Thyroid carcinoma

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Thyroid tumors

**PRIMARY TUMORS**

Tumors of the follicular epithelium:
- Tumors of the follicular cell:
  - benign – follicular adenoma
  - malignant: well differentiated: papillary carcinoma
    follicular carcinoma
    Hürtele cell carcinoma
    poorly differentiated: insular, tall-cell, diffuse sclerosing.
  - undifferentiated: anaplastic carcinoma

- Tumor of the parafollicular C cells: medullary carcinoma

Nonepithelial tumors: sarcoma, malignant lymphoma ...

**SECONDARY TUMORS**
Tumor thyroid disease

**Benign tumors** - adenomas (scintigraphic "hot" or "cold"), adenomatous goiter, cysts

**Malignant tumors** - carcinoma
- papillary 80%
- follicular 10% (≈ Hürthle cell ca. 2%)
- medullary 7% (5%)
- poorly differentiated 2%
- anaplastic <1%
- metastasis of other tumors in the thyroid
Malignant tumors of the thyroid

- the annual incidence 0.5-10/100 000 people
- 1% of all malignant carcinomas
- 90% of all malignant endocrine tumors
- very good prognosis for differentiated tumors of the thyroid
Scintigraphic “cold” nodules
NODULAR CHANGES
The number, size, echostructure, location
1. cysts and cystic changed nodes
2. solitary nodes- hypoechoic, isoechogenic, degeneratively changed (benign goiter)
3. multinodular goiter
4. nodes in lymphomatosus goiter
NODULAR CHANGES: adenomas, carcinomas
Echographical criteria of malignancy

Hypoechoogenicity

Microcalcifications

Without hypoechogetic edge, irregular borders

Intranodular vascularisation

Regional lymphadenopathy
Papillary carcinoma: The most common carcinoma of the thyroid (80%). Today, owing to ultrasonography, they are detected early in the course (about half of the detected papillary carcinoma is up to 1 cm).
Subtypes of thyroid papillary carcinoma:

- follicular variant
- tall cell- columnar cell
- solid trabecular
- diffuse sclerosing

-Some of them have aggressive behavior
Papillary carcinoma at the time of diagnosis

At presentation

- 60% Intrathyroid
- 38% With regional lymph node metastasis
- 1-2% With distant metastasis

90-95% long-term cure

5-10% recurrent disease

Local recurrence in cervical lymph node or thyroid bed (80-90% of cases)

10-30% dead of disease

Distant metastasis (10-20% of cases)

50-90% dead of disease

Fig. 18A.5 Flow chart to depict the natural history of papillary thyroid carcinoma.
Follicular carcinoma
It occurs much less frequently (10%), older age, more common in areas with endemic goiter. No reliable diagnostic possibility to distinguish them from adenoma, except possibly present metastases. It may have a similar echographic image as papillary carcinoma (hypoechogenicity, irregular margin, invasive growth, small calcifications-microcalcifications), but it is usually larger than papillary carcinoma. Sometimes it appears as isoechogenic or degeneratively changed node.

Hürthl carcinoma (2%) is frequently isoechogenic on US, does not differ from the nodular goiter.
Subtypes of thyroid follicular carcinoma:

- minimally-invasive
- invasive
- Hürthle cell
- insular

- Some of them have aggressive behavior
Follicular carcinoma

The prognosis is good if no distant metastases.

Distant metastases, in the lungs and in the bones.

Metastases are usually functional and can be treated with radioiodine.

Large doses of iodine, particularly in bone metastases can lead to damage to the bone marrow.

Distant metastases - worse prognosis.
Follicular adenoma or carcinoma

- Impossibility of cytological diagnosis.

