PAPER

Need for a Revised Staging Consensus in Medullary Thyroid Carcinoma

Sarah Y. Boostrom, MD; Clive S. Grant, MD; Geoffrey B. Thompson, MD; David R. Farley, MD; Melanie L. Richards, MD; Tanya L. Hoskin, MS; Ian D. Hay, MD, PhD

Hypothesis: Assessing prognosis for medullary thyroid cancer remains challenging and inexact. We hypothesize that the 1997 TNM staging criteria, especially for stage IV, are more accurate than the current 2002 staging system.

Design: Retrospective cohort study.

Setting: Tertiary referral center.

Patients: One hundred seventy-three patients surgically treated for medullary thyroid cancer from January 1, 1980, to December 31, 2007.

Main Outcome Measures: Patients were staged according to 1997 and 2002 TNM criteria and according to treatment result: biochemically cured (normal calcitonin level); clinically cured (elevated calcitonin level but no evidence of disease by imaging); or not cured. Survival was calculated from initial surgery to death or last follow-up. Analysis used McNemar test to compare paired proportions and Kaplan-Meier estimation with log-rank tests.

Results: A significantly higher proportion of patients were classified as having stage IV cancer using 2002 criteria compared with 1997 criteria (33% vs 7%, respectively; \( P < .001 \)). Stage IV, 5-year overall survival was 82% (95% confidence interval, 72%-93%) with 2002 criteria vs 46% (95% confidence interval, 22%-93%) with 1997 criteria. Despite 15 of 36 clinically cured patients (42%) being classified as having stage IV cancer (13 patients with stage IVa cancer, 2 patients with stage IVb cancer) by the 2002 criteria, the observed overall survival of the clinically cured group at 5, 10, and 15 years was 100%, 100%, and 79%, respectively (\( P = .7 \) compared with those biochemically cured).

Conclusions: The current 2002 TNM staging for medullary thyroid cancer appears inadequate, especially for patients with stage IV cancer. Elevated but stable calcitonin levels often do not portend unfavorable outcome. Patients with lymph node metastases, irrespective of their location, but without distant disease would seem best classified as having stage III cancer.

Arch Surg. 2009;144(7):663-669

Medullary thyroid carcinoma (MTC) accounts for 5% to 10% of thyroid cancers and is characterized by distinctive biochemical markers and genetic linkage.\(^1\,^2\) The biological behavior of MTC is highly variable, ranging from decades of indolent disease to a rapidly progressive fatal malignant neoplasm. Thus, assessing prognosis for MTC remains challenging and inexact. Hereditary MTC represents a prime example of the benefits of translational science. The RET proto-oncogene, responsible for the predictable development of hereditary MTC, has been localized, its mutations have been defined, and when identified by a blood test the cancer can be totally prevented by preemptive thyroidectomy. However, approximately 80% of MTC tumors are discovered clinically, which implies macroscopic tumors in the thyroid often with associated lymph node metastases (LNMs). Cure can be achieved if the disease is confined to the thyroid, but LNMs are usually viewed as a major barrier preventing biochemical cure, or normalization of the calcitonin level. Considerable attention has been focused on eradicating LNMs producing various types of extraordinarily meticulous, highly aggressive, extensive lymph node dissections including bilateral modified radical neck dissections plus median sternotomy and mediastinal lymphadenectomy.\(^3\) Unfortunately, sustained eucalcitoninemia has been achieved in only a small minority of patients with LNMs. Nevertheless, many patients with MTC may enjoy prolonged survival and remain clinically well with no evidence of disease by examination or imaging but with persistently elevated calcitonin levels. Apparently influenced by the statisti-

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤1 cm, limited to the thyroid</td>
<td>Tumor ≤2 cm, limited to the thyroid</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;1 to ≤4 cm, limited to the thyroid</td>
<td>Tumor &gt;2 to ≤4 cm, limited to the thyroid</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;4 cm, limited to the thyroid</td>
<td>Tumor &gt;4 cm, limited to the thyroid or minimal extrathyroid extension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size extending beyond the thyroid capsule</td>
<td>T4a: tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve; T4b: tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels</td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis; N1a: metastasis in ipsilateral cervical lymph nodes; N1b: metastasis to level VI mediastinal lymph nodes; N1c: metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph nodes</td>
<td>Regional lymph node metastasis; N1a: metastasis to level VI (pretaracheal, paratracheal, and prelaryngeal); N1b: metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes</td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Table 2. Comparison of the 1997 and 2002 Cancer Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Category</th>
<th>N Category</th>
<th>M Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Iva</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Ivb</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IVc</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

©2009 American Medical Association. All rights reserved.

