

Prospective Study Confirms that Radioiodine Remnant Ablation Is Not Necessary in Low-Risk Differentiated Thyroid Cancer

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Differentiated thyroid carcinoma (DTC) accounts for more than 80% of all thyroid cancers. An increasing incidence of DTC over the last decades has been reported worldwide, and is mainly due to the discovery of small papillary carcinomas [1] with an excellent prognosis. Such favorable prognosis may be due to the biological properties of these tumors and/or the effectiveness of the primary therapy [2, 3]: near total thyroidectomy followed by radioactive iodine (RAI) remnant ablation with ¹³¹I.

The aim of postsurgical ablation of the thyroid remnant with RAI is to facilitate the early detection of recurrence based on serum thyroglobulin (Tg) measurement and RAI whole body scan. In addition, RAI ablation may represent an adjuvant therapy by cleaning persistent microscopic foci of cancer, which can be present in the thyroid remnant. While the first aim – remnant ablation – is related to follow-up in any patient regardless of his specific risk, the second one – adjuvant therapy – is advocated as a tool to reduce the rates of disease recurrence or cause-specific mortality [4], and thus its use must be justified according to a real risk of recurrence.

In the past, RAI ablation was indicated in almost every patient with a diagnosis of DTC. Nowadays, careful revision of patients' outcome has introduced the concept or risk-based selection of patient candidates to RAI ablation. The individual risk depends on initial prognostic indicators obtained at surgery and on results of serum Tg measurements and neck ultrasonography obtained after surgery [5]. According to these parameters, the American Thyroid Association (ATA) has defined three groups of

patients with different risk of recurrence [5]. The benefits of postoperative ¹³¹I differs between the following groups:

- *ATA High-Risk Category.* Patients are defined to be at high risk if they have macroscopic extrathyroidal extension, incomplete tumor resection, distant metastases, and postoperative serum Tg suggestive of distant metastases, large-volume lymph node involvement (any metastatic lymph node ≥ 3 cm in largest dimension), and follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion or extracapsular vascular invasion). The published literature supports ¹³¹I ablation for high-risk patients.
- *ATA Intermediate-Risk Category.* This includes patients with lymph node metastases (clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension), intrathyroidal papillary thyroid cancer with a primary tumor of 1–4 cm that is BRAF mutated (if known), and multifocal papillary microcarcinoma with extrathyroidal extension and BRAF mutated (if known). In these patients, the decision to administer ¹³¹I should be individualized according to risk factors such as adverse thyroid cancer histology, lymph node disease outside the central neck, and advancing age.
- *ATA Low-Risk Category.* This includes patients with intrathyroidal PTC without vascular invasion, with or without small-volume lymph node metastases (clinical N0 or ≤ 5 pathologic N1 micrometastases of a few millimeters in size), intrathyroidal encapsulated follicular variant of papillary thyroid cancer or intrathyroidal well-differentiated follicular cancer with capsular or minor vascular invasion (<4 vessels involved), and

intrathyroidal papillary microcarcinomas. In the low-risk category, the risk of disease-specific mortality and of persistent/recurrent disease is so low that it is unlikely to be improved by RAI ablation; therefore, it is not recommended [2, 3, 6, 7]. The same applies to papillary microcarcinoma (<1 cm, uni- or multifocal) in absence of other higher-risk features [8].

While all the previous studies were mostly retrospective in nature and thus submitted to the risk of bias intrinsic to retrospective studies, a recent study by Janovsky et al. [9] in this issue of the *European Thyroid Journal* is the first prospective study to address the utility of RAI ablation in low-risk DTC. Among 550 DTC patients, the authors found 57 patients who were classified as at low risk for disease recurrence according to the ATA stratification, based on the following criteria: a tumor measuring <4.0 cm restricted to the thyroid gland and nonaggressive histology. They had negative Tg antibodies, no family history of thyroid cancer, no history of head and neck irradiation, and no extracapsular involvement. Patients were enrolled in a prospective follow-up study without receiving RAI ablation. They were evaluated during a follow-up period of 36–84 months. Twenty-four patients (42%) had a tumor <1 cm, 25 patients (44%) had a tumor between 1 and 2 cm, and 8 patients (14%) had a tumor >2 cm. Histology was classical papillary thyroid cancer in 31 (55%), a follicular variant of papillary in 21 (38%), an oncocytic variant in 4 (7%), and minimally invasive follicular carcinoma in 1. Twenty-one patients (37%) showed multifocal tumors.

