Hürthle Cell Carcinoma

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Contents

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Case Presentation

A 74-year-old man was referred to the endocrine surgeon in February 2020 because of an incidental finding of a lesion in the left thyroid lobe that was visualized on a magnetic resonance (MR) scanning of the spine. The indication for MR was pain in the neck and shoulder, and there was suspicion of a spinal hernia. The thyroid lesion was observed to bulge into, deviate, and partially compress the trachea.

The patient presented with a palpable lump, about 5 cm in diameter. Interestingly, the patient had not noticed the lump himself nor noted any local symptoms of dysphagia or airway obstruction. The patient was a nonsmoker with no history of malignancy; he had a history of past surgical procedures due to inguinal hernia and meniscectomy, yet had no medicinal treatment other than painkillers and antihypertensives. Ultrasound examination visualized an almost solid hypoechoic lesion where the shape was wider-than-tall, measuring 2.9 cm in anterioposterior, 3.4 cm in transverse, and 5.1 cm in longitudinal diameter. The lesion was surrounded by a halo, contained some microcalcifications, and the margin was well defined. According to the EU-TIRADS, the lesion would be categorized as having an intermediate risk of malignancy or, according to ACR-TIRADS, as moderately suspicious for malignancy. The right thyroid lobe was normal with the exception of a cyst 4 mm in size.

Fine-needle aspiration cytology showed increased cellularity with predominance (about 90%) of Hürthle cells, absence of background colloid or chronic inflammation, and classified as Bethesda IV. The proliferation rate was low (Ki-67 <1%).

The patient underwent a left-sided hemithyroidectomy. No lymph nodes were removed.

The histopathological examination verified a radically removed Hürthle cell carcinoma with multifocal invasion of the tumor capsule, yet without lymphovascular invasion or extrathyroidal extension. The pTNM was classified as pT3aNx (Figs. 7.1, 7.2, 7.3, and 7.4). The cells were characterized by large, bulky, and eosinophilic cytoplasm and carried a low nuclei-cytoplasmic ratio. The nuclei were relatively monomorphic with compact chromatin, and puncta formed nucleoli without nuclear changes characteristic for papillary thyroid cancer. The growth pattern was mixed: solid, trabecular, and microfollicular. Less than 1 mitosis per 10 high-power fields was observed and no obvious tumor necrosis was seen. Immunohistochemical analyses showed immuno reactivity against TTF-1, PAX8 and thyroglobulin, with the latter positive in 75–100% of cells. The Ki-67-index was 2.1%. According to the local routine, molecular genetic examination of tumor DNA

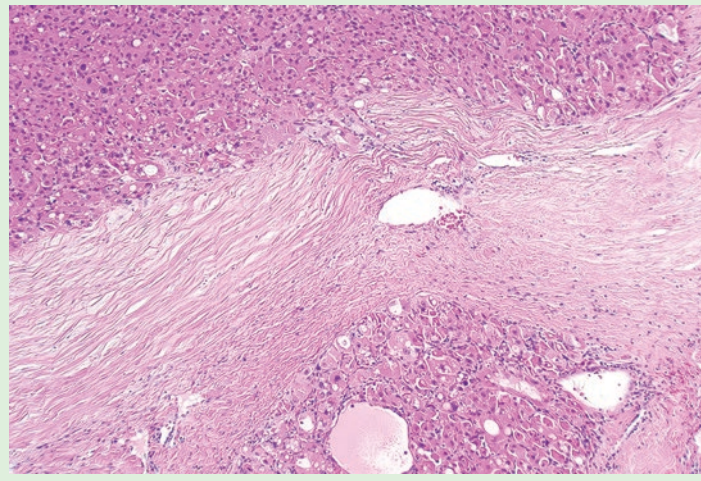

Fig. 7.1 Hürthle cell carcinoma; capsular invasion, original magnification ×100; hematoxylin and eosin (H&E) stain. (All histology images provided by C. Christofer Juhlin, Associate Professor, Department of Pathology and Cytology, Karolinska University Hospital, Stockholm, Sweden)

