



Nemours Vincent. *Landscape with Figures*. From the collection of Amy and David Quinlan.

Definition of risk groups has assisted decisions regarding the extent of surgery for differentiated thyroid cancer.

Thyroid Cancer: Extent of Thyroidectomy

Ashok R. Shaha, MD, FACS

Background: Surgical resection is the key to management of thyroid cancer, but determining the optimal surgical procedure for individual cases has been controversial.

Methods: The author reviews several large data bases that allow examination of prognostic criteria for long-term outcomes.

Results: Patients can be classified into good- or poor-risk groups that assist defining the optimal surgical procedure. Routine use of total thyroidectomy in all patients with thyroid cancer is best avoided; however, patients with medullary cancer generally need total thyroidectomy.

Conclusions: The definition of risk groups has clarified the options regarding choice of primary surgical therapy for differentiated thyroid cancer.

Introduction

Determining the extent of thyroidectomy in the management of differentiated thyroid cancer is controversial. The principal reason of this controversy is the fact that the majority of patients with differentiated thyroid cancer do extremely well; patients survive for decades. Most patients present at a low-risk stage, where survival is excellent. Statistically, it would be impossible to detect any meaningful impact of the rou-

tine use of radioactive iodine (RAI) therapy in low-risk patients. The routine application of total thyroidectomy in all patients with differentiated thyroid cancer is likely to lead to significant incidence of complications, with considerable long-term morbidity. No randomized, prospective trials have been conducted regarding the extent of thyroidectomy in differentiated thyroid cancer. This is mainly due to the excellent survival and the need of a large number of patients to be followed for a considerable period of time. A study of this kind would be almost impossible to conduct, especially in good-risk thyroid cancer patients.

Approximately 18,000 new cases of thyroid cancer will occur in the United States in the year 2000.¹ Of these, only 200 to 300 patients are expected to die of differentiated thyroid cancer. The majority of the mortality in thyroid cancer is related to either anaplastic thyroid cancer or medullary thyroid cancer. Currently,

From Cornell University Medical College and Memorial Sloan-Kettering Cancer Center, New York, New York.

Address reprint requests to Ashok R. Shaha, MD, FACS, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

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thyroid surgery is considered to be the safest surgical procedure, with minimal morbidity and rare mortality.

In 1909, Emil Theodor Kocher became the first surgeon to win the Nobel Prize in Medicine for his contributions to the understanding of thyroid physiology and for perfecting the technique of thyroidectomy. In the past two decades, we have learned a great deal about the biology of thyroid cancer, the prognostic factors, the risk groups, and the application of risk groups to the extent of thyroidectomy and adjuvant therapy. The National Cancer Data Base reported a large series of 53,856 patients with thyroid carcinoma between 1985 and 1995.² The 10-year overall relative survival rates for patients with papillary, follicular, Hürthle cell, medullary, and undifferentiated/anaplastic carcinoma was 93%, 85%, 76%, 75%, and 14%, respectively. Their large data base at 5 years did not translate into compelling differences in survival for any subgroup of papillary or follicular carcinoma based on extent of surgery. The percentage distribution of various types of thyroid carcinoma, by histologic subgroups, was papillary (79.9%), follicular (14.2%), medullary (3.7%), Hürthle cell (2.7%), and undifferentiated/anaplastic (1.6%).

Risk Groups in Differentiated Thyroid Cancer

An understanding of the risk groups in differentiated thyroid cancer is necessary before the extent of thy-

roidectomy can be discussed. Our knowledge of the prognostic factors comes from univariate and multivariate analysis of various prognostic factors that have been studied over the past two to three decades. The initial study came from the European Organization for Research and Treatment of Cancer (EORTC) Thyroid Cancer Cooperative Group in 1979.³ Similar studies were performed in the United States at the Mayo Clinic (Minn),⁴ the Lahey Clinic (Mass),⁵ University of Chicago (Ill), and Memorial Sloan-Kettering Cancer Center (NY).⁶ The major prognostic factors in all of these studies were patient age, tumor grade, distant metastasis, tumor size, and extrathyroidal extension. The prognostic factors in differentiated thyroid cancer are well described by Dean and Hay elsewhere in this issue. (pp 229-239) Similarly, they report the most important prognostic factors in the evaluation of patients with thyroid cancer as patient age, tumor grade, distant metastasis, extrathyroidal invasion, tumor size, and completeness of resection. Based on their low- and high-risk groups, survival is excellent in the low-risk group, while the disease can frequently be fatal in the high-risk group.

