The Oncologist®
Endocrinology

Follicular Adenoma and Carcinoma of the Thyroid Gland

CHRISTOPHER R. MCHENRY,[a] ROY PHITAYAKORN[b]

[a]Department of Surgery, MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio, USA; [b]Department of Surgery, Division of General and Gastrointestinal Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Key Words. Follicular thyroid carcinoma • Follicular adenoma • Follicular neoplasm

Disclosures

Christopher R. McHenry: None; **Roy Phitayakorn:** None.

Section Editor **Herbert Chen** discloses research funding received from Novartis.

Section Editor **Stan Sidhu** discloses no financial relationships.

Reviewer "A" discloses no financial relationships.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial basis. On the basis of disclosed information, all conflicts of interests have been resolved.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the differentiation of follicular adenoma from follicular carcinoma.
2. Explain novel developments in the diagnosis and treatment of follicular carcinoma.

ABSTRACT

Follicular neoplasms of the thyroid gland include benign follicular adenoma and follicular carcinoma. Currently, a follicular carcinoma cannot be distinguished from a follicular adenoma based on cytologic, sonographic, or clinical features alone. The pathogenesis of follicular carcinoma may be related to iodine deficiency and various oncogene and/or microRNA activation. Advances in molecular testing for genetic mutations may soon allow for preoperative differentiation of follicular carcinoma from follicular adenoma. Until then, a patient with a follicular neoplasm should undergo a diagnostic thyroid lobectomy and isthmusectomy, which is definitive treatment for a benign follicular adenoma or a minimally invasive follicular cancer. Additional therapy is necessary for invasive follicular carcinoma including completion thyroidectomy, postoperative radioactive iodine ablation, whole body scanning, and thyrotropin suppressive doses of thyroid hormone. Less than 10% of patients with follicular carcinoma will have lymph node metastases, and a compartment-oriented neck dissection is reserved for patients with macroscopic disease. Regular follow-up includes history and physical examination, cervical ultrasound and serum TSH, and thyroglobulin and antithyroglobulin antibody levels. Other imaging studies are reserved for patients with an elevated serum thyroglobulin level and a negative cervical ultrasound. Systemic metastases most commonly involve the lung and bone and

Correspondence: Christopher R. McHenry, M.D., Vice-Chairman, Department of Surgery, MetroHealth Medical Center, Professor of Surgery, Case Western Reserve University, General, Neck and Endocrine Surgery, 2500 MetroHealth Drive, H-917, Cleveland, Ohio 44109-1998, USA. Telephone: 216-778-4753; Fax: 216-778-3774; e-mail: cmchenry@metrohealth.org Received December 2, 2010; accepted for publication February 21, 2011; first published online in ***The Oncologist*** *Express* on April 11, 2011.
1083-7159/2011/$30.00/0 doi: 10.1634/theoncologist.2010-0405

less commonly the brain, liver, and skin. Microscopic metastases are treated with high doses of radioactive iodine. Isolated macroscopic metastases can be resected with an improvement in survival. The overall ten-year survival for patients with minimally invasive follicular carcinoma is 98% compared with 80% in patients with invasive follicular carcinoma. ***The Oncologist*** 2011;16:585–593

INTRODUCTION

Follicular adenoma and follicular carcinoma of the thyroid gland are tumors of follicular cell differentiation that consist of a microfollicular architecture with follicles lined by cuboidal epithelial cells. A follicular adenoma is a benign encapsulated tumor of the thyroid gland. It is a firm or rubbery, homogeneous, round or oval tumor that is surrounded by a thin fibrous capsule. A follicular adenoma is a common neoplasm of the thyroid gland. In two autopsy series, the incidence of thyroid adenoma was 3 and 4.3% [1, 2]. The ratio of follicular adenoma to follicular carcinoma in surgical specimen is approximately 5 to 1 [3].

Most patients with a follicular adenoma are clinically and biochemically euthyroid. Approximately 1% of follicular adenomas are "toxic adenomas," which are a cause of symptomatic hyperthyroidism. Hyperthyroidism usually does not occur until a functioning follicular adenoma is ≥3 cm in size. On radioiodine thyroid scintigraphy, functioning follicular adenomas avidly concentrate radioiodine and may suppress iodine uptake in the rest of the thyroid gland. In contrast, most follicular adenomas are hypofunctioning on thyroid scintigraphy.

Follicular carcinoma has microscopic features that are similar to a follicular adenoma. However, a follicular carcinoma tends to be more cellular with a thick irregular capsule, and often with areas of necrosis and more frequent mitoses. A follicular carcinoma cannot be distinguished from a follicular adenoma based on cytologic features alone. It is distinguished from a follicular adenoma on the basis of capsular invasion, vascular invasion, extrathyroidal tumor extension, lymph node metastases, or systemic metastases. Capsular invasion is defined as tumor extension through the entire capsule. A follicular neoplasm with tumor invasion into but not through the entire capsule is considered a follicular adenoma [4]. Vascular invasion is defined as tumor penetration into a large caliber vessel within or outside the capsule. Tumor invasion of a large vessel with an identifiable wall and an endothelial lining is definitive morphologic evidence of vascular invasion. Vascular invasion is the most reliable sign of malignancy.

