? World J Surg. 1988;12(4):488–95.
23. Gosain AK, Clark OH. Hurthle cell neoplasms. Malignant potential. Arch Surg. 1984;119(5):515–9.
24. Bondeson L, et al. Oxyphil tumors of the thyroid: follow-up of 42 surgical cases. Ann Surg. 1981;194(6):677–80.
25. Samaan NA, et al. The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. J Clin Endocrinol Metab. 1992;75(3):714–20.
26. Samaan NA, et al. Pulmonary metastasis of differentiated thyroid carcinoma: treatment results in 101 patients. J Clin Endocrinol Metab. 1985;60(2):376–80.
27. Har-El G, et al. Hurthle cell carcinoma of the thyroid gland. A tumor of moderate malignancy. Cancer. 1986;57(8):1613–7.
28. Thoresen SO, et al. Survival and prognostic factors in differentiated thyroid cancer – a multivariate analysis of 1,055 cases. Br J Cancer. 1989;59(2):231–5.
29. Sugino K, et al. Hurthle cell tumor of the thyroid: analysis of 188 cases. World J Surg. 2001;25(9):1160–3.
30. Besic N, et al. The role of radioactive iodine in the treatment of Hurthle cell carcinoma of the thyroid. Thyroid. 2003;13(6):577–84.
31. Lopez-Penabad L, et al. Prognostic factors in patients with Hurthle cell neoplasms of the thyroid. Cancer. 2003;97(5):1186–94.
32. Mills SC, et al. Hurthle cell carcinoma of the thyroid: retrospective review of 62 patients treated at the Royal Marsden Hospital between 1946 and 2003. Eur J Surg Oncol. 2009;35(3):230–4.
33. Carcangiu ML, et al. Follicular Hurthle cell tumors of the thyroid gland. Cancer. 1991;68(9):1944–53.
34. Arturi F, et al. Iodide symporter gene expression in human thyroid tumors. J Clin Endocrinol Metab. 1998;83(7):2493–6.
35. Dohan O, et al. The sodium/iodide symporter (NIS): characterization, regulation, and medical significance. Endocr Rev. 2003;24(1):48–77.
36. Dadachova E, Carrasco N. The Na/I symporter (NIS): imaging and therapeutic applications. Semin Nucl Med. 2004;34(1):23–31.
37. Grunwald F, et al. Redifferentiation therapy-induced radioiodine uptake in thyroid cancer. J Nucl Med. 1998;39(11):1903–6.
38. Schmutzler C, et al. Retinoic acid increases sodium/iodide symporter mRNA levels in human thyroid cancer cell lines and suppresses expression of functional symporter in nontransformed FRTL-5 rat thyroid cells. Biochem Biophys Res Commun. 1997;240(3):832–8.
39. Park JW, Clark OH. Redifferentiation therapy for thyroid cancer. Surg Clin North Am. 2004;84(3):921–43.
40. Braga-Basaria M, Ringel MD. Clinical review 158: beyond radioiodine: a review of potential new therapeutic approaches for thyroid cancer. J Clin Endocrinol Metab. 2003;88(5):1947–60.
41. Spitzweg C, Morris JC. Gene therapy for thyroid cancer: current status and future prospects. Thyroid. 2004;14(6):424–34.
42. Gruning T, et al. Retinoic acid for redifferentiation of thyroid cancer – does it hold its promise? Eur J Endocrinol. 2003;148(4):395–402.
43. Clark OH, Hoelting T. Management of patients with differentiated thyroid cancer who have positive serum thyroglobulin levels and negative radioiodine scans. Thyroid. 1994;4(4):501–5.
44. Chao TC, Lin JD, Chen MF. Surgical treatment of Hurthle cell tumors of the thyroid. World J Surg. 2005;29(2):164–8.
45. Chen H, Nicol TL, Udelsman R. Follicular lesions of the thyroid. Does frozen section evaluation alter operative management? Ann Surg. 1995;222(1):101–6.
