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REVIEW

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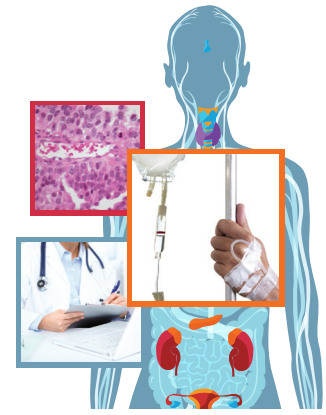

International Journal of Endocrine Oncology

# Surgery for lymph node metastases of medullary thyroid carcinoma

Linda X Jin[1] & Jeffrey F Moley*[,2,3]

**Practice points**

- No known effective systemic therapy exists for medullary thyroid carcinoma (MTC), and surgery remains the first-line treatment for curative therapy.
- Lymph node involvement in MTC affects prognosis, and nodal status is incorporated into the American Joint Committee on Cancer MTC staging classification, in addition to tumor size, invasion and distant metastases.
- Hereditary medullary thyroid cancer syndromes include MEN 2A, MEN 2B and familial MTC and are associated with germline mutations in the RET proto-oncogene on chromosome 10q11.2. Knowledge of the specific RET mutation allows clinicians to stratify patients in risk groups based on age of onset and aggressiveness of MTC.
- In patients with palpable disease but without evidence of local invasion, cervical node metastases or distant metastases, total thyroidectomy accompanied by a central node dissection (level VI nodes) is the appropriate primary treatment.
- Systematic, compartment-oriented approach to the removal of nodal tissue improves survival rates and reduces recurrence rates, and should be performed instead of procedures with removal of only grossly involved nodes.
- The majority of patients with palpable MTC have regional metastases at the time of diagnosis, for which surgical clearance is the only effective therapy.
- Ipsilateral neck dissection, also called 'functional' or 'modified radical' neck dissection, in which all or portions of levels II, III, IV and V nodes are removed, should be considered in all patients with clinically evident MTC.
- The burden of lymph node metastasis in the central compartment can help predict lateral compartment involvement.
- In MEN 2A and familial MTC with high-risk mutations, an ipsilateral or bilateral central neck dissection (level VI) should be performed in the presence of palpable or radiologically identifiable lymphadenopathy or elevation of calcitonin level >40 pg/ml. Patients with low-risk mutations (level I) with calcitonin level <40 pg/ml and no evidence of nodal disease should receive a total thyroidectomy, leaving the parathyroid *in situ*.
- Patients with MEN 2B should receive thyroidectomy at infancy, as MTC is often present at birth, with additional central neck dissection if the calcitonin level is elevated.
- All patients should be followed with calcitonin levels measured postoperatively and semiannually thereafter.
- Reoperation should be considered for patients with elevated calcitonin levels in the setting of an inadequate initial operation, imaging evidence of recurrent or persistent local disease, or for threat of compression or invasion of the trachea or major vessels.
- A significant reduction in stimulated calcitonin levels after reoperation can be achieved through a thorough microdissection, which involves dissection of all lymph node and fatty tissue of the central and lateral zones of the neck, both recurrent nerves, as well as nodes of the lateral neck.

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Medullary thyroid carcinoma (MTC) is a neuroendocrine malignancy of the thyroid C cells, and can commonly spread to cervical and mediastinal lymph nodes. MTC cells do not concentrate radioactive iodine and are not sensitive to hormonal manipulation, and therefore surgery is the only effective option for curative therapy, reduction in tumor burden or effective palliation. In patients undergoing preventative operations for hereditary MTC, central lymph node dissection should be considered if the calcitonin level is above 40 pg/ml. Systematic removal of at-risk or involved lymph node compartments should be performed in all patients with palpable primary tumors and recurrent disease, and a 'berry-picking' approach should be avoided.

**KEYWORDS**
• lymph node metastases
• medullary thyroid cancer
• multiple endocrine neoplasia • recurrence
• surgery

Medullary thyroid carcinoma (MTC) is a neuroendocrine malignancy of the calcitonin producing thyroid C cells, also known as parafollicular cells. Parafollicular C cells are of neural crest derivation, and are dispersed throughout the normal thyroid gland. C cells secrete calcitonin, a hormone involved in calcium metabolism. Elevated calcitonin level is a sensitive and specific marker for the presence of MTC. It is valuable in both screening and follow-up of patients with MTC. MTC accounts for 4% of all thyroid cancers, and displays a variety of clinical behaviors ranging from indolent to aggressive [1,2].

