Current Approaches to the Treatment of Well-Differentiated Thyroid Cancer

By Peter Angelos, MD, PhD

Most patients with well-differentiated thyroid cancer initially present with a thyroid nodule. The role of the primary care physician is critical at this stage, because the majority of patients are diagnosed only after a nodule is palpable on physical examination. Nevertheless, the increasing use of diagnostic imaging such as carotid duplex scanning and computed tomography (CT) scanning (for other reasons) has led to more frequent identification of thyroid nodules before they are palpable. Once a nodule is identified, the appropriate diagnostic work-up includes a careful history with attention to risk factors such as radiation exposure, previous thyroid cancer, or less commonly, family history of well-differentiated thyroid cancer.[2] Hoarseness or lymphadenopathy associated with a palpable thyroid mass is particularly suspicious for carcinoma. Numerous imaging modalities are available for evaluating thyroid nodules. In most instances, an ultrasound of the neck will provide accurate and detailed information about the nodule as well as the status of the remainder of the thyroid, including any possible lymphadenopathy in the cervical region. Increasingly, microcalcifications in association with a thyroid nodule have been identified as suspicious for papillary thyroid carcinoma.[3] Thyroid scintigraphy continues to be helpful if the functionality of a nodule is being questioned. CT scanning and magnetic resonance imaging (MRI) are generally less helpful in the initial evaluation. Positron-emission tomography (PET) scanning in conjunction with fluorine-18 fluorodeoxyglucose (FDG) has shown promise in identifying thyroid malignancies, but it is not yet clear what the most appropriate role for this imaging modality will be.[4,5]

Cytologic Evaluation

A diagnosis of well-differentiated thyroid cancer is often made preoperatively with the use of fine-needle aspiration (FNA) cytology. A diagnosis of papillary thyroid carcinoma is readily made on cytologic evaluation. The cells characteristically have enlarged nuclei with dense chromatin and,
frequently, intranuclear cytoplasmic inclusions. The cytologic diagnosis of follicular thyroid carcinoma is more problematic. The distinction between benign adenoma and malignant carcinoma for this type of tumor is not based primarily on cellular features, but rather, on the presence of capsular or vascular invasion.[6] In other words, the cells in a benign follicular adenoma and a malignant follicular carcinoma may be identical. The distinction between benign and malignant depends largely on where the cells are located. If there is no capsular or vascular invasion, then the lesion is considered benign.

The nature of this distinction often leads to an indeterminate cytologic evaluation, even when a follicular thyroid carcinoma has been aspirated. Such nodules are usually characterized as "follicular neoplasms," since benign lesions cannot be distinguished from malignant lesions on the basis of cytology alone. When the results of the aspiration are indefinite, and because the issue of capsular or vascular invasion cannot be determined no matter how many times the cells in a nodule are sampled, most physicians recommend at least a partial thyroidectomy (lobectomy or hemithyroidectomy). Only after the pathologist has completely evaluated the entire nodule for capsular and vascular invasion can such a tumor be categorized as a benign follicular adenoma.

**Hürthle Cell Neoplasm**

Follicular neoplasms can be further subcategorized into Hürthle cell neoplasms. These uncommon tumors consist of large acidophilic or oncocytic cells. Some authors have suggested that Hürthle cell carcinomas have a worse prognosis than the usual follicular carcinoma.[7,8] This finding may be related to the greater likelihood that Hürthle cell carcinomas are locally invasive and concentrate radioiodine less avidly.

**Surgical Treatment**

Surgical considerations in well-differentiated thyroid cancer are frequently complicated by the need to operate on patients with indeterminate nodules based on FNA. When a follicular or Hürthle cell neoplasm is the preoperative diagnosis, the surgeon should at least perform a total lobectomy of the involved side. Such an approach avoids the increased risk of complications to the parathyroids and nerves if a second operation is necessary.

Whether a patient initially undergoes a lobectomy or a total thyroidectomy for an indeterminate nodule has much to do with specific considerations of the individual patient and the preference of the surgeon. In patients with nodules in the other lobe, many surgeons favor a total thyroidectomy. If the nodule is large, a total thyroidectomy may also be favored because of the greater risk of vascular or capsular invasion with increasing size of the nodule.

