Moderator
Jatin Shah, New York

Panelists
Henning Dralle – Germany
Akira Miyauchi - Japan
Robert Gagel – USA
Richard Kloos – USA
Jeff Moley – USA
Nelson Wolhk - Chile
Panel Discussion Format

• Presentation of facts
• Questions to the Panelists
• Case presentations
Background

- Natural history
  - Indolent disease
  - Usually diagnosed on physical examination as a solitary nodule
  - Early spread to regional lymph nodes is common
  - Distant metastases occur to the lung, liver, bone, and brain
  - Overall more aggressive than differentiated cancers
  - Sporadic (SMTC) = 75%, Inherited (IMTC) = 25%
  - SMTC usually is unilateral
  - IMTC are typically multicentric and bilateral
  - Produce several tumor markers (Calcitonin, CEA, Corticotropin, Serotonin, Melanin \(\rightarrow\) paraneoplastic syndromes)
  - Does not concentrate iodine (RAI not effective!)
Questions

• If this is an indolent disease, would you consider leaving it alone, and observation only? When and in whom?

• What is the most common way the patients with this disease present themselves?
Pathology

- Occurs in C cells which are most abundant in upper midportion of the gland
- Variety of histopathological patterns
  - Usually **bland, round or oval cells in nests or trabeculae**
  - May be spindle shaped
- Stromal **amyloid deposits in >25% of cases**
- **Immunohistochemistry**
  - Calcitonin +, CEA +, TGb -ve
Questions

• Is FNAC satisfactory for diagnosis?
• What cytological features are diagnostic?
• Is there ever a need for an open biopsy?
Background

- **RET proto oncogene**
  - Plasma membrane–bound tyrosine kinase enzyme
  - Chromosome 10
  - Mutations → overactive Ret protein → C-cell hyperplasia → Cancer
- **IMTC**: 98% RET germline mutations (AD inheritance pattern)
- **SMTC**: 40-50% RET somatic mutations
Ret Prot oncogene Mutations in 306 Families with Hereditary MTC

Eng et al JAMA 1996.
Questions

• When should testing be done for Genetic mutations? Pre op? Immediate Post Op / or later ?

• Who should do it ? What is the role of the Geneticist?
Questions

• Do any of these mutations reflect the aggressiveness of Medullary Carcinoma?
• Who amongst the family members of the patient need to be tested?
• Does gender of the patient matter?
THE SPECTRUM OF MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES AND HEREDITARY MEDULLARY THYROID CARCINOMA

MEN I — MEN-IIa — MEN-IIb — Familial MTC

MEN Syndromes — Hereditary MTC

Werner’s Syndrome — Sipple’s Syndrome — MTC — MTC
Pituitary adenomas — MTC — Pheochromocytoma — Pheochromocytoma
Pancreatic islet cell tumor — Pheochromocytoma — Marfanoid habitus
Adrenal cortical adenomas — Hyperparathyroidism — Multiple mucosal intestinal ganglioneuromas
Hyperparathyroidism — Hyperparathyroidism

MEN = multiple endocrine neoplasia;
MTC = medullary thyroid carcinoma
Multiple Endocrine Neoplasia, Type 2

**MEN 2A**
- Medullary Thyroid Carcinoma: > 90-100%
- Parathyroid Hyperplasia: 10-20%
- Pheochromocytoma: 40-60%

**MEN 2B**
- Medullary Thyroid Carcinoma: > 98%
- Mucosal Neuromas: > 98%
- Pheochromocytoma: 40-60%
### Aggressive Medullary Thyroid Cancer

#### Genotype – Phenotype Correlations and Risk Levels

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Exon</th>
<th>ATA risk level²</th>
<th>MTC risk level⁶</th>
<th>FMTC⁵</th>
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*Risk from aggressive MTC: level D is highest risk.

²Risk from aggressive MTC from the Seventh International Workshop on MEN (2): level 1, high risk; level 2, higher risk; level 3, highest risk.

⁶Presence (+) of inherited MTC in the absence of PHPT or PHEO has been described, although the number of family members and number of family generations studied and duration of follow-up is variable. Historically, mutations initially considered diagnostic of FMTC have eventually demonstrated some penetrance of the MEN 2A phenotype. The absence (-) of association with FMTC indicates that inheritance of MTC in isolation is very unlikely.

