

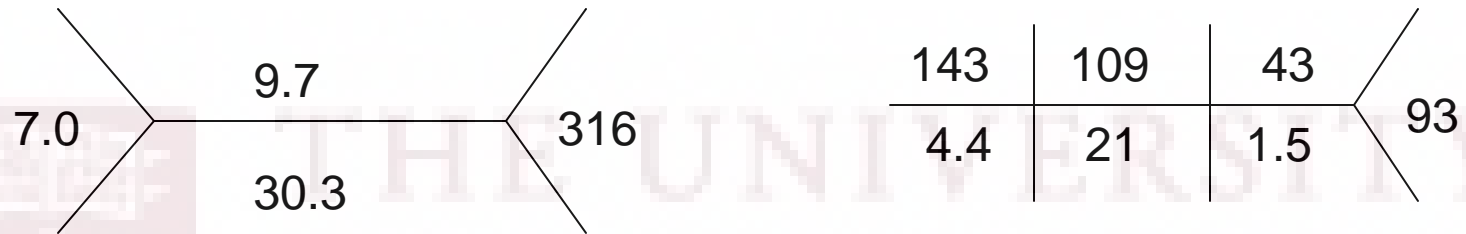
# 65 year old female with toxic multinodular goiter

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MD,  
Endorama, 10/25/2012

# History of past illness

- 65 year old woman who was diagnosed with diffuse goiter.
- Underwent partial thyroidectomy in 1998.
- Goiter recurred 2 years later.
- Patient remained euthyroid since her diagnosis.
- Presented with new onset A.fib in 06/19/2008.
- Received cardioversion on 06/30/2008
- A. fib recurred on 07/02/2008
- Thyroid labs were checked on 07/03/2008

# Labs:



## Thyroid labs:

TSH < 0.01, T3 210 (80-195 pg/dL), T4 11.7 (5-11.7 ng/dL)

Thyroglobulin AB  
neg, anti-TPO  
20480

Ca 9.0 mg/dL

Mg 2.1 mg/dL

Phos 3.6  
mg/dL

# Thyroid uptake and scan

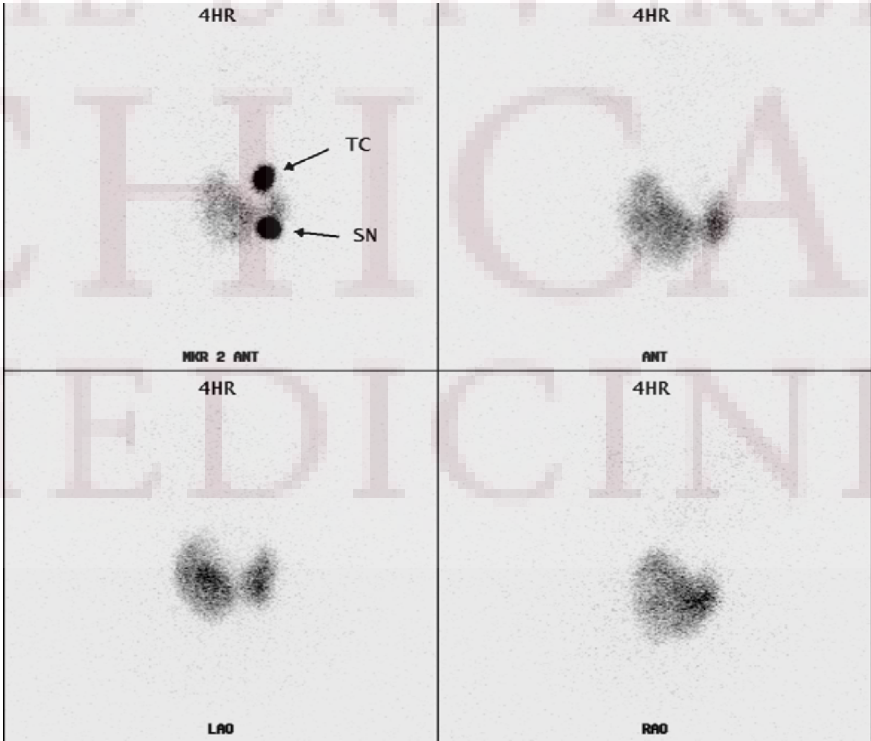
TECHNIQUE: 537 uCi I-123 (sodium iodide) p.o.

COMPARISON: None.

FINDINGS: The thyroid images demonstrate uniform activity in a gland with a small residual left lobe consistent with a history of partial resection. No foci of increased or decreased activity are seen. The 4-hour radioactive iodine uptake is 11% and the 24-hour uptake is 35% (normal range 10-30%).

IMPRESSION: Uniform mildly elevated thyroid uptake. In the setting of laboratory hyperthyroidism, this is suggestive of mild Graves' disease.

# Thyroid uptake and scan



# History of past illness

- The patient was started on methimazole and remained euthyroid on a very low dose of methimazole (5mg/day) till 05/02/2012

	Ref. Range	5/2/2012 11:30
Thyroxine, Free	Latest Range: 0.9-1.7 ng/dL	2.71 (H)
Thyrotropin	Latest Range: 0.30-4.00 mcU/mL	0.01 (L)

# Past medical history

- Past medical history:
  - Hypertension
  - Paroxysmal A.fib
  - ESRD on HD
  - Anemia of chronic kidney disease
  - Gout
- Medications: allopurinol, aspirin, clonidine, losartan, metoprolol, nifedipine, pravastatin, sevelamer, methimazole, warfarin.
- Family history: hypertension – mother, no history of thyroid problems or autoimmune disease in her family.
- Social history: no smoking, alcohol or illegal drugs, retired, denied any exposure to radiation or iodine.
- ROS: positive for palpitations in the chest, heat intolerance, nervousness, insomnia, weakness and fatigue.

