



RADIOIODIO: LE INDICAZIONI DELLA SOCIETÀ EUROPEA DI MEDICINA NUCLEARE

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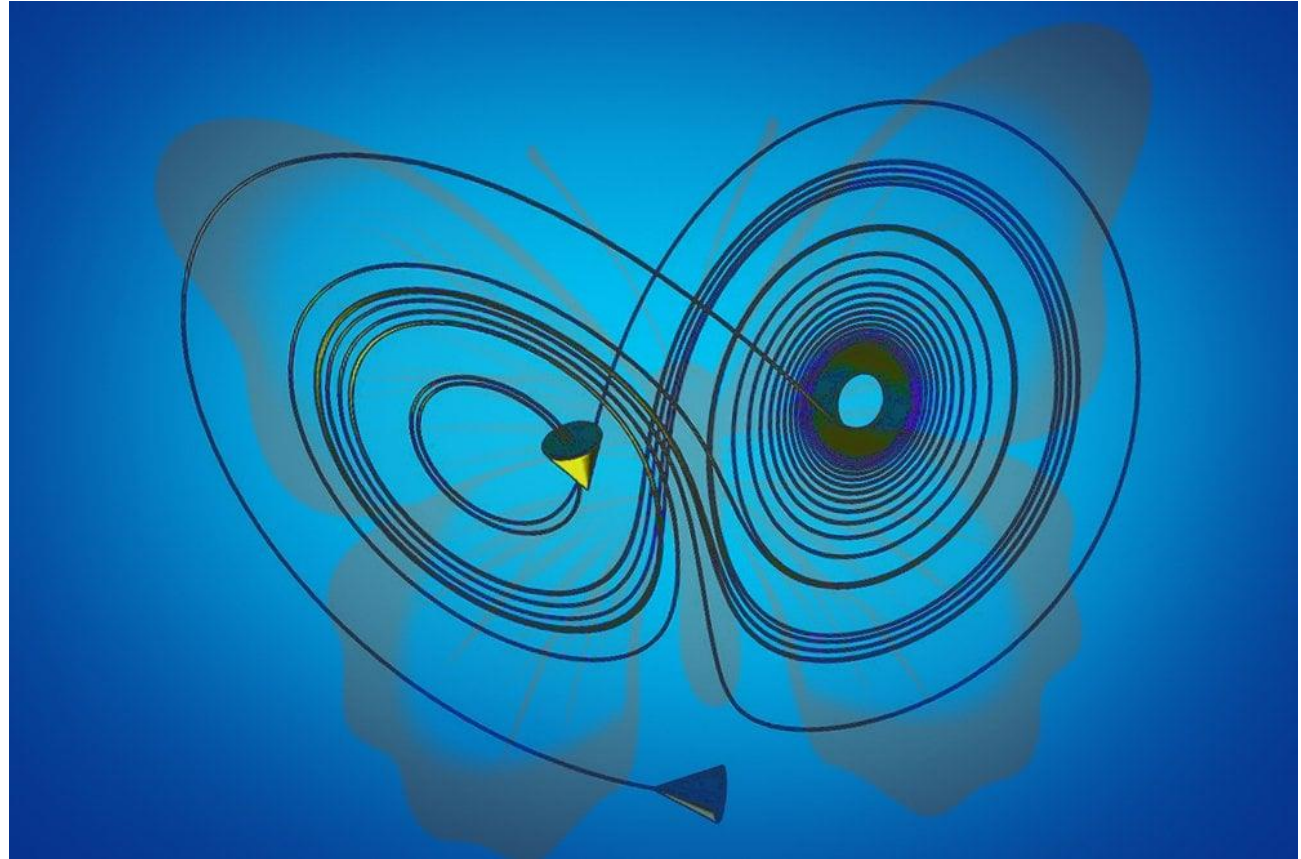
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Ente Ospedaliero Cantonale

Linee Guide e Raccomandazioni

- ATA
- SNMMI/EANM
- ETA
- ESMO
- NCCN
- Varie Nazionali



DTC: debated issues

- RAI therapy
- Neck-dissection
- Lobectomy
- (Thermal ablations)
- Active surveillance



Incidentalomas and ultrasound screening




De-escalation: the first step!

Endocrine

<https://doi.org/10.1007/s12020-023-03316-8>

VIEWPOINT

Radioiodine therapy in differentiated thyroid cancer. There is (still) a great chaos under heaven: is the situation excellent?

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Recommendation 51

-RAI remnant ablation **is not routinely recommended** after thyroidectomy for **ATA low-risk DTC patients**.

