Do All Cancers Need to Be Treated?
The Role of Thyroglobulin in the Management of Thyroid Cancer

The 2006 Hayes Martin Lecture

Keith S. Heller, MD

Hayes Martin died on Christmas Day 1977. I was a fellow on the head and neck service at Memorial Hospital, New York, New York, at that time. I never met Dr Martin because he had been an invalid for many years. I felt his influence constantly, though, because my teachers, my attending physicians, had all been his students, his fellows, or his colleagues. Dr Martin’s first article, co-written in 1928 with Dr Quick, described how to perform a gastrostomy. We had little else to offer our patients at that time. His last article, published in 1962, emphasized the importance of tying 1-handed knots to expedite the performance of head and neck surgical procedures. There is no one procedure that we can attribute to Dr Martin. Perhaps his most important single contribution to head and neck oncology was his recognition of the value of fine-needle aspiration biopsy (FNAB). What Dr Martin did, through his teachings and his writings, was to create a structure, not a building, but a structure within which one could provide total care for patients with head and neck cancer. His greatest contribution, his true legacy, is not what he did but those whom he trained, others whom they trained, and yet others whom we will continue to train.

When our president, Dr Jack Coleman, invited me to give this lecture, my first reaction was surprise, my second was gratitude for this honor, and my last was anxiety and apprehension. It is a great responsibility to be the Hayes Martin lecturer. I knew that I could not hope to be as entertaining as Dr Chris O’Brien when he took us on a magical mystery tour of head and neck surgery accompanied by Sgt Pepper, or as brilliant as Dr Eugene Myers as he meticulously dissected the history of the treatment of metastatic disease to the neck, and certainly not as eloquent as my friend and mentor Dr Joseph Attie as he painted a picture with words of the contributions of physicians to the arts. I am going to talk to you today about what I know best—the care of patients with thyroid cancer and share with you my concerns about the directions in which the treatment of this disease is heading.

When I was a fellow, I was taught that thyroid cancer is rare. Even today when I tell patients of their diagnosis of thyroid cancer, many react by saying, “I never heard of that. I never knew anybody who had thyroid cancer.” Thyroid cancer is no longer rare. It is estimated that this year there will be more than 30,000 new cases in the United States. This is roughly the same number as cancers of the oral cavity and oropharynx combined, far more than new cancers of the larynx, more than cancers of the ovary, about the same as cancers of the pancreas, and almost half as common as all lymphomas.

In addition, we seem to be facing an epidemic of thyroid cancer. After a relatively long period of stability, the incidence of thyroid cancer has virtually doubled in the past 20 years. At a time when the incidence of most cancers is either decreasing, relatively stable, or increasing only minimally, thyroid cancer is increasing at a rate far greater than any other cancer in this country; a rate that is now approaching 7% a year.

Why is this happening? Is this increase real? Might we be seeing a delayed
effect of radioactive fallout from the atmospheric nuclear tests of the early 1950s? I think it is unlikely. Is it possible that other environmental influences are contributing to this? It is certainly possible, but none have been identified. We have known for many years that clinically occult thyroid cancer is very common. Autopsy studies have shown thyroid cancer in as many as 36% of patients with no antecedent history of thyroid cancer. In a recent article in JAMA, the authors observed that the increased incidence of thyroid cancer is almost exclusively due to an increase in incidence of papillary cancer, about 50% of this increase is due to cancers smaller than 1 cm, and 87% is due to cancers smaller than 2 cm.9

I do not believe that this epidemic is real. It is due to improved diagnostic scrutiny, ultrasonography, and other imaging studies and the increasing use of ultrasound-guided FNAB. We may be diagnosing and treating cancers that have no clinical significance. I would like to share with you some of my own data. I have been privileged, in the 28 years that I have been in practice, to have personally operated on and cared for almost 1000 patients with thyroid cancer, including the initial operating surgeon on about 800 patients with differentiated thyroid cancer (DTC). I compared 100 consecutive patients operated on between 1991 and 1995 with the most recent 100 patients with DTC and determined the way in which these thyroid cancers were initially discovered (Table 1). There has been a profound change in these 15 years. In the earlier group, neck masses were felt by the physician or patient in about 90%, including 9% with palpable nodes. In recent times, patients presenting with palpable nodes have been rare, but 27% of cancers were discovered with imaging studies. These have included carotid duplex scans, magnetic resonance imaging scans of the neck to evaluate neck pain, and more recently positron emission tomographic scans performed to evaluate other malignant lesions. They also include what I consider unindicated thyroid imaging, for example, in patients who have vague complaints that are not an appropriate indication for ultrasonography. We are finding cancers now that would not have been found 15 years ago.

