Surgical Management of Medullary Thyroid Carcinoma

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Moderator: Dr Anjali Mishra
Introduction

• 4-7% of all thyroid cancers
  – 0.18- 0.23/ 100,000 population
• Difficult to cure
• Familial : 20-25%
  – MEN-2A : MTC, PCC, PHPT
  – MEN-2B : MTC, PCC, Characteristic phenotype
  – FMTC
• Para-neoplastic syndromes
  – Diarrhea (Pg, VIP, CGRP)
  – Cushing’s (CRH)
  – Carcinoid (5- HT)
MTC vs DTC

- Origin different- Neural crest cells
- Prognosis intermediate between DTC and ATC
- Clinical course- extremely indolent to aggressive variant
- Higher rate of nodal metastasis- c/l cervical and mediastinal compartments
- 20-30 % familial
  - High penetrance- MEN 2 syndrome
- Does not concentrate Radioactive iodine
Genetics
Genetics

• Gene involved is ret – proto-oncogene which is an autosomal dominant gene
• Codes for RET protein which is a tyrosine kinase receptor
• Situated at long Arm of chromosome 10 at position 11.2 (between base pairs 42,892,532 – 42,944,954)
• Spread through 21 Exons with 60 – 287 base pairs
• Is the only gene associated with MEN syndromes
• Penetrance >90% in MEN 2A and >95% in MEN 2B*
RET protein

• Is a trans cell membrane receptor with an extracellular and an Intracellular portion.
• Transmits signals for growth depending upon stimulation by growth factors which attaches to the extracellular portion of receptor
• Has got activating and deactivating mutations
• Plays role in development of
  - Intestinal neurons
  - Autonomic nervous system
  - Normal kidney Development
  - Spermatogenesis
## Age of Manifestation

<table>
<thead>
<tr>
<th>Codon</th>
<th>Age of MTC</th>
<th>Age of Lymph node Mets</th>
<th>Age of distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest Risk</strong></td>
<td>&lt; 1yr</td>
<td>2.5 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td>883,918,922</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>&lt;1yr (634) - &lt;5 yrs (rest)</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; Decade</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Decade</td>
</tr>
<tr>
<td>611,618,620,634</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Least High Risk</strong></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; to 3&lt;sup&gt;rd&lt;/sup&gt; decade</td>
<td>2nd to 4&lt;sup&gt;th&lt;/sup&gt; decade</td>
<td>&gt;4&lt;sup&gt;th&lt;/sup&gt; Decade</td>
</tr>
<tr>
<td>609,768,790,804,891</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of evidence</td>
<td>RET risk category&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mutated RET codon</td>
<td>MTC N0</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------</td>
<td>-------------------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age, years</td>
<td>[Ref. No.]</td>
</tr>
<tr>
<td>V</td>
<td>Highest</td>
<td>918</td>
<td>0.75 (9 months)</td>
</tr>
<tr>
<td>V</td>
<td>High</td>
<td>630</td>
<td>1</td>
</tr>
<tr>
<td>V</td>
<td>High</td>
<td>609</td>
<td>5</td>
</tr>
<tr>
<td>V</td>
<td>High</td>
<td>611</td>
<td>7</td>
</tr>
<tr>
<td>V</td>
<td>Least high</td>
<td>791</td>
<td>21</td>
</tr>
<tr>
<td>V</td>
<td>Least high</td>
<td>804</td>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on the 1999 consensus statement from the Seventh International Workshop on Multiple Endocrine Neoplasia, with minor adjustments for carriers of RET mutations in codon 609 and 630 to accommodate recent literature.<sup>23</sup>

<sup>b</sup>Based on 90 RET families.<sup>24</sup>

<sup>c</sup>Deaf of disease at age 55 years (distant metastasis not explicitly stated).

<sup>d</sup>Lymph node status unspecified.