MTC has several distinctive features. First, MTC may be sporadic (75% of cases) or hereditary (25% of cases), occurring in all patients with multiple endocrine neoplasia type 2 (MEN 2) syndromes [3]. Sporadic cases of MTC usually present with a palpable thyroid mass, while hereditary cases may be detected and treated on the basis of genetic testing once the syndrome is diagnosed in a family. Second, although MTC is more aggressive than differentiated thyroid carcinoma, it is still an indolent malignancy, with reported 10-year survival rates from 69 to 89% [1,4–5]. Finally, unlike differentiated thyroid cancer, no known effective systemic therapy exists for MTC, although recent trials with small molecule inhibitors are promising. MTC cells do not concentrate radioactive iodine and are not sensitive to the manipulation of thyroid-stimulating hormone. All these features influence the choice for therapy in patients with MTC. While newly approved targeted molecular therapies offer wider treatment options for symptomatic, locally advanced, metastatic progressive unresectable MTC, surgery remains the first-line treatment for curative therapy.

Primary MTC tumors may invade adjacent structures, including the larynx, trachea, recurrent laryngeal nerve and esophagus. In familial forms, tumors are usually bilateral and multifocal. Once the primary tumor is established, metastasis to regional lymph nodes occurs earlier than in differentiated thyroid cancer [6,7]. Nodes in the central compartment (levels VI and VII) are most often involved, followed by levels II–V on the ipsilateral, and frequently the contralateral side **(Figure 1)**. Involved lymph nodes seen on preoperative ultrasound may appear enlarged, with lack of a fatty hilum and microcalcifications, as well as abnormal blood flow pattern **(Figure 2)**. We do not routinely use fine needle aspiration to evaluate lymph nodes preoperatively as abnormal appearance on ultrasound is already an indication for intraoperative removal. Metastatic spread to the upper and anterior mediastinum may also be observed. Hematogenous spread occurs variably in the course of MTC, generally to the liver, lungs and bone. Distant metastases often occur in a fine miliary pattern that is not well visualized on CT scans or other anatomic imaging.

Lymph node involvement in MTC affects prognosis, and nodal status is incorporated into the American Joint Committee on Cancer MTC staging classification, in addition to tumor size, invasion and distant metastases. In several studies, 10-year cause-specific survival was most influenced by age, stage and postoperative basal calcitonin levels [5,9]. This was confirmed in a recent review, which again showed that the most sensitive predictors of survival were age at diagnosis and tumor stage [10]. In this series, differences in survival time were correlated with biochemical and radiographic remission. In those who did not, 10-year survival was slightly reduced to 73%. These observations confirm the indolent nature of the disease and suggest the benefit of therapeutic interventions that keep tumor burden at a minimum, including reoperative surgery when technically possible.

## Hereditary medullary thyroid cancer

Hereditary MTC syndromes include MEN 2A, MEN 2B and familial MTC (FMTC). These syndromes are associated with germline

