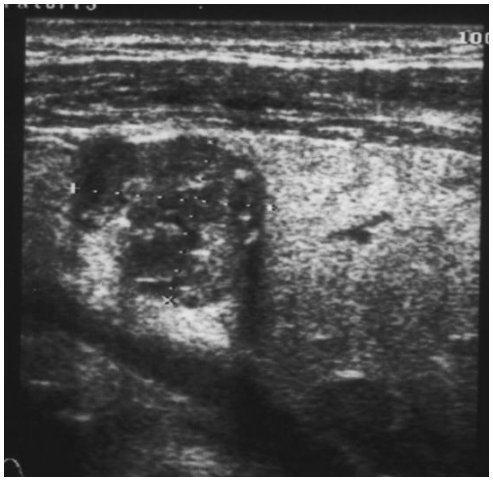
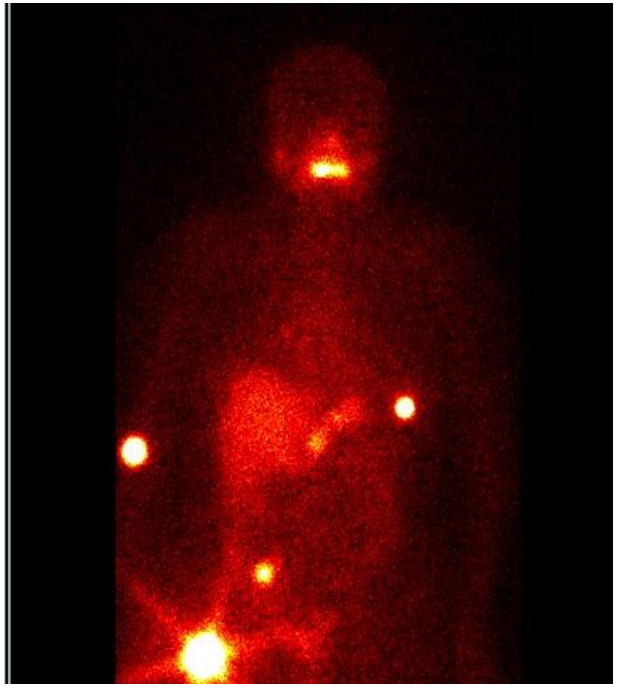
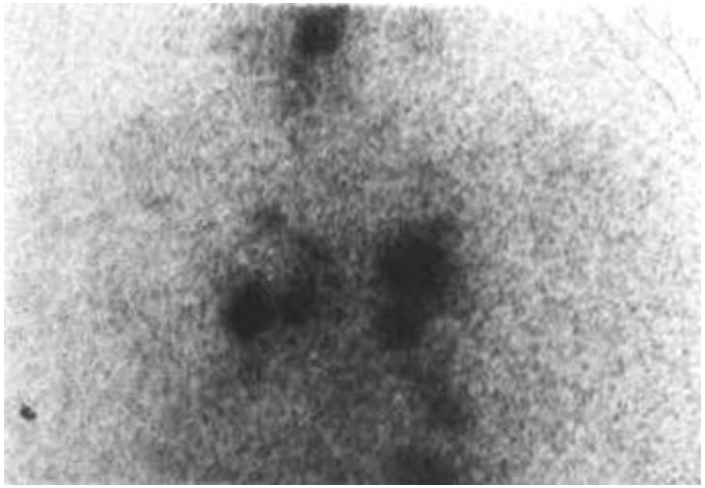
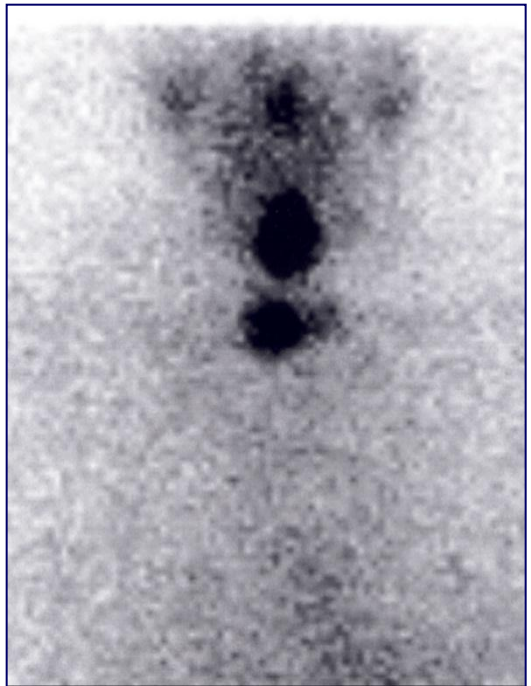
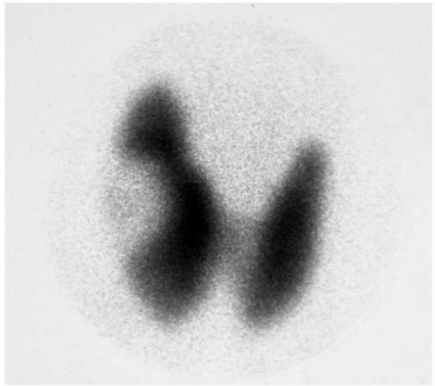
Thyroid carcinoma











Assoc. prof. V. Marković, MD, PhD

Assoc. prof. A. Punda, MD, PhD

D. Brdar, MD, nucl. med. spec.

Thyroid tumors

PRIMARY TUMORS

Tumors of the follicular epithelium :

- Tumors of the follicular cell:
  - benign – follicular adenoma
  - malignant: well differentiated: **papillary carcinoma**
    follicular carcinoma
    Hürtle 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

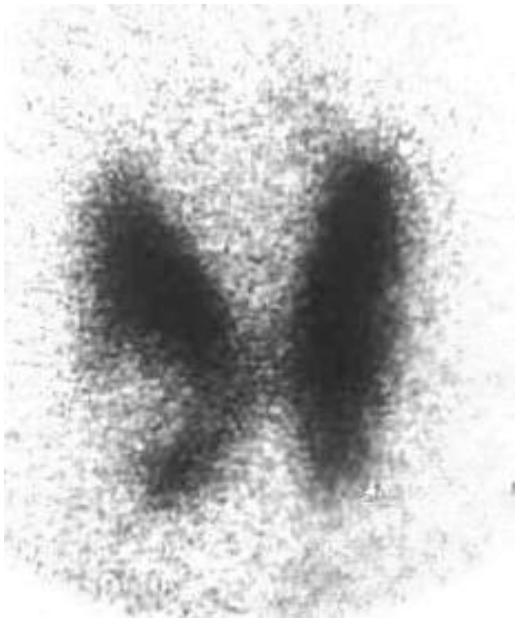
Benign tumors- adenomas (scintigraphic "hot" or "cold"), adenomatous goiter, cysts

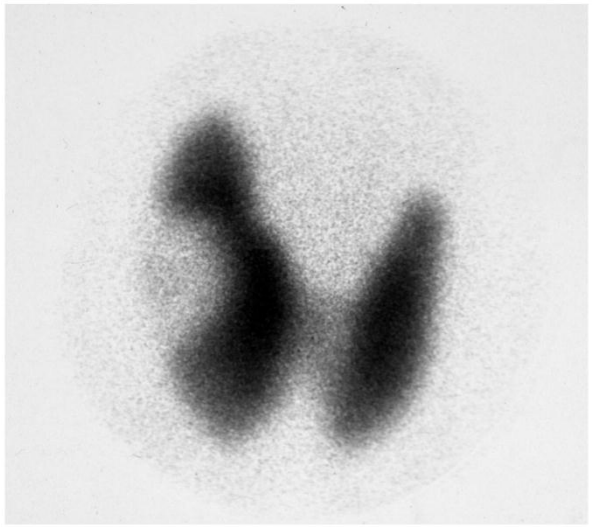
Malignant tumors- carcinoma
papillary 80%
follicular 10% (+ Hürthl cell ca. 2%)
medullary 7% (5%)
poorly differentiated 2%
anaplastic <1%
metastasis of other tumors in the thyroid

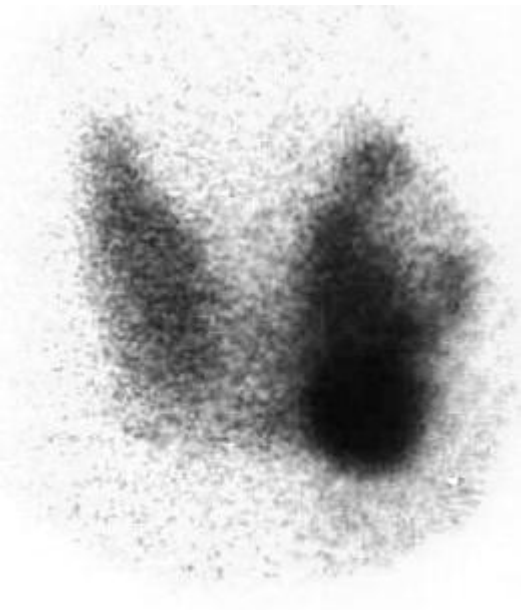
Malignant tumors of the thyroid

- 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



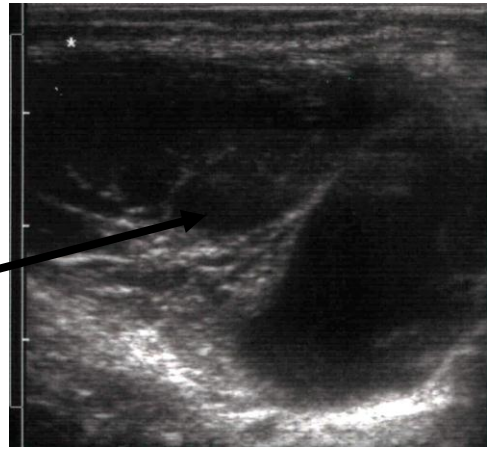


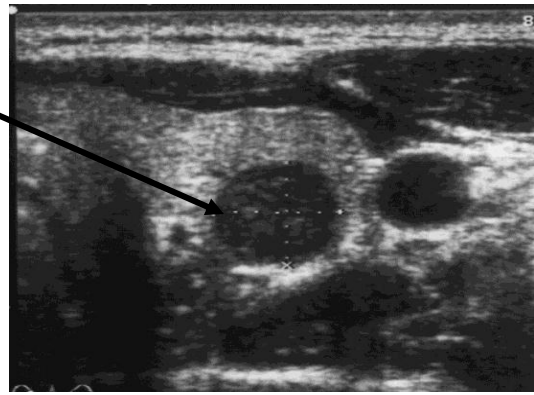


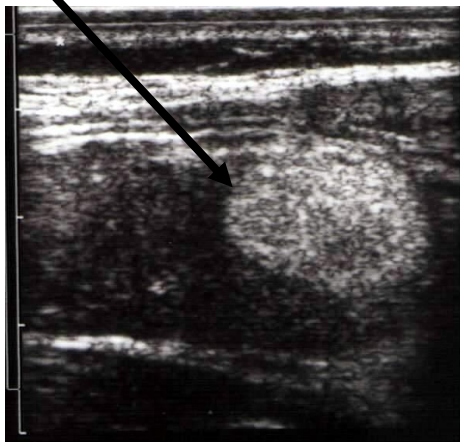
NODULAR CHANGES

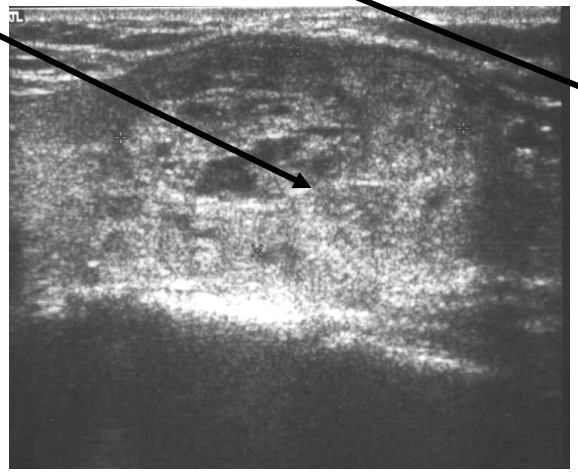
The number, size, echostructure, location

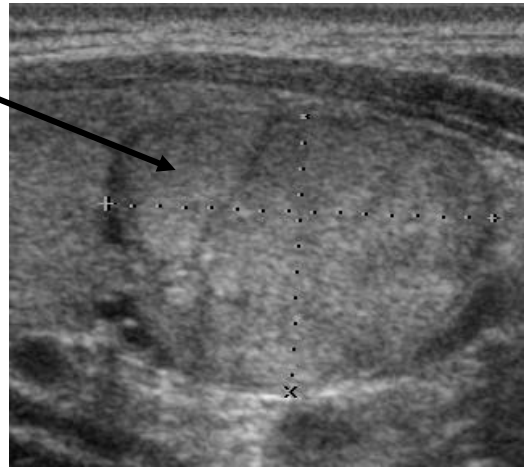
1. cysts and cystic changed nodes
2. solitary nodes- hypoechoic, isoechogenic, degeneratively changed (benign goiter)
3. multinodular goiter
4. nodes in lymphomatous goiter



