PAPER

Long-term Results of Reoperation and Localizing Studies in Patients With Persistent or Recurrent Medullary Thyroid Cancer

Electron Kebebew, MD; Shoichi Kikuchi, MD, PhD; Quan-Yang Duh, MD; Orlo H. Clark, MD

Hypothesis: Reoperation benefits patients with locoregional, persistent, or recurrent medullary thyroid cancer (MTC). Currently available localizing studies have limited utility for detecting all foci of residual MTC.

Design: A retrospective study with a mean follow-up time of 7.5 years (median, 13 years; range, 2.2-29 years).

Setting: A tertiary referral medical center.

Patients: Thirty-three patients who underwent 46 reoperations for locoregional residual MTC.

Results: Sixty-four percent of residual MTC was located in the lateral cervical nodes, 22% in the central cervical nodes or thyroid bed, and 14% in the anterior mediastinum (197 of 1128 nodes resected were positive for MTC). After reoperation, basal calcitonin levels were undetectable in 2 patients, reduced by greater than 50% in 10 patients, and either increased or were not reduced by greater than 50% in the remaining patients. On reoperation, one patient had a thoracic duct injury that required reexploration and ligation. Patients who had a greater than 50% decrease in calcitonin levels after reoperation were less likely to develop distant metastases compared with patients who did not have a greater than 50% decrease ($P<.05$). The sensitivities of magnetic resonance imaging (n=31), computed tomographic scan (n=16), ultrasound (n=9), and dimercaptosuccinic acid scan (n=3) were 91%, 86%, 88%, and 100%, respectively.

Conclusions: Although reoperation in patients with residual MTC rarely results in biochemical cure, cervical reexploration is safe and in selected patients may limit MTC progression. Lateral cervical node dissection could be beneficial at the time of initial surgical treatment because of the high frequency of residual MTC in the lateral cervical nodes. Noninvasive imaging studies were helpful but far from perfect for guiding the reexploration for locoregional residual MTC.

Arch Surg. 2000;135:895-901

From the Department of Surgery, University of California–San Francisco and Mount Zion Medical Center, San Francisco (Drs Kebebew, Kikuchi, and Clark), and Surgical Services, Veterans Affairs Medical Center, San Francisco (Dr Duh).

MEDULLARY thyroid cancer (MTC) accounts for 3% to 10% of all thyroid cancers, and originates from the parafollicular or C cells of the thyroid gland.[1-3] The neuroendocrine C cells of the thyroid gland secrete calcitonin, a relatively accurate tumor marker for MTC.[3] Plasma basal and stimulated (with pentagastrin or calcium) calcitonin measurements have been used in the past to screen patients who are at risk of developing MTC and today remain indispensable for the detection of residual MTC after initial surgical treatment.[3,4] The implementation of fine-needle aspiration cytology has also improved the accuracy of the preoperative diagnosis of MTC. It has also allowed the selection of the appropriate initial extent of surgical resection.[3] Furthermore, the identification of the germline *RET* proto-oncogene point mutations responsible for hereditary MTC (MEN 2A and MEN 2B, and familial non-MEN MTC) and its application in genetic screening of patients at risk for hereditary MTC have led to earlier diagnosis of MTC and the use of prophylactic surgical treatment before any neoplasm develops.[5-9]

Although there has been tremendous improvement in the early diagnosis and treatment of MTC, more than 50% of patients still present with a thyroid mass, and up to 75% of these patients have locoregional lymph node metastases.[3,10,11] The overall survival rate of patients with MTC is intermediate to that of patients with differentiated thyroid cancer and anaplastic thyroid cancer.[1,2] In contrast to patients with residual locoregional or metastatic differentiated thyroid cancer of follicular cell origin, postoperative radioiodine ablation therapy is generally ineffective in patients with residual MTC because the C cells of MTC do not trap

PATIENTS AND METHODS

Between 1971 and 1998, 33 patients underwent locoregional reoperation for persistent or recurrent MTC at the University of California, San Francisco (UCSF) hospitals. *Persistent MTC* refers to patients who had an elevated postoperative plasma calcitonin level. *Recurrent MTC* was defined as new evidence of locoregional or distant MTC in which the basal postoperative plasma calcitonin level was normal after initial surgical resection for at least 6 months. *Residual MTC* in this report refers to either persistent or recurrent MTC.

