ORIGINAL ARTICLE

POSTOPERATIVE RADIOTHERAPY FOR ADVANCED MEDULLARY THYROID CANCER—LOCAL DISEASE CONTROL IN THE MODERN ERA

David L. Schwartz, MD,[1,2] Vishal Rana, MD, MPH,[1] Stephanie Shaw, MD,[3] Cynthia Yazbeck, MD,[3] Kie-Kian Ang, MD, PhD,[1] William H. Morrison, MD,[1] David I. Rosenthal, MD,[1] Ana Hoff, MD,[3] Douglas B. Evans, MD,[4] Gary L. Clayman, DMD, MD,[5] Adam S. Garden, MD,[1] Steven I. Sherman, MD[3]

[1] Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas. E-mail: docdls@mdanderson.org
[2] Department of Experimental Diagnostic Imaging, The University of Texas M. D. Anderson Cancer Center, Houston, Texas
[3] Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas M. D. Anderson Cancer Center, Houston, Texas
[4] Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas
[5] Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Accepted 24 October 2007
Published online 22 January 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20791

Abstract: *Background.* The purpose of this study is to catalog modern-era postoperative radiotherapy (external beam radiotherapy [EBRT]) outcomes for advanced medullary thyroid cancer.

Methods. Thirty-four consecutive patients with stage IVa–c disease were evaluated. Ten patients had recurrent disease, 16 had mediastinal involvement, and 10 had distant metastasis. Positive surgical margins were present in 12 cases. Median pre-EBRT serum calcitonin was 556. All patients received conformal EBRT or intensity-modulated radiotherapy. Median EBRT dose was 60 Gy and median follow-up was 46.5 months.

Results. Kaplan–Meier estimates of locoregional relapse–free survival, disease-specific survival, and overall survival at 5 years were 87%, 62%, and 56%, respectively. Disease in 3 patients with gross residual disease was controlled locoregionally. Distant disease at the time of EBRT did not predict survival. Two (9%) patients reported symptomatic chronic morbidity.

Conclusion. Surgery followed by EBRT provided durable locoregional disease control with limited morbidity. Postoperative EBRT merits consideration in cases of advanced disease at high risk for locoregional recurrence. ©2008 Wiley Periodicals, Inc. *Head Neck* **30:** 883–888, 2008

Keywords: medullary thyroid carcinoma; radiotherapy; IMRT; postoperative; adjuvant; outcomes

Correspondence to: D. L. Schwartz

Results from this work were presented at the 49th Scientific Meeting of the American Society of Therapeutic Radiology and Oncology in October 2007.

Contract grant sponsor: National Cancer Institute; contract grant number: P01 CA06294.

Dr. Sherman has reported a financial interest/relationship with Astra Zeneca as a consultant and a recipient of financial support for the research of medullary thyroid cancer.

Medullary thyroid carcinoma (MTC) is a neuroendocrine neoplasm originating from calcitonin-secreting C cells in the upper lateral lobes of the gland. It is an uncommon diagnosis, representing 5% to 10% of all thyroid cancers. One fourth of

cases are associated with 1 of 3 autosomal dominant hereditary cancer syndromes: multiple endocrine neoplasia type 2A (MEN 2A), MEN 2B, and familial non-MEN MTC.[1] Genotyping of affected kindred has identified germline mutations in the RET oncogene, which are now known to be responsible for all hereditary cases.[2]

Although MTC typically grows slowly, it is lymphotropic and frequently (especially in hereditary cases) presents with multifocal and/or bilateral glandular involvement. Up to 80% of patients with palpable disease have nodal involvement,[3] with the central compartment most commonly affected, followed by the ipsilateral and contralateral cervical nodal chains and superior mediastinum.

MTC is classically managed with surgery alone.[4,5] Unlike differentiated thyroid cancers, MTC is not iodine-avid and cannot be treated with systemic radioiodine. MTC has garnered a reputation as being resistant to external beam radiotherapy (EBRT); not surprisingly, patterns-of-care data confirm that EBRT is delivered to less than 15% of patients with MTC.[6] Limited data exist to substantiate or refute this practice. Available institutional outcomes data, however, do suggest that radiotherapy improves locoregional disease control in high-risk cases, despite the lack of an impact on overall survival (OS).[7–11] These are generally very small or dated series that document the results of treatment delivered up through the 1990s.

