Sporadic/Hereditary
Medullary Thyroid Cancer

B. Niederle

Chirurgische Endokrinologie
Universitätsklinik für Chirurgie
Thyroid Cancer

Follicular cell-derived
- Papillary thyroid cancer
- Follicular thyroid cancer
- Anaplastic thyroid cancer

C-Cell
- Medullary thyroid cancer
  - sporadic
  - hereditary
Medullary Thyroid Cancer

- Parafollicular cells, neural chrest
Medullary Thyroid Cancer

- Parafollicular cells, neural crest
- 3 – 10 % of all thyroid cancers
Thyroid Neoplasms

1991-2001
n = 556

PTC 330 (59%)
FTC 81 (15%)
MTC 110 (20%)
ITC 7 (1%)
ATC 14 (3%)
others 14 (3%)

Department of Surgery, Medical University, Vienna
Thyroid Neoplasms

Germany [1996]
n = 2537

- PTC: 1685 (66%)
- FTC: 691 (27%)
- ATC: 91 (4%)
- MTC: 70 (3%)

Hölzer S. et al.: Cancer 89 (2000); 192-201
Thyroid Neoplasms

USA [1996]

n = 5583

- PTC: 4522 (81%)
- FTC: 788 (14%)
- ATC: 96 (2%)
- MTC: 177 (3%)

Hundahl, S.A. et al.: Cancer 89 (2000); 202-217
Medullary Thyroid Cancer

- Parafollicular cells, neural chrest
- 3 – 10% of all thyroid cancers
- Incidence 1 – 2 / million inhabitants / year
- f / m = 1.5 / 1
- Age at diagnosis (4. – 7. decade)
# Medullary Thyroid Cancer

## Clinical Presentation

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Age</th>
<th>Sex</th>
<th>TH</th>
<th>LNN</th>
<th>M1</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saad</td>
<td>1984</td>
<td>125</td>
<td>46±16</td>
<td>1:10</td>
<td>94</td>
<td>52</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>Bergholm</td>
<td>1989</td>
<td>186</td>
<td>-</td>
<td>1;1,3</td>
<td>83</td>
<td>44</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Rosenberg</td>
<td>1989</td>
<td>33</td>
<td>41±14</td>
<td>1:1,4</td>
<td>75</td>
<td>45</td>
<td>28</td>
<td>30</td>
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<tr>
<td>Kallinowski</td>
<td>1993</td>
<td>33</td>
<td>-</td>
<td>-</td>
<td>45</td>
<td>42</td>
<td>12</td>
<td>12</td>
</tr>
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</table>
Sporadic Medullary Thyroid Cancer

Disease Free Survival

n = 33

Department of Surgery, Medical University, Vienna - 1990
## Medullary Thyroid Cancer

### Survival

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>5 Years</th>
<th>10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rougier</td>
<td>1983</td>
<td>75</td>
<td>72%</td>
<td>54%</td>
</tr>
<tr>
<td>Saad</td>
<td>1984</td>
<td>161</td>
<td>78%</td>
<td>61%</td>
</tr>
<tr>
<td>Schröder</td>
<td>1988</td>
<td>60</td>
<td>67%</td>
<td>47%</td>
</tr>
<tr>
<td>Bergholm</td>
<td>1990</td>
<td>249</td>
<td>80%</td>
<td>68%</td>
</tr>
<tr>
<td>Kohlwagen</td>
<td>1991</td>
<td>480</td>
<td>81%</td>
<td>61%</td>
</tr>
<tr>
<td>Längle (SMENA)</td>
<td>1994</td>
<td>88</td>
<td>81%</td>
<td>73%</td>
</tr>
<tr>
<td>Winter (Ger MEN)</td>
<td>1994</td>
<td>709</td>
<td>94%</td>
<td>85%</td>
</tr>
</tbody>
</table>
Medullary Thyroid Cancer

Treatment

There are no conservative treatment regimes – Surgery is the treatment of choice!
Medullary Thyroid Cancer