Medical records, including operative notes, pathology reports, and localizing imaging study results were reviewed. Follow-up information was obtained from clinic visits and through the UCSF Cancer Registry. On follow-up and prior to undergoing locoregional reexploration for residual MTC, all patients had preoperative chest radiographs and most patients routinely had a computed tomographic (CT) scan or magnetic resonance imaging (MRI) study of the chest to identify MTC lung metastasis. Furthermore, patients with residual MTC had a preoperative abdominal CT scan to detect liver metastasis as well as measurements of liver function tests in some patients. In patients with symptoms suggesting bony metastasis or patients with highly elevated plasma calcitonin, a bone scan was done. The type of MTC was classified into 4 groups: sporadic MTC, familial non-MEN MTC, MEN 2A or MEN 2B, as previously described.[11] Within 4 months after reoperation, all patients had at least their basal plasma calcitonin level measured, and some had stimulated plasma calcitonin level measurement(s). Patients with elevated postreoperative calcitonin levels were considered to have residual MTC. During the study period, different biochemical assays for calcitonin measurement were used. Therefore, the percent reduction of plasma calcitonin after reoperation was used (percent calcitonin reduction = [1 – basal postreoperative calcitonin level / basal prereoperative calcitonin level] × 100%.

A similar technique of cervical lymphadenectomy as described by Tissel et al,[14] Dralle et al,[15] and Moley et al[13] was used, although we prefer to preserve normal parathyroid glands in situ rather than autotransplanting them. Central neck node clearance consisted of the removal of lymphatic and fibrofatty tissue from the carotid sheath (laterally) and hyoid bone (superiorly) to the clavicle (inferiorly), removing upper mediastinal tissue through a cervical incision. Modified radical neck dissection (functional) with or without mediastinal lymphadenectomy refers to resection of tissue from the hyoid bone (superiorly), the trapezius muscle (laterally) to the clavicle, and anterior mediastinum (inferiorly). Patients who had residual MTC in the deep anterior mediastinum identified by localizing studies had a median sternotomy performed in addition to cervical reexploration.

The accuracy of the localizing studies were determined by comparing the results of the imaging study with those of the pathologic examination of the resected specimen. Because all of the patients had MTC, the specificity of the localizing studies is undefined (ie, no true-negative results). We evaluated the influence of several clinical and pathologic factors on the outcome of reoperation for residual MTC. The Student t test was used for continuous variables, and the Fisher exact and χ^2 tests were used for categorical data.

iodine.[12] Additionally, chemotherapy and radiation treatment for MTC are usually ineffective.[3,11] Surgical resection, therefore, remains the only definitive treatment for patients with residual MTC.

Unfortunately, residual MTC as indicated by elevated plasma basal or stimulated calcitonin levels is common even after apparent complete initial surgical resection.[3,4,10,11] Although all patients diagnosed with MTC should have at least a total thyroidectomy with central neck node clearance, some patients are still treated with lesser procedures. Several investigators, using microdissection of the cervical lymph node compartments, have reported that reoperation on selected patients with persistent MTC may provide biochemical cure in up to 38% of patients.[13-15] On the other hand, others have documented that patients with residual MTC may have a long survival time without surgical reintervention if no gross disease is clinically identified.[11,16] Although the presence of residual MTC can accurately be diagnosed by measuring the postoperative serum calcitonin levels, the localization of residual MTC remains a clinical challenge.[3,4,11]

Patients with residual MTC can be grouped into 2 categories: (1) patients who have had an appropriate initial surgical resection (ie, at least a total thyroidectomy with central neck node clearance); or (2) patients who have had lesser initial surgical procedures. Many surgeons agree that patients with residual MTC who have had an inadequate initial surgical resection warrant a cervical reexploration. This usually includes a complete removal of cervical and mediastinal lymphatic and fibrofatty tissue. However, the utility of cervical reexploration in asymptomatic patients with residual MTC remains unclear.[13-16] Furthermore, only a few investigators have evaluated localizing studies in a small group of patients with residual MTC.[3] Some investigators have suggested that a more extensive initial lateral cervical lymphadenectomy should be performed because of the relatively high frequency of locoregional metastasis and the high risk of residual MTC.[10,15] We reviewed our experience with reoperation for locoregional persistent or recurrent MTC to determine (1) the benefit, if any, of cervical reoperation for persistent or recurrent MTC; (2) the morbidity and mortality rate associated with reoperation for residual MTC; (3) the pattern of residual MTC occurrence; and (4) the accuracy of readily available noninvasive localizing studies.

RESULTS

Thirty-three patients underwent a total of 46 locoregional reoperations for persistent (n=29) or recurrent (n=4) MTC. The indications for reoperation in patients with residual MTC were (1) increasing hypercalcitoninemia (59%); (2) local symptoms (28%); and (3) pal-

liative (13%). The clinical and pathologic characteristics of the patients with persistent and recurrent MTC is summarized in the **Table**. The mean follow up time was 7.5 years (median, 13 years; range, 2.2-29 years). Sixty-one percent of the patients had a follow-up time of more than 10 years. Of the 46 reoperations, 13% had central neck node clearance, 67% had modified radical neck dissection, and 20% had mediastinal lymphadenectomy. One patient (2%) had a complication; patient developed a postoperative chyle leak from a thoracic duct injury. This patient had reexploration and ligation of the duct.