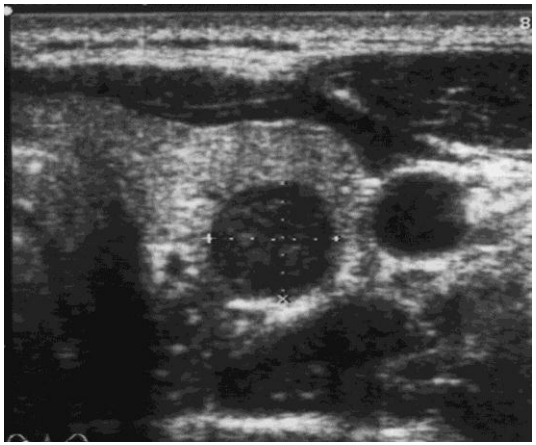


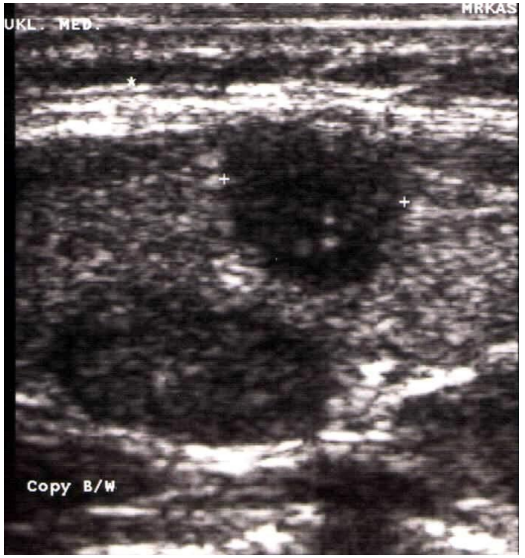


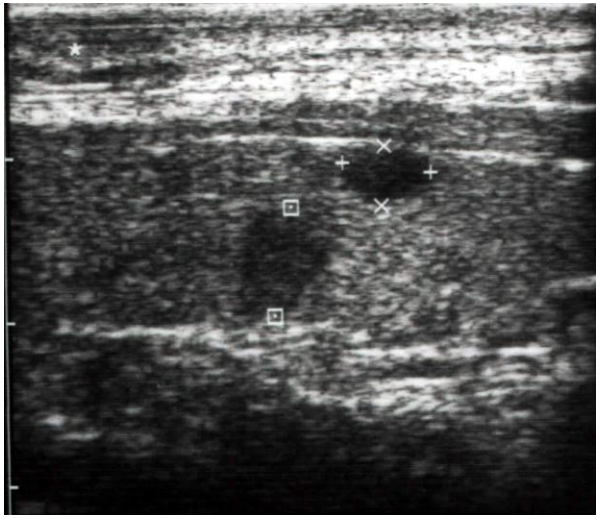


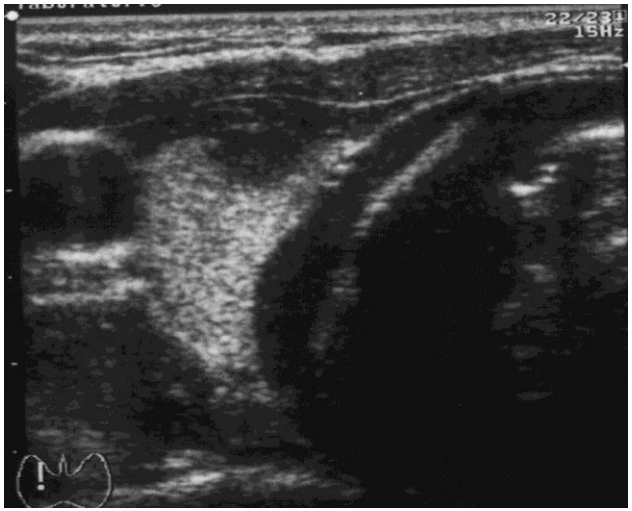


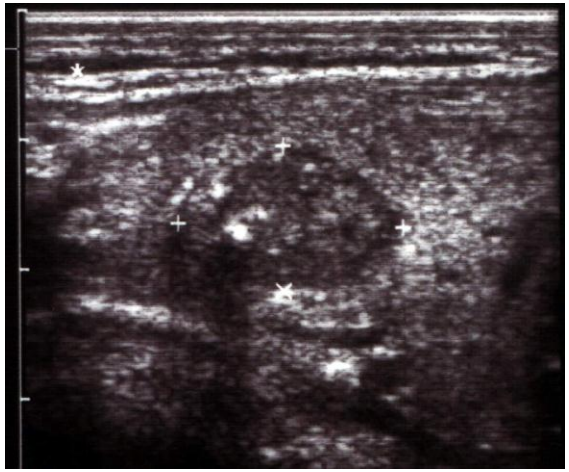
NODULAR CHANGES: adenomas, carcinomas





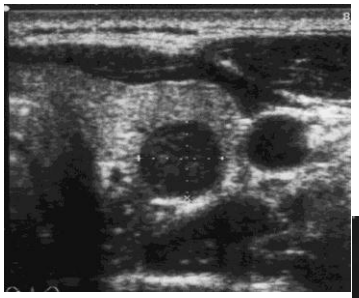




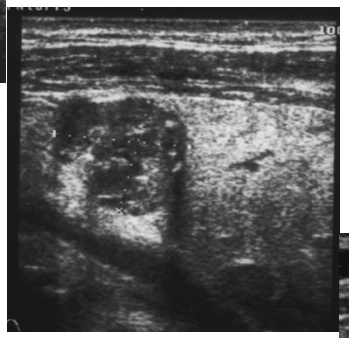


Echographical criteria of malignancy

Hypoehogenicity



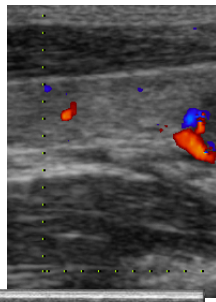
Microcalcifications



Without hypoehogenic edge,

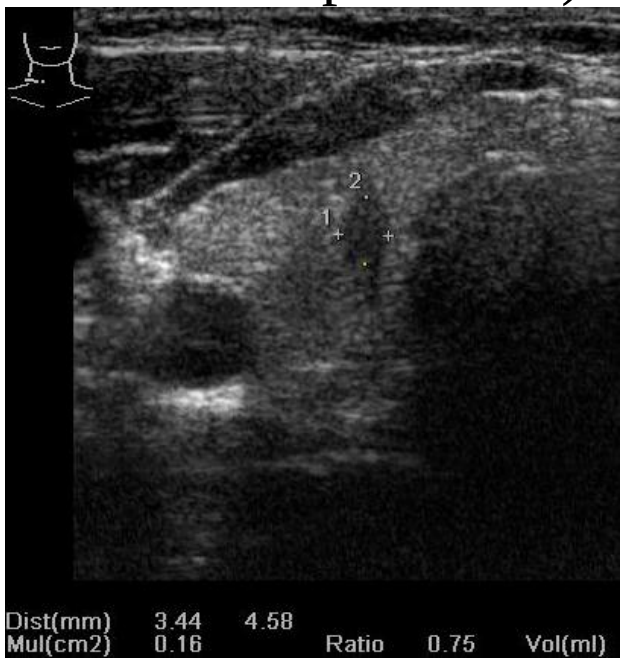
irregular borders

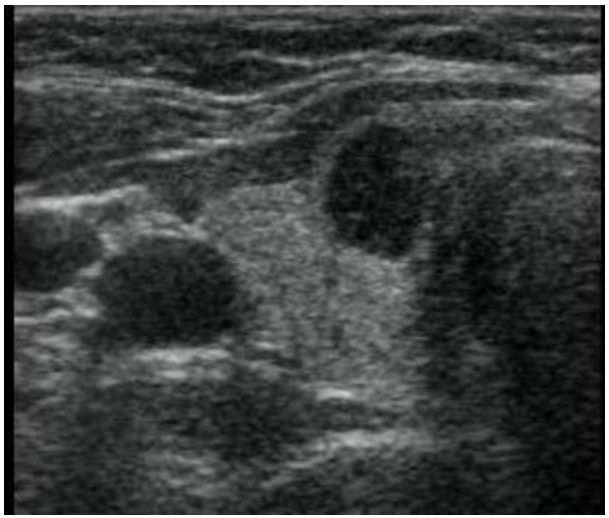
Intranodular vascularisation

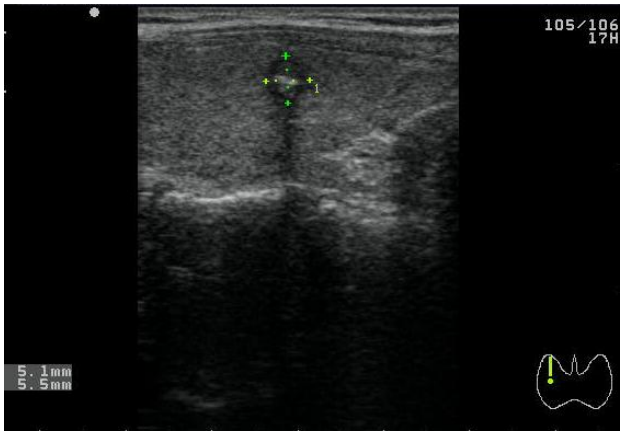


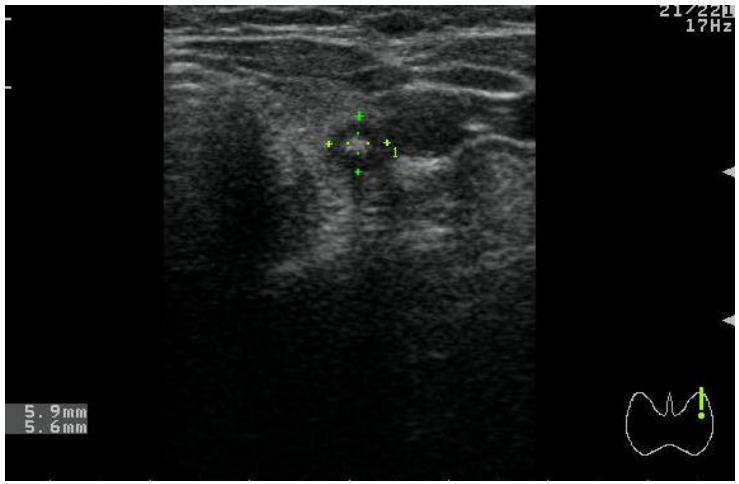
Regional lymphadenopathy

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

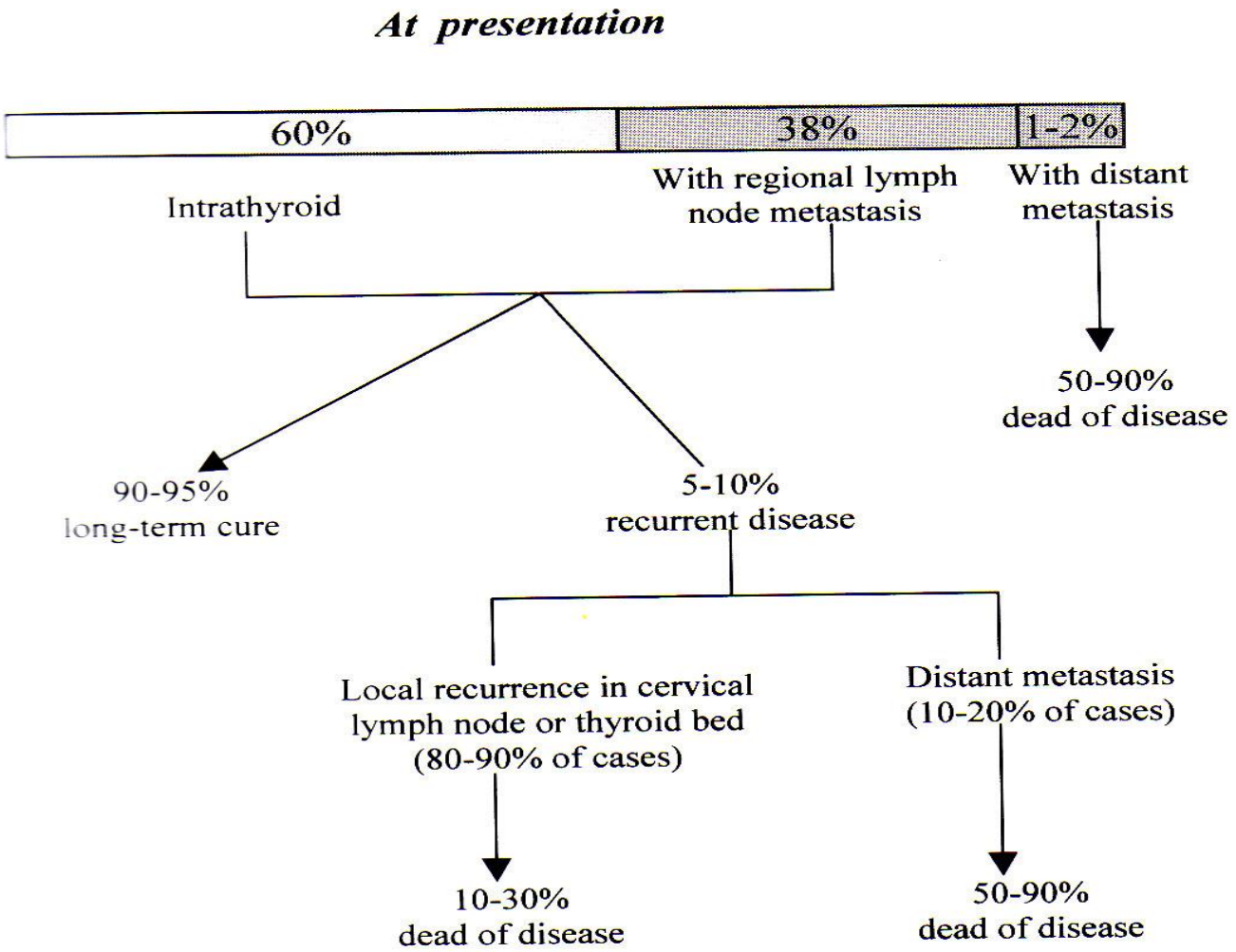


Fig. 18A.5 Flow chart to depict the natural history of papillary thyroid carcinoma.