Treatment

There are no conservative treatment regimes –
Surgery is the treatment of choice!
Extent of surgery still under discussion
Sporadic Medullary Thyroid Cancer

pT1-3 vs pT4

n = 33

Department of Surgery, Medical University, Vienna - 1990
Sporadic Medullary Thyroid Cancer

pT1-3: M0 vs Mpos

n = 29

Department of Surgery, Medical University, Vienna - 1990
Sporadic Medullary Thyroid Cancer

pT1-3 M0: N0 vs Npos vs NX

n = 27

Department of Surgery, Medical University, Vienna - 1990
Sporadic Medullary Thyroid Cancer

pT1-3 M0: radical vs less radical surgery

n = 27
Medullary Thyroid Cancer

Prognostic Factors

Univariate/ (multivariate) Analysen (EBM III)

- Distant metastasis
- Lymph node metastasis
- Extent of surgery
- Tumor size
- Age
Medullary Thyroid Cancer

Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1, N0, M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>T2-4, N0, M0</td>
</tr>
<tr>
<td>Stage 2</td>
<td>T1-4, N1, M0</td>
</tr>
<tr>
<td>Stage 3</td>
<td>T1-4, N0-1, M1</td>
</tr>
</tbody>
</table>

UICC 1997
Medullary Thyroid Cancer

Survival

Poor prognosis $\rightarrow$ Late diagnosis
Medullary Thyroid Cancer

Tumour Marker

Calcitonin

32 aminoacid polypeptide
Medullary Thyroid Cancer

Calcitonin Assay (I)

CIS (France) – IRMA manual, 2-step
Nichols (USA) – ICMA automated, 1-step
Medgenix (Belgium) – IRMA manual, 1-step

Calcitonin Stimulation Tests

Pentagastrin:
0.5 µg / kg / BW (diluted in 5-10 ml NaCl; i.v. Bolus; 5-10 sec)
Blood samples: 0, 2, (3), 5, (10) min

Calcium:
3 mg / kg / KG (10 min)
Medullary Thyroid Cancer

Calcitonin „Screening“

Early diagnosis may improve the clinical and biochemical outcome of MTC!
Medullary Thyroid Cancer

„Screening“

A „preoperative“ diagnosis of MTC allows adequate initial surgery!
Medullary Thyroid Cancer

Calcitonin Screening

… not recommended in work-up of thyroid diseases!
### Calcitonin

**Routine biochemical test**

<table>
<thead>
<tr>
<th></th>
<th>Solitary nodule</th>
<th>Multinodular goiter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATA</strong></td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>ETA</strong></td>
<td>43%</td>
<td>32%</td>
</tr>
</tbody>
</table>

Hegedüs et al Endocrine Rev 24 (2003); 102-132
Sporadic Hypercalcitoninemia

Indication for Stimulation Test

Basal Calcitonin level: > 10 pg/ml

Calcitonin Assay: Nichols or CIS
Sporadic Hypercalcitoninemia

Indication for Surgery

Stimulated Calcitonin level: > 100 pg/ml

Calcitonin Assay: Nichols or CIS
Sporadic Hypercalcitoninemia

Calcitonin Screening

The interpretation of basal and stimulated Calcitonin levels allows a prediction of C – cell morphology
Calcitonin Screening

Pathological Workup

The entire surgical specimens (thyroid, lymph nodes) must be blocked and C-cell disorders may be documented by conventional histology and immunohistochemistry

Kaserer K. et al; Wien klin Wschr 2002: 114; 274 - 278
Calcitonin Screening

bCT $> 10$ pg/ml and Pentagastrin-stimulation $> 100$ pg/ml
n = 260

Male n = 167 (67%)
Female n = 93 (36%)
f : m = 1 : 1.8
57 $\pm$ 13.44 years
Calcitonin Screening

Morphology

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>CCH</td>
<td>126 (48.5%)</td>
<td></td>
</tr>
<tr>
<td>MTC</td>
<td>134 (51.5%)</td>
<td></td>
</tr>
<tr>
<td>Σ</td>
<td>260 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

