

**^{131}I treatment for differentiated thyroid carcinoma -
clinical and radiation protection aspects**

**François Jamar, UCL Brussels
GBS/VBS Symposium on Radiation protection
Brussels,
March 12, 2016**

¹³¹I treatment for differentiated thyroid carcinoma - Scope

- Clinical presentation of DTC
- Staging and risk stratification
- Radioiodine therapy: practical aspects
- Some questions that need an answer
- RAI refractory patients
- Radiation protection issues

¹³¹I treatment for differentiated thyroid carcinoma

Clinical presentation

- Palpable nodule (including self palpation)
- Rapidly progressive nodule
- Local compression including voice changes
- Neck lymph nodes
- Incidentaloma (CT-scan, PET-scan, carotid US,...)
- Incidentaloma at surgery for benign disease
- Rarely metastases as first presentation
- Rare familial cases (screening)

- **Treatment:** total thyroidectomy & ¹³¹I in some cases

Pathological classification of DTC

Staging (AJCC 7th edition)

TABLE 4. TNM CLASSIFICATION SYSTEM FOR DIFFERENTIATED THYROID CARCINOMA

	<i>Definition</i>
T1	Tumor diameter 2 cm or smaller
T2	Primary tumor diameter >2 to 4 cm
T3	Primary tumor diameter >4 cm limited to the thyroid or with minimal extrathyroidal extension
T4 _a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4 _b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
TX	Primary tumor size unknown, but without extrathyroidal invasion
NO	No metastatic nodes
N1 _a	Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1 _b	Metastasis to unilateral, bilateral, contralateral cervical or superior mediastinal nodes
NX	Nodes not assessed at surgery
MO	No distant metastases
M1	Distant metastases
MX	Distant metastases not assessed

Pathological classification of DTC

Additional 'Staging' information

- More aggressive sub-types
- Vascular and lymphatic invasion
- Number of LN in N+ patients
- Extracapsular spread in LN
- Size of LN invasion in affected LN
- BRAF V600E mutation and other genetic abnormalities
- Age and potential risk factors

Risk Stratification of DTC

Need for radioiodine treatment (ATA 2009)

TABLE 5. MAJOR FACTORS IMPACTING DECISION MAKING IN RADIOIODINE REMNANT ABLATION

Factors	Description	Expected benefit			RAI ablation usually recommended	Strength of evidence
		Decreased risk of death	Decreased risk of recurrence	May facilitate initial staging and follow-up		
T1	1 cm or less, intrathyroidal or microscopic multifocal	No	No	Yes	No	E
	1–2 cm, intrathyroidal	No	Conflicting data ^a	Yes	Selective use ^a	I
T2	>2–4 cm, intrathyroidal	No	Conflicting data ^a	Yes	Selective use ^a	C
T3	>4 cm					
	<45 years old	No	Conflicting data ^a	Yes	Yes	B
	≥45 years old	Yes	Yes	Yes	Yes	B
	Any size, any age, minimal extrathyroidal extension	No	Inadequate data ^a	Yes	Selective use ^a	I
T4	Any size with gross extrathyroidal extension	Yes	Yes	Yes	Yes	B
Nx,N0	No metastatic nodes documented	No	No	Yes	No	I
N1	<45 years old	No	Conflicting data ^a	Yes	Selective use ^a	C
	>45 years old	Conflicting data	Conflicting data ^a	Yes	Selective use ^a	C
M1	Distant metastasis present	Yes	Yes	Yes	Yes	A

Risk Stratification of DTC

Need for radioiodine treatment

EJE 2006 and EANM 2008

- **Very low risk patients:** T1<1cm, unifocal and intra-thyroid; and N0 (no capsular invasion, no previous irradiation, no unfavourable histology, [tall, columnar and sclerosing]): **No benefits, no indication for I131**
- **High risk patients:** T3-4, N1, M1, persistent disease: treatment with a high activity (3.7 GBq or more) following withdrawal until remission
- **Low risk patients:** the other patients: Benefits of I131 controversial. Ablation may be performed with a low/high activity and following rhTSH/withdrawal

Risk Stratification of DTC

Need for radioiodine treatment (ATA 2009): But...!

Table 3. Patients With Persistent Disease at the End of Follow-up

		Epidemiological, Clinical, and Pathological Features at the Time of Ablation								Biochemical and Imaging Data at the End of Follow-up				
Patient	Group	Age at Diagnosis, y	Sex	Histotype	TNM	Stage	De Groot's Class	Risk Stratification	Basal Tg, ng/mL	rhTSH-Tg, ng/mL	Neck US ^a	Post-therapy WBS	CT Scan	Outcome
1	Hypo	55	M	PVE	T3N1M0	III	3	I	<0.5	2.3	Negative	R	nd	BD
2 ^b	Hypo	63	M	PVC	T4bN1bM0	IV B	3	H	17.5		LFN	R + LC-LFN	LC-LFN	SD
3	Hypo	39	M	PVC	T4aN1bM0	II	3	H	<0.5	4.15	Negative	Negative	Nd	BD
4	Hypo	38	F	PVC	T4bN1aM0	II	3	H	<0.5	1.6	Negative	R	Negative	BD
5	Hypo +	57	M	PVE	TxN1M1	IV C	4	H	1.22	2.25	LFN	LC-LFN + Md/LFN	Lung USSx	SD
	rhTSH													
	Eu +	26	F	PVS	T1aNO/M0	I	1	L			2.05	33.4	LFN	R + LC-LFN
	rhTSH													
	Eu + rhTSH	56	F	PVE	T3N1aM0	III	3	I			25.3		LFN	Negative
	Eu + rhTSH	17	F	PVC	T1bNO/M0	I	1	L			<0.5	2.9	Negative	Negative
	Eu + rhTSH	41	F	PVC	T1aNO/M0	I	1	L			<0.5	2.46	Negative	R
	rhTSH													
10	Hypo +	37	F	PVC	T2NO/M0	I	3	I	<0.5	24.4	LFN	Negative	Nd	BD
	rhTSH													
11	Eu +	27	F	PVC	T2NO/M0	I	1	L	1.18	11.8	LFN	Negative	LFN	SD
	rhTSH													
12 ^d	Eu +	26	F	PVS	T1aNO/M0	I	1	L	2.05	33.4	LFN	R + LC-LFN	Nd	SD
	rhTSH													
13 ^e	Eu + rhTSH	56	F	PVE	T3N1aM0	III	3	I	25.3		LFN	Negative	LC-LFN	SD
14	Eu + rhTSH	17	F	PVC	T1bNO/M0	I	1	L	<0.5	2.9	Negative	Negative	Nd	BD
15	Eu + rhTSH	41	F	PVC	T1aNO/M0	I	1	L	<0.5	2.46	Negative	R	Nd	BD
16	Eu + rhTSH	39	F	PVC	T2NO/M0	I	1	L	<0.5	1.2	Negative	Negative	Negative	BD

