28 year old woman with metastatic thyroid cancer

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Dr. Cohen does not have any relevant financial relationships with commercial interests.

History at Presentation

- 1997 – 8 year old girl who developed UTI symptoms. She saw her pediatrician, who noted a multinodular goiter on exam. She was referred to Dr. Rosenfield.
- **US** (per note): thyroid replaced by nodules. **Technetium scan**: Multiple cold nodules. **Chest CT**: multiple bilateral pulmonary nodules (largest 4 mm); bilateral infiltrating thyroid mass extending into upper anterior mediastinum
- Dr. Kaplan performed a **total thyroidectomy, central and mediastinal node dissection, right modified neck dissection, and left jugular node dissection**.
- Path:

  -**Multicentric papillary carcinoma, follicular variant**.

  -Tumor invades through the capsule into the surrounding soft tissue and to the inked surgical margin in several areas.

  Lymph node dissection

  -Left central and left mediastinal: Metastatic thyroid carcinoma in eight of eight nodes (8/8).

  Right modified neck dissection:

  -Metastatic thyroid carcinoma in seven of fourteen nodes (7/14).

  "Jugular lymph nodes":

  -Metastatic tumor in two of two nodes (2/2).

  "Lymph node":

  -Metastatic thyroid carcinoma in one node (1/1).

History (Continued)

- Referred to Dr. De Groot
- 9/15/97 Diagnostic **^{131}Iodine scan** revealed: 1. Bilateral foci in upper anterior neck likely representing nodes. 2. Faint focus adjacent to these foci likely representing thyroid bed activity. 3. Faint region in right chest that is only minimally different from left chest
- 9/18/97 **Neck CT**: diffuse cervical adenopathy
- 9/18/97 **Chest CT** (infused): multiple small pulmonary nodules throughout both lungs, increased slightly in number in the right lung.
- Plan: Further surgery prior to consideration of RAI

History (Continued)

- 12/97 – The patient underwent bilateral anterior jugular node dissection
- Pathology: “The histology of the metastatic tumor is similar to the thyroid tumor that was diagnosed as follicular variant of papillary carcinoma”

  -"right neck (anterior) jugular, right neck mass":
  one out of two lymph nodes with metastatic adenocarcinoma.
  (1/2) See comment.
  -"right neck, highest lymph node tissue":
  one lymph node with no evidence of metastatic tumor (0/1)
  -"left jugular lymph nodes":
  six lymph nodes with no evidence of metastatic tumor (0/6)

- The patient was then withdrawn from levothyroxine in anticipation of RAI

History (Continued)

- 8/98 TSH =154 mcU/ml. Tg = 88 ng/ml. ^{131}Iodine scan revealed uptake in the neck bilaterally, as well as possible lung uptake (R > L). Treated with **50.9 mCi ^{131}Iodine** (no post-therapy scan).
- 8/99 Follow-up **^{131}Iodine scan**: Neck uptake is now resolved. Mild diffuse activity noted in lungs.
  - %uptake in neck: 0.14
  - % uptake in chest: 0.25
- 8/00 **^{131}Iodine scan**: Faint diffuse radiotracer uptake in both lungs that is more prominent in the right base is re-demonstrated with no significant interval change
- Last saw Dr. DeGroot in 2003, and he noted that there was only very faint uptake in lungs. Plan: "Check CT scan. But Rx a ?"
- Dr. De Groot retired and left the U of C for Brown University, and the patient followed up with me a few years later.

History, Physical Exam, Labs, and Initial Plan in 2006

- I first saw patient in 2006, when she was 17 years old:
  - At that time, she felt well. No SOB. No specific concerns.
  - No history of radiation exposure
  - No family history of thyroid cancer
  - No other significant PMH.
  - Physical exam was unremarkable other than the absence of her thyroid
  - TSH 0.06 mcU/ml
  - Tg was 38 ng/ml (negative Abs)
- What is the best plan? Should we continue to monitor or treat with RAI?

