

Judicious use of RAI in management of Differentiated Thyroid Cancer

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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

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26 year old female
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	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

Evolving Management Recommendations

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

	2000	2015	2025
Detection	Palpation	Incidental finding	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 mIU/L
Shared Decision Making	?	Better	Guided decision making

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

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

Purpose of RAI

- **Remnant Ablation**

- Destroying normal thyroid tissue remaining after surgery to facilitate monitoring

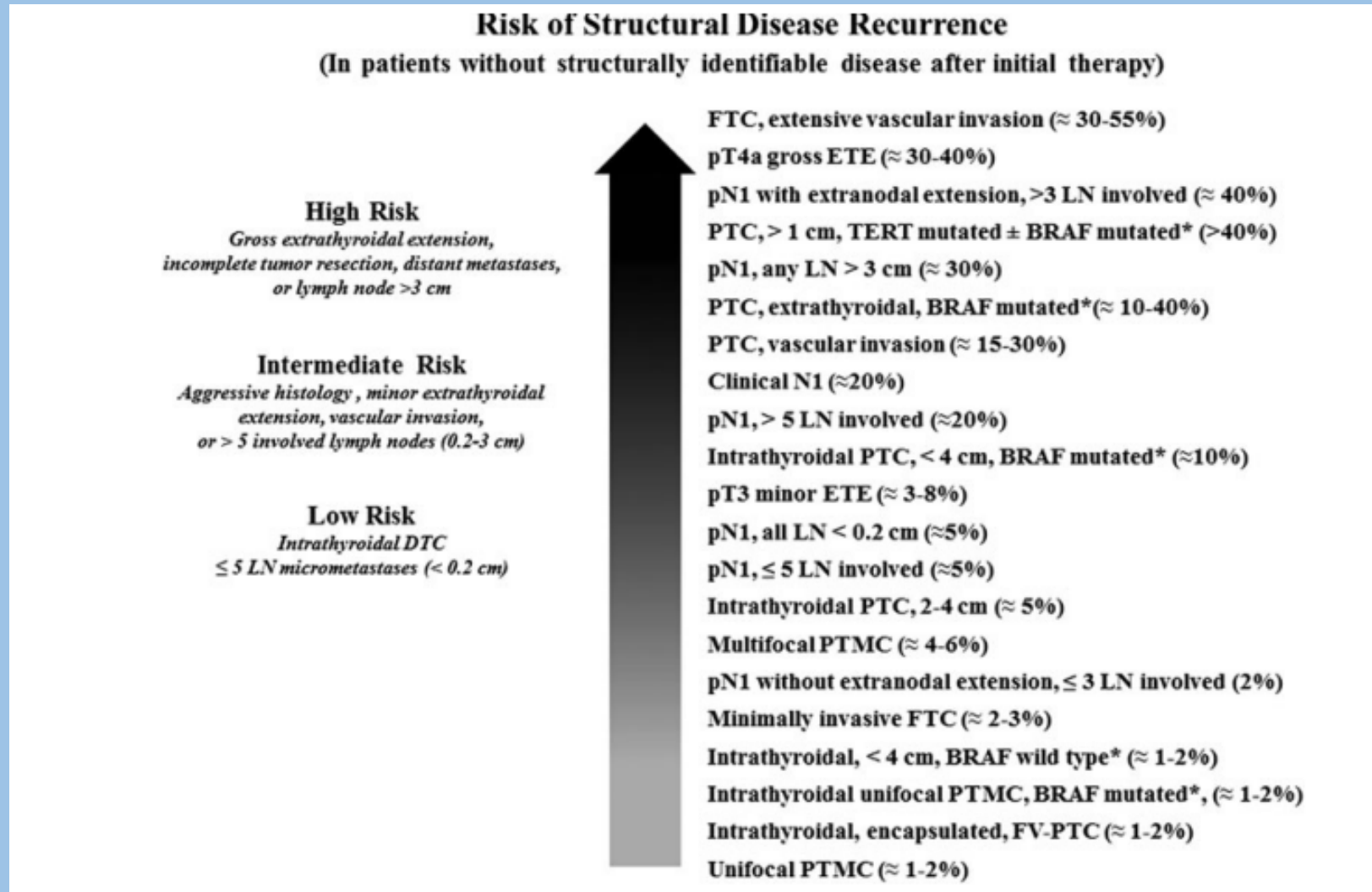
- **Adjuvant therapy**

- Small persistent disease is suspected based on initial risk and RAI is administered to reduce the risk of recurrence

