Judicious use of RAI in management of Differentiated Thyroid Cancer

Jyotika Fernandes , MD
Wendy and Keith Wellin Endowed Chair in Endocrinology
Professor of Medicine
Div of Endocrinology , Dept of Medicine , MUSC
Endocrine Section Chief RHJ VA Medical Centre

1

Disclosures

- No financial disclosures or conflicts of interest
- Non financial : The presenter has no relevant nonfinancial relationship to disclose

2

Evolving Management Recommendations

26 year old female
1.4 cm intrathyroidal right lobe Papillary thyroid cancer

	2000	2015	2025
Detection	Palpation		
Thyroid Surgery	Total thyroidectomy		
Adjuvant RAI	Yes		
TSH goal	0.1mIU/L		
Shared Decision Making	?		

Cooper, Thyroid 2006; Haugen Thyroid 2015; Tuttle Uptodate 2024

3

Evolving Management Recommendations

26 year old female
1.4 cm intrathyroidal Right lobe Papillary thyroid cancer

	2000	2015	2025
Detection	Palpation	Incidental finding	
Thyroid Surgery	Total thyroidectomy	Total thyroidectomy or lobectomy	
Adjuvant RAI	Yes	Probably	
TSH goal	0.1mIU/L	0.5-1.5mIU/L	
Shared Decision Making	?	Better	

Cooper, Thyroid 2006; Haugen Thyroid 2015; Tuttle Uptodate 2024

4

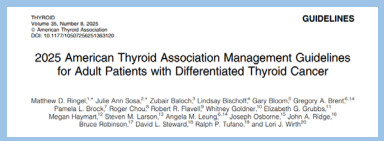
Evolving Management Recommendations

26 year old female
1.4 cm intrathyroidal Right lobe Papillary thyroid cancer

	2000	2015	2025
Detection	Palpation	Incidental finding / Cancer Screening	
Thyroid Surgery	Total thyroidectomy	Total thyroidectomy or lobectomy	Lobectomy / Observation?
Adjuvant RAI	Yes	Maybe	No
TSH goal	0.1mIU/L	0.5-1.5mIU/L	1-3 mL/L
Shared Decision Making	?	Better	Guided decision making

Cooper, Thyroid 2006; Haugen Thyroid 2015; Tuttle Uptodate 2024

5


GUIDELINES

2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer

THYROID , Vol 35, Number 8, August 2025

6

Evidence behind the use of RAI in DTC

- **Purpose of RAI**
- Evidence based data on RAI use in
  - **LOW** Risk of recurrence
  - **INTERMEDIATE** risk of recurrence
  - **HIGH RISK of** recurrence and metastatic disease
- Role of RAI in Oncocytic Thyroid ca

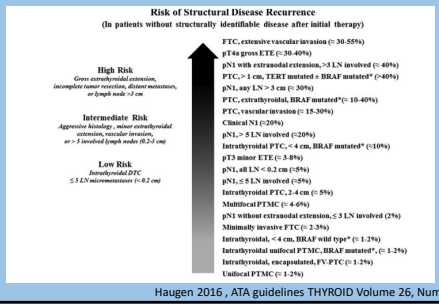
7

Purpose of RAI

- **Remnant Ablation**
  - Destroying normal thyroid tissue remaining after surgery to facilitate monitoring
- **Adjuvant therapy**
  - Small persistent disease is suspected based on initial risk and RAI is administered to reduce the risk of recurrence
- **Treatment**
  - Treatment of known disease

