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Medullary Thyroid Carcinoma: Review of 27 Cases

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Abstract: Medullary thyroid carcinoma (MTC) may present in various clinical forms, either sporadic or a counterpart of hereditary endocrine disorders. The appropriate surgical procedure for MTC is total thyroidectomy combined with central neck clearance. The aim of this study was to document the initial clinical presentation, surgical treatment and clinical course of MTC in 27 patients. Thirteen (48.1%) cases were diagnosed as hereditary, either MEN 2a(7/27, 25.9%) or 2b syndrome (1/27, 3.7%) or familial non-MEN MTC (5/27, 18.5%), and fourteen cases were diagnosed as sporadic. Eighteen primary thyroid operations and twelve reoperative surgical procedures were performed on 24 patients. Eleven of the primary thyroid operations were total thyroidectomy combined with central neck clearance and bilateral modified radical neck dissection. Approximately half of the patients (45.5%) who underwent primary and total thyroidectomy had regional lymph node

metastasis. There was no recurrent nerve palsy or hypoparathyroidism. One patient died of acute respiratory insufficiency. External radiation therapy was performed in 9 of 24 patients. Postoperative follow-up periods ranged from 3 to 97 months, the mean being 38 months. Local recurrence occurred in three (13.6%) patients, two of whom developed distant metastasis as well. The overall five-year survival rate was found to be 85%. MTC is often diagnosed in advanced stages, especially in sporadic cases; however, total thyroidectomy combined with central neck clearance and modified radical neck dissection followed by external radiation provide long-term survival. Performance of an adequate surgical procedure during the initial intervention and detection of patients with MTC at earlier ages by screening improve the survival rates.

Key Words: Medullary thyroid carcinoma, Surgical treatment.

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Introduction

Medullary thyroid carcinoma comprises about 5-10% of all thyroid cancers and is more aggressive than well-differentiated thyroid carcinoma (1, 2, 3, 4). MTC may present in different clinical forms, either sporadic or a component of one of three familial endocrinopathies: multiple endocrine neoplasia (MEN) 2a or 2b syndromes and familial non-MEN MTC. The disease is inherited as an autosomal dominant trait in familial forms and may be associated with pheochromocytoma and primary hyperparathyroidism in MEN 2 a syndrome. MEN 2 b is distinguished by a characteristic phenotype of mucosal neuromas, ganglioneuromatosis and marfanoid habitus in addition to occasional pheochromocytoma. There are no

associated endocrine disorders in familial non-MEN MTC. The age of presentation, initial symptoms and the clinical course of the disease vary among these different clinical entities. The age at the time of diagnosis is lower in hereditary cases than in sporadic cases (5, 6, 7). The behaviour of MTC also varies according to the associated disorders, being most aggressive in MEN 2 b syndrome. The others, in decreasing order of aggressivity, are the sporadic form, MEN 2a syndrome and familial non-MEN MTC (8, 9).

The serum calcitonin level is a specific marker in diagnosis, detection of recurrent or persistent disease and screening family members of patients with MTC. Identification of the gene responsible for the familial form

Table 1. The distribution of thyroid cancer among 2570 patients.

	n:	(%)
Thyroid carcinoma	214	(8.3)
Papillary carcinoma	143	(66.8)
Follicular carcinoma	18	(8.4)
Medullary carcinoma	27	(12.6)
Anaplastic carcinoma	20	(9.4)
Hurthle cell carcinoma	3	(1.4)
Undifferentiated carcinoma	3	(1.4)

	Sporadic (n:14)	Familial (n:5)	MEN 2a (n:7)	MEN 2b (n:1)
Mean age (yrs)	44.6	36.4	33.0	40.0
	n: (%)	n: (%)	n: (%)	n: (%)
Solitary thyroid nodule	7(50)	1(20)	2(28.6)	
Diffuse enlargement	2(14.3)			
Cervical lymph nodes	5(35.7)			
Pheochromocytoma			3(42.8)	1(100)
Screening		4(80)	2(28.6)	
Distant metastasis	2(14.3)			
	2(28.6)			

Table 2. Initial clinical presentation of patients with MTC and patients having distant metastasis at the time of initial presentation.

of MTC has established an absolute method of diagnosing such patients at earlier ages (10).