For as long as I have been coming to meetings of this society or of its predecessor societies we have entertained each other with stimulating, provocative, passionate presentations and panel discussions arguing the merits of total thyroidectomy vs lobectomy. We have related the epic tales of heroic operations performed for mass at these meetings. Much of the early work on risk stratification was first presented at these meetings. But while we have been focusing on the surgical treatment of thyroid disease, our colleagues in endocrinology have moved in a different direction. There has been a paradigm shift in the treatment of patients with thyroid cancer from the treatment of clinically obvious macroscopic disease to the detection and eradication of all disease, macroscopic and microscopic, identified using increasingly sensitive diagnostic tests. There is no longer a controversy about the extent of surgery to be performed or the need for radioactive iodine (RAI) ablation. Most endocrinologists in this country believe that the appropriate initial treatment for almost all DTC is total or near-total thyroidectomy followed by RAI ablation. I know that there are those of you who disagree strongly with this approach, but I believe this is the standard of care for most patients in the United States today.

Earlier this year, the American Thyroid Association published its guidelines for the management of patients with thyroid nodules and DTC.10 The group that wrote these guidelines was relatively ecumenical. In addition to endocrinologists it included a surgeon and a sonographer. These guidelines are evidence-based and include the references that support each recommendation. They represent a true consensus of most of those treating thyroid cancer in the United States. The guidelines are in the form of 85 specific recommendations. Each one is a question followed by the supporting evidence and then the answer. I would like to concentrate on 6 of these recommendations.

The first 2 are related to cervical lymph nodes. Guideline R21 states that preoperative ultrasonography to evaluate the contralateral lobe and bilateral cervical lymph nodes, central and lateral, should be performed in all patients undergoing surgery for a biopsy-proven thyroid cancer. Guideline R22 states that a neck dissection should be performed if metastatic adenopathy is detected either clinically or by imaging followed by FNAB. The consequences of these recommendations are significant. We know that occult lateral cervical lymph node metastases are common. In 1971, Attie et al11 presented their experience with elective neck dissection for DTC. In 115 patients who underwent elective neck dissection, 69% had positive nodes. In their patients with positive nodes there were no recurrences or deaths. In 1996, Grebe and Hay12 published an excellent review of the literature, including all articles correlating the presence of metastatic disease in the neck with prognosis. Not a single article demonstrated a correlation between positive nodes and ultimate survival in patients with papillary cancer. The vast majority of articles showed no correlation with prognosis in patients with follicular or mixed papillary and follicular carcinoma. I do believe, and I think Hughes and colleagues13 at Memorial Hospital have shown us, that older patients with grossly positive nodes have a decreased survival rate. We need to consider very seriously the consequences of this aggressive search for metastatic nodes in the neck. We will be performing many neck dissections with their associated morbidity without proof that those neck dissections will improve survival.

I would like to devote most of the remainder of my talk to a discussion of the role of thyroglobulin in the

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Table 1. Manner in Which Well-Differentiated Thyroid Cancer Was Discovered in 2 Groups of 100 Consecutive Patients Each, Treated From 1991-1995 and 2004-2005

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Patient or physician</td>
<td>79</td>
<td>66</td>
</tr>
<tr>
<td>Incidental imaging</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Thyroid imaging</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Cervical nodes</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

a Data are given as number of patients.
management of DTC. That role is summarized in these 4 recommendations from the guidelines. Thyroglobulin levels should be measured every 6 to 12 months (Guideline R43). In low-risk patients who have had thyroidectomy and RAI ablation, stimulated thyroglobulin levels should be measured about 1 year after the initial treatment (Guideline R45). Cervical ultrasonography should be performed on a regular basis. How often and for how long depends on the patient’s risk of recurrence and thyroglobulin level (Guideline R48). Finally, RAI therapy might be considered in patients without documented metastatic or recurrent cancer but who have an elevated or rising thyroglobulin level (Guideline R78).