- **Treatment**

- Treatment of known disease

Risk Stratification ATA guidelines



Estimated Risk of Structural Recurrence

PTC AND SUBTYPES [Ⓢ]	FTC/IEFVPTC [Ⓢ]	OTC [Ⓢ]
RISK OF RECURRENCE	RISK OF RECURRENCE	RISK OF RECURRENCE
T3a + microscopic ETE, T3b, or T4; or ANY T with any of the following: - Poorly differentiated or high grade - Gross incomplete resection (R2) - cN1 ≥ 3 cm - Extranodal extension (ENE) - Distant metastasis (M1)	T3a + microscopic ETE, T3b, or T4; or ANY T with any of the following: - Poorly differentiated or high grade - Widely invasive - Encapsulated angioinvasive: extensive vascular invasion ≥ 4 vessels - cN1 ≥ 3 cm** - Extranodal extension (ENE) - Distant metastasis (M1)	T3a + microscopic ETE, T3b, or T4; or ANY T with any of the following: - Poorly differentiated or high grade - Widely invasive - Encapsulated angioinvasive: extensive vascular invasion ≥ 4 vessels - cN1 ≥ 3 cm** - Extranodal extension (ENE) - Distant metastasis (M1)
T1, T2, or T3a with any of the following: - Bilateral multifocality >1 cm - Clinically evident lateral LN mets (cN1b) <3 cm 2+ Low-intermediate risk factors - Aggressive histology - Vascular invasion	T1, T2, or T3a with any of the following: - Clinically evident lateral LN mets (cN1b) <3 cm** 2+ Low-intermediate risk factors	T1, T2, or T3a with any of the following: - Clinically evident lateral LN mets (cN1b) <3 cm** 2+ Low-intermediate risk factors
T3a or; T1 or T2 with any of the following: - Unilateral multifocality - Microscopic ETE - cN1a or pN1a >2mm* or >5LNs - Negative margins or microscopic + posterior margin (R1)	T3a or; T1 or T2 with any of the following: - Microscopic ETE - Limited vascular invasion <4 vessels[Ⓢ] - cN1a or pN1a >2mm* or >5LNs** - Negative margins or microscopic + posterior margin (R1)	T3a or; T1 or T2 with any of the following: - Microscopic ETE - Limited vascular invasion <4 vessels[Ⓢ] - cN1a or pN1a >2mm* or >5LNs** - Negative margins or microscopic + posterior margin (R1)
T1 and T2 (≤4cm): - Unifocal - pN0a, or cN0 and pN1a (≤5 LNs, all ≤2 mm) - Negative margins or only microscopic + anterior margin (R1)	T1 and T2 (≤4cm): - Minimally invasive: capsular invasion only[Ⓢ] - pN0a, or cN0 and pN1a (≤5 LNs, all ≤2 mm)** - Negative margins or only microscopic + anterior margin (R1)	T1 and T2 (≤4cm): - Minimally invasive: capsular invasion only[Ⓢ] - pN0a, or cN0 and pN1a (≤5 LNs, all ≤2 mm)** - Negative margins or only microscopic + anterior margin (R1)

LEGEND: PTC: Papillary Thyroid Carcinoma FTC/IEFVPTC: Follicular Thyroid Carcinoma/Invasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma OTC: Oncocytic Thyroid Carcinoma Ⓢ: WHO 2022 definition

*: No clear cutoffs for LNs between low-intermediate and high-intermediate risk groups. In general, smaller size and fewer lymph node metastases are associated with lower risk of recurrence.

** : LN mets are uncommon in OTC and FTC/IEFVPTC

Low Risk ATA

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

<i>Propensity Stratum for adjuvant RAI (1 = lowest likelihood, 5 = highest likelihood)</i>	<i>Adjuvant RAI</i>			<i>No adjuvant RAI</i>			<i>RR</i>	<i>95% CI</i>	<i>p</i>
	<i>N</i>	<i>% of stratum</i>	<i>5 yr DFS, %</i>	<i>N</i>	<i>% of stratum</i>	<i>5 yr DFS, %</i>			
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.