Risk of Structural Disease Recurrence

(In patients without structurally identifiable disease after initial therapy)

High Risk (>20%)

pT4
M1-R1, R2
Inappropriate post-op Tg

Intermediate Risk (5%-20%)

pT3 N0 Nx
pT1-3, N1a-N1b
Aggressive histology or vascular invasion
RAI uptake outside the thyroid bed

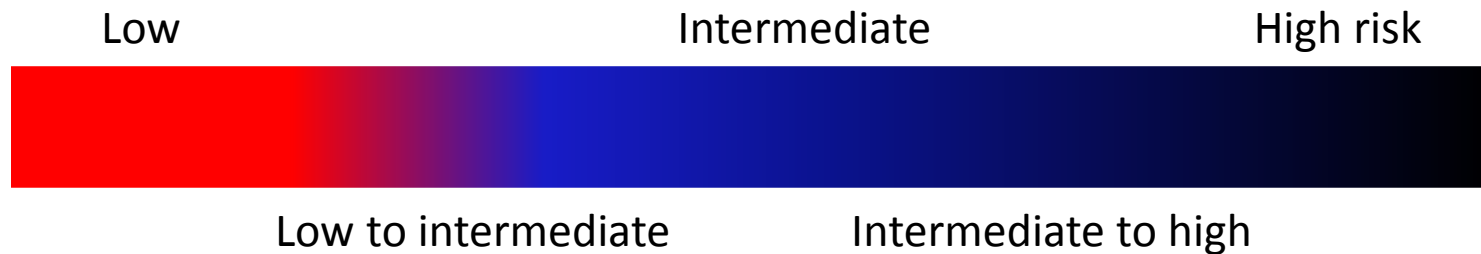
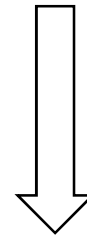
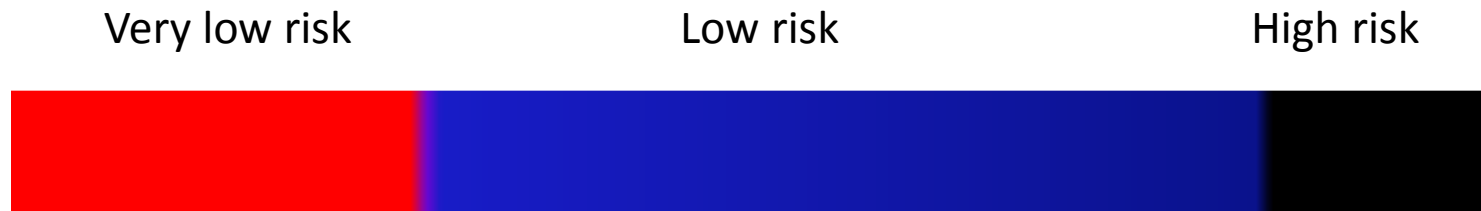
Low Risk (<5%)

pT1-T2 N0/Nx
No aggressive histology, no vascular invasion



FTC, extensive vascular invasion (\approx 30-55%)
pT4a gross ETE (\approx 30-40%)
pN1 with extranodal extension, >3 LN involved (38%)
pN1, any LN > 3 cm (\approx 30%)
BRAF mutated, not intrathyroidal (\approx 10-40%)
PTC, vascular invasion (\approx 15-30%)
Clinical N1 (\approx 20%)
pN1, > 5 LN involved (\approx 20%)
BRAF mutated, intrathyroidal, < 4 cm (\approx 10%)
pT3 minor ETE (\approx 3-8%)
pN1, all LN < 0.2 cm (\approx 5%)
pN1, < 5 LN involved (\approx 5%)
Intrathyroidal 2-4 cm PTC (\approx 5%)
Multifocal PMC (\approx 4-6%)
pN1 with extranodal extension, \leq 3 LN involved (2%)
Minimally invasive FTC (\approx 2-3%)
BRAF wild type, intrathyroidal, < 4 cm (\approx 1-2%)
BRAF mutated, intrathyroidal unifocal PMC (\approx 1-2%)
Intrathyroidal, encapsulated, FV-PTC (\approx 1-2%)
Unifocal PMC (\approx 1-2%)

Risk Stratification of DTC



New paradigm (ATA 2015)

Radioiodine therapy for ablation of remnants following thyroidectomy

General recommendations

- Treatment should be given shortly after surgery (<3mo)
- Usual activity: 100 mCi for ablation
- No evidence of usefulness of pre R_x ^{131}I imaging (stunning)
- Higher activities for residual disease, metastases
- Preparation with rh-TSH (2 im) or L-T4 withdrawal (4 weeks)
- Always followed by WBS and suppressive L-T4
(TSH < 0.1 for 12-24 mo, than < 1)
- Radiation protection issues

Radioiodine therapy in DTC following thyroidectomy

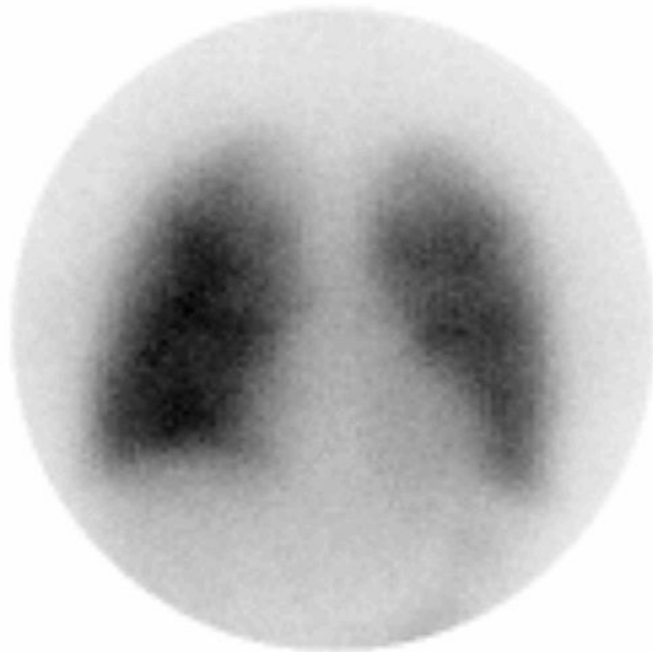
General recommendations

- In metastatic patients, higher activities
- In metastatic patients, L-T4 withdrawal
- Steroids to prevent edema when CNS lesions
- I-131 can be given once in Tg+ pts with negative Dx scan (not more if post-therapy scan remains negative)