- Diagnostic criteria of minimally invasive carcinoma: complete invasion through the capsule and intravascular invasion.
Follicular carcinoma at the time of diagnosis

- 75-90% Intrathyroid
  - 70-80% long-term cure

- 5-20% With regional lymph node metastasis
  - 20-30% recurrent disease
    - Local recurrence (80-90% of cases)
      - 10-30% dead of disease
    - Distant metastasis (10-20% of cases)
      - 50-90% dead of disease

- 2-5% With distant metastasis
  - 50-90% dead of disease
Poor prognostic sign for differentiated thyroid carcinomas: interruption of the lobe capsule (capsule invasion), the invasion of the trachea or esophagus (rarely seen), or invasion of blood vessels, due to tumor or metastases to lymph nodes. Preoperative diagnosis of metastatic lymph nodes - required extensive surgery.
Poorly differentiated and anaplastic thyroid carcinomas

- Insular carcinoma
- Trabecular
- Solid
Anaplastic carcinoma <1%

- one of the most malignant cancers in humans
- the elderly with pre-existing goiter
- rapidly growing tumor, hard consistency
- already at diagnosis inoperable because of extensive invasion of surrounding structures; regional and distant metastases
- prognosis is poor, median survival of 3-4 months, most dying in 6-12 months.
- dd: sarcoma, metastasis, parathyroid carcinoma, Riedel's struma- immunohistochemistry, clinical data
• Mucoepidermoid thyroid cancer is rare; two variants: mucoepidermoid carcinoma and sclerosing mucoepidermoid carcinoma

• Rare tumors of the thyroid:
  • SETTLE tumori: spindled and epithelial tumor with thymus like differentiation
  • CASTLE tumori: tumor-carcinoma with thymus like differentiation
Microcarcinoma of the thyroid gland
Well differentiated thyroid carcinomas <1 cm

- Detected by ultrasound and FNAC (owing to US a significant number of nowday detected thyroid cancers are smaller than 1 cm)
- Incidental microcarcinoma: histologically detected in thyroid tissue, which is operated for another reason
- Clinical (former Occult) microcarcinoma: discovered as a source (starting point) of metastases in the neck lymph nodes or distant metastases
- Latent microcarcinoma which is detected accidentally at autopsy
Medullary carcinoma

• Malignant tumor originated from parafollicular C cells
• Produces calcitonin and many other peptides
• 70-80% sporadic
• 20-30% hereditary: younger age, multicenter, bilateral
Medullary carcinoma
5-10% of patients with ca. thyroid; echographically hypoechogenic nodules, of varying sizes, often with calcification, irregular margin, with the infiltration of the neighbouring tissues.

Medullary carcinoma with tiny calcifications
Preoperatively, except with FNAC, medullary ca. can be diagnosed with calcitonin measurement in the serum and aspirate.
- **Sporadic form-** 70-80%

- **Family form-** 20-30%, a examination of relatives (ultrasonography, determination of basal calcitonin in serum and after provocation, and genetic testing) for early diagnosis and preventive surgical therapy.

**Prognosis**

- **good:** if early detected and operated without local metastases and without elevated serum calcitonin.
- **worse:** metastases present at the time of surgery, not enough radical surgery, calcitonin elevated after surgery (dissemination of disease- local recurrences and distant metastases).
FAMILIAL MEDULLARY THYROID CARCINOMA SYNDROMES

Medullary Carcinoma Alone

MEN IIA (II)
C Cell Hyperplasia – Medullary Carcinoma
Adrenal Medullary Hyperplasia – Pheochromocytoma
Parathyroid Hyperplasia – Adenoma

MEN IIB (III)
C Cell Hyperplasia – Medullary Carcinoma
Adrenal Medullary Hyperplasia – Pheochromocytoma
Gastrointestinal and Ocular Ganglioneuromas
Skeletal Abnormalities
MEN IIb - tongue neurinomas
Primary lymphoma of the thyroid

Rare primary tumor

Associated with Hashimoto's thyroiditis

Women, middle-aged

B immunophenotype
indolent (MALT)
aggressive (tall-cell)
PRIMARY THYROID LYMPHOMA

- Rare neoplasm
  - 0.5-1% of all lymphomas
  - 5% of all neoplasms of the thyroid

- Incidence
  - 3-5/1,000,000
Metastatic tumors

- Lung adenocarcinoma
- Breast cancer
- Melanoma
- Renal cancer
Treatment of thyroid tumors

Benign tumors: extirpation, lobectomy

Malignant tumors:

1. **total thyroidectomy**
   (with neck dissection in the case of lymph node metastasis)
   Complications:
   hypoparathyroidism (5%) and paresis of recurrent laryngeal nerve (1-2%)