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

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

Intermediate ATA Risk

Estimated Risk of Structural Recurrence

PTC AND SUBTYPES^Φ



FTC/IEFVPTC^Φ



OTC^Φ



T1, T2, or T3a with any of the following:

- Bilateral multifocality >1 cm
- Clinically evident lateral LN mets (cN1b) <3 cm
- 2+ Low-intermediate risk factors
- Aggressive histology
- Vascular invasion

**INTERMEDIATE-HIGH
≥16-30%**

T1, T2, or T3a with any of the following:

- Clinically evident lateral LN mets (cN1b) <3 cm**
- 2+ Low-intermediate risk factors

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**INTERMEDIATE-HIGH
≥16-30%**

T3a or; T1 or T2 with any of the following:

- Unilateral multifocality
- Microscopic ETE
- cN1a or pN1a >2mm* or >5LNs
- Negative margins or microscopic + posterior margin (R1)

**LOW-INTERMEDIATE
10-15%**

T3a or; T1 or T2 with any of the following:

- Microscopic ETE
- Limited vascular invasion <4 vessels^Φ
- cN1a or pN1a >2mm* or >5LNs**
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- Negative margins or microscopic + posterior margin (R1)

**LOW-INTERMEDIATE
10-15%**

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

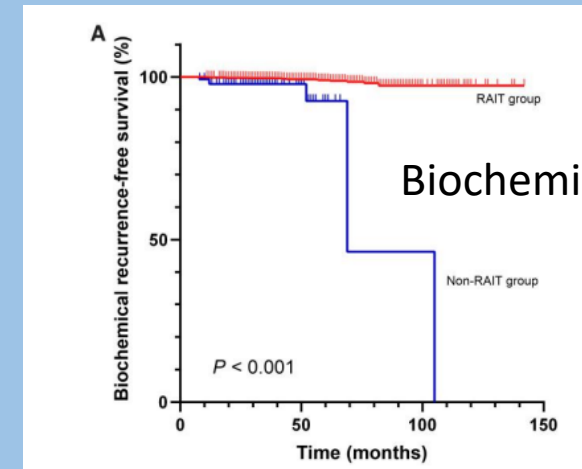
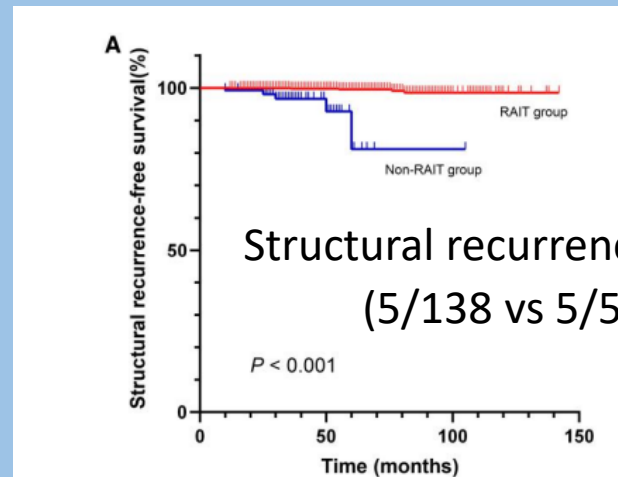
Adjuvant therapy may be beneficial in intermediate risk group

- 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 1349 patients 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)

