Selective Surgical Management of Well-Differentiated Thyroid Cancer

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There has been a rapid rise in the incidence of thyroid cancer in the United States, along with more incidentalomas of the thyroid. Treatment of thyroid cancer revolves around appropriate surgical intervention, minimizing complications, and the use of adjuvant therapy in select circumstances. Prognostic features and risk-group analysis are crucial in determining the appropriate treatment. Thyroid cancers are divided into low-, intermediate-, and high-risk groups. Surgical treatment should adhere to the risk-group analysis. The prognostic features in thyroid cancer are age, gender, size and grade of the tumor, extrathyroidal extension, and completeness of resection. The patient presenting with extrathyroidal extension needs extra attention in the operating room to remove all gross tumor during the initial surgical procedure to avoid future recurrences. Nodal metastasis generally has minimal implications; however, in older patients and those with poorly differentiated histology, it has major implications. Grading of the tumor is important, especially for understanding the poorly differentiated varieties of thyroid cancer, such as tall cell and insular. These patients do not respond well to RAI and are best followed with a PET scan. Overall survival in patients with well-differentiated thyroid cancer exceeds 95%.

Key words: thyroid cancer; incidentaloma; prognostic features; risk groups in thyroid cancer; surgical treatment of thyroid cancer

Introduction

There appears to be a rapid rise in the incidence of thyroid cancer over the last two decades. Approximately 32,000 new patients with thyroid cancer were expected to be seen in the year 2007 in the United States.[1] A large number of these appear to be incidental findings. Whether this rapid rise is due to increasing diagnostic utilization or a true rise in the incidence of thyroid cancer remains unclear. Another tumor with such a rapid rise is cutaneous malignant melanoma. Even though the incidence of thyroid cancer has tripled in the United States, mortality from thyroid cancer has remained essentially unchanged (Fig. 1). The majority of deaths from thyroid cancer are related to anaplastic or medullary thyroid cancer. Recently, pathologists have been able to distinguish poorly differentiated thyroid carcinoma where the incidence of local recurrence and distant metastasis is quite high with a high mortality rates. The prognostic factors in thyroid cancer have been well described in recent years from Mayo Clinic, Lahey Clinic, and Memorial Sloan-Kettering Cancer Center.[2–5] These prognostic factors include age, sex, grade of tumor, extrathyroidal extension, size of tumor, and distant metastasis. Gender, multicentricity, and lymph node metastasis do not have a major prognostic bearing on thyroid cancer. Memorial Sloan-Kettering Cancer Center has divided its thyroid cancer patients into low-, intermediate-,

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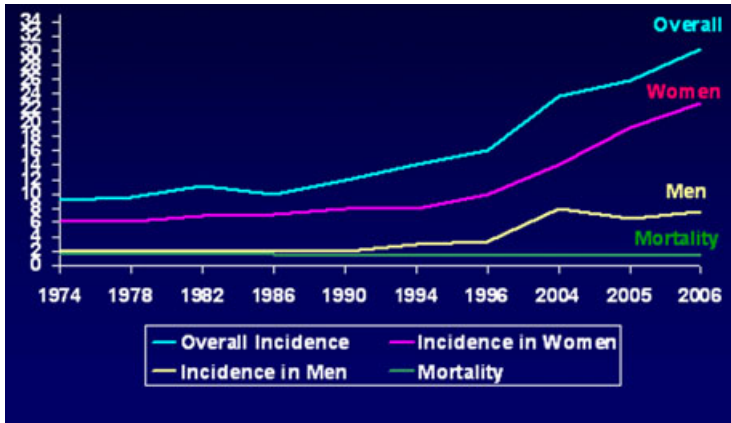
Figure 1. Thyroid cancer: incidence & mortality, 1974–2006. (In color in *Annals* online.)