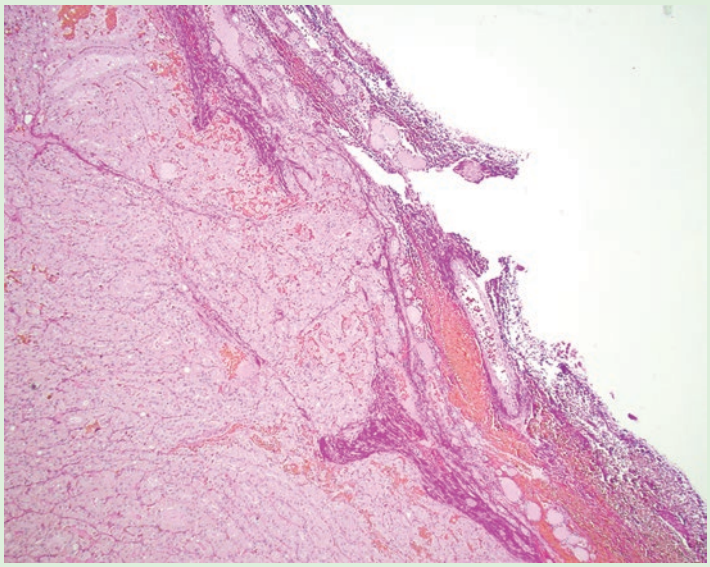

Fig. 7.2 Hürthle cell carcinoma; capsular invasion, original magnification ×20; Van Gieson stain

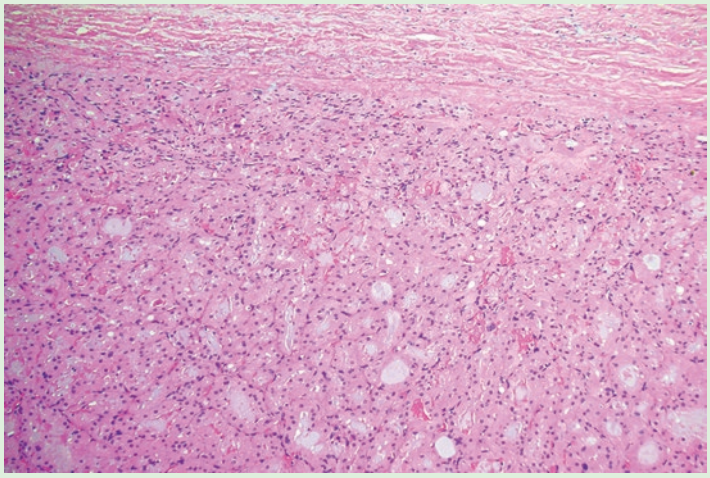

Fig. 7.3 Hürthle cell carcinoma; cellular attributes, original magnification ×100; H&E stain

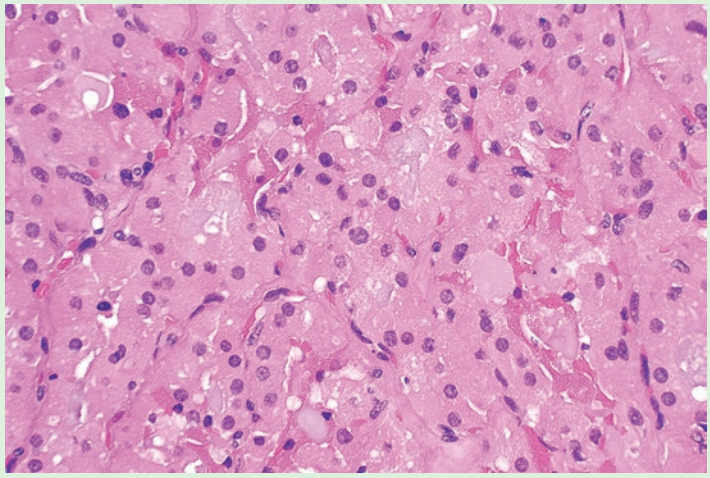

Fig. 7.4 Hürthle cell carcinoma; cellular attributes, original magnification ×400 H&E stain

with *TERT* promoter sequencing was performed and verified a *TERT* promoter mutation, C228T.

The patient underwent completion thyroidectomy. The subsequent histopathological examination revealed a colloid nodule but no sign of tumor. Thyroxine treatment followed and included a daily dose of 125 micrograms in order to maintain a circulating thyroid-stimulating hormone concentration below 0.01 mIU/L. Based upon a multidisciplinary board decision, the patient received radioiodine treatment in the dose of 3.7 gigabecquerel (GBq) (100 Millicurie (mCi)). A full-body scan after the procedure showed local uptake of radioactivity in the thyroid bed.

