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Original Article

Surgical therapy of medullary thyroid cancer and our clinical experiences

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Abstract

Aim: Medullary thyroid cancer (MTC) is a rare neuroendocrine tumor that originates from the thyroid parafollicular C cells and produces calcitonin. It is a quite aggressive disease with a potential to cause serious morbidity and mortality. In this study we aimed to report treatment outcomes of MTC, which has a bad prognosis and is difficult to manage.

Material and Methods: The medical records of 1287 patients who were operated on for thyroid cancer between 2009 and 2018 were retrospectively assessed. Twenty-one patients (1.6%) were diagnosed with MTC.

Results: Eleven (52.4%) patients were females. The age range of the patients was 54(14-85) years. Sixteen (76.2%) cases were sporadic and 5 (23.8%) were familial. Twelve patients underwent bilateral total thyroidectomy + central and unilateral neck dissection, 5(23.8%) bilateral total thyroidectomy + central and bilateral neck dissection, 4(19%) bilateral total thyroidectomy. Pathology examination revealed lymph node metastasis in 13(61.9%) patients. Three (14%) patients had simultaneous papillary thyroid cancer. Mean duration of follow-up was 52(3-96) months. Five (23.8%) patients suffered recurrence cervical lymph nodes (6 months later), lungs and bone metastasis (at 12th and 18th months), lungs (at 12thmonth), mediastinal lymph nodes (at 15th months), liver metastasis (at 6th months). Seven (33%) patients underwent chemo-radiotherapy.

Conclusion: Surgery is the gold standard to control loco-regional disease and the only curative method among the available therapies in MTC treatment. Despite having a low incidence, MTC may still lead to serious mortality and morbidity in delayed cases and/or when loco-regional control cannot be achieved.

Keywords: Medullary Thyroid Cancer; Surgery; Recurrence.

INTRODUCTION

Medullary thyroid cancer (MTC) is a rare neuroendocrine tumor that originates from the thyroid parafollicular C cells and produces calcitonin (1). It was first defined by Hazard in 1959 (2). The disease can be seen in hereditary and sporadic forms and constitutes 1-2% of all thyroid cancers (3). Its incidence has shown a rapid increase in the last two decades (4-6). MTC is unresponsive to radioactive iodine therapy and hormone suppression therapy and can be cured only by eliminating tumor and loco-regional metastases (1).

In this study we aimed to report surgical treatment and outcomes of MTC, a difficultto manage disease with poor prognosis.

MATERIAL and METHODS

We retrospectively reviewed the medical records of 1287 patients who were operated on for thyroid cancer at Başkent University General Surgery Clinic between 2009 and 2018. Twenty-one (1.6%) patients were diagnosed with MTC. The patients were evaluated with respect to age, sex, family history, physical examination, preoperative radiological examinations, calcitonin, CEA, calcium, fine needle aspiration biopsy (FNAB), operation type, complications, metastasis status, mortality, and follow-up duration.

Statistical analysis: Data analysis was done with SPSS 23.0 software package. Categorical variables were expressed as number and percentage and continuous

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measurements as mean and standard deviation (median and minimum-maximum when necessary). Chi-square test was used for comparison of categorical variables. Statistical significance was set at 0.05.

RESULTS

Eleven (52.4%) patients were females and 10 (47.6%) were males. The mean age was 54 (14-85) years. Sixteen (76.2%) cases were sporadic and 5 (23.8%) were familial. The most common physical examination finding was thyroid nodule in 13 (61.9%) patients and lymphadenopathy at the side of the nodule in 2 patients. the most common complaints of 5 patients with hereditary transmission were palpitations, and muscle weakness and pain. Prior to operation, all patients underwent thyroid ultrasonography which revealed thyroid nodule in all of them. Eleven patients underwent whole neck MRI. The preoperative calcitonin level was 881 (0-8200), calcium 8.9 (8.2-10.4), and CEA 16 (0-74).Demographics and laboratory data of the patients are presented in Table 1.