To understand the basis for these recommendations I would like to review with you in detail some of the articles that have led to these guidelines. The importance of thyroglobulin as a tumor marker was first reported in 1982 by Colacchio et al. They studied 37 patients known to have recurrent or metastatic DTC. Thyroglobulin was elevated in 29 of these patients while they were taking suppressive doses of thyroid hormone. When thyroid hormone treatment was withdrawn and the patients were allowed to become hypothyroid, thyroglobulin level was elevated in all but 3. Among patients with elevated thyroglobulin levels, the total body scan results were negative in 6. Three patients had positive scan results and no elevation of thyroglobulin. In 30 control patients with very small cancers who were assumed to be cured and disease free, none had either suppressed or stimulated thyroglobulin elevation. They recommended that thyroglobulin stimulated by T3 and T4 withdrawal be measured at the same time that RAI scanning was performed and that if the results were negative, further follow-up could be with thyroglobulin alone. Thyroglobulin measurement, both suppressed and stimulated by thyroid hormone withdrawal, joined RAI scanning as part of the routine follow-up of patients with DTC.

This was the standard of care until recombinant human thyroid-stimulating hormone (rhTSH) became available. It was first necessary to prove that rhTSH stimulation was the equivalent of thyroid hormone withdrawal for the performance of RAI scanning and thyroglobulin measurement. In a multicenter study of 229 patients, each of whom was studied with both thyroid hormone withdrawal and rhTSH stimulation, it was shown that there was concordance in the results in 89% of patients and that rhTSH stimulation was more sensitive than thyroid hormone withdrawal in 4% and less sensitive in 8%. For the measurement of thyroglobulin elevation, rhTSH stimulation and thyroid hormone withdrawal were also equivalent. The authors concluded that the combination of rhTSH-stimulated thyroglobulin measurements and RAI scanning would detect 93% of patients with either recurrent disease or residual thyroid tissue in the thyroid bed and 100% of patients with metastatic cancer.

The need for RAI scanning in the follow-up of patients with DTC was also questioned. Three studies reached similar conclusions. David et al. studied 33 low- and high-risk patients with DTC treated with total thyroidectomy and RAI ablation. Of these, 29 had undetectable, suppressed thyroglobulin levels. Stimulation with rhTSH caused no increase in thyroglobulin in 25 patients, who also had negative RAI scans. Stimulated thyroglobulin increased in 4, only 2 of whom had positive scan results. In the 4 patients with elevation of suppressed thyroglobulin, all of whom had distant metastases, stimulated thyroglobulin increased in all 4, but the RAI scan findings were positive in only 3. In this study, RAI scanning did not improve the sensitivity of rhTSH-stimulated thyroglobulin measurement. In a similar study, Wartofsky et al. described 300 low-risk patients treated for DTC, all of whom had low or unmeasurable suppressed thyroglobulin levels up to 10 years after total thyroidectomy and RAI ablation. In 18%, rhTSH-stimulated thyroglobulin levels increased significantly, including 11% whose increases were more than 5 ng/mL. In 62% of these patients, RAI scanning had been negative. This study, too, suggests that RAI scanning is not as sensitive as rhTSH-stimulated thyroglobulin measurement. Mazzaferri and Kloos studied 107 patients, of whom 50% were considered at high risk for development of metastatic disease. All had undetectable suppressed thyroglobulin. Eleven of 20 patients with stimulated thyroglobulin levels higher than 2 ng/mL were found to have metastatic disease. In none of these was the site of metastatic disease identified on the RAI scan.

The magnitude of the increase in stimulated thyroglobulin level correlates with the likelihood of metastatic disease. Haugen et al. described 83 patients initially treated with thyroidectomy and RAI ablation, 17 of whom had negative total body scan findings but elevated stimulated thyroglobulin levels. When the stimulated thyroglobulin level was less than 10 ng/mL, only 1 patient was found on ultrasonography to have positive nodes. When the stimulated thyroglobulin level was greater than 10 ng/mL, 6 of 7 patients were found to have metastatic disease. Undetectable stimulated thyroglobulin at the initial follow-up is highly predictive of complete and persistent remission. Pacini et al. studied 315 patients treated with total thyroidectomy and RAI ablation who had undetectable stimulated thyroglobulin at the time of their initial follow-up RAI scan. Findings on RAI scanning were negative or showed minimal uptake in the thyroid bed. Only 2 patients developed recurrent disease, both to cervical lymph nodes, after a follow-up of at least 12 years. It seems safe to conclude that not only does an elevated stimulated thyroglobulin detect disease but an undetectable stimulated thyroglobulin at the first initial follow-up evaluation is predictive of cure and that RAI scanning provides little additional information.