TABLE 1. Risk-Group Definitions in Differentiated Carcinoma of the Thyroid

	Low risk	Intermediate risk	Intermediate risk	High risk
Age (years)	<45	<45	>45	>45
Distant metastasis	M0	M+	M0	M+
Tumor size	T1, T2 (<4 cm)	T3, T4 (>4 cm)	T1, T2 (<4 cm)	T3, T4 (>4 cm)
Histology and grade	Papillary	Follicular and/ or high-grade	Papillary	Follicular and/ or high-grade
5-year survival	100%	96%	96%	72%
20-year survival	99%	85%	85%	57%

and high-risk groups (Table 1). This risk stratification is critical in understanding the biology of thyroid cancer, its prognosis, and the appropriate treatment modalities, including adequate surgical extirpation.[6]

Low-risk thyroid cancers are generally in young patients (low-risk patients) and are small tumors (less than 4 cm) without extrathyroidal extension and with well-differentiated histology. High-risk thyroid cancers include high-risk patients (above the age of 45) and high-risk tumors (larger than 4 cm) with extrathyroidal extension or poor histology. The intermediate-risk group includes young patients with aggressive thyroid cancer or older patients with small tumors. This risk stratification appears to be consistent in various published series. The treatment decisions and the role of adjuvant therapy, such as radioactive iodine and external radiation therapy, are well defined based on this risk stratification. The subject of thy-roid cancer has generated considerable debate, with a large volume of published literature and continued controversy among surgeons and endocrinologists.[7] There are strong proponents and opponents of total versus less-than-total thyroidectomy. What is important is to identify the risk groups and apply appropriate surgical treatment based on patient and tumor characteristics. The entire idea of selective surgical treatment rests on understanding the biology of the tumor, applying the appropriate surgical procedure based on the aggressiveness of the cancer, not over-treating every patient with thyroid cancer, and using adjuvant therapy selectively.

Surgical Treatment of Thyroid Cancer

The surgical treatment of thyroid cancer can be divided into treatment of primary tumor,

treatment of regional nodes, and treatment of distant metastasis.

Surgical Treatment of Primary Thyroid Tumor

A patient presenting with a thyroid nodule and suspected to have thyroid cancer needs either a thyroid lobectomy or total thyroidectomy, depending upon the extent of the disease. Patients in the high-risk group, or those with aggressive thyroid cancer, will require a total thyroidectomy. This is mainly because total thyroidectomy will allow the patients to receive adjuvant radioactive iodine. Patients who are likely to require radioactive iodine treatment should undergo total thyroidectomy to facilitate postoperative radioactive iodine ablation. The advantages of thyroid lobectomy include minimizing over-treatment and the high incidence of complications in total thyroidectomy. These include nerve injury and temporary or permanent hypoparathyroidism. Also a selected group of patients do not require thyroid supplementation in follow-up. The pros of total thyroidectomy include: the complication rate in the hands of good thyroid surgeons is not higher than that in thyroid lobectomy, the ease of radioactive iodine scanning and ablation and the ease of follow-up of patients with thyroglobulin.

Both thyroid lobectomy and total thyroidectomy appear to render similar long-term results in low- and selected intermediate-risk group patients.[8] There are no randomized prospective trials in patients presenting with low-risk thyroid cancer with total or less-than-total thyroidectomy. Obviously, the philosophy of extent of thyroidectomy will depend on the surgical center, the approach taken by individual surgeons, and the patient's preference. However, a Google search will convince the majority of patients with thyroid cancer to undergo total thyroidectomy so that they can get radioactive iodine ablation and thyroglobulin follow-up. Unfortunately, the thyroglobulin follow-up is

TABLE 2. Thyroid Cancer: A Unique Human Neoplasm

- Age is the most important prognostic factor
- No stage III & IV cancers in patients < 45
- Multicentricity of thyroid cancer is frequent, though without prognostic impact
- No prognostic impact of microscopic tumor – "laboratory cancer"
- Nodal metastasis has no impact on outcome
- Impact of extrathyroidal spread is high with local recurrence
- Grade of the tumor & histologic poorly differentiated features have impact on outcome

likely to show an incidental lymph node metastasis, the treatment of which continues to be most debatable.