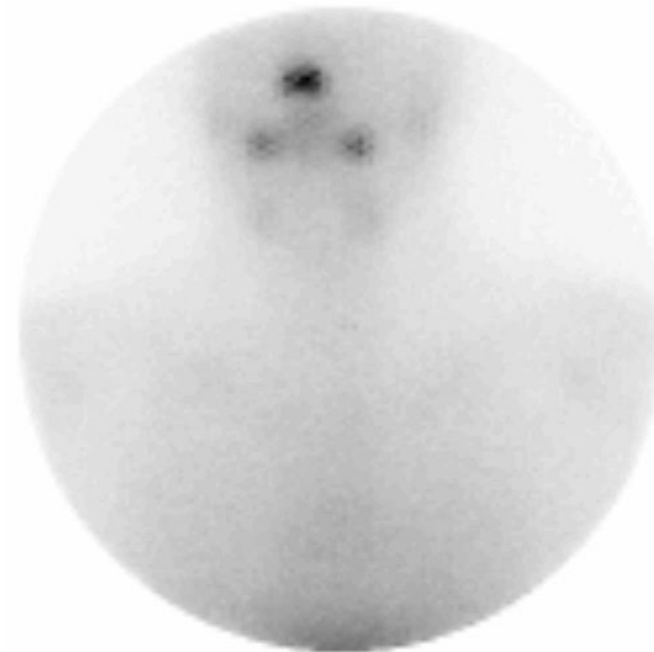
- Avoid iodine contamination, low-iodine diet 3-4 weeks
- Good hydration, salivary gland protection (lemon)
- Avoid constipation and vomiting

Standard ^{131}I activity (100mCi) after L-T4 withdrawal for remnants ablation following thyroidectomy

A myth: the magic bullet



11/98



07/01

Radioiodine therapy in DTC following thyroidectomy

Questions to be answered – secondary cancer

THYROID
Volume 25, Number 8, 2015
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DOI: 10.1089/thy.2014.0557

THYROID RADIOLOGY AND NUCLEAR MEDICIN

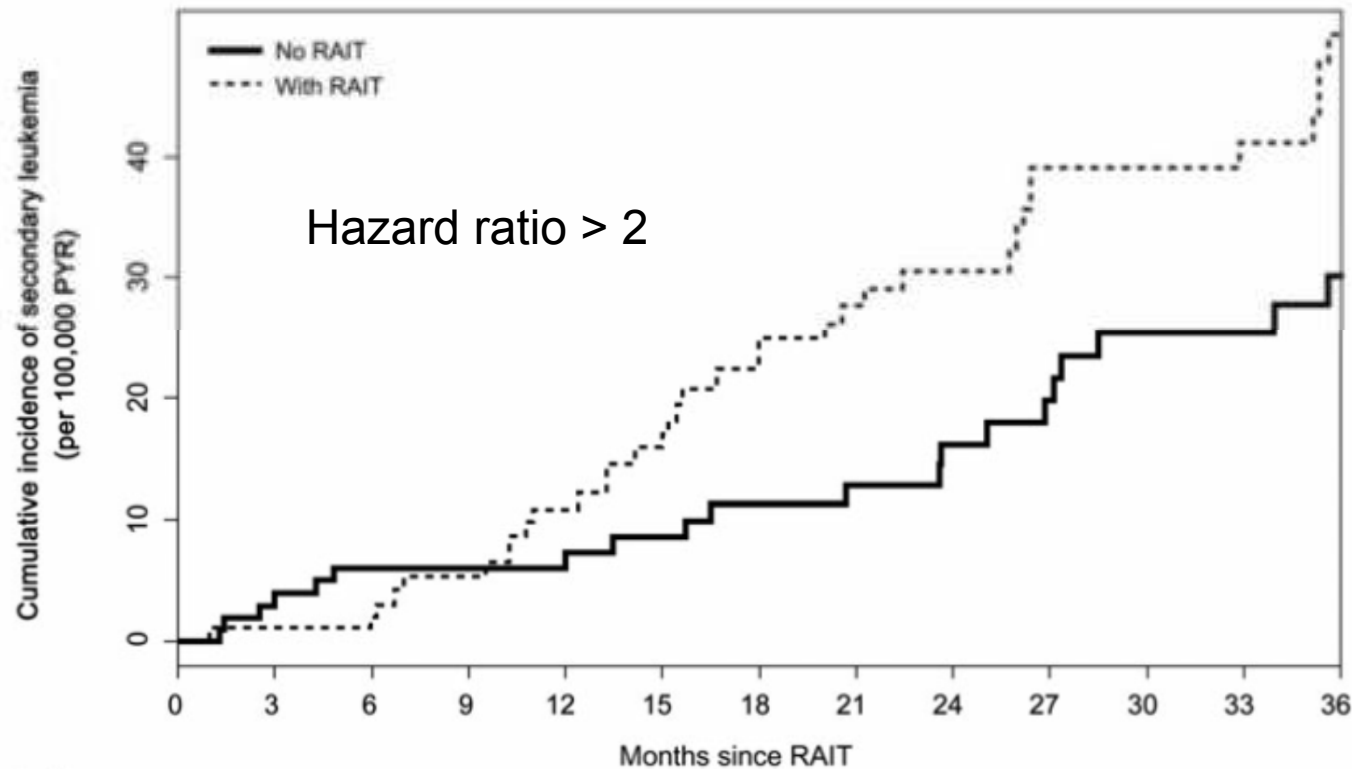
Increased Risk of Leukemia After Radioactive Iodine Therapy in Patients with Thyroid Cancer: A Nationwide, Population-Based Study in Korea

Gi Hyeon Seo,¹ Yoon Young Cho,² Jae Hoon Chung,² and Sun Wook Kim²

Radioiodine therapy in DTC following thyroidectomy

Questions to be answered – secondary cancer?

LEUKEMIA AFTER RADIOACTIVE IODINE



Note: relative risk: Low dose < no RAI = moderate dose < very high dose < high dose

Radioiodine therapy in DTC following thyroidectomy

Questions to be answered

- The incidence of DTC has been tripled over the last 40 yr
- The mortality rate remains unchanged
- Most patients have limited disease
- Maybe we overtreat some patients, maybe not...
- Radiation protection issues (eg. secondary cancer) are raised and relevant

[Get rid of L-thyroxin withdrawal
Reduce I131 activities
Rationalize the use of I131 therapy

Radioiodine therapy in DTC following thyroidectomy

Evolution of recommendations

Everything that can guarantee the efficiency of care to DTC patients with less radiation burden is welcome

Use of rh-TSH for ablation of remnants following thyroidectomy

Results

- Randomized, multicentric study, 5 Europe/5 US
- 63 eligible patients (T1: 13 / T2: 44 / T4: 6 / N+: 22)
- Age: 20-68 yr F/M 50/13
- 30 hypothyroid / 33 euthyroid
- 100 mCi I131
- Endpoints: ablation success, dosimetry, QoL

Use of rh-TSH for ablation of remnants following thyroidectomy

Results

TABLE 2. Results of thyroid remnant ablation at month 8 based on ^{131}I thyroid bed uptake

Uptake in thyroid bed	Hypothyroid (n = 28), n (%)	Euthyroid (n = 32), n (%)
No visible uptake or uptake <0.1%	28 (100)	32 (100)
No visible uptake	24 (85.7)	24 (75.0)
Visible uptake <0.1%	4 (14.3)	8 (25.0)
Visible uptake >0.1%	0	0

CI, Confidence interval.