MTC N0 / N1 / M1: node-negative, node-positive, metastatic (to distant sites) medullary thyroid carcinoma; N/A: not available (no data available from the international literature).
**Codon specific Age related MTC progression in familial syndromes**

<table>
<thead>
<tr>
<th>Codon</th>
<th>Mean Age</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CCHP</td>
<td>Node $-$ve MTC</td>
<td>Node $+$ve MTC</td>
</tr>
<tr>
<td>609,611,618,620,630,634(n=165)</td>
<td>8.3</td>
<td>10.2</td>
<td>17.1</td>
</tr>
<tr>
<td>768,791,804,891(n=27)</td>
<td>11.2</td>
<td>16.6</td>
<td>-</td>
</tr>
<tr>
<td>*918(n=17)</td>
<td>3.0</td>
<td>16.0</td>
<td></td>
</tr>
<tr>
<td>634(n=129)</td>
<td>6.9</td>
<td>10.1</td>
<td>16.7</td>
</tr>
</tbody>
</table>

*Codon 918, 611, 791 no statistical difference
609,630,891- No or scarce data
hence needs further verification

Study 1- n=207 age<20,T<1.0cm
Study 2 – n=167


Diagnosis and management of Medullary Thyroid Cancer
Method of testing

Peripheral blood
  - Lymphocyte pellet
  - DNA extraction by Proteinase

PCR

1) Direct DNA sequencing
2) Analysis of restriction sites introduced or deleted by mutation
3) Gel shift Analysis
Familial MTC Syndromes
### MEN 2 and its Related syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Characteristic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN2A</td>
<td>MTC</td>
</tr>
<tr>
<td></td>
<td>Adrenal medulla (pheochromocytoma)</td>
</tr>
<tr>
<td></td>
<td>Parathyroid glands</td>
</tr>
<tr>
<td>FMTC</td>
<td>MTC</td>
</tr>
<tr>
<td>MEN2A with cutaneous lichen amyloidosis</td>
<td>MEN2A and a pruritic cutaneous lesion located over the upper back</td>
</tr>
<tr>
<td>MEN2A or FMTC with Hirschsprung’s disease</td>
<td>MEN2A or FMTC with Hirschsprung’s disease</td>
</tr>
<tr>
<td>MEN2B</td>
<td>MTC</td>
</tr>
<tr>
<td></td>
<td>Adrenal medulla (pheochromocytoma)</td>
</tr>
<tr>
<td></td>
<td>Intestinal and mucosal ganglioneuromatosis</td>
</tr>
<tr>
<td></td>
<td>Characteristic habitus, marfanoid</td>
</tr>
</tbody>
</table>

#### RET Mutations

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Codon of Ret Mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN 2A</td>
<td>609</td>
</tr>
<tr>
<td>FMTC</td>
<td>611</td>
</tr>
<tr>
<td></td>
<td>615</td>
</tr>
<tr>
<td></td>
<td>620</td>
</tr>
<tr>
<td></td>
<td>630</td>
</tr>
<tr>
<td></td>
<td>634</td>
</tr>
<tr>
<td></td>
<td>760</td>
</tr>
<tr>
<td>Familial MTC</td>
<td>768</td>
</tr>
<tr>
<td></td>
<td>769</td>
</tr>
<tr>
<td></td>
<td>804</td>
</tr>
<tr>
<td></td>
<td>801</td>
</tr>
<tr>
<td>MEN2A/CLA</td>
<td>634</td>
</tr>
<tr>
<td></td>
<td>532</td>
</tr>
<tr>
<td></td>
<td>528</td>
</tr>
<tr>
<td>MEN 2A/</td>
<td>518</td>
</tr>
<tr>
<td>Hirschsprung</td>
<td>520</td>
</tr>
<tr>
<td>MEN 2B</td>
<td>883</td>
</tr>
<tr>
<td></td>
<td>618</td>
</tr>
</tbody>
</table>

#### RET Domain

- **Cysteine-rich**
- **Tyrosine kinase domain**
Familial Medullary thyroid cancer syndromes

- MEN 2A
- MEN 2B
- FMTC
MEN – 2A

• Diagnosis:
  – Families with MTC, Pheo, HPT
  – Families with MTC, Pheo in at least 1 at risk relative
  – Families with MTC, HPT in at least 1 at risk relative

