

Medullary thyroid carcinoma: Results of a standardized surgical approach in a contemporary series of 80 consecutive patients

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Background. The surgical management and follow-up strategy in patients with medullary thyroid carcinoma (MTC) remain controversial because of the lack of data on the natural history of these tumors and their patterns of progression.

Methods. We reviewed the records of all patients who underwent a cervical operation for MTC between 1991 and 2002. Compartment-oriented surgery (COS) was performed to minimize the risk of cervical recurrence.

Results. We identified 92 consecutive patients who underwent a cervical operation for MTC: 80 had invasive MTC, and 12 had C-cell hyperplasia after prophylactic thyroidectomy for familial MTC. Ten (13%) of the 80 patients with invasive MTC presented with distant metastases and underwent COS to achieve local-regional control; cervical recurrence developed in none, but three have died of MTC. The remaining 70 patients underwent COS for primary ($n = 23$) or recurrent ($n = 47$) MTC. Disease recurred in 18 (26%) of these 70 patients at a median follow-up of 35 months, with 10 (14%) of the recurrences being cervical. Recurrent disease was associated with a basal calcitonin level of >250 pg/mL in all but four patients, two of whom showed tumor dedifferentiation. In contrast, only 5 (11%) patients without evidence of recurrence had basal calcitonin levels of >250 pg/mL at last follow-up.

Conclusions. Complete COS minimizes cervical recurrence. Radiographic evidence of recurrent disease is unlikely when the calcitonin level is ≤ 250 pg/mL. These data could be used to develop a logical, cost-effective treatment and follow-up strategy for patients with MTC. (Surgery 2003;134:890-901.)

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MEDULLARY THYROID CARCINOMA (MTC) is an uncommon malignancy that arises from the C-cells of the thyroid as either a sporadic event or the result of a germline mutation in the *RET* proto-oncogene, which is transmitted in an autosomal dominant mode of inheritance.¹ Familial MTC may occur as part of multiple endocrine neoplasia (MEN) type 2A or type 2B, or in the absence of other endocrinopathies (familial non-MEN MTC).² MTC typically spreads to regional lymph nodes

early in its course, a finding first appreciated by Miller et al in 1972.³ All grossly visible disease can usually be removed from the neck during the initial operation; however, cure in patients with apparently localized disease cannot be gauged solely on the basis of operative or pathologic criteria. A more reliable criterion was recognized by Tashjian and Melvin, who in 1968 first measured the calcitonin (CT) level in the serum and thyroid tissue from a patient with MTC.⁴ CT has proved to be an extremely sensitive biochemical tool for identifying microscopic MTC.

MTC is a unique solid tumor for two reasons. First, it is usually an indolent disease that is associated with prolonged survival, yet spreads to regional lymph nodes and occasionally distant sites before the primary thyroid tumor is diagnosed. Second, serum CT measurement can detect MTC long before regional lymph node or distant metastases become visible on imaging studies.

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The obvious difficulty for the clinician is that most patients who undergo thyroidectomy with or without some form of regional lymph node dissection subsequently have an elevated CT level but no clinical or radiographic evidence of disease. This clinical quandary has prompted surgeons to perform a more extensive lymph node dissection either at the initial or a subsequent operation in an effort to achieve a biochemical cure, as defined by a normal basal or stimulated CT level.⁵⁻¹⁰ Unfortunately, biochemical cure after cervical reoperation remains infrequent, occurring in only 14% to 38% of patients.^{8,10-12}

It is generally agreed that patients with elevated postoperative CT levels have residual MTC; however, currently, there are no available data to guide the management of such patients. When physical examination and cervical ultrasound findings are otherwise normal, many patients undergo an exhaustive radiographic evaluation in search of extracervical metastatic disease. Slowly progressive increases in serum CT levels cause further frustration for the patient and physician. In an effort to better manage this challenging disease, we have attempted, over the past decade, to standardize our approach to the surgery and follow-up of patients with sporadic and familial MTC.¹¹ This has led us to use a compartment-oriented surgical approach to the neck, as initially described by Dralle et al,⁶ that is consistent with standard principles of surgical oncology. Herein we report the results of our experience with MTC in a consecutive series of patients treated over the last decade to define the natural history of this disease and the impact of compartment-oriented surgery (COS) on the rates of cervical recurrence and CT levels.

METHODS

We reviewed the medical records of patients in our prospective database who underwent a prophylactic or therapeutic cervical operation for MTC in the Department of Surgical Oncology at The University of Texas M. D. Anderson Cancer Center between 1991 and 2002. All patients were divided into one of five groups according to the nature of their initial operation at M. D. Anderson: (1) *initial surgery*: therapeutic primary resection for invasive MTC in a patient with no prior history of cervical surgery; (2) *reoperation for persistent disease*: prior incomplete resection of thyroid or regional nodal disease performed within 6 months of referral; (3) *reoperation for recurrent disease*: radiographic or biopsy-proven cervical recurrence more than

6 months after previous cervical operation; (4) *elective reoperation*: reoperative neck dissection for an elevated basal CT level with no clinical or radiographic evidence of cervical or distant metastasis; and (5) *prophylactic surgery*: elective primary surgery in affected members of kindreds with familial MTC.