Investigators at the Memorial Sloan-Kettering Cancer Center⁶ divided the prognostic factors based on patient-related and tumor-related factors. Patients were divided into groups according to low, intermediate, or high risk. The low-risk group consisted of low-risk patients (under the age of 45) with low-risk tumor, and the high-risk group consisted of high-risk patients (above the age of 45) with high-risk tumor. The inter-

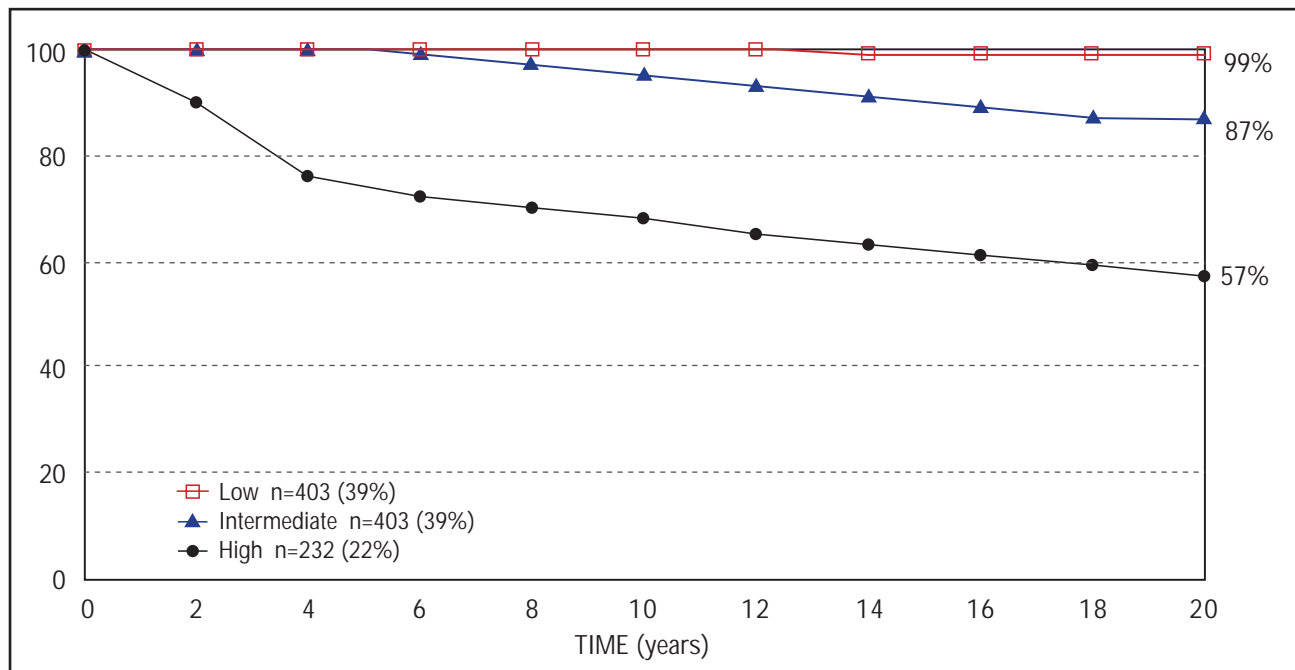


Fig 1. — Long-term survival of patients with differentiated thyroid cancer, according to risk group (based on a review of Memorial Sloan-Kettering Cancer Center thyroid data base, 1,038 patients). The separate risk categories (low, intermediate, and high) show a significant statistical difference in long-term survival.

mediate-risk group consisted of two categories: low-risk patients (under the age of 45) with high-risk tumor or high-risk patients (above the age of 45) with low-risk tumor. Based on these separate risk-group categories, investigators were able to show significant statistical differences in the survival rate. Long-term survival was 99% in the low-risk group, 87% in the intermediate-risk group, and 57% in the high-risk group.