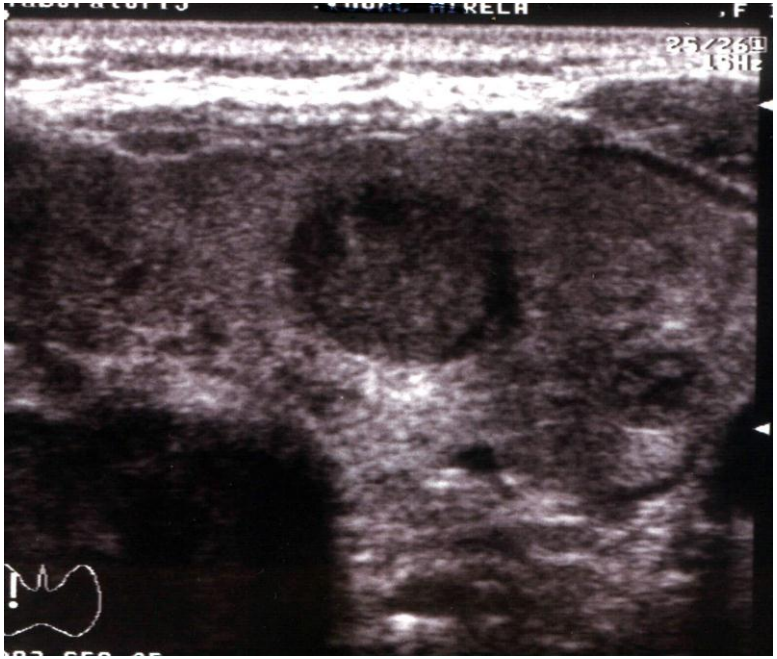
Follicular carcinoma

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.

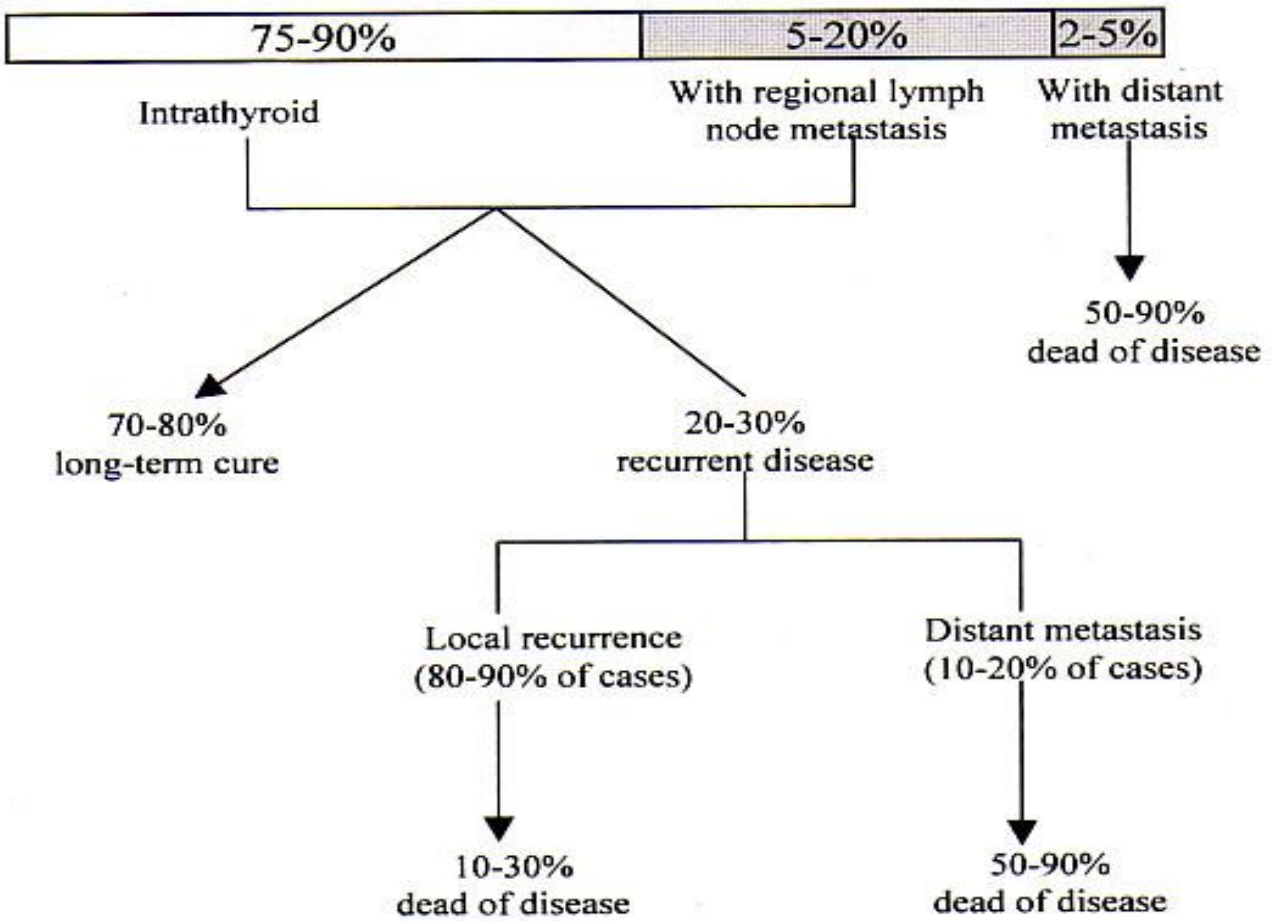
Large doses of iodine, particularly in bone metastases can lead to damage to the bone marrow.

Distant metastases - **worse prognosis.**

Follicular adenoma or carcinoma

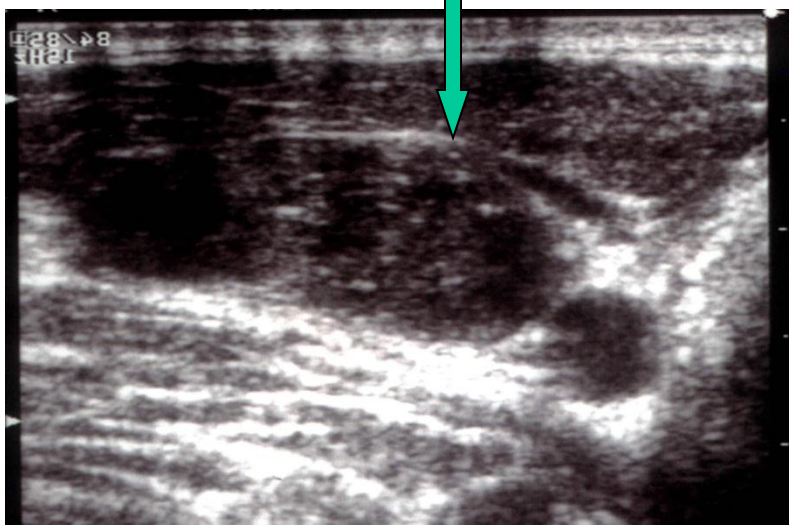
- Impossibility of cytological diagnosis.
- Diagnostic criteria of minimally invasive carcinoma: complete invasion through the capsule and intravascular invasion.

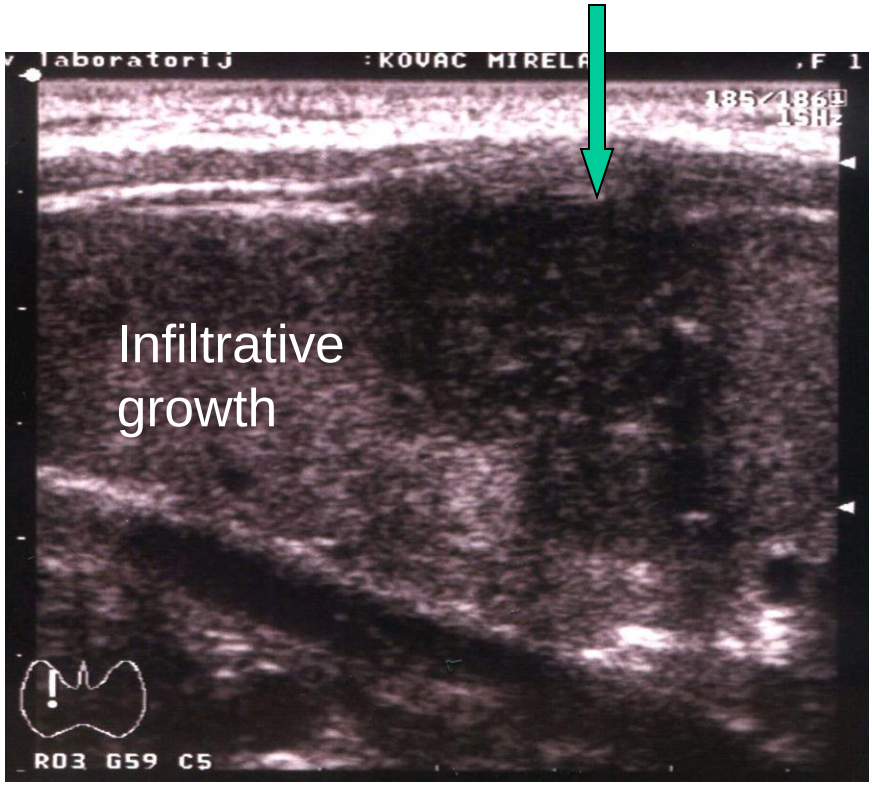
Follicular carcinoma at the time of diagnosis



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.

