

Thyroid Cancer: Less is more?

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Background

- Increased incidence of DTC, primarily PTC, rising from 4.9 per 100,000 in 1975 to 14.3 per 100,000 in 2009 in US
- By 2019, one study predicts that PTC will become the 3rd most common cancer in women at a cost of \$19-21 billion in the U.S
- Similar figures in Europe (*Elisei 2010*)
- The Epidemic of Thyroid Cancer in the United States:
The Role of Endocrinologists and Ultrasounds
Robert Udelsman. Thyroid. March 2014, 24(3): 472-479
.
Increased detection of thyroid cancer results in therapeutic interventions including surgery and radioactive thyroid treatment that may be of limited benefit.



Current controversies in Low risk DTC

- Low risk DTC
- 49% $\leq 1\text{cm}$ and 87% $\leq 2\text{cm}$
- 58% of patients aged $< 50\text{yrs}$ (*Edwards 2002*)
- 10-year mortality rate of 1.7% for PTC and 3.4% for combined PTC/FTC (*Sawka et al., 2004*)

- Benefit of intervention vs treatment induced morbidity
- **Surgery:**
 - Extent?
- **Radioiodine (RAI):**
 - yes or no?
 - Dose?
- **TSH suppression:**
 - how much?
 - how long?



Less extensive surgery?

- Experienced thyroid surgeons
- Careful case selection based on patient and tumour factors
- Shared decision with patient explaining benefit/risk
- Structured FU scheme
- Tg, USS, other tests as required for minimum 10 yrs, probably for life



BTA 2014

Key recommendation

- iii) The evidence for an advantage of total thyroidectomy compared to hemithyroidectomy in patients with unifocal tumours $>1-\leq 4$ cm in diameter, age <45 years, with no extra-thyroidal spread, no familial disease, no evidence of lymph node involvement, no angioinvasion and no distant metastases, is unclear. In such cases Personalised Decision Making is recommended (Chapter 2.4, and Table 2.4) (4, D).



To ablate or not to ablate?

- *Mazzaferri and Young 1981*
 - 576 patients, 10 yrs follow-up
 - RAI reduced mortality and recurrence
- In an era of better stratification does this still hold?
- A “one size fits all” is no longer acceptable
- Concern over RAI induced second primary malignancy and other morbidity



Clear indications for RAI or no RAI

- **Indicated in high and intermediate risk of recurrence**
 - >4cm, gross extrathyroidal extension, aggressive histology, distant metastases leading to reduced recurrence and improved survival
(Mazzaferrri and Young, 1981; Yamashita et al., 1997; Brierley et al., 2005)
- **Not indicated in very low risk**
 - tumor <1cm including multifocal microcarcinoma without any high risk features



Grey area for role of RAI

- Simpson et al (1998)
 - RRA of benefit if microscopic residual disease post surgery but if not no benefit
- Mazzaferri and Kloos (2001)
 - 1510 patients, followed-up 40 years
 - RRA reduced locoregional recurrence, distant metastases, and cancer death.
- Hay et al 2002
 - 2444 patients
 - RRA showed no benefit in already excellent cause specific mortality and tumor recurrence in low risk following near TT
- Schvartz et al. (2012)
 - 1298 low risk patients
 - median follow up of 10 years
 - no survival benefit of RAI after surgery in low risk
- **adequacy of surgery** was the main reason for different results in these studies



Why lower the dose of radioiodine?

- Patient benefits:
 - reduces duration of hospital isolation
 - reduces total body absorbed radiation dose
 - reduced risk of second malignancy
 - reduces radioiodine toxicities
 - improves quality of life for patient
- Wider benefits to society:
 - reduced radiation exposure to environment
 - reduced burden on health services
 - reduced exposure to healthcare workers
 - Fewer overall societal cost-less time off work



Efficacy of lower radioiodine ablation dose

- Two randomised controlled studies NEJM 2012
 - HiLo study in UK
 - ESTIMABL study in France

