Medullary Thyroid Cancer

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Current Treatment Options in Oncology 2000, 1:359-367
Current Science Inc. ISSN 1527-2729
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Opinion statement
Patients with clinically evident medullary thyroid cancer should have a total extra-capsular thyroidectomy with bilateral central neck dissection and an ipsilateral prophylactic or therapeutic modified (functional) radical neck dissection when the primary tumor is greater than 1 cm and when the central neck nodes are positive. A prophylactic contralateral neck dissection should be done when the primary tumor is bilateral and when there is extensive lymphadenopathy on the side of the primary tumor. Patients who have gross, unresectable residual medullary thyroid cancer should receive postoperative external radiotherapy.

Patients who are carriers of germ-line RET proto-oncogene point mutations or have an elevated (basal or stimulated) calcitonin levels on screening should have a prophylactic total thyroidectomy before age 6 years. In patients with an elevated basal or stimulated plasma calcitonin level and an intrathyroidal nodule on ultrasound, a total thyroidectomy and central neck lymph node dissection should be done.

Patients with persistent or recurrent medullary thyroid cancer should have a complete thyroidectomy (if not done initially) and bilateral central and modified radical neck dissection, including upper mediastinal lymphadenectomy.

Patients who are symptomatic from distant medullary thyroid cancer metastases (diarrhea, flushing, weight loss, or bone pain) should be treated with somatostatin analogs. Bone metastases should be resected if possible, and symptomatic lesions that are unresectable should be treated with external radiotherapy. Cytoreductive procedures such as radiofrequency ablation or cryoablation for liver metastases should be considered in symptomatic patients to reduce tumor burden. Localized pulmonary metastases should be resected. Chemotherapy or radioactive immunotherapy (iodine 131 labeled carcinoembryonic antigen monoclonal antibody) protocols should be considered in patients with nonoperative widely metastatic progressing medullary thyroid cancer.

Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) was first described by Hazard et al. [1] as a unique thyroid neoplasm, and exciting advances in the understanding of MTC pathogenesis, molecular biology, and tumor behavior have occurred. MTC is a rare malignancy originating from the neuroendocrine-derived parafollicular or C (calcitonin secreting) cells of the thyroid gland. It accounts for about 7% of all thyroid cancers and occurs as a sporadic or hereditary disease [2–4]. Hereditary MTC accounts for about 25% of all cases of MTC and has an autosomal dominant pattern of inheritance. Pene-trance is virtually 100% [5]. Familial non-multiple endocrine neoplasia (MEN), MEN 2A, and MEN 2B comprise the hereditary forms of MTC. Germ-line point mutations in the RET proto-oncogene are responsible for hereditary MTC. Genetic screening for RET germ-line point mutations is accurate in identifying at-risk individuals [4]. It has replaced basal and stimulated plasma calcitonin measurement for screening at most medical centers. Genetic screening is more effective than biochemical testing for the following reasons: 1) yearly testing is not required if a family member has no mutations in a family with a known RET mutation; 2) provocative calcitonin testing may be associated with side effects; 3) it is more accurate; and 4) it can be done at an earlier age [6]. However, basal or stimulated calcitonin measurement remains indispensable for detecting persistent or recurrent MTC [7].
Except for those diagnosed by screening, most patients with MTC present with a thyroid mass, or with cervical lymphadenopathy and local symptoms. They rarely present with systemic symptoms from metastatic disease [4•]. Fine needle aspiration cytology is highly accurate for establishing the diagnosis of MTC, especially with immunohistochemical staining for calcitonin, carcinoembryonic antigen (CEA), and amyloid. Locoregional lymph node metastases are common in patients with MTC at the time of diagnosis. About two-thirds of ipsilateral cervical lymph nodes and one-third of the contralateral cervical lymph nodes are involved (Fig. 1) [8]. Because this tumor commonly occurs in the upper posterior two-thirds of the thyroid gland, local MTC invasion into the trachea, recurrent laryngeal nerve, and surrounding structures may be present. On late patient presentation or in patients with long-standing persistent or recurrent MTC, distant MTC metastases can occur in the liver, lung, and bone [4•,7].

Although MTC is a relatively rare thyroid cancer, it is one of the more aggressive thyroid cancers accounting for about 14% of all thyroid cancer deaths [1,2]. Furthermore, more than 50% of the patients with apparently curative surgical treatment have persistent or recurrent MTC [6,9]. Unlike differentiated thyroid cancer of follicular cell origin, postoperative radioiodine therapy is ineffective in most patients with MTC [10].

Surgery is the primary treatment for MTC. There is a general consensus that patients with clinically evident MTC should have at least a total or near-total thyroidectomy and regional cervical lymph node dissection. The extent of initial cervical lymph node dissection should include at least central neck node dissection with or without unilateral or bilateral modified radical neck dissection. Asymptomatic patients at risk for MTC should have a prophylactic total thyroidectomy with prophylactic bilateral central neck node dissection when the basal or stimulated calcitonin level is increased or when lesions are identified by ultrasound within the thyroid gland. It is controversial whether routine locoregional postoperative external radiotherapy is beneficial, but it should be considered in patients with residual MTC for local control. Chemotherapy for patients with metastatic MTC is currently generally ineffective. Based on our experience and others, this chapter discusses the optimal treatment strategies in patients who present with 1) clinically evident MTC, 2) asymptomatic MTC (found to be at risk of developing MTC by screening tests), 3) persistent or recurrent MTC, and 4) metastatic MTC.

**PROGNOSIS**

The overall survival of patients with MTC is about 75% (ranging from 61% to 88%) at 10 years follow-up [2,3,4•]. However, the prognosis of patients with MTC...