Pediatric Thyroid Cancer: Treatment Controversies; I-131 Radiotherapy

Marguerite T. Parisi, M.D., M.S. Ed.
Associate Professor, Departments of Radiology and Pediatrics
University of Washington School of Medicine
Division Head, Ultrasound
Children’s Hospital and Regional Medical Center
Seattle, Washington
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Thyroid Cancer

- Most common endocrine malignancy
- 1-2% of all malignancies
- 5-6% of head and neck malignancies
- Wide interethnic and geographic variations
- 100 cases /million/year in adults
- 14-17,000 new cases a year in the USA
- 1% of cancer mortality; 1100 deaths/year
Thyroid Cancer

• 4 types:
  – Papillary
  – Follicular
    • Hurtle Cell
  – Medullary
  – Anaplastic
Papillary Cell Carcinoma

- 80% of all thyroid cancers
- Mean age at presentation in 3rd decade
- Cervical node metastases in 30-40%
- Distant metastases in 2-14%
- 30-85% multifocal on routine versus thin histologic sectioning
- 90% survival at 20 years
Follicular Cell Carcinoma

- 10-20% of all thyroid cancers
- Mean age of presentation in 4th decade
- Lower incidence of cervical node metastases
- Higher incidence (33%) of distant metastases
- Usually solitary
- 8% multifocal; occurs more often in association with benign thyroid conditions and in areas of iodine deficiency
- 70-75% survival at 20 years
 Pediatric Thyroid Cancer

- 10% of all thyroid cancers occur in those <21
- Increased incidence with puberty but can occur at any age
- In England & Wales:
  - 0.19 cases/million/year up to age 14
  - 3 cases/million/year between ages 15-25
- In USA:
  - 5 cases/million/year in those <19 years.
Pediatric Thyroid Cancer

BIOLOGIC BEHAVIOR IS DIFFERENT THAN THAT IN ADULTS

• Typically well-differentiated papillary or follicular subtypes
• Female:male ratio: 2:1 vs 3:1 in adults
Pediatric Thyroid Cancer

CHILDREN TYPICALLY PRESENT WITH ADVANCED DISEASE

- Extensive regional nodal involvement in 60-80%
- Higher rate of distant metastases
  - Lung in 10-20%
  - Bone metastases rare; <5%
- Higher local and distant recurrence rates
Pediatric Thyroid Cancer

- Rapid response to therapy
- Excellent prognosis
- 10 year mortality <10%
- Overall survival >95% at 20 years
  - versus 40%-5 year and 20% -10 year survival rates in adults with distant/pulmonary metastases
- Unfortunately, progression occurs in a significant proportion of patients
- Progression free survival is only 65-70% at 5 years.
Thyroid Cancer: Etiology

• Known sequellae of radiation to the head and neck
  – 1st reported in 1950 by Duffy and Fitzgerald
  – Winship and Rosvoll: latency period between XRT and development of thyroid cancer averages 8.5 years.
  – Risk continues for up to 30 years following exposure
  – Risk greatest when exposure occurs at a younger age, in females, when higher TSH level at exposure and with higher radiation rates
  – Following Chernobyl, 1986: 100 fold increase in incidence of pediatric thyroid cancer in exposed populations.
Thyroid Cancer: Etiology

Current sources of thyroid irradiation:

• Treatment of malignant disease.
• Radio-iodine therapy of Graves disease
• Nuclear Irradiation
• Diagnostic X-rays
Thyroid Cancer: Etiology

- Increased incidence of secondary cancers in those with prior XRT or chemotherapy:
  - Overall incidence of secondary malignancies: 3-12%
  - Risk of development:
    - 36.6 times normal if age <4 at time of Rx;
    - 3-4 times normal if XRT doses >10GY
- Increased incidence in those with immunosuppression e.g. following BMT or organ transplant
  - Risk of secondary malignancies 8X normal by 10 years post BMT
- Genetic determinants in Medullary Thyroid Carcinoma
- Familial non-medullary carcinoma infrequent; 1.7% occurrence
History:
9 yo patient presents for surveillance CT 6 years post diagnosis and therapy of bilateral Wilm’s tumor (including whole lung irradiation for metastases) and 2 years post renal transplant. CT demonstrates a (asymptomatic) mass in the right lobe of the thyroid. Biopsy performed with ultrasound guidance revealed bilateral PTC with lymph node metastases.
Thyroid Cancer: Clinical Presentation

• One or more asymptomatic neck masses
  – 4-5% of adults have thyroid nodules; 5% are malignant
  – 1-2% of kids have thyroid nodules; 33-40% malignant.
• Increased likelihood of cancer if mass is:
  – Hard
  – Adherent to surrounding tissues
  – Associated with lymphadenopathy or vocal cord paralysis
  – If previous history of radiation exposure to head and neck
Thyroid Cancer: Diagnosis

- History
- Physical Examination
- Laboratory Studies:
  - Triiodothyronine-T3
  - Thyroxine-T4
  - TSH
  - Thyroglobulin
  - Antithyroid antibodies
  - Calcitonin (MTC and C-cell hyperplasia)
  - DNA analysis for ret mutations (MEN-2)
  - Genetic testing at birth for those at risk for MEN-2
- Imaging
- Fine needle biopsy: value in children questionable due to difficulty of procedure and histologic heterogeneity
Thyroid Cancer: Imaging

• Ultrasound:
  – Distinguish cystic from solid lesions
    • Cystic lesions typically benign BUT
    • Up to 50% of malignant lesions have cystic component
    • 8% of cystic lesions represent malignancies
  – Detect non-palpable lesions
  – Guidance of needle biopsies

• CT / MRI
  – Useful in assessing local invasion and determining the presence of nodal and distal metastases
History:

11 yo presenting with multiple neck masses. US confirms multifocal solid masses in right lobe of thyroid and cervical lymphadenopathy in this patient with extensive metastatic PTC.
History:

18 yo with persistent slowly enlarging midline neck mass.

CT: Heterogenous multicystic and solid mass

Excisional biopsy: PTC arising in a thyroglossal duct cyst.
## Thyroid Cancer: Nuclear Imaging

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<thead>
<tr>
<th>Tc-99 Pertechnetate</th>
<th>I-123</th>
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<tr>
<td>• More stable</td>
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<td>• Readily available</td>
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<td>• Scan at 20 minutes</td>
<td>• Scan at 4/24 hours</td>
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<td>• Shows trapping, not organification</td>
<td>• Shows both trapping and organification</td>
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<td>• Patient dose: 0.1 rad</td>
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History: 16 yo presents with one year history of enlarging neck mass. Previous history of bilateral retinoblastoma, left enucleation, XRT to right eye and later to neck for recurrent metastatic disease in cervical lymph nodes. S/p total thyroidectomy; final path: multinodular goiter.
History: Previously healthy 4 yo with enlarging neck mass found to represent metastatic follicular variant PTC.
Thyroid Cancer: Nuclear Imaging

• I-123 necessary if hot nodule identified
  – 0.7% incidence of malignancy in hyperfunctioning nodules

• Other Radiotracers:
  – Tl-201 and MIBI: may be useful in identifying metastases and/or recurrences in treated patients in whom I-131 diagnostic scans are negative
  – 18-FDG:
Pediatric Thyroid Cancer: Treatment

• While extensively investigated, treatment of thyroid cancer remains **controversial**
  – Small number of patients with the disease
  – Difficulty in obtaining a large, single institution series
  – Differences in treatment methods at different as well as at the same institution over time
  – No large retrospective study of pediatric patients with a well-defined treatment protocol
  – Lack of a controlled randomized prospective study
Pediatric Thyroid Cancer: Treatment

• Extent of thyroidectomy remains controversial in those with a solitary thyroid cancer
  – Society of Surgical Oncology recommends lobectomy for low risk DTC patients
  – American Thyroid Assn and American Assn of Clinical Endocrinologists recommend near total or total thyroidectomy for all except pT1M0N0.

• For multifocal, bilateral or advanced thyroid cancer (infiltration of surrounding tissues, local or distant metastases), total thyroidectomy is mandated
Pediatric Thyroid Cancer: Treatment

Advantages of Lobectomy:

• Lower risk of complications
• >50% of local recurrences can be cured with surgery
• <5% of the recurrences occur in the thyroid bed
• Tumor multicentricity has little clinical significance
• Excellent prognosis of those who underwent less than total thyroidectomy.
Pediatric Thyroid Cancer: Treatment

Advantages of Total Thyroidectomy:

• Radioactive iodine can be used to detect and treat residual thyroid tissue, local and distant metastases

• Serum thyroglobulin level is a more sensitive marker of persistent or recurrent disease when all normal thyroid tissue has been removed

• Up to 85% of patients with PTC have microscopic foci in the contra-lateral lobe which are then eliminated as sites of possible disease recurrence
Pediatric Thyroid Cancer: Treatment

Advantages of Total Thyroidectomy:

• Recurrence develops in contra-lateral lobe in 7% of patients; 1/2 of these patients die of their disease
• Recurrence is lower in patients who underwent bilateral procedures or total thyroidectomy
• 1% risk of anaplastic transformation in thyroid remnant is decreased
• Re-operation is associated with increased risk of complications
Radio-iodine

- Introduced by Seidlin in 1946
- Short-ranging $B$ radiation
- Maximum range: 2 mm
- T1/2 of 8 days
- In adults, radio-iodine uptake is seen in:
  - 80% of FTC
  - 70% of PTC
  - 10% of HCT
I-131 Therapy

Post-operative RAI remains controversial

• Improved survival, decreased progression and lower recurrence rates in those with low risk DTC who received post-op RAI
  – Mazzaferri et al, 1994
  • recurrence 6.4%; 97% disease free at 5 years ff surgery + I-131
  • 11% recurrence; 40-60% relapse between 5-10 years ff surgery alone
  – Van Herle et al,
  • Recurrence rates decreased from 17% to 6% following post-surgical RAI treatment
I-131 Therapy

Indications:

• Adjuvant prophylactic ablation of thyroid remnants following thyroidectomy
• Curative and/or palliative treatment of inoperable cancer or tumor not removable; of local recurrences, nodal or distant metastases

Contraindications: Pregnancy; breast feeding
Facts influencing RAI uptake:

1. Amount of normal thyroid tissue remaining
2. Serum iodine level
   - I-131 or I-123 in initial evaluation post-thyroidectomy
   - “Stunning” vs lesion detectability, cost and inability to obtain dosimetry
3. Serum TSH level (must be >30 mU/l)
4. Degree of tumor differentiation; tumor type
5. Patient age
I-131 Therapy: Preparation

Diagnostic I-131 scan and uptake (1-3mCi dose)

- Performed 8-12 weeks post surgery
- Avoidance of interfering materials
- T4, T3 withdrawal 4 and 2 weeks pre-scan
  - Use of exogenous stimulation by recombinant TSH as opposed to thyroid hormone withdrawal
- Low-iodine diet for 7-10 days prior to scan
- Immediately (1-3 days) prior to scan
  - Oncologist performs physical exam and
  - Obtains labs: TSH, Thyroglobulin, antithyroid antibodies, urinary iodine, pregnancy test
I-131 Therapy: Preparation

On day of administration of diagnostic dose:

• Check lab results
• Verify patient identification
• Ensure patient/family have educational materials
• Discuss plans for possible hospital admission and performance of therapy one day after diagnostic scanning
I-131 Therapy: Preparation

On day of diagnostic scanning:

- Imaging: 72 hours post ingestion of tracer
- Large field of view; high energy collimator
- Patient lying supine
- Anterior and posterior images; spots for 5-10 minutes/view; pinholes to differentiate normal thyroid residual from residual cancer and nodal metastases
- If hospitalization warranted for therapy, ensure nursing update, room and equipment preparation
I-131 Therapy

Dose remains controversial
• If post-op I-131 scan shows uptake confined to the thyroid bed and >20%: re-operation
• For low risk patients: If uptake confined to thyroid bed and <10% at 48-72 hours: perform I-131 ablation
  – Little difference between low and hi dose radio-ablation: DeGroot & Reilly; Johansen et al; Mazzafferi & Jhiang
  – > 80-90% chance that 30 mCi will produce ablation
History: 4 yo with palpable neck mass

I-131 scan post subtotal thyroidectomy for metastatic PTC.

Iodine uptake at 72 hours: measured 32%
I-131 Therapy

- In high risk patients: in-patient Rx; 100-200 mCi
  - Regional nodal involvement: 150-175 mCi
  - Lung metastases: 175-200 mCi
  - Bone metastases: 200-250 mCi
- In those post-thyroidectomy, absent I-131 uptake but elevated Tg levels: 100 mCi (Kebebew)
  - On post-therapy scanning: 1/3 will have I-131 uptake and resultant decreasing Tg levels
  - McDougall asks “What is being treated?”; what is the correct dose? What is the risk/benefit ratio?
I-131 Therapy

Day of Therapy:

• Verify compliance with preparatory regimen
• Admit to lead-lined room
• Verify patient identification
• Obtain witnessed, written, informed consent
• Start prophylactic IV for fluid hydration; stress need for oral hydration; use of lemon drops
• Verify dose
• Personally witness and/or administer dose
• Hospitalized until emissions <7 mR/hr@ 3 feet
I-131 Therapy

7 days post-therapy: Imaging

• Dose-related sensitivity in disease detection--increase dose, increase the number of detectable lesions (Waxman; Catz; Petit; Starr)

• Post-therapy scans may detect new lesions in 46%

• Implications of liver activity: felt to indicate the presence of cancer somewhere in the body since iodine is only concentrated in the liver when it has been organified (Chung, 1997)
History:
12 yo presenting with neck mass. CT demonstrates mass in left lobe of thyroid gland and bilateral cervical and upper mediastinal lymphadenopathy.

Patient underwent total thyroidectomy and lymph node resection for PTC.
Post-Therapy Imaging

Diagnostic I-131

Post-therapy I-131

One year later
Post-Therapy Imaging

History:
11 year old s/p total thyroidectomy for PTC with metastatic lymph node involvement. Post-therapy images clearly show diffuse lung metastases not seen on diagnostic imaging.
Post-Therapy Imaging

15 year old s/p total thyroidectomy and I-131 Rx for metastatic PTC. Post-Rx scan shows mediastinal disease not identified on earlier imaging.
I-131 Therapy: Risks

Those occurring during or shortly post-Rx:

• Mild nausea/emesis from radiation gastritis: 50%
• Acute sialadenitis: 30%
• Painful swelling of remnant/metastases: 10-20 %
• Reduced salivary gland function: 40%; Xerostomia: 4%
• Transient, mild, thrombocytopenia: 66%
• Transient amenorrhea (lasting up to 10 months): 8%; menstrual irregularities: 12% (Vini, et al, 2001)
• Transient elevations of FSH in males
I-131 Therapy: Risks

Late Effects: Fertility

- No cases of permanent ovarian failure (1398pts; Vini)
- Smith, 1994; 154 kids; 68 females <20 years: I-131 doses up to 250 mCi not associated with long term risk of infertility
- I-131 therapy does NOT result in demonstrable adverse effects in subsequent pregnancies (Lin et al, 1998; Dottorini et al, 1994; Schlumberger et al, 1995; Schlumberger et al, 1996)
- Increased risk of miscarriage; 13% (Schlumberger et al, 1995)
- Birth defects reported (2-Smith, 1994; 4-Ayala, 1998) in those who conceived within 6 months of I-131 Rx
- Earlier onset of menopause ff I-131 (Ceccarelli, et al, 2001)
- Azoospermia, oligospermia, increased FSH levels (Handelsman, 1980; Ahmed, 1984; Pacini, 1994; Winters, 1997)
I-131 Therapy: Risks

Late Effects:

• Pulmonary fibrosis:
  – Occurs in those with lung metastases
  – Risk correlates with the intensity of I-131 uptake (Reiners et al, 1994)
  – Risk varies inversely with age of patient:
    • 1% in adults; 10% in kids
I-131 Therapy: Risks

Late Effects: Risk of Secondary Malignancies

- Brinker, 1973: 2% frequency of leukemia ff I-131 Rx
- Holm, 1980: No increased incidence of malignant thyroid tumors following I-131 Rx for Graves disease.
- Hoffmann, 1984: Increased risk of cancer in organs that concentrate iodine ff I-131 Rx (salivary glands, gut, bladder)
- Smith & Edmonds, 1986: Small, significant excess of deaths from leukemia and bladder cancer
- Hall, 1991-1992: No specific cancer or groups of cancers could be linked to hi dose I-131 Rx.
Follow-Up

• Periodic physical examination
• Labs:
  – Verify that thyrotropin secretion (TSH) suppressed
  – Serum thyroglobulin:
    • Differentiated thyroid carcinomas secrete Tg
    • Post-removal/ablation of normal thyroid tissue, serum Tg >2-3ug/L is diagnostic of recurrence
• Use of radio-iodine scanning
  – Verify ablation or in cases of recurrence
Conclusion

• Despite the aggressive nature of pediatric thyroid cancer, overall survival—even in those with distant metastases—is 100% at 10 years
• Recurrent disease may not be seen until after 1 decade
• 5-7% succumb to progressive disease
• 5-7% develop lethal treatment related complications or secondary malignancies
• Lifelong surveillance needed
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