Consideration of specific features of the individual patient that could modulate recurrence risk, disease follow-up implications, and patient preferences are relevant to RAI decision-making (Weak recommendation, Low-quality evidence)

-RAI adjuvant therapy **should be considered** after total thyroidectomy in **ATA intermediate-risk level DTC patients** (Weak recommendation, Low-quality evidence)

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

Haugen B, et al. *Thyroid*. 2016; 26:1-133.

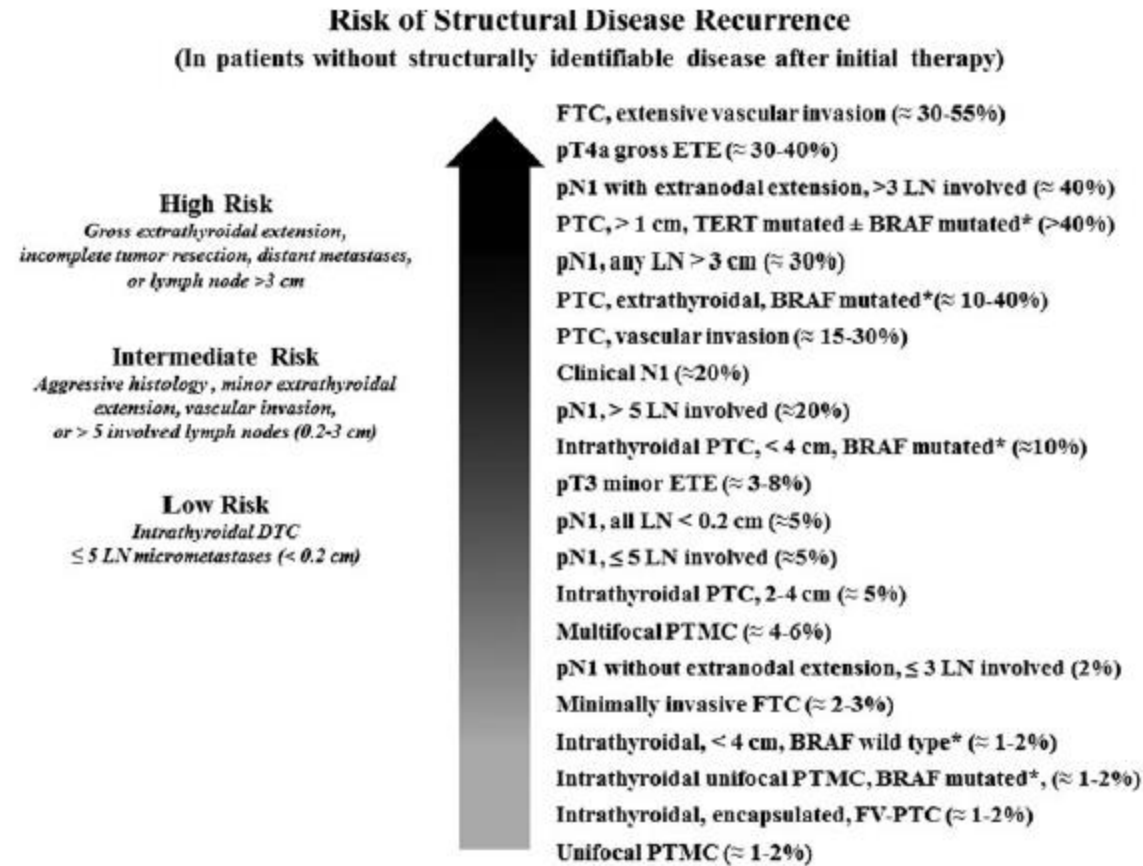
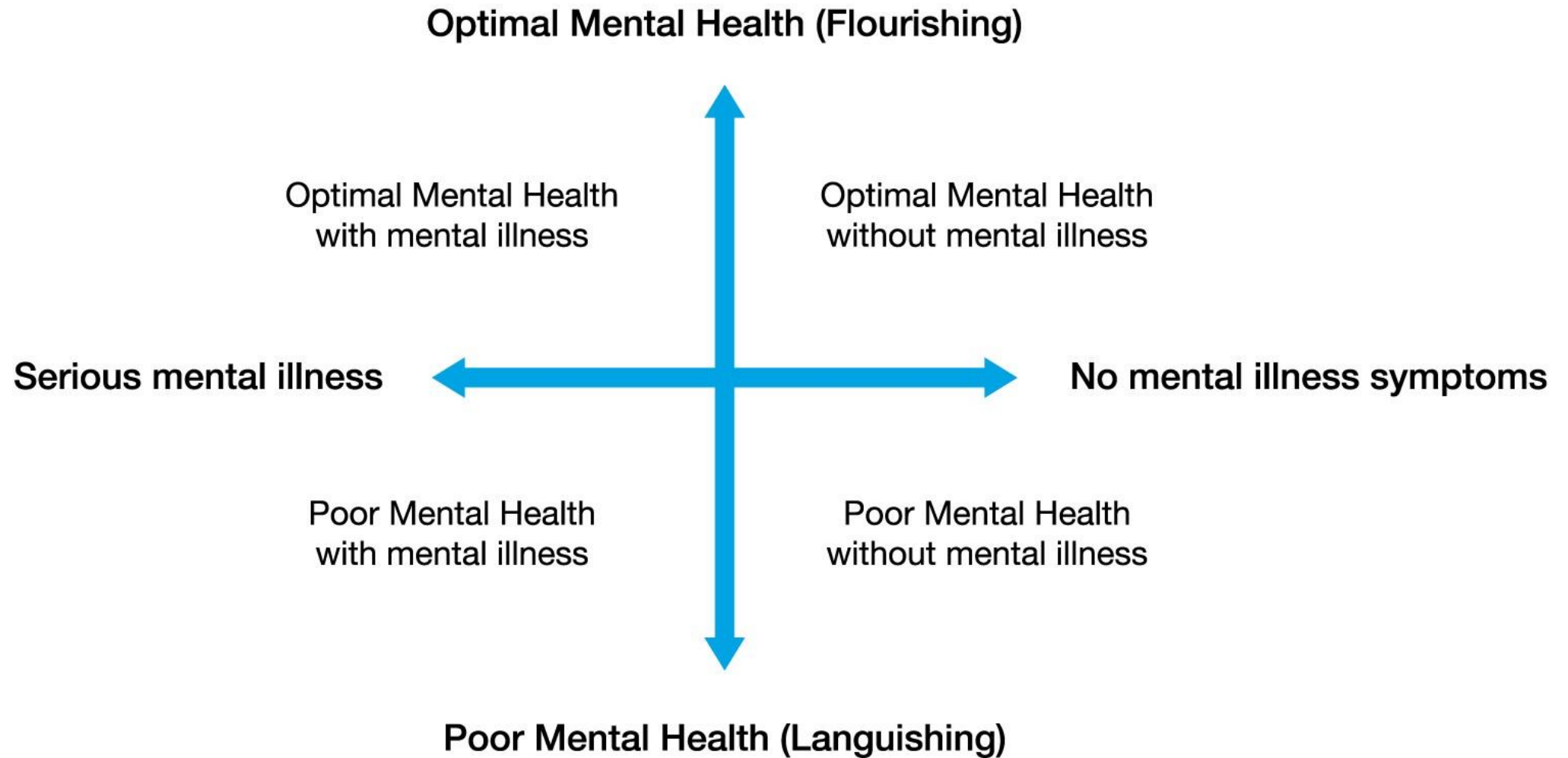