Follicular carcinoma is divided into minimally invasive and invasive variants based on morphologic criteria. Minimally invasive follicular carcinoma is an encapsulated tumor with microscopic penetration of the tumor capsule without vascular invasion [4, 5]. Minimally invasive follicular carcinoma is a less aggressive tumor with a disease-free survival that has been reported to be similar to a benign follicular adenoma [6, 7]. However, there are reports of some patients dying of minimally invasive follicular carcinoma [4]. Patients with minimally invasive follicular carcinoma tend to be younger than patients with invasive follicular carcinoma, and it has been suggested that minimally invasive follicular carcinoma may be a precursor to its invasive counterpart [8].

Invasive follicular carcinoma is defined as a follicular carcinoma with vascular invasion and/or extension beyond the tumor capsule into the adjacent thyroid parenchyma. It is associated with a worse prognosis. It has been subdivided into moderately invasive and widely invasive variants based on the presence of angioinvasion with or without capsular invasion versus extensive invasion of the capsule and the thyroid parenchyma [4]. Van Heerden and colleagues reported a 10-year disease-specific mortality of 15%–28% in patients with invasive follicular carcinoma [6].

Follicular carcinoma accounts for ~10% of all cases of thyroid malignancy in iodine-sufficient areas and 25%–40% of thyroid malignancies in areas of iodine deficiency [3, 9]. The incidence of follicular carcinoma in the United States has decreased, most likely secondary to dietary iodine supplementation and the elimination of iodine deficiency and the more accurate diagnosis of follicular variant of papillary cancer and Hürthle cell cancer [10]. It occurs more often in women and older patients with a female-to-male ratio of 3:1 and a mean age of 60 years at the time of diagnosis. Most follicular cancers are nonfunctional, but there are rare cases of functioning follicular cancers. Follicular carcinoma is usually unifocal, and <10% of patients will have lymph node metastases [4, 11]. Follicular carcinoma has a propensity for hematogenous spread. Ten to 15% of patients with follicular carcinoma will present with metastatic disease, most commonly involving the lung followed by bone. The brain, liver, and skin are less common sites of systemic metastases.

PATHOGENESIS

Iodine deficiency and endemic goiter are thought to be factors predisposing one to the development of follicular cancer. An increased risk of follicular thyroid cancer has been

reported in areas of iodine deficiency and in areas of endemic goiter [12, 13]. The addition of iodide to the diet has resulted in a decreased incidence of follicular cancer and a relative increase in the incidence of papillary thyroid cancer [12, 14].

Oncogene activation is common in follicular carcinomas. Approximately 80% of follicular carcinomas contain RAt Sarcoma (RAS) gene mutations or a paired box gene 8/peroxisome proliferator-activated receptor gamma (PAX8-PPARγ) gene rearrangement [15]. The RAS genes code for multiple G proteins that are involved in intracellular signaling through the RAF-MEK-MAPK kinase pathway. Point mutations in the N-RAS, H-RAS, and K-RAS genes occur in ~40% of follicular cancers, producing continuously activated signaling proteins leading to uncontrolled growth [16, 17].

The PAX8-PPARγ gene rearrangement has been found in 4%–13% of follicular adenomas and 29%–56% follicular carcinomas [18]. PAX8 is a gene that codes for a nuclear protein product of a thyroid-specific transcription factor that is involved in follicular cell differentiation. Mutations in PAX8 cause it to become fused with PPARγ and impair PPARγ function, leading to loss of growth inhibitory controls [19].

Weber and colleagues have reported that four micro-RNAs (miR-192, miR-197, miR-328, and miR-346) have a significantly greater expression in follicular carcinoma than follicular adenoma [20]. Micro-RNAs are small noncoding segments of ribonucleic acid that contain ~25 nucleotides that negatively regulate gene transcription by binding to gene promoters, ultimately affecting apoptosis and cell proliferation. Mutations in the phosphatase and tensin homologue suppressor gene and the phosphatidylinositol 3-kinase pathway may be an important factor in the development of more aggressive thyroid cancers and may be more common in follicular cancer [21]. Other factors that have been implicated in the pathogenesis of follicular thyroid cancer include gene mutations in p53, c-myc, c-fos, and the thyrotropin (TSH) receptor [22, 23].

Functioning follicular adenomas occur as a result of a monoclonal expansion of thyroid follicular cells with a high prevalence of activating mutations in the gene for the TSH receptor and less frequently in the adenylate cyclase-stimulating G alpha protein gene that result in increased thyroid hormone secretion independent of TSH [24–26]. Approximately 20% of nonfunctioning follicular adenomas possess oncogene mutations that may predispose them to progression to follicular carcinoma [27, 28]. N-RAS and K-RAS mutations may be present in patients with follicular adenoma and have been implicated as playing a role in the evolution of follicular adenoma to follicular carcinoma [29].

Clinical Presentation

Most patients with a follicular adenoma or follicular carcinoma of the thyroid gland present with a solitary thyroid nodule in an otherwise normal thyroid gland. However, both may occur in association with thyroiditis and/or nodular hyperplasia. Most patients are euthyroid and asymptomatic. Patients with larger tumors may present with dyspnea, coughing or choking spells, hoarseness, or dysphagia as a result of compression of the trachea, recurrent laryngeal nerve, or esophagus. They may complain of neck pain as a result of sudden tumor enlargement from intratumoral hemorrhage or cystic degeneration. Rare patients may present with hyperthyroidism.