Similar results for thyroglobulin

Use of rh-TSH for ablation of remnants following thyroidectomy

Results

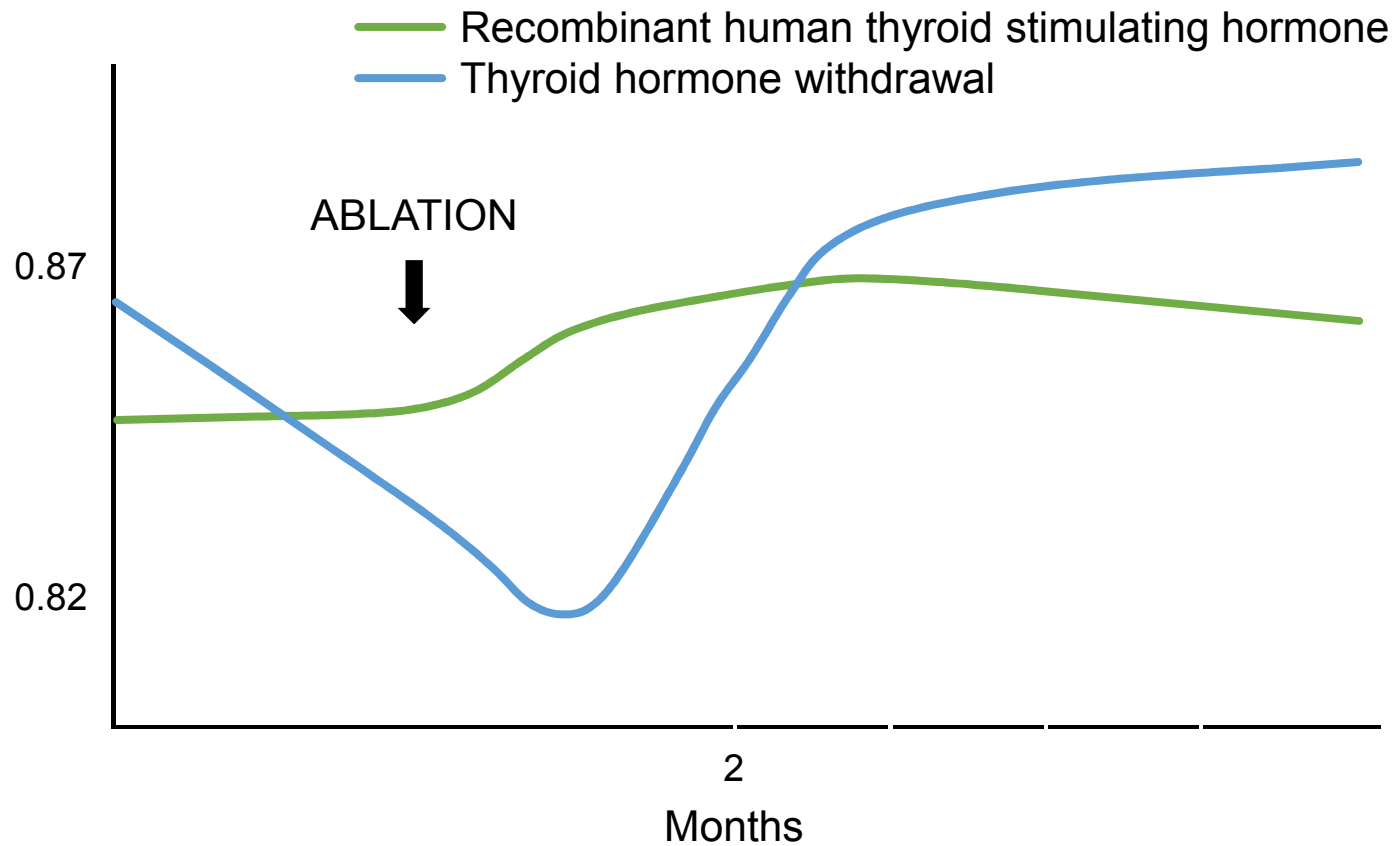
- 51 pts of Pacini's series after median FU of 3.7 yr
- Ablation rate equal in both arms (92 vs 90 %)
- Stimulated Tg > 2 in two patients (1rh/1THW)
- 9 recurrences retreated (4rh/5THW), all in remission at FU

Use of rh-TSH for ablation of remnants following thyroidectomy

Advantages vs L-T4 withdrawal

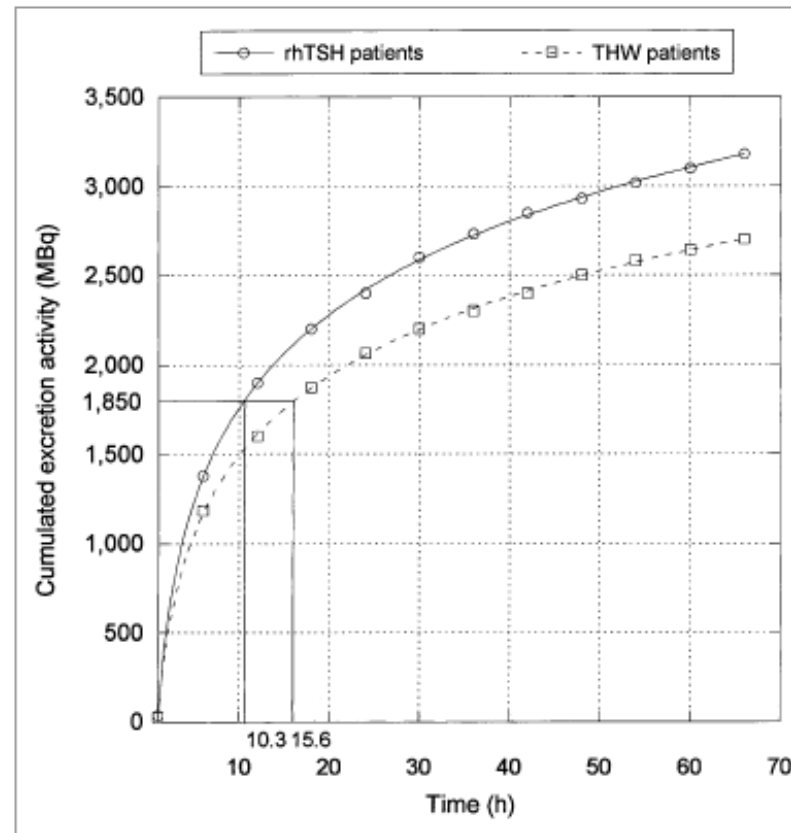
- No symptoms of hypothyroidism
- No medical contra-indication (exc. hypersensitivity)
- Improved compliance
- Maintained quality of life
- Pharmaco-economic benefit
- Reduction of whole-body dose with I-131
- Less proliferative effect than endogenous TSH
- Few side effects

