

# **FDG PET & PET•CT in the Evaluation of Thyroid Cancer**

## Thyroid carcinoma

- 37,340 estimated new cases with 1,590 estimated deaths in 2008
  - 28,410 will occur in women, and 8,930 in men
- Most frequent in iodine rich areas, radiation major etiological factor
- Five year survival approximately 97%
- 20% patients develop locoregional metastases
- Metastasis to regional lymph nodes common (53% of all mets.)
- Distant metastases in 5 -10% cases - mostly follicular cancer
- Adverse prognostic factors include: age>45; metastases at time of diagnosis; larger primary tumor; anaplastic histology; poor radioiodine accumulation

## T categories for Thyroid Cancer

TX	<b>Primary tumor cannot be assessed</b>
T0	<b>No evidence of primary tumor</b>
T1	<b>Tumor is 2 cm or smaller across, limited to the thyroid</b>
T2	<b>Tumor 2 - 4 cm across , limited to the thyroid</b>
T3	<b>Tumor is larger than 4 cm or has begun to grow into nearby tissues outside the thyroid</b>
T4a	<b>Tumor of any size and has grown extensively beyond the thyroid gland into nearby tissues of the neck</b>
T4b	<b>Tumor has grown either back toward the spine or into nearby large blood vessels</b>

# N and M categories for Thyroid Cancer

<b>NX</b>	<b>Regional (nearby) lymph nodes cannot be assessed</b>
<b>N0</b>	<b>No spread to nearby lymph nodes</b>
<b>N1</b>	<b>Spread to nearby lymph nodes</b>
	<b>N1a: Spread to lymph nodes around the thyroid in the neck (cervical)</b>
	<b>N1b: Spread to lymph nodes in the sides of the neck (lateral cervical) or the upper chest (upper mediastinal)</b>
<b>MX</b>	<b>Presence of distant metastasis cannot be assessed</b>
<b>M0</b>	<b>No distant metastasis</b>
<b>M1</b>	<b>Distant metastasis is present, involving distant lymph nodes, internal organs, bones, etc.</b>

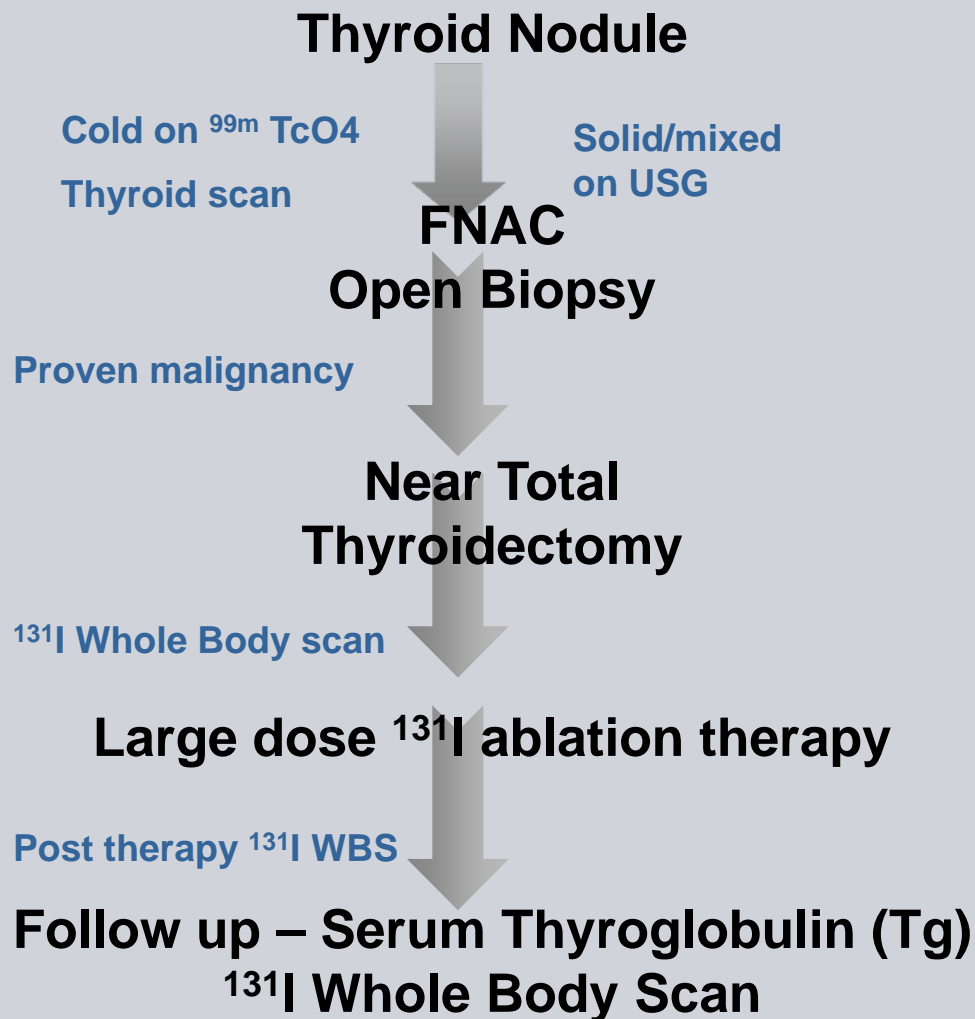
## Papillary carcinoma

- Most common of all thyroid malignancies
- Peak incidence 35-45 yrs age group
- Low grade malignancy
- Usually multi-centric histology
- Excellent prognosis
- Lymph nodes usual site of metastasis
- Lung metastases occasionally seen
- Distant metastases rare
- Most important prognostic factor: age of patient

## Follicular carcinoma

- Tend to occur in older patients
- Slow growing but metastasize to bone, liver and lungs (not lymph nodes)
- May closely resemble an adenoma
- Prognosis: tumor invasion, metastases, tumor differentiation
- Some patients present with distant metastases

## Standard approach to diagnosis & management



Tg elevation highly sensitive for thyroid ca recurrence

<sup>131</sup>I WBS requires withdrawal of thyroxine for TSH stimulation

Presence of metastases requires multiple large dose radio iodine therapy

Combination radiotherapy often used for complicated metastasis

## Thyroid cancer staging

- Majority of tumor recurrence, lymph node and distant metastases associated with high thyroglobulin (Tg) levels and iodine avidity on  $^{131}\text{I}$  whole body scans
- Some distant metastases do not take up iodine - unfavorable prognosis
- Lack of iodine uptake related to low expression of Na-I symporter gene
- $^{131}\text{I}$  uptake higher in well differentiated tumors
- Metastatic tumors may dedifferentiate and lose iodine avidity
- Most metastases associated with elevated Tg levels
- Rising serum Tg > 10 ng/ml ~ indicates metastases in majority of patients
- FDG PET shows high glucose uptake in  $^{131}\text{I}$  negative Tg positive metastasis
- Flip flop phenomenon- Low  $^{131}\text{I}$  / High FDG uptake
- High  $^{131}\text{I}$  / Low FDG uptake
- High FDG uptake- sign of increased mitotic activity/ tumor dedifferentiation/adverse prognostic indicator

## FDG and $^{131}\text{I}$ uptake in thyroid cancer

- 41 pts with differentiated thyroid cancer post surgery &  $^{131}\text{I}$  ablation studied with FDG PET and  $^{131}\text{I}$  WBS
- **In 90% cases alternating uptake pattern visualized-  $^{131}\text{I}$  trapping metastases with no FDG uptake and FDG trapping metastases with no  $^{131}\text{I}$  uptake**
- In 6 pts with rising Tg levels and negative  $^{131}\text{I}$  WBS- FDG PET demonstrated avid neck node metastases
- Tumors with remaining functional differentiation for hormone synthesis and iodine uptake have low glucose metabolism in more than 95% of cases
- Tumors without functional differentiation with low  $^{131}\text{I}$  uptake show high glucose metabolism
- **FDG uptake seems to be an indicator of poor functional differentiation, and possibly higher malignancy, in thyroid cancer.**

## FDG PET in papillary thyroid cancer

- 54 pts with papillary cancer, post surgery and  $^{131}\text{I}$  ablation with negative  $^{131}\text{I}$  scan underwent FDG PET
- 33 pts proven to have metastasis by biopsy & follow up; 21 pts in remission
- FDG PET +ve for metastasis in 31 (94%) pts. Thyroglobulin levels higher in 18 (55%) pts
- 15 pts with mets – normal Tg levels- 14 pts had +ve FDG PET
- 21 pts without mets- 16 pts with normal Tg levels- 20 pts had –ve FDG PET
- FDG PET Sensitivity 94% Specificity 95%
- Thyroglobulin Sensitivity 55% Specificity 76%
- High incidence of false –ve Tg- high +ve rate of anti thyroglobulin antibodies
- 5 pts- FDG PET +ve for mets- -ve Tg- metastatic small cervical/mediastinal nodes- -ve Tg probably related to small tumor mass
- Pts with distant metastasis- all +ve Tg +FDG PET
- **PET determined superior to Tg in sensitivity for  $^{131}\text{I}$  negative papillary ca**

Value of FDG PET in papillary thyroid cancer with negative  $^{131}\text{I}$  whole body scan.

Chung et al, JNM 1999; 40(6):986-92

## Clinical impact on patient management

- 37 pts with thyroid cancer, post surgery &  $^{131}\text{I}$  ablation with **rising Tg and negative  $^{131}\text{I}$  whole-body scan** studied with FDG PET
- FDG PET performed while patient on thyroxine therapy
- **FDG PET demonstrated metastases sites in 28 pts (76%) and accurately localized disease in 89% of tumor sites**
- 10 pts (Gr I) showed positive on conventional imaging (USG, CT, MR): 9 pts positive with PET. PET confirmed 17 out of 18 known tumor sites. PET also detected additional 11 tumor sites not detected by other imaging modalities
- 27 pts (Gr II) were negative on conventional imaging: PET positive in 19 pts. PET demonstrated 44 tumor sites in these patients
- **Detection rate with PET higher stages III and IV (80%) than for stages I and II (47%)**
- PET findings changed management in 27 pts – 23 pts underwent surgery for residual tumor; 4 pts underwent external RT

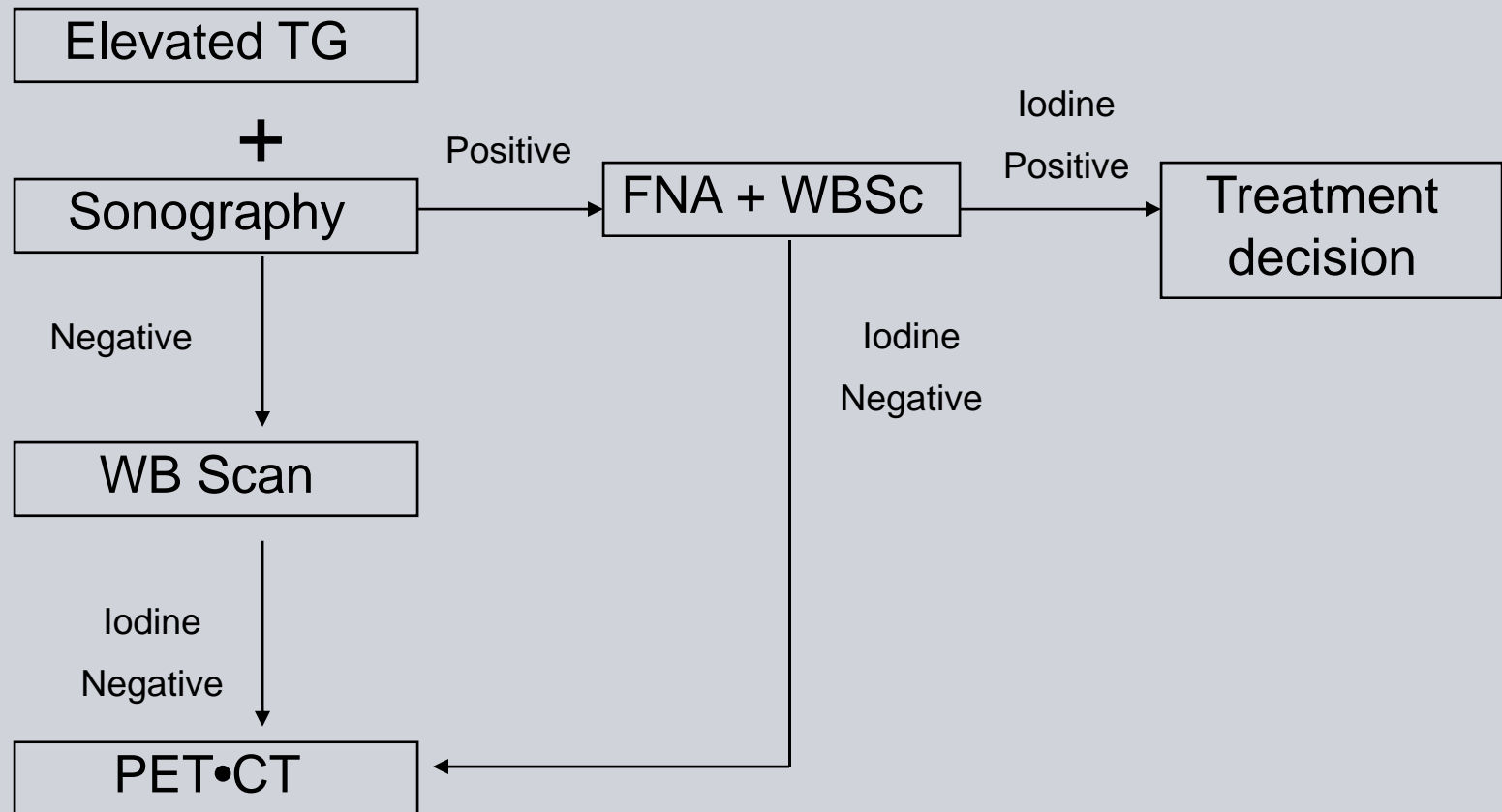
Clinical impact of FDG PET in thyroid ca pts with elevated thyroglobulin levels and negative  $^{131}\text{I}$  scanning results after therapy. Helal et al, *JNM* 2001; 42:1464-1469

## Diagnostic accuracy and impact on pt management

- 40 pts with DTC with suspected iodine negative tumor tissue evaluated with FDG PET•CT – (Tg +ve and <sup>131</sup>I WBS –ve)
- 127 lesions in 40 pts evaluated - PET•CT; PET only; PET & CT side by side
- **Diagnostic accuracy - 93% PET•CT 78% PET only**
- Sensitivity 79% Specificity 76% by FDG PET only
- 17 out of 23 pts with suspicious FDG foci - PET•CT improved localization vs. side by side PET and CT
- 57% of all lesions(73/127) were discordant on side by side PET and CT reading and required integrated PET•CT for correct evaluation
- **PET•CT led to change in management in 48% cases**
- In 10 pts surgical resection was extended by FDG PET•CT identification of additional sites of Iodine negative recurrence
- 3 patients w/ small lung metastases(<6mm) diagnosed by PET•CT but –ve on PET alone
- Futile surgery prevented in 3 patients

Integrated PET•CT in differentiated thyroid cancer: Diagnostic accuracy and impact on patient management. Palmedo et al: JNM April 2006 47:616-624

# Algorithm for clinical use of PET•CT with <sup>18</sup>F FDG in differentiated thyroid carcinoma



Integrated PET/CT in Differentiated Thyroid Cancer: Diagnostic Accuracy and Impact on Patient Management. Palmedo et al, JNM April 2006; 47: 616-624

## Papillary thyroid carcinoma: PET•CT with stimulation with TSH

- 15 pts with Papillary Ca Thyroid- <sup>131</sup>I WBS –ve Tg +ve evaluated with FDG PET•CT
- Patients were prepared for PET•CT imaging with thyroid hormone withdrawal ( $n = 7$ ) or recombinant human TSH ( $n = 8$ )
- PET•CT scans revealed active foci in 9 pts (40%) - 4 prepared with hypothyroidism, and 5 with exogenous TSH
- FDG PET•CT showed active disease in patients with persistently elevated but relatively low Tg values (~ 14 µgm/lit)
- Thyroid-stimulating hormone (TSH) stimulation with thyroxine withdrawal or recombinant TSH administration improves lesion detectability and sensitivity of FDG PET•CT

Thyroid-Stimulating Hormone–Stimulated Fused PET/CT in the Evaluation of Recurrence in <sup>131</sup>I-Negative Papillary Thyroid Carcinoma. Saab et al, Thyroid Mar 2006; Vol. 16, 3: 267-272

## Differentiated thyroid ca: TSH stimulates FDG uptake

- 30 pts with +ve thyroglobulin and –ve  $^{131}\text{I}$  WBS and –ve CT/MR underwent FDG PET under TSH suppression with thyroxine replacement and under exogenous TSH stimulation by injection of rhTSH
- FDG uptake quantitated using tumor to background ratio (TBR) and SUV
- FDG PET identified more lesions with rhTSH as compared to that with TSH suppression with thyroxine replacement
- FDG PET with TSH suppression identified 45 lesions in 9 patients and 82 lesions in 19 patients with rhTSH
- Mean TBR of +ve FDG lesions was 2.54 under TSH suppression and 5.51 with rhTSH
- Mean SUV of FDG +ve lesions under TSH suppression was 2.05 and 2.77 with rhTSH
- TBR and SUV increased only marginally under TSH stimulation in inflammatory nodes
- **Study proves that TSH stimulates FDG uptake in differentiated thyroid ca and that FDG PET is more accurate under rhTSH than under TSH suppression by thyroxine replacement**

Influence of rhTSH on [(18)F]fluorodeoxyglucose uptake by differentiated thyroid carcinoma.  
Petrich et al, EJNM 2002 May; 29(5): 641-7

## **Diagnostic value of CT in pulmonary metastases in differentiated thyroid carcinoma**

- Lung mets occur in 2-20% of all thyroid cancers- more common in papillary cancer
- Good response to <sup>131</sup>I therapy for functioning lung mets
- Chest X-ray normal in 50% of pts with lung mets
- Micronodules <1 cm common with lung mets

## Diagnostic value of CT in pulmonary metastases in differentiated thyroid carcinoma.....continued

- 42 pts with lung mets studied- 30 papillary 12 follicular cancer
- All had increased Tg and +ve  $^{131}\text{I}$  scan for lung mets
- All pts underwent large dose  $^{131}\text{I}$  therapy- 10 pts completely disease free after therapy
- 22 pts with lung mets underwent HRCT shortly after diagnosis of lung met
- 18 out of 22 pts positive on HRCT
- 14 pts normal Chest X-ray--- 10 of these had +ve HRCT
- 8 pts abnormal Chest X-ray- All +ve on HRCT
- 4 pts- -VE HRCT +VE  $^{131}\text{I}$  WBS for lung mets
- HRCT –VE lung mets and micronodular lung mets- best survival

**Conclusion:** HRCT misses  $^{131}\text{I}$  +ve early lung metastases for thyroid ca

## Diagnostic value of CT in pulmonary metastases in differentiated thyroid carcinoma.....continued

- 82 pts with non functioning  $^{131}\text{I}$  –ve metastatic thyroid cancer evaluated with HRCT &  $^{99\text{m}}\text{Tc}$  MIBI SPECT
- 8 pts positive for lung metastases with HRCT &  $^{99\text{m}}\text{Tc}$  MIBI- disease confirmed on follow-up

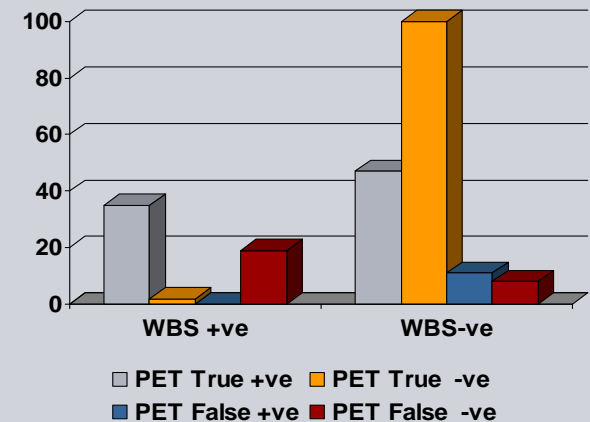
**Conclusion:** HRCT accurate for nonfunctioning lung metastases in thyroid carcinoma

## Relationship between FDG PET results and thyroglobulin levels in thyroid cancer

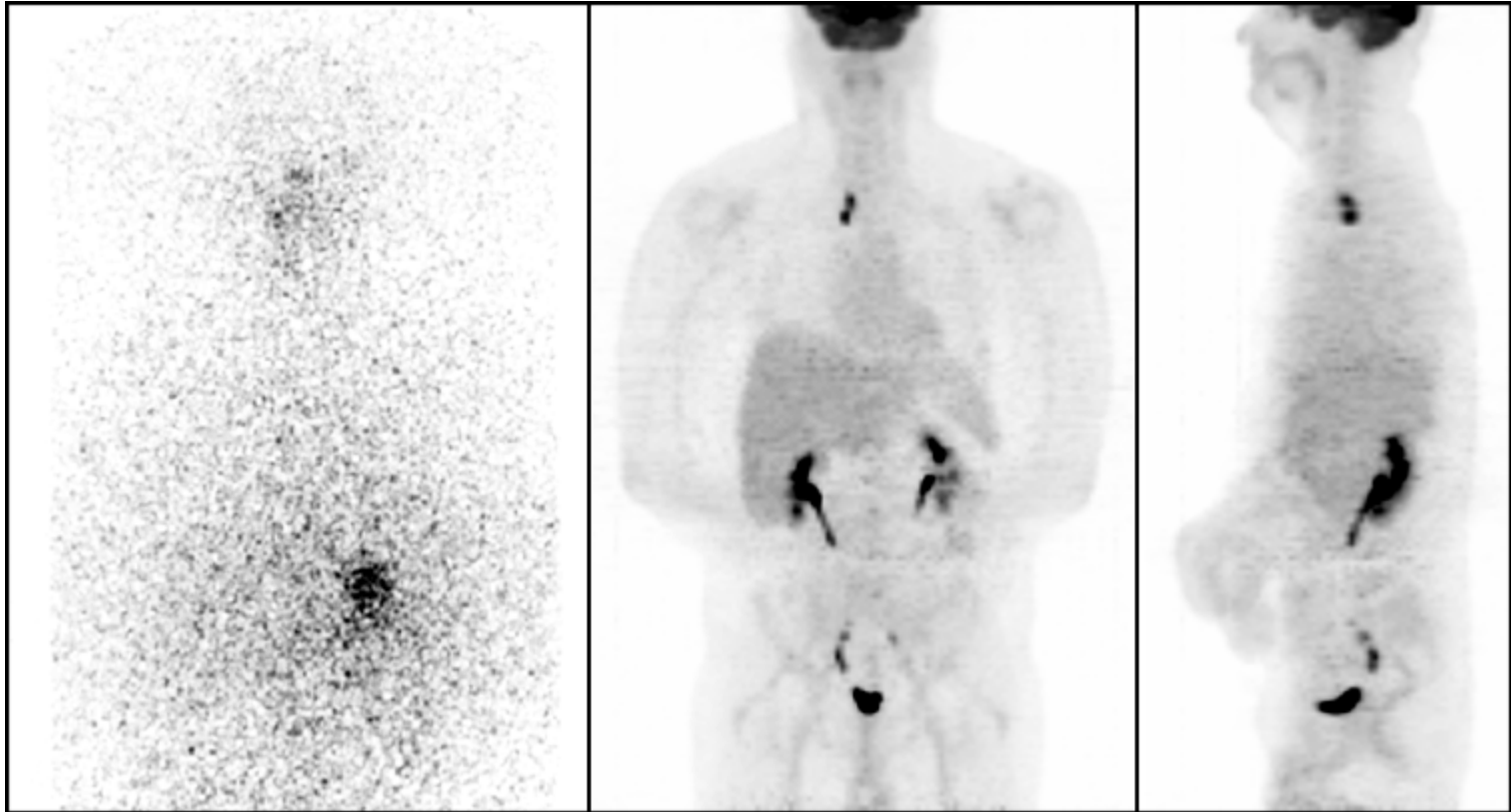
- FDG PET shows higher sensitivity for lesion detection in pts with higher Thyroglobulin levels in pts with negative  $^{131}\text{I}$  WBS
- Low Thyroglobulin levels ( $<5\mu\text{g/L}$ ) associated with lower detection rate with FDG PET- often related to small nodal metastasis- smaller tumor volume
- TSH stimulation increases Tg level and FDG uptake in pts with small tumor volume – increased sensitivity

## FDG PET in thyroid carcinoma- results of a multicentre study

- 222 pts studied with Tg,  $^{131}\text{I}$  WBS and FDG PET. 166 pts had –ve  $^{131}\text{I}$  WBS
- Sensitivity for FDG PET – 75% for whole patient group; 85% for  $^{131}\text{I}$  WBS –ve patient group(166pts)
- Overall sensitivity of FDG PET was 77.3% for pts with Tg <5  $\mu\text{g}/\text{ml}$  & 75.6% for pts with Tg > 5 $\mu\text{g}/\text{ml}$
- Patients with  $^{131}\text{I}$  WBS +ve mets- FDG PET sens. 72.7% with Tg<5  $\mu\text{g}/\text{ml}$  & 64.3% for with Tg > 5 $\mu\text{g}/\text{ml}$
- Patients with  $^{131}\text{I}$  WBS –ve mets- FDG PET sensitivity 81% with Tg <5 $\mu\text{g}/\text{ml}$  & 87.5% with Tg >5 $\mu\text{g}/\text{ml}$
- Specificity of FDG PET-90% for whole patient group
- $^{131}\text{I}$  WBS – Sensitivity 50% Specificity 99% for whole patient group
- Combined analysis of FDG PET and  $^{131}\text{I}$  WBS- Tumour tissue missed in only 7% cases
- Study included 20 Hurthle cell tumors- 18 WBS –ve 2 WBS +ve- 19 FDG PET +ve

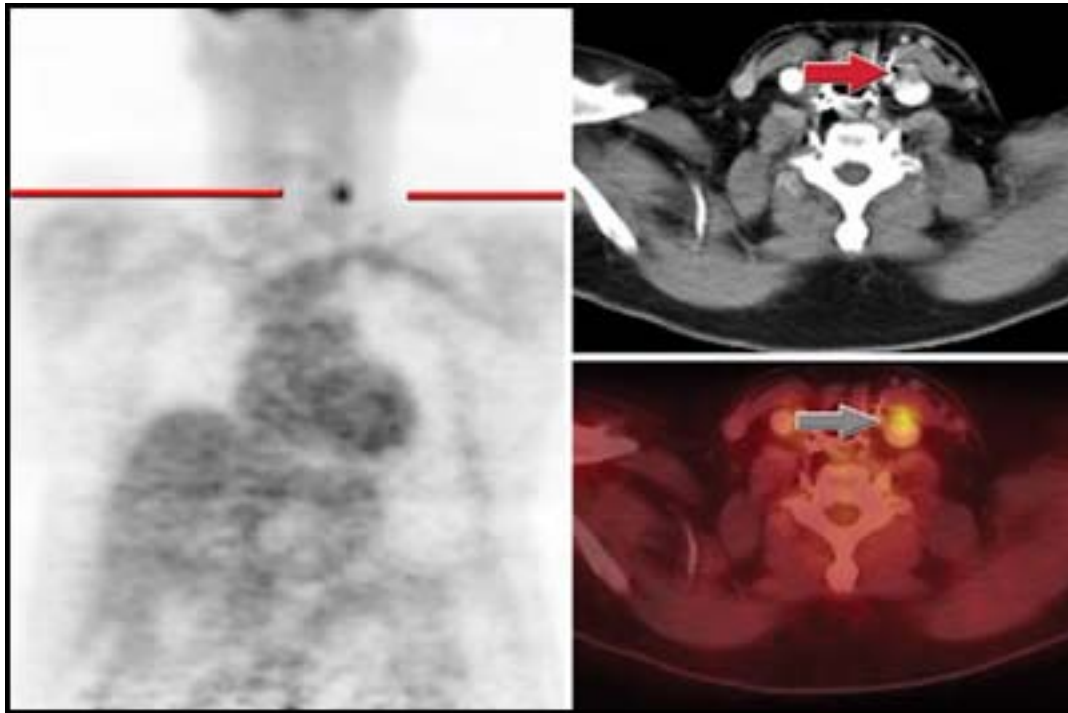


## Recurrent papillary thyroid cancer $^{131}\text{I}$ / FDG flip-flop



As thyroid cancer cells dedifferentiate, they lose the ability to concentrate iodine, become more aggressive and metabolically active, concentrating FDG

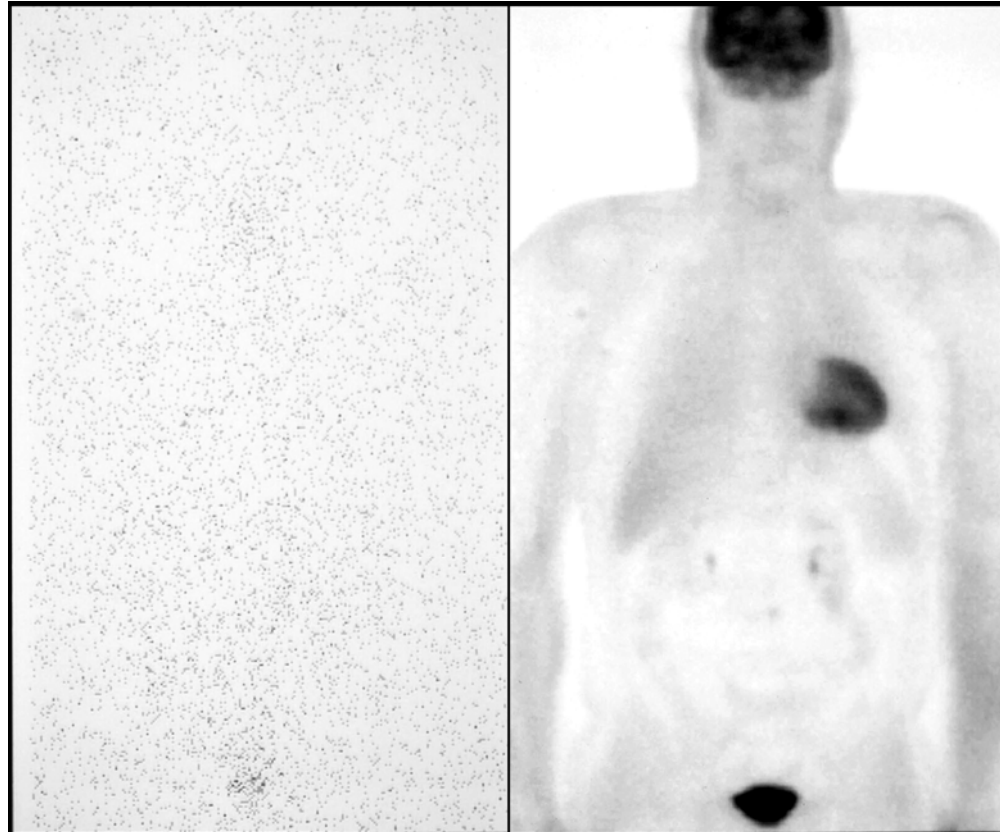
## Restaging papillary thyroid cancer



56 year old s/p thyroidectomy with rising Tg and negative  $^{131}\text{I}$  scan. PET demonstrates focal area of increased uptake of FDG in the left neck inferiorly, localized on PETCT to a small left level 4 lymph node. This small, normal sized jugulodigastric lymph node was resected and found to be positive for recurrent papillary carcinoma.

## Restaging papillary thyroid cancer

$^{131}\text{I}$  WBS



FDG PET

55 year old man, s/p thyroidectomy, now asymptomatic with elevated thyroglobulin level and negative  $^{131}\text{I}$  scan. PET demonstrated single focal area of FDG uptake in lumbar spine region

# Papillary thyroid cancer

**FDG PET**



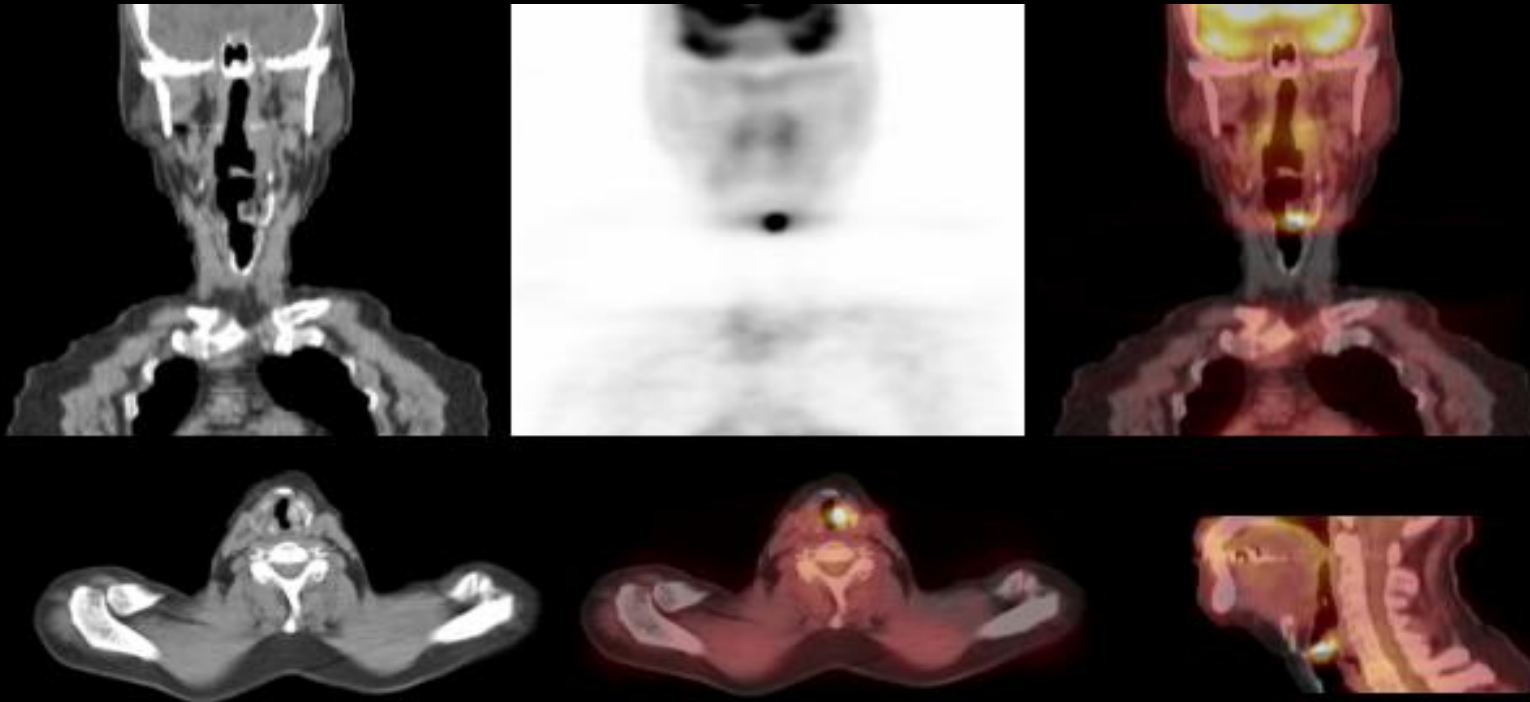
**MRI**

**Sagittal View L Spine**

PET confirmed an isolated metastasis by MRI.

Patient received external beam radiation therapy with good long term outcome

## Recurrent thyroid cancer vs. second primary



Status post near total thyroidectomy and  $^{131}\text{I}$  Rx 1995. Rising thyroglobulin level, negative  $^{131}\text{I}$  scan, negative CT of the chest and neck.

PET findings: positive FDG uptake anterior neck. PETCT localized lesion to area of L false vocal cord – mets versus second primary.

## Conclusion

- **FDG PET shows high sensitivity in differentiated thyroid carcinoma which is  $^{131}\text{I}$  whole body scan negative**
- **FDG PET sensitivity and specificity higher in patients with thyroglobulin values  $>5$   $\mu\text{g/ml}$**
- **Lower radioiodine uptake and increased FDG uptake related to aggressive tumor and poor prognosis**
- **TSH stimulation increases FDG accumulation in tumor tissue stages cervical and ovarian cancers with high diagnostic accuracy**
- **PET•CT is superior to PET only for lesion localization and overall sensitivity and accuracy**