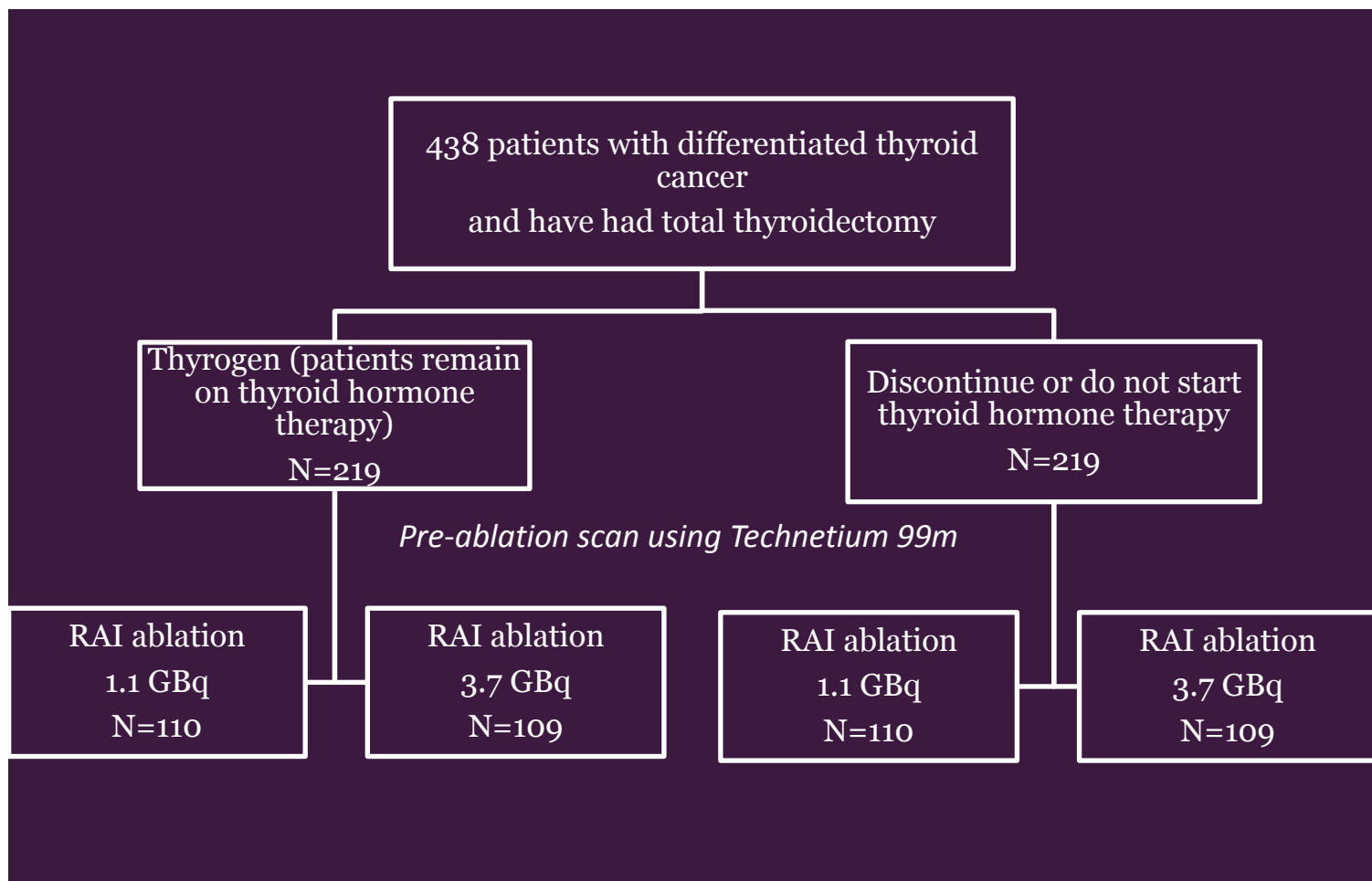


ORIGINAL ARTICLE

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., Jonathan Wadsley, F.R.C.R., Susan Clarke, F.R.C.P., Laura Moss, F.R.C.P., Alice Nicol, Ph.D., Penelope M. Clark, F.R.C.Path., Kate Farnell, R.C.N., Ralph McCready, D.Sc., James Smellie, M.D., Jayne A. Franklyn, F.Med.Sci., Rhys John, F.R.C.Path., Christopher M. Nutting, M.D., Kate Newbold, F.R.C.R., Catherine Lemon, F.R.C.R., Georgina Gerrard, F.R.C.R., Abdel Abdel-Hamid, F.R.C.R., John Hardman, F.R.C.R., Elena Macias, M.D., Tom Roques, F.R.C.R., Stephen Whitaker, M.D., Rengarajan Vijayan, F.R.C.R., Pablo Alvarez, M.Sc., Sandy Beare, Ph.D., Sharon Forsyth, B.Sc., Latha Kadalayil, Ph.D., and Allan Hackshaw, M.Sc.