All patients underwent fine needle aspiration biopsy. Thirteen (51.9%) patients received a diagnosis of suspected malignancy, 4 (19%) MTC, 3 (14.3%) follicular neoplasm, and 1 (4.8%) papillary thyroid cancer.

Twelve (67.1%) patients underwent bilateral total thyroidectomy +central and unilateral neck dissection, 5 (23.8%) bilateral total thyroidectomy +central and bilateral neck dissection, 4 (19%) bilateral total thyroidectomy. Pathology examination revealed lymph node metastasis in 13 (61.9%) patients and the mean number of lymph nodes was 12 (4-39). Three (14%) patients had simultaneous papillary thyroid cancer. Four (19%) patients had a complication (permanent hoarseness, hypocalcemia, and bleeding, pulmonary embolism). The mean duration of hospital stay was 3 (1-12) days. The mean follow-up duration was 52 (3-96) months. Five (23.8%) patients had recurrence (cervical lymph nodes (6 months later), lung and bone metastasis (at 12th and 18th months), lung (at 12th months), mediastinal lymph nodes (at 15th months), and liver metastasis (at 6th months). Seven (33%) patients received chemo-radiotherapy. No mortality was observed.

DISCUSSION

Medullary thyroid cancers constitute 1-2% of all thyroid cancers and areresponsible for approximately 13.4% of thyroid cancer-related deaths (3,7-8). MTC does not show regional differences, it is not affected by iodine imbalance, does not coexist with other thyroid disorders, and no exogenous factor is responsible for its development (9-11). Approximately 25% of medullary thyroid cancers is hereditary, which involves a pathology of the RET proto-oncogene. In such patients the genetic transmission is autosomal dominant and associated with multiple endocrinological neoplasms (3,12). In our study the incidence of MTC was 1.6% and the hereditary transmission rate was 23.8%, both compatible with literature data.

The first-ever symptom of medullary thyroid cancer may show differences depending on whether the disease is sporadic or hereditary. Sporadic cases may be seen more commonly as a solitary nodule and/or a palpable neck mass, hoarseness, dysphagia, dyspnea, and pain. Hereditary cases, on the other hand, may become symptomatic depending on other simultaneous disorders (pheochromocytoma, parathyroid hyperplasia, marfanoid stature, mucosal neuromas etc.). In our study, 5(23.8%) patients with hereditary transmission most commonly had palpitations, muscle weakness and pain. The sporadic cases most commonly had neck swelling (n=10, 47%).

MTC may show regional or distant metastasis at the time of diagnosis. The most common sites of metastasis are regional lymph nodes, liver, lung, and bone (13-14). In our study none of our patients had distant metastases but 5 (23.8%) showed recurrence (cervical lymph nodes (6 months later), lung and bone metastasis (at 12th and 18th months), lung (at 12th months), mediastinal lymph nodes (at 15th months), liver metastasis (at 6th months). Furthermore, the most common finding on physical examination at the time of diagnosis was a nodule in the thyroid gland in 13 (61.9%) patients and lymphadenopathy on the side of nodule.

All patients with a preoperative diagnosis of MTC should underwent detailed neck ultrasonography, serum calcitonin and carcinoembryonic antigen (CEA) measurement. Basal serum calcitonin levels are usually associated with tumor burden and also provide information about tumor differentiation (3). All patients in our study underwent thyroid ultrasonography which revealed a thyroid nodule prior to operation. All patients underwent serum calcium measurement, 16 patients' serum calcitonin measurement, and 14 patients' serum CEA level measurement. In patients considered to have hereditary MTC, an abdominal ultrasonography (for pheochromocytoma), parathormone level measurement, and scintigraphy examinations were done for a detailed evaluation. In our study serum calcitonin level was 881 (0-8200) which showed parallelism with tumor size and lymph node metastasis, as reported in the literature. Additionally, serum calcitonin level is considered for management decisions of patients without ultrasonography/FNAB-proven lymph node metastasis and the need for lymph node dissection (3).