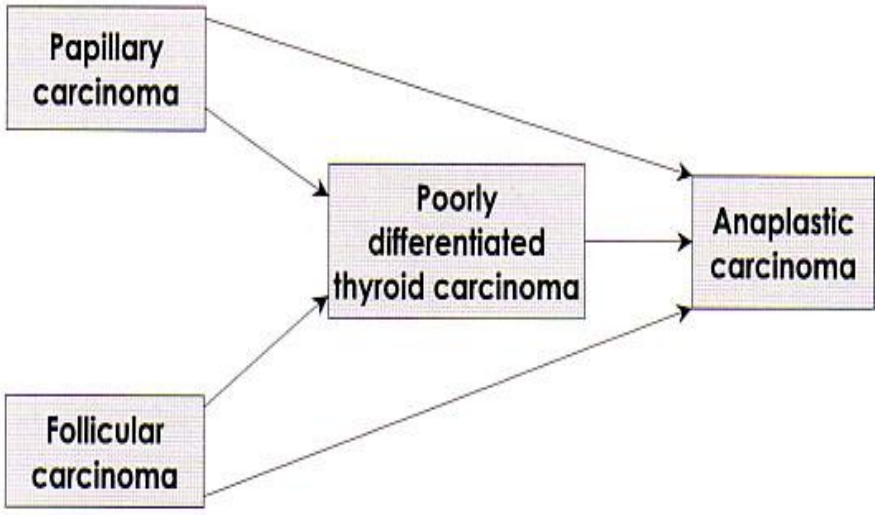
Metastatic lymph node

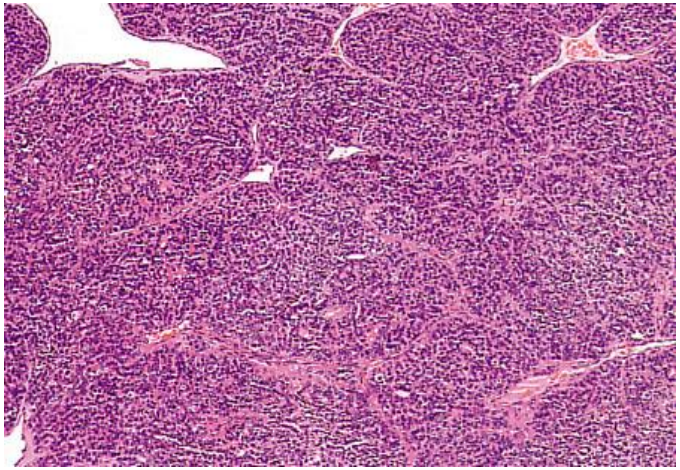


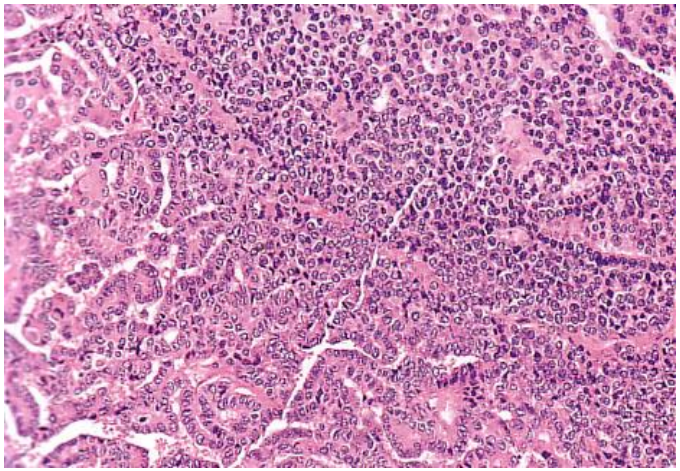


Poorly differentiated and anaplastic thyroid carcinomas

- 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

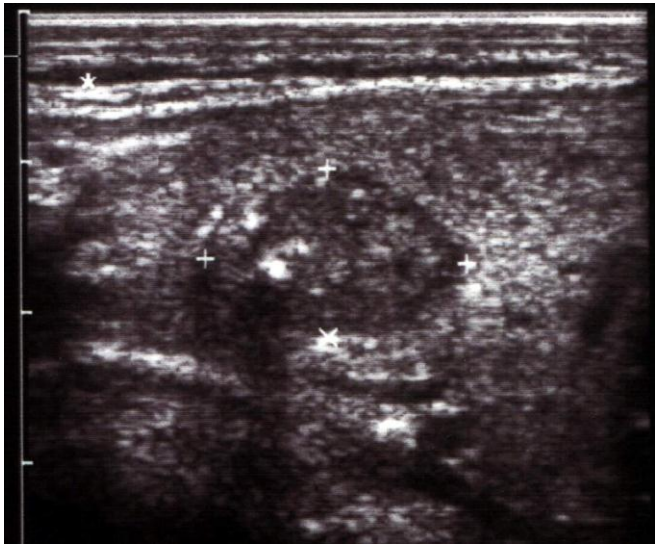
- **Detected by ultrasound and FNAC** (owing to US a significant number of nowday detected thyroid cancers are smaller than 1 cm)
- **Incidental** microcarcinoma: histologically detected in thyroid tissue, which is operated for another reason
- **Clinical (former Occult)** microcarcinoma: discovered 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 llB- 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)

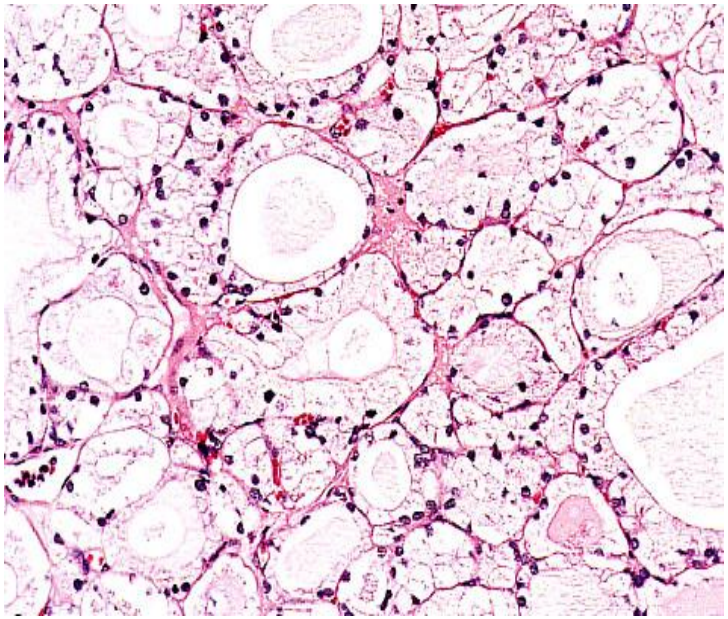
PRIMARY THYROID LYMPHOMA

- 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 recurent laryngeal nerve (1-2%)