COS was used for both the central (level VI) and lateral (levels IIA, III, IV, and V) neck compartments; "node plucking" was not performed.^{6,11} Postoperative external-beam radiation therapy (EBRT) was administered at the discretion of the treating physicians and was frequently recommended in patients who had bulky cervical disease with histologic evidence of soft tissue extension or reoperation for recurrent disease when COS was previously performed at M. D. Anderson.^{13,14} Postoperative cervical ultrasonography and chest, abdominal, and bone imaging were performed at the physician's discretion.

Clinicopathologic factors, basal CT levels, and the *RET* codon mutation status (for patients with familial MTC) were obtained from the patients' records. The following basal CT levels were noted: preoperative level, that is, prior to the M. D. Anderson operation; postoperative level, that is, lowest value within 6 months after the M. D. Anderson operation; and the level obtained at the last clinical follow-up or at the time of recurrence. Initial pathologic tumor, node, metastasis staging¹⁵ was determined by the histopathologic findings of all operations performed within 6 months of the patient's first operation (prereferral or at M. D. Anderson). Patients' vital and disease status at last follow-up was categorized as follows: *no evidence of disease* (NED), as shown by physical examination and radiographic imaging; *alive with disease* (AWD), although biopsy was not routinely done to confirm radiographically evident distant metastases; *dead of disease* (DOD); and *dead of other causes*.

All CT levels recorded were measured at M. D. Anderson. Prior to June 2000, basal CT levels were measured using a two-site immunoradiometric isotope assay (IRMA; Nichols Institute Diagnostics, San Juan Capistrano, Calif). This assay had a lower detection limit of 10 pg/mL; the upper limit of the normal reference range was <26 pg/mL for males and <17 pg/mL for females. Since June 2000, basal CT levels have been measured using an automated chemiluminescence immunoassay (Nichols Institute Diagnostics, San Juan Capistrano, Calif). This assay has a lower detection limit of 0.7 pg/mL; the upper limit of the normal reference range was ≤11.5 pg/mL for males and ≤4.6 pg/mL for females.

Table I. Demographics and outcome of all 92 patients*

| Parameter | Total | Total recurrences (%) | CR | DM | CR and DM | DOD |
|---------------------------------|-------|-----------------------|----|----|-----------|-----|
| Total no. of patients | 92† | 18 (20) | 7 | 8 | 3 | 6 |
| M0 at first MDACC surgery | 82 | 18 (22) | 7 | 8 | 3 | 3 |
| Indication for surgery | | | | | | |
| Initial surgery: therapeutic | 18 | 3 (17) | 2 | 1 | 0 | 0 |
| Initial surgery: prophylactic | 17‡ | 0 | 0 | 0 | 0 | 0 |
| Reoperation: persistent disease | 12 | 3 (25) | 1 | 2 | 0 | 1 |
| Reoperation: recurrent disease | 20 | 8 (40) | 3 | 4 | 1 | 1 |
| Reoperation: elective | 15 | 4 (27) | 1 | 1 | 2 | 1 |
| M1 at first MDACC surgery | 10 | NA | 0 | NA | NA | 3 |
| Indication for surgery | | | | | | |
| Initial surgery: therapeutic | 4 | NA | 0 | NA | NA | 2 |
| Reoperation: persistent disease | 1 | NA | 0 | NA | NA | 0 |
| Reoperation: recurrent disease | 5 | NA | 0 | NA | NA | 1 |
| Etiology of MTC | | | | | | |
| Sporadic | 49 | 16 (33) | 6 | 7 | 3 | 5 |
| Hereditary | 43 | 2 (5) | 1 | 1 | 0 | 1 |
| MEN2 | 31 | 1 (3) | 1 | 0 | 0 | 1 |
| Familial MTC | 12 | 1 (8) | 0 | 1 | 0 | 0 |

CR, Cervical recurrence; DOD, Dead of disease; DM, Distant metastatic recurrence; MDACC, M. D. Anderson Cancer Center; M0, No evidence of distant metastasis; M1, Evidence of distant metastasis; MEN2, Multiple endocrine neoplasia type 2; MTC, Medullary thyroid carcinoma; NA, Not applicable.

*All values are numbers of patients.

†80 of the 92 patients had invasive MTC; 12 had C-cell hyperplasia.

‡12 of the 17 patients had C-cell hyperplasia and no evidence of invasive MTC.

For those patients deemed NED after surgery, recurrence-free survival (RFS) was computed from the date of the first surgery at M. D. Anderson to the date of the first evidence of recurrence or to the date of the last follow-up for those remaining free of disease. The Kaplan-Meier method was used to estimate RFS for patients based on preoperative and postoperative CT levels. Differences in the distributions were assessed by the log-rank test.

RESULTS

From May 1991 to December 2002, 92 patients underwent therapeutic (n = 75) or prophylactic (n = 17) cervical operations for sporadic or hereditary MTC (Table I). Five of the 17 patients who underwent prophylactic thyroidectomy were found to have invasive MTC and 12 had C-cell hyperplasia. Therefore, of the 80 patients with invasive MTC, 10 presented to M. D. Anderson with distant metastatic disease (M1) and the remaining 70 had disease confined to the neck (M0). The median follow-up interval from the time of the initial operation at M. D. Anderson was 35 months.