• Penetrance of MTC is 90%

• MTC is the first manifestation
MEN 2B & FMTC

• MEN 2B Diagnosed:
  – Families with MTC associated or not with pheochromocytoma and musculoskeletal anomalies and mucosal neuromas and other phenotypical fetures
  – May have associated intestinal ganglioneuromatosis

• FMTC – is familial form of MTC
• Diagnosis is made if only medullary thyroid cancer is the presentation in
  – >10 kindred as carriers
  – Multiple carriers or affected members >50 yrs
  – No other components of MEN syndromes
Intervention issues
Intervention - issues

• Surgery for MTC in familial setting
• Prophylactic Thyroidectomy – Total Thyroidectomy Vs less than total
• Age at which prophylactic surgery offered
• Role of prophylactic neck dissection
• The extent of lymph node surgery for clinical MTC in MEN2
• Management of associated pathology (HPT & Pheo)
## Lymph node metastasis

<table>
<thead>
<tr>
<th>Type of Metastasis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central compartment disease</td>
<td>81%</td>
</tr>
<tr>
<td>Ipsilateral lateral nodal metastasis</td>
<td>14-80%</td>
</tr>
<tr>
<td>Contralateral lateral nodal metastasis</td>
<td>19-49%</td>
</tr>
</tbody>
</table>

8/21/2013

*Diagnosis and management of Medullary Thyroid Cancer*
Timing of Thyroidectomy in ret gene carriers

- Risk level:* (Codon)
- Thyroidectomy (age, year):
- Central lymph node dissection:
- Bilateral lymph node dissection:

** Risk levels as defined in Table 2

- Any (any)
  - Immediately**
    - Tumour > 10 mm or node-positive

- Increased

- Normal
  - High (883, 918, 922)
    - < 1
  - Intermediate (609, 611, 618, 620, 630, 634)
    - 5
  - Least high (768, 790, 791, 804, 891)
    - 5–10 (< 20)

* 2 Timing of thyroidectomy in RET gene carriers (University of Halle Algorithm). *Risk levels as defined in Table 2. **Preferably immediately. 
COPS (Codon Oriented Prophylactic surgery)

- Removes at risk organ prior to its developing clinically significant disease
- Extent of surgery – debated
- TT- to be done
- CCND- debated
- Clinically occult disease with nodal metastasis- 6% patients

<table>
<thead>
<tr>
<th>Treatment initiated after identification of thyroid nodule</th>
<th>Mortality 15-20 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early prophylactic thyroidectomy in carriers</td>
<td>Mortality &lt; 5 %</td>
</tr>
</tbody>
</table>

JCEM 86(12):5658-5671 2001
What is the role of preventive surgery for carriers of MEN2A
What is the role of preventive surgery for carriers of MEN2A?

- At risk family members with positive mutation will certainly develop MTC at some point of life before the age of 30
- Likely to benefit from prophylactic thyroidectomy
Preventive Surgery for Carriers of MEN 2A Gene..

• In older MEN 2A series, with treatment initiated after the identification of a thyroid nodule, MTC progressed and showed 15-20% of cancer mortality.

• Carrier diagnosis before adulthood has an impact (proven in long term studies with measurement of serum CT) that is only now evident.

• Early thyroidectomy may have lowered the mortality from hereditary MTC to less than 5%, well below the cancer mortality in MEN-I.
Prophylactic thyroidectomy in MEN2A

- Bilateral and multicentric MTC is the most common cause of death in patients with MEN2A
- MTC follows an orderly pattern of development- from C-cell hyperplasia to microscopic MTC to a visible focus
- Another important finding was of an age-dependent progression of early MTC specific to the RET codon. This resulted in codon – directed prophylactic surgery
- Enough evidence to show that total thyroidectomy that is performed before MTC develops or spreads beyond the gland is currently the only curative treatment
How can we utilize this genetic information for therapeutic purposes?
Prophylactic Surgery