Our institutional practice has been to offer postoperative EBRT to patients with high-risk disease, as defined by the presence of gross or microscopic residual disease, soft tissue extension, nodal disease, or mediastinal involvement. In this report, we summarize the clinical outcomes in high-risk patients treated with modern 3-dimensional image guided adjuvant EBRT after the year 1995.

MATERIALS AND METHODS

After obtaining approval from our Institutional Review Board, we retrospectively reviewed the medical records of 47 patients who presented to our department following surgical management of medullary thyroid cancer between November 1995 and December 2004. We excluded 13 patients from the analysis on the basis of treatment delivery at an outside facility, yielding a study cohort of 34 patients.

Patient characteristics are detailed in Table 1. Twenty-nine percent of patients had locally recurrent disease, 47% had mediastinal involvement, and 29% had distant metastasis. All patients had node-positive stage IVa–IVc disease with high-risk surgical-pathologic features, such as presence of gross or microscopic residual disease, soft tissue extension, nodal metastases, or mediastinal involvement. All underwent primary or salvage total thyroidectomy with central compartment and cervical neck dissection. Eighteen (53%) patients underwent mediastinal dissection as part of their surgery, as noted in formal opera-

Table 1. Patient characteristics.

	No. (%)
Sex	
Male	27 (79)
Female	7 (21)
Age, y	
Median	48.3
Range	25.5–80.5
AJCC stage	
IVa	23 (68)
IVb	1 (3)
IVc	10 (29)
Hereditary status	
Sporadic MTC	30 (80)
MEN2a	2 (6)
MEN2b	1 (3)
Familial MTC	1 (3)
No. of positive nodes	
Median	10
Range	1–55
Nodal extracapsular spread	
Positive ECE	22 (65)
Negative ECE	12 (35)
Mediastinal spread	
Yes	16 (47)
No	18 (53)
Pre-XRT disease status	
Index diagnosis	14 (41)
Recurrent	10 (29)
Metastatic	10 (29)
Surgical margin status	
Gross +	3 (9)
Microscopic +	12 (35)
Negative	19 (56)
Pre-XRT serum calcitonin	
Median	556
Range	0–88,000
Intent of XRT	
Curative	25 (74)
Palliative	9 (26)
XRT dose, Gy	
Median	60
Range	36–70
No. of XRT fractions	
Median	30
Range	12–35
3DRT	27 (79)
IMRT	7 (21)

Abbreviations: AJCC, American Joint Committee on Cancer; MTC, medullary thyroid carcinoma; MEN, multiple endocrine neoplasia; ECE, extracapsular extension; XRT, radiotherapy; Gy, gray; 3DRT, 3-dimensionally guided radiotherapy; IMRT, intensity-modulated radiotherapy.

tive reports. The majority of patients were men (80%) with sporadic disease (88%), with a median age of 48 years (range, 25.5–80.5). Median number of metastatic nodes was 10 (range, 1–55), with extracapsular nodal extension in 65% cases. Operative beds contained microscopically positive margins in 12 cases, or residual gross disease in 3 cases. Median pre-EBRT serum calcitonin was 556 (range, 0–88,000). Median pre-EBRT serum calcitonin for patients with known distant metastatic disease was 12,630 (range, 1714–88,000) versus 327 (range, 0–5628) for those patients with locoregional involvement. Immediate and longitudinal postoperative serum calcitonin levels were not uniformly obtained and therefore were not cataloged for analysis.