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Questions

1. In which of the following would you establish the diagnosis of Hürthle cell carcinoma?
   1. Cytology specimen from a solid thyroid nodule showing greater than 70% of Hürthle cells
   2. Cytology specimen from a solid thyroid nodule showing greater than 70% of Hürthle cells, classified as Bethesda V
   3. Intraoperative frozen section of intrathyroidal lesion containing greater than 70% of Hürthle cells
   4. Histopathological verification of intrathyroidal lesion with full-thickness capsular invasion containing greater than 70% of Hürthle cells
      (a) All are correct.
      (b) Only 2, 3, and 4 are correct.
      (c) Only 2 and 4 are correct.
      (d) Only 4 is correct.
      (e) None are correct.
2. What is true about Hürthle cells?
   1. Presence of Hürthle cells, per se, increases the risk of malignancy.
   2. Hürthle cells are also called oncocytes.
   3. Hürthle cells can be present in benign goiter.
   4. Hürthle cells are characterized by a high content of mitochondria.
      (a) All are correct.
      (b) Only 3 and 4 are correct.
      (c) Only 2, 3, and 4 are correct.
      (d) Only 4 is correct.
3. How would you classify a Hürthle cell carcinoma?
   1. A variant of follicular thyroid cancer
   2. A variant of papillary thyroid cancer
   3. A variant of differentiated thyroid cancer
   4. A separate entity
      (a) All are correct.
      (b) Only 1, 2, and 3 are correct.
      (c) Only 3 and 4 are correct
      (d) Only 4 is correct.
      (e) None are correct.

4. Which of the following preoperative preparative examinations are advisable for patients with Hürthle cell neoplasia, presenting with hoarseness?
   1. Ultrasound
   2. Laryngoscopy
   3. MR scanning to detect extrathyroidal extension
   4. Contrast-enhanced CT scanning to detect extrathyroidal extension
      (a) All are correct.
      (b) Only 1 and 2 are correct.
      (c) Only 1, 2, and 4 are correct
      (d) All but 4 are correct
5. Which of the following statements are correct about ultrasound?
   1. Thyroid Imaging Reporting and Database Systems are developed to provide a structured ultrasound reporting template.
   2. Ultrasound is effective for detection of lymph node metastases in region VI.
   3. Ultrasound is effective for differentiation between Hürthle cell carcinoma and adenoma.
   4. Protrusion into adjacent structures and disruption of the capsular margin indicate extrathyroidal extension.
      (a) All are correct.
      (b) Only 1 is correct.
      (c) Only 1 and 2 are correct.
      (d) Only 1 and 4 are correct.
6. Which of the following statements are correct for Bethesda classification?
   1. Introduced to standardize the terminology for reporting of thyroid cytopathology.
   2. Grouped into six categories based on the risk of malignancy.
   3. Hürthle cell carcinoma are often classified as follicular lesion of undetermined significance.
   4. Cytology may be diagnostic for Hürthle cell carcinoma in patients with metastatic disease.
      (a) Only 1 and 2 is correct.
      (b) Only 1, 2, and 3 are correct.
      (c) Only 1, 2, and 4 are correct.
      (d) All are correct.
7. Which are the goals of radioiodine therapy?
   1. Remnant ablation meant to facilitate detection of recurrent disease
   2. Adjuvant therapy intended to destroy suspected residual disease
   3. Therapy intended to treat persistent disease
   4. Therapy intended to improve disease-specific and disease-free survival
      (a) All are correct.
      (b) Only 1 is correct.

(c) Only 1 and 2 are correct.
(d) Only 1, 3, and 4 are correct.
(e) Only 2 and 3 are correct.

