THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

"A 63 year old with a history of thyroid cancer presents with leg swelling"

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

ENDORAMA
A 63 year old with a history of thyroid cancer presents with leg swelling

Laura Dickens

September 15, 2016

Chief complaint

Mr. LBJr is a 63 year old man with a past medical history of metastatic papillary thyroid cancer, HTN, and OSA presents from oncology clinic with one week of progressive bilateral lower extremity swelling and 10lbs weight gain.

Thyroid Cancer History

- January 1995 (age 42) – thyroid nodule with FNA suggestive of papillary carcinoma
- February 1995 – Thyroidectomy and L radical neck dissection
  - Invasive **moderately to poorly differentiated follicular carcinoma** (4.5cm in greatest extent) virtually replacing the left lobe. No apparent extension of the tumor beyond the confines of the thyroid capsule.
  - 12/13 mediastinal lymph nodes showing complete replacement by metastatic thyroid carcinoma
  - 7/21 jugular lymph nodes with metastatic thyroid carcinoma and foci of extranodal extension of tumor
- March 1995 → 100 mCi RAI

Thyroid cancer staging and risk assessment

TABLE 10. AJCC 7TH EDITION/TNM CLASSIFICATION SYSTEM FOR DIFFERENTIATED THYROID CARCINOMA

	Definition
T0	No evidence of primary tumor
T1a	Tumor ≤1 cm, without extrathyroidal extension
T1b	Tumor >1 cm but ≤2 cm in greatest dimension, without extrathyroidal extension
T2	Tumor >2 cm but ≤4 cm in greatest dimension, without extrathyroidal extension.
T3	Tumor >4 cm in greatest dimension limited to the thyroid ***or*** Any size tumor with minimal extrathyroidal extension (e.g., extension into sternothyroid muscle or perithyroidal soft tissues).
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.
T4b	Tumor of any size invading prevertebral fascia or encasing carotid artery or mediastinal vessels
N0	No metastatic nodes
N1a	Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes).
N1b	Metastases to unilateral, bilateral, or contralateral cervical (levels I, II III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII)
M0	No distant metastases
M1	Distant metastases

Patient age <45 years old at diagnosis			
I	Any T	Any N	M0
II	Any T	Any N	M1

TABLE 11. ATA 2009 RISK STRATIFICATION SYSTEM WITH PROPOSED MODIFICATIONS

ATA low risk	Papillary thyroid cancer (with all of the following): • No local or distant metastases; • All macroscopic tumor has been resected • No tumor invasion of loco-regional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan • No vascular invasion • Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)[a] Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer[a] Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion[a] Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF*^{V600E} mutated (if known)[a]
ATA intermediate risk	Microscopic invasion of tumor into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension[a] Multifocal papillary microcarcinoma with ETE and *BRAF*^{V600E} mutated (if known)[a]
ATA high risk	Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension[a] Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)[a]

[a]Proposed modifications, not present in the original 2009 initial risk stratification system. See sections [B19]–[B23] and Recommendation 48B.

Thyroid. 2016 Jan;26(1):1-133.

Thyroid Cancer History, continued

- September 1995 – mediastinal node dissection
  - R superior lymph node and mediastinal mass showing poorly differentiated follicular carcinoma
- September 1995 → 150 mCi RAI
- Early 2000 – bony spinal metastases at T11-L1, pulmonary metastases
- February 2000 → 201 mCi RAI
- September 2001 → 200 mCi RAI
- April 2002 → 203 mCi RAI

Thyroid Cancer History, continued

- March 2012 – uptake and scan shows no uptake in thyroid bed, multiple foci in both lung fields, questionable sacral metastasis in the L pelvis
- March 2012 → 192 mCi RAI
- January 2013 – CT shows slight increase in bilateral pulmonary mets, L4 and R iliac lytic bone lesions
- April 2013 – transitions oncology care to UCMC

Treatment summary

- Surgery
  - Total thyroidectomy and neck dissection
- RAI treatment total = **1,046 mCi**
  - March 1995 – 100 mCi masonic
  - September 1995 – 150 mCi Rush
  - February 2000 – 201 mCi NWMH
  - September 2001 – 200 mCi NWMH
  - April 2002 – 203 mCi NWMH
  - March 2012 – 192 mCi Stroger
- TSH suppression
  - Levothyroxine 300 mcg daily

Thoughts about his treatment to date?