FIG. 4. Risk of structural disease recurrence in patients without structurally identifiable disease after initial therapy. The risk of structural disease recurrence associated with selected clinico-pathological features are shown as a continuum of risk with percentages (ranges, approximate values) presented to reflect our best estimates based on the published literature reviewed in the text. In the left hand column, the three-tiered risk system proposed as the Modified Initial Risk Stratification System is also presented to demonstrate how the continuum of risk estimates informed our modifications of the 2009 ATA Initial Risk System (see Recommendation 48). *While analysis of *BRAF* and/or *TERT* status is not routinely recommended for initial risk stratification, we have included these findings to assist clinicians in proper risk stratification in cases where this information is available. FTC, follicular thyroid cancer; FV, follicular variant; LN, lymph node; PTMC, papillary thyroid microcarcinoma; PTC, papillary thyroid cancer.



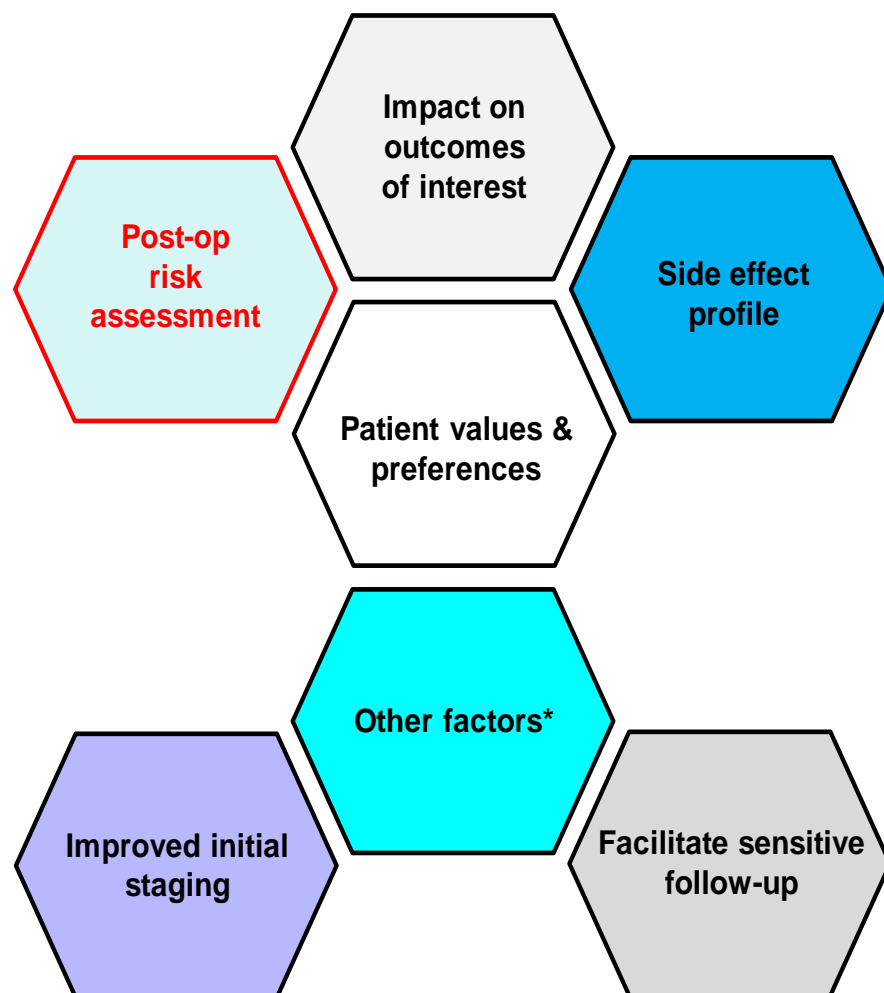


Martinique's Principles

2. The goal of I-131 therapy should be characterized as remnant ablation, adjuvant treatment, or treatment of known disease using standardized definitions.
3. Assessment of post-operative disease status is required to optimize proper patient selection for I-131 therapy (i.e. ablation, adjuvant treatment).
4. Post-operative disease status evaluations should be standardized and integrated into routine clinical care.
5. Optimal patient selection for I-131 adjuvant treatment requires consideration and evaluation of multiple factors beyond post-operative disease status and risk stratification.

Optimal patient selection for I-131 adjuvant treatment requires consideration and evaluation of multiple factors beyond post-operative disease status and risk stratification.