All patients received 3-dimensional image-guided radiotherapy following CT-based simulation. CT imaging included the entire thorax to permit incorporation of both lung volumes into treatment planning. Median EBRT dose was 60 Gy (range, 30–70 Gy) in 30 fractions (12–35 Gy). Patients treated at the time of initial diagnosis received a median dose of 60 Gy (56–70 Gy), patients with recurrent disease received a median dose of 60 Gy (60–70 Gy), and patients with distant metastases received a median dose of 50.5 Gy (36–62 Gy). Patients with negative or microscopically positive surgical margins received a median dose of 60 Gy (36–70 Gy), whereas those with gross disease received a median dose of 66 Gy (62–70 Gy). Twenty-seven patients received conventional EBRT to a median dose of 60 Gy (36–70 Gy) via extended opposed anterior/posterior (AP/PA) fields supplemented by off-cord photon boost fields or enface electron fields after delivery of 45 Gy. Seven patients received intensity-modulated radiotherapy (IMRT) to a median dose of 60 Gy (56–70 Gy) after mid-2001. With either technique, the superior mediastinum was treated to a prophylactic dose of 45–50 Gy. Definitive postoperative doses and extended inferior coverage of the middle or inferior mediastinum was pursued if these regions were involved with disease and/or if the patient underwent mediastinal nodal dissection.

IMRT was delivered via a step-and-shoot, multileaf collimation through a static treatment gantry. From 2001 through August 2003, IMRT treatment planning was performed with a CORVUS treatment planning system (CORVUS v.4.0; Nomos Corporation, Pittsburg, Pennsylvania). A Pinnacle3 system (version 6.2b or later; Philips Medical Systems, Andover, Massachusetts) was used after August 2003. Five patients were prescribed 60 Gy to a high-dose clinical target volume (CTV) 1 encompassing the surgical resection bed with a 1- to 2-cm (minimum, 0.5 cm) circumferential margin. One patient with gross residual disease was prescribed 70 Gy to CTV1, whereas another patient with documented distant disease was prescribed 56 Gy to CTV1 encompassing the surgical resection bed which had positive microscopic surgical margins. All patients received 30 once-daily fractions of 2 Gy to CTV1. An intermediate CTV2 encompassing immediately adjacent soft tissues and draining nodal basins was treated to a postoperative dose of 56 Gy in 30 daily fractions. Finally, prophylactic coverage of at-risk cervical and mediastinal nodal stations was provided by a CTV3 treated to 54 Gy in 30 daily fractions. Constraints for normal tissue structures were set at 45 Gy for spinal cord, 26 Gy for parotid glands, and 20 Gy to whole lungs, whereas larynx and esophagus were contoured as avoidance structures with low priority weighting to prevent compromising intended CTV1 or CTV2 coverage. The mean dose delivered to CTV1 ranged from 59.8 to 72.6 Gy (median, 62.4 Gy). The mean percentage of the prescribed dose delivered to CTV1 ranged from 102.0% to 106.8% (median, 104.0%). The volume of CTV1 receiving less than the prescribed dose ranged from 0.0% to 3.5% (median, 2.5%).

The endpoints of this study were locoregional relapse–free survival (LRFS), disease-specific survival (DSS), and OS. These were defined from the date of completion of radiotherapy and were estimated by the Kaplan–Meier method. Survival outcomes were analyzed for significance by the log-rank test for disease- and treatment-related variables. Potentially significant predictors were subsequently added in a forward stepwise fashion to a multivariate Cox proportional hazards model to test for significance. As appropriate, the significance of differences in proportions was calculated with chi-square testing and the significance of differences in means was calculated with a Student's *t* test, using a threshold of .05.

RESULTS

Median follow-up from completion of radiation was 46.5 months (range, 5.5–113) for all patients in the study cohort, and 65 months for surviving patients (range, 6.6–113).

Survival and Patterns of Failure. At last follow-up, 18 (53%) patients were alive and 30 (88%)

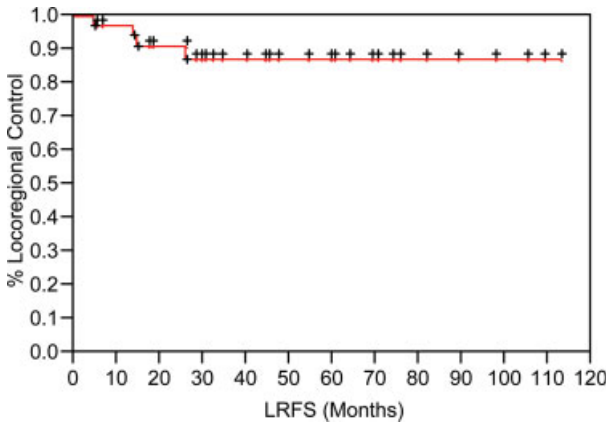

FIGURE 1. Locoregional relapse–free survival (LRFS) for the study cohort. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

patients remained free of disease locoregionally. All 4 locoregional failures occurred within 26 months of completion of EBRT. Ten of 24 (42%) patients who were initially seen with locoregionally confined disease eventually developed some component of distant failure following EBRT. Kaplan–Meier estimates of LRFS, DSS, and OS at 5 years were 87%, 62%, and 56%, respectively (Figures 1–3).