RAI refractory thyroid cancer

- Definition of RAI refractory disease [1]
  - Malignant/metastatic tissue never concentrates RAI
  - Tumor tissue loses ability to concentrate RAI
  - RAI concentrates in some lesions but not others
  - Metastatic disease progresses despite significant concentration of RAI
- Management
  - If disease is asymptomatic, stable, or minimally progressive → monitoring on TSH suppressive therapy with serial imaging is an option
  - If disease is symptomatic, rapidly progressive, imminently threatening → consider advanced treatment options (clinical trail, TKI, chemotherapy)

Risks of RAI Therapy

- RAI dose and risk of secondary malignancies
  - Study in 2003 evaluated risk of second primary malignancies (SPM) in a European Cohort of thyroid cancer patients
  - 6841 patients, 62% received I-131
  - Patients who received RAI had increased rates of cancer involving salivary glands (RR 7.5), bone and soft tissue (RR 4.0), female genital (RR 2.2), CNS (RR 2.2), and leukemia (RR 2.5)
  - Increased risk of solid tumors and leukemias was seen with increasing cumulative activity of I-131

Table 4 Excess of relative risk per cumulative activity of ^{131}I in GBq (ERR) according to external radiotherapy for major types of SPMs

	No external radiotherapy		External radiotherapy		All the patients		
Type of SPM	**ERR per GBq of ^{131}I[a] (95% CI)**	**Test of trend[b]**	**ERR per GBq of ^{131}I[a] (95% CI)**	**Test of trend[b]**	**ERR per GBq of ^{131}I[c] (95% CI)**	**Test of trend[b]**	**Test of heterogeneity[d]**
Solid cancers[e]	0.03 (0.002–0.08)	0.03	0.04 (0.00006–0.09)	0.05	0.04 (0.009–0.07)	<0.01	0.6
Soft-tissue and bone cancer	0.29 (?–1.74)[f]	0.2	1.04 (?–3.93)[f]	<0.001	0.61 (?–2.41)[f]	<0.001	0.9
Colorectal cancer	0.15 (0.02–0.38)	0.01	0.02 (?–0.20)[f]	0.7	0.10 (0.08–0.27)	0.03	0.4
Breast cancer	0.002 (?–0.07)[f]	1.0	–0.02 (?–0.04)[f]	0.3	–0.01 (?–0.04)[f]	0.6	0.3
Leukaemias	0.22 (?–1.30)[f]	0.2	0.59 (?–2.34)[f]	<0.01	0.39 (?–1.54)[f]	0.01	0.4

[a]Stratified on study group. [b]Test of trend for a linear dose–effect relationship: *P*-value. [c]Adjusted on external radiotherapy and stratified on study group. [d]Test of heterogeneity of the ERR between patients exposed and nonexposed to external radiotherapy. [e]All cancers except leukaemias, thyroid cancers, and nonmelanoma skin cancers. [f]Lower bound not calculable.

Br J Cancer. 2003 Nov 3;89(9):1638-44.

Table 2 Observed number of SPMs, standardized incidence ratio (95% confidence interval) and risk of SPM in relation to ^{131}I administration, among the 6841 patients treated for a papillary or follicular thyroid cancer