Patients with a follicular adenoma or a follicular carcinoma usually present with a thyroid nodule that is palpable on physical examination or identified on an imaging study. Palpable thyroid nodules occur in 4%–7% of the population and up to 60%–70% will have a nonpalpable nodule that can be identified by imaging the thyroid gland with ultrasound [30–32]. It has been estimated that ~10–20 million Americans have clinically detectable thyroid nodules at any given time [33]. Patients with follicular carcinoma may rarely present with lung or bone metastases identified on an imaging study.

Diagnostic Evaluation

The diagnostic evaluation of a patient who presents with a thyroid nodule consists of a routine fine needle aspiration biopsy, an ultrasound examination of the neck, and a screening serum TSH level. Fine needle aspiration biopsy remains the most important diagnostic modality for evaluating patients with a thyroid nodule. A major limitation of fine needle aspiration biopsy, however, is the inability to distinguish a follicular adenoma from a follicular carcinoma.

Fine needle aspiration biopsy in patients with a follicular adenoma and patients with a follicular carcinoma is characterized by abundant follicular epithelial cells in sheets with crowding and overlapping of cells, microfollicle formation, and scant or no colloid [3, 34]. According to the Bethesda system for reporting thyroid cytopathology, this cytologic appearance is classified as follicular neoplasm or suspicious for follicular neoplasm. A fine needle aspiration biopsy specimen consistent with a follicular neoplasm accounts for ~20% of all fine needle aspiration biopsy results [35–37] and has a 15%–30% risk of malignancy [34]. The differential diagnosis for a patient with a thyroid nodule and a fine needle aspiration biopsy result consistent with a follicular neoplasm is a follicular adenoma, adenomatous hyperplasia, follicular carcinoma, follicular variant of papillary carcinoma, and classic papillary

carcinoma. Cytomorphologic criteria alone cannot distinguish a follicular adenoma from a follicular carcinoma.

Some patients with a follicular adenoma or follicular carcinoma have a fine needle aspiration biopsy specimen that consists of follicular cells with abnormal architecture and atypia that is more significant than usually seen with benign lesions but not sufficient enough to call it a follicular neoplasm. According to the Bethesda classification system, these patients are categorized as having "atypia of undetermined significance" or "follicular lesion of undetermined significance." This cytologic category is associated with a 5%–15% risk of malignancy and normally warrants repeat fine needle aspiration biopsy [34]. The management of patients with this fine needle aspiration biopsy result may also be dependent on other clinical and sonographic factors.

An ultrasound examination of the thyroid gland is recommended in all patients with a thyroid nodule to help characterize the nodule as well as to examine the rest of the thyroid gland for other nodules. Sonographic features that are associated with a higher risk of malignancy include hypoechogenicity, punctuate microcalcifications, indistinct or irregular margins, absent halo sign, a nodule that is taller than it is wide, and an increased intranodular blood flow. Sonographic features alone cannot distinguish a follicular adenoma from a carcinoma. However, recent studies using duplex Doppler ultrasonography have demonstrated that the assessment of blood flow in a follicular neoplasm is associated with a 96% negative predictive value but only a 15% positive predictive value for carcinoma [38]. The absence of intranodular blood flow in a follicular neoplasm makes it unlikely to be a carcinoma. In a patient with a follicular neoplasm, ultrasound demonstration of nodular disease in the contralateral lobe has important implications for operative management.

All patients with nodular thyroid disease should have a serum TSH level measured to evaluate the functional status of the thyroid gland. A low serum TSH level suggests the possibility of a "toxic adenoma." In these patients, a free thyroxine and a free triiodothyronine level should be measured and an iodine-123 thyroid scan should be obtained to distinguish a hyperfunctioning nodule from a hypofunctioning nodule. In patients with a fine needle aspiration biopsy consistent with a follicular neoplasm, the incidence of malignancy with a hyperfunctioning nodule is $<1\%$, compared with 20% with a hypofunctioning nodule [39].

Recently, molecular testing for genetic mutations has been investigated to help improve the accuracy of thyroid fine needle aspiration biopsy. Nikiforov and colleagues reported the results of a large prospective study testing for a panel of mutations in preoperative fine needle aspiration biopsy specimens obtained for assessment of thyroid nodules. Their results revealed that molecular testing of thyroid nodules for a panel of mutations can be effectively performed in a clinical setting and that its combination with cytology produced a significant improvement in diagnostic accuracy. The presence of any mutation was a strong indicator of malignancy, with 31 of 32 (97%) mutation positive nodules found to be malignant after surgery. Despite a specificity of 99.7%, the sensitivity of molecular testing alone was only 62%. A RAS mutation conferred an 87% probability of malignancy, justifying a recommendation for surgery in all patients with RAS positive nodules [40].

Moses and colleagues reported that genetic testing for common somatic genetic alterations was feasible in a fine needle aspiration biopsy specimen, and in patients with an indeterminate or suspicious fine needle aspiration biopsy result, positive genetic testing could allow for definitive total thyroidectomy. However, the negative predictive value is too low to reduce the need for diagnostic thyroidectomy [41].