In patients with thyroid nodules, serum calcitonin measurement is routinely done with or without pentagastrin administration (15). In some studies, it has been reported to have a greater diagnostic sensitivity and specificity for MTC compared to FNAB findings (15-18). When basal calcitonin levels are above > 200 pg/mL, there occurs an occult lymph node metastasis in the contralateral neck at a rate of 14% (19). Therefore, when a preoperative image is positive on the ipsilateral neck and basal serum calcitonin level is greater than200 pg/mL, a prophylactic contralateral lateral compartment neck dissection should be considered (3). Moreover, ATA guidelines recommend that prophylactic ipsilateral lateral neck dissection in patients with serum basal calcitonin levels areabove 20 pg/mL (3).

Table 1. Demographics, clinical and laboratory data of the patients

Patient	Age (year)	Gender	Family History	Physical Examination	Ultrasound Findings	FNAB	Preoperative Calcitonin Level (pg/ml)	Preoperative CEA Level (ng/ml)	Preoperative Ca Level (mg/dl)	Operation Type	Follow-Up Duration (Months)	Complications	Metastasis
1	40	F	+	Neck Mass	Soliter Nodule (3 cm)	Suspected Malignancy	71.9	0	8,9	BTT + C and U ND	72	-	-
2	27	F	+	Thyroid Nodule	MNG	Suspected Malignancy	0	0	8,5	BTT	84	-	-
3	58	M	-	Thyroid Nodule	MNG	Suspected Malignancy	0	0	8,2	BTT + C and U ND	45	-	-
4	67	M	-	Thyroid Nodule	MNG	Suspected Malignancy	0	0	8,3	BTT + C and U ND	64	-	-
5	58	F	-	Lymphadenopathy	Soliter Nodule (1.5 cm)	Papillary Thyroid Ca	0	0	8,3	BTT + C and U ND	36	-	-
6	48	F	-	Normal	Soliter Nodule (1cm)	Suspected Malignancy	167	0,9	9,5	BTT + C and U ND	72	-	-
7	61	F	-	Normal	Soliter Nodule (2 cm)	Follicular Neoplasm	91,3	0	8,8	BTT	48	-	-
8	14	M	+	Thyroid Nodule	MNG	MTC	8200	74	9,4	BTT + C and B ND	60	-	Cervical Lymph Nodes
9	70	M	-	Thyroid Nodule	Soliter Nodule (3 cm)	MTC	1400	20	10,4	BTT + C and U ND	13	Hypocalcemia	-
10	54	M	-	Guatr	MNG	Suspected Malignancy	2	1,6	9,4	BTT	15	-	-
11	54	F	-	Thyroid Nodule	MNG	Suspected Malignancy	2	23,9	9	BTT	20	-	-
12	82	F	+	Thyroid Nodule	MNG	Suspected Malignancy	7,4	37	9,4	BTT + C and U ND	56	Hoarseness	-
13	58	F	+	Thyroid Nodule	MNG	Suspected Malignancy	23	5	9,2	BTT + C and U ND	44	-	Lung And Bone Metastasis
14	57	M	-	Lymphadenopathy	Soliter Nodule (1 cm)	MTC	704	1.8	10,2	BTT + C and B ND	10	-	-
15	26	F	+	Guatr	MNG	Suspected Malignancy	1500	3,5	8,7	BTT + C and B ND	68	-	-
16	36	M	-	Thyroid Nodule	Soliter Nodule (2,5 cm)	Suspected Malignancy	0	0	8,7	BTT + C and B ND	3	Pulmonary embolism	-
17	35	M	+	Thyroid Nodule	MNG	Follicular Neoplasm	1424	58	9,4	BTT + C and U ND	18	-	-
18	85	F	-	Thyroid Nodule	MNG	Suspected Malignancy	1200	2.5	8,8	BTT + C and U ND	84	-	Mediastinal Lymph Nodes
19	67	F	-	Thyroid Nodule	MNG	MTC	2400	26	9,5	BTT + C and B ND	96	Bleeding	Liver Metastasis
20	48	M	-	Thyroid Nodule	MNG	Suspected Malignancy	1300	70	8,8	BTT + C and U ND	52	-	Lung Metastasis
21	45	M	-	Normal	Soliter Nodule (1.5 cm)	Follicular Neoplasm	21	26	8,8	BTT + C and U ND	48	-	-