8. Why treat patients with recombinant TSH?
   1. To suppress TSH
   2. To avoid negative effects on Quality of Life from thyroxin withdrawal
   3. To achieve a TSH greater than 30 mIU/L
   4. To increase the effect of radioiodine treatment
      (a) All are correct.
      (b) Only 4 is correct.
      (c) Only 2 and 3 are correct.
      (d) Only 2, 3 and 4 are correct.
9. Which of the following risk factors have been found to be negative prognostic signs in Hürthle cell carcinoma?
   1. Age over 45 years
   2. Female gender
   3. Tumor size and extension at diagnosis
   4. Hot nodule with hyperfunction
      (a) All are correct.
      (b) Only 3 is correct.
      (c) Only 1 and 3 are correct.
      (d) Only 1, 3, and 4 are correct.
10. Which of the following statements are true for Hürthle cell carcinoma?
    1. Accounts for about 3% of all thyroid malignancies.
    2. 10-year survival of 92.6% has been reported.
    3. The majority presents with local disease.
    4. $_{18}$FDG-PET/CT can be useful for detection of recurrent disease.
       (a) All are correct.
       (b) Only 3 is correct.
       (c) Only 1 and 3 are correct.
       (d) Only 1, 3, and 4 are correct.

7.1 Introduction

Hürthle cell carcinoma is defined as a malignant thyroid tumor that is predominantly (at least 75%) composed of metaplastic thyroid follicular cells with abundant granular eosinophilic cytoplasm. These cells, also called oncocytes, may also be present in nontumor tissue such as nodular goiter, lymphocytic thyroiditis, and other variants of thyroid neoplasia [1, 2]. The granular eosinophilic cytoplasm results from excessive accu-

mulation of mitochondria. The name is actually a misnomer; the cells, as described by Hürthle in 1894, were actually parafollicular C cells [3]. Hürthle cell carcinoma accounts for about 3% of thyroid malignancies [4]. Traditionally, Hürthle cell carcinoma has been considered a histopathological variant of follicular carcinoma, yet is now defined as a separate entity based upon its unique biological behavior, genetic alterations, and differences in prognosis as compared to follicular carcinoma [5, 6]. Hürthle cell carcinoma has historically been found to be more aggressive, carrying a higher risk for distant metastases and poor prognosis when compared to other differentiated thyroid cancers; however, the survival rate has improved dramatically over time [7–9]. The majority of patients with Hürthle cell carcinoma can today be effectively treated.

7.2 Clinical Presentation

Most Hürthle cell cancer patients present with a single, painless thyroid nodule. In a recent analysis of 2101 patients with Hürthle cell carcinoma identified in the database from the Surveillance, Epidemiology and End Results (SEER) and who were diagnosed between 2004 and 2016 with an average age of 55, +/− 15 years, it was found that 29% were men and 83% had local disease at the time of diagnosis. Patients with distant disease were older, more often males, and more often exhibited extensive and multifocal tumors [10].

Compared to follicular thyroid carcinoma, Hürthle cell carcinoma seems to be diagnosed in older patients and in more advanced stages where lymph node metastases are more frequent; however, T1 tumors do occasionally exhibit metastatic disease [1, 11–14]. Symptoms such as hoarseness, airway obstruction, dysphagia, and hyperthyroidism can exist in advanced cases [12, 15]. Hürthle cell carcinoma is sometimes detected as an incidental finding of other imaging for nonthyroidal disorders, especially in an $_{18}$FDG-PET [16]. Both malignant and benign forms of Hürthle cell neoplasia have high FDG avidity. The increased utilization of $_{18}$FDG-PET during the diagnostic workup of several malignant and nonmalignant disorders leads to the detection of an increasing number of focal thyroid lesions requiring workup [17].

Hürthle cell carcinoma is divided into two types based on the pathological presentation: minimally invasive Hürthle cell carcinoma and widely invasive Hürthle cell carcinoma. Generally, minimally invasive Hürthle cell carcinoma demonstrates much less aggressive behavior compared to widely invasive Hürthle cell carcinoma, which is associated with a higher rate of distant metastases [18].

7.3 Natural History

The natural history of Hürthle cell carcinomas has not been systematically studied. The biological behavior varies. Often, Hürthle cell carcinomas have been included as a part of follicular thyroid carcinomas. Some are slow-growing lesions, while others grow aggressively and spread hematogenously. Also, Hürthle cell carcinomas may be diagnosed as incidental findings of microcarcinoma, while others exhibit extrathyroidal spread [1, 10, 13, 19]. A history of childhood head and neck radiation has been associated with risk of more extensive and bilateral thyroid lobe involvement [20]. Hürthle cell carcinomas have been reported to differ from follicular carcinomas by having a higher prevalence of lymph node metastases and more frequent locoregional recurrence as soft tissue implants [21, 22]. Recent independent categorization of Hürthle cell carcinoma as a separate entity from follicular carcinoma, together with advances in molecular pathology, will facilitate future studies and in time our understanding [5].