Key Elements in Adjuvant Treatment Decision Making



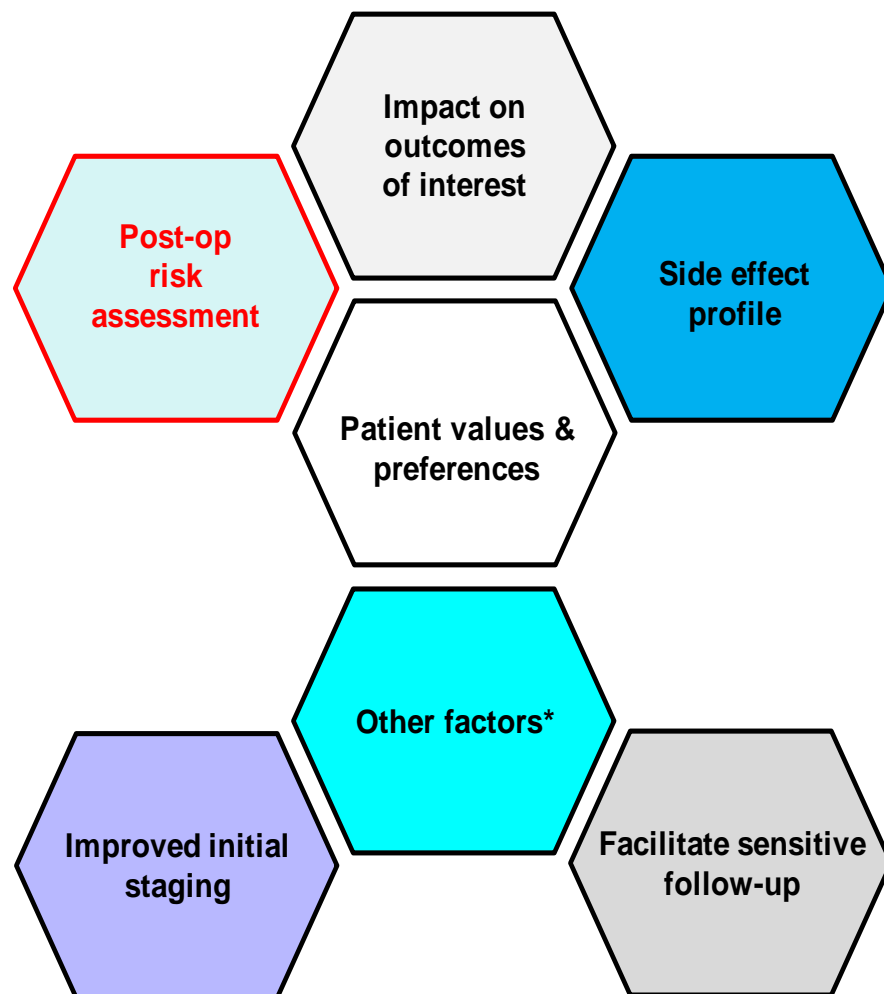
***Other factors**

- Availability and quality of:
 - Pre and post-op US
 - RAI imaging
 - Tg assays
 - Experienced thyroid surgeon
- Presence of anti-Tg antibodies
- Preferences of local disease management team

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

Furio Pacini¹, Dagmar Fuhrer², Rossella Elisei³, Daria Handkiewicz-Junak⁴, Sophie Leboulleux⁵, Markus Luster⁶, Martin Schlumberger⁹ and Johannes W Smit⁷

- 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 the intermediate-risk category, RAI therapy **may be indicated** and should be tailored according to individual cases.
- 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**. Low-risk patients with post-operatively detectable serum Tg, in particular when it is above the institutional cut-off of, for example, 2 ng/mL on l-T4 or >5-10 ng/mL after TSH stimulation or with abnormal ultrasound findings have a higher risk of recurrence, and RAI therapy may be considered, although there is no evidence that it can improve disease-free survival



In ESTIMABL-1 the rate of patients with persistent structural disease after ^{131}I ablation was similar in 3 subgroups of stimulated Tg ranges (i.e. <1 , 1–5 and 5–10 ng/mL)

Hindie E, Taieb D, Avram AM, Giovanella L. Lancet Diabetes Endocrinol. 2018

Individualized treatment of differentiated thyroid cancer: The value of surgery in combination with radioiodine imaging and therapy

A German position paper from Surgery and Nuclear Medicine

Individualisierte Behandlung von differenziertem Schilddrüsenkrebs: Der Wert der Operation in Kombination mit Radiojodbildgebung und -therapie

Ein deutsches Positionspapier aus der Chirurgie und Nuklearmedizin

Authors

Matthias Schmidt^{1, 12, 13}, Peter Bartenstein^{2, 13}, Jan Bucerius³, Markus Dietlein^{4, 13}, Alexander Drzezga¹, Ken Herrmann⁴, Constantin Lapa^{5, 11}, Kerstin Lorenz^{6, 14}, Thomas J. Musholt^{7, 14}, James Nagarajah^{8, 12, 13}, Christoph Reiners⁹, Carsten O. Sahlmann^{3, 12}, Michael C. Kreissl^{10, 12}

RECOMMENDATION 1 (ETA CONSENSUS STATEMENT)

The decision for post-operative radioiodine therapy should be taken based on initial prognostic indicators for thyroid cancer related death and recurrence, including among others the surgical and pathological report and on the results of serum thyroglobulin measurements and neck ultrasonography obtained after surgery.

MODIFIED RECOMMENDATION 1

The decision to proceed with post-operative RIT should be based on the recommendation of an interdisciplinary tumor board incorporating initial prognostic indicators for thyroid cancer related death and recurrence, including not only the surgical and pathology report, and patient age but also the results of postoperative laboratory and imaging results. The patient should be involved in the decision-making process ("shared decision making").

RECOMMENDATION 3 (ETA CONSENSUS STATEMENT)

In the intermediate-risk category*, RIT therapy may be indicated and should be tailored according to individual cases.

