De-escalating radioactive iodine in patients with differentiated thyroid cancer:

When to use it and how much?

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Conflict of Interest Statement

I have no relevant conflicts of interest

Post-operative RAI

35 year old female
Total thyroidectomy, central neck dissection

Pathology
2.5 cm classic PTC
No vascular invasion
No extrathyroidal extension
2/7 lymph nodes with PTC
Largest LN 4 mm
No extranodal extension

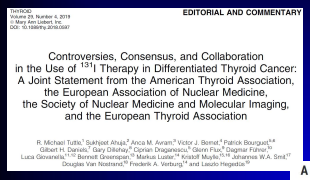
6 weeks post-op
Tg < 0.2 ng/mL, Tg Ab negative
TSH 0.5 mIU/L
US shows no abnormal LN's

Should see get RAI therapy? If so, what administered activity?

What is the potential benefit? What is the potential harm?

What is the goal of RAI therapy?

Key Elements in Adjuvant Treatment Decision Making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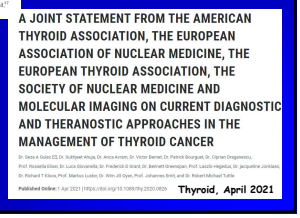
EDITORIAL AND COMMENTARY

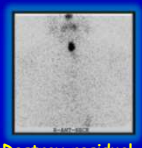
Controversies, Consensus, and Collaboration in the Use of ^{131}I Therapy in Differentiated Thyroid Cancer: A Joint Statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association


A JOINT STATEMENT FROM THE AMERICAN THYROID ASSOCIATION, THE EUROPEAN ASSOCIATION OF NUCLEAR MEDICINE, THE EUROPEAN THYROID ASSOCIATION, THE SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING ON CURRENT DIAGNOSTIC AND THERANOSTIC APPROACHES IN THE MANAGEMENT OF THYROID CANCER

Thyroid, April 2021

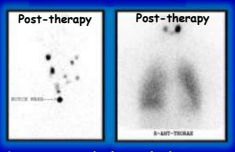
Goals of I-131 Therapy

Remnant Ablation



Destroy residual normal tissue to improve initial staging and facilitate follow-up

Adjuvant Treatment



Destroy subclinical disease that may or may not be present in patients with no biochemical, functional or structural evidence of disease

Treatment of Known Disease

Treatment of RAI Avid Mets

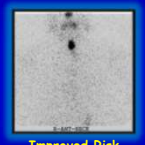
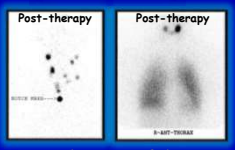
Van Nostrand, Endo Metab Clin NA 2017; Haugen et al, ATA Guidelines, Thyroid 2015
Tuttle et al, Martinique Principles, Thyroid 2019

Adjuvant Therapy for Cancer

- Additional treatments given after surgical resection of known tumor and metastatic foci to destroy subclinical tumor foci that may or may not be present.
- The goal is to decrease recurrence rates and improve disease specific survival.
- Because adjuvant therapy is given for a risk, rather than for demonstrable disease, it is accepted that a proportion of patients who receive adjuvant therapy will already have been cured by their primary surgery.
- Therefore, selection for adjuvant therapy traditionally involves an analysis of the risk of recurrence/death, potential side effects, and evidence for improved clinical outcomes.

Tuttle et al, Martinique Principles, Thyroid 2019

Trend to More Selective Use of RAI

Remnant Ablation	Adjuvant Treatment	Treatment of Known Disease
		
Improved Risk Stratification	Where most of the controversy exists	Time course of effectiveness
Highly sensitive Tg	Potential benefit?	Curative vs palliative
Neck US	Potential risks?	Re-differentiation
Low yield of diagnostic RAI scans	Personalized therapy	Genomics

Very Selective Use Approach

Philosophical underpinnings

- The vast majority of DTC patients that are adjuvant therapy candidates will do well with disease specific survival rates in excess of 99% and with structural disease recurrence rates of < 5-10%.
- Delayed intervention (radioactive iodine, additional surgery), when necessary, is effective and has no impact on disease specific survival.
- Minimal residual disease is common and of little clinical importance.
- Early detection and treatment of a very small volume structural incomplete response has little clinical benefit.