• If first operation by teenage/adulthood likely hood of metastasis is higher
• If there is a raised stimulated or basal calcitonin then TT + CCLND is the minimum surgical procedure indicated
• Lateral neck dissection indicated if there is evidence of involved nodes in neck
• Re operation indicated if no distant metastasis and stimulated/basal calcitonin still high
• Management of metastatic setting
  – Surgery palliative 1) local 2)systemic
# ATA Risk Level

## Table 6. American Thyroid Association Risk Level and Prophylactic Thyroidectomy Testing and Therapy

<table>
<thead>
<tr>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>ASAP and within the 1st year of life</td>
<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>
</tr>
<tr>
<td>C</td>
<td>&lt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>Before age 5 years</td>
</tr>
<tr>
<td>B</td>
<td>&lt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>&gt;3–5 years</td>
<td>Consider surgery before age 5. May delay surgery beyond age 5 years if stringent criteria are met.¹</td>
</tr>
<tr>
<td>A</td>
<td>&lt;3–5 years</td>
<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.¹</td>
</tr>
</tbody>
</table>

¹A normal annual basal±stimulated* serum Ct, normal annual neck US, less aggressive MTC family history, and family preference. ASAP, as soon as possible.
## Age of Surgery

<table>
<thead>
<tr>
<th>Codon</th>
<th>Time of surgery</th>
<th>Extent of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest Risk</strong></td>
<td>With in 6 months of life – preferably in 1st month</td>
<td>TT + CCLND</td>
</tr>
<tr>
<td>883,918,922</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>With in 5 yrs of age</td>
<td>TT ± CCLND</td>
</tr>
<tr>
<td>611,618,620,634</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Least High Risk</strong></td>
<td>5 – 10yrs of age</td>
<td>TT ± CCLND</td>
</tr>
<tr>
<td>609,768,790,804,891</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For symptomatic carriers with established MTC surgical strategy same as sporadic MTC

*Brandi et al. J Clin Endocrinol Metab 2001;86(12):5658-5671*
Prophylactic node dissection

• Need for preemptive neck dissection not clear from literature

• For carriers of highest risk mutation (Codon918) cervical lymph node dissection mandatory

• Recommended for carriers of high risk mutation from 5 yrs of age (codon 634) and 10 yrs for 609,611,618,620 and 630

• Least high risk category no clear indication – suggested beyond 20yrs of age

Prophylactic thyroidectomy...?

• What is the benefit of prophylactic Thyroidectomy?
  – In older MEN 2 patients presented with thyroid nodule there was increased cancer mortality (15-20%)* compared to the ones who underwent early thyroidectomy (<5%)#

• Is there a reliable method of identifying patients in whom Cancer in a specific organ will develop?
  – RET mutation is the only mutation associated with MEN 2 syndromes
  – Sensitive and reliable in predicting development of MTC

Prophylactic thyroidectomy...?

• Is the Organ Expendable or its function amenable to replacement?
  – Thyroxine replacement is easy and hassle free

• Is the removal of organ concerned associated with minimal risk to the patient?
  – Yes, Total thyroidectomy is relatively a safe procedure in experienced hands and well tolerated even by Infants

• Is there a reliable method to determine whether the patient has been rendered free of disease and remains so after the removal of organ?
  – Stimulated calcitonin with calcium/pentagastrin is a reliable method to assess for Persistent/recurrence
Evaluation & Management of Clinically Evident MTC
FNAC

- Plasmacytoid, small round cells, large/spindle cells, cytoplasmic granules with amyloid
- Amyloid – in 60-70%
- Preoperative diagnosis of MTC: Fine needle aspiration cytology as compared with serum calcitonin measurement
  - Higher sensitivity of serum CT measurement as compared with FNAC to diagnose MTC (98% vs. 63%)
- Immunocytochemistry

- Maria João M. Bugalho et al, JSO, vol 91,1:56-61,2002
Options for screening

- Calcitonin Assay
- RET mutation analysis
S. Calcitonin

- Rough estimation of amount of tumor tissue
- To establish diagnosis in sporadic cases
- Normal values < 10 pg/ml
- > 100 pg/ml - diagnostic of MTC
- 10-40 pg/ml - nodal metastasis start developing
- Distant metastasis - > 150 pg/ml & frequently > 1000 pg/ml
- Most sensitive & specific marker of MTC for primary diagnosis & follow up
  - Sensitivity - 98-100%
  - Specificity - 95-100%

