Radioiodine Therapy in Papillary Thyroid Cancer

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Case 1

- A 40-year-old man with type 2 diabetes and hypertension underwent Doppler ultrasound assessment of the carotid arteries as part of a primary cardiovascular prevention program
- He was referred because the examination disclosed an asymptomatic nodule in the right lobe of the thyroid.
- Ultrasonography (US) of the thyroid and neck performed revealed a hypoechoic nodule measuring 15 mm with signs of punctate microcalcification.No suspicious lymph nodes were seen
- The nodule was subjected to fine-needle aspiration biopsy (FNAb) , and the cytological findings were suggestive of papillary thyroid cancer (PTC) (Bethesda class V)

Case 1

- The patient underwent total thyroidectomy . Pathology examination of the surgical specimen revealed a classical PTC measuring 14 mm with no evidence of extrathyroidal extension or vascular invasion [pT1b, Nx (stage 1) according to theAJCC/TNM 2017 Edition]

- The risk of recurrence was classified as low according to the modified American Thyroid Association (ATA) staging system (2026)

- Four weeks after surgery, TSH=40mIU/l, Tg=0.9ng/ml and Anti Tg= below assay sensitivity (<4.11 U/mL)

Case 1

- After discussion of these findings and the pros and cons of radioactive iodine remnant ablation (RRA), the patient chose to forego ablation and to be followed with simple surveillance.
- Eight weeks later, he was taking LT4 8 pills per week.
- At that time ,TSH= 0.2mIU/l, Tg= 0.02ng/ml , Anti Tg= negative
- Six months later, neck ultrasound revealed no abnormal finding

Case 2

- A 56year-old woman was referred to the endocrine clinic for a 2.0 cm right thyroid nodule found on a “routine” thyroid ultrasound.

- Because of suspicious sonographic characteristics, she underwent a fine-needle aspiration biopsy that suggested papillary thyroid cancer (PTC).

- Preoperative neck ultrasound showed tow suspicious lymph nodes in zone VI

Case 2

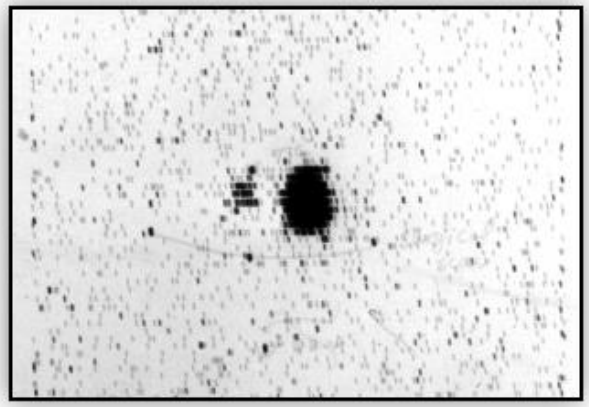
- A total thyroidectomy with central neck dissection was performed, and the pathology showed a 19 cm classic PTC in the right lobe, with 4 lymph nodes (out of 15) with metastatic foci; the larger was 1.0 cm

- Four weeks after surgery, TSH=40mIU/l, Tg= 10 ng/ml and Anti Tg= below assay sensitivity (<4.11 U/mL).

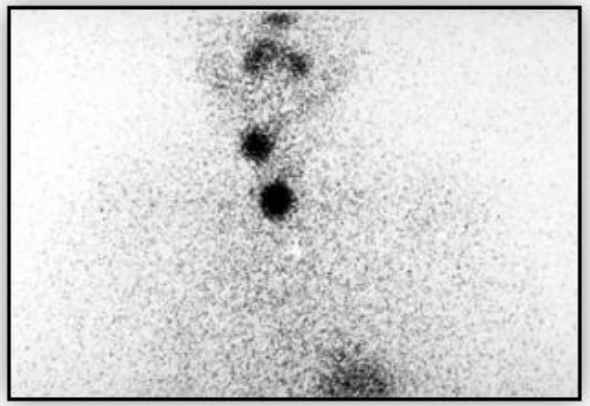
- No abnormal sonographic finding was found at this time

RAI Use in Thyroid Cancer

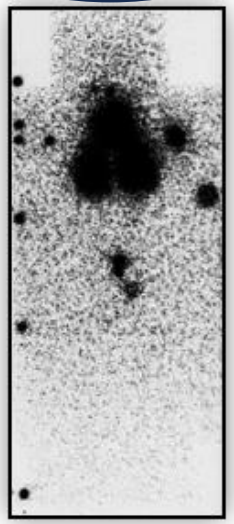
RRA



Adjuvant Rx



^{131}I Rx



Goals of Radioiodine Remnant Ablation

- Destroy presumably benign thyroid tissue
- Improve value of serum Tg in follow-up
- Increase sensitivity of subsequent WBS
- Maximize therapeutic benefit of subsequent RAI Rx
- Postablative scan may identify additional disease sites

Adjuvant Treatment

- Use of 131-I to destroy subclinical tumor deposits that may or may not be present after surgical resection of all known primary tumor tissue and metastatic foci

- Since adjuvant treatment is given based on the risk of having persistent/recurrent disease without definitive evidence of biochemical or structural evidence of disease, it is accepted that some patients selected for adjuvant treatment might already have been treated sufficiently by their primary surgery

Treatment of known disease

- Use of 131-I to destroy known locoregional and/or distant metastasis with the objectives of potential cure, reduced recurrence and mortality from thyroid cancer, and/or palliation

Terminology that should be used to communicate the goals of 131I therapy

	^{131}I Therapy		
Goal	Remnant Ablation	Adjuvant Treatment	Treatment of Known Disease
Initial staging	√	√	√
Facilitate follow-up	√	√	√
Improve disease-specific survival	-	√	√
Decrease recurrence	-	√	-
Improve progression-free survival	-	√	√
Curative intent	-	√	√
Palliative intent	-	-	√

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Importance of risk stratification

- The adequate risk stratification in a malignant neoplastic disease is crucial to avoid on one hand the overtreatment of low-risk patients and on the other hand the under treatment of high-risk subjects

- This issue is particularly important in thyroid carcinoma, generally characterized by good outcomes with 10-year overall survival (OS) rates for patients with papillary (PTC), follicular (FTC) of 93% and 85% respectively

Tuttle RM, et al. Thyroid. 2010; 20: 134-49

Tools for risk classification

- TNM and prognostic scoring tools such as MASIC for prediction of **disease specific mortality**
- Clinico-pathological staging system for prediction of **recurrence**
- Dynamic reclassification

TNM

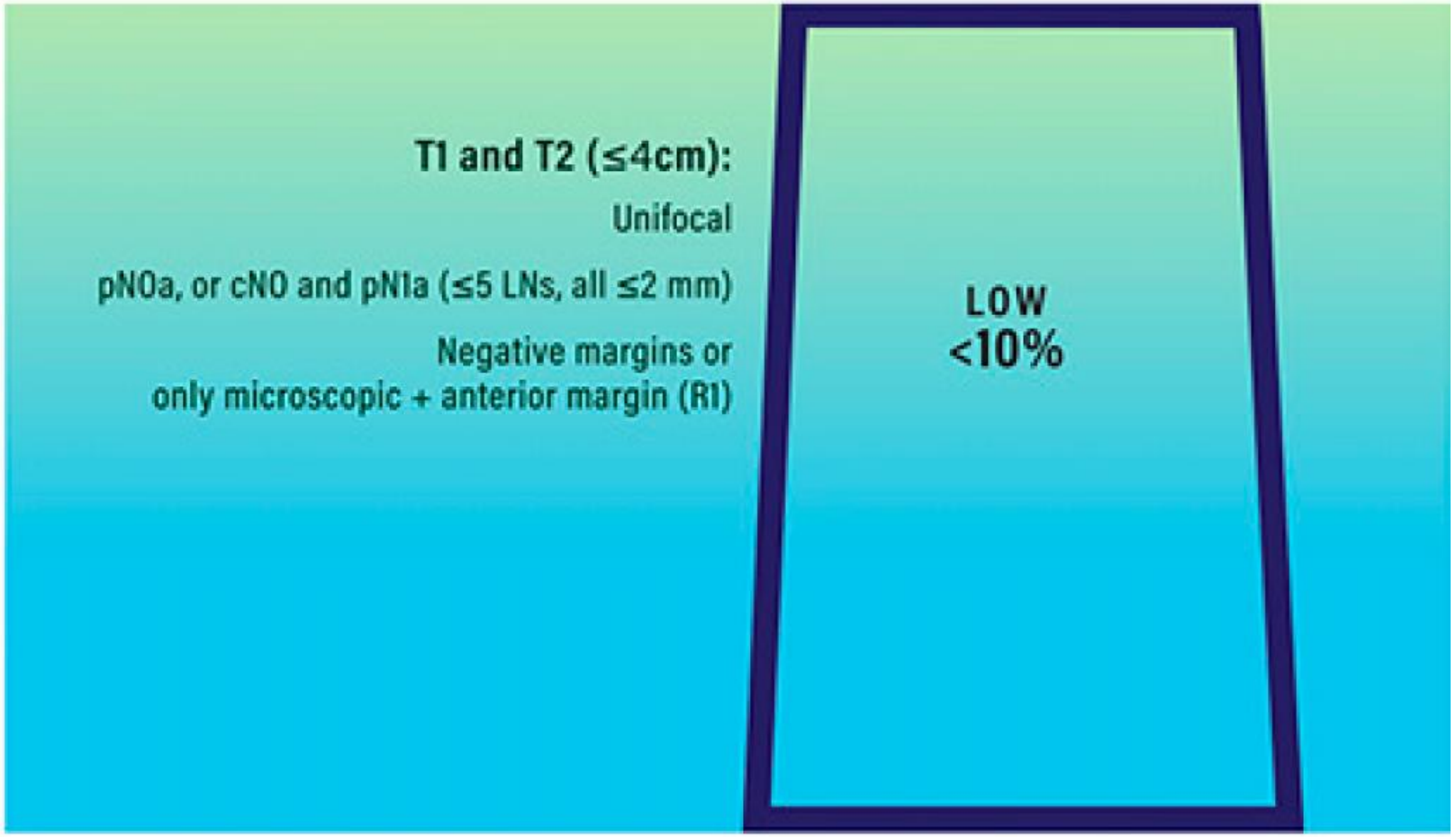
CATEGORY[a]	*Code*	*Description*
Primary tumor (pT)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	T1	Tumor ≤2 cm limited to thyroid
	• T1a	Tumor ≤1 cm limited to thyroid
	• T1b	Tumor >1 cm but ≤2 cm limited to thyroid
	T2	Tumor >2 cm but ≤4 cm limited to thyroid
	T3	Tumor >4 cm or minimal extrathyroidal extension
	• T3a	Tumor >4 cm limited to thyroid
	• T3b	Gross extrathyroidal extension to strap muscles
	T4	Gross extrathyroidal extension to major neck structures
	• T4a	Invading soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve
	• T4b	Invading prevertebral fascia or encasing carotid/mediastinal vessels