Basic surgical treatment of MTC should be total thyroidectomy with central neck clearance (4, 10, 11, 12). Less thorough procedures may be followed by local or distant recurrence and multiple reoperations.

Our aim was to document the initial form of diagnosis, the extent of surgical procedure and the differences in the clinical course of the disease according to primary surgical treatment.

Material and Method

Between January 1986 and October 1996, 2570 patients were treated for various thyroid disorders at the Endocrine Surgery Unit of the Department of Surgery of Istanbul Medical Faculty. Two hundred fourteen cases of thyroid carcinoma were diagnosed (8.3%), 27 (12.6%) of which were MTC (Table 1). Four patients who had been subjected elsewhere primary thyroid operations for goiter were admitted to our institution for total thyroidectomy. Two patients belonged to a family with MEN 2 a syndrome. They were screened after another member of this family was treated for MTC in our

institution. One had had total thyroidectomy elsewhere 5 years before and the other had undergone bilateral adrenalectomy for pheochromocytoma elsewhere. Both patients have been reluctant to undergo further evaluation and follow-up.

Seven (25.9%) cases were classified as MEN 2a, and one (2.7%) as MEN 2b syndrome. Five (18.5%) cases were classified as familial non-MEN and 14 (51.9%) as sporadic cases of MTC. If preoperative or peroperative diagnosis of MTC was available, total thyroidectomy plus central neck clearance was performed as the minimum surgical procedure. Central neck clearance consists of removal of all central lymph nodes and fibrofatty tissue

from the brachiocephalic vein inferiorly to the hyoid bone superiorly and between the carotid arteries (1). Modified radical neck dissection (removal of cervical lymph nodes lateral to the carotid sheath with preservation of the sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve) was performed in patients with palpable lymphadenopathy (1, 4). Family members of patients having MTC were screened by means of basal and stimulated calcitonin assays. Patients having locally invasive or unresectable diseases underwent external radiation. Student's t test was used for statistical analysis and p<0.05 was accepted as significant.

Results

Preoperative Results

Of 27 patients, 18 (66.7%) were female and 9 (33.3%) were male. Ages ranged from 13 to 68 years, the mean being 40. Initial mode of presentation, mean age at presentation and patients with distant metastasis are shown in Table 1. MTC was diagnosed at earlier ages in hereditary forms than in the sporadic form (p<0.01). A solitary thyroid nodule was found to be the most frequent initial symptom, especially in sporadic MTC. The

Table 3. Primary thyroid operations for MTC (n:18)

	n:	(%)
Total thyroidectomy BMRND, CNC	11*	(61.1)
Total thyroidectomy CNC	3	(16.7)
Total thyroidectomy	2	(11.1)
Lobectomy, isthmusectomy, contralateral wedge resection	2	(11.1)

*One patient underwent anterior superior mediastinal lymph node dissection as well.
BMRND: Bilateral modified radical neck dissection, CNC: Central neck clearance

Table 4. Histological results of primary thyroidectomy (n:18)

	n:	(%)
Tumor in both lobes	12	(66.7)
Tumor confined to one lobe	6	(33.3)
Lymph node metastasis Central: 1 Lateral: 4	5	(27.8)
Capsule invasion	4	(22.2)
Adjacent tissue invasion	4	(22.2)

Table 5. Histological results of completion thyroidectomies (n:5)

	n:	(%)
Residual tumor	3	(60)
No tumor found	2	(40)
Lymph node metastasis (central and lateral)	5	(100)
Adjacent tissue invasion	2	(40)

initial symptom in approximately half of the patients with sporadic MTC was palpable cervical lymph nodes. Four (14.8%) patients were found to have distant metastasis. Multiple liver metastasis was shown by computerized tomography in two patients. Of the remaining two

patients, one had intracranial metastasis, and the other had multiple lung metastasis. The mean values of preoperative serum calcitonin and CEA levels were 517.6 pg/dl (range:2.4-1520 pg/dl) and 112.3 ng/dl (range: 0.1-400 ng/dl), respectively. The mean value of serum calcitonin in patients with hereditary MTC (375.6 pg/dl) was lower than in patients with sporadic MTC (554.3 pg/dl) ($p<0.01$).