- Elisei R et al, JCEM 2004;89:163-8
Screening For MTC with Routine Ct Estimation

• Multiple European studies → routine measurement of serum calcitonin in patients with thyroid nodules is effective in the detection of clinically occult MTC

• Cost–effectiveness study → addition of calcitonin screening to current ATA guidelines for the evaluation of thyroid nodules → US$11,793 per life-year-saved (LYS)

• Additional 113,000 life-years at a cost increase of 5.3%
Calcitonin vs Genetic screening

<table>
<thead>
<tr>
<th>*Stimulated Calcitonin</th>
<th>% of MTC</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td>Elevated</td>
<td>98</td>
<td>32</td>
</tr>
</tbody>
</table>

False positive rate in calcitonin assay 8%
False postive rate in RET analysis 0%

- Early detection of MTC can alter the Clinical course
- RET testing is better in picking up true +ve compared to calcitonin tests
- Abnormal Ct tests – 5-10% false positive Ct testing
- Only 50% of the kindreds are affected
- Easy to perform, single time
- Provocative testing is unpleasant
- Genetic analysis of exons 10,11,13,14,15 and 16 of RET to exclude hereditary disease with a probability of greater than 99%

Carcinoembryonic antigen (CEA)

- Elevated in > 50% of MTC
- > 30 pg/ml - highly predictive of inability to cure with operative intervention
- > 100 pg/ml - lymphnode mets/ distant mets
- Increasing CEA in presence of stable Calcitonin - sign of dedifferentiation of tumor & worse prognosis
IHC

• Stains for Calcitonin & CEA
• Staining pattern- variable- usually diffuse, may be focal
  • *Absence of calcitonin reactivity* – in 5-25 % of MTC cases
• Calcitonin is lost with dedifferentiation of MTC but CEA is retained
  • **CEA** - to assess MTC that lack/ present only focal reactivity for calcitonin

• Erickson LA, Adv Anat Pathol 2004;11:175-189
• Syndromic association
  – Relevant investigation

• Biochemical Screening
  – Serum Calcitonin Assay (Basal & stimulated)
  – 24 hr Urinary / Plasma metanephrines
  – Serum Calcium, PTH
Extent of Imaging
ATA Guidelines 2009

• Preoperative neck USG → recommended for all patients when an FNA or Ct level is diagnostic or suspicious for MTC

• Chest CT, neck CT, liver CT or contrast-enhanced MRI → recommended when local lymph node metastases are detected (N 1) or the serum Ct is > 400 pg /mL
PET in MTC

- FDG, F 18 DOPA
- Useful in post-op follow up to detect residual/recurrent tumor
- FDG uptake co-relates with poor differentiation & higher proliferative activity

- Sensitivity
  - Higher- 95 %- higher calcitonin> 1000 pg/ml (higher than CT/MRI)
  - Lower- 20%- calcitonin < 500 pg/ml

- More sensitive in detecting cervical, supraclavicular and mediastinal lymph nodes but failed to detect small lesions in lung & liver

- V Rufini et al, Minerva Endocrinol 2008;33:67-73
Radio-nuclide imaging in MTC

<table>
<thead>
<tr>
<th></th>
<th>I-131MIBG sensitivity</th>
<th>Tc-99m MDP sensitivity</th>
<th>Tc-99m DMSA sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>10%</td>
<td>100%</td>
<td>94%</td>
</tr>
<tr>
<td>Local</td>
<td>20%</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Distant mets</td>
<td>13%</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

DMSA has advantages over both MIBG and Tc 99m MDP in imaging patients with metastatic MTC

Treatment Overview

- Surgery
- Adjuvant- Thyroxin replacement therapy
- No role of RAIA therapy
- Limited role of RT, CT, Palliative symptomatic therapy
# Staging in MTC