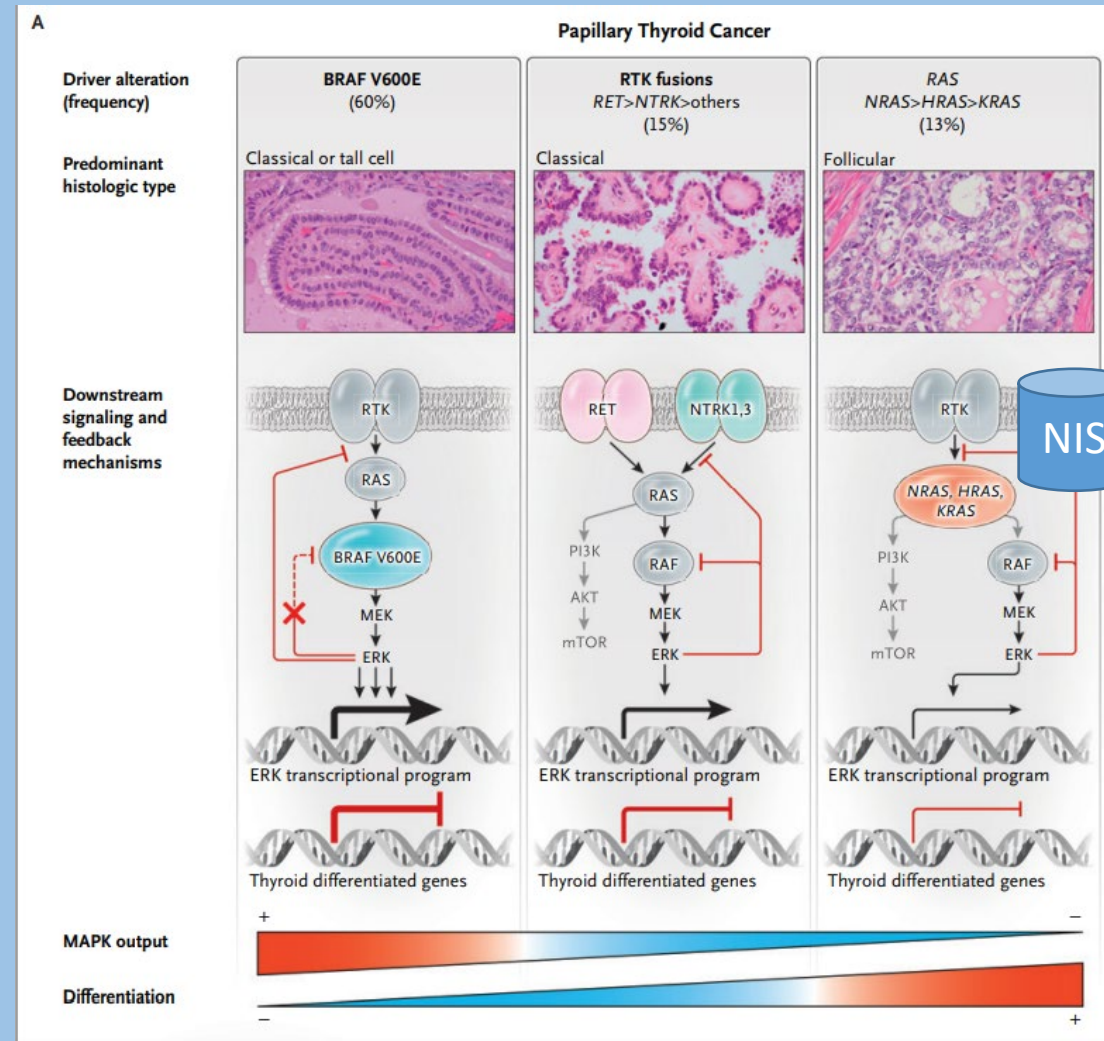
Tian Tan JCEM, 2023; 108 (8):2033-2041



Biochemical recurrence-free survival

