Surgical Management of Thyroid Carcinoma

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Abstract
Thyroid carcinoma has a unique biologic behavior characterized by early spread to regional lymph nodes and occasional extrathyroidal soft tissue extension but a low incidence of distant metastasis and infrequent disease-related death. Therefore, controversy exists over the proper extent of thyroidectomy and regional lymph node dissection in patients with differentiated thyroid carcinoma (DTC) and medullary thyroid carcinoma (MTC). The modest disease-specific mortality makes it unlikely that the extent of surgery will ever be the subject of a prospective randomized trial. Although more extensive cervical surgery may have only a limited effect on the duration of survival in patients with DTC, it may significantly improve quality of life by minimizing cervical recurrence. The high rates of cervical recurrence in patients with DTC and MTC have alerted physicians to the importance of fine-needle aspiration biopsy and ultrasonography for the diagnosis, preoperative staging, and follow-up of thyroid cancer. In patients with MTC, death caused by disease is uncommon in the absence of radiographically evident distant metastasis at the time of thyroidectomy. Cervical recurrence is even more common with MTC, and the need for compartment-oriented lymphadenectomy is accepted as standard surgical treatment to minimize disease recurrence. Postoperatively, calcitonin (CT) levels can be used to guide clinical management, but basal CT levels should not be used to direct the timing of prophylactic thyroidectomy in affected high-risk patients with familial MTC. (JNCCN 2005;3:458–466)

The incidence of thyroid cancer has been increasing over the past three decades, with 23,690 new cases expected in the United States in 2005. However, thyroid cancer-related deaths are expected to number only 1,490 (6%) during the year. The modest death rate and the visible nature of surgical complications, such as injury to the recurrent laryngeal nerve and hypoparathyroidism, may lead surgeons to take a conservative surgical approach for local-regional disease in patients with differentiated thyroid carcinoma (DTC). Although the optimal surgical management of patients with low-risk DTC (T1-2, N0, M0, and age less than 45) remains controversial, there is little argument that removal of tumor tissue from the neck will maximize local-regional tumor control. The liberal use of fine-needle aspiration (FNA) biopsy and the availability of accurate preoperative ultrasonography (US) for staging have enhanced the ability of surgeons to completely remove all gross disease at surgery. In addition, the National Comprehensive Cancer Network (NCCN) practice guidelines for the treatment of thyroid carcinoma advocate the use of preoperative FNA biopsy, the practice of total thyroidectomy in high-risk patients (age greater than 45, T3-4, and N1), and extirpation of all disease evident on physical examination and preoperative imaging studies. This treatment strategy is also supported by the fact that cervical recurrences occur in up to 31% of patients with DTC and in up to 65% of patients with medullary thyroid carcinoma (MTC), suggesting that many patients have macroscopic lymph node metastasis at the time of initial surgery. If such metastatic adenopathy was detected preoperatively and removed, patients could potentially avoid subsequent repeat surgery for recurrence in the neck. Cervical recurrence necessitating repeat surgery does not necessarily predict the development of extra cervical metastatic disease and may not significantly affect the duration of survival, especially in patients with low or intermediate risk. However, reoperation is a traumatic event for patients and may be...
associated with complications such as injury to the recurrent laryngeal nerve, hypoparathyroidism, palsy of the spinal accessory nerve, and the cosmetic concerns from cervical incisions.6–8

**Indications for Surgery on the Basis of FNA Findings**

Most patients with DTC present with asymptomatic thyroid nodules, although fewer than 5% of palpable thyroid nodules seen in the adult population are malignant. Whatever the presentation, FNA biopsy has now supplanted most other tests (scintigraphy with iodine-123 [123I] or technetium-99m [99mTc] pertechnetate) for preoperative evaluation of thyroid nodules.9,10