ESTIMABL: mean change in EQ-5D utility score during post-op RAI treatment



Use of rh-TSH for ablation of remnants following thyroidectomy

Advantages: radiation dose



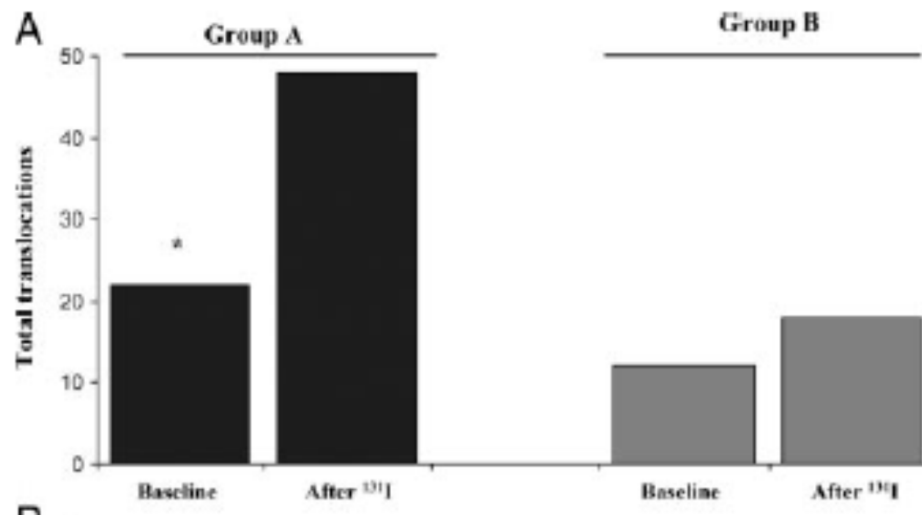
Remy et al. JNM, 2008

FIGURE 1. Cumulated urinary excretion activity: comparison between withdrawal patients (THW) and rhTSH patients.

Use of rh-TSH for ablation of remnants following thyroidectomy

Advantages: radiation dose

Chromosome Translocation Frequency after Radioiodine Thyroid Remnant Ablation: A Comparison between Recombinant Human Thyrotropin Stimulation and Prolonged Levothyroxine Withdrawal



Which ^{131}I activity to use for ablation following thyroidectomy?

- The universal standard is **100 mCi** (*ie.* **3.700.000.000 Bq**)
- First (Non-RCT study in 1976! – Mc Cowen, Am J Med)
- 8/10 studies demonstrated equal results with 30 or 50 mCi

- Direct comparative trials between
 - 30 vs 100 mCi
 - and rh-TSH vs withdrawal
 - ESTIMABL (France, 752/684 pts)
 - HILO (UK, 438/421 pts)

Which I-131 activity to use for ablation following thyroidectomy?

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MAY 3, 2012

VOL. 366 NO. 18

Strategies of Radioiodine Ablation in Patients with Low-Risk Thyroid Cancer

Martin Schlumberger, M.D., Bogdan Catargi, M.D., Ph.D., Isabelle Borget, Pharm.D., Ph.D., Désirée Deandreis, M.D.,

Which I-131 activity to use for ablation following thyroidectomy?

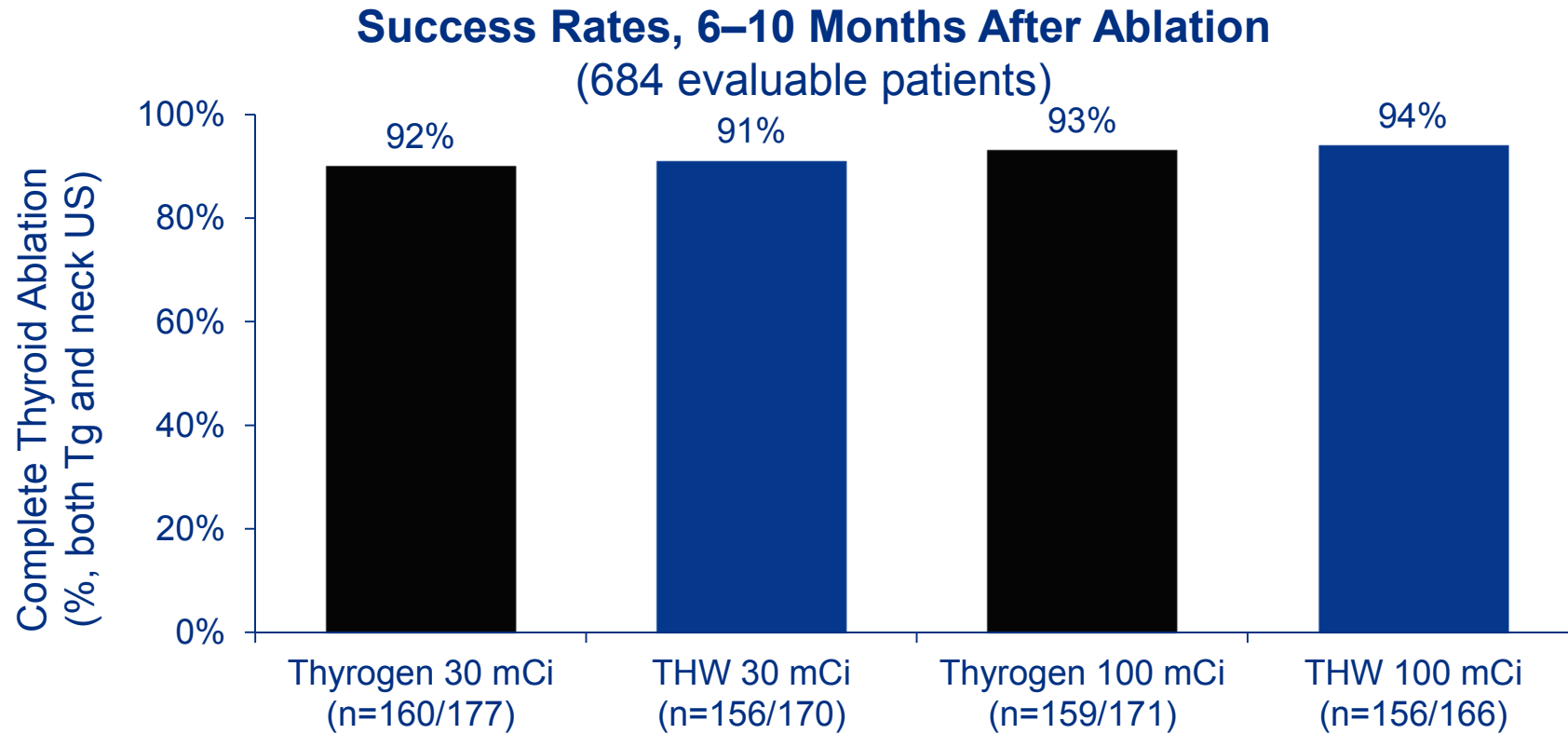
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ablation with Low-Dose Radioiodine and Thyrotropin Alfa in Thyroid Cancer