N Engl J Med 2012;366:1674-85.



Assessments post-ablation:

- *7 days: Whole body ¹³¹I scan*
- *3 months: QoL*
- *6-9 months: Success/failure of ablation using ¹³¹I diagnostic scan (140-185 MBq) and stimulated Thyroglobulin*

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., Slimane Zerdoud, M.D., Boumédiène Bridji, M.D., Ph.D., Stéphane Bardet, M.D., Laurence Leenhardt, M.D., Ph.D., Delphine Bastie, M.D., Claire Schvartz, M.D., Pierre Vera, M.D., Ph.D., Olivier Morel, M.D., Danielle Benisvy, M.D., Claire Bournaud, M.D., Françoise Bonichon, M.D., Catherine Dejax, M.D., Marie-Elisabeth Toubert, M.D., Sophie Leboulleux, M.D., Marcel Ricard, Ph.D., and Ellen Benhamou, M.D.,
for the Tumeurs de la Thyroïde Refractaires Network for the Essai Stimulation Ablation Equivalence Trial*

French study, ESTIMABL

- n= 684
- similar design (T1-2, N0)
- also showed equivalence
- Rates of ablation 89-93%



Conclusions from HiLo and Estimabl

- 1.1 GBq \approx 3.7GBq ablation success rate
- rhTSH \approx THW ablation success rate following 1.1 GBq
- The same conclusion for T3 or N1 disease or Hurthle cell
- 1.1 GBq spent less time in hospital isolation (reduced overall costs)
- rhTSH +1.1GBq possibly be treated as a day case
- 1.1GBq has fewer acute side effects
- rhTSH better QoL
- Lead to practice change

Radioiodine treatment questions for the audience...

Should these patients follow a low iodine diet?

How long to patients have to avoid contact with children?

Can patients be in same house as family after radioiodine?

Can patients fly after radioiodine?

Does it cause infertility?

No ablation?

- Both HiLo and ESTIMABL showed
 - small remnants on pre-ablation scans (USS or WBS)
 - only 2.3% had significant remnant in HiLo
- Stimulated Tg < 1 (No Tg Ab) in 20-60% in HiLo and ESTIMABL
- Therefore successful remnant ablation with surgery alone
- Following appropriate surgery, the majority of patients with low-risk disease and even some patients with more advanced-stage or regional metastases have low rates of recurrence and high rates of survival when managed without radioiodine



Iodine or Not (IoN) - UK

- Phase II: monthly patient accrual rates
- Phase III: 5-year Disease-Free Survival based on
 - Histologically confirmed structural loco-regional recurrent or residual disease
 - Distant Recurrence



IoN UK

- Post TT randomised to receive RAI (1.1 GBq) or not
- diagnostic I131 scan, neck ultrasound
- Assessment of success of ablation with stimulated thyroglobulin at 6-9 months
- Identifying residual disease and recurrence early is crucial.
- For 5 years
 - Tg measured every 6 mths whilst on T4
 - Neck USS \pm FNA every 6 mths in first year and then annually.
- Most recurrences are locoregional and will be detected using these techniques.



Contemporary approach to treatment selection

- Risk Stratification
 - clinical staging cTNM
 - pathological staging pTNM
 - molecular profiling
 - dynamic response to treatment stratification
- Risk adapted treatment
 - individualisation of treatment based on predicted therapeutic gain