Ten patients presented to M. D. Anderson with distant metastases (liver in five, lung in three, bone in one, and extracervical lymph node in one) and required a cervical operation for local-regional disease control. The median age of these patients at diagnosis was 33 years (range: 10 to 60 years), and

the median age at the time of their operation at M. D. Anderson was 40 years (range: 12 to 70 years). Four patients had sporadic MTC and six had hereditary MTC. The M. D. Anderson operation was the initial cervical operation in four patients and was a reoperation for persistent (n = 1) or recurrent (n = 5) disease in 6 patients. Five of 10 patients subsequently received systemic therapy. At last follow-up, none of the 10 patients had developed a cervical recurrence; six were AWD, three were DOD, and one had been lost to follow-up.

Clinicopathologic factors and vital statistics for the 70 patients without distant metastatic disease (M0 MTC) at presentation to M. D. Anderson are summarized in Table II. The median age at diagnosis in these patients was 41 years (range: 5 to 78 years), and the median age at the time of operation at M. D. Anderson was 45 years (range: 5 to 78 years). The etiology of MTC was sporadic in 45 (64%) and hereditary in 25 (36%). The initial surgery was performed at M. D. Anderson in 23 (33%) patients, whereas 47 (67%) were referred for reoperation.

The outcomes of the 45 patients with sporadic M0 MTC are summarized in Table III. Thirty-seven (82%) patients had evidence of cervical lymph node metastases, of whom 32 had N1b disease (levels IIA, III, IV, or V). Disease recurred in 16 (36%) of these 45 patients, a median of 23 months (range: 9 to 125 months) after their initial operation at M. D. Anderson. Of the six patients with an isolated

Table II. Demographics, recurrence data, and vital status of 70 patients with M0 medullary thyroid carcinoma*

| Parameter | Total | Total recurrences (%) | CR | DM | CR and DM | NED | AWD | DOD | Dead, other† |
|-------------------------------|-------|-----------------------|----|----|-----------|-----|-----|-----|--------------|
| Total no. of patients | 70 | 18 (26) | 7 | 8 | 3 | 58 | 8 | 3 | 1 |
| Age at diagnosis | | | | | | | | | |
| ≤45 years | 42 | 10 (24) | 5 | 5 | 0 | 37 | 5 | 0 | 0 |
| >45 years | 28 | 8 (29) | 2 | 3 | 3 | 21 | 3 | 3 | 1 |
| Gender | | | | | | | | | |
| Male | 29 | 11 (38) | 4 | 5 | 2 | 22 | 5 | 2 | 0 |
| Female | 41 | 7 (17) | 3 | 3 | 1 | 36 | 3 | 1 | 1 |
| Etiology of MTC | | | | | | | | | |
| Sporadic | 45 | 16 (36) | 6 | 7 | 3 | 34 | 7 | 3 | 1 |
| Hereditary | 25 | 2 (8) | 1 | 1 | 0 | 24 | 1 | 0 | 0 |
| First MDACC surgery | | | | | | | | | |
| Initial surgery: therapeutic | 18 | 3 (17) | 2 | 1 | 0 | 16 | 1 | 0 | 1 |
| Initial surgery: prophylactic | 5 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| Reoperation: therapeutic‡ | 32 | 11 (34) | 4 | 6 | 1 | 25 | 5 | 2 | 0 |
| Reoperation: elective | 15 | 4 (27) | 1 | 1 | 2 | 12 | 2 | 1 | 0 |

AWD, Alive with disease; CR, Cervical recurrence; DOD, Dead of disease; DM, Distant metastatic recurrence; MDACC, M. D. Anderson Cancer Center; M0, No evidence of distant metastasis; MTC, Medullary thyroid carcinoma; NED, No evidence of disease.

*All values are numbers of patients.

†One patient died of congestive heart failure without known evidence of recurrent or metastatic disease.

‡Reoperation for persistent or recurrent MTC.

Table III. Pathologic staging, recurrence data, and vital status of 45 M0 patients with sporadic medullary thyroid carcinoma*†

| Parameter | Total | Total recurrences (%) | CR | DM | CR and DM | NED | AWD | DOD | Dead, other‡ |
|--------------------------|-------|-----------------------|----|----|-----------|-----|-----|-----|--------------|
| Sporadic disease | 45 | 16 (36) | 6 | 7 | 3 | 34 | 7 | 3 | 1 |
| Primary tumor (T) | | | | | | | | | |
| T1 | 18 | 4 (22) | 4 | 0 | 0 | 18 | 0 | 0 | 0 |
| T2 | 16 | 6 (38) | 2 | 2 | 2 | 11 | 3 | 1 | 1 |
| T3 | 9 | 4 (44) | 0 | 3 | 1 | 5 | 3 | 1 | 0 |
| T4a | 2 | 2 (100) | 0 | 2 | 0 | 0 | 1 | 1 | 0 |
| Regional lymph nodes (N) | | | | | | | | | |
| N0 | 4 | 1 (25) | 0 | 1 | 0 | 3 | 1 | 0 | 0 |
| N1a | 5 | 1 (20) | 1 | 0 | 0 | 5 | 0 | 0 | 0 |
| N1b | 32 | 14 (44) | 5 | 6 | 3 | 22 | 6 | 3 | 1 |
| NX | 4 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| Stage grouping | | | | | | | | | |
| Stage I | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Stage II | 2 | 1 (50) | 0 | 1 | 0 | 1 | 1 | 0 | 0 |
| Stage III | 6 | 1 (17) | 1 | 0 | 0 | 6 | 0 | 0 | 0 |
| Stage IVA | 32 | 14 (44) | 5 | 6 | 3 | 22 | 6 | 3 | 1 |
| Stage not assessed§ | 4 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |

AWD, Alive with disease; CR, Cervical recurrence; DOD, Dead of disease; DM, Distant metastatic disease; M0, No evidence of distant metastasis; NED, No evidence of disease.

