THYROID NODULES AND THYROID CANCER

DEPARTMENT OF ENDOCRINOLOGY, DIABETES AND ISOTOPE THERAPY
WROCLAW MEDICAL UNIVERSITY
JACEK DAROSZEWSKI, ANNA BRONA
THYROID NODULES

J. Daroszewski
THYROID NODULES

Benign

- Colloid-filled follicles
- Adenomas
- Cysts
- Lymphocytic thyroiditis
- Painful (subacute, deQuervain) thyroiditis

Malignant

- Papillary
- Follicular
- Medullary
- Anaplastic
- Lymphoma
- Metastases
Prevalence of thyroid nodules

- Clinical findings: 7-15%
- US findings: 30-40%
- Autopsy findings: 50%
- DTC (autopsy): 4-8%

J. Daroszewski
CAUSES OF THYROID NODULES

**Primary factors**

- Functional heterogeneity of normal follicular cells, cause unknown, possibly genetic and acquisition of new inheritable qualities by replicating epithelial cells
- Subsequent functional and structural abnormalities in growing goiters

**Secondary factors (Stimuli to New Follicle Generation)**

- TSH (induced by, e.g., iodine deficiency, goitrogens, inborn errors of thyroid hormone synthesis)
- Other thyroid-stimulating factors (TGF-B, EGF, IGF)
- Usually the goiter *grows gradually* for a period of a few to many years, and then becomes stable with little tendency for further growth

- Spontaneous *reduction* in the size of the thyroid gland is *very rare*
Rarely, if ever, do the patients become hypothyroid and if they do, the diagnosis is more probably Hashimoto's thyroiditis than nodular goiter.

If the goiter is present for a long time, thyrotoxicosis develops in a large number of patients (8-10%).
Multinodular goiter – indications for surgical treatment

Vena cava superior syndrome – dilatation of superficial chest veins
Toxic Multinodular Goiter

- More common in places with lower iodine intake
  - Accounts for less than 5% of thyrotoxicosis cases in iodine-sufficient areas and up to 50% in iodine-deficient areas
- Evolution from sporadic diffuse goiter to toxic multinodular goiter is gradual
- TSH receptor mutations mutations have been found in some patients with toxic multinodular goiters
- Surgery or $^{131}$I is recommended – (radical treatment)
SIGNS AND SYMPTOMS OF GOITER
(usually asymptomatic)

- Presence of an enlarging mass in the neck
- Dysphagia, cough, and hoarseness
- Paralysis of a recurrent laryngeal nerve (very unusual – suggesting cancer)
- Horner's syndrome (rather rare)
- Symptoms suggesting constriction of the trachea (dyspnoe)
Multinodular goiter and single nodule – management

- Prophylaxis – on national level
- Exclusion of malignancy
- Follow – up
- LT4 treatment – rarely in young subjects, efficacy not confirmed
- Thyroidectomy

J.Daroszewski
DIAGNOSTIC TESTS

- TSH, fT4
- AntiTPO, TRab
- USG
- Isotope scintigraphy (?)
- Chest X-ray
- FNAB
Ultrasound of thyroid

- rapid, simple, inexpensive
- extremely sensitive
- thyroid and nodule measurement (follow up)
- nodule solid or cystic
- US assisted FNAB
Thyroid scintigraphy

- $^{99m}$Tc, $^{131}$I
- function of the nodule: cold, warm, toxic
- sensitivity (cold + warm) 96%
- specificity for TC 17%
SCINTIGRAPHY OF THE HEART Tc-99m
Scyntygrafia Tarczycy Tc-99m
SCYNTYGRAFIA TARCZYCY  Tc-99m
SCINTIGRAFIA TARCZYCY Tc-99m

TT AP[1]
FNAB
Indications for FNAB

- Single palpable tumour
- Multinodular goiter
  - solid hypoechoogenic nodules,
  - microcalcifications
  - poorly defined or irregular margins
  - intranodular vascularity
  - enlarged lymph nodes on the site of the nodule
- Painful goiter or goiter of increased compactness
- Foci found on US > 1 cm (especially hypoechoogenic)
Advantage of Fine Needle Aspiration Biopsy