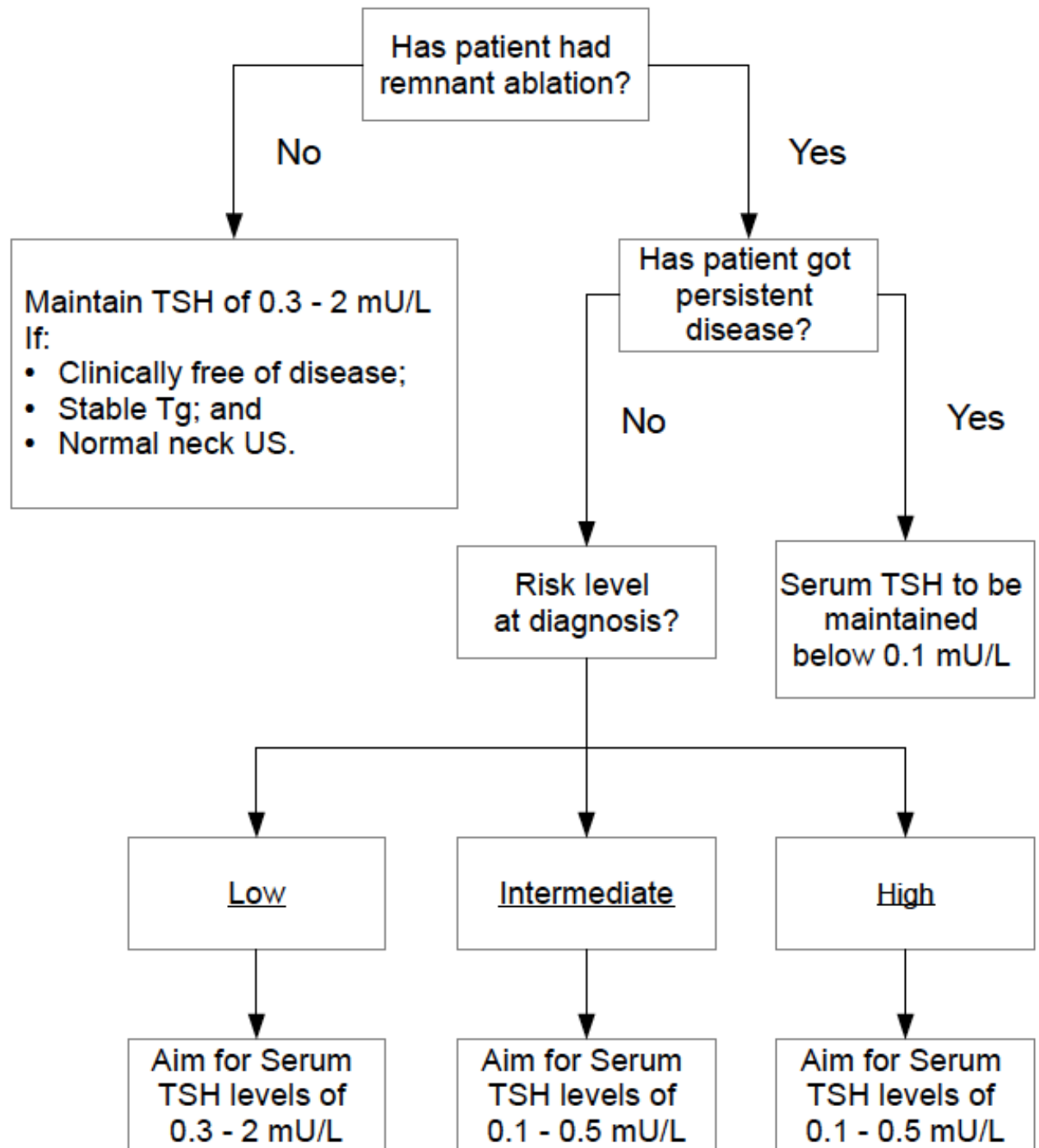


Risk adapted approach

- **High Risk, aggressive disease**
 - 50% 10 year survival
 - may need multimodality treatment akin to that in other solid tumours
 - TT+ND + High dose RAI (Empiric or dosimetry)
 - TT+ND+ High dose RAI + adjuvant targeted therapy
- Cautious dose escalation studies?
Higher absorbed dose for higher risk
- **Intermediate Risk**
 - more judicious use of surgery
 - RAI 1.1-3.7GBq
- **Low Risk**
Is *low* dose or *no* dose an option for low risk disease?