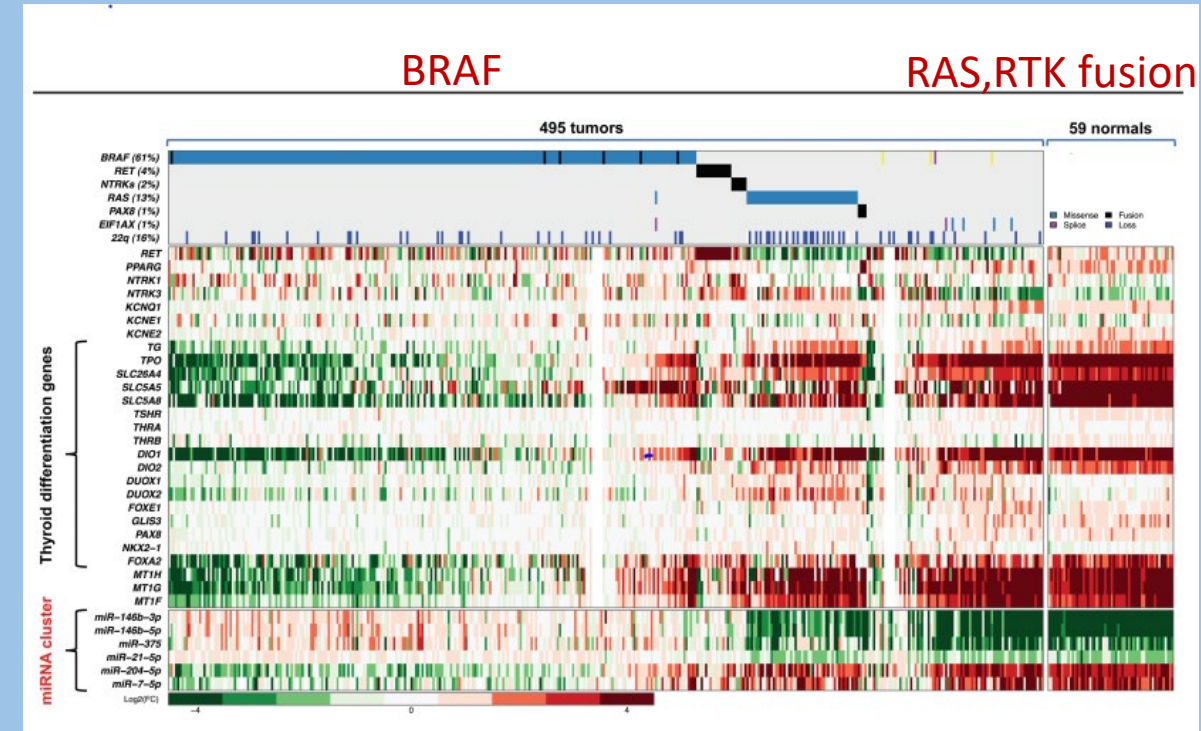
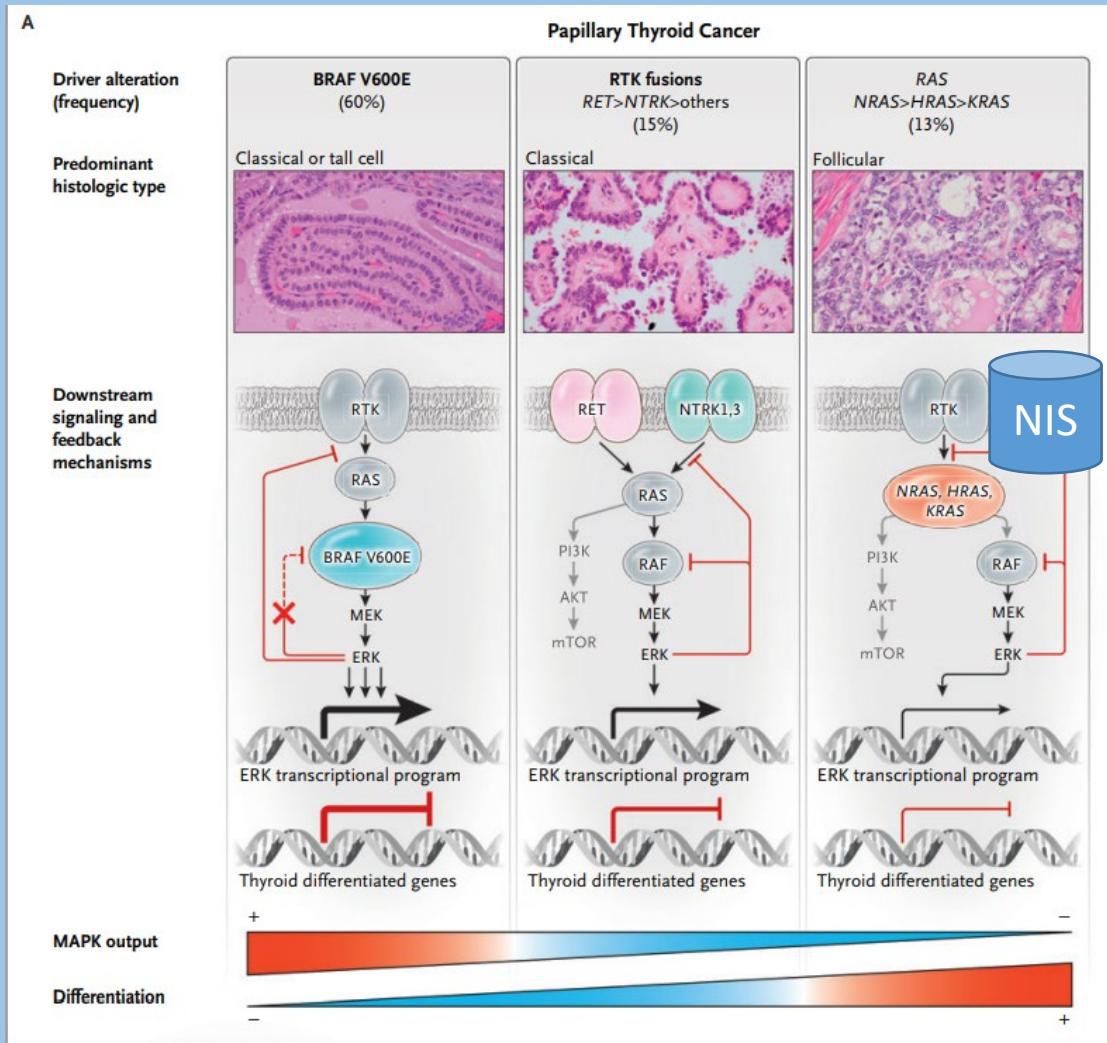
(6/138 vs 4/552, P=.005)

Biologic and RAI Responsiveness Thyroid Cancer



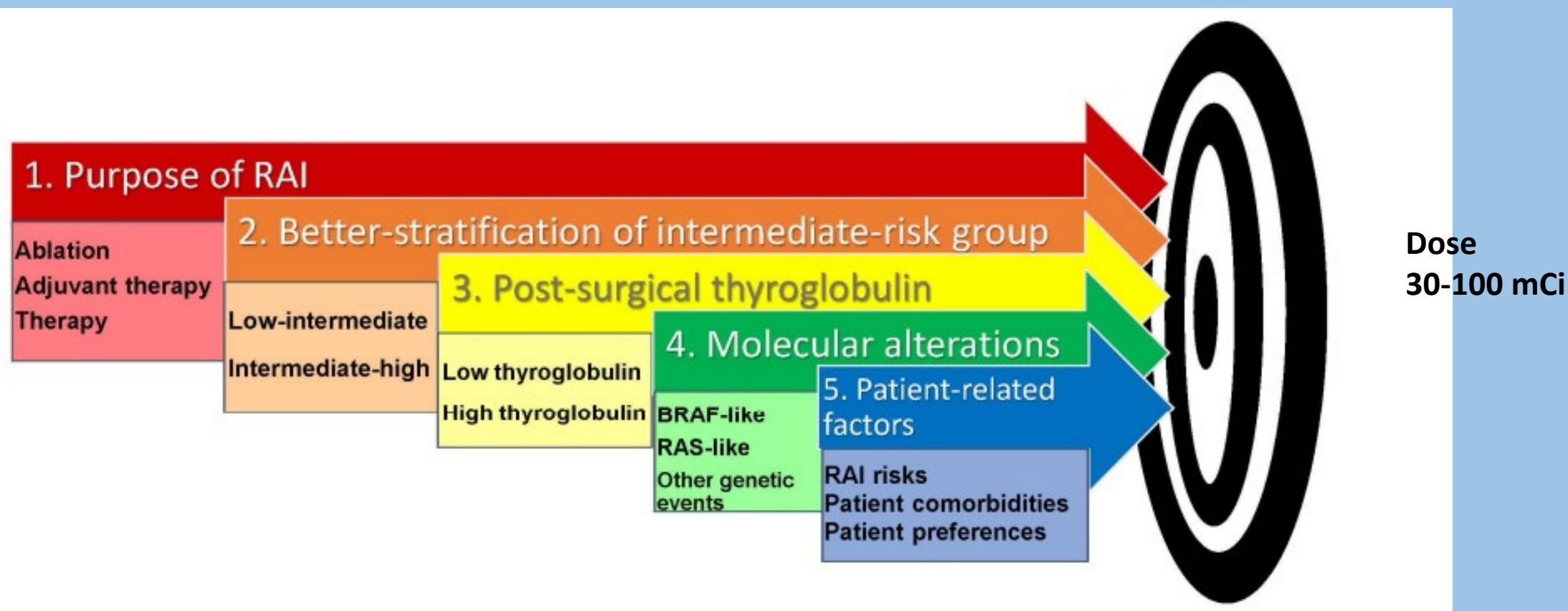
Fagin, N Engl J Med 2016;375:1054-67

Biologic and RAI Responsiveness Thyroid Cancer



Boucai JCEM 2022; 107 (4);1030

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



Conclusion – Intermediate risk

Adjuvant therapy may be beneficial in intermediate risk group

High ATA Risk

Improved survival following RAI in Stage III & IV DTC

N= 5000

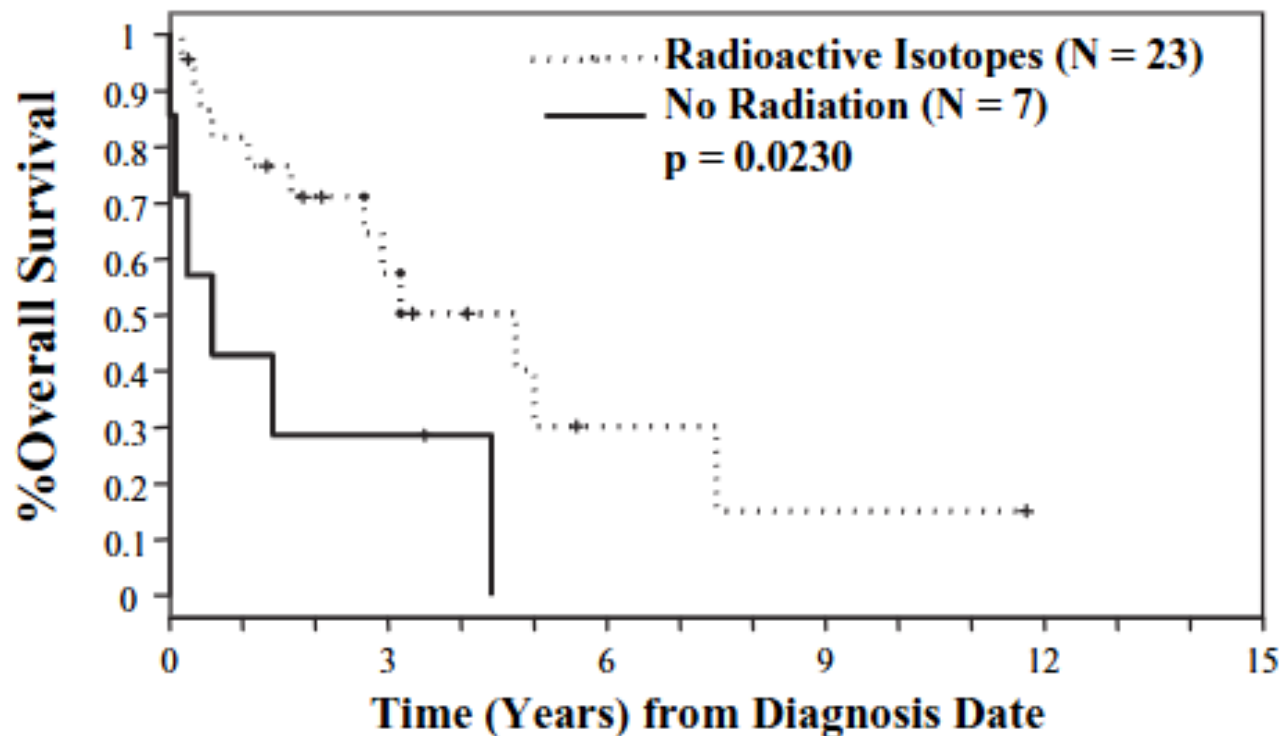
	<i>Overall Survival</i>			<i>Disease-Specific Survival</i>			<i>Disease-Free Survival</i>		
