ORIGINAL ARTICLE

Treating medullary thyroid carcinoma in a tertiary center. Current trends and review of the literature.

Prokopakis E, Doulaptsi M, Kaprana A, Velegrakis S, Vlastos Y, Velegrakis G

Department of Otorhinolaryngology, University Hospital of Heraklion, Heraklion Crete, Greece

Abstract

Objectives: We present the clinical outcome and long-term survival in patients with medullary thyroid carcinoma treated in a tertiary center. A thorough review of published series and current therapeutic approaches is also addressed.

Study Design: A retrospective review

Setting: An Academic Tertiary center

Subjects/Methods: An analysis of oncologic outcomes from 25 patients treated in our department for medullary thyroid carcinoma is performed, together with a comparison of relevant studies over the literature.

Results: The incidence of patients alive free of disease and the 5-year survival rate has been noticed to be slightly higher than the rate reported in most series.

Conclusions: Total thyroidectomy and neck dissection remains the gold standard in the treatment of medullary thyroid carcinoma. Early diagnosis and aggressive surgical treatment lead to lower rates of recurrence and invasiveness. Tyrosine-kinase inhibitor, especially vantetanib, appears to be a promising target for treatment. Hippokratia 2014; 18 (2):130-134.

Keywords: Medullary thyroid carcinoma, sporadic, calcitonin, thyroidectomy, neck dissection, Tyrosine-kinase inhibitor

Corresponding author: George Velegrakis, MD, Professor, Department of Otorhinolaryngology, University Hospital of Heraklion, University Avenue, A Building 3rd Floor, Heraklion 71110, Crete, Greece, tel: +302810392348, fax: +302810542106, e-mail: gvel@med.uoc.gr

Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor originating from the parafollicular C cells of the thyroid gland. It is a calcitonin producing tumour, fact that plays a major role in the diagnosis, as well as in patient's follow up. Medullary thyroid carcinoma (MTC) represents the most challenging disease in thyroid surgery. Even though it is considered an uncommon malignancy, its major clinical and investigational interest relies in its hereditary pattern, and the close correlation with other neuroendocrine disorder, as part of Multiple Endoctine Neoplasia (MEN) syndromes type 2A and 2B. Solid MTC was first described by Hazard et al in 1958, and only a few years later in 1961, the first association between thyroid carcinoma, and pheochromocytoma was reported, while the distinction between the 2 phenotypes of MEN2 (Sipple's Syndrome) was made in 1974[1]. In 1993, germline activating mutations of RET (rearranged during transfection) proto-oncogene, which encodes a tyrosine kinase receptor expressed primarily in neuroendocrine cells (including thyroid C cells and adrenal medullary cells) were identified in 98% of the individuals with MEN2[2]. Since then, there has been a constant progress in the fields of genetic testing and familial consultation for hereditary MTC, as well as in the development of novel therapeutic strategies[3].

Medullary thyroid carcinoma can be sporadic, or familial (FMTC), which occurs as part of MEN 2A or MEN 2B syndrome, and non-MEN FMTC. In several studies, MTC represents 5-10% of all thyroid cancers. In a previous Greek study, this rate has been reported as 4%[4]. Most of the MTC cases are sporadic (70-75%), and the prevalence of familial MTC 25-30%[5]. In this study, MTC represented 5.12% of all thyroid carcinomas reviewed. This is consistent with the universal literature. Familial MTC was confirmed in 20% of individuals.

We report the clinical outcome, as well as long-term survival in patients with MTC treated in our institution. A thorough review of published series and current therapeutic approaches is addressed.