1994 - 2004
C - Cell Hyperplasia
C - Cell Hyperplasia

Definition

(Aside from tumor tissue) - at least one area with more than 50 C-cells per low power field (magnification x100) in both thyroid lobes
(only visible in immunohistochemistry!)
C - Cell Hyperplasia / Cancer

Pathogenesis
C - Cell Hyperplasie

Morphology

focal
diffuse

nodular
neoplastic
Calcitonin Screening

C – Zell Hyperplasie (CCH)

<table>
<thead>
<tr>
<th>Morphologie</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>diffus</td>
<td>28 (22%)</td>
</tr>
<tr>
<td>nodulär</td>
<td>39 (31%)</td>
</tr>
<tr>
<td>neoplastisch (Ca in situ?)</td>
<td>59 (47%)</td>
</tr>
<tr>
<td><strong>Σ</strong></td>
<td>126 (100%)</td>
</tr>
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1994 - 2004
Calcitonin Screening

Morphology

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<td>Σ</td>
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Medullary Thyroid Cancer

Definition

Areas of C-cell proliferation suspected of early infiltration are regarded as carcinoma if a focal loss or reduplication of basement membrane is observed through immunohistochemistry (or in electron microscopy) using antibodies against collagen IV.
Medullary Thyroid Cancer
Calcitonin Screening

bCT >10 pg/ml and Pentagastrin-stimulation >100 pg/ml
n = 260

Male n = 167 (67%)
Female n = 93 (36%)
f : m = 1 : 1.8
57 ± 13.44 years
Sporadic Hypercalcitoninemia

bCT >10 pg/ml and Pentagastrin Stimulation >100 pg/ml

Medullary Thyroid Cancer (MTC)

<table>
<thead>
<tr>
<th>Stimulated Calcitonin pg/ml</th>
<th>n</th>
<th>MTC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>m / w</td>
<td>male n (%)</td>
<td>female (%)</td>
</tr>
<tr>
<td>100 - 200</td>
<td>90 / 18</td>
<td>13 (14)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>201 - 400</td>
<td>36 / 9</td>
<td>5 (14)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>401 - 600</td>
<td>8 / 7</td>
<td>5 (63)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>601 - 800</td>
<td>5 / 1</td>
<td>5 (100)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>801 -</td>
<td>28 / 58</td>
<td>28 (100)</td>
<td>58 (100)</td>
</tr>
<tr>
<td>Σ</td>
<td>167 / 93</td>
<td>56 (34)</td>
<td>78 (84)</td>
</tr>
</tbody>
</table>

1994 - 2004
Sporadic Hypercalcitoninemia

CT >10 pg/ml and Pentagastrin Stimulation >100 pg/ml

MTC – Lymph node involvement - Persistence

<table>
<thead>
<tr>
<th>Stimulated Calcitonin pg/ml</th>
<th>n</th>
<th>MTC</th>
<th>follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N0</td>
<td>N1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>100-200</td>
<td>20</td>
<td>17 (85)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>201-400</td>
<td>12</td>
<td>10 (83)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>401-600</td>
<td>10</td>
<td>9 (90)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>601-800</td>
<td>6</td>
<td>5 (83)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>801-</td>
<td>86</td>
<td>54 (63)</td>
<td>32 (37)</td>
</tr>
<tr>
<td>Σ</td>
<td>134</td>
<td>95 (71)</td>
<td>39 (29)</td>
</tr>
</tbody>
</table>

1994 - 2004
Medullary Thyroid Cancer

- Parafollicular cells, neural crest
- 4 – 10% of all thyroid cancers
- Incidence 1 – 2 / million inhabitants / year
- f / m = 1.5 / 1
- Age at diagnosis (4. – 7. decade)
- Sporadic and hereditary
Thyroid Neoplasms

USA [1996]
n = 5583

- FTC: 788 (14%)
- PTC: 4522 (81%)
- ATC: 96 (2%)
- SMTC: 150 (2.5%)
- HMTC: 27 (0.5%)