*All values are numbers of patients.

†Staging (AJCC, 6th edition)¹⁵ based on histopathologic results from all operations performed within 6 months of initial operation.

‡One patient died of congestive heart failure without known evidence of recurrent or metastatic disease.

§Stage could not be assessed because of incomplete prereferral pathology report issued more than 6 months before MDACC reoperation.

cervical recurrence, all originally presented with lymph node metastases (N1b in 5, N1a in 1), underwent reoperation, and are currently NED. Isolated distant metastases developed in seven patients (liver in four, bone in four, and lung in two), and both cervical and distant recurrences

developed in three patients (liver in three, lung in two, and bone in two). Of these 10 patients, two (20%) presented with T4a disease and nine (90%) with N1b (stage IVA) disease. At last follow-up, seven of the 10 patients with distant metastases were AWD and three have died of MTC.

Table IV. Basal calcitonin levels in 70 M0 patients with medullary thyroid carcinoma

| Time | Median basal calcitonin levels (pg/mL)* | | | | |
|---------------------------------|---|-------------------------|----------------------------|--------------------------|----------------------|
| | No evidence of recurrence (range) | CR (range) | DM (range) | CR and DM (range) | Total (range) |
| Preoperative | 340 (5 to 39,348) | 1,345 (114 to 3,100) | 3,734 (1,064 to 13,160) | 694 (76 to 1,013) | 585 (5 to 39,348) |
| Postoperative | 20 (0.7 to 2,835) | 245 (48 to 488) | 531 (25 to 3,410) | 339 (10 to 442) | 46 (0.7 to 3,410) |
| At last follow-up or recurrence | 33 (0.7 to 3,052) | 320 (55 to 4,044) | 1,754 (32 to 6,574) | 1,009 (125 to 36,000) | NA |

CR, Cervical recurrence; DM, Distant metastatic recurrence; M0, No evidence of distant metastasis; NA, Not applicable.

*Basal calcitonin levels were unavailable for four of 70 patients preoperatively, seven of 70 postoperatively, six of 52 at last follow-up, and one of 18 at the time of recurrence.

As expected, the 25 patients with hereditary M0 MTC had early-stage disease at presentation (T1 in 21 [84%], T2 in two [8%], and T3 in one [4%], and TX in one patient). The nodal status in these patients was as follows: N0, 14 (56%) patients; N1a, three (12%) patients; N1b, four (16%) patients; and NX, four (16%) patients. The *RET* mutations were known in 23 of the 25 patients and consisted of 10 (43%) mutations at codon 634, three (13%) at codon 891, three (13%) at codon 918, two (9%) at codon 609, two (9%) at codon 620, and one each at codons 611, 618, and 804. At last follow-up, only two (8%) of the 25 patients had recurrent disease develop (Table II). A cervical recurrence developed in one patient 8 years after initial operation at M. D. Anderson. The patient was treated with a repeat central neck dissection and is NED 24 months after this repeat surgery. Bone metastases developed in the other patient 16 months after the first surgery at M. D. Anderson, and the patient is currently alive with stable metastatic disease 52 months after initial surgery.

The relationship between the CT level and recurrence in patients with M0 MTC is shown in Table IV and Figures 1 and 2. Preoperative CT levels were available for 66 of the 70 patients (median: 585 pg/mL, range: 5 to 39,348 pg/mL). The recurrence rate was higher in the patients with preoperative CT levels equal to or above the median than in those with preoperative CT levels below the median (Fig 1). The estimated 5-year RFS rates were 0.54 and 0.89 for patients with CT levels equal to or above and below the median, respectively ($P < .01$). Postoperative CT levels were available for 63 of the 70 patients with M0 MTC (median: 46 pg/mL, range: undetectable to 3,410 pg/mL). Once again, the recurrence rate was higher in the patients with postoperative CT levels equal to or above the median than in those with postoperative CT levels

below the median (Fig 2). The estimated 5-year RFS rates were 0.54 and 0.90 for patients with CT levels equal to or above and below the median, respectively ($P < .01$). Of the 63 patients with postoperative CT levels, three had undergone prophylactic thyroidectomy. Excluding these three patients, postoperative CT levels were undetectable in 13 (22%) of the remaining 60 M0 patients, 10 after therapeutic operation and three after elective reoperation. Twelve (92%) of these 13 patients remain NED, and one patient has died of recurrent disease. However, CT levels at last follow-up remain undetectable in only six (50%) of the 12 patients; the other six have detectable levels of CT despite no radiographic or clinical evidence of disease.

CT levels at the time of recurrence were available for 17 of the 18 patients in whom recurrence developed (median: 804 pg/mL, range: 32 to 36,000 pg/mL). Recurrent disease was associated with a CT level >250 pg/mL in all but four patients, two with isolated cervical disease and two with distant metastases with evidence of tumor dedifferentiation and clinical evidence of rapid tumor progression. Carcinoembryonic antigen (CEA) levels at the time of recurrence in these four patients were normal. In contrast, among the 46 patients without recurrence in whom CT values were documented, only five (11%) had CT levels >250 pg/mL at last follow-up.