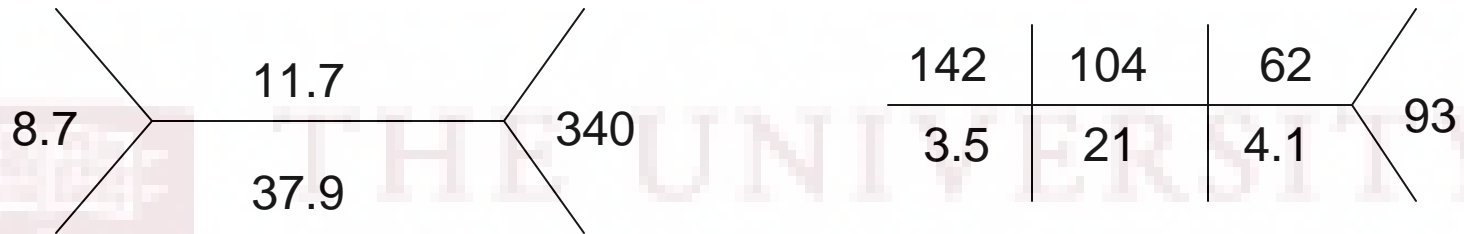
# Physical exam:

- Head: Normocephalic and atraumatic.  
Mouth/Throat: Oropharynx is clear and moist. No oropharyngeal exudate.
- Eyes: EOM are normal. Pupils are equal, round, and reactive to light. No scleral icterus.
- Neck: Normal range of motion. Neck supple. No JVD present. No tracheal deviation present. Thyromegaly present. **Palpable goiter mostly located on the right side of her neck**
- Cardiovascular: **Irregularly irregular rhythm**, normal heart sounds and intact distal pulses. Exam reveals no gallop and no friction rub. No murmur heard.
- Pulmonary/Chest: Effort normal and breath sounds normal. No respiratory distress. She has no wheezes. No rales. No tenderness.
- Abdominal: Soft. Bowel sounds are normal. No distension and no mass. There is no tenderness. There is no rebound and no guarding.
- Musculoskeletal: Normal range of motion. No edema and no tenderness. She has no cervical adenopathy.
- Neurological: She is alert and oriented to person, place, and time. No cranial nerve deficit. Normal muscle tone. Coordination normal. **Brisk reflexes in upper and lower extremities**
- Skin: Skin is warm. No rash noted. Not diaphoretic. No erythema. No pallor.
- Psychiatric: normal mood and affect, behavior is normal. Judgment and thought content normal.





# Labs:



Thyroid labs:

TSH < 0.01, free T3 510  
(230 – 420 pg/dL), free  
T4 1.98 (0.9 – 1.7 ng/dL)

TSI 2.8 (<=1.3)

Ca 9.6 mg/dL

Mg 2.0 mg/dL

Phos 3.4  
mg/dL

# US of thyroid

RIGHT LOBE MEASUREMENTS: 3.9 x 5.2 x 10.1 cm

LEFT LOBE MEASUREMENTS: 2.0 x 2.8 x 5.9 cm

ISTHMUS MEASUREMENTS: Variable, but approximately 5 mm

RIGHT LOBE: Numerous complex nodules throughout the right lobe. The largest measures 3.0 x 4.7 x 4.7 cm and is located superiorly.

LEFT LOBE: Numerous complex nodules throughout the left lobe. The largest is located at the equator measuring 1.4 to 1.6 x 2.3 cm

ISTHMUS: No significant abnormality noted.

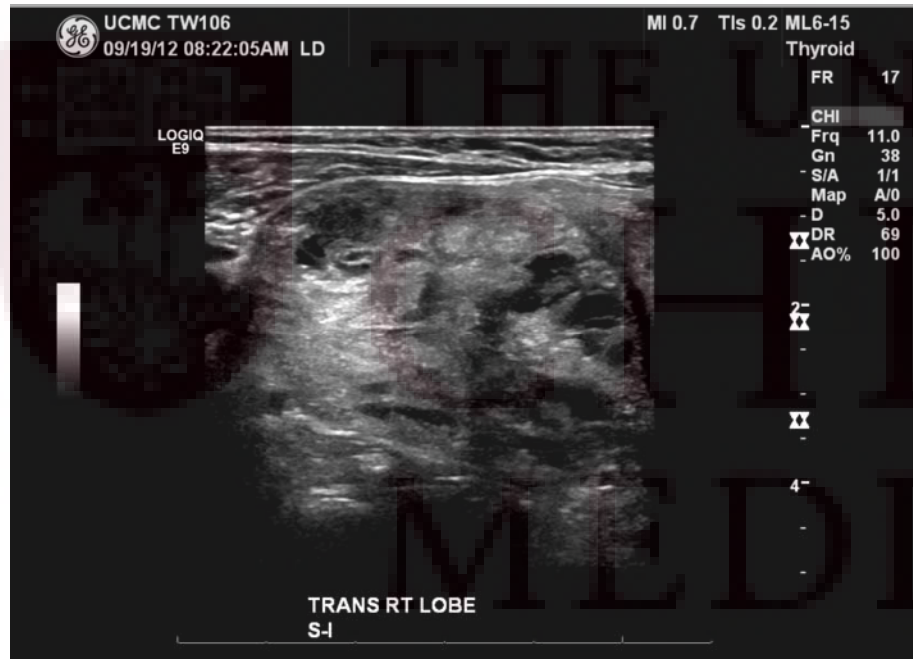
PARATHYROID GLANDS: No significant abnormality noted.

LYMPH NODES: Small bilateral lymph nodes measuring up to 1.9 cm in diameter.

OTHER: No significant abnormality noted.

IMPRESSION: Goiter with numerous complex nodules bilaterally.

