The Journal of Clinical Endocrinology & Metabolism, 2023, **00**, 1–2
https://doi.org/10.1210/clinem/dgad171
Advance access publication 25 March 2023
Commentary

Adjuvant Radioiodine for Intermediate-Risk Papillary Thyroid Cancer—To Treat or Not to Treat

Evert F. S. van Velsen[1,2,3] **and Frederik A. Verburg**[2,4]

[1]Department of Internal Medicine, Erasmus Medical Center, 3015 CE, Rotterdam, The Netherlands
[2]Academic Center for Thyroid Diseases, Erasmus Medical Center, 3015 CE, Rotterdam, The Netherlands
[3]Erasmus MC Bone Center, Erasmus Medical Center, 3015 CE, Rotterdam, The Netherlands
[4]Department of Radiology and Nuclear Medicine, Erasmus Medical Center, 3015 CE, Rotterdam, The Netherlands

Correspondence: Evert F. S. van Velsen, MD, PhD, Department of Internal Medicine, Erasmus Medical Center, Dr. Molewaterplein 40, 3015 CE, Rotterdam, The Netherlands. Email: e.vanvelsen@erasmusmc.nl.

Key Words: papillary thyroid cancer, radioiodine therapy, ATA, American Thyroid Association, intermediate-risk

Abbreviations: ATA, American Thyroid Association; DTC, differentiated thyroid cancer; PSM, propensity score matched; PTC, papillary thyroid cancer; RAI, radioiodine; Tg, thyroglobulin.

The incidence of differentiated thyroid cancer (DTC), the most common endocrine cancer, has steadily increased over the last 2 decades (1). DTC comprises both papillary (PTC) and follicular (FTC) thyroid cancer, of which PTC is the most common. The vast majority of the patients with PTC have either stage I or stage II disease at presentation, with the 10-year disease-specific survival approaching 100% in stage I disease (2). Therefore, predicting the risk of recurrence and/or persistent disease as a basis for guiding the appropriate extent of therapy has become much more important in day-to-day clinical practice. The American Thyroid Association (ATA) risk stratification system is designed to predict response to therapy and recurring disease in patients with DTC, and patients are stratified as either low-, intermediate-, or high-risk (3).

Historically, treatment of DTC is based on a combination of thyroid surgery followed by radioiodine (RAI) therapy (3). The current 2015 ATA guidelines roughly state that RAI therapy can be omitted in low-risk, should be considered in intermediate-risk, and is recommended in high-risk patients. The recommendation not to give RAI therapy in low-risk patients is based on systematic reviews which did not find a significant benefit of RAI therapy on cancer-related death (3). Recently, Leboulleux et al showed prospectively that in low-risk DTC patients, omitting low-activity RAI remnant ablation is noninferior to a treatment regimen including low-activity RAI remnant ablation with respect to the occurrence of functional, structural, and biologic events after 3 years (4), but longer follow-up is needed to have more robust conclusions as these patients usually have excellent disease-free survival rates (5). For intermediate-risk patients, the evidence on the impact of RAI therapy on disease recurrence is conflicting thus far, showing beneficial effects in some and no benefit in others (6). Benefits regarding survival or recurrence can be expected to be larger in intermediate-risk patients with higher risk of recurrent or persistent disease, but more studies are needed to characterize RAI treatment efficacy in these intermediate-risk patients as the evidence is of low-quality and heterogeneous (3).

Recently, Tian et al published the results of a propensity score matched (PSM) analysis of RAI therapy in patients with intermediate-risk PTC with low thyroglobulin (Tg) levels (7). In this study, 1487 adult patients with unstimulated Tg ≤ 1 ng/mL or stimulated Tg ≤ 10 ng/mL after total thyroidectomy were enrolled retrospectively. Patients were matched using PSM, and those who received RAI therapy, with an activity of 3.7 GBq iodine-131 which is consistent with adjuvant intent, were compared with those who did not receive this therapy. Both groups were compared with respect to biochemical and structural recurrence. A total of 690 patients could be matched (552 RAI group, 138 non-RAI group) having a median follow-up of 51 months. Overall recurrence rates were 1.6% (9/552) in the RAI group and 7.9% (11/138) in the non-RAI group ($P < .001$), while these rates were 0.9% and 3.6% with respect to structural recurrence ($P = .007$), and 0.7% and 4.3% with respect to biochemical recurrence ($P = .005$), respectively. The authors therefore justifiably conclude that postoperative RAI therapy decreases the risk of structural and biochemical recurrence in patients with intermediate-risk PTC with low Tg levels.