	All the patients (PYR = 77 955)			^{131}I therapy (PYR = 37 702)			No ^{131}I therapy (PYR = 40 253)			
Cancer site (ICD9 code)	Number of SPMs	SIR[a]	(95% CI)	Number of SPMs	SIR[a]	(95% CI)	Number of SPMs	SIR[a]	(95% CI)	Relative risk[b]: ^{131}I *vs* no ^{131}I (95% CI)
Oral cavity (140–145)	13	2.0	(1.0–3.4)	10	2.6	(1.2–4.8)	3	0.8	(0.2–2.2)	2.8 (0.8–13.0)
Salivary glands (142)[c]	7	–		6	–		1	–		7.5 (1.2–143)
Pharynx (146–149)	3	0.5	(0.09–1.6)	1	0.3	(0.02–1.5)	2	0.9	(0.2–2.9)	0.4 (0.02–4.7)
Digestive tract (150–159)	126	1.3	(1.0–1.5)	61	1.2	(0.9–1.5)	65	1.4	(1.0–1.8)	1.1 (0.8–1.5)
Stomach (151)	20	1.1	(0.6–1.7)	10	1.0	(0.5–1.7)	10	1.0	(0.5–1.7)	1.3 (0.5–3.2)
Colon and rectum (153–154)	69	1.3	(0.9–1.6)	37	1.4	(0.9–1.9)	32	1.1	(0.7–1.7)	1.3 (0.8–2.0)
Respiratory organs (161–163)	37	0.9	(0.6–1.3)	20	1.0	(0.6–1.6)	17	0.8	(0.4–1.4)	1.1 (0.5–2.3)
Lung cancer (162)	32	1.0	(0.6–1.4)	18	1.0	(0.6–1.6)	14	0.9	(0.4–1.7)	1.1 (0.5–2.3)
Bone and soft tissue (170–171)	19	5.9	(3.6–9.0)	14	5.8	(2.5–11.2)	5	1.8	(0.3–5.5)	4.0 (1.5–12.4)
Skin melanoma (172)	25	2.5	(1.6–3.7)	11	2.1	(1.1–3.8)	14	2.9	(1.6–4.9)	0.8 (0.3–1.8)
Breast (174)	128	1.3	(1.0–1.5)	54	1.2	(0.9–1.6)	74	1.3	(1.0–1.7)	0.8 (0.5–1.1)
Female genital organs (179–183)	57	0.7	(0.5–1.0)	36	0.9	(0.6–1.3)	21	0.6	(0.3–0.9)	2.2 (1.3–3.9)
Uterus (179–182)	39	1.0	(0.7–1.4)	25	1.1	(0.7–1.7)	14	0.8	(0.4–1.4)	2.3 (1.2–4.7)
Ovary (183)	20	0.5	(0.3–0.8)	12	0.7	(0.3–1.2)	8	0.4	(0.1–0.8)	2.0 (0.8–5.2)
Male genital organs (185–186)	30	1.6	(1.0–2.4)	16	1.3	(0.6–2.3)	14	2.0	(1.1–3.4)	1.1 (0.5–2.3)
Urinary tract (188–189)	50	1.8	(1.3–2.4)	31	2.1	(1.4–3.1)	19	1.4	(0.7–2.3)	1.5 (0.9–2.8)
Bladder (188)	19	1.2	(0.7–1.9)	12	1.4	(0.7–2.3)	7	0.4	(0.1–1.2)	1.6 (0.6–4.5)
Kidney (189)	31	2.6	(1.7–3.8)	19	2.6	(1.5–4.4)	12	2.6	(1.3–4.5)	1.5 (0.7–3.3)
Central nervous system (191–192)	21	2.5	(1.5–3.8)	13	3.0	(1.6–5.2)	8	1.9	(0.8–3.7)	2.2 (0.9–5.7)
Endocrine glands (194)	18	3.1	(1.6–5.3)	10	5.2	(2.4–9.7)	8	1.5	(0.4–1.4)	1.6 (0.6–4.3)
Lymphoma (200–202)	17	1.1	(0.6–1.8)	10	1.1	(0.5–2.2)	8	1.2	(0.5–2.5)	1.0 (0.4–2.8)
Multiple myeloma (203)	6	1.4	(0.5–2.9)	4	1.6	(0.5–3.6)	2	0.6	(0.03–2.6)	1.4 (0.3–0.7)
Leukaemia (204–208)[d]	18	1.6	(0.8–2.7)	12	1.9	(0.8–3.6)	6	1.2	(0.4–2.8)	2.5 (1.0–7.4)
Other[e]	21	0.9	(0.5–1.5)	8	0.6	(0.2–1.3)	13	1.2	(0.6–2.1)	0.6 (0.2–1.5)
At least one cancer[f]	576	1.3	(1.2–1.4)	301	1.3	(1.1–1.5)	275	1.3	(1.1–1.4)	1.2 (1.0–1.4)