Obviously, if the preoperative ultrasound shows thyroid nodularity involving the contralateral lobe, patients should undergo total thyroidectomy. Subtotal and near-total thyroidectomy should be abandoned for patients with suspected or known thyroid cancer. There is always a small amount of thyroid tissue left behind after these procedures, which can be seen on radioactive iodine scanning in the postoperative period. Recently, postoperative dosimetry and ablation have been performed with recombinant thyroid stimulating hormone (TSH), which has helped improve quality of life for patients who otherwise would have undergone approximately 6 weeks of hypothyroidism (Table 2).

Management of Neck Nodes in Thyroid Cancer

Many series reported in the literature have shown that regional nodal metastasis in well-differentiated thyroid cancer has no major prognostic implications.[9–11] However, with the recent increasing use of preoperative ultrasound, a large number of patients with well-differentiated thyroid cancer are noted to have nodal metastasis.[12] Obviously, these patients will require appropriate nodal clearance.

TABLE 3. Surgical Decisions for Metastatic Cervical Nodes from Thyroid

- Modified neck dissection for palpable nodes
- Evaluate jugular and superior mediastinal nodes at the time of surgery
- Modified neck dissection
  – "Berry picking"
  – Preserve sternocleidomastoid (SCM), internal jugular vein (IJV), XI (accessory) nerve
  – Submandibular gland
  – Selective or compartment-oriented neck dissection

Standard radical neck dissection is rarely performed for well-differentiated thyroid carcinoma. The berry picking operation, which was a popular operation approximately two decades ago, is rarely used today. There was a high incidence of multiple positive nodes in the neck, and berry picking will allow further recurrence of nodal metastasis, requiring additional neck surgery. The standard surgical procedure utilized now is a modified neck dissection, with the removal of lymph nodes at levels II, III, IV, and V. The incidence of nodal metastasis at level I from well-differentiated thyroid carcinoma is quite low, and generally, the region is not dissected routinely, as there may be a high incidence of injury to the lower division of the facial nerve (ramus mandibularis). Some authors use the terms, "compartment oriented dissection" or "selective nodal dissection," for removal of the selected groups of lymph nodes[12] (Table 3). The incidence of nodal metastasis above the accessory nerve is quite low, and skeletonization of the accessory nerve is not necessary in all patients with cervical nodal metastasis.

The most important aspect of neck dissection is central compartment clearance. Again, there continues to be considerable controversy as to routine use of central compartment clearance. Practically every patient undergoing surgery for thyroid cancer should have a thorough and complete central compartment evaluation. This is generally a clinical evaluation at the time of surgery. If the nodes appear to be enlarged or suspicious, they should be removed with appropriate central compartment clearance. A frozen section may be of help in patients with Hashimoto's thyroiditis to see if these are benign or metastatic lymph nodes. Routine paratracheal clearance is likely to result in a high incidence of temporary and permanent hypoparathyroidism and is best avoided, unless there is a strong suspicion of nodal metastasis. However, it is important to undertake appropriate paratracheal clearance in individuals with locally aggressive, large thyroid cancers, or suspected paratracheal lymph node metastasis. In patients undergoing surgery for medullary carcinoma of the thyroid, routine central compartment clearance is a standard procedure, as there appears to be a high incidence of nodal metastasis in patients with medullary thyroid carcinoma. The superior mediastinal lymph nodes should also be dissected in these individuals. However, superior mediastinal clearance is generally not indicated in well-differentiated thyroid carcinoma unless there is an obvious clinical suspicion of superior mediastinal lymph nodes during surgery.