# US of thyroid

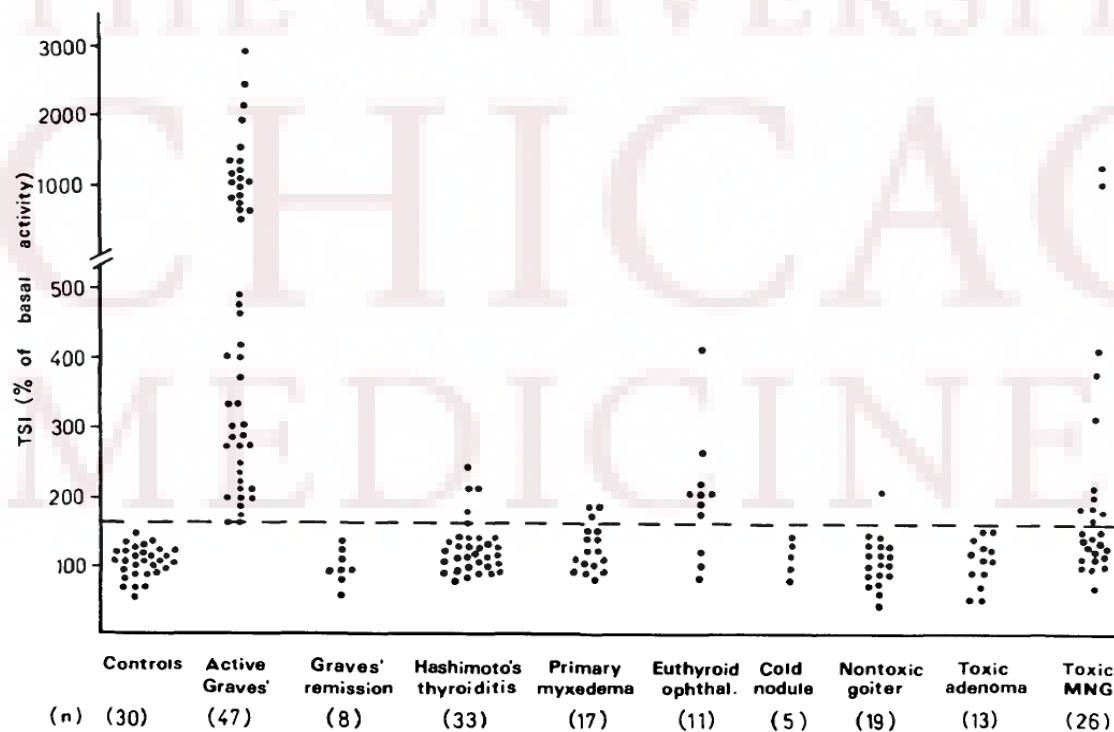


# Differential diagnosis for hyperthyroidism:

- ***Hyperthyroidism with a normal or high radioiodine uptake:***
  - Autoimmune thyroid disease: Graves disease, hashitoxicosis.
  - Autonomous thyroid tissue: toxic adenoma, toxic multinodular goiter, toxic adenoma.
  - TSH-mediated hyperthyroidism: TSH-producing pituitary adenoma, non-neoplastic TSH-mediated hyperthyroidism.
  - Human chorionic gonadotropin-mediated hyperthyroidism: hyperemesis gravidarum, trophoblastic disease.
- ***Hyperthyroidism with a near absent radioiodine uptake:***
  - Thyroiditis: subacute granulomatous (de Quervain's) thyroiditis, painless thyroiditis (silent thyroiditis, lymphocytic thyroiditis), amiodarone (also may cause iodine-induced hyperthyroidism), radiation thyroiditis, palpation thyroiditis.
  - Exogenous thyroid hormone intake: excessive replacement therapy, intentional suppressive therapy, factitious hyperthyroidism.
  - Ectopic hyperthyroidism: struma ovarii, metastatic follicular thyroid cancer.

## Questions:

- Is it Graves or toxic multinodular goiter? Can the combination of two coexist?
- Surgical vs radioactive iodine treatment vs ATD for toxic multinodular goiter
- Risk of relapse
- Is toxic multinodular goiter with autoimmunity has a higher chances of relapse post RAI treatment?



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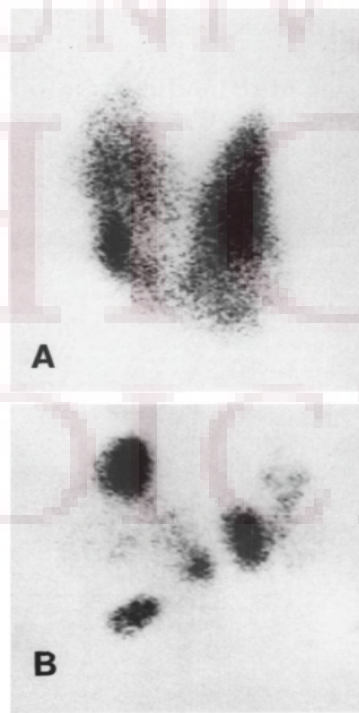


FIG. 1. Thyroid scintiscans of toxic multinodular goiter patients (anterior views). Type A, Diffuse but uneven (patchy) distribution of the radioisotope (technetium). Type B, Localization of the radioisotope in multiple discrete nodules of varying size and function.



TABLE 1. Clinical and laboratory data of patients with toxic multinodular goiter

Scintiscan pattern A <sup>a</sup>							Scintiscan pattern B <sup>b</sup>						
Patient no.	Age (yr), sex	Ophthal <sup>c</sup>	LSG <sup>d</sup>	Antimicro antibody <sup>e</sup>	Anti-Tg antibody <sup>f</sup>	TSI (% basal)	Patient no.	Age (yr), sex	Ophthal	LSG	Antimicro antibody	Anti-Tg antibody	TSI (% basal)
1	58, F	+	-	ND <sup>g</sup>	1:2560	1233	19	81, F	-	-	1:400	ND	212
2	31, F	-	-	ND	ND	1037	20	75, F	-	+	ND	ND	155
3	31, M	-	-	>1:1.6 × 10 <sup>6</sup>	1:20	412	21	67, F	-	-	1:100	ND	144
4	59, F	-	-	>1:1.6 × 10 <sup>6</sup>	1:20	379	22	55, M	-	-	ND	ND	130
5	55, F	-	-	>1:1.6 × 10 <sup>6</sup>	ND	313	23	83, F	-	+	1:1600	1:160	124
6	48, F	-	-	>1:1600	ND	203	24	81, M	-	+	1:100	ND	124
7	75, F	-	-	>1:1.6 × 10 <sup>6</sup>	ND	186	25	63, F	-	+	ND	ND	123
8	38, M	-	-	ND	ND	173	26	61, M	-	-	ND	ND	107
9	33, F	+	-	ND	ND	171							
10	67, M	+	-	ND	ND	164							
11	60, F	-	-	ND	ND	156							
12	49, F	-	-	1:100	ND	128							
13	51, F	-	-	>1:1.6 × 10 <sup>6</sup>	1:40	116							
14	75, F	-	-	ND	ND	114							
15	47, F	-	-	ND	1:10	111							
16	45, M	-	-	>1:1.6 × 10 <sup>6</sup>	ND	110							
17	67, M	-	-	ND	ND	107							
18	51, F	-	+	ND	ND	83							

<sup>a</sup> Pattern of diffuse but uneven distribution of technetium.