TNM		
CATEGORY[a]	*Code*	*Description*
Regional lymph node (pN)	NX	Regional lymph nodes cannot be assessed
	N0	No evidence of regional lymph node metastasis
	• N0a	One or more cytological or histologically confirmed benign lymph nodes
	• N0b	No radiological/clinical evidence of metastasis
	N1	Metastasis to regional nodes
	• N1a	Metastasis to level VI or VII (pretracheal, paratracheal, prelaryngeal / Delphian or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease
	• N1b	Metastasis to unilateral, bilateral or contralateral lateral neck lymph nodes (levels I, II, III, IV or V) or retropharyngeal lymph nodes

8th edition (age of patient <55 years)			
I	Any T	Any N	M0
II	Any T	Any N	M1
8th edition (age of patient ≥55 years)			
I	T1 or T2	N0 or Nx	M0
II	T1 or T2	N1	M0
	T3a or T3b	Any N	M0
III	T4a	Any N	M0
IVa	T4b	Any N	M0
IVb	Any T	Any N	M1

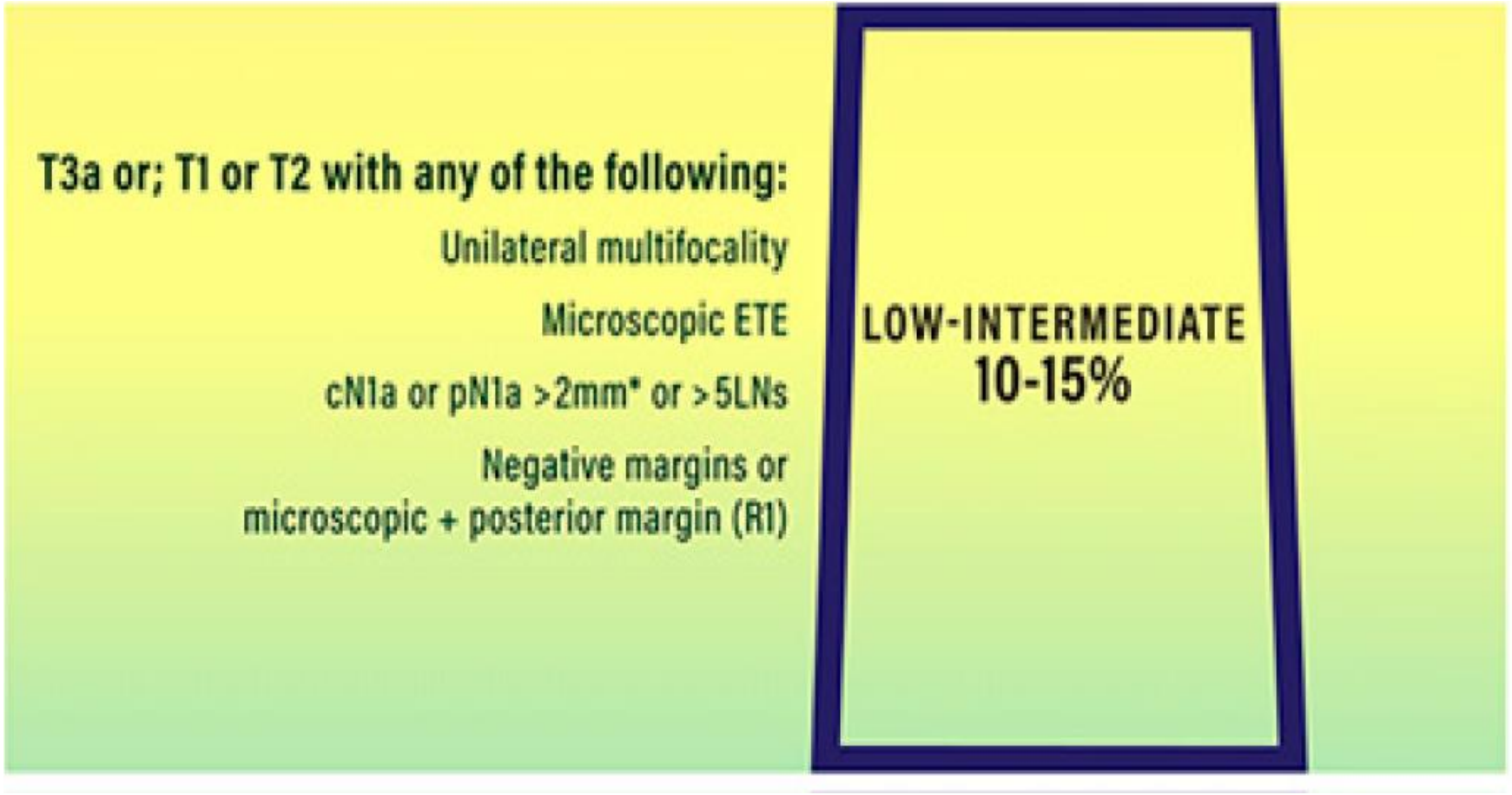
ATA Guideline 2025

Low risk — Risk of recurrence

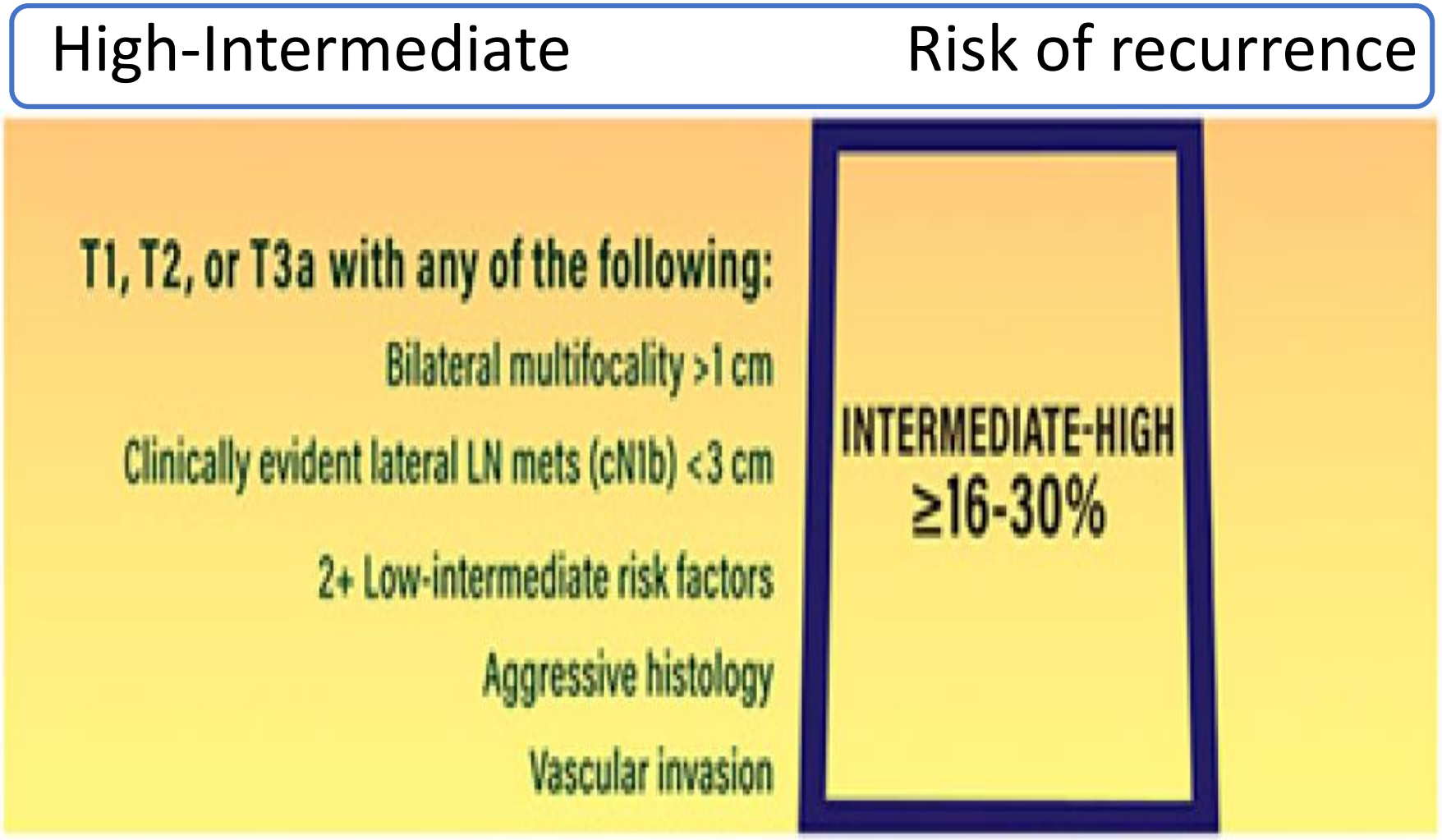


ATA Guideline 2025

Low-Intermediate Risk of recurrence

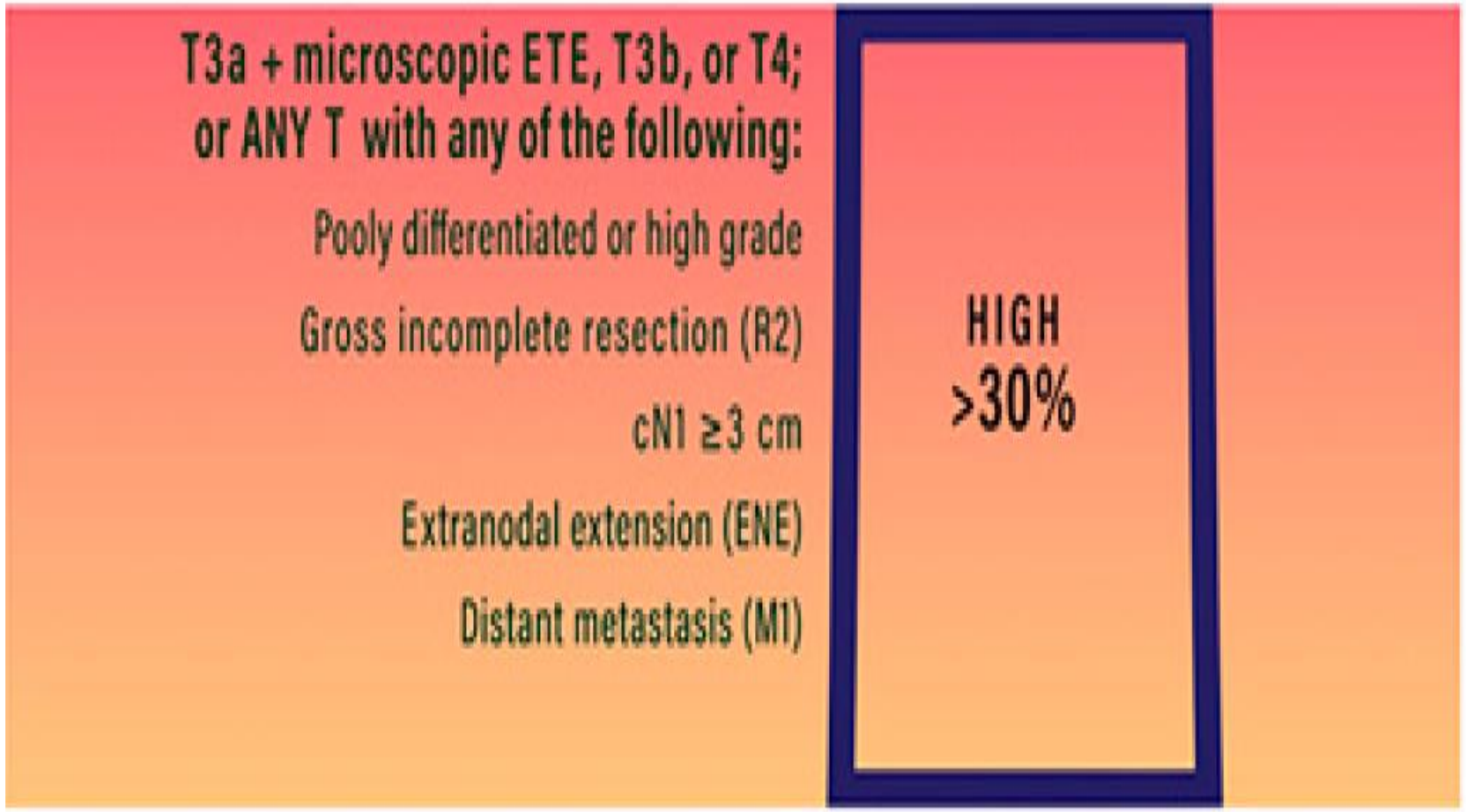


ATA Guideline 2025



ATA Guideline 2025

High Risk	Risk of recurrence



Dynamic Reclassification

- Before 2015 ATA guideline, there was a static and single risk evaluation was done only at the time of diagnosis. For the first time Tuttle proposed the dynamic risk stratification

- In dynamic risk stratification about 50-73% of patients with initial ATA high risk status move to low-risk category and nearly 6-12% of patients from ATA low risk groups are reclassified as high risk.

Tuttle RM, et al. Thyroid. 2010; 20: 134-49
Castagna MG, et al. EJE. 2011; 165: 441-6.
Ozkan E,etal. Nucl Med Commun.2017;38:1055-59

Response	Definition (2015 American Thyroid Association guidelines)[21]	Risk of recurrence (%)
Excellent response	• No abnormal finding on imaging and basal thyroglobulin <0.2 ng/ml or stimulated thyroglobulin <1 ng/ml • And no thyroglobulin antibodies	<1–4
Biochemical incomplete response	• No abnormal finding on imaging • And basal thyroglobulin ≥1 ng/ml or stimulated thyroglobulin ≥10 ng/ml or rising thyroglobulin antibodies over time	20