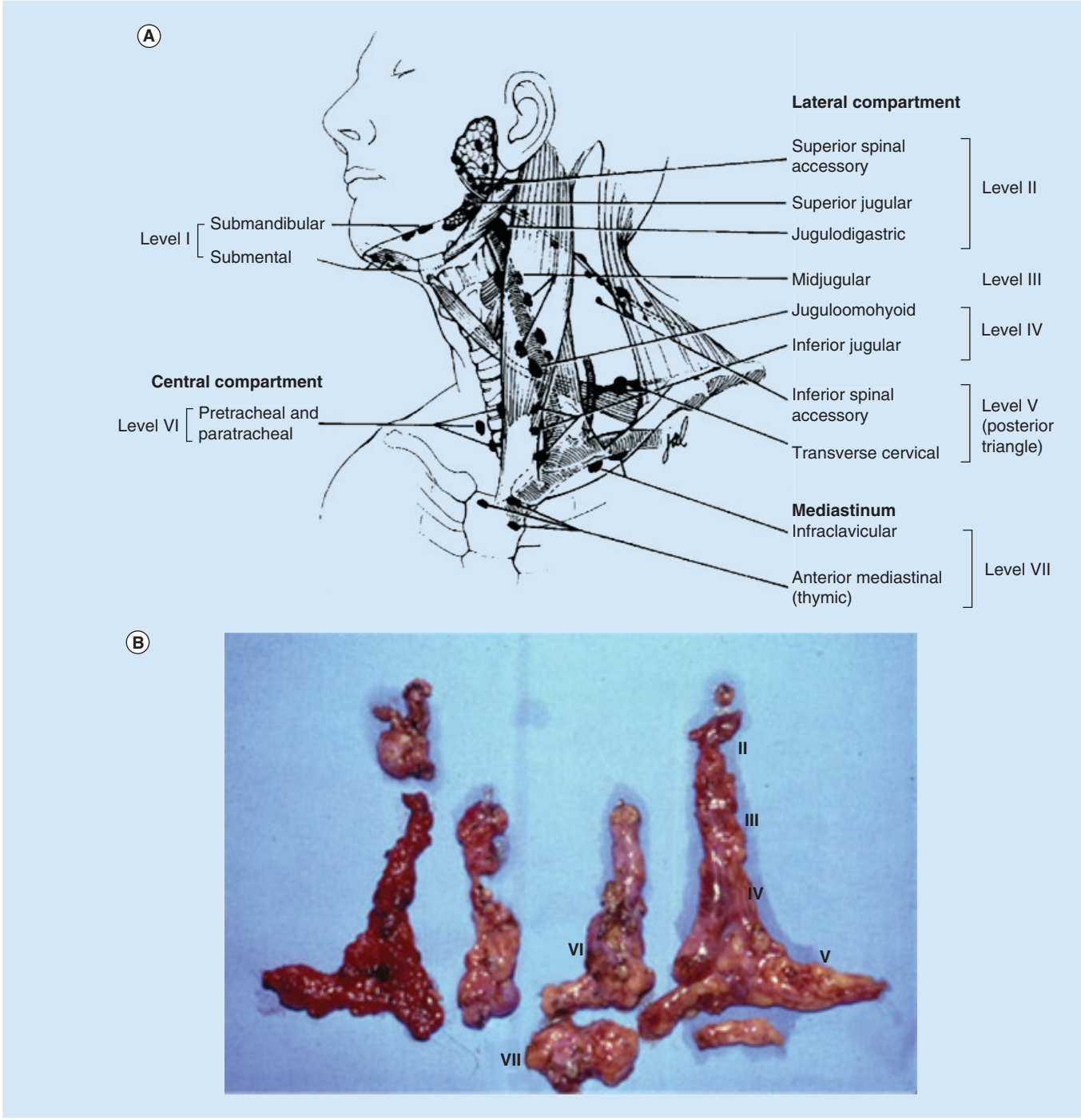


**Figure 1. Lymph node dissection during surgery for medullary thyroid carcinoma. (A)** Lymph node groups in the neck. **(B)** Specimen from a patient following central and bilateral neck dissection. Level II nodes are from the high jugular nodes; level III, mid-jugular nodes; level IV, low jugular nodes; level V, posterior triangle nodes; level VI, paratracheal nodes; level VII, superior mediastinal nodes. Reproduced with permission from [8].

mutations in the RET proto-oncogene on chromosome 10q11.2. [11–13] This gene encodes a tyrosine kinase receptor protein involved in growth, differentiation and migration of developing tissues. In MEN 2A and FMTC, mutations within codons specifying cysteine residues in the extracellular ligand-binding domain of the RET gene product are most

commonly found. In MEN 2B, a mutation is found in the intracellular tyrosine kinase domain. Changes in protein structure and function that result from these mutations predispose to neoplasia by a dominant oncogenic mechanism [14].

Each of the hereditary MTC syndromes has unique associated endocrine abnormalities, but all have near-complete penetrance of MTC. Progression from C-cell hyperplasia to intrathyroidal MTC with eventual lymphatic and metastatic spread is age dependent and related to expression of specific RET mutation phenotypes [15,16]. Knowledge of the specific RET mutation allows clinicians to stratify patients in risk groups based on age of onset and aggressiveness of MTC: highest (level III), high (level II) and low (level I) level risk [17].

MEN 2A is characterized by multifocal, bilateral MTC, pheochromocytoma (42% penetrance) and hyperparathyroidism (10 to 30% penetrance). It is associated with RET mutations affecting extracellular cysteine residues [11–12,14,18–20]. Cutaneous lichens amyloidosis and Hirschsprung's disease has also been described in patients with MEN 2A. MEN 2A has a variable course based on codon mutation. Mutations in codon 611, 618, 620 and 634 pose a level II risk. Patients with mutations in the 634 codon have an increasing, cumulative age-related risk of lymph node metastasis, starting from the mid-teens and reaching a >40% cumulative risk by the age of 20. MEN 2A with mutations in codons 768, 790, 804 or 891 are less aggressive (level I risk) and often present in the second or third decade of life.