<sup>b</sup> Pattern of technetium being localized in multiple discrete nodules of varying size and function.

<sup>c</sup> Ophthalmopathy.

<sup>d</sup> Long-standing goiter of at least 4-yr duration before the onset of hyperthyroidism (+), compared to concurrent development of goiter and hyperthyroidism (-).

<sup>e</sup> Antimicrosomal antibody. Measured by passive hemagglutination assay. Normal values, ≤1:400.

<sup>f</sup> Antithyroglobulin antibody. Measured by passive hemagglutination assay. Normal values, <1:100.

<sup>g</sup> Not detectable.

## Surgical vs radioactive iodine treatment for toxic multinodular goiter

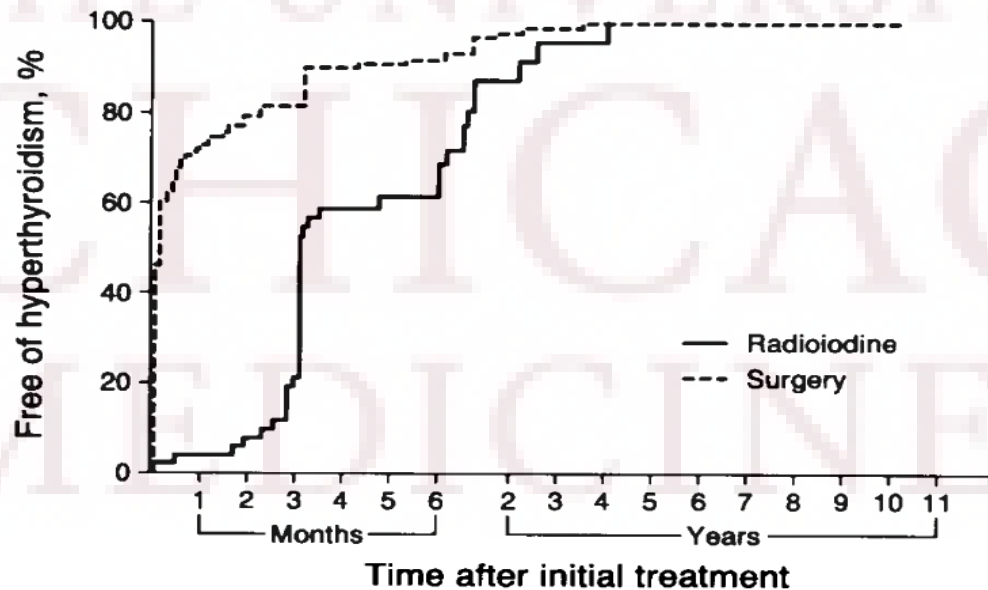


FIG. 1. Percentage of treatment success (hypothyroid or euthyroid) as a function of time after initial treatment stratified by  $^{131}\text{I}$  and surgical treatment.

## Surgical vs radioactive iodine treatment for toxic multinodular goiter

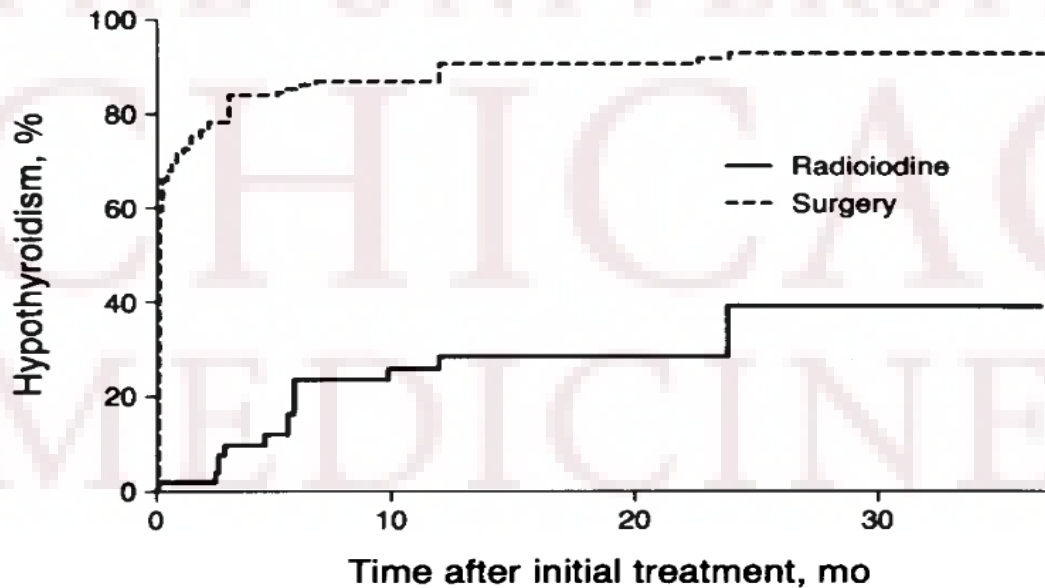
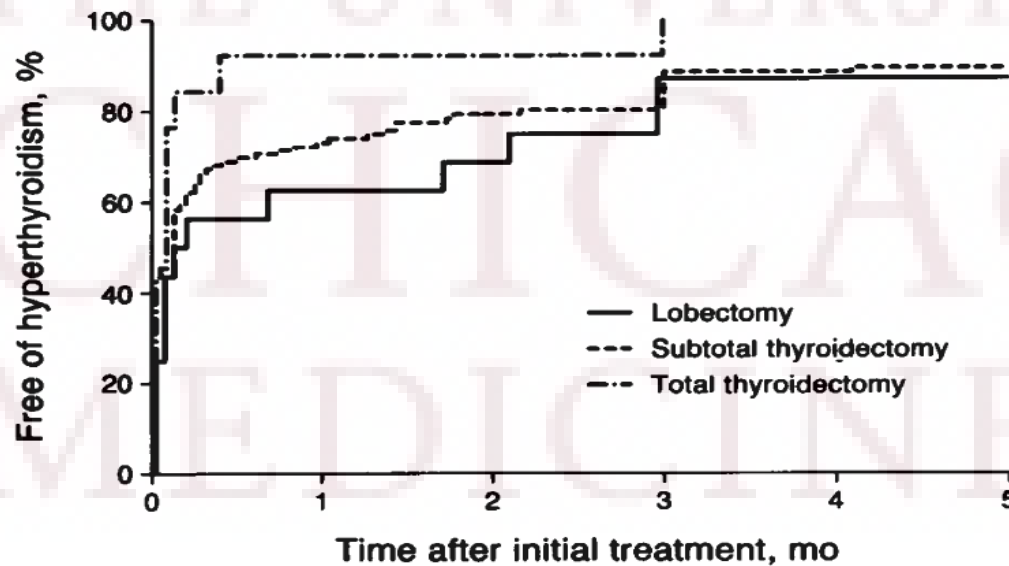