Indeterminate response	• Nonspecific findings on imaging • And/or basal thyroglobulin ≥0.2 to <1 ng/ml or stimulated thyroglobulin ≥1 to <10 ng/ml or stable or declining thyroglobulin antibodies over time	15–20
Structural incomplete response	Abnormal findings on imaging	100

TABLE 9. RESPONSE CRITERIA AFTER INITIAL THERAPY BASED ON TYPE OF INTERVENTION

Response to therapy	*Post total thyroidectomy and/or neck dissection with RAI ablation or therapy*	*Post total thyroidectomy and/or neck dissection without RAI ablation*	*Post hemithyroidectomy*	*TSH goal*
Excellent	Nonstimulated Tg <0.2 or stimulated Tg <1 and negative imaging	Nonstimulated Tg <2.5	Normal or low-risk nodules in the contralateral lobe, or contralateral lobe nodules with benign biopsy AND no abnormal lymph nodes on imaging	TSH within normal reference range
Indeterminate	Nonspecific findings on imaging studies or nonstimulated Tg 0.2–1 or stimulated Tg 1–10 or stable/ declining TgAb levels	Nonspecific findings on imaging studies or nonstimulated Tg 2.5–5, or stable/ declining TgAb levels	N/A[a]	TSH within normal reference range[b]
Biochemically incomplete	Non-stimulated Tg >1 or stimulated Tg >10 or increasing TgAb levels and negative imaging	Nonstimulated Tg >5 or increasing TgAb levels and negative imaging	N/A[a]	TSH below normal reference range[c]
Structurally incomplete	Structural evidence of disease (suspicious imaging or biopsy proven local or distant metastatic disease)	Structural evidence of disease (suspicious imaging or biopsy proven local or distant metastatic disease)	Structural evidence of disease (suspicious imaging or biopsy proven local or distant metastatic disease)	TSH below normal reference range[c]

Different outcomes

- Successful ablation
- Recurrence
- Disease free survival
- Disease specific survival
- Progression free survival
- Overall survival

Definitions of outcomes

- **Disease-Free Survival (DFS):**Time from treatment (e.g., surgery or therapy) until disease “recurrence” or “death from any cause”

- **Disease-Specific Survival (DSS):**Time from diagnosis/treatment until death “specifically from the disease being studied”, excluding deaths from other causes

- **Progression-Free Survival (PFS):**Time from treatment until “disease progression” or “death from any cause”