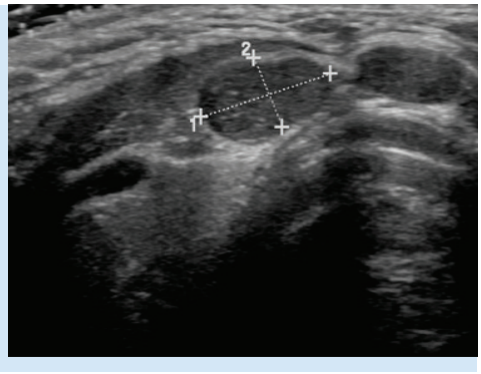

**Figure 2. Metastatic sporadic medullary thyroid cancer to central lymph nodes anterior to the trachea.** The nodes are enlarged, there is lack of a fatty hilum and microcalcifications, and there is an abnormal blood flow pattern.

FMTC represents a clinical variant of MEN 2A in which only MTC is seen. FMTC is caused by the same genetic mutations as MEN 2A as well as by less common mutations in the intracellular portion of the gene product [11,15–16,18]. Commonly associated mutations occur in codons 609, 611, 618 and 620 in exon 10; codon 768 in exon 13 and codon 804 in exon 14 [17,21]. Generally, FMTC-related mutations are least aggressive (level I risk).

MEN 2B is characterized by MTC with onset at a very young age, pheochromocytoma (40% penetrance), multiple mucosal neuromas, ganglioneuromatosis of the GI tract and megacolon. MEN 2B is most commonly caused by a methionine to threonine mutation in codon 918 of the catalytic domain of tyrosine kinase. MTC in the setting of MEN 2B is typically the most aggressive (level III risk), with invasive carcinoma in the first year of life and early lymph node metastasis.

The surgical approach in older RET mutation carriers should be individualized based on calcitonin level, presence of palpable disease, imaging results, RET mutation and family history.

## Initial surgical treatment of clinically evident disease

The surgical treatment of MTC is guided by several key principles. First, the biology and behavior of MTC is very different from those of differentiated thyroid cancer. MTC cells do not take up iodine and radioactive iodine therapy is ineffective. Unlike differentiated thyroid cancer, MTC does not respond to thyroid suppression using levothyroxine; thus surgery is the only effective therapeutic modality. Second, MTC is multicentric in 90% of patients with hereditary forms of the disease and in 20% of patients with the sporadic form. Third, nodal metastases are present in more than 70% of patients with palpable disease [22,23]. Last, the ability to measure postoperative stimulated calcitonin levels allows the adequacy of surgical extirpation to be assessed.

In patients with palpable disease but without evidence of local invasion, cervical node metastases or distant metastases, total thyroidectomy accompanied by a central node dissection (level VI nodes) are the appropriate primary treatment **(Figure 3)** [3]. Systematic, compartment-oriented approach to removal of nodal tissue was reported to improve survival rates and reduce