After reexploration for residual locoregional MTC, 5 patients developed distant metastases: 1 to the liver, 3 to the lung, and 1 to the liver and lung with extension into the thoracic rib cage. The basal calcitonin levels were 1396 to 25150 ng/L prior to reoperation in these patients. After reoperation, the calcitonin level was undetectable in only 2 patients. In these patients, the prereoperative basal calcitonin level was 53 ng/L and 322 ng/L with only 3 of 33 and 3 of 53 lymph nodes removed positive for MTC, respectively. The basal calcitonin level was reduced by more than 50% in 10 patients and was not reduced by greater than 50% in 21 patients, despite removing locoregional metastatic MTC in all patients. Patients who had a less than 50% reduction in basal calcitonin levels after reoperation were more likely to develop distant metastases ($P<.05$, with no significant difference in the follow-up time). Age at diagnosis or at reoperation, stage of MTC (by TNM classification), sex, tumor size, the presence of nodal metastases at the time of initial surgery, MTC multicentricity, number of reoperations, and number of positive nodes removed at reoperation were not significant predictors of a greater than 50% reduction in the basal calcitonin level after reoperation. Four patients were dead at follow-up (12% mortality rate at 10 years). All 4 patients died of widely metastatic MTC without airway compromise. There was no statistically significant difference in the number of positive nodes removed or percentage of calcitonin reduction between the patients who died and those who were not dead at last follow-up.

In 46 reoperations for residual MTC, a total of 1128 lymph nodes were removed and 197 were positive for metastatic MTC. Twenty-two percent of residual MTC was located in the central neck compartment, 64% in the lateral neck compartment, and 14% in the anterior mediastinum. In patients who had an initial total thyroidectomy and central neck node dissection, 70% of residual MTC was located in the lateral neck, 15% in the central neck, and 15% in the mediastinum.

Patients who had cervical reoperation for residual MTC had 1 or more noninvasive localizing studies consisting of MRI, CT scan, high-resolution ultrasound, and dimercaptosuccinic acid (DMSA) scan. The sensitivity of MRI (n=31), CT scan (n=16), ultrasound (n=9), and DMSA scan (n=3) was 90.9%, 85.7%, 87.5%, and 100%, respectively. When more than 1 imaging study was used, the percent correlation (true positive) of the imaging studies was 80% for MRI and CT scan (n=5), 66% for MRI and ultrasound (n=3), 100% for MRI and DMSA (n=2), and 100% for CT scan and ultrasound (n=3).

Clinical and Pathologic Characteristics of Patients Undergoing Reoperation for Persistent and Recurrent MTC*

Characteristic	Persistent MTC	Recurrent MTC
Sex, M/F	17/12	4/0
Average age, y	38.7	56
Type of MTC		
Sporadic	26	4
Familial	2	0
MEN 2A	1	0
MEN 2B	0	0
Indications for reoperation		
Hypercalcitoninemia	13	3
Symptomatic†	12	0
Palliative‡	4	1
TNM stage		
I	2	0
II	8	0
III	15	3
IV	4	1
Lymph node metastasis	15	4
Distant metastasis	4	1
Dead/alive	4/25	0/4

**MTC indicates medullary thyroid cancer. Values represent number of patients unless otherwise indicated.*

†Symptomatic refers to patients who had a cervical mass, or complained of neck pain, dysphagia, and hoarseness attributable to locoregional residual MTC.

‡Palliative refers to patients who had local symptoms from locoregional residual MTC in the setting of known MTC distant metastases.

COMMENT

After initial surgical treatment, residual MTC, manifested by elevated plasma calcitonin levels (basal or stimulated), is unfortunately common in patients with clinically evident MTC and remains a frustrating clinical dilemma. All of these patients should undergo an extensive workup for metastatic MTC. It remains unclear whether patients with biochemical evidence of residual MTC should be closely observed until MTC is identified by various localizing studies, or whether an aggressive surgical approach consisting of locoregional removal of all lymphatic and soft tissue should be done in the central, ipsilateral, or both lateral neck compartments.[4,13-15] Although to our knowledge there have been no prospective studies comparing observation with reoperation, several investigators have documented that both approaches are reasonable. Van Heerden et al[16] documented that patients who had apparently curative surgical treatment with residual MTC and no identifiable MTC may enjoy a long survival time. In contrast, others have reported that reoperative meticulous "microdissection" may lead to biochemical normalization in about a third of patients with occult residual MTC.[13-15] Our study offers a longer follow-up time than previous studies evaluating the results of reoperation for residual MTC.[13-15] We believe that a longer follow-up time is imperative to evaluate the benefit of reoperation because MTC is generally a slow-growing tumor, and residual MTC may occur later. Our surgical approach in patients with residual MTC has been to first determine if an adequate initial surgical resection was done (ie, at least a total or near-total thyroidectomy with bilateral central neck node clearance).