FIG. 2. Percentage of cases of hypothyroidism as a function of time after initial treatment stratified by  $^{131}\text{I}$  and surgical treatment.

## Surgical vs radioactive iodine treatment for toxic multinodular goiter



**FIG. 3.** Percentage of treatment success (hypothyroid or euthyroid) as a function of time after initial treatment stratified by type of operation.

## Surgical vs radioactive iodine treatment for toxic multinodular goiter

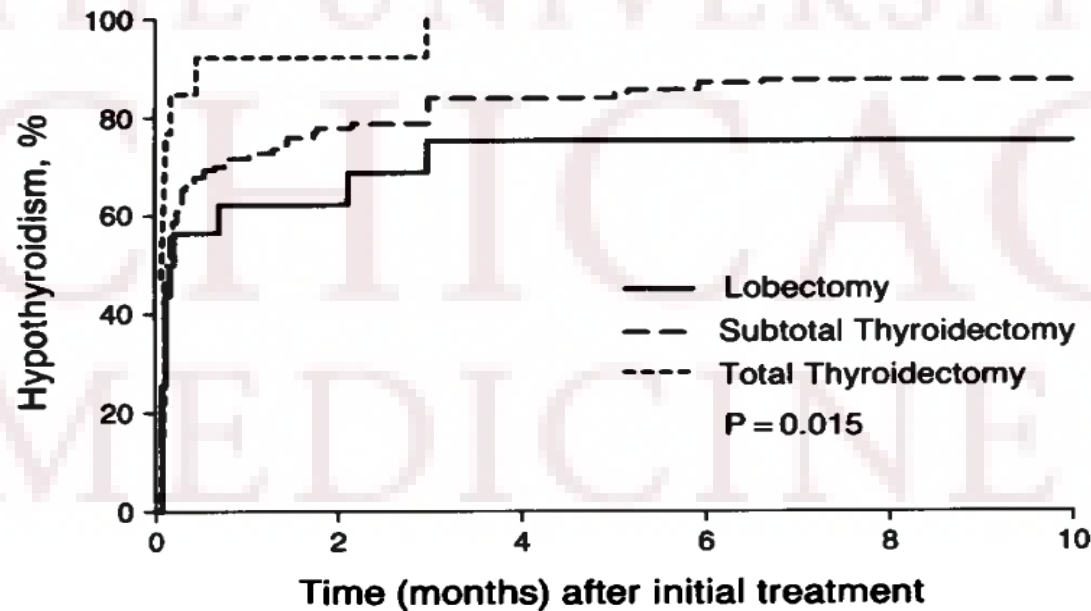


FIG. 4. Percentage of cases of hypothyroidism for three different surgical modalities as a function of time.

# ATD in treatment of toxic multinodular goiter vs Graves

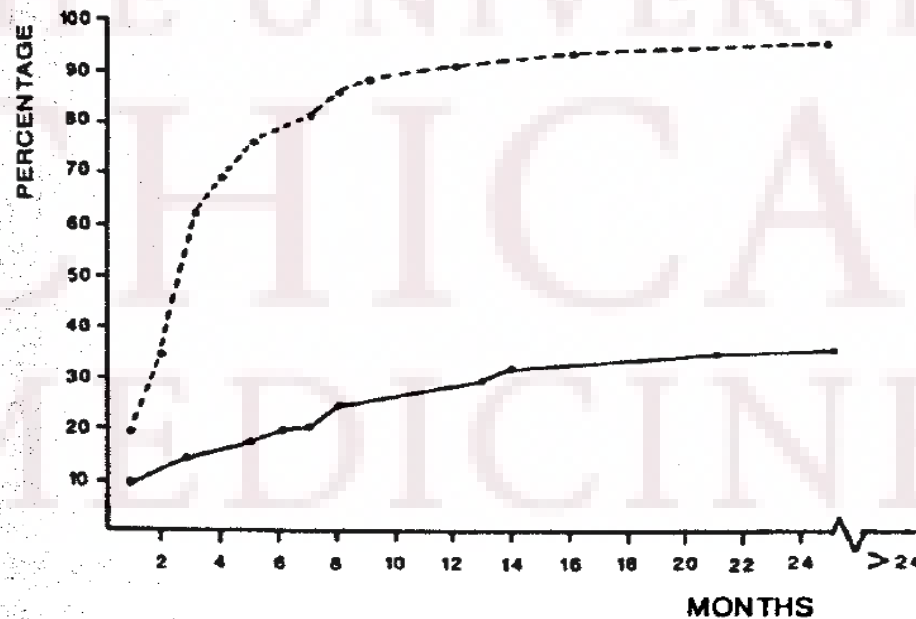


Fig. 1 - Cumulative percentage of total number of patients after discontinuation of drug therapy.