- **Overall Survival (OS):**Time from treatment until :death from any cause: (most definitive endpoint)

The NEW ENGLAND JOURNAL of MEDICINE

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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*

N Engl J Med 2012;366:1663-73

Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial

Martin Schlumberger, Sophie Leboulleux, Bogdan Catargi, Desiree Deandreis, Slimane Zerdoud, Stephane Bardet, Daniela Rusu, Yann Godbert, Camille Buffet, Claire Schvartz, Pierre Vera, Olivier Morel, Danielle Benisvy, Claire Bournaud, Marie-Elisabeth Toubert, Antony Kelly, Ellen Benhamou, Isabelle Borget

Lancet Diabetes Endocrinol 2018 Aug;6(8):618-626

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., 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

Recurrence after low-dose radioiodine ablation and recombinant human thyroid-stimulating hormone for differentiated thyroid cancer (HiLo): long-term results of an open-label, non-inferiority randomised controlled trial

Hakim-Moulay Dehbi, Ujjal Mallick, Jonathan Wadsley, Kate Newbold, Clive Harmer, Allan Hackshaw

Lancet Diabetes Endocrinol 2019; 7: 44–51

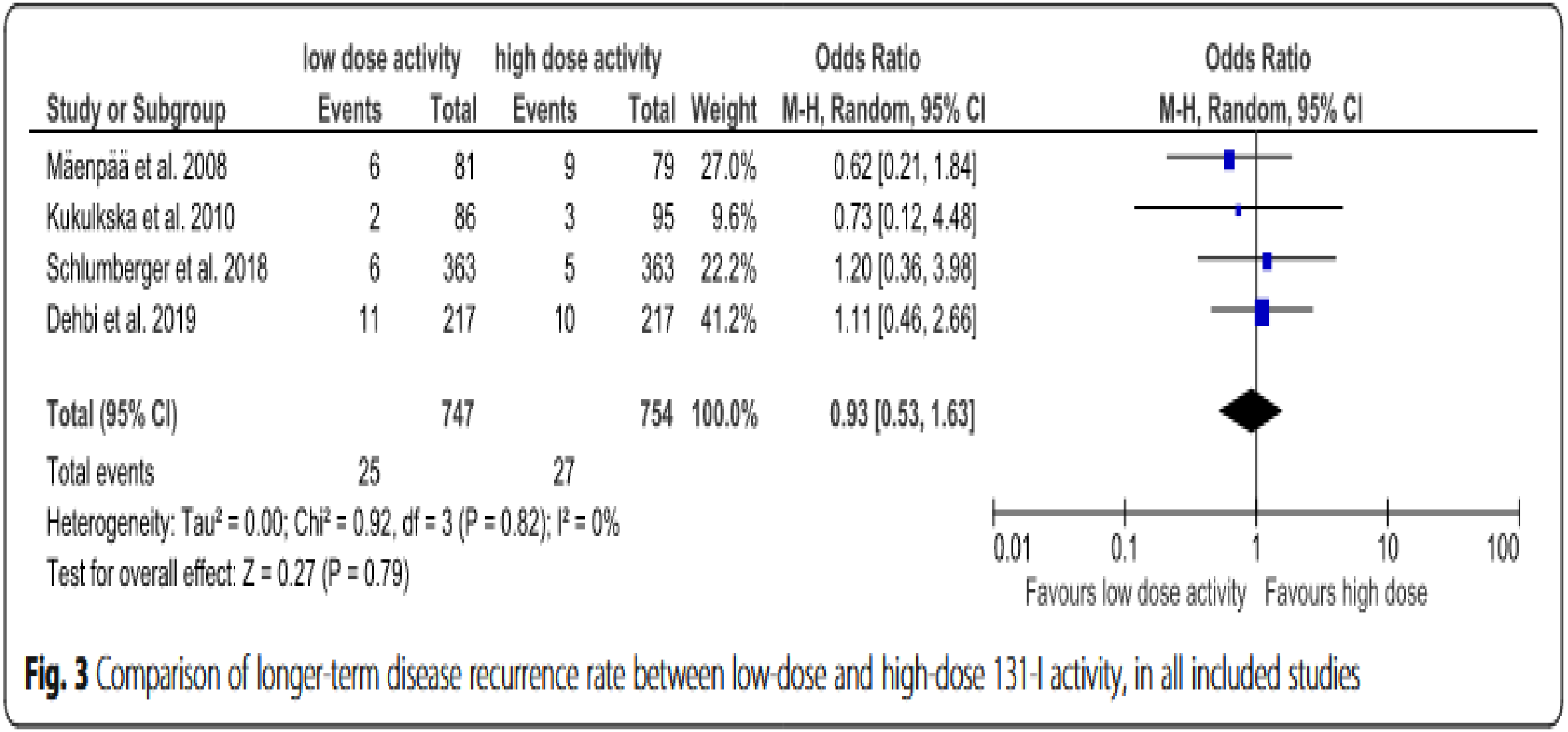
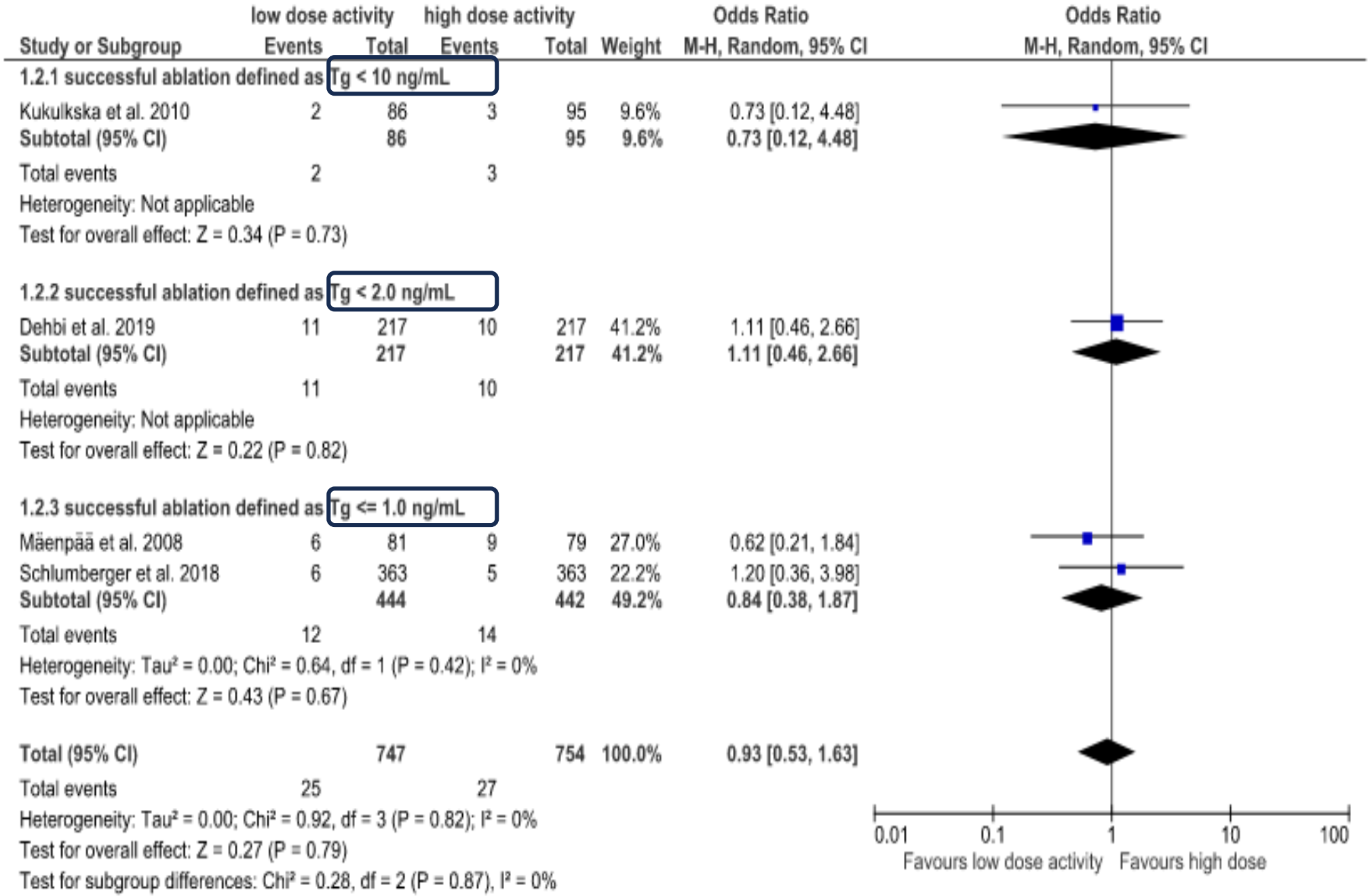
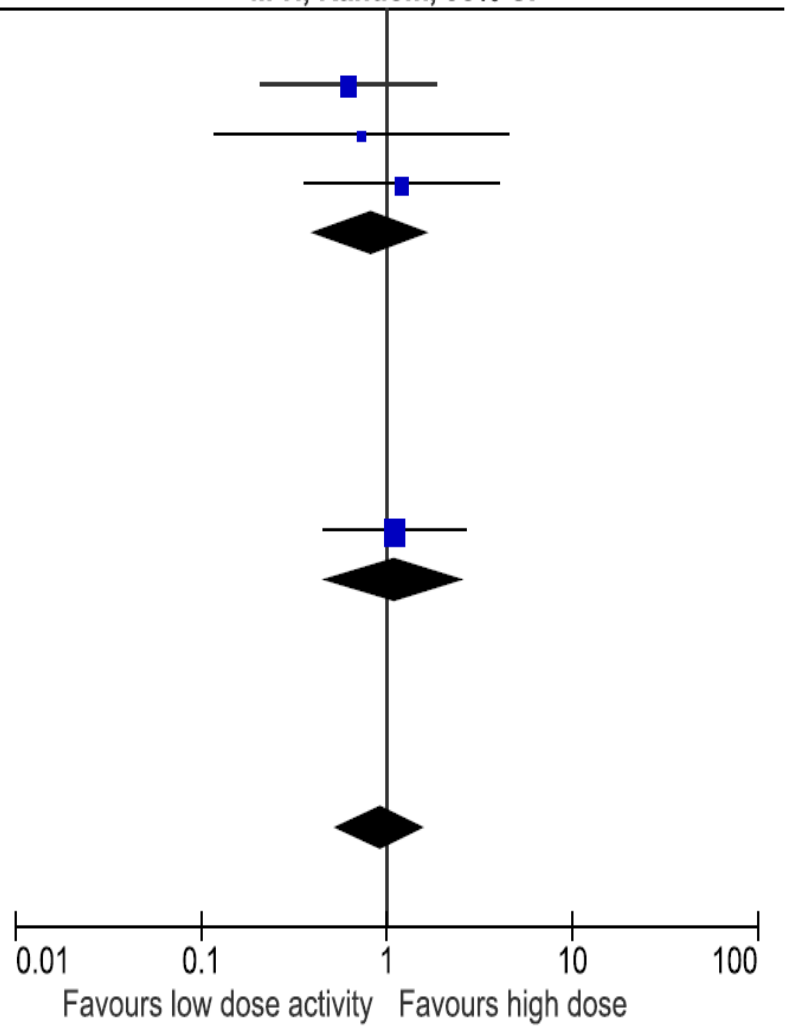
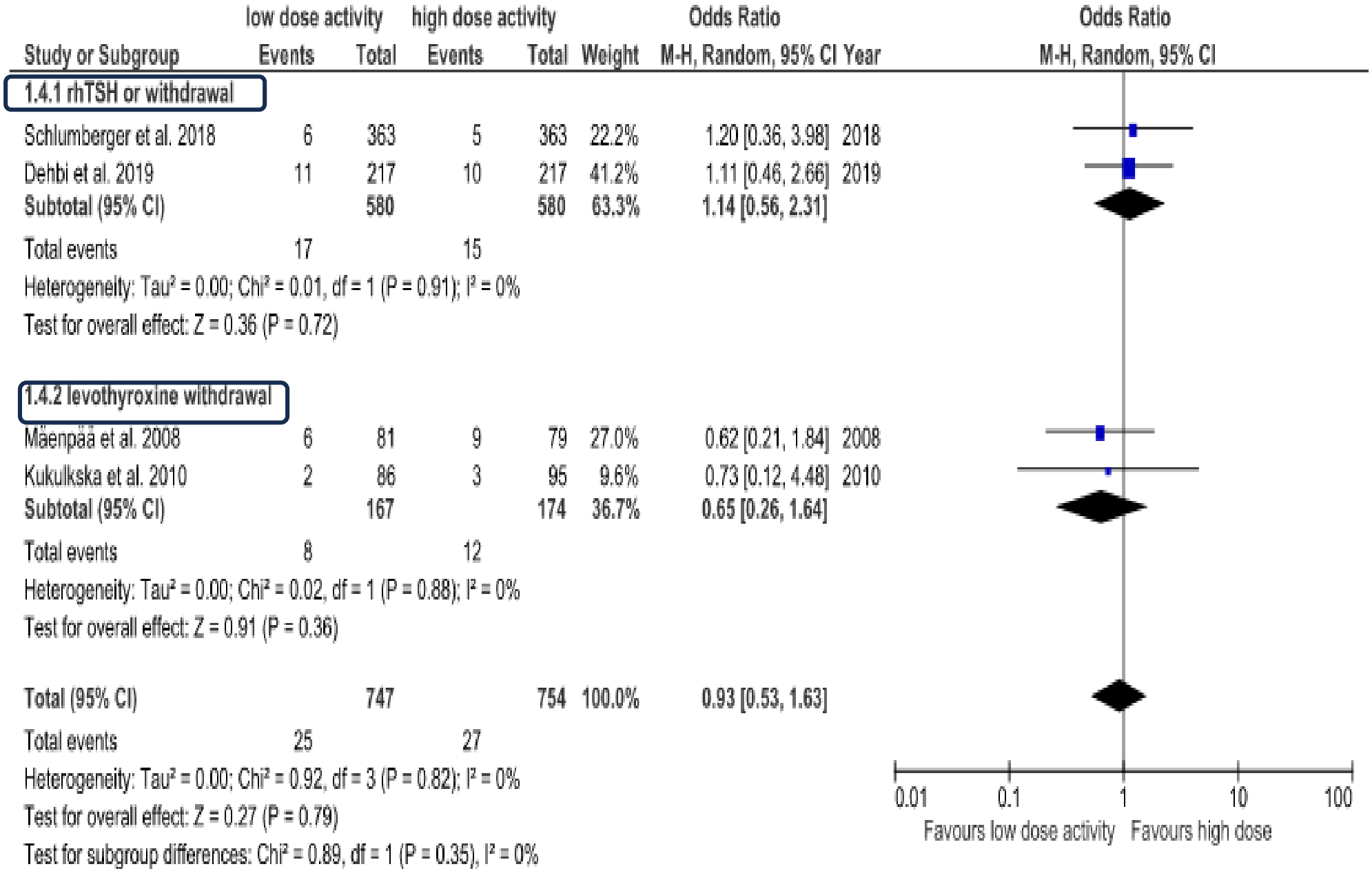