In patients who had lesser procedures, we have performed locoregional reoperation removing any remaining thyroid tissue as well as cervical and upper mediastinal lymph nodes. If the initial surgical treatment was at least a total or near-total thyroidectomy with central neck node clearance, the following were indications for reoperation: (1) increasing plasma calcitonin levels with or without residual MTC localized by imaging studies, or (2) the presence of symptomatic locoregional residual MTC with or without metastatic MTC.

The normalization of calcitonin levels after locoregional reoperation in our study was lower (10.5% of asymptomatic patients with hypercalcitoninemia) than that reported by other investigators, but our study had a longer follow-up time.[13-15] This emphasizes that a long follow-up time is necessary before patients can be assured of being "cured" of MTC after reoperation for residual MTC.[10] Interestingly, patients with residual MTC who had a greater than 50% reduction in the plasma basal calcitonin levels after reoperation were less likely to develop distant metastases. Although this may reflect a selection bias, there was no statistically significant difference in the absolute calcitonin levels before reoperation, stage of MTC, or length of follow-up time. This suggests that reoperation in patients with locoregional residual MTC may limit MTC progression. Furthermore, we found that reoperation for symptomatic locoregional residual MTC was effective in relieving symptoms, and may potentially prevent later airway compromise and death by suffocation in these patients. The former is consistent with the findings of other investigators who evaluated reoperation for residual MTC in palliating symptomatic metastatic MTC.[17]

Complication rates from locoregional reoperation for residual MTC have been reported to range from 5% to 14% and have mainly consisted of recurrent laryngeal nerve injury, hypoparathyroidism, and thoracic duct injury.[13-17] Our complication rate was lower than that of most reports. This would suggest that the benefit of reoperation for residual MTC outweighs the low risk of reoperative morbidity and mortality. Such low morbidity and mortality rates have been observed by experienced surgeons. Therefore, these patients should be referred to institutions experienced with reoperative thyroid surgery.

We and other investigators have documented that the initial extent of thyroidectomy is an important factor in the risk of residual MTC and the prognosis of patients with MTC.[11,18,19] Compared with lesser procedures, total thyroidectomy and central neck node dissection is associated with a lower risk of residual MTC, improved survival, and the need for fewer reoperations.[11] Cervical node dissection, therefore, has a therapeutic role for MTC and allows for more than just accurate staging of MTC. Some patients, however, continue to be treated with inadequate initial surgical resections. Even when total thyroidectomy with central neck node clearance is used, a higher than acceptable rate of residual MTC has been observed.[11] The extent of MTC lymph node involvement at the time of resection cannot be reliably determined intraoperatively to guide the optimal extent of cervical node dissection required. This is best exemplified in a study by Moley and DeBenedetti,[10] who reported a sensitivity of 64% and specificity of 71% for an experienced surgeon to accurately identify MTC lymph node metastases. Furthermore, even small primary MTC foci are associated with up to 80% ipsilateral cervical node and 44% contralateral node MTC metastases.[10] On reoperation, we similarly found residual MTC in the lateral cervical node compartments in 70% of patients, suggesting that these patients should perhaps have had an initial lateral neck dissection. By doing so, reoperative neck node dissection could be avoided, reducing the morbidity of reoperation. In patients diagnosed at a young age by genetic screening, lateral cervical node clearance may be unnecessary because cervical node MTC metastasis occurs infrequently (8.6%) in patients undergoing prophylactic surgical treatment.[7,9]

The accuracy of localizing imaging studies for locoregional residual MTC depends on (1) the size and site of residual MTC, (2) the experience of the radiologist interpreting the imaging study, (3) technical imaging factors, and (4) the confirmation of imaging results by pathologic examination. Localizing study results have been reported without uniform confirmation of the presence of MTC and have made the interpretation of the accuracy of several imaging modalities difficult. In our study, all of the localizing study results were confirmed by pathologic examination of the specimens removed. The high sensitivity of plasma calcitonin level, especially stimulated calcitonin level, for detecting residual occult MTC makes it difficult to detect foci of residual MTC by using standard imaging studies and these may not be detectable until these patients are observed for a longer period.[20] Although selective venous catheterization with measurement of a calcitonin (basal or stimulated) gradient has been reported to have a high sensitivity, especially for liver metastasis, residual MTC can only be localized to a region.[3] Furthermore, this technique is invasive, expensive, technically challenging, and not widely available. Only a limited number of investigators have evaluated MRI for locoregional MTC.[21] Medullary thyroid cancer foci enhance on MRI T2-weighted imaging and areas of fibrosis may be distinguished from MTC. Although MRI may identify suspicious lesions, it is not highly specific (false-positive rate of 16% in our study). However, it is not associated with any radiation exposure to the patient and is especially helpful for detecting residual MTC in the mediastinum. Van Heerden et al[16] have advocated high-resolution ultrasound scanning for identifying residual MTC in the neck, whereas other investigators have reported more limited success.[22-24] Ultrasound scanning is relatively inexpensive, and a fine-needle aspiration biopsy can be done on suspicious lesions to confirm residual MTC. On the other hand, ultrasound is not useful for detecting mediastinal residual MTC and would have missed 14% of the residual MTC found in the mediastinum. Overall there was no significant difference in the sensitivities of MRI, CT scan, and ultrasound scanning for locoregional residual MTC. Computed tomographic scan images may be difficult to interpret because of surgical clip artifacts from prior surgery. We have had limited experience with technetium Tc 99m DMSA scintigraphy scanning and variable sensitivities (ranging from 0%-100%) have been reported.[25] The potential advantage of technetium Tc 99m DMSA