Management of Locally Aggressive Thyroid Cancer

One of the most important prognostic features in well-differentiated thyroid cancer is the presence of extrathyroidal extension.[13] This has been shown to be the most important prognostic feature in various series around the world. When the thyroid tumor is intrathyroidal, the outcome is excellent. However, once the tumor comes out of the thyroid gland and invades the surrounding structures, the incidence of local recurrence is high (Fig. 2). The majority of these tumors happen to be in older individuals and generally with a more aggressive histology, such as tall cell, insular, or poorly differentiated thyroid cancer. It is very important for the pathologist to differentiate these various types of poorly differentiated thyroid cancers.

The structures that are commonly involved in locally aggressive thyroid cancer are the anterior structures and the posterior structures.
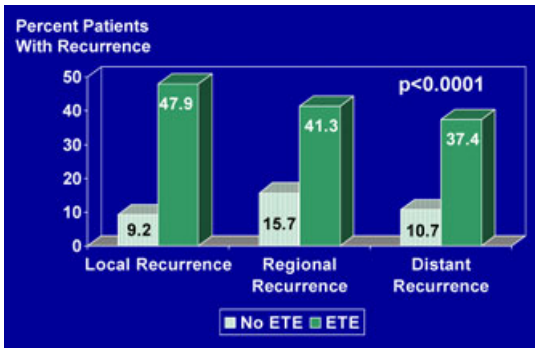
Figure 2. Thyroid carcinoma with extrathyroid extension (ETE) treatment failure. (Memorial Sloan-Kettering data.) (In color in *Annals* online.)

The anterior structures include the sternohyoid and sternothyroid muscles. These generally do not have major prognostic implications, as they can be easily resected. However, when the tumor invades the posterior structures, such as the recurrent laryngeal nerve, esophageal musculature, and tracheal wall, the overall outcome is quite poor, and surgical resection may be quite difficult. If the tumor invades the recurrent laryngeal nerve and the recurrent laryngeal nerve is known to be paralyzed preoperatively, it should be resected at the time of surgery for better resection of locally aggressive thyroid cancer. Preoperative evaluation of the vocal cords is essential. When the tumor is adherent to the esophageal musculature, it can be easily resected. However, when the tumor is adherent to the tracheal wall, it is important to evaluate the exact extent of the tumor invasion into the trachea.[14–16] If the tumor is adherent to the tracheal wall, it can be easily shaved off. It is vitally important to leave no gross tumor behind. Obviously, the microscopic tumor in these individuals requires adjuvant therapy, such as radioactive iodine or external radiation therapy. However, if the tumor is invading the trachea with submucosal or intraluminal extension, tracheal resection is generally recommended. A sleeve resection is advisable with end-to-end anastomosis.[15] Obviously, the radicality of surgery changes with tracheal resection, and when such findings are noted intra-operatively, the decision making may be quite difficult, unless the surgeon has considerable experience in these procedures.

Occasionally, secondary surgical intervention may be necessary, if the primary surgeon is not prepared for radical resection. However, the extent of the radicalness should depend upon the extent of the locally aggressive thyroid cancer. The basic oncologic principle that should be adhered to is the removal of all gross tumor at the time of the first surgical procedure. Preoperative evaluation in these individuals is crucial, including evaluation of the vocal cord function. Extent of the disease in the central compartment should be evaluated with imaging studies, such as CT scan or MRI of the neck. If the CT scan is to be performed, the contrast dye may interfere with postoperative radioactive iodine ablation, and MRI or CT without contrast should be considered. If the tumor is minimally invading the trachea, a partial tracheal resection can be performed. However, reconstructing partial defects may be more difficult than classical sleeve resection. If the tumor invades the cricothyroid junction or the laryngeal structure, the treatment becomes extremely complex, as primary total laryngectomy is rarely indicated in well-differentiated thyroid carcinoma. However, occasionally, the larynx is considerably destroyed, and if there is extensive involvement of the laryngeal framework, total laryngectomy may be required. A partial laryngectomy may be attempted in selected patients if all gross tumor could be removed, and the laryngeal function can still be maintained.

