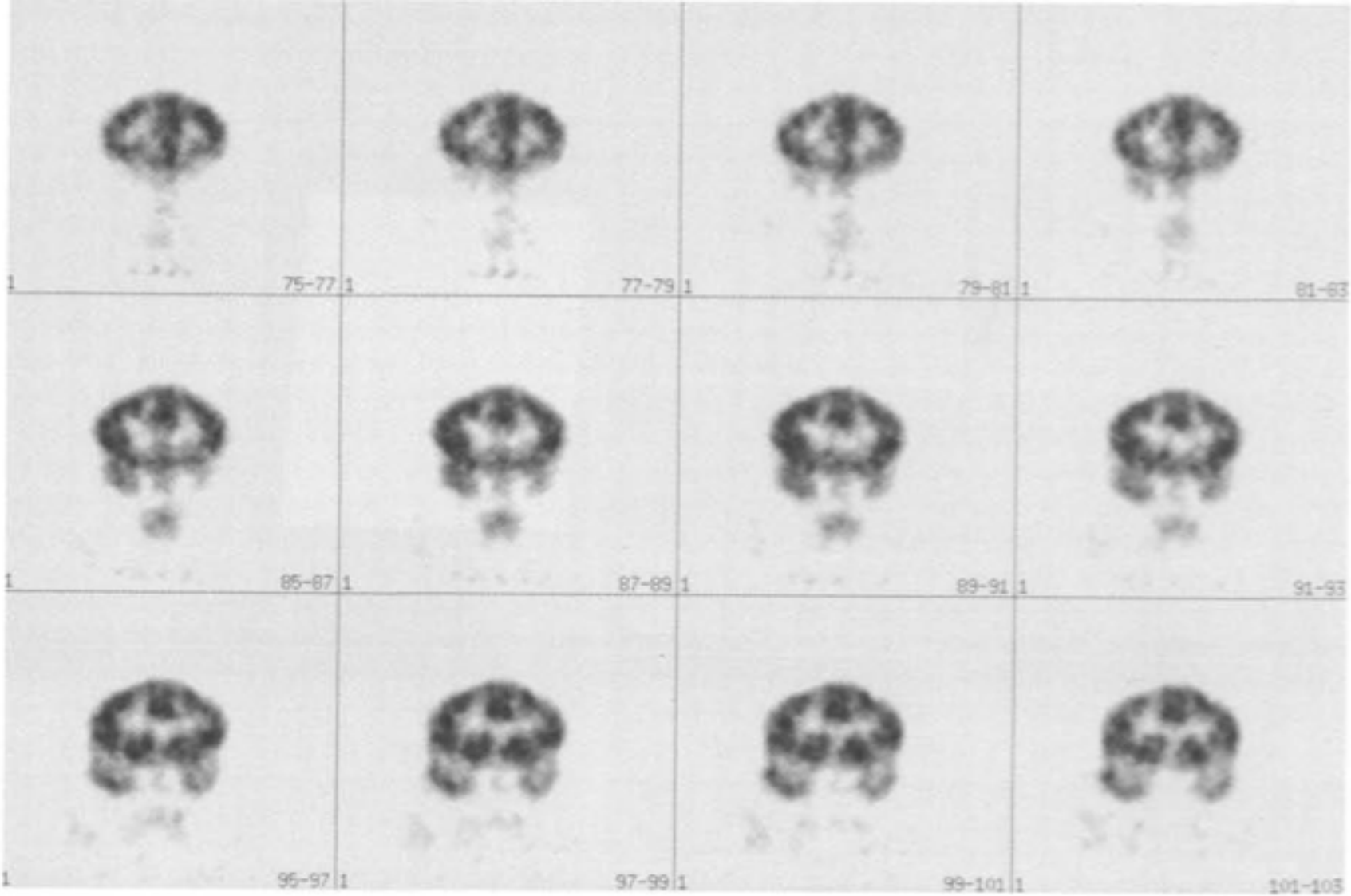
Cerebral infarct

1. F18- FDG is dependent on glucose metabolism
2. SPECT Tc-99m HMPAO/ ECD are cerebral perfusion agents that are lipid soluble, distribute according to blood flow (gray to white matter ratio, 3:1 to 4:1) and fix intracellularly
3. Wedge shape severe decreased metabolism in the left posterior parietal region
4. Cerebral hemorrhage/ infarct/ neoplasm

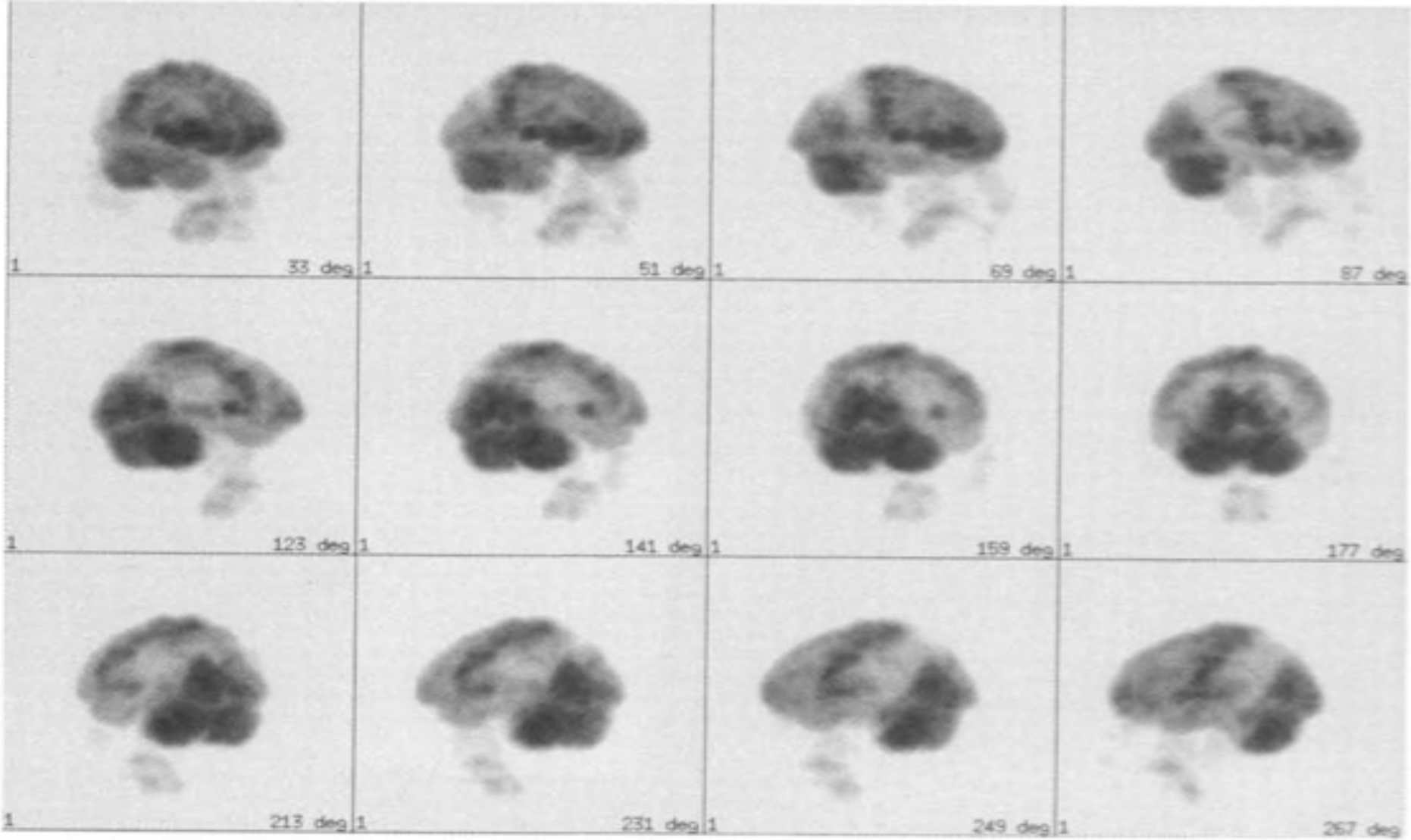


A patient has a seizure disorder unresponsive to medical therapy and is being considered for surgical treatment.

1. Describe the image finding on these coronal ^{18}F FDG-PET slices.
2. What is the differential diagnosis of this image finding if no history was available?
3. What is the probable seizure focus site?
4. What is the utility of PET or SPECT in seizure disorders?

Seizure disorder

1. Decreased metabolism in the left temporal lobe.
2. Temporal lobe infarct, benign mass or lower grade tumor, post RT changes, interictal left temporal lobe seizure focus.
3. Interictal left temporal lobe seizure focus.
4. Conformation of the location of the seizure focus in a candidate for temporal lobe lobectomy. Study is an alternative to surgical depth electrode placement.

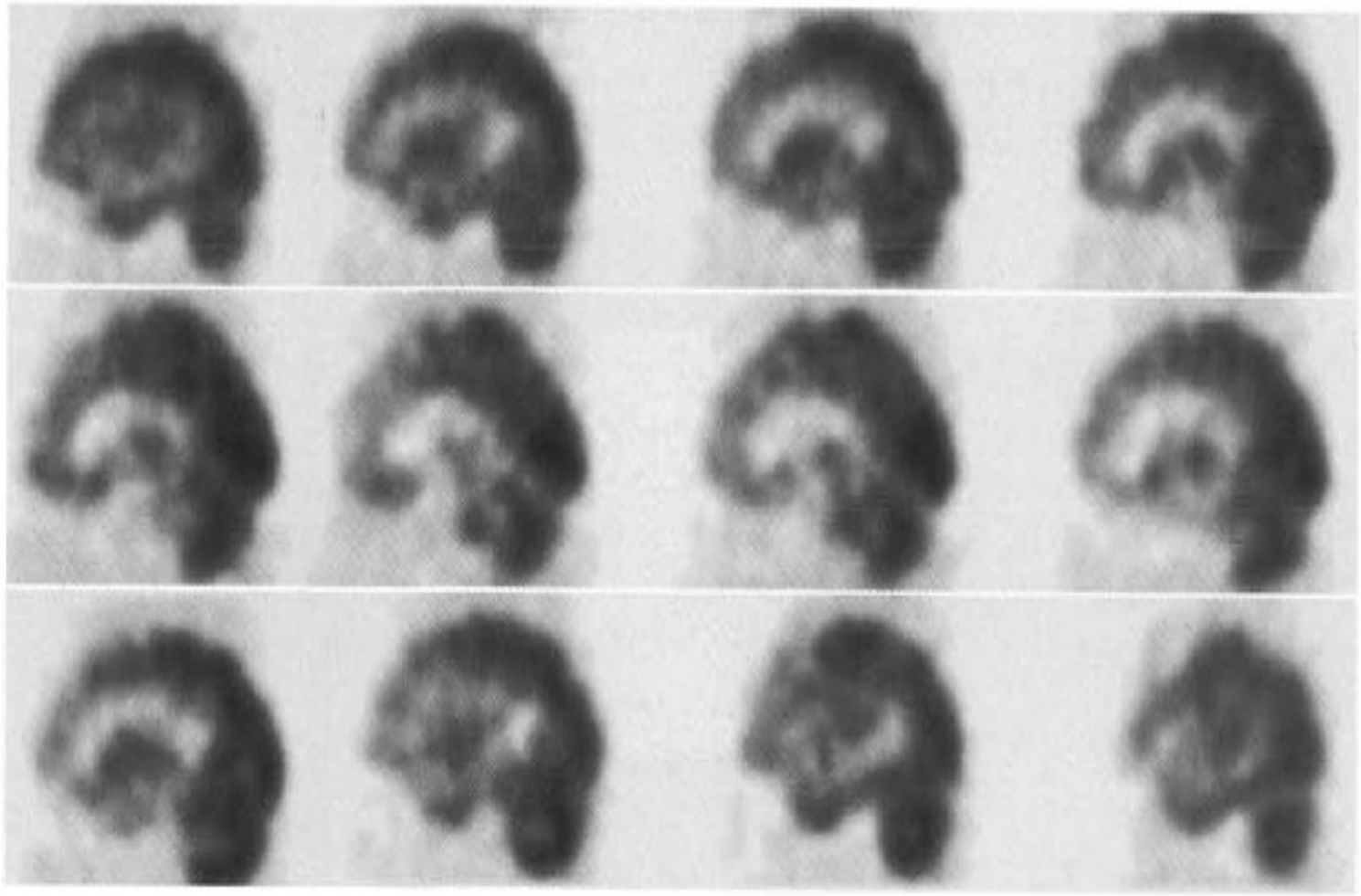


A 55-year-old man has had worsening dementia over 10 months.

1. Give a clinical differential diagnosis for dementia.
2. How can SPECT or PET aid in this differential diagnosis?
3. Describe the ^{18}F FDG-PET findings on the reconstructed three-dimensional volume display.
4. What is the diagnosis and with what degree of certainty?

Alzheimer's disease

1. Multiinfarct, Alzheimer's disease, AID's related, substance abuse, alcoholism, Parkinson's disease, Prick's, Creutzfeldt-Jacob disease, depression, metabolic.
2. Diagnostic pattern using Tc-99m HMPAO, ECD or FDG PET: multiinfarct dementia or Alzheimer's.
3. Hypometabolism (decreased FDG uptake) of the posterior parietal and temporal lobes bilaterally and to a lesser extent the frontal lobes.
4. Alzheimer's disease > 80%

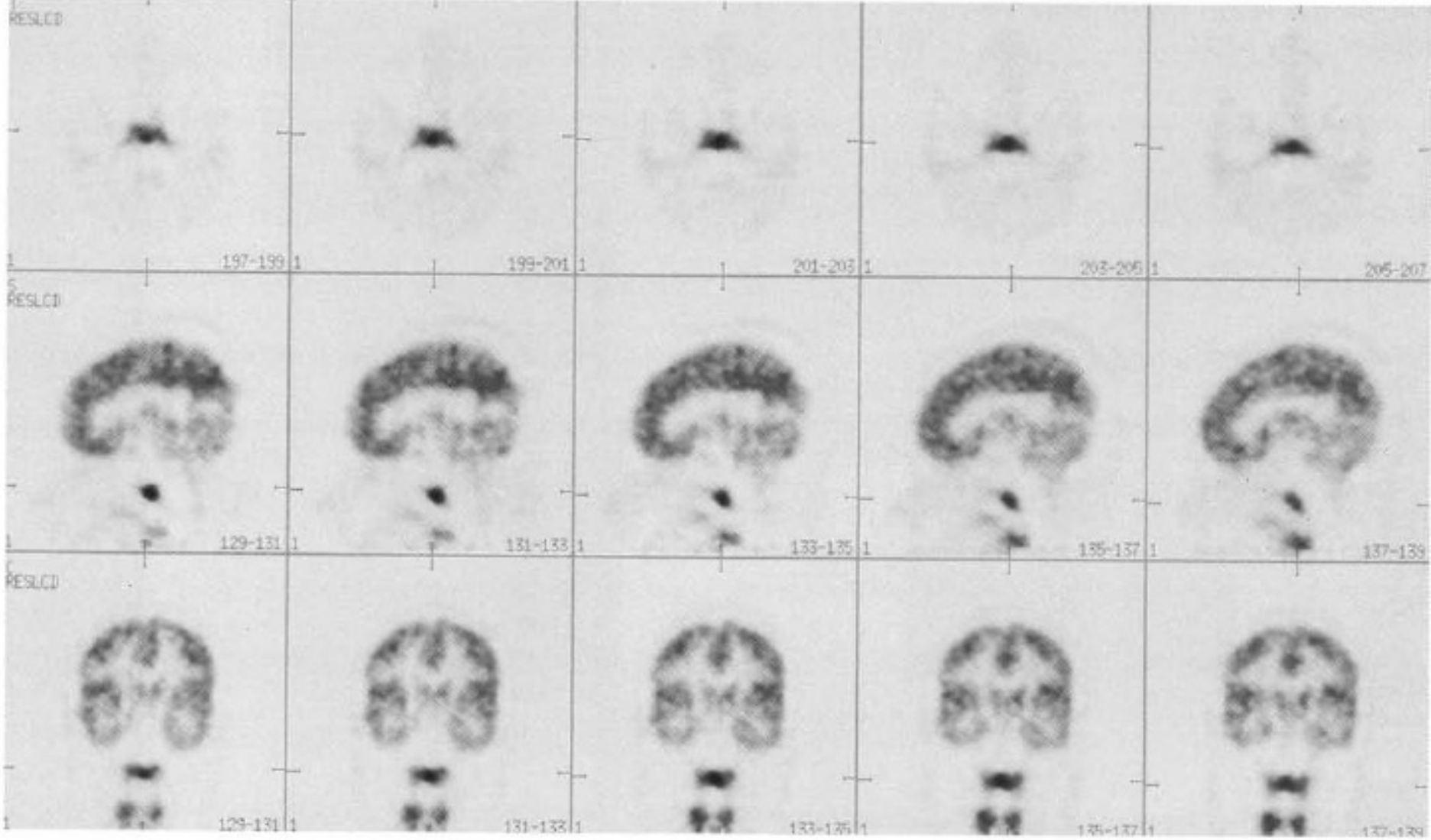


A 55-year-old man has increasing dementia. Recently he had a normal MRI. Sagittal SPECT sections are submitted.

1. List the most common causes of dementia in the elderly.
2. Describe the mechanism of uptake of the radiopharmaceutical used.
3. What causes of dementia are associated with characteristic SPECT perfusion patterns?
4. Describe the findings and the most likely diagnosis.

Prick's disease

1. Alzheimer's disease, multiinfarct, late stage Parkinson's disease, metabolic, drug related and depression.
2. The lipophilic Tc-99m HMPAO or ECD, cross the intact BBB and have rapid intracellular uptake in proportion to cerebral blood flow. They are fixed intracellularly. Subsequent imaging provide a snapshot of the blood flow pattern at the time of injection.
3. Alzheimer's, multi infarct or Prick's disease
4. Decreased blood flow in the frontal cortex bilaterally as a result of frontal lobe dementia.

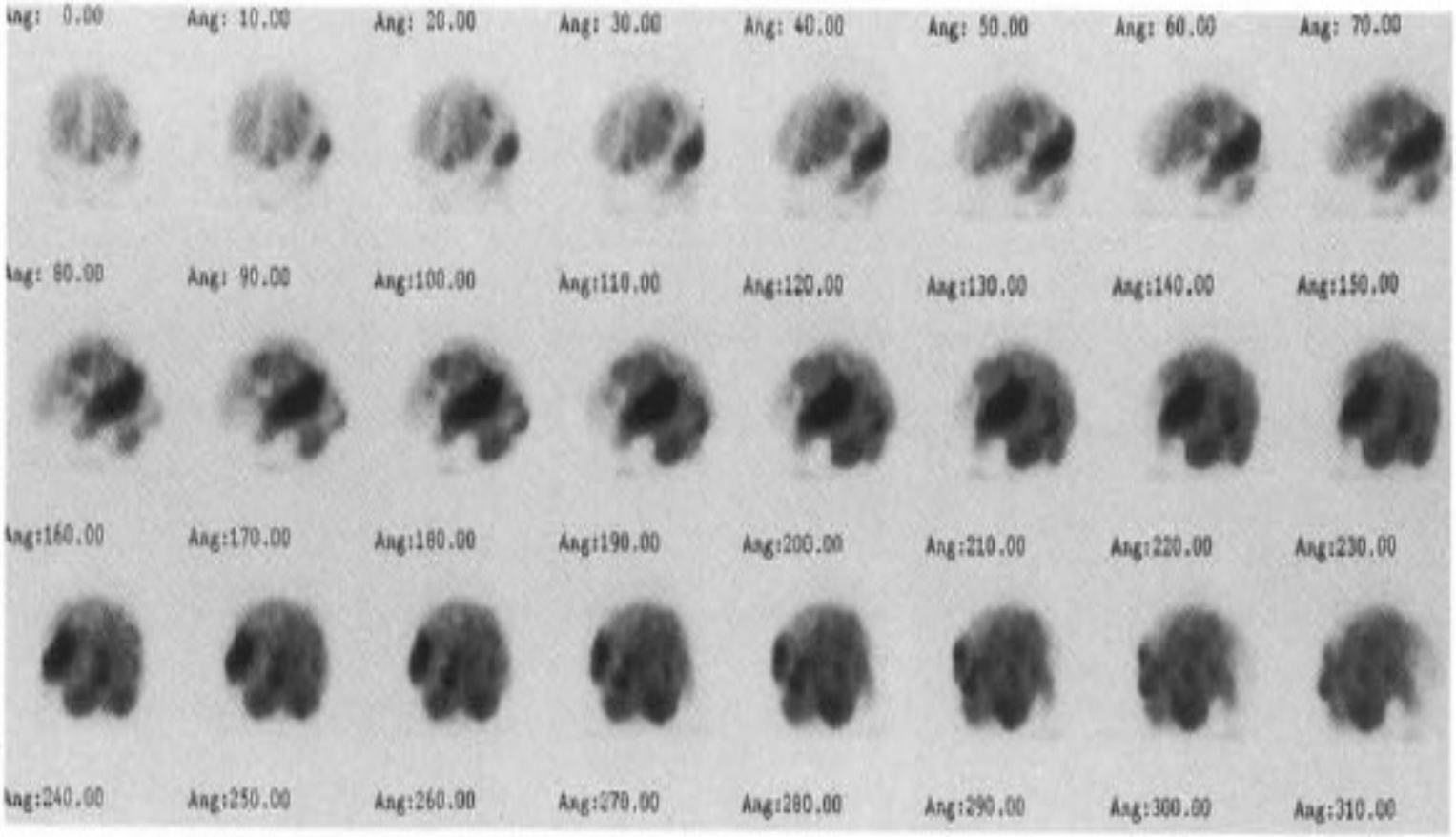


A 51-year-old man with AIDS. MRI scan (not shown) showed a cystic mass in the medulla oblongata.

1. What is the differential diagnosis in this clinical setting?
2. What are the FDG-PET imaging findings? Transverse *(above)*, sagittal *(middle)*, coronal *(below)*.
3. What is your interpretation?
4. Can this differentiation of tumor versus infection be made using single photon radiopharmaceuticals?

Brain lymphoma vs. infection in AIDS

1. Tumor, especially lymphoma, versus infection e.g..: toxoplasmosis
2. Increased FDG uptake in the medulla oblongata
3. Consistent with malignancy
4. Yes, with Tl-201 or Tc-00m sestaMIBI

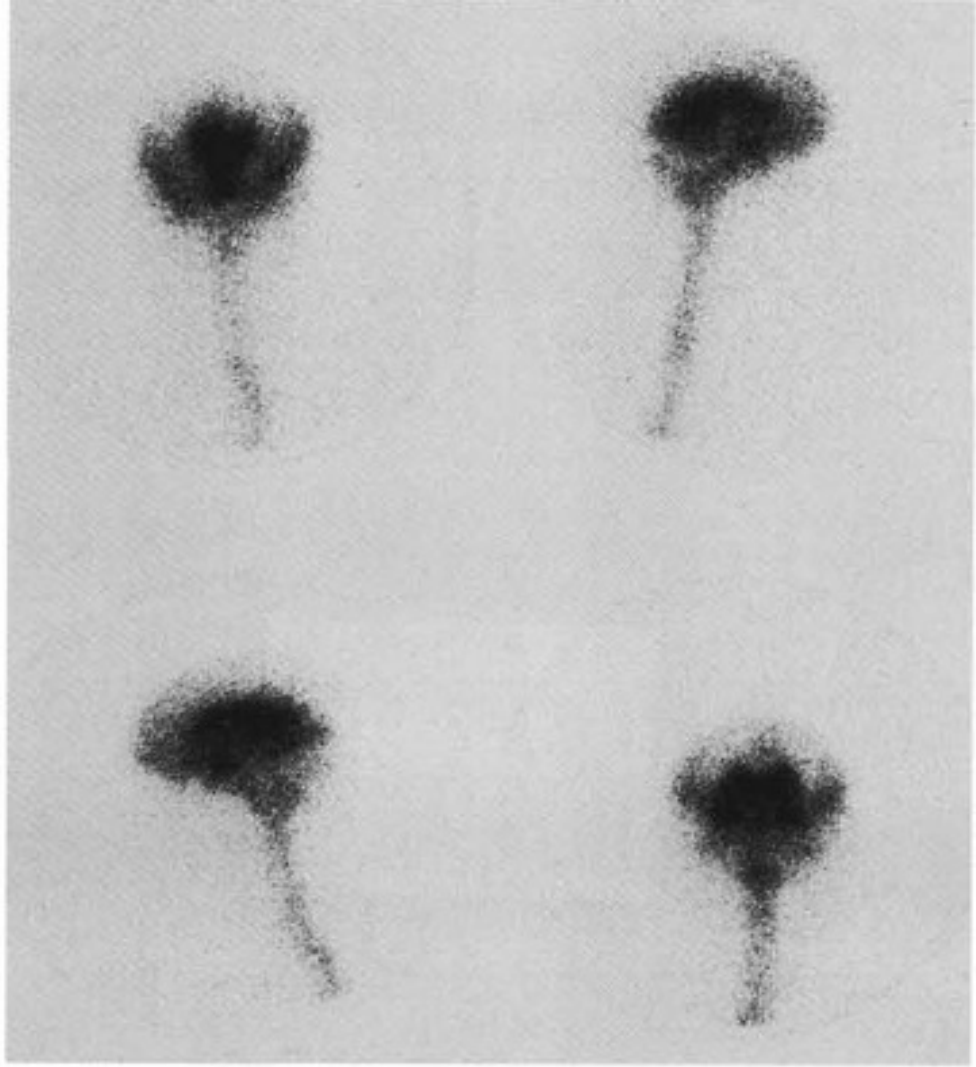


A 29-year-old man with recent onset of fever and headache has no prior medical problems.

1. Describe the ^{99m}Tc HM-PAO SPECT reconstructed volume display in this patient. Angle 0 is the anterior projection, angle 90, the left lateral view, and so forth.
2. What is the physiological correlate of this imaging pattern?
3. What is the differential diagnosis of this scintigraphic pattern in this patient?
4. What is the likely diagnosis considering the patient's history?

Herpes Encephalitis

1. Increased uptake in the temporal lobe
2. Increased blood flow in this region
3. Seizure focus (ictal injection), infection or tumor
4. Herpes encephalitis

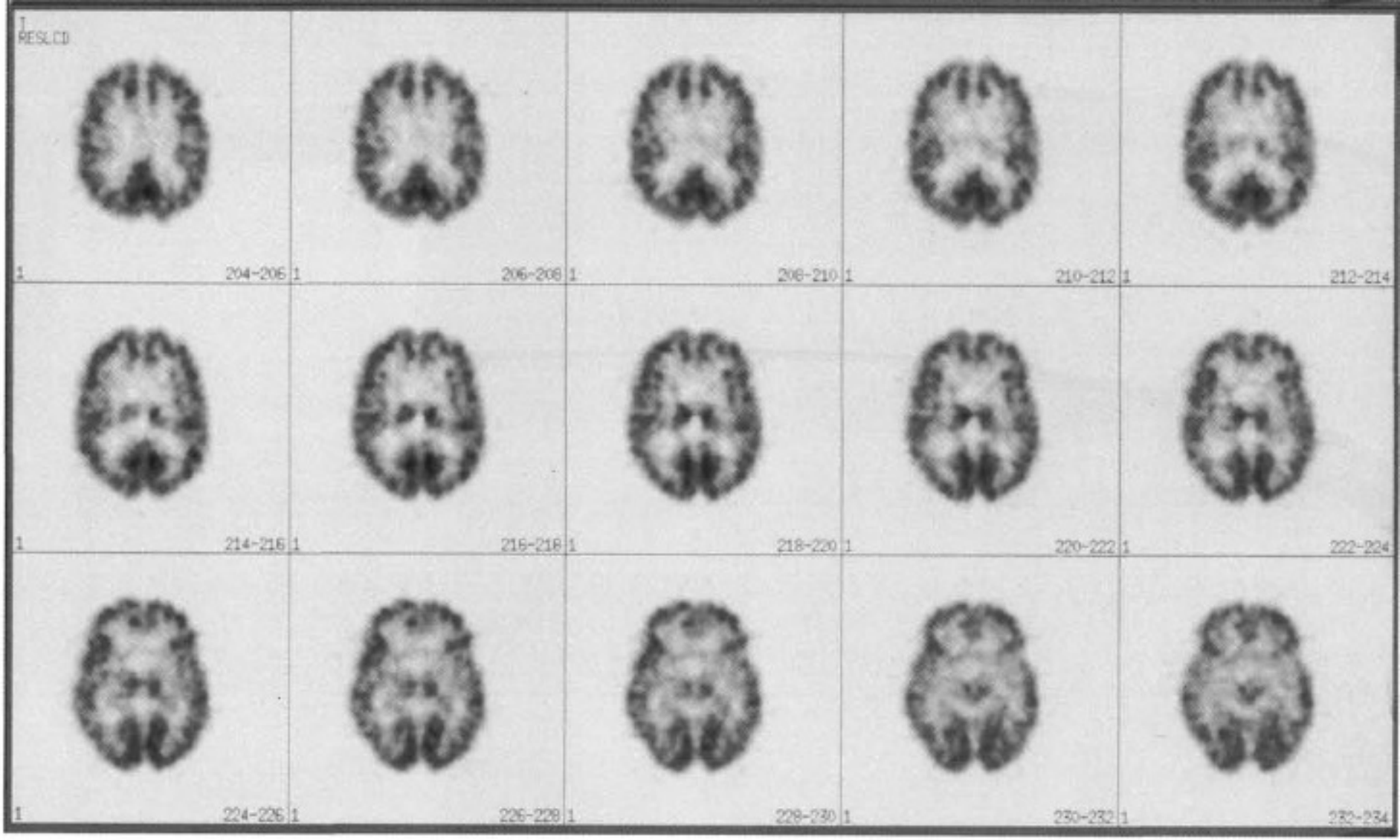


A 65-year-old man was referred for radionuclide cisternography. CT showed enlarged cerebrospinal spaces.

1. What is the radiopharmaceutical and route of administration?
2. Describe the findings on these images acquired at 24 hours after injection. *Top row:* anterior and right lateral. *Bottom row:* left lateral and posterior.
3. What is the diagnosis?
4. What are the patient's likely symptoms?

Normal pressure hydrocephalus

1. In-111 DTPA administered intrathecally by lumbar puncture
2. Ventricular reflux and convexity block with no flow over the cerebral hemispheres above the sylvian fissure
3. Communicating hydrocephalus, in this case is normal pressure hydrocephalus
4. Triad of dementia, ataxia and incontinence

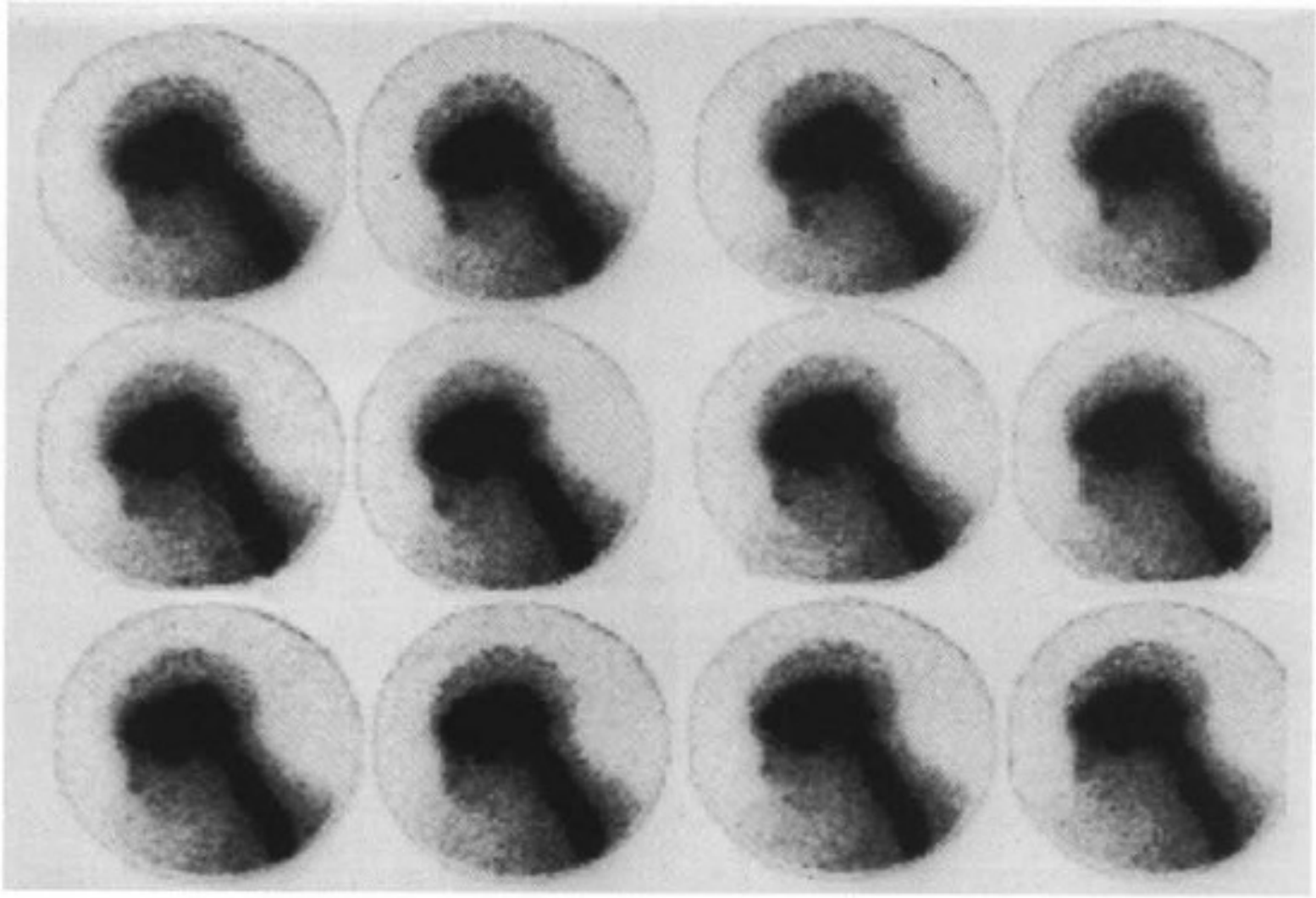


A 33-year-old man with neurological disorder was referred for a ^{18}F FDG-PET brain scan.