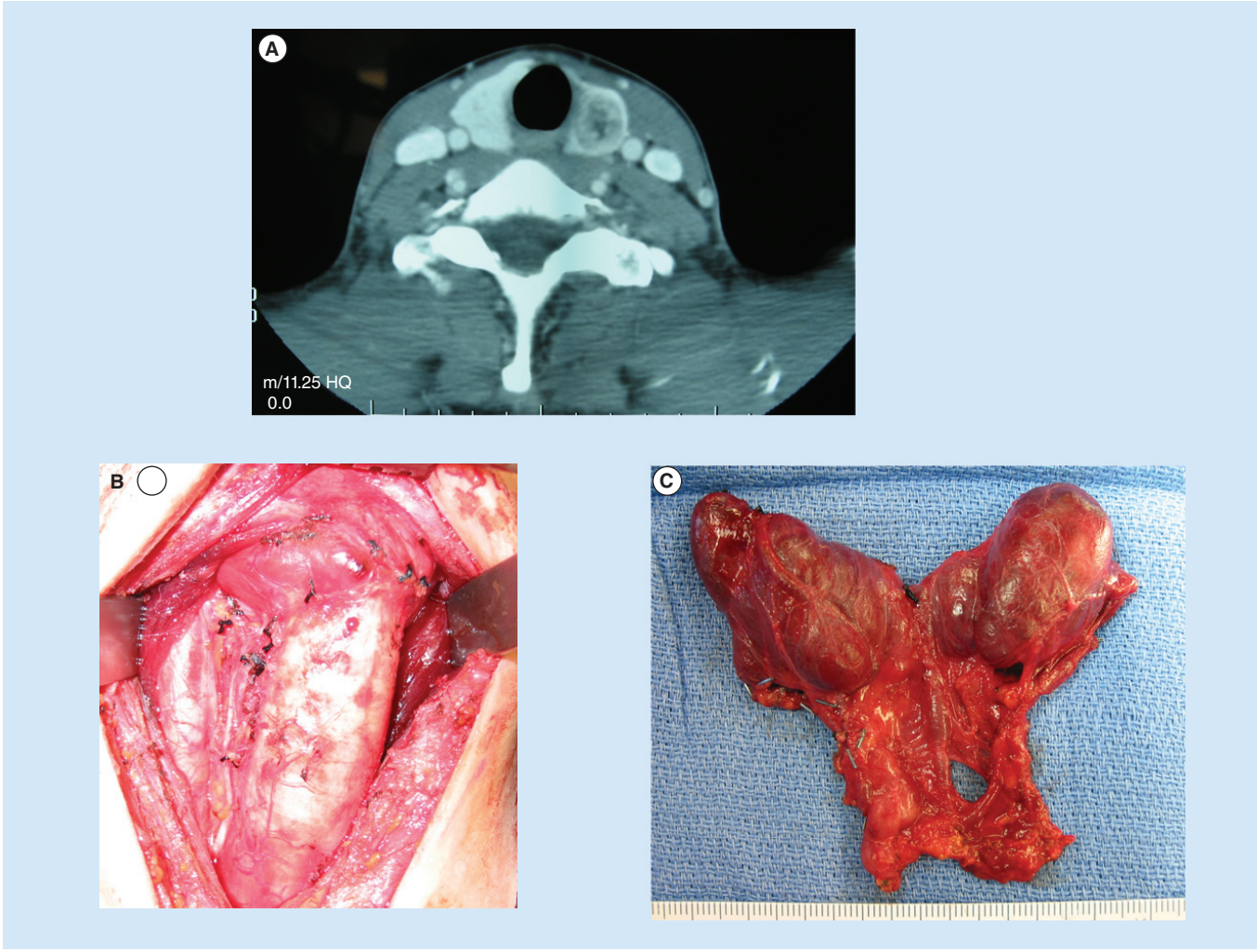


**Figure 3. Lymph node metastases in medullary thyroid carcinoma.** **(A)** Computerized tomography showing left-sided medullary thyroid cancer; **(B)** intraoperative photo showing the thyroidecomy and central neck dissection bed; **(C)** operative specimen after thyroidectomy and central neck dissection.

recurrence rates when retrospectively compared with procedures with removal of only grossly involved nodes ('berry picking') [24]. During this dissection, all thyroid and nodal tissue are removed from the level of the hyoid bone to the innominate vessels. All four parathyroid glands should be identified if possible. Central nodal tissue on the anterior surface of the trachea is removed, exposing the superior surface of the innominate vein behind the sternal notch. Fatty and nodal tissue between the carotid sheaths and the trachea should be removed, including paratracheal nodes along the recurrent nerves. On the right, the junction of the innominate and right carotid arteries is exposed, and on the left, nodal tissue is removed to a comparable level behind the head of the left clavicle.

MTC tumors sometimes involve the recurrent laryngeal nerve. If the nerve is functioning on preoperative laryngoscopy, attempts should be made to preserve it, though this is sometimes not possible. In cases where the nerve is not functioning at the end of the case, special care must be taken to preserve the contralateral normal nerve. If the patient has stridor postoperatively due to bilateral nerve dysfunction (which is not uncommon if one nerve is removed, and the other manipulated during thyroidectomy), airway patency can be achieved by one of several methods. These include keeping the patient intubated until the noninjured nerve recovers, using steroids and helium–oxygen mixtures to combat airway obstruction, and surgical lateralization of the nonfunctioning vocal cord on

the side of the resected nerve for effective temporary opening of the airway. It is not advisable to place a tracheostomy in a field where central nodes have just been cleared down into the upper mediastinum, as there will be no tissue between the innominate vessels and the tracheostomy. This can lead to leaks, mediastinitis and innominate blowout. If a tracheostomy must be done, a vascularized muscle pedicle should be placed between the tracheal opening and the innominate vessels to protect them.