Materials and Methods

A retrospective review was done on total thyroidectomies performed in the Department of Otorhinolaryngology of the University Hospital of Crete, from January 1990 to December 2011. Only patients with complete medical record, including biochemical measurements, operative notes, pathology reports, and imaging studies such as neck ultrasound and more if appropriate, were placed in a data base. Patients with insufficient data, and those who were treated initially in another institution were excluded from the study. All cases with suspected medullary cancer from fine-needle aspiration (FNA) cytology results or serum calcitonin level underwent complete diagnostic protocol for MTC[6]. Pre-operative assessment included measurement of basal calcitonin level in the blood, the

standard tumor marker for MTC, carcinoembryonic-antigen (CEA), calcium (albumin-corrected or ionized), while imaging with neck sonography, or computed tomography (CT) scan gave us adequate information on staging and thus valid surgical planning[7]. Patients with palpable neck mass underwent investigation for distant metastasis with chest X-ray, and abdominal sonography. Total thyroidectomy plus central neck lymph node dissection with or without ipsilateral or bilateral modified neck dissection was performed depending on its case. All patients were evaluated three months after surgery with calcitonin, CEA serum measurement and neck ultrasound. Six-monthly, calcitonin and CEA surveillance followed for asymptomatic cases with negative imagine[8,9]. At the end of the follow up period (median 41.5 months), patients were classified in four groups according to the serum measurements, imaging results and clinical outcome at the last evaluation.1) Alive free of disease, when calcitonin, CEA, and imaging study were negative, 2) Alive with disease when biochemical measurements or imaging were positive for recurrent or residual disease, 3) Deceased due to MTC, and 4) Deceased due to other causes (Table 1).

Statistical analysis was performed with univariate tests. Minitab version 16.0 was used for this purpose. Systematic search in PubMed for relevant studies (in English literature) was performed (Table 1). From over 100 references initially identified, 8 articles comprised the basis of this review. Inclusion and exclusion criteria were defined according to "The Prisma Statement"[17]. Overall clinical outcome was the primary endpoint.

Results

In our academic tertiary Otorhinolaryngologic center, between January 1990 and December 2011, a total of 2089 thyroidectomies were performed. Thyroid cancer was confirmed in 488 of the patients (23.36%). The diagnosis of papillary carcinoma was made in 436 patients representing 89.35% of all cases, while twenty-seven individuals (5.53%) had follicular thyroid carcinoma. Medullary thyroid carcinoma was confirmed in 25 patients (5.12%). Mean age to the MTC group was 48 and male:female ratio was 1.1:1. After the biochemical and genetic screening of all individuals, 20 patients (80%) were found to have sporadic, four (16%) familiar non-MEN MTC, and one (4%) had MEN2a MTC. In our study group, no patient was found to have MEN2b MTC (Table 2). Only one patient had distant metastases at the time of presentation. According to the American Joint Committee on Cancer (AJCC) staging system, there were 12 patients with stage I, 6 patients with stage II, 5 patients with stage III, 1 patient with stage IVA, 1 patient with stage IVC. All individuals underwent surgical procedure and post-operative follow up as indicated above.

After a median post-surgical follow up of 53.5 months (range 6-120 months), n=19 or 76% of patients were living disease free, n=4 or 16% were living with disease, n=1 or 4% was deceased due to MTC, and n= 1 or 4% was deceased due to another cause (Table 1).

Discussion

It is noticeable that all forms of MTC are responsible for 13.4% of the total deaths attributable to thyroid can-

Table 1. Review of the literature regarding medullary thyroid carcinoma with primary endpoint the overall clinical outcome.

Series	POS	Subjects	AMR	MPS	ADF	AWD	DOD	DOC
Dottorini ME et al (1996)[10]	1986-2006	53	46.11	54	36%	20%	38%	6%
Jason B et al (1999)[11]	1991-1997	40	N/A	35	93%	7%	0%	0%
Kebebew E et al (2000)[12]	1960-1998	104	38	60	49.4%	38.3%	10.7%	1.6%
Esic O, et al (2002)[13]	1960-1999	91	N/A	72	64%	64%	26%	10%
Cupisti K et al (2007)[14]	1986-2006	289	32	N/A	41%	31%	20%	8%
Pelizzo MR et al (2007)[15]	1967-2004	157	47.3	68	42.9%	39.8%	3.2%	3.1%
Lenine G et al (2009)[16]	1982-2006	53	36	75	41.5%	43.4%	7.6%	7.5%
Prokopakis E et al (current study)	1990-2011	25	48	53.5	76%	16%	4%	4%
Total	1960-2011	812	-	-	-	-	15.14%	5.78%

POS: Period of study, AMR: Age mean range, MPS: Median post-surgical follow up (months), ADF: Alive disease free, AWD: Alive with disease, DOD: Deceased due to MTC, DOC: Deceased due to other causes, N/A: Data not available.