Fig. 3 Comparison of longer-term disease recurrence rate between low-dose and high-dose 131-I activity, in all included studies


low dose activity
high dose activity
Odds Ratio
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
1.2.1 successful ablation defined as Tg < 10 ng/mL
Kukulkska et al. 2010 2 86 3 95 9.6% 0.73 [0.12, 4.48]
Subtotal (95% CI) 86 95 9.6% 0.73 [0.12, 4.48]
Total events 2 3
Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)
1.2.2 successful ablation defined as Tg < 2.0 ng/mL
Dehbi et al. 2019 11 217 10 217 41.2% 1.11 [0.46, 2.66]
Subtotal (95% CI) 217 217 41.2% 1.11 [0.46, 2.66]
Total events 11 10
Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.82)
1.2.3 successful ablation defined as Tg <= 1.0 ng/mL
Mäenpää et al. 2008 6 81 9 79 27.0% 0.62 [0.21, 1.84]
Schlumberger et al. 2018 6 363 5 363 22.2% 1.20 [0.36, 3.98]
Subtotal (95% CI) 444 442 49.2% 0.84 [0.38, 1.87]
Total events 12 14
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
Total (95% CI) 747 754 100.0% 0.93 [0.53, 1.63]
Total events 25 27
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Chi² = 0.28, df = 2 (P = 0.87), I² = 0%
0.01
0.1
1
10
100
Favours low dose activity
Favours high dose

Study or Subgroup	low dose activity Events	Total	high dose activity Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.3.1 patients with total thyroidectomy included							
Mäenpää et al. 2008	6	81	9	79	27.0%	0.62 [0.21, 1.84]	2008
Kukulkska et al. 2010	2	86	3	95	9.6%	0.73 [0.12, 4.48]	2010
Schlumberger et al. 2018	6	363	5	363	22.2%	1.20 [0.36, 3.98]	2018
Subtotal (95% CI)		**530**		**537**	**58.8%**	**0.82 [0.39, 1.71]**	
Total events	14		17				
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 2 (P = 0.72); I² = 0%							
Test for overall effect: Z = 0.53 (P = 0.59)							
1.3.2 patients with total thyroidectomy or near-total thyroidectomy included							
Dehbi et al. 2019	11	217	10	217	41.2%	1.11 [0.46, 2.66]	2019
Subtotal (95% CI)		**217**		**217**	**41.2%**	**1.11 [0.46, 2.66]**	
Total events	11		10				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.22 (P = 0.82)							
Total (95% CI)		**747**		**754**	**100.0%**	**0.93 [0.53, 1.63]**	
Total events	25		27				
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 3 (P = 0.82); I² = 0%							
Test for overall effect: Z = 0.27 (P = 0.79)							
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%							




low dose activity
high dose activity
Odds Ratio
Odds Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
Year
M-H, Random, 95% CI
1.4.1 rhTSH or withdrawal
Schlumberger et al. 2018 6 363 5 363 22.2% 1.20 [0.36, 3.98] 2018
Dehbi et al. 2019 11 217 10 217 41.2% 1.11 [0.46, 2.66] 2019
Subtotal (95% CI) 580 580 63.3% 1.14 [0.56, 2.31]
Total events 17 15
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)
1.4.2 levothyroxine withdrawal
Mäenpää et al. 2008 6 81 9 79 27.0% 0.62 [0.21, 1.84] 2008
Kukulkska et al. 2010 2 86 3 95 9.6% 0.73 [0.12, 4.48] 2010
Subtotal (95% CI) 167 174 36.7% 0.65 [0.26, 1.64]
Total events 8 12
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)
Total (95% CI) 747 754 100.0% 0.93 [0.53, 1.63]
Total events 25 27
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.35), I² = 0%
0.01
0.1
1
10
100
Favours low dose activity
Favours high dose

Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer

S. Leboulleux, C. Bournaud, C.N. Chougnet, S. Zerdoud, A. Al Ghuzlan, B. Catargi, C. Do Cao, A. Kelly, M.-L. Barge, L. Lacroix, I. Dygai, P. Vera, D. Rusu, O. Schneegans, D. Benisvy, M. Klein, J. Roux, M.-C. Eberle, D. Bastie, C. Nascimento, A.-L. Giraudet, N. Le Moullec, S. Bardet, D. Drui, N. Roudaut, Y. Godbert, O. Morel, A. Drutel, L. Lamartina, C. Schvartz, F.-L. Velayoudom, M.-J. Schlumberger, L. Leenhardt, and I. Borget

- In this prospective, phase 3 trial, patients with **low-risk** differentiated thyroid cancer who were undergoing thyroidectomy were randomized to receive ablation with postoperative administration of radioiodine (1.1 GBq) after injections of recombinant human thyrotropin **(radioiodine group)** or to receive no postoperative radioiodine **(no-radioiodine group)**

N Engl J Med 2022;386:923-32

Methods

- **Primary End Point**: To assess non inferiority in the no-radioiodine group as compared with the radioiodine group with respect to the percentage of patients without a functional, structural, or biologic event during **3 years** after randomization.

- **Noninferiority** was defined as a between-group difference of **less than 5 percentage** points in the percentage of patients who did not have events that included the presence of abnormal foci of radioiodine uptake on whole-body scanning that required subsequent treatment (in the radioiodine group only), abnormal findings on neck ultrasonography, or elevated levels of thyroglobulin or thyroglobulin antibodies

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Radioiodine (N=389)	No Radioiodine (N=387)
Age — yr	52.2±13.4	52.6±13.5
Female sex — no. (%)	319 (82.0)	323 (83.5)
Interval between thyroidectomy and randomization — days	92.1±23.2	91.2±23.6
Histologic analysis — no. (%)		
Papillary	372 (95.6)	372 (96.1)
Follicular	13 (3.3)	11 (2.8)
Oncocytic: Hürthle cell	4 (1.0)	4 (1.0)
Largest tumor dimension — mm	13.4±3.6	13.7±3.9
Primary tumor–node–metastasis stage — no. (%)		
pT1aN0	26 (6.7)	23 (5.9)
pT1aNx	56 (14.4)	42 (10.9)
pT1bN0	143 (36.8)	148 (38.2)
pT1bNx	164 (42.2)	174 (45.0)
Multifocality — no. (%)	178 (45.8)	156 (40.3)
Neck dissection performed — no. (%)†	171 (44.0)	171 (44.2)
Central only	69 (17.7)	77 (19.9)
Central and lateral	74 (19.0)	65 (16.8)
Lateral only	26 (6.7)	27 (7.0)
Unknown	2 (0.5)	2 (0.5)

Table 2. Number and Type of Events Occurring during 3 Years (Per-Protocol Population).*

Variable	Radioiodine (N=363)		No Radioiodine (N=367)		Between-Group Difference†
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	*percentage points (90% CI)*
Primary composite end point					
No primary event during 3 yr	348	95.9 (93.3 to 97.7)	351	95.6 (93.0 to 97.5)	−0.3 (−2.7 to 2.2)
Occurrence of event during 3 yr	15	4.1 (2.3 to 6.7)	16	4.4 (2.5 to 7.0)	

Table 4. Response to Treatment at 10 Months and 3 Years.

Response	Radioiodine	No Radioiodine
Evaluation at 10 mo		
No. of patients	325	342
Distribution of response — no. (%)		
Excellent*	282 (86.8)	295 (86.3)
Structurally incomplete: abnormal imaging	4 (1.2)	1 (0.3)
Biochemically incomplete†	8 (2.5)	13 (3.8)
Indeterminate‡	31 (9.5)	33 (9.6)
Evaluation at 3 yr		
No. of patients	363	367
Distribution of response — no. (%)		
Excellent§	265 (73.0)	272 (74.1)
Structurally incomplete: abnormal imaging	4 (1.1)	3 (0.8)
Biochemically incomplete¶	2 (0.6)	12 (3.3)
Indeterminate‖	40 (11.0)	37 (10.1)
Missing data for central laboratory assessment	52 (14.6)	43 (11.7)

Key message

- In patients with low-risk thyroid cancer undergoing thyroidectomy, a follow-up strategy that did not involve the use of radioiodine was noninferior to an ablation strategy with radioiodine regarding the occurrence of functional, structural, and biologic events at 3 years

Thyroidectomy without radioiodine in patients with low-risk thyroid cancer: 5 years of follow-up of the prospective randomised ESTIMABL2 trial

- Here, we report a pre-specified analysis after 5 years of follow-up

- An event was defined as abnormal foci of ^{131}I uptake on the post-treatment whole-body-scan requiring subsequent treatment , abnormal neck ultrasonography, elevated thyroglobulin levels, increasing titers or appearance of thyroglobulin antibody (using the same laboratory assay), or a combination of these definitions.

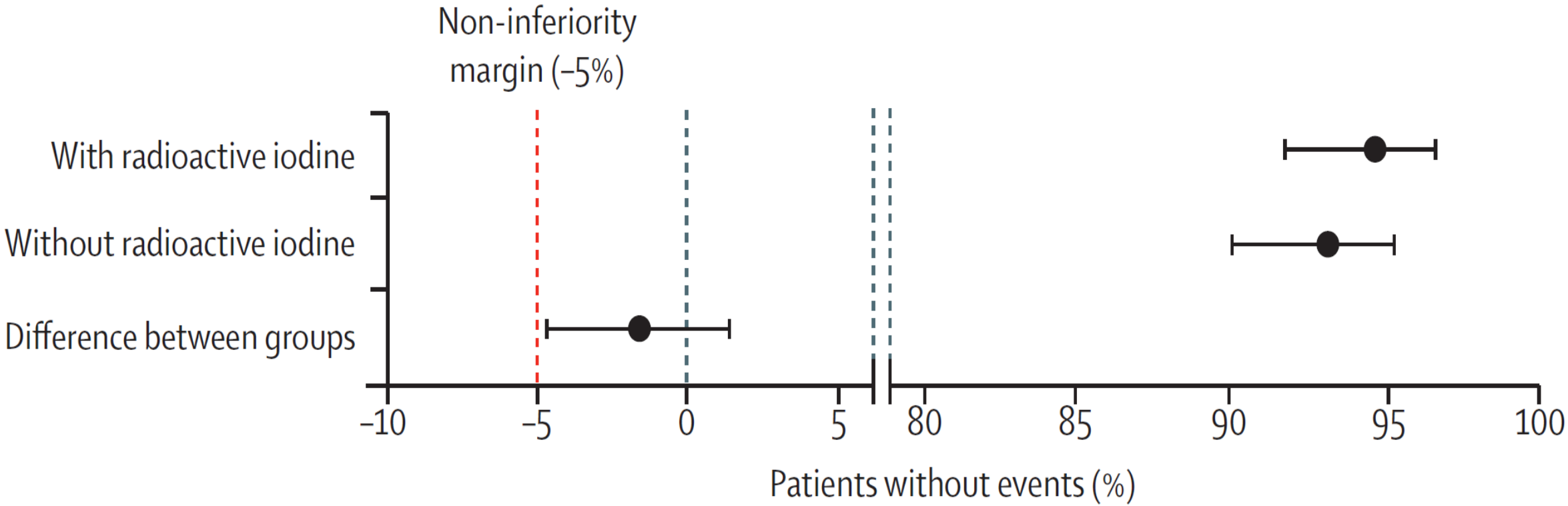
- Non-inferiority of the proportion of patients without an event in one group compared with the other at 5 years after randomization was shown if this proportion and its CI did not differ by more than -5%