Prognostic Factors. In this cohort with advanced stage disease, no patient/treatment characteristic predicted for LRFS on univariate analysis. Age as a continuous variable predicted for DSS (RR = 1.07/year, $p = .001$) and OS (RR = 1.05/year, $p = .005$) on Cox proportional hazards analysis. Presence of gross residual or metastatic disease at the time of radiation did not predict for outcome. All 3 patients with gross residual disease were controlled locoregionally with a minimum follow-up of 28 months. Distant disease at the time of EBRT did not predict for worse OS, and the estimated 5-year OS for such patients was 54% (Figure 3B).

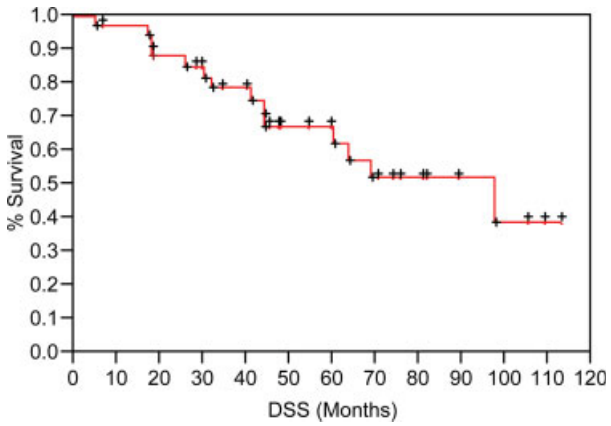

FIGURE 2. Disease-specific survival (DSS) for the study cohort. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

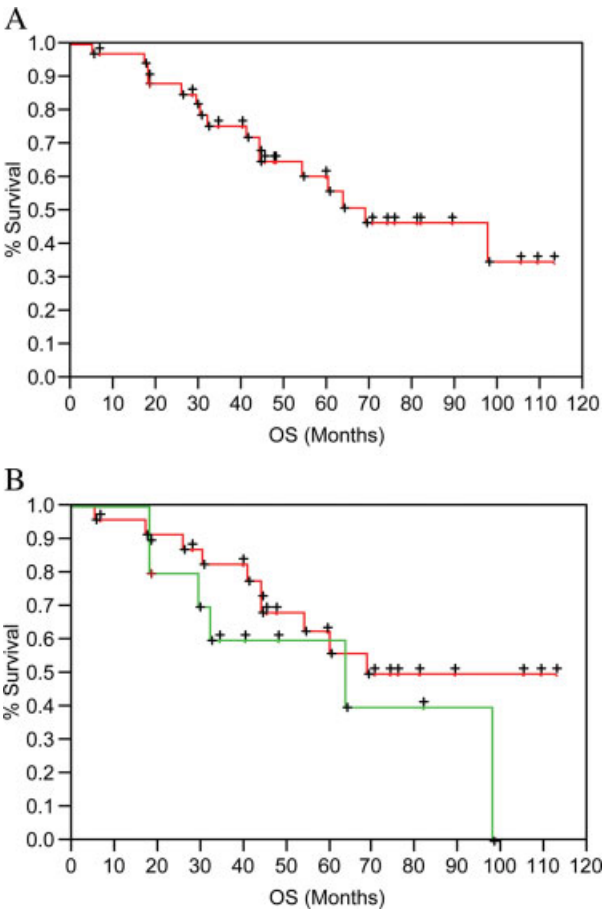

FIGURE 3. Overall survival (OS) for the entire study cohort (**A**), and according to presence/absence of metastatic disease at the time of radiation (**B**) ($p = .26$ by log-rank testing). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Posttreatment Morbidity. Two (9%) patients were noted to have symptomatic chronic EBRT morbidity. One patient who received 56 Gy/28 fractions of conventional EBRT with treatment extending superiorly to include high level II regions had chronic grade 2 xerostomia, but otherwise remained alive and disease free 109 months posttreatment. The second patient had multiple recurrent disease with gross residual disease in the left cervical neck and parapharyngeal region following salvage neck dissection. She received 70 Gy/35 fractions of IMRT with concurrent platinum-based chemotherapy (the only patient in the study cohort to receive concurrent systemic treatment).