Prophylactic thyroidectomy was performed in 17 patients (four with familial MTC, 13 with MEN2) at a median age of 7 years (range: 4 to 30 years). *RET* mutations included eight (47%) at codon 634, three each (18%) at codon 609 and 620, and two (12%) at codon 618, with screening for *RET* mutations not performed in one patient. Stage I invasive MTC was found in five (29%) of these 17 patients at a median age of 12 years (range: 5 to 30 years). The median preoperative CT level in these

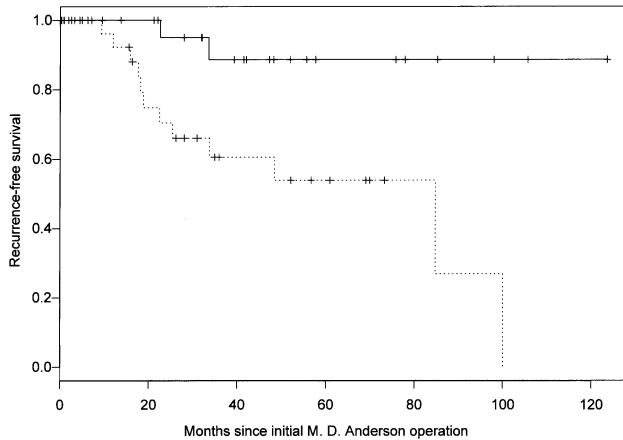


Fig 1. Recurrence-free survival in the M0 patients with MTC vis-à-vis preoperative CT levels. Preoperative CT levels were available for 66 of the 70 M0 patients. There were 18 recurrences in the 70 patients; 12 occurred in patients with preoperative CT levels equal to or above the median, and two occurred in patients with preoperative CT levels below the median. The remaining four recurrences were in patients lacking documented preoperative CT levels. The recurrence rate was higher in patients with preoperative CT levels equal to or above the median (*dashed line*) than in those with preoperative CT levels below the median (*solid line*), $P < .01$.

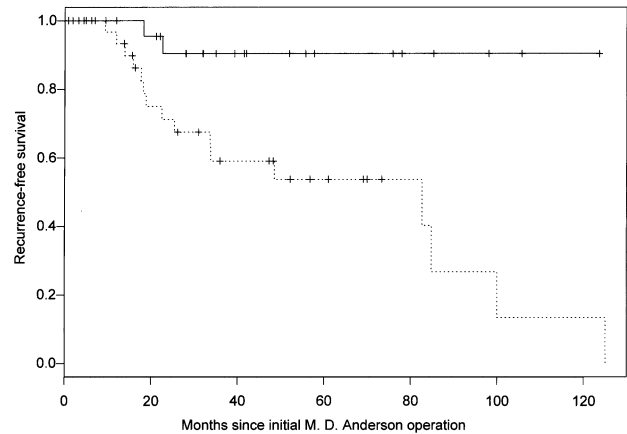


Fig 2. Recurrence-free survival in the M0 patients with MTC vis-à-vis postoperative CT levels. Postoperative CT levels were available for 63 of the 70 M0 patients. Of the 18 recurrences in these patients, 16 occurred in patients with postoperative CT levels equal to or above the median and two occurred in patients with postoperative CT levels below the median. The recurrence rate was higher in patients with postoperative CT levels equal to or above the median (*dashed line*) than in those with postoperative CT levels below the median (*solid line*), $P < .01$.

five patients was 32 pg/mL (range: 20.5 to 204 pg/mL). The median preoperative CT level for the patients with normal histology or C-cell hyperplasia (available in 10 of 12 patients) was 21 pg/mL (range: 3.6 to 26.4 pg/mL). There was no correlation between preoperative CT levels and the finding of invasive MTC on histopathology in the patients undergoing prophylactic thyroidectomy for hereditary MTC (Fig 3). One patient with invasive MTC was not included in Figure 3 because the CT level was 204 pg/mL, a value so high that MTC was suspected prior to operation.

Fifteen patients with elevated CT levels but no clinical or radiographic evidence of disease underwent elective reoperative neck dissection (Table V). The median age at diagnosis in these patients was 44 years (range: 9 to 66 years), and the median age at the time of their first operation at M. D. Anderson was 45 years (range: 11 to 66 years). Histopathologic evidence of MTC was found in the surgical specimens of 12 (80%) of the 15 patients. No patient received adjuvant EBRT. Four recurrences were diagnosed during the follow-up period, all of which occurred in patients with sporadic MTC. Three of the four patients had stage IVA disease; cervical recurrences developed in all three, two of whom had concomitant distant metastases. The fourth patient had stage II disease

and developed isolated bone metastases. At last follow-up, 12 (80%) of the 15 patients were NED, two were AWD, and one was DOD. Preoperative CT levels were available in 14 of the 15 patients (median: 226 pg/mL, range: 5 to 7,100 pg/mL). Postoperative CT levels were available in 12 of the 15 patients (median: 24 pg/mL, range: undetectable to 4,430 pg/mL), and as stated above, were undetectable in three (25%) of 12 patients. At last follow-up, all three patients remain NED; however, all three had detectable CT levels. The relationship between preoperative and postoperative CT levels and recurrence in this subgroup of patients is depicted in Figures 4 and 5.