*patients with 1) microscopic invasion of tumor into the perithyroidal soft tissues; 2) aggressive histology (e. g., tall cell, hobnail variant, columnar cell carcinoma); 3) PTC with vascular invasion; 4) clinical N1 or > 5 pathologic N1 with all N1 < 3 cm in largest dimension; 5) multifocal papillary microcarcinoma with microscopic invasion of tumor into the perithyroidal soft tissues and BRAFV600E mutation (if known)

MODIFIED RECOMMENDATION 3

In the intermediate-risk category, RIT therapy is indicated.

RECOMMENDATION 4 (ETA CONSENSUS STATEMENT)

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

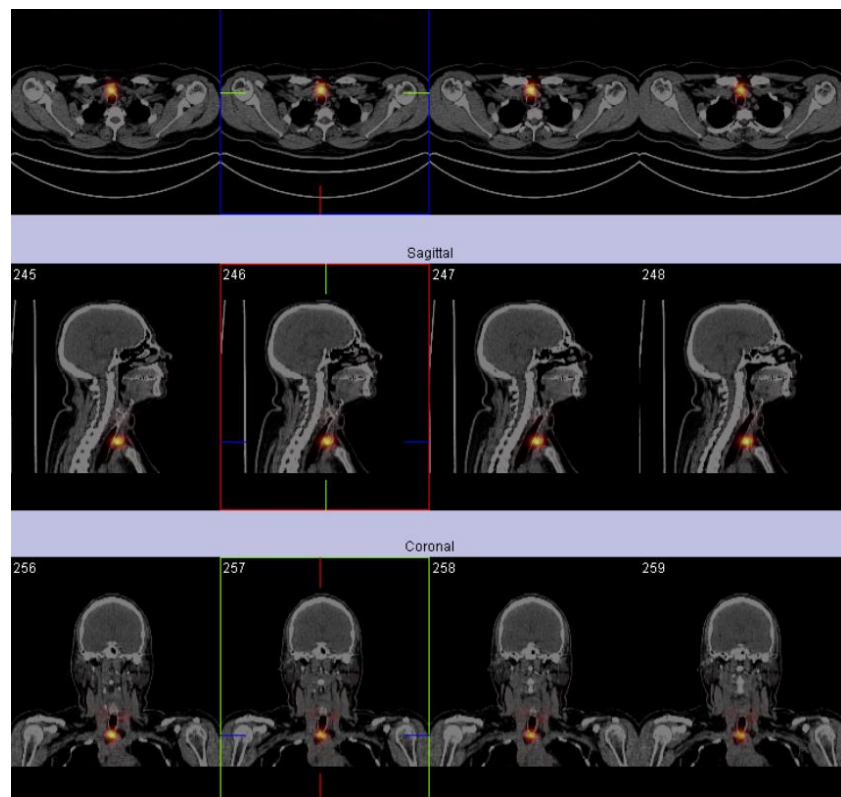
§ patients with 1) intrathyroidal PTC without vascular invasion, with or without small volume lymph node metastases (clinical N0 or ≤ 5 pathologic N1, all < 0.2 cm in largest dimension); 2) intrathyroidal encapsulated follicular variant of papillary thyroid cancer or intrathyroidal well differentiated follicular cancer with capsular or minor vascular invasion (< 4 vessels involved); 3) intrathyroidal papillary microcarcinomas that are either BRAF wild type or BRAF mutated (if known)

MODIFIED RECOMMENDATION 4

In low-risk patients, RIT therapy should be performed in patients at stages pT1b-2, N0-1; in stage pT1a RIT may be performed but under consideration of additional risk modifiers (e. g. multifocality, aggressive histology, BRAF mutation).

SNMMI Procedure Standard/EANM Practice Guideline for Nuclear Medicine Evaluation and Therapy of Differentiated Thyroid Cancer: Abbreviated Version

Anca M. Avram (cochair)¹, Luca Giovanella (cochair)², Bennett Greenspan³, Susan A. Lawson⁴, Markus Luster⁵, Douglas Van Nostrand⁶, Justin G. Peacock⁷, Petra Petranović Ovčariček⁸, Edward Silberstein⁹, Mark Tulchinsky¹⁰, Frederik A. Verburg¹¹, Alexis Vrachimis¹²



The goal of therapeutic ^{131}I administration after total thyroidectomy is outlined based on standardized definitions as follows: remnant ablation, adjuvant treatment, or treatment of known disease (19,20). Upon integration of various parameters, including clinical/pathologic data and laboratory and imaging information, ^{131}I therapy is administered for the following reasons: (1) to eliminate normal thyroid tissue remnant in low-risk patients, thereby ensuring undetectable or minimal serum Tg levels (in the absence of neoplastic tissue), which facilitates follow-up (remnant ablation); (2) to irradiate suspected but unproven sites of neoplastic cells in low-intermediate- and intermediate-risk patients as determined by histopathologic features, thereby reducing the risk of disease recurrence (adjuvant treatment); and (3) to treat persistent or recurrent disease in patients with demonstrated metastatic disease (treatment of known disease).