By 2003, the data on rhTSH-stimulated thyroglobulin as a monitoring method were so compelling that a consensus report was published. A meta-analysis of more than 1000 patients identified 784 whose initial posttreatment thyroglobulin levels while receiving suppressive doses of thyroid hormone was less than 1 ng/mL. Of this group, 168 had an rhTSH-stimulated thyroglobulin higher than 2 ng/mL, of whom 53 were found to have metastases. In this group, RAI scanning identified metastases in only 11 patients. The authors conclude with the following recommendations:

1. TSH-stimulated thyroglobulin measurement is sufficient for the follow-up of low-risk patients with no clinical evidence of disease.
2. If the stimulated thyroglobulin level is higher than 2 ng/mL, further evaluation is necessary.
3. If the initial stimulated thyroglobulin level is less than 0.6 ng/mL, further follow-up can be limited to l-thyroxin–suppressed thyroglobulin and physical examination.

Ultrasonography has assumed an increasingly important role in the evaluation of patients with DTC. Pacini et al22 described 294 patients with undetectable suppressed thyroglobulin. Of these, 250 had undetectable stimulated thyroglobulin. In that group, high-resolution ultrasonography and FNAB detected 3 patients with metastatic cancer in lateral cervical lymph nodes. In the group with elevated stimulated thyroglobulin levels (≥ 2 ng/mL), RAI scanning identified positive nodes in 4 patients. Ultrasonography showed positive nodes in 2 additional patients. In this group, ultrasonography identified 5 patients, 2% of the total, with lymph node metastases that would not otherwise have been identified.

Finally, Torlontano et al23 studied 456 patients with low-risk papillary cancer, of whom 38 were identified with ultrasonography to have positive nodes 1 to 5 years after their initial treatment. Seven patients had undetectable stimulated thyroglobulin. All of the nodes identified in this group were smaller than 1 cm. All were identified by the detection of thyroglobulin messenger RNA (with polymerase chain reaction) in the lymph node aspirate, not with standard histologic stains. In the 18 patients whose stimulated thyroglobulin level was less than 10 ng/mL, the largest node was 1.5 cm. Eight of these were identified with polymerase chain reaction only. Even in the group with stimulated thyroglobulin levels higher than 10 ng/mL, the largest node was only 1.5 cm; 5 of 13 were identified only with polymerase chain reaction.

All of these studies, guidelines, and recommendations lack data that prove that the presence of these minimally involved lymph nodes in any way affects the patient’s prognosis nor are there any data that the removal or treatment of these nodes improves their survival. I find these guidelines very troubling for those reasons.

Thyroid cancer has become relatively common. Death from thyroid cancer remains rare. Of the 30,000 new cases of thyroid cancer expected this year, only 1500 will result in deaths.6 While the incidence of thyroid cancer has increased dramatically, the death rate has been stable. How is this explained? One might assume that our treatments are getting better. I do not really believe that is the case. It is helpful to identify which patients actually die of thyroid cancer. The National Cancer Database includes more than 50,000 patients with thyroid cancer treated between 1985 and 1995.24 In that cohort, 2% of patients had anaplastic thyroid cancer, with a mortality of 85%. Extrapolating that to our current number of thyroid cancers per year we would expect roughly 500 deaths this year from anaplastic cancer. A similar calculation for medullary cancer yields an additional 300 deaths. Patients with DTC who present with stage IV disease were found to have 50% mortality. That would account for another 150 deaths. About 1000 of the 1500 deaths expected this year would be due to these aggressive cancers. In addition, other aggressive histologic subtypes such as tall cell and insular carcinoma need to be considered as well as other high-risk patients. Even if these calculations overestimate the number of aggressive cancers, the obvious conclusion is that very few patients die of apparently curable, low-risk thyroid cancer. Most patients who ultimately die of thyroid cancer can be identified at the time of their initial treatment and followed up aggressively and appropriately.

The Mayo Clinic has carefully studied its large series of 2300 patients with thyroid cancer who were treated between 1940 and 1999.25 All of these had complete resection of all disease in the neck and were followed up for a median of 15 years. The cancer-specific mortality of these patients was 4%. All deaths occurred in the first 15 years. The recurrence rate in the group treated between 1950 and 1999 was only 13%. While recurrences continue for at least 25 years, most occur within the first 5 years after treatment. Most important, in low-risk patients, defined as having pTNM stage I and II disease or MACIS (distal metastasis, patient age, completeness of resection, local invasion, and tumor size) score less than 6, and including almost 85% of all patients, the cancer-specific 10-year mortality was zero. None of these patients died. The 10-year recurrence rate was less than 10%. How can we improve on this by using polymerase chain reaction to detect microscopic metastases in cervical lymph nodes?