Detection of circulating tumor cells in the blood using a reverse transcriptase-polymerase reaction for TSH receptor and thyroglobulin messenger RNA may help differentiate follicular adenoma from follicular carcinoma. TSH receptor and thyroglobulin mRNA transcripts found in the peripheral blood have been reported to be sensitive and specific for thyroid cancer [42]. Milas and colleagues reported that a preoperative TSH receptor mRNA $>$ 1 ng/ug in patients with a follicular neoplasm or suspicious cytology had a 96% predictive value for carcinoma and an undetectable level with no abnormal sonographic features had a 95% predictive value for benign disease [43]. Sato and colleagues reported that detection of carcinoembryonic antigen mRNA in the blood was useful in differentiating follicular adenoma from follicular carcinoma [44].

Because fine needle aspiration biopsy has been unable to distinguish a benign follicular adenoma from a follicular carcinoma, considerable effort has been given to try to identify clinical factors for their potential in predicting carcinoma and determining the extent of thyroidectomy. We have previously reported that, in patients with an indeterminate fine needle aspiration biopsy, there was no significant difference in age, gender, nodule size, or cytologic atypia in patients with or without carcinoma [37, 45]. In patients with a fine needle aspiration biopsy consistent with a follicular neoplasm, clinical factors, except for a prior history of head or neck radiation, do not affect preoperative or intraoperative decision-making.

Treatment of a Patient with a Follicular Neoplasm

A patient with a fine needle aspiration biopsy consistent with a follicular neoplasm should, at minimum, undergo a

diagnostic thyroid lobectomy and isthmusectomy. Patients with a follicular neoplasm and a prior history of head or neck radiation or nodular disease involving the contralateral lobe of the thyroid gland should be treated with a definitive total thyroidectomy. Frozen section examination has not been helpful for intraoperative decision-making because it rarely distinguishes a follicular adenoma from a follicular carcinoma. This has been confirmed by a randomized clinical trial [46].

The sensitivity, specificity, and accuracy of frozen-section examination are similar to fine needle aspiration biopsy, and frozen-section examination rarely provides any additional information in patients with a fine needle aspiration biopsy consistent with a follicular neoplasm [47]. In 95% of patients with a follicular neoplasm, the frozen-section exam diagnosis that is rendered at operation is "consistent with a follicular neoplasm" and a definitive diagnosis is deferred until all of the permanent sections have been reviewed [47]. Chen and colleagues reported that, in patients with a follicular neoplasm, frozen-section exam rendered no useful information in 87% and was inaccurate in 5% [48].

The assessment of capsular invasion by frozen-section examination can be extremely difficult, particularly with an irregular capsule of variable thickness [47, 49, 50]. Frozen-section diagnosis of vascular invasion is difficult related to vessel distortion and collapse and sectioning artifact, which can "drag" tumor cells into thyroid vessels and give the appearance of vascular invasion [50, 51]. The diagnosis of capsular and vascular invasion can be very subjective and often dependent on the expertise of the pathologist. Franc and colleagues reported that the interobserver agreement for diagnosis of capsular invasion and vascular invasion was only 27% and 20%, respectively [52]. Frozen-section examination for assessment of both capsular and vascular invasion is also limited by sampling error. It requires multiple sections through the nodule capsule interface to adequately assess for capsular and vascular invasion. The use of immunohistochemical techniques to identify PAX8/PPARγ mutation in frozen-section specimens from patients with a follicular neoplasm has been investigated with a reported increase in sensitivity from 84% to 96% but a decrease in the specificity from 100% to 90% [53]. To date, the immunohistochemical techniques are too time-consuming for intraoperative use.

Thyroid lobectomy and isthmusectomy is definitive treatment for patients with a benign follicular adenoma and patients with minimally invasive follicular cancer. Invasive follicular carcinoma is a more aggressive tumor with a propensity for systemic metastases and a worse prognosis. Patients with invasive follicular carcinoma are treated with a total thyroidectomy. Prophylactic central neck dissection is not a consideration in patients with follicular carcinoma because $<10\%$ will have lymph node metastases. Central and modified neck dissections are reserved for patients with abnormal lymph nodes and biopsy confirmation of metastatic disease. Completion thyroidectomy is preferably performed within the first week of initial surgery or 3 months later to avoid operation during the period of maximal scarring. Delay in performing completion thyroidectomy beyond 6 months following initial thyroidectomy may be associated with a higher risk of metastases and reduced survival [54].

Patients with a solitary toxic nodule, which is most often a functioning follicular adenoma, may be treated with iodine-131 therapy or unilateral thyroid lobectomy. The advantages of surgical therapy are immediate resolution of hyperthyroidism and compressive symptoms, avoidance of radiation exposure to the normal thyroid tissue, removal of the nodule, and treatment of rare cases of carcinoma. Persistent or recurrent hyperthyroidism is uncommon. The incidence of hypothyroidism is low with a reported rate of 14% compared with 22% for radioiodine therapy [55, 56].

Postoperative Follow-Up

Numerous systems have been developed to stratify patients with differentiated thyroid cancer into risk groups. The most important prognostic factors are the age of the patient, tumor size, extent of the tumor, and the presence of distant metastases. Seventy to 85% of patients are at low risk for recurrence and mortality, and as a result their postoperative management and follow-up does not need to be as aggressive as in patients with high-risk cancer. Low-risk follicular cancer is defined as a well or moderately differentiated tumor <4 cm in size that is confined to the thyroid gland without metastases in a patient <45 years of age. High-risk follicular cancer is defined by a poorly differentiated tumor, tumor size >4 cm, extrathyroidal tumor spread, distant metastases, or patient age of 45 years or older.