7.4 Diagnosis

Patients with Hürthle cell carcinoma often exhibit a solitary thyroid nodule, either as a palpable nodule or as an incidental finding on an imaging modality for reasons not related to clinical suspicion of a thyroid disorder. Some may be autonomously hyperfunctioning [14, 15]. The recommendation for evaluation of clinically or incidentally detected thyroid lesions follows the guidelines for thyroid nodules and differentiated thyroid cancer [23, 24].

Generally, only nodules larger than 1 cm in size need to be evaluated, with the exception of those associated with clinical symptoms or associated lymphadenopathy, which require the need for further evaluation [19, 25]. A diagnostic ultrasonography of the thyroid and the cervical lymph nodes should be performed in order to evaluate size, location, sonographic characteristics of thyroid lesions, and the presence or absence of any suspicious cervical lymph nodes in the central or lateral compartments [23, 24]. Based upon the sonographic appearance, ultrasound-based risk stratification systems are devel-

oped and modified to identify lesions that warrant fine-needle biopsy or sonographic follow-up [26–28]. Follow-up should be considered for nodules that do not meet criteria for fine-needle aspiration at the initial ultrasound examination. For optimal planning of all procedures related to thyroid nodules, such as fine-needle cytology and surgical procedures, access to a high-resolution system, a high-frequency linear probe, and, last but not least, an experienced ultrasound operator are all essential [24]. The main limitations of thyroid ultrasound are the operator dependency and the difficulty of analyzing lymph nodes in the central compartment [16, 29]. The Thyroid Imaging Reporting and Database System (TIRADS) has been introduced to allow for systematic reporting of sonographic characteristics of thyroid nodules and to simplify communication. Different variants, including web-based versions, have been introduced and found to provide high sensitivity, negative predictive value, and interobserver reproducibility for stratification of malignancy [26, 30]. Generally, only lesions classified as intermediate or high risk for malignancy are referred for surgery [26].

At this time, neither ultrasound nor any other imaging has provided the ability to distinguish between Hürthle cell carcinoma and adenoma, except for when extrathyroidal extension or lymph node metastases are confirmed. The differentiation between benign and malignant is dependent on histopathological verification of full-thickness capsular and/or vascular invasion. Hürthle cells are typically large, polygonal follicular cells with a prominent nucleolus and display eosinophilic cytoplasm on hematoxylin and eosin stains (H&E) [3]. The eosinophilic granularity of the cytoplasm is due to accumulation of mitochondria [31, 32]. Hürthle cell lesions are defined as lesions with a predominating expression of Hürthle cells (>75% of the cellular population). Based on the latest WHO classification, Hürthle cell carcinoma is defined as a separate entity without subclassification [5]. Expression of Hürthle cells, per se, does not increase the risk of malignancy. It is often possible to differentiate between neoplasia and nontumor tissue, such as nodular goiter and lymphocytic thyroiditis but not between cancer and adenoma. The Bethesda System for reporting thyroid cytopathology was introduced in 2007 to help standardize the terminology for reporting of thyroid cytopathology and has been shown to be reliable and valid [33]. The results are grouped into six Bethesda categories based on risk of malignancy: nondiagnostic (I); benign (II); atypia of undetermined significance/follicular lesion of undetermined significance (III), follicular neoplasm/ suspicious for follicular neoplasm (IV), suspicious for malignancy (V) and malignant (VI). An increased risk of malignancy of specimens defined as benign (Bethesda II) has been reported [34–36]. Fine-needle cytology from Hürthle cell carcinoma is often classified into category IV with the expected risk of cancer as 20–30%. In the context of mul-

tiple thyroid noduli, fine-needle specimens showing predominant expression of Hürthle cells are often classified as follicular lesion of undetermined significance (Bethesda III) rather than suspicious for Hürthle cell neoplasm (Bethesda IV). It was recently shown that the risk of malignancy did not differ between cases with or without multiple nodules or the presence of lymphocytic thyroiditis [37]. In the latest WHO classification, Hürthle cell carcinoma was defined as a specific entity without subclassification [5]. However, in practice, the tumors are often further categorized, based on their extent of invasion, into minimally and widely invasive. Encapsulated Hürthle cell carcinoma with microscopically identifiable foci of capsular and/or a few foci(<4) of vascular invasion are often defined as minimally invasive, in contradistinction to tumors with extrathyroidal and/or extensive vascular invasion, categorized as widely invasive [23]. However, controversy still remains concerning the prognostic importance of the degree of angioinvasion and, if encapsulated, tumors with angioinvasion should be defined as a separate group [24].