2. radioiodine ablation and therapy

3. suppressive therapy

4. chemotherapy, external radiation- rarely (mostly anaplastic ca.,
   incomplete because of extensive invasion of surrounding structures
   or widespread disease with iodine-negative metastases.)
Metastases on the left side of the neck.
Metastases on the left side of the neck

Metastasis

v. jug. int.
Metastatic lymph nodes
Neck metastases
Neck dissection

- Paratracheal neck dissection - region VI
- Selective neck dissections
- Modified radical neck dissection type I, II and III
- Radical neck dissection
- Extended radical neck dissection
Basic treatment of differentiated thyroid cancer:

*a total or near-total thyroidectomy and radioiodine ablation of thyroid remnant*

- ablation dose: 1.1-3.7 GBq J-131 (30-100 mCi)

-low iodine diet: < 50 μg/day, ↑uptake 68%, (Maxon 1983., Maruca 1984.)

-diagnostic whole body scintigraphy with 74-185 MBq I-131 (2-5 mCi) before ablation?? (stunning)
Procedure after thyroid carcinoma surgery

- 4 weeks after total thyroidectomy **ablation dose** of 30-100 mCi 131I for residual thyroid tissue
- TSH above 30 µU/mL (possibly exogenous TSH-Thyrogen)
- whole body scintigraphy
- therapeutic dose of 100-200 mCi for the treatment of metastases
- measurement of Tg
Total thyroidectomy $\approx 2\%$
“Something always remains” (98%) – thyroid remnant tissue after "total" thyroidectomy - scintigraphy with I-131
Why is the ablation of thyroid remnant with a I-131 necessary?

Why radioiodine ablation? ↓ number of recurrences, metastases and mortality.

(Mazzaferri and Massoll, 2002.)
Why is the ablation of thyroid remnant with a I-131 necessary?

Ablation of thyroid remnant destroys possible microfoci of thyroid ca., destroys possible micrometastases and promotes Tg to tumor marker (the only source of Tg is thyroid tissue or metastases).

It creates conditions for the detection and treatment of possible metastases.
Exogenous stimulation with rhTSH (Thyrogen)

Two-dose Regimen

<table>
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<tr>
<th>Sun</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thu</th>
<th>Fri</th>
<th>Sat</th>
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<tr>
<td>THYROGEN - day 1</td>
<td>THYROGEN - day 2</td>
<td>I31I - day 3</td>
<td></td>
<td>WBS and Tg Test - day 5</td>
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</tr>
</tbody>
</table>

- 0.9 mg Thyrogen i.m. on day 1 and 2
- TSH on day 3 and 5
- 74-185 MBq I-131 on day 3
- Diagnostic I-131 WBS on day 5
- Tg measurement on day 5
Exogenous stimulation with rhTSH (Thyrogen)

1. day injection of Thyrogen
2. day injection of Thyrogen
3. day - diagnostic (or ablative- therapeutic ) dose of I-131
5. day - Tg and whole body scintigraphy
Treatment of functional metastases with I-131
Metastases in the lymph nodes - Therapy with I-131

Metastases in the lymph nodes of the neck - Scan after therapy with 100 mCi J-131
Functional metastases in the lung - Therapy with I-131

Metastases in the lung - scan after 200 mCi I-131
Functional metastases in the bones - Therapy with I-131

Metastases in the bones - scan after 200 mCi I-131
Bone metastases
External radiation

- inoperable tumor
- residual, deeply infiltrating tumor of the esophagus, trachea
- bone metastases: a) after J-131  b) prevention of pathological fractures
- brain metastases
- with massive mediastinal metastases for which there is low probability of total control with I-131
- Recurrent metastases after the maximum therapeutic dose of I-131 (1Ci or 37 GBq)
- obstruction of the vena cava superior
- dose: 35-45 Gy for bone metastases, 65 Gy for inoperable tm.
Chemotherapy

* Progressive disease after surgery, therapy application of I-131 and external radiation

* The most commonly used adriamycin

* The therapeutic response is partial
Prognosis and follow-up

Good prognosis:
no accumulation of I-131, unmeasurable Tg, normal echographic findings in the neck

Poor prognosis:
Distant metastases (lung, bones).
High thyroglobulin.
Nonfunctional distant metastases (that don’t accumulate radioiodine).
A lot of residual tissue after surgery, residual local metastases.