Controversy exists over the optimal management of the parathyroid glands in operations for MTC. Some surgeons prefer to leave the parathyroid glands *in situ*, ensuring that the vascular pedicle is preserved [25,26]. Others routinely perform four-gland parathyroidectomy with autotransplantation and argue that adequate central node dissection is not possible if the parathyroid glands are left in place [27]. Although various approaches exist, it is important to emphasize that the individual surgeon should do whichever procedure he/she is most comfortable with to achieve a universal goal of preserving parathyroid function. Our approach is to resect the two parathyroids ipsilateral to the primary tumor and the contralateral inferior parathyroid, leaving the contralateral superior parathyroid intact on a vascular pedicle. Removed parathyroids are then minced into 1 × 3 mm fragments and transplanted into individual muscle pockets with two to three fragments per pocket. The pockets are then closed with a 4–0 suture [28]. Choice of muscle for transplantation is based on disease process. We use the sternocleidomastoid muscle in patients with sporadic MTC, FMTC and MEN 2B and the nondominant forearm in patients with MEN 2A, due to the risk of developing graft-dependent hyperparathyroidism. In MEN 2A patients who have concurrent hyperparathyroidism at the time of operation, a four-gland parathyroidectomy should be performed, with at least 100 mg of parathyroid tissue being transplanted. All residual tissue should be viably frozen [29]. The parathyroid autografts generally function well within 4–6 weeks, at which time calcium supplementation can be stopped.

### • Management of regional lymph nodes in clinically evident disease

Regional nodal metastases are present in the majority of patients with palpable MTC. Because these tumors do not take up iodine, nodal metastases cannot be ablated with radioactive iodine. Surgical clearance is the only effective strategy for eliminating these metastases [24,30–31]. Ipsilateral neck dissection, also called 'functional' or 'modified radical' neck dissection, in which all or portions of levels II, III, IV and V nodes are removed, should be considered in all patients with clinically evident MTC and especially in patients suspected to have locally advanced disease. At our institution, we evaluated the incidence and pattern of nodal metastases in patients with palpable MTC [22]. In this series, 73 patients with palpable MTC underwent thyroidectomy with concurrent or delayed central and bilateral cervical node dissection. The number and location of lymph node metastases in the central (levels VI and VII) and lateral (levels II–V) nodal groups were noted and correlated with the size and location of the primary tumor. In patients with unilateral intrathyroidal tumors, nodal metastases were present in 81% in central level VI, in 81% in ipsilateral levels II–V and in 44% in contralateral levels II–V nodal groups. In patients with bilateral intrathyroidal tumors, nodal metastases were present in 78% of central level VI nodal groups, in 71% of level II through V nodes ipsilateral to the largest intrathyroidal tumor and in 49% of level II through V nodes contralateral to the largest intrathyroidal tumor. This is an alarmingly high incidence of nodal involvement. In this same series, we found that intraoperative nodal assessment by the surgeon had a low sensitivity (64%) and specificity (71%) for detecting positive nodes [22]. Therefore, reliance on intraoperative assessment and a 'berry picking' strategy may miss clinically involved nodes up to a third of the time. If central nodes are positive on frozen section, it is an indication for further dissection of lateral nodes. However, it is not our practice to routinely use intraoperative frozen section and rely more on preoperative imaging characteristics and preoperative calcitonin as discussed above.

The burden of lymph node metastasis in the central compartment can help predict lateral compartment involvement. In one retrospective analysis, the presence of zero positive central nodes correlated with a 10% risk of metastatic involvement of ipsilateral level II–V nodes. However, the risk of lateral compartment involvement increased to 77% with one to three positive central nodes, and to 98% with four or more positive central nodes [32]. Contralateral level II–V metastases were observed in 4.9%

of cases when zero central nodes were positive, in 28% when one to nine central nodes were positive and in 77% of cases when ten or more central nodes were positive [32]. Therefore, the decision to perform lateral neck dissection is influenced by the extent of central compartment nodal involvement as well as preoperative imaging assessment. If extensive central node metastases are present, even with negative preoperative imaging, serious consideration should be given to performing an ipsilateral functional neck dissection given the high likelihood of microscopic nodal involvement. A recent study has also showed that in patients with preoperative basal calcitonin levels <200 pg/ml, the risk of contralateral neck involvement was low, but in patients who crossed that threshold, the risk of contralateral neck involvement increased significantly [33]. These data suggest that in addition to central compartment lymph node burden, the level of basal preoperative calcitonin may also help inform the decision of whether to perform a bilateral lateral neck dissection.