Table 1. Comparison of the 1997 and 2002 TNM Criteria

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Category</th>
<th>N Category</th>
<th>M Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Iva</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Ivb</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IVc</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>


性格 rare restoration of normal calcitonin levels in patients with internal jugular LNMs, the sixth edition of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer TNM classification for thyroid carcinoma was revised (Table 1 and Table 2). In contrast to the fifth edition where all LNMs (without distant disease) were classified as stage III, the sixth edition included any lateral internal jugular LNMs in stage IV disease. The accompanying AJCC observed survival graph depicted stage IV disease with a 5-year survival of about 20% (Figure 1). This change carries with it very important ramifications. Just as a single example, until recently, nonsurgical treatments of MTC had very limited success. However, recent early evidence offers hope for antitumor targeted therapy. Accurate tumor staging with corresponding predictable clinical outcomes would seem important in differentiating patients who would benefit from such treatment while sparing po-

Figure 1. Five-year observed survival by combined American Joint Committee on Cancer stage for medullary carcinoma of the thyroid gland, 1985 to 1991. The 95% confidence intervals (CIs) correspond to survival rates at year 5. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, sixth edition (2002) published by Springer Science and Business Media LLC, http://www.springerlink.com.
tially toxic side effects and expense for patients who may not need additional treatment. We hypothesize that the new stage IV classification in the sixth edition, which portrays a bleak prognosis, inappropriately encompasses many patients with well-controlled disease who have a much better survival. Thus, we propose that the 1997 fifth edition TNM staging criteria, especially for stage IV, are more accurate than the current 2002 sixth edition TNM staging criteria.

METHODS

A retrospective institutional review board–approved review of the 180 consecutive patients who underwent primary surgery for MTC between January 1, 1980, and December 31, 2007, at Mayo Clinic, Rochester, Minnesota, was performed. Seven patients were excluded based on final pathological analysis of C-cell hyperplasia. Data elements included demographics, presentation, type of MTC, preoperative imaging results, operative and pathology details, and postoperative complications. Specifically, a central neck lymph node dissection was defined either by the surgeon’s specific comment in the operative note or by 5 or more central nodes verified on the pathology report. Central lymph node sampling was defined similarly as either a specific note or fewer than 5 nodes indicated on the pathology report. A modified radical neck dissection included compartment dissections of level III, level IV, and the anterior aspect of level V, with or without the addition of level II lymph nodes. Through review of patient histories and direct contact, we recorded follow-up imaging results, laboratory values, and outcome. Cancer was staged according to the 1997 and 2002 TNM criteria. In addition, patients were categorized as “biochemically cured” (no evidence of disease by examination or imaging but an elevated calcitonin level), “clinically cured” (no evidence of disease by examination or imaging but an elevated calcitonin level), or not cured. Survival was calculated from initial surgery to death or last follow-up. The analyzed end points were disease-free and overall survival according to stage and biochemically vs clinically cured. Analysis was performed using McNemar test to compare paired proportions and Kaplan-Meier estimation with log-rank tests. Statistical significance was set at $P<.05$.

RESULTS

Of the 180 patients, 7 were found to have only C-cell hyperplasia on final pathological diagnosis and were excluded, leaving a study group of 173 patients (86 males and 87 females). The mean age was 45.5 years (range, 2-92 years). Patients were followed up until death or, in surviving patients, for a mean of 84.4 years (range, 0-23.4 years). Sporadic, multiple endocrine neoplasia type 2A, familial, and multiple endocrine neoplasia type 2B subtypes of MTC were found in 97 patients (56%), 47 patients (27%), 25 patients (15%), and 4 patients (2%), respectively. A total or near-total thyroidectomy was performed in 162 patients (94%), a lobectomy was performed in 10 patients (6%), and 1 patient underwent a debulking procedure. The median tumor size was 1 cm and multicentricity was found in 54 patients (31%). Central neck lymph node dissection and sampling were performed in 114 patients (66%) and 29 patients (17%), respectively, with an average of 6.7 nodes dissected. Central neck nodes were not pathologically evaluated in 30 patients (17%). Of the patients with central nodes evaluated, 77 (54%) had positive nodes, with an average of 2 metastatic nodes. Fifty-three patients (31%) underwent a modified radical neck dissection with an average of 22 nodes dissected. Eight patients (5%) underwent lateral lymph node sampling, and lateral nodes were not pathologically evaluated in 112 patients (65%). Of the patients with lateral nodes evaluated, 51 (84%) had positive lateral nodes with an average of 7.4 nodes positive for metastatic disease. Operative complications included hypoparathyroidism in 10 patients (6%) and unintentional recurrent laryngeal nerve paralysis in 2 patients (1%).