Follow-up

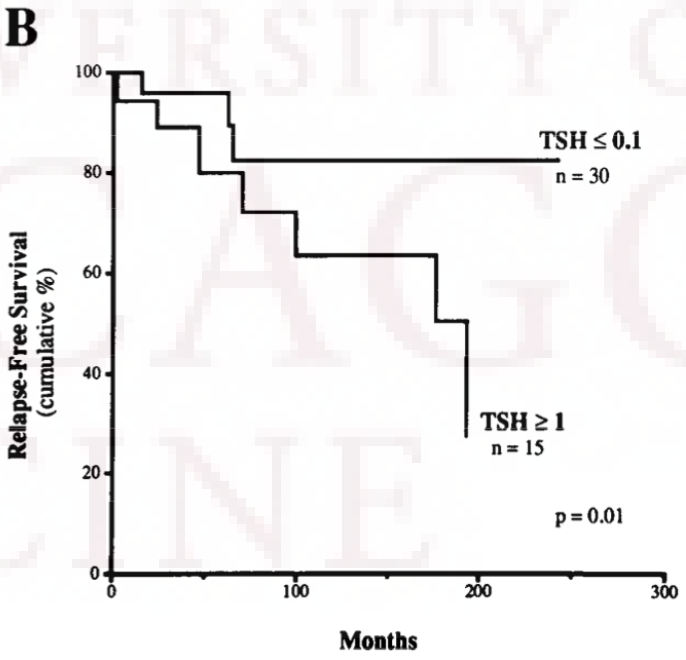
- The patient and her family declined RAI.
- Since that time, the patient has been followed by periodic surveillance studies:
  - Neck ultrasound: No evidence of recurrence
  - Chest CT scan, most recently in 2015: Bilateral innumerable lung nodules, not increased in either size or number from prior studies
  - Thyroglobulin measurements: Stable, generally in 30-50 ng/ml range
  - Mild TSH suppression

Recent Visit

- Last seen about a month ago.
- Doing well. Working as a pharmacist. Recently married. Tg 34 ng/ml (stable). Clinically euthyroid. TSH 0.65 mcU/ml (last year, TSH was 0.08 on the same LT4 dose)
- She is interested in starting a family soon, and wants to know your opinion. Is this safe for her to get pregnant? What are the issues involved?

TSH Suppression and Relapse-Free Survival

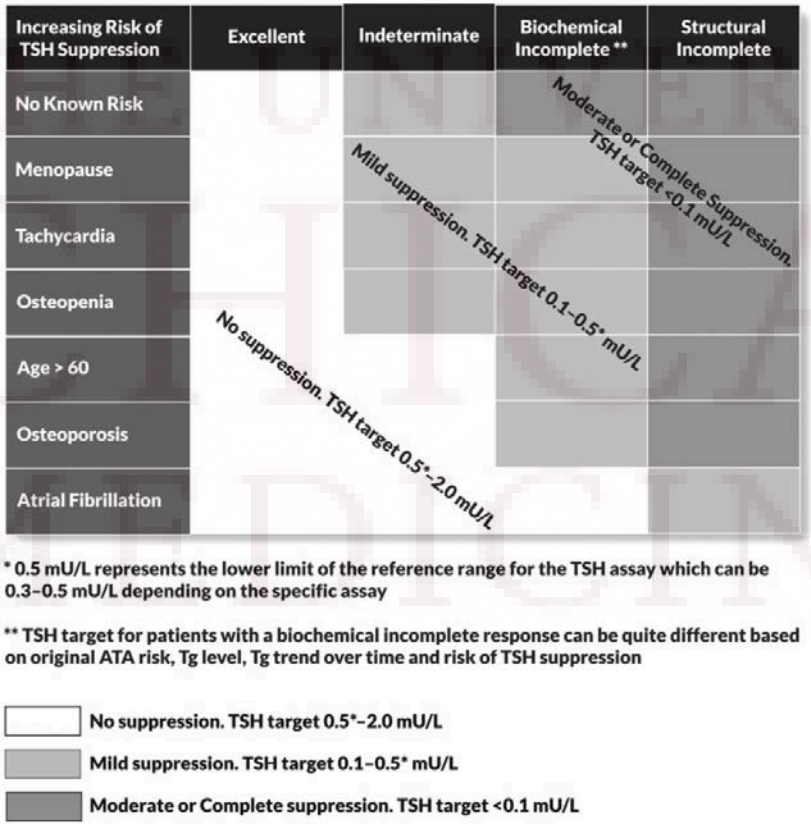
- 141 patients from 1970-1993 with DTC
- All patients underwent surgery (126 total; 15 subtotal)
- 126 patients received one or more doses RAI (mean dose 143 mCi)
- Follow-up: TSH, Tg, and CXR yearly; 131-Iodine scan yearly x 3 years



Pujo, et al, JCEM, 1996, 81: 4318

2015 ATA Guidelines for TSH Suppression in DTC

TABLE 15. THYROTROPIN TARGETS FOR LONG-TERM THYROID HORMONE THERAPY



Haugen, et al, Thyroid, 2016, 26: 1-133.

