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EDITORIAL COMMENTARY

A low thyroglobulin level cannot be used to avoid adjuvant ^{131}I therapy after thyroidectomy for thyroid carcinoma

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Thyroglobulin (Tg) measurements are the mainstay of the follow-up of patients with differentiated thyroid cancer. Reports of patients with a negative ^{131}I whole-body scan (WBS) and positive Tg are common. Much less common are reports of patients with a positive ^{131}I scan and negative stimulated Tg levels.

In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Park and colleagues [1] report a retrospective analysis of 824 consecutive patients with differentiated thyroid cancer who received ^{131}I treatment, either in the postsurgical ablation setting or as repeat therapy for various reasons. They found that 52 patients (6.3%) had negative serum Tg levels despite the presence of residual/recurrent thyroid cancer, identified by therapeutic ^{131}I WBS. The disease was localized to cervical or mediastinal lymph nodes in the majority of patients, but seven patients had distant metastases to the lungs or bones. The authors excluded from the study those patients with high titres of anti-Tg antibodies (Tg Abs), as well as those in whom TSH levels in the hypothyroid state were lower than 30 mIU/l. Tg measurements were reassessed using several kits so as to verify that Tg negativity is not due to technical problems.

Park et al. [1] considered as negative a stimulated serum Tg level of ≤2 ng/ml with a Tg Ab level of <100 U/ml. Although recent Tg diagnostic tests may have much better sensitivity [2], the cut-off chosen by the authors (2 ng/ml after thyroid hormone withdrawal) is an appropriate trade-off between sensitivity and specificity for the detection of recurrent disease [3]. For patients submitted to rhTSH stimulation, a more appropriate Tg threshold would be 1 ng/ml [3]. As for Tg Abs, the cut-off of 100 U/ml for patient exclusion may seem more arbitrary. Some authors [4] consider that Tg measurements are not reliable in patients with detectable Tg Abs, regardless of the level.

Among the 52 patients with suspicious ^{131}I foci and negative Tg, many were identified in the setting of postsurgical ^{131}I ablation WBS. Thus, the study by Park et al. [1] points to the importance of postsurgical ^{131}I ablation. A limitation of the study is that in the majority of patients no guided biopsy of ^{131}I foci was obtained. So one cannot formally exclude the possibility that some of these patients may have had residual noncancerous thyroid tissue located outside the thyroid bed, for example substernal goitre or ectopic foci along the thyroglossal duct [5].

Postoperative ^{131}I therapy is currently widely recommended as adjuvant therapy in patients with differentiated thyroid cancer, especially in high-risk patients [6, 7]. Ablation allows the discovery of metastatic foci at an early stage, improves the sensitivity and specificity of Tg measurements during follow-up and probably reduces the recurrence rate by killing occult micrometastases and clusters of cancer cells too small to be detected by modern gamma cameras [6, 7].

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It has been shown that Tg levels before ablation may have a prognostic value for the risk of metastatic disease [8, 9]. However, one important message of the study by Park et al. [1] is that Tg levels cannot be used to decide whether postsurgical ablation should be performed or not. This is in agreement with other data showing that the number of patients with lung or bone metastases can be discovered during ^{131}I ablation even in the presence of low or nonsuspicious Tg levels and negative radiological studies [10–12]. At this stage, a complete remission can be obtained using a limited number of ^{131}I courses; hence the importance in clinical practice of not relying on Tg alone. In the present study by Park et al. [1], after repeated treatment with ^{131}I, metastatic disease, mostly in lymph nodes, disappeared in 70.2% of Tg-negative patients, was ameliorated in 8.5% and remained stable in 21.3%. No patient experienced progression. This confirms that ^{131}I is a highly effective therapy in iodine-avid metastases.

One factor that has helped adjuvant ^{131}I therapy gain wide acceptance is its relative safety. Lacrimal and salivary gland damage is usually transient and is almost never a serious problem [7]. Rubino et al. [13] have estimated an excess absolute risk of 0.8 leukaemia cases per GBq of ^{131}I and 10^5 person-years of follow-up. Based on this estimate, in a group of 100 patients having received an ablation activity of 100 mCi and followed-up for 10 years, 0.03 cases of leukaemia would be expected. Moreover, it should be noted that these estimates were obtained by extrapolation from much higher activities (>22 GBq; 600 mCi) that are used for the treatment of patients with lung and/or bone metastases (sometimes in association with external beam radiotherapy); no increase in leukaemia has been reported for the usual ablation doses. Considering the excess in solid cancers, and the type of tumours concerned, the data are highly divergent in the literature. Some authors [13] have reported a link between ^{131}I therapy and some solid cancers, which has not been confirmed by other studies [14].

The study by Park et al. [1] underlines the limitations of basing follow-up solely on Tg measurements. In 15–20% of patients, Tg results are unexploitable due to the presence of Tg Abs [4, 15]. Low Tg levels in the presence of residual thyroid cancer tissue may be found if the tumour burden is small [16], if the cancer is aggressive or poorly differentiated with a low Tg secretion capacity [17], or if the circulating Tg is a form variant that has reduced recognition by routine radioimmunoassays [17].

Since Tg cannot safely be used as a single marker for residual disease, a major issue would be how to verify that a patient is free of residual disease 4 to 6 months after total thyroidectomy and ^{131}I ablation. Neck ultrasonography (with additional guided fine-needle biopsy and/or aspiration for Tg measurement) now plays an important role in the follow-up of patients with differentiated thyroid cancer. Therefore, it would have been interesting to know the results of neck ultrasonography in the population described by Park et al. [1]. The complementary role of nuclear imaging should not be minimized [18]. This is particularly important in high-risk patients (such as patients of any age with T4 tumours, but also patients older than 45 years with T3 tumours, lymph node metastases with extracapsular extension, or aggressive histology subtypes). These patients still require nuclear imaging as part of the first follow-up examination after ablation, which can be done using either ^{131}I or ^{123}I isotopes coupled to WBS and SPECT-CT, or the positron emitter ^{124}I with PET-CT. Alternatively, the use of a second therapy dose of ^{131}I, coupled to a posttherapy scan, may also be justified in the management of high-risk patients. Finally, the role of ^{18}F-FDG PET-CT in high-risk patients with elevated Tg levels has been underlined by many authors [19].

In conclusion, low levels of Tg should not be used to indicate that ^{131}I ablation should not be performed. Moreover, the limitation of Tg as a single marker for follow-up calls for the use of complementary diagnostic tools. The role of nuclear medicine modalities should not be minimized, especially in high-risk patients.

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