Residual tissue on the neck after total thyroidectomy
Why does it take a long follow-up of patients with thyroid carcinoma?
Follow-up of patients with differentiated thyroid carcinoma

- Methods in the follow-up
- Follow-up strategy
The most important methods in the follow-up:

Thyroglobulin (Tg)

Scintigraphy with I-131

Neck ultrasonography
Thyroglobulin

- negative Tg (T4 or TSH) =<0,5 ng/ml
- sensitivity *:
  
  Tg/T4= 78%
  
  Tg/TSH= 96%  (hypothyroidism )
  
  Tg/rhTSH= 92%

- TgAb#

- Tg> 2 ng/ml: recurrence? metastases? where are they?
  are they iodine positive or negative?


Thyroid antibodies

Chiovato. 2003
The new definition of successful ablation !?

Negative Tg (<0,5 ng/ml) under TSH stimulation (thyroxine ex or rhTSH)*

Whole body scintigraphy with I-131

- diagnostic:
  - withdrawal of thyroid hormone: hypothyroidism...
  - rhTSH
  - 185 MBq (5 mCi) I-131
  - if high dose therapy is intended with I-131, only 74 MBq or **ommitted** (stunning)

- post-ablation and post-therapy (10-26% additional meta. foci): 3.7-1 GBq I-131 (100-300 mCi)?

- sensitivity*:
  - d-WBS = 49%
  - pt-WBS= 79%

The percentage of false negative results in patients with metastases diagnosed at pt-WBS (N=35)

(Haugen BR et al. A comparison of recombinant human thyrotropin.... J Clin Endocrinol Metab.1999;84:3877-3885.)
Neck ultrasonography

- 20-50% patients with differentiated thyroid carcinoma have metastases in cervical lymph nodes*
- negative Tg---- US positive
- fine needle aspiration (FNA) + Tg in aspirate (Tg/a)
- sensitivity#: 
  - FNAC = 85 - 91%
  - FNA + Tg/a = 100%

New definition of successful ablation?

**Negative Tg** (<0.5 ng/ml) under TSH stimulation (thyroxine ex or rhTSH)*

+ Negative neck US!?

*Disease free patients

Follow-up strategy for patients with differentiated thyroid carcinoma

Preoperative staging*

1. **Low-risk patients** (80%): T1, N0, M0

2. **High-risk patients** (20%): T>1, or N1, M1

Postoperatively and after ablation

1. **Low-risk:** tm. removed completely, no invasion tm. in the surrounding structures, tm. no aggressive histology, no accumulation of I-131 outside the thyroid bed on the neck, no local nor distant metastases.

2. **High-risk:** incomplete tm. resection, tm. invasion in the surrounding structures, aggressive histology, accumulation of I-131 outside the thyroid bed on the neck, distant metastases.

AMES criteria for the definition of low and high risk groups in papillary and follicular carcinoma

<table>
<thead>
<tr>
<th>Parameters assessed in the AMES (age, metastases, extent of primary cancer, and tumor size) risk-group definition system:</th>
<th>Low-risk</th>
<th>High-risk</th>
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<tr>
<td>Parameter</td>
<td>Low-risk</td>
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<tr>
<td>Age</td>
<td>Male ≤40 years</td>
<td>Male &gt;40 years</td>
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<td></td>
<td>Female ≤50 years</td>
<td>Female &gt;50 years</td>
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<tr>
<td>Metastases</td>
<td>No distant metastasis</td>
<td>Distant metastasis</td>
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<tr>
<td>Extent of primary cancer</td>
<td>Intrathyroidal papillary carcinoma</td>
<td>Extrathyroidal papillary carcinoma</td>
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<td>Minimally invasive follicular carcinoma</td>
<td>Widely invasive follicular carcinoma</td>
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<tr>
<td>Size</td>
<td>&lt;5 cm</td>
<td>&gt;5 cm</td>
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### Table 4. TNM Classification System for Differentiated Thyroid Carcinoma