PYR = Number of person-years of follow-up. [a]Standardised incidence ratio adjusted on external radiotherapy. [b]Relative risk stratified on study group and adjusted on external radiotherapy. [c]No SIR could be calculated for this cancer since French reference rates are lacking for this localization. [d]One woman developed a leukaemia less than 1 year after the occurrence of a breast cancer. [e]Including the following sites (ICD9 code): 160, 164, 165, 175, 184, 187, 190, 195–199. [f]Number of patients with at least one cancer excluding thyroid cancers and nonmelanoma skin cancers: 13 patients with two second malignancies within 2 years.

Br J Cancer. 2003 Nov 3;89(9):1638-44.

Management at UCMC

- April 2013 – initial oncology visit
  - Patient asymptomatic, **plan to monitor with serial imaging**
- November 2013 – pathologic R hip fracture at site of bony metastasis
- March 2015 – oncology follow up
  - On Levothyroxine 350mcg daily
  - Bisphosphonate initiated
- April 2015 – PET scan shows extensive bony disease, metastasis in liver and lungs
- May 2015 – started on treatment with **Lenvatinib**
- Over the next year serial CT show stable disease, patient develops multiple side effects from Lenvatinib (fatigue, weight loss) leading to dose reduction

	Ref. Range	**3/30/15**	**7/20/15**	**9/14/15**	**11/6/15**	**1/6/16**	**4/4/16**	**6/22/16**
TG	<29 ng/mL	46000 (H)	5000 (H)	5250 (H)	12500 (H)	20000 (H)	46000 (H)	84000 (H)
TSH	0.30 - 4.00 mcU/mL	<0.01 (L)	<0.01 (L)	<0.01 (L)	<0.01 (L)	<0.01 (L)	<0.01 (L)	<0.01 (L)

Kinase Inhibitors for RAI-Refractory DTC

[C42] Kinase inhibitors

■ **RECOMMENDATION 96**

(A) Kinase inhibitor therapy should be considered in RAI-refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches. Kinase inhibitors that are FDA approved for differentiated thyroid carcinoma or other available kinase inhibitors (preferably within the context of therapeutic clinical trials) can be considered since the impact of these agents on overall survival and quality of life remains to be defined.

- Three TKIs have showed improved progression-free survival
  - Vandetanib
  - Sorafenib
  - Lenvatinib
- No studies have shown overall survival benefit or improved quality of life

Thyroid. 2016 Jan;26(1):1-133.