**Type and Size of Neoplasm**

Among follicular neoplasms that are cold on nuclear medicine scanning, approximately 20% prove to be malignant.[9] In older patients and in those with nodules greater than 4.0 cm in diameter, the risk of malignancy is higher.[10] For this reason, many patients with follicular neoplasms greater than 4.0 cm in diameter are initially managed with a total thyroidectomy. Patient input is critical in deciding whether or not to perform a total thyroidectomy or lobectomy. If a lobectomy has been performed and the patient is diagnosed with follicular or Hürthle cell carcinoma postoperatively, then a return to the operating room for a completion total thyroidectomy is usually encouraged. The extent of surgery for optimal treatment of well-differentiated thyroid cancer, even when the diagnosis is known preoperatively, is controversial. For papillary thyroid carcinomas greater than 1.0 cm in diameter or with extension outside the thyroid capsule, angioinvasion, or involvement of lymph nodes, we favor total thyroidectomy with removal of any involved lymph nodes. Papillary thyroid cancers that are less than 1.0 cm in size and that do not have extension outside the thyroid capsule, angioinvasion, or spread into lymph nodes are generally referred to as "microcarcinomas" or "minimal papillary carcinomas."[11] In 100 consecutive autopsies from the University of Michigan, these small thyroid cancers had a prevalence of 13%. [12] They are associated with a low risk of progression or spread. Such minimal papillary carcinomas may be effectively treated with an ipsilateral thyroid lobectomy. Similarly, if a patient has undergone a thyroid lobectomy for any reason and a minimal papillary carcinoma is incidentally noted within the specimen, a completion total thyroidectomy is unnecessary.

For a patient with a follicular thyroid carcinoma, our practice is to perform a total thyroidectomy. When Hürthle cell carcinoma is suspected preoperatively, a more extensive lymph node dissection should be performed, because these tumors do not take up radioiodine well. When referring to well-differentiated thyroid cancer in the following pages, we will assume that the patient does not have "minimal papillary carcinoma," but rather, has more extensive disease.
Benefits of Total Thyroidectomy
Although other authors have argued in favor of thyroid lobectomy for most young patients with well-differentiated thyroid cancer,[13] a more extensive surgical approach has three primary benefits. First, if a total (or even near-total) thyroidectomy has been performed, radioactive iodine can be used to ablate any residual thyroid tissue in the neck or thyroid cancer cells in lymph nodes or elsewhere in the body. If an entire thyroid lobe is preserved in the patient, radioactive iodine cannot effectively be used to detect or treat spread outside the thyroid. Once a total thyroidectomy has been performed, the development of distant metastases (for tumors other than Hürthle cell carcinomas) can usually be identified and treated with iodine-131.

The second benefit is that once all thyroid tissue has been successfully eradicated, thyroglobulin levels can be used to follow patients for recurrence. This may be particularly important in patients with Hürthle cell carcinomas, because radioactive iodine cannot be used as an accurate means of identifying recurrent disease.

Third, in the patient with disease in both lobes, total thyroidectomy eliminates the risk of leaving a focus of carcinoma in the remaining lobe. The risk of bilateral lobar involvement of papillary thyroid cancer has been reported in 19% of patients in a large series from the Mayo Clinic, with 26% of patients having multifocal disease.[14,15]

If a patient undergoes a hemithyroidectomy and is subsequently found to have significant well-differentiated thyroid cancer within the specimen, completion total thyroidectomy should be performed, optimally within 2 weeks. Reoperation within this time frame minimizes the increased risk of complications associated with scarring near the parathyroids and nerves. If it is not possible to reoperate within this short period after the initial procedure, it is best to wait approximately 8 to 12 weeks to allow postoperative tissue changes from the initial procedure to resolve.