scintigraphy and other radionuclide scanning methods is that they allow whole-body scanning and therefore may detect sites of distant MTC metastases. In a recent study by Conti et al,[26] positron emission tomography imaging correctly identified residual MTC in all 6 patients with hypercalcitoninemia. Unfortunately, only in 2 patients who had surgical resection were the positron emission tomography results confirmed. Our problem with all currently available localizing studies is that they often fail to correctly diagnose involved locoregional nodes when they are smaller than 1 cm. It seems that to achieve biochemical cure of patients with nodal MTC metastases they must be small, few, and without extranodal invasion.[15,27,28]

Tung et al[29] have reported that routine diagnostic laparoscopy identified 8 of 41 liver metastases from MTC not detected by standard imaging studies, probably due to the miliary nature of MTC liver metastases. We have not performed routine laparoscopy before reoperation for locoregional MTC. This technique might have identified liver metastases in the 2 patients who later developed liver metastases. However, we do not believe that routine diagnostic laparoscopy to detect liver metastasis is necessary to select patients for reoperation. This is because reoperation for residual locoregional MTC can lead to symptomatic relief even in patients with widely metastatic MTC and decreases the risk of death from locoregional MTC causing airway obstruction or invasion into the great vessels.[17]

In summary, locoregional reoperation for residual MTC rarely results in long-term biochemical cure, but seems to limit MTC progression. Prophylactic lateral cervical node clearance at the time of initial surgical resection for patients with MTC may reduce the high frequency of residual MTC and avoid the need for reoperation. Noninvasive imaging studies are helpful in detecting residual MTC but are not sensitive or accurate enough to be used to guide the extent of resection required on reoperation for residual MTC.

Presented at the 71st Annual Session of the Pacific Coast Surgical Association, San Francisco, Calif, February 21, 2000.

Philip H. G. Ituarte, MPH, PhD, provided assistance with statistics.

Corresponding author: Electron Kebebew, MD, Department of Surgery, University of California–San Francisco, 513 Parnassus Ave, Mail Stop S343, San Francisco, CA 94134-0470.