## Management of lymph nodes during preventative surgery for hereditary MTC

The goal of curative therapy for patients with hereditary MTC is complete surgical resection prior to malignant transformation or spread beyond the thyroid gland, regardless of calcitonin levels. RET mutation carriers often harbor foci of MTC in the thyroid gland even when stimulated calcitonin levels are normal [34–36]. A recent study in pediatric patients with hereditary MTC compared nine patients who had age appropriate thyroidectomy with 19 patients who had thyroidectomy at a later age according to North American Neuroendocrine Tumor Society guidelines. Patients who had age appropriate thyroidectomy were cured with no disease recurrence, while patients who had thyroidectomy past the recommended age had a 42% recurrence rate [37]. However, other groups have suggested that following patients with known hereditary disease using stimulated calcitonin levels may also be a safe way to individualize timing of surgery [38].

In MEN 2A and FMTC, the timing of thyroidectomy remains controversial. High-risk (level II) mutations associated with MEN 2A (codons 611, 618, 620, 634) should have thyroidectomy at or before age 5 or 6 years. An ipsilateral or bilateral central neck dissection (level VI) is additionally recommended in the presence of palpable or radiologically identifiable lymphadenopathy or elevation of calcitonin level >40 pg/ml. However, patients with low-risk mutations (level I) associated with MEN 2A and FMTC have extremely low risk of nodal metastasis in patients under the age of 8, or if the calcitonin level is <40 pg/ml [27]. For this reason, it is our practice to perform a total thyroidectomy, leaving the parathyroid *in situ* if the calcitonin level is <40 pg/ml and there is no evidence of nodal disease. Patients with elevated calcitonin level, a thyroid nodule over 5 mm in size (at any age), or with radiographic evidence of lymph node metastasis should undergo total thyroidectomy with central node dissection. An ipsilateral dissection of levels II–V should also be considered if the calcitonin is >40 pg/ml, and certainly should be done if there is ultrasound evidence of nodal metastases [33]. This operation should only be performed by surgeons familiar with thyroid and parathyroid operations in children [36]. We reported long-term follow-up results from a series of 50 pediatric patients with MEN 2A following thyroidectomy, central node dissection and total parathyroidectomy with autotransplantation [36]. Long-term disease control was excellent and long-term parathyroid function was normal (no supplementation) in 93% of patients. Other groups reported good results with selective removal of lymph nodes and parathyroids in young at-risk patients [34,35].

Highest risk (level III) mutations, associated with MEN 2B require a different approach. In these patients, thyroidectomy should be performed in infancy, as MTC is often already established at birth. Central neck dissection should be performed if the calcitonin level is elevated. This requires that the surgeon has identified and preserved the parathyroids, either by autotransplantation or preservation on an intact vascular pedicle. The consequences of hypoparathyroidism in an infant are disastrous, and all possible steps must be taken to avoid this. The parathyroid glands at this age are extremely small and translucent, and often obscured by prominent cervical thymic tissue, making identification difficult for even the most experienced parathyroid surgeon. If the surgeon is unable to identify and preserve the parathyroids, a central neck dissection should be deferred until a later age or a surgeon with more extensive experience is available. For both MEN 2A and 2B cases with concurrent

pheochromocytoma, the pheochromocytoma should be treated first.

## Management of recurrent or persistent disease

After primary surgery for MTC, persistent or recurrent elevation of the basal or stimulated calcitonin levels indicates the presence of residual or recurrent tumor. Patients with normal calcitonin levels following MTC surgery have achieved 'biochemical cure'. Patients with mildly elevated but stable serum calcitonin levels (<150 pg/ml) following adequate primary surgery have biochemical evidence of residual disease. MTC can be a very indolent disease, and many patients with persistently high levels of calcitonin after thyroidectomy and node dissection continue to do well without evidence of disease for many years. However, patients with more aggressive forms of MTC can have a rapidly progressive course. One series from Mayo Clinic reported a 66% mortality rate in node-positive patients with hereditary MTC after a median follow-up of 15.7 years [39,40]. Therefore, all patients should be followed with calcitonin levels measured postoperatively and semiannually thereafter.