Patients with a final diagnosis of follicular adenoma or minimally invasive follicular carcinoma require no additional therapy. Thyrotropin-suppressive doses of thyroid hormone are unnecessary. Thyroid hormone is only given for treatment of hypothyroidism, which occurs in one third of patients following thyroid lobectomy [57]. A serum TSH level is obtained 4–6 weeks after surgery to assess for hypothyroidism. Radioiodine ablation and whole-body scanning are not indicated for minimally invasive follicular carcinoma. A yearly neck examination, cervical ultrasound exam, and a screening serum TSH level are recommended for follow-up.

Postoperatively, patients with invasive follicular carci-

noma are treated with 30 mCi iodine-131 as an outpatient to destroy residual thyroid tissue or microscopic malignancy. A whole-body scan is recommended following ablation for identification of metastatic disease. A 30 mCi dose of iodine-131 is successful in ablating residual normal thyroid tissue in 80% of patients [58]. An additional 30 mCi dose of iodine-131 may be given 6–12 months later in the 20% of patients in whom the first dose is not successful in ablating the residual thyroid tissue. Radioiodine ablation reduces the risk of recurrence. It also eliminates normal thyroid tissue as a source for thyroglobulin and iodine uptake, enhancing the sensitivity of serum thyroglobulin monitoring and iodine whole-body scanning for detection of recurrent disease.

Patients with invasive follicular carcinoma are treated with thyroid hormone to prevent TSH-induced growth of residual cancer cells and reduce recurrence. In patients with low-risk follicular cancer who are free of disease, serum TSH levels are maintained between 0.3 and 2.0 uIU/ml. In patients with high-risk follicular carcinoma, serum TSH levels are maintained between 0.1 and 0.5 uIU/ml. In patients with persistent or metastatic disease, serum TSH levels are maintained < 0.1 uIU/ml [59].

An estimated 11%–39% of patients with follicular carcinoma will develop recurrent disease [6, 60–64]. Recurrent thyroid cancer most commonly develops within the first two years after surgical therapy. As a result, patients with invasive follicular carcinoma are followed with history, physical examination, and serum TSH, thyroglobulin, and antithyroglobulin antibody levels at 3–6 month intervals for the first two years and then yearly thereafter. Cervical ultrasound is performed at 6 and 12 months after surgery and yearly thereafter for 3–5 years depending on the patient's risk for recurrent disease and results of thyroglobulin monitoring [59]. A TSH-stimulated thyroglobulin level obtained after withdrawal of thyroid hormone or after administration of recombinant human TSH is obtained one year following radioiodine ablation to establish the absence of residual disease [59]. For patients who are found to be free of disease, unstimulated serum thyroglobulin levels are followed. An unstimulated thyroglobulin level above 2 ng/ml that increases over time may be indicative of recurrent disease, and a repeat TSH-stimulated thyroglobulin level is obtained.

Routine iodine whole-body scanning is unnecessary for patients without clinical evidence of disease who have an undetectable serum thyroglobulin level, a negative ultrasound of the neck, and a prior negative iodine whole-body scan. Repeat whole-body scanning is obtained when a patient has an elevated serum thyroglobulin level and a negative cervical ultrasound. Computed tomography (CT) of the head, neck, and chest; magnetic resonance imaging (MRI) of the spine, pelvis, and femurs; and positron emission tomographic imaging with 18 fluorodeoxyglucose (FDG-PET) are reserved for patients with elevated thyroglobulin levels, a negative ultrasound of the neck, and a negative iodine-131 whole-body scan. Thin-cut or spiral CT is the best imaging modality for identifying pulmonary metastases. MRI is the best modality for identifying bone metastases. FDG-PET imaging has both a diagnostic and prognostic role. FDG-PET positive lesions are associated with a worse prognosis.

Treatment of Local Recurrence and Metastatic Disease

Surgical resection with tumor-free margins is the mainstay of therapy for local recurrence along with removal of any remaining thyroid tissue. Macroscopic lymph node metastases in the central neck are treated with a central neck dissection, which entails removal of all fibrofatty and nodal tissue between the common carotid arteries from the hyoid bone superiorly to the innominate artery inferiorly. Macroscopic lymph node metastases in the lateral neck are treated by a modified neck dissection, which involves removal of all nodal and fibrofatty tissue from levels II–V in the neck. This includes the upper, mid, and lower cervical, the posterior cervical, and the supraclavicular lymph nodes. Macroscopic metastases that are isolated to the lung, bone, or brain that can be resected result in improved survival [59].

Surgery also has a role in patients with metastases involving the vertebral bodies or long bones to prevent fractures and for palliation of neurologic sequelae. Bone metastases are most often osteolytic and most commonly occur in the vertebral bodies followed by the pelvis, femur, skull, and ribs. Patients with vertebral body metastases and neurologic symptoms from vertebral collapse or tumor compression are candidates for spine stabilization with tumor resection or percutaneous vertebroplasty [64]. Surgery may also be indicated for severe pain refractory to medical therapy and for metastases that do not concentrate radioiodine.