Hundahl, S.A. et al.: Cancer 89 (2000); 202-217
Medullary Thyroid Carcinoma

Sporadic vs Hereditary
n = 177

SMTC 150 (85%)
HMTC 27 (15%)

Hundahl, S.A. et al.: Cancer 89 (2000); 202-217
Sporadic / Hereditary Medullary Thyroid Cancer

Surgical Strategy

- **Diagnosis before/during surgery**
  - Total thyroidectomy
  - Hereditary: Completion thyreoidectomie
  - Sporadic: Completion thyroidectomy,
    - If PG-stimulation is positive

**Incl. adequate lymph node surgery**
Medullary Thyroid Cancer

Treatment

• Thyreoidectomy

• Central neck dissection (bilateral)
• functional - or modified radical (systematic) laterale neck dissection

• transcervical or transsternale mediastinal dissection (on demand)

• Thyroid hormone (substitution)
Medullary Thyroid Cancer

Treatment

- Thyreoidectomy
- Central neck dissection (bilateral)
- functional - or modified radical (systematic) laterale neck dissection
- transcervical or transsternale mediastinal dissection (on demand)
- Thyroid hormone (substitution)
Medullary Thyroid Cancer

Treatment

• Thyreoidectomy

• Central neck dissection (bilateral)
• functional - or modified radical (systematic) laterale neck dissection

• transcervical or transsternale mediastinal dissection
  (on demand)

• Thyroid hormone (substitution)
Calcitonin Screening

## Tumor Diameter

<table>
<thead>
<tr>
<th>MTC</th>
<th>Tumor diameter [mean value $\pm$ SD (mm)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>134</td>
<td>12.9 $\pm$ 4.45 (0.6 – 90)</td>
</tr>
</tbody>
</table>
Calcitonin Screening

Lymph node surgery

<table>
<thead>
<tr>
<th>MTC</th>
<th>Examined lymph nodes [n - mean number]</th>
</tr>
</thead>
<tbody>
<tr>
<td>134</td>
<td>71 (2 -188)</td>
</tr>
</tbody>
</table>
Sporadic Medullary Thyroid Cancer

pT - Classification

n = 116

- pT1: 73 (63%)
- pT2-3: 31 (27%)
- pT4: 12 (11%)

Calcitonin screening 1994 – 2004
UICC 1997
**Sporadic Medullary Thyroid Cancer**

\[ pT_{1-4} \ n = 116 \]

<table>
<thead>
<tr>
<th>( pT_a )</th>
<th>( pT_b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>unifocal</td>
<td>multifocal</td>
</tr>
<tr>
<td>93 (80%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>1 (1%)</td>
<td>22 (19%)</td>
</tr>
</tbody>
</table>

Calcitonin screening 1994-2004
### Sporadic Medullary Thyroid Cancer

#### Lymph-node Metastases

<table>
<thead>
<tr>
<th>pN</th>
<th>pT 1 n (%)</th>
<th>pT 2, 3 n (%)</th>
<th>pT 4 n (%)</th>
<th>all pT n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65 (89)</td>
<td>20 (65)</td>
<td>1 (8)</td>
<td>86 (74)</td>
</tr>
<tr>
<td>1</td>
<td>8 (11)</td>
<td>11 (35)</td>
<td>11 (92)</td>
<td>30 (26)</td>
</tr>
<tr>
<td>All</td>
<td>73 (63)</td>
<td>31 (26)</td>
<td>12 (10)</td>
<td>116 (100)</td>
</tr>
</tbody>
</table>

Calcitonin screening 1994 - 2004
Hereditary Medullary Thyroid Cancer

pT – Classification UICC 1997

n = 18

3 (17%) pT1
7 (39%) pT2-3
8 (44%) pT4

Hereditary Medullary Thyroid Cancer

(Bilateral) C – cell hyerplasia – **Precursor lesion** of the hereditary medullary thyroid cancer

# Hereditary Medullary Thyroid Cancer

\[ pT_{1-4} \ n = 18 \ \text{(Index)} \]