In otherwise asymptomatic patients, endocrine surgeons prefer to operate only on those with cancer, thereby avoiding possible injury of the recurrent laryngeal nerve, hypoparathyroidism, and thyroid hormone dependence in patients with benign thyroid nodules. The use of FNA biopsy in the preoperative evaluation of thyroid nodules can prevent intraoperative indecision and facilitate accurate preoperative staging of the neck by US if a diagnosis of carcinoma is confirmed.6,13 FNA biopsy findings are categorized as positive, negative for malignancy, indeterminate, or nondiagnostic. These cytologic findings guide patient management with specific reference to the need for thyroidectomy (Fig. 1). Patients with biopsy findings positive for malignancy can undergo a definitive

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**Figure 1** Diagnostic algorithm for patients with thyroid nodules currently in practice at the Department of Surgical Oncology at The University of Texas M. D. Anderson Cancer Center. Patients with thyroid-stimulating hormone levels below the normal range (0.50 to 5.50 mU/L) are evaluated using 123I scintigraphy. Patients with cold nodules on scintigraphy and those with normal or elevated thyroid-stimulating hormone levels undergo fine-needle aspiration biopsy. Management of patients is straightforward after fine-needle aspiration shows the presence or absence of malignancy. Surgical management of patients with indeterminate biopsy findings is more complicated and requires additional evaluation with 123I scintigraphy and careful consideration of other patient factors, such as age, nodule size, and treatment preferences.
planned surgical procedure, including total thyroidectomy, without the need for frozen-section analysis.

In patients with negative biopsy findings, serial follow-up with or without a repeat FNA biopsy is safe unless other factors raise the possibility of a false-negative finding, such as voice change, dysphagia, or worrisome findings on physical examination. Indeterminate FNA biopsy findings can be subclassified as suspicious for papillary carcinoma or follicular or Hurthle cell neoplasms. Patients with biopsy findings suspicious for papillary carcinoma have a high likelihood (up to 82%) of actually having papillary carcinoma. In such cases, total thyroidectomy is advised. In contrast, the risks of invasive carcinoma in patients with biopsy findings that suggest follicular or Hurthle cell neoplasms are only 15% to 20%. Thus, the obvious dilemma is whether patients with follicular or Hurthle cell neoplasms should undergo thyroidectomy and, if so, what extent of thyroid resection (lobectomy vs. total or subtotal thyroidectomy) should be performed. Thyroid lobectomy and frozen-section analysis appear to be an obvious solution. However, frozen-section histopathologic analysis may miss vascular or capsular invasion (the hallmark finding that confirms malignancy), because of the limited number of sections examined in centers not equipped to perform high-volume, more complete frozen-section analyses. In our previously published series, frozen-section analysis failed to diagnose all follicular carcinomas. In patients with follicular carcinoma with vascular invasion or moderate- to high-risk papillary carcinoma in whom total thyroidectomy is preferred, a second surgery would be required if the initial procedure was a unilateral thyroid lobectomy. Investigators have attempted to determine which patients with follicular and Hurthle cell neoplasms have the highest risk of harboring an invasive carcinoma on the basis of preoperative patient and tumor characteristics. Our most recent study suggested that the only patient factor suggestive of an increased risk for invasive carcinoma in patients with follicular neoplasms (by FNA) was a nodule diameter greater than 2 cm. Cytologic features of indeterminate FNA biopsy specimens that suggest carcinoma include marked crowding with a 3-dimensional grouping of cells, an increased number of single cells, irregular follicles, and nuclear changes such as pleomorphism, enlargement, hyperchromasia, macronucleoli or prominent nucleoli, and atypical mitotic figures. Although such cytologic findings raise concern over the possibility of invasive carcinoma, they may also be present in benign nodules, especially colloid nodules with cystic degeneration, which are frequently associated with focal atypia, nuclear pleomorphism, and cytologic characteristics of Hurthle cell change.