Surgical Steps
Patients are prepared for thyroidectomy in the same manner as for other procedures involving general anesthesia. All patients who have had previous neck operations, or any patient with a change in voice or hoarseness should undergo a preoperative examination of vocal cord function. The technical aspects of thyroidectomy involve making large subplatysmal flaps to allow a small skin incision to be moved up and down in the neck. Dissection on the side of the dominant nodule is performed first. The strap muscles can be effectively retracted and rarely need to be divided. After ligating and dividing the middle thyroid vein or veins (if present), the superior and inferior pole vessels are ligated at the level of the thyroid capsule. All tissue on the lateral aspect of the thyroid gland can then be carefully dissected off the thyroid capsule using sharp and blunt dissection. This approach minimizes the risk that the parathyroid glands will be injured or devascularized. The tubercle of Zuckerkandl is elevated from its position posterior to the recurrent laryngeal nerve. Branches of the inferior thyroid artery are individually ligated and divided, with care taken to identify and preserve the recurrent laryngeal nerve. No electrocautery is used in proximity to the nerve. The pyramidal lobe is identified and traced to its most cranial point. During this portion of the dissection, any Delphian lymph nodes situated over the cricothyroid membrane should be identified and removed. The same surgical steps are then repeated on the remaining lobe.[16]

If the surgeon is concerned that the recurrent laryngeal nerve or parathyroids have not been safely preserved on the first side of the dissection, a near-total lobectomy on the contralateral side from the dominant nodule may be performed to decrease the risk of hypoparathyroidism or bilateral nerve injury. This approach preserves the posterior capsule of the thyroid along with a small remnant of thyroid tissue (usually less than 1.0 g) in the region of the nerve and parathyroid glands. Alternatively, the surgeon may choose to perform an autotransplant of a parathyroid gland.

The extent of lymph node dissection in the management of well-differentiated thyroid cancer has been controversial. Certainly, at the time of the thyroidectomy, nodes in the central and lateral compartments should be carefully assessed for enlargement. There is general agreement that any abnormal lymph nodes found should be removed. Radical lymph node dissection is not indicated in the treatment of well-differentiated thyroid cancer, although the role of prophylactic lymph node dissection has also been controversial. At Northwestern University Medical School, we believe that all enlarged lymph nodes should be removed. As long as iodine-131 scanning is used postoperatively, however, prophylactic lymph node dissection may not have a role, because most cases of well-differentiated thyroid cancer will take up radioactive iodine.

Postoperative Management
After a total thyroidectomy, serum calcium levels should be checked in the first 24 hours because a small percentage of patients will require calcium supplementation. We have found that it is generally unnecessary to check calcium levels prior to 16 hours after surgery.[17] Although some surgeons...
recommend outpatient thyroidectomies, we believe that most patients should be discharged on the day after surgery. Even if all patients were sent home on calcium supplementation, the primary reason for keeping patients in the hospital overnight is that the rare patient may develop a potentially life-threatening neck hematoma. Recurrent laryngeal nerve injury or permanent hypoparathyroidism should be rare occurrences when the procedure is in the hands of an experienced thyroid surgeon. In most large series, the incidence of either of these complications is less than 2%.\[18-20\] In patients undergoing thyroid reoperation, the incidence of vocal cord paralysis or permanent hypoparathyroidism is increased and has been reported to range from 2% to 5%.\[21,22\]

**Radioisotope Therapies**

After surgery, the initial goal of medical management is to prepare the patient for radioactive iodine scanning. Different protocols for thyroid hormone replacement can be used to allow hypothyroidism to develop. One common approach is to delay use of levothyroxine after total thyroidectomy. Usually, within 4 to 6 weeks, thyroid-stimulating hormone (TSH) levels will rise to concentrations greater than 30 µIU/mL, which is considered adequate for stimulation of radioiodine uptake in metastatic lesions.\[23\]

Alternatively, patients may be treated with approximately 50 µg of oral triiodothyronine (25 µg bid). Because triiodothyronine has a shorter half-life, this hormone will be cleared from the body within 2 weeks. This approach shortens the period of hypothyroidism; it also shortens the period during which patients have elevated TSH levels that may stimulate some thyroid cancer cell growth. Prior to radioactive iodine scanning, patients should consume an iodine-deficient diet for at least 2 weeks.\[24\] Patients should also undergo tests to determine blood TSH level, thyroglobulin level, and antithyroglobulin antibody level, as well as a pregnancy test, if appropriate. An outpatient diagnostic whole-body scan can be used to measure the amount of uptake in the neck or elsewhere. Numerous investigators have raised the possibility that the diagnostic radioactive iodine scan may stun thyroid cancer cells so that their ability to concentrate iodine-131 in the therapeutic scan is diminished.\[25-27\] However, if small doses of radioiodine are used for the diagnostic scan, the stunning effect on cancer cells seems to be minimized.