MNG: Multi noduler guatr BTT: Bilateral total thyroidectomy BTT + C and U ND: Bilateral total thyroidectomy +central and unilateral neck dissection BTT + C and B ND: Bilateral total thyroidectomy +central and bilateral neck dissection FNAB: Fine needle aspiration biopsy

Fine needle aspiration biopsy (FNAB) is the standard approach for the diagnosis of thyroid cancers. All of our patients underwent FNAB but only 4 (19%) patients received a diagnosis of MTC. Thyroid and whole neck ultrasonography provides information about both thyroid gland and regional lymph node metastases. Furthermore, it also provides guidance for FNAB in non-palpable thyroid nodules and lymph nodes. We performed preoperative neck ultrasonography for all of our patients.

ATA and NCCN guidelines recommend bilateral central compartment lymph node dissection (level VI) and total thyroidectomy for patients diagnosed with sporadic MTC when the disease is limited to neck region and there is no metastasis in cervical lymph nodes and distant organs in preoperative imaging studies (3,20). However, in patients with a small intrathyroidal MTC with a preoperative calcitonin level of <20 pg / mL, prophylactic central neck dissection is unnecessary because lymph node metastasis risk is negligible when basal calcitonin level is lower than 20 pg/mL (normal reference level <10) (19). Furthermore, in patients with MTC and limited lymph node metastasis, total thyroidectomy, bilateral central lymph node dissection (level VI), and selective neck dissection (level II-Volume) should be performed (3,20). In our study 12 (57.1%) of our patients were operated on with bilateral total thyroidectomy + central and unilateral neck dissection, 5 (23.8%) with bilateral total thyroidectomy + central and bilateral neck dissection, 4 (19%) with bilateral total thyroidectomy. Four patients undergoing bilateral thyroidectomy alone had no preoperative diagnosis of MTC. In these patients calcitonin level was low and thus no central lymph node dissection was performed, and follow-up was recommended.

Another debated topic is the need for lateral lymph node dissection as a part of primary surgery in patients with no clinically or ultrasonically detectable lymph node metastasis. When there is no evidence of neck metastasis on ultrasonography or distant metastasis, dissection of lymph nodes in the lateral compartment (Level II-V) is recommended as a Grade 1 recommendation by American Thyroid Association (ATA) (based on basal calcitonin levels) (3). In patients with limited metastasis to neck and cervical lymph nodes, bilateral total thyroidectomy, central and lateral compartment lymph node dissection should be done (3). In our study 17 (80%) patients underwent unilateral or bilateral lymph node dissection at the 1th or 2thsession. Pathology examination revealed lymph node metastasis in 13 (61.9%) patients and the mean number of lymph nodes was 12 (4-39).

In cases with residual and recurrent disease, or when there aremetastases, it is still controversial what the ideal therapy should be (1). Radioactive iodine therapy is not effective for MTC (21). Palliative surgery has an important role in metastatic disease. Acute spinal cord compression or airway or esophagus compression requires palliative surgery. The aim of the latter is to provide symptomatic relief (3). Systemic chemotherapy is ineffective for MTC (21-22). Metastatic disease (inoperable neck/mediastinal mass or bone metastasis) may prompt palliative radiotherapy. However, the usefulness of radiotherapy for MTC is debated owing to the lack of prospective randomized studies (23-27). As a general rule, adjuvant radiotherapy has been shown to be ineffective for patients with lymph node metastasis (28). Furthermore, radiofrequency ablation is performed for patients with liver metastases (3,21). Intravenous bisphosphonates may be administered in patients with lytic bone lesions. Today, tyrosine kinase inhibitors targeting RET proto-oncogene products are promising for the treatment of metastatic medullary thyroid cancer (3,12,21).