Peroperative Results

Twenty primary operations were performed on 21 patients referred initially to our institution. The majority (61.1%) of the primary thyroid operations consisted of total thyroidectomy and central neck clearance combined with bilateral modified radical neck dissection due to palpable lateral cervical lymph nodes (Table 3). In one patient, the anterior superior mediastinal lymph nodes were dissected as well. Although thyroidectomy was not possible in two patients due to extreme local invasion, it was performed in 18(85.7%) of 21 patients. Biopsy was performed in these two patients with unresectable tumors. One patient with multiple lung metastasis was not operated on. Twelve reoperative procedures were performed on 7 patients. Five of seven patients who initially underwent lobectomy and contralateral wedge resection were subjected to total thyroidectomy with central neck clearance and bilateral modified radical neck dissection. Bilateral (2) or unilateral (3) modified radical neck dissections were performed for palpable lymph nodes. Tumor metastasis was shown histologically in only three of these five lymph node dissections. The remaining two reoperative procedures were excision of anterior mediastinal and later intrathoracic recurrent mass by sternotomy and thoracotomy, respectively, in the same patient. Four patients underwent one reoperative intervention. Two patients were subjected to two reoperations. Four reoperative procedures were performed on one patient. This patient, who had previously been operated on for goiter elsewhere, underwent total thyroidectomy, central neck clearance and modified radical neck dissection. Unilateral modified radical neck dissection was performed two months after total thyroidectomy. Fifteen months later, the patient underwent sternotomy due to recurrent disease in the anterior mediastinum. Three months after sternotomy, a mass adjacent to the right pulmonary vein was removed by right thoracotomy. At present, 30 months after total thyroidectomy, metastasis to the thoracic vertebra has been demonstrated by magnetic resonance.

Postoperative Results

There was no hypoparathyroidism or recurrent nerve

palsy. One patient died of acute respiratory insufficiency on the fourth postoperative day. Histological results of primary and total thyroidectomies are summarized in Tables 4 and 5. MTC was found to be bilateral in two thirds of patients undergoing primary thyroidectomy (12/18). Residual tumors were detected histologically in 3 out of 5 patients undergoing total thyroidectomy. Lymph node metastasis was present in 10(45.5%) out of 22 patients who underwent primary or total thyroidectomy. External radiation therapy was performed in nine (37.5%) out of 24 patients who had histologically determined extraglandular disease or postoperative residual tumor due to locally invasive disease, or in whom MTC was unresectable.

Mean postoperative serum calcitonin and CEA levels were found to be 187.8 pg/dl (range: 1.2-1222 pg/dl) and 11.2 ng/dl (range: 0.3-45.9 ng/dl), respectively. Serum calcitonin levels returned to their normal values in 5 patients during the first postoperative month; however, elevation of the calcitonin level occurred in one of these patients. Serum calcitonin levels remained elevated in the other 17 patients, still remaining lower than the postoperative value. The decline of the calcitonin level was more marked in patients with sporadic MTC (from 554.3 pg/dl to 124.4 pg/dl) than in patients with familial MTC (from 375.6 pg/dl to 163.7 pg/dl) ($p < 0.05$). Patients with hypercalcitoninemia were subjected to DMSA scanning every six months, and further imaging techniques were used in the event of abnormal uptake.

The postoperative follow-up period ranged from 3 to 98 months, the mean being 38 months. During this period, local recurrence occurred in three of 22 (13.6) patients, and these patients underwent reoperation. Distant metastasis to lung and vertebra developed in two of these three patients as well. Although one of these two patients underwent right thoractomy for removal of a tumoral mass, surgical intervention was not attempted on the other patient due to multiple metastasis. External radiation was performed on all three patients who developed local or distant metastasis. All patients with local recurrence or distant metastasis had undergone subtotal thyroidectomy elsewhere and were admitted to our institution for total thyroidectomy.