- MTC- age is not taken in account

<table>
<thead>
<tr>
<th>Stage</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1N0M0</td>
<td>T2N0M0</td>
<td>T3N0M0 T1/2/3N1aM0</td>
<td>IV A Potentially resectable T4a N0/1a M0 T1-4a N1b M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV B locally unresectable T4b N any M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV C Distant Metastasis T any N any M1</td>
</tr>
<tr>
<td>Survival rate at 10 years</td>
<td>100%</td>
<td>93%</td>
<td>71%</td>
<td>20%</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor diameter 2 cm or smaller</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Primary tumor diameter &gt; 2 to 4 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Primary tumor diameter &gt; 4 cm limited to the thyroid or with minimal extrathyroidal extension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4_a</td>
<td>Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4_b</td>
<td>Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor size unknown, but without extrathyroidal invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>No metastatic nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1_a</td>
<td>Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)</td>
<td></td>
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<tr>
<td>N1_b</td>
<td>Metastasis to unilateral, bilateral, contralateral cervical or superior mediastinal mode metastases</td>
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<tr>
<td>NX</td>
<td>Nodes not assessed at surgery</td>
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<tr>
<td>MO</td>
<td>No distant metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastases not assessed</td>
<td></td>
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</tr>
</tbody>
</table>
Surgical treatment of Primary Sporadic MTC

- TT+CCLND
- Ipsilateral MRND-
- **Therapeutic Vs Prophylactic**
  - primary tumor>1cm / +ve nodes in CC
- **Contra lateral MRND**-
  - bilateral tumors/ extensive lateral adenopathy on side of primary tumor
- **Despite aggressive surgical resection of all neck lymph nodes- 32 % undetectable Calcitonin levels postoperatively**
Total thyroidectomy with central compartment dissection
Thyroidectomy - Technique

- Knowledge of anatomy
- Preserve all parathyroids
- Protect RLN
- Leaving no area of residual tissue
- Lateral approach to thyroidectomy (for re-operative surgery)
Important Anatomical relations
Identifying Parathyroid and RLN: a critical step
Parathyroids

Line of dissection
ATA Guidelines 2009..

Parathyroid glands

- Devascularized normal parathyroid glands from patients with MEN 2B or FMTC should be autografted into the sternocleidomastoid muscle of the neck.

- Devascularized normal parathyroid glands from patients with MEN 2A in a kindred with strong family history of PHPT, or a RET mutation carrying a significant risk of PHPT, should be autografted into the forearm.
ATA Guidelines 2009..
Parathyroid glands

• Devascularized normal parathyroid glands from patients with a RET mutation associated with both MEN 2A with a low risk of PHPT and FMTC, whose kindred suggests FMTC $\rightarrow$ autograft of the parathyroid tissue into either the forearm or sternocleidomastoid muscle
Lateral approach


Diagnosis and management of Medullary Thyroid Cancer
Subplatysmal plane
Surgery in MTC with Distant Metastasis

- Unfavorable course doesn’t warrant extended surgery apart from TT+ CCLND+ selective removal of symptomatic lymph nodes / tumor infiltrates
- For palliation of paraneoplastic syndrome
Cure definition

• Biochemical cure- normalization of postoperative CT levels after pentagastrin / calcium stimulation
Postoperative surveillance

• Disease confine to thyroid gland only-
  – very low risk of recurrence & rare mortality

• Nodal disease at presentation-
  – very high risk of recurrence/ persistence- need close follow up postoperatively

• Follow up started at 3 months postoperatively
• Follow up every 6 months x 2 years then annually
• S Calcitomin, CEA, TFT
  – Undetectable- annual follow up with S Calcitomin, CEA
  – Rise in serum marker- further imaging
Adjuvant therapy

- Thyroxine replacement therapy (1.5-1.8 µg/kg/day)
Radiation Therapy

- External beam Radiation Therapy - not much significant role
- Complications - cervical fibrosis, dysphagia, radiation tracheitis, paraplegia
- Help palliative local disease when surgery not feasible
- Palliate bone metastasis
- High risk patients - Surgery +Rt - recurrence rate 14 % compared to Surgery alone - 48 %
  - Brierley J et al, Thyroid 1996;6:305-310
Systemic therapy