<table>
<thead>
<tr>
<th>( pT_a )</th>
<th>unifocal</th>
<th>( pT_b )</th>
<th>multifocal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (5.5 %)</td>
<td>unilateral</td>
<td>1 (5.5 %)</td>
<td>bilateral</td>
</tr>
</tbody>
</table>

Calcitonin screening 1994-2004
# Hereditary Medullary Thyroid Cancer

## Lymph-node Metastases

### Index Patients

<table>
<thead>
<tr>
<th>pN</th>
<th>pT</th>
<th>all pT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 n (%)</td>
<td>2, 3 n (%)</td>
</tr>
<tr>
<td>0</td>
<td>6 (75)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>1</td>
<td>2 (25)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>All</td>
<td>8 (44)</td>
<td>7 (39)</td>
</tr>
</tbody>
</table>

Calcitonin screening 1994 - 2004
Calcitonin Screening

Molecular Genetics

<table>
<thead>
<tr>
<th>Morphology (n)</th>
<th>sporadic n</th>
<th>hereditary n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCH (126)</td>
<td>122</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>MTC (134)</td>
<td>116</td>
<td>18 (13%)</td>
</tr>
<tr>
<td>∑ (260)</td>
<td>238</td>
<td>22 (8%)</td>
</tr>
</tbody>
</table>

1994 - 2004
Multiple Endocrine Neoplasia (MEN)

Definition

Hyper- and/or neoplastic proliferation of more than one endocrine organ
## Medullary Thyroid Cancer

<table>
<thead>
<tr>
<th></th>
<th>FMTC</th>
<th>MEN 2A</th>
<th>MEN 2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTC</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Parathyroid hyperplasia</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Mucosal ganglioneuromas</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Musculoskeletal abnormalities (Marfanoid habitus)</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Markedly enlarged peripheral nerves</td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
## Multiple Endocrine Neoplasia 2A

### Frequency - Literature

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTC</td>
<td>100%</td>
</tr>
<tr>
<td>Phäochromozytom</td>
<td>40-60%</td>
</tr>
<tr>
<td>PHPT</td>
<td>10-40%</td>
</tr>
</tbody>
</table>
Medullary Thyroid Cancer

Chromosome 10 (10q 11.2) - RET Proto - Oncogen
Medullary Thyroid Cancer

RET Proto – Oncogen (Chromosome 10)

7 exons
(8, 10, 11, 13, 14, 15, 16)

22 codons
(533, 600, 609, 611, 618, 620, 630, 634, 635, 637, 768, 781, 790, 791, 804, 806, 826, 883, 891, 907, 912, 918)
Calcitonin Screening

RET Proto-Oncogen - Mutations
Index patients: n = 22

1994 - 2004

Exon 11
6 (27%)

Exon 13
6 (27%)

Exon 14
4 (18%)

Exon 15
2 (9%)

Exon 8
1 (5%)

Exon 10
3 (14%)
Calcitonin Screening

Molecular Genetics

<table>
<thead>
<tr>
<th>Morphology (n)</th>
<th>sporadic n</th>
<th>hereditary n</th>
</tr>
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<tbody>
<tr>
<td>CCH (126)</td>
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1994 - 2004
Calcitonin Screening

C – Cell Hyperplasie (CCH)

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<th>Morphology</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>diffuse</td>
<td>28</td>
</tr>
<tr>
<td>nodulär</td>
<td>38 (+1)*</td>
</tr>
<tr>
<td>neoplastic (Ca in situ?)</td>
<td>56 (+3)*</td>
</tr>
<tr>
<td><strong>∑</strong></td>
<td><strong>122 (+4)</strong>*</td>
</tr>
</tbody>
</table>

* hereditary

1994 - 2004
# Calcitonin Screening

## Index Patients - Phenotype

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MTC</th>
<th>Pheo uni</th>
<th>Pheo bi</th>
<th>PHPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMTC „only“</td>
<td>9 (+4)</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MEN 2A - 1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MEN 2A – 2</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>MEN 2A – 3</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td><strong>∑</strong></td>
<td>22</td>
<td>18</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