⁷Organ-specific penetrance: MA, majority; MI, minority; R, rare.

⁸Mutations based on limited families/case reports and may represent variants of unknown significance.

Phenotype associated with corneal nerve thickening.

Phenotype associated with mucosal neurillemomas.
# ATA Risk Levels

**Prophylactic Thyroidectomy Testing and Therapy**

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<th>ATA risk level</th>
<th>Age of RET testing</th>
<th>Age of required first US</th>
<th>Age of required first serum Ct</th>
<th>Age of prophylactic surgery</th>
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<td>ASAP and within the 1st year of life</td>
<td>6 months, if surgery not already done</td>
<td>ASAP and within the 1st year of life</td>
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<td>Consider surgery before age 5. May delay surgery beyond age 5 years if stringent criteria are met.</td>
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<td>&gt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>May delay surgery beyond age 5 years if stringent criteria are met.</td>
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* A normal annual basal ± stimulated* serum Ct, normal annual neck US, less aggressive MTC family history, and family preference. ASAP, as soon as possible.
Ret Prot oncogene
Mutations in 306 Families with Hereditary MTC

Surgery < 5 yrs old
Surgery < 6 mo old
Eng et al JAMA 1996.
Presentation

- Upper lobe nodule common
- 50% metastatic cervical nodes initially
- 15% airway compression or invasion
- Most patients in fourth decade of life
  - Sporadic patients older (5-6\textsuperscript{th} decade) than FMTC or MEN IIA (3rd decade)
  - Most MEN IIB in 1st or 2nd decade
- Gender distribution equal
Questions

• Should Serum Calcitonin and CEA be routinely ordered as a part of work up for any patient with a thyroid nodule?

• Are there patients with Medullary Ca., with ‘normal’ Calcitonin and high CEA, or vice versa?
Evaluation

- Thorough history for symptoms
  - Assessment for local invasion
  - Systemic assessment for
    - Pheochromocytoma
    - Distant mets (diarrhea, bone pain)
- Comprehensive family history
- Complete head and neck examination
Preoperative Evaluation

- Serum tumor markers
  - Calcitonin (nl <10 pg/ml)
  - CEA
- Screen for pheochromocytoma
  - 24-hour urine catecholamines and metanephrines
  - If co-existing, treat prospectively
- Screen for hyperparathyroidism
  - Serum calcium; if elevated, PTH
Questions

• What is the extent of imaging studies required for a patient with a recently diagnosed MTC, in a solitary thyroid nodule?
• Does every patient need work up for Pheochromocytoma?
Treatment

- **Surgery** is the only curative treatment
- I-131 and thyroid suppression Rx ineffective unlike well-diff thyroid ca
- Plan surgery appropriate for individual patient
- **Calcitonin** serves as a marker for persistent or recurrent disease
- Adjuvant **post-op XRT** in selected cases
Primary Tumor Management

- **Total thyroidectomy** - general agreement
- Glandular involvement multifocal
  - Familial forms - 90%
  - Sporadic - 20% (intraglandular spread)
  - 20% “sporadic” prove to be familial
- **Resect tumor completely** if local invasion
- Thyroid replacement therapy post-op
Questions

- Extent of thyroid surgery
  - Does everyone need a total thyroidectomy?
- Extent of neck surgery
  - Does everyone need central compartment node dissection?
  - Who needs a lateral neck dissection?
  - Unilateral or bilateral?
Surgical Management and Outcomes

• American Thyroid Association (ATA) MTC management guidelines

• Review of data supporting “Recommendation 61-65” related to best surgical management in Sporadic MTC
Surgical Management and Outcomes

Recommendations are made on 3 main clinical scenarios:

- Surgery for low volume (intra-thyroidal) disease
- Surgery for limited local and limited or no distant disease
- Surgery for advanced local and extensive distant metastasis
Surgical Management and Outcomes

Recommendation 61:

Patients with known or highly suspected MTC with no evidence of regional or distant disease:

Total thyroidectomy and prophylactic central compartment (level VI) neck dissection (Grade B)

- Importance of central neck clearance at the initial surgery was recognized (decrease recurrence and central neck complications)
- Prophylactic lateral neck dissection was omitted
- Best reserved for patients with preoperative positive imaging
Surgical Management and Outcomes