None of the 22 patients who underwent primary or total thyroidectomy died during the follow-up period. Two (14.8) out of 27 patients died as result of MTC during the follow-up period. Two were members of a family with a history of MEN 2a syndrome and had undergone operative procedures elsewhere. These patients were called in for further evaluation, and

multiple liver metastasis due to MTC was detected. No surgical intervention was performed on in these patients, and they were finally lost due to hepatic failure.

Discussion

Medullary thyroid carcinoma originating from parafollicular cells is not a common thyroid tumor. The initial presentation of MTC may be one of the wide range of local or systemic symptoms, such as a single thyroid nodule, cervical lymph nodes, diarrhea, symptoms associated with pheochromocytoma or hyperparathyroidism or symptoms related to distant metastasis. More than half of the patients have extension to regional lymph nodes, and a considerable number have distant metastasis at the time of initial diagnosis (5, 11, 13). In the present study, we determined that 35.7% and 14.3% of patients having sporadic MTC had lymph node metastasis and distant metastasis, respectively, at the time of initial diagnosis. Thus, MTC is often detected in an advanced stage. The preferred form of initial diagnosis in the familial varieties of MTC is through screening tests, by which the disease may be detected at the stage of C cell hyperplasia (6, 7). A single thyroid nodule was the leading initial symptom of sporadic MTC, in this study, while the second most common symptom was palpable cervical lymph nodes. The clinical findings of pheochromocytoma preceded MTC in patients with MEN 2a syndrome. Most patients with familial non-MEN MTC were diagnosed through screening tests.

Unlike other types of thyroid carcinoma, MTC has a specific diagnostic marker, the serum calcitonin level. Serum calcitonin assay, either basal or stimulated by pentagastrin, is widely used for the screening of family members of patients with sporadic or familial MTC. Stimulated calcitonin assay, repeated annually, is the fundamental method for detecting affected individuals of a family with familial MTC (6, 7). The age of initial diagnosis has been reduced to the third decade by means of screening tests, and the majority of cases are detected long before they would otherwise have been (19). In our study, almost half of the patients (n:6/13) with hereditary MTC were diagnosed through screening tests, and patients diagnosed with hereditary MTC were significantly younger than those diagnosed with sporadic MTC ($p < 0.01$). Serum calcitonin assay, however, has limitations as a screening test, as not all members of families adhere to an annual stimulation test for screening. It is important to detect the affected individuals in much earlier years than 30, and stimulated

calcitonin assay may give false positive results (5, 10, 20).

By improvement of molecular endocrinology, the gene responsible for the hereditary forms of MTC, defined as the RET protooncogene, has been found to be located on chromosome 10 (10, 21). The identification of RET protooncogene provides an absolutely reliable method of screening family members of patients with MTC. In familial forms of the disease, RET protooncogene mutations can be demonstrated in the DNA extracts of the peripheral blood leukocytes (germline mutations); however, RET mutations are present only in the tumor tissue (somatic mutations) of patients with sporadic MTC (10). Precise identification of germline or somatic mutations enables precise differential diagnosis between sporadic or familial disease (10). Development of a new molecular means of detecting individuals with germline mutations that will result in MTC largely outdated the use of calcitonin assay as a screening procedure. However, this method is still valuable for postoperative follow-up of the patients (4, 5, 10, 22).

The importance of early diagnosis arises from the fact that surgery is the basic treatment of MTC, and other treatment modalities, such as external radiation, radioiodine treatment and chemotherapy, have no widely proved benefit, although postoperative external radiation has been reported to lower the rate of locoregional recurrence and improve survival in high risk patients (10, 14, 15, 16, 17). Total thyroidectomy at the stage of C cell hyperplasia results in absolute cure. Controversy exists over how to approach lateral and superior mediastinal lymph nodes. Some authors suggest testing the lateral and anterior superior mediastinal lymph nodes and performing lymphadenectomy if the tumor is positive (11). Block and Duh et al., however, advise removal of the lateral and anterior superior mediastinal nodes in "palpable" MTC in spite of the lack of ipsilateral cervical lymphadenopathy, or modified radical lymph node dissection in tumors larger than 2 cm (4, 5). All patients with palpable MTC are considered to have at least occult metastases in cervical and anterior mediastinal lymph nodes which will result in slightly elevated calcitonin level postoperatively (4). Anterior superior mediastinal nodes were present in half of the patients who underwent surgery for regional nodal metastasis, and mediastinal disease was associated with a poorer prognosis than lateral cervical metastasis (23). In our group, of ten patients with regional lymph node metastasis, both lateral and central nodes were present in nine.