Lancet Diabetes Endocrinol,2025; 13: 38–46

	Radioiodine group (n=389)	No radioiodine group (n=387)
Age, years	52·2 (42·3–62·7)	52·9 (42·7–63·9)
Sex		
Female	319 (82·0%)	323 (83·5%)
Male	70 (18·0%)	64 (16·5%)
Days from thyroidectomy to randomisation	92·1 (23·2)	91·2 (23·6)
Histology		
Papillary	372 (95·6%)	372 (96·1%)
Follicular	13 (3·3%)	11 (2·8%)
Oncocytic	4 (1·0%)	4 (1·0%)
Largest tumour size, mm	13 (11–15)	14 (11–17)
pTNM stage		
pT1amN0	26 (6·7%)	23 (5·9%)
pT1amNx	56 (14·4%)	42 (10·9%)
pT1bN0	143 (36·8%)	148 (38·2%)
pT1bNx	164 (42·2%)	174 (45·0%)

	Radioiodine group (n=389)	No radioiodine group (n=387)
Multifocality	178 (45·8%)	156 (40·3%)
Neck dissection performed	171 (44·0%)	171 (44·2%)
Type of neck dissection performed		
Central only	69 (17·7%)	77 (19·9%)
Central and lateral	74 (19·0%)	65 (16·8%)
Lateral only	26 (6·7%)	27 (7·0%)
Unknown	2 (0·5%)	2 (0·5%)
Thyroglobulin levels at randomisation in the 597 patients without thyroglobulin antibodies	N=304	N=293
Median (IQR)	0·26 (0·10–0·59)	0·20 (0·10–0·40)
<0·2 ng/mL	94 (30·9%)	104 (35·5%)
0·2–1·0 ng/mL	161 (53·0%)	155 (52·9%)
>1·0 ng/mL	32 (10·5%)	18 (6·1%)
Missing value	17 (5·6%)	16 (5·5%)

Proportion of patients without events during the 5 years after randomization



	Radioiodine group	Non Radioiodine group
Excellent response	260 of 344 patients (75·6%)	295 of 354 patients(83·3%)
Indeterminate response	68 (19·8%)	26 (7·3%)
Structural disease	0	3 (0.9%)

Key message

- The non-inferiority of a follow-up strategy compared with postoperative ^{131}I administration in low risk differentiated thyroid cancer was confirmed at 5 years

- There is no loss of opportunity in following these patients without postoperative ablation

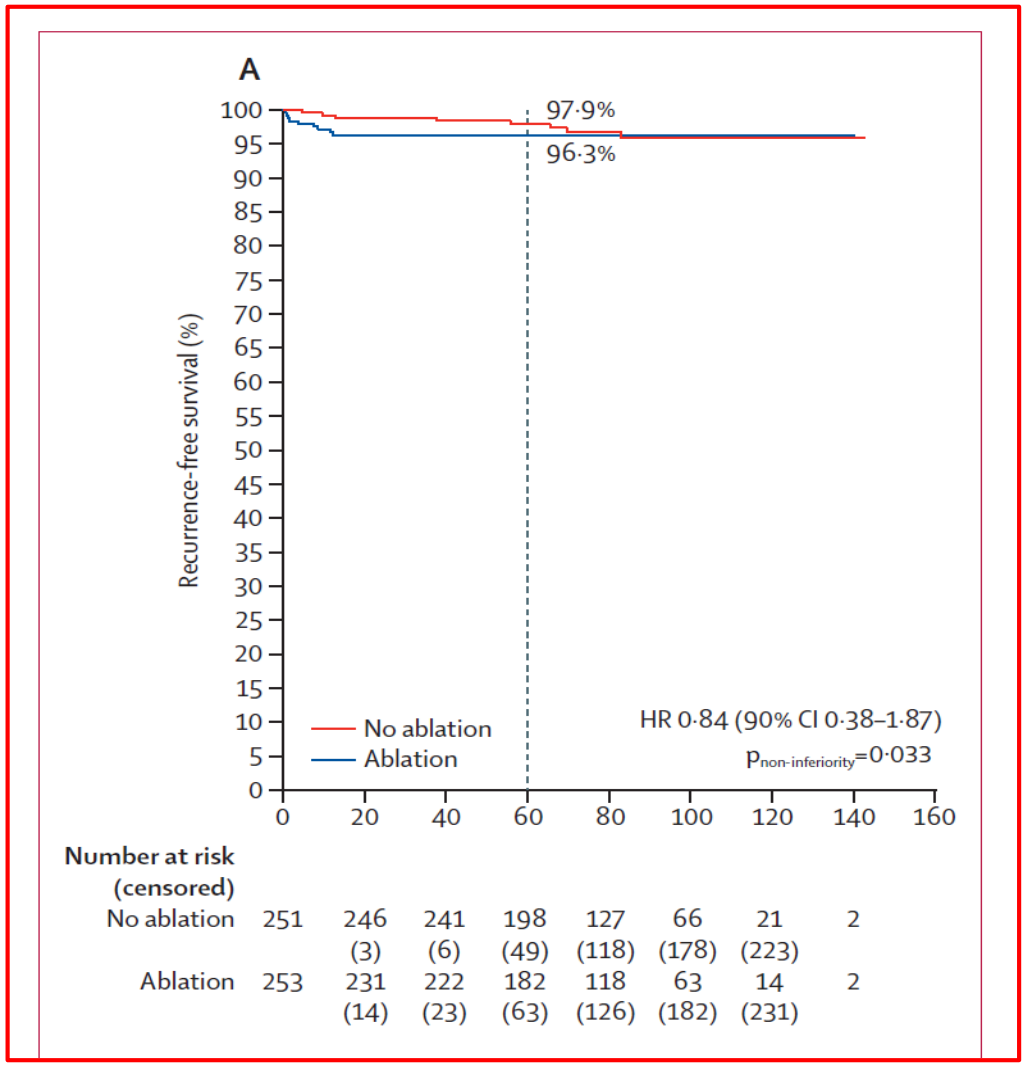
Thyroidectomy with or without postoperative radioiodine for patients with low-risk differentiated thyroid cancer in the UK (IoN): a randomised, multicentre, non-inferiority trial

Ujjal Mallick, Kate Newbold*, Matthew Beasley, Kate Garcez, Jonathan Wadsley, Sarah J Johnson, Tim Stephenson, Mark Gaze, Andrew Goodman, Sarah Jefferies, Suganya Sivabalasingham, Nicholas Slevin, David P Wilkinson, Elena Macias-Fernandez, Danielle Power, Tom Roques, Lesley Speed, Christopher Nutting, George Mochloulis, Georgina Gerrard, Charles Candish, Sally Morgan, Devashish Tripathi, Peter Truran, Claire Arthur, Andrzej Wieczorek, Krishnaswamy Madhavan, Jillian Maclean, David Boote, Dae Kim, Abigail Pascoe, Gayani Pitiyage, Sharon Forsyth, Emily Ambrose, Elizabeth Chang, Kate Farnell, Allan Hackshaw**

- The IoN trial was designed to assess whether recurrence-free survival was non-inferior after no ablation compared with ablation in patients with low-risk differentiated thyroid cancer.
- Eligible patients had complete (R0) resection following total thyroidectomy; stage pT1, pT2, pT3 (according to Tumour, Node, Metastasis staging version 7 [TNM7]), or pT3a (according to TNM8) disease; and N0, Nx, or N1a disease.
- The primary endpoint was 5-year recurrence-free survival, defined by the absence of locoregional recurrent or persistent structural disease, distant metastases, or death from thyroid cancer.
- Non-inferiority was assessed with a margin of 5 percentage points

Lancet 2025; 406: 52–62

	No ablation (N=251)	Ablation (N=253)
Age, years	48 (17–77)	47 (17–80)
Time from thyroidectomy to random assignment, months	2·3 (0·4–5·9)	2·1 (0·6–5·7)
Unstimulated post-surgical thyroglobulin, ng/mL*	0·5 (0·01–14·4)	0·4 (0·01–70·2)
Sex		
Female	191 (76%)	199 (79%)
Male	60 (24%)	54 (21%)
Histology		
Papillary	192 (76%)	204 (81%)
Follicular	52 (21%)	38 (15%)
Oncocytic†	7 (3%)	11 (4%)
Multifocal		
Yes	89 (35%)	97 (38%)
No	162 (65%)	156 (62%)
Stage		
pT1	117 (47%)	118 (47%)
pT2	111 (44%)	112 (44%)
pT3 or pT3a‡	23 (9%)	23 (9%)
Nodal status		
Nx	57 (23%)	57 (23%)
N0§	171 (68%)	172 (68%)
N1a§	23 (9%)	24 (9%)
Stage and nodal status		
pT1 and N0 or Nx	102 (41%)	107 (42%)
pT2 and N0 or Nx	107 (43%)	102 (40%)
pT3 or pT3a and N0 or Nx	19 (8%)	20 (8%)
pT1 and N1a	15 (6%)	11 (4%)
pT2 and N1a	4 (2%)	10 (4%)
pT3 or pT3a and N1a	4 (2%)	3 (1%)
Total thyroidectomy		
One-stage	101 (40%)	107 (42%)
Two-stage	149 (59%)	142 (56%)
Unknown	1 (<1%)	4 (2%)
Central compartment neck dissection	40 (16%)	51 (20%)