In the postoperative period, serum calcitonin and CEA levels should be measured 3 months after the first operation and when they are undetectable, the measurements should be repeated every 6 months (3,20,29-30). Distant metastatic disease should be considered when serum calcitonin level exceeds 150 pg/mL. In such patients, thoracic CT, contrast MRI, or triphasic CT of liver, bone scintigraphy, or pelvic and axial skeletal MRI should be performed (3,20). Patients with normal serum CEA and undetectable serum calcitonin levels are biochemically considered to be cured and have an excellent prognosis. The risk of recurrence is 1-8.5% and the survival 97-99% at 5-10 years (30-34).

The disease-specific mean survival duration is 8.6 years (3,35,36). The prevalence of distant metastases varies between n13% and 20% (35,37-41). In our study no distant organ metastasis was detected and no patient died at a follow-up of 4.3 years.

CONCLUSION

The lower incidence of MTC and its unresponsiveness to RAI complicates its treatment. Both ATA and NCCN issued guidelines for the treatment and diagnosis of MTC. The only current treatment option for MTC is surgery; with central compartment lymphadenectomy and thyroidectomy at minimum constitute the base of treatment. Physical examination, calcitonin and CEA levels, FNAB, whole neck ultrasonography, and genetic test for RET germline mutation should be done in newly diagnosed MTC cases. For locally advanced and metastatic disease novel low molecule therapies are being developed and studies on neo-adjuvant therapy are ongoing.

Loco-regional surgery is the gold standard for the control of loo-regional disease and is the only curative option among available treatment options. Despite having a low incidence, MTC is a source of serious mortality and morbidity for patients whose disease is delayed and/or loco-regional control cannot be achieved.