- Somatostatin analogues
- Interferon alpha
- Chemotherapy - limited efficacy
- Complete response – very rare
- Partial response - in < 1/3\textsuperscript{rd} patients
- Doxorubicin, Dacarbazine, Capcetabine, 5-Fu - partial response up to 24-29 %

Somatostatin analogues

• Impact on symptoms & production of Calcitonin but do not reduce tumor mass or improve survival rate

• Inhibit neuroendocrine tumor cell growth through inhibition of release & activity of
  – Growth promoting hormones/ factors
  – Angiogenesis
  – Modulate immunologic activity
  – Direct effect on Somatostatin receptors

  – Vitale G et al, JCEM 2000;85:983-8
Newer therapies

• Tyrosine kinase inhibitors- Imatinib Mesylate
• Motesanib diphosphate
• 20 % partial response
• 30 % stable response
• VEGF inhibitor-Vandetanib
Persistent/recurrent disease

- Recurrence – 50%
- Calcitonin & stimulated Calcitonin levels
- Re-operations for loco-regional recurrence-associated with significant risks
- Symptomatic loco-regional recurrence even in metastatic setting—surgery + RT
- Re-operations normalize Calcitonin in $1/3^{rd}$ patients
Functional- Radionuclide imaging in follow up

• To detect metastatic sites & aid surgical planning
• Somatostatin analogues, 201-Thallium, Tc-99m sestamibi, Tc-99m tetrofosmin, Tc-99m DMSA(V) scans
• Tc-99m DMSA(V) scan- sensitivity for detecting recurrence- 71.4%
ATA Guidelines 2009..

Follow up

• MTC serum tumor markers (Ct and CEA) should be measured 2–3 months postoperatively
Evaluation of metastatic disease

- Neck USG
- CECT Chest, Abdomen
- Functional imaging - PET, MIBG
- Liver - miliary pattern - not picked up by conventional imaging - advice Selective venous sampling, Diagnostic Laparoscopy
ATA Guidelines 2009..

Recurrent or persistent MTC

• In the absence of residual anatomically identifiable disease (neck US and CT) in a thyroidectomized patient with a measurable Ct level who has not previously undergone a level VI compartmental dissection, an empiric central compartment dissection may be considered but remains controversial.

  – Grade C Recommendation
ATA Guidelines 2009..
Recurrent or persistent MTC

- Serum Ct levels $\geq 150$ pg/mL with small (< 1 cm) locoregional metastatic disease that is asymptomatic and nonthreatening, and with distant metastases $\implies$ immediate intervention towards the locoregional disease is of unknown benefit $\implies$ such lymph nodes may be observed
ATA Guidelines 2009..

Recurrent or persistent MTC

• Postoperative MTC patients with serum Ct levels ≥ 150 pg /mL with symptomatic and/or progressive locoregional disease > 1 cm should be considered for locoregional therapy (e.g., surgery)

• Symptomatic distant metastases – consider clinical trials and palliative therapies eg surgery, EBRT, percutaneous interventions hepatic embolization
ATA Guidelines 2009..
Recurrent or persistent MTC

• Routine use empiric liver or lung biopsies, hepatic vein sampling, systemic vascular sampling, or hepatic angiography prior to re-operation not recommended
ATA Guidelines 2009..
Distant Metastasis

• Patients with isolated or limited brain metastases → consider surgical resection

• EBRT (including stereo-tactic radiosurgery) may be indicated for brain metastases not amenable to surgery
ATA Guidelines 2009..

