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 12th month), mediastinal lymph nodes (at 15th month), 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.
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 23 (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), 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 undergo 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 than 200 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 are above 20 pg/mL (3).
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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 are metastases, 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 loco-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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