46. Lowe VJ, et al. 18F-FDG PET of patients with Hurthle cell carcinoma. J Nucl Med. 2003;44(9):1402–6.
47. Lazzi S, et al. Oncocytic (Hurthle cell) tumors of the thyroid: distinct growth patterns compared with clinicopathological features. Thyroid. 1999;9(2):97–103.
48. McDonald MP, et al. Hurthle cell carcinoma of the thyroid gland: prognostic factors and results of surgical treatment. Surgery. 1996;120(6):1000–4. discussion 1004–5.
49. Besic N, et al. Is patient's age a prognostic factor for follicular thyroid carcinoma in the TNM classification system? Thyroid. 2005;15(5):439–48.
50. Bhattacharyya N. Survival and prognosis in Hurthle cell carcinoma of the thyroid gland. Arch Otolaryngol Head Neck Surg. 2003;129(2):207–10.
51. Kushchayeva Y, et al. Prognostic indications for Hurthle cell cancer. World J Surg. 2004;28(12):1266–70.
52. Belchetz G, et al. Hurthle cell tumors: using molecular techniques to define a novel classification system. Arch Otolaryngol Head Neck Surg. 2002;128(3):237–40.
53. Tala H, et al. Five-year survival is similar in thyroid cancer patients with distant metastases prepared for radioactive iodine therapy with either thyroid hormone withdrawal or recombinant human TSH. J Clin Endocrinol Metab. 2011;96:2105–11.
54. Klubo-Gwiezdzinska J, Burman KD, Van Nostrand D, Mete M, Jonklaas J, Wartofsky L. Thyroid. radioiodine treatment of metastatic thyroid cancer: relative efficacy and side effect profile of preparation by thyroid hormone withdrawal versus recombinant human thyrotropin. Thyroid. 2012;22(3):310–7.
55. Mazzaferri EL, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab. 2003;88(4):1433–41.
56. Yen TC, et al. The role of technetium-99m sestamibi whole-body scans in diagnosing metastatic Hurthle cell carcinoma of the thyroid gland after total thyroidectomy: a comparison with iodine-131 and thallium-201 whole-body scans. Eur J Nucl Med. 1994;21(9):980–3.
57. Plotkin M, et al. Implication of 2-18fluor-2-deoxyglucose positron emission tomography in the follow-up of Hurthle cell thyroid cancer. Thyroid. 2002;12(2):155–61.
58. Simpson WJ, et al. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. Int J Radiat Oncol Biol Phys. 1988;14(6):1063–75.
59. Brierley JD, Tsang RW. External-beam radiation therapy in the treatment of differentiated thyroid cancer. Semin Surg Oncol. 1999;16(1):42–9.
60. Ford D, et al. External beam radiotherapy in the management of differentiated thyroid cancer. Clin Oncol (R Coll Radiol). 2003;15(6):337–41.
61. Schuck A, et al. Acute toxicity of adjuvant radiotherapy in locally advanced differentiated thyroid carcinoma. First results of the multicenter study differentiated thyroid carcinoma (MSDS). Strahlenther Onkol. 2003;179(12):832–9.
62. Grunwald F, et al. Redifferentiation therapy with retinoic acid in follicular thyroid cancer. J Nucl Med. 1998;39(9):1555–8.
63. Foote RL, et al. Is there a role for radiation therapy in the management of Hurthle cell carcinoma? Int J Radiat Oncol Biol Phys. 2003;56(4):1067–72.
64. Lin JD, et al. Results of external beam radiotherapy in patients with well differentiated thyroid carcinoma. Jpn J Clin Oncol. 1997;27(4):244–7.
65. Nikiforov YE. Thyroid carcinoma: molecular pathways and therapeutic targets. Mod Pathol. 2008;21 Suppl 2:S37–43.
66. Nikiforova MN, Nikiforov YE. Molecular genetics of thyroid cancer: implications for diagnosis, treatment and prognosis. Expert Rev Mol Diagn. 2008;8(1):83–95.
67. Li H, et al. Cost-effectiveness of a novel molecular test for cytologically indeterminate thyroid nodules. J Clin Endocrinol Metab. 2011;96(11):E1719–26.