$^{131}$I Radiotherapy of Pediatric Thyroid Cancer

Steven Waguespack, MD
Associate Professor

Dept of Endocrine Neoplasia and Hormonal Disorders
Department of Pediatrics-Patient Care

University of Texas M.D. Anderson Cancer Center
Houston, Texas, USA

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Objectives:

• Review the general approach to the treatment of pediatric PTC
• Discuss the role of $^{131}$I in pediatric PTC
• Review evolving approaches to the use of RAI to treat pediatric PTC
ARS QUESTION

A 7-year-old, 25 kg girl is diagnosed with a follicular variant PTC, mT3N1bMx, and is status post total thyroidectomy and a comprehensive compartment-focused neck dissection by an experienced thyroid surgeon who performs over 100 thyroid cancer surgeries a year. A CXR at diagnosis was negative for pulmonary metastases and the lung fields on a pre-operative contrast-enhanced CT neck did not reveal pulmonary metastases in the upper lung fields. After a documented normal 24-hour urine iodine level, she is now ready for further evaluation and possible treatment with $^{131}$I. Recognizing that the treatment of pediatric PTC is evolving, which of the following statements is correct?
ARS QUESTION, cont’d

A. A diagnostic scan using $^{123}$I is unlikely to add any additional diagnostic information; based upon her pathological findings and high risk of pulmonary metastases, the patient should receive an empiric dose of 150 mCi $^{131}$I and have a post-treatment scan performed 7 days after treatment.

B. Dosimetry should be planned and the patient administered the highest $^{131}$I dose that will limit her blood/bone marrow radiation dose to <200cGy.

C. If pulmonary metastases are identified, due to her increased risk of death from PTC, a second high dose of $^{131}$I should be planned for 6 months after the first dose.

D. Treatment using rhTSH (instead of thyroid hormone withdrawal) is preferred because large randomized clinical trials have demonstrated safety and efficacy in pediatric patients with similar clinical presentations.

E. A diagnostic scan using $^{123}$I and a stimulated thyroglobulin at the time of the diagnostic scan may help to determine the appropriate dose of RAI, if needed.
Thyroid Carcinoma

Follicular Cell

WDTC

Papillary Thyroid Cancer

90+%

Follicular Thyroid Cancer

5-10%

Parafollicular C Cell

Medullary Thyroid Cancer

<5%

Pathology courtesy of Adel el-Naggar, MD
DTC Differences in Behavior

- More likely to metastasize to regional lymph nodes
- Hematogenous mets to the lungs (usually with extensive neck disease)
- Often multifocal and bilateral

- Usually no lymphatic spread unless a less differentiated variant
- More prone to initial hematogenous mets—bone & lung
- Usually unifocal
Pediatric Thyroid Cancer Survival

Hogan et al. *Journal of Surgical Research*, 156, 167-72, 2009
Cause-Specific Mortality in 215 Mayo PTC Patients Aged <21 Years

- Cumulative occurrence (%)
- Years after initial surgery

Median FU 28.7 yrs

2 patients who died 28 and 30 yr. after diagnosis

Prognosis relates to patient age, size of metastases, & RAI avidity

- <40 yrs old, micronodular mets
- >40 yrs old, micronodular mets or <40 yrs old, macronodular mets
- >40 yrs old, macronodular lung or multiple bone mets

10 yr survival: 76% vs. 25%

Durante et al. J Clin Endocrinol Metab. 91(8):2892-9; 2006
PTC Differences in Behavior—Kids Vs Adults

Children present with larger tumors, a greater incidence of LN mets, a greater incidence of lung mets, and a higher chance of recurrence

BUT

The prognosis for cancer death is much better in children

– more TSH dependent
– mutational differences (RET/PTC vs BRAF)
– lack of progression to poorly differentiated tumors
– More beneficial immunologic mechanisms
Approach to PTC

- Surgery (total thyroidectomy +/- lymph node dissection) by an experienced thyroid cancer surgeon

- Possible treatment with RAI ($^{131}$I)

- TSH suppression and long-term monitoring with blood tests (TG) & imaging studies (neck US, thyroid scan, etc.)
131I

- Physical half-life is 8.04 d; effective half-life in the living body is about 7.6 d
- Emits two types of particles:
  - beta (β−; electron), used for treatment
  - gamma (γ), used for diagnosis
- Available as sodium iodide in gelatin capsules/drinking solution
$^{131}$I-A History

- **1938**
  - $^{131}$I first produced from tellurium by a cyclotron at UC, Berkeley

- **1941**
  - First patients treated for thyrotoxicosis

- **1946**
  - Seminal papers in *JAMA* reporting the use of $^{130}$I/$^{131}$I treatment in hyperthyroidism

131I-A History

- **1942**
  - Thyroid cancer shown to concentrate radiiodine.

- **1946**
  - First publication in thyroid cancer treatment
    - Adult pt with functional thyroid cancer successfully treated with 130I/131I
Radio-iodine halts one type of cancer.

Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors.

The man shown in the contrasting portraits at right is a Brooklyn shoe salesman named Bernard Brunstein who is destined to become one of the most famous patients in medical history. Brunstein is the first person known to be cured (insofar as a cure can be established by medical tests on a living patient) of metastatic cancer, a form of the disease in which the malignancy spreads through the body from an original tumor. Metastatic cancer has always been 100% fatal. But Brunstein’s tumors were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine.

When Brunstein was admitted to New York’s Montefiore Hospital seven years ago, he appeared to be suffering from an overactive thyroid gland rather than cancer. Last May, a section of Brunstein’s skull was removed for a microscopic examination. The mass was found to be cancerous and dead cells were expelled.

Dr. S. M. in radio-iodine therapy for hyperthyroidism, he discovered that the tumors receded, grew to be normal size, and never returned. Of the four doses, now, the tumors slowly began to diminish in size and eventually disappeared altogether.

Radio-iodine is chemically identical with ordinary iodine, giving off a powerful radiation that can kill any tissue that absorbs it in sufficient concentration. The chemical had never been effectively used as a treatment for cancer, but Brunstein agreed to try it in the hope that it might help. It did. Three months after he drank his first glassful of the tasteless, colorless liquid, his heart began to slow down and he started to put on weight. Geiger counters placed over the tumor sites revealed that there was a heavy concentration of radio-iodine in these areas. After three additional doses the tumors slowly began to diminish in size and eventually disappeared altogether.

Bernard Brunstein in 1942 (left); as he looks today.

“...the first person known to be cured...of metastatic cancer: by drinking 4 doses of radioactive iodine.”

Life, Oct 31 1949
$^{131}$I for DTC

- **Remnant Ablation**
  - To facilitate detection of recurrent disease & initial staging

- **Adjuvant Therapy**
  - To decrease risk of recurrence & disease-specific mortality by destroying suspected, but unproven metastatic disease

- **RAI Therapy**
  - To treat known persistent disease

Cooper DS et al. Revised ATA Guidelines. *Thyroid*. Volume 19, Number 11; 2009
Disease-free survival improved with adjuvant radioiodine

Adapted from Mazzaferri & Kloos, *J Clin Endocrinol Metab*, 2001
\(^{131}\)I Therapy in Children Appears to Increase Disease Free Survival


N=102

Univariate Analysis
Lack of Impact of Ablation on Nodal Recurrence in 161 PTC Patients <21 Yrs

Fig. 6 Lack of impact of RRA in reducing neck nodal recurrences in PTC patients younger than 21 years of age and who had initial NT or TT at Mayo Clinic during 1950 through 2008

Survival after radioiodine: Stage I

- Median follow-up: 5.3 yrs
- Total patient-years: 30,000

- No significant association between radioiodine treatment and overall survival in adult stage I patients

Jonklaas et al., Thyroid, 2010
### Table 5. Major Factors Impacting Decision Making in Radioiodine Remnant Ablation

<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
<th>Expected benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1 cm or less, intrathyroidal or microscopic multifocal</td>
<td>Decreased risk of death, Decreased risk of recurrence, May facilitate initial staging and follow-up, RAI ablation usually recommended, Strength of evidence</td>
</tr>
<tr>
<td>T2</td>
<td>&gt;2-4 cm, intrathyroidal</td>
<td>No, Conflicting data&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T3</td>
<td>&gt;4 cm</td>
<td>No, Conflicting data&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T4</td>
<td>Any size with gross extrathyroidal extension</td>
<td>Yes, Yes</td>
</tr>
<tr>
<td>Nx,N0</td>
<td>No metastatic nodes documented</td>
<td>No, No</td>
</tr>
<tr>
<td>N1</td>
<td>&lt;45 years old</td>
<td>No, Conflicting data&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
<td>Yes, Yes</td>
</tr>
</tbody>
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<sup>a</sup>Because of either conflicting or inadequate data, we cannot recommend either for or against RAI ablation for this entire subgroup. However, selected patients within this subgroup with higher risk features may benefit from RAI ablation (see modifying factors in the text).
$^{131}$I Considerations

- Low iodine Diet/Use of Lithium
- Withdrawal vs rhTSH
- Empiric Dosing vs Dosimetry
- Inpatient vs outpatient treatment
- Diagnostic and Post-treatment scans
- Risks vs Benefits
- Treatment of Lung Metastases
\[^{131}\text{I} \text{ Dosing}\n\]

• **Empiric**
  - 1.0-1.5 mci (37-55 MBq)/kg
  - \((\text{Wt in kg}/70) \times \text{empiric dose for adults}\)
    - 30-100 mCi (1.1-3.7 GBq) for remnant ablation
    - 150-175 mCi (5.5-6.5 GBq) for soft tissue metastases
    - 200-250 mCi (7.4–9.2 GBq) for bony disease

• **Dosimetric**
  - Limit Blood/Bone Marrow Dose to 200 cGy and whole body retained dose to <80mCi (2.96 GBq) at 48 hrs
  - Lesion Based Dosimetry—80Gy to metastasis
Dosimetry for Significant Lung Disease
Low vs High Dose RAI

- Two large randomized trials in Europe
  - Thyroid hormone withdrawal or rhTSH-stimulated ablation with 30mCi (1.11 GBq) equally effective as 100 mCi (3.7 GBq) in low-risk patients

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<thead>
<tr>
<th></th>
<th>HiLo</th>
<th>ESTIMABL</th>
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<tbody>
<tr>
<td>30 mCi</td>
<td>85%</td>
<td>91%</td>
</tr>
<tr>
<td>100 mCi</td>
<td>89%</td>
<td>94%</td>
</tr>
<tr>
<td>rTSH</td>
<td>87%</td>
<td>92%</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>87%</td>
<td>93%</td>
</tr>
</tbody>
</table>

The Diagnostic Scan

• $^{123}$I preferred over $^{131}$I
• May change management:
  – Iodine-avid neck disease best treated with surgery
  – Iodine-avid distant disease that may change dose
  – Iodine non-avid disease or no thyroid disease that may not require Rx
  – Caveat—Dx scan may be negative in RAI-avid disease; stim TG and clinical Hx important
Utility of the Post-Rx Scan

DIAGNOSTIC WB 1123 SCAN 4/24/2008

POST THERAPY WB 1131 SCAN 5/2/2008

Diagnostic Scan

Post Therapy Scan
SPECT-CT Imaging

• Can be done on Dx or Post-Rx Scan
• Precisely localizes iodine uptake, which may change management and can facilitate FU

$^{131}$I for DTC—Side Effects

- **Early**
  - Sialadenitis
  - Nausea, vomiting, diarrhea
  - Transient cytopenias

- **Late**
  - Xerostomia/salivary calculi
  - Lacrimal Duct Obstruction
  - Pulmonary fibrosis/BM suppression
  - Secondary Malignancies---bladder, colon, breast, leukemias, salivary gland, stomach
9yo with PTC lung mets

April 2005

June 2003
Increased risk of second malignancies after RAI

Brown et al., J Clin Endocrinol Metab 2008
Increased risk of second malignancies after RAI

In low risk patients:

SIR of 1.21 (0.93-1.54)
- Salivary Gland
- Leukemia (esp <age 45)

EAR 4.6 excess cases/10K PYR

SIR=standardized incidence ratio
EAR=excess absolute risk
PYR= person-years at risk

Iyer et al., Cancer 2011
Lung Metastasis in PTC

- Persistent but non-progressive disease frequent
- Generally 100% 10 yr survival
- Delayed responses to RAI can be seen:

- Tg levels in 20 children (mean age at Dx 10.4 yrs) with disseminated pulmonary mets
- Mean of 5.5 RAI courses and dose of 24.2 GBq (654mCi)

Long-term Survival with Pulmonary Metastases
Pulmonary Fibrosis

- 69 Chernobyl pts with pulm metastases
- 1.35 mCi (50 MBq) of $^{131}$I/kg followed by 2.7 mCi

“Based on the characteristics of affected individuals, the number of radioiodine courses may have to be limited, especially in young children....”

Younger at Dx
- 2 also treated with chemo
- 1 death

RAI in Pediatric PTC

Slow and Steady Wins the Race!
1\textsuperscript{31}I for PTC—A Personalized Approach

Papillary Thyroid Cancer

Total thyroidectomy\textsuperscript{1} & lymph node dissections as indicated (see text)

3-12 wks post-op in most patients; TSH > 30 \textmu/U/ml:
1) Diagnostic whole body scan with \textsuperscript{123}I or \textsuperscript{131}I
2) Stimulated Tg & Tg Ab

No RAI:
- Low risk patient\textsuperscript{2}
- Little or no thyroid bed uptake
- Stimulated Tg <5ng/ml\textsuperscript{3}

Consider RAI:
- High risk patient\textsuperscript{2}
- Thyroid bed uptake only
- Stimulated Tg <5ng/ml\textsuperscript{3}

RAI:
- High risk patient\textsuperscript{2}
- Thyroid bed uptake only
- Stimulated Tg >5ng/ml\textsuperscript{3}

RAI:
- Low or high risk patient\textsuperscript{2}
- Lung or other distant uptake

RAI or Surgery\textsuperscript{4}:
- Low or high risk patient\textsuperscript{2}
- Neck uptake outside of thyroid bed

\textsuperscript{1}Rare cases where lobectomy may suffice (see text)
\textsuperscript{2}Low risk: Primary tumor does not grossly invade the trachea, recurrent laryngeal nerve, esophagus or other vital structures; non-bulky lymph node presentation; no evidence of distant metastatic disease. High risk: Any of the previous features present
\textsuperscript{3}Assumes negative Tg Ab
\textsuperscript{4}RAI if no macroscopic disease on US; surgery if macroscopic disease on US
Diagnostic $^{131}$I scan:

Wt is 27.4 kg
TSH 119 MCU/ml
TG 142 ng/ml (neg Ab)

What dose to give?

60 mCi of 131I given
Diagnostic $^{131}$I scan:

- Wt is 27.4 kg
- TSH 119 MCU/ml
- TG 142 ng/ml (neg Ab)

Would you treat?  
Yes
Pediatric PTC-Personalized Rx

Diagnostic $^{131}$I scan:

Wt is 27.4 kg
TSH 119 MCU/ml
TG 142 ng/ml (neg Ab)

Would you treat?

YES, with Surgery
Diagnostic $^{131}$I scan:

Wt is 27.4 kg
TSH 119 MCU/ml
TG 1.2 ng/ml (neg Ab)

Would you treat?
No
SUMMARY

• Pediatric PTC is typically an indolent malignancy that, despite an advanced clinical presentation, is not associated with a poor prognosis during childhood.

• Surgery is the primary therapy and the best chance for cure—surgeon experience is vital.

• Routine RAI ablation is not necessary in all cases.

• RAI treatment of iodine-avid distant metastases remains important but patience is key.
ARS QUESTION

A 7-year-old, 25 kg girl is diagnosed with a follicular variant PTC, mT3N1bMx, and is status post total thyroidectomy and a comprehensive compartment-focused neck dissection by an experienced thyroid surgeon who performs over 100 thyroid cancer surgeries a year. A CXR at diagnosis was negative for pulmonary metastases and the lung fields on a pre-operative contrast-enhanced CT neck did not reveal pulmonary metastases in the upper lung fields. After a documented normal 24-hour urine iodine level, she is now ready for further evaluation and possible treatment with $^{131}$I. Recognizing that the treatment of pediatric PTC is evolving, which of the following statements is correct?
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ARS QUESTION

REFERENCES


QUESTIONS?

swagues@mdanderson.org

Vincent Van Gogh
Sunflowers 1888
Neue Pinakothek, München

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Department of Endocrine Neoplasia and Hormonal Disorders
Making Cancer History®