A nondiagnostic FNA specimen may be a result of either the characteristics of the thyroid nodule or inadequate sampling. Thyroid nodules that are sclerotic or calcified and those with large areas of cystic degeneration or necrosis are extremely difficult to aspirate. An adequate specimen may not be obtained if needle placement is suboptimal. For patients with thyroid nodules in which FNA yields inadequate diagnostic material, repeat aspiration under US guidance can improve specimen acquisition, especially in patients with small thyroid nodules or nodules that are difficult or impossible to detect on physical examination. Because we routinely use transcutaneous cervical US to determine the presence or absence of regional adenopathy before surgery, we now perform the vast majority of FNA biopsies under US guidance. False-positive FNA biopsy findings are uncommon, usually ranging from 2% to 7%. In our most recent report, the false-negative rate was 4%. The more routine use of US-guided FNA biopsy will probably minimize but not prevent false-negative findings, although inadequate sampling is not the only cause of false-negative cytologic readings. For example, follicular carcinomas occasionally have a macrofollicular pattern, with large amounts of background colloid, making the differentiation between adenomatoid colloid nodules and follicular neoplasms quite difficult.

**Role of Preoperative Ultrasonography in the Surgical Management of Thyroid Cancer**

The goal of surgical intervention for thyroid carcinomas is to remove all cancerous tissue from the neck. Therefore, the entire thyroid gland and affected cervical lymph nodes should be resected. The realization that preoperative physical examination is inadequate for the detection of extrathyroidal cervical metastasis has caused clinicians to consider transcutaneous US for preoperative staging in patients diagnosed with thyroid carcinoma by FNA biopsy. High-quality US is helpful in determining the size and location of tumors and is now considered an established diagnostic tool for detecting local-regional metastatic thyroid
disease as small as 3 to 4 mm in diameter. We recently reported our data concerning the effect of preoperative US on the surgical management of patients with thyroid cancer. We found that the planned surgical procedure was modified in 34% of patients with DTC and in 43% of those with MTC because of unsuspected clinically occult soft tissue or lymph node metastasis that were revealed by US. Patients with US-proven cervical lymph node metastasis should be treated with a compartment-oriented surgical (COS) intervention using standard techniques of neck dissection in an effort to prevent recurrence in the neck.

US is both sensitive and specific for the diagnosis of soft tissue or lymph node metastasis. However, false-negative US findings may be seen in the central neck compartment, especially in patients with an in situ thyroid gland. US cannot be used to assess the central compartment with the high sensitivity that is possible after thyroidectomy. Therefore, we have adopted the practice of removing the ipsilateral paratracheal lymph nodes in patients with papillary carcinoma or Hürthle cell carcinoma.

Metastasis in lymph nodes may be difficult to detect intraoperatively, especially when they are located behind the carotid artery or internal jugular vein or in the paratracheal groove posterior to the recurrent laryngeal nerve. Preoperative staging with US will allow for a more complete initial surgery (thereby minimizing patient confusion and physician indecision when evaluating postoperative radioiodine scans and serum thyroglobulin levels), prevent the indiscriminate and sometimes unnecessary use of radioiodine therapy, and minimize cervical recurrence with its negative effect on the physical and emotional state of the patient.

In contrast to opinion on DTC, experts generally agree that patients with invasive MTC should undergo routine dissection of at least the level VI (central) cervical compartment. Therefore, preoperative US findings may not alter the surgical procedure. However, the knowledge of the extent and locations of regional metastasis will alert the surgeon to the need for a more detailed dissection, and surgeons less experienced with neck dissection may wish to refer such patients with invasive MTC to a center more experienced in the operative management of locally advanced thyroid cancer.

Controversy Over Total Versus Lobe Thyroidectomy for Patients with DTC

Controversy persists over whether total or near total thyroidectomy (leaving no more than 3 g of thyroid tissue) is the preferred initial surgical procedure for all patients with DTC. The importance of total or near total thyroidectomy in decreasing recurrence and death in high-risk patients is now well accepted. The rationale for total or near total thyroidectomy in patients with low or intermediate risk include the facts that as many as 80% of papillary carcinomas are multifocal and approximately one third are bilateral, that complete removal of the thyroid tissue allows for delivery of adjuvant radioiodine and facilitates postoperative monitoring for recurrences with serum thyroglobulin, and facilitates more effective suppression of thyroid-stimulating hormone because the patient is thyroid hormone dependant.