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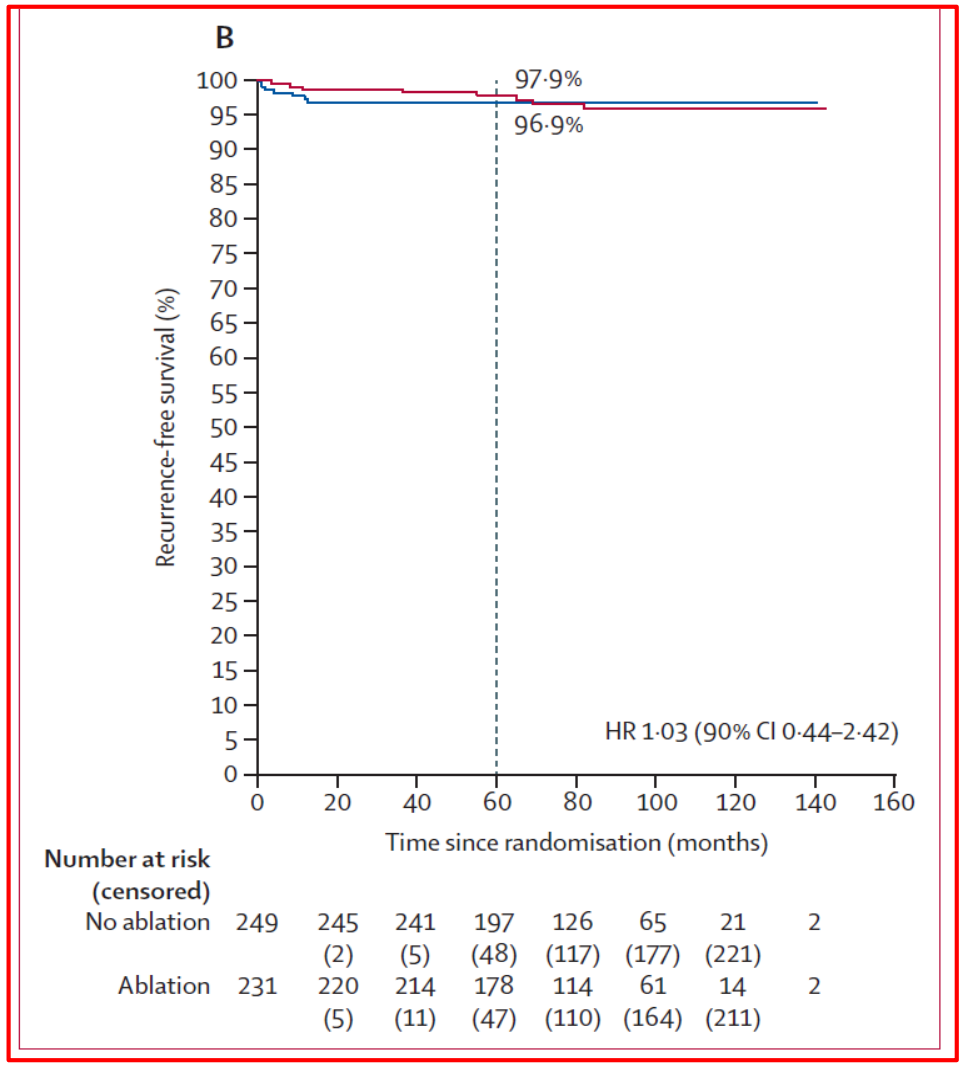

Per Protocol

	No ablation	Ablation	HR or risk difference
Intention-to-treat analysis			
Number of patients	251	253	..
Number of events	8	9	0·84* (90% CI 0·38 to 1·87)
3-year recurrence-free survival	98·8% (95% CI 97·4–100·0)	96·3% (95% CI 93·9–98·7)	0·4† (90% CI −1·5 to 2·3; 95% CI −1·8 to 2·7)
5-year recurrence-free survival	97·9% (95%CI 96·1–99·7)	96·3% (95% CI 93·9–98·7)	0·5† (90% CI −1·8 to 2·7; 95% CI −2·2 to 3·2)
3-year or 5-year recurrence-free survival	..	..	0·6‡ (90% CI −3·1 to 2·3; 95% CI −4·2 to 2·5)
Per-protocol analysis			
Number of patients	249	231	..
Number of events	8	7	1·03* (90% CI 0·44 to 2·42)
3-year recurrence-free survival	98·8% (95% CI 97·4–100·0)	96·9% (95% CI 94·7–99·1)	−0·1† (90% CI −1·8 to 1·7; 95% CI −2·2 to 2·0)
5-year recurrence-free survival	97·9% (95% CI 96·1–99·7)	96·9% (95% CI 94·7–99·1)	−0·1† (90% CI −2·2 to 2·0; 95% CI −2·6 to 2·5)
3-year or 5-year recurrence-free survival	..	..	−0·1‡ (90% CI −4·2 to 1·7; 95% CI −5·5 to 1·9)

All events were recurrences: no deaths from thyroid cancer occurred. An event is confirmed structural locoregional recurrent or residual disease, or distant recurrence. Units for risk differences are percentage points. HR=hazard ratio. *Unadjusted HR; the HR adjusted for the randomisation stratification factors (age, T stage, and nodal status) was 0·76 (90% CI 0·34–1·70) for the intention-to-treat analysis and 0·95 (0·40–2·25) for the per-protocol analysis. †Risk difference, estimated using regression standardisation.[17] ‡Risk difference, estimated by applying the unadjusted HR and 90% CI to the observed recurrence-free rate in the ablation group.[16] The risk differences are the same at 3 years and 5 years because the rates in the ablation group are the same.

Table 2: **Summary of recurrence-free survival**

Factors influencing post-operative RAI therapy

- Cancer related death(TNM classification)
- Risk of recurrence (ATA risk category)
- Post surgical ultrasound
- Post surgical Tg measurement

Stage/Risk Stratification	Recommendations
ATA guidelines	
ATA low-risk differentiated thyroid cancer patients	RAI ablation is not routinely recommended after thyroidectomy[a] (weak recommendation, low-quality evidence).
Unifocal papillary microcarcinoma in absence of other adverse features	RAI ablation is not routinely recommended (strong recommendation, moderate-quality evidence).
Multifocal papillary microcarcinoma in absence of other adverse features	RAI ablation is not routinely recommended[a] (weak recommendation, low-quality evidence).
ATA intermediate-risk level differentiated thyroid cancer	RAI adjuvant therapy should be considered (weak recommendation, low-quality evidence).
ATA high-risk patients	RAI adjuvant therapy is routinely recommended (strong recommendation, moderate-quality evidence).

Thyroid 2016;26(1):1–133

CONSENSUS STATEMENT

2022 ETA Consensus Statement: What are the indications for post-surgical radioiodine therapy in differentiated thyroid cancer?

Recommendation 4: In low-risk patients, the benefit of I-131 therapy is a matter of intensive scientific debate and the decision on whether to perform RAI therapy should be based on the presence of individual risk modifiers.

Recommendation 3: In the intermediate-risk category, RAI therapy may be indicated and should be tailored according to individual cases.

Recommendation 2: The use of I-131 therapy as adjuvant treatment or treatment of known disease is indicated for patients in the high risk of recurrence category or with known structural disease. In this setting, high activities (≥3700 MBq) of radioiodine are preferred over low activities.

Eur Thyroid J. 2022 Jan 1;11(1):e210046

ATA Guideline 2025

RAI after thyroidectomy in the primary management of DTC?

- Remnant ablation is not recommended routinely after total thyroidectomy for patients with ATA low-risk DTC. **(Strong recommendation, High certainty evidence)**

- RAI adjuvant therapy may be considered after total thyroidectomy in patients with ATA low-intermediate and intermediate-high risk of recurrent DTC**(Conditional recommendation**, **Low certainty evidence)**

- RAI adjuvant therapy is recommended routinely after total thyroidectomy for patients with ATA high-risk DTC. **(Strong recommendation, Moderate certainty evidence)**

- In patients with an initial diagnosis of DTC with distant metastases, RAI therapy is recommended routinely after total thyroidectomy. **(Strong recommendation, Moderate certainty evidence)**

ATA Guideline 2025

RAI after thyroidectomy in the primary management of DTC?

TABLE 10. SUMMARY OF RECOMMENDATIONS FOR INITIAL RAI FOLLOWING THYROIDECTOMY[a]

Risk category	*Typical RAI recommendation*	*Recommended ^{131}I activity level*	*Goals of therapy*
Low	No	1.1–1.85 GBq (30–50 mCi)	None or remnant ablation
Intermediate-low and intermediate-high	Consider	1.1–3.7 GBq (30–100 mCi)	Remnant ablation +/– adjuvant therapy
High	Yes	3.7–5.55 GBq (100–150 mCi)	Remnant ablation and adjuvant therapy
Distant metastases	Yes	3.7–7.4 GBq (100–200 mCi) or consider dosimetry	Treatment of known disease, remnant ablation

[a]Note that these recommendations represent guidelines and that a variety of additional features including patient preference, comorbid conditions, access to care, pre-therapy imaging, and others may influence the decision to treat with RAI as well as the resulting activity level. Consistent with the Martinique documents, the final recommendation for administered activity should be based on multidisciplinary management recommendations.[760]