RESEARCH SUMMARY

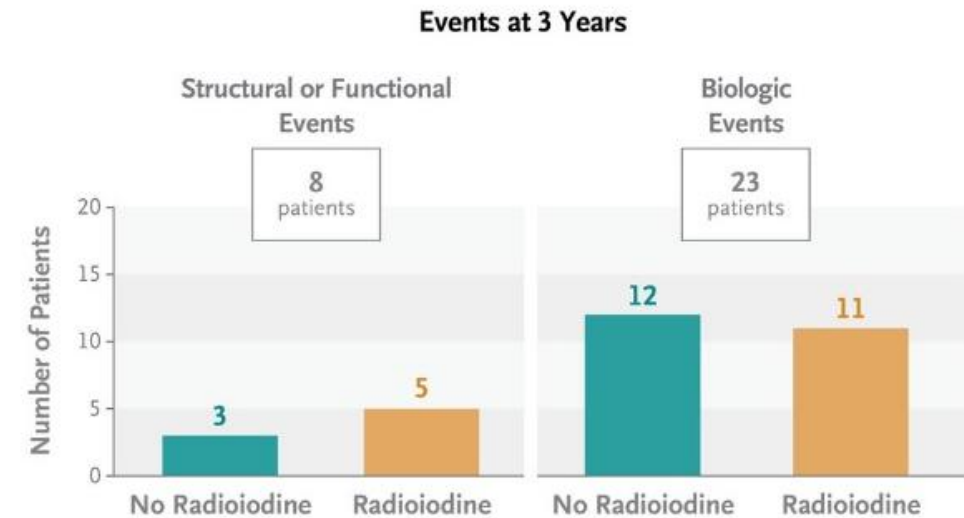
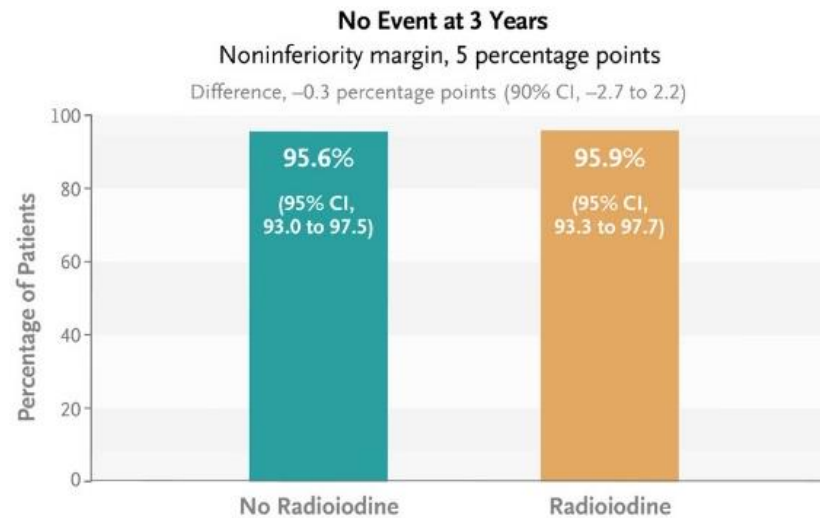
Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer

Leboulleux S et al. DOI: 10.1056/NEJMoa2111953

Radioiodine Ablation N=389



Follow-up Alone (No Radioiodine) N=387



LIMITATIONS AND REMAINING QUESTIONS

- The findings need to be confirmed over longer follow-up.
- A higher risk of events was observed in patients with a tumor size of <14 mm, an unexpected finding without a clear explanation.

Links: Full Article | NEJM Quick Take | Editorial

CONCLUSIONS

In patients undergoing thyroidectomy for low-risk differentiated thyroid cancer, follow-up alone without radioiodine therapy was noninferior to radioiodine therapy in terms of events at 3 years.