— = Graves' disease; ---- = Toxic multinodular goiter.

# Induction of autoimmunity in patients with toxic multinodular goiter by radioiodine treatment

Table 1 Clinical and laboratory data of patients with toxic multinodular goitre type A before and after <sup>131</sup>I therapy

Pat. No.	Age (yr)/ Sex	Before RAI treatment					Reevaluation after RAI treatment										
		hTRAK (IU/l) (<2)	anti-TPO (U/ml) (<60)	anti-TG (U/ml) (<60)	TSAB (%)	TSBAB (%)	<sup>131</sup> I dose Gray	<sup>131</sup> I activity (MBq)	time (months)	hTRAK (IU/l) (<2)	anti-TPO (U/ml) (<60)	anti-TG (U/ml) (<60)	TSAB (%)	TSBAB (%)	LT <sub>4</sub> (µg/d)	ATDT (mg/d)	loss of thyroid size (ml)
1	68/m	0	4014	5242	0	0	233	390	3	52	8662	7281	0	0	0	0	6
2	61/f	0	2456	0	0	0	353	525	11	40	7007	7007	0	0	0	0	0
3	71/f	0	2100	103	0	0	358	420	9	13.6	4054	132	0	0	0	0	15
4	78/f	0	0	0	0	0	502	193	9	2.4	0	0	0	0	25	0	8
5	56/m	0	0	0	0	0	342	677	9	0	2632	0	0	0	0	0	n.d.
6	80/f	0	0	0	0	0	184	1201	9	0	236	0	0	0	0	5	22
7	48/f	0	0	0	0	0	563	189	11	0	79	0	0	0	0	0	9
8	69/m	0	0	0	0	0	70	1012	10	0	0	0	0	0	0	0	6
9	65/m	0	0	0	0	0	181	1501	10	0	0	0	0	0	0	0	20
10	79/f	0	0	0	0	0	264	456	9	0	0	0	0	0	50	0	2
11	52/f	0	0	0	0	0	181	1223	11	0	0	0	0	0	0	0	30

ATDT = methimazole; n.d. = not determined.

# Induction of TSH-receptor antibodies in patients with toxic multinodular goiter by radioiodine treatment

TABLE 1. FIFTEEN PATIENTS WITH DEVELOPMENT OF POSTRADIOIODINE IMMUNOGENIC HYPERTHYROIDISM

Pt. no.	Diagnosis	Preradioiodine therapy (Pre-RITH)									RITH dosis [Gy]	Post-radioiodine therapy (Post-RITH)							
		Thyroid volume [mL]	Uptake pattern	Tc-uptake [%]	FT <sub>3</sub> [pg/mL]	FT <sub>4</sub> [ng/100 mL]	TSH [ $\mu$ U/mL]	TPO [U/mL]	TRAK [U/L]	Thyroid volume [mL]		Uptake pattern	Tc-Uptake [%]	FT <sub>3</sub> [pg/mL]	FT <sub>4</sub> [ng/100 mL]	TSH [ $\mu$ U/mL]	TPO [U/mL]	TRAK [U/L]	
1	UFA	2.5 (31)	F	1.7	3.9	1.6	0.1	2	0.9	550	31	D	1.6	7.4	2.5	0.0	<b>840</b>	<b>6.7</b>	
2	UFA	2.0 (15)	F	0.7	2.9	1.2	0.1	22	1.0	430	13	D	1.3	6.9	2.3	0.0	<b>548</b>	<b>4.8</b>	
3	UFA	10 (21)	F	1.2	3.7	1.4	0.0	36	0.0	400	19	D	2.9	6.1	1.9	0.0	44	<b>13.8</b>	
4 <sup>a</sup>	UFA	14 (33)	F	2.6	6.0	1.7	0.0	96	0.3	330	13	D	2.5	8.4	2.2	0.0	<b>925</b>	<b>3.5</b>	
5	UFA	1.3 (8)	F	1.3	3.0	1.0	0.1	107	2.1	850	7	D	2.3	9.2	1.2	0.0	<b>256</b>	<b>18.3</b>	
6	UFA	4.5 (17)	F	0.4	2.9	1.1	0.1	110	2.0	330	11	D	1.9	6.0	1.7	0.0	<b>811</b>	<b>19.4</b>	
7	UFA	3.5 (29)	F	2.2	4.3	1.3	0.0	<b>1477</b>	1.3	410	27	D	7.5	12.5	3.4	0.0	<b>2117</b>	<b>21.5</b>	
8	UFA	22 (40)	F	0.8	4.8	1.3	0.0	<b>1749</b>	3.5	250	35	D	0.6	9.8	3.0	0.0	<b>3417</b>	<b>4.5</b>	
9	MFA	54	MF	1.5	4.1	1.2	0.0	5	0.5	130	38	D	1.8	7.0	2.2	0.0	13	2.3	
10	MFA	50	MF	0.8	3.7	1.3	0.0	18	0.3	110	40	D	9.4	17.7	5.0	0.0	33	<b>13.2</b>	
11	MFA	60	MF	2.4	3.3	1.3	0.1	22	0.0	160	40	D	6.7	17.9	6.3	0.0	56	<b>21.5</b>	
12	MFA	53	MF	1.4	3.9	2.0	0.0	27	0.6	240	53	D	4.2	21.0	5.9	0.0	<b>1101</b>	<b>17.4</b>	
13	MFA	36	MF	1.4	3.4	1.2	0.0	73	0.7	170	30	D	1.2	5.8	2.1	0.0	<b>322</b>	<b>14.0</b>	
14	MFA	100	MF	1.1	3.2	1.3	0.1	<b>1128</b>	0.2	140	68	D	3.9	10.0	3.4	0.0	<b>40814</b>	<b>16.8</b>	
15	DIFF	18	D	0.9	3.7	1.4	0.1	<b>566</b>	0.0	230	17	D	1.6	7.4	2.5	0.0	<b>5673</b>	<b>5.8</b>	

<sup>a</sup>Patient 4 developed endocrine orbitopathy postradioiodine therapy.