Lenvatinib for RAI-refractory thyroid cancer

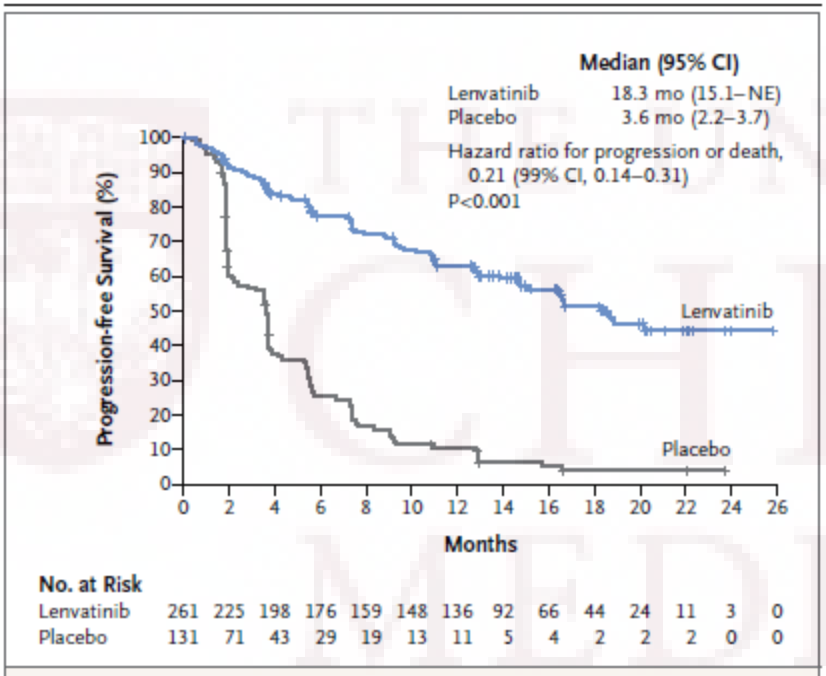

Figure 2. Kaplan–Meier Estimate of Progression-free Survival in the Intention-to-Treat Population.

Tumor responses were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by independent centralized radiologic review. Tumor responses were calculated as the maximum percentage change from baseline in the sum of the diameters of target lesions. CI denotes confidence interval, and NE not estimable.

- Randomized, double blind, placebo controlled trial
- 392 patients enrolled
  - 261 for Lenvatinib and 131 for placebo
- Primary end point was progression-free survival
  - Lenvatinib 18.3 months
  - Placebo 3.6 months Hazard ratio for progression or death 0.21, P<0.001)
- At a median follow up time of 17 months, disease progression occurred in
  - 35.6% of patients on Lenvatinib
  - 83.2% of patients on placebo

N Engl J Med. 2015 Feb 12;372(7):621-30.

Lenvatinib Adverse Effects

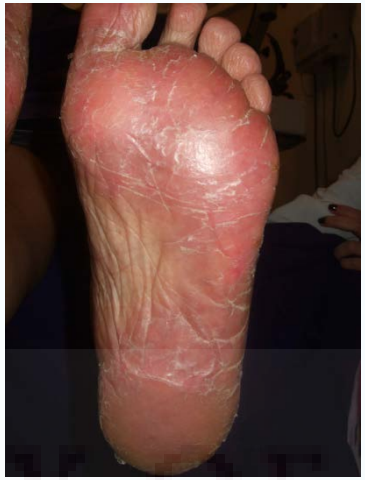

Table 3. Adverse Effects.

Effect	Lenvatinib (N=261)		Placebo (N=131)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any treatment-related adverse effect — no. of patients (%)	254 (97.3)	198 (75.9)	78 (59.5)	13 (9.9)
Adverse effect developing during treatment — no. of patients (%)				
Serious*				
Total	130 (49.8)		30 (22.9)	
Treatment-related	79 (30.3)		8 (6.1)	
Fatal				
Total†	20 (7.7)		6 (4.6)	
Treatment-related	6 (2.3)		0	

- 75.9% of patients on Lenvatinib had treatment-related adverse effects of grade 3 or higher
  - HTN (any grade 69.3%, grade >=3 42.9%)
  - Proteinuria (any grade 32.2%, grade >=3 10.0%)
  - Other adverse effects: arterial and venous thromboembolic events, renal failure, liver failure, GI fistula, prolonged QT, PRES
- Six deaths in patients on Lenvatinib (2.3%) were treatment related

N Engl J Med. 2015 Feb 12;372(7):621-30.

Moving forward his to hospital admission…

HPI: Pt was recently started on diuretics for LE swelling, over the past week noticed worsening swelling and decreased urination. Denies chest pain, orthopnea, PND, cough, fever.

ROS: +fatigue +weight loss (100lbs past year) +DOE +leg swelling

PMH: Thyroid cancer, HTN, OSA

PSH: Thyroidectomy and node dissection x2, spinal fusion, R hip replacement

Meds:

- Carvedilol 3.125mg BID
- Furosemide 40mg daily,
- Levothyroxine 300mcg daily,
- Metolazone 2.5mg daily,
- Tadalafil 10mg PRN
- Lenvatinib held x1 month

Social: Retired surgical tech, divorced, lives alone. Former smoker (quit 1971), no ETOH or drugs. No known exposure to radiation.