1994 - 2004
## Calcitonin Screening

### Index Patients – Genetic Screening

<table>
<thead>
<tr>
<th></th>
<th>Gene-carrier</th>
<th>Surgery</th>
<th>MTC</th>
<th>CCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index patients</td>
<td>22</td>
<td>38</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>1994 - 2004</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Calcitonin Screening

### Index Patients – Genetic Screening - MTC

<table>
<thead>
<tr>
<th>Index patients</th>
<th>Gene-carrier</th>
<th>Surgery</th>
<th>MTC</th>
<th>CCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>31</td>
<td>26</td>
<td>16</td>
<td>10</td>
</tr>
</tbody>
</table>

1994 - 2004
## Calcitonin Screening

### Index Patients – Genetic Screening - CCH

<table>
<thead>
<tr>
<th>Index patients</th>
<th>Gene-carrier</th>
<th>Surgery</th>
<th>MTC</th>
<th>CCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>4*</td>
<td>3</td>
<td>0</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

* Exon 13, Codon 791; TAT>TAC; tyr>phen

1994 - 2004
Hereditary Medullary Thyroid Cancer

Genetic Screening

Preclinical diagnosis of hereditary MTC improves survival!!
Genetic screening is the „golden standard“ for confirmation of hereditary medullary thyroid cancer (and MEN II) and can suggest therapeutic approach and outcome.
Hereditary Medullary Thyroid Cancer

Prophylactic Thyroidectomy:
Thyreoidectomy before tumour development

Early thyreoidectomy:
Thyreoidectomy in a preclinical stage
## Hereditary Medullary Thyroid Cancer

<table>
<thead>
<tr>
<th>Surgical strategy</th>
<th>proph.</th>
<th>early</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroidectomy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Centrale neck dissection (bilateral)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lateral neck dissection (functional bilateral)</td>
<td>-</td>
<td>(+)</td>
</tr>
<tr>
<td>Transsternale mediasinal dissection</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Hereditary Medullary Thyroid Cancer

Patients (prophylactic/early surgery)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Age (p)</th>
<th>Age (e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMTC &quot;only&quot;</td>
<td>13</td>
<td>5, 24, 52</td>
<td>19, 20, 24, 25, 28, 30, 43, 56, 69, 71</td>
</tr>
<tr>
<td>MEN 2A – 1</td>
<td>4</td>
<td>7</td>
<td>4, 5, 10</td>
</tr>
<tr>
<td>MEN 2A – 2</td>
<td>21</td>
<td>6, 6, 21, 22,</td>
<td>8, 15, 27, 35, 38, 42, 50, 52, 54, 56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22, 25, 33,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>36, 37, 45,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>60,</td>
<td></td>
</tr>
<tr>
<td>∑</td>
<td>38</td>
<td>5 – 60 (15)</td>
<td>4 – 71 (23)</td>
</tr>
</tbody>
</table>

Department of Surgery, Medical University of Vienna; (12/2005)
Hereditary Medullary Thyroid Cancer
# Hereditary Medullary Thyroid Cancer

## Complications

<table>
<thead>
<tr>
<th>Thyroidectomy</th>
<th>n</th>
<th>Parese (N.L.R)</th>
<th>Hypoparathyreoidism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>transient</td>
<td>permanent</td>
</tr>
<tr>
<td>Prophylactic</td>
<td>15</td>
<td>0/15</td>
<td>0/15</td>
</tr>
<tr>
<td>Early</td>
<td>23</td>
<td>0/23</td>
<td>0/23</td>
</tr>
<tr>
<td><strong>Σ</strong></td>
<td>38</td>
<td>0/38</td>
<td>0/38</td>
</tr>
</tbody>
</table>

Department of Surgery, Medical University of Vienna; (12/2005)
# Hereditary Medullary Thyroid Cancer