The choice of whether to use radioactive iodine is another controversial one. Either on the basis of this diagnostic scan or the risk group the patient falls in, a therapeutic dose of iodine-131 (usually requiring an inpatient stay) is decided upon and administered. Some thyroid specialists favor giving approximately 30 mCi to low-risk patients with uptake only in the thyroid bed and 100-200 mCi to high-risk patients or those with tumor outside the thyroid bed. Other physicians believe that if radioiodine is to be used at all, a dose closer to 150 mCi should be used. We favor this latter approach, because the risks associated with a single such dose of radioiodine are low.

**Hormonal Management**

After radioactive iodine ablation, patients should be started on levothyroxine with the goal of suppressing TSH to less than 0.1 mIU/mL without associated hyperthyroidism. Many endocrinologists give triiodothyronine along with levothyroxine for several days after radioactive iodine, to return the patient to the euthyroid state more quickly. TSH levels should be checked approximately 6 weeks after initiating a dose of thyroid hormone and modifications in dosing made as needed based on these results.

Because only normal thyroid and well-differentiated thyroid cancer cells can make thyroglobulin, once a patient has undergone ablation therapy with radioactive iodine, thyroglobulin levels can be used to follow the patient for recurrence of cancer. Thyroglobulin production is stimulated by TSH. Consequently, the higher the TSH level, the higher the thyroglobulin level will be. Baseline levels of thyroglobulin are checked when the patient is hypothyroid prior to receiving radioactive iodine. In addition, antithyroglobulin antibody levels should be checked in all patients. As long as the patient does not have high levels of antithyroglobulin antibodies, the thyroglobulin level can be followed after radioactive iodine is administered. Should such levels rise, the patient can then be closely evaluated for recurrent disease. Because Hürthle cell carcinomas do not take up radioactive iodine well, the thyroglobulin level is the best means of following these patients for recurrence.

**Surveillance**

Surveillance of patients with a history of well-differentiated thyroid cancer includes a physical examination, monitoring of thyroglobulin and TSH levels, and repeat radioactive iodine scanning for
recurrence. Patients are usually rescanned a year after the initial radioactive iodine treatment so that any residual or recurrent disease can be detected and treated. Although recombinant human TSH (thyrotropin alfa [Thyrogen]) is commercially available, it has not been approved for the initial radioactive iodine scan or treatment after surgery. Recombinant TSH has been used effectively to prepare a patient for a follow-up diagnostic scan.[28,29] This approach avoids the need to withdraw the patient from levothyroxine prior to scanning. Once a patient has had a negative scan, further follow-up scans are not generally required, because thyroglobulin levels can be followed for recurrence.

Clinicians are faced with a dilemma when a rising thyroglobulin level suggests recurrent disease but the diagnostic radioiodine scans are negative. One should be certain that these thyroglobulin-positive, radioiodine scan-negative patients were not iodine-loaded prior to scanning, as this would suppress iodine uptake. Some investigators have found that the majority of patients with a truly negative diagnostic iodine-131 scan will actually have areas of uptake evident on scanning after being given a therapeutic dose of radioactive iodine.[30,31] Controversy surrounds whether therapeutic doses of radioactive iodine should be given to thyroglobulin-positive, scan-negative patients. Other imaging modalities including ultrasound studies of the neck or FDG-PET scanning of the body should be considered, as they may reveal sites of recurrent disease.[32]

Apart from patients with Hürthle cell carcinoma, few patients with well-differentiated thyroid cancer actually have tumors that do not take up radioactive iodine. When such tumors are found, they are more challenging to manage because radioactive iodine therapy is no longer a treatment option. These tumors are thought to be less differentiated and, therefore, less able to take up radiiodine. Some investigators have suggested that treatment with retinoic acid may "redifferentiate" the tumor so that it will regain its iodide-trapping ability.[33,34] Despite apparent successes with this approach in small numbers of patients, further study is necessary to determine whether such a strategy should be more widely recommended.