Family: Pancreatic cancer (mother), lung cancer (father, smoker), no family history of thyroid cancer

Physical exam

VITALS: Temp 35.9, BP 128/53, HR 66, RR 16, O2 sat 95% on RA, BMI 28

General: No apparent distress. Sitting in bed, appears comfortable

HEENT: NC/AT. No pharyngeal erythema, PERRL, EMOI

Neck: Golf ball sized mass in the L neck, mildly tender. Thyroid surgically absent, well healed midline horizontal and L vertical scars.

CV: Normal rate, regular rhythm. Extremities warm. Bilateral lower extremity edema, 4+, symmetric

Pulmonary: Clear bilaterally. No increased WOB, rales, or wheezes.

GI: Soft, non-tender, non-distended abdomen. No rebound or guarding.

MSK: No deformities. No joint swelling. Normal tone.

Neuro: AOx3, no focal deficits.

Skin: No rash, no acanthosis nigricans

Psych: Normal mood, appropriate

Admission Labs

135	94	74
5.4	23	**2.5**

136

Cr baseline 1.1-1.3

Ca 9.0
Mg 2.5
Ph **5.1**

6.5	3.2
1.6	0.8
139	**89**

195

	9.2
4.9	136

MCV 75.1

BNP= **3,025**
Troponin= <0.03
TSH <0.01

UA: -LE –nitrite, no protein, no bacteria, many hyaline casts

LE dopplers: negative for DVT

Focused differential diagnosis?

Evaluating for CHF -> TTE

- Left ventricle: Mildly dilated, normal wall thickness and diastolic performance. Systolic performance is normal with **EF 60-65%.** No RWMA.
- Right ventricle: Moderately dilated. Systolic performance is normal.
- Atria: Left and right atrial severely dilated. **Dilated IVC** suggestive of increased RA pressure
- Valves: Mild mitral regurgitation, mild-moderate tricuspid regurgitation, elevated RV systolic pressure consistent with **severe pulmonary hypertension** (peak 68mmHg + RA). Increased transaortic velocities consistent with increased flow, no aortic stenosis or regurgitation. No pulmonic stenosis or regurgitation.

Right Heart Catheterization

FINDINGS:
RA = 17 mmHg
RV = 62/20 mmHg
PA = 66/20 mmHg with a mean of 35 mmHg
Wedge pressure = 25 mmHg
PA saturations = 73.8%.
Systemic saturation = 96% on pulse ox.
Cardiac output by Fick = 12.2 L/minute
Cardiac index by Fick = 5.6 L/min/m2
SVR 393 (dyne*sec)/cm-5
PVR 0.82 Wood

CONCLUSIONS:
1. Elevated right-sided hemodynamics in the setting of elevated wedge pressure.
2. **High cardiac output**.

Differential for High Output HF

- **Hyperthyroidism**
- Carcinoid syndrome
- Sepsis
- Obesity
- Liver disease
- AV shunts
- Myeloproliferative disorders
- Anemia
- Beriberi

Additional TFTs…

- TSH <0.01
- Free T4 = **0.25** *(ref 0.9-1.7)*
- Total T3 = **310** *(ref 80-195)*
- Free T3 = **617** *(ref 230-420)*

How do you interpret these TFTs?