Ujjal Mallick, F.R.C.R., Clive Harmer, F.R.C.P., Beng Yap, F.R.C.P.,

Ablation Success with rhTSH vs THW

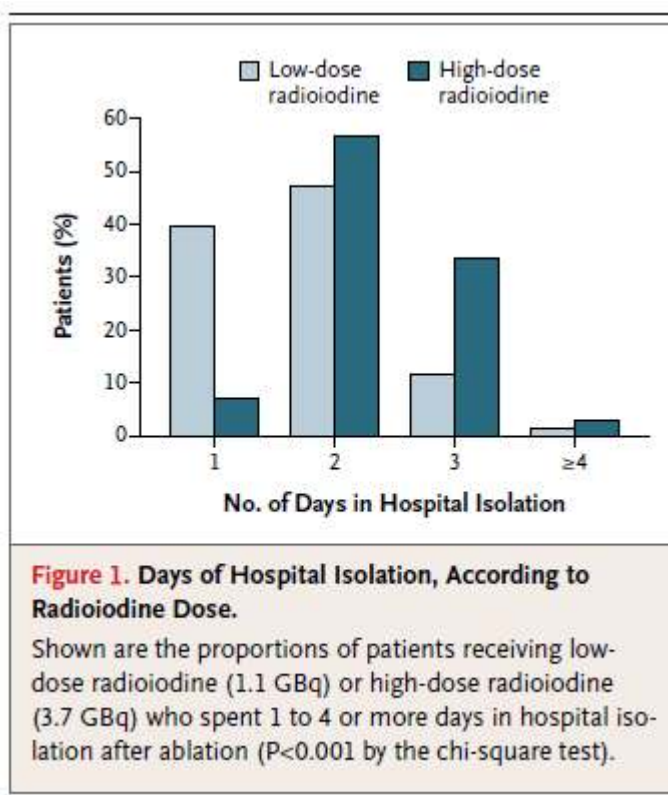


Which I-131 activity to use for ablation following thyroidectomy?

- rh-TSH and withdrawal preparation give equal results
- 30 and 100 mCi give equal results
- Limitations: mainly T1-T2*, N0, M0 patients
- Endpoints: clinical results (ablation rate within Y1, recurrences, retreatment), costs, QoLi

*: HILO: ~25% 'size' T3

Which I-131 activity to use for ablation following thyroidectomy?



Costs

Low-dose THW	776£
Low-dose rh-TSH	1.356£
High-dose THW	1.056£
High-dose rh-TSH	1.582£

Costs of sick-leave and QoL not considered

Which I-131 activity to use for ablation following thyroidectomy?

- **10-yr FU** of 159 patients (T_4 withdrawal or rh-TSH)
- 4/115 ablated patients showed recurrence (1 later cured)
- 16/44 non ablated patients with persistent disease (those with early Tg < 5.4 will be cured)

- In total, 19/159 have persistent disease at 10yr

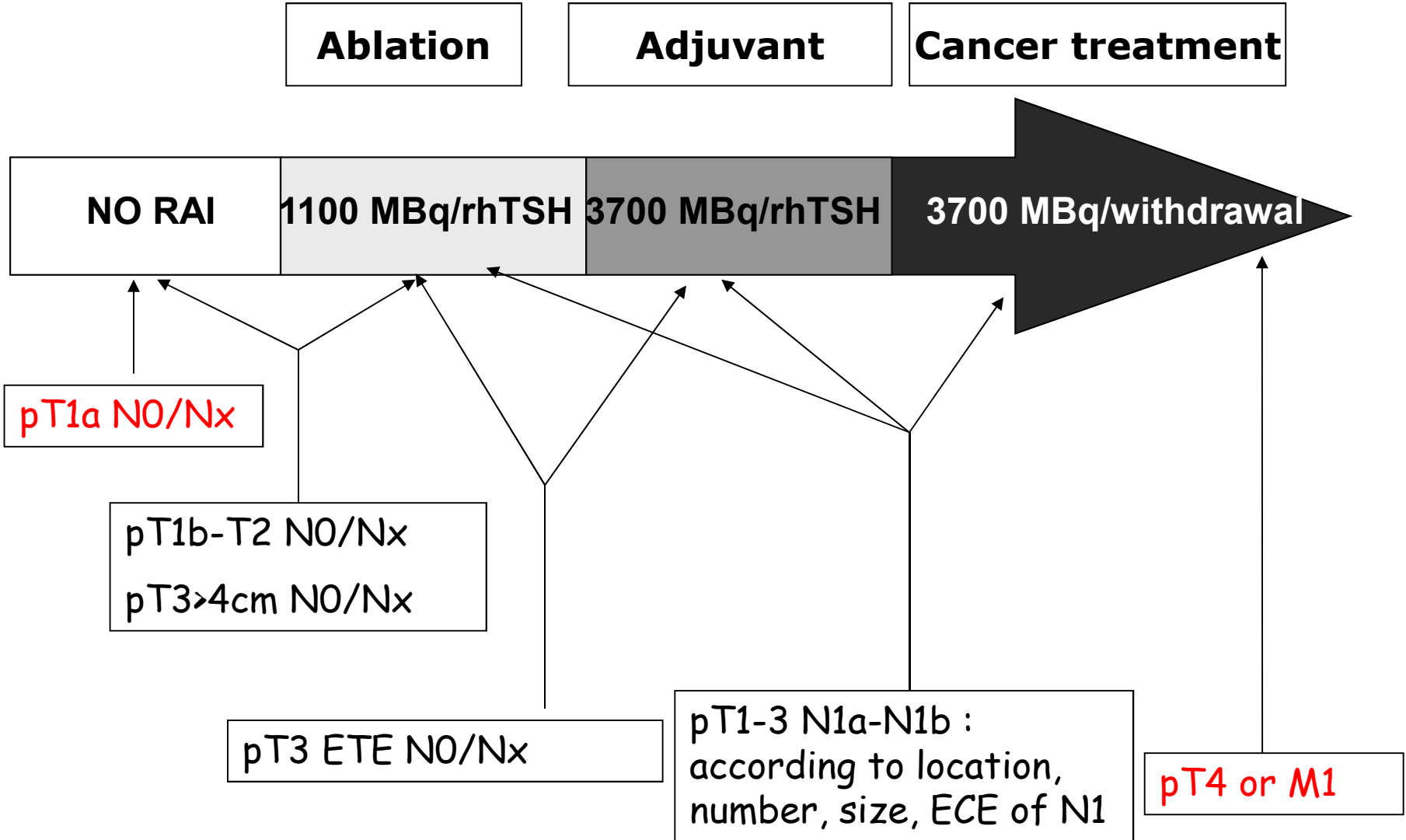
- Results **seem** similar to standard treatment
- Not randomized, no direct comparison

Which I-131 activity to use for ablation following thyroidectomy?