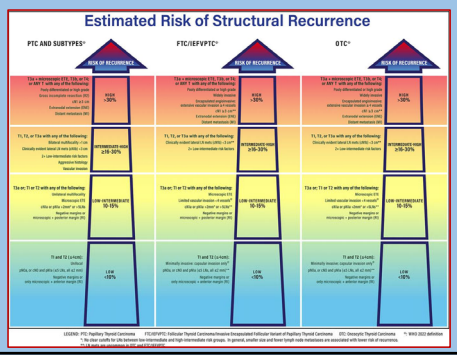
8

Risk Stratification ATA guidelines



Haugen 2016 , ATA guidelines THYROID Volume 26, Number 1, 2016

9



10

Low Risk ATA

11

National Thyroid Cancer Treatment Cooperative Study Group

Outcomes of patients with differentiated thyroid carcinoma following initial therapy
3000 pts from 11 North American Institutions

Propensity score analysis of RAI therapy for registry stage I patients, overall cohort

Propensity Stratum for adjuvant RAI (1 = lowest likelihood, 5 = highest likelihood)	*Adjuvant RAI*			*No adjuvant RAI*					
	N	*% of stratum*	*5 yr DFS, %*	*N*	*% of stratum*	*5 yr DFS, %*	*RR*	*95% CI*	*p*
1	35	18%	92%	164	82%	95%	0.61	0.25–1.67	0.3
2	88	44%	86%	111	56%	94%	0.66	0.37–1.15	0.15
3	175	77%	92%	53	23%	88%	1.22	0.63–2.18	0.53
4	124	85%	89%	22	15%	100%	0.0008	*	0.12
5	167	88%	78%	23	12%	86%	0.83	0.33–1.52	0.59

RR = risk ratio for outcome, no adjuvant RAI/adjuvant RAI. RR > 1 indicates a better outcome associated with adjuvant RAI. * = lower limit of 95% CI approaches 0.

Jonklass , Thyroid 2006 Dec 6 (12) : 1229- 42

12

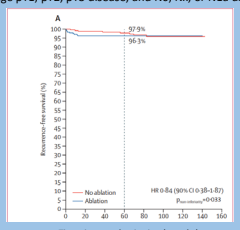
Remnant ablation for Low -Risk PTC

- ESIMABL-2
  - 730 pts – 3 year FU
  - Recurrence **No RAI group 4.4 % and 4.1 % RAI group**
  - Leoulleux, NEJM 2022,10 (386) 923
  - **At 5 year - No RAI group 6.8 % and 5.2 % RAI group**
  - Leoulleux Lancet Diabetes Endocrinol 2025 Jan 13(1) 38-46
- HiLo 438 pts – 30 mCi or 100 mCi – same rate of recurrence
  - At 3 years 1.5% vs 2.1%
  - At 7 years 5.9% vs 7.3% ., HR 1.1(0.47-2.59) p =0.83
  - Dehbi Lancet Diab Endocrinol 2019 Jan 7 (1):44-51
- ESTMABL-1 726 pts randomized to 30 or 100 mCi
  - At 5.4 years 11 recurrences – 6 in 30 grp ,5 in 100 grp
  - Schlumberger Lancets Diabetes Endocrinol 2018, Aug 6(8),618-626

13

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

- IoN was a multicenter -33 UK cancer centers.
- Stage pT1, pT2, pT3 disease; and N0, Nx, or N1a disease



Mallick, Lancet, June 2025; 406: 52–62

14

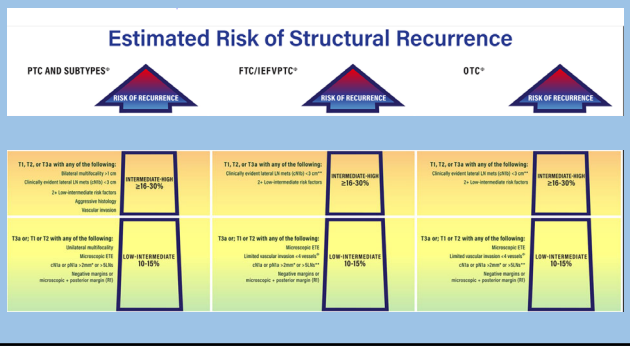
Conclusion : Low Risk

- RAI is **not indicated** for remnant ablation of low risk thyroid cancer based on retrospective and prospective randomized trials.
- If RAI is considered , **low dose** of 30 -50 mCi is recommended