The involvement of the carotid artery and prevertebral fascia are generally considered to present an inoperable situation, and such individuals are best considered for palliative treatment. Postoperative radioactive iodine ablation is routinely considered in these individuals. However, it must be remembered that the effectiveness of radioactive iodine ablation is much inferior in poorly differentiated thyroid carcinoma. Such individuals are best followed

with a PET scan, since these tumors are 18 Florodeoxy Glucose (FDG) avid. External radiation therapy is used in selected individuals, especially with poor histologic features. External radiation therapy has been shown to improve local control in patients with locally aggressive thyroid carcinoma. There is clearly a high incidence of distant metastases in these individuals. Total thyroidectomy should be routinely performed in these patients to facilitate radioactive iodine ablation. Appropriate neck evaluation should be considered at the time of primary surgery, since there is generally a higher incidence of regional recurrence in patients with locally aggressive thyroid carcinoma (Fig. 2).

Management of Distant Metastases in Well-Differentiated Thyroid Carcinoma

Although rare, the most frequent areas where the tumor generally metastasizes include the lungs, bones, and the brain.[17] Pulmonary metastases are fairly common in young individuals, in patients with locally aggressive or advanced primary tumor. It is also well known in patients with bulky nodal metastases. The chest x-ray may be normal, and even the CT scan of the chest may be normal; however, the best way to identify pulmonary metastases is radioactive iodine ablation. The majority of these patients present miliary diffuse pulmonary metastases. In patients with diffuse pulmonary metastases, there is no role for surgical intervention. However, if the patient has developed massive pleural effusion, pleurodesis or sclerotherapy may be considered in selected individuals.

The bony metastases, though rare, are seen most commonly in patients with follicular carcinoma or Hurthle cell carcinoma. These individuals generally present with backache or hip pain. Occasionally, they may present with pathological fracture. It is not uncommon to see a patient presenting with bony metastasis as an initial sign of thyroid cancer. These individuals are best treated with total thyroidectomy and radioactive iodine ablation. External radiation therapy may be used for pain control from bony metastases.

Brain metastases are fairly rare in patients with well-differentiated thyroid carcinoma. However, they may be part of a diffuse metastatic process. Brain metastases are best evaluated with an imaging study, such as a CT, MRI, or PET scan. Occasionally, a craniotomy may be necessary for diagnostic purposes for a space-occupying lesion. These patients are best treated with radioactive iodine ablation, or with external radiation therapy. During external radiation therapy, patients may develop brain edema and may need steroid supplementation. Overall prognosis in patients with bone and brain metastases is quite poor. The highest thyroglobulin levels are generally seen in bony metastases.

Conclusion

There continues to be considerable controversy regarding the optimal extent of thyroidectomy in patients presenting with low-risk well differentiated thyroid carcinoma. The debate continues primarily due to varying philosophies of the individual treating physicians, the consideration of use of radioactive iodine ablation, and concerns about the complications of total thyroidectomy. In low-risk patients, generally there is hardly any difference in the overall outcome, whether the patient has undergone total versus less-than-total thyroidectomy. The decisions regarding the extent of thyroidectomy should be made in the operating room, based on a variety of factors, including risk-group stratification, extent of the disease, condition of the opposite lobe, involvement of the central compartment lymph nodes, and opportunities for long-term follow-up of these patients.