Comparing disease staging from the fifth (1997) and sixth (2002) edition systems, there was a shift of about 10% from stage II to stage I. More dramatic, however, was the stage IV increase from only 7% to 33% ($P<.001$) with a corresponding decrease in stage III (Table 3). Overall survival at 5 years was 46% (95% confidence interval, 22%-93%) in patients with stage IV cancer using the 1997 criteria, whereas patients with stage IV cancer per the 2002 criteria had 3-year survival of 82% (93% confidence interval, 72%-93%) (Figure 2 and Figure 3). In addition, overall survival was similar ($P=.54$) between stages III and IVa (96% and 94%, respectively, at 5 years) using 2002 criteria, whereas overall survival in stages IVb and IVc was significantly lower (30% and 56%, respectively, at 5 years) (Figure 4).
At a mean follow-up of 8.4 years, 82 patients (47%) had elevated calcitonin serum levels, 78 (45%) had normal calcitonin serum levels, and 13 (8%) were lost to follow-up. Thirty-six patients (21%) had elevated calcitonin serum levels but no evidence of disease on imaging (ie, they were clinically cured). Seventy-eight patients (45%) had no evidence of disease and normal calcitonin levels (ie, they were biochemically cured). Forty-six patients (27%) had elevated calcitonin levels as well as imaging-confirmed recurrence and are alive with disease but considered not cured.

Overall survival by treatment group comparing biochemically cured patients, clinically cured patients, and patients not cured is shown in Figure 5. Although 15 of the 36 clinically cured patients (42%) were classified as having stage IV cancer (13 patients with stage IVa cancer, 2 patients with stage IVb cancer) by the sixth edition criteria, the observed overall survival of the clinically cured group at 5, 10, and 15 years was 100%, 100%, and 79%, respectively. Overall 5-year survival was similar between stages III and IVa (96% and 94%, respectively) according to the sixth edition criteria, whereas stages IVb and IVc demonstrated poorer outcomes (50% and 56%, respectively). Strikingly similar survival over 20 years was achieved by patients who were biochemically cured compared with those who were clinically cured, in marked contrast to those categorized as not cured. It is readily apparent that when the sixth edition of the AJCC criteria for stage IV MTC are applied to our patient population, the 5-year survival of 82% is vastly superior to the approximate 20% survival depicted on the AJCC published survival curves. Even when the fifth edition stage IV criteria are applied, our 5-year survival of 46% far exceeds the 20% survival from the AJCC.

In contrast to the AJCC survival data, recently published 5-year survival estimates (Table 4) suggest approximately 80% to 85% for lymph node–positive patients and roughly 50% to 60% for patients with distant disease. Oskam et al. noted a less than 20% disease-free survival at 3 years with incomplete resection. Modigliani et al. reported a 10-year overall survival of 71% for patients with MTC and LNMs and 21% for those with distant disease. Of these patients, biochemical cure (normal calcitonin level) was achieved in 16% of the patients with LNMs and only

**COMMENT**

In our study, 25% of patients with stage III cancer by the AJCC fifth edition (1997) staging criteria would be reclassified as having stage IV cancer according to the sixth edition (2002) criteria. Yet, the stage IV, 5-year overall survival was 82% with the sixth edition criteria vs 46% with the fifth edition criteria. Moreover, despite 15 of 36 clinically cured patients (42%) being classified as having stage IV cancer (13 patients with stage IVa cancer, 2 patients with stage IVb cancer) by the sixth edition criteria, the observed overall survival of the clinically cured group at 5, 10, and 15 years was 100%, 100%, and 79%, respectively. Overall 5-year survival was similar between stages III and IVa (96% and 94%, respectively) according to the sixth edition criteria, whereas stages IVb and IVc demonstrated poorer outcomes (50% and 56%, respectively). Strikingly similar survival over 20 years was achieved by patients who were biochemically cured compared with those who were clinically cured, in marked contrast to those categorized as not cured. It is readily apparent that when the sixth edition of the AJCC criteria for stage IV MTC are applied to our patient population, the 5-year survival of 82% is vastly superior to the approximate 20% survival depicted on the AJCC published survival curves. Even when the fifth edition stage IV criteria are applied, our 5-year survival of 46% far exceeds the 20% survival from the AJCC.