TSH suppression

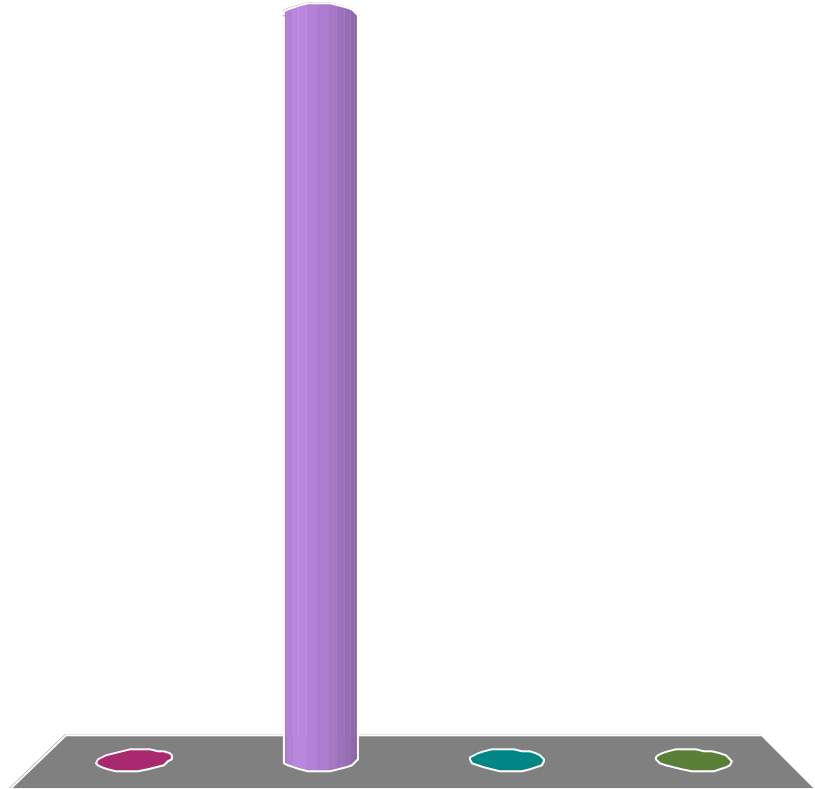


TSH suppression questions



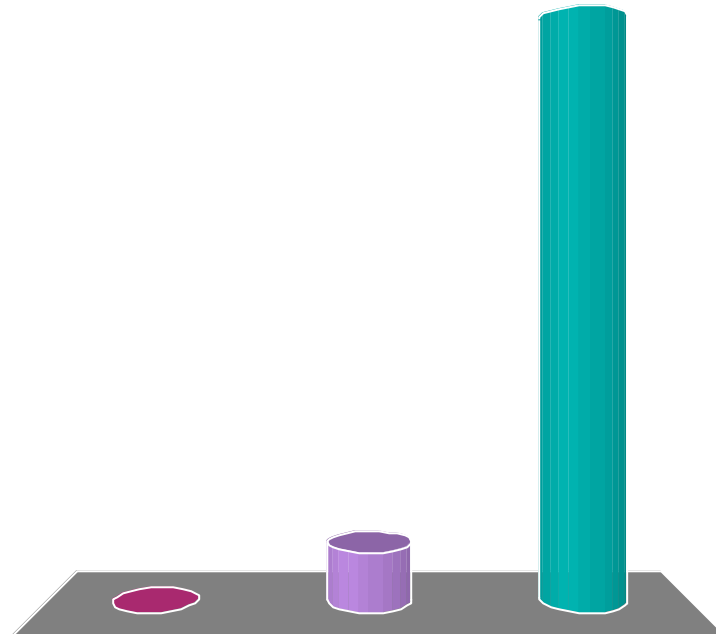
In which setting should TSH be suppressed?

- A. PTC
- B. FTC
- C. MTC
- D. ATC



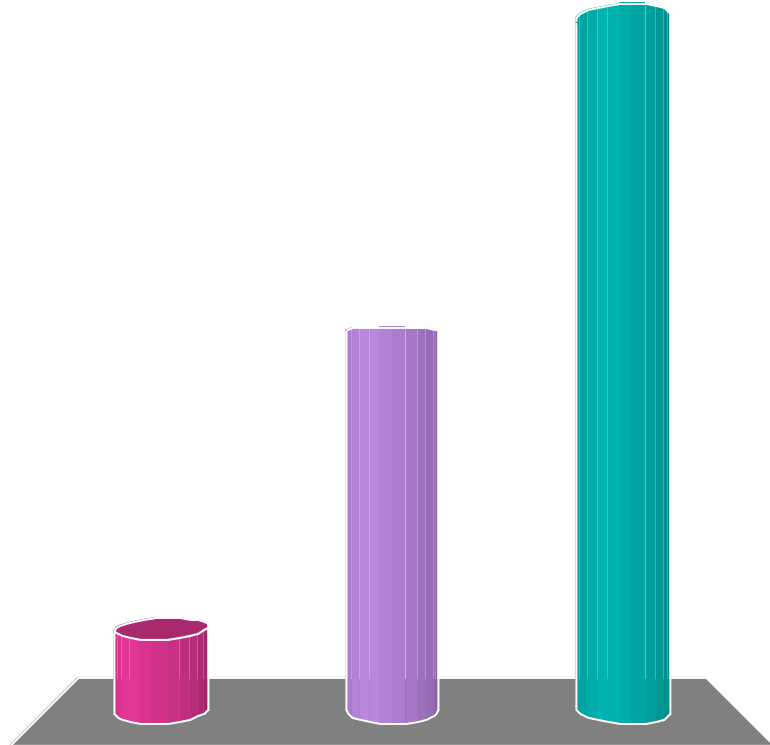
Long term TSH suppression can cause which of the following?