15

Intermediate ATA Risk

16



17

Adjuvant therapy may be beneficial in intermediate risk group

- 11 studies showing benefits vs 13 studies showing no recurrence benefits
  - Lamartina , JCEM .2015, May; 100 (5):1748-61
- 21, 870 from NCDB, 15 418 (70.5%) received RAI and 6452 (29.5%) did not. FU 6 years.
  - RAI was associated with improved OS in all patients
  - 29% risk reduction in death
  - 36% reduction death in pts <45 years – Subgroup analysis
    - Ruel , JCEM 2015 April;100 (4):1529-36
    - No propensity score matching
    - No recurrence benefit reported
    - No disease –specific survival

18

Slide 13

J1 JFernandes, 9/20/2025

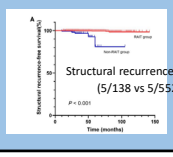
Adjuvant therapy <u>may be beneficial in intermediate risk group</u>

- 11 studies , some demonstrating **recurrence** benefit others did not

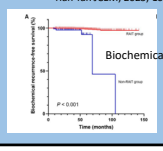
Verburg et al . Eur J of Nuc Med Mol Imaging . 2020 Jan ;47(1);78-83

- Single Centre (China) 1487 intermediate risk PTC with Tg <1ng/ml
  - Propensity score matching was used
  - Compared 1349patients who received RAI (90.7%) to 138 (9.3%) who did not
  - Median FU 51 months
  - 5/552 + **RAI grp** (less after propensity matching) vs 5/138 (**non RAI group)** had structural recurrence. (P=.005)

Tian Tan JCEM, 2023; 108 (8):2033-2041



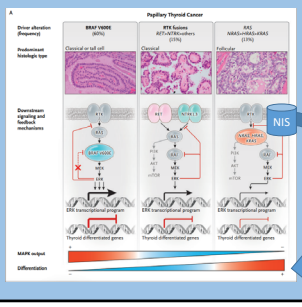
Structural recurrence-free survival
(5/138 vs 5/552, P= .046)



Biochemical recurrence-free survival
(6/138 vs 4/552, P=.005

19

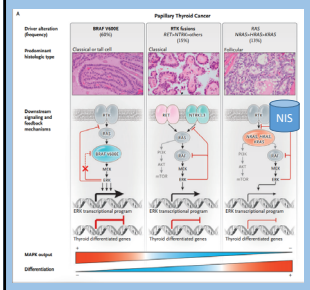
Biologic and RAI Responsiveness Thyroid Cancer

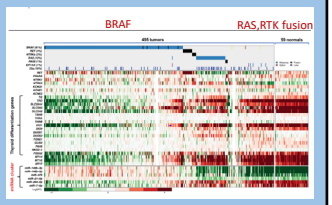


Fagin,N Engl J Med 2016;375:1054-67

20

Biologic and RAI Responsiveness Thyroid Cancer



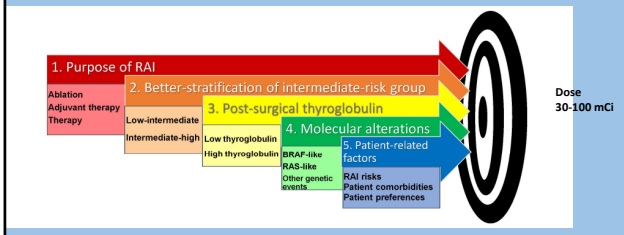


Boucai JCEM 2022; 107 (4);1030

Fagin,N Engl J Med 2016;375:1054-67

21

Key variables in the decision-making process for RAI use in patients with DTC at intermediate risk of recurrence