- nodules > 10 mm
- high sensitivity
- high specificity
- simple ??
<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy, %</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or unsatisfactory</td>
<td>1-4</td>
<td>Repeat FNA with ultrasonographic guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Atypia of undetermined significance or follicular lesion of undetermined significance</td>
<td>5-15</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Follicular neoplasm or suspicious for a follicular neoplasm</td>
<td><strong>NF</strong> 5+10%</td>
<td>Surgical lobectomy</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60-75</td>
<td>Near-total thyroidectomy or surgical lobectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
<td>Near-total thyroidectomy</td>
</tr>
</tbody>
</table>
Increased risk of malignancy – ultrasound

- Metastatic lymph nodes
- Infiltration of surrounding organs
- Microcalcifications
- Hypoechogenic
- Irregular margins
- More tall than wide
- Intranodular vascularisation
Decreased risk of malignancy - ultrasound

- Hyperehogenic
- Simple cyst
- Spongiform nodule
- Isolated macrocalification
- Toxic nodule - scintigraphy
Clinical features of malignancy

- Metastases to lymph nodes or distant meta
- Familial history
- Exposition on external radiation in history
- Speed growth of a nodule
- Firm consistency
- Fixation to environment
- Diameter > 4 cm
- Age at diagnosis < 20 and > 60
Multinodular goiter – indications for surgical treatment

URGENT

- Compression of tracheae with ventilation disturbances
  chest X-ray, US, CT, SPECT-CT

- Vena cava syndrome - due to compression of retrosternal goiter

- Dysphagia
Multinodular goiter – indications for surgical treatment

X-ray - dislocation and stenosis of trachea
Multinodular goiter – indications for surgical treatment

SCHEDULED

- Reasonable suspicion of malignancy - based on clinical features and/or FNAB
- Some risk factors of malignancy in multinodular goiter
- Retrosternal, mediastinal goiter
- High calcitonin level, MEN2 syndrome, RET mutation (molecular tests)
Multinodular goiter – indications for surgical treatment

RELATIVE

- Large goiter
- Cosmetic reasons – patient’s choice
Epidemiology of thyroid cancer

- Infrequent
- 0.5-1.5% of all malignancies
- 90% of cancers in endocrinology
THYROID CANCER

- quite rare
- accounting for only 1.5% of all cancers in adults
- accounting for 3% of all cancers in children
- the rate of new cases increasing in recent decades
- in contrast to other cancers, thyroid cancer - almost always curable
THYROID CANCER

- the most common endocrine malignancy
- arising from follicular cells (adenoma, carcinoma, and follicular/papillary carcinoma) - a broad range of overlapping clinical and cytologic features
- follicular and papillary thyroid cancers - differentiated thyroid cancers
- together making up 95% of thyroid cancer cases
THYROID CANCER EPIDEMIOLOGY AND CHARACTERISTICS

- Of all thyroid cancers, 74-80% of cases are papillary cancer.
- Of all thyroid cancers, 17-20% are follicular ones.
- Follicular carcinoma incidences are higher in regions where goiter is common.
- The most common presentation of thyroid cancer is an asymptomatic thyroid mass or a nodule that can be felt in the neck.
# Types of thyroid carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Poland</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary (PTC)</td>
<td>65%</td>
<td>80%</td>
</tr>
<tr>
<td>follicular (FTC)</td>
<td>20%</td>
<td>&gt;5%</td>
</tr>
<tr>
<td>Medullary (MTC)</td>
<td>5%</td>
<td>&gt;5%</td>
</tr>
<tr>
<td>Anaplastic (ATC)</td>
<td>10%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

DTC

C-cells

J.Daroszewski
Factors influencing carcinogenesis of TC:

- Log-term TSH stimulation: DTC
- Ionising radiation: PTC(+++), FTC(+)
- I deficiency: FTC
- I excess: PTC
- Genetic factors: MTC
- Thyroiditis: lymphoma
- Neoplasms persisted after 131-I treatment: ATC
Papillary thyroid carcinoma characteristics