Reoperation should be considered for patients with elevated calcitonin levels in the setting of an inadequate initial operation, imaging evidence of recurrent or persistent local disease, or for threat of compression or invasion of the trachea or major vessels. Reoperative surgery for locoregional disease, in experienced hands, can achieve long-term control and biochemical cure in up to a third of patients [41–44]. Metastatic workup is necessary before proceeding with neck reoperation with curative intent. Palliative tumor debulking procedures are helpful in patients who have pain, systemic symptoms of flushing and diarrhea, or those with tumor that threatens to cause airway or vascular compromise.

A significant reduction in stimulated calcitonin levels after reoperation can be achieved through a thorough microdissection. This involves a meticulous dissection of all lymph node and fatty tissue of the central and lateral zones of the neck, including the thyroid bed, both recurrent nerves, and nodes of the lateral neck, extending from the level of the mastoid process down to the innominate vein and subclavian arteries and out laterally to the level of the spinal accessory nerve. In some cases, a median sternotomy and resection of upper mediastinal nodes may also be necessary. Previously, we reported two series of reoperations for MTC. In the first series, 37 reoperations were done in 32 patients. In 28% of patients, calcitonin was reduced to undetectable levels following reoperation, and in an additional 42% of patients, calcitonin levels were decreased by 40% or more [45]. In the second series, we sought to improve our results through better selection of patients most likely to benefit from reoperation. This was achieved by obtaining a systematic metastatic workup prior to reoperation, including routine staging laparoscopy [46,47]. In 45 patients who had reoperation with curative intent, the mean decrease in postoperative-stimulated calcitonin level was 73%, and in 86% of patients, postoperative-stimulated calcitonin levels were within the normal range or lower. More recently, we reported the long-term follow-up results after reoperation. Of the 56 patients with 8–10-year follow-up data, 25 (46%) had normal or stable basal calcitonin levels and no radiologic evidence of disease recurrence [40,44]. These results support the use of a systematic microdissection approach to reoperation in patients with a persistent or recurrent elevation of calcitonin levels after surgery for MTC.

Re-exploration of the neck carries a higher risk of complications, including thoracic duct leak, injury to the recurrent laryngeal nerve and hypoparathyroidism. Use of intraoperative nerve monitoring devices and bipolar cautery in redo surgery is helpful. In children, central neck reoperations are especially dangerous due to the small size of the parathyroids. These should be avoided unless bulky central disease threatening the airway or the great vessels makes the operation absolutely necessary. A 'back-door' or lateral approach helps to facilitate redo central neck dissection. This operation has been described in detail by our group elsewhere. In this procedure, the strap muscles are mobilized off the carotid artery and the space between the carotid and the trachea is entered through a previously undissected tissue plane [48–50]. As always, it is imperative to identify the recurrent laryngeal nerve and parathyroids to ensure safe removal of recurrent or residual central disease and lymph nodes [48–50]. Preoperative imaging, clinically palpable nodes and presence of central compartment lymph node disease should be used as indications for lateral neck dissections (levels II–V).

## Conclusion

The propensity for MTC to metastasize to cervical lymph nodes is a defining feature of this disease that informs surgical management in all clinical settings: prophylactic surgery in RET mutation carriers, primary operations for established tumors, reoperations for persistent and recurrent disease, and palliative procedures for symptomatic tumors. Eradication of involved nodes can result in long-term cure or disease control. A working knowledge of cervical lymph node anatomy and the natural history of MTC spread within these nodal groups is important to surgeons managing these patients. The parathyroid glands are intimately related to the central nodes. Careful, correct management of the parathyroid glands in these situations will minimize the risk for hypoparathyroidism, which especially must be avoided in young children.

## Future perspective

The propensity for MTC to metastasize to cervical lymph nodes is a defining feature of this disease that informs surgical management in all clinical settings: prophylactic surgery in RET mutation carriers, primary operations for established tumors, reoperations for persistent and recurrent disease, and palliative procedures for symptomatic tumors. Eradication of involved nodes can result in long-term cure or disease control and is currently the treatment option of choice. Reoperation should be considered for patients with persistently or recurrently elevated calcitonin levels after primary surgery. However, although it is outside the scope of the current review, promising advances in targeted systemic therapy are an exciting area of development in the treatment of MTC. Radioactive iodine, external beam radiation therapy and traditional chemotherapy agents are not effective treatment modalities for progressive advanced MTC. In the future, the availability of effective systemic therapy such as small molecule tyrosine kinase inhibitors may obviate the need for reoperation in patients with recurrent disease. Though newly approved systemic therapies targeting RET tyrosine kinase activity have shown promising results in treating disease progression, further work is needed to fully understand the role in the treatment for advanced disease.

## Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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