Newman, Cancers 2024, 16, 3096

22

Conclusion – Intermediate risk

Adjuvant therapy <u>may be beneficial in intermediate risk group</u>

23

High ATA Risk

24

Improved survival following RAI in Stage III & IV DTC

Nα 5000

	Overall Survival			Disease-Specific Survival			Disease-Free Survival		
	RR	*95% CI*	*p*	*RR*	*95% CI*	*p*	*RR*	*95% CI*	*p*
Stage I	0.0006	*	0.013	0.00063	*	0.1	0.64	0.47–0.85	0.0013
Stage II	1.71	1.07–2.74	0.026	1.21	0.26–3.92	0.76	1.03	0.75–1.39	0.84
Stages III & IV	1.43	1.17–1.72	0.0006	1.46	1.13–1.87	0.0045	1.32	1.02–1.68	0.035

RR = risk ratio for outcome, no RAI/RAI = radioactive iodine-131. RR > 1 indicates a better outcome associated with RAI. * = lower limit of 95% CI approaches 0. Registry staging is used.

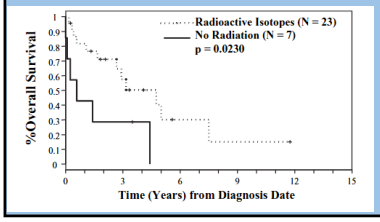
Jonklass,Thyroid ,Volume 16, Number 12, 2006

25

Use of radioactive iodine in high risk patients

TABLE II. Multivariate Analysis of 14,545 Patients With Papillary or Papillary Variant Thyroid Carcinoma

Source	Risk ratio	Lower CL	Upper CL	L-R chi-square	Prob > chi-square
LN_inv_YN [LN Involve]	1.279224	1.136022	1.436753	16.054664	0.0001
SizeGT2 [<2 cm]	0.85152	0.761247	0.951645	8.16144928	0.0043
AgeGT45 [age < 45]	0.359538	0.305036	0.41878	239.946615	0.0000
MetsYN [mets present]	2.110436	1.652917	2.625294	28.2825829	0.0000



SEER Database 1973-2001

>45 years
Tumor >2cm
LN+
Distant Mets

Podonos,J. Surg. Oncol. 2007;96:3–7

26

Long-Term Outcomes Following Therapy in Differentiated Thyroid Ca: NTCTCS Registry Analysis 1987–2012

Multivariate analysis of overall survival after initial treatment therapies

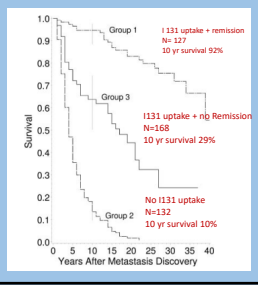
4941 pts – FU 6 years

Any RAI vs None	RR	95% CI	P RR	P model
Stage I	0.79	0.35-1.89	0.58	0.50
Stage II	0.67	0.36-1.28	0.22	0.13
Stage III	**0.66**	**0.46-0.98**	**0.04**	**0.01**
Stage IV	**0.70**	**0.46-1.10**	**0.12**	**.049**

Carhill, JCEM ,2015 ; 100,3270

27

Long-Term Outcome of 444 Patients with Distant Metastases from Papillary and Follicular Thyroid Carcinoma



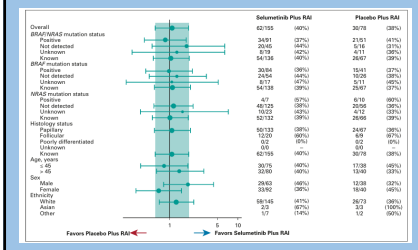
2/3 of pts with metastatic disease become refractory to RAI

Durante J, Clin Endocrinol Metab 91: 2892–2899, 2006

28

Redifferentiation of Differentiated Thyroid Cancer:

Selumetinib Plus Adjuvant Radioactive Iodine in Patients With High-Risk Differentiated Thyroid Cancer: A Phase III, Randomized, Placebo-Controlled Trial (ASTRA)



Four hundred patients were enrolled
233 randomly assigned
(selumetinib, n = 155 [67%];
placebo, n = 78 [33%]).
No statistically significant difference in CR

Ho,2022;J Clin Oncol 40:1870-1878.