2. radioiodine ablation and therapy

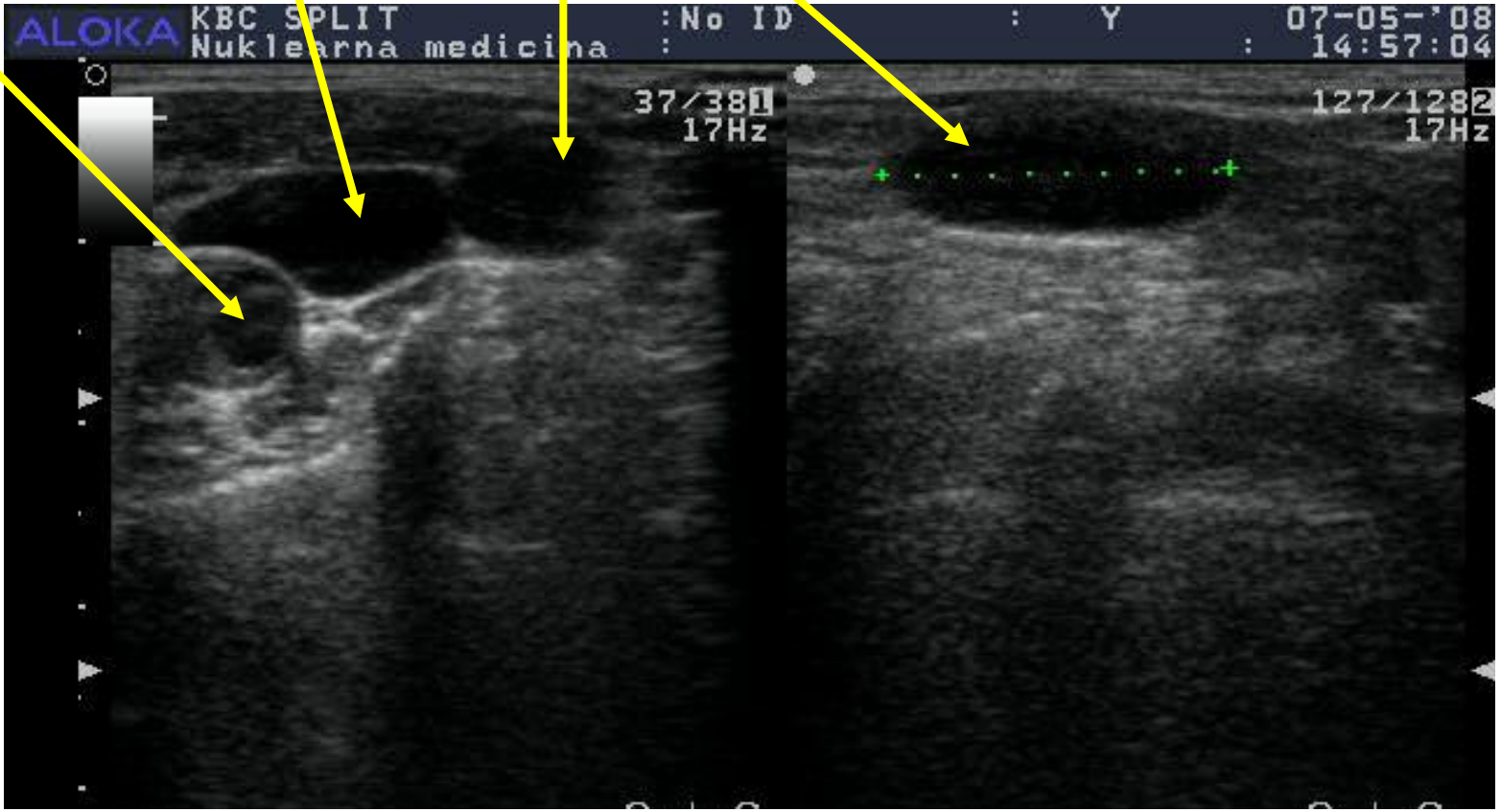
3. suppressive therapy

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

metastasis

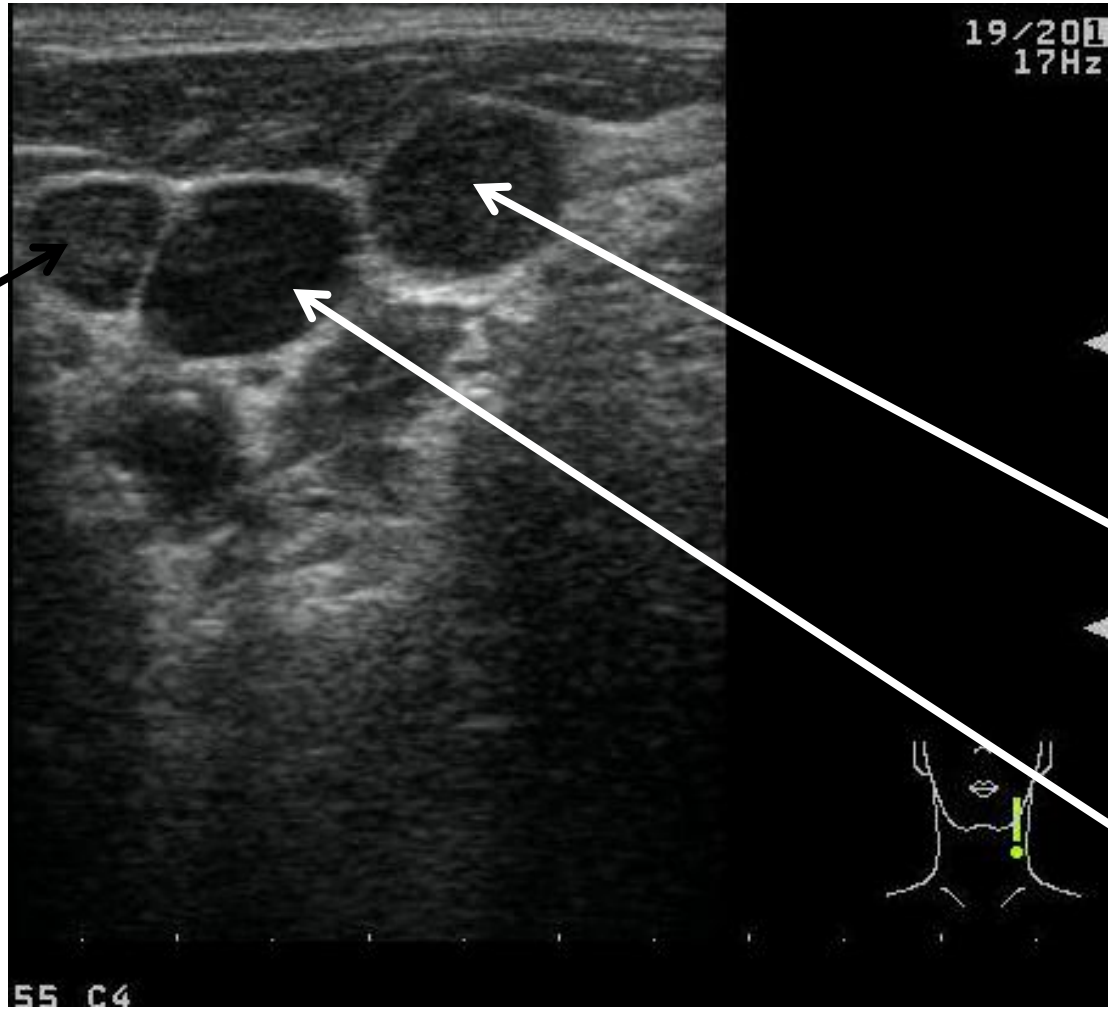
v. int. jugular

a.c.c.-partially occluded



Metastases on the left side of the neck

Metastases on the left side of the neck

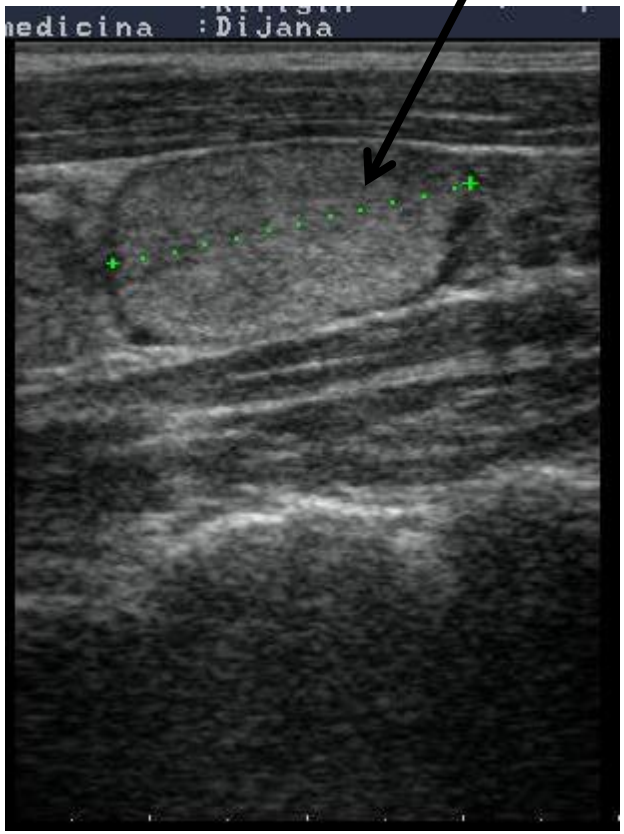


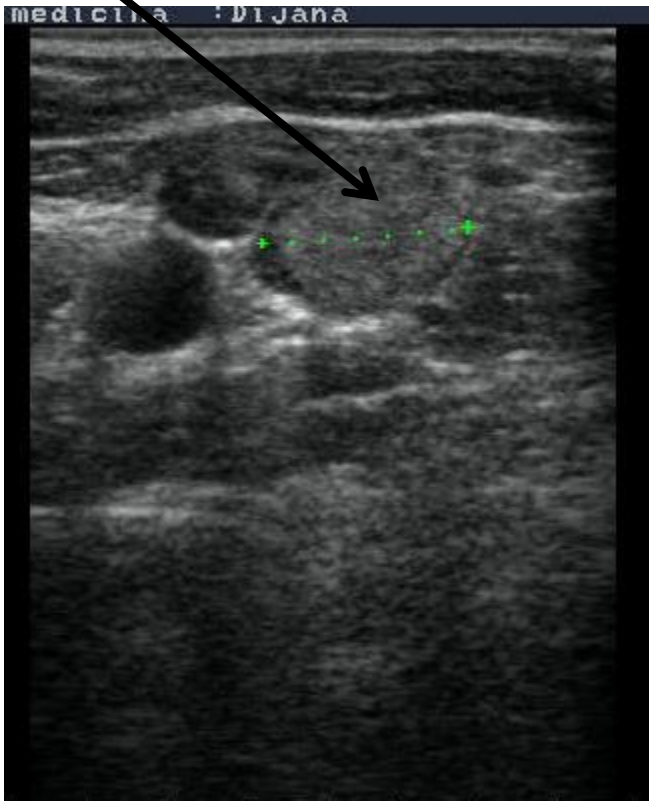
Metastasis

Metastasis

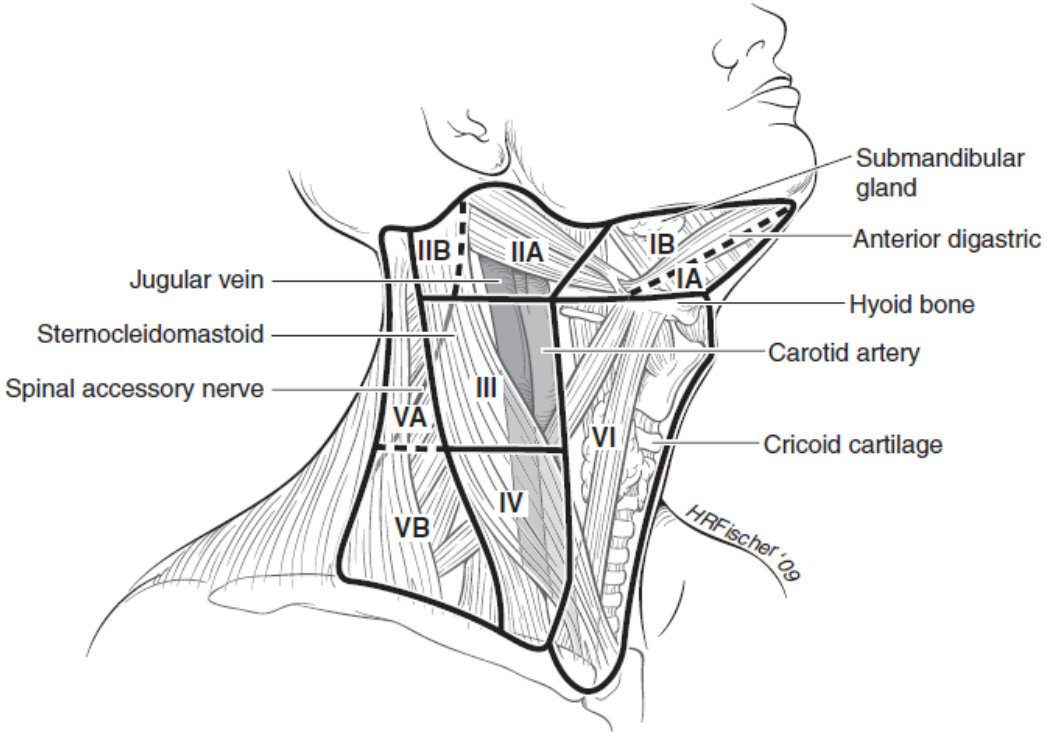
v. jug. int.

Metastatic lymph nodes

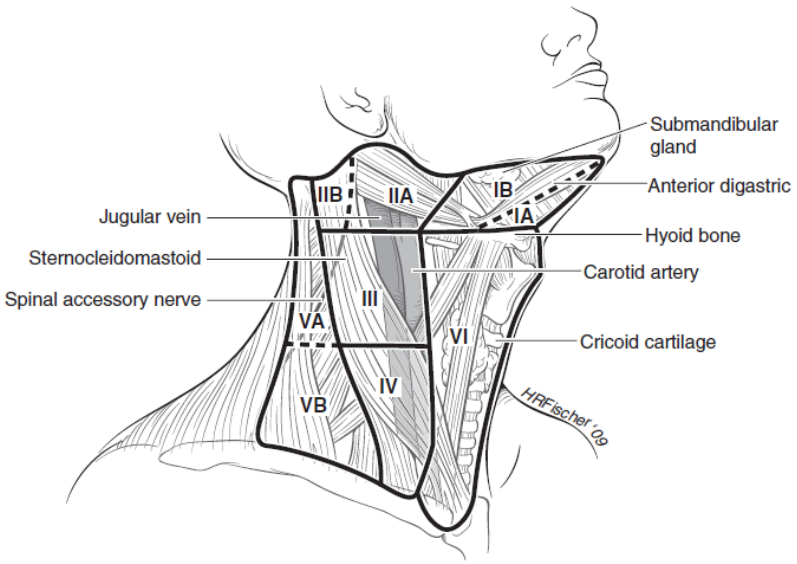




Neck metastases



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

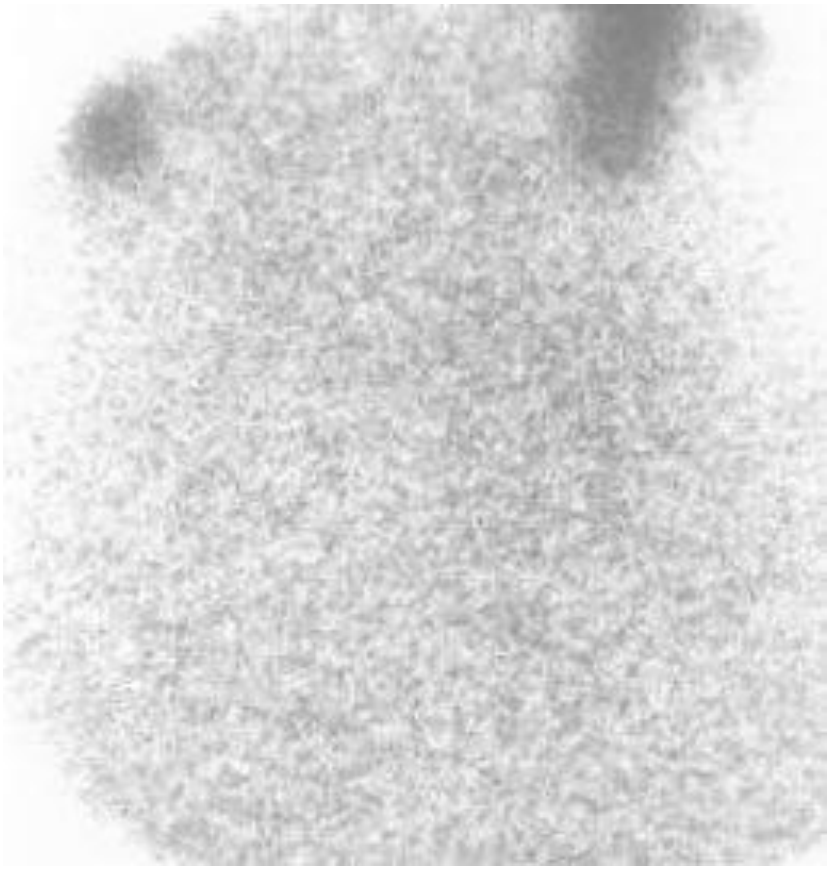
- TSH above 30 μU/mL (possibly exogenous TSH-Thyrogen)

- whole body scintigraphy

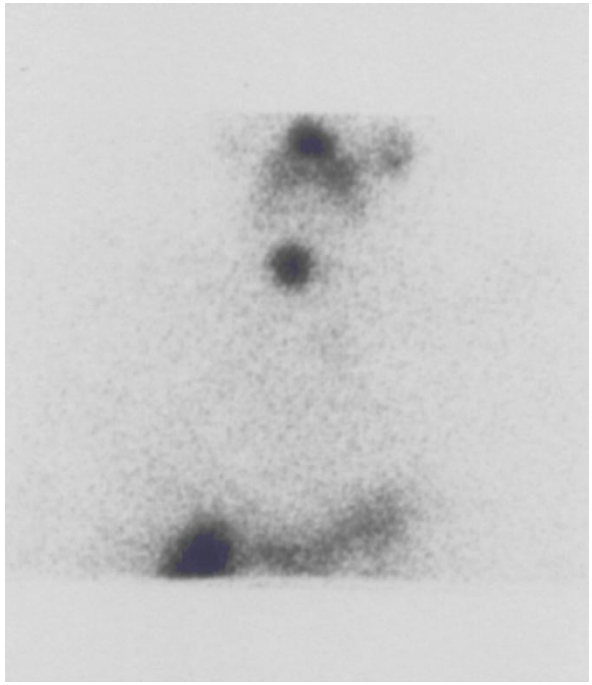
- therapeutic dose of 100-200 mCi for the treatment of metastases

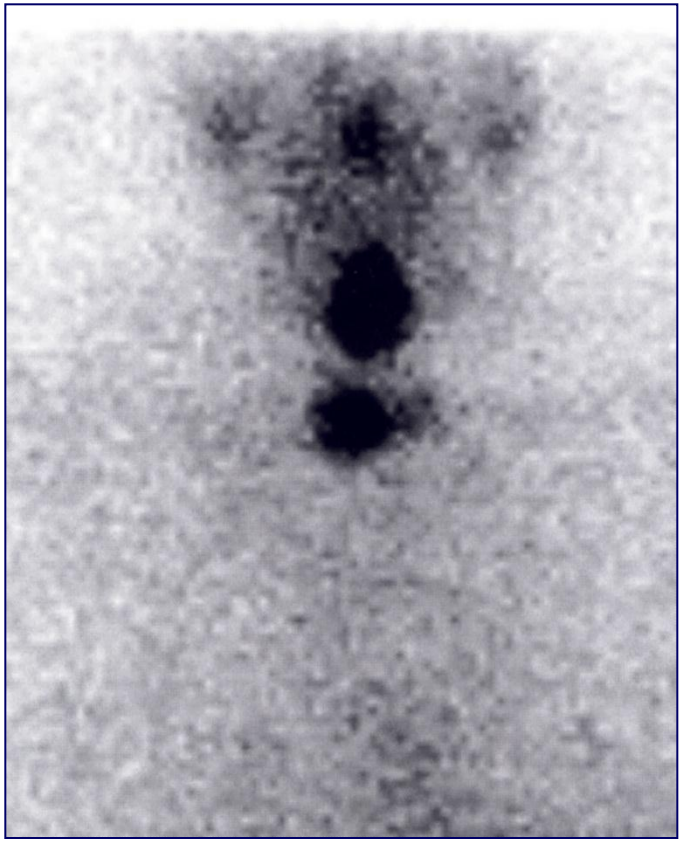
- measurement of Tg

Total thyroidectomy ≈ 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?