- most common (65%)
- mostly in young (< 45 yrs)
- multifocal
- local metastases to lymph nodes
- very good prognosis

J.Daroszewski
- the most common form of well-differenciated thyroid cancer
- the most common form of thyroid cancer to result from exposure to radiation
- propensity to invade lymphatics but are less likely to invade blood vessels.
PAPILLARY THYROID CANCER PATHOGENESIS

- Several chromosomal rearrangements in papillary thyroid carcinoma
- Chromosomal rearrangements involving the rearranged during transfection (RET) proto-oncogene, which arises from a paracentric inversion of chromosome 10
- Molecules that physiologically regulate the growth of the thyrocytes (interleukin-1, interleukin-8), or other cytokines (e.g., insulin-like growth factor-1, transforming growth factor-beta, epidermal growth factor) could play a role in the pathogenesis of this cancer.
- mutation in the *BRAF* gene - prominent in papillary thyroid carcinoma

- the *BRAF* V600E mutation is associated with aggressive clinicopathological characteristics of papillary thyroid carcinoma, (including lymph node metastasis, extrathyroidal invasion, and loss of radioiodine avidity)
a clear association between radiation exposure (from radiotherapy or fallout) and incidence of papillary thyroid carcinoma

Port et al report:

- papillary thyroid cancers in patients exposed to radiation from the Chernobyl accident could be completely distinguished from sporadic papillary thyroid cancers in patients with no history of radiation exposure, on the basis of gene expression patterns involving seven genes (i.e., SFRP1, MMP1, ESM1, KRTAP2-1, COL13A1, BAALC, PAGE1)
Approximately 7% of individuals exposed to the atomic bombs in Japan developed thyroid cancers.

Individuals, especially children, who lived in Ukraine during the time of the Chernobyl nuclear event may have increased risk of papillary thyroid cancer.
A study by Yu et al found that papillary thyroid microcarcinomas are generally associated with an excellent prognosis; however, 0.5% of patients may die.
Thyroid microca. has a perfect prognosis

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>n</th>
<th>Follow-up (Yrs)</th>
<th>Specif. mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baudin, 1998</td>
<td>281</td>
<td>7</td>
<td>4%</td>
</tr>
<tr>
<td>Hay, 2008</td>
<td>900</td>
<td>17</td>
<td>0.3%</td>
</tr>
<tr>
<td>Chow, 2003</td>
<td>203</td>
<td>8</td>
<td>1%</td>
</tr>
<tr>
<td>Noguchi, 1996</td>
<td>867</td>
<td>13</td>
<td>0.2%</td>
</tr>
<tr>
<td>Yamashita, 1999</td>
<td>1743</td>
<td>12</td>
<td>0.2%</td>
</tr>
<tr>
<td>Buffet, 2012</td>
<td>669</td>
<td>7</td>
<td>0%</td>
</tr>
</tbody>
</table>
SYMPTOMS OF THYROID CANCER

- The principal sign of thyroid carcinoma - a palpable nodule, usually solitary
- In the thyroid area that has the following characteristics:
  - Painless
  - Hard consistency
  - Average size of less than 5 cm
  - Ill-defined borders
  - Fixed in respect to surrounding tissues
  - Moves with the trachea at swallowing
  - Cervical lymphadenopathy (if present)
    - palpable on either the ipsilateral or contralateral
    - tight or full feeling in the neck, hoarseness, or signs of tracheal or esophageal compression.
THERAPY OF THYROID CANCER

- Surgery - the definitive management of papillary thyroid cancer
- Total thyroidectomy
- Radioiodine therapy - approximately 4-6 weeks after surgical thyroid removal
- Radioiodine therapy
  - Detection and destruction of any metastasis and residual tissue in the thyroid
- A diagnostic dose of radioiodine ($^{131}$I or $^{123}$I)
- A whole-body scintiscan
- If any normal thyroid remnant or metastatic disease is detected, a therapeutic dose of $^{131}$I is administered to ablate the tissue.
- Thyroid hormone replacement (levothyroxine) therapy.
- Lifelong thyroid hormone replacement therapy, especially after total thyroidectomy
Treatment and follow-up of DTC - summary

- Primary surgery - (near) total thyroidectomy lobe + isthmus
- Secondary surgery
- Radioiodine therapy – $^{131}$I
- TSH suppression with LT$_4$
- Thyroglobulin (TG) is a marker in follow-up
Follicular thyroid carcinoma

- 20% of all thyroid cancers
- TSH-dependent
- all ages
- blood vessels invasion
- distant metastases: lungs, bone
- mean survival ca. 10 – 15 yrs.