1. What is the FDG-PET scan abnormality?
2. What symptoms are likely?
3. What is the pathological condition?
4. What is the diagnosis?

Huntington's disease

1. Hypometabolism of the basal ganglion
2. Progressive motor abnormalities of involuntary choreiform movements and akinetic rigidity with progressive cognitive deteriotion
3. Neuronal degeneration in the striatum, with the caudate more involved than the putamen
4. Huntington's disease



A 53-year-old woman has a history of head trauma, headache, and rhinorrhea. Left lateral views over 1 hour.

1. Name the appropriate radiopharmaceutical(s).
2. How is the radiopharmaceutical administered?
3. What is the imaging finding and interpretation?
4. How can the site of leakage be further defined?

CSF leak

1. In-111 or Tc-99m DTPA
2. Intrathecal injection
3. Activity in the region of the nose, indicating CSF leak, probably at the cribriform plate
4. Anterior views. With the use of nasal pledgets placed in the superior, middle and inferior nasal turbinates

Thyroid

Pearls & Pitfalls

Thyroid

- A normal 24-hour iodine uptake in most lab ranges between 10% and 30% to 35%.
- Common indications for radionuclide thyroid imaging are to differentiate between various types of hyperfunction (Grave's disease, toxic MNG or autonomous adenoma) and to assess nodularity (cold or hot) and ectopic tissue.

Pearls & Pitfalls

Thyroid

- Salivary glands are usually seen on Tc-99m pertechnetate scan unless the patient has Grave's disease. They are not seen on an I-123 scan.
- A lingual thyroid is usually located in the midline at the base of tongue, with no thyroid seen in the normal location. The ectopic gland is often hypofunctional.

Pearls & Pitfalls

Thyroid

- A thyroid gland with an organification defect is usually seen as a normal gland on a Tc-99m pertechnetate scan but manifests no activity on an iodine scan in a child with a high TSH level.
- A large gland with intense homogenous activity is usually Grave's disease.

Pearls & Pitfalls

Thyroid

- A large gland with patchy activity is usually a MNG but could also be chronic thyroiditis or an infiltrative process.
- Most hot nodules are benign hyperfunctioning adenomas. They can be single or multiple and can suppress the normal portions of the glands.

Pearls & Pitfalls

Thyroid

- Subacute thyroiditis classically presents with a markedly depressed radioiodine uptake and nonvisualization of the gland in a patient with thyrotoxicosis and a tender, swollen thyroid.
- Chronic thyroiditis can mimic numerous thyroid conditions but on imaging is usually patchy and decreased in activity.

Pearls & Pitfalls

Thyroid

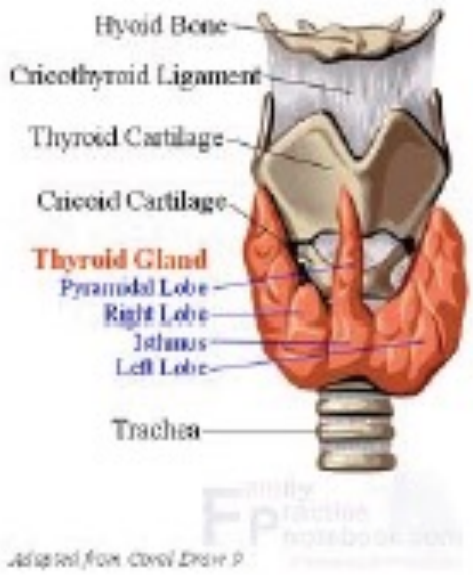
- Thyroid cancer is usually a single focal cold lesion and only rarely is seen to be diffuse or multifocal on thyroid scan.
- Thyroid cancer can concentrate Tc-99m sestamibi and persist on delayed images. They are typically cold on Tc-99m pertechnetate scans.

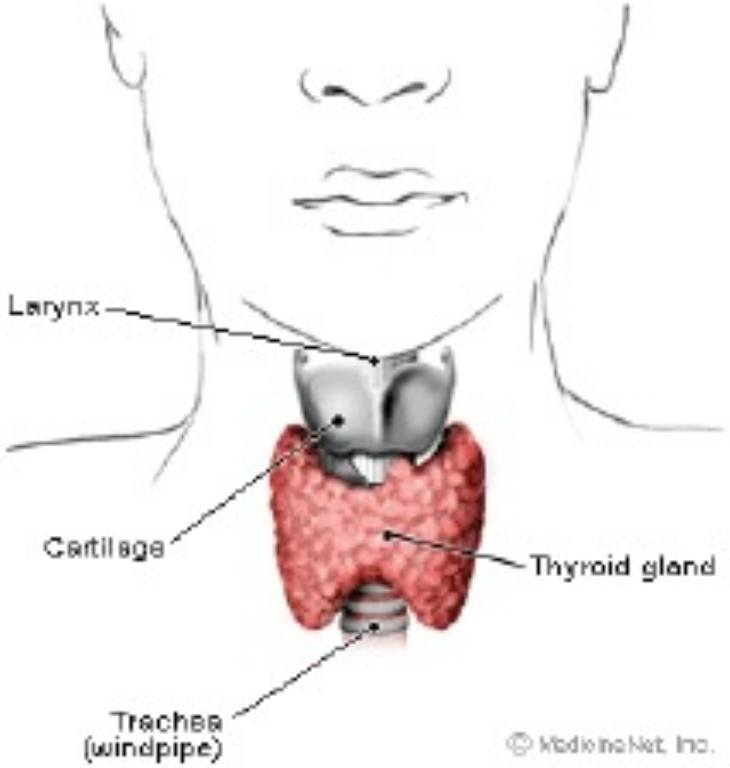
Pearls & Pitfalls

Thyroid

- Activity in the bladder, stomach and bowel and diffuse activity in the liver is usually normal on a WBS of I-131.
- After successful RAI ablation of residual thyroid tissue, serum Tg are sensitive to detect recurrent thyroid cancer.

ANATOMY





'Thyroid' derived from Greek word 'thureos'

Usual weight - 20 - 25 gms

↑ size with age

Embryological Development

- 1st endocrine gland to develop ~ day 24
- Originates between 1st and 2nd pharyngeal pouch
- Bilobed structure by 6-7th weeks, becomes detached and descends into the neck
- Remaining remnant connected to tongue is thyroglossal duct
- Duct solidifies and becomes obliterated ~7-10th wk of gestation
- Pyramidal lobe is remnant of thyroglossal duct
- Complete descent ~ 7th wk of gestation

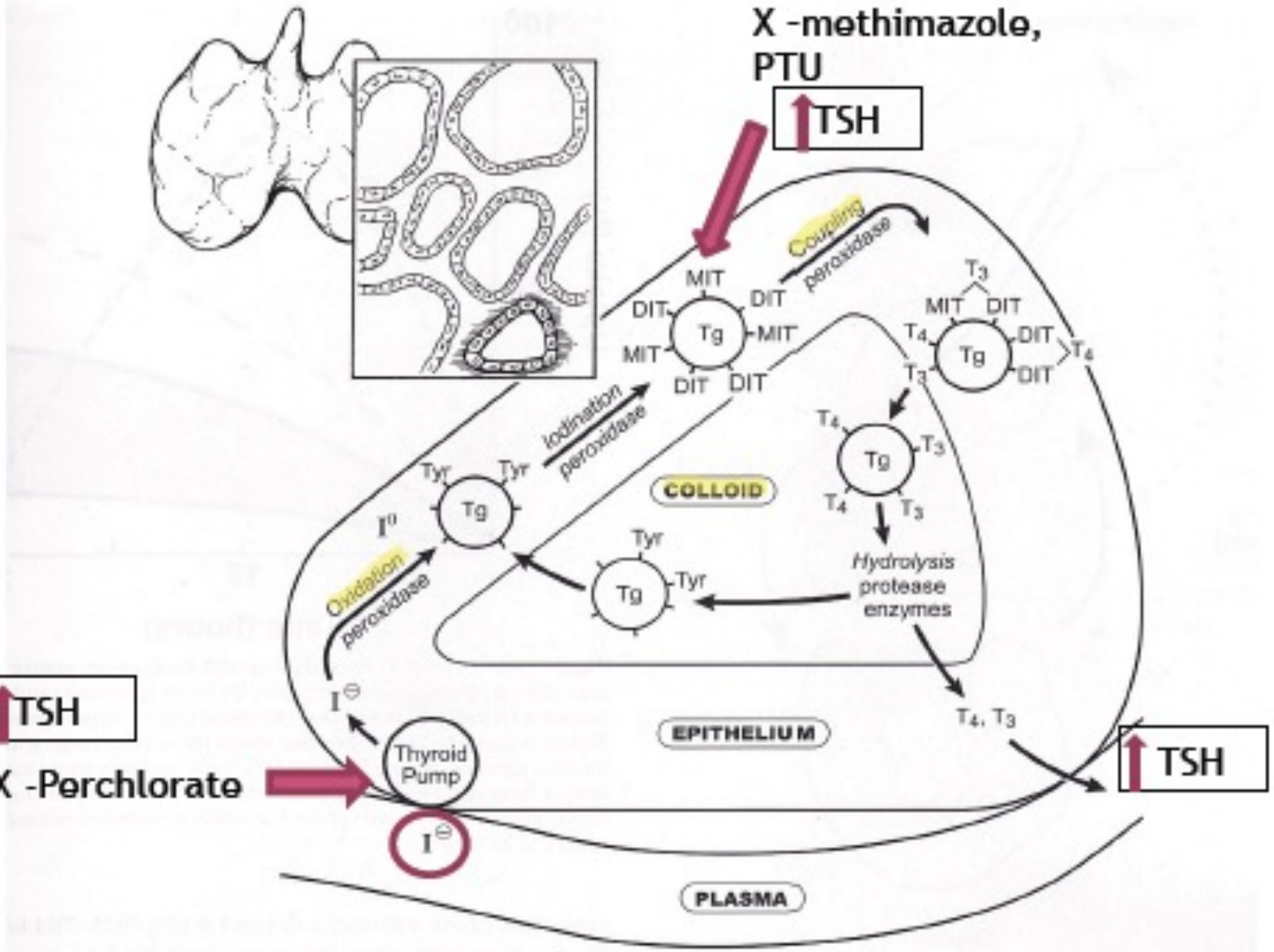
Physiology

- Anions I- , TcO_4^- selectively trapped by thyroid, salivary glands, stomach and choroid plexus
- Conc ratio (Thyroid : Serum)

Iodide	30:1
Tc-pertchn -	12:1
*Thyrotoxicosis	500 : 1

- Iodide further 'organified'
- Trapping phase can be evaluated by Tc-pertechn
- Non-organified iodine or Tc can be washed out by perchlorate
- Stable iod. block binding of radioactive iodine → ↓ upt.
- More than 90% iodide absorbed within 60 min
- Thyroid extraction - 20%, urinary excr - 80%

IODINE METABOLISM



THYROTOXICOSIS VS HYPERTHYROIDISM

- Thyrotoxicosis: a group of symptoms and signs due to elevated thyroid hormones in the body of any cause.
- Hyperthyroidism: a group of symptoms and signs due to increased production of thyroid hormones by hyper- functioning thyroid gland.

PHYSICAL PROPERTIES

I-131	I-123	Tc-99m
Reactor-produced	Cyclotron-produced	Generator elution
Decay by beta (β^-) emission	Decay by electron capture	Decay by isomeric transition
$T_{½}$ = **8 days**	$T_{½}$ = **13.2 hours**	$T_{½}$ = **6 hours**
The β^- decay is followed by γ-ray emission of **364 keV** (90%), beta emission (606keV)	γ-ray emission of **159 keV** During production, potential contaminated with other iodine isotopes such as I-124 ($T_{½}$ = 4.2 days) & I-125($T_{½}$ =60 days).	γ-ray emission of **140 keV** (88%)
I-131 vial may turn brown owing to radiolysis.	.	Trapped not organified

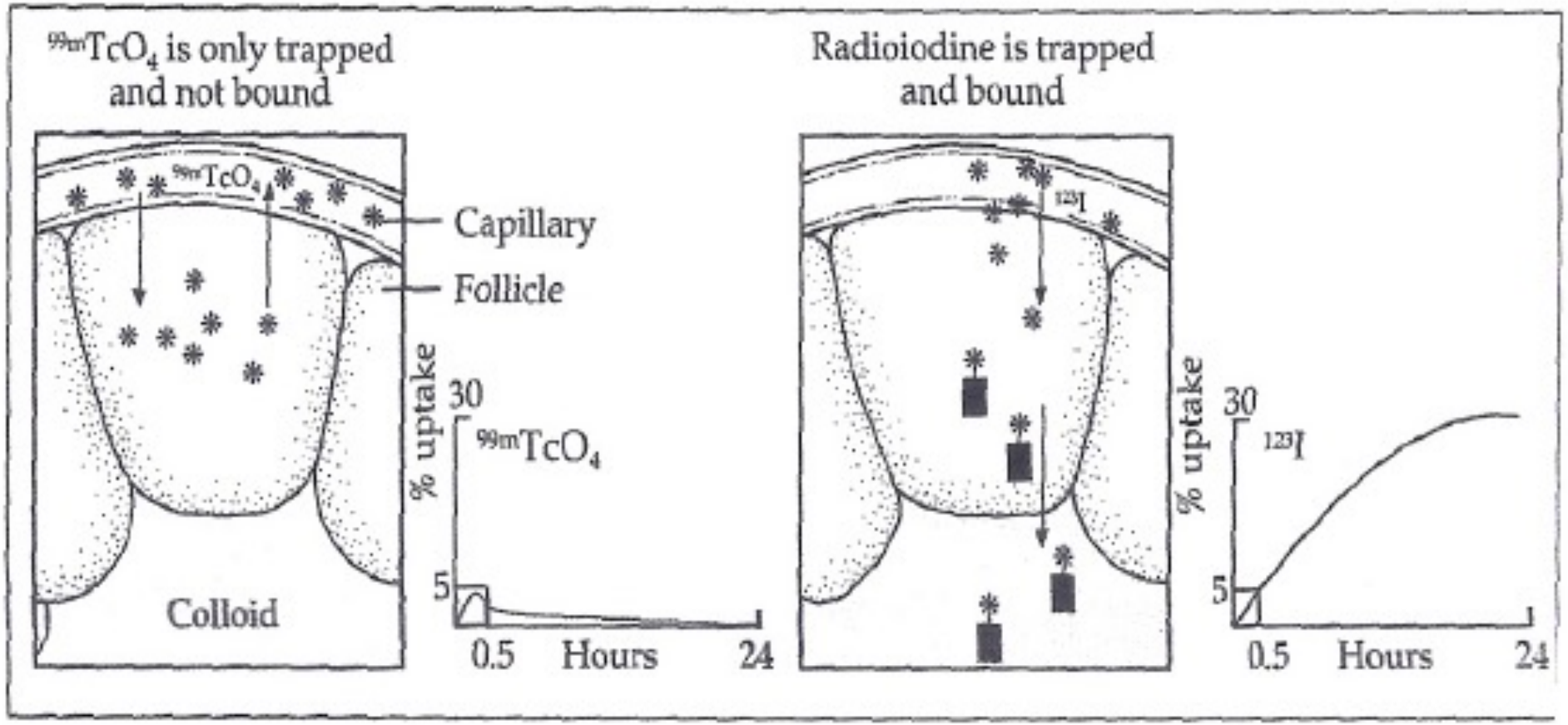
RADIOIODINE- 131 AND 123

- ideal physiological tracer
- rapid absorption, prompt uptake
- selectively trapped and organified and incorporated into thyroid hormone
- Detected in gld within few min, reaches thy lumen by 20-30 min, progressively increase over 24 hours
- Excretion through kidneys (~50% in 24hrs) and GIT

TECHNETIUM-99M

- pertechn ion similar in size to iodide ion
- trapped but not organified
- about 0.5 to 3.75% of administered dose is found in the thyroid at 20-30 mins
- 30% excreted in the urine in the first 24 hr then fecal excretion

RADIONUCLIDES
99M TCO AND RADIOIDOINE UPTAKE MECH.



CLINICAL INDICATION OF THYROID SCAN

- Structural & Functional status(hot,cold) of thyroid gland/nodule
- Cause of thyrotoxicosis
- Locate ectopic thyroid tissue (lingual thyroid)
- Evaluation of congenital hypothyroidism
- Diagnosis of mediastinal mass (substernal goiter)
- Differentiate thyroiditis from Graves'
- Thyroid cancer (whole body scan -WBS)

METHODOLOGY

A. Patient preparation: [Radioiodine]

- ascertain pregnant status or lactating
- avoidance of interfering materials

  i) medications (thyroid horm and ATD)

  ii) iodine-containing foods (eg kelp) and medications (eg iodinated contrast, etc)

- lab and relevant Ix results
-nil orally x 4 hrs

IODINE CONTAINING FOODS & SUBSTANCES

Table 2
Dietary Sources of Iodine

Iodized salt
Milk/dairy products
Eggs
Seafood
Seaweed and kelp products
Commercial bread made with iodide conditioners
Chocolate
Iodide-containing multivitamins
FDC red dye #3

DRUG INTERACTIONS

Type of Medication/Substance	Duration of stopping Tx prior to RAIT
Antithyroid eg PTU, CBM, methimazole, multivitamins	3 days for antithyroid drugs NB; beta blockers can be cont. 7 days for multivitamins
Thyroxine / T3	4-6 weeks / 2 weeks
Expectorants,agar, Lugols iodine Potassium iodide (SKKI)	2-3 weeks depending on iodine content
Radiographic contrast agents Intravenous (water soluble)	3-4 weeks (assuming normal RF)
Amiodarone	3-6 months or longer

Adapted from Society of NM Guidel(18)Martin A Walter,Mathias Briel,et al. BMJ 2007(26);334;514

IMAGING PROCEDURE

Radionucl: 3-5 mCi i.v (TcO_4^-) or
p.o 200-300 µCi I-123/5 mCi I-131

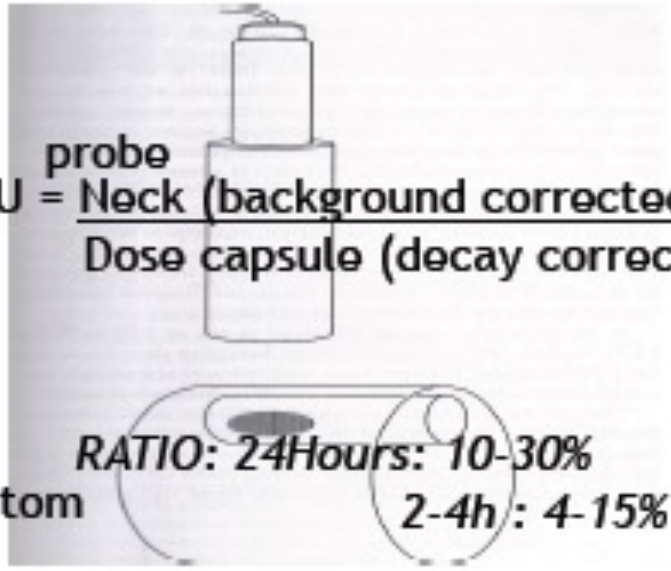
Imaging : 15-30 min after Tc injection or 3-24hrs after
I-123/3-5 days post I-131

Position : supine, head extended
Views : ant, lat, obl.

Markers **- thyroid cart and sternal notch**
- palpable nodules

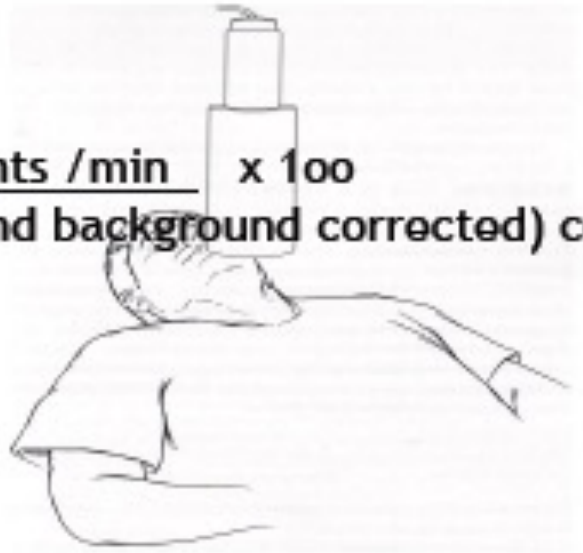
THYROID UPTAKE STUDIES-METHOD

- Provide quantitative information of % uptake of administered activity
- %RAIU elevated in Grave's ds, suppressed in other causes of thyrotoxicosis eg thyroiditis
- 5-10 µCi I-131, 50-100 µCi I-123



$$\%RAIU = \frac{\text{Neck (background corrected) counts /min}}{\text{Dose capsule (decay corrected and background corrected) counts/min}} \times 100$$

RATIO: 24Hours: 10-30%
2-4h : 4-15%



TC-99M PERTECHNETATE % UPTAKE

- Scintillation probe not used
- Gamma camera technique
- Syringe counting before and after Tc-99m inj
- Thyroid scan
- ROI drawn over thyroid, (background), syringes
- Normalization for pixel size and time of acquisition
- Calculate percent uptake -

$$\text{Tc-99 pertech \% uptake} = \frac{\text{thy cnts - bckgrd cnts}}{\text{inj cnts - R cnts}} \times 100$$

Ratio: 0.3-4.5%

THYROID UPTAKE STUDY

- NTT (neck to thigh) ratio may be calculated.
- ROI over the thyroid (neck) and thigh.
- Uptake measurement:

a) Count patient's neck for 1 min

b) Count patient's thigh for 1 min

- count rate of the thyroid by the count rate of the thigh which will give the ratio (Normal: 5-10)

DIFFERENTIAL DIAGNOSIS OF THYROTOXICOSIS-BASED INCREASE OR DECREASE %RAIU

- INCREASE UPTAKE

-Hyperthyroidism

-Toxic MNG

-Hashitoxicosis

-Central hypothyroidism

-Hidatidiform mole, trophoblastic tumour, chorioca

-Metastatic thyroid cancer

- DECREASE UPTAKE

-Subacute thyroiditis

-Iodine-induced thyrotoxicosis

-Amiodarone-induced thyrotoxicosis

-Thyrotoxicosis factitia

-Struma ovarii

Thyroid function	Increased thyroid uptake	Normal thyroid uptake	Decreased thyroid uptake
Thyrotoxicosis	Grave's disease	Antithyroid drugs PTU/CBZ	Expended iodide pool
			Thyrotoxic phase of subacute thyroiditis
	Hashitoxicosis		Thyrotoxicosis factitia
			Antithyroid drugs
			Struma ovarii
Euthyroid	Rebound after antithyroid drug withdrawal		
	Recovery from subacute thyroiditis		
Hypothyroid	Hashimoto's disease	Hashimoto's disease after RAI therapy	Hypothyroidism: primary/ secondary
		Subacute thyroiditis	

Trapping/organification

- Potassium perchlorate discharge test:uptake pre and post 400mg KCl.if reduction in uptake > 20%,suggestive of organification defect (e.g Pendred's syndrome)

T3 SUPPRESSION

- T 3 100 uG daily X5 days.
- Suppression more than 2% suggests autonomy or GRAVES' DISEASE

Solitary cold nodule in thyroid scan	Thyroid adenoma
	Parathyroid adenoma
	Lymphoma
	TB
	Colloid cyst
	Metastatic carcinoma
	Primary thyroid carcinoma

Percentage to become thyroid carcinoma

Nodules	Cold	15 – 20%
	Indeterminate	15 – 20%
	MNG	5%
	Hot	<1%

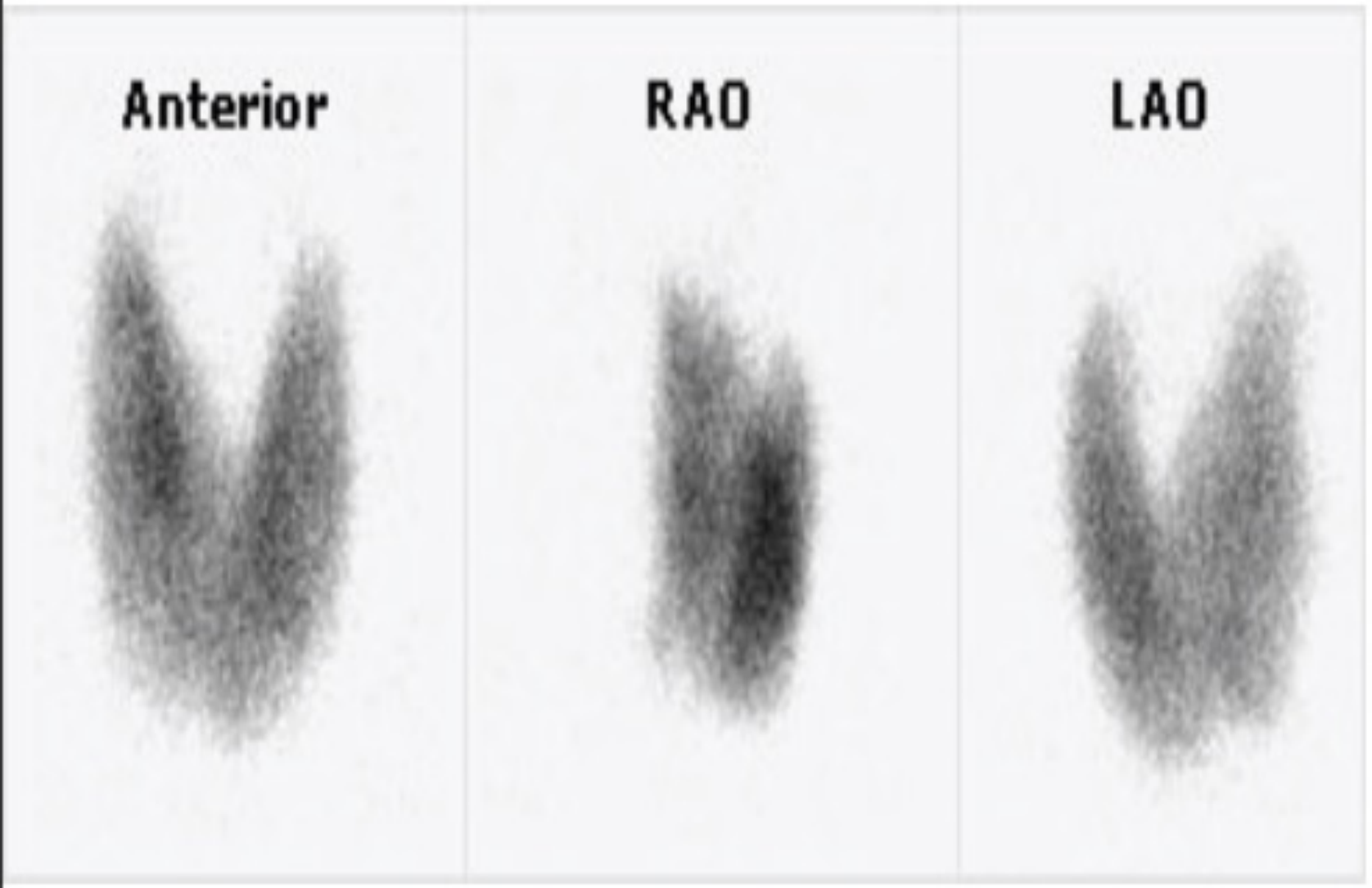
20% malignant = trapping but not organified

Discordant nodule (thyroid adenoma)	**Hot nodule of Tc-99m**
	Cold nodule of I-131

Small amount of functioning thyroid tissue with intact trapping and organified

Reverse discordant nodule (thyroid adenoma/ Hashimoto's thyroiditis/ thyroglassal duct)	**Cold nodule of Tc-99m**
	Hot nodule of I-131

Owl's eye sign	**Photopenic area in center of functioning autonomous thyroid nodule = cystic degeneration within solitary functioning thyroid nodule**
Fish eye sign	Central core of functioning tissue surrounded by a rim of decreased uptake = functioning adenoma with cystic degeneration at periphery



Normal Thyroid Scan

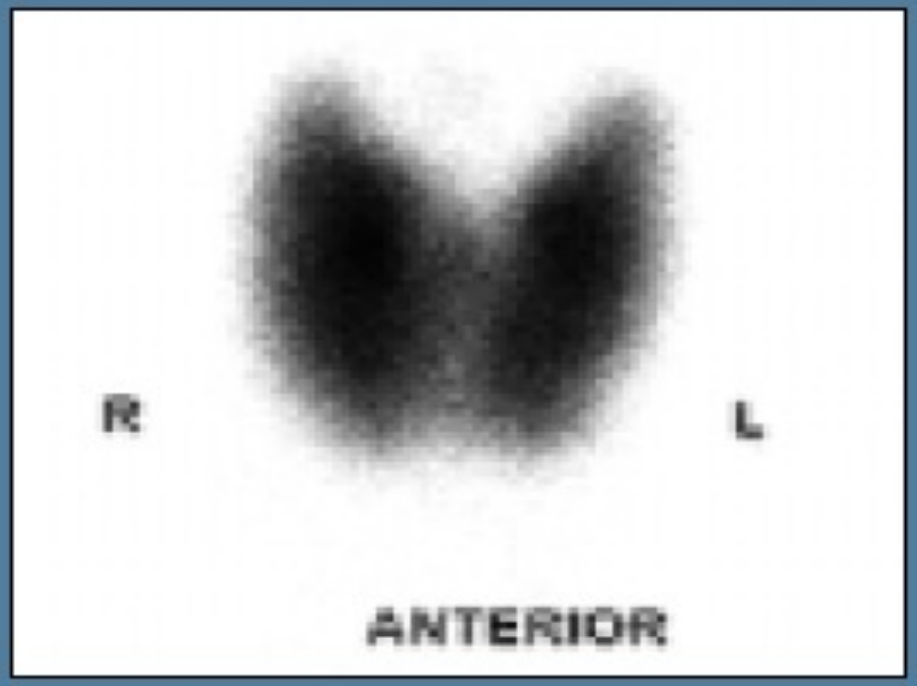


Fig 1.
Graves' Disease

Case 2

46 y/Mal/Female
Enlarging goitre a/w toxic symptoms
resistant to conserv mx

Scan: Diffuse Toxic Goitre (Graves' Ds)

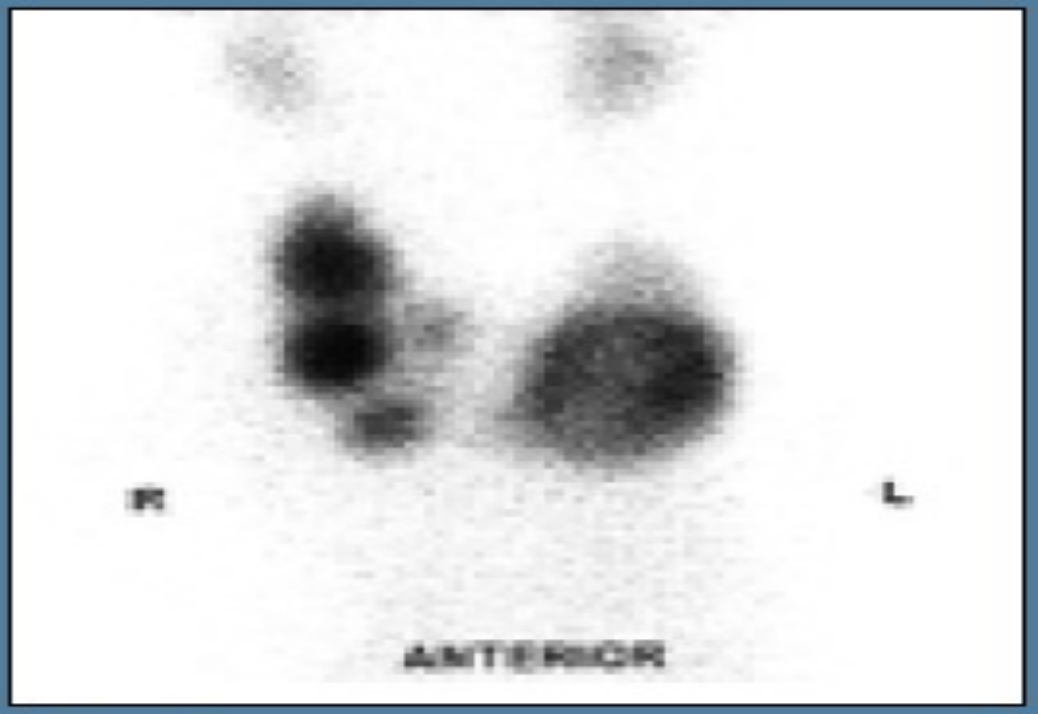
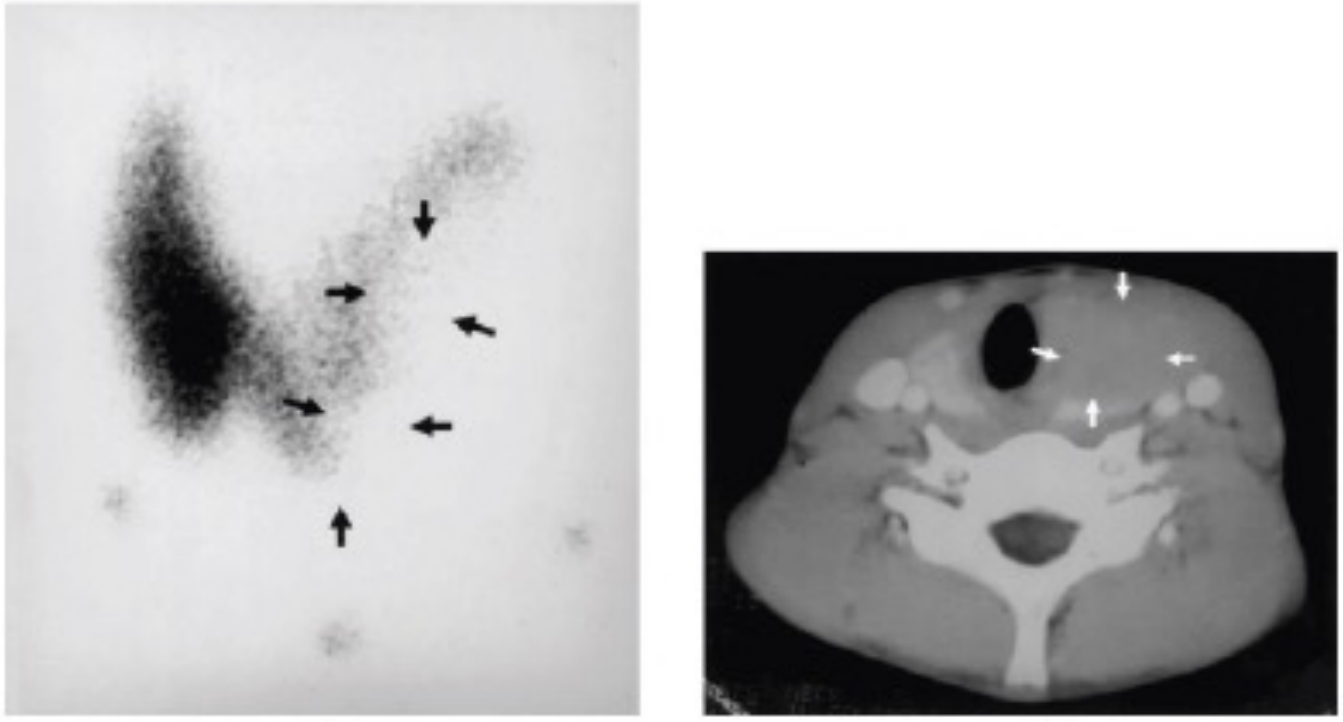


Fig 2.
Toxic multinodular goitre

Case 1

THYROID NODULES



(a) (b)

Figure 5. (a) Isotope scan of thyroid demonstrating a photopenic area within the left lobe. (Reproduced with permission of Springer-Verlag [12]). (b) Axial contrast enhanced CT of the same patient shows a solid mass within left lobe of thyroid (arrows). Lymphoma was proven by biopsy.

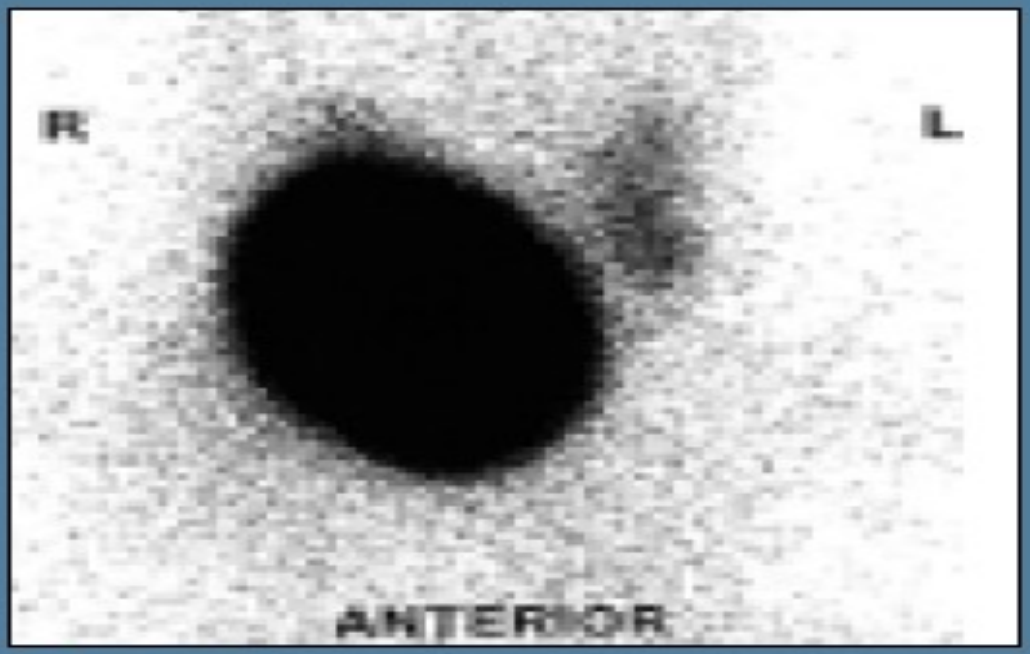
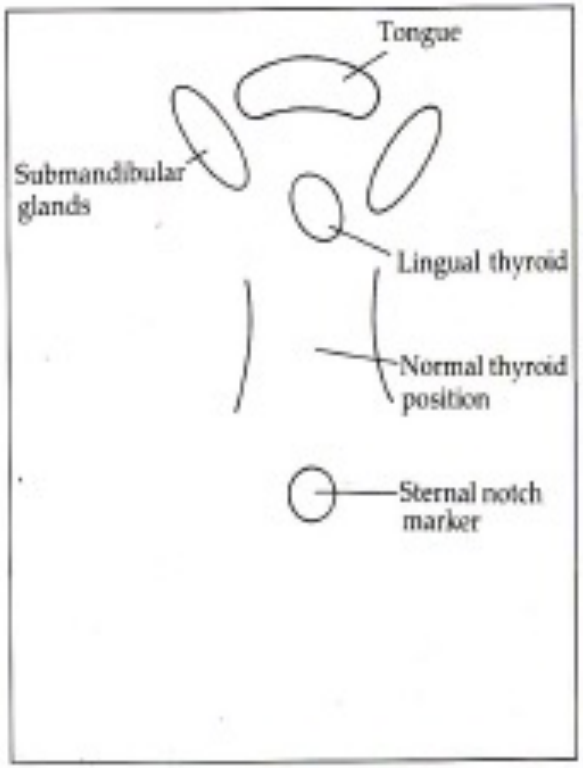


Fig 3.
Autonomous toxic nodule

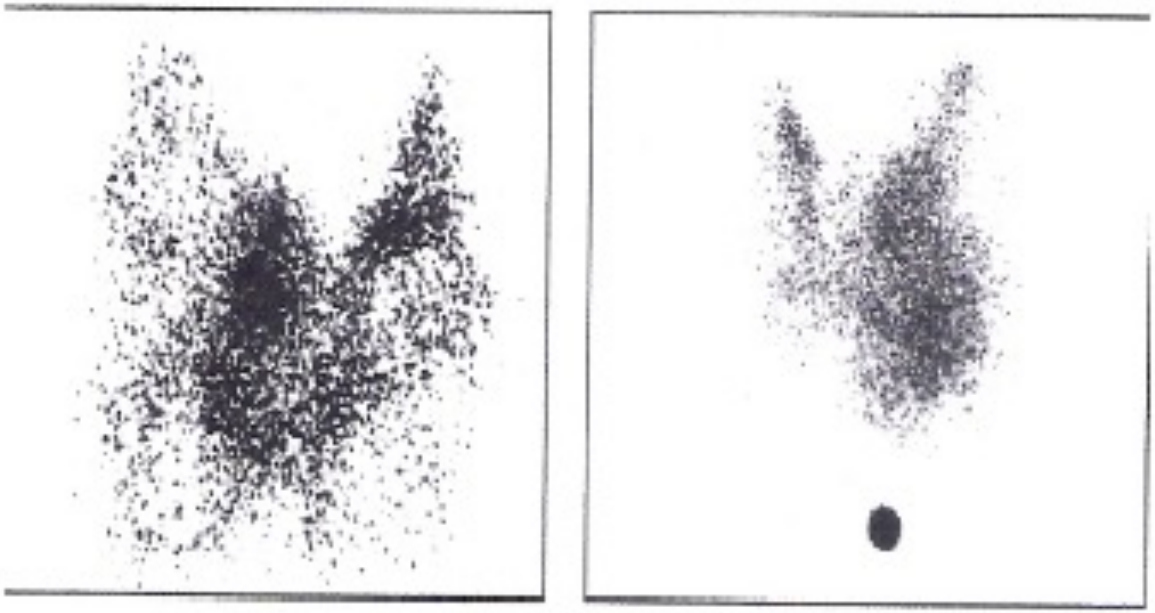
Case 5

C/O POST TONGUE MASS



99mTc-Thyroid Scan-
Lingual thyroid

52 Y/ IND/ FEM
LONGSTANDING NOD GOITRE X 20 YRS
ASYMPTOMATIC
USG- MULTINODULAR GOITRE, SUGG THYR SCAN FOR FURTHER EVALUATN

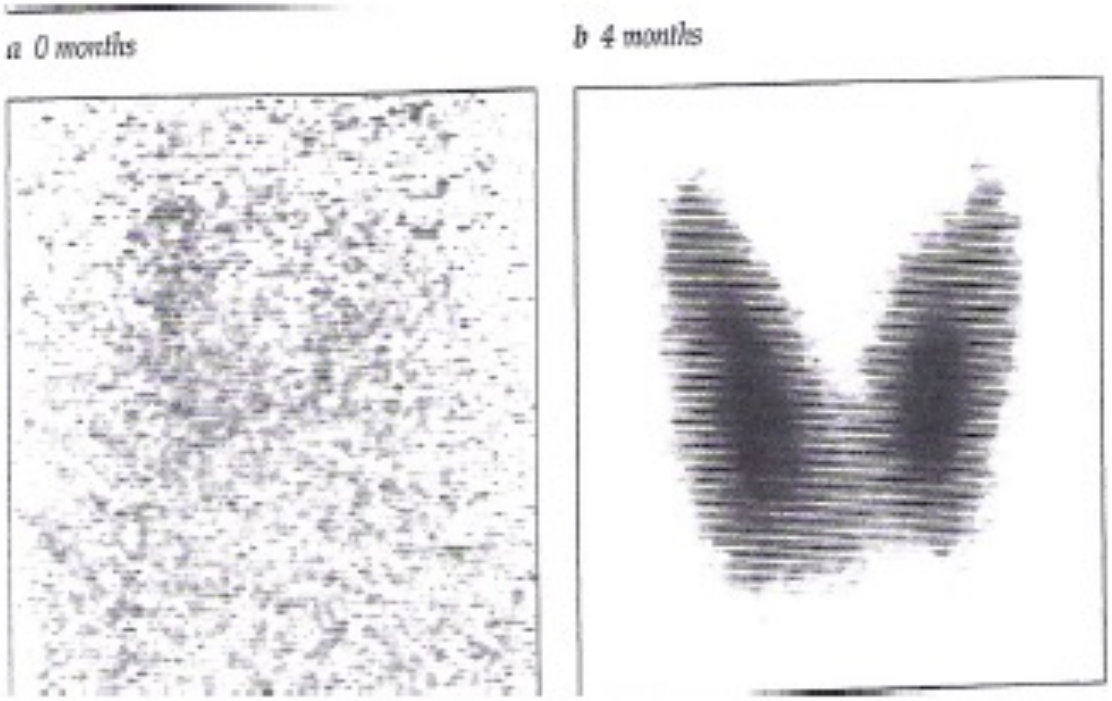


Scan : Non-toxic
Multinodular G

Fig 4.
Subacute thyroiditis

Case 6

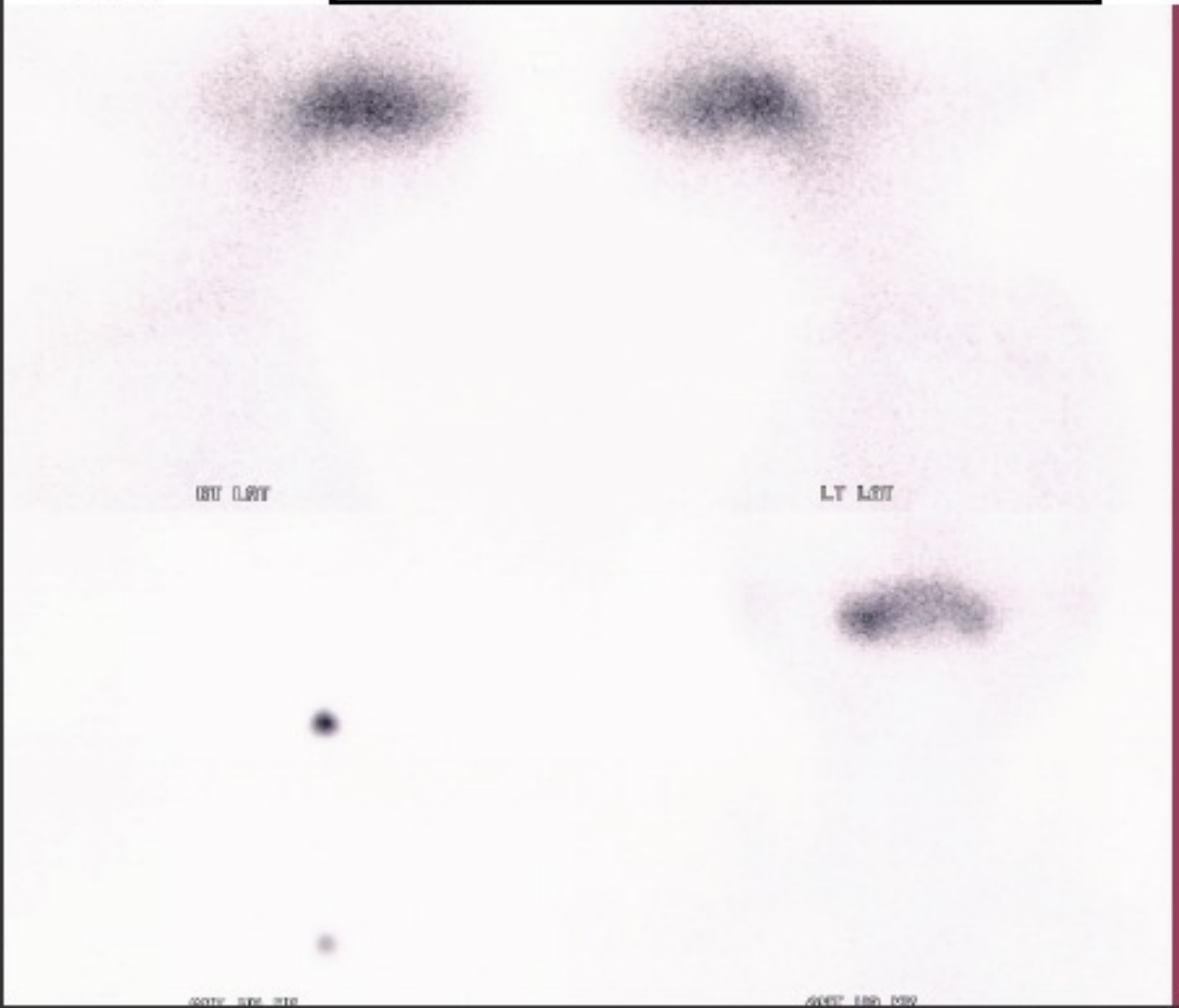
C/o painful swelling of thyroid w biochem hyperthyroid



SCAN: GENERALISED REDUCED RADIOACTIVITY DUE TO SUBACUTE VIRAL THYROIDITIS

Case 7

Congenital Hypothyroid



^{131}Iodine– Physical Characteristics

- reactor produced
- T ½ 8.02 days
- ß and γ emitter
  - ß - 606 keV max, 191 keV mean
  - γ - 364 & 637 keV
- Clinical Form – Sodium Iodide

Mechanism of cell damage

- Energy from ionizing radiation →disrupts chemical bonds throughout the cell → damage of the DNA molecule →cellular dysfunction → ultimately cell death.
- Most of the radiation dose is delivered by ß-particles. ß-particles do not penetrate deep into tissue (2 mm in depth, at most). 10% of the total radiation dose comes from γ radiation

Causes of hyperthyroidism

Grave's Disease
Toxic multinodular Goitre
Toxic adenoma

→ Antithyroid drugs
Surgery
Radioiodine

Thyroiditis
- Hashimoto's
- Subacute (De Quervain's)
- Silent (post partum)

→ Self limiting
Symptomatic

Factitious
Iodine and iodine-containing drugs agents
Drugs - amiodarone
Trophoblastic disease

→ Treatment of causes

Treatment Choices

Antithyroid drugs (thionamides)

- inhibit thyroxine production
- immunomodulation

Surgery

- reduce thyroid bulk to decrease thyroxine production

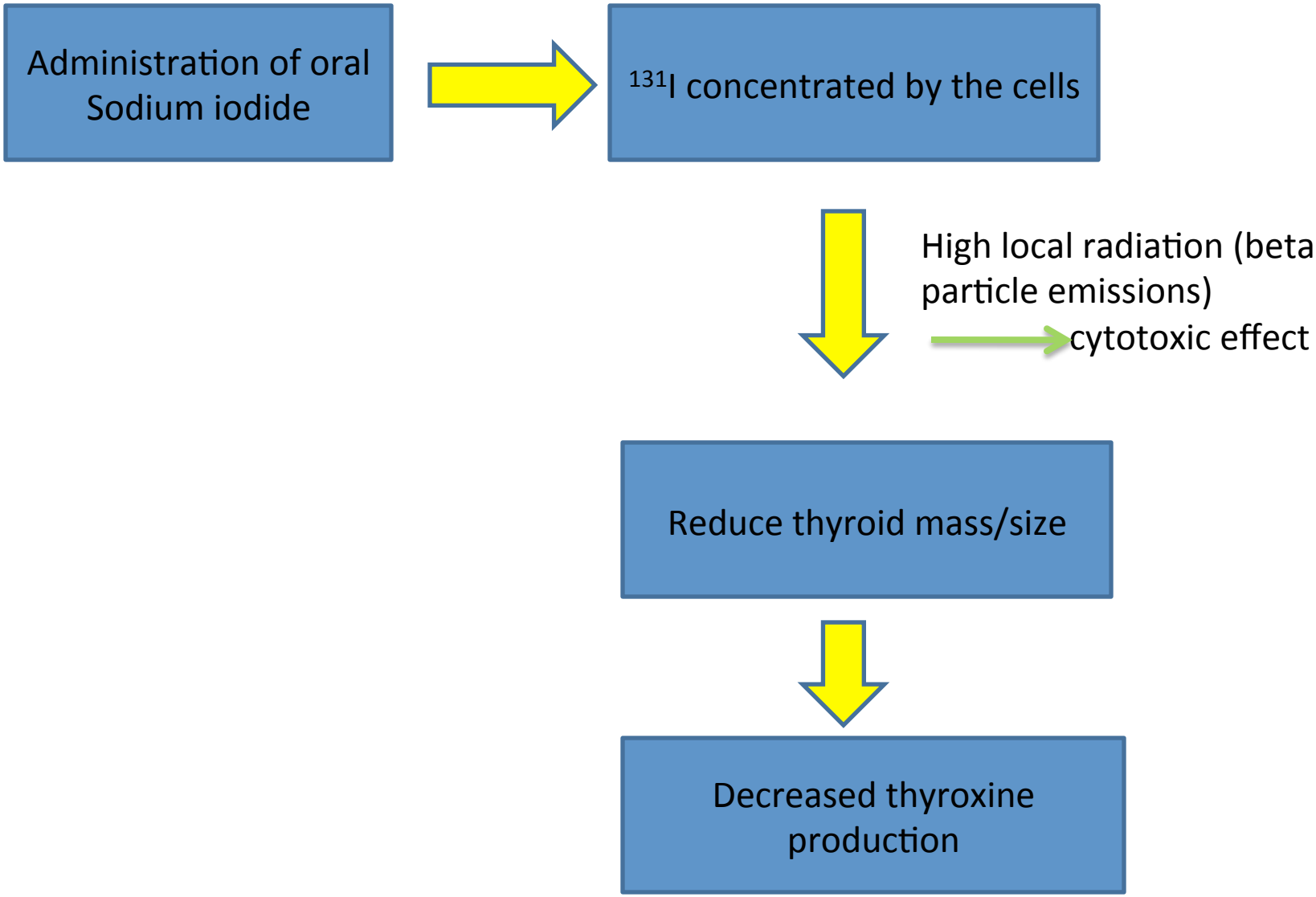
Radioiodine

- same principle as surgery

Physical Characteristics of 131Iodine

- reactor produced
- T ½ 8.02 days
- ßeta and gamma emitter
- ßeta - 606 keV max, 191 keV mean
- Beta-particle emission tissue range – 0.8mm (local therapeutic effect)
- gamma - 364 & 637 keV
- Clinical Form : Sodium Iodide

Physiological Basis of Radioiodine Treatment



Radioiodine therapy in Benign Thyroid Disease

Indications:-

1. Grave's Diisease
2. Toxic Multinodular Goitre
3. Solitary Autonomously Functioning Nodules
4. Nontoxic Multinodular Goitre
5. Goitre recurrence
6. Post-operative ablation of benign thyroid remnant(s) after thyroidectomy

- Subclinical hyperthyroidism

Contraindications

- Pregnant women

  a. cross the placenta – accumulate in the fetal thyroid gland – severe neonatal hypothyroidism

  b. irradiation – ↑ risk of thyroid cancer

  c. retained activity in maternal bladder – direct exposure to the fetus

- Lactating mother

Drug interactions

Type of Medication/Substance	Duration of stopping Tx prior to RAIT
Antithyroid eg PTU, CBM, methimazole, multivitamins	3 days for antithyroid drugs NB; beta blockers can be continued 7 days
Expectorants,agar, Lugols iodine Potassium iodide (SKKI)	2-3 weeks depending on iodine content
Radiographic contrast agents Intravenous (water soluble)	3-4 weeks (assuming normal RF)
Amiodarone	3-6 months or longer

Adapted from Society of NM Guidel(18)Martin A Walter,Mathias Briel,et al. BMJ 2007(26);334;514

Patient's Preparation

- No solid foods or drink dairy products for at least two hours before and after treatment.
- Low iodine diets for about 3 - 7 days
- GD patients should be counseled regarding the risks of ophthalmopathy.
- Render patients euthyroid before treatment with ^{131}I or thyroidectomy.
  - older patients (> 50–60 years old)
  - very thyrotoxic patients (symptomatic)
  - patients with cardiac problems.

Special Considerations Pre- Therapy

- **Pre- treatment Antithyroid drugs**

  - initial treatment esp with overt hyperthyroid
  - withdrawn at least 2 days before RAI
  - restarted 1 week after RAI
  - ** β adrenergic antagonists helpful for symptom relief*

- **Graves' ophthalmopathy**

  - prednisolone cover

New Engl J Med 1998;338:73-8

Patient's Preparation

- Follow drug interactions notes

- Antithyroid drugs - resumed 3 to 10 days following
treatment, or earlier, if clinically necessary

- Beta blockers medications - to reduce symptoms which may occur during treatment:
propranolol, 80–160 mg/day, or
atenolol, 50–150 mg/day, or
diltiazem 30 – 180mg/day (bronchospasm)

Doses

Two common approaches:

1. Fixed Dose

2. Calculated Dose - based on the size of the thyroid & percentage uptake at 24 h.

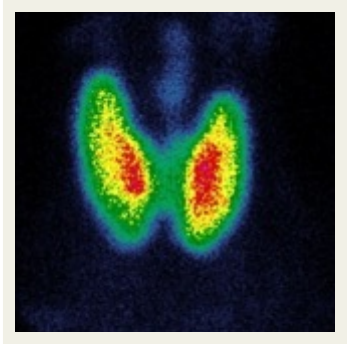
Doses

- Although treatments based on dose calculations appear efficacious, they have not proven superior to the use of empirically selected administered activities.

- Fixed dose advantages – simple & successful outcome in an acceptable number of patients.

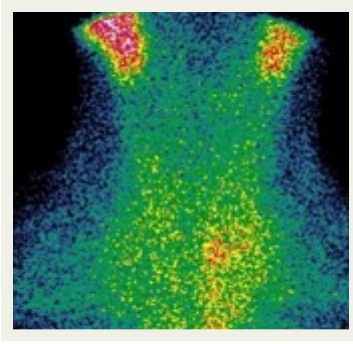
Initial Therapy

Grave's Disease



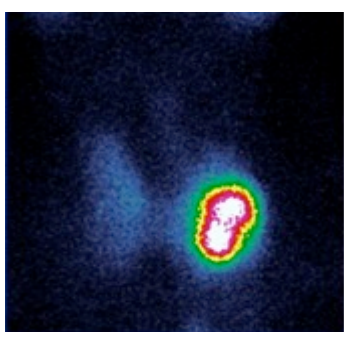
B-block
Antithyroid

Subacute Thyroiditis



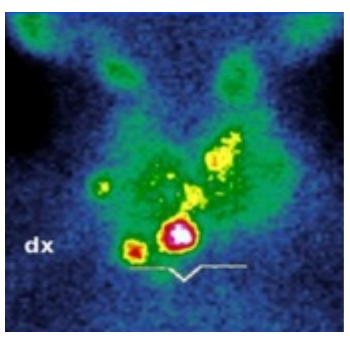
B-block
Steroids until resolution of symptoms

Toxic adenoma (Plummer Disease)



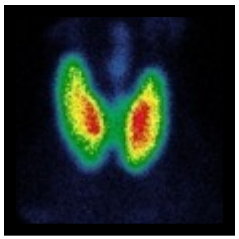
B-block
Antithyroid

Hyperfunctioning Multinodular Goiter



B-block
Antithyroid

Grave's Disease



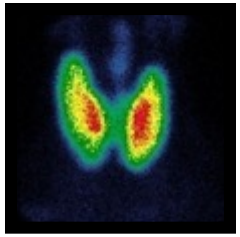
B-blockers
Carbimazole or PTU

Modulate therapy
until normalization
of TSH, FT3, FT4
(18 – 24 months)

Withdrawal of B-blocker
Progressively reduce
Carbimazole or PTU

Check TSH, FT4, FT3
Every 3 month

Grave's Disease - 1° relapse



B-blockers
Carbimazole or PTU

- Inform the pt on alternative advantages and limitations of ^{13l} I therapy and surgery
- Needs of substitutive Tx in both cases

- Pt's age and gender
- Size of goiter
- Tracheal compression
- Narcosis risks
- Complications of thyroid surgery

Fixed dose

- Vary but are commonly in the range of 185–555 MBq (5–15 mCi)
- Depending on the size of the gland

Calculation of Administered Activities for Treatment of Benign Thyroid Diseases

Use the following equation to correct for 24-hour RAI uptake in target thyroid tissue:

Administered activity = Thyroid tissue mass (g) x Activity per g tissue/RAI uptake at 24 hours

with RAI uptake expressed as a fraction of 100% uptake.

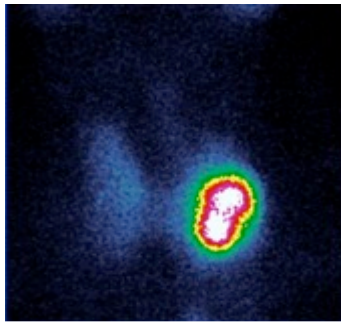
Graves' disease

Strategies for Removing Hyperthyroidism of Graves Disease

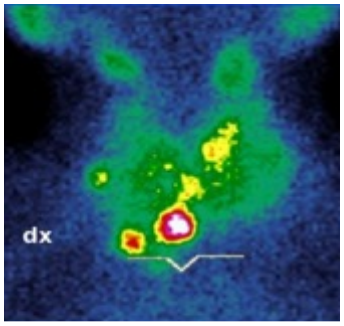
Strategy	Advantages	Disadvantages
ATD control for 1 or more years	Permanent hypothyroid 4-13%	Require pt compliance Recurrence in 50% Toxicity in 3-4%
Thyroidectomy	Effective if 98% removed Relieves obstruction from large goitres No radiation	Require hospitalization Risk of laryngeal/parathy Hypothyroid common
Use of Iodine-131	Simplest therapy Usually 1 dose sufficient Outpatient Safe No toxicity	Hypothyroid v.common Somewhat slow in action Improvement in 4-6 wks Hyperthyroid gone in 10-12 weeks Radiation

Long Term Therapy

Toxic adenoma (Plummer Disease)



Hyperfunctioning Multinodular Goiter



^{131}I THERAPY vs. SURGERY

- Pt's age and gender
- Size of goiter
- Tracheal compression
- Narcosis risks
- Complications of thyroid surgery

Toxic Nodular Goitre

- Definitive treatment is more commonly accomplished with RAI or surgery
- > RAI resistant than GD
- Large doses
- Standardized administered activities:

  740 – 1110 Mbq (20 - 30 mCi)
- Administered less than 370 MBq (10mCi)

  – common Tx failure

(Estour B, Millot L, Vergely N, et al. Efficacy of low doses of radioiodine in the treatment of autonomous thyroid nodules: importance of dose/area ratio. Thyroid 1997; 7(3):357–361.)

- Large solitary nodules – percutaneous ethanol injection.

(Del Prete S, Caraglia M, Russo D, et al. Percutaneous ethanol injection efficacy in the treatment of large symptomatic thyroid cystic nodules: ten-year follow-up of a large series. Thyroid 2002; 12(9):815–821.)

Total thyroidectomy for clinically benign disease of the thyroid gland

Incidence of:

- temporary recurrent laryngeal nerve palsy 2.3%
- temporary hypoparathyroidism 14.4%
- Permanent recurrent laryngeal nerve palsy 1.1%
- permanent hypoparathyroidism 2.4%
- Neither the initial clinical diagnosis nor a history of previous treatment significantly influenced the rate of complications.

Bron LP, O'Brien CJ. Br J Surg. 2004 May;91(5):569-74.

Euthyroid Multinodular Goitre

- Surgery – first-line treatment esp. for enlarged goiter
- Preferable for patients > 65 years old
- > 90% of patients demonstrate a decrease in goiter size
  - Average reduction of 40% at 1 year .

  (Freitas JE. Therapeutic options in the management of toxic and nontoxicnodular goiter. Semin Nucl Med 2000; 30(2):88–97.)

- A small percentage may developed transient hyperthyroidism

- Approximately 4% developed autoimmune thyroid disease.

  (Huysmans AK, Hermus RM, Edelbroek MA, et al. Autoimmune hyperthyroidism occurring late after radioiodine treatment for volume reduction of large multinodular goiters. Thyroid 1997; 7(4):535–539.)

- RAI > effective than L-thyroxine suppression for reducing the size of nontoxic goitre

Goals and outcomes

- 80% response rate should be expected.
- Primary goal of treatment is to resolve hyperthyroidism
- Hypothyroidism is preferable to persistent hyperthyroidism - if not optimally treated, may produce significant morbidity.
- Hypothyroidism tends to occur more frequently in patients with small thyroid glands & lower 24-hour uptake measurements
- Significantly reduce thyroid gland size in patients with GD - 50% to 80% reduction in gland volume

Outcomes

- Euthyroid
- Hypothyroid
  - transient
  - permanent → early
  - permanent → late
- Hyperthyroid

Side Effects

Generally it is mild, infrequent and self-limiting.

General

- Thyroid tenderness
- Salivary gland swelling
- Nausea

} NSAIDs

- Vocal cord paresis – extremely rare

Hormonal related

- Transient hypothyroidism, permanent hypothyroidism
- Transient hypoparathyroidism
- Exacerbation of hyperthyroidism – Beta blockers
- Thyroid storm is uncommon

Side Effects

Severe side effects > likely in patient with large goitre – risk of tracheal compression.

Ophthalmopathy

- Ophthalmopathy may be particularly severe in 3% to 5% of patients with GD.
- Progression of ophthalmopathy - approximately 15% of patients especially:
  - who smoke
  - have pre-existing eye disease
  - high levels of TSH-receptor antibody
  - severe manifestations of thyroid disease

Side Effects

- Prednisone, 0.4–0.5 mg/kg per day, beginning immediately after radioiodine treatment, continued for one month, and then tapered over three months, has been shown to be effective in a randomized controlled trial.

  (Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998; 338(2):73–78.)

- Referral to Ophthalmologist is recommended.

Side Effects

Cancer Risk

- remains controversial
- Ron et al, a study of >35,000 hyperthyroid patients found that the incidence of thyroid cancer in RAI-treated patients over a 27-year period was not significantly different from its incidence in the general population.

Genetic Effects to Offspring

- no evidence that exposure to radioiodine affects the long-term outcomes of subsequent pregnancies and offspring.

Patient's Instruction & Precautions

- First 72 hours after treatment:
- Drink plenty of fluids.
- Do not spend prolonged periods of time closer than 3 feet to any adult, or within the same room as any child.
- For the next 4–7 days:
- Void as often as possible. Flush toilet twice after use.
- Wash hands thoroughly and routinely.
- Do not share eating utensils or towels. Wash utensils or clothing separately.
- Avoid close contact with children and pregnant women (not closer than 2 feet) for long periods of time.
- Sleep in a separate bed.
- Avoid kissing and sexual intercourse.

Follow up

- To assess the need for
  - further ^{131}Iodine treatment
  - L-thyroxine replacement

- Symptoms of uncontrolled hyperthyroidism should be described, and patients should be informed to seek medical attention if such symptoms occur.

- 4 to 6 weeks and at regular intervals thereafter.

Children with hyperthyroidism

- Incidence of side effects from antithyroid medications is higher & less consistent in taking the medications → remission rates are lower.
- Surgery - may have the highest cure rates but thyroidectomy is technically more difficult in young children.
- Several authorities have promoted the administration of ^{131}I earlier in the management of pediatric patients and even as the primary treatment.
- Children as young as 3 year old can be treated.

Chronic Renal Failure and Dialysis Patients

- Holst et al. reviewed the medical literature and concluded that:

> ^{131}I dose does not need to be adjusted. However, recommended ^{131}I administration as soon as possible after dialysis and a delay in subsequent dialysis until the maximum ^{131}I uptake has occurred in the thyroid.

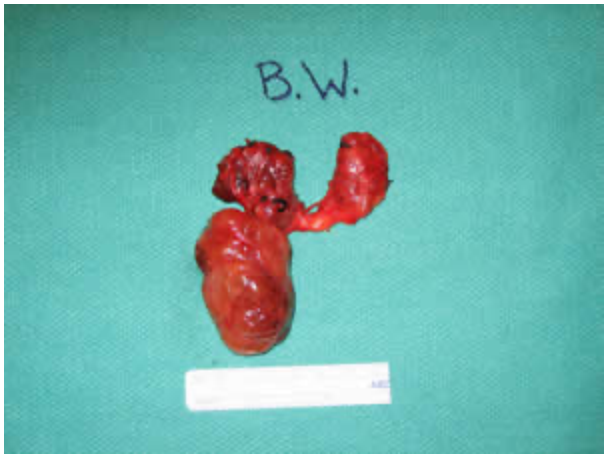
Temperature	37.2-37.6	5
	37.7-38.2	10
	38.3-38.7	15
	38.8-39.3	20
	39.4-39.9	25
	>40	30
CNS	Mild agitation	10
	Moderate delirium/psychosis	20
	Seizure/coma	30
GI/liver dysfunction	Diarrhea/vomiting/abd pain	10
	Unexplained jaundice	20
Cardiovascular dysfunction	99-109	5
	110-119	10
	120-129	15
	130-139	20
	>140	25
Heart failure	Pedal edema	5
	Bibasilar rates	10
	APO	15
	AF	20
Precipitant history	negative	0
	positive	10

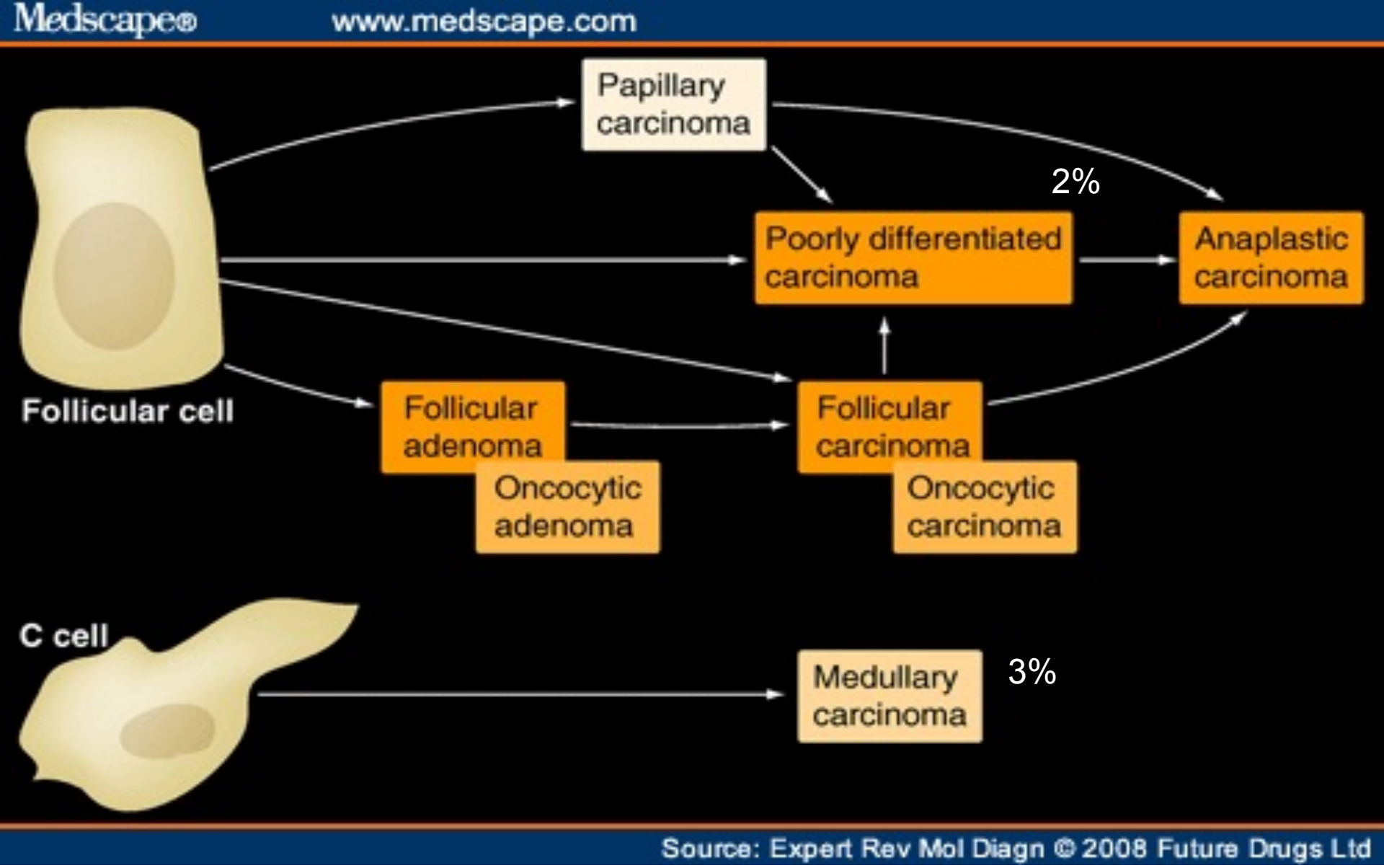
Score >45 suggestive of thyroid storm, 25 – 44 supports the diagnosis and < 25 unlikely thyroid storm

Molecular genetic of thyroid carcinoma

Introduction

- Thyroid cancer- most common malignant tu of endocrine system & accounts for 1% of all newly diagnosed cancer cases.
- Most thyroid cancers originate from thyroid follicular cells .
- Type of thyroid malignancy :
- papillary ca 80%,
- follicular ca 15% may be of conventional or oncocytic (Hurthle cell) type.[4]
- Follicular ca develop either from pre-existing benign follicular adenomas or directly, bypassing the stage of adenoma.





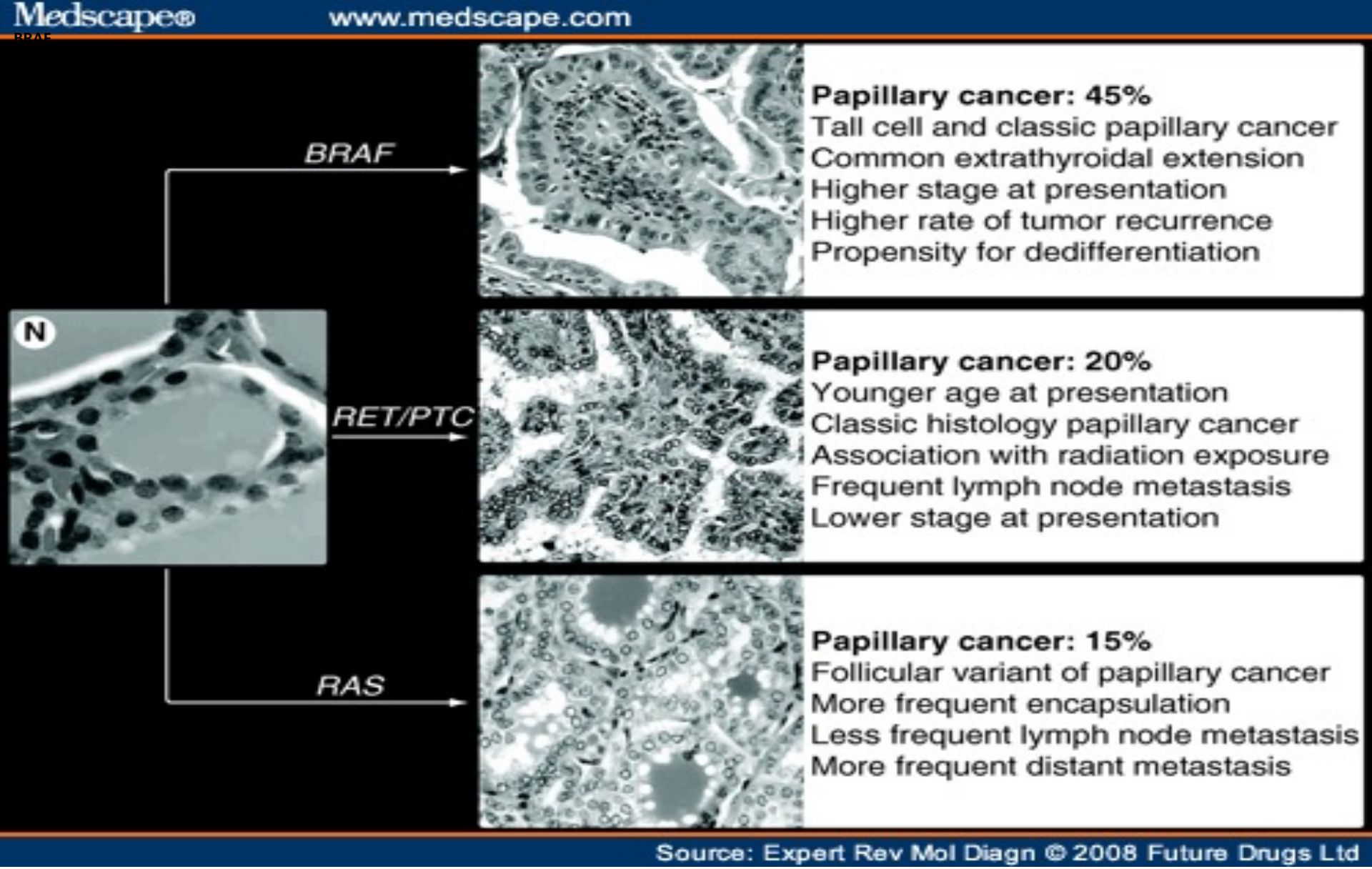
Schematic representation of thyroid ca origin and its putative progression. Oncocytic adenoma and ca are considered to be variants of follicular adenoma and ca. Papillary ca may be of the classical type or manifests as one of its variants, including oncocytic variant of papillary ca

Tumor type	Prevalence (%)
Papillary carcinoma	
BRAF	45
RET/PTC	20
RAS	10
TRK	<5
Follicular carcinoma	
RAS	45
PAX8-PPAR	35
PIK3CA	<10
PTEN	<10
Poorly differentiated carcinoma	
RAS	35
β-catenin (CTNNB1)	20
TP53	20
BRAF	15
Anaplastic carcinoma	
TP53	70
β-catenin (CTNNB1)	65
RAS	55
BRAF	20
PIK3CA	20
PTEN	>10
Medullary carcinoma	
Familial forms *RET*	>95
Sporadic *RET*	40

Source: Expert Rev Mol Diagn © 2008 Future Drugs Ltd

Papillary Ca

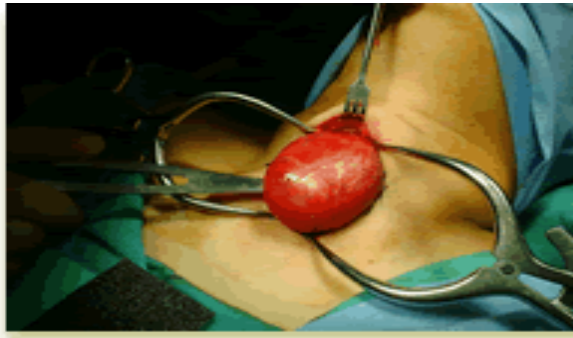
- Activating mutations of BRAF, RET or RAS genes seen in 70% papillary ca.
- Genes mutations rarely overlap in the same tumor, suggesting that activation MAPK signaling is essential for tumor initiation
- Alteration of a single effector of the pathway is sufficient for cell transformation



Mol p/way in thyroid papillary ca & typical microscopy & clin feat of tu assoc with specific mutations

BRAF mutation

- Involve nucleotide 1799 and result in a val-to-glut substitution at residue 600 (V600E).
- Other mech include K601E point mut, small in-frame insertions or del surrounding codon 600,[14–16] & AKAP9-BRAF rear which is more common in papillary ca a/w radiation exposure.[17]



With BRAF mutation….

- Extrathyroidal extension , advanced tu stage @ presentation, tu recurrences & lymph node or distant mets.
- BRAF V600E is independent predictor of tu recurrence even in stage 1-2.
- Decreased ability of tu to trap radioiodine & dysregulation of function of Na iodide symporter (NIS) & other genes metabolizing iodides in follicular cells

BRAF mut as therapeutic target…..

- BRAF inhibitors like BAY 43-9006, a multikinase inhibitor with potent activity against RAF & other protein kinases.
- BAY 43-9006 effectively blocks the wild-type BRAF and the mutant V600E BRAF kinase activity. [13,31]
- Sudies showed that BAY 43-9006 inhibit BRAF signaling and growth of all thyroid cancer cell lines carrying mutant *BRAF* and it impair the growth of the cell line xenografts in nude mice.[32]

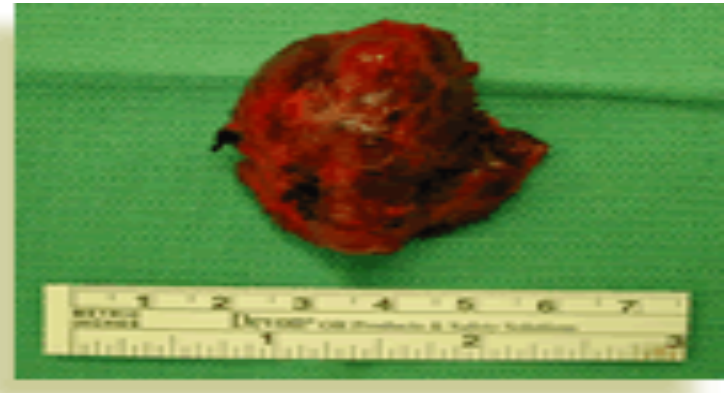
RET/PTC rear in papillary thyroid ca

N	*RET/PTC* type	Partner gene	Chromosomal positions	Frequency among all *RET/PTC* types	Ref.
1	RET/PTC1	H4 (CCDC6, D10S170)	inv10(q11.2;q21)	70%	[36]
2	RET/PTC2	PRKAR1A	t(10;17)(q11.2;q23)	3%	[40]
3	RET/PTC3 (RET/PTC4)	NCOA4 (RFG, ELE1)	inv10(q11.2;q10)	30% (higher in radiation-induced tumors)	[37–39]
4	RET/PTC5	GOLGA5 (RFG5)	t(10;14)(q11.2;q32)	Rare	[41]
5	RET/PTC6	HTIF1 (TRIM24)	t(7;10)(q32;q11.2)	Rare	[42]
6	RET/PTC7	TIF1G (RFG7, TRIM33)	t(1;10)(p13;q11.2)	Rare	[42]
7	ELKS/RET	ELKS (RAB6IP2)	t(10;12)(q11.2;p13.3)	Rare	[47]
8	RET/PTC8	KTN1	t(10;14)(q11.2;q22.1)	Rare	[44]
9	RET/PTC9	RFG9	t(10;18)(q11.2;q21)	Rare	[43]
10	PCM1/RET	PCM1	t(8;10)(p21;q11.2)	Rare	[45]
11	RFP/RET	RFP (TRIM27)	t(6;10)(p21;q11.2)	Rare	[46]
12	HOOK3/RET	HOOK3	t(8;10)(p11.21;q11.2)	Rare	[48]

Source: Expert Rev Mol Diagn © 2008 Future Drugs Ltd

RET/PTC

- Fusion between the 3´-portion of the *RET* receptor tyrosine kinase gene and the 5´-portion of various genes.
- Two most common rear types, *RET/PTC1* and *RET/PTC3*, are paracentric inversions, because both *RET* and its respective fusion partner, *H4* or *NCOA4 (ELE1)*, reside on the long arm of chromosome 10.[36–39]



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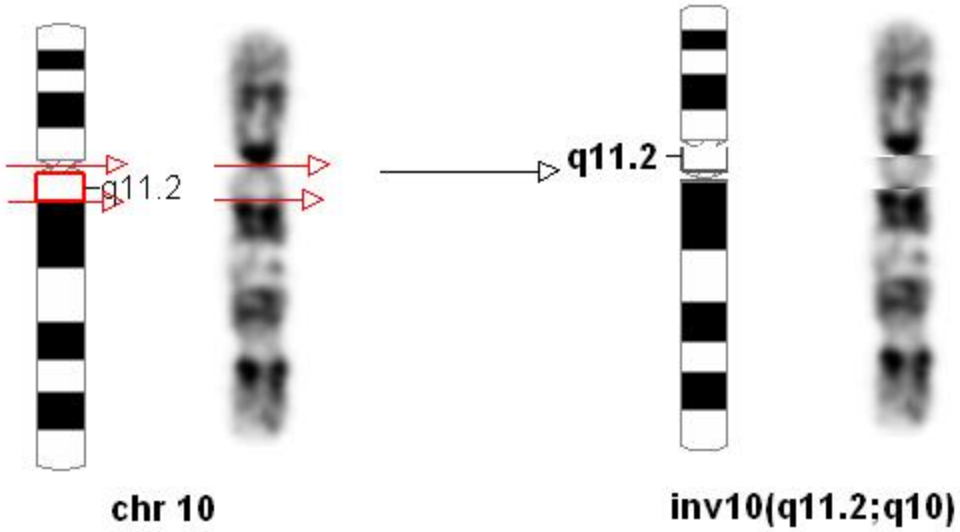
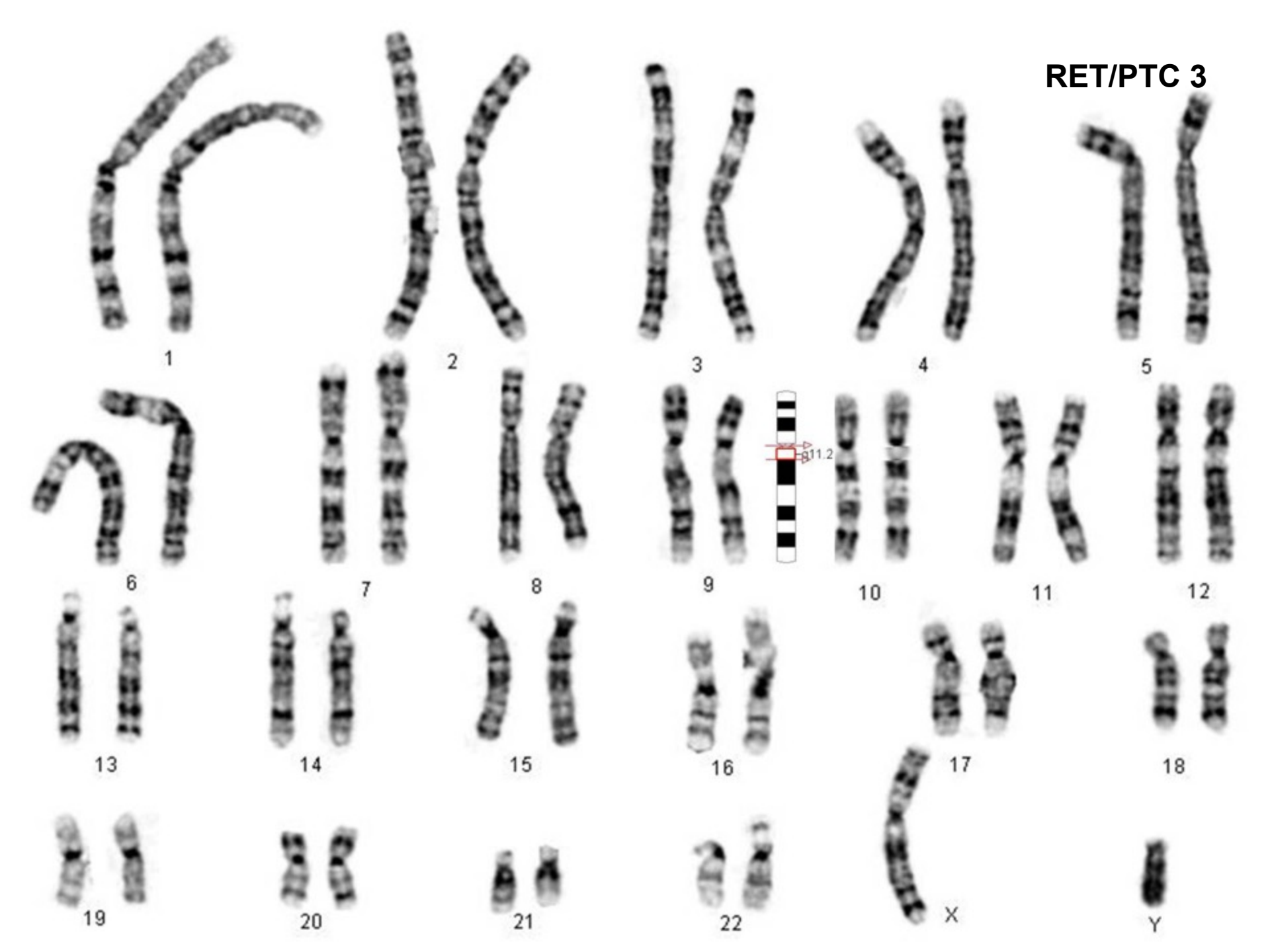


RET/PTC 3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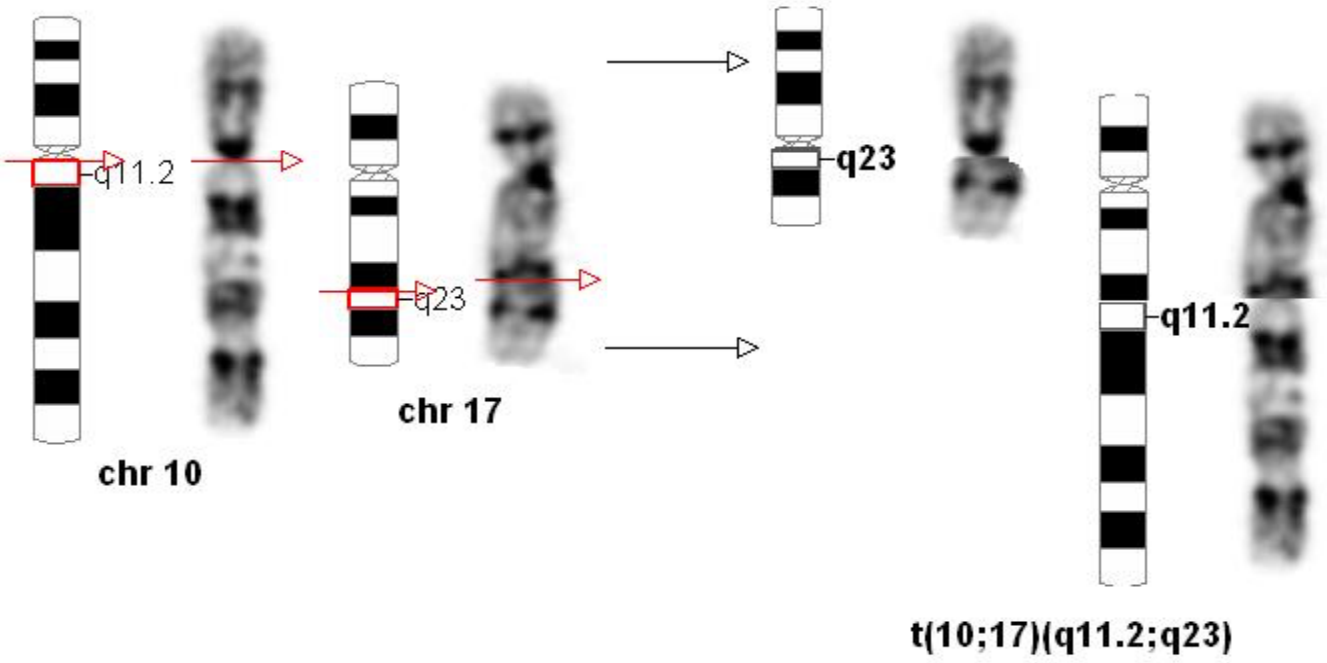
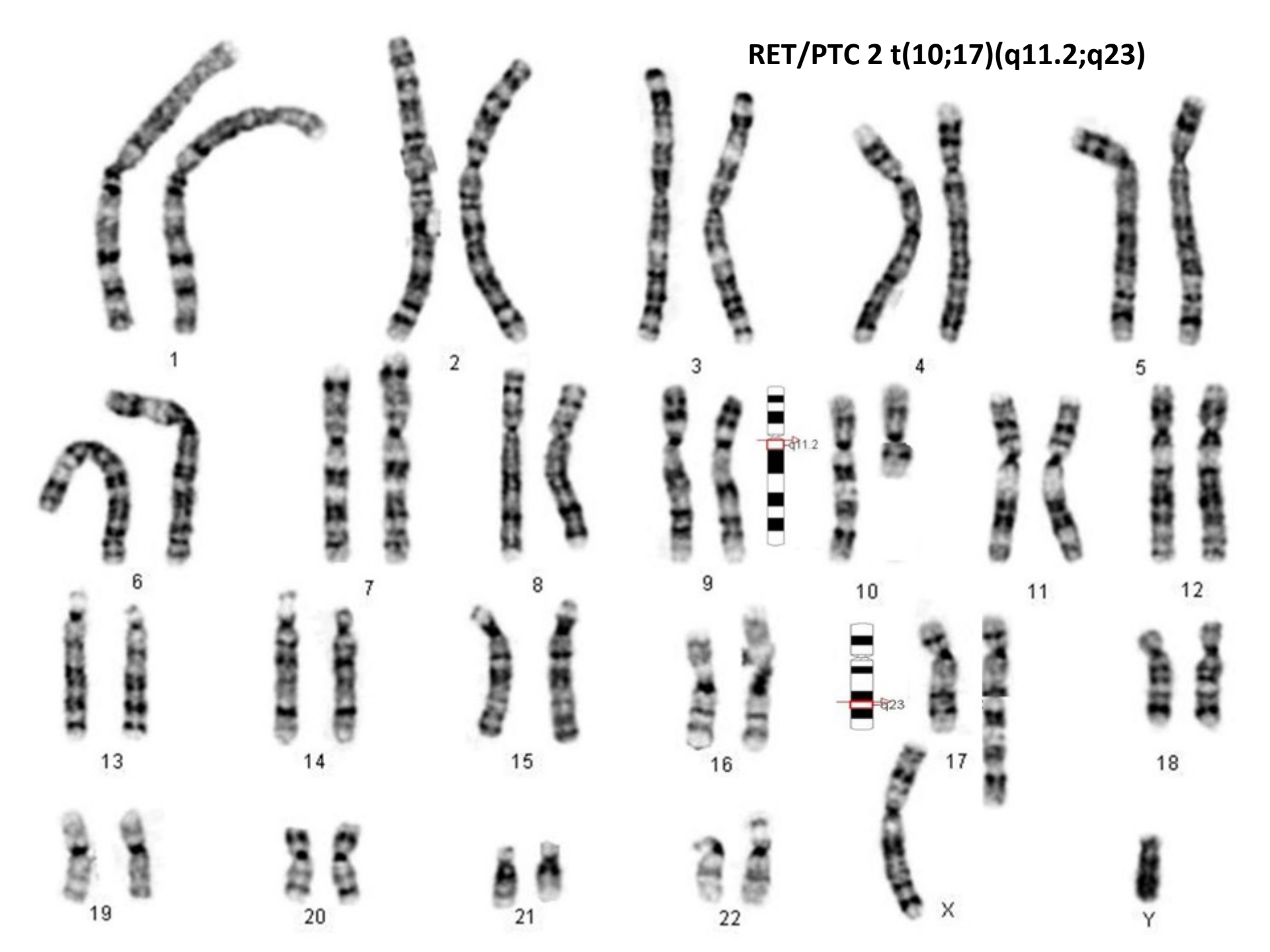
RET/PTC

- Most of these rare *RET/PTC* seen in papillary ca fr pts with a h/o environmental or therapeutic exposure to ionizing radiation,[40–46] & in children & young adult.
- In papillary ca assoc/w exposure to ionizing radiation (i.e. post Chernobyl), RET/PTC1 a/w classic papillary histology, RET/PTC3 more common in solid variant

RET/PTC 2 t(10;17)(q11.2;q23)



RET/PTC2 **and nine more recently identified types of** ***RET/PTC*** **are all interchromosomal translocations**


RET/PTC 2 t(10;17)(q11.2;q23)
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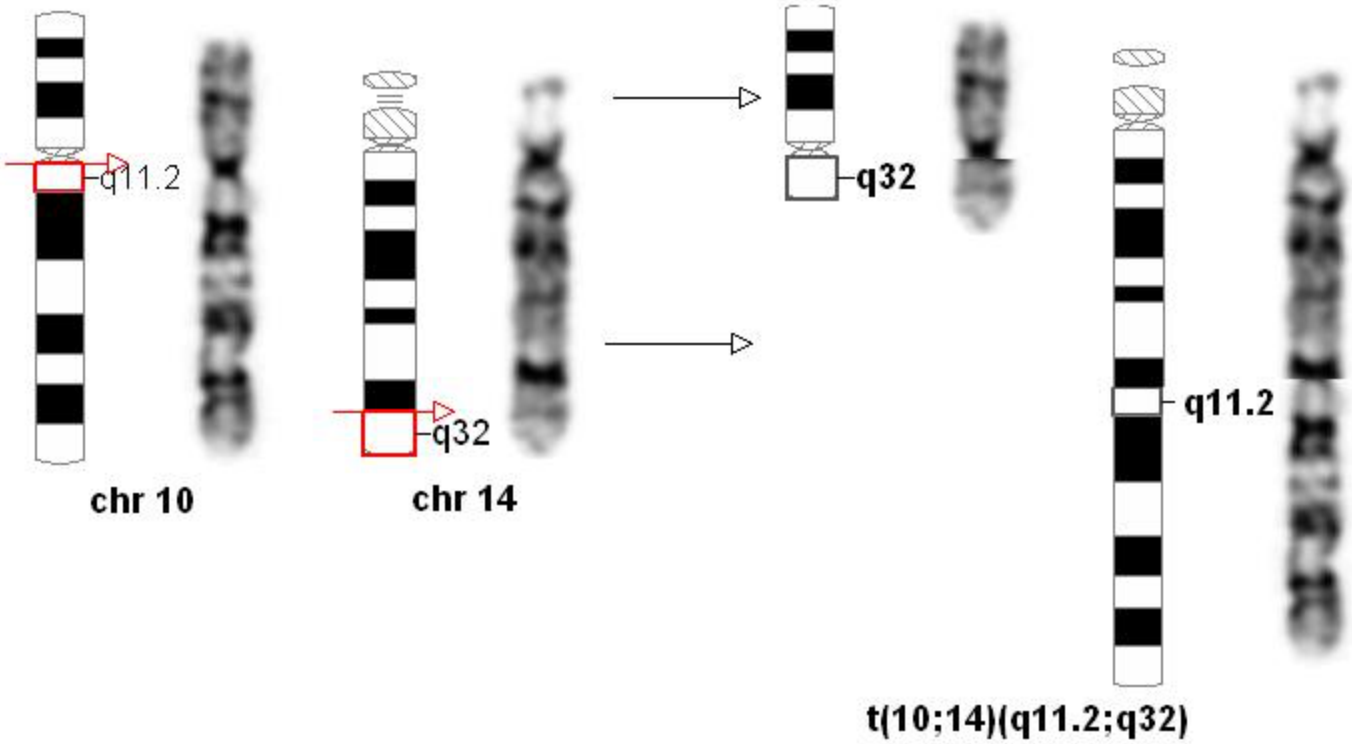
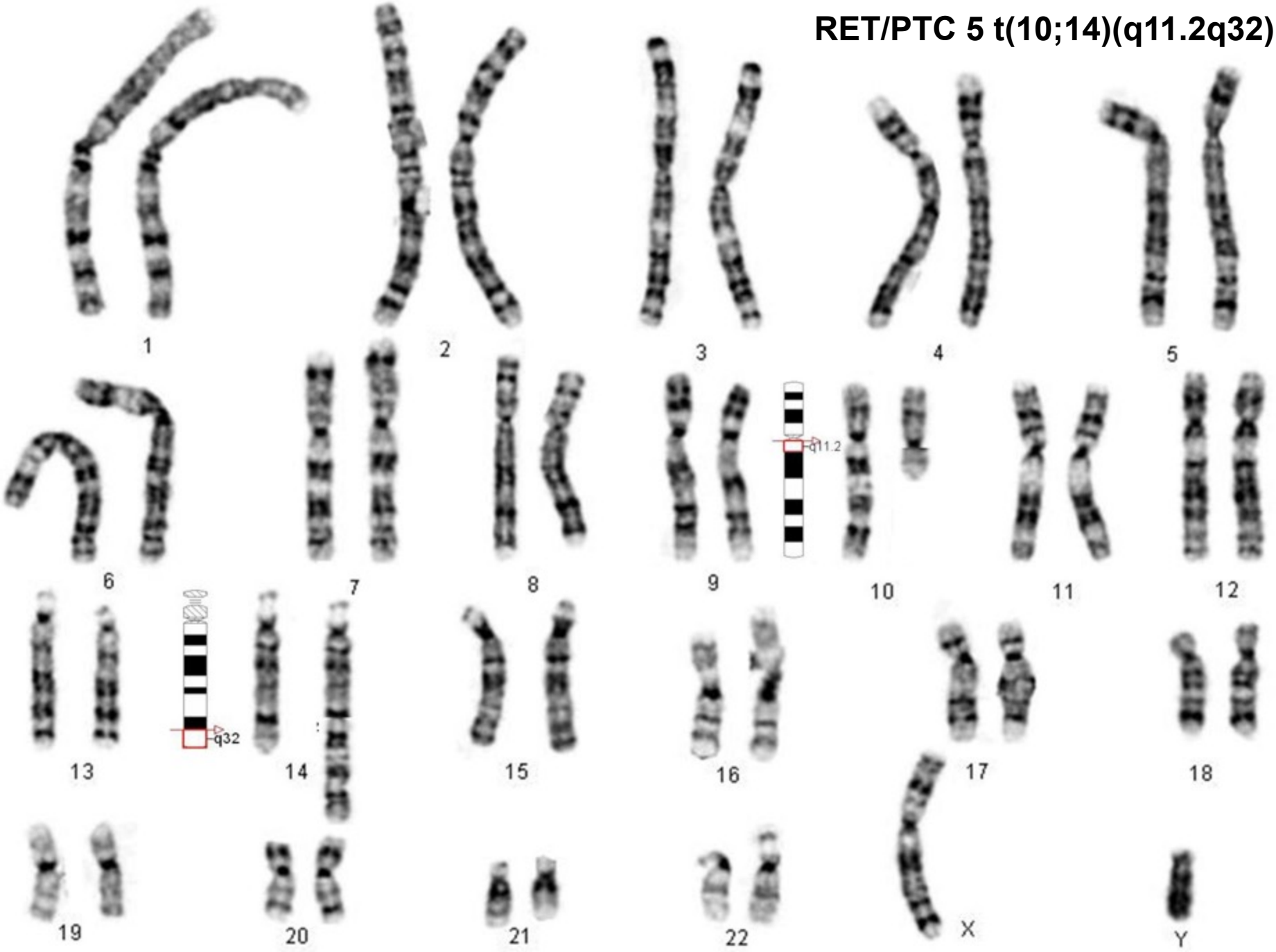
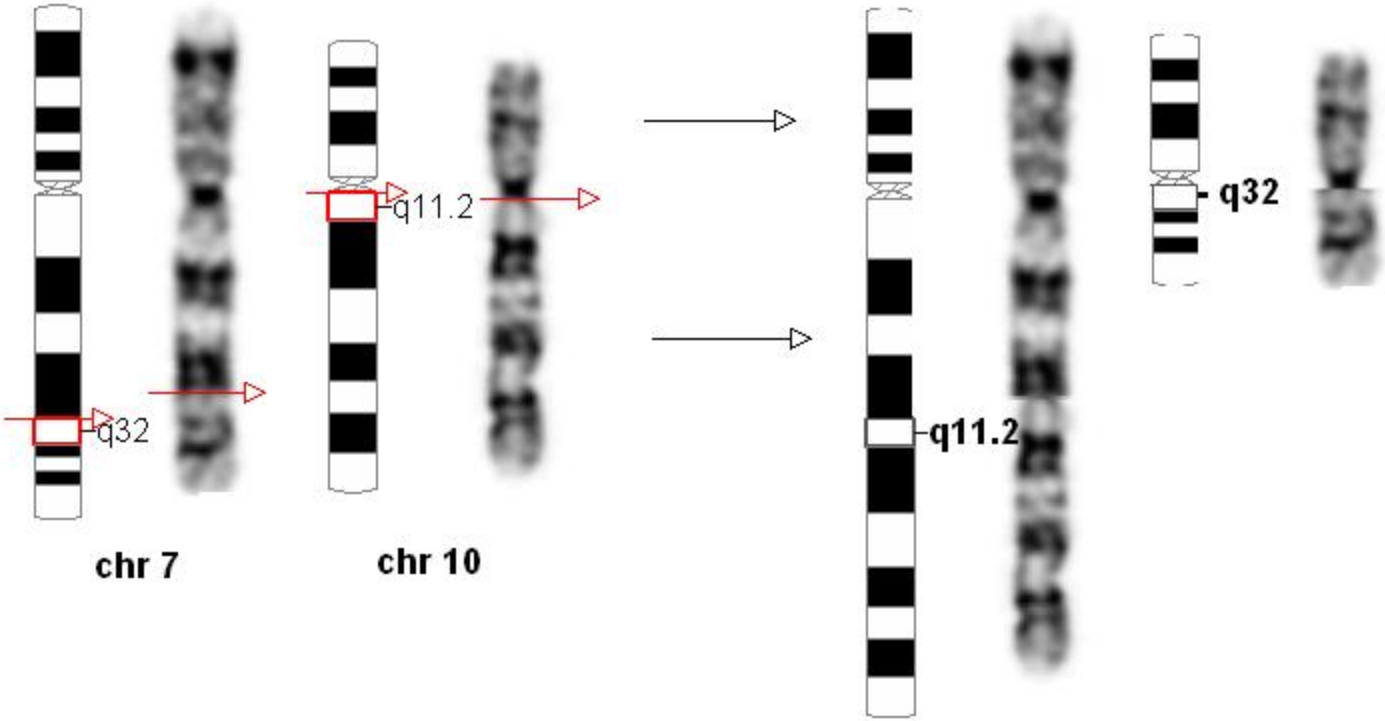


RET/PTC 5 t(10;14)(q11.2q32)

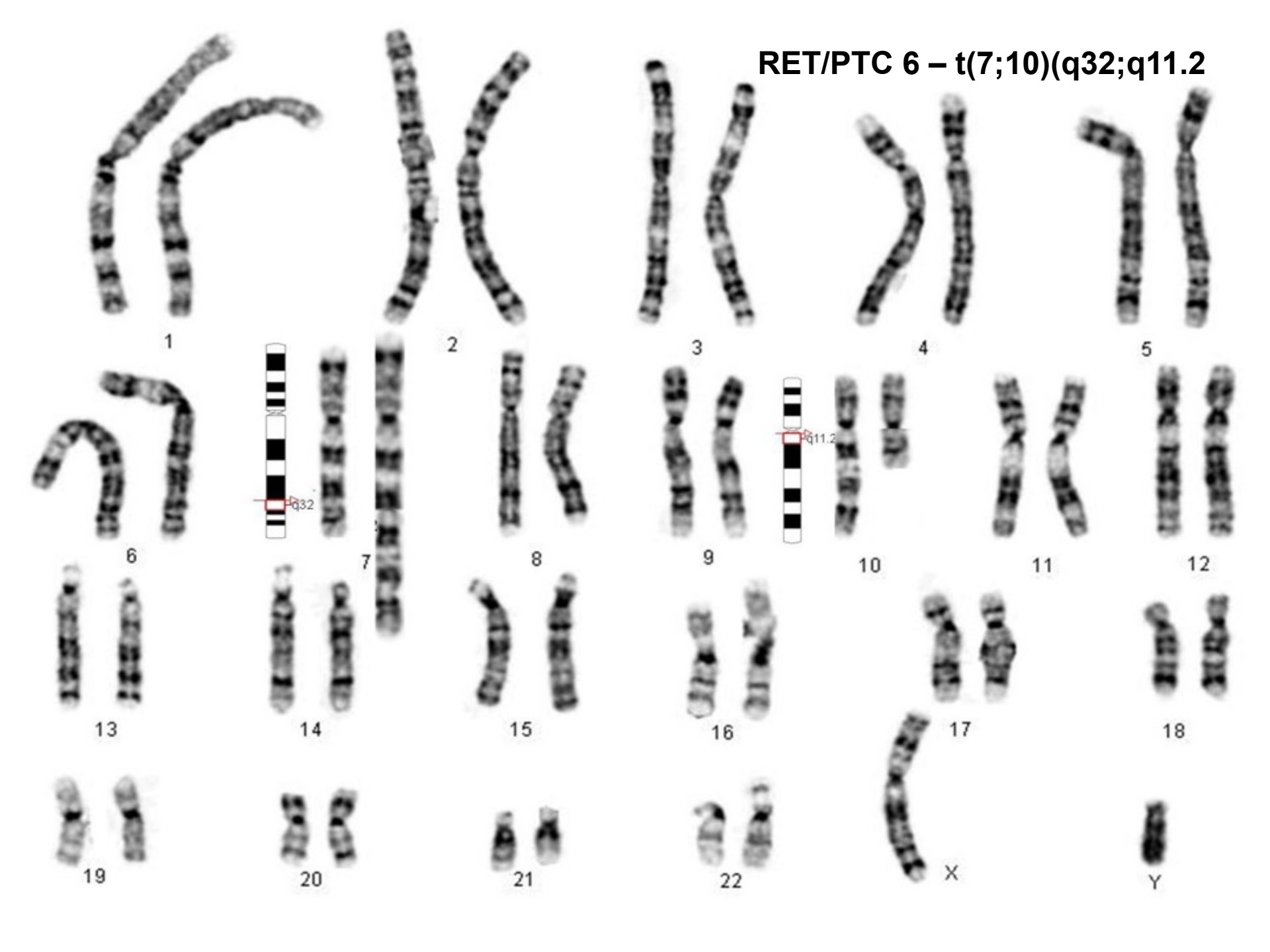
RET/PTC 5 t(10;14)(q11.2q32)

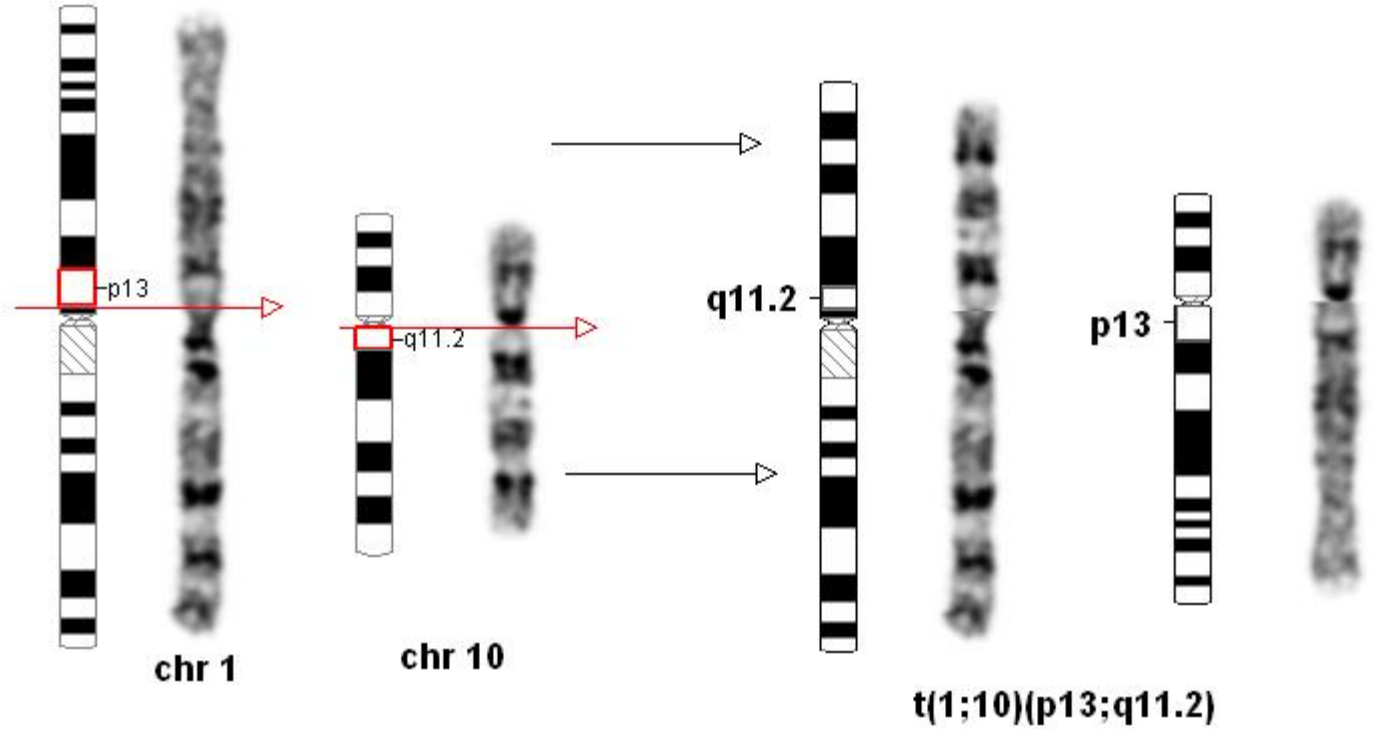




RET/PTC 6 – t(7;10)(q32;q11.2)

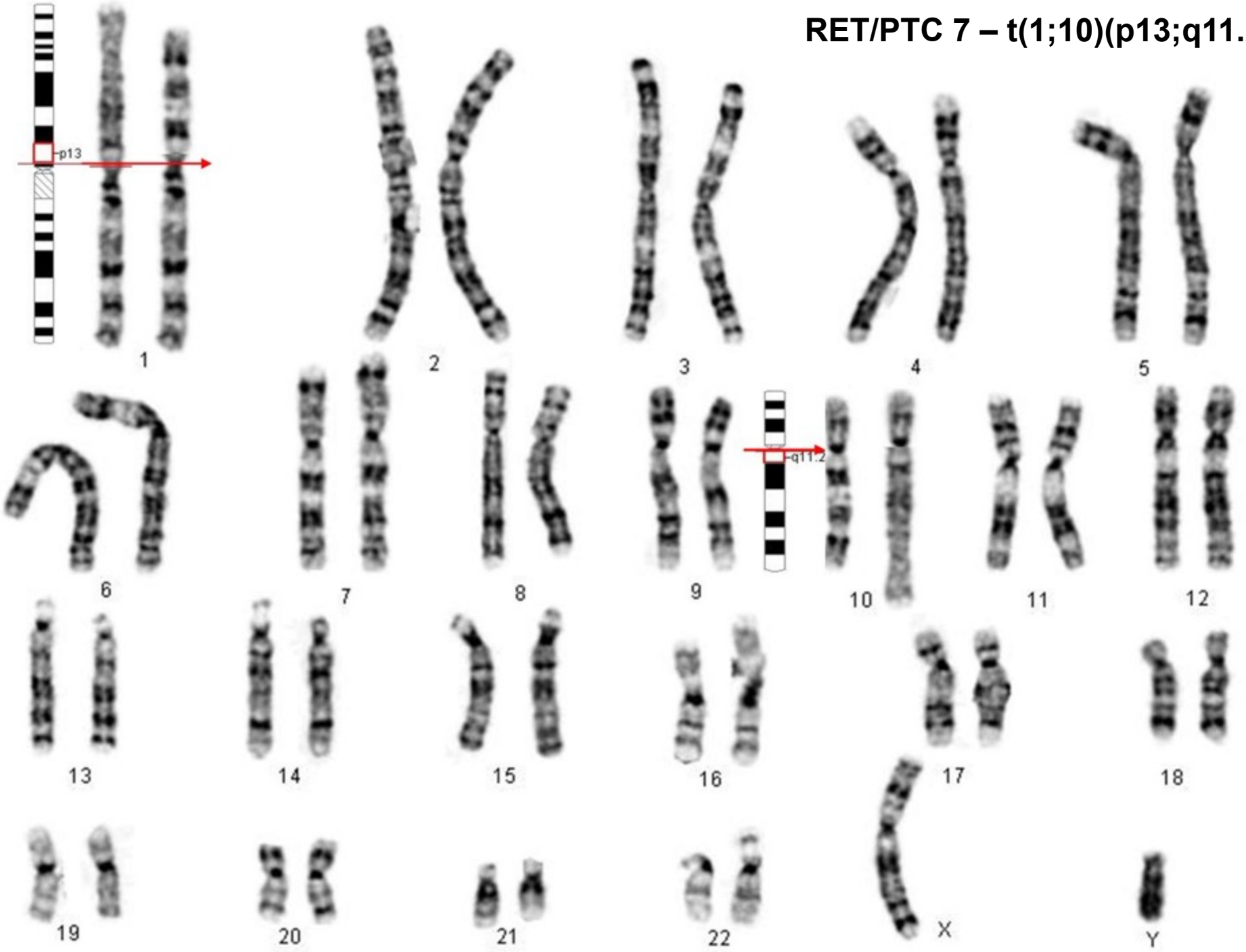
RET/PTC 6 – t(7;10)(q32;q11.2

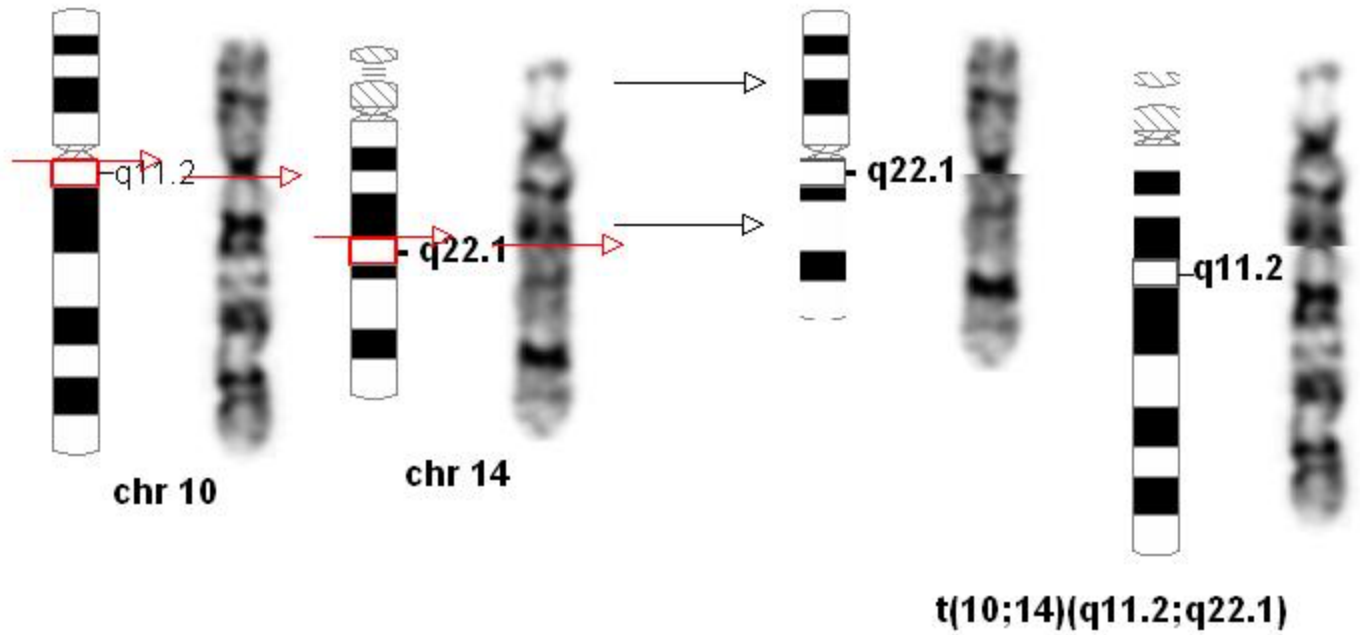




RET/PTC 7 – t(1;10)(p13;q11.2)

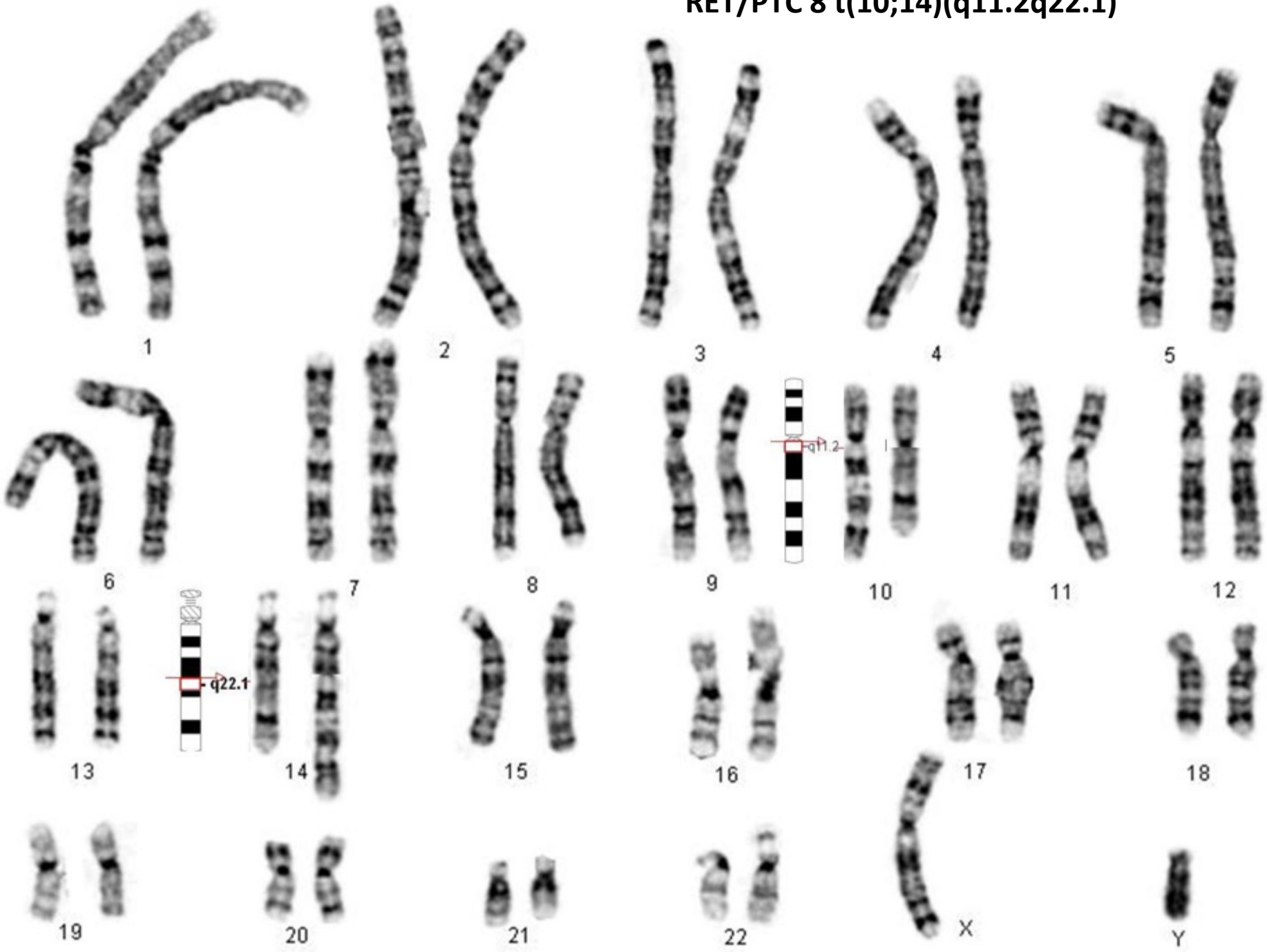
RET/PTC 7 – t(1;10)(p13;q11.2)

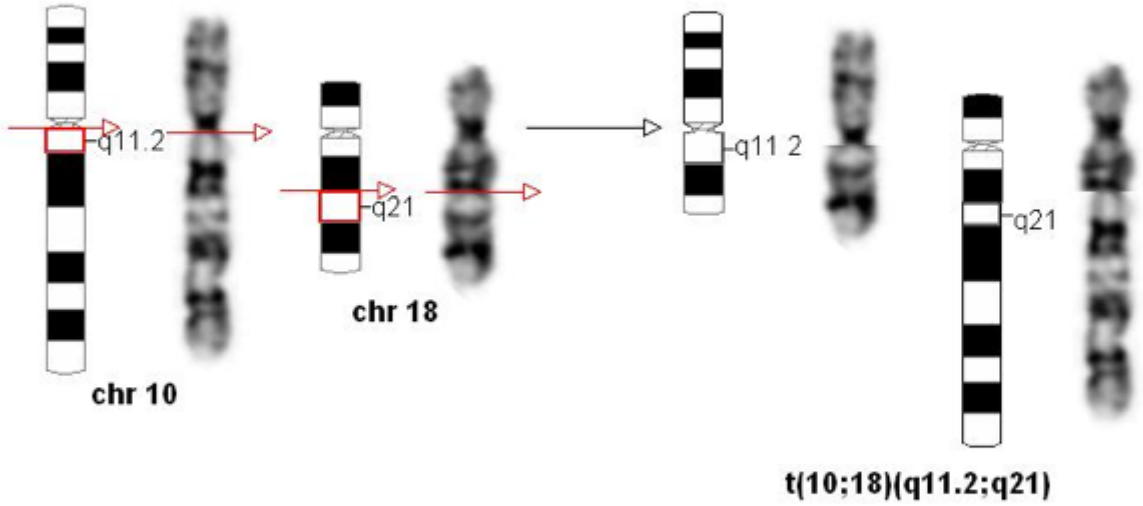




RET/PTC 8 – t(10;14)(q11.2;q22.1)

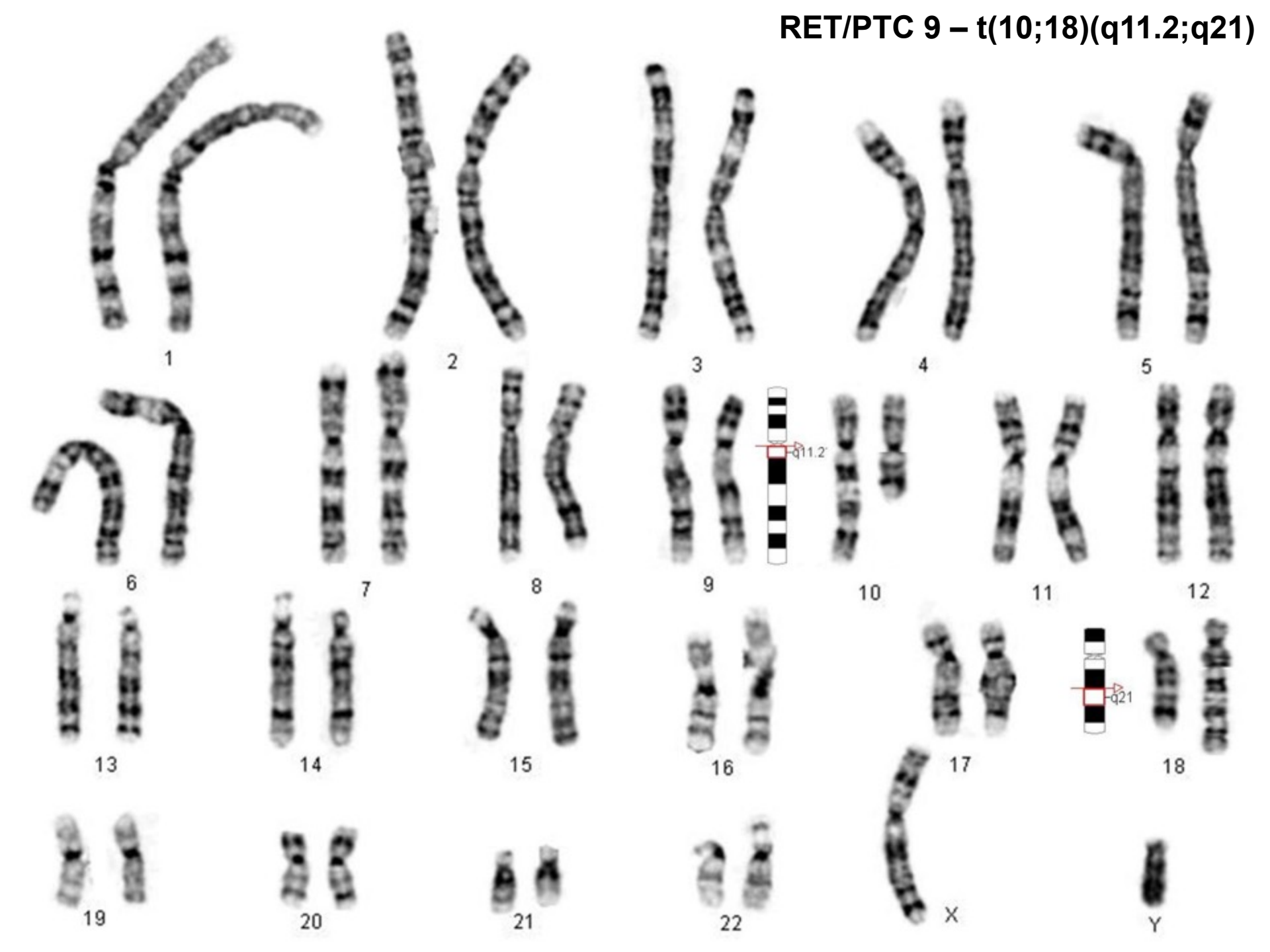
RET/PTC 8 t(10;14)(q11.2q22.1)

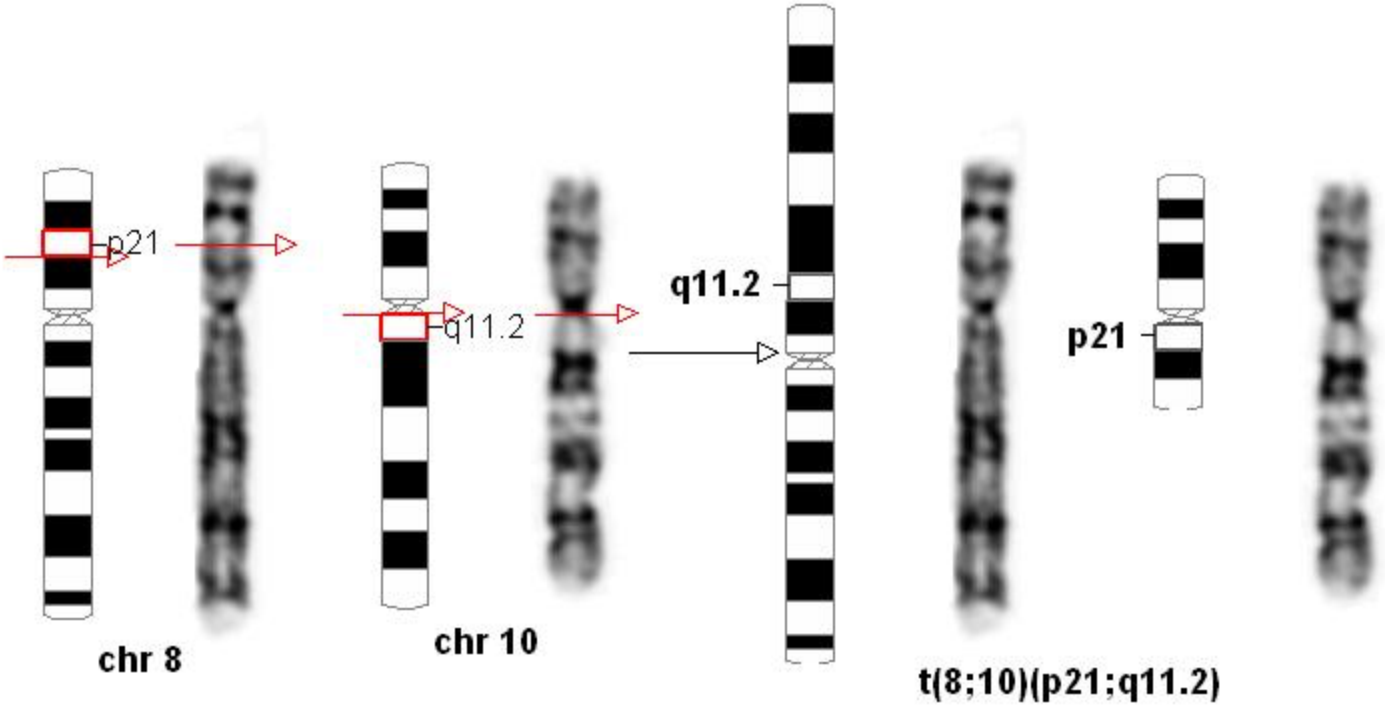




RET/PTC 9 – t(10;18)(q11.2;q21)

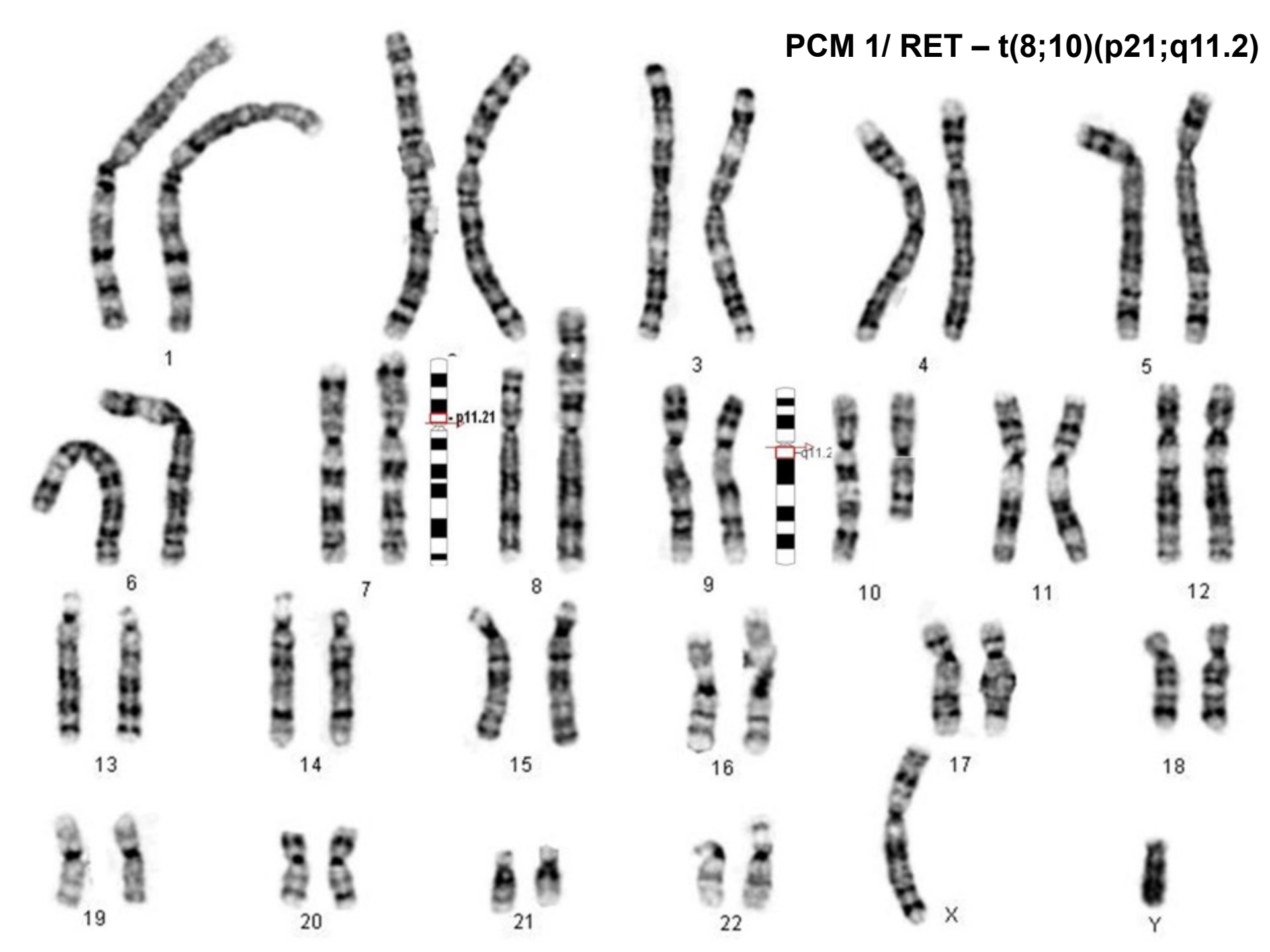
RET/PTC 9 – t(10;18)(q11.2;q21)

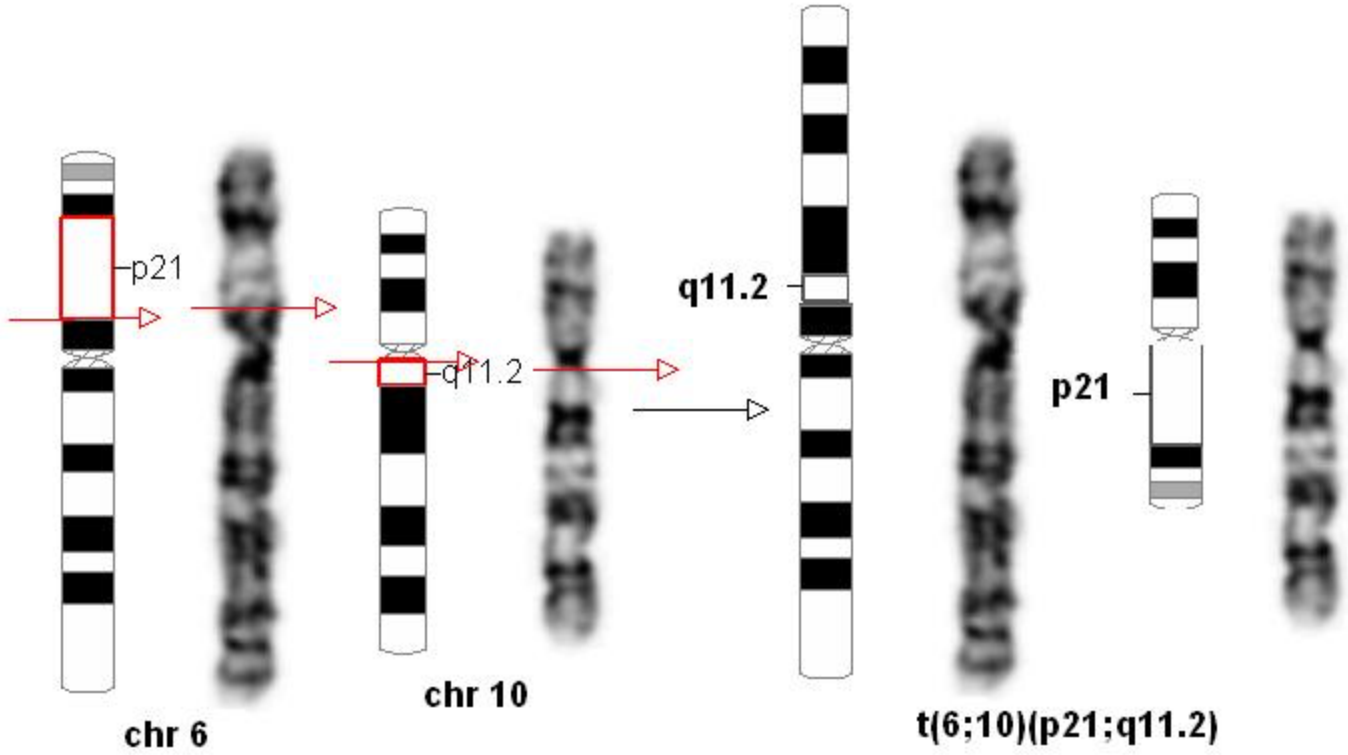




PCM 1/ RET – t(8;10)(p21;q11.2)

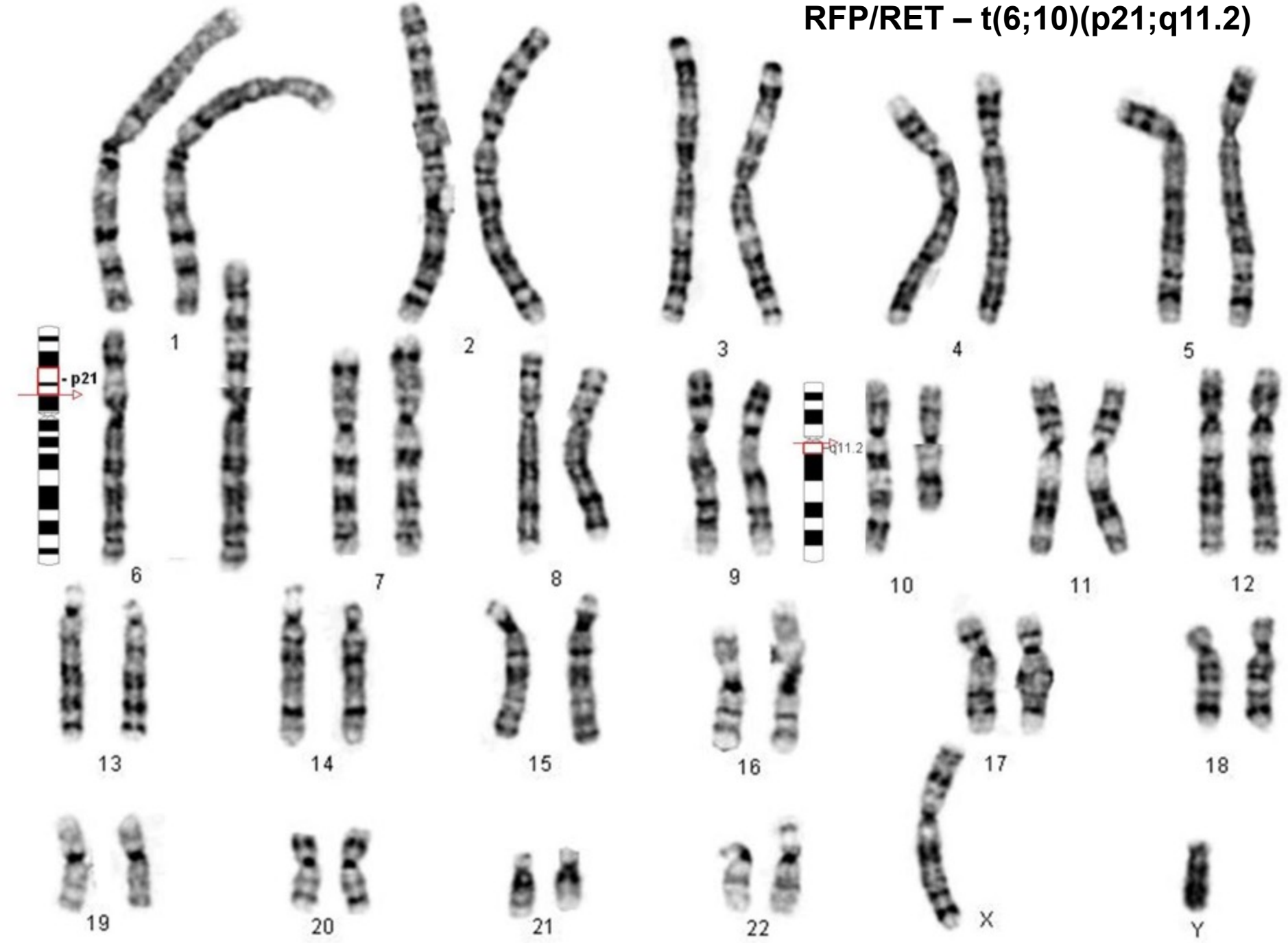
PCM 1/ RET – t(8;10)(p21;q11.2)





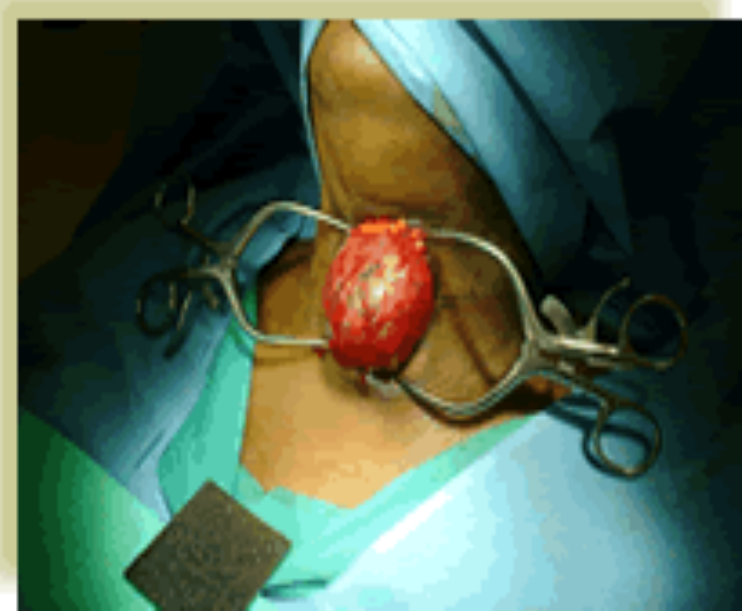
RFP/RET – t(6;10)(p21;q11.2)

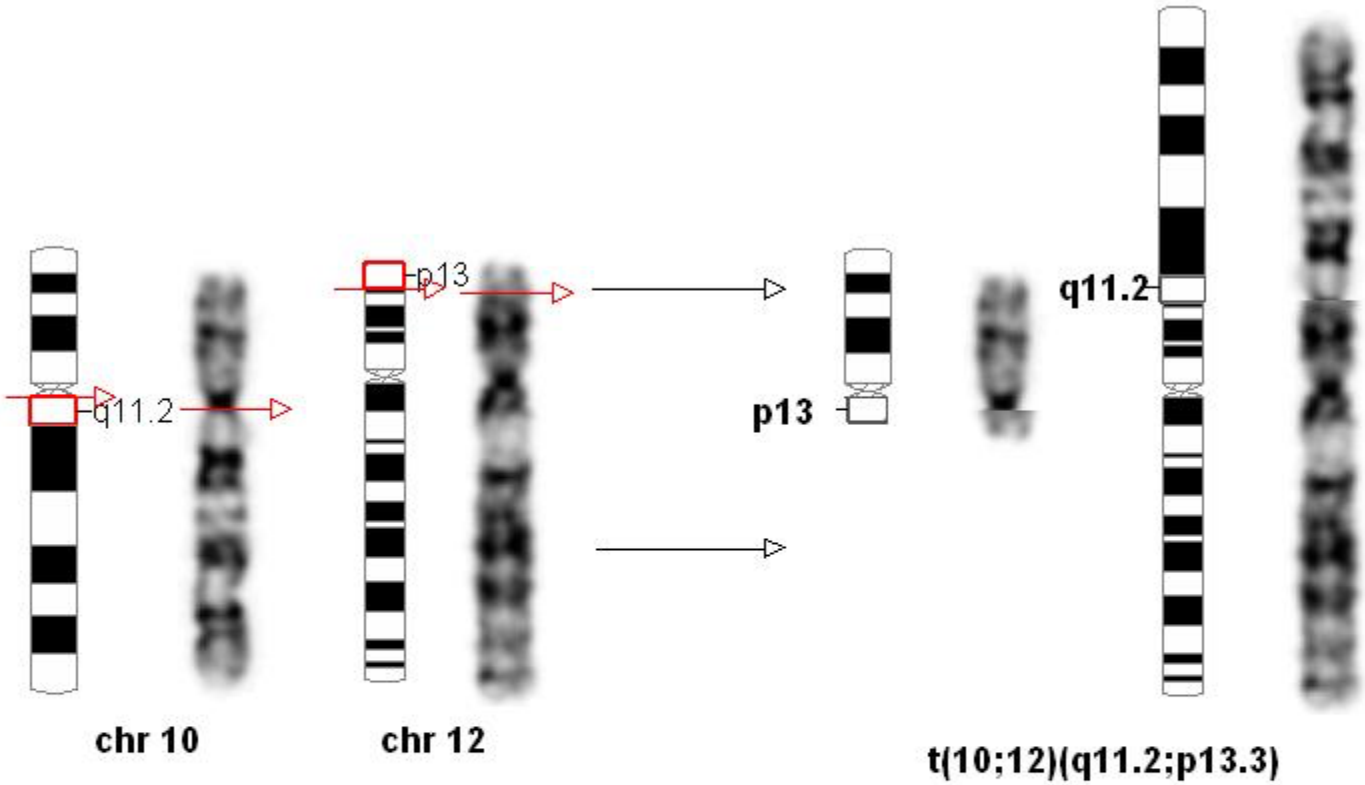
RFP/RET – t(6;10)(p21;q11.2)



RET/PTC

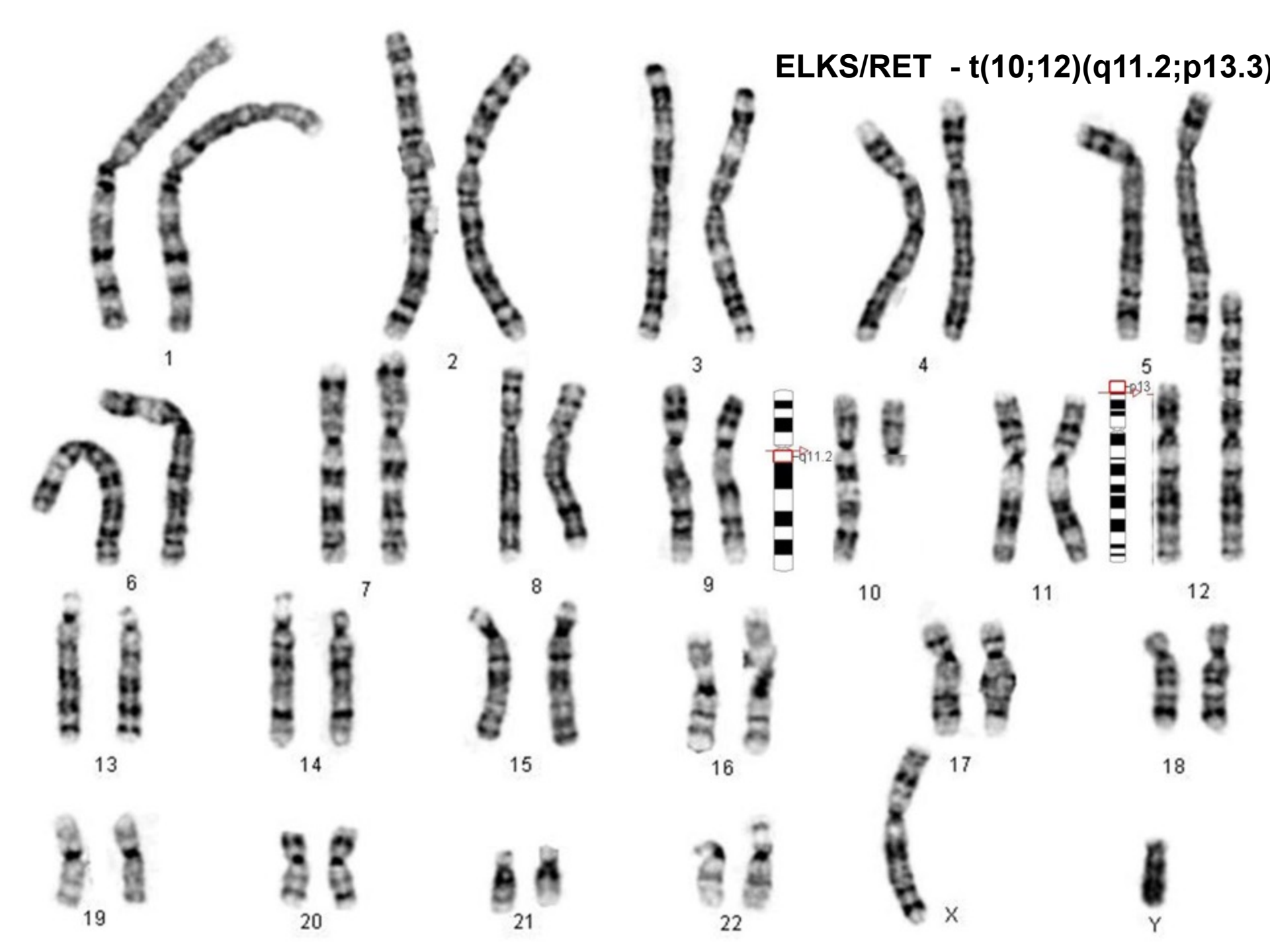
- *ELKS-RET* and *HOOK3-RET* fusions identified in papillary ca with no apparent h/o of radiation exposure.[47,48]

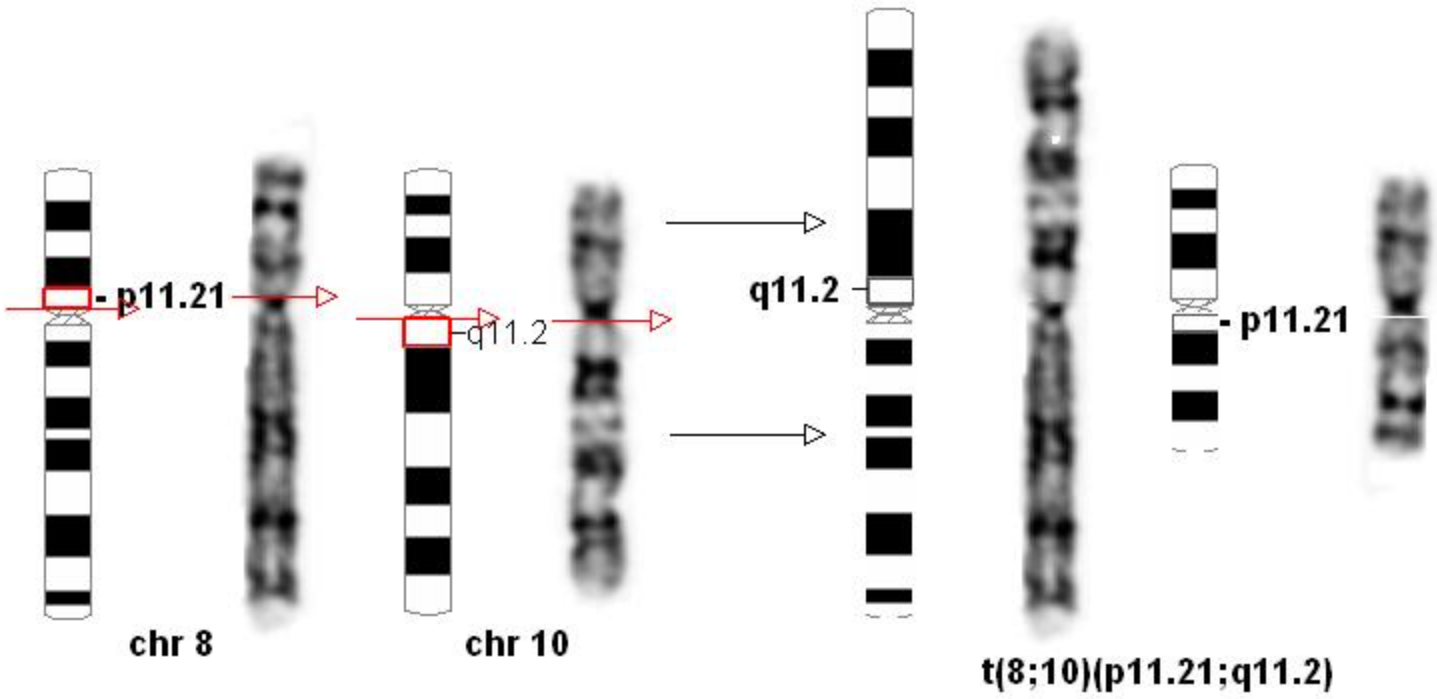




ELKS/RET - t(10;12)(q11.2;p13.3)

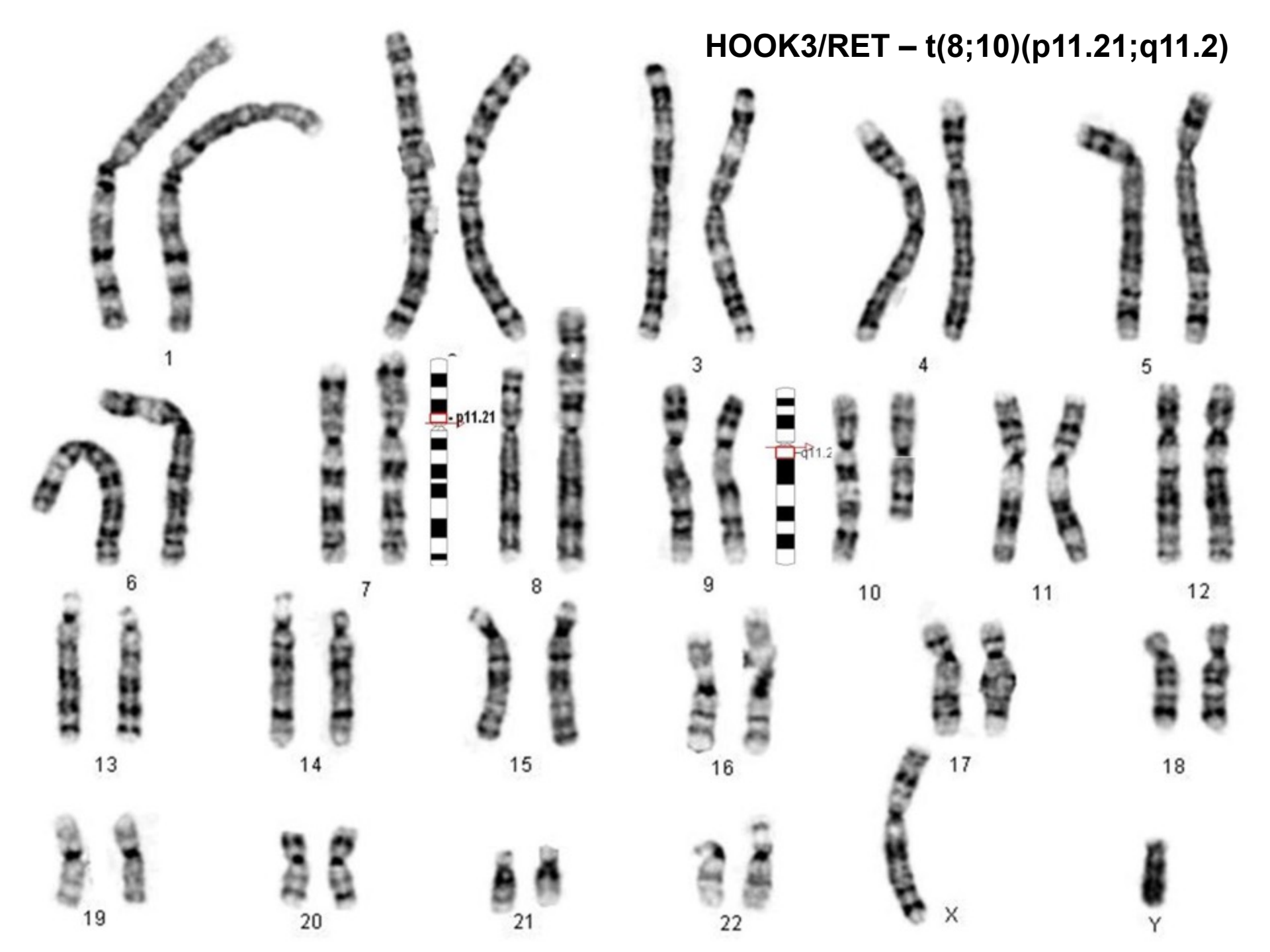
ELKS/RET - t(10;12)(q11.2;p13.3)





HOOK3/RET – t(8;10)(p11.21;q11.2)

HOOK3/RET – t(8;10)(p11.21;q11.2)



- All fusions leave the tyrosine kinase domain of the RET receptor intact and enable the RET/PTC oncoprotein to bind SHC and activate the RAS-RAF-MAPK cascade.[49]

RET/PTC mut as therapeutic target….

- ZD6474, orally active low m.w receptor kinase inhibits VEGVR-2 & blocks RET tyrosine kinase.
- ZD6474 block phosphorylation and signalling from RET/PTC3 *in vitro*, induce growth arrest of human papillary ca cell lines carrying RET/PTC1 and prevent growth of RET/PTC3-transformed fibroblasts in nude mice.[64,65]

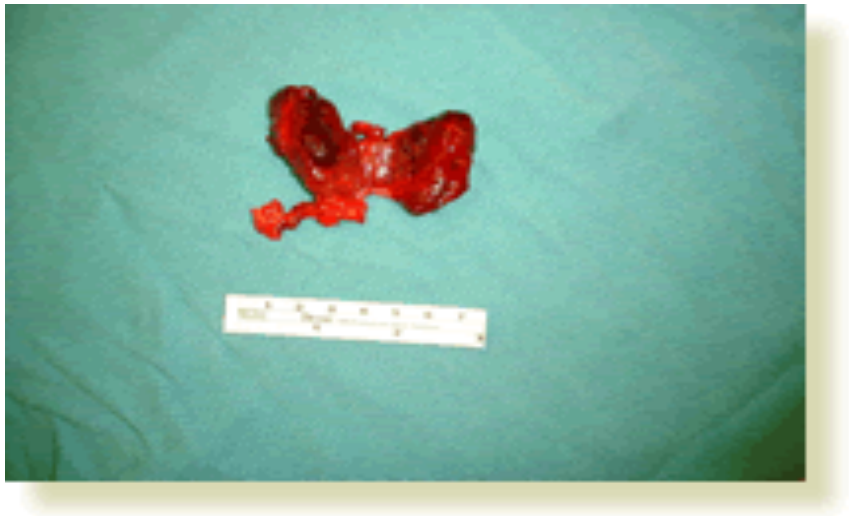
RET/PTC mut as therapeutic target……..

- SU 12248 (multikinase inhibitor - sunitinib) effectively inhibit signalling from RET/PTC kinase in the experimental models and has been tested in Phase II clinical trial in radioiodine-refractory, unresectable differentiated thyroid cancer.[66]

RAS

- *RAS* genes (*HRAS*, *KRAS* and *NRAS*) encode G-proteins important in the intracellular transduction of signals arising from cell membrane receptors.
- In its inactive state, RAS protein is bound to GDP.
- Upon activation, it releases GDP and binds GTP, activating MAPK and PI3K/AKT.

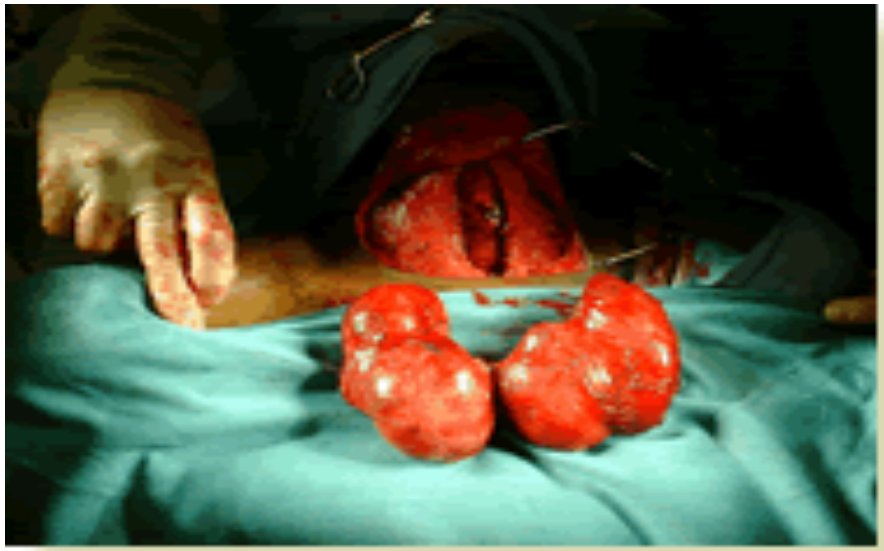
- Normally, the activated RAS-GTP protein becomes quickly inactive due to its intrinsic GTPase activity and the action of cytoplasmic GTPase-activating proteins.

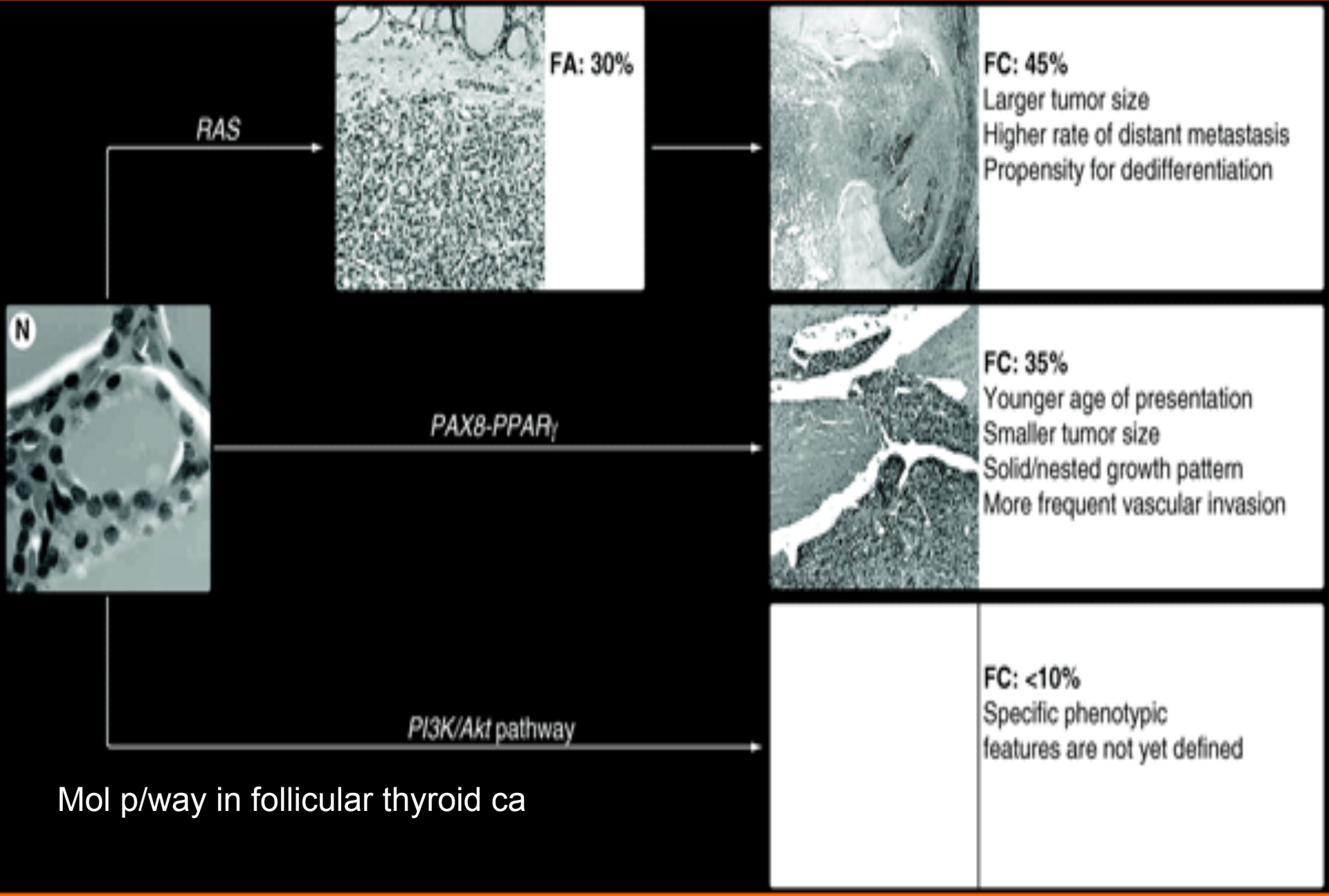


- Point mut in the discrete domains of the *RAS* gene either increase its affinity for GTP (mut in codons 12 and 13) or inactivate its autocatalytic GTPase function (mut in codon 61).
- As a result, the mutant protein becomes permanently switched in the active position and continuously activates its downstream targets

Follicular Ca & Adenoma

- RAS
- PAX8-PPAR
- PIK3CA
- PTEN





Mol p/way in follicular thyroid ca

Source: Expert Rev Mol Diagn © 2008 Future Drugs Ltd

Foll Ca & Adenoma - RAS

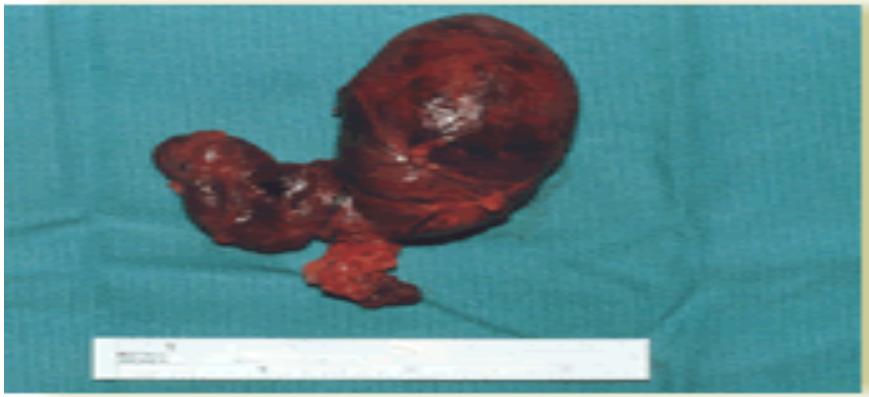
- Mutations found in 40 to 50% conventional foll ca & in 20 to 40% adenomas.
- Hotspots – NRAS codon 61 & HRAS codon 61.
- Mutations seen in 15 to 25% oncocytic cell ca.
- Mut correlates with tu dedifferentiation & metastasis

Foll Ca & Adenoma - PAX8-PPARy

- Due to t(2,3)(q13;p25)
- Leads to fusion of PAX8 & PPARy genes.
- 35% of conventional foll ca & lower in hurtle cell ca.
- A/w younger age, smaller size, solid/nested growth pattern & vas invasion
- If seen in adenoma – ? Insitu (preinvasive foll ca, ?invasion overlooked in histo)

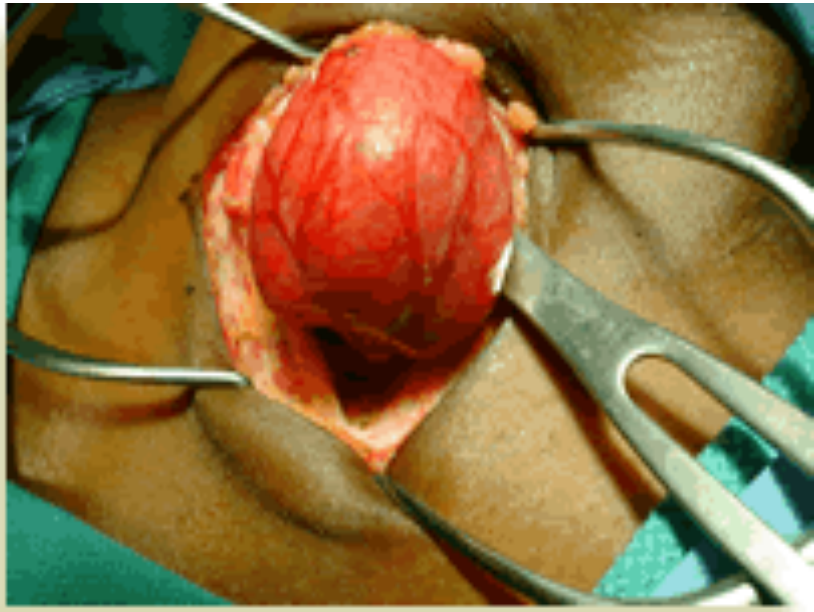
Foll Ca & Adenoma – other mut

- P13K/AKT pathway mut seen in 6-13% foll ca & 0-6% of foll adenoma
- In exons 20 & 9 of PIK3CA genes.
- LOH in regions harboring different tu supp genes..
- Del of 2p, 3p, 9q,10q,11p,15q & 17p.
- LOH assoc/w aggressiveness & recurrences



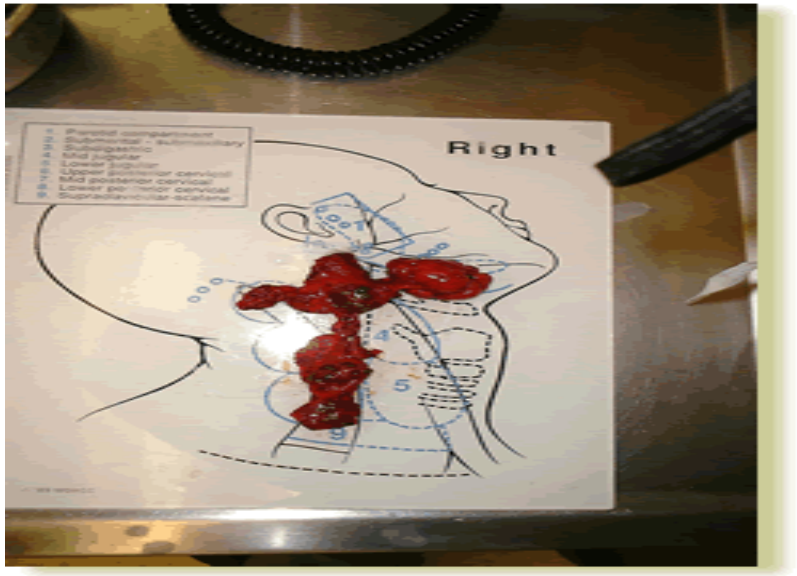
Oncocytic Ca

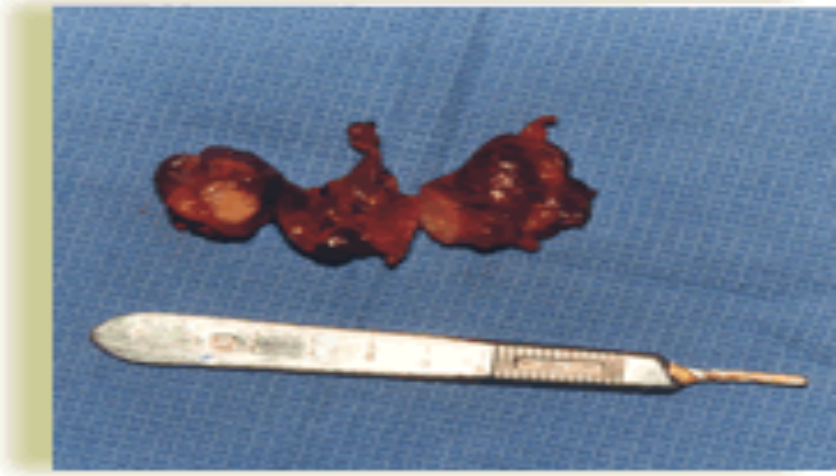
- LOH on chr 3q,18q,1p,2p,8q,14q
- Mut of GRIM-19 in 15% oncocytic ca
- GRIM-19 encodes a protein linked to retinoid-interferon-induced p/way of cell death & involved in mitochondrial met.



Poorly diff & Anaplastic Ca

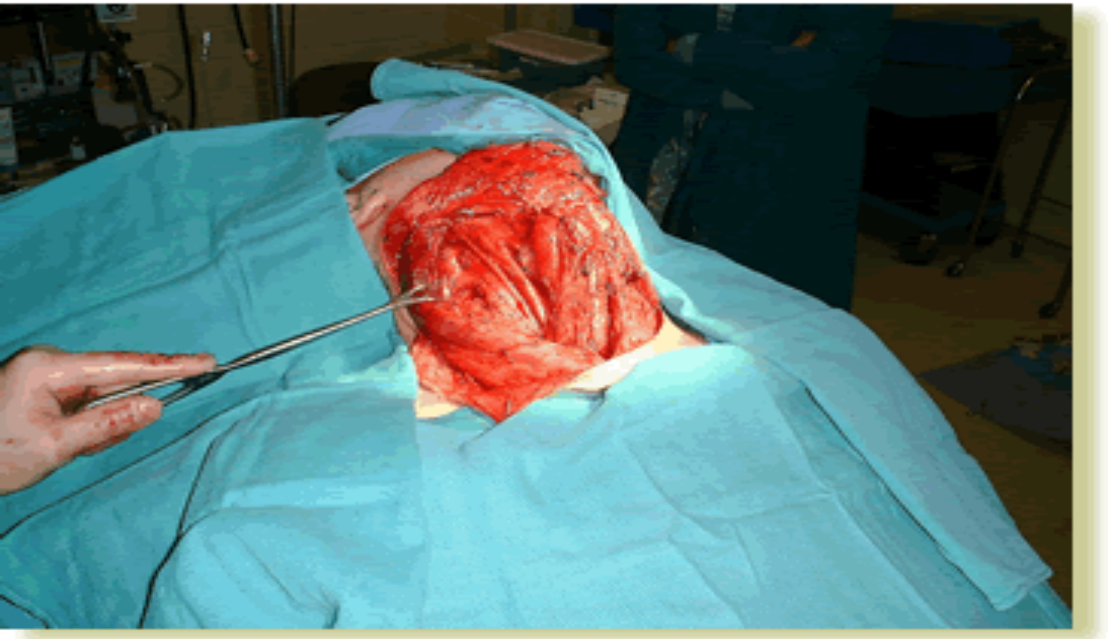
- TP53
- CTNNB1 (Beta catenin)
- RAS
- BRAF
- PIK3Ca
  PTEN





Poorly diff Ca & Anaplastic Ca-TP53

- Point mut of TP53 are late events
- Most involve exons 5-8 of gene & alter DNA binding properties
- Assoc/w accelerated cell growth & progressive

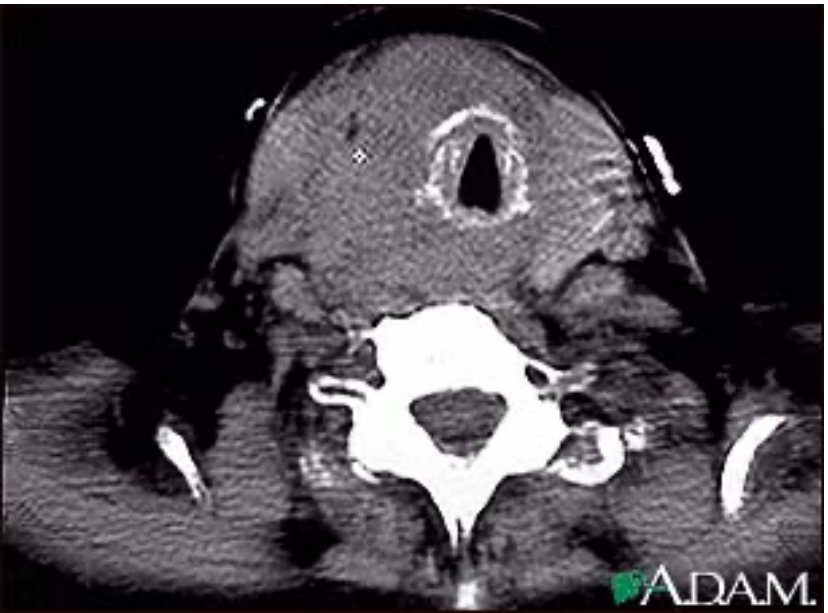


This is the neck after removal of the cancerous lymph nodes

Medullary Thyroid Ca

- *RET* is activated by point mutation vs chr rear in papillary ca.
- Germline mutations in specific functional regions of *RET* found in almost all pts with familial medullary ca.
- MEN 2A & familial medullary ca, mutations are typically located in the extracellular domain, within the cysteine-rich region.[124]
- 90% of MEN 2A mutations affect a single codon 634, whereas in familial medullary ca they are more evenly distributed along the cysteine rich region.[125]

- In MEN 2B, the majority of germline mutations occur in codon 918 in the intracellular tyrosine kinase domain of *RET*.
- This alter the substrate specificity of RET kinase, resulting in phosphorylation of unusual intracellular proteins.[126]



This CT scan shows a thyroid cancer tu in the throat, encircling,narrowing, & displacing the windpipe(trachea)

- Sporadic medullary ca, somatic mutations of the *RET* gene in 20–80% of cases.[127,128]
- Mut affect codon 918 mostly, some have heterogeneous distribution within the tu & detected only in a subset of metastatic nodules.[128]

- RET kinase inhibitors ZD6474 and SU12248 (sunitinib), now in Phase II clinical trials in pts with familial & sporadic medullary thyroid cancer.[63,66]

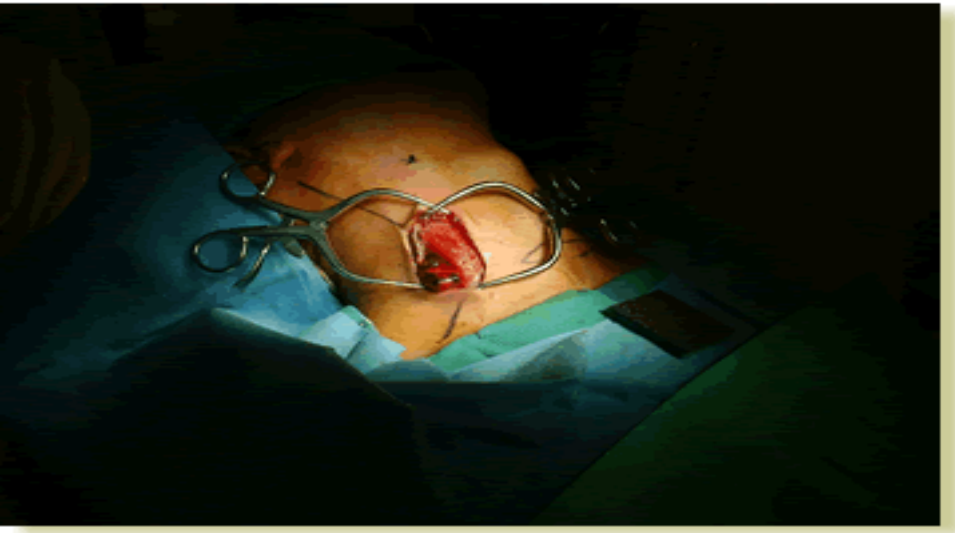
Summary

- FNA dx of thyroid nodules can be improved by testing for *BRAF*, *RET/PTC* and other mutations.
- *BRAF*, *RET/PTC* and *RAS* mutations correlate with specific phenotypical features of papillary ca.
- *BRAF* is a reliable diagnostic marker for malignancy and an independent prognostic marker for tumor recurrence and more aggressive behaviour of papillary carcinomas.

These are lymph nodes that received cancer cells fr the primary ca in the thyroid gld

Summary

- *PAX8-PPAR γ* & *RAS* mut correlate with specific phenotypical feat of follicular ca.
- Limitations…..Papillary ca (~30%), conventional follicular cas (~20%) & oncocytic follicular ca (>50%) do not harbour any of the known mutations.



Black discoloration of cancerous lymph nodes.Papillary ca is sometimes black in color especially afer having spread to lymph nodes

Therapy in Differentiated Thyroid Cancer

Cancer of thyroid:-

2 varieties –

- Follicular epithelium
- Parafollicular or C cells

Follicular epithelium

- Papillary Ca - 70%

- 2nd to 3rd decade, slow growing (to LNs)
- local invasion rare
- microscopically divided into well-differentiated and poorly-differentiated

Follicular epithelium

- Follicular Ca - 15-20%
- Older age group, mean age 55 yrs
- More aggressive
- Poorer prognosis
- Spread via bloodstream to lung and bone
- Mixed Pap-Follicular variety

◊ *Hurthle cell* tumour (rare subtype)

- Anaplastic - 5%

- Worse prognosis

Parafollicular / C cells

- Medullary carcinomas - 5 – 10%
  - sporadic
  - familial (MEN type 2A or 2B; non-MEN)
  - secrete thyrocalcitonin
  - non- iodine avid
  - mainstay of treatment : surgery

Tx	Primary tumor cannot be assessed	Same as fifth edition
T0	No evidence of primary tumor	Same as fifth edition
T1	Tumor size ≤ 1 cm	Tumor size ≤2 cm
T2	Tumor size >1 and ≤ 4 cm, intrathyroidal	Tumor size >2 and £4 cm, intrathyroidal
T3	Tumor size >4 cm, intrathyroidal	Tumor size >4 cm intrathyroidal or any tumor with minimal extrathyroidal extension (e.g. extension to sterno thyroid muscle or perithyroid soft tissues)
T4	Tumor of any size extending beyond the thyroid capsule (i.e. extrathyroidal)	T4a: any tumor invaded to subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve T4b: any tumor invaded to prevertebral fascia or encasing carotid artery or mediastinal vessels
Nx	Regional lymph nodes cannot be assessed	Same as fifth edition
N0	No regional lymph node metastasis	Same as fifth edition
N1a	Metastasis in ipsilateral cervical lymph node(s)	Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/delphian lymph nodes)
N1b	Metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph node(s)	Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes
Mx	Distant metastases cannot be assessed	Same as fifth edition
M0	No distant metastasis	Same as fifth edition
M1	Distant metastasis	Same as fifth edition

Table 5.1. TNM classification of thyroid cancer

pTX	Primary tumor is not assessable
pT0	No evidence of primary tumor
pT1	Tumor < 2 cm, limited to the thyroid
pT2	Tumor > 2 cm and < 4 cm, limited to the thyroid
pT3	Tumor > 4 cm, limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissue)
pT4a	Tumor extends over the thyroid capsule and invades any of the following structures: subcutaneous soft tissue, larynx, trachea, esophagus, recurrent laryngeal nerve
pT4b	Tumor invades prevertebral fascia, mediastinal vessels, or encases carotid artery
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1a	Lymph node metastasis of the central compartment
pN1b	Lymph node metastasis of the ipsilateral or contralateral cervical compartment, mediastinal lymph node metastasis
pMX	Distant metastasis cannot be assessed
pM0	No distant metastasis
pM1	Distant metastasis

Biologic considerations

- Defects in metabolism of radioiodine in cancer cells
  - iodine uptake, via the sodium-iodide symporter (NIS), is always decreased and is undetectable in about a third of patients;
  - iodine organification is markedly reduced;
  - the effective half-life of iodine in tumor tissue is always shorter

However, response to TSH stimulation is usually present, even in the absence of clinically evident ^{131}I uptake

Good ^{131}I uptake → better results

Administered ^{131}I activities

- Empirical
  - Fixed amounts of radioiodine are given based upon the presence and location of metastases*
    - Residual thyroid bed activity only: 100 mCi
    - Regional Metastases (Cervical Nodes): 150-175 mCi
    - Lung Metastases: 175-200 mCi (100-300 for pulmonary micrometastases @)
    - Skeletal Metastases: 200 mCi
- Calculated based on measured iodine uptake
  - dose to bone marrow <2 Gy from a single treatment

*JNM1992; 33: 2214-21

@Thyroid 2006; 16: 1-25

- no study has yet demonstrated that maximal activities based on dosimetry or high standard activities of ^{131}I are more effective than standard treatment with fixed activities of 3.8–5.6 GBq (100–150 mCi).

Dosimetry considerations

- Sgouros et al. [PET scanning & administered ^{131}I activity of 3.8 to 16 GBq (100 – 420 mCi)] estimated tumour doses to range from 1.2 to 540 Gy
  - wide variations in the absorbed dose distribution between lesions and even within lesions.

JNM 2004;45:1366–1372

Preparation for ^{131}I Tx or Dx

- TSH stimulation
- Low Iodine Diet
- No iodine contrast containing media (if prior radiological investigations)

TSH stimulation (>30mIU/L)

Two alternative methods:

1. Thyroid hormone withdrawal:
   - LT4 treatment is withdrawn for ~~4–6~~ weeks.

2. rhTSH injections:
   - rhTSH (0.9 mg) is injected i.m. for 2 consecutive days (days 1 and 2) and
   - ^{131}I is administered on the day after the second injection (day 3).
   - Serum Tg is measured on the third day after the second injection (day 5)

rhTSH stimulation

For

- Patients unable to raise endogenous TSH, or
- prolonged withdrawal is contraindicated or poorly tolerated

^{131}Iodine Whole Body Scanning

- performed to assess for
  - residual functioning thyroid tissue
  - the presence of metastatic lesions
- Preparation
  - Stop L-thyroxine 4 - 6 weeks prior to scan
  - Low iodine diet
- Negative result needs validation against TSH result (must be >30uIU/ml)

- Traditionally done post surgery, before RAI ablation – currently generally omitted
- WBS after RAI ablation
  - more sensitive than with low dose

Examples of Scans

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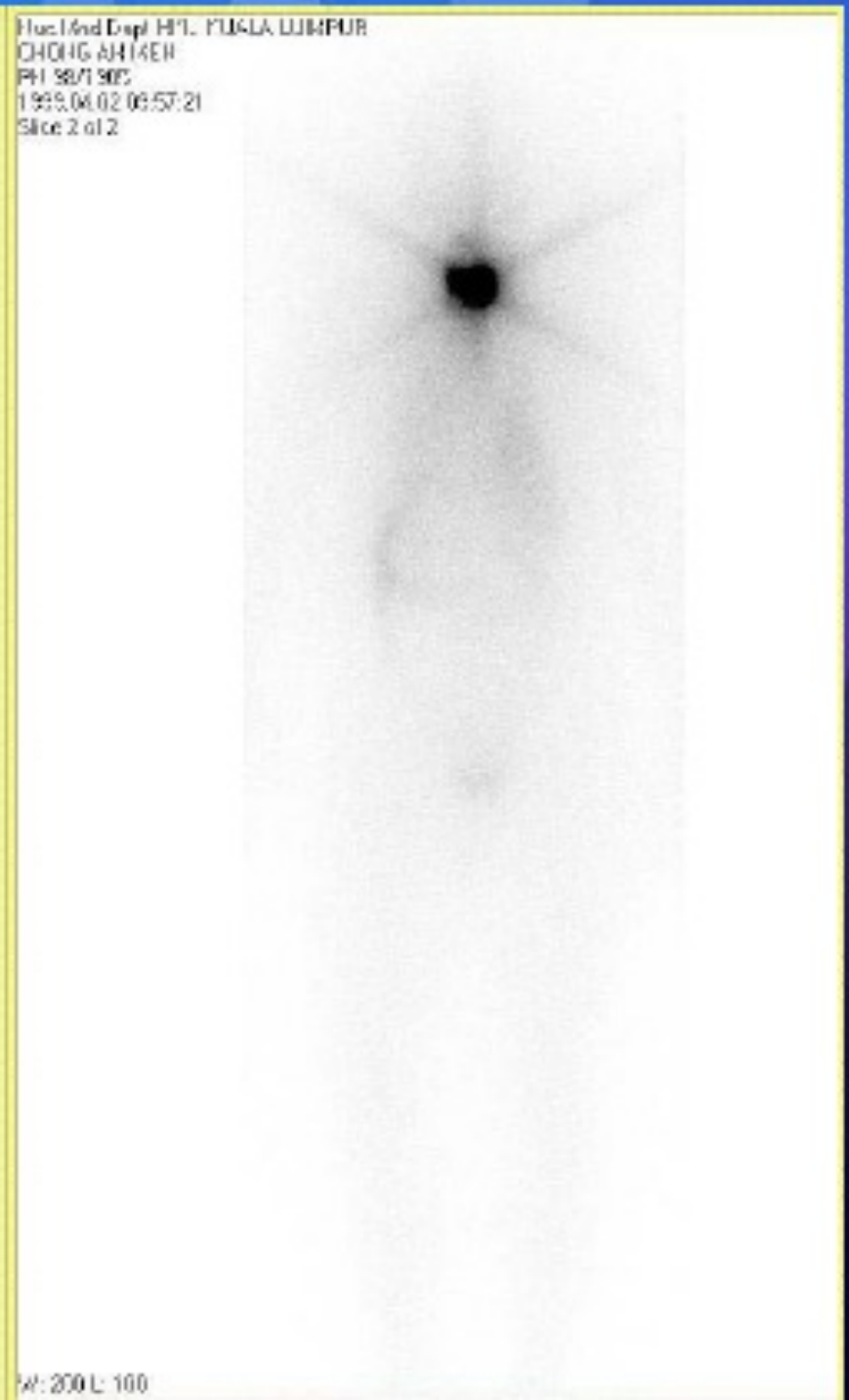
1999.04.02 09:57:21
Slice 1 of 2
W: 200 L: 100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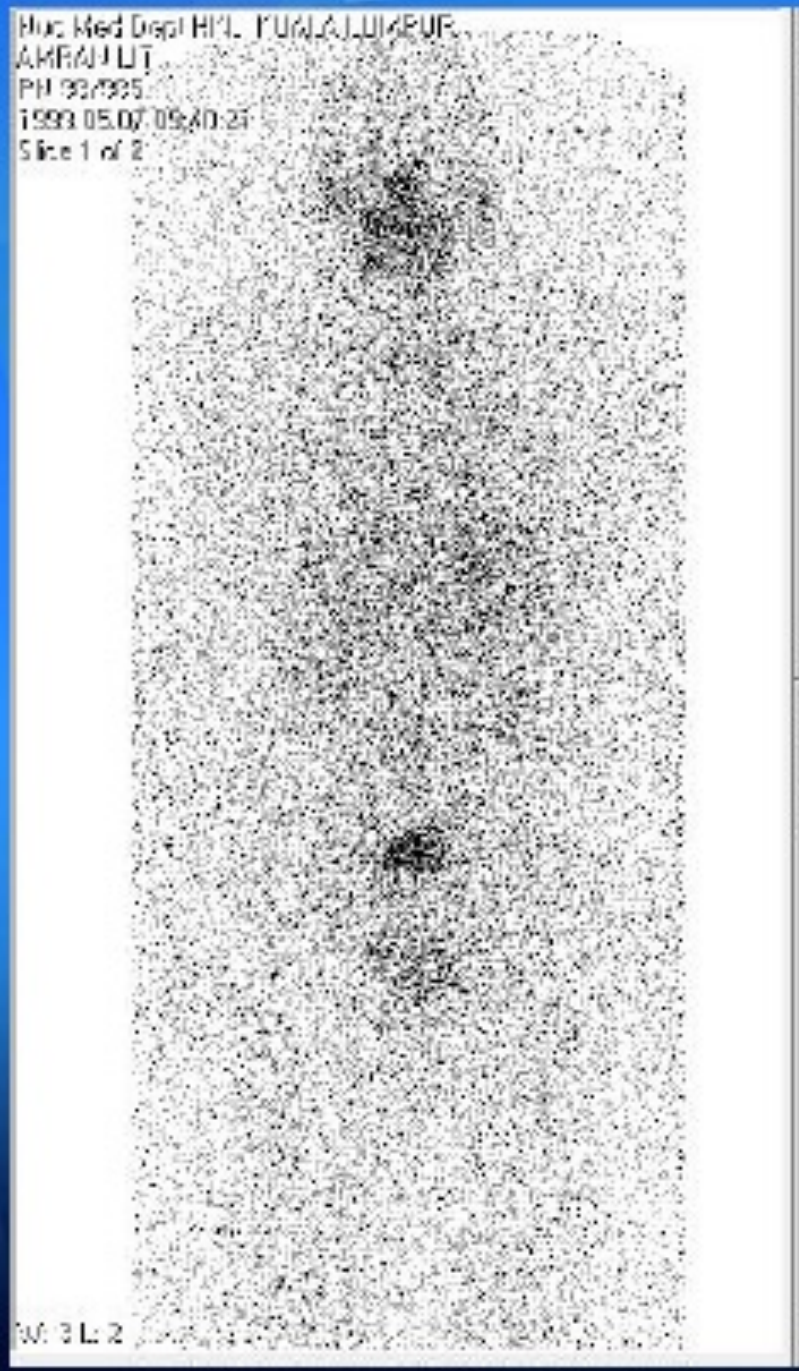
Slice 2 of 2
W: 200 L: 100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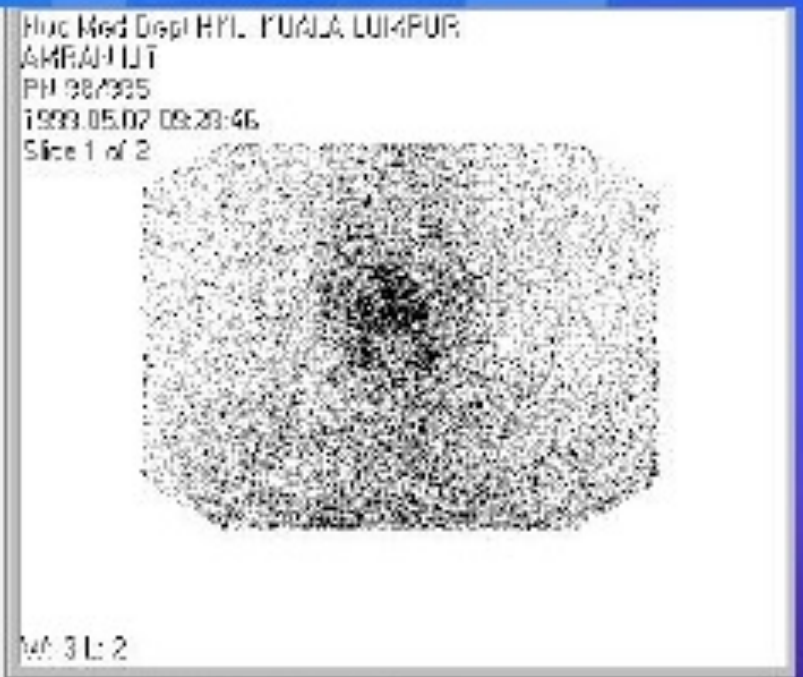
AMRAN UT
PH 98/995
1998.05.07 09:40:21
Slice 1 of 2
W: 3 L: 2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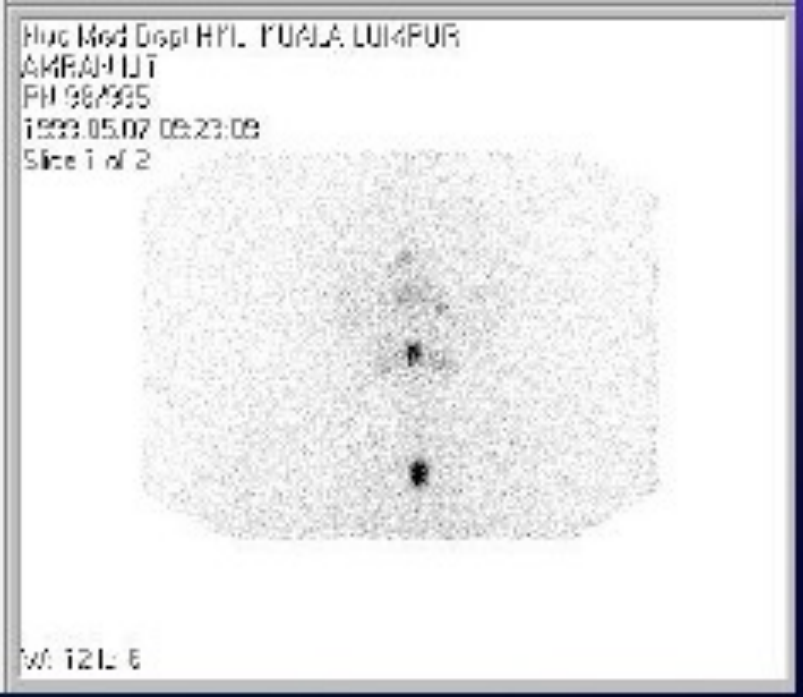
AMRAN UT
PH 98/995
1998.05.07 09:28:46
Slice 1 of 2
W: 3 L: 2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PH 98/995
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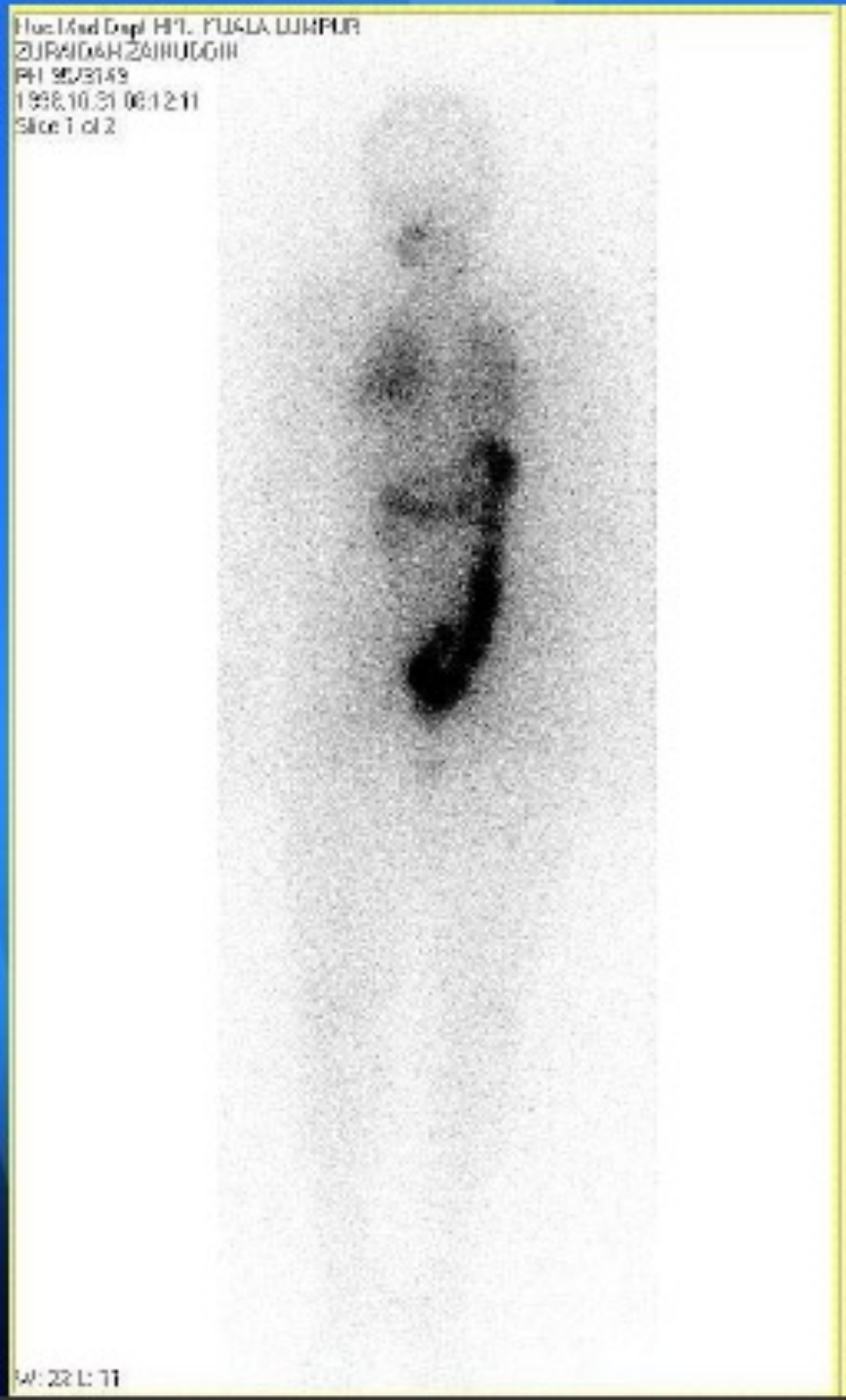
Slice 1 of 2
W: 12 L: 6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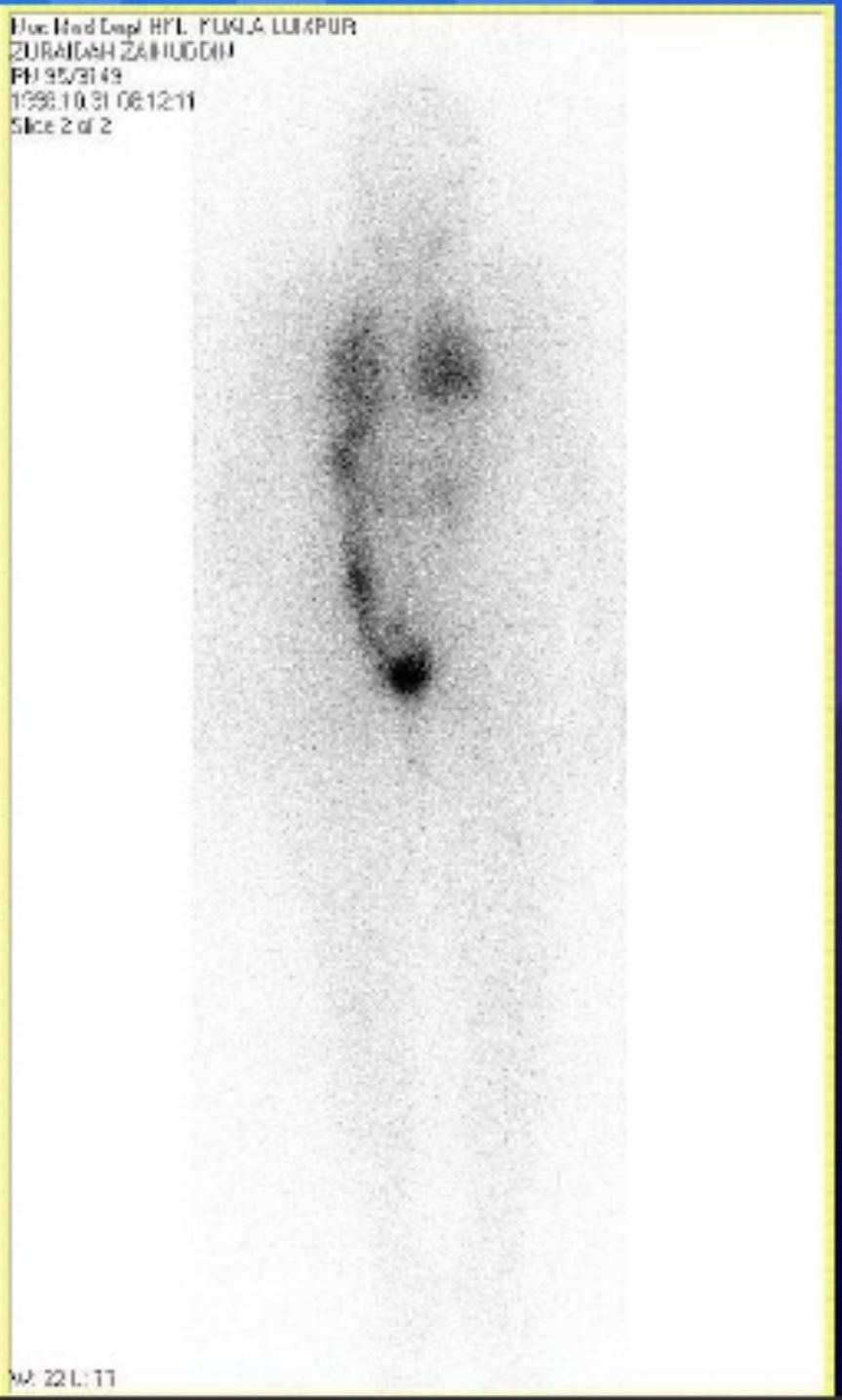
ZURAIDAH ZAINUDDIN
PH 95/3149
1998.10.31 06:12:11
Slice 1 of 2
W: 22 L: 11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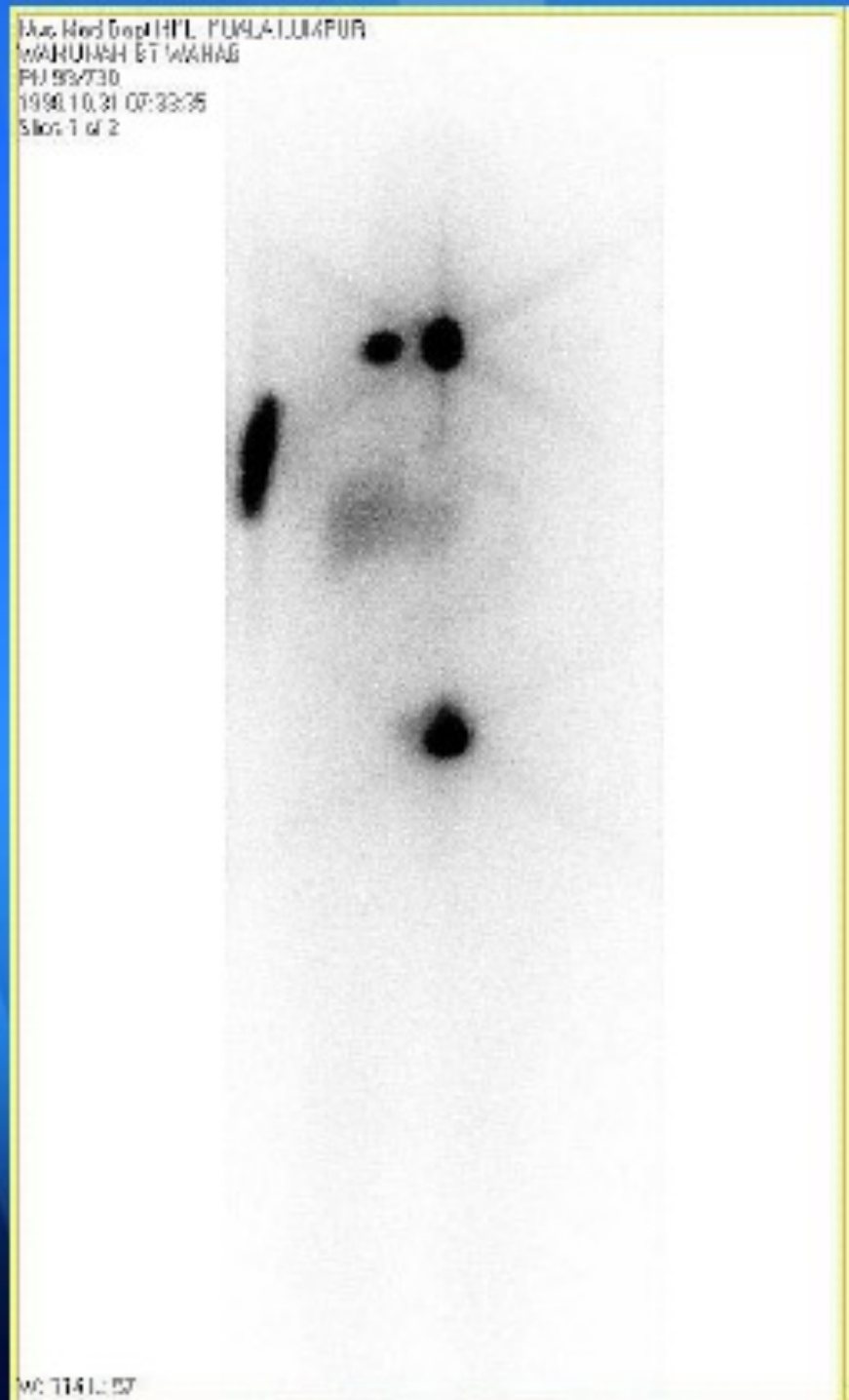
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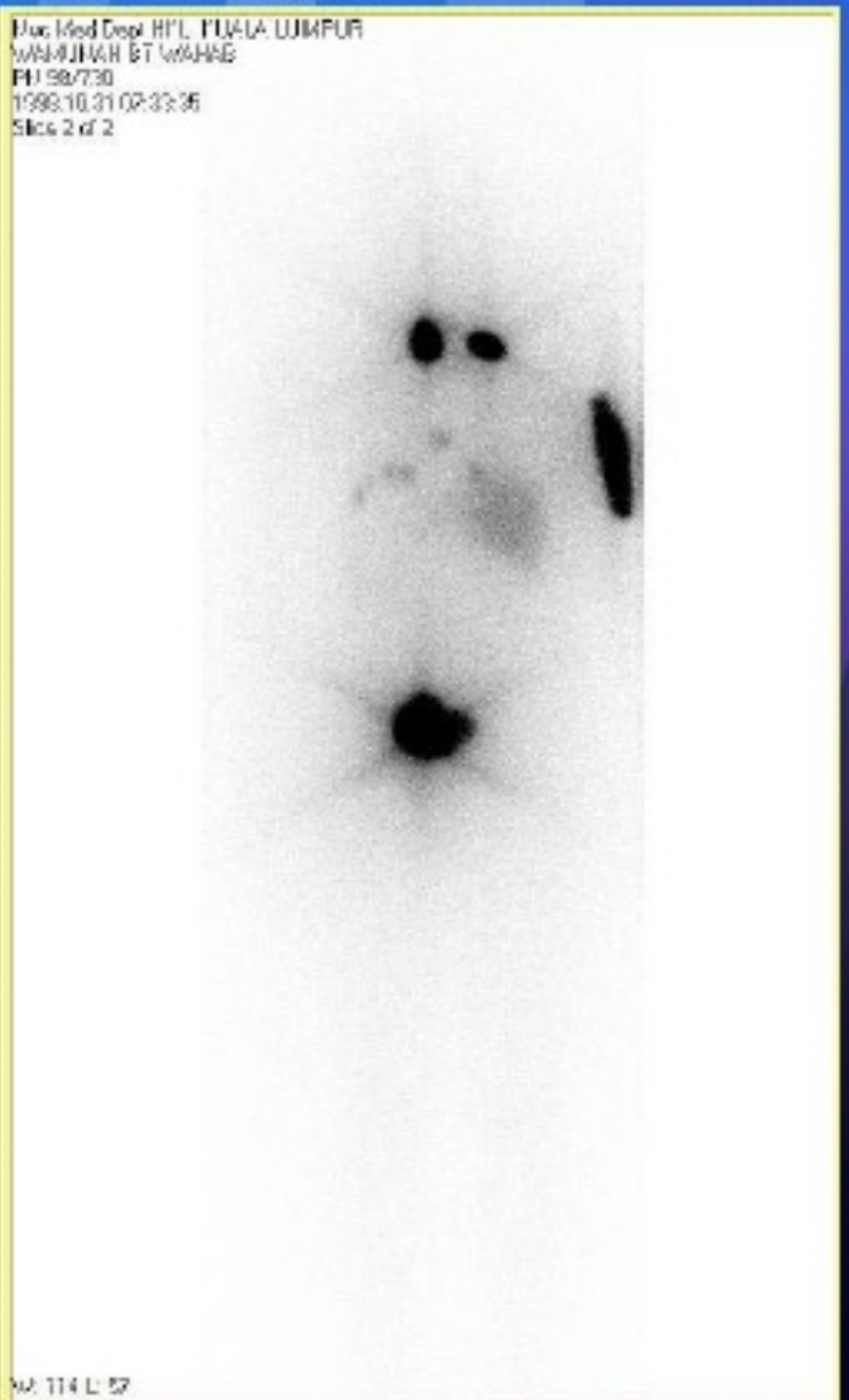
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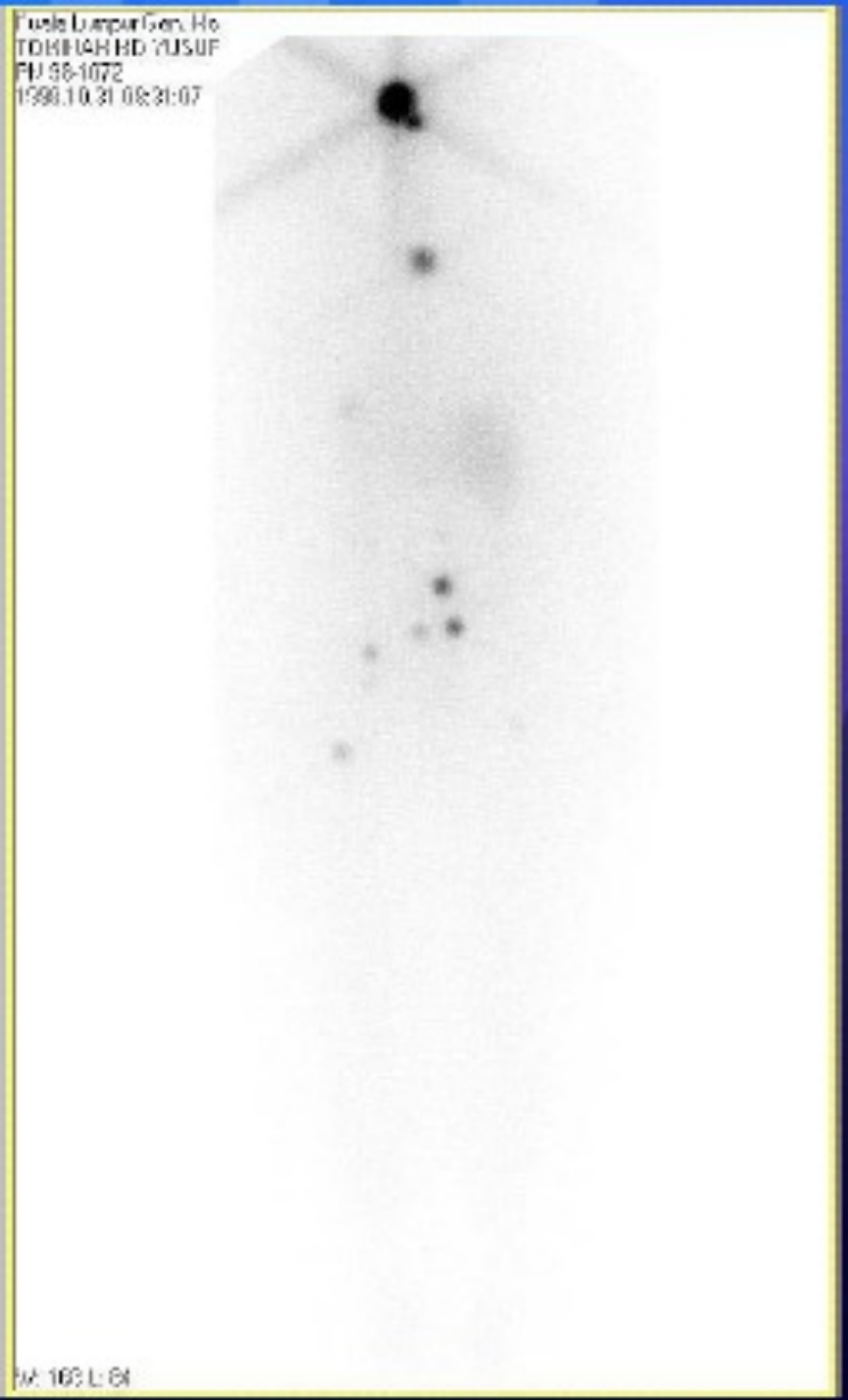
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Treatment with ^{131}Iodine

Pertinent Surgical Note From European Consensus 2006*

- solitary well differentiated thyroid cancer less than 1 cm in diameter with no evidence for nodal or distant metastases, and no history of previous radiation exposure - may be operated on by less than total thyroidectomy,
- the standard surgical treatment is total (or near-total) thyroidectomy. This procedure decreases the risk of local recurrence and is performed with almost no morbidity under expert hands. Moreover, it facilitates postsurgical radioiodine ablation and adequate follow-up

*European J. of Endocrinology,2006; 154; 787-803

^{131}Iodine Ablation

- Follows surgery (Total thyroidectomy)
- Indications
  - To destroy the thyroid tissue remaining in the neck after surgery
  - For the treatment of functional metastases
  - Possibly for the treatment of patients with elevated thyroglobulin levels, but a negative ^{131}Iodine scan

^{131}Iodine Ablation - HKL

- Dose:
  - 80 – 100mCi ^{131}Iodine (if only thyroid bed uptake)
  - 120 – 150mCi ^{131}Iodine (if Extrathyroidal lesions)
- Preparation – as for diagnostic WBS
- Treatment after administering Iodine-131
  - antiemetics, analgesics
  - steroids if lungs, brain involved
- Post therapy WBS– may detect new lesions.
- patient discharged with L-thyroxine

^{131}I FOR THYROID REMNANT ABLATION (RRA)

- since 1970s
- widely adopted in the United States and Europe and is supported by several learned medical societies
- European consensus – risk stratification
  - Very Low risk – no indication
  - High risk – definite indication
  - Low risk – no consensus, but generally given

European consensus 2006

Indications

No indication (low risk of relapse or cancer-specific mortality) Very low risk	**Definite indication** (use high activity after thyroid hormone withdrawal) High risk	**Probable indication** (use high or low activity) Low risk
• Complete surgery • Favorable histology • Unifocal T<= 1cm, N0 M0 • No extrathyroidal extension	• Distant metastases or • Incomplete tumor resection or • Complete tumor resection but high risk for recurrence or mortality: -tumor extension beyond the thyroid capsule (T3 or T4) -lymph node involvement	• Less than total thyroidectomy or • No lymph node dissection or • Age< 18 years or • T1>1cm and T2 N0 M0 • Unfavorable histology: -Papillary: tall cell, columnar cell, diffuse sclerosing -Follicular: widely invasive or poorly differentiated

- Robbins et al* recommend RRA for any individual with
  - a carcinoma >1.5 cm or
  - with a thyroid carcinoma of any size with obvious lymph node involvement, extrathyroidal extension, or multicentricity.
  - incomplete surgical resection.

*JNM 2005;46(Suppl);28S-37S

- less need for RRA in low-risk patients who have had a true total thyroidectomy
- a greater need when large remnants are present or in patients who are at high risk for recurrence, based on histology, age, or extrathyroidal extension.

Benefit of RRA

- Sawka et al. (2004)* - evidence from pooled analyses on RRA - supported the reduction of relative risk of local and distant metastases
- All individuals who have RRA should have a whole-body scan after therapy to screen for unexpected metastatic lesions.

*J Clin Endocrinol Metab. 2004;89:3668–3676

^{131}I FOR LOCOREGIONAL RECURRENCES

- therapy of choice is - surgical resection
- large lymph node metastases (>1 cm in diameter) - surgery - first-line treatment
- small lymph node metastases (<1 cm in diameter) can be treated with ^{131}I alone
  - if any abnormality (such as ^{131}I uptake or abnormalities on neck sonography) persists after 2 or 3 treatment courses → surgery

^{131}I FOR DISTANT METASTASES

- most common distant metastatic sites - lungs, spine, and bone
- administered activity empiric or according to dosimetric studies
  - no evidence that one approach results in a better outcome than the other
- Steroids used in patients with metastases to brain or lung

- Favourable - young age and small volume disease, especially diffuse micronodular lung disease
- bone metastases are generally resistant to commonly used activities of ^{131}I
- Older age and multiple organ sites - only significant predictors of cancer mortality

- trend toward using radioiodine therapy for thyroid cancer survivors who have elevated serum Tg levels, even in the absence of identifiable lesions

Advantages of ^{131}Iodine treatment

- Decreases local recurrence*
- Improves survival in patients following local recurrence
- Prolongs survival in patients with lung or bone mets even though rate of actual cure is low*
- Eliminates the thyroid gland as source of thyroglobulin

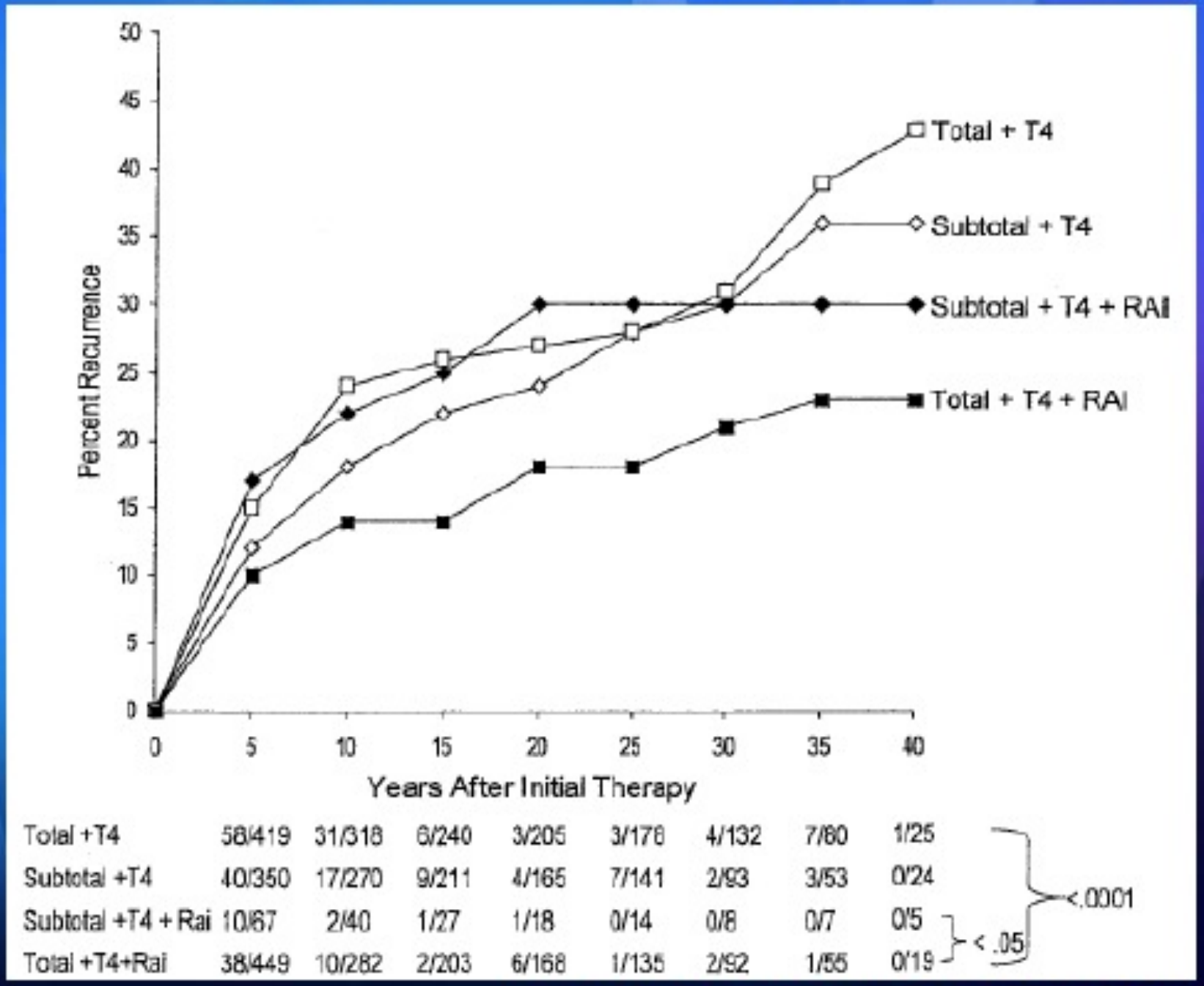
*Cancer 2002 Aug 1;95(3):488-98 & Thyroid 2006; 16: 1-25

Impact of ^{131}Iodine Therapy

- Reduce long term recurrence
- Reduce mortality (some studies)
  - Mazzaferri et al. 2001*
    - Remnant thyroid ablation in patients with tumors larger than 1.5 cm

    à significantly lower cancer recurrence, distant recurrence, and cancer death rates (the latter for patients >40 yr)

*J. Cl.Endocrinology & Metabolism, 2001; Vol. 86 No. 4

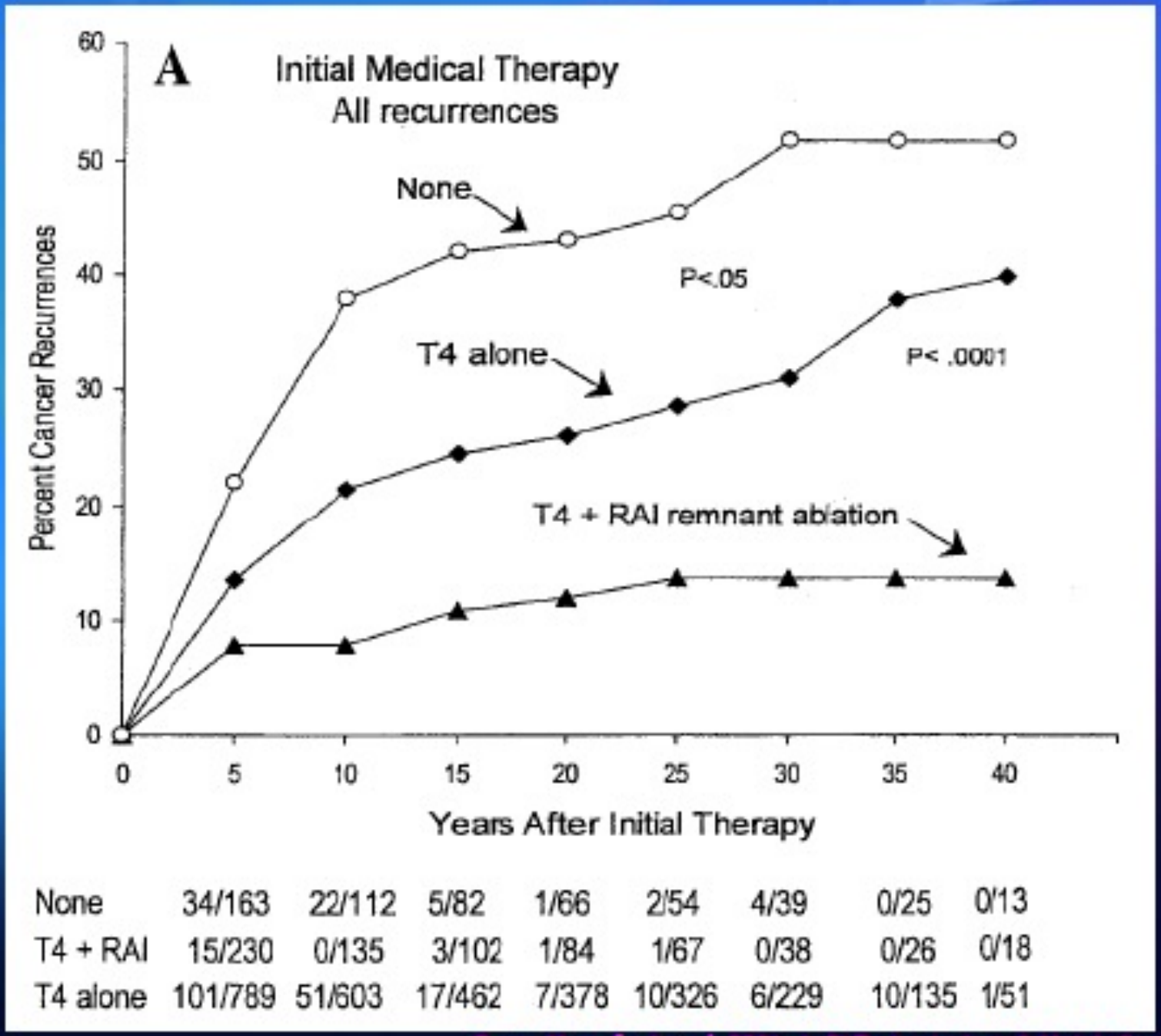


Total +T4	58/419	31/318	6/240	3/205	3/176	4/132	7/80	1/25
Subtotal +T4	40/350	17/270	9/211	4/165	7/141	2/93	3/53	0/24
Subtotal +T4 + Rai	10/67	2/40	1/27	1/18	0/14	0/8	0/7	0/5
Total +T4+Rai	38/449	10/282	2/203	6/168	1/135	2/92	1/55	0/19

<.0001

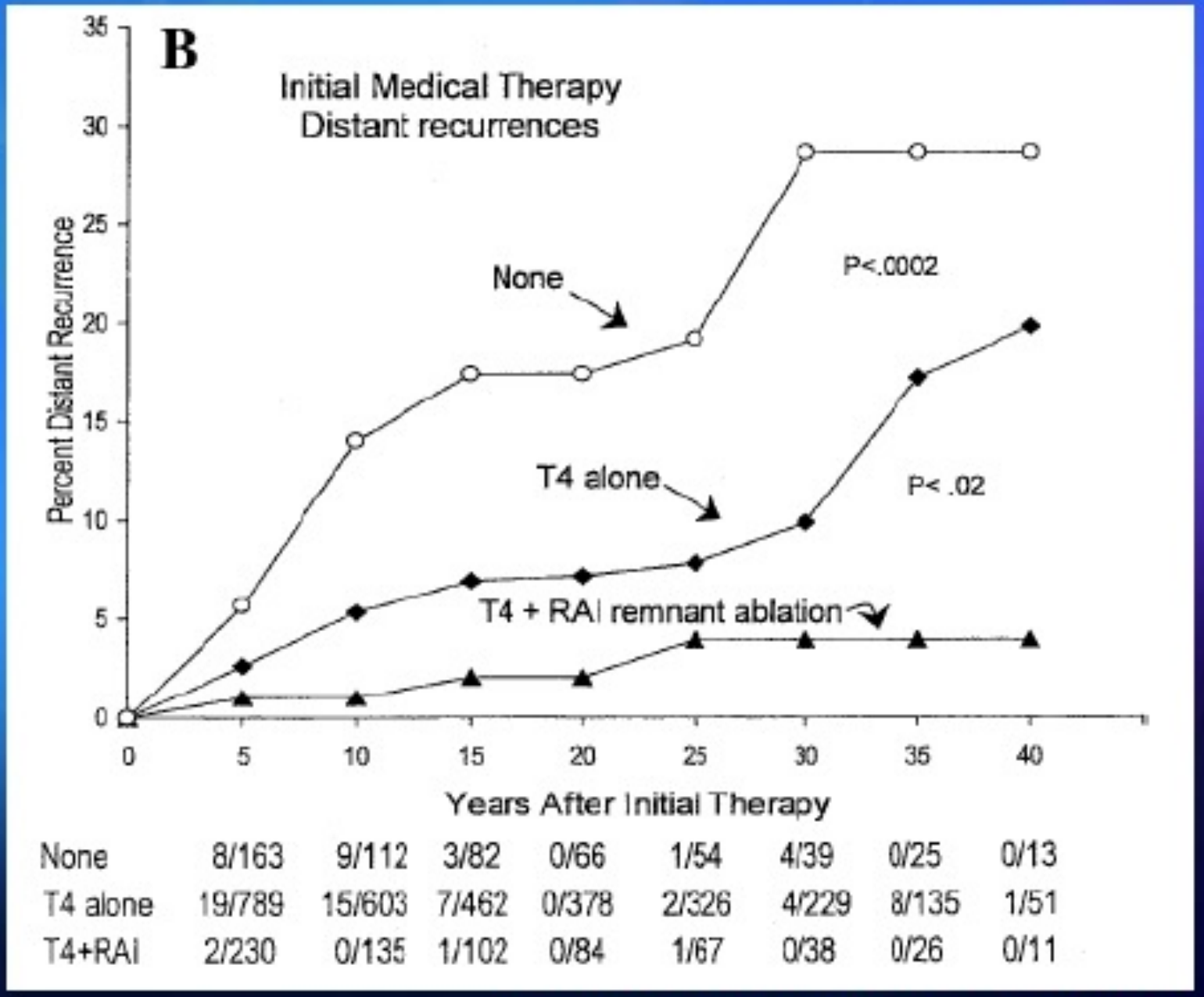
< .05

From: Mazzaferri et al., J. Cl.Endocrinology & Metabolism 2001 Vol. 86 No. 4



None	34/163	22/112	5/82	1/66	2/54	4/39	0/25	0/13
T4 + RAI	15/230	0/135	3/102	1/84	1/67	0/38	0/26	0/18
T4 alone	101/789	51/603	17/462	7/378	10/326	6/229	10/135	1/51

From: Mazzaferri et al. 2001, J. Cl.Endocrinology & Metabolism Vol. 86 No. 4



From: Mazzaferri et al. 2001, J. Cl.Endocrinology & Metabolism Vol. 86 No. 4

^{131}Iodine Thyroid Ablation Therapy

Acute Complications

- Salivary gland inflammation
- Loss of taste (Acute/Chronic)
- GI symptoms / Radiation Gastritis
- Minimal bone marrow suppression
- Radiation pneumonitis and pulmonary fibrosis
- Thyroid storm
- Transient amenorrhea
- Decreased testicular function/fertility
- Cerebral edema or spinal cord compression
- Radiation sickness

^{131}Iodine Thyroid Ablation Therapy

Chronic Complications

There is NO increased risk of thyroid tumors and no evidence of reduced fertility or genetic abnormalities in patient's offspring due to ^{131}Iodine therapy.

^{131}Iodine Thyroid Ablation Therapy

Chronic Complications

1- Secondary Tumors

- The risk of secondary tumor is low and lacks clinical impact [JNM, Jan. 95, p.21-27].
- Slightly increased risk for AML, bladder carcinoma, breast carcinoma, salivary carcinoma especially if large doses given over short period of time.

2- Hypoparathyroidism

- Post ^{131}Iodine treatment hypoparathyroidism is extremely rare.

Follow up ^{131}I WBS

- Done not earlier than 3 months following treatment with RAI
- Generally 2 negative WBSs 6 months apart before decision on f/u with Se Tg alone

- no need for subsequent ^{131}I whole-body scans in patients with an undetectable serum Tg after rhTSH, because virtually all patients with distant metastases had detectable serum Tg in that situation*

*J Clin Endocrinol Metab. 1999;84:3877–3885

In the investigation of hyperthyroidism

A. In Grave's disease, uptake of Tc-99m is usually uniform
B. If, after 2 years following I-131 treatment for Grave's disease the patient is still euthyroid, the incidence of subsequent development of hypothyroidism is negligible
C. A normal isotope scan exclude Grave's disease
D. Hypothyroidism following I-131 treatment of a solitary hyperfunctioning nodule is more common than in Grave's disease
E. Low tracer uptake into the thyroid gland may occur in untreated hyperthyroidism

In the investigation of hyperthyroidism

- TFFFT