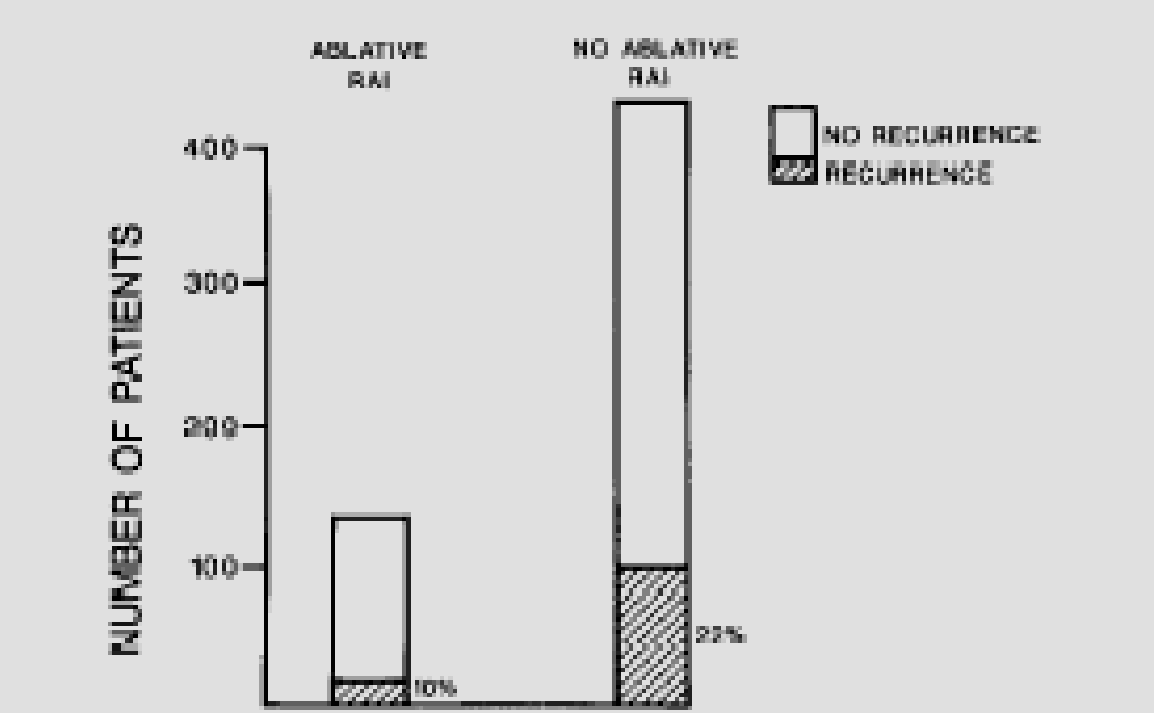


FIG. 4. Comparison of recurrence rates between ablative and nonablative ^{131}I therapy (RAI). Patients with no ablation had a higher recurrence rate. [Reproduced with permission from N. A. Samaan *et al.*: *J Clin Endocrinol Metab* 56:1131–1136, 1960 (15). © The Endocrine Society.]

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

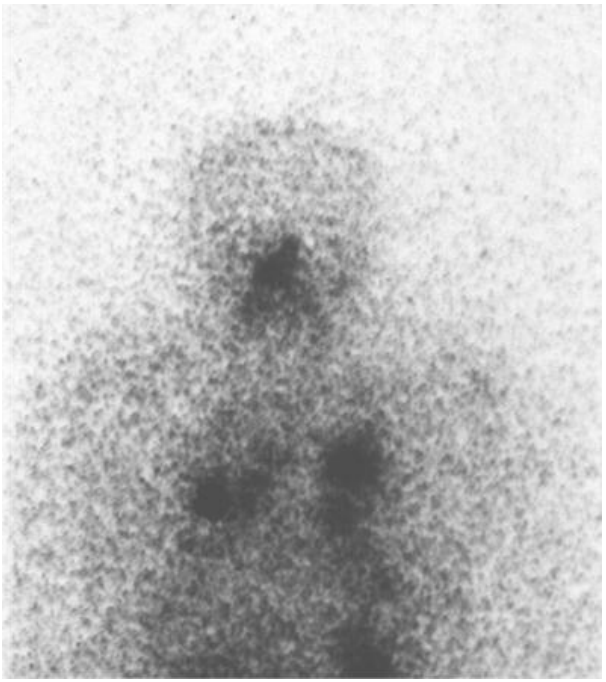
Sun	Mon	Tue	Wed	Thu	Fri	Sat
	THYROGEN ▼ day 1	THYROGEN ▼ day 2	^{131}I ▼ day 3	day 4	WBS and Tg Test ▼ day 5	

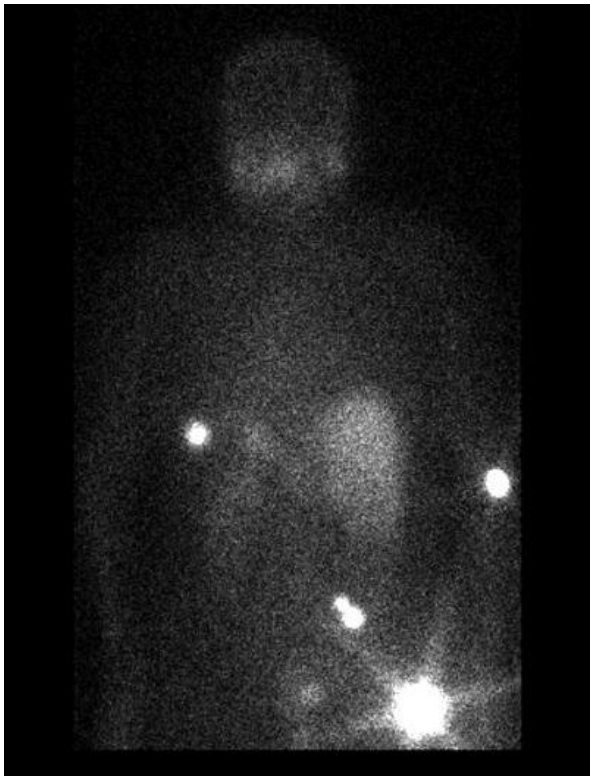
- 0.9 mg Thyrogen i.m. on day 1 and 2
- TSH on day 3 and 5
- 74-185 MBq I-131 on day 3
- Diagnostic I-131 WBS on day 5
- Tg measurement on day 5

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

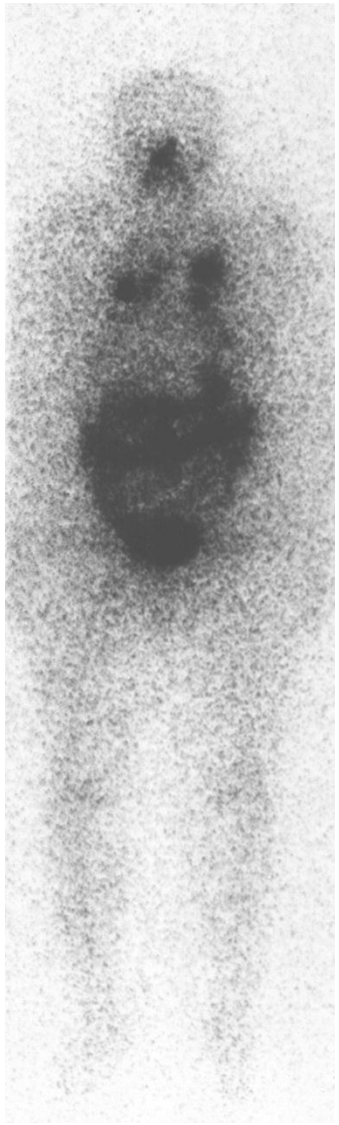


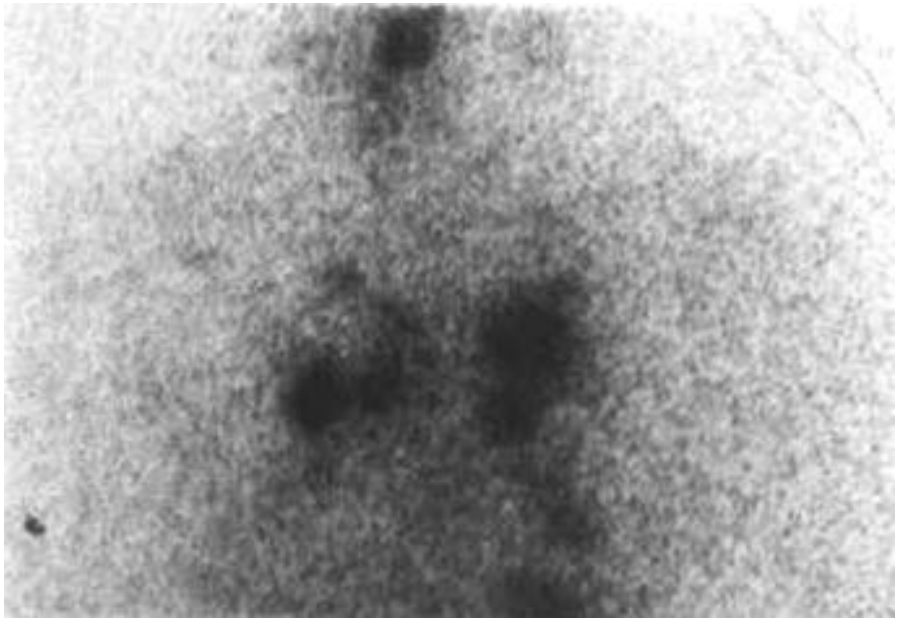


Metastases in the lymph nodes - Therapy with I-131

Metastases in the lymph nodes of the neck - Scan after therapy with 100 mCi J-131

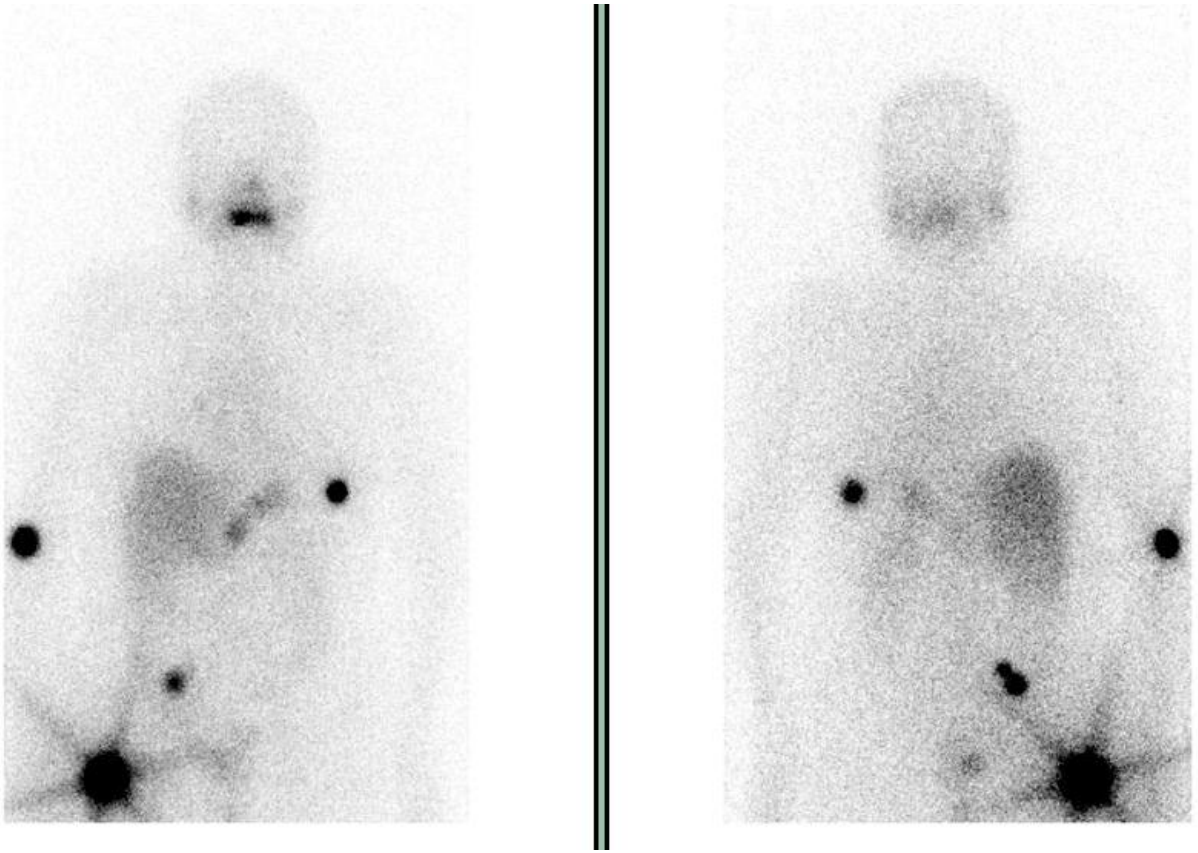
Functional metastases in the lung- Therapy with I-131