J.Daroszewski
Follicular thyroid carcinoma (FTC)
a well-differentiated tumor
resembles the normal microscopic pattern of the thyroid
originates in follicular cells
the second most common cancer of the thyroid, after papillary carcinoma.
may be overtly or minimally invasive
Activating point mutations in the ras oncogene
Especially in poorly differentiated (55%) and anaplastic carcinoma (52%)
Several reports have shown a relationship between iodine deficiency and the incidence of thyroid carcinoma.

Incidence of FTC has decreased in geographic areas of endemic goiter after iodized salt was introduced.
Medullary thyroid carcinoma characteristics

- derives from parafollicular C cells
- 5-10% thyroid malignancies
- 10% familiar (autosomal dominant) - MEN IIA, MEN IIB
  - isolated
- calcitonin (CT) - marker of MTC
  (basal and after pentagstrin, Ca, or omeprazol stimulation)
- Thyroid surgery with adenomectomy
- Teleradiotherapy

J.Daroszewski
Medullary Carcinoma

Epidemiology

- Medullary carcinoma of the thyroid (MTC)
- A distinct thyroid carcinoma
- Originates in the parafollicular C cells of the thyroid gland
- C cells - calcitonin
- Sporadic, or isolated, MTC accounts for 75% of cases
- Inherited MTC constitutes the rest
- Inherited MTC occurs in association with multiple endocrine neoplasia (MEN) type 2A and 2B syndromes, but non-MEN familial MTC also occur.
MEDULLARY CARCINOMA SYMPTOMS

- Medullary thyroid cancer (MTC)
- on physical examination - a solitary neck nodule
- common - early spread to regional lymph nodes
- distant metastases in the liver, lung, bone, and brain
- Sporadic MTC usually unilateral
- In association with multiple endocrine neoplasia (MEN) syndromes always bilateral and multicentric
Mutations in the RET (REarranged during Transfection) proto-oncogene

A receptor protein tyrosine kinase encoded on chromosome 10

Prophylactic thyroidectomy can now be offered to specific types of patients with this genetic abnormality.
A specific constellation of symptoms of medullary thyroid carcinoma (MTC) is not usually noted; however, one or more of the following symptoms may be observed:

- Patients may describe a lump at the base of the neck, which may interfere with or become more prominent during swallowing.
- Patients with locally advanced disease may present with hoarseness, dysphagia, and respiratory difficulty.
- Physical examination may demonstrate a dominant thyroid nodule at the base of the neck.
- Palpable cervical lymphadenopathy signifies disease that has progressed locally.
MEDULLARY CANCER MANAGEMENT

- Perform a total thyroidectomy and central neck dissection for cases of symptomatic (clinically detected) MTC.

- Prophylactic thyroidectomy is indicated for carriers of RET mutations who have no apparent disease but are at risk for aggressive MTC.
Anaplastic thyroid carcinoma characteristics

- older age (over 60 yrs)
- rapid local invasion, distant metastases - lungs
- survival 4-6 months after diagnosis
- 5-10% of thyroid cancers
- Surgery, chemotherapy – not effective
<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
<th>Age</th>
<th>Spread</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>65</td>
<td>Young &lt;45 y</td>
<td>Lymph</td>
<td>Excellent</td>
</tr>
<tr>
<td>Follicular</td>
<td>20</td>
<td>Middle age</td>
<td>B.V.</td>
<td>Good</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>10</td>
<td>Elderly</td>
<td>Local</td>
<td>Poor</td>
</tr>
<tr>
<td>Medullary</td>
<td>5</td>
<td>Elderly, familial</td>
<td>All</td>
<td>Variable</td>
</tr>
</tbody>
</table>