In patients with locally aggressive thyroid cancer, one needs to be aggressive for removal of the entire gross tumor. The first surgical

procedure should be the most appropriate and adequate with the use of adjuvant therapy, such as radioactive iodine ablation and external radiation therapy, in selected individuals. Most of these patients may have aggressive histology, such as tall cell or poorly differentiated thyroid carcinoma. The treatment of nodal metastases should include appropriate nodal clearance by modified neck dissection. Follow-up in these individuals includes radioactive iodine ablation, thyroglobulin monitoring, and ultrasound evaluation of the neck. If the ultrasound reveals obvious metastatic disease, appropriate neck dissection should be considered. However, resection of subcentimeter lymph nodes should be considered against the complications of surgery and the need for further surgeries. The management of distant metastases generally is palliative, including radioactive iodine ablation and external radiation therapy in select circumstances. Bony metastases pose the worst prognosis. Patients with advanced, well-differentiated thyroid carcinoma should be treated in a multidisciplinary fashion, with appropriate involvement of thyroid surgeons, endocrinologists involved in thyroid cancer management, and nuclear physicians.

Thyroid cancer continues to be a unique human neoplasm, different from other human cancers, generally with an excellent prognosis and unique biological behavior (Table 2).

Conflicts of Interest

The author declares no conflicts of interest.

References

1. Jemal, A., R. Siegel, E. Ward, *et al.* 2007. Cancer statistics, 2006. *CA Cancer J. Clin.* **56:** 106–130.
2. Hay, I.D., C.S. Grant, W.F. Taylor, *et al.* 1987. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. *Surgery* 1088–1095.
3. Hay, I.D., E.J. Bergstralh, J.R. Goellner, *et al.* 1993. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery* **102**(6): 947–953.
4. Cady, B. 1997. Hayes Martin Lecture. Our AMES is true: how an old concept still hits the mark, or risk group assignment points the arrow to rational therapy selection in differentiated thyroid cancer. *Am. J. Surg.* **174**(5): 462–468.
5. Shaha, A.R. 2004. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. *Laryngoscope* **114:** 393–402.
6. Shaha, A. 2006. Treatment of thyroid cancer based on risk groups. *J. Surg. Oncol.* **94:** 683–691.
7. Mazzaferri, E.L. & S.M. Jhiang. 1994. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am. J. Med.* **97**(5): 418–428.
8. Shaha, A.R., J.P. Shah & T.R. Loree. 1997. Low-risk differentiated thyroid cancer: the need for selective treatment. *Ann. Surg. Oncol.* **4:** 328–333.
9. Noguchi, M. *et al.* 1993. Multivariate study of prognostic factors of differentiated thyroid carcinoma: The significance of histologic subtype. *Int. Surg.* **78**(1): 10–15.
10. Sugitani, I., N. Kasai, Y. Fujimoto & A. Yanagisawa. 2004. A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. *Surgery* **135:** 139–148.
11. Sherman, S.I., J.D. Brierley, M. Sperling, *et al.* 1998. Prospective multicenter study of thyroid carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. *Cancer* **83**(5): 1012–1021.
12. Grubbs, E.G. & D.B. Evans. 2007. Role of lymph node dissection in primary surgery for thyroid cancer. *J. Natl. Compr. Canc. Netw.* **5:** 623–630.
13. Patel, K.N. & A.R. Shaha. 2005. Locally advanced thyroid cancer. *Curr. Opin. Otolaryngol. Head Neck Surg.* **13:** 112–116.
14. Shaha, A.R. 2000. Controversies in the management of thyroid nodule. *Laryngoscope* **110**(2 Pt 1): 183–193.
14. Czaja, J.M. & T.V. McCaffrey. 1997. The surgical management of laryngotracheal invasion by well-differentiated papillary thyroid carcinoma. *Arch. Otolaryngol. Head Neck. Surg.* **123**(5): 484–490.
15. Grillo, H.C. & P. Zannini. 1986. Resectional management of airway invasion by thyroid carcinoma. *Ann. Thorac. Surg.* **42**(3): 287–298.
16. Anderson, P.E. *et al.* 1995. Differentiated carcinoma of the thyroid with extrathyroidal extension. *Am. J. Surg.* **170**(5): 467–470.
17. Cohen, E.G., R.M. Tuttle & D.H. Kraus. 2003. Postoperative management of differentiated thyroid cancer. *Otolaryngol. Clin. North Am.* **36:** 129–157.