DTC Risk Categories

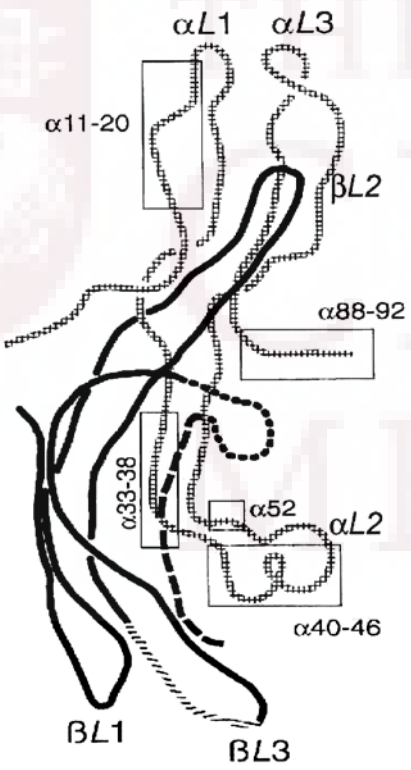
TABLE 13. CLINICAL IMPLICATIONS OF RESPONSE TO THERAPY RECLASSIFICATION IN PATIENTS WITH DIFFERENTIATED THYROID CANCER TREATED WITH TOTAL THYROIDECTOMY AND RADIOIODINE REMNANT ABLATION

Category	*Definitions*[a]	*Clinical outcomes*	*Management implications*
Excellent response	Negative imaging ***and either*** Suppressed Tg <0.2 ng/mL[b] ***or*** TSH-stimulated Tg <1 ng/mL[b]	1%–4% recurrence[c] <1% disease specific death[c]	An excellent response to therapy should lead to an early decrease in the intensity and frequency of follow up and the degree of TSH suppression
Biochemical incomplete response	Negative imaging ***and*** Suppressed Tg ≥1 ng/mL[b] ***or*** Stimulated Tg ≥10 ng/mL[b] ***or*** Rising anti-Tg antibody levels	At least 30% spontaneously evolve to NED[d] 20% achieve NED after additional therapy[a] 20% develop structural disease[a] <1% disease specific death[a]	If associated with stable or declining serum Tg values, a biochemical incomplete response should lead to continued observation with ongoing TSH suppression in most patients. Rising Tg or anti-Tg antibody values should prompt additional investigations and potentially additional therapies.
Structural incomplete response	Structural or functional evidence of disease With any Tg level With or without anti-Tg antibodies	50%–85% continue to have persistent disease despite additional therapy[e] Disease specific death rates as high as 11% with loco-regional metastases and 50% with structural distant metastases[a]	A structural incomplete response may lead to additional treatments or ongoing observation depending on multiple clinico-pathologic factors including the size, location, rate of growth, RAI avidity, ^{18}FDG avidity, and specific pathology of the structural lesions.
Indeterminate response	Nonspecific findings on imaging studies Faint uptake in thyroid bed on RAI scanning Nonstimulated Tg detectable, but <1 ng/mL Stimulated Tg detectable, but <10 ng/mL ***or*** Anti-Tg antibodies stable or declining in the absence of structural or functional disease	15%–20% will have structural disease identified during follow-up[a] In the remainder, the nonspecific changes are either stable, or resolve[a] <1% disease specific death[a]	An indeterminate response should lead to continued observation with appropriate serial imaging of the nonspecific lesions and serum Tg monitoring. Nonspecific findings that become suspicious over time can be further evaluated with additional imaging or biopsy.

Haugen, et al, Thyroid, 2016, 26: 1-133.

HCG and TSH

Model of TSH based on structure of HCG



Grossmann, et. al., Endo Rev, 1997

- HCG and TSH are composed of α and β subunits
- The α subunits of HCG and TSH are the same
- Only the β subunits are different, and provide specificity at the TSH receptor

Does Pregnancy Worsen Outcomes in Patients with DTC?