In contrast to the AJCC survival data, recently published 5-year survival estimates (Table 4) suggest approximately 80% to 85% for lymph node–positive patients and roughly 50% to 60% for patients with distant disease. Oskam et al. noted a less than 20% disease-free survival at 3 years with incomplete resection. Modigliani et al. reported a 10-year overall survival of 71% for patients with MTC and LNMs and 21% for those with distant disease. Of these patients, biochemical cure (normal calcitonin level) was achieved in 16% of the patients with LNMs and only
6% of patients with distant metastases. Similarly, Boikos and Stratakis stated that even with persistently elevated calcitonin levels, the 5- and 10-year expected survivals would be 80% and 70%, respectively. In analyzing Surveillance, Epidemiology, and End Results Program data, Roman et al found that the extent of lymphadenectomy did not appear to impart additional benefit (to the extent of thyroidectomy) with regard to survival. Therefore, it appears that our results are commensurate with prior published survival rates for patients grouped with LNMs and for patients grouped separately with distant disease. Additionally, even though the pure definition of cure is a return to a normal calcitonin level, the survival curves for biochemical and clinical cure are not significantly different even 15 to 20 years postoperatively.

What might have been the rationale for the changes between the fifth and sixth editions of the AJCC staging criteria? The oncologic progression of MTC outside of the thyroid gland follows a reasonably predictable pattern, first to locoregional cervical lymph nodes, then to local surrounding structures, followed by lung, liver, and bone metastases. For individual patients, however, sometimes even within the same family with the same RET mutation, the rate and extent of disease progression may be markedly different. The AJCC and International Union Against Cancer TNM classification applied generally to malignant neoplasms reserves stages I and II for favorable prognosis with a low risk of mortality. Stage III follows a moderate risk of mortality, and stage IV usually reflects systemic disease with a high risk of mortality, quite often within 5 years of diagnosis. To be meaningful, survival curves by stage should show separation—distinctly different outcomes.

In the last decade, great emphasis has been placed on the near futility of surgically restoring calcitonin levels to normal in the face of LNMs. Wells and Nevins stated that patients with MTC presenting as a thyroid nodule “are usually incurable because the cancer has already metastasized to regional lymph nodes or distant sites.” Machens et al found that only one-third of patients undergoing surgery for node-positive MTC could have their calcitonin levels restored to normal, and if there were more than 9 LNMs, if there were central compartment (level VI) LNMs plus LNMs in one of the lateral jugular chains, or if mediastinal LNMs were present, virtually no patient could be biochemically cured. In fact, the same group concluded a year later that “once lymphatic dissemination has occurred, biochemical cure . . . may be beyond reach despite radical surgery on the neck and mediastinum.” The M. D. Anderson Cancer Center group stages cancer in their patients according to physical examination and imaging results rather than reporting cure according to calcitonin levels. In part, this may be owing to the fact that of 60 patients with no distant disease and excluding those undergoing surgery for only screen-detected disease, only 6 (10%) had persistently undetectable calcitonin levels. Perhaps the sixth edition was revised to reflect the rare biochemical curability of lateral jugular LNMs by shifting patients with positive nodes outside of compartment VI to being classified as having stage IVa cancer.

The AJCC and International Union Against Cancer TNM classification is effectively and widely used for differentiated thyroid carcinoma. Appropriate, careful analysis of papillary thyroid carcinoma has led to incorporating age as a crucial factor in disease staging. Analogous prognostic factors may improve the staging classification when applied to patients with MTC. Such factors that have been proposed include age, sex, and calcitonin doubling times.

Cancer staging overall is an essential component of management and aids in successful treatment, prognostication, and information exchange between clinicians and institutions involved in patient care. Importantly, staging may impact decisions regarding subsequent surgical procedures and applicability of other adjuvant therapies. For clinical application and success, staging systems should exhibit predictability, reproducibility, and applicability. Furthermore, classification systems should bear a direct relationship with outcome. However, the applicability of the current AJCC criteria for MTC is questionable. While the fifth edition survival curves follow a predicted pattern of patient disease and survival that is stage dependent, the sixth edition survival curves lack this reproducibility. Patients classified as having stage III and IV disease have similar disease-free and overall survival curves.