Recent advances in cancer genomics and molecular testing have enabled evolvement of tests that have progressed from single gene to broad genomic panels. Identification of distinct genomic alterations in Hürthle cell carcinoma with widespread losses of heterozygosity/chromosomes and prominent mitochondrial DNA mutations has formed the basis for recently available, modified next-generation sequencing tests [6, 31, 38]. At the present time, genomic panels have shown accuracy in correctly classifying hyperplastic nodules as likely to be benign, yet are not adequate for differentiating malignant Hürthle neoplasia from benign. The amount of nucleic acids needed is very low. An input as low as 2.5 nanograms is sufficient as long as the concentration of tumor cells is at least 12% [31]. Prospective clinical studies with long-term ultrasound follow-ups are needed in order to determine when molecular rule-in tests for cytology samples with potential malignancy can guide surgical decision-making [24, 31, 39]. Testing for prognostic markers such as *TERT*- and *TP53*-mutations that are interpreted in the context of the *BRAF*-mutation status may be helpful in the planning of treatment and accurate follow-up [24, 31, 40, 41].

For patients with advanced disease or with clinically evident extensive lymph node involvement, cross-sectional imaging, such as magnetic resonance imaging (MRI) or computer tomography without contrast, may be necessary for effective surgical planning. After contrast administration, radioiodine treatment needs to be withheld for at least 3 months [24].

7.5 Treatment

The basic goals of treatment are to improve survival, reduce risk of persistent or recurrent disease, and to permit accurate risk stratification while minimizing unnecessary therapy and morbidity related to therapy. Adequate surgery is the primary and most important treatment, while treatment with radioactive iodine, TSH suppression, as well as other treatments play adjunctive roles [23, 24]. Before surgery, accurate staging including clinical examination, ultrasound, and fine-needle cytology is mandatory. For patients with clinical suspicion of advanced disease, cross-sectional images are recommended as is discussed in the previous section.

In the majority of cases, it is not possible to distinguish between Hürthle cell adenoma and carcinoma preoperatively. The first step is usually ipsilateral hemithyroidectomy/isthmusectomy. Partial thyroidectomy can be sufficient for single tumors without extrathyroidal invasion, yet the acceptable size limit for partial thyroidectomy is controversial. For patients with indeterminate nodules that are cytologically or sonographically suspicious for malignancy, large (>4 cm), positive for known mutations associated with a higher cancer risk, familial disease, or history of radiation exposure, an initial total thyroidectomy may be performed [23, 24]. Still, there is no evidence for benefit of total compared to partial thyroidectomy [10]. For patients planning to receive radioactive iodine treatment postoperatively, near-total or total thyroidectomy is necessary in order to enable efficient radioiodine therapy [23, 24]. Hürthle cell carcinoma has been reported to more likely be associated with lymph node metastases than follicular thyroid cancer [21]. The risk of lymph node metastases is related to size of lesion, age, and male gender. Prophylactic ipsilateral central neck dissection at the time of initial operation has been suggested for older male patients with HCC greater than 5 cm [21]. The current guidelines do not address Hürthle cell carcinoma specifically [23, 24]. Prophylactic central-compartment dissection is only recommended for patients with papillary thyroid cancer and an advanced primary tumor or clinically involved lateral neck nodes [23, 24].

Due to the less aggressive behavior of a minimally invasive Hürthle cell carcinoma as compared to the more aggressive behavior of a widely invasive Hürthle cell carcinoma, a lesion that is less than 4 cm in size can be treated with thyroid lobectomy alone, because it does not require adjuvant treatment with radioactive iodine. This approach is applied to the tumor that has been removed during a thyroid lobectomy for "follicular neoplasm" or "follicular lesion of undetermined significance" and diagnosed as a minimally invasive Hürthle cell carcinoma on final pathological evaluation [18].

