West Yorkshire & Harrogate Cancer Alliance

Guidelines on the Management of Medullary Thyroid Cancer (MTC)

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i Document Control

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Contributors to current version		
Contributor	**Author/Editor**	**Section/Contribution**
G Gerrard & YCN Thyroid NSSG	Former YCN Thyroid NSSG	General
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ii Information Reader Box

Title	Guidelines on the Management of Medullary Thyroid Cancer (MTC)
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iii Table of Contents

1.1 Pre op investigations when FNAC suggests MTC

1.1.1 Blood & urinary tests;

- Calcitonin
- CEA
- Corrected calcium
- Two 24 hour urine collections for catecholamines or plasma metanephrines

1.1.2 Scans (see appendix);

- initially request "CT neck, chest, abdomen & pelvis with dual phase contrast liver scan"
- iodine 123 mIBG scintigraphy in patients with supected nodal disease and / or phaeochromocytoma (time permitting)

MTC commonly metastasises to nodes, lungs, liver and bone (if bone pain present or abnormal bone biochemistry, consider investigations for bone mets – see appendix)

The above tests are performed to

- assess the extent of surgery required (by staging the cancer)
- exclude a phaeochromocytoma and primary hyperparathyroidism (pHPT) pre –op
- glean prognostic information

- in USA look for RET gene pre op to guide extent of surgery

1.2 Types of medullary thyroid cancer

1.2.1 Sporadic

1.2.2 Familial

a) as part of multiple endocrine neoplasia type 2A (MEN2).
b) as part of multiple endocrine neoplasia type 2B (MEN3).
c) as familial medullary thyroid cancer without other endocrine disease (FMTC) but now viewed as a phenotypic variation of MEN2A with reduced penetrance for phaeochromocytoma and primary hyperparathyroidism (pHPT). Inheritance of MTC in isolation is very rare.

The tumour is most indolent in FMTC and most aggressive in MEN2B.

The familial forms are inherited autosomal dominant conditions - there is a 50/50 chance of any child of an affected parent inheriting the condition.

50% present with advanced disease.

75% of patients with palpable primaries have lymph node involvement.

Suspect in -

1. Upper pole tumour.
2. Painful/tender thyroid lump.
3. Family history for diarrhoea.

All patients should be referred to a geneticist - absence of family history does not preclude the patient from being the index case for a new kindred.

Important prognostic factors

- Pre and post operative calcitonin.
- Calcitonin and CEA doubling times.
- Size of primary.

1.3 Treatment of MTC

1.3.1 Surgery

Surgery should be centralised in Leeds and MTC patients should be referred to JW or ML.

a) **If medullary thyroid cancer is diagnosed pre operatively**

1. Minimum of total thyroidectomy and level VI/VII neck dissection - if no palpable or radiologically suspicious nodes (even if there are distant metastases but only a limited amount of mets). Consider ipsilateral prophylactic selective lateral neck dissection if high risk of / positive central neck nodes.
2. Total thyroidectomy, level VI/VII neck dissection and selective lateral neck dissection if there are suspicious nodes in the lateral neck on palpation or ultrasound (even if limited distant metastases).
3. Consider palliative/debulking surgery/thyroidectomy if advanced local or distant disease with the aim of providing good local control and preservation of speech and swallowing. A level VI/VII neck dissection may or may not be required but the risks of hyperparathyroidism should be avoided if possible.

A level VI/VII neck dissection is recommended in the first two situations above, because there is a high rate of lymph node involvement in this level which are not all detectable by ultrasound or palpation and re operation is associated with a higher complication rate.

b) **If MTC diagnosed post operatively after lobectomy**

Consider completion thyroidectomy and level VI/VII neck dissection +/- ipsilateral prophylactic selective lateral neck dissection if, tumour multifocality, c cell hyperplasia, thyroid capsule invasion, positive margin, nodal metastases, family history of MEN2, Ultrasound suspicious of central node metastases or contralateral tumour, raised calcitonin or RET mutation.

There is absence of data and decisions should be made on an individual basis weighing the risks and benefits.

1.3.2 Radionuclide therapy

Iodine mIBG therapy – approximately 30% of MTC take up enough mIBG for therapy and this should be considered for inoperable and or metastatic disease.
Lutathera therapy should also be considered if sufficient uptake.
Radioiodine has no role in medullary thyroid cancer.

1.3.3 Biological therapy

has a role in palliation and considered in preference to chemotherapy. For more information see BTA 2014 guidelines.

1.3.4 Chemotherapy

has a very small role in palliation and now rarely used for MTC. Chemotherapy could be offered to patients with symptomatic rapidly progressing disease with fast calcitonin doubling times. These patients should not be amenable to clinical trials or other palliative therapies e.g. MIBG treatment, embolisation or radiofrequency ablation.

1.3.5 External beam radiotherapy

Radiotherapy is controversial & consider each case individually. Plan for RT if the surgeon thinks there is significant residuum which cannot be removed by a second operation.
External beam radiotherapy may increase local control in high risk patients e.g. inoperable, macroscopic residual disease (R2 resection).
Consider if previous large volume disease and R1 resection or residual extra nodal soft tissue extension when post op calcitonin raised in absence of distant mets.
Need > 2 month post operative calcitonin and CEA before decision is made.
Note that it can take several months for calcitonin to fall after surgery.

1.3.6 Other palliative treatment

For more information see BTA 2014 guidelines.

1.3.7 Management of post op patients

An elevated but stable calcitonin maybe managed conservatively, provided treatable disease has been excluded radiologically. Rising calcitonin should trigger imaging.

a) **Investigation of modestly elevated post operative calcitonin**

- Ultrasound neck and no further investigations initially or perform the following base line tests;
  CT neck, chest, abdomen & pelvis with dual phase contrast liver scan,
  bone scan / MRI spine & pelvis.
  If all these scans are negative or inconclusive for a FDG PET-CT.
  If the PET-CT is normal, consider mIBG scintigraphy (unless already performed recently), and / or Indium – 111 Octreotide scintigraphy or Gallium 68 Somatostatin Receptor PET-CT (if available). If the mIBG or Octreotide scans show tumour uptake – consider radionuclide therapy.

b) **Investigation of a significantly elevated post operative calcitonin**

- all the above tests in section 'a' are recommended.
  Empirical liver biopsies and hepatic venous sampling are not recommended.

If a suspicious node is found on the above scans but is < 1 cm in diameter and no distant metastasis are seen then the choice is observation or re operation. If there are distant metastases then observation is recommended rather than re operation.

If there is a suspicious node that is > 1 cm or the patient is symptomatic or the disease is

progressing (and there are no distant metastases) then consider surgery.

If there are distant metastases then to consider palliative treatment and clinical trials.

Very occasionally patients can have **progressive disease with no measurable calcitonin** and very occasionally can have tumours that do not produce calcitonin or CEA these are more likely to be poorly differentiated medullary thyroid cancers.

Calcitonin positive but image negative

Follow up intervals should be judged individually based on disease behaviour and doubling times. Calculate the calcitonin and CEA doubling times by performing six monthly blood tests. At least 4 values are required to calculate doubling times via an on line calculator. These are predictive of the rate of progression and useful to determine the interval of follow up. If there are long doubling times then annual follow up would be reasonable but if doubling times are short then recommend approximately six monthly follow up. If calcitonin & CEA have risen since previous anatomical imaging, repeat ultrasound neck. If calcitonin is significantly high perform other tests as above in section 'a'.

1.4 Follow up of MTC patients

Follow up by endocrinologist +/- surgeon if calcitonin normal.

Follow up by endocrinologist and oncologist if calcitonin raised/metastasis/advanced local regional disease and metastasis likely but not yet discovered.

Patients should have at least annual calcitonin, CEA and calcium tests. If a patient has a familial type of MTC, and residual adrenal tissue, they also need 24 hour urine collections for metanephrines (or plasma metanephrines) & 6 to 12 monthly monitoring of blood pressure. In some patients, urinary metanepharines are normal but plasma metanephrines are raised & the later should be performed annually (bilateral phaeos can occur).

1.5 Appendix

Rationale for radiological investigations

1.5.1 Initial staging (ideally to be done pre op but MTC not always suspected)

MTC commonly metastasises to nodes, lungs, liver and bones.
Request "CT neck, chest, abdomen & pelvis with dual phase contrast liver scan"

- neck scan to look for nodes,extent of primary tumour & bone mets
- chest scan to look for lung mets, mediastinal nodes & bone mets
- abdomen / pelvis scans to look for phaeos, liver mets & bone mets
- bone scan / MRI spine & pelvis if bone pain present or abnormal bone biochemistry to look for bone mets
- (Time permitting for a mIBG scan to look for nodes or phaeo or if the above

scans show inoperable mets to assess suitability for MIBG therapy)

1.5.2 Rising calcitonin / CEA

- for CT neck, chest, abdomen & pelvis with dual phase contrast liver
    - scan, bone scan / MRI spine & pelvis .Consider MRI liver as more sensitive for liver met detection
- if the above scans are normal, for a FDG PET-CT
- if the PET-CT is normal, consider a mIBG scan (unless already performed recently), and / or Indium – 111 Octreotide scintigraphy or Gallium 68
    - Somatostatin Receptor PET-CT (if available)

1.5.3 Recurrent lump in neck

- initially request an US neck and FNAC

Note that the management / investigations are tailored to each patient and discussed at MDT meetings (and may not conform exactly to the above which is to be used as a simplified guide)

1.6 References

BTA guidelines 2014
ETA guidelines 2012
ATA guidelines 2009