Thyroid Cancer: Imaging Techniques (Nuclear Medicine)

Andrei Iagaru, MD
Introduction

- There are approximately 56,460 new cases of thyroid carcinoma annually in the United States, and the overall incidence continues to rise.
- Women are more likely to have thyroid cancer at a ratio of 3:1.
- Thyroid cancer can occur in any age group, although it is most common after age 30 and its aggressiveness increases significantly in older patients.

Incidence of thyroid cancer

Thyroid cancer cases and deaths

>56,460 in 2012

Total cases, women, men: Total deaths, women, men

Deaths
2012 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
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<tr>
<td>Kidney</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
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<tr>
<td>Oral cavity</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
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</tbody>
</table>

2012 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>289,550</td>
<td>270,100</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Liver &amp; bile duct</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26%</strong></td>
<td><strong>26%</strong></td>
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</table>

Thyroid cancer: ethnic influence

- 3.3/100,000 African American women
- 6.2/100,000 Hispanic women
- 6.5/100,000 White women
- 9.1/100,000 Hawaiian women
- 10.5/100,000 Vietnamese women
- 14.6/100,000 Filipino women
- 32.5/100,000 Filipino women 55-69 yrs
- Papillary thyroid cancer (PTC) is the most common of all thyroid cancers, comprising approximately 70-75% of follicular cell derived cancers.

- Papillary cancer can occur in any age group, although its peak incidence is in the fourth and fifth decades of life.

- It is more common in women than in men (2.5:1).
The main risk factors for the development of PTC include a history of childhood head and neck radiation for benign conditions, or a family history of papillary cancer.

PTC typically has an excellent prognosis, with overall 10-year survival rates estimated at 80-90%.

Age over 45 years at time of diagnosis, tumor size over 4 cm, extrathyroidal extension of tumor, lymph node recurrence, and distant metastases negatively influence survival.
PTC: FNA shows large cells and nuclei, and their cytoplasm has a “ground glass” appearance. Nucleoli are prominent and the nuclei have clefts, grooves and “holes” due to intranuclear cytoplasmic inclusions.
PTC: Surgical specimen showing the classical histologic appearance of papillary cancer, with papillary structure and no follicles or colloid.
Unlike papillary and follicular thyroid cancers, which arise from thyroid hormone producing cells, medullary thyroid cancer (MTC) is a neuroendocrine tumor of the parafollicular or C cells of the thyroid gland.

A characteristic feature of this tumor is the production of calcitonin.

The C cells originate from the embryonic neural crest; as a result, medullary carcinomas often have the clinical and histologic features of other neuroendocrine tumors such as carcinoid and islet-cell tumors.
MTC constitutes about 5-10% of all thyroid malignancies.

Most medullary thyroid carcinomas are sporadic. However, some are familial as part of the multiple endocrine neoplasia type 2 (MEN2) syndrome.

Overall 10-year survival rates are 90% when all the disease is confined to the thyroid gland, 70% with spread to cervical lymph nodes, and 20% when spread to distant sites is present.
MTC: FNA with immunostaining for calcitonin reveals nuclei of the tumor cells placed eccentrically, larger and more pleomorphic than those of normal follicular cells. Immunocytologic staining for calcitonin is positive. The background contains many RBC’s that nonspecifically take up the stain.
MTC: Surgical specimen showing typical histologic appearance of medullary carcinoma.
Tg Synthesis

Tg

Thyroperoxidase

I-

I-Tg

Lysosomal Digestion

T4, T3

MIT, DIT

Pendrin

I-

Colloid

Capillary

Tg

T4, T3

Na+

NIS

L

I-

T4, T3
Diagnostic whole body $^{123}$I scan

- Proof of elevated TSH
  - How high should it be?
  - Withdrawal of thyroid hormone
  - rhTSH

- Measurement of Tg when TSH is stimulated

- Low iodine diet

- Which radionuclide of iodine?
How high should TSH be?

- 25 mU/L
- 30 mU/L
- 50 mU/L
- In one of our published reports the mean TSH value was 121 mU/L

ATA Management Guidelines: “TSH > 30 mU/L”
Rating B
Withdrawal of thyroid hormone vs. rhTSH

- 4-6 week delay before testing and treatment
- Physical symptoms and signs of hypothyroidism
- Psychological symptoms of hypothyroidism

- 2 week delay for testing and treatment
- No signs and symptoms of hypothyroidism
Thyroglobulin

- Tg values depend on amount of thyroid tissue present
- Tg levels increase with increase in TSH
- About 25% of patients with papillary cancer have antibodies to Tg
  - Antibodies alter validity of measurement
  - Antibodies probably benefit prognosis

ATA recommendation: Tg measured every 6-12 months using IRMA (same laboratory with antibody assay)
Rating A
Day 13 of low iodine diet

Christmas card from patient, presented with permission

ATA recommendation: Low-iodine diet for 1-2 weeks
Rating B
Iodine uptake and iodine excretion

Unusual sites of iodine uptake

Tissues that have NIS receptor
- Breast
- Thymus
- Salivary glands

Secretion and excretion of iodine

Other pathologies

Carlisle, Lu and McDougall
Nucl Med Comm 2003;24:715-735

Shapiro et al in Thyroid Cancer edited by Wartofsky and Van Nostrand Humana Press 2006, Chap 16

Courtesy of Dr McDougall
\( ^{123}\text{I}/^{131}\text{I} \): false positive scans

Unusual sites of Iodine uptake

- Tissues with NIS receptor
- Secretion and excretion of iodine
- Other pathologies

- Saliva
- Milk
- Gastric fluid
- Bile/stool
- Sweat

Courtesy of Dr McDougall
$^{131}$I trapping in thymus is uncommon, but not rare!

Davidson and McDougall
*Nucl Med Comm*
2000;27:425-430
$^{123}\text{I}/^{131}\text{I}$: false negative scans
$^{124}$I PET/CT in DTC
52 women, 17 men; 17 - 83 years old (average: 46)

124I PET/CT and a whole body scan were done, before and after 131I ablation, respectively

124I PET/CT and 131I WBS matched in 58/67 patients (86.6%)

124I PET/CT detected more disease than 131I WBS in 5/67 patients (7.5%), mainly lymph node involvement

131I WBS detected more disease than 124I PET/CT in 4/67 patients (4.9%), including lymph nodes and disseminated 131I-avid lung metastases
Disseminated iodine-avid lung metastases in differentiated thyroid cancer: a challenge to $^{124}$I PET

- 39 women, 31 men; 12 - 83 years old (average: 50)
- $^{124}$I PET/CT and a whole body scan were done, before and after $^{131}$I ablation, respectively
- Quantitative data consisted of absolute lung $^{124}$I activity concentrations and lung-to-background (L/B) $^{124}$I uptake ratios
- Only 1/7 patients with disseminated lung metastases on the $^{131}$I WBS had visible disseminated lung uptake on the $^{124}$I PET/CT
- L/B ratios overlapped between the subjects with/without $^{124}$I uptake in disseminated lung metastases to an extent that an unequivocal diagnosis based solely on this criterion was impossible in some patients
Some differentiated thyroid cancers lose the ability to trap iodine.

How would you determine extent of disease in this situation?
Normal thyroid: little or no uptake of $^{18}\text{F}$ FDG
Diffusely increased uptake in the thyroid

Diffuse uptake most likely chronic lymphocytic thyroiditis

$^{18}$F FDG PET in 1,102 healthy subjects

Diffuse uptake in the thyroid in 36 patients

- 33 women
- 27 positive thyroid antibodies

Ultrasound consistent with chronic thyroiditis or with Graves’ disease if the patient is thyrotoxic

Yasuda et al. Radiology 1998;207:775-8
123I scan positive; Tg 1,000 ng/ml

PET very positive; surgery and XRT
63-year-old woman with follicular thyroid cancer. Whole body $^{123}$I scintiscan is negative. FDG PET/CT shows multiple lung metastases.
57-year-old man with papillary thyroid cancer. $^{123}$I scintigraphy and FDG PET/CT show lesions in the thyroid bed (arrows), mediastinal lymph nodes (black arrowheads) and the left hip (white arrowheads).
\(^{123}\text{I}\) scan positive; Tg >3,000 ng/ml

PET very positive; surgery and XRT
\(^{18}\)F FDG PET/CT is commonly used when there is discordance between elevated Tg and negative \(^{123}\)I whole-body scans (WBS)

When used in combination, \(^{18}\)F FDG PET/CT and \(^{123}\)I WBS may result in tumor foci being missed in as few as 7% of cases, suggesting a complementary role for the two imaging modalities
2-Deoxy-2-\(^{18}\text{F}\)fluoro-d-glucose-Positron Emission Tomography and Positron Emission Tomography/Computed Tomography Diagnosis of Patients with Recurrent Papillary Thyroid Cancer

Andrei Iagaru, MD, Rinat Masamed, MD, Peter A. Singer, MD, Peter S. Conti, MD, PhD

- 14 women & 7 men, 26-75 years old (average: 50 ± 16)
- All patients had papillary cancer
Serum Tg levels were 1.0-10.0 ng/ml (average: 4.5 ng/ml) in the patients with negative PET scans (white) and 1.0-38.0 ng/ml (average: 16.8 ng/ml) in the patients with positive scans (black) – $P$: 0.029
Local thyroid cancer recurrence, as well as pulmonary metastases in a 75-year old woman with Tg=36 ng/ml.
The sensitivity and specificity of $^{18}$F FDG PET for disease detection in this cohort were 88.2% (95% CI: 65.7-96.7) and 75% (95 % CI: 30.1-95.4), respectively.

Detectable levels of Tg, even in the presence of a negative $^{123}$I WBS or anatomic imaging, should prompt imaging with $^{18}$F FDG PET/CT.

Tg values less than 10 ng/ml can produce both positive and negative PET scans, while levels higher than 10 ng/ml appear to correlate with successful tumor identification on PET scans.
F-18 FDG PET/CT in the Management of Thyroid Cancer

Andrei Iagaru, MD, Judith Kalyniak, MD, PhD, and I. Ross McDougall, MD, PhD

- 44 women & 32 men, 20-81 years old (average: 51.1±18.1)
- 68 patients had papillary and 8 had follicular cancer
- 98 PET/CT scans were analyzed (59 patients had 1 scan, 12 patients had 2 scans and 5 patients had 3 scans)
Sensitivities and specificities of PET/CT in differentiated thyroid cancer

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<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
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<tr>
<td><strong>Based on patients (n=76)</strong></td>
<td>88.6 (78.8-94.3)</td>
<td>89.3 (71.9-97.1)</td>
</tr>
<tr>
<td><strong>Lesions in thyroid bed</strong></td>
<td>87.5 (73.4-95.1)</td>
<td>96.5 (87.6-99.7)</td>
</tr>
<tr>
<td><strong>Metastases (overall)</strong></td>
<td>88.9 (78.5-94.8)</td>
<td>94.3 (80.4-99.4)</td>
</tr>
<tr>
<td><strong>Lymph nodes metastases</strong></td>
<td>87.7 (76.4-94.2)</td>
<td>97.1 (83.8-99.9)</td>
</tr>
<tr>
<td><strong>Other metastases</strong></td>
<td>88.9 (65.9-98.1)</td>
<td>96.4 (80.8-99.9)</td>
</tr>
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</table>
Tg levels ranged 0.5-123.0 ng/ml (average: 9.72) in pts with negative PET/CT and 0.5-28,357 ng/ml (average: 1203) for those with positive PET/CT scans \( (P = 0.0389) \)

TSH values ranged 0.01-225 mIU/L (average: 32.21) in pts with negative PET/CT and 0.004-262 mIU/L (average: 51.22) in pts with positive scans \( (P = 0.258) \)

<table>
<thead>
<tr>
<th></th>
<th>Positive PET/CT</th>
<th>Negative PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg ng/ml mean (range)</td>
<td>1203 (0.5-28,357)</td>
<td>9.7 (0.5-123)</td>
</tr>
<tr>
<td>SUV max (thyroid bed)</td>
<td>10.8 (2.5-32)</td>
<td></td>
</tr>
<tr>
<td>SUV max (metastases)</td>
<td>7.53 (2.5-26.2)</td>
<td>( P ) value: 0.0114</td>
</tr>
<tr>
<td>TSH mIU/l mean (range) in 73 scans</td>
<td>51 (&lt;0.01-262)</td>
<td>32 (0.01-225)</td>
</tr>
</tbody>
</table>
38 women, 25 men; 25 - 77 years old (average: 52)

PET/CT was performed before (basal PET) and 24-48 h after rhTSH administration (rhTSH-PET) in 63 patients (52 PTC and 11 FTC)

rhTSH-PET was significantly more sensitive than basal PET for the detection of lesions (95 vs. 81%; P = 0.001) and tended to be more sensitive for the detection of involved organs (94 vs. 79%; P = 0.054)

However, basal PET and rhTSH-PET did not have significantly different sensitivity for detecting patients with any lesions (49 vs. 54%; P = 0.42)

Treatment changes due to true positive lesions occurred in 6% of cases
Imaging MTC
When MTC is diagnosed by fine needle aspiration biopsy, ultrasonography, CT and/or MRI scanning of the neck are indicated to look for cervical lymph node involvement.

- $^{123}$I MIBG, $^{111}$In Octreotide, and $^{99m}$Tc DMSA-V were investigated for evaluation of MTC and are currently used in detection of metastatic/recurrent disease.

- $^{18}$F FDG PET detects more lesions than $^{99m}$Tc DMSA-V and $^{111}$In Octreotide, as well as bone scintigraphy combined with morphologic imaging such as ultrasound, CT, or MRI.
Detection of Occult Medullary Thyroid Cancer Recurrence with 2-Deoxy-2-[F-18]fluoro-d-glucose-PET and PET/CT

Andrei Iagaru, MD,¹,* Rinat Masamed, MD,² Peter A. Singer, MD,² Peter S. Conti, MD, PhD¹

- 7 women & 6 men, 15-62 years old (average: 48 ± 13)
- All patients had histologic diagnosis of MTC
- The PET scan request was triggered by rising levels of calcitonin and negative anatomical imaging studies
The calcitonin levels ranged from 52 to 5090 pg/ml (average: 1996 pg/ml) in patients with negative PET scans (black) and from 132 to 9500 pg/ml (average: 3757 pg/ml) in patients with positive studies (gray) – $P$: 0.26
Whole body FDG PET of a 49-year old female with MTC recurrence in the thyroid bed and superior mediastinum. Her calcitonin levels prior to the PET examination were 9500 pg/ml.
Negative scan of a 42-year old female with calcitonin levels of 5090 pg/ml.
FDG PET scan of a 62-year old male with recurrent cervical (arrows) and hepatic disease (arrowheads), and calcitonin levels of 5290 pg/ml.
The lesions were located in superior mediastinum (4), cervical lymph nodes (3), thyroid bed (2), lung (1) and liver (1).

The sensitivity and specificity of F-18 FDG PET for recurrence/residual disease detection in this cohort were 85.7% (95% CI: 48.7-97.4) and 83.3 % (95 % CI: 43.6-96.9), respectively.

An overlap of measured calcitonin levels in patients with positive/negative scans was noted.
Imaging ATC
PET in anaplastic thyroid cancer

- To stage disease
- To define local extent of cancer
- To evaluate response to therapy
Focal uptake of $^{18}$FDG
Scan done for non thyroidal cancer

✓ Incidentaloma
✓ Metaboloma

Approximately 40-50% chance of thyroid cancer, usually papillary

BUT

Metastasis to thyroid can occur
THANK YOU!

http://nuclearmedicine.stanford.edu

http://mips.stanford.edu