Therefore, in contrast to the current staging criteria that subdivide stage IV, revision of the current system may provide a more accurate assessment of disease status and prognosis. For now, patients with LNMs, irrespective of their location, but without distant disease would seem best classified as having stage III cancer. This would certainly be concordant with other stage III diseases with intermediate curability and survival.

The value and implication of calcitonin levels are not yet well elucidated. There seems to be no debate that an elevated calcitonin level must mean disease exists, but whether it is clinically meaningful is difficult to assess, at least in real time. The overall survival curves showing equivalent outcomes for biochemical cure compared with clinical cure would seem to indicate that at least when calcitonin levels are elevated but stable, they often do not portend unfavorable outcome. We must continue to strive for an even better understanding and definition of MTC disease behavior to allow introduction of newly evolving targeted therapies at optimal times in the course of the disease.

Accepted for Publication: January 19, 2009.
Correspondence: Clive S. Grant, MD, Department of Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (cgrant@mayo.edu).
Author Contributions: Study concept and design: Boostrom and Grant. Acquisition of data: Boostrom and Grant. Analysis and interpretation of data: Boostrom, Grant, Thompson, Farley, Richards, Hoskin, and Hay. Drafting of the manuscript: Boostrom and Grant. Critical revision of the manuscript for important intellectual content: Boostrom, Grant, Thompson, Farley, Richards, Hoskin, and Hay. Statistical analysis: Hoskin. Obtained funding: Boostrom and Grant. Administrative, technical, and material support: Boostrom, Grant, Thompson, and Farley. Study supervision: Grant.
Financial Disclosure: None reported.
Previous Presentation: This paper was presented at the 116th Annual Meeting of the Western Surgical Association; November 11, 2008; Santa Fe, New Mexico; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

REFERENCES


DISCUSSION

Terry Lairmore, MD, Temple, Texas: The authors are to be commended for a very concise manuscript and thoughtfully analyzed data. This is a retrospective study from a single referral institution that analyzes stage, surgical treatment, and outcome in a large cohort of patients with medullary thyroid carcinoma, including sporadic and familial tumors, over almost a 30-year period.

This study carefully examines the relationship between AJCC stage and outcome for medullary thyroid carcinoma and specifically compares the 1997 fifth edition AJCC staging system to the revised staging system established in the 2002 sixth edition. The principal conclusion of the manuscript is that patients with regional lymph node metastases in the ipsilateral jugular lymph nodes should not be classified as stage IV because even with persistently elevated calcitonin levels, these patients may do well for an extended period of time. As you have just heard succinctly summarized, the authors contend that the new system reclassifies an inordinate percentage of patients as stage IV who have regional lymph node metastases to lateral cervical nodes but no distant disease. Moreover, they argue that their data support an excellent overall survival of 100% at 10 years and 79% at 15 years in the group they define as clinically cured who are nevertheless classified as stage IV under the 2002 system.

I will briefly make some important general observations that impact the current understanding of clinical outcome, staging, and treatment modalities for medullary thyroid carcinoma, many of which were made in the manuscript. I then offer a limited number of directed, pertinent questions for the authors. Medullary carcinoma is a relatively infrequent histopathologic variety of thyroid cancer that may occur either sporadically or in association with specific genetic changes that confer a diverse spectrum of associated aggressiveness of the malignancy. Medullary thyroid cancer spreads early and frequently to regional lymph nodes and is effectively treated only with surgery, as radioactive iodine is not selective for the tumor cells. Nevertheless, some patients do well for an extended period of time with known persistent disease, whether evident biochemically, radiographically, or clinically, while some patients progress early and succumb to their disease at a young age. The most effective management of these patients requires an accurate understanding of the important prognostic variables and the natural history of medullary thyroid carcinoma, the appropriate extent of surgical treatment, and the role of newer targeted therapies.

I would like to ask the authors to respond to the following specific questions:

1. Complete central zone cervical lymphadenectomy was performed in only 66% of the patients when defined as either characterization as such in the surgeon’s note or pathologic examination of 5 or greater lymph nodes. Central lymph node sampling occurred in an additional 17% of patients. While it is understood that this cohort was treated over almost 3 decades by a variety of surgeons and that patients presented in diverse ways ranging from a palpable nodule to directed familial screening, this is a somewhat low frequency of central lymph node dissection. The accepted current treatment for medullary thyroid carcinoma recognized preoperatively is total thyroidectomy and completion central zone lymphadenectomy. Can you comment on rate of central lymph node dissection in this study, and could this impact the staging of patients without regional node metastases and affect the observed outcomes?