EBRT was delivered to 20 (25%) of the 80 patients with invasive MTC at presentation (13 with M0 disease and seven with M1 disease) because they had bulky cervical disease with histopathologic evidence of extrathyroidal or extranodal soft tissue extension, or because of concern over a microscopically positive margin of resection. The EBRT doses ranged from 42 to 76 Gy; 11 patients received 60 Gy. EBRT was given after the first M. D. Anderson operation in 14 patients and after a second M. D. Anderson operation in the remaining six patients. Of the 14 patients who received EBRT after their first M. D. Anderson operation, only one (7%) developed a cervical recurrence, which was diagnosed 14 months after the completion of EBRT.

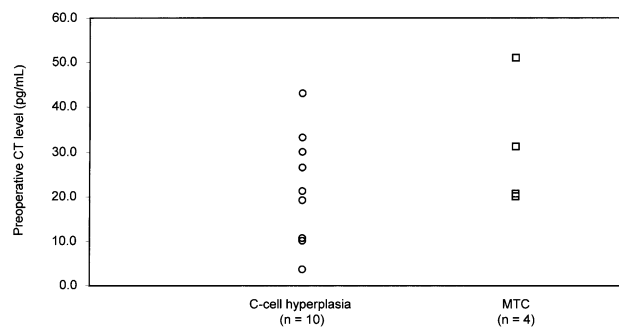


Fig 3. Scatter plot of preoperative CT levels in 14 of the 17 patients undergoing prophylactic thyroidectomy for hereditary MTC (MEN2 or familial MTC). Preoperative CT values were available for 15 of the 17 patients. One patient who had invasive MTC was not included because her CT level of 204 pg/mL was so high that she was suspected of having invasive MTC before operation. Final histopathology of the 17 patients showed 12 to have C-cell hyperplasia and 5 to have invasive MTC. The distribution of preoperative CT values in this group suggests that CT level is not an accurate predictor of histology in patients undergoing prophylactic thyroidectomy.

This patient was treated with repeat central neck dissection and is currently NED. Of the six patients who received EBRT after their second M. D. Anderson operation, no patient developed a subsequent cervical recurrence. In contrast, cervical recurrence developed in nine (14%) of the 66 patients who did not receive EBRT after their first M. D. Anderson operation. CT levels before and after EBRT (up to 3 months post-EBRT) were available in six patients with no evidence of extracervical disease. The median pre- and post-EBRT CT levels were 136 pg/mL (range: 15 to 1,000 pg/mL) and 108 pg/mL (range: 13 to 1,363 pg/mL), respectively.

Ten (13%) of the 80 patients with invasive MTC at presentation underwent a total of 11 reoperations for recurrent cervical disease after their initial operation at M. D. Anderson. The median time to recurrence was 23 months (range: 14 to 126 months). One (10%) of these 10 patients received adjuvant EBRT after the first M. D. Anderson operation. Six of the remaining nine patients received EBRT after their second M. D. Anderson operation for recurrent cervical disease. At last follow-up, seven of these 10 patients were NED, one was AWD, and two were DOD.

Surgical morbidity included resection of the ipsilateral recurrent laryngeal nerve ($n = 3$), permanent hypoparathyroidism ($n = 4$; defined as the need for both calcium and vitamin D at 6 months after surgery), postoperative hemorrhage requiring reoperation ($n = 2$), chylous fistula ($n = 2$),

chylothorax ($n = 1$), transient palsy of the spinal accessory nerve ($n = 2$), and Horner's syndrome ($n = 1$). Four additional patients had permanent hypoparathyroidism prior to their M. D. Anderson operation. Therefore, the total frequency of permanent hypoparathyroidism was eight (9%) of 92 patients.

DISCUSSION

Our findings in the 92 patients referred for surgical treatment of biopsy-proven or presumed MTC suggest the following: (1) death from MTC is uncommon in the absence of radiographically evident distant metastases at the time of surgery (3/70, 4%); (2) the likelihood of cervical recurrence can be minimized with COS in patients with either primary or recurrent MTC (10/80, 13%); (3) postoperative CT levels can be used to guide clinical management; (4) basal CT levels cannot be used to direct the timing of prophylactic thyroidectomy in affected at-risk patients with familial MTC; and (5) EBRT should be considered in high-risk patients who have undergone COS for regionally advanced MTC.

Our data support the finding from previous natural history studies that MTC progresses relatively slowly.^{16,17} In fact, we recorded only six MTC-related deaths: three in the 10 patients who presented with distant metastatic disease (M1) and three (4%) in the 70 patients who presented with primary or recurrent M0 MTC. Overall, distant metastases developed in 11 (16%) of the 70 patients with M0 disease at presentation, including the three patients who ultimately died of disease. Ten (91%) of these 11 patients presented with advanced cervical disease (N1b). Bone metastasis developed in one patient without cervical lymph node metastases, demonstrating the very unusual biology this tumor can occasionally display. Nine of 11 patients showed a progressive rise in serum CT levels; two patients exhibited rapidly progressive, radiologically apparent metastatic disease in the absence of an elevation in CT or CEA levels, suggesting tumor dedifferentiation. Therefore, eight of the 11 patients in whom distant metastases developed had large-volume cervical disease, and their serum CT level progressively rose during follow-up, prompting a radiographic search for distant disease in lung, liver, and bone.