Table 2. Data of patients treated for medullary thyroid carcinoma in the department of Otorhinolaryngology of the University Hospital of Crete, from January 1990 to December 2011.

	Number of Patients	**%**
Ca	488	100%
MTC	25	5.12%
Sporadic MTC	20	80%
Familiar non MEN MTC	4	16%
MENIIA	1	4%
MENIIB	0	0%

Ca: Thyroid Carcinoma, MTC: Medullary Thyroid Carcinoma, MEN: Multiple Endocrine Neoplasia.

cer[18]. The overall 10-year survival rate reported in large series range between 72%, and 87%, while a number of prognostic factors have been studied[15]. In our series, after a median post-surgical follow up of 53.5 months (range 6-120 months), 19 or 76% of patients were living disease-free, 4 or 16% were living with disease, 1 or 4% was deceased due to MTC, and 1 or 4% was deceased due to another cause. We have previously reported a potential correlation of the increased incidence of papillary thyroid carcinoma in Crete between 1995 and 2000, with the Chernobyl fallout[19]. Though, an association of MTC and radiation exposure cannot be established.

Systematic reviews and meta-analyses are very important for clinicians, as these keep them up to date, and are often used as a starting point for developing clinical practice guidelines. The PRISMA statement (Preferred reporting items for systematic reviews, and meta-analyses) helps authors to improve the quality of their reporting. It is focused on randomized trials, but we used it as a basis for our systematic review[17]. Thus, the meta-analysis of these published series reveals that among 812 individuals treated for MTC the last 51 years, 123 patients (15.14%) deceased due to their disease, and 47 individuals (5.78%) deceased due to other cause. Table 1 compares same surveillance rates to other studies in the literature. Safe overall survival rates cannot be determined due to lack of evidence data. Though, in most reviewed series 5-year survival rate reaches approximately 70-80%. The incidence of patients alive, free of disease and the 5-year survival rate in our study has been noticed to be slightly higher than the rate reported in most series, possibly due to early diagnosis and aggressive surgical treatment.

The relevant small sample size, did not allow us to identify any variable as an independent prognostic factor. However, age of diagnosis has been reported to be a stronger predictor of survival for patients with MTC, as well as in follicular carcinoma, than for patients with papillary carcinoma[20]. Gender (male), TNM stage at the time of presentation, MTC subtype (sporadic/hereditary), and type of operative procedure have also prognostic value, but their significance remains controversial.

If MTC is suspected, pre-operative assessment should include serum basal calcitonin level measurement, carcinoembryonic-antigen (CEA), calcium (albumin-corrected, or ionized), and detection of local metastasis with neck sonography[6]. Exclusion of comorbid conditions, such as hyperparathyroidism, or pheochromocytoma is critical. Pheochromocytoma is unlikely with negative plasma free metanephrine and normetanephrine counts, or negative adrenal CT, or magnetic resonance imaging. Patients with palpable neck mass should undergo chest X-ray, and abdominal sonography to exclude distant metastasis[6,7]. The pentagastrin-stimulation test can be useful to diagnose familiar forms of MTC, because the clinical examination and imaging can be negative, and calcitonin, as well as carcinoembryonic-antigen (CEA) are serum markers for the post-surgical monitoring, as they allow the detection of recurrent disease. However, this test is not part of patient's standard preoperative assessment, as is not available in many parts of the world. Germline DNA-based testing of the RET gene identifies mutations in more than 95% of cases with MEN2A and MEN2B and in about 88% of individuals with FMTC. In familial forms genetic testing, in combination with calcitonin measurements and ultrasound are key tools. Similar to the evaluation of all thyroid nodules, fine-needle aspitation (FNA) plays a significant role in diagnosing MTC. However, it can be mistaken for parathyroid carcinoma or anaplastic thyroid carcinoma when spindle-shaped cells are present. Therefore, specimen is stained for calcitonin, chromographin A, or CEA, substances that confirm the diagnosis[21].