Finally, I would like to share with you my own data. Between 1979 and 2005, I operated on 809 patients with previously untreated DTC. The current status of all of these patients was obtained by contact with the patient and his or her physician or by accessing the social security database. The median follow-up period in this group of patients was more than 5 years and the average follow-up was 82 months. Of the 360 patients younger than 45 years at the time of initial treatment, 99% are alive at

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Table 2. Cancer-Related Deaths Among Patients With Differentiated Thyroid Cancer, 1979-2005

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>Stage</th>
<th>Pathology</th>
<th>Survival, y</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/69</td>
<td>T4a N1a–IV</td>
<td>Papillary</td>
<td>5</td>
<td>Lung and bone metastases</td>
</tr>
<tr>
<td>F/69</td>
<td>T4a N0–IV</td>
<td>Papillary</td>
<td>5</td>
<td>Local/regional recurrence</td>
</tr>
<tr>
<td>M/50</td>
<td>T3 N1a–III</td>
<td>Tall cell</td>
<td>7</td>
<td>Local/regional recurrence</td>
</tr>
<tr>
<td>F/83</td>
<td>T1N1b–III</td>
<td>Papillary</td>
<td>8</td>
<td>Bone and kidney metastases</td>
</tr>
<tr>
<td>M/67</td>
<td>T2N1b–III</td>
<td>Papillary</td>
<td>6</td>
<td>Local/regional recurrence</td>
</tr>
<tr>
<td>M/64</td>
<td>T2N1b–III</td>
<td>Poorly differentiated papillary</td>
<td>6</td>
<td>Lung and bone metastases</td>
</tr>
<tr>
<td>F/70</td>
<td>T3N1a–III</td>
<td>Poorly differentiated papillary</td>
<td>4</td>
<td>Local/regional and lung metastases</td>
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<tr>
<td>F/61</td>
<td>T3N1a–III</td>
<td>Poorly differentiated papillary</td>
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<td>M/39</td>
<td>T3N0–I</td>
<td>Hürthle cell</td>
<td>5</td>
<td>Bone metastases</td>
</tr>
</tbody>
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the time of this writing. Three died of non–cancer-related causes. One patient died of thyroid cancer. Of the 449 patients aged 45 years or older, 91% are alive at the time of this writing. Of the 40 patients who died, only 8 died of thyroid cancer. Table 2 summarizes the characteristics of the patients who died. The only patient younger than 45 years was a 39-year-old man with a T3 Hurthle cell cancer treated aggressively with total thyroidectomy and RAI ablation, who died 5 years later of widespread bony metastases. The disease did not recur in the neck. The other 8 deaths were of patients older than 45 years, with most being older than 60 years. At their initial presentation, it was apparent that all these patients were at high risk of recurrence and death. Four had aggressive histologic changes, 2 presented with stage IV disease limited to the neck, and 2 were elderly patients with bulky lateral cervical lymph node metastases. A good prognosis would not have been predicted at the time of initial treatment in any of these patients, with the possible exception of the 39-year-old.

We have embarked on a quixotic quest to rid our patients of microscopic and probably clinically unimportant thyroid cancer. We need to refocus our efforts, not to detect more occult disease, but to identify and cure those few patients whose disease is likely to shorten their lives. We need to improve our accuracy in the evaluation of the indeterminate thyroid nodule. We are performing far too many unnecessary thyroidectomies. We need to have a greater appreciation of the importance of risk stratification in predicting not only those who will do well, but those who will almost certainly do poorly. We need to concentrate less on the detection of subclinical disease and more on the identification of patients with clinically low-risk disease who are at a higher risk of recurrence. We need to learn to identify those patients with small cancers who perhaps do not need any treatment at all. Finally, we need to improve our treatment of patients with advanced and aggressive disease.

It is very appropriate that I have had the opportunity to present these thoughts at this meeting, a combined meeting of basic scientists and clinicians. I am a clinician and these are clinical problems. Their solution, however, will come not from the clinic but from the laboratory through a better understanding of the molecular and genetic basis of thyroid cancer.

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Additional Information: I would like to dedicate this lecture to the memory of Dr George Sisson, a giant among head and neck surgeons, a founder of the American Society for Head and Neck Surgery, and a former Hayes Martin lecturer, who recently died, and to Dr Martin.