Microscopic metastases are treated with high doses of radioiodine. Metastases from follicular carcinoma will concentrate radioiodine in 75% of patients [58]. A 150 mCi dose of iodine-131 is used for treatment of microscopic lymph node metastases. A 200 mCi dose of iodine-131 is used for treatment of systemic metastases. Radioiodine therapy is most effective for micronodular pulmonary metastases that are detected on iodine-131 whole-body imaging in young patients with a normal chest x-ray. Multiple doses are often required for treatment of micronodular pulmonary metastases with a reported 10-year survival rate of

90%, and it can be curative in 35%–45% of patients [66]. Macronodular pulmonary metastases that are identified on chest x-ray are less responsive to radioiodine therapy, and the 10-year patient survival is only 11% [66].

Bone metastases are less likely to concentrate radioiodine and are associated with a worse prognosis than pulmonary metastases. High-dose radioiodine is used for treatment of bone metastases that concentrate radioiodine. Patients are rarely cured but they may experience a partial tumor response or stabilization of disease with symptomatic improvement. It is estimated that iodine-131 therapy is effective in only 55% of patients and only 17% of patients develop a remission [67, 68]. External radiation therapy may be used for palliation of bone pain and control of tumor growth of metastases that do not take up radioiodine. Periodic intravenous infusions of bisphosphonate drugs may help reduce pain, pathologic fractures, and progression of bone metastases. Patients with asymptomatic bone metastases that do not concentrate radioiodine can be treated with levothyroxine therapy alone with appropriate monitoring. In contrast to patients with differentiated thyroid carcinoma and isolated pulmonary metastases who have an overall 54% and 49% 10- and 20-year survival, the 10- and 20-year survival for patients with bone metastases is 12% and 8%, respectively [67].

Brain metastases account for $<1\%$ of the systemic metastases from follicular carcinoma. They are associated with a poor prognosis with a median survival of only 1 year. When surgical resection is not an option, external radiation can be used for palliation. Radioiodine therapy can be problematic because of the potential to cause cerebral edema. Corticosteroid therapy is given to help prevent development of cerebral edema. Consideration should be given to using investigational therapy with a tyrosine kinase inhibitor such as sorafenib or sunitinib for patients with progressive radioiodine-resistant metastatic disease or entering them into a clinical trial [69].

Outcome

Shaha reported an overall survival at 5, 10, and 20 years for patients with follicular thyroid cancer of 85%, 80%, and 76%, respectively [36]. When patients with follicular carcinoma were divided into low-, intermediate-, and high-risk groups based on age, T stage, distant metastases, histologic type, and grade, their survival rates were 98%, 88%, and 56% at 10 years and 97%, 87%, and 49% at 20 years, respectively. D'Avanzo and colleagues reported that patients with minimally invasive follicular carcinoma have a 98% 10-year survival, compared with 80% at 10 years for patients with angioinvasive follicular carcinoma with or without capsular invasion and 38% with extensive invasion of the tumor capsule and the thyroid parenchyma [4]. The cause of death is most commonly from progression of distant metastases [70].

Author Contributions

Conception/Design: Christopher R. McHenry
Provision of study materials or patients: Christopher R. McHenry, Roy Phitayakorn
Collection and/or assembly of data: Christopher R. McHenry, Roy Phitayakorn
Data analysis and interpretation: Christopher R. McHenry
Manuscript writing: Christopher R. McHenry, Roy Phitayakorn
Final approval of manuscript: Christopher R. McHenry

References

1 Silverberg SG, Vidone RA. Adenoma and carcinoma of the thyroid. Cancer 1966;19:1053–1062.

2 Bisi H, Fernandes VS, de Camargo RY et al. The prevalence of unsuspected thyroid pathology in 300 sequential autopsies, with special reference to the incidental carcinoma. Cancer 1989;64:1888–1893.

3 Rosai J, Carcangiu ML, DeLellis RA. Tumors of the thyroid gland. In: Atlas of tumor pathology, 3rd series, fas 5. Washington, DC: Armed Forces Institute of Pathology, 1992:21–48.

4 D'Avanzo A, Treseler P, Ituarte PH et al. Follicular thyroid carcinoma: Histology and prognosis. Cancer 2004;100:1123–1129.

5 Collini P, Sampietro G, Rosai J et al. Minimally invasive (encapsulated) follicular carcinoma of the thyroid gland is the low-risk counterpart of widely invasive follicular carcinoma but not of insular carcinoma. Virchows Arch 2003;442:71–76.

6 van Heerden JA, Hay ID, Goellner JR et al. Follicular thyroid carcinoma with capsular invasion alone: a nonthreatening malignancy. Surgery 1992; 112:1130–1136, discussion 1136–1138.

7 Sanders LE, Silverman M. Follicular and hurthle cell carcinoma: predicting outcome and directing therapy. Surgery 1998;124:967–974.

8 Serra S, Asa SL. Controversies in thyroid pathology: the diagnosis of follicular neoplasms. Endocr Pathol 2008;19:156–165.

9 Correa P, Chen VW. Endocrine gland cancer. Cancer 1995;75:338–352.

10 LiVolsi VA. Pure versus follicular variant of papillary thyroid carcinoma: clinical features, prognostic factors, treatment, and survival. Cancer 2003; 98:1997; author reply 1997–1998.