Variation in practice patterns exist because of low incidence of MTC which limits both widespread clinical expertise and definitive large randomized clinical trials[22]. Radioactive iodine, external beam radiation therapy, and conventional chemotherapy have not been effective. Nevertheless, the consensus is that early diagnosis, together with aggressive surgical management, including prophylactic thyroidectomy for patients with hereditary MTC, improves the prognosis[23]. Before the operation, the presence of pheochromocytoma must be excluded, and treated in advance, if found[6].

According to the American Thyroid Association (ATA), primary treatment usually consists of surgical resection that includes total thyroidectomy followed by central neck node compartmental dissection[6]. Lateral neck dissection is indicated in patients with suspected limited local metastatic disease to regional lymph node. Some authors advocate the necessity of a more aggressive approach (ipsilateral, or bilateral modified radical

neck dissection) primarily even without evidence of suspicious lymph nodes[6].

Primary treatment usually consists of surgical resection that includes a total thyroidectomy, central neck nodal dissection, and functional lateral neck nodal dissection[24,25]. Most patients have nodal disease present at the time of operation, and nodal involvement is often bilateral especially in case of familial MTC, and MEN2. Lymph node metastasis is present in 50-80% of patients presenting with a palpable neck mass or nodule[26]. The central (level VI) followed by the lateral compartments (levels II–V) are the most common sites. Further spread can occur to the contralateral cervical lymph nodes, and then to the mediastinal (level VII) nodes. Distant metastases can occur via haematogenous spread to the lungs, liver, bone, and brain. Since the first operation in MTC remains a key predictor of outcome for unilateral tumours less than 1 cm, total thyroidectomy is recommended with the dissection of the level VI nodes being justified, given that in those cases nodal involvement has been reported in significant rates (10-33%). For MTC tumours greater than, or equal to 1 cm or multifocal disease, total thyroidectomy with routine central neck dissection is advocated[6]. For ipsilateral or contralateral cervical lymph nodes metastasis, ipsilateral or bilateral modified neck dissection (levels IIA, III, IV, and V) is the treatment of choice[6,27]. Many authors recommend less aggressive neck operation in the presence of distant metastases, or advanced local features in order to preserve parathyroids glands, and vocal cord function[6]. Even with an aggressive surgical approach, parathyroid function, and vocal cord function should be preserved if at all possible. The timing of prophylactic surgery for familiar carriers can be dictated by the specific genotype. Most writers suggest that thyroidectomy should be performed before the age of 5 years for the patients with MEN2A, or FMTC who have high risk mutations, and even earlier for patients with MEN2B, and mutations at the highest risk[28,29].

Elevated level of serum calcitonin after initial surgery is a sign of residual disease or recurrent tumor. Clinical recurrence will display at different time depending to the extent of residual disease and tumor growth rate. Calcitonin doubling time is an important clinical predictor for the biological behavior of residual and recurrent MTC. In one study, a calcitonin doubling time less than six months carried a 75% risk of cancer related death during the following five years, whereas doubling times more than two years were not associated with cancer related death[30]. If disease is not anatomically defined with neck ultrasonography, computed tomography, chest CT, bone scanning, determination of basal calcitonin, and CEA must be repeated every six months. Otherwise, whenever residual or recurrent disease can be anatomically localized in the neck, a second surgical procedure is a treatment option offering excellent prevention of recurrence. Patients with symptomatic distant metastases might require palliative therapies, such as surgery, hepatic embolization, and cryotherapy. Individuals with metastatic MTC can be asymptomatic, and stable for long periods, therefore, no intervention and close imaging observation every six months is an accepted option.

Recently, a retrospective study revealed an increase in micro-MTC, whereas recurrence and invasiveness of disease is decreased over the years. Distant metastasis, cervical lymph node invasion at diagnosis were more frequent in patients treated before 2000. Furthermore, subjects who underwent multiple surgeries more frequenlty, had more distant metastases at follow up, and more progressive disease. In contrast, patients treated over the last two decades had less advanced stage at diagnosis, underwent fewer surgeries, and had less progressive disease. This could be due to early diagnosis with routine thyroid examination, hormonal measurement (calcitonin) coupled with neck ultrasound, increased awareness in familial cases, and finally aggressive surgical treatment[31,32].