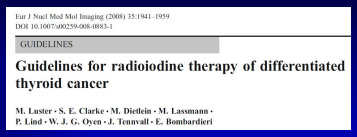
Trend Toward More Selective Use of RAI

Routine Use	Selective Use
RAI to nearly every DTC patient	Post-op Risk Assessment
	Impact on outcomes of interest
	Side effect profile

Tuttle et al, Martinique Principles, Thyroid 2019

Nearly Routine Use Approach

European Association of Nuclear Medicine



Eur J Nucl Med Mol Imaging (2008) 35:1941–1959
DOI 10.1007/s00259-008-0883-1

GUIDELINES

Guidelines for radioiodine therapy of differentiated thyroid cancer

M. Luster · S. E. Clarke · M. Dietlein · M. Lassmann · P. Lind · W. J. G. Oyen · J. Tennvall · E. Bombardieri

- "RAI ablation after total or near-total thyroidectomy is a standard procedure in patients with DTC."
- "The only exception is patients with unifocal papillary thyroid carcinoma ≤1 cm in diameter who lack: evidence of metastasis, thyroid capsule invasion, history of radiation exposure and unfavorable histology (tall cell, columnar cell, or diffuse sclerosing subtypes)."

Nearly Routine Use Approach

German Society for Nuclear Medicine

Verfahrensanweisung

Radioiodtherapie beim differenzierten Schilddrüsenkarzinom

Verfahrensanweisung – Version 4 (Stand 30.10.2015)

Markus Dietlein[1,3]; Wolfgang Eschner[1,2,3]; Frank Grünwald[1,4]; Michael Lassmann[1,2,5]; Frederik A. Verburg[1,6]; Markus Luster[1,7]

Nuklearmedizin. 2016 Jun 28;55(3):77-89.

- RAI post-op for all tumors > 1 cm
- RAI < 1 cm in the presence of high risk features such as multifocality, capsule infiltration, poorly differentiated subtypes, infiltrative growth, desmoplastic fibrosis, BRAF V600E mutation

Nearly Routine Use Approach

Society of Nuclear Medicine

Journal of Nuclear Medicine, published on July 11, 2012 as doi:10.2967/jnumed.112.105148

The SNM Practice Guideline for Therapy of Thyroid Disease with ^{131}I 3.0*

Edward B. Silberstein[1] (Chair), Abass Alavi[2], Helena R. Balon[3], Susan E.M. Clarke[4], Chaitanya Divgi[5], Michael J. Gelfand[6], Stanley J. Goldsmith[7], Hossein Jadvar[8], Carol S. Marcus[9], William H. Martin[10], J. Anthony Parker[11], Henry D. Royal[12], Salil D. Sarkar[13], Michael Stabin[14], and Alan D. Waxman[15]

131I ablative or tumoricidal treatment of differentiated thyroid cancer with radioiodine "should be considered"

- Tumors > 1 cm
- Tumors < 1 cm with high risk features
  - Aggressive histology
  - Lymphatic or vascular invasion
  - Distant metastases
  - Multifocal disease
  - Capsular invasion or penetration
  - Perithyroidal soft tissue involvement
  - Elevated anti-Tg antibody

Selective Use Approach

Organization	Wording for patient selection for ablation/adjuvant therapy
ATA 1996	Individualized and based on clinical experience
ATA 2006	All M1/gross ETE, most older N1, others selective use
ATA 2009	No, selective use, yes
ATA 2015	No, not routine, consider, generally favored, yes
AACE/ACE/AAES 2011	Case by case decision is recommended
NCCN 2017	Not typically, recommended, or typically recommended
European Consensus Conference/Report 2005, 2006	No indication, definite indication, probably indicated
BTA 2014	No indications, uncertain indications, definite indications
JSES/JSTS 2016	Selective use
Cancer Care Ontario 2017	Not recommended, selective use, routine use
LATS 2009	Recommended, could be performed, not mandatory
ESMO 2012	Not indicated, may be indicated, indicated