11 Phitayakorn R, McHenry CR. Follicular and Hurthle cell carcinoma of the thyroid gland. Surg Oncol Clin N Am 2006;15:603–623, ix–x.

12 Pettersson B, Adami HO, Wilander E et al. Trends in thyroid cancer incidence in Sweden, 1958–1981, by histopathologic type. Int J Cancer 1991; 48:28–33.

13 Grebe SK, Hay ID. Follicular thyroid cancer. Endocrinol Metab Clin North Am 1995;24:761–801.

14 Burgess JR, Dwyer T, McArdle K et al. The changing incidence and spectrum of thyroid carcinoma in Tasmania (1978–1998) during a transition from iodine sufficiency to iodine deficiency. J Clin Endocrinol Metab 2000;85:1513–1517.

15 Nikiforova MN, Lynch RA, Biddinger PW et al. Ras point mutations and pax8-ppar gamma rearrangement in thyroid tumors: evidence for distinct

molecular pathways in thyroid follicular carcinoma. J Clin Endocrinol Metab 2003;88:2318–2326.

16 Downward J. Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer 2003;3:11–22.

17 Medema RH, Bos JL. The role of p21ras in receptor tyrosine kinase signaling. Crit Rev Oncog 1993;4:615–661.

18 Kato MA, Fahey TJ 3rd. Molecular markers in thyroid cancer diagnostics. Surg Clin North Am 2009;89:1139–1155.

19 Martelli ML, Iuliano R, Le Pera I et al. Inhibitory effects of peroxisome poliferator-activated receptor gamma on thyroid carcinoma cell growth. J Clin Endocrinol Metab 2002;87:4728–4735.

20 Weber F, Teresi RE, Broelsch CE et al. A limited set of human MicroRNA is deregulated in follicular thyroid carcinoma. J Clin Endocrinol Metab 2006;91:3584–3591.

21 Wu G, Mambo E, Guo Z et al. Uncommon mutation, but common amplifications, of the PIK3CA gene in thyroid tumors. J Clin Endocrinol Metab 2005;90:4688–4693.

22 Führer D, Tannapfel A, Sabri O et al. Two somatic TSH receptor mutations in a patient with toxic metastasising follicular thyroid carcinoma and nonfunctional lung metastases. Endocr Relat Cancer 2003;10:591–600.

23 Nikiforov YE. Genetic alterations involved in the transition from well-differentiated to poorly differentiated and anaplastic thyroid carcinomas. Endocr Pathol 2004;15:319–327.

24 Rastad JKF. Surgical management of Graves' disease: prospective preparation and extent of surgery. Problems Gen Surg 1997;14:132–154.

25 Castro P, Eknaes M, Teixeira MR et al. Adenomas and follicular carcinomas of the thyroid display two major patterns of chromosomal changes. J Pathol 2005;206:305–311.

26 Plummer HS. The clinical and pathologic relationships of hyperplastic and nonhyperplastic goiter. J Am Med Assoc 1913;61:650–651.

27 Marques AR, Espadinha C, Catarino AL et al. Expression of PAC8-PPAR gamma 1 rearrangements in both follicular thyroid carcinomas and adenomas. J Clin Endocrinol Metab 2002;87:3947–3952.

28 Kondo T, Ezzat S, Asa SL. Pathogenetic mechanisms in thyroid follicular-cell neoplasia. Nat Rev Cancer 2006;6:292–306.

29 Challeton C, Bounacer A, Du Villard JA et al. Pattern of ras and gsp oncogene mutations in radiation-associated human thyroid tumors. Oncogene 1995;11:601–603.

30 Ezzat S, Sarti DA, Cain DR et al. Thyroid incidentalomas. Prevalence by palpation and ultrasonography. Arch Intern Med 1994;154:1838–1840.

31 Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 1997;126:226–231.

32 Deandrea M, Mormile A, Veglio M et al. Fine-needle aspiration biopsy of the thyroid: Comparison between thyroid palpation and ultrasonography. Endocr Pract 2002;8:282–286.

33 Cramer H. Fine-needle aspiration cytology of the thyroid: an appraisal. Cancer 2000;90:325–329.

34 Ali SZ CE: The Bethesda system for reporting thyroid cytopathology. Definitions, criteria and explanatory notes. New York: Springer Science + Business Media, 2010.

35 Gharib H, Papini E, Paschke R. Thyroid nodules: a review of current guidelines, practices, and prospects. Eur J Endocrinol 2008;159:493–505.

36 Shaha AR. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. Laryngoscope 2004;114:393–402.

37 McHenry CR, Thomas SR, Slusarczyk SJ et al. Follicular or Hurthle cell neoplasm of the thyroid: can clinical factors be used to predict carcinoma and determine extent of thyroidectomy? Surgery 1999;126:798–802, discussion 802–794.

38 Iared W, Shigueoka DC, Cristofoli JC et al. Use of color Doppler ultrasonography for the prediction of malignancy in follicular thyroid neoplasms: systematic review and meta-analysis. J Ultrasound Med 2010;29:419–425.

39 McHenry CR, Slusarczyk SJ, Askari AT et al. Refined use of scintigraphy in the evaluation of nodular thyroid disease. Surgery 1998;124:656–661, discussion 661–652.