Cytotoxic chemotherapy, external beam radiation, radioiodine ablation, bi-specific antibodies direct against carcinoemryonic antigen, and treatment with diethylene triamine pentaacetic acid (DTPA) provide low response rates in patients with metastatic or rapidly progressive disease[33,34]. Most common used agent in MTC was doxorubicin, with or without cisplatin. Tumor response in such treatment is low, and lasts only few months. Postoperative radioactive iodine is only recommended in the presence of concomitant epithelial cell-derived differentiated thyroid cancer[6].

In the last decade, targeted molecular therapies are under investigation. Germline activating mutations of RET (rearranged during transfection) proto-oncogene, encodes a tyrosine-kinase receptor expressed in 98% of the individuals with MEN2B, and 30-50% of sporadic MTC tumors[10]. Tyrosine-kinase inhibitors (TKI), especially vantetanib, showed significant advantages over placebo in terms of response rate, disease control rate and biochemical response in a phase III study. Vandetanib was approved by the US Food and Drug Administration (FDA) for the treatment of adults with symptomatic or progressive MTC, and appears to be a promising agent for treatment[26]. More recently, European Medicine Agency approved this agent for the treatment of locally advanced and/or metastatic disease on the basis of the phase III results[11]. Adverse effects usually include diarrhea, anorexia, fatigue, and skin toxicities. Less often cardiac toxicity, and cytopenia may occur. In addition to vandetanib, cabozantinib has also been approved.

Medullary thyroid cancer remains fascinating due to its unique characteristics. Excluding patients with advanced disease stage, or MEN2b MTC, who are more likely to have clinical recurrence, and die of their disease, many subjects have long-term survival free-of, or with disease. Our data compared with that of current literature, according to the Prisma statement criteria, show slightly higher survival rates. Overall, total thyroidectomy and neck dissection remains the gold standard in the treatment of MTC. Further trials should be done in the direction of other adjacent or comprehensive treatment.

Conflict of Interest

No competing financial interests exist.