According to guidelines, the decision of adjuvant treatment and surveillance after radical surgical removal of a differentiated thyroid cancer is based on stratification of risk for recurrence into three groups: low, intermediate, and high risk. Hürthle cell carcinoma is not specifically addressed in the guidelines. In the WHO classification from 2017, Hürthle cell carcinoma is defined as a specific entity without subclassification. In everyday practice, the stratification of Hürthle cell carcinoma often follows that for follicular thyroid carcinoma.

Initial TSH suppression treatment is recommended for patients with follicular-derived thyroid cancers of high and intermediate risk and is based on the reported effect on overall survival and the documented stimulating effects of TSH on growth and proliferation of follicular thyroid cells [23, 24, 42]. Data regarding the optimal intensity and duration of TSH suppression therapy are weak. For patients with persistent disease, treatment is life-long; however, for patients with high risk of adverse effects on heart and bone, the benefits should be weighed against the potential risks [23].

Data concerning the benefits on outcome of radioiodine treatment are conflicting. Generally, the European experts prefer a wider use of radioactive treatment as compared to the ATA. In the ATA guidelines, radioiodine treatment is considered for patients with aggressive histology, vascular invasion, and tumor size larger than 4 cm or having extrathyroidal extension [23]. In the European revised version, radioiodine administration is classified by goal as remnant ablation meant to facilitate staging and detection of recurrent disease by measurement of thyroglobulin or scintigraphy; also adjuvant therapy intended to improve disease-free survival by destroying suspected but unproven residual disease and as therapy intended to treat persistent disease and improve disease-specific and disease-free survival [24]. Based on observational research, the goal is to elevate TSH to greater than 30mIU/L in preparation for radioiodine treatment. Treatment with recombinant human thyrotropin should be considered before thyroid hormone withdrawal due to the aspects for quality of life [23, 24]. In terms of radioiodine treatment used as therapy, higher versus lower initial activities and fewer high-activity administrations versus more numerous low-activity administrations are preferred [24]. The use of remnant ablation solely for facilitating follow-up is questioned. Survival benefits with or without postoperative radioiodine will be analyzed in two on-going European randomized, multicenter studies [24].

Generally, Hürthle cell carcinoma is less sensitive to radioactive radioiodine therapy than other differentiated thyroid cancers, yet survival benefits from adjuvant radioiodine treatment have been exhibited. In a study including 2799 patients with Hürthle cells from the SEER database, an increase of overall survival was observed for patients (n = 1529) receiving

adjuvant radioiodine treatment [43]. It has also been verified that some but not all distant metastases of Hürthle cells can concentrate radioiodine [44, 45]. In one study where Hürthle cells and follicular thyroid cancer were analyzed together, two-thirds of 394 patients with lung and/or bone metastases had verified radioactive iodine uptake, but only 46% achieved complete response and the age of the patient seemed to affect the uptake. Uptake with response was coupled to a 15-year survival rate of 89% as compared to 8% for patients who did not achieve response [46].

Surveillance is guided by dynamic risk stratification. Patients that have undergone treatment with thyroidectomy and radioiodine ablation are usually examined with full-body scintigraphy within 6–9 months in order to evaluate the effect of ablation. After 9–12 months, a risk re-evaluation is performed based on clinical examination, measurement of thyroglobulin, and neck ultrasound, after which the TSH suppression therapy may be substituted with TSH supplementation. Patients with persistent disease continue with lifelong TSH suppression therapy.

For advanced or metastatic Hürthle cell carcinoma refractory to radioactive iodine therapy, several different anticancer agents outside or inside clinical trials are available. The challenge remains to correctly identify which patients will benefit from these treatments and when to start and when to end treatment. For patients who are asymptomatic, stable, or minimally progressive, TSH-suppressive thyroid hormone therapy and close monitoring may be preferable. Conventional cytotoxic chemotherapy is not recommended. Treatment with kinase inhibitors has been shown to improve progression-free survival in prospective trials and should therefore be considered; preliminary data also indicate the option of resensitization to radioiodine treatment [23, 24]. Focal palliative approaches such as bronchial stenting or bronchial laser therapy may be considered [24]. For patients with pathological fractures and spinal cord compression, external radiation and antiresorptive agents such as bisphosphonates should be considered [47].