UFA, unifocal autonomy; MFA, multifocal autonomy; DIFF, diffuse thyroid disease; total thyroid volume [mL] as measured by ultrasound (UFA: volume of the node is given first and the entire thyroid volume is given second [in brackets]); Uptake pattern: F, focal; MF, multifocal; D, diffuse or homogeneous uptake. Two patients (patient 1 and patient 5) required thyrostatic medication to control overt hyperthyroidism and one patient (patient 10) was on levothyroxine for thyrotropin (TSH) suppression. The remaining patients had subclinical hyperthyroidism. All patients developed clinically and biochemically overt hyperthyroidism after radioiodine therapy and were put on thyrostatic medication after radioiodine therapy. Normal values for free triiodothyronine (FT<sub>3</sub>) were 2.0–4.6 pg/mL; for free thyroxine (FT<sub>4</sub>), 0.6–1.8 ng/100 mL; and for TSH, 0.4–4.0  $\mu$ U/mL. Pathologic thyroid peroxidase (TPO) values (>200 U/L) and pathologic TRAK values (>4 U/L) are printed in bold font.



# Induction of TSH-receptor antibodies in patients with toxic multinodular goiter by radioiodine treatment

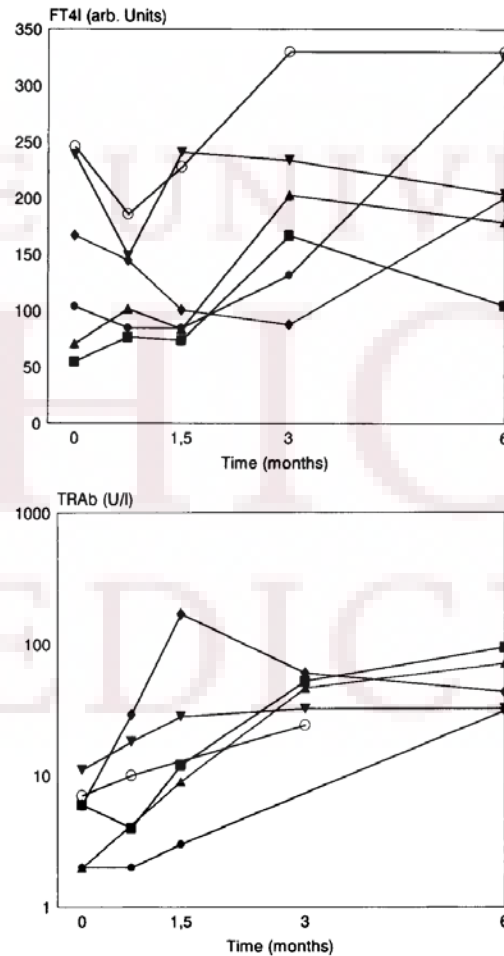


FIG. 2. Top: Changes in FT<sub>4</sub>I in 6 patients developing elevated thyrotropin receptor antibodies (TRAb) levels and a Graves'-like hyperthyroidism related to <sup>131</sup>I therapy of toxic nodular goiter. Bottom: Changes in TRAb in 6 patients developing elevated TRAb levels and a Graves'-like hyperthyroidism related to <sup>131</sup>I therapy of toxic nodular goiter.

# Induction of TSH-receptor antibodies in patients with nontoxic multinodular goiter by radioiodine treatment

TABLE 1. Patient data of <sup>131</sup>I-treated patients with nontoxic goiter

Patient no.	Age (yr), sex	<sup>131</sup> I dose (MBq)	Scintiscan	Thyroid vol at the time of treatment (mL)	Thyroid vol 1 yr after treatment (mL)	TSH at the time of treatment (U/mL)	Anti-TPO at the time of treatment (U/mL)	TRAb at the time of treatment (U/L)	Max. TRAb value (U/L)
1	53, F	555	Multinodular	52	39	0.48	646	6	35
2	56, F	481	Multinodular	49	23	0.97	50	4	324
3	35, F	444	Diffuse with a small solitary adenoma	83	26	0.02	48	3	30
4	33, F	370	Multinodular	58	42	0.73	330	3	120
5	50, F	370	Multinodular	38	19	0.01 <sup>a</sup>	4081	7	368
6	48, F	555	Multinodular			0.18	554	6	57
7	48, F	370	Multinodular	53	40	0.22	2000	5	? (38 after 1 yr)
8	31, F	370	Multinodular			0.39			
9	56, F	740	Multinodular	100	60	0.27	988	6	12
10	46, F	259	Diffuse	37	22	1.50	483	2	3
11	50, F	740	Multinodular	116	108	1.20	6347 (1 month)	3	3
12	71, F	740	Multinodular	140	111	0.01	30	1	2
13	45, F	222	Multinodular			0.09	2605	1	4
14	36, F	444	Multinodular			0.18	50	1	1
Ten patients who remained euthyroid		8F/2M	7 multinodular, 3 diffuse	(n = 10)	(n = 10)				
Median, range		50, 39–69	370,259–740	55, 37–140	40, 19–111	0.20,0.02–1.1	<50, <50–61	1, <9	3, <9

Patients 1–9 developed hyperthyroidism 3 months after treatment; patients 10–14 developed radiation thyroiditis.

<sup>a</sup> Treated with L-T<sub>4</sub>.