Recommendation 62:
Patients with limited local (CN) and limited or no distant disease:
Total thyroidectomy and central compartment neck dissection (Grade B)

Recommendation 63:
Patients with limited locoregional (CN+LN) and limited or no distant disease:
Total thyroidectomy with central and lateral compartment neck dissection (Grade B)

Recommendation 64:
Patients with presence of distant metastatic disease:
Less aggressive surgical approach appropriate to preserve function of speech, swallowing and PTG
Maintain locoregional disease control and prevent central neck morbidity (Grade C)
Surgical Management and Outcomes

Recommendation 65:

*Surgery for advanced local or distant metastasis*

*Less aggressive neck surgery may be appropriate to maintain local disease control and function* (Grade C)

Recommendation 66:

Patients with extensive distant disease

*A palliative neck procedure may still be needed (pain, tracheal compression). Otherwise, neck disease may be observed and surgery deferred* (Grade C)
Questions

- Adjuvant therapy? What and in whom?
- What defines cure from Medullary Carcinoma?
- What do you do when patients have persistently elevated Calcitonin?
- Does the level of post. Op Calcitonin matter?
Radiation Therapy

- Slight improvements in locoregional disease-free survival in select cases reported

- Consider for:
  - Extraglandular invasion
  - Microscopic residual disease
  - Nodal ECS
  - Inoperable locoregional tumors
  - Symptomatic bone metastases

- Weigh benefits against sequelae
• Review article
• Despite aggressive surgery, patients at high risk for local recurrence may benefit from adjuvant EBRT?
• Although the role of EBRT in the management of these tumors has thus far been poorly defined, EBRT should be considered as a treatment option for patients with locally advanced MTC to optimize locoregional control
• EBRT may impact locoregional control, however the literature has failed to find evidence of improved survival in these patients
Follow-Up

• **Calcitonin and CEA**, 2 to 3 months post-op

• If calcitonin >100, evaluate for residual neck disease +/- distant metastases

• MEN-IIA and MEN-IIB:
  Annual screen for pheochromocytoma and hyperparathyroidism
Questions

- When should the first post operative Calcitonin be ordered?
- At what level of Calcitonin, should there be concern about persistent or metastatic disease?
- Does post operative Calcitonin continue to decline over time?
Persistent Hypercalcitonemia

- Baseline calcitonin
- Serial calcitonin levels
- **Calcitonin doubling time (< or > 1 yr)**
- Symptoms
- Work-up – imaging studies (CT, MRI, PET, Octreotide scanning)
- Treatment – symptomatic relief (surgery, RT, systemic chemotherapy, targeted therapy)
Management of metastatic disease

- Complex and unpredictable and a topic in itself!

- Surgery/chemo/embolization/EBRT and new investigational drug therapies should all be considered
Questions

• What are the drugs currently approved / available for systemic treatment?
• Results of systemic treatment?
• What are the drugs currently under investigation?
• What are the currently active clinical trials?
Systemic Therapy

Targeted Drugs

- **Tyrosine Kinase Inhibitors**
  - Sorafenib, Sunitinib, Pazopznib, *C*abozentinib
  - Motesanib, Axitinib, *V*andetinib

- **BRAF inhibitors**
  - Vemurafenib, Dabrafenib, Selumetinib

- **Anti Angiogenesis drugs**
  - Bevacizumab, Lenelidomide, *L*envatinib
Vandetanib in Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial
Cabozen tinib Outcomes

- Statistically significant PFS prolongation of 7.2 mo was observed; median PFS for cabo was 11.2 mo vs 4.0 mo for P (HR 0.28, 95% CI 0.19-0.40, p<0.0001)
- An interim analysis of OS (44% of the 217 required events) did not show a difference between cabo and P.