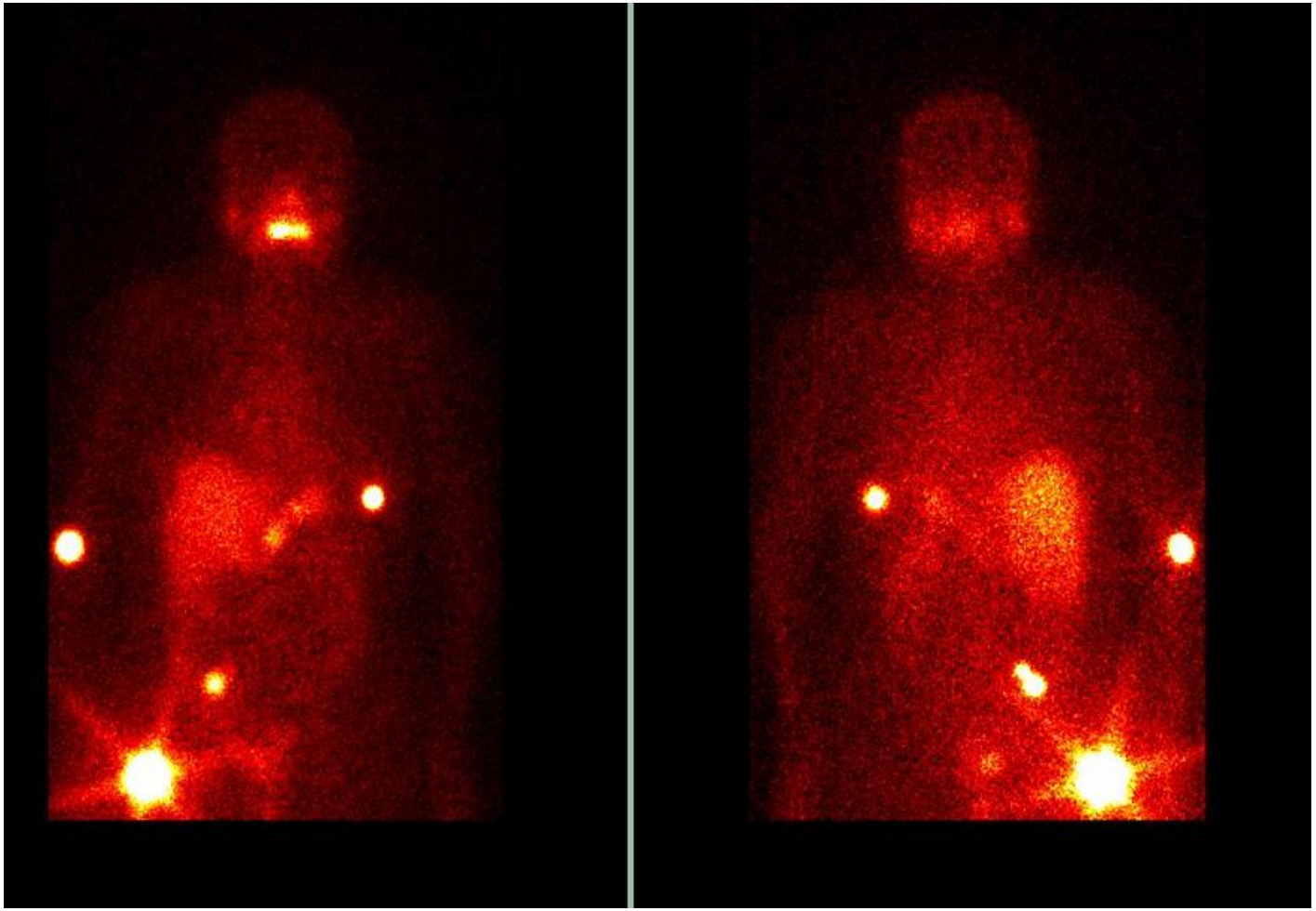
Metastases in the lung- scan after 200 mCi I-131

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

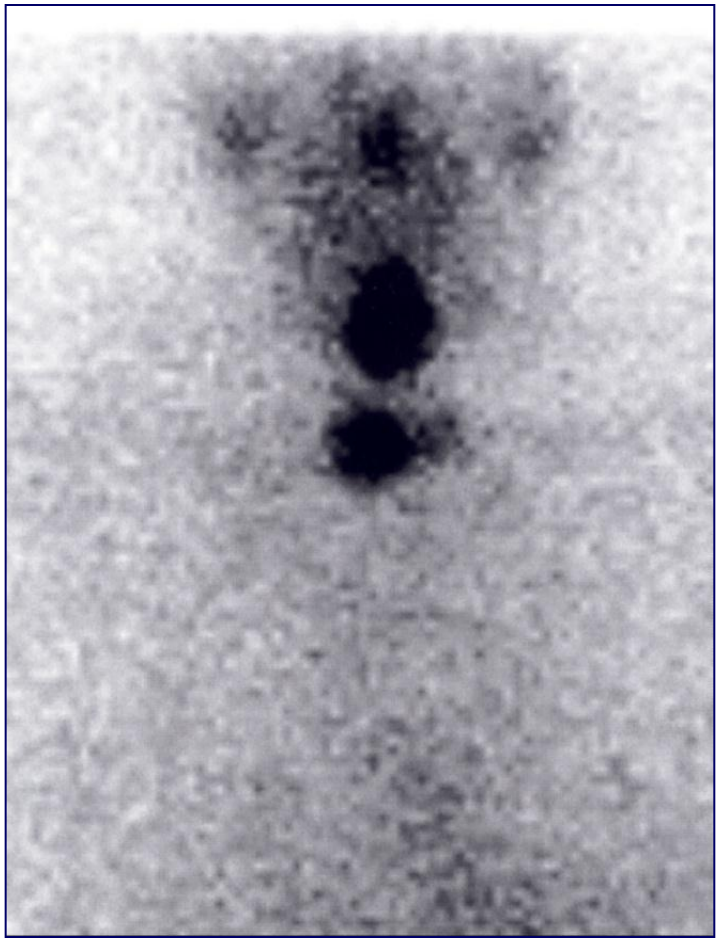
* The therapeutic response is partial

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.

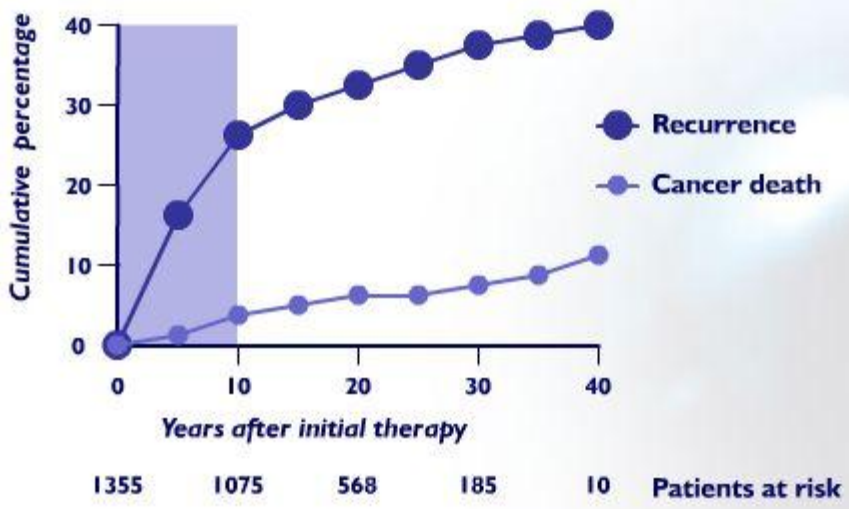


Residual tissue on the neck
after total thyroidectomy

Why does it take a long follow-up of patients with thyroid carcinoma?

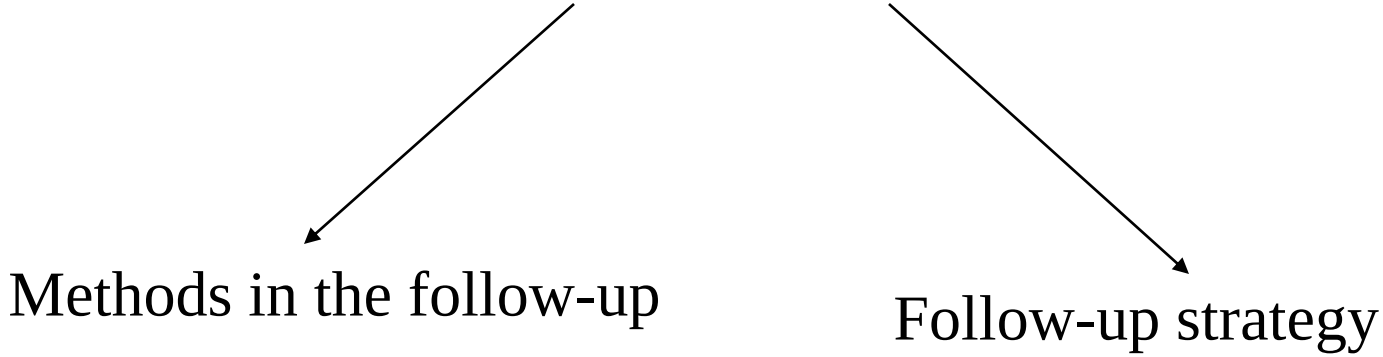
Cumulative Recurrence & Death After Initial Therapy:

High survival rate, but also high recurrence rates - lifetime monitoring required



Mazzaferri et al. AM J Med. 1994; 418 - 428

Follow-up of patients with differentiated thyroid carcinoma



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%

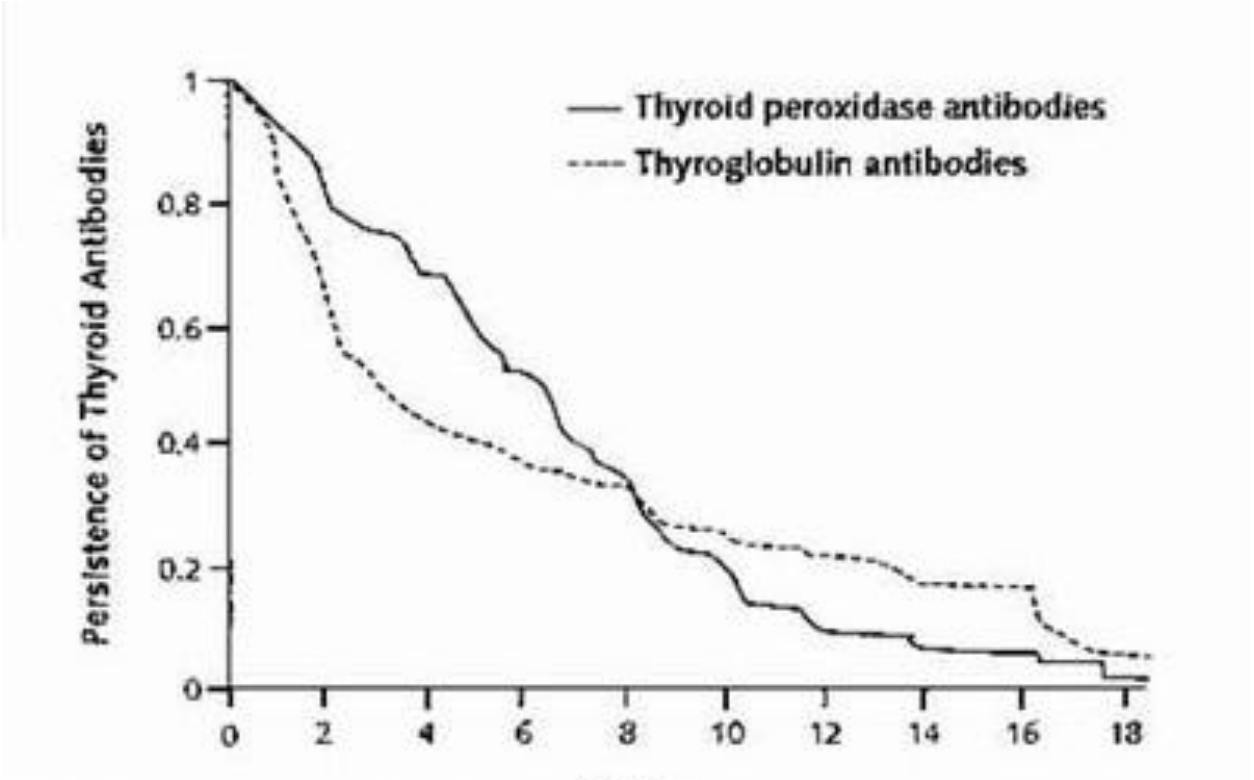
- TgAb#

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

Eustatia-Rutten CF et al. Diagnostic value of serum thyroglobulin mesurements... ClinEndocrrinol (Oxf). 2004; 61-74.