2. Biochemical cure is defined as postoperative normalization of calcitonin levels. The most strict definition of biochemical cure would be undetectable stimulated calcitonin levels. Thyroidectomized patients with detectable calcitonin levels or levels in the normal range after stimulation can reasonably be considered to have persistent C-cell disease. This may represent too strict a distinction for the purposes of the clinical staging system, as you have argued that patients with biochemical cure and clinical cure have a similar outcome. Were patients defined as biochemically cured based on stimulated or basal calcitonin levels?

3. This represents a retrospective study of a large number of patients seen at a major referral center. Nearly half of the patients in the study had familial disease with a diagnosis of either MEN 2A [multiple endocrine neoplasia type 2A], familial MTC, or MEN 2B [multiple endocrine neoplasia type 2B]. This is an unexpectedly large percentage and may represent a referral bias. Patients with familial disease are often identified earlier by systemic prospective screening. While patients were compared stage for stage, there is also the suggestion that the biologic behavior...
of MTC conferred by the specific mutations in familial MTC and to some degree MEN 2A is more indolent as compared with sporadic tumors. Could this significant representation of familial patients have influenced the favorable outcome in patients with stage IV disease by the 2002 criteria in your study?

4. I would also like to ask the authors to discuss their indications for lateral (modified radical) lymph node dissection in patients with MTC. While this issue may not have direct bearing on the conclusions of this manuscript, this is an important clinical controversy. It is recognized that early regional lymph node metastases are frequent in this disease. Because we do not have the ability to administer a selective agent such as radioactive iodine for differentiated thyroid cancer, surgical extirpation is the only effective way to treat microscopic or macroscopic lymph node metastases. As the authors have pointed out, very aggressive surgical dissections have been performed in some patients with arguable but nevertheless potential benefit in selected patients. The importance of rational surgical decision making with regard to extent of surgery is emphasized by the fact that some patients will do well with known persistent disease and some will progress rapidly and have a poorer outcome. In your opinion, what are the indications for ipsilateral or contralateral modified radical neck dissection?

Dr Grant: Central compartment lymphadenectomy (CCL).

1. There are 2 reasons that only two-thirds of the patients underwent cervical lymphadenectomy:

a. CCL has received dramatically increased focus only since the turn of the millennium, but [it is] principally related to papillary thyroid cancer. In regards to medullary thyroid cancer (MTC), only in the late 1990s in this country, with the pioneering efforts of Dr Jeff Moley and the group at Washington University, was the vital importance of the central compartment lymph nodes fully appreciated. Prior to this, covering 15 to 20 years of our study, the central compartment was less diligently dissected.

b. Many of these patients were operated as a result of screening by either direct assessment of the RET proto-oncogene or gene linkage. Most of these patients still had MTCs, if only a few millimeters. So with these small MTCs, the central lymph nodes were less compulsively dissected. Many of these patients had normal postoperative calcitonin levels and were stage I.

2. Regarding definition of biochemical cure: most of our patients had basal calcitonin levels, only a few had stimulated levels. While we acknowledge the most stringent definition of cure is stimulated calcitonin, particularly after reviewing these data, we are not prompted to institute calcitonin stimulation testing. Stable low levels of calcitonin, even though mildly elevated, seem rarely to progress to clinically relevant disease.

3. Regarding the biologic behavior specific to individual RET mutations, we have found that the sporadic and MEN 2B patients did have higher stage disease and mortality, whereas the MEN 2A and FMTC [familial MTC] patients have lower stage disease and mortality. This was certainly influenced by screening as you suggested. We do not have all of the codon-specific information for every hereditary MTC patient, and therefore we have not grouped them into the 3-tiered risk groups.

4. Regarding indications for lateral neck dissection, this remains a major point of debate. Some experts around the world advise lateral node dissection either when any central nodes are metastatically involved or even when disease in the respective thyroid lobe is macroscopic, ie, larger than several millimeters. However, this must be balanced against the extent of the scar and the multiple potential complications associated with lateral neck dissection. We have investigated a subpopulation of this MTC cohort of patients specifically regarding the value of preoperative ultrasound. We have found, similar to our papillary thyroid cancer patients, that a positive ultrasound affords us a very accurate threshold to proceed with lateral neck dissection.

Financial Disclosure: None reported.