Posttreatment course was complicated by fibrosis, trismus, and carotid artery bleeding events, necessitating chronic gastrostomy tube placement and carotid artery embolization and surgical repair. The patient succumbed 54 months after completion of radiotherapy with no evidence of disease.

DISCUSSION

MTC is a rare diagnosis. Limited experience is available to guide the use of EBRT following resection of advanced disease for frontline or salvage treatment. Early discouraging reports,[12,13] including data from our own institution, led to a nihilistic view of radiotherapy's role in treating this cancer, which lingers to this day. Contemporary[14,15] and subsequent series,[7–11] however, support an alternative view that EBRT may improve locoregional control of MTC, especially in patients with locally advanced disease. For example, Brierly et al[7] from the University of Toronto reported results from patients treated between 1954 and 1992 with 20 to 75.5 Gy (median, 40 Gy). In high-risk patients with microscopic residual disease, extraglandular spread, or lymph node metastasis, the LRFS was 86% at 10 years with postoperative EBRT (25 patients) versus 52% without irradiation (15 patients, $p = .049$). Fife et al[8] from the Royal Marsden Hospital presented results from 51 patients treated between 1960 and 1992. The local control rate at 5 years was 100% for patients with negative margins, and 65% for positive margins. LRFS, however, did fall to 24% for patients with gross residual disease. Actuarial OS was 69% and 52% at 5 and 10 years, respectively.

Our current series presents outcomes from a cohort of patients with very high-risk disease features treated over a brief 10-year time period in the modern era. All patients had stage IVa–IVc disease according to 2002 American Joint Committee on Cancer staging criteria, including patients with primary disease extending beyond the thyroid capsule into surrounding resectable structures (T4a) or prevertebral fascia, carotid artery, or mediastinal vessels (T4b), nodal metastases to cervical or mediastinal stations (N1b), and/or distant metastases (stage IVc). Ten patients had locally recurrent disease, 16 had mediastinal extension, and 10 had distant spread. All underwent at least primary or salvage total thyroidectomy with central compartment and cervical neck dissection, and 18 required mediastinal dissection. Despite these adverse features, LRFS, DSS, and OS at 5 years for the cohort outperformed previously published results and were 87%, 62%, and 56%, respectively. Presence of gross or metastatic disease at the time of radiation did not impact LRFS, although this could be due to selection of patients with limited volume of disease. Disease in all 3 patients with gross residual disease was controlled locoregionally at the time of last follow-up. Given the low number of disease events in our series, no prognostic factors for outcomes were identified. It is important to note that potential explanations for our encouraging survival outcomes relative to previous series include patient selection biases, improvements in disease localization and staging, and advances in perioperative and longitudinal supportive care.

Radiotherapy-related morbidity was low. Acute toxicity did not limit treatment delivery in any case and evolved into symptomatic chronic issues in 2 patients. Modern radiotherapy techniques, especially IMRT, promise to improve the cost/benefit ratio of EBRT by permitting safe delivery of high-dose treatment to residual tumor while sparing neighboring structures. This is supported by early clinical results from Rosenbluth et al[16] from Memorial Sloan-Kettering Cancer Center, who have reported no serious chronic morbidity with the early use of high-dose IMRT for thyroid cancer.