29

Examples of Redifferentiation Procedures

Ho et al.[1]	Selumetinib 75 mg po bid×4 weeks. If ^{124}I PET scan was positive, then selumetinib continued to perform dosimetry and subsequently discontinued 2 days after ^{131}I therapy.
Rothenberg et al.[2]	Dabrafenib 150 mg po qd for 25 days before ^{131}I scan. If positive, dabrafenib was continued to day 37, tx with 150 mCi of ^{131}I, and dabrafenib was continued for five more days.
Dunn et al.[6]	Vemurafenib 960 mg po bid for approximately 4 weeks. If ^{124}I PET scan had radioiodine uptake and at least one "index tumor" (≥5 mm) met the lesional dosimetry criteria [≥2000 cGy) with ≤300 mCi of ^{131}I, that patient was considered as a responder and then patient continued on vemurafenib and treated with ^{131}I activity determined by dosimetry. Vemurafenib was discontinued 2 days after ^{131}I therapy.
Iravani et al.[7]	For *NRAS*: trametinib 2 mg po qd×4 weeks
Iravani et al.[7]	For *BRAF*^{V600E}: combination of dabrafenib 150 mg po qd and trametinib 2 mg po qd×4 weeks (or vemurafenib 960 mg po bid×4 weeks and cobimetinib 60 mg po qd×4 weeks). Calculation of the therapy activity of ^{131}I is complicated and beyond the scope of this review.
Groussin et al.[9]	Larotrectinib 100 mg po bid (duration not listed)
Leboulleux et al.[10]	Dabrafenib 150 mg po bid and trametinib 2 mg po qd for 42 days. On day 28, a radioiodine scan was performed. After 35 days, a therapy of ^{131}I was administered.
Groussin et al.[12]	Selpercaptinib 160 mg po bid for×3 weeks

PET, positron emission tomography.

Nostrand, Thyroid ;Volume 33, Number 6, 2023

30

Conclusion – High Risk

- RAI adjuvant therapy is **recommended** after TT for ATA high risk DTC (Strong recommendation, High certainty evidence)
- In patients with an initial diagnosis of DTC with **distant metastases** , RAI therapy is **routinely recommended** after TT (Strong recommendation, High certainty evidence)

31

Recommendations for Initial RAI following Thyroidectomy

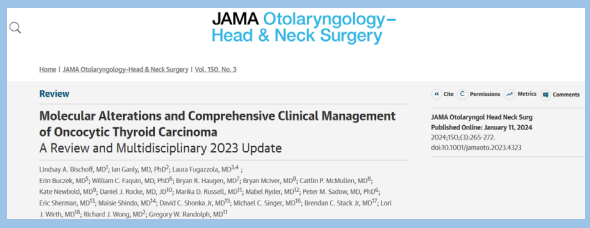
Risk Category	RAI recommendations	Recommended I131 (mCi)	Goals of therapy
Low	No	30-50	None or remnant ablation
Intermediate Low	Consider	30-100	Remnant ablation +/- adjuvant therapy
Intermediate High	Yes	100-150	Remnant ablation and adjuvant therapy
Distant Metastases	Yes	100-200	Treatment of known disease and remnant ablation

32

Recommendation ATA 32

- Remnant ablation is **not routinely** recommended after total thyroidectomy for ATA low risk DTC patients . However ,considerations including patient preference and specific risk factors may make RAI an appropriate choice in select patients
  - **(Strong recommendation , High certainty of evidence)**
- RAI adjuvant therapy **may be** considered after total thyroidectomy in pts with ATA low-intermediate and intermediate high risk of recurrence
  - **(Conditional recommendations ,Low certainty evidence)**
- RAI adjuvant therapy is **recommended** after TT for ATA high risk DTC (Strong recommendation, High certainty evidence)
- In patients with an initial diagnosis of DTC with **distant metastases** , RAI therapy is **routinely recommended** after TT (Strong recommendation, High certainty evidence)