The main limitations of this study include the retrospective nature in which bias is introduced due to physician and/or patient preferences, even though PSM was used to overcome this problem. Further, only those with unstimulated Tg ≤ 1 ng/mL or stimulated Tg ≤ 10 ng/mL after total thyroidectomy were enrolled, as most patients with higher Tg values tend to receive RAI therapy at their doctor's recommendation. Also, it is unclear how the patients were initially diagnosed with their PTC, as recent literature suggests that the risk of recurrence is significantly higher when PTC was diagnosed after a palpable mass was found (8), suggesting that the underlying risk profile of the tumor is important. Finally, all patients received total thyroidectomy with central neck dissection, which is no

Received: 16 March 2023. **Editorial Decision:** 18 March 2023. **Corrected and Typeset:** 11 April 2023

longer common practice in many parts of the world thus potentially hampering generalizability (3).

The study of Tian et al adds another study in favor of postoperative adjuvant RAI therapy in intermediate-risk DTC patients. Although retrospective in design, one of the strong points of this study is the use of PSM to try to overcome the problem of confounding-by-indication. What is also striking in this study is that adjuvant RAI therapy seems to significantly benefit even those with low Tg values after initial surgery. Conventionally, such low Tg values after initial surgery are usually assumed to predict freedom of disease (3), obviating the need for adjuvant postoperative RAI therapy. Therefore, in contrast with the decreased radioiodine use the past decade, this provides evidence supporting the use of adjuvant RAI therapy in intermediate-risk patients. Thus, adjuvant RAI therapy, stated in the 2015 ATA guidelines as to be "considered," might, and perhaps even should, be considered more strongly than before in the light of this new evidence.

Notwithstanding this supportive evidence, however, we should not neglect to endeavor toward providing highest quality evidence in the form of prospective, randomized studies with a follow-up of sufficient duration. Considering that all retrospective studies have inherent weaknesses, opening the result, whichever way it falls, for nonacceptance by those who, based on their experience and own study of the literature thus far, believe otherwise, such prospective studies are the method to confirm or deny retrospective findings such as the present one and will finally enable us to identify those patients benefiting (or not) from adjuvant postoperative RAI therapy with an acceptable degree of evidence-based certainty.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author Contributions

E.V.V. and F.A.V. wrote the manuscript.

Disclosures

F.A.V. has received consultancy fees from Sanofi and GE Healthcare (all fees paid to employer) as well as speaker honoraria from AstraZeneca (all fees paid to employer). E.V.V. declares no conflicts of interest and no competing financial interests exist.

References

1. La Vecchia C, Malvezzi M, Bosetti C, *et al*. Thyroid cancer mortality and incidence: a global overview. *Int J Cancer*. 2015;136(9):2187-2195.
2. van Velsen EFS, Visser WE, Stegenga MT, *et al*. Finding the optimal age cutoff for the UICC/AJCC TNM staging system in patients with papillary or follicular thyroid cancer. *Thyroid*. 2021;31(7):1041-1049.
3. Haugen BR, Alexander EK, Bible KC, *et al*. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133.
4. Leboulleux S, Bournaud C, Chougnet CN, *et al*. Thyroidectomy without radioiodine in patients with low-risk thyroid cancer. *N Engl J Med*. 2022;386(10):923-932.
5. Verburg FA, Mader U, Reiners C, Hanscheid H. Long-term survival in differentiated thyroid cancer is worse after low-activity initial post-surgical 131I therapy in both high- and low-risk patients. *J Clin Endocrinol Metab*. 2014;99(12):4487-4496.
6. Lamartina L, Durante C, Filetti S, Cooper DS. Low-risk differentiated thyroid cancer and radioiodine remnant ablation: a systematic review of the literature. *J Clin Endocrinol Metab*. 2015;100(5):1748-1761.
7. Tian T, Qi Z, Huang S, Wang H, Huang R. Radioactive iodine therapy decreases the recurrence of intermediate-risk PTC with low thyroglobulin levels. *J Clin Endocrinol Metab*. Published online January 30, 2023. doi:10.1210/clinem/dgad045
8. Lee IA, Moon G, Kang S, *et al*. Predictive factors indicative of hemithyroidectomy and close follow-up versus bilateral total thyroidectomy for aggressive variants of papillary thyroid cancer. *Cancers (Basel)*. 2022;14(11):2757.