40 Nikiforov YE, Steward DL, Robinson-Smith TM et al. Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules. J Clin Endocrinol Metab 2009;94:2092–2098.

41 Moses W, Weng J, Sansano I et al. Molecular testing for somatic mutations improves the accuracy of thyroid fine-needle aspiration biopsy. World J Surg 2010;34:2589–2594.

42 Chiappetta G, Pentimalli F, Monaco M et al. Thymosin beta-10 gene expression as a possible tool in diagnosis of thyroid neoplasias. Oncol Rep 2004;12:239–243.

43 Milas M, Shin J, Gupta M et al. Circulating thyrotropin receptor mRNA as a novel marker of thyroid cancer: clinical applications learned from 1758 samples. Ann Surg 2010;252:643–651.

44 Sato T, Nakano S, Yamashita J. Carcinoembryonic antigen mRNA in blood: distinguishing follicular thyroid carcinoma from adenoma. Thyroid 2003;13:891–892.

45 McHenry CR, Huh ES, Machekano RN. Is nodule size independent predictor of thyroid malignancy? Surgery 2008;144:1062–1069.

46 Udelsman R, Westra WH, Donovan PI et al. Randomized prospective evaluation of frozen-section analysis for follicular neoplasms of the thyroid. Ann Surg 2001;233:716–722.

47 McHenry CR, Raeburn C, Strickland T et al. The utility of routine frozen section examination for intraoperative diagnosis of thyroid cancer. Am J Surg 1996;172:658–661.

48 Chen H, Nicol TL, Udelsman R. Follicular lesions of the thyroid. Does frozen section evaluation alter operative management? Ann Surg 1995;222:101–106.

49 Kraemer BB. Frozen section diagnosis and the thyroid. Semin Diagn Pathol 1987;4:169–189.

50 Franssila KO, Ackerman LV, Brown CL et al. Follicular carcinoma. Semin Diagn Pathol 1985;2:101–122.

51 Ghossein R. Problems and controversies in the histopathology of thyroid carcinomas of follicular cell origin. Arch Pathol Lab Med 2009;133:683–691.

52 Franc B, de la Salmoniere P, Lange F et al. Interobserver and intraobserver reproducibility in the histopathology of follicular thyroid carcinoma. Hum Pathol 2003;34:1092–1100.

53 Sahin M, Allard BL, Yates M et al. PPARgamma staining as a surrogate for PAX8/PPARgamma fusion oncogene expression in follicular neoplasms: clinicopathological correlation and histopathological diagnostic value. J Clin Endocrinol Metab 2005;90:463–468.

54 Scheumann GF, Seeliger H, Musholt TJ et al. Completion thyroidectomy in 131 patients with differentiated thyroid carcinoma. Eur J Surg 1996;162:677–684.

55 Miccoli P, Minuto MN, Galleri D et al. Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. ANZ J Surg 2006;76:123–126.

56 Eyre-Brook IA, Talbot CH. The treatment of autonomous functioning thyroid nodules. Br J Surg 1982;69:577–579.

57 McHenry CR, Slusarczyk SJ. Hypothyroidism following hemithyroidectomy: incidence, risk factors and management. Surgery 2000;128:994–998.

58 Maxon HR 3rd, Smith HS. Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer. Endocrinol Metab Clin North Am 1990;19:685–718.

59 Cooper DS, Doherty GM, Haugen BR et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–1214.

60 DeGroot LJ, Kaplan EL, Shukla MS et al. Morbidity and mortality in follicular thyroid cancer. J Clin Endocrinol Metab 1995;80:2946–2953.

61 Tsang RW, Brierley JD, Simpson WJ et al. The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. Cancer 1998;82:375–388.

62 Witte J, Goretzki PE, Dieken J et al. Importance of lymph node metastases in follicular thyroid cancer. World J Surg 2002;26:1017–1022.

63 Chow SM, Law SC, Mendenhall WM et al. Follicular thyroid carcinoma: prognostic factors and the role of radioiodine. Cancer 2002;95:488–498.

64 Tzavara I, Vlassopoulou B, Alevizaki C et al. Differentiated thyroid cancer: a retrospective analysis of 832 cases from Greece. Clin Endocrinol (Oxf) 1999;50:643–654.

65 Kushchayev S, Kushchayeva Y, Theodore N et al. Percutaneous vertebroplasty for thyroid cancer metastases to the spine. Thyroid 2010;20:555–560.

66 Schlumberger M, Tubiana M, De Vathaire F et al. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. J Clin Endocrinol Metab 1986;63:960–967.

67 Durante C, Haddy N, Baudin E et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 2006;91:2892–2899.

68 Proye CA, Dromer DH, Carnaille BM et al. Is it still worthwhile to treat bone metastases from differentiated thyroid carcinoma with radioactive iodine? World J Surg 1992;16:640–645, discussion 645–646.

69 Cabanillas ME, Waguespack SG, Bronstein Y et al. Treatment with tyrosine kinase inhibitors for patients with differentiated thyroid cancer: the M. D. Anderson experience. J Clin Endocrinol Metab 2010;95:2588–2595.

70 Kitamura Y, Shimizu K, Nagahama M et al. Immediate causes of death in thyroid carcinoma: clinicopathological analysis of 161 fatal cases. J Clin Endocrinol Metab 1999;84:4043–4049.