# Induction of TSH-receptor antibodies in patients with nontoxic multinodular goiter by radioiodine treatment

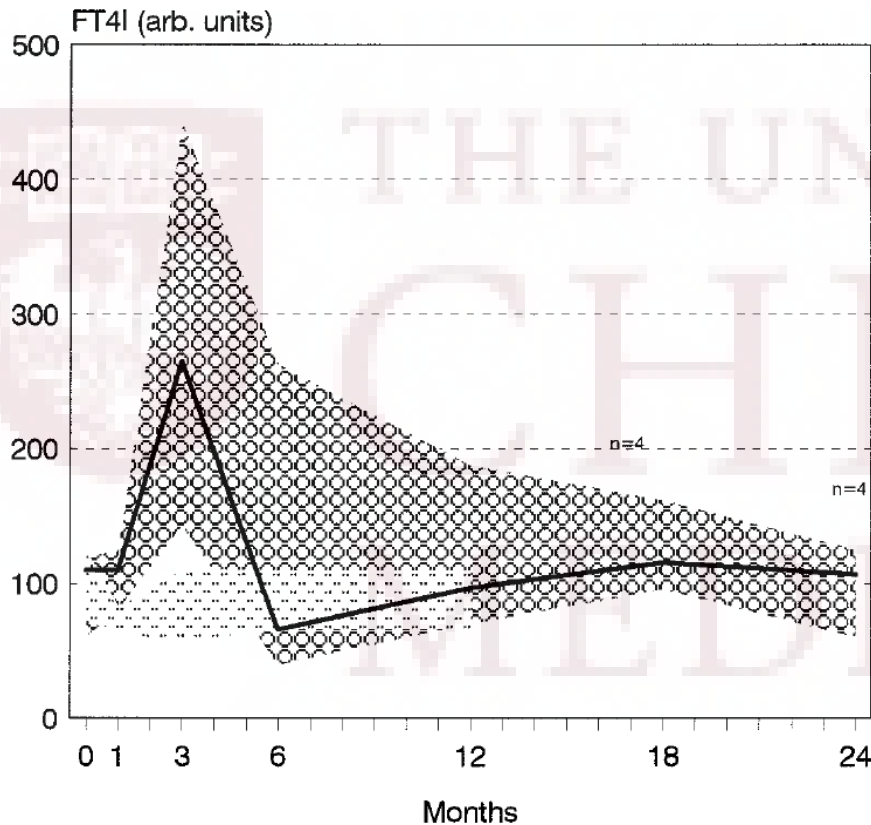


FIG. 1. Changes in serum FT<sub>4</sub>I related to time after <sup>131</sup>I treatment of nontoxic goiter in 6 patients (no. 1–6) developing hyperthyroidism (median, *black line*; range, ○○○) and range of FT<sub>4</sub>I in 10 control patients (·····).

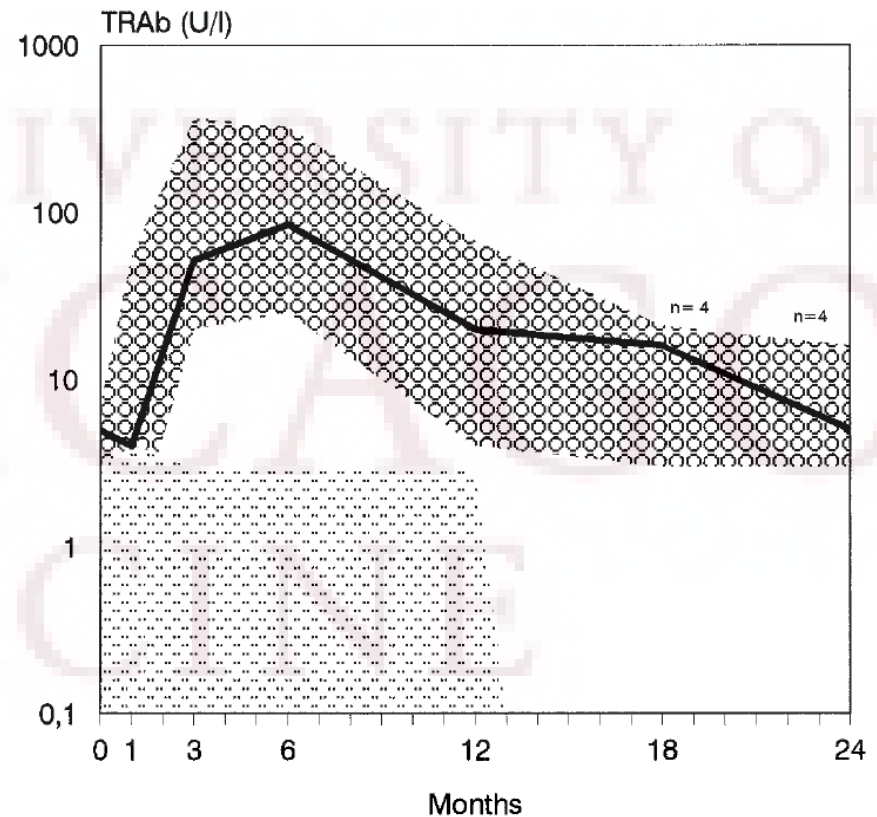


FIG. 2. Changes in serum TRAb concentration related to time after <sup>131</sup>I treatment of nontoxic goiter in 6 patients (no. 1–6) developing hyperthyroidism (median, *black line*; range, ○○○) and range of serum TRAb in 10 control patients (·····). A logarithmic scale was used.

## Back to our patient:

	Ref. Range	8/31/2012 15:22	10/12/2012 13:54
Triiodothyronine, Free	Latest Range: 230-420 pg/dL	510 (H)	1001 (H)
Thyroxine, Free	Latest Range: 0.9-1.7 ng/dL	1.98 (H)	3.40 (H)
Thyrotropin	Latest Range: 0.30-4.00 mcU/mL	0.01 (L)	<0.01 (L)

## Take home points:

- Toxic multinodular goiter with autoimmunity.
- Majority of patients achieve euthyroidism with surgery or RAI treatment, but time to achieve euthyroid state is faster with surgery.
- Patients with toxic multinodular goiter have higher chances of relapse when treated with ATD.
- Patients with toxic multinodular goiter and autoimmunity have higher risk of relapse post RAI.

# References:

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