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EDITORIAL COMMENTARY

Less is more: reconsidering the need for regular use of diagnostic whole body radioiodine scintigraphy in the follow-up of differentiated thyroid cancer

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Changes in thyroid cancer epidemiology and management

By far, differentiated thyroid cancer (DTC) is the most common form of thyroid cancer (TC) accounting for about 90% of all TC in most industrialized countries [1]. Incidence has increased throughout the world during recent decades and is mostly attributed to an increase of very small (<10 mm in maximum diameter) to small tumors [1, 2]. The widespread use of imaging technologies, namely ultrasound for the work-up of nodular thyroid disease and TC screening have been identified as probable causes of this epidemiological trend [3].

In general, survival rates of DTC are very high, reaching up to more than 95% over long term periods (> 10 year observation) [4]. Recurrence rates vary considerably dependent on patient age at initial presentation, histology, primary tumor size, the presence of lymph node, or distant metastases, which all are integrated into postoperative staging systems (TNM, AJCC/UICC) [5].

Over the years (near-)total thyroidectomy has evolved as the standard of care in many countries worldwide also for very low and low risk patients, i.e. intrathyroidal papillary carcinoma with a tumor diameter < 40 mm and the absence of clinical manifested lymph node metastasis [6]. However, the shift in favor of the use of thyroidectomy has been questioned, and lobectomy is recommended as the initial surgical strategy by the American Thyroid Association (ATA) and the German guidelines for low risk DTC patients [5, 7].

Impact of thyroid cancer epidemiology on patient follow-up

Changes in thyroid cancer epidemiology, clinical assessment, and surgical strategies make it necessary to reassess regularly follow-up guidelines with respect to their diagnostic and prognostic value and their utility in clinical routine.

Recently, modified follow-up procedure guidelines have been issued by ATA with respect to the changes in surgical strategies, patient population, and risk stratification based on imaging, biochemical, and genetic factors [5]. This concept is titled dynamic risk stratification acknowledging the fact that initial risk estimates may change over longer periods of time [5].

In principle, all follow-up strategies for DTC are based on neck ultrasound examinations and the measurement of i. endogenous and preferably exogenously stimulated thyroglobulin (Tg) using an assay which is calibrated against CRM 457 standard and ii. anti-Tg antibodