Pediatric Thyroid Cancer
Lung Metastases

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Differentiated thyroid cancer (DTC)

- The 3rd most common solid tumor in childhood and adolescence

- Accounting for 1.5%-3% of all childhood cancers
  - 1% of cancer cases in prepubertal children
  - 7% of cancer cases in adolescents aged 15–19 years old

- SEER (Surveillance, Epidemiology, and End Results) registry
  - An increasing incidence of thyroid cancer in the pediatric population - a rising of 1.1%/year over the 31 year period*

* Howlader *et al* SEER Cancer Statistics Review, 1975-2010, SEER web site, April 2013
**Differentiated thyroid cancer (DTC)**

- **Incidence**: 0.5-1.5 in 100,000/year
- **Median age**: 12-13 years
- **Peak incidence**: 15-19 years
- **Male : Female**: 1:2.8 (adolescence 1:5)
DTC characteristics - presentation

Extensive disease at presentation (*especially in younger children*)

- Large tumor: 88 - 95%
- Involvement of both lobes / multifocal disease: 30 - 50%
- Local invasion: 20 - 60%
- Lymph node metastases: 40 - 90%
- Distant metastases (lungs): 20 - 30%
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Diagnostic work-up

- Thyroid function tests …
- Neck US of thyroid gland and cervical lymph nodes
- FNA

**Bethesda classification**

1. Non-diagnostic (unsatisfactory)
2. Benign
3. AUS/FLUS (atypia/follicular lesion of undetermined significance)*
4. Follicular (or suspicious for follicular) neoplasm
5. Suspicious for malignancy
6. Malignant

- (Chest imaging)
- (Thyroglobulin levels)

* 20-30% indeterminate cytology
Initial treatment

- Total thyroidectomy +/- neck dissection
- RAI ablation / therapy
- TSH-suppressive LT4 therapy

Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer

Gary L. Francis, Steven G. Waguespack, Andrew J. Bauer, Peter Angelos, Salvatore Benveniga, Janete M. Cerutti, Catherine A. Dinauer, Jill Hamilton, Ian D. Hay, Markus Luster, Marguerite T. Parisi, Marianna Rachmiel, Geoffrey B. Thompson, and Shunichi Yamashita
## Definition of risk-groups for recurrent/persistent disease according to “post-operative-staging” classifications

<table>
<thead>
<tr>
<th>Post-operative staging</th>
<th>Low risk (Grade 1)</th>
<th>Intermediate risk (Grade 2)</th>
<th>High risk (Grade 3)</th>
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<tr>
<td>ATA</td>
<td>Disease confined to the thyroid  No local or distant metastases  No invasion of locoregional tissues</td>
<td>Extensive LN metastases to cervical level VI compartment or minimal invasion to cervical levels I, II, III, IV, or V</td>
<td>Regionally extensive disease or locally invasive disease <strong>with or without distant metastasis</strong>*</td>
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*Distant metastasis, except in the lungs in DTC, is rare among the younger age group*
Figure 6  Papillary thyroid carcinoma metastatic to lungs. A 15-year-old girl with PTC, Stage II (T4a, N1b, M1); this is the same patient as in Fig. 2. A 5-mm coronal (A) and axial (B) maximum-intensity-projection image from a non-contrast-enhanced CT of the lung demonstrate numerous bilateral peripheral lung nodules. Pulmonary metastases occur in as many as 20% of children with PTC.
Lung metastases in the pediatric age group

- Occur in 25% (9%–30%) of pediatric patients with DTC

- Children with DTC are more likely to have pulmonary metastases compared with adults

- The chance of having pulmonary metastases
  - Is inversely related to patient age
  - Increases when the post operative Tg levels are high

Pulmonary metastasis in most pediatric patients could be diagnosed only after performing WBS following $^{131}$I.

Chest x-rays* and CT-scan are not sensitive to detect lung metastasis.

* x-ray–positive pulmonary metastases in children are often misinterpreted.

Bal et al. THYROID 2004; 14:217-225
FIG. 2. A 16-year-old male, in whom although postsurgical 48-hour radioiodine uptake (RAIU) was 27%, x-ray and high-resolution computed tomography (CT)-negative pulmonary metastasis was revealed by first postsurgical low-dose whole-body scan (WBS). His pulmonary metastasis responded well to $^{131}$I and was ablated with one dose of $^{131}$I. A: Normal chest x-ray. B: Normal high-resolution CT scan. C: Postsurgical low-dose $^{131}$I WBS revealing pulmonary metastasis (looks like perfusion lung scan). D: Last posttherapy WBS showing no $^{131}$I concentration in the lungs.
The patterns of lung metastases

- **Diffuse (miliary)**
  - excellent $^{131}$I uptake

- **Micronodular defined radiologically as <1 cm in diameter**
  - good $^{131}$I uptake

- **[Macronodular defined radiologically as >1 cm in diameter**
  - poor $^{131}$I uptake (surgical resection)]

The majority of children with pulmonary metastases have micronodular disease
Treatment of lung metastases

Treatment is based on $^{131}\text{I}$ with a WBS performed 3–5 days after the dose

- Iodine-avid pulmonary metastases benefit from $^{131}\text{I}$ treatment
- $^{131}\text{I}$ could successfully destroy micronodular pulmonary lesions, especially in younger patients ([Schlumberger et al 2001](#))

- In microscopic and small volume lung disease - complete remission
- With increasing burden of disease - administration of multiple $^{131}\text{I}$ treatment
The optimal frequency of $^{131}$I treatment is not determined

- **Past:** Treatment is repeated every 10 - 12 months until the disappearance of any uptake on the scan

- **Present:** Less-aggressive use of $^{131}$I
  
  A continuous improvement in serum Tg levels for years following discontinuation of $^{131}$I therapy in children with pulmonary metastases

- The maximal clinical and biochemical response from an administered activity of $^{131}$I may not be reached for up to 15 – 18 months
- The effects of therapy can be seen beyond the first years after treatment
- Longer intervals between $^{131}$I therapy would seem prudent in the child who does not demonstrate progressive disease

Padovani et al Thyroid 2012; 22:778–783*
A cascade of alveolar damage with inflammatory response and subsequent fibrotic changes

Occurs in 10% of pediatric thyroid cancer patients with diffuse pulmonary metastases treated with $^{131}\text{I}$

The risk correlates with
- The intensity of $^{131}\text{I}$ uptake
- The age of the patient

The risk is increased
- When the retained $^{131}\text{I}$ activity exceeds 80 mCi (3 GBq) at 24 hours
- When cumulative activities of administered $^{131}\text{I}$ is about 352 mCi (13 GBq).
Classification of pulmonary fibrosis*

- **Stage 0 fibrosis**: Normal CT images, no signs of fibrosis
- **Stage 1 fibrosis**: Discrete signs of fibrosis in the periphery of the lungs (subpleurally, <2 cm) or thickening of septa or irregularities of the pleura
- **Stage 2 fibrosis**: Discrete streaks of fibrosis in the center of the lungs
- **Stage 3 fibrosis**: Net-like fibrosis in the center of the lung without destruction of architecture
- **Stage 4 fibrosis**: Honeycomb changes in the center of the lung with destruction of lung architecture

* Based on the principles of the SOMA/LENT scoring system

Pulmonary fibrosis

Is diagnosed by

CT scan

Pulmonary function testing

Lung metastases - outcome

Cure

- **Definition:** complete biochemical remission - Tg < 2 ng/liter
  - negative WBS
- In > 80% of children with lung metastases
- After 2-3 courses of $^{131}$I treatment

Persistent disease

- In ~20% of children with lung metastases
- The vast majority of whom will demonstrate stable metastatic disease and low disease-specific mortality
FIGURE 5. $^{131}$I WBS of posterior chest after treatment. Thyroid-stimulating hormone level was 40 mU/L, and Tgb level was 850 μg/L. 14-y-old girl was seen 6 y after initial diagnosis of juvenile papillary thyroid carcinoma. She had been treated with surgery, EBRT (115 Gy), and 4 doses of $^{131}$I.

FIGURE 6. $^{131}$I WBS of anterior chest after diagnostic $^{131}$I dose (thyroid-stimulating hormone level, 45 mU/L; Tgb level, 13 μg/L) of same patient as in Figure 5 but 2 y later.
Pulmonary metastases can remain stable for extended periods.

The growth rate of lung metastases is usually very slow on L-T4 suppressive therapy.

Persistent disease may cause death several decades after initial treatment.

Pawelczak et al. THYROID 2010; 10:1095-1101
**DTC in SCMCI (1997 – 2017)**

Pediatric DTC

63 patients

Without lung metastases

48 (76%)

With lung metastases

Prepubertal

8 (75%)

Nodal

4

Miliary

4

Persistent

3

Pubertal

5 (20%)

Nodal

3

Miliary

2

Persistent

1

(ND 1)

Post pubertal

2 (10%)

Nodal

1

Miliary

1

Persistent

1
There is a need for developing the best management strategy in pediatric patients with DTC and lung metastases

- Early detection of the pulmonary metastases
- Administer the most effective treatment
- Meticulous follow-up including pulmonary function testing

in order to optimize the survival profile
THANKS