REFERENCES

1. Gilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma: a population-based study of 15 698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973-1991. *Cancer*. 1997;79:564-573.
2. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A national cancer database report on 53 856 cases of thyroid carcinoma treated in the U.S., 1985-1995. *Cancer*. 1998;83:2638-2648.
3. Marsh DJ, Learoyd DL, Robinson BG. Medullary thyroid carcinoma: recent advances and management update. *Thyroid*. 1995;5:407-420.
4. Moley JF, DeBenedetti MK, Dilley WG, Tisell LE, Wells SA. Surgical management of patients with persistent or recurrent medullary thyroid cancer. *J Intern Med*. 1998;243:521-526.
5. Mulligan LM, Kwok JB, Healey CS, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. *Nature*. 1993;363:458-460.
6. Donis-Keller H, Dou S, Chi D, et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. *Hum Mol Genet*. 1993;2:851-856.
7. Wells SA, Chi DD, Toshima K, et al. Predictive DNA testing and prophylactic thyroidectomy in patients at risk for multiple endocrine neoplasia type 2A. *Ann Surg*. 1994;220:237-247.
8. Lips CJ, Landsvater RM, Hoppener JW, et al. Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. *New Engl J Med*. 1994;331:828-834.
9. Kebebew E, Treseler PA, Siperstein AE, Duh QY, Clark OH. Normal thyroid pathology in patients undergoing thyroidectomy for finding a RET gene germ-line mutation: a report of three cases and review of the literature. *Thyroid*. 1999;9:127-131.
10. Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. *Ann Surg*. 1999;229:880-888.
11. Kebebew E, Ituarte P, Siperstein AE, Duh QY, Clark OH. Medullary thyroid cancer: clinical characteristics, treatment, prognostic factors and a comparison of staging systems. *Cancer*. 2000;88:1139-1148.
12. Saad MF, Guido JJ, Samaan NA. Radioactive iodine in the treatment of medullary carcinoma of the thyroid. *J Clin Endocrinol Metab*. 1983;57:124-128.
13. Moley JF, Dilley W, DeBenedetti M. Improved results of cervical re-operation for medullary thyroid carcinoma. *Ann Surg*. 1997;225:734-743.
14. Tisell L, Hansson G, Jansson S, Salander H. Re-operation in the treatment of asymptomatic metastasizing medullary thyroid carcinoma. *Surgery*. 1986;99:60-66.
15. Dralle H, Damm I, Scheumann GF, et al. Compartment-oriented microdissection of regional lymph nodes in medullary thyroid carcinoma. *Surg Today*. 1994;24:112-121.
16. Van Heerden JA, Grant CS, Gharib H, Hay ID, Ilstrup DM. Long-term course of patients with persistent hypercalcitoninemia after apparent curative primary surgery for medullary thyroid carcinoma. *Ann Surg*. 1990;212:395-401.
17. Chen H, Roberts JR, Ball DW, et al. Effective long-term palliation of symptomatic, incurable metastatic medullary thyroid cancer by operative resection. *Ann Surg*. 1998;227:887-895.
18. Duh QY, Sancho JJ, Greenspan FS, et al. Medullary thyroid carcinoma: the need for early diagnosis and total thyroidectomy. *Arch Surg*. 1989;124:1206-1210.
19. Moley JF. Medullary thyroid cancer. *Surg Clin North Am*. 1995;75:405-420.
20. Tisell LE, Dilley WG, Wells SA. Progression of postoperative residual medullary thyroid carcinoma as monitored by plasma calcitonin levels. *Surgery*. 1996;119:34-39.
21. Dorr U, Sautter-Bihl ML, Bihl H. The contribution of somatostatin receptor scintigraphy to the diagnosis of recurrent medullary carcinoma of the thyroid. *Semin Oncol*. 1994;21:42-45.
22. Frank-Raue K, Raue F, Buhr HJ, et al. Localization of occult persisting medullary thyroid carcinoma before microsurgical reoperation: high sensitivity of selective venous catheterization. *Thyroid*. 1992;2:113-117.
23. Gorman B, Charboneau JW, James EM, et al. Medullary thyroid carcinoma: role of high resolution US. *Radiology*. 1987;162:147-150.
24. Raue F, Winter J, Frank-Raue K, et al. Diagnostic procedure before reoperation in patients with medullary thyroid carcinoma. *Horm Metab Res Suppl*. 1989;21:31-34.
25. Mojiminiyi OA, Udelsman R, Soper NDW, Shepstone BJ, Dudley NE. Pentavalent Tc-99m DMSA scintigraphy: prospective evaluation of its role in the management of patients with medullary carcinoma of the thyroid. *Clin Nuc Med*. 1991;16:259-262.
26. Conti PS, Durski JM, Bacqai F, Grafton ST, Singer PA. Imaging of locally recurrent and metastatic thyroid cancer with positron emission tomography. *Thyroid*. 1999;9:797-804.
27. Moley JF, Wells SA, Dilley WG, Tissell LE. Reoperation for recurrent or persistent medullary thyroid cancer. *Surgery*. 1993;114:1090-1096.
28. Gimm O, Ukkat J, Dralle H. Determinative factors of biochemical cure after primary and reoperative surgery for sporadic medullary thyroid carcinoma. *World J Surg*. 1998;22:562-567.
29. Tung WS, Vesely TM, Moley JF. Laparoscopic detection of hepatic metastases in patients with residual or recurrent medullary thyroid cancer. *Surgery*. 1995;118:1024-1029.

DISCUSSION

Nis Schmidt, MD, Vancouver, British Columbia: I prepared some overheads just to help us focus on the contents of this paper. It is a privilege and a pleasure to be invited by Dr Clark and his group to respond to this paper on medullary cancer of

the thyroid gland. Medullary cancer of the thyroid is an infrequent malignant disease of the thyroid, as we have heard. Only in a very specialized and focused practice of surgery such as that of Dr Clark and his group would one accumulate a large experience with this endocrine tumor of APUD tissue origin. Fortunately, medullary cancer continues to produce calcitonin and, in the presence of neoplasia, this is fortuitous for identifying genetically determined disease in infants to residual recurrent or metastatic disease in the adult. This is not the occasion to present another paper on this phenomenon. We are here to consider medullary cancer and how one attempts to localize and treat with curative intent.