Selective Use Approach

Factors impacting use of RAI for ablation/adjuvant therapy

- Extent of disease
- Adequacy of resection
- Age
- Worry about disease specific mortality
- Patient willingness to accept RAI

- Socioeconomic status
- Education level
- Employed/unemployed
- English language proficiency
- Insurance status
- Specialty training
- Region of the country

Marti Thyroid 2015, Haymart Cancer 2013, Papaleontiou Thyroid 2013, Schuessler, Ann Surg Oncol 2013, Haymart JCEM 2013, Zevallos Thyroid 2014, Goldfarb Endo Practice 2014

Literature Review Specific to Adjuvant Treatment

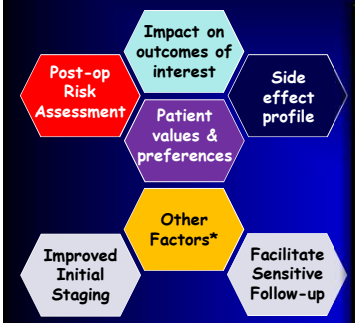
Despite multiple publications, several meta-analyses, and countless arguments, the available data does not allow for definitive recommendations with regard to the impact of adjuvant RAI therapy on recurrence or disease specific survival.

Problems with the current literature

- Lack of randomized controlled trials
- More than 16 different staging systems used to define "risk"
- Definition of "low risk" varies across studies
- None incorporate response to therapy assessments
- Little data specific to the "adjuvant therapy" cohort
- Histological heterogeneity of differentiated thyroid cancer
- Likelihood of RAI avidity not considered
- Event rates are often small
- Events can occur decades after diagnosis
- Pre-op imaging has improved over time
- Methods for detecting recurrent disease have improved over time

Modified from Sacks, Thyroid 2010

Key Elements in Adjuvant Treatment Decision Making



*Other Factors
Availability and quality of:
Pre and Post-Op US
RAI imaging
Tg Assays
Experienced Thyroid Surgeon

Presence of anti-Tg antibodies

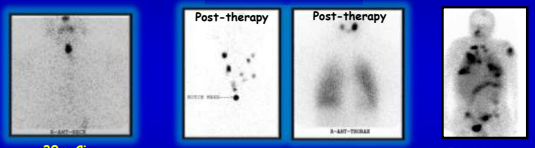
Preferences of the local disease management team

Likelihood of RAI avidity (histology, imaging, genomics)

Tuttle et al, Martinique Priniciples, Thyroid 2019

Administered Activities

Remnant Ablation | Adjuvant Treatment | Treatment of Known Disease



30 mCi (1.11 GBq)

30-150 mCi (1.11 - 5.5 GBq)

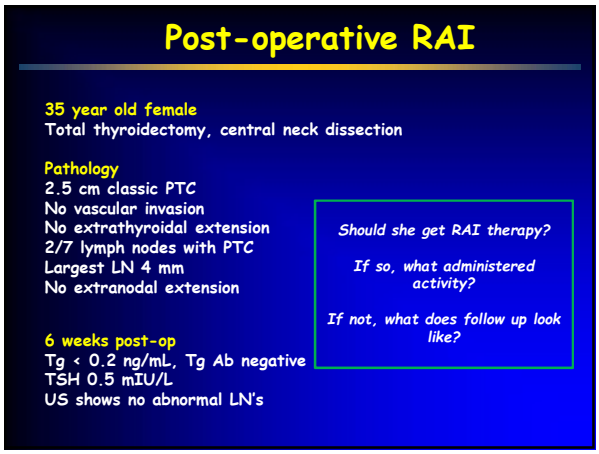
MSKCC
Diagnostic scan & 100 mCi

Empiric

150-300 mCi (5.5 - 11 GBq)

Empiric
Or
Dosimetry Based

Van Nostrand, Endo Metab Clin NA 2017; Haugen et al, ATA Guidelines, Thyroid 2015
Tuttle et al, Martinique Principles, Thyroid 2019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US shows no abnormal LN's
Should she get RAI therapy?
If so, what administered activity?
If not, what does follow up look like?