#### Definition

<table>
<thead>
<tr>
<th>T1</th>
<th>Tumor diameter 2 cm or smaller</th>
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<tbody>
<tr>
<td>T2</td>
<td>Primary tumor diameter &gt;2 to 4 cm</td>
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<tr>
<td>T3</td>
<td>Primary tumor diameter &gt;4 cm limited to the thyroid or with minimal extrathyroidal extension</td>
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<tr>
<td>T4a</td>
<td>Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve</td>
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<tr>
<td>T4b</td>
<td>Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels</td>
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<tr>
<td>TX</td>
<td>Primary tumor size unknown, but without extrathyroidal invasion</td>
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<tr>
<td>N0</td>
<td>No metastatic nodes</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)</td>
</tr>
<tr>
<td>N1b</td>
<td>Metastasis to unilateral, bilateral, contralateral cervical or superior mediastinal nodes</td>
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<tr>
<td>NX</td>
<td>Nodes not assessed at surgery</td>
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<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
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<tr>
<td>MX</td>
<td>Distant metastases not assessed</td>
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#### Stages

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<th>Patient age &lt;45 years</th>
<th>Patient age 45 years or older</th>
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<td>Stage I</td>
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<td>Stage III</td>
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<td>Stage IVA</td>
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<td>Stage IVB</td>
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<td>Stage IVC</td>
<td>Any T, Any N, M1</td>
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</table>
Patients without signs of disease - disease free patients*

- Most of the patients after tot. thyroidectomy and radioiodine ablation, without clinical and scintigraphic evidence of disease, with negative Tg / T4 and Tg / TSH and negative neck US

- Follow-up: **Tg/T4 and neck US per year**

- d-WBS not required: sensitivity of Tg/T4 is higher than sensitivity of d-WBS (78% vs. 49%)

Follow-up high-risk patients*

The follow-up strategy for these patients is more aggressive, and in case of recurrence or metastatic disease, the following procedures are applied, depending on iodine positive or negative recurrences or metastases:

- curative or palliative surgery
- I-131 therapy
- external radiation
- experimental chemotерapeutic trial
- watchful waiting in patients with stable, asymptomatic and slow progressive disease

Iodine - positive metastases - 66%
- The treatment of choice: I-131 every 6-12 months
- dedifferentiation

Iodine - negative, Tg positive meta. - 33%
- diagnosis - Tl-201, Sestamibi, Tetrofosfin, bone sc., rtg., MR, CT, F18-FDG PET
- treatment:
  a) single meta.: surgery., radiation, I-131? (6-9%)
  b) multiple: redifferentiation using retinoic acid?
     26% ↑ uptake, 16%↓ meta. *
  c) chemotherapy-partial, modest response (25%)

F-18- FDG PET

- Malignant tumors show elevated glucose metabolism and accumulate also F-18 FDG
- The follow up of thyroid cancer belongs to a la indication for FDG PET according to the Consensus Conference 2000
- Whereas I-131 is accumulated mainly in well differentiated recurrences and metastases, F-18 FDG accumulation mainly represents poor differentiation of tumor cells
Why suppressive therapy?

[B22] What is the role of TSH suppression therapy? DTC expresses the TSH receptor on the cell membrane and responds to TSH stimulation by increasing the expression of several thyroid specific proteins (Tg, sodium-iodide symporter) and by increasing the rates of cell growth (268). Suppression of TSH, using supra-physiologic doses of LT₄, is used commonly to treat patients with thyroid cancer in an effort to decrease the risk of recurrence (127,214,269). A meta-analysis

Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer

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Suppressive therapy

- The aim of TSH suppression therapy (TSH<0.1 mU / L) with supraphysiological doses of T4 is to reduce the risk of recurrence or metastasis.

- Improves outcomes in high risk patients while there is no evidence for improving outcomes in low risk patients.

- suppressive therapy = subclinical, latent thyrotoxicosis

Recommendation*:

- low-risk patients without evidence of disease: 0.5-2 mU / L
- high-risk patients without evidence of disease: 0.1-0.5 mU / L
- patients with persistent disease: <0.1 mU / L

Suppressive therapy

- **Thyroxine** (Euthyrox, Letrox) 100-150 µg daily

- The goal of therapy: suppressed TSH and normal values of thyroid hormones

- Treatment of hypoparathyroidism: Vitamin D (AT 10 drops or Rocaltrol)
SURVIVAL vs HISTOTYPE (n=1150)

SURVIVAL

% 100 50 0

YEARS

0 2 5 10 15 20

PTC
FTC
MTC
ATC

Dept. Endocrinology University of Pisa

The end!