Our excellent locoregional disease control outcomes and limited number of radiotherapy complications argue for consideration of aggressive use of adjuvant EBRT in patients with advanced disease, even in patients with preexisting, small/moderate-volume distant metastases. In our series, distant disease at the time of EBRT did not predict for OS, and estimated 5-year OS for such patients was just over 50%. MTC is an attractive diagnosis for testing biological therapy, given the well-characterized involvement of the RET tyrosine kinase receptor in its etiology. Current early-phase clinical trials are investigating the use of agents targeted against RET such as imatinib mesylate, ZD6474, and 17-AAG in advanced hereditary or sporadic MTC, among others.[17,18] As improvements are made in the control of distant disease with systemic therapy, the need for durable locoregional control will become increasingly important. The combined use of targeted agents with EBRT is an appealing topic for future clinical study, especially in patients with unresectable gross disease.

In summary, our results document durable locoregional disease control with relatively limited morbidity in an advanced-stage cohort

treated with modern postoperative EBRT techniques. Patients with locally advanced or metastatic MTC frequently enjoy durable OS, making optimal locoregional management an imperative. We currently recommend consideration of postoperative EBRT in cases of advanced MTC at high risk for locoregional recurrence.

REFERENCES

1. Quayle FJ, Moley JF. Medullary thyroid carcinoma: including MEN 2A and MEN 2B syndromes. J Surg Oncol 2005;89:122–129.
2. Kouvaraki MA, Shapiro SE, Perrier ND, et al. RET proto-oncogene: a review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. Thyroid 2005;15:531–544.
3. Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. Ann Surg 1999; 229:880–887; discussion 887–888.
4. Cohen MS, Moley JF. Surgical treatment of medullary thyroid carcinoma. J Intern Med 2003;253:616–626.
5. Yen TW, Shapiro SE, Gagel RF, Sherman SI, Lee JE, Evans DB. Medullary thyroid carcinoma: results of a standardized surgical approach in a contemporary series of 80 consecutive patients. Surgery 2003;134:890–899; discussion 899–901.
6. Hundahl SA, Cady B, Cunningham MP, et al. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the united states during 1996. U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on Cancer Patient Care Evaluation study. Cancer 2000;89:202–217.
7. Brierley J, Tsang R, Simpson WJ, Gospodarowicz M, Sutcliffe S, Panzarella T. Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. Thyroid 1996;6:305–310.
8. Fife KM, Bower M, Harmer CL. Medullary thyroid cancer: the role of radiotherapy in local control. Eur J Surg Oncol 1996;22:588–591.
9. Peixoto Callejo I, Americo Brito J, Zagalo CM, Rosa Santos J. Medullary thyroid carcinoma: multivariate analysis of prognostic factors influencing survival. Clin Transl Oncol 2006;8:435–443.
10. Chow SM, Chan JK, Tiu SC, Choi KL, Tang DL, Law SC. Medullary thyroid carcinoma in Hong Kong Chinese patients. Hong Kong Med J 2005;11:251–258.
11. Esik O, Tusnady G, Tron L, et al. Markov model-based estimation of individual survival probability for medullary thyroid cancer patients. Pathol Oncol Res 2002;8: 93–104.
12. Williams CR, Brewer DB. Medullary carcinoma of the thyroid. Br J Surg 1969;56:437–443.
13. Samaan NA, Schultz PN, Hickey RC. Medullary thyroid carcinoma: prognosis of familial versus sporadic disease and the role of radiotherapy. J Clin Endocrinol Metab 1988;67:801–805.
14. Tubiana M, Lacour J, Monnier JP, et al. External radiotherapy and radioiodine in the treatment of 359 thyroid cancers. Br J Radiol 1975;48:894–907.
15. Tubiana M, Haddad E, Schlumberger M, Hill C, Rougier P, Sarrazin D. External radiotherapy in thyroid cancers. Cancer 1985;55(9, Suppl):2062–2071.
16. Rosenbluth BD, Serrano V, Happersett L, et al. Intensity-modulated radiation therapy for the treatment of nonanaplastic thyroid cancer. Int J Radiat Oncol Biol Phys 2005;63:1419–1426.
17. Drosten M, Putzer BM. Mechanisms of Disease: cancer targeting and the impact of oncogenic RET for medullary thyroid carcinoma therapy. Nat Clin Pract Oncol 2006;3: 564–574.
18. Moley JF, Fialkowski EA. Evidence-based Approach to the Management of Sporadic Medullary Thyroid Carcinoma. World J Surg 2007;31:946–956.