- Is it safe for this patient to become pregnant?
- What are the chances of disease progression during pregnancy?

Does Pregnancy Worsen Outcomes in Patients with DTC?

- Retrospective study of 235 patients at MSKCC
- Included patients with DTC who had a full-term pregnancy after an initial treatment for DTC between 1997-2015
- Clinical Status:
  - **Excellent** (Tg < 0.6 ng/ml and no Abs);
  - **Indeterminate** (Tg between 0.6 and 1 ng/ml, Tg Abs that are stable or declining, or nonspecific structural findings on imaging)
  - **Biochemical Incomplete**: Tg> 1 ng/ml or increasing Ab titer;
  - **Structural Incomplete**: persistent locoregional or distant mets);
- "Structural progression" defined by an increase of 3 mm or more of any lesion; or the development of a new metastatic focus
- "Clinically significant" defined as progression that was either symptomatic or led to additional treatment in the first 18 months after pregnancy
- "Biochemical progression" defined as an increase in Tg or Tg antibodies. Increase of Tg > 0.2 ng/ml above a baseline of < 1 ng/ml; increase by > 1 ng/ml above baseline of 1.1-10 ng/ml; or increase by > 20% above baseline of Tg> 10 ng/ml

Pre-pregnancy Clinical Status	n	Clinically Significant Structural Disease Recurrence/Progression Leading to Additional Therapy	Minor Structural Disease Recurrence/Progression Not Requiring Additional Therapy	Post-partum Tg Elevated Above Pre-pregnancy Baseline
Excellent	148	0%	0%	6.8% (10/148)
Indeterminate	29	0%	0%	6.9% (2/29)
Biochemical Incomplete	20	0%	0%	20% (4/20)
Structural Incomplete	38	8% (3/38)	21% (8/38)	31.6% (12/38)

Rakhlin, Fish, and Tuttle, Thyroid, 2017, In Press.

Characteristics of the 11 Patients With Structural Disease Progression

	Patient	Race/Ethnicity	Age at diagnosis (yrs)	Age at delivery (yrs)	Histology	Primary tumor size (cm)	Known nodal involvement at diagnosis	Distant metastasis at diagnosis	ATA Risk 2009	TNM/ AJCC	Structural progression prior to pregnancy	Structural progression during pregnancy	Follow up after delivery
	1	Caucasian	25	40	Follicular variant, papillary	1.9	No	No	Intermediate	1	No	Yes	Observation
	2	Caucasian	29	33	Classic papillary	1.9	Yes	No	High	1	No	Yes	Observation
	3	Caucasian	32	35	Classic papillary	1.5	Yes	No	Intermediate	1	Yes	Yes	Observation
	4	Caucasian	23	28	Classic papillary	2.5	No	No	Intermediate	1	Yes	Yes	Observation
→	5	Caucasian	22	23	Poorly differentiated	5.5	Yes	Yes-lung	High	2	Yes	Accelerated	Chemotherapy
→	6	Asian	23	44	Classic papillary	3.6	Yes	Yes-lung	High	2	Yes	Yes	Observation
→	7	Unknown	31	34	Classic papillary	1.6	No	Yes-lung	High	2	No	Yes	Observation
	8	Caucasian	35	38	Classic papillary	5.5	Yes	No	Intermediate	1	No	Yes	Observation
	9	Caucasian	41	44	Classic papillary	1.1	Yes	No	Intermediate	1	Yes	Yes	Observation
**	10	Caucasian	25	32	Classic papillary	2.4	No	No	High	1	Yes	Yes	Neck dissection
**	11	Caucasian	19	20	Classic papillary	Unknown	Yes	No	Intermediate	1	Yes	Accelerated	Neck dissection

*All had undergone total thyroidectomy and radioactive iodine ablation at diagnosis.

** Requiring further therapy

→ Presentation included lung mets

Rakhlin, Fish, and Tuttle, Thyroid, 2017,In Press.

Conclusions

- Risk of progression is probably low, except in patients with a structural incomplete response
- However, it is not clear for this patient the likelihood of disease progression.
- It may be reasonable for her to become pregnant, with careful monitoring, but there are also risks.