References

1. Carney JA. Familial multiple endocrine neoplasia: the first 100 years. Am J Surg Pathol. 2005; 29: 254-274.
2. Mulligan LM, Kwok JB, Healey CS, Elsdon MJ, Eng C, Gardner E, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature. 1993; 363: 458-460.
3. Wells SA Jr, Santoro M. Targeting the RET pathway in thyroid cancer. Clin Cancer Res. 2009; 15: 7119-7123.
4. Gkountouvas A, Nikas M, Chatjimarkou F, Thomas D, Georgiadis P, Kaldrimidis P. Thyroid cancer in Greece. A tertiary center experience. J BUON. 2010; 15: 674-678.
5. Moo-Young TA, Traugott AL, Moley JF. Sporadic and familial medullary thyroid carcinoma: state of the art. Surg Clin North Am. 2009; 89: 1193-1204.
6. American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, Evans DB, Francis GL, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid. 2009; 19: 565-612.
7. Pichon MF, Basuyau JP, Gory-Delabaere G, Eche N, Daver A, Blanc-Vincent MP, et al. [Standards, options and recommendations for blood tumor markers in thyroid cancers]. Bull Cancer. 2001; 88: 775-792.
8. Fialkowski EA, Moley JF. Current approaches to medullary thyroid carcinoma, sporadic and familial. J Surg Oncol. 2006; 94: 737-747.
9. Pitt SC, Moley JF. Medullary, anaplastic, and metastatic cancers of the thyroid. Semin Oncol. 2010; 37: 567-579.
10. Dottorini ME, Assi A, Sironi M, Sanqalli G, Spreafico G, Colombo L, et al. Multivariate analysis of patients with medullary thyroid carcinoma: Prognostic significance and impact on treatment of clinical and pathologic variables. Cancer. 1996; 77: 1556-1565.
11. Fleming JB, Lee JE, Bouvet M, Schultz PN, Sherman SI, Sellin RV, et al. Surgical strategy for the treatment of medullary thyroid carcinoma. Ann Surg. 1999; 230: 697-707.
12. Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. Cancer. 2000; 88: 1139-1148.
13. Esik O, Tusnády G, Trón L, Boér A, Szentirmay Z, Szabolcs I, et al. Markov model-based estimation of individual survival probability for medullary thyroid cancer patients. Pathol Oncol Res. 2002; 8: 93-104.
14. Cupisti K, Wolf A, Raffel A, Schott M, Miersch D, Yang Q, et al. Long-term clinical and biochemical follow-up in medullary thyroid carcinoma: a single institution's experience over 20 years. Ann Surg. 2007; 246: 815-821.
15. Pelizzo MR, Boschin IM, Bernante P, Toniato A, Piotto A, Pagetta C, et al. Natural history, diagnosis, treatment and outcome of medullary thyroid cancer: 37 years experience on 157 patients. Eur J Surg Oncol. 2007; 33: 493-497.
16. Brandão LG, Cavalheiro BG, Junqueira CR. Prognostic influence of clinical and pathological factors in medullary thyroid carcinoma: a study of 53 cases. Clinics (Sao Paulo). 2009; 64: 849-856.
17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010; 8: 336-341.
18. Jiménez C, Hu MI, Gagel RF. Management of medullary thyroid carcinoma. Endocrinol Metab Clin North Am. 2008; 37: 481-496.
19. Prokopakis EP, Lachanas VA, Velegrakis GA, Tsiftsis DD, Moschandreas J, Chalkiadakis GE. Increased incidence of papillary thyroid cancer among total thyroidectomies in Crete. Otolaryngol Head Neck Surgery. 2007; 136: 560-562.
20. 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.
21. Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. CA Cancer J Clin. 2013; 63: 373-394.
22. Wu LS, Roman SA, Sosa JA. Medullary thyroid cancer: an update of new guidelines and recent developments. Curr Opin Oncol. 2011; 23: 22-27.
23. Allen SM, Bodenner D, Suen JY, Richter GT. Diagnostic and surgical dilemmas in hereditary medullary thyroid carcinoma. Laryngoscope. 2009; 119: 1303-1311.
24. Cohen MS, Moley JF. Surgical treatment of medullary thyroid carcinoma. J Intern Med. 2003; 253: 616-626.
25. Lachanas VA, Prokopakis EP, Mpenakis AA, Karatzanis AD, Velegrakis GA. The use of Ligasure Vessel Sealing System in thyroid surgery. Otolaryngol Head Neck Surg. 2005; 132: 487-489.
26. 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 887-8.
27. Tuttle RM, Ball DW, Byrd D, Daniels GH, Dilawari RA, Doherty GM, et al; National Comprehensive Cancer Network. Medullary carcinoma. J Natl Compr Canc Netw. 2010; 8: 512-530.
28. You YN, Lakhani V, Wells SA Jr. New directions in the treatment of thyroid cancer. J Am Coll Surg. 2007; 205: S45-S48.
29. Danko ME, Skinner MA. Surgical intervention in children with multiple endocrine neoplasia type 2. Curr Opin Pediatr. 2006; 18: 312-315.
30. Costante G, Durante C, Francis Z, Schlumberger M, Filetti S. Determination of calcitonin levels in C-cell disease: clinical interest and potential pitfalls. Nat Clin Pract Endocrinol Metab. 2009; 5: 35-44.
31. Alevizaki M, Saltiki K, Rentziou G, Papathoma A, Sarika L, Vasileiou V, et al. Medullary thyroid carcinoma: the influence of policy changing in clinical characteristics and disease progression Eur J Endocrinol. 2012; 167: 799-808.
32. Karga H, Giagourta I, Papaioannou G, Doumouchtsis K, Polymeris A, Thanou S, et al. Changes in risk factors and Tumor Node Metastasis stage of sporadic medullary thyroid carcinoma over 41 years, before and after the routine measurements of serum calcitonin. Metabolism. 2011; 60: 604-608.
33. Almeida MQ, Hoff AO. Recent advances in the molecular pathogenesis and targeted therapies of medullary thyroid carcinoma. Curr Opin Oncol. 2012; 24: 229-234.
34. Schlumberger M, Massicotte MH, Nascimento CL, Chougnet C, Baudin E, Leboulleux S. Kinase inhibitors for advanced medullary thyroid carcinoma. Clinics (Sao Paulo). 2012; 67n Suppl 1: 125-129.