<table>
<thead>
<tr>
<th>Calcitonin (preop)</th>
<th>MTC</th>
<th>Lymph node metastasis</th>
<th>M</th>
<th>Thyroidectomy and</th>
</tr>
</thead>
<tbody>
<tr>
<td>bCT [n], sCT [n]</td>
<td>rare (2/14) [12 CCH]</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>bCT [n], sCT [e]</td>
<td>probable (9/12)</td>
<td>? (0/12)</td>
<td>0</td>
<td>Central neck dissection - bilateral</td>
</tr>
<tr>
<td>bCT [e], sCT [e]</td>
<td>always (12/12)</td>
<td>possible (1/12)</td>
<td>0</td>
<td>Central neck dissection bilateral Functional neck dissection bilateral</td>
</tr>
</tbody>
</table>

Department of Surgery, Medical University Vienna, (12/2005)
Hereditary Medullary Thyroid Cancer

Codon / Calcitonin Specific Surgical Strategy

Basal and/or stimulated Calcitonin

increased

Any

[3] highest
918, 922, 883

[2a] very high
634, 630

[2b] high
620, 618, 611, 609

[1] low
768, 790, 791, 804, 891

6-12 mo
1-2 y
5 y
5-10 y

Risk category: (Codon)

Thyroidectomy at age:

Immediately

Lymph node dissection:

• central comp.
• lateral comp.

Synchronously

Tumour>10mm or node pos

Dralle H, Machens A: Surgery 139 (2006); 279-282
# Medullary Thyroid Cancer

## Follow-up

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Sporadic MTC</th>
<th>Hereditary MTC</th>
<th>Σ</th>
</tr>
</thead>
</table>
|                               | Cured        |                | N0    | N1    | N0 | N1
| Cured                         | 94 (81%)     | 11 (61%)       | 105   | (78%) |
| N0                            | 82           | 8              | 90    |       |
| N1                            | 12           | 3              | 15    |       |
| Persisting Disease (M?)       | 22 (19%)     | 7 (39%)        | 29    | (22%) |
| N0                            | 3            | 1              | 4     |       |
| N1                            | 19           | 6              | 25    |       |

Calcitonin screening: 1994 - 2004
Medullary Thyroid Cancer

Is it possible to improve the prognosis?

YES!
EARLY DIAGNOSIS
Conclusion

Total thyroidectomy and lymph node dissection
(bilateral central neck dissection, bilateral later neck dissection [transsternale mediastinal dissection])
lead to the best long-term results in clinically apparent sporadic/hereditary MTC –
nevertheless the chance to “cure“ is low!
Medullary Thyroid Cancer

Conclusion

Screening for MTC and early treatment has a nearly 100% cure rate (pT1 73/116 [63%]).
Calcitonin Screening

Conclusion

• Basal Calcitonin measurements „must“ be performed in all patients independent the „thyroid morphology“
• bCT >10pg/ml → Pentagastrin stimulation
• sCT > 100 pg/ml → Surgery
• Genetic Screening!
Multiple Endocrine Neoplasia (MEN) MEN IIA

Conclusion

Genetic screening (blood) has to be done in all patients with medullary thyroid cancer or pheochromocytoma to exclude MEN II.
Hereditary Medullary Thyroid Cancer

Genetic Screening

Preclinical diagnosis of hereditary MTC improves survival
Conclusion

Hereditary medullary thyroid disease (HMTC) is a “model” disease. **Prophylactic thyroidectomy** avoids malignancy!
Hereditary medullary thyroid disease (HMTC) is a “model“ disease

*early* (preclinical) **thyroidectomy**

“cures“ (up to 98%)!
Hereditary Medullary Thyroid Cancer

Genetic Screening

Genetic screening for HMTC can suggest time for surgery and the extent of surgery!
New members!

WELCOME!
CONTACT

Secretary-Treasurer

bruno.niederle@meduniwien.ac.at

FAX ++43-1-40400 6827
European Society of Endocrine Surgeons

ESES Workshop Vienna

MAY 17-19, 2007
Topic

Endoscopic Surgery in Neuroendocrine Pancreatic Tumors
http://www.meduniwien.ac.at/chir-endokrin

Chirurgische Endokrinologie