Three months after surgery, all 57 patients presented no evidence of abnormal residual tissues or metastatic lymph nodes on neck ultrasound (US). Fifty-four patients had serum Tg <1 ng/ml and only 3 patients had Tg >1 ng/ml. Six months after surgery, the mean rhTSH-stimulated

Tg was 2.9 ± 3.9 ng/ml. After 18 months of follow-up, all patients had negative neck US and a mean serum Tg level of 0.28 ng/ml (range: 0.10–2.1) without suppressed TSH levels. Tg levels showed a spontaneous drop to undetectable levels in almost all patients. Twenty-four months after surgery, the results showed that the thyroid bed uptake and the stimulated Tg levels were much lower when compared with the first control. At the end of follow-up, very few patients continued to have detectable serum Tg levels, but the temporal trend tended to decline. All neck US scans were negative, and the patients were considered to have no evidence of disease.

Several conclusions can be derived from this study. First, after a rather long follow-up, low-risk patients not submitted to RAI ablation are in complete remission. Second, despite the possible presence of residual thyroid tissue, neck US is highly informative in ruling out the presence of persistent or recurrent disease in the thyroid bed or the lateral neck. Third, even without ablation, Tg levels become undetectable in almost all patients both in the basal condition and after TSH stimulation, thus demonstrating that serum Tg is an informative tumoral marker also in patients not submitted to remnant ablation.

There is no evidence to suggest that postsurgical RAI ablation improves the risk of recurrence in low-risk patients. In these patients, ^{131}I should be administered selectively, based on prognostic indicators and on Tg level, and neck US performed after surgery. The overall risk of persistent disease will be <3% and even lower when serum Tg is undetectable.

Disclosure Statement

The author has nothing to disclose.

References

- 1 Aschebrook-Kilfoy B, Ward MH, Sabra MM, et al: Thyroid cancer incidence patterns in the United States by histologic type, 1992–2006. *Thyroid* 2011;21:125–134.
- 2 Nascimento C, Borget I, Al Ghuzlan A, et al: Persistent disease and recurrence in differentiated thyroid cancer patients with undetectable postoperative stimulated thyroglobulin level. *Endocr Relat Cancer* 2011;18:R29–R40.
- 3 Ross DS, Litofsky D, Ain KB, et al: Recurrence after treatment of micropapillary thyroid cancer. *Thyroid* 2009;19:1043–1048.
- 4 Pacini F, Schlumberger M, Harmer C, et al: Post-surgical use of radioiodine (^{131}I) in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report. *Eur J Endocrinol* 2005;153:651–659.
- 5 Haugen BR, Alexander EK, Bible KC, Doherty G, Mandel SJ, Nikiforov YE, Pacini F, Randolph G, Sawka A, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward D, Tuttle RM, Wartofsky L: 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2015, Epub ahead of print.
- 6 Schwartz C, Bonnetain F, Dabakuyo S, et al: Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients. *J Clin Endocrinol Metab* 2012;97:1526–1535.
- 7 Rosario PW, Mourão GF, Siman TL, et al: A low postoperative nonstimulated serum thyroglobulin level excludes the presence of persistent disease in low-risk papillary thyroid cancer patients: implication for radioiodine indication. *Clin Endocrinol (Oxf)* 2014, Epub ahead of print.
- 8 Baudin E, Travagli JP, Ropers J, et al: Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. *Cancer* 1998;83:553–559.
- 9 Janovsky CCPS, Maciel RMB, Camacho CP, Padovani RP, Nakabashi CC, Yang JH, Malouf EZ, Ikejiri ES, Mamone MCOC, Wagner J, Andreoni DM, Biscolla RPM: A prospective study showing an excellent response of patients with low-risk differentiated thyroid cancer who did not undergo radioiodine remnant ablation after total thyroidectomy. *Eur Thyroid J* DOI: 10.1159/000442048.