7.6 Surgical Details

Surgical resection is the primary and curative treatment of Hürthle cell carcinoma. Substantial controversy still surrounds the selection of initial partial or near-total/total thyroidectomy and or lymph node clearance [23, 24]. Since it is generally not possible to distinguish between Hürthle cell adenoma and carcinoma preoperatively, ipsilateral lobectomy and isthmusectomy are frequently the initial routine procedures for patients with a single dominant nodule. The surgical risks of two-stage thyroidectomy (lobectomy followed by completion thyroidec-

tomy) are similar to those of one-stage total thyroidectomy. Initial thyroidectomy is recommended for patients with obvious malignant disease when the strategy includes radioactive iodine treatment postoperatively. Findings elicited during the preoperative workup may indicate the need for more extensive procedures including the need for sternotomy and/or tracheal or laryngeal resection and reconstruction. Total thyroidectomy is also preferred for patients with a history of cervical head and neck radiation in childhood, which has shown to be associated with an increased incidence of multifocal disease and concomitant papillary cancer [23]. The pros and cons of choice of the surgical procedure must be carefully considered in each case, and the surgeon should communicate the surgical risks to the patient. Contralateral nodular disease/goiter or a high risk for a second surgical procedure could advocate for a one-stage total thyroidectomy [23]. For minimally invasive Hürthle cell carcinoma, the risk of recurrence is very low and lobectomy may be sufficient [1]. For widely invasive Hürthle cell carcinoma, completion thyroidectomy and subsequent radioiodine ablation are often advocated to facilitate follow-up and earlier detection of recurrence; however, controversies regarding indication for thyroidectomy still remain [8].

A preoperative laryngoscopy should be routinely performed. The correlation between vocal symptoms and actual vocal status is poor. Vocal cord paralysis is indicative of invasive disease. The surgical procedure should include a careful exploration to detect tumor invasion into adjacent structures, contralateral nodular disease, and metastatic nodal and soft tissue disease in the central neck [23, 24]. Frozen section is neither diagnostic nor informative in the differentiation between Hürthle cell carcinoma and Hürthle cell adenoma [48]. Care should be taken to preserve the parathyroid glands and their blood supply. Visual identification of the recurrent laryngeal nerve is required in all cases, and during dissection of the superior pole, care should be taken to preserve the external branch of the superior laryngeal nerve. Intraoperative neuromonitoring is favored in order to help prevent bilateral paresis by avoiding contralateral resection when nerve paralysis is detected on the initial side [24]. Neuromonitoring may also facilitate nerve identification and protection. If completion thyroidectomy is recommended based upon the histopathological examination, the surgeon should check a laryngeal exam prior to the completion surgery.

7.7 Outcomes or Prognosis

The majority of patients with HCC can be treated effectively. From the SEER's database, 5-year and 10-year survival rates of 95.4% and 92.6%, respectively, have been reported [10].

Compared to other differentiated thyroid cancers, Hürthle cell carcinoma has been found to be more aggressive, carrying a higher risk of distant metastases and poor prognosis, yet the rate of survival has improved dramatically over time [7, 8]. Size and extension of the tumor at diagnosis, presence of vascular invasion and/or of residual tumor after surgery, patients age over 45 years, and male gender have all been identified as negative prognostic factors [1, 10, 13, 49–51]. Patients with Hurthle cell microcarcinomas more oftenly present with distant metastases and have compromised survival as compared to patients with papillary thyroid microcarcinoma and carry less than a 10-year overall survival rate of 89.3% versus 94.3% for the latter [19, 25].

For dynamic risk stratification, one may take advantage of the postoperative doubling-time for thyroglobulin levels and assess imaging with an 18FDG-PET/CT in order to optimize staging and plans for follow-ups and eventual treatment therapy [24, 52, 53]. The value of 18FDG-PET/CT in the initial diagnostic workup is limited due to the fact that even benign adenoma may present with high FDG avidity [17].

Answers to the Questions

1. (d); 2. (c); 3. (c); 4. (d); 5. (d); 6. (b); 7. (a); 8. (d); 9. (c); 10. (a)

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