- A. Weight loss
- B. Arrhythmia
- C. Osteoporosis



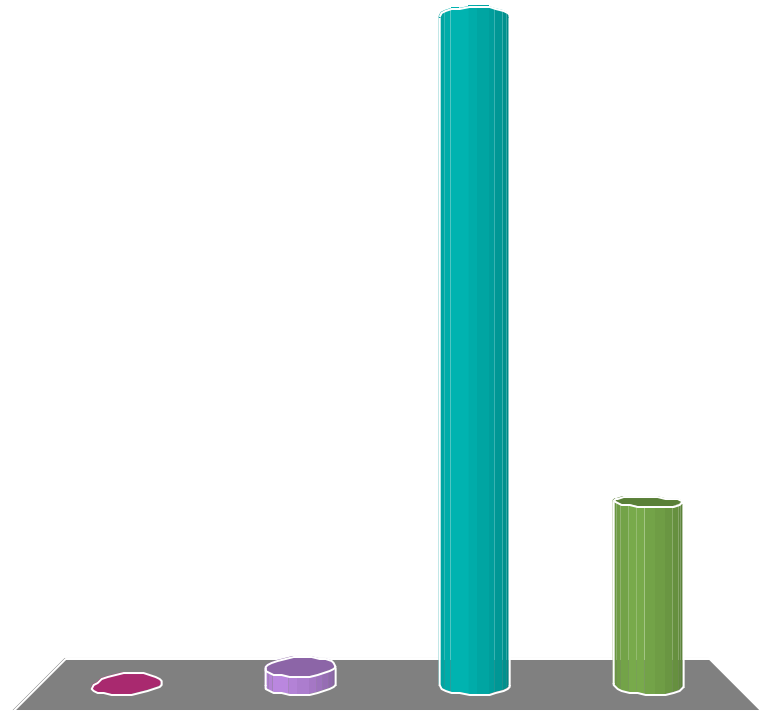
At which time point can TSH suppression be relaxed?

- A. Never
- B. 10 years
- C. 1 year



How often should the thyroxine dose be changed when trying to achieve TSH target range?

- A. Weekly
- B. Monthly
- C. 2 monthly
- D. 6 monthly



Watchful waiting in Thyroid cancer?

- *Ito et al World J Surgery 2010; Thyroid 2014*
 -option for papillary microcarcinoma active surveillance or thyroidectomy.
 -Active surveillance involved neck USS at 6 mths then annually

TABLE 3. THE NUMBER OF PATIENTS AT RISK AND INCIDENCE RATES OF THE THREE EVENTS IN EACH SUBSET

<i>Observation periods</i>	<i>5-year</i>	<i>10-year</i>	<i>15-year</i>
Size enlargement			
Patients at risk (<i>n</i>)	157/225/45	36/82/11	6/18/0
Incidence rates (%)	4.0/5.0/9.1	4.0/9.1/12.1	
Novel appearance of node metastasis			
Patients at risk (<i>n</i>)	160/229/49	36/87/13	5/20/2
Incidence rates (%)	0.5/1.4/5.2	0.5/2.3/16.1	
Progression to clinical disease			
Patients at risk (<i>n</i>)	157/229/48	36/87/13	6/19/2
Incidence rates (%)	2.2/4.0/9.5	2.5/4.9/22.5	

Data are presented as number or percent of patients in each age group (old/middle-aged/young).



Conclusions

- HiLo and ESTIMABL first step, multi-centre RCT establishing non-inferiority of lower activity of RAI with rhTSH in low risk DTC
- Quest for level 1/robust evidence continues for the “grey” areas
 - IoN UK
 - ESTIMABL 2 France
- Refinement of stratification of risk of recurrence will lead to individualised treatment packages
- “Less can be more” BUT only after careful selection
- The Pendulum should not swing too early or too far



The Royal Marsden Thyroid Unit

Oncology

- Dr Kate Newbold
- Prof Chris Nutting
- Prof Kevin Harrington

Endocrinology

- Dr Steve Hyer
- Dr Daniel Morganstein

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- Mr John Watkinson

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