- Endocrinology consulted

T3 Thyrotoxicosis in Metastatic Follicular Thyroid Cancer

Thyrotoxicosis Associated With Distant Metastatic Follicular Carcinoma of the Thyroid

CAPT WILLIAM D. BOWDEN, MC, and MAJ ROBERT E. JONES, MC, San Francisco, Calif

Clinical Endocrinology (1994) 40, 429–434

Case of the Month

Metastatic thyroid cancer presenting as thyrotoxicosis: report of three cases

Case Report

Metastatic Follicular Thyroid Carcinoma Secreting Thyroid Hormone and Radioiodine Avid without Stimulation: A Case Report and Literature Review

Case Reports of Thyrotoxicosis in Metastatic Thyroid Cancer

TABLE 2. Present Case and Previously Reported Survivors

Case No. (Reference)	*Age at Diagnosis, Sex*	*Type of Tumor*	*Years to Metastasis*	*Years to Toxicosis*	*Response to Therapy*			*Total Dose of ^{131}I (mCi)*	*Length of Follow-up After Toxicosis*
					Metabolic		*Tumor*		
					*AT**	*^{131}I*	*^{131}I*		
12 (1)	30, M	Adenocarcinoma	15	15	+	+		Unknown	3 years
13 (12)	46, F	Follicular	8	16.5		+	+	Unknown	2 years
14 (13)	61, F	Unknown	0	0		+	+	198	6 months
15 (14)	57, F	Follicular	5	5	+	+		250	8 months
16 (3)	53, F	Follicular	0	0		+	+	300	2 years
17 (3)	27, F	Unknown	5	11	+	+	+	170	7 months
18 (15)	70, F	Adenocarcinoma	0	0		+	+	200	7 months
19 (15)	56, F	Follicular	0	0		+	+	400	1 year
20 (16)	46, F	Follicular	0	3		+		228	1 year
21 (16)	58, F	Follicular	0	0		+		128	2 months
22 (16)	56, M	Trabecular	0	4		+	+	336	9 months
23 (17)	68, F	Follicular	0	0		+	+	200	1 year
24 (18)	45, M	Follicular	0	0	+	+	+	280	1.5 years
25 (19)	30, F	Adenocarcinoma	9	9			+	150	2 months
26 (9)	57, F	Follicular	10	13		+	+	>100	3 years
27 (20)	57, M	Follicular	0	10	+	+	+	125	3 months
28 (Present case)	64, M	Follicular	0	0.2		+	+	386	1 year

*AT = antithyroid therapy.

South Med J. 1986 Apr;79(4):483-6.

Prevalence of Elevated T3 in Follicular Thyroid Carcinoma

TABLE 1. Thyroid function data for the patient groups

	Patients with massive metastatic thyroid cancer			Patients without recurrence	Significance of difference
	Papillary	Follicular	Medullary		
TSH (μIU/ml)	0.246 ± 0.804	0.068 ± 0.156	0.114 ± 0.216	0.219 ± 0.349	NS
FT_4 (ng/dl)	1.53 ± 0.29	1.38 ± 0.35	1.32 ± 0.16	1.45 ± 0.29	NS
FT_3 (pg/ml)	2.87 ± 0.62	3.53 ± 1.40	3.03 ± 0.41	2.69 ± 0.36	$P < 0.01$[a]
Tg (ng/ml)	1940 ± 2603	2089 ± 2916	NE	<0.5	NS[b]
Levothyroxine (μg/d)	135 ± 34	138 ± 34	114 ± 28	113 ± 25	$P < 0.05$[c]
FT_3/FT_4	1.91 ± 0.46	3.44 ± 4.43	2.31 ± 0.39	1.93 ± 0.47	$P < 0.05$[a]
Patients with positive Tg antibody	2	4	NE	0	

Normal values are as follows: TSH, 0.3–5 μIU/ml; FT_4, 0.7–1.6 ng/dl; FT_3, 1.7–3.7 pg/ml; thyroglobulin, less than 35 ng/ml. For statistical calculation of TSH values, values less than the detectable level (<0.003 μIU/ml) were regarded as zero. Tg values of patients with positive Tg antibody were excluded from statistical analysis. NE, Not evaluated; NS, not significant.

[a] Papillary and without recurrence vs. follicular.

[b] Papillary vs. follicular.

[c] Papillary and follicular vs. medullary and without recurrence.