33



34

Oncocytic Thyroid Cancer - OTC

- Metastasizes locally and regionally and distantly
- **Rarely iodine avid**
- Commonly FDG avid

35

RAI in Oncocytic Thyroid Carcinoma (OTC)

- Data are of **poor quality** and **conflicting**
- Standard of care has been to give RAI to high-risk follicular derived thyroid cancer
- Potential concerns of using RAI in OTC:
  - Delay in other imaging for staging
  - Delay in initiating systemic therapy

36

OTC and RAI

Source	Study design	Sample size, No.	Patient population	Systemic therapy and/or EBRT	Patients who had RAI, No. (%)	Median cumulative dose (mCi)	Positive WBS, No. (%)	Median follow-up, y	10-y DSS after RAI, %	Reported survival benefit
Besic et al,[51] 2016	Retrospective review	32	OTC with distant metastasis	13 systemic therapy; 18 EBRT	30 (94)	922	16 (53)	8.3	60	Yes
Haigh et al,[46] 2005	SEER review	172	OTC	Unknown	56 (33)	Unknown	Unknown	9.4	73	No
Jillard et al,[47] 2016	National Cancer Database review	1909	OTC without low-risk pathology	Unknown	1162 (61)	Unknown	Unknown	NR	74	Yes
Jin et al,[48] 2021	Retrospective review	97	All OTC	Unknown	40 (41)	Unknown	Unknown	8.5	92	No
Lopez-Penabad et al,[40] 2003	Retrospective review	89	All OTC	Yes; 27%/48%	14 (16)	223	14/37 (38) with known metastasis	8.1	64	No
Oluic et al[41] 2017	Retrospective review	239	All OTC	Unknown	65 (37)	Unknown	Unknown	7.5	92.5	No
Wang et al,[49] 2022	SEER review	2279	TT for OTC without EBRT	No EBRT, unknown systemic therapy	1438 (63)	Unknown	Unknown	7.6	92	No
Yang et al,[50] 2019	SEER review	2799	All OTC	Unknown EBRT, yes systemic therapy	1529 (55)	Unknown	Unknown	5.2	90	OS benefit, DSS no benefit

37

Studies evaluating sensitivity and specificity of PET in OTC

Author and year	Sample size N	Pt population	PET positivity N(%)	WBS positive N(%)	PET sensitivity (%)	PET specificity (%)
Pryma 2006	44	OTC	24(54)	6(14)	96	95
Lowe 2003	12	OTC	10(83)	1/6 (17)	92	67
Plotkin 2002	17	OTC with positive Tg	13 (76)	4/11(36)	92	80

Bischoff;JAMA Otolaryngology–Head & Neck Surgery March 2024 Volume 150, Number 3

38

Should radioiodine be administered for OTC treatment?

- **RECOMMENDATION 33 ATA**
- Outcome data are limited in OTC; thus, specific recommendations regarding use of RAI are **not certain**. If RAI is not administered empirically, evaluation of iodine avidity with a diagnostic whole-body scan (WBS) may be considered.
- ***(Conditional recommendation, Very low certainty evidence)***

39

Conclusion- RAI after Total Thyroidectomy

- Remnant ablation is **not routinely** recommended for ATA low risk DTC patients
- RAI adjuvant therapy **may be considered** in pts with ATA intermediate risk of recurrence
- RAI adjuvant therapy is **recommended** for ATA high risk DTC
- In patients with an initial diagnosis of DTC with **distant metastases** , RAI therapy is **routinely recommended**
- **Redifferentiation strategies** may be considered in some patients
- Role of **RAI unclear** in Oncocytic Thyroid Cancer pts

40