	<i>RR</i>	<i>95% CI</i>	<i>p</i>	<i>RR</i>	<i>95% CI</i>	<i>p</i>	<i>RR</i>	<i>95% CI</i>	<i>p</i>
Stage I	0.0006	*	0.013	0.00063	*	0.1	0.64	0.47–0.85	0.0013
Stage II	1.71	1.07–2.74	0.026	1.21	0.26–3.92	0.76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

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.

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

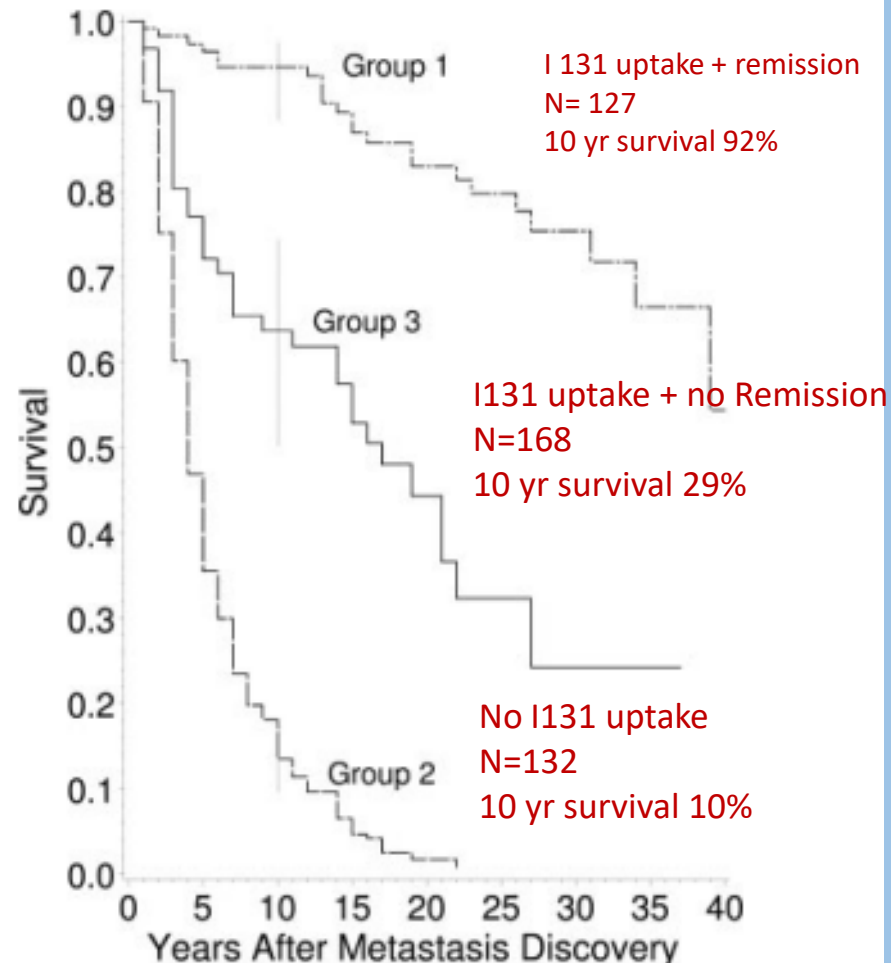
Long-Term Outcomes Following Therapy in Differentiated Thyroid Ca: NTCTCS Registry Analysis 1987–2012