- An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients (pts) with documented RECIST progression at baseline.
Medullary Carcinoma

Outcomes

- Outcomes variable
- **Overall survival** 70% 5-year
  55% 10-year
- Children with detected MEN-IIA and FMTC
  - Most cured after thyroidectomy
- Palpable tumor at presentation
  - 50% have persistent disease post-op
- Some patients have indolent disease despite distant metastases
Prognostic Factors

Clinical, pathologic, and biochemical/molecular factors:

- **Stage**
- **Type:** Sporadic, MEN-IIB, MEN-IIA, FMTC
- **RET codon mutations 768,790,791,804**
- **ECS; bilateral nodes**
- **Older age; male gender**
- **Elevated CEA, calcitonin (>10,000 pg/ml)**
- **CEA & Calcitonin doubling time(< or > 1 yr)**
Summary

• MTC - uncommon thyroid malignancy
• Neuroendocrine C-cell tumor, secretes calcitonin, allows for diagnosis and f/u
• Various forms, sporadic and hereditary, with spectrum of clinical behavior
• RET gene mutations identify at-risk patients
• Surgery is the only effective treatment
• Better adjuvant therapy is needed
Case 1

- 45 yo district court judge presents with an incidentally noted right thyroid nodule by his general practitioner on routine clinical evaluation
- Appropriate work-up included a fine needle aspiration biopsy
- Cytology was suggestive of medullary carcinoma of the thyroid
Case 1

- What are cytological features suggestive of medullary carcinoma of the thyroid?
- Preop work-up?
- In the absence of family history, is it important to rule out pheochromocytoma?
- Should genetic testing be done before or after surgery?
Case 1

- Patient’s preop work-up showed calcitonin to be 345 and CEA of 7.
- Operative intervention – extent of thyroid surgery?
- Management of the neck - central compartment – ipsilateral, contralateral; lateral neck – ipsilateral, contralateral?
- Mediastinal nodes
Case 1

- Patient underwent total thyroidectomy, central compartment clearance on both sides
- Final pathology report shows 1.7 cm medullary carcinoma of the thyroid
- All lymph nodes in central compartment were negative
- Postop calcitonin was 33
- 9 months after surgery, calcitonin is 754
- Further work-up and investigations?
Case 1

- Role of PET scan?
- Role of calcitonin stimulation test?
- Patient’s ultrasound showed a 2 cm lymph node in the right upper neck
- Fine needle aspiration biopsy was consistent with medullary carcinoma of the thyroid
- Further treatment?
- Extent of neck dissection?
Case 1

- Patient underwent right modified neck dissection
- 7 positive nodes noted
- Postop calcitonin was 110
Case 1

- 3 years later patient comes in totally asymptomatic with calcitonin of 10,515
- Work-up?
- Role of PET scan?
- Ultrasound?
- MIBG scan?
- Laparoscopy?
Case 1

- Patient has multiple liver metastases on laparoscopy

- Further treatment and prognosis?
Case 2

- 73 yo high US official comes with hoarseness of voice for 6 months
- Clinical examination revealed 7 cm right thyroid mass with paralyzed vocal cord
- Mass is semi-fixed
- Fine needle aspiration biopsy = medullary carcinoma of the thyroid
- Multiple R neck nodes
- Patient’s calcitonin is 35,000
Case 2

- Preop work-up?
- Extent of surgery?
- Postop follow-up?
Case 2

- Patient’s postop calcitonin is 3,344
- Follow-up?
Case 3

• 73 yo male presents with malaise, discomfort in the neck and throat, and mild hoarseness

• Clinical examination revealed 8 cm semi-fixed left neck mass with sluggish vocal cord

• Patient has diffuse pulmonary metastasis and liver metastasis

• Clinically, he appears to be in good health
Case 4

- 75 yr female comes with an incidentally noted large thyroid mass
- Fine needle aspiration biopsy = medullary carcinoma of the thyroid
- Patient underwent total thyroidectomy, right modified neck dissection and recovered well from surgery
Case 4

- Genetic testing showed 804 mutation
- Patient has 4 children, ages 39, 44, 48 and 50
- Three of them have 804 mutation
- Advise extent of surgery, etc.
Case 5

- 37 yo gastroenterologist was worked-up extensively for incidentally noted CEA of 13
- Multiple GI investigations were reported to be negative
Case 5

- Routine CT scan of the chest revealed a large thyroid mass measuring 4.5 cm
- Fine needle aspiration biopsy was consistent with medullary carcinoma of the thyroid
- Patient’s calcitonin level was 3,444
Case 5

- Extent of surgery for the primary?
- Extent of surgery for the neck?
- Patient’s genetic testing showed 634 mutation
- Patient has 3 children, ages 5, 12, 17
- Advise for the children?