The argument against total thyroidectomy is that for most patients younger than 45 years with tumors confined to the thyroid gland, possible complications such as recurrent laryngeal nerve injuries and hypoparathyroidism after total thyroidectomy outweigh any potential oncologic benefit. However, for the vast majority of patients with little or no risk of death from DTC, the endpoint for assessing treatment benefit, including the extent of surgery, should be the development of cervical recurrence rather than overall survival. To date, no randomized, prospective trial has compared survival and recurrence rates after thyroid lobectomy and total thyroidectomy. Such a prospective trial is not likely to be feasible. A cause-specific mortality trial would be easiest to perform, although even that would need to include approximately 3,100 patients and would require a long follow-up.

Therefore, the treatment for patients with DTC is based on several large retrospective studies. In such a retrospective study of 1,685 low-risk patients, statistically significant differences in cancer-specific mortality and distant metastasis were seen between patients who received total thyroidectomy and those who underwent thyroid lobectomy. The 20-year rates for local recurrence and nodal metastasis after unilateral lobectomy were 14% and 19%, respectively, significantly higher (P = .0001) than the respective 2% and 6% rates seen after bilateral thyroid resection. As a result, Hay et al. concluded that bilateral thyroid resection is the preferred initial surgical approach in patients with low-risk papillary cancer. Predicting which...
low-risk patients will have recurrent disease is difficult. Of the patients found to be at low risk by age, metastases, extent, and size (AMES), 11% had recurrence and 33% of those subsequently died of the cancer.44

To determine the optimal extent of thyroidectomy, Kebebew et al.45 used a well-designed decision analysis model. The probabilities of complications from thyroidectomy and the risk of recurrence and death from thyroid cancer were analyzed by comparing lobectomy with total thyroidectomy. Thyroid lobectomy was the preferred surgical approach only if a complication rate was 33 times higher for thyroidectomy. The authors concluded that this decision analysis model provided an objective approach to the extent of surgical intervention on the basis of patient preference regarding health outcome, institution specific outcome data on cancer recurrence and mortality, and the surgeon specific complication rate.45 We also used a decision analysis model to identify the optimal treatment strategy for patients with papillary thyroid carcinoma, stratified by risk group classification.8 The conclusion of our study was that total thyroidectomy maximized the quality-adjusted life expectancy in both low- and high-risk patients with papillary thyroid carcinoma.8 All recommendations for total thyroidectomy assume that the procedure can be performed safely and with a low complication rate.

Management of Recurrences

Up to 31% of patients with DTC experience cervical recurrences, mostly regional lymph node metastasis,2–4 and up to 65% of patients with MTC have recurrences.5 Some are related to incomplete initial treatment (recurrent disease in a thyroid remnant or lymph nodes), and others indicate the presence of an aggressive tumor (in the thyroid bed after total thyroidectomy or in soft tissues). We recently reviewed all patients who required repeat surgery for recurrent papillary carcinoma at our institution from 1992 to 2003 and found that 49% of the reoperations may have been preventable.46 Half of these patients underwent an incomplete initial operation, including patients in whom preoperative imaging or intraoperative findings suggested more extensive disease than was successfully removed by the surgeon. Clearly, surgeon experience may have contributed to the need for reoperation in some of these patients. In the remaining patients, lymph node metastasis recurred in the same cervical compartment in which node plucking had previously been performed.47,48 We support the use of COS, which can minimize the incidence of neck recurrence and is far superior to node plucking.11 Importantly, dissection of the lateral neck compartments (levels IIA through V) is associated with minimal morbidity in the absence of injury to the spinal accessory nerve (Fig. 2).49–50