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

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

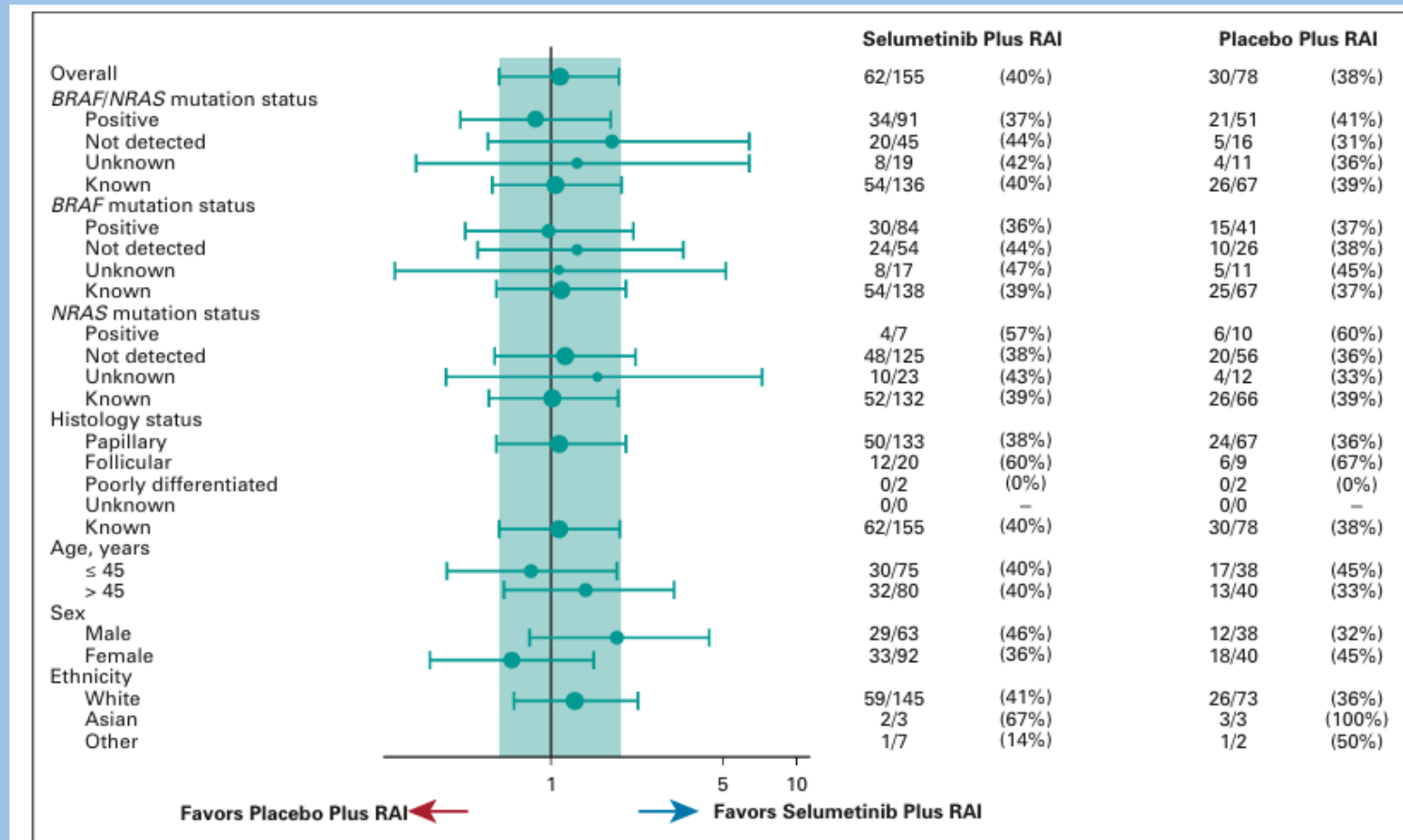


2/3 of pts with metastatic disease become refractory to RAI

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

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**

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)

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

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)

Oncocytic Thyroid Cancer - OTC

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

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

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

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

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)***

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