To give or not to give? A critical appraisal of a clinical trial on radioiodine treatment

Murat Tuncel^{1,2} · Alexis Vrachimis^{1,3} · Alfredo Campenni^{1,4} · Bart de Keizer^{1,5} · Frederik A. Verburg⁶ · Michael C. Kreissl^{1,7} · Petra Petranovic Ovcaricek^{1,8} · Tamara Geliashvili^{1,9} · Luca Giovannella^{1,10}

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Activity selection

1.1 GBq vs no RAI (ablation but adjuvant activity)

Surgery

- R0, total thyroidectomy without US-detected remnant
- High number of patients underwent central neck dissection (> 6 lymph nodes)
- A number of patients also underwent lateral neck dissection

Randomization

The chance of having an event increased by the Tg level at randomization. However, as the authors failed to show a balanced distribution of Tg levels in the study groups, a selection bias may be suspected here.

Composite outcome strategy

- RAI ablated: any uptake outside the thyroid bed

Thyroglobulin

- basal in nonablated
- rhTSH stimulated in ablated
- arbitrary cutoff

Thyroglobulin antibodies

- Patients with positive and negative TgAb were included

Observation period

The 3-year period applied is too short to draw definitive conclusions

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Villejuif, le 22 mars 2022

New England Journal of Medicine Pas de bénéfice de l'iode radioactif dans le cancer de la thyroïde à faible risque

Les patients atteints d'un cancer différencié de la thyroïde à faible risque de rechute ne devraient plus recevoir un traitement à base d'iode radioactif après chirurgie thyroïdienne. Ce changement de paradigme qui plaide pour une désescalade de la prise en charge de ces patients a été démontré avec l'essai clinique prospectif randomisé de phase III, ESTIMABL2, promu par Gustave Roussy et qui a été principalement mené par des médecins-chercheurs de Gustave Roussy, de l'Inserm et de l'Université Paris-Saclay. Accompagnée d'une vidéo pédagogique, l'étude, publiée dans the *New England Journal of Medicine* du 10 mars 2022 et saluée dans l'éditorial de la revue donne lieu à un nouveau standard de traitement.

<https://www.nejm.org/doi/full/10.1056/NEJMoa2111953>

Les cancers différenciés de la thyroïde sont parmi les plus fréquents des cancers endocriniens (90 %) et présentent dans la majorité des cas (75 %) un faible risque de récurrence à cinq ans. Pour ces patients, un traitement standard à base d'iode radioactif était jusqu'à présent utilisé après une résection de la glande thyroïde par chirurgie (thyroïdectomie) pour éliminer les reliquats thyroïdiens et les potentielles cellules cancéreuses. L'administration d'iode radioactif se déroule dans le cadre d'une hospitalisation de trois à cinq jours. Elle comporte peu d'effets secondaires hormis de rares nausées ou des problèmes des glandes salivaires et lacrymales. Par ailleurs, les grossesses sont contre-indiquées dans les six mois qui suivent un traitement par iode radioactif.

L'ajout d'iode radioactif après une thyroïdectomie est pratiqué depuis plus de 60 ans suite aux résultats d'études rétrospectives ayant montré un bénéfice sur la diminution des rechutes et de la mortalité dans les cancers différenciés de la thyroïde tous risques confondus. La question de son utilisation dans les cancers à faible risque restait posée suite à un précédent grand essai clinique randomisé et prospectif en 2012, ESTIMABL1 publié dans *The New England Journal of Medicine* qui démontrait qu'une dose d'iode trois fois moins élevée (1,1 GBq) apportait le même bénéfice qu'une dose de 3,7 GBq, sur la récurrence de ce cancer.

ESTIMABL2 vient changer les pratiques

La Dr Sophie Leboulleux, endocrinologue spécialiste des cancers de la thyroïde et ancienne cheffe du service de médecine nucléaire de Gustave Roussy jusqu'en 2021, a coordonné l'essai Stimulation Ablation 2 (ESTIMABL2). Dans ce vaste essai prospectif randomisé de phase III, 776 patients atteints d'un cancer différencié de la thyroïde à faible

Conclusions

- ❑ Unfortunately, robust evidence is still lacking in most, if not all, scenarios, and most recommendations are **expert opinions** rather than **evidence-based** recommendations.
- ❑ In daily clinical practice of specialized centers, such “ideological” differences are frequently compounded in patient-centered discussions (i.e., tumor boards) but this may be not the case for colleagues operating in non-dedicated centers.
- ❑ Accordingly, instead of proposing unilateral guidelines, medical societies should be committed to produce joint guidelines for the benefit of patients.

THANKSGIVING

EANM Thyroid Committee 2.0

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The Martinique Working Group