It is clear from these risk groups that the discussion regarding the extent of thyroidectomy should be based primarily on the risk-group analysis of the patient in the operating room. In the low-risk group, where radioactive iodine treatment is generally not necessary, the removal of all gross disease — most probably with lobectomy — is satisfactory, while in the high-risk group, total thyroidectomy is indicated to facilitate RAI therapy. In the intermediate-risk group, decisions regarding the extent of thyroidectomy should be based mainly on tumor-related factors. For example, for high-risk tumor, where RAI therapy may be necessary postoperatively, a total thyroidectomy should be considered. The presence or absence of poorly differentiated carcinoma is important since these patients have more aggressive tumors, a higher chance of local recurrence, and a strong consideration for RAI and external radiation therapy. A large number of patients with poorly differentiated carcinoma do not take up RAI. Various other prognostic factors (eg, DNA ploidy, adenylate cyclase response, epidermal growth factor receptor, cathepsin, and telomerase) are analyzed in the evaluation of thyroid cancer. We will learn more about these biological prognostic factors in the future through molecular biology in thyroid cancer. Comparative genomic hybridization has been utilized in 60 patients with differentiated thyroid cancer. To clarify the role of thyroidectomy and postoperative radiation, the American College of Surgeons Oncology Group is considering instituting randomized, prospective trials to evaluate the extent of surgery and postoperative radiation. Nevertheless, with currently available information, patients can be placed in low-, intermediate-, high-risk groups (Fig 1) with long-term survival rates of 99%, 87%, and 57%, respectively. These risk groups affect the decision of optimal type of surgical resection.

Surgical Procedures for Thyroid Cancer

A major controversy involves the routine use of total thyroidectomy in differentiated thyroid cancer compared with less than total thyroidectomy. Surgical procedures such as nodulectomy and partial thyroidectomy should be abandoned for patients suspected of thyroid cancer. The minimal operation should be ipsilateral lobectomy with isthmusectomy. Routine

subtotal thyroidectomy should also be avoided for fear of leaving behind microscopic thyroid cancer and for difficulty in ablating the remaining thyroid tissue. Some reports recommend a near-total thyroidectomy, which involves leaving behind some thyroid tissue in order to preserve the blood supply to the parathyroids and the recurrent laryngeal nerve. However, if the extent of the disease and the risk-group interpretation require aggressive surgical procedure, then total thyroidectomy should be performed with an intention to leave behind no thyroid tissue. It is common that some thyroid tissue may be left behind in certain areas, eg, near the recurrent laryngeal nerve, the ligament of Berry, or the superior pole, or in the area of the pyramidal lobe. Such residual thyroid tissue can be easily ablated postoperatively. It is also important to preserve the recurrent laryngeal nerves and the parathyroids with their blood supply to minimize the complications from thyroid surgery.

Total vs Less Than Total Thyroidectomy

Proponents of routine total thyroidectomy cite several factors to support their preference: the high incidence of microscopic disease in the opposite lobe, the use of RAI dosimetry and ablation, the monitoring of recurrence with RAI scan and serum thyroglobulin, decreasing the small risk of development of undifferentiated thyroid cancer in the thyroid remnant, reducing the recurrence rate in the opposite lobe of the thyroid, and increasing the sensitivity of early detection of pulmonary metastasis and the treatment with RAI.

While these factors seem logical, they prove to be unfounded based on risk-group analysis. In the low-risk group, where long-term survival is 99%, the routine use of total thyroidectomy has no fundamental basis.⁷ Supporters of routine total thyroidectomy claim that the reduction of local recurrence and the improvement of long-term survival suggest that in high-risk patients, total or near-total thyroidectomy with RAI therapy improves survival. However, this has no implication in the low-risk group. Because most studies are retrospective and because prospective studies are difficult to conduct, the controversy will continue. In addition, most retrospective studies are difficult to interpret and involve considerable biases, depending on the institutional practice. Philosophical differences exist among surgeons, endocrinologists, and nuclear medicine physicians. The routine application of RAI dosimetry or ablation may be excessive in low-risk patients. The question is not, "What can be done?" but rather, "What is the most optimal and rational treatment?" A prospective, randomized study of total vs less than total thyroidectomy is impossible due

Indications for Total Thyroidectomy

- High-risk patients with high-risk tumor
Young patients with bulky nodal disease requiring RAI ablation
Patients with:
- gross disease in both lobes of the thyroid
 - gross extrathyroidal tumor requiring RAI ablation
 - preoperative diagnosis of poorly differentiated tumor
 - medullary thyroid carcinoma
 - thyroid cancer and a history of radiation
 - operable anaplastic thyroid carcinoma
 - distant metastasis requiring RAI ablation

to the excellent outcome in the low-risk group, the requirement of long-term follow-up, and the large number of patients needed to show any statistical difference in long-term survival outcome.