Previous investigators have supported the use of reoperative cervical lymphadenectomy to achieve a clinical and biochemical systemic cure, as assessed by serum levels of CT.⁶⁻⁹ Their rationale was that because indolent diseases such as MTC may

Table V. Demographics, recurrence data, and vital status of 15 M0 patients undergoing elective reoperation for medullary thyroid carcinoma*

| Parameter | Total | Total recurrences (%) | CR | DM | CR and DM | NED | AWD | DOD |
|--|-------|-----------------------|----|----|-----------|-----|-----|-----|
| Total no. of patients | 15 | 4 (27) | 1 | 1 | 2 | 12 | 2 | 1 |
| Age at diagnosis | | | | | | | | |
| ≤45 years | 9 | 1 (11) | 1 | 0 | 0 | 9 | 0 | 0 |
| >45 years | 6 | 3 (50) | 0 | 1 | 2 | 3 | 2 | 1 |
| Etiology of MTC | | | | | | | | |
| Sporadic | 9 | 4 (44) | 1 | 1 | 2 | 6 | 2 | 1 |
| Hereditary | 6 | 0 | 0 | 0 | 0 | 6 | 0 | 0 |
| Stage grouping† | | | | | | | | |
| Stage I | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Stage II | 2 | 1 (50) | 0 | 1 | 0 | 1 | 1 | 0 |
| Stage III | 3 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| Stage IVA | 7 | 3 (43) | 1 | 0 | 2 | 5 | 1 | 1 |
| Stage not assessed‡ | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Interval from initial surgery to MDACC reoperation | | | | | | | | |
| ≤16 months | 8 | 3 (38) | 1 | 0 | 2 | 6 | 1 | 1 |
| >16 months | 7 | 1 (14) | 0 | 1 | 0 | 6 | 1 | 0 |

AWD, Alive with disease; CR, Cervical recurrence; DM, Distant metastatic recurrence; DOD, Dead of disease; MDACC, M. D. Anderson Cancer Center; MTC, Medullary thyroid carcinoma, NED, No evidence of disease.

*All values are numbers of patients.

†Staging (AJCC, 6th edition)¹⁵ based on histopathologic results from all operations performed within 6 months of initial operation.

‡Stage could not be assessed because of incomplete prereferral pathology report issued more than 6 months before MDACC reoperation.

metastasize to regional lymph nodes in the absence of distant organ metastases, a more extensive lymphadenectomy might result in long-term cure. However, the controversy surrounding elective or prophylactic neck dissection in patients with MTC has hindered a more thorough analysis of cervical recurrence rates and the importance of surgery in maximizing local-regional disease control. Regardless of one's view on the use of cervical lymphadenectomy to reduce serum CT levels, the rates of cervical recurrence seen in patients with MTC (20% to 60%) mandate that greater attention be paid to the operative approach to the neck used in these patients.^{6,18,19} The modest cervical recurrence rates observed in this study (13%) provide preliminary evidence supporting the use of COS in patients with MTC. The approach we take in patients depends on the extent of their disease. In patients with sporadic MTC and no clinical or radiologic evidence of cervical nodal disease, we perform total thyroidectomy, central compartment dissection, and ipsilateral modified neck dissection. In patients with sporadic MTC and clinical or radiographic evidence of lymph node metastases in any cervical compartment, we perform total thyroidectomy and central and bilateral neck dissection. In patients with familial MTC and grossly evident disease, we also perform total thyroidectomy and central and bilateral neck dissection.

Our study shows that postoperative CT levels can be used to guide the clinical management of patients with MTC. Specifically, our data suggested that a CT value ≤250 pg/mL is unlikely to be associated with radiographically visible recurrent disease. This information should be used to help guide the overall care of the patient. For example, a patient with sporadic MTC who undergoes surgery for a histopathologic T1-T2, N1a MTC with a postoperative CT level of 100 pg/mL is unlikely to have distant metastases, and chest and abdomen computed tomography and bone scintigraphy (in the absence of symptoms) are very unlikely to yield positive findings. We recommend that such a patient be followed up with serial measurements of serum CT and CEA levels at 6- to 12-month intervals and yearly ultrasonography of the neck. The radiographic evaluation of liver, lung, and bone should be performed if there is a sudden or progressive rise in the CT or CEA level or if clinical symptoms develop.

The scatter plot in Figure 3 demonstrates the inaccuracy of using basal CT levels to determine whether invasive MTC is present in the affected children of familial MTC kindreds. As demonstrated by previous authors, one cannot reliably distinguish patients who have benign C-cells from those with malignant C-cells on the basis of the basal CT levels.²⁰⁻²³ This is of major clinical relevance in

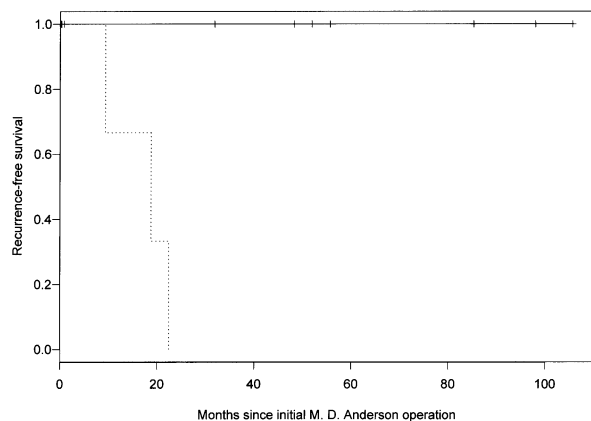


Fig 4. Recurrence-free survival in the 15 patients undergoing elective neck reoperation vis-à-vis preoperative CT levels. Preoperative CT levels were available for 14 of the 15 patients. There were 4 recurrences in the 15 patients; 3 patients had preoperative CT levels equal to or above the median; the preoperative CT level was not available for the fourth patient. The recurrence rate was higher in patients with preoperative CT levels equal to or above the median (*dashed line*) than in those with preoperative CT levels below the median (*solid line*), $P < .01$.

patients with level two (high-risk) *RET* mutations (codon 611, 618, 620, 634) in whom the current recommendation is to perform prophylactic thyroidectomy by the age of 5 years.²⁴ Because of the inability of serum CT levels to differentiate C-cell hyperplasia from invasive MTC, and in light of our anecdotal experience in this analysis with one patient with a codon 634 mutation who had invasive MTC after prophylactic thyroidectomy at age 5 years, we currently prefer to perform thyroidectomy before the age of 5 in patients with level two *RET* mutations.