Special Considerations

Recurrence
Few patients treated with total thyroidectomy, radioiodine ablation, and TSH suppression with levothyroxine will develop recurrent papillary thyroid cancer. When recurrences do develop, they most commonly manifest as lymph node metastases. Less commonly, recurrences are seen in the thyroid bed itself. Palpable disease should be treated surgically whenever possible. Patients in whom no tumor can be identified, even on ultrasound, FDG-PET scanning, and MRI, are best treated with radioiodine. That said, few patients with recurrent papillary thyroid carcinoma will have a recurrence that is inoperable. Approximately a quarter of these patients with recurrent, inoperable, papillary thyroid carcinoma will be unable to concentrate radioiodine. Some will respond to redifferentiation therapy with retinoic acid, as discussed above. Consideration should also be given to the use of external-beam radiation therapy for selected patients.[35]

Pediatric Patients
Well-differentiated thyroid cancer is rarely diagnosed in children. Among pediatric patients in whom the disease is found, many will have extensive nodal disease at the time of diagnosis. In fact, 30% to 70% of children with well-differentiated thyroid cancer present with lymphadenopathy.[36,37] The approach to management of this disease in the pediatric population is not significantly different from that in the adult. Total or near-total thyroidectomy by an experienced endocrine surgeon with removal of involved lymph nodes is the optimal initial step in treatment.[38] The argument against lobectomy alone for the treatment of well-differentiated thyroid cancer is stronger in the pediatric population because of the higher incidence of multifocal disease in this age group. Indeed, 30% to 40% of children and adolescents diagnosed with well-differentiated thyroid cancer have multiple foci of disease.[39] Radioactive iodine ablation should be used, and patients should be treated with levothyroxine to ensure long-term suppression of TSH.

Pregnant Patients
Occasionally, patients are diagnosed with well-differentiated thyroid cancer during pregnancy. In such situations, total thyroidectomy is best performed during the second trimester. The surgeon should attempt to remove any involved lymph nodes, because radioiodine cannot be safely administered during or immediately after the pregnancy. After surgery, patients are started on replacement doses of levothyroxine, and TSH levels are closely monitored throughout the remainder
of the pregnancy. Radioactive iodine ablative therapy should be delayed until after the delivery and after lactation has ended, when the woman’s breasts have returned to normal.

**Risk Group Classification**

The majority of patients diagnosed with well-differentiated thyroid cancer have an excellent prognosis.[40] In an attempt to predict which patients are at higher risk for a poor prognosis, several classification systems have been proposed.[41] The most basic risk classification can be made on the basis of age and gender. All patients less than 45 years old at the time of diagnosis of papillary thyroid carcinoma are considered low-risk unless distant metastases are present. All older patients are considered high-risk. More complex postoperative risk classification systems have also been proposed: AGES (age, grade, extent, size); AMES (age, metastases, extent, size); and MACIS (metastases, age, completeness of surgery, invasion of cancer, size).[42-44] The most complex of these, the MACIS system, defines a prognostic score as follows:

\[
\text{MACIS} = 3.1 \text{ (if age} \leq 39 \text{ years)} \\
\text{or } 0.08 \times \text{age (if age} \geq 40 \text{ years)} \\
+ 0.3 \times \text{tumor size (in centimeters)} \\
+ 1 \text{ (if incompletely resected)} \\
+ 1 \text{ (if extrathyroidal invasion)} \\
+ 3 \text{ (if distant metastases present)}
\]

Four risk groups are defined on the basis of the MACIS score: < 6.0, 6.0-6.9, 7.0-7.9, \geq 8.0. Patients with a score < 6.0 are in the low-risk group. Hay and colleagues reported that approximately 84% of papillary thyroid carcinomas from the Mayo Clinic series fall into this low-risk group.[45] The 20-year cause-specific survival rates for patients with MACIS scores < 6.0, 6.0-6.99, 7.0-7.99, and \geq 8.0 were 99%, 89%, 56%, and 24%, respectively. The recurrence rate was significantly lower in patients in all groups who had bilateral surgery, and survival was better in high-risk patients who underwent bilateral procedures.

**Conclusions**

Patients with well-differentiated thyroid cancer can be readily diagnosed and effectively treated. In order to ensure that these patients have an optimal prognosis, all physicians involved in their care must continue to pursue aggressive means of diagnosis and treatment. The contemporary management of this disease truly requires a multidisciplinary approach.

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