Dr Kebebew presented the paper clearly and succinctly. Thirty-three patients studied retrospectively had a total of 46 procedures to attempt further surgical eradication of recurrent disease evidenced by rising or high calcitonin levels after initial surgical management or increasing local symptoms. Initial surgical management of medullary cancer of the thyroid is a real issue. Initial diagnosis of medullary cancer should be highly accurate if ABC (ie, aspiration, biopsy, cytology) is practiced on thyroid nodules and calcitonin levels are measured preoperatively. Depending on the referral pattern of practice, all thyroid lumps should have a cytologic diagnosis before going to the operating room. If not definitive, at least there should be some opinion as to the histologic diagnosis. The basic operation then for medullary cancer should be a total thyroidectomy with central clearing and ipsilateral or bilateral dissection for grossly evident disease or nodal enlargement. My own experience with this disease has taught me this. I stress this basic procedure in my practice and in my teaching. I have seen medullary cancer (nonpalpable in the thyroid and nonpalpable in nodes) present in the soft tissue around the thyroid without any evidence of disease in nodes histologically, so it is a vexacious disease that can spread surreptitiously around the area as we have seen from the contents of this paper.

Unfortunately, even this infrequently results in the return of serum calcitonin levels to normal. Hence the dilemma: when is enough surgery enough? In the situation of palpable or symptomatic recurrence of medullary cancer or in follow-up, if serum calcitonin levels remain high or increase, the future for the patient is distinctly worrisome. There is a mortality to this disease. There is also severe morbidity of locoregional recurrence with tracheal, vascular, neurologic, even bony invasion, in addition to the morbidity of difficult reoperative neck procedures.

Localization studies in this situation are not reassuring. As we have heard, none of the noninvasive modalities, including x-rays and ultrasounds and the like, are particularly definitive. Invasive venous sampling is imprecise and the literature is full of series of localization studies comparing without conclusion one modality with the other. Chemotherapy and radiation if used in the treatment by isotope or external means are disappointing, and, if done to the maximum, usually preclude any further local therapy or surgery. Does one then embark on radical reoperation in all cases of high serum calcitonin? Obviously not.

What is still needed is a better localization test, which, if done early, could sort out medullary cancer of the thyroid that is confined to the gland or that is locoregional at the outset and deserves early aggressive therapy. If it is already shown to be systemic and beyond more surgical effort, we might be operating in the neck for a disease that is really systemic from the start or is both local and systemic. A decision has to be made as to the effectiveness of further surgery the first, second, or third time around.

In the last 5 years, increasing publications, interest, and availability and experience are accumulating with positron emission tomography. It may be key for the future to use a fluorinated glucose molecule, increased cellular enzyme activity, and increased cellular membrane transport of glucose, allowing the FDG or 2-fluoro-2-deoxyglucose molecule to be trapped inside the cell. This, when labeled with a positron-emitting fluorine 18 molecule, is accumulated and will provide a unique biochemical scan and whole-body image.

Once again the study may be limited, the surgery may be limited, but with this new technology that is expensive but becoming more available, our surgical science may in fact win the day. So, thank you for the opportunity of responding to this paper.

I have a couple of questions. It is so critical as to how the first operation is done on these patients. How does one try to educate other surgeons who may be tackling some of these tumors? Secondly, do you have any experience as yet with the PET scanning?

Claude H. Organ, Jr, MD, Oakland, Calif: A lot of these endocrine lesions we are curing biochemically, but the patients are continuing to be symptomatic. We have bounced around the concept of lateral aberrant thyroid tissue and benign metastasizing goiter; however, I want to call the Association's attention to the fact that calcitonin liberated by C cells comes from lateral anlages (the ultimobranchial body or the fourth pharyngeal pouch). It is a lateral anlage and where medullary cancer is concerned, we have to be very careful about what we are looking at. Two questions: (1) Please define recurrent as opposed to persistent disease. (2) Can I conclude from your manuscript that these metastases are not functioning metastases?

Theodore X. O'Connell, MD, Los Angeles, Calif: I have 2 questions for the authors. First, although I do believe that these extensive node dissections probably control local disease and I agree with the authors, there is no data in the paper that proves it because there is no comparative treatment or treatment group. The second question is, since the biochemical cure is so low, even with these extensive neck dissections, do they have any experience with any adjuvant therapy such as external beam radiation to see if there is increased biochemical cure with adjuvant therapies?

Lawrence A. Danto, MD, Stockton, Calif: I also thought this was an excellent presentation and discussion by Dr Schmidt. Sentinel node identification and biopsy is a vexing disease as has been pointed out. Early operation for cure is very important. What is the role of sentinel node identification?

David R. Byrd, MD, Seattle, Wash: The key to the surgical management of this disease seems to be with the first operation. I think many of us have struggled with the extent of lymphadenectomy at the first operation. Would the authors comment on (1) any imaging at the initial diagnosis to help guide the extent of lymphadenectomy, and (2) could one use postoperative basal and/or stimulated calcitonin levels (since it has such a short half life) after total thyroidectomy and central neck dissection to guide surgical management of the ipsilateral and/or contralateral neck nodes?