It is premature to drastically change the current empirical activity of '100 'mCi in **all** patients.

Several trials have shown promise in low-risk patients; it is obvious that if the radiation burden (to patient, staff and public) can be reduced, it will be a major step forward.

Indications: Post-op RAI administration (ATA 2015)



Courtesy of M. Schlumberger, 2015

¹³¹I treatment for DTC: 2016 proposal*

T=rhTSH W= T4 withdrawal

	Nx (cN0)	N0	N1a-b** ECS-	N1a-b ECS+
pT1a	(-)	(-)	100 T	100 W
pT1b	30 T	30 T	100 T	100 W
pT2	30 T	30 T	100 T	100 W
pT3	100 T	100 T	100 T	100 W
pT4	100 W	100 W	100 W	100 W
M+	100 W	100 W	100 W	100 W

*: if no additional risk factors: previous radiation, unfavourable histology, vascular or lymphatic invasion, genetic variants

Any pT: R1 upstaged to T3; R2 upstaged to T4

** : if complete lymphadenectomy and < 5 LN < 2mm, considered as N0

Treatment of DTC

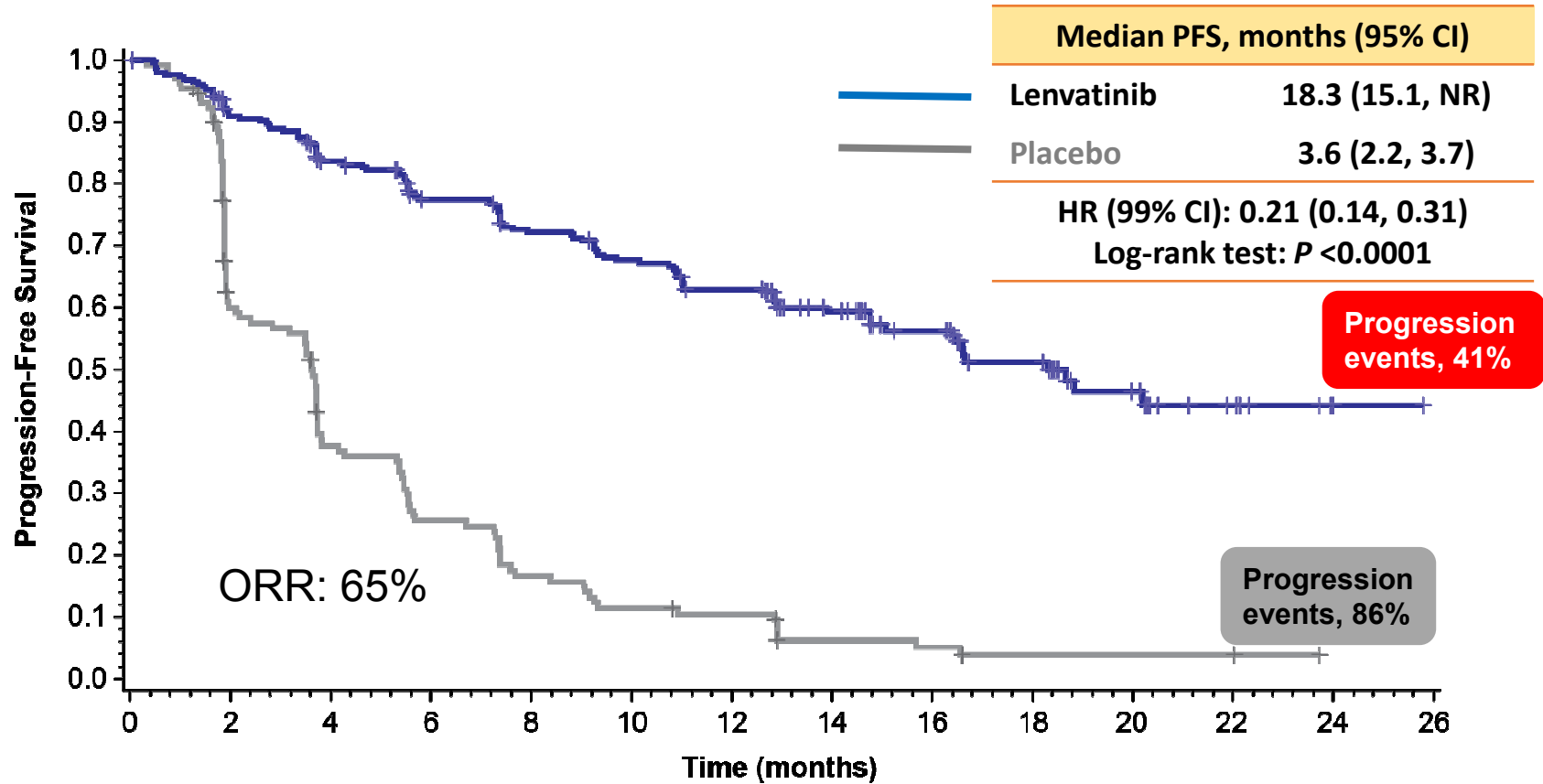
High-risk – RAI *refractory* patients

- **What is a RAI *refractory* patient?***
 - No RAI uptake
 - Disproportionate RAI uptake by comparison with Tg
 - No clinical/radiological response in spite of RAI uptake
 - PET+/RAI- numerous lesions
 - Risks of ^{131}I Rx outweighs benefits (eg. lung fibrosis)

*: *non-responsive, non-avid, refractory, resistant, see Haugen et al .Endocr Rev, 2013, 439-455*