The serum calcitonin level decreases or returns to

normal values after an adequate surgical procedure in about one month, as observed in the present study. Postoperative elevation of basal or stimulated calcitonin levels indicates recurrent or residual disease. Persistent hypercalcitoninemia is frequently encountered after the operation. Although the serum calcitonin level decreases, it remains slightly elevated in most patients despite an adequate surgical procedure. Persistent elevation is probably due to occult disease in the lateral cervical or anterior superior mediastinal lymph nodes (4).

Determination of calcitonin gradient by selective venous catheterization has been found to be the most precise method for localizing occult persistent MTC compared to CT, ultrasonography and physical examination (24). Microsurgical dissection of central, lateral or anterior superior mediastinal lymph nodes guided by preoperative selective venous catheterization has been found to improve or normalize serum calcitonin levels in patients with persistent hypercalcitoninemia (24, 25). The influence of extensive microsurgical operations on survival in patients with residual occult carcinoma has not yet been determined. On the other hand, patients with occult residual disease resulting in an elevated calcitonin level may be treated by a conservative approach for many years (26). Serum calcitonin levels remained slightly elevated after an adequate surgical treatment in the majority of our patients without any clinically apparent disease. Although the number of patients and the follow-up period were not adequate for a precise conclusion, persistent stable hypercalcitoninemia did not seem to require an aggressive approach for localization and reoperation in patients who had undergone appropriate surgery. However, sudden elevation of calcitonin, which may indicate growth of residual MTC, requires detailed evaluation for localization and surgical removal of the recurrent mass.

Several factors have been proven to affect the prognosis of MTC. Early detection of the disease significantly improves survival rates (5). Small tumors, absence of regional lymph node metastasis, absence of extraglandular or vascular invasion, absence of diarrhea as one of the initial complaints, younger age and female gender were all found to be associated with a significantly higher survival rate (8, 13, 27). Presence of extraglandular invasion, residual disease after surgical treatment, postoperative abnormal calcitonin level and lack of staining of the tumor tissue for amyloid histologically were found to be significant predictors of poor survival (13). The chance of cure depends on proper surgical treatment following early detection of the disease. An adequate initial surgical procedure has been

shown to lower the rate of recurrence (8). Reoperations are associated with increased morbidity and preclusion of optimal surgical procedure due to scar tissue (28, 29). In our group, there was no recurrence in patients who underwent adequate primary surgery; however, there was recurrence in the majority of patients who initially underwent insufficient resection followed by total thyroidectomy. The higher recurrence rate in patients undergoing total thyroidectomy is probably related to inadequate resection in order to prevent injury to important structures, and to the aggressive behaviour of the tumor in these patients.

Adjuvant treatment methods are generally used for palliation of unresectable tumors. External radiation is probably the most widely used adjuvant method. Several studies have documented that patients who are more likely to develop recurrence as a result of a locally extensive disease benefit from external radiation following surgical treatment (13). Although a

considerable number of patients had advanced tumors in our group, the rate of local or distant metastasis was relatively low. This result may be attributed to the role of external radiotherapy applied to patients with advanced tumors. The follow-up period, however, is not long enough to reach a statistically significant conclusion. Radioiodine treatment is of practically no use in MTC (15). The results of chemotherapy, documented in small groups, have been disappointing (15, 16).

In conclusion, total thyroidectomy and central neck clearance is the basic surgical treatment for MTC. Modified radical neck dissection should be performed in the presence of palpable or cervical lymph nodes. An initial adequate surgical procedure followed by external radiotherapy in patients with extraglandular disease or postoperative local residual tumor results in low recurrence rates. Reoperation due to incomplete resection at the primary operation bear a high risk of morbidity or recurrence.

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