- Study included 58 patients with metastatic thyroid cancer: 31 papillary, 20 follicular, seven medullary
- 4/20 patients (20%) with follicular carcinoma had abnormally high FT3 levels and FT3/FT4 ratio >3.5

J Clin Endocrinol Metab. 2008 Jun;93(6):2239-42.

What are the potential mechanisms of T3 thyrotoxicosis in metastatic thyroid cancer?

Increased Deiodinase Activity

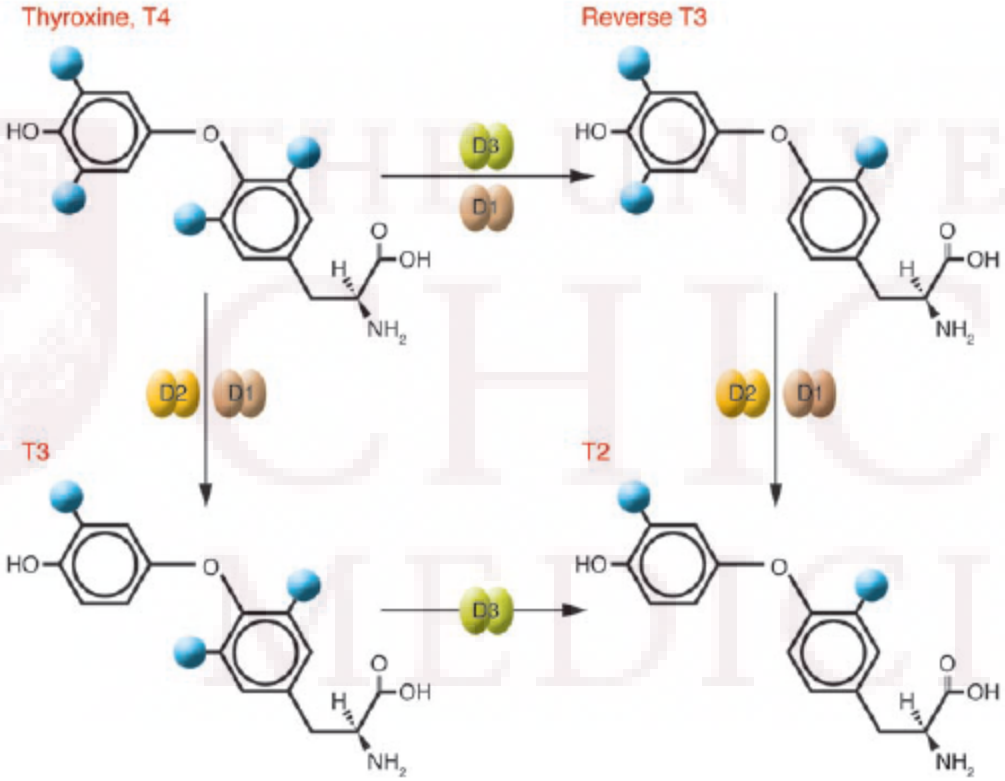

Figure 1
Basic deiodinase reactions. The reactions catalyzed by the deiodinases remove iodine moieties (blue spheres) from the phenolic (outer rings) or tyrosil (inner rings) rings of the iodothyronines. These pathways can activate T4 by transforming it into T3 (via D1 or D2) or prevent it from being activated by converting it to the metabolically inactive form, reverse T3 (via D1 or D3). T2 is an inactive product common to both pathways that is rapidly metabolized by further deiodination.

J Clin Invest. 2006 Oct;116(10):2571-9.

Next step in management?
How can you determine the cause?

Case, continued

- LT4 held
- Repeat TFTs show rapid drop in total T3 and free T4
- LT4 reinitiated at lower dose
- Diuresed on inotrope support, LE edema significantly improved
- Endo f/u this week

	23-Aug	25-Aug	27-Aug	29-Aug
TSH	<0.01			
FT4	0.48	0.12	<0.10	<0.10
Total T3	310	151	59	59
Free T3	617		121	136
rT3		66		
	8/23 Last dose LT4 300		8/28 start LT4 50mcg	

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