The use of EBRT in patients with MTC remains controversial. However, our data support the conclusion of previous investigators that EBRT may improve local-regional disease control in high-risk patients with MTC.^{13,14,25} In particular, of the 20 patients who received EBRT in this study, cervical recurrence developed in only one (5%). Our indications for EBRT include bulky cervical disease with histologic evidence of extranodal or soft tissue invasion or a microscopically positive margin of resection. We do not advise the use of EBRT in patients with an elevated postoperative CT level in the absence of these histopathologic findings.

In summary, our data provide valuable natural history information on patients with MTC who undergo a standardized surgical approach. COS may minimize the risk of cervical recurrence and

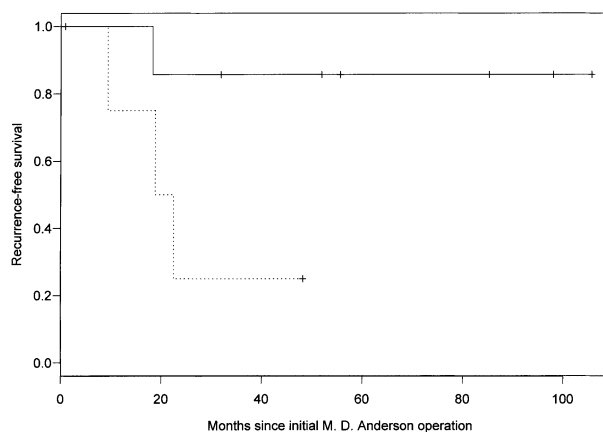


Fig 5. Recurrence-free survival in the 15 patients undergoing elective neck reoperation vis-à-vis postoperative CT levels. Postoperative CT levels were available for 12 of the 15 patients. Of the 4 recurrences, 3 were in patients with postoperative CT levels equal to or above the median and 1 was in a patient with a postoperative CT level below the median. There was thus a trend toward higher recurrence rates in patients with postoperative CT levels equal to or above the median (*dashed line*) than in those with postoperative CT levels below the median (*solid line*), $P = .06$.

will alleviate concern on the part of both the patient and referring endocrinologist that an elevated postoperative CT level is the result of disease in one or two lymph nodes not removed during the primary surgery. Patients can then be followed up with serial measurements of CT and CEA levels and radiographic imaging on the basis of the absolute level of CT and its change over time. For patients who undergo COS and have a persistently elevated CT level of less than approximately 250 pg/mL, follow-up is limited to physical examination, annual cervical ultrasonography, and serial measurements of CT and CEA levels. Further radiographic imaging should be performed if symptoms arise or the CT or CEA levels progressively increase.

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DISCUSSION

Dr Ashok R. Shaha (New York, NY). I enjoyed your paper. Very nice data and good analysis in a prospective fashion. In spite of that, certain questions come up.

You did talk about compartment-oriented surgery. If there is a paratracheal node that is level VI, the question is, do you dissect levels II, III, and IV in that patient, especially one with medullary thyroid cancer? In papillary thyroid cancer, you may not consider doing that, but I just want to know your philosophy in medullary thyroid cancer.

Next, you didn't explain about the contralateral prophylactic dissection, either paratracheal or compartment-oriented dissection. What about the mediastinal nodes?

The last is, do you rely on the size of the primary tumor or the preoperative calcitonin level to decide how extensive a neck dissection you should consider?

Dr Yen. I think that question can be partly answered by this slide. Our surgical approach depends on the various compartments, as you stated, as well as an individualized approach for each patient. In a patient who has sporadic MTC and no obvious clinical or radiographic evidence of nodal disease, we prefer the standard total thyroidectomy, central neck dissection, and ipsilateral neck dissection. If this patient or the referring physician is going to fixate on the postoperative calcitonin levels, then we would discuss with the patient preoperatively the value of performing bilateral neck dissection.

With respect to contralateral dissection, again, that is discussed preoperatively.

Regarding mediastinal nodes, we routinely do not perform median sternotomy to address level 7 nodes unless, preoperatively, there is evidence of disease in the mediastinum.

Lastly, tumor size may play a role in preoperative discussion as to how aggressively we recommend lateral neck dissection in some of these patients.

Dr Jeffrey F. Moley (St. Louis, Mo). That was a very nice paper. I have a couple of questions.

First of all, you stated that death from disease is uncommon, but in the abstract, it states that your average follow-up is only 36 months. As we know, these patients can take a lot longer to have metastatic disease develop and then die, and I would suggest that the mortality will be a bit higher if you see these patients for a longer period.

Secondly, as far as radiation therapy is concerned, you suggest that it is helpful in these patients, but you didn't really present any data to support that. Did radiation