A local or regional recurrence that is palpable or grossly visualized with US or computed tomography and appears surgically resectable should be excised. Our surgical approach to patients with recurrent DTC and suspected or proven central or lateral compartment lymph node metastasis emphasizes standard principles of neck dissection. When performed, central compartment dissection involves removal of all lymph nodes and soft tissues in level VI, usually with the overlying sternothyroid muscle (Fig. 2). In patients with DTC (in contrast to MTC), the level VI dissection is largely limited to the ipsilateral tracheoesophageal groove, unless preoperative imaging suggests metastatic disease in the contralateral paratracheal region. Lateral compartment dissection (modified radical neck dissection) involving removal of all lymph nodes and soft tissues in levels IIA, III, IV, and V with preservation of the sternocleidomastoid muscle, jugular vein, carotid artery, vagus nerve, phrenic nerve, and spinal accessory nerve...
is reserved for patients with radiographic evidence of lateral neck disease. In patients with papillary or Hürthle cell carcinoma and no evidence of regional lymph node metastasis, we routinely remove the ipsilateral paratracheal lymph nodes; however, the lateral compartment is not dissected in the absence of clinical or US evidence of lymph node metastasis. In patients with DTC, in contrast to selected patients with MTC, we do not consider elective reoperation because of an elevated thyroglobulin level in the absence of clinical or US evidence of lymph node metastasis. We believe that COS consisting of formal dissection of the central (level VI) and lateral (levels IIA through V) neck compartments, when performed for gross disease (palpable or visible on US), will minimize subsequent lymph node recurrences.

Considerations in the Surgical Management of MTC

In contrast to DTC, the most common thyroid malignancy, MTC is rare, accounting for less than 5% of all thyroid cancers. MTC arises from the C-cells of the thyroid and can occur as a sporadic event or as part of familial MTC or multiple endocrine neoplasia type 2. MTC typically spreads to regional lymph nodes early in its course; therefore, central compartment (level VI) lymphadenectomy is the standard of care for all patients with macroscopic MTC during the initial surgery. MTC is a unique solid tumor for two reasons. First, it is usually an indolent disease associated with long-term survival, yet it often spreads to regional lymph nodes and occasionally distant sites before the primary thyroid tumor is diagnosed. Second, serum calcitonin measurement can detect MTC long before regional lymph node or distant metastasis becomes visible on imaging studies. Because most patients who undergo thyroidectomy, with or without some form of regional lymph node dissection, still have an elevated calcitonin level after surgery, surgeons routinely perform a more extensive lymph node dissection than is accepted for the treatment of DTC. However, although most surgeons perform a central neck dissection (level VI) at the time of thyroidectomy, elective dissection of the lateral neck compartments (levels IIA, III, IV, and V) remains controversial. A more aggressive neck dissection to include the lateral neck compartments is based on the hypothesis that MTC may metastasize to regional lymph nodes in the absence of distant organ metastasis. Therefore, a more extensive lymphadenectomy may prevent cervical recurrence and occasionally result in a long-term clinical and biochemical cure. Therefore, in patients with sporadic MTC and no clinical or radiographic evidence of cervical lymph node metastases, we perform total thyroidectomy, central compartment dissection, and ipsilateral modified neck dissection. In patients with sporadic MTC and clinical or radiographic evidence of lymph node metastasis in any cervical compartment and in patients with familial MTC and grossly evident disease, we perform total thyroidectomy along with central and bilateral neck dissection.

Postoperative calcitonin levels and radiographic imaging based on the absolute level of calcitonin and its change over time can be used to guide the clinical management of patients with MTC. A slowly progressive increase in serum calcitonin levels causes anxiety and frustration for the patient and physician. Our published data suggest that a calcitonin level of < 250 pg/mL is rarely associated with radiographically detectable disease. For patients who have undergone COS and have a persistent elevation of calcitonin < 250 pg/mL (approximately), follow-up is limited to physical examination, annual cervical US, and serial measurement of calcitonin and carcinoembryonic antigen at 6- to 12-month intervals. Further radiographic imaging is performed if clinically indicated on the basis of patient symptoms or a progressive increase in calcitonin or carcinoembryonic antigen. For example, radiographic evaluation of liver, lung, and bone should be performed if a sudden or progressive rise in calcitonin levels is seen or if clinical symptoms develop. Because most patients will have persistent elevation in calcitonin levels after initial thyroidectomy, a COS approach to the neck simplifies patient management and minimizes cervical recurrence and the need for reoperation. We previously reported a cervical recurrence rate of 13% in our MTC population, significantly lower than previous reports, which suggest cervical recurrence rates ranging from 20% to 60%.