#Cooper DS et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association Guidlines Taskoforce. Thyroid. 2006;16:1-33.

Thyroid antibodies



Chiovato, 2003

The new definition of successful ablation !?

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

*Schlumberger M et al. Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. Eur J Endocrinol. 2004;150:105-112.

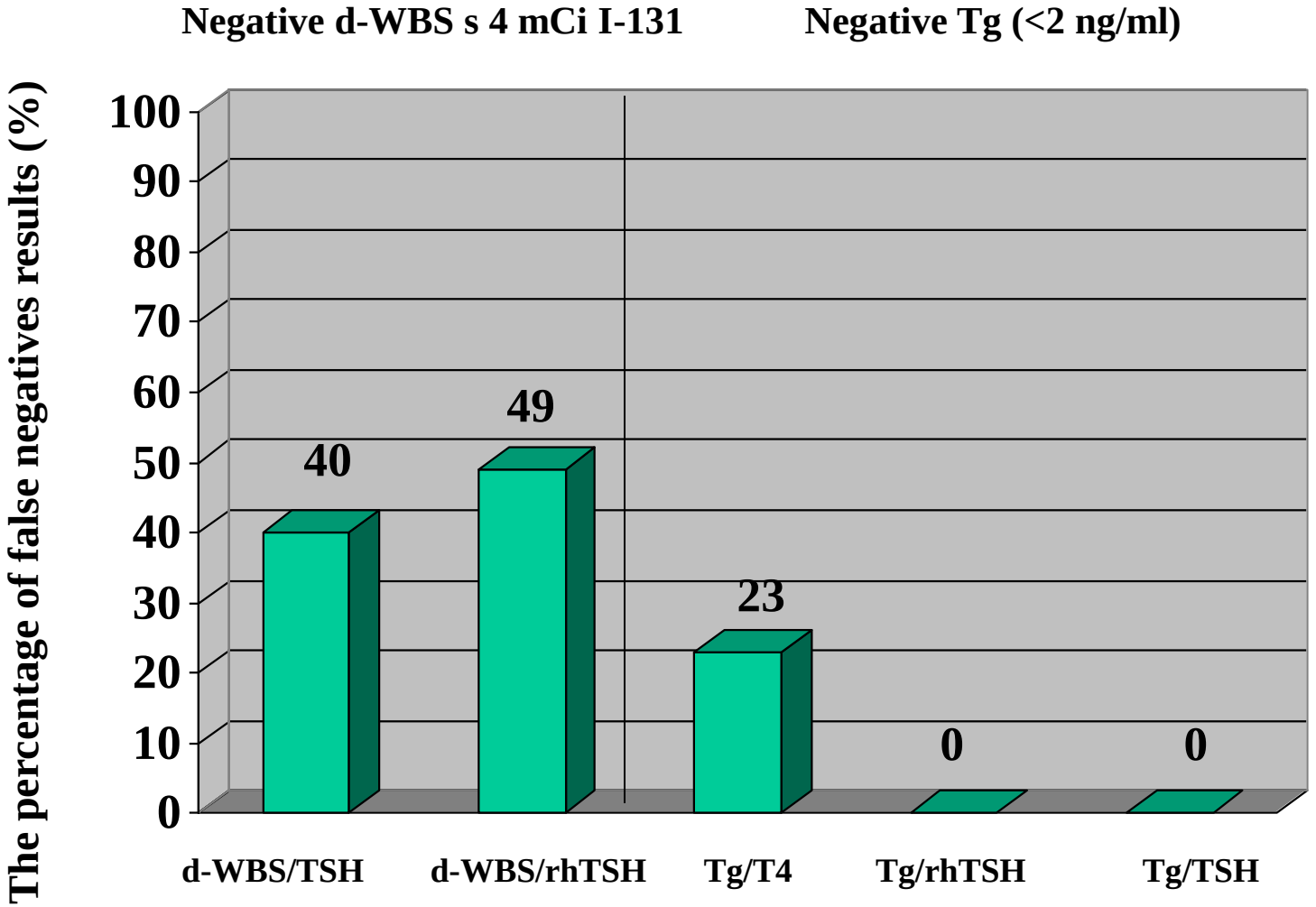
Whole body scintigraphy with I-131

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

*Mazzaferri EL et al. A consensus report of the role.... J Clin Endocrinol Metab. 2003;99:1433-1441.



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%

*Cooper DS et al. Management guidelines..... The American Thyroid Association Guidelines Taskoforce. Thyroid. 2006.16:1-33.

#Pacini F et al. Detection of thyroglobuin in fine needle aspirates.. J Clin Endocrinol Metab. 1992;74:1401-1404.

New definition of successful ablation!?

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

+

Negative neck US!?

Disease free patients

*Schlumberger M, et al. Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. Eur J Endocrinol. 2004;150:105-112.

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.

*Cooper DS et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association Guidelines Taskoforce. Thyroid. 2006;16:1-33.

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

Table 18A.8 Stratification of patients by risk group for well-differentiated thyroid carcinomas (papillary and follicular carcinoma)

Parameters assessed in the AMES (age, *m*etastases, extent of primary cancer, and tumor *s*ize) risk-group definition system:		
Parameter	**Low-risk**	**High-risk**
Age	Male ≤40 years Female ≤50 years	Male >40 years Female >50 years
Metastases	No distant metastasis	Distant metastasis
Extent of primary cancer	Intrathyroidal papillary carcinoma Minimally invasive follicular carcinoma	Extrathyroidal papillary carcinoma Widely invasive follicular carcinoma
Size	<5 cm	>5 cm

Table 4. TNM Classification System for Differentiated Thyroid Carcinoma

	Definition	
T1	Tumor diameter 2 cm or smaller	
T2	Primary tumor diameter >2 to 4 cm	
T3	Primary tumor diameter >4 cm limited to the thyroid or with minimal extrathyroidal extension	
$T4_a$	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve	
$T4_b$	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels	
TX	Primary tumor size unknown, but without extrathyroidal invasion	
N0	No metastatic nodes	
$N1_a$	Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)	
$N1_b$	Metastasis to unilateral, bilateral, contralateral cervical or superior mediastinal nodes	
NX	Nodes not assessed at surgery	
M0	No distant metastases	
M1	Distant metastases	
MX	Distant metastases not assessed	
Stages		
	Patient age <45 years	*Patient age 45 years or older*
Stage I	Any T, any N, M0	T1, N0, M0
Stage II	Any T, any N, M1	T2, N0, M0
Stage III		T3, N0, M0
		T1, $N1_a$, M0
		T2, $N1_a$, M0
		T3, $N1_a$, M0
Stage IVA		$T4_a$, N0, M0
		$T4_a$, $N1_a$, M0
		T1, $N1_b$, M0
		T2, $N1_b$, M0
		T3, $N1_b$, N0
		$T4_a$, $N1_b$, M0
Stage IVB		$T4_b$, Any N, M0
Stage IVC		Any T, Any N, M1

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%)

*Cooper DS et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association Guidelines Taskoforce. Thyroid. 2006;16:1-33.

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 chemoterapeutic trial

- watchful waiting in patients with stable, asymptomatic and slow progressive disease

*Cooper DS et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association Guidelines Taskoforce. Thyroid. 2006;16:1-33.

Metastases

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%)

*Simon D et al. Clinical impact of retinoids in redifferentiation therapy of advanced thyroid cancer: final results of o pilot study. Eur J Nucl Med Mol Imag.2002;29:775-782.

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 Ia indication for FDG PET according to the Consensus Conference 2000
- Wheras 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 LT_4, is used commonly to treat patients with thyroid cancer in an effort to decrease the risk of recurrence (127,214,269). A meta-analysis

THYROID
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ORIGINAL STUDIES, REVIEWS, AND SCHOLARLY DIALOG

THYROID CANCER AND NODULES

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

David S. Cooper, M.D.[1] (Chair)*, Gerard M. Doherty, M.D.,[2] Bryan R. Haugen, M.D.,[3]
Richard T. Kloos, M.D.,[4] Stephanie L. Lee, M.D., Ph.D.,[5] Susan J. Mandel, M.D., M.P.H.,[6]
Ernest L. Mazzaferri, M.D.,[7] Bryan McIver, M.D., Ph.D.,[8] Furio Pacini, M.D.,[9] Martin Schlumberger, M.D.,[10]
Steven I. Sherman, M.D.,[11] David L. Steward, M.D.,[12] and R. Michael Tuttle, M.D.[13]

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

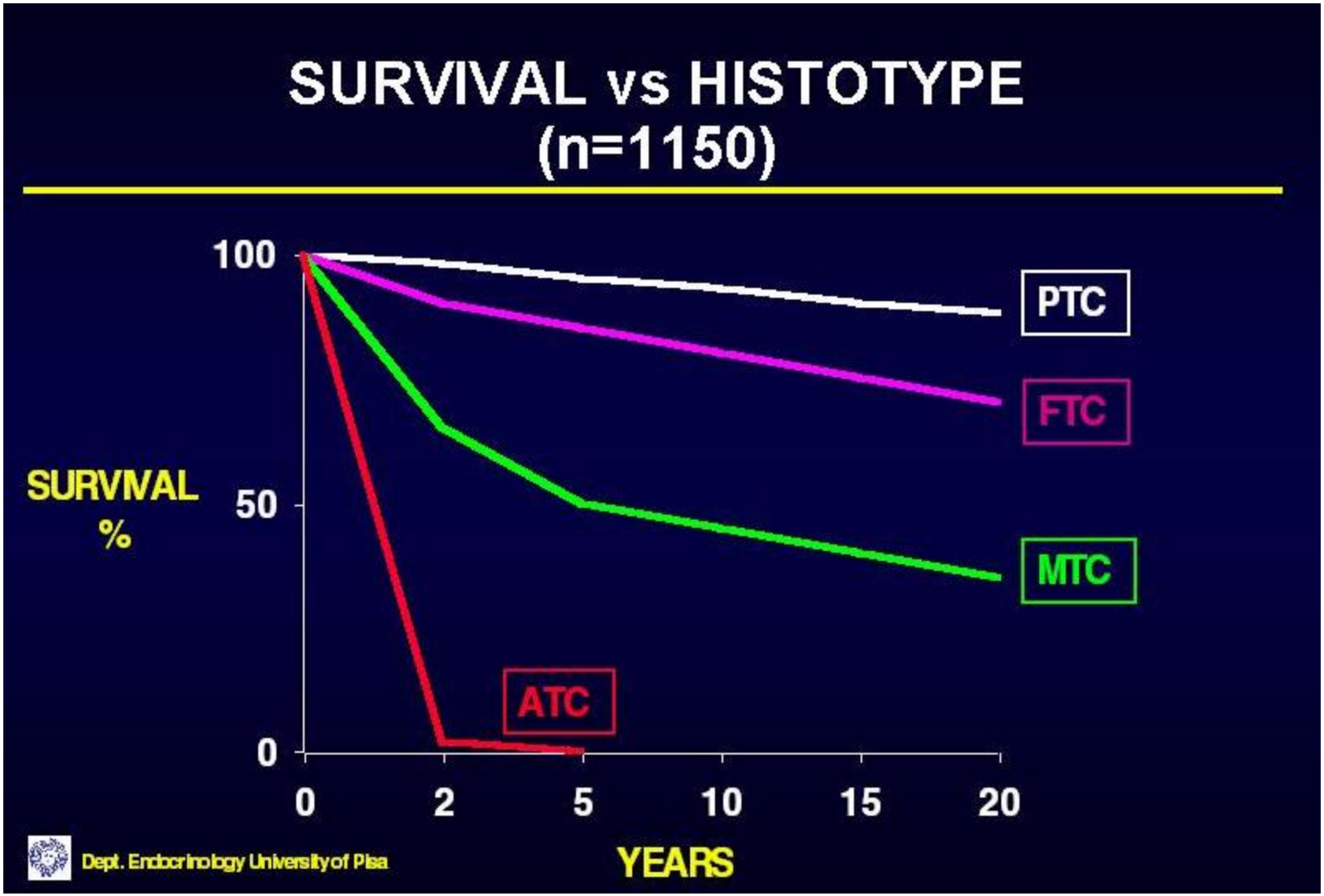
* The American Thyroid Association Guidelines Taskforce, 2009.

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)
100
50
0
SURVIVAL
%
PTC
FTC
MTC
ATC
0
2
5
10
15
20
YEARS
Dept. Endocrinology University of Pisa

The end!