I-131 AND PET IN THYROID CANCER IMAGING AND TREATMENT
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INDICATIONS FOR I-131 THERAPY

- Thyrotoxicosis
  - Graves’ Disease
  - Toxic Nodular Goiter
- Differentiated Thyroid Cancer
  - Papillary; 10-year cancer specific mortality 7%
  - Follicular; 10-year cancer specific mortality 15%
  - Hurthle cell; 10-year cancer specific mortality 25%
- Neuroendocrine Tumors

ISOTOPES OF IODINE

- I-123: gamma emitter, half life 13 hours
- I-124: positron emitter
- I-125: very low keV; not useful in vivo imaging
- I-131: beta emitter, primarily used for therapy

Iodine 131

- Reactor produced
- Physical half-life 8.02 days
- Beta emitter (90% of absorbed radiation)
- Major gamma rays: 364 keV and 637 keV
- Supplied: liquid solution or capsules
  - Capsules safer to handle, with less mucosal irradiation
- Rapidly absorbed in upper intestine
- Can be administered intravenously
I-131 DOSE IN DIFFERENTIATED THYROID CANCER

- Dose range: 30 mCi to 200 mCi
- Remnant ablation: 30 mCi to 100 mCi
- Treatment of recurrent disease: 100 mCi to 200 mCi
- Doses above 200 mCi require pretreatment dosimetry estimates of marrow dose. This is currently rarely indicated.

DOSIMETRY

\[ D = kA \sum n_i E_i \]

- \( D \): absorbed dose (rad or Gy)
- \( A \): cumulated activity
- \( n_i \): number of particles with energy \( E_i \)
- \( E_i \): energy per particle
- \( m \): mass of target region (grams)
- \( k \): proportionality constant

RADIOBIOLOGICAL CONSIDERATIONS

- Organ tolerance data primarily from high dose fractionated external beam data
- Radionuclide therapy is low dose but continuous
- There appears to be a higher tolerance for internal sources compared to external beam treatments for same dose; more work is needed to clarify

Stabin M, Dosimetric Considerations, Nuclear Medicine, Ell and Gambhir Eds, 2004.

RADIOBIOLOGY OF I-131

- Beta particles penetrate 2 mm or less
- Virtually no irradiation outside of tumor targets
- Cellular heterogeneity will result in inhomogenous irradiation of tumor targets
- Gamma radiation produces 10% of the absorbed dose, but virtually all of the externally detectable dose (scans, environment)
TUMOR BIOLOGY ISSUES

- Iodine uptake (sodium-iodine symporter-NIS) is decreased
- Iodine organification is reduced
- Effective half time of iodine in tumor is shortened
- Response to TSH is usually present, even in absence of visible I-131 uptake on scans


SIDE EFFECTS OF I-131 THERAPY

- Usually minimal and transient
- Nausea, gastric pain rare
- Transient loss of taste
- Sialadenitis; rarely progresses to xerostomia
  - Prophylaxis; fluids and sialogogues


TUMOR BIOLOGY ISSUES

- Iodine uptake is heterogeneous in both normal thyroid and tumor because of heterogeneous expression of NIS and low expression of thyroid genes that transport and organify iodine
- Heterogenous iodine uptake and short path length of beta particles can result in suboptimal tumor treatment response
- Therefore, intense TSH stimulation is needed in radioiodine therapy of differentiated thyroid CA


INFERTILITY, GONADAL FAILIURE AND GENETIC EFFECTS

- Absolutely contraindicated in pregnancy
- No evidence of long term genetic effects in offspring
- Some increase in miscarriage rate post I-131 treatment; recommendation to avoid elective pregnancy for 1 year post treatment

OVARIAN DAMAGE

- No permanent sterility in women cumulatively receiving up to 300 mCi I-131, but occurs in up to 60% of those receiving in excess of 800 mCi
- Miscarriage rate increases after 100 mCi
- Recommend delay in conception for 1 year post high dose (100 mCi or more), but has no clear effect with hyperthyroid doses


TESTICULAR DAMAGE

- Testis is more sensitive to irradiation than is the ovary
- Sterility in less than 10% of men given cumulative doses of 300 mCi, and in up to 90% with cumulative doses over 800 mCi
- Consider sperm banking when greater than 100 mCi treatment used


CARCINOGENIC EFFECTS

- Results controversial because of sample sizes and other factors
- Increased risk of leukemia for cumulative doses higher than 500 mCi, especially when associated with external beam therapy
- Below 500 mCi, results vary; some studies show no increased cancer risk, some show small risk (breast, colorectal, salivary gland)

**LIMITATIONS OF BROWN ET AL**

- No information on dose effects: this is a critical issue in assessing risk for a given patient
- Molecular links: Papillary (not follicular) cancer has mutation in RET protooncogene (Jiang, Oncogene 2000). This oncogene linked to leukemia, prostate cancer, breast cancer

**RADIATION SAFETY**

- ALARA: as low as reasonably achievable
- Time, distance, shielding
- Hospital admission virtually never needed for hyperthyroid I-131 treatments, for cancer patients admission may be required for doses above 50 mCi.
- UCSF protocol permits outpatient treatments with doses up to 200 mCi

Robbins R and Schlumberger M. Journal of Nuclear Medicine 46:S298-S378, 2005
GOALS OF I-131 THERAPY IN DIFFERENTIATED THYROID CANCER

- Destroy any microscopic foci of disease remaining after surgery
- Destroy any remaining normal thyroid tissue
  - Improve the value of serum Tg as a tumor marker (increased specificity in the absence of normal thyroid tissue)
  - Increase specificity of I-131 scanning

REMNANT ABLATION

- Long term benefits in low risk patients uncertain
- 10 year event rate for all histologies with/without I-131 ablation were 4% and 10% for locoregional recurrence, and 2% and 4% for distant metastases
- Without remnant ablation, half of lung metastases in children cannot be identified
- No effect on cancer specific mortality

Sawka et al. J Clin Endo Metab 89: 3668, 2004
Mazzaferri E. J Clin Endo Metab 89: 3662, 2004

FIG. 1. Survival after the discovery of metastases according to the presence or absence of 131I uptake in the metastases
FIG. 3. Survival after the discovery of distant metastases

Group 1: I-131 + who became -
Group 2: I-131 + who did not become -
Group 3: No I-131 uptake

I-131 whole body scan with remnant and lymph node metastasis following surgery
Sensitivity of I-131 whole body scanning is low and depends on dose administered
Sensitivity approximately 45% to 75% and is somewhat lower with papillary compared to follicular carcinomas.

FIG. 1. 99mTc-depreotide scan (total body anterior view (A), coronal SPECT slice (B)) shows increased activity at a locoregional recurrence in a radioiodine-negative patient with follicular thyroid carcinoma (patient 5, Table 1).

Bronchoalveolar Carcinoma of Lung Mimicking Iodine Avid Metastasis

PET/CT IN THYROID CANCER

- Normally very little FDG uptake in thyroid
- Intense and diffuse uptake suggests chronic thyroiditis (Hashimoto’s) or Graves’ disease
- Focal, intense regions of uptake have 30% - 50% incidence of primary thyroid malignancies or metastases


I-131 \( ^{131}I \) SPECT/CT demonstrates lesion in posterior mediastinum rather than in bone

Lind P and Kohlfurst S. Seminars in Nuclear Medicine 36:194, 2006
NEGATIVE RADIOIODINE SCAN AND POSITIVE THYROGLOBULIN (Tg)
- TSH stimulated Tg > 10 ng/mL
- I-131 or I-123 scan negative
- Options: PET/CT or empiric I-131 therapy
- McDougall et al: 87 patients with PET/CT
  - Sensitivity 87%
  - Specificity 80%

RELATIONSHIP OF TSH TO PET FDG UPTAKE IN THYROID CANCER

<table>
<thead>
<tr>
<th>Low TSH</th>
<th>High TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients positive</td>
<td>9</td>
</tr>
<tr>
<td>Lesions positive</td>
<td>22</td>
</tr>
</tbody>
</table>

INDICATIONS FOR PET/CT IN THYROID CANCER PATIENTS
- Primary role is in less well differentiated cancer
- Thyroglobulin (Tg) positive/radioiodine negative
- Hurthle cell (usually Tg positive, iodine negative)
- Anaplastic (usually Tg and iodine negative)
- Medullary carcinoma (iodine negative, calcitonin positive)
- Lymphoma
- Metastases to thyroid

Sensitivity 87%
Specificity 80%

PET/CT in Thyroid Cancer:
- Prediction of Absorbed Dose to Normal Organs in Thyroid Cancer Patients Treated with $^{131}$I by Use of $^{124}$I PET and 3-Dimensional Internal Dosimetry Software

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RELATIONSHIP OF TSH TO PET FDG UPTAKE IN THYROID CANCER
- Low TSH | High TSH
  - Patients positive | 9 | 19
  - Lesions positive | 22 | 78

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How should Tg positive post-thyroidectomy patients be managed?

- Negative post-treatment whole body I-131 scan:
  - “If an empiric dose (100mCi - 200 mCi) of radioiodine fails to localize the persistent disease, FDG PET scanning should be considered…”

- Negative post-treatment whole body I-131 scan and Tg positive:
  - “Tg positive, iodine negative patients with disease that is incurable with surgery and is evident on FDG-PET can be managed with hormone suppression therapy, external beam radiotherapy, chemotherapy, RFA…”

- Negative post-treatment whole body I-131, Tg positive with no structural evidence of disease: “can be followed with serial imaging studies and serial Tg measurement...when and how often to repeat FDG PET is less certain.”

57 y/o male with recurrent papillary/follicular thyroid carcinoma, level III and IVa nodes

Non-contrast CT limits CT definition of disease, but FDG PET compensates.

DIFFUSE FDG UPTAKE IN THYROID GLAND

- Review of 1102 healthy subjects
- Diffuse FDG uptake in 36
  - 33 women
  - 27 positive thyroid antibodies
  - Ultrasound was consistent with chronic thyroiditis or, if thyrotoxic, Graves' disease

Yasuda et al, Radiology 277: 775-778, 1998
Diffuse FDG Uptake in Thyroid Gland
Suggests Thyroiditis: Could It Be Contrast Artifact?

Not an artifact; persists on attenuation uncorrected images

Corrected MIP  Uncorrected MIP

RECURRENT AND METASTATIC PAPILLARY THYROID CARCINOMA
79 y/o male, Stage IVc

RECURRENT AND METASTATIC PAPILLARY THYROID CARCINOMA
13 y/o female with anaplastic thyroid carcinoma

3 months previously

Current

Courtesy of Diego Ruiz MD, Palo Alto Medical Foundation
I-131 TREATMENT FOR DCT WITH END STAGE RENAL FAILURE

- Empiric treatment activity of 40-50% of that used for patients with normal renal function
- More rigorous dosimetric estimates in selected patients can be useful

Alevizaki C et al, Hormones 5:276, 2006
International, randomized, multicenter trial to compare efficacy and safety of rTSH versus hormone withdrawal for remnant ablation of thyroid tissue with 100 mCi I-131

Comparable remnant ablation rates in both groups

Decreased blood radiation exposure in rTSH group