Thyroid Cancer
Radioiodine Ablation Therapy

Saeid Abdelrazek

Department of Nuclear Medicine

Medical University of Bialystok

Thyroid Cancer- Incidence

- Differentiated thyroid cancers (DTC) are slow-growing tumors with very low disease-specific mortality rates for local - regional disease (5-y survival: 99.9% for localized disease, 98.3% for regional metastatic disease)
- Distant metastatic disease is associated with significantly worse prognosis (5-y survival: 54.9%)
- Standard-of-care management for DTC includes risk-adapted surgery, postoperative 131I therapy, and thyroid hormone therapy.
- In uncommon cases of radioiodine-refractory tumors, additional therapy may include reoperative surgical intervention, external radiotherapy, and interventional radiology for treatment of locoregional metastases and multikinase or tyrosine kinase inhibitors for treatment of distant metastatic disease

Thyroid Cancer- Incidence

- Thyroid neoplasms are the most common endocrine tumors, with an annual incidence of 829 cases/100000 people, with substantial variability between and within populations.
- DTC accounts for > 90% of cases, is more frequent in women, and has excellent specific mortality and prognosis in most cases
- The rising incidence of thyroid cancer observed in the last 30 y is mainly due to detection of small (< 2 cm) tumors as a result of increased and improved imaging

Thyroid Cancer- Incidence

- However, larger tumors (> 2 and > 5 cm) have also increased in incidence
- DTC is biologically and functionally heterogeneous, with different molecular pathways impacting cancer cell biology
- The BRAF V600E mutation is particularly associated with reduced expression of all thyroid-specific genes involved in iodine metabolism, resulting in variably decreased responsiveness to 131I therapy

AJCC TNM SYSTEM

TABLE 5. AMERICAN JOINT COMMITTEE ON CANCER TNM CLASSIFICATION SYSTEM FOR DIFFERENTIATED THYROID CARCINOMA[a]

Primary tumor (T)		
TX		Size not assessed, limited to the thyroid
T1	T1a	≤ 1 cm, limited to the thyroid
	T1b	> 1 cm but ≤ 2 cm, limited to the thyroid
T2		> 2 cm but ≤ 4 cm, limited to the thyroid
T3		> 4 cm, limited to the thyroid, or any tumor with minimal extrathyroid extension
T4	T4a	Tumor extends beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
	T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
Lymph nodes (N)		
NX		Regional lymph nodes not assessed
N0		No regional lymph node metastasis
N1	N1a	Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/ Delphian lymph nodes)
	N1b	Metastasis to unilateral, bilateral, or contralateral cervical levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII)
Distant metastasis (M)		
MX		Distant metastasis not assessed
M0		No distant metastasis
M1		Distant metastasis

Thyroid Cancer- Incidence

- **Very low risk**

pT1a N0 M0 (Tumour ≤ 1cm, restricted to thyroid)

- **Low risk**

pT1b N0 M0
pT1m N0 M0
pT2 N0 M0

- **High risk**

Any pT3, any PT4
Any N1
Any

Method in following up Differentiating Thyroid Carcinoma

1. Serum Thyroglobulin
2. US and us-FNAB
3. I-131 Whole body scintigraphy (I-131 WBS)
4. Tl-201 WBS
5. Tc-99m Sestamibi/ Tc-99m Tetrofosmin WBS
6. F-18 FDG PET

Serum Thyroglobulin (Tg)

- Tg is a 660-Kd glycoprotein produced in the thyroid cells and is specific for thyroid cells
- Tg is one of the most sensitive tumor markers in oncology; Tg IRMA is the gold standard for Tg measurement in thyroid cancer
- Test assay (IRMA) with a functional Sensitivity below 1 ng/ml

Serum Thyroglobulin (Tg) Precondaitions

- Complete ablation of normal thyroid tissue
- TSH above 30 mU/L either after withdrawal of thyroid hormones or under exog administration of rhTSH
- After thyroidectomy and radioiodine remnanet ablation Tg should be undetectable (<0.5 ng/ml) under T4 off or rhTSH inj

Serum Thyroglobulin (Tg) Precondaitions

- Increase of Tg: recurrence or metastases
- Sensitivity (T4 on; TSH < 0.03 mU/L) : 84%
- Sensitivity (T4 off/rhTSH; TSH >30 mU/L): 98%

Imaging methods in Increasing Tg

1. US and us-FNAB
2. I-131 Whole body scintigraphy (I-131WBS)
3. Tl-201 WBS
4. Tc-99m Sestamibi/ Tc-99m Tetrofosmin WBS
5. F-18 FDG PET
6. Somatostatin receptor (SSR) imaging with radiolabeled somatostatin analogs (99mTc-depreotide, 99mTc-EDDA/HYNIC-Tyr3-octreotide [Tektrotyd], 111In-octreotide, and 68Ga-DOTATATE/TOC/NOC)

I-131 Whole body scintigraphy

- I-131 is the most specific radionuclide to image well differentiated local recurrences, lymph node metaseases or distant metaseases
- Several preconditions are needed to perform (I-131WBS)
- Only 2/3 of metastases show I-131 uptake

I-131 Whole body scintigraphy preconditions

- TSH >30 mU/L after 3-4 weeks withdrawal of thyroid hormones or i.m inj of rhTSH (thyrogen 2x0.9mg)
- No thyroid tissue should be left after total thyroidectomy and I-131 remnant ablation
- Urinary iodine excreation <100 ug/g Crea
- rhTSH used in Low risk and/or multimorbidity
- Endogenous hypothyrosis prefered in High risk

I-131 Whole body scintigraphy preconditions

- rhTSH (thyrogen 2x0.9mg) i.m injection or s.c inj if patient is on anticoagulant
- Radioiodine given 1 day after 2nd dose of rhTSH inj
- Serum Tg testing is performed 3-4 days after 2nd rhTSH inj
- If dx WBS it takes place after 48-72 hr after radioiodine is applied
- Rx WBS is performed 2-7 days following radioiodine administration
- rhTSH used in high risk and/or multimorbidity

I-131 Whole body scintigraphy

- Administration of 74-185 MBq I-131
- WBS after 24 i 48 hr
- Spot imaging: 10 min per image
- Large field gamma camera
- High energy all purpose collimator
- In case of faint uptake: late scan 72 hr after I-131 administration

I-131 Whole body scintigraphy

- For routine follow up : 185 MBq I-131
- In case of elevated Tg, if high dose I-131 therapy is intended, only 74 MBq I-131 should be given to avoid thyroid stunning
- After I-131 therapy a pt-I-131 WBS should be performed 5 days after therapy
- Sensitivity (D-I-131 WBS) : 56%
- Sensitivity (a pt-I-131 WBS) : 79%

I-131 Whole body scintigraphy

- Because only 2/3 of recurrences and metastases show I-131 uptake, imaging methods using non-specific tracers are needed to detect I-131 negative metastases
  - in case of elevated Tg but –ve I-131 WBS
  - in case of marked elevation of Tg but only faint uptake in I-131 WBS, when additional I-131 negative metastases are suspected
  - elevated Tg in case of oxyphilic histology

I-131 Whole body scintigraphy

- The value of low dose diagnostic I-131 WBS (74-185 MBq) is questionable due to the low sensitivity (<60%) – stunning
- WBS using I-123 is performed in some centers and does not lead to stunning
- The sensitivity of post – therapeutic I-131 WBS (3700-11100 MBq) is much higher (>70) compared to a diagnostic WBS

F-18- FDG PET

- Malignant tumors show elevated glucose metabolism and accumulate also F-18 FDG
- The follow up of thyroid cancer belong to a Ia indication for FDG PET according GCC
- Where as I-131 is accumulated mainly in well differentiated recurrences and metastases, F-18 FDG accumulation mainly represents poor differentiation of tumor cells

F-18- FDG PET

- F-18 FDG detects most iodine –ve mets and represents rapid tumor growth and poor differentiation/prognosis
- Most of the I-131 –ve mets demonstrate F-18 FDG uptake
- F-18 FDG PET/CT imaging is particularly useful not only for identification and localization of non-iodine–avid metastases but also for predicting the course of disease as aggressive or indolent.
- F-18 FDG PET/CT has demonstrated prognostic value for survival in metastatic DTC, predicting a survival disadvantage for patients with positive PET compared with those with negative PET results

F-18- FDG PET

- In advanced DTC, brain MRI is recommended, because patients may have brain metastases in the absence of neurologic signs or symptoms and 18F-FDG PET is not reliable in the brain due to high brain glucose metabolism.
- Although DTC osseous metastases are typically osteolytic and highly vascularized, bone metastases can occasionally be detected on 99mTc-MDP bone scintigraphy or 18F-NaF PET/CT when 18F-FDG PET/ CT is negative

F-18- FDG PET

- Widespread use of 18F-FDG PET/CT imaging for evaluation of Tg+/scan– patients replaced routine use of mitochondrial imaging, the different uptake mechanisms of 99mTc-sestamibi and 18F-FDG in neoplastic cells provides the rationale for selected use of 99mTc-sestamibi in difficult patients with suspected metastatic disease not identified by other conventional imaging modalities (e.g., negative 131I WBS, US, 18F-FDG PET/CT, and CT)

F-18- FDG PET

- Somatostatin receptor (SSR) imaging with radiolabeled somatostatin analogs (99mTc-depreotide, 99mTc-EDDA/HYNIC-Tyr3-octreotide [Tektrotyd], 111In-octreotide, and 68Ga-DOTATATE/TOC/NOC)
- A substantial percentage of aggressive histologic variants of DTC (e.g., Hurthle cell, tall cell, insular variants) associated with locoregionally advanced and/or metastatic DTC exhibit cellular expression of SSR, which can be found independently of glucose transporter overexpression (in patients with negative 18F-FDG PET/CT imaging)
- SSR PET imaging also often provides complementary information in 18F-FDG + patients and appears to be especially promising in poorly differentiated and oxyphilic subtypes (Hurthle cell) metastatic DTC

DTC - RI Therapy for Ablation

➢ **Indications:**

- Standard procedure in High risk and low risk group
- Not indicated in very low risk group in case of large thyroid remnants (e.g. hemithyroidectomy
- Individual decision to be taken in very low risk group after total thyroidectomy

RAIT

- After total thyroidectomy, patients with thyroid cancer can receive radioactive iodine therapy (RAIT), according to different indications.

- Three main goals related to RAIT:

I. Remnant ablation
II. Adjuvant therapy
III. Therapy for persistent disease

UANM guidelines recommend a similar degree of TSHS to the American Thyroid Association guidelines based on the risk stratification of DTC.

The target baseline TSH level

HIGH-RISK GROUP

below 0.1 mIU / L during the course of thyroxine suppressive therapy

INTERMEDIATE RISK

0.1–0.5 mIU / L

LOW-RISK

0.5–2.0 mIU / L - patients who received RTI after thyroidectomy and had a TG level lower than the limit of detection

1. Clinical goals of RIT

2. Which patients benefit from RIT?

3. Management of RIT?

Radioiodine therapy

- Remnant ablation
- Adjuvant therapy
- Treatment of known disease

High risk DTC

RAI recommended in both publications
beneficial
patients with known persistent disease after surgery
patients with a high risk of recurrence

Intermediate risk DTC

SNMMI/EANM - 131I adjuvant treatment for all
ETA - selective use
Patient’s age
Histology of the tumour
Volume of nodal disease
Extranodal extension
Affected region of the neck

Low-risk DTC

RAI not recommended routinely for patients with <1cm DTC without locoregional and/or distant metastases
ETA - selective use
Tg, nodal metastases
SNMMI/EANM
Absolute Tg threshold cannot be established
Tg values - determine which activity to choose

Preparation for RIT

ETA
rhTSH preferred, except in metastatic disease
LID may be advised
SNMMI/EANM
rhTSH or THW
THW preferred in metastatic disease
1-2 weeks of LID

Approaches to RIT

SNMMI/EANM
risk-stratification
Functional imaging-guided
ETA
risk-stratification

131-I activity

ABLATION
ETA if performed 1.1 GBq
SNMMI/EANM 1.1 – 1.85 GBq
ADJUVANT
ETA ⩾ 3.7 GBq in high risk category
SNMMI/EANM 1.85 – 3.7 GBq
VIABLE DISEASE
ETA ⩾ 3.7 GBq
SNMMI//EANM: 3.7 – 5.6 GBq (small volume locoregional disease)
5.6 – 7.4 GBq (advanced locoregional and/or small volume distant metastatic disease)
⩾ 7.4 GBq or maximum tolerable safe activity (diffuse distant metastatic disease)

131-I activity

- Risk-adapted 131I therapy 1.11–1.85 GBq (30–50 mCi) 131I Remnant ablation
- Risk-adapted 131I therapy 1.85–3.7 GBq (50–100 mCi) 131I Adjuvant treatment
- Risk-adapted 131I therapy 3.7–5.6 GBq (100–150 mCi) 131I Treatment of small volume locoregional disease
- Risk-adapted 131I therapy 5.6–7.4 GBq (150–200 mCi) 131I Treatment of advanced locoregional disease and/or small volume distant metastatic disease
- Whole-body/-blood dosimetry > 7.4 GBq (> 200 mCi) 131I, maximum tolerable safe 131I activity Treatment of diffuse distant metastatic disease

Ablative I-131 Therapy - Preparation

- TSH >30 mU/L after 3-4 weeks withdrawal of thyroid fhormones or i.m inj of rhTSH (thyrogen 2x0.9mg)
- No thyroid tissue should be left after total thyroidectomy and I-131 remnant ablation
- Urinary iodine excreation <100 ug/g Crea
- RhTSH used in Low risk and/or multimorbidity
- Endogenous hypothyrosis prefered in High risk

Ablative I-131 Therapy - Procedure

- Fasting 4 h before and 1 hr after RI administration
- Single dose activity 1-5 (2-4) GBq
- Oral hydration
- Radiation protection
- Measurement of residual whole body activity at least daily
- WBS with residual activity (<250 MBq)

Evaluation of Ablative I-131 Therapy -

- Diagnostic I-131 WBS
- hTG serum measurement

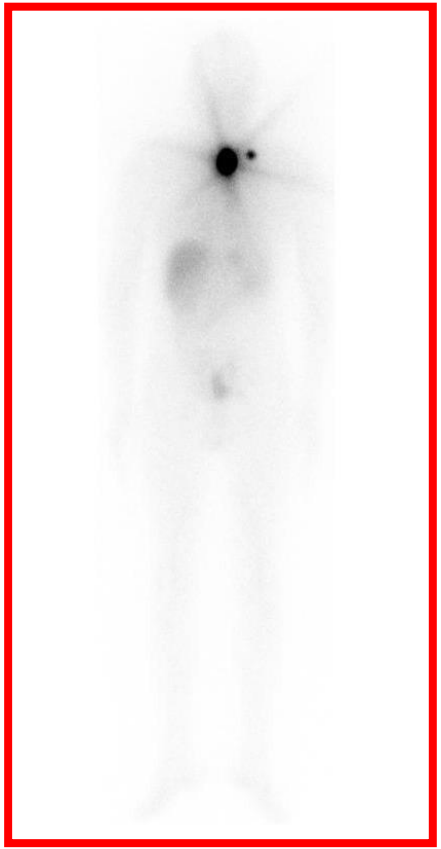
Under exogenous TSH stimulation

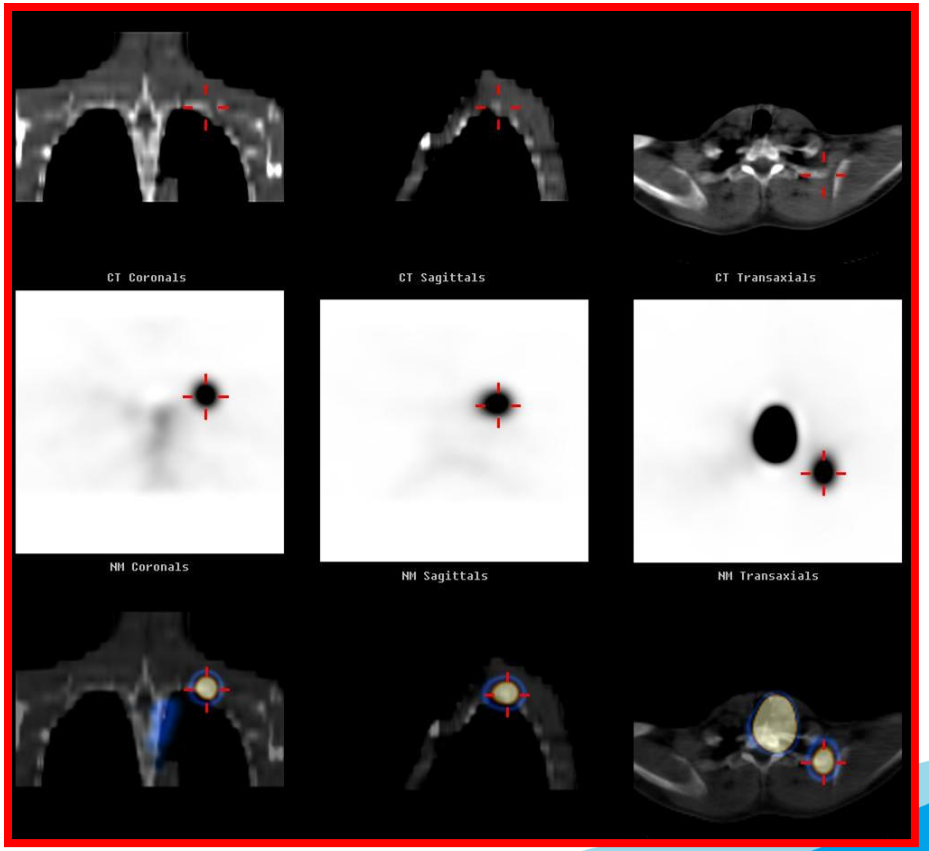
3-6 months post ablation

Criteria for verifivation of Complete Ablation

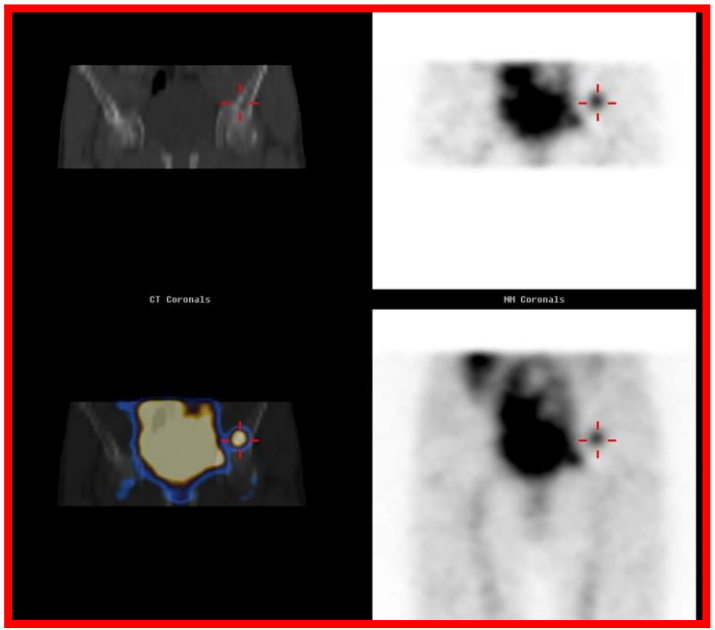
- No I-131 accumulation in neck, no pathological locations of I-131 activity
- hTG < 0.3 -1 ng/ml, depending on sensitivity of test

WBS after therapeutic dose of ^{131}I for DTC

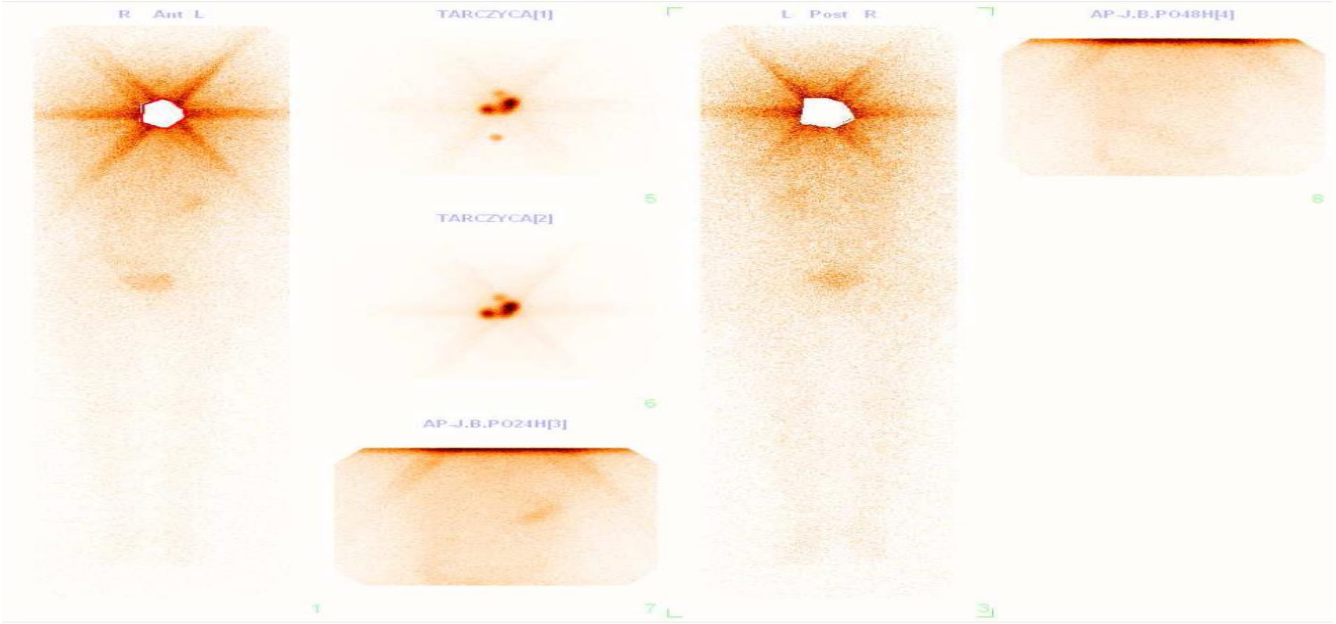




WBS after therapeutic dose of ^{131}I for DTC

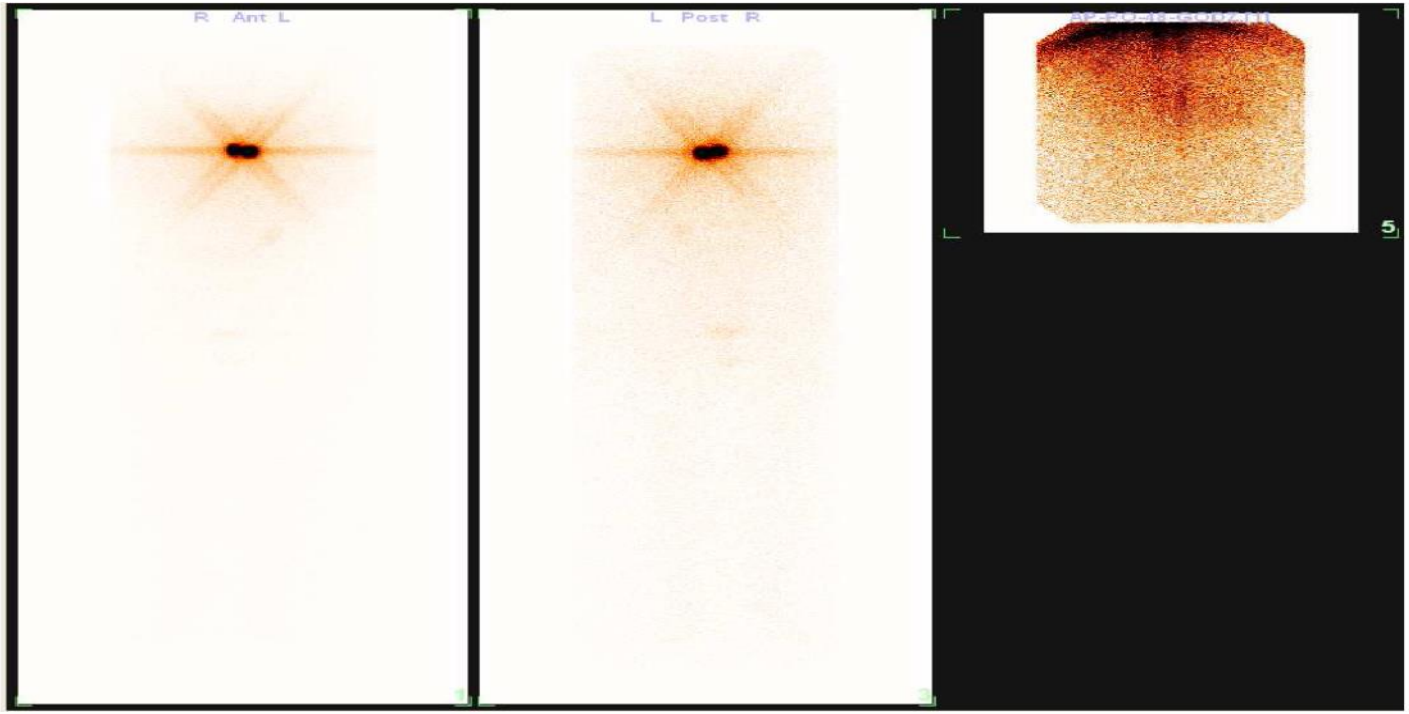


I-131 WBS



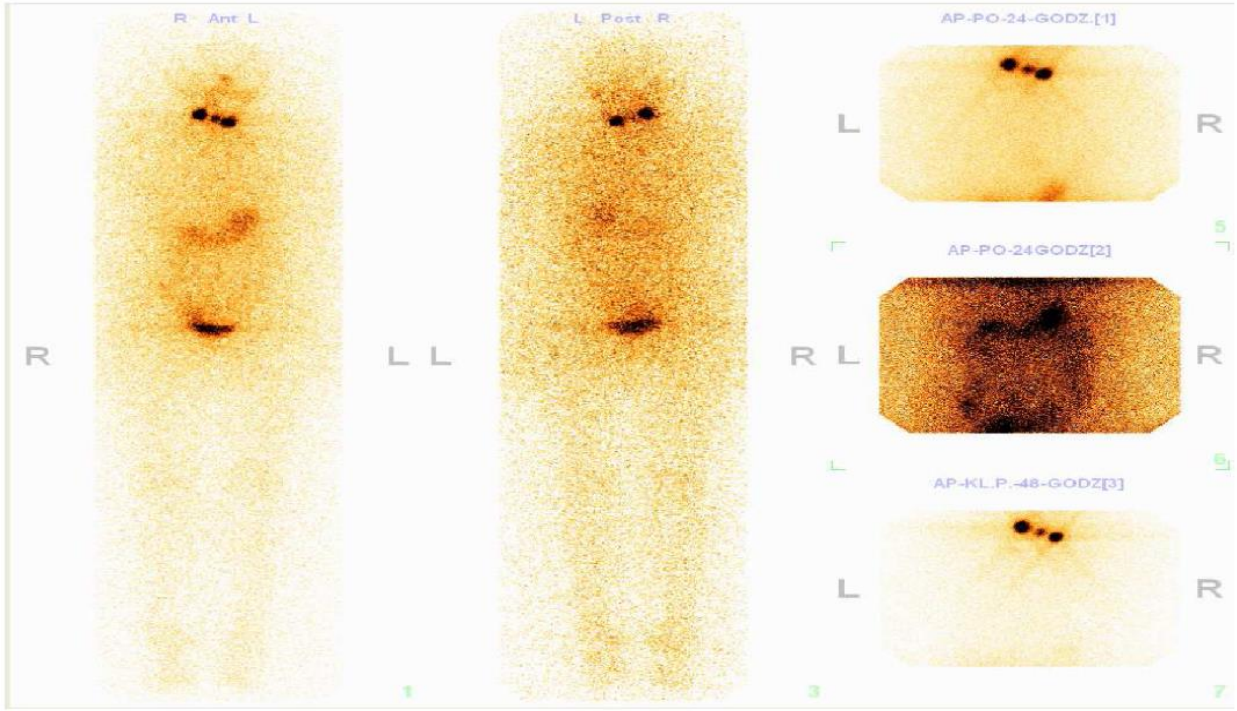
)pis:
V obrazie scyntygraficznym całego ciała po podaniu I-131 (120MBq) uwidoczniły dwa
większe ogniska odpowiadające kikutom płatów tarczycy(wychwyt ok 18%). W pozostałej
części fizjologiczne gromadzenie znacznika w rzucie żołądka, jelit, pęcherza moczowego.
Badanie wykonano przy poziomie TSH=49,09uIU/ml

I-131 WBS



Opis:
W obrazie scyntygraficznym całego ciała uwidoczniły się dość duże dwa ogniska gromadzenia znacznika w rzucie tarczycy(wychwyt ok12%). Ponadto stwierdza się fizjologiczne gromadzenie znacznika w rzucie pęcherza moczowego, jelit. Badanie wykonano przy poziomie TSH 21uIU/ml

I-131 WBS



Opis:
W obrazie scyntygraficznym całego ciała po podaniu I-131 (120MBq) uwidoczniły się dwa większe ogniska oraz jedno mniejsze w rzucie tarczycy (wychwyt ok 1,4%). W pozostałym układzie stwierdza się gromadzenie znacznika w rzucie żołądka, jelit, pęcherza moczowego. Badanie wykonano przy poziomie TSH=33,37 uIU/ml

Conclusion

- **In the follow up of differentiated thyroid cancer US and Tg (T4 off or under rhTSH) are most effective and should be performed at each visit**
- **The sensitivity of post – therapeutic I-131 WBS (3700-11100 MBq) is much higher (>70) compared to a diagnostic WBS**

Conclusion

- **F-18 FDG PET is a new methods to follow up patients with DTC**
- **F-18 FDG detects most iodine –ve mets and represents rapid tumor growth and poor differentiation/prognosis**

Thank you for your attention