Recurrent or persistent MTC

• Surgery is indicated in weight-bearing bone metastases with fracture or impending fracture
Diarrhea in MTC

- In 20-30% patients of MTC
- Causes: calcitonin, prostaglandin, serotonin, VIP
- Abolished/palliated by tumor reduction
- Somatostatin analogue can palliate diarrhea
Ectopic Cushing’s syndrome

• In 4 % patients of MTC
• Diarrhea- watery- 10-12 stools / day
• Rapid onset of symptoms & progressive clinical course
• Treatment- Bilateral adrenalectomy– cytoreductive surgery
Prognostic factors in MTC

- Predictors of improved survival
  - female gender, younger age at diagnosis, localized disease, well/moderately differentiated histological grade, intra-thyroidal tumor, no lymph node metastasis, complete surgical resection
- Age > 65 years – poor prognosis
- Risk of dying increased by 5.2% for each additional year of age
  - Sanziana Roman et al, Cancer 2006;107:2134-42
### Prognosis

<table>
<thead>
<tr>
<th>Disease extent</th>
<th>50 % intrathyroidal</th>
<th>30 % locally invasive/lymphnode metastasis</th>
<th>13 % Distant metastasis</th>
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</thead>
<tbody>
<tr>
<td>Survival rate</td>
<td>10 year- 95 %</td>
<td>5 year- 75 %</td>
<td>10 year- 40 %</td>
</tr>
</tbody>
</table>
Genetic testing in diagnosis and management of MEN

Patient with MTC (index case)

Germline ret mutation analysis

Ret +ve patient (hereditary disease)

Ret mutation analysis in all first degree relatives

Ret negative

No further evaluation

Ret positive

surgery

Ret -ve patient

Pentagastrin test in 3 first degree relatives

Negative pentagastrin test - insignificant risk

For those refusing surgery/ subjects with exon 13,14,15 mutations

Pentagastrin test

positive

surgery

negative

Annual pentagastrin test

8/21/2013
**ATA Guidelines 2009**

**Diagnosis and management of Medullary Thyroid Cancer**

- **FNA or calcitonin diagnostic or suspicious for MTC**
  - Mandatory skilled neck US to include the superior mediastinum, central and bilateral lateral neck compartments
  - Serum calcitonin, CEA, and calcium
  - RET mutation analysis
  - Treat PHEO before MTC. PHEO excluded if negative: 1) RET and family history, or 2) plasma free metanephrines and normetanephrines, or 24-hour urine metanephrines and normetanephrines, or 3) adrenal CT or MRI

**Flowchart**

- **N₀ + calcitonin < 400 pg/mL**
  - Thyroidectomy + level VI compartmental dissection

- **N₁ or calcitonin > 400 pg/mL**
  - Obtain:
    - Chest CT
    - Neck CT
    - 3-phase contrast-enhanced multidetector liver CT, or contrast enhanced MRI

- **M₀ or minimal M₁**
  - Extensive M₁
  - Thyroidectomy + level VI compartmental dissection
  - Lateral neck compartmental dissection of image or biopsy positive compartments.
  - In the presence of M₁ disease or advanced local features, consider less aggressive neck surgery to preserve: speech and swallowing, and maintain locoregional disease control to prevent central neck morbidity.
  - Consider EBRT for high risk patients (controversial)

- **Palliative neck operation if needed for trachea compromise or local pain**
  - Consider clinical trials, and palliative therapies including surgery, EBRT, percutaneous interventions, and hepatic embolization.
**Treatment approach of MTC**

1. **Screen for Pheochromocytoma**
   - Positive (+ve) → **Adrenalectomy**
   - Negative (-ve) → Surgery

2. **Surgery**
   - Genetic test

3. **Thyroxine replacement therapy**
   - Post op Calcitonin 3 months post surgery

4. **Post op Calcitonin 3 months post surgery**
   - Increased
     - Imaging
     - No detection → Selective venous catheterization → Surgery
   - Normal
     - Follow up

5. **Disease detected**
   - Loco-regional → CT, RT, Biotherapy → Surgery
   - Distant mets
Follow up of MTC patient with post operative hypercalcitoninemia

Persistent hypercalcitoninemia

Neck, liver USG, Bone scan
CT Scan - neck, thorax, abdomen

Positive

Appropriate follow up and treatment

Negative

Venous sampling catheterization with CT measurement

Gradient outside neck

Present

Appropriate follow up

Absent

Gradient in neck/mediastinum

Surgery
Thank You