Importantly, one cannot reliably distinguish between benign and malignant C-cells on the basis of basal calcitonin levels in kindreds with familial MTC. This is of great clinical importance in patients with level 2 (high-risk) RET mutations (codon 611, 618, 620, or 634), for whom the current recommendation is to perform prophylactic thyroidectomy by age 5 years. Because of the inability of serum calcitonin levels to differentiate C-cell hyperplasia from invasive MTC and
Surgical Management of Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinoma is rare and is one of the most aggressive human malignancies. The prognosis for a patient with anaplastic thyroid carcinoma is dismal, with a disease-specific mortality of almost 100%. Anaplastic thyroid carcinoma is usually seen in elderly patients, most often in women, as a rapidly enlarged neck mass, often associated with dysphagia, dyspnea, and hoarseness. As with other types of thyroid carcinoma, the diagnosis of anaplastic carcinoma can be confirmed by FNA biopsy. In the absence of extracervical disease, imaging studies (computed tomography or magnetic resonance imaging) are necessary to accurately stage the local-regional tumor extension. Cure can be achieved only after complete tumor resection in the neck, but it is rarely possible because most patients present with widespread local invasion, distant metastasis, or both. Even radical surgery alone cannot significantly extend survival. The mainstay of treatment is multimodality therapy prioritizing chemoradiation and performing close monitoring of the airway and tracheostomy when necessary. A Swedish cooperative study reported adriamycin to limit growth and enhance effectiveness of external beam radiation. In a trial that included 33 patients, 23 of the 33 patients (70%) had tumor debulking between neoadjuvant and adjuvant chemoradiation. This treatment strategy seemed to be moderately effective, because 48% of patients experienced local control of tumor. A recent published in vivo study has shown encouraging results regarding the epidermal growth factor receptor (EGFR) as a potential target for molecular therapy of anaplastic thyroid carcinoma in animal models. However, future human clinical trials will be necessary to prove this effect.

Conclusions

In summary, although thyroid carcinoma is a slow-growing malignancy with an excellent survival rate for most patients, local-regional recurrence in the neck remains common in patients with DTC as well as MTC. FNA biopsy is a safe, inexpensive, and reliable method of confirming the diagnosis. Total thyroidectomy is the recommended surgical procedure in patients with a preoperative diagnosis of thyroid cancer. Preoperative US should be routinely performed before surgery to identify the extent of regional nodal disease and allow for complete, compartment-directed dissection to maximize local-regional disease control. For patients with DTC, we frequently remove the lymph nodes in the ipsilateral tracheoesophageal groove in an effort to prevent central neck recurrence, while lateral compartment dissection is reserved for patients with evidence of regional lymph node metastasis on physical examination or preoperative US. For patients with MTC, complete central compartment lymphadenectomy is routinely performed. We also favor lateral neck dissection on the side of the primary tumor in patients with sporadic MTC, even in the absence of clinical evidence of involved regional nodes to maximize local-regional disease control. Bilateral lateral compartment dissection is performed in patients with sporadic MTC with clinically evident regional nodal disease, and in patients with familial MTC with clinically identified disease. Because the vast majority of patients with DTC or MTC will not die of the disease regardless of the surgery performed, mortality is an invalid endpoint for assessing treatment strategies. Cervical recurrence rates remain unacceptably high, in part because of greater emphasis being placed on possible surgery-related complications (injury to the recurrent laryngeal nerve and hypoparathyroidism) than disease recurrence. Safe and complete removal of all gross disease in the neck can be achieved if the surgery is performed by an experienced surgeon after accurate preoperative radiographic staging to determine the extent of cervical disease.

References