John T. Vetto, MD, Portland, Ore: I have 1 technical question. The authors advocate what is almost a complete dissection: removing memorial levels 2, 3, and 4, which they call "central," and 5, which is actually posterior (they call it "lateral" in the paper). Do the authors remove level 1 as well, or do they find that these nodes are almost never involved? Those are the submandibular nodes. Also, do they spare normal structures? In other words, are they performing selective dissections, complete dissections, or modified complete dissections?

Dr Duh: Dr Schmidt, thank you very much for your comments. You asked about PET scans. We have limited experience with PET scans. Recently we have had a few patients who have had PET scans, and they seemed to be useful. I believe you also find PET scans to be a relatively sensitive test. Unfor-

tunately, although tumors were found by PET scanning and were removed, the calcitonin levels remained elevated.

Dr Organ, we use 6 months to define recurrent vs persistent disease. Disease is present if there are clinical signs of disease or if serum calcitonin is elevated. We routinely observe these patients for their serum calcitonin and CEA levels.

Whether all of the tumors are functioning or not is a good question. We believe that almost all of the tumors that we find are functioning. A common clinical dilemma is having an elevated basal or stimulated serum calcitonin level and not being able to find the disease.

Dr O'Connoll, regarding the rationale for the extensive surgical treatment and whether there are other therapies, there are no other effective therapies available besides surgery. Although we are aggressive surgically, we have not been as aggressive as some of our German colleagues who routinely do the compartment dissection including a mediastinal cleanout during the first operation. Surgeons who perform extensive microdissection, including mediastinal cleanout, report a lower level of calcitonin when a more extensive operation is done. We do not yet know whether such aggressive surgery prolongs patient survival.

Dr Danto, we do not have any experience with sentinel nodes for medullary thyroid cancer, although we have considered this approach for low-risk patients. It is common for medullary cancer to metastasize to the lymph nodes very early, but it is difficult to predict which lymph nodes are involved. The rule of thumb for patients with a clinically obvious nodule and medullary thyroid cancer is that two-thirds have positive central nodes, two-thirds have positive ipsilateral lateral nodes, one third have positive contralateral nodes, and one third have positive mediastinal nodes. Since the nodal involvement is difficult to predict, identifying sentinel node may be a good idea. Patients with occult tumors measuring 1 cm are less likely to have involved nodes.

Dr Byrd, regarding preoperative imaging studies prior to the first operation, we have become more aggressive in doing prophylactic neck dissections. Imaging studies such as ultrasonography may be useful for locally invasive tumors in planning the operation. At operation, we routinely perform a total thyroidectomy, central neck clearance, and an ipsilateral lateral neck dissection for almost all patients with a palpable medullary thyroid cancer that is larger than 1 cm. We usually use size of tumor to determine the extent of initial operation.

Dr Vetto, we do not routinely do a level I dissection.

IN OTHER AMA JOURNALS

ARCHIVES OF INTERNAL MEDICINE

Predictors of Recurrence After Deep Vein Thrombosis and Pulmonary Embolism: A Population-Based Cohort Study

John A. Heit, MD; David N. Mohr, MD; Marc D. Silverstein, MD; Tanya M. Petterson, MS; W. Michael O'Fallon, PhD; L. Joseph Melton III, MD

Background: The appropriate duration of oral anticoagulation after a first episode of venous thromboembolism (VTE) is uncertain and depends upon VTE recurrence rates.
Objective: To estimate VTE recurrence rates and determine predictors of recurrence.
Methods: Patients in Olmsted County, Minnesota, with a first lifetime deep vein thrombosis or pulmonary embolism diagnosed during the 25-year period from 1966 through 1990 (N = 1719) were followed forward in time through their complete medical records in the community for first VTE recurrence.
Results: Four hundred four patients developed recurrent VTE during 10 198 person-years of follow-up. The overall (probable/definite) cumulative percentages of VTE recurrence at 7, 30, and 180 days and 1 and 10 years were 1.6% (0.2%), 5.2% (1.4%), 10.1% (4.1%), 12.9% (5.6%), and 30.4% (17.6%), respectively. The risk of recurrence was greatest in the first 6 to 12 months after the initial event but never fell to zero. Independent predictors of first overall VTE recurrence included increasing age and body mass index, neurologic disease with paresis, malignant neoplasm, and neurosurgery during the period from 1966 through 1980. Independent predictors of first probable/definite recurrence included diagnostic certainty of the incident event and neurologic disease in patients with hospital-acquired VTE. Recurrence risk was increased by malignant neoplasm but varied with concomitant chemotherapy, patient age and sex, and study year.
Conclusions: Venous thromboembolism recurs frequently, especially within the first 6 to 12 months, and continues to recur for at least 10 years after the initial VTE. Patients with VTE with neurologic disease and paresis or with malignant neoplasm are at increased risk for recurrence, while VTE patients with transient or reversible risk factors are at less risk. (*2000;160: 761-768*)

Reprints: John A. Heit, MD, Hematology Research, Plummer 549, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: heit.john@mayo.edu).