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REFERENCES

1. Kim BH, Kim IJ. Recent updates on the management of medullary thyroid carcinoma. Endocrinol Metab (Seoul) 2016;31:392-99.
2. Hazard JB, Hawk WA, Crıle G Jr. Medullary [solid] carcinoma of the thyroid: a clinicopathologic entity. J Clin Endocrinol Metab 1959;19:152-61.
3. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25:567-610.
4. Aschebrook-Kilfoy B, Schechter RB, Shih YC, et al. The clinical and economic burden of a sustained increase in thyroid cancer incidence. Cancer Epidemiol Biomarkers Prev 2013;22:1252-9.
5. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic": screening and overdiagnosis. N Engl J Med 2014;371:1765-7.
6. Kim TY, Kim WG, Kim WB, et al. Current status and future perspectives in differentiated thyroid cancer. Endocrinol Metab (Seoul) 2014;29:217-25.
7. Gilliland FD, Hunt WC, Morris DM, et al. 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;79:564-73.
8. Hundahl SA, Fleming ID, Fremgen AM, et al. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see commetns]. Cancer 1998;83:2638-48.
9. Burgess JR, Dwyer T, McArdle K, et al. The changing incidence and spectrum of thyroid carcinoma in Tasmania (1978-1998) during a transition from iodine sufficiency to iodine deficiency. J Clin Endocrinol Metab 2000;85:1513-7.
10. Lawal O, Agbakwuru A, Olayinka OS, et al. Thyroid malignancy in endemic nodular goitres: prevalence, pattern and treatment. Eur J Surg Oncol 2001;27:157-61.
11. From G, Mellemgaard A, Knudsen N, et al. Review of thyroid cancer cases among patients with previous benign thyroid disorders. Thyroid 2000;10:697-700.
12. Ménez C, Hu MI, Gagel RF. Management of medullary thyroid carcinoma. Endocrinol Metab Clin North Am 2008;37:481-96.
13. Koçak S, Özbaş S. Medüller tiroid kanseri. Türkiye Klinikleri J surg med Sci 2005;1:59-64.
14. Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. Ann Surg 1999;229:880-7.
15. Elisei R, Bottici V, Luchetti F, et al. Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. J Clin Endocrinol Metab 2004;89:163-8.
16. Vierhapper H, Raber W, Bieglmayer C, et al. Routine measurement of plasma calcitonin in nodular thyroid diseases. J Clin Endocrinol Metab 1997;82:1589-93.
17. Costante G, Meringolo D, Durante C, et al.Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 2007;92:450-5.
18. Cheung K, Roman SA, Wang TS, et al. Calcitonin measurement in the evaluation of thyroid nodules in the United States: a cost-effectiveness and decision analysis. J Clin Endocrinol Metab 2008;93:2173-80.
19. Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. J Clin Endocrinol Metab 2010;95:2655-63.
20. NCCN Clinical Practice Guidelines in Oncology Medullary thyroid carcinoma. 2016. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.
21. Burinicardi F Charles Schwartz's principels of surgery. In: Lal G, Clark HO. Thyroid, parathyroid, adrenal. McGraw Hill Company, Ninth Edition, Newyork, 2010:1343-408.
22. Ball WD. Medullary thyroid cancer: Monitoring and therapy. Endocrinol Metab Clin North Am 2007;36:823-37
23. Brierley JD, Tsang RW. External beam radiation therapy for thyroid cancer. Endocrinol Metab Clin North Am 2008;37:497-509.
24. Martinez SR, Beal SH, Chen A, et al. Adjuvant external beam radiation for medullary thyroid carcinoma. J Surg Oncol 2010;102:175-8.
25. Fife KM, Bower M, Harmer CL. Medullary thyroid cancer: the role of radiotherapy in local control. Eur J Surg Oncol 1996;22:588-91.
26. Terezakis SA, Lee NY. The role of radiation therapy in the treatment of medullary thyroid cancer. J Natl Compr Canc Netw 2010;8:532-40.
27. Brierley J, Tsang R, Simpson WJ, et al. Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. Thyroid 1996;6:305-10.
28. Konstantinidis A, Stang M, Roman SA, et al. Surgical management of medullary thyroid carcinoma. Updates Surg 2017;69:151-60.
29. Ismailov SI, Piulatova NR. Postoperative calcitonin study in medullary thyroid carcinoma. Endocr Relat Cancer 2004;11:357-63.
30. Elisei R, Pinchera A. Advances in the follow-up of differentiated or medullary thyroid cancer. Nat Rev Endocrinol 2012;8:466-75.
31. Lindsey SC, Ganly I, Palmer F, et al. Response to initial therapy predicts clinical outcomes in medullary thyroid cancer. Thyroid 2015;25:242-9.
32. Tuttle RM, Ganly I. Risk stratification in medullary thyroid cancer: moving beyond static anatomic staging. Oral Oncol 2013;49:695-701.
33. Yang JH, Lindsey SC, Camacho CP, et al. Integration of a postoperative calcitonin measurement into an anatomical staging system improves initial risk stratification in medullary thyroid cancer. Clin Endocrinol [Oxf] 2015;83:938-42.
34. Barbet J, Campion L, Kraeber-Bode´re´ F, et al. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab 2005;90:6077-84.
35. Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer 2006;107:2134-42.
36. Veiga LH, Neta G, Aschebrook-Kilfoy B, et al. Thyroid cancer incidence patterns in Sao Paulo, Brazil, and the U.S. SEER program, 1997-2008 Thyroid 2013;23:748-57.
37. Machens A, Schneyer U, Holzhausen HJ, et al. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. J Clin Endocrinol Metab 2005;90:2029-34.
38. Scollo C, Baudin E, Travagli JP, et al. Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer. J Clin Endocrinol mETAB 2003;88:2070-5.
39. Machens A, Hauptmann S, Dralle H. Prediction of lateral lymph node metastases in medullary thyroid cancer. Br J Surg 2008;95:586-91.
40. Bumming P, Ahlman H, Nilsson B, et al. Can the early reduction of tumour markers predict outcome in surgically treated sporadic medullary thyroid carcinoma? Langenbecks Arch Surg 2008;393:699-703.
41. Pelizzo MR, Boschin IM, Bernante P, et al. Natural history, diagnosis, treatment and outcome of medullary thyroid cancer: 37 years experience on 157 patients. Eur J Surg Oncol 2007;33:493-7.