Medullary thyroid carcinoma – update and present management controversies

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ABSTRACT

INTRODUCTION Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy arising from the parafollicular C cells. It accounts for 5–10% of thyroid malignancies and occurs in sporadic and hereditary forms. There are still many controversial aspects relating to the diagnosis and management of this unusual tumour in its various forms. The present article addresses the more important of these issues.

METHODS A literature review was performed using Pubmed database combined with additional original papers obtained from citations in those articles identified in the original literature search. Only those articles which related specifically to the controversial issues addressed in this review were included.

RESULTS Genetically determined tumours constitute approximately 25% of MTC and have special clinical interest because of their association with other endocrinopathies including pheochromocytoma and hyperparathyroidism in the multiple endocrine neoplasia syndromes (MEN IIa and MEN IIb). Familial medullary thyroid carcinoma (FMTC) is a rare form not associated with any other endocrinopathies. The genetic basis for these familial tumours derives from a series of missense germline mutations in the RET proto-oncogene. Genetic testing by DNA analysis facilitates identification of family members at risk who can now be offered early 'prophylactic thyroidectomy' with an increased prospect of surgical success and long-term survival. MTC is a tumour which does not take up radioactive iodine, is relatively radioresistant and poorly responsive to chemotherapy. Therefore, surgery is the only treatment which can offer the prospect of cure. Total thyroidectomy with central and lateral nodal dissection can achieve biochemical cure (normocalcaemia) in more than 80% of cases. Compartmental orientated microdissection of cervical nodes has significantly improved the results of primary surgery but even so a group of 20% of patients will prove to have recurrent or residual disease. These cases require detailed investigation by a variety of techniques including ultrasound, cross-sectional imaging, nuclear imaging and laparoscopy with liver biopsy to exclude disseminated disease and select those patients who can be offered a prospect of cure by further neck surgery. Such an approach may be associated with successful normalisation of calcitonin levels in about 40%.

CONCLUSIONS It is hoped that in the near future new medical therapies may become available to treat MTC which still has a 10-year survival of only 60–80% in spite of the application of meticulous surgical techniques.

KEYWORDS

Medullary thyroid carcinoma – Sporadic – Genetic – Current therapy

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Medullary thyroid carcinoma (MTC) arising from the parafollicular C cells continues to provoke a degree of interest and controversy concerning management, out of proportion to its incidence. This tumour accounting for about 5–10% of all cases of thyroid carcinoma was initially described at the turn of the 20th century in the German literature as 'malignant goitre with amyloid'.¹ The definitive description was provided by Hazard *et al.*² in 1959 referring to the tumour as 'solid non-follicular carcinoma with co-existing amyloid'. Williams^{3,4} further defined the histology of the tumour in 1966 and suggested that the thyroid parafollicular C cells, derived from the neural crest, were the cells of origin of the growth. C cells

have the ability to produce and secrete calcitonin, a most valuable immunohistochemical and biochemical marker for MTC, but also have the potential to secrete a multitude of other hormones and humoral agents.

On rare occasions, excessive secretion of ACTH from this tumour may result in the dramatic clinical picture of Cushing's syndrome.⁵

The severe diarrhoea seen in some patients with advanced extensive disease has been attributed to prostaglandin secretion by the tumour.⁶

Although approximately 75% of cases of MTC are of a sporadic variety, it is the remaining 25%, genetically deter-

mined as part of the MEN IIa, MEN IIb, or FMTC syndromes which have in recent years created special challenges for the endocrine surgeon.⁷ The multiple endocrine neoplasias type IIa, IIb (MEN IIa and MEN IIb) and also familial medullary thyroid carcinoma (FMTC) are characterised by bilateral multifocal MTC invariably in a background of C-cell hyperplasia, the inherited predisposing abnormality.