*: *revised by Schlumberger et al. Lancet Diabetes-endocrinology, 2014*

SELECT: Lenvatinib vs placebo Progression Free Survival

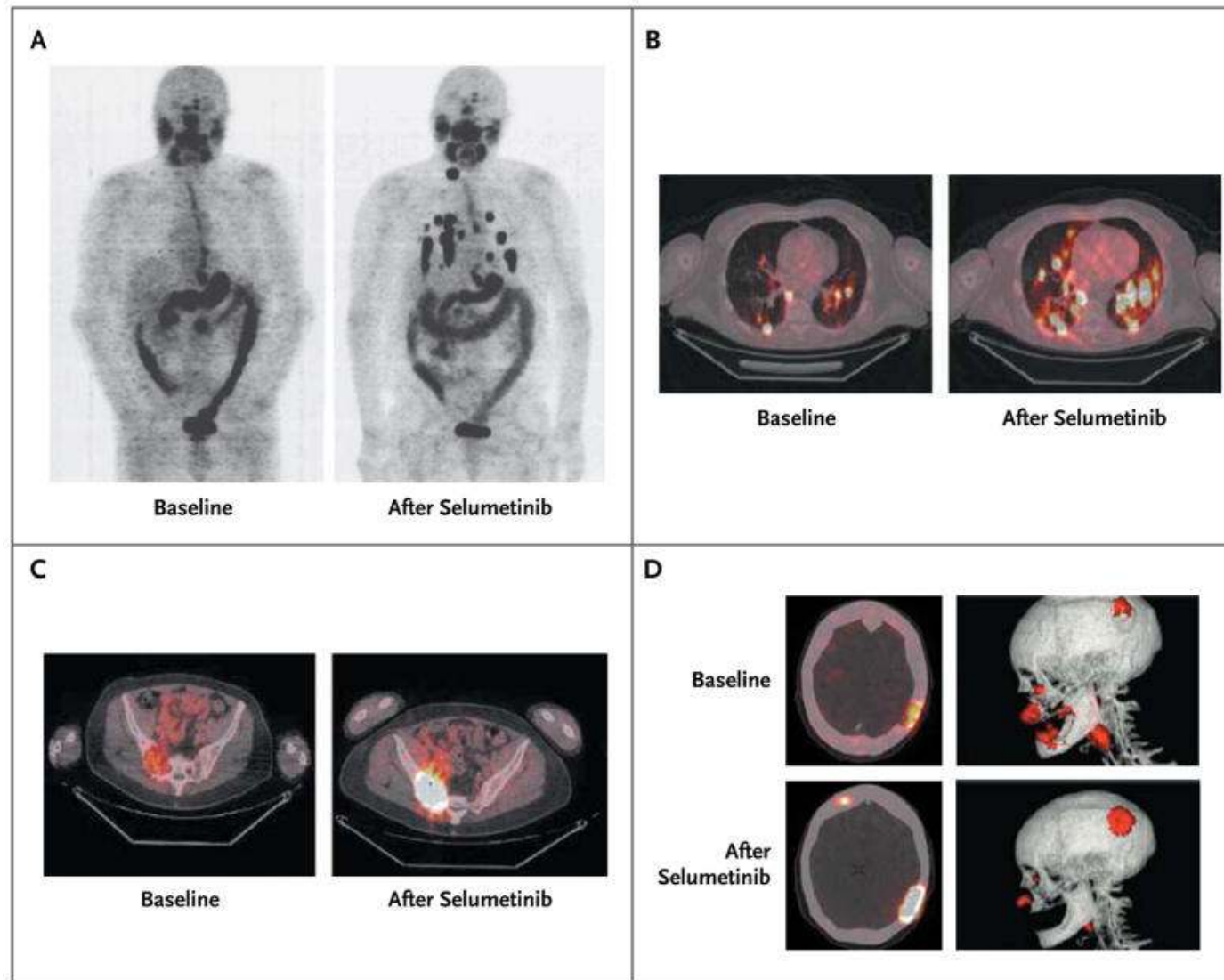


Number of subjects at risk:

Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

High-risk – RAI *refractory* patients



Radioiodine therapy in DTC

Radiation protection issues for the patient

- **Well-balanced indications (justification)**
- **Prevention of acute side effects (deterministic)**
 - Local pain (swelling) – symptomatic R/
 - Nausea – vomiting: Avoid absolutely! – R/ domperidone
 - Sialadenitis: 5-10d, mainly females, dose-dependent
 - Hematologic complications very rare
- **Delayed side effects (mainly stochastic)**
 - Negligible: leukemia for high doses, solid cancer unclear, earlier menopause even for low dose (1-2 yr), no effect on fertility and offspring, *xerostomia, xerophthalmia, lung fibrosis*

Radioiodine therapy in DTC

Radiation protection issues for the patient

- **Patient preparation**
 - Plenty of fluids!
 - Citric acid (lemon, candies,...)
 - Prevention of iodine contamination
- **Contraception: a must!**
 - Treatment during pregnancy is not permitted
 - Conception during 4-6 mo after treatment must be avoided
 - Thorough review of medical history is required
 - Hormonal contraception preferred, otherwise measures x2
 - This also applies to male patients
- **Information about radiation protection**

Radioiodine therapy in DTC

Radiation protection for the family, relatives and public

- **Patient discharge from hospital:**
 - allowed when dose-rate $< 20\mu\text{Sv/h}$ at 1 m
 - unless urinary incontinence, mental incapacity, no intention to follow rules, sojourn in hospice, presence of young children, ...than $10\mu\text{Sv}$
- **External irradiation (gamma 364 keV)**
 - TDS rules
- **Internal (external) contamination**
 - medium energy beta
 - high affinity for the thyroid tissue

Radioiodine therapy in DTC

Radiation protection for the family, relatives and public

- **External irradiation (gamma 364 keV)**
 - **Contact restrictions** (1m / 30'/d) for **100 mCi**
 - separate bed rooms
 - refrain from sexual activity, no kiss, hugging OK
 - no unnecessary travel by car and public transport
 - Distance x 2, dose /4!!!
 - 2 days: adults, children > 6y
 - 1w: children <6y, pregnant women, public and work places

Radioiodine therapy in DTC

Radiation protection for the family, relatives and public
Superior Health Council Report 7221

2. Traitement pour cancer de la thyroïde

Tableau clinique*	Durée des restrictions**		
	Mesures vis-à-vis du partenaire (lits séparés, ...)	Mesures vis-à-vis du public et des collègues de travail	Mesures vis-à-vis des femmes enceintes et des enfants < 6 ans à domicile ou au travail
dose ablative	2 - 5 jours	1 sem.	1 sem.
localisation métastatique identifiée ⁶	1 - 2 sem.	1 - 2 sem.	1 - 2 sem.

Radioiodine therapy in DTC

Radiation protection for the family, relatives and public

- **Internal irradiation (beta)**
 - Contamination: urine >>> saliva, sweat
 - Avoid personal belongings in therapy room (eg. laptop, tablet, jewels, books,...)
 - Hygiene, washing hands, toilets, ...
 - Measures are rather simple and logical
- **Exceptional situation: premature death**
 - Rules for burial/cremation, see FANC
(www.fanc.fgov.be/GED/000000000/2900/2941.pdf)

Radioiodine therapy in DTC

Radiation protection – Real life

- Young mother (1 & 2 yr old)
- Old lady (82 yr), fear for secondary cancer
- Old lady (77 yr), cats and dogs...or parrots
- Claustrophobia and being in peace...

Radioiodine therapy in DTC

Radiation protection – **take home message**

- There are **rules and laws**
- Radiation protection issues are *mainly* for other people
- One must remain realistic
- No-conception is a must (male and females!)
- **Face to face information is absolutely necessary**