There are definite indications for total thyroidectomy, as presented in the Table. If there is a gross disease in both lobes, then a total thyroidectomy should be considered. The major argument for total thyroidectomy is the presence of microscopic disease in the opposite lobe, which may extend between 40% and 70%. However, the clinical evidence of recurrence in the opposite lobe is less than 5%. The presence of microscopic multicentric disease, noted as "laboratory cancer," has little prognostic significance. It is important to appreciate that 80% of patients will do well with lobectomy alone, 15% will require a total thyroidectomy (due to the extent of the disease) and adjuvant RAI or external radiation therapy to control locally advanced disease, and 5% will die of thyroid cancer regardless of the extent of thyroidectomy and adjuvant treatment. These are the patients in the high-risk group with locally aggressive tumor or poorly differentiated histologies.

The routine use of RAI therapy, which necessitates total thyroidectomy, remains controversial. When patients are divided into low-, intermediate-, and high-risk groups, with 99% survival in the low-risk group, no specific indications exist for the routine use of RAI ablation. It is unlikely that RAI therapy will have a major impact in the long-term survival of these patients. Indeed, in the low-risk group, the planning for RAI treatment will produce hypothyroidism for 6 to 8 weeks and may necessitate a second or third RAI dosimetry. The argument for total thyroidectomy, based on the thyroglobulin, does not appear to have a significant effect in the low-risk patient group. Thyroglobulin is a non-specific and weak tumor marker, and more studies are necessary to understand the impact of thyroglobulin in the low-risk group. In reviewing the arguments for and against total vs less than total thyroidectomy, the minimal operation for patients with solitary thyroid nodule should be lobectomy and isthmusectomy. For the

majority of patients, it is also the maximum operation. Our experience with a large number of patients with differentiated thyroid cancer indicated that tumor size was not a prognostic factor in tumors of <1 cm, 1 to 2 cm, and 2 to 3 cm until the size reached 3 to 4 cm. Specific indications for total thyroidectomy include a grossly abnormal opposite lobe, massive nodal metastasis, a high-risk patient with an extrathyroidal tumor or a large primary tumor with extracapsular tumor extension, or an elderly patient with follicular carcinoma exhibiting major capsular or vascular invasion. The routine use of total thyroidectomy in every patient with a solitary thyroid nodule is an overtreatment; more is not necessarily better, and less may mean more.

A common clinical finding is a solitary thyroid nodule in a patient undergoing thyroid lobectomy, where the frozen section is reported as follicular neoplasm and the final pathology report indicates follicular carcinoma, based on minimal capsular invasion. Controversy exists around this group of patients. A common "knee-jerk response" is to schedule completion thyroidectomy. The surgeon should re-review the pathology slides and discuss the capsular invasion with the pathologist. Minimal capsular invasion or vascular invasion (popularly called *nonthreatening malignancy* by van Herden et al⁸) indicates that additional treatment is generally not necessary unless major vascular invasion or other poor prognostic factors are present. The routine application of completion thyroidectomy in this group of patients is likely to lead to more complications with no survival benefits.

One of the major complications of routine total thyroidectomy is permanent hypoparathyroidism, which appears to be directly proportional to the extent of thyroidectomy and inversely proportional to the experience of the surgeon. The average surgeon confronted with differentiated thyroid cancer can choose virtually any operation and find support for it in the literature. However, it is important to understand the biology of the thyroid cancer, the prognostic factors, and the risk-groups, and then individualize the treatment based on risk groups. Removal of all gross tumor in patients who present with major extrathyroidal extension is also important. A common clinical problem is extrathyroidal extension with the tumor adhering to the tracheal wall or recurrent laryngeal nerve. Preoperatively, the operating surgeon must appreciate the function of the vocal cords. If the recurrent laryngeal nerve is functioning preoperatively, every effort should be made to preserve the recurrent laryngeal nerve — unless the tumor is directly invading the recurrent laryngeal nerve or there is a likelihood of leaving gross tumor behind. If the tumor is adhering to the tracheal wall, in most cases it can be easily shaved off the

tracheal wall without leaving gross tumor behind. Microscopic tumor, under these circumstances, can be managed with aggressive RAI treatment and external radiation therapy, if needed. If the tumor directly invades the tracheal wall with luminal extension, every effort should be made to remove all gross tumor, which requires sleeve resection of the trachea and end-to-end anastomosis. Strap muscles should be removed if they have been invaded by the tumor. Again, removing all gross tumor is important in this group of patients. Pathology slides should be re-reviewed to rule out poorly differentiated thyroid cancer (eg, tall cell or insular variety). In these patients, adjuvant postoperative external radiation therapy may be considered. Although experience with external radiation therapy is limited in the United States, it may be an important therapeutic modality in truly high-risk thyroid cancer patients where microscopic cancer may be left behind after surgical procedure or in high-grade tumors.

The issue of extent of thyroidectomy in well-differentiated thyroid cancer continues to be controversial. The extent of thyroidectomy should be based on prognostic factors and risk groups; the routine total thyroidectomy as a definitive surgical procedure in all patients with thyroid cancer should be avoided. As Thomas⁹ commented, "Routine use of total thyroidectomy in all patients with thyroid cancer is best avoided. An operation not worth doing is not worth doing well."

Management of Cervical Lymph Nodes

The treatment of cervical lymph nodes in differentiated thyroid cancer is generally less controversial. Even though the incidence of microscopic metastasis in the cervical lymph nodes is 30% to 50%, the standard procedure is to evaluate the paratracheal and tracheoesophageal groove to determine if any grossly enlarged lymph nodes are present. Generally, elective neck dissections are not recommended in patients with differentiated thyroid cancer since the presence of nodal metastasis has not had a major impact on the long-term outcome.¹⁰ The cervical lymph node metastasis may have a minor effect on local recurrence in the neck in high-risk patients above the age of 45.¹¹ However, in the low-risk patient, the presence or absence of nodal metastasis has no long-term survival benefit. Thus, elective neck dissection is generally not recommended at the time of thyroid surgery. However, the operating surgeon should review the tracheoesophageal groove, the superior mediastinum, and the jugular area to determine if any obvious enlarged lymph nodes are present. If so, the appropriate central compartment clearance should be undertaken. If clinically apparent metastases are evident, especially in the supraclavicular fossa, a

modified neck dissection should be considered while preserving the sternomastoid, accessory nerve, and internal jugular vein. Level I or submandibular lymph nodes are rarely involved in patients with differentiated thyroid cancer, and submandibular salivary gland excision is generally not recommended in these patients. Young patients presenting with massive nodal disease are likely to have microscopic pulmonary metastasis and should undergo a routine total thyroidectomy with modified neck dissection followed by RAI ablation.

Extent of Thyroidectomy for Medullary Thyroid Cancer

Medullary thyroid cancer is an autosomal-dominant familial disease that may present as either a sporadic or familial variety, including the multiple endocrine neoplasia type 1 (MEN-1) or type 2 (MEN-2) syndrome.¹² Patients with medullary thyroid cancer should undergo total thyroidectomy with appropriate central compartment clearance, including removal of the paratracheal nodes, the tracheoesophageal groove nodes, the nodes around the internal jugular vein, and the superior mediastinal nodes. Lateral neck dissection is generally not indicated unless enlarged lymph nodes are evident in the jugular area. In clinically apparent cervical lymph nodes in patients with medullary thyroid cancer, appropriate neck dissection should be undertaken, which may require the removal of the sternomastoid muscle or jugular vein for proper clearance. Every effort should be made to preserve the accessory nerve if it is not involved directly by the tumor. The appropriate central compartment clearance and total thyroidectomy may result in higher incidence of temporary or permanent hypoparathyroidism in this group of patients. The operating surgeon should be quite familiar with autotransplantation of the parathyroid under these circumstances, especially if the blood supply to the parathyroid gland is damaged.

Extent of Thyroidectomy for Anaplastic Thyroid Cancer

The anaplastic thyroid cancer represents one of the most aggressive cancers in the human body. For the majority of patients with anaplastic thyroid cancer, outcomes are generally fatal. The average survival in this group is 6 to 9 months, with rapid involvement of the central compartment leading to airway mortality or massive pulmonary disease. Total thyroidectomy is rarely feasible in this group of patients. However, if the patient has minimal disease and a true anaplastic thyroid cancer that appears to be surgically resectable, then appropriate total thyroidectomy with neck dissec-

tion should be considered. The surgeon's role in anaplastic thyroid cancer is to make the appropriate diagnosis and rule out lymphoma or small cell anaplastic thyroid cancer. Once the diagnosis of giant and spindle cell thyroid cancer is confirmed, with either a core biopsy or open biopsy, most of these patients are treated with aggressive chemotherapy and radiation therapy.¹³ The use of Taxol or combination chemotherapy and hyperfractionated radiation therapy seems to have some beneficial impact. However, further studies are needed on this subject.

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