Phaeochromocytomas, frequently bilateral and multiple, occur in 35–50% of MEN IIa and MEN IIb. Hyperparathyroidism due to multigland disease, often asymmetrical, develops in about 25% of cases of MEN IIa but is never seen in MEN IIb. Very characteristic phenotypic abnormalities are found in MEN IIb and these include mucosal neuromata and ganglioneuromas typically in the lips, tongue, buccal membranes, conjunctivae and lacrimal regions, gastrointestinal tract resulting in megacolon, skeletal abnormalities, marfanoid habitus without the cardiac abnormalities, and hypertrophied peripheral nerves typically seen in the cornea. None of these associated endocrinopathies occur in FMTC.

In these familial settings, MTC is a malignant tumour whose inheritance is autosomal dominant with high penetrance and variable expressivity for the other neoplastic features of the syndromes.⁸

The discovery and delineation of a series of missense mutations in the extracellular and intracellular domains of the RET proto-oncogene on chromosome 10 provided the spectacular advance of DNA analysis and testing to facilitate identification of family members at risk for inheriting these syndromes.^{9,10} Inevitably this provided the possibility of performing 'prophylactic thyroidectomy' before the development of thyroid cancer in individuals who had inherited the mutation.

Medullary thyroid carcinoma is a heterogeneous disease in terms of biological behaviour with a clinical course which is extremely variable and unpredictable. Overall, the tumour is more aggressive than differentiated thyroid cancer arising from the thyroid follicular cell. FMTC and MEN IIa are thought to have the most favourable prognosis and MTC in the setting of MEN IIb syndrome the least.¹¹ Patients with sporadic MTC may have a less favourable prognosis than FMTC and MEN IIa although the earlier diagnosis of hereditary cases by biochemical screening and mutational analysis may be a significant factor influencing the comparison.

The molecular background of these types of MTC are very different and, in inherited tumours, there is a clear correlation between genotype and phenotype.¹² At the present time, differing phenotypes in patients sharing identical genetic mutations remain unexplained. The neurotrophic ligands for RET which include glial cell-derived neurotrophic factor (GDNF) activate a series of different signal transduction pathways ultimately modulating tumour cell growth. The downstream influence of other genetic factors may account for some of the variability seen in clinical tumour behaviour occurring in patients who have identical RET mutations.¹⁵

Surgery is the only effective treatment for MTC as this is a tumour which is not usually responsive to chemotherapy or external radiation. Radioactive iodine is ineffective as C cells are incapable of taking up the agent and, in contrast to differentiated papillary thyroid carcinoma, administration of L-thyroxine and TSH suppression are of no value. Not surprisingly many of the most important controversies concerning the management of MTC relate to surgical issues such as extent and timing of intervention.

Extent of thyroidectomy

Because this tumour is multifocal and bilateral in virtually all patients with hereditary disease and in at least 20% of patients with sporadic disease, total thyroidectomy has been the logical treatment of choice. Although multifocality and bilaterality is less frequent in sporadic tumours compared with those in an hereditary setting, it is well recognised that intraglandular lymphatic spread can also occur in sporadic disease. Furthermore, at the time of performing primary surgery, it may not always be apparent whether one is dealing with hereditary or sporadic disease. When there are no positive clinical indicators of familial disease (*e.g.* bilateral disease or a positive family history), subsequent genetic mutational analysis will reveal that the patient is an index case of MEN IIa in up to 16% of cases.¹⁴

However, in spite of these observations, it has been argued that when pre-operative mutational analysis has shown no RET germline mutation there may be a case for performing only hemithyroidectomy and isthmusectomy. In a group of highly selected patients with sporadic tumours, Miyauchi and colleagues¹⁵ were able to demonstrate that successful outcome and biochemical cure with a normal postoperative calcitonin level were not compromised by performing unilateral resection. However, 18.3% of their series had intraglandular metastatic spread but these were all cases noted to have extensive nodal metastases. Such nodal disease or tumour extending beyond the isthmus were considered to be indications for total thyroidectomy.

The incidentally discovered MTC may also prove to be a special case. Raffel and colleagues¹⁶ proposed that complete total thyroidectomy and neck dissection might not be necessary when a small pT1 tumour is incidentally identified by postoperative histology of a thyroid gland removed for other reasons, providing hereditary disease is excluded by DNA analysis.

As MTC occurs in 0.6% of thyroid nodules,¹⁷ it has been suggested that all patients undergoing assessment for nodular thyroid disease should have at least basal calcitonin measurement in order to avoid the undesirable surprise of the incidentally discovered MTC.¹⁸ However, an elevated calcitonin level does not always indicate MTC and cannot distinguish between C-cell hyperplasia and tumour especially when only mildly raised.

In the series reported by Kraimps and colleagues,¹⁹ 38 of 67 patients with raised calcitonin levels undergoing thyroidectomy for nodular disease did not have MTC but 30 of these did have C-cell hyperplasia. It was recommended that a pentagastrin-stimulated calcitonin level should be measured in all patients with only a mildly raised basal calcitonin. These data from two French groups clearly have considerable significance with regard to the assessment of thyroid nodular disease.

At present, surgical excision is the only effective treatment for MTC. Therefore, a universal strategy of performing total thyroidectomy as the primary operation in clinically overt tumours seems the safest option most likely to offer the best chance of cure.

It must be emphasised that it is mandatory that all patients undergoing surgery for MTC should have pre-operative measurement of urinary catecholamines in order to exclude a pheochromocytoma, even when there is no specific evidence to suggest the thyroid tumour is of the hereditary variety. The major surgical procedure of thyroidectomy on a patient with an undiagnosed and, therefore, unprepared pheochromocytoma is likely to precipitate a physiological disaster. If excessive catecholamine secretion is demonstrated, adrenal surgery after appropriate adrenergic blockade should be performed before thyroidectomy.

Extent of lymph node dissection

MTC has a phenomenal propensity for spread to regional lymph nodes in addition to its ability to metastasise to bone, liver and lungs. Notwithstanding the enormous variation seen in clinical outcome between different types of MTC (sporadic versus hereditary), there is also frequently vastly different tumour behaviour within members of the same MEN family.

Prognosis is most accurately predicted by TNM tumour classification and the presence of lymph node metastases has a dominant influence on survival. A report from the Mayo clinic indicated that two-thirds of hereditary MTC patients with positive nodes ultimately died of their disease and no patient with positive nodes had a normal postoperative calcitonin level after a median follow-up of 15.7 years.²⁰

Previously, many studies of patients who had not undergone systematic cervical lymph node dissection at the time of primary surgery underestimated the true incidence of lymph node metastases. In an historical series of 60 cases treated for MTC in Cardiff, only 51% underwent a formal cervical lymph node dissection. This reflects early clinical practice before the pathology and natural history of MTC were understood. Therefore, the true incidence of nodal disease in these cases treated by thyroidectomy alone would have been grossly understated, (Al-Rawi M and Wheeler MH, unpublished data).

It is now known that when the primary tumour is palpable, the case in the majority of sporadic patients and index MEN

cases, nodal metastases occur in more than 70%.²¹ This is in marked contrast to the cases detected by genetic screening where positive lymph nodes are extremely rare.²² In spite of these observations, the issue of the extent of surgical nodal dissection remains controversial.

Dralle²³ has popularised the concept of 'compartmental hierarchy' of local regional lymph node involvement in MTC and has proposed a compartmental classification consisting of right cervicocentral (C1a), left cervicocentral (C1b), right cervicolateral (C2), left cervicolateral, (C3) right upper mediastinal, and (C4a) left upper mediastinal (C4b).

The cervicocentral compartments extend from the hyoid bone superiorly to the brachiocephalic vein inferiorly and are flanked laterally by the carotid sheaths. Included within these compartments are the pretracheal and paratracheal lymph node chains.

The cervicolateral compartments extend from the mastoid processes superiorly to the subclavian veins inferiorly and are essentially triangular regions bounded by the internal jugular veins medially and the trapezium muscles laterally. The principal nodal groups are those in relation to the jugular vein and those within the posterior triangle of the neck. The mediastinal compartments extend from the infrabrachiocephalic level to the tracheal bifurcation.

This elegant, yet simple, classification is more meaningful when applied to medullary thyroid carcinoma than the classical Robbins' level classification previously used for other tumours in the head and neck including squamous cancer and melanoma. The 'compartmental hierarchy' concept facilitates a better understanding of the disease and its potential for spread and, thereby, offers the surgeon a sound and logical premise upon which to base surgical strategy.

The rate of lymph node metastases correlates with the pT category of the TNM classification in patients undergoing primary surgery for MTC.²⁴ The central compartment nodes will be positive in about one-third of even pT1 cases with tumours less than 1 cm in size. As tumour stage rises there is an increasing incidence of metastases in the contralateral central neck, ipsilateral lateral neck and contralateral lateral neck compartments. It is extremely unusual for metastatic spread to occur to the lateral nodes without first involving the ipsilateral central nodes. Mediastinal nodal involvement will be found in about 50% of pT4 cases.

Surgical excision is the only effective therapy for these metastases. Therefore, these data dictate a positive and structured approach to the cervical nodes at the time of the total thyroidectomy procedure.

The central neck compartments (C1a, C1b) should be dissected in all pT1 tumours. If central disease is sufficiently gross to be apparent either on ultrasound or intra-operatively, both lateral nodal compartments should also be dissected. The lateral nodal dissection should be performed with preservation of the spinal accessory nerve, sternomas-

toid muscle and internal jugular vein unless any of these structure are actually invaded by tumour.

All pT2–4 tumours should be treated by complete central and bilateral lateral compartmental excision. These guidelines apply to sporadic tumours but even more so to hereditary tumours with their virtually universal propensity for bilateral pathology.

However, it has been proposed that a decision whether or not to perform lateral nodal dissection in sporadic disease should be based on intra-operative nodal biopsy results.⁷ This approach is obviously subject to potential sampling errors. Inadequate nodal surgery at the time of the primary thyroidectomy procedure is a potent cause of surgical failure and recurrent disease.

Although a strategy of resecting only significant and clinically involved nodes may, at times, be reasonable in the treatment of differentiated thyroid carcinoma where there are back up treatment modalities including radioactive iodine, such a conservative policy has no place in the management of MTC, a tumour which does not take up radioiodine.

The initial surgical intervention is the golden opportunity for both patient and surgeon to achieve a cure.

Based on the above considerations, Dralle²⁵ has advocated a microsurgical *en bloc* dissection technique of the nodal compartments and shown that biochemical cure with a normal postoperative calcitonin level can be achieved in 100% of pT1 and more than 80% of pT2/pT3 sporadic tumours; a marked improvement on previous historical data.

When there is suspected mediastinal nodal disease, selected cases will require a median sternotomy and mediastinal dissection. This situation is most common in pT4 disease but, even with an aggressive surgical strategy, postoperative normalisation of the calcitonin level is unlikely.

Biochemical cure is the best marker, at present, of a successful surgical outcome but it is not yet known whether an aggressive nodal clearance even though accompanied by an improved postoperative normocalcitemia rate will ultimately lead to fewer distant metastases and longer survival.

The surgeon often faces the dilemma of the patient with MTC who has obvious or suspected metastatic disease at presentation. Although at this stage one cannot predict the likely clinical course, it is well recognised that some patients may have indolent disease and survive for years in spite of the metastases.²⁶ However, inadequately treated local disease may progress to severe morbidity with invasion of adjacent organs including oesophagus, jugular veins, carotid arteries, trachea and recurrent laryngeal nerve. Therefore, a positive approach is required with respect to the cervical pathology the policy being to control local disease by total thyroidectomy and selective nodal excision.

Surgery for residual and recurrent disease

Although the application of total thyroidectomy and systematic nodal microdissection has made a significant impact on the

biochemical cure rate there remains a group of about 20% of patients, frequently those who had nodal metastases at the time of the initial surgery, who have residual or recurrent disease as evidenced by a positive postoperative basal or stimulated calcitonin level.

The clinical course of such patients is variable, dependent upon the aggressivity of the individual tumour. Many patients with raised calcitonin levels after thyroidectomy may do well for years before eventually succumbing to the disease. Therefore, some workers have advised a conservative ‘watch and wait’ approach, not advising surgical re-intervention unless there are impending local complications.²⁶ Others have advanced a more active approach but often with little success.

Tisell and his colleagues²⁷ were the first to report improved results using a meticulous microdissection technique although they were still only able to restore the calcitonin level to normal in 4 of 11 cases. Later, in a further series of 32 re-operative cases, Moley *et al.*²⁸ achieved a 28% rate of postoperative normocalcitemia.

Clearly, the success of re-operative surgery in the neck is absolutely dependent upon excluding metastatic disease elsewhere. Although there is a plethora of localisation techniques available, few possess adequate sensitivity for precise diagnosis. Ultrasonography of the neck is a valuable modality and will facilitate a confirmatory biopsy. Cross-sectional imaging with CT and/or MRI is helpful but not specific. There are also numerous nuclear imaging methods available including MIBG (*meta*-iodobenzylguanidine), DMSA (dimercaptosuccinic acid), octreotide, anti-CEA monoclonal antibodies and FDG-PET (fluorodeoxyglucose positron emission tomography). Unfortunately, these all have less than ideal sensitivity and, therefore, limited utility.

More specific and sensitive methods are invasive and include selective venous catheterisation (SVC) and sampling for calcitonin in order to exclude or identify a calcitonin source outside the neck.

Laparoscopy and guided liver biopsy obviate the problem created by many liver deposits which are small, multiple, military and situated on the surface of the liver thereby making them virtually impossible to detect by conventional imaging and scintigraphy.

Moley *et al.*²⁹ utilised a systematic work-up and routine staging laparoscopy in order to more carefully select patients with persistent disease who would be likely to benefit from re-operation. From an initial group of 115 patients, 45 were selected to undergo 51 operations. Stimulated calcitonin levels were restored to normal in 17 (38%). It was concluded that this increased success resulted from a policy of detailed pre-operative staging and patient selection coupled with a meticulous systematic re-operative surgical technique.

Applying almost identical principles and methods but including liberal mediastinal nodal dissection, Gimm and Dralle³⁰ reported similar re-operative biochemical cure

rates. It was noted that no patient with extrathyroidal tumour could be cured biochemically.

Although MTC is not very radiosensitive occasionally external DXR can be used to treat recurrent cervical disease for which it is no longer possible to perform further neck surgery. Good control of local disease and relief of symptoms may sometimes be achieved. But the most valuable application of DXR is for painful bony metastases.

Symptomatic distant metastases may also be amenable to a direct surgical approach. We have successfully carried out excision of bony metastases and performed lung resections with excellent palliation (Al-Rawi M and Wheeler MH, unpublished data).

Preventative thyroidectomy

In hereditary MTC (MEN IIa, MEN IIb, FMTC), C-cell hyperplasia is the genetically determined precursor which subsequently progresses to frank MTC in virtually all cases. Obviously, C-cell hyperplasia has the best prognosis and advanced medullary malignancy the worst. Therefore, detection of the disease at the pre-malignant C-cell stage has been the major clinical objective since the first descriptions of the familial syndromes.

Initially, screening of family members at risk was based on measurement of calcitonin levels after stimulation by pentagastrin and/or calcium. Such testing had the distinct disadvantage of being unpleasant for the patient, required annual testing until at least the fifth decade and did not possess the sensitivity to discriminate between C-cell hyperplasia and tumour. Furthermore, it was soon recognised that some individuals might have a normal stimulated calcitonin result but still be found subsequently to have MTC.³¹ Also, because of the autosomal dominant nature of the disease inheritance, approximately 50% of the family members would not be at risk of MTC development and, therefore, undergo years of unnecessary testing. Nevertheless, patients detected by biochemical screening either as probands or later converters certainly had a higher rate of biochemical and clinical cure after a timely thyroidectomy.

Identification of the RET proto-oncogene mutations responsible for inherited MTC provided a dramatic breakthrough which soon paved the way for genetic screening using DNA analysis. Early series of young patients submitted to 'prophylactic total thyroidectomy' based on genetic testing, many with normal calcitonin levels, clearly demonstrated the potential benefits of this approach.³²

In a study from Germany and Austria of 75 children and adolescents with hereditary medullary thyroid carcinoma undergoing prophylactic thyroidectomy, C-cell disease (either hyperplasia or even frank MTC) was found in up to 61% and lymph node metastases in 4%.³³ Nevertheless, early follow-up data testify to the efficacy of 'prophylactic

thyroidectomy' with the prospect of an extremely high cure rate. Longer follow-up and, of course, continued surveillance for the development of pheochromocytoma will be required to assess the true benefits.

Many important questions arise, not the least being when should prophylactic thyroidectomy be performed? The very fact that some patients undergoing thyroidectomy based on genetic testing already had microscopic disease means that surgery was not truly 'prophylactic' but early therapeutic. This is an issue which strikes at the very heart of the timing of both testing and subsequent surgery. Genetic analysis should be performed at the earliest possible opportunity and, in the case of MEN IIb cases, blood taken from the umbilical cord at birth. The present consensus is that MEN IIa and MTC patients detected in childhood should undergo thyroidectomy by 6 years of age. In the case of MEN IIb children, surgery should be performed in the first year in view of the aggressive nature of the disease. No biochemical cure is likely if surgery is left until the 'teens'.

How extensive should nodal surgery be in these young subjects? It would seem that nodal metastases are extremely uncommon in children under 10 years of age. It has, therefore, been suggested that, provided calcitonin levels are normal, central lymph node dissection is not required in children up to age 10 years.³⁵

Therefore, early surgery not only offers the potential reward of removing a thyroid gland before MTC has developed but also permits a strategy which does not involve lymph node dissection in the central compartment with all its attendant risks of damage to small paediatric parathyroid glands and recurrent laryngeal nerves.

More extensive dissections including lateral compartments and occasionally even mediastinal will be required in older children, those with clinically involved nodes and those with elevated calcitonin levels.

Advising prophylactic surgery in such young patients places a great responsibility on the surgeon who must be sure that thyroidectomy in these circumstances can be performed with a low complication rate. Present results suggest that the incidence of permanent hypoparathyroidism and recurrent laryngeal nerve injury is comparable to that seen in adult operations.³⁵

The future

1. Refinement of genetic testing should allow positive patients to be categorised into low- and high-risk groups based on the precise mutations identified. Guidelines for optimal timing of surgery will then be possible.
2. The correlation of genotype and phenotype already permits identification of patients who are likely to develop pheochromocytoma and hyperparathyroidism as part of the MEN IIa syndrome.

3. MTC is an excellent model to illustrate the concept of interventional therapy based on genetic analysis, a trend which is likely to continue in other areas of surgical oncology.
4. There is also the hope that medical, non-surgical measures may be developed to treat MTC. Already trials of pharmacological agents to produce tyrosine kinase receptor blockade are underway (Moley JF, personal communication).
5. Other manipulations of genetic mechanisms await development.¹⁵

Implementation of these exciting advances with continued refinement of meticulous surgical technique will hopefully impact favourably upon the present overall 10-year survival rate of about 65%.⁷

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