Medullary Thyroid Carcinoma

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Background

- Hazard et al described Medullary Thyroid Carcinoma (MTC) in 1959
- MTC represents 4 -5% of all thyroid cancers
- 75% of MTCs are sporadic
- 25% are inherited MTCs
- Hereditary MTCs can occur as part of MEN 2a, MEN 2b, or Familial MTC syndromes
- Steiner et al described MEN 2 syndrome in 1968

Medullary Thyroid Carcinoma

- MTC arises from parafollicular C cells, not from thyroid follicular cells.
- C cells originate from the embryonic neural crest.
- They migrate into the thyroid after its descent.
- Parafollicular cells produce calcitonin and Carcinoembryogenic antigen (CEA)

Inherited MTC

- MEN 2a (60% of MEN2):
  - MTC, Pheochromocytoma, Hyperparathyroidism
- MEN 2b (5% of MEN2):
  - MTC, Pheochromocytoma, Marfanoid, mucosal/intestinal ganglioneuromas
- FMTC (35% of MEN2):
  - MTC only

Inherited MTC

- Autosomal dominant inheritance
- Multifocal disease
- Parafollicular cell hyperplasia present
- Patients with FMTC present in their 4th decade, MEN 2a in their 3rd decade, and MEN 2b during childhood.

Sporadic MTC

- Unifocal disease usually
- Usually without parafollicular cell hyperplasia
- No associated endocrinopathy
- Patients present in the 4th decade of life with disease

Molecular Biology

- Mutation in various codons of RET proto-oncogene found in:
  - 97% MEN 2a, 95% MEN 2b, 86% FMTC, and 30% sporadic MTC patients
- RET codes for a transmembrane tyrosine kinase receptor
- Mutations lead to autophosphorylation of RET, and growth stimulation.

Clinical Presentation

- Present with a mass, and/or symptoms of local invasion and/or of hormone secretion
- Symptoms associated with local invasion:
  - dysphagia, stridor, or hoarseness
- Symptoms associated with hormone secretion:
  - flushing, diarrhea, and Cushings disease

Disease Course

- Behavior is indolent to aggressive
- Aggressiveness of disease
  - MEN 2b > MEN 2a = Sporadic > FMTC
- Early local and regional metastasis to cervical and mediastinal nodes.
- Late distant metastasis to lung, liver, bone, and brain

Staging

- Tumor
  - T1: < = 1cm
  - T2: >1 cm , < = 4 cm
  - T3: > 4cm no extracapsular spread
  - T4: Extracapsular spread
- Nodal status
  - N0: No lymph node mets
  - N1: lymph node mets present
- Metastasis
  - M0: No metastasis
  - M1: Metastasis present

Stage	TNM
I	T1N0M0
II	T2-4N0M0
III	T1-4N1M0
IV	T1-4N0-1M1

Diagnostic Work-Up

- FNA with calcitonin immunohistochemical screening
- Calcitonin testing: baseline level, as well as Pentagastrin stimulation test.
- CEA level
- Calcium, PTH, urinary catecholamines, vanillylmandelic acid, and metanephrines
- Genetic testing for RET mutations
- Radiographic testing including CT scan, MRI

Prognostic Factors

- Advanced Stage
- MTC subtype
- Age > 40 yrs
- Pre-op Calcitonin level
- Male gender
- Histologic characteristics

Therapeutic Options

- Surgery - best and only option for a cure
- Chemotherapy - late stage, aggressive disease and relief of symptoms related to hormone secretion
- External beam radiation - microscopic residual disease and palliation.
- Targeted, radionuclide-labeled molecules including anti-CEA antibodies are untested

Surgery

- Total thyroidectomy is advocated due to the often multifocal nature of MTC.
- Extent of nodal dissection is controversial and depends on
  - Size of disease, Extent of disease, and Pre-op calcitonin level
- All four parathyroids should be visualized to determine parathyroid disease.

Extent of Lymphatic Disease

- *Palpable, unilateral, intrathyroid tumors: metastases found in,
  - 81% of central neck dissections
  - 81% of ipsilateral, lateral neck dissections
  - 44% of contralateral neck dissection specimens
- MTC < 1 cm: metastases found in
  - 22% of contralateral, neck dissections
- Cervical lymph node recurrence = 45%

*Moley et al Annals of Surgery 229 (6) pp 880

Lymph Node Dissection

- Non-palpable disease, with normal calcitonin levels: Central nodal dissection
- Palpable primary, N0 disease: Central nodal dissection + Bilateral functional neck dissections.
- N1 or greater disease: Central/ lateral/ mediastinal compartment dissections
- Calcitonin levels

Post-operative follow-up

- Calcitonin levels (basal and stimulated) are checked immediately post-op and again starting 2 months after surgery.
- CEA levels are also checked
- Metastatic search is warranted if Calcitonin levels remain high, or are increasing post-op
- Metastatic search includes
  - CT scan, MRI, Ultrasound, bone scan, nuclear scans, exploratory laparoscopy, selective venous catheterization

Prognosis

- 10-year survival for Stage I & II
  - 95%
- 10-year survival for Stage III & IV
  - 55%
- MTC recurs in one third of patients after surgery
- Survival best for patients with FMTC, and worst for those with MEN 2b

Hereditary MTC Screening

- RET mutation screening at birth
- Follow serum Calcitonin levels and Pentagastrin stimulation tests regularly.
- Pentagastrin testing screen on all 1st degree relatives of patients with sporadic MTC
- MEN 2b: Micro-foci of MTC detected in children 6 mo. Old

Prophylactic Thyroidectomy

- MEN 2a: Recommended at age 4-6 yrs old
  - Some will follow patients with Pentagastrin stimulation test and serum calcitonin levels
- MEN 2b: Recommended at age <1 yr old
- FMTC: Follow with Pentagastrin stimulation test and serum calcitonin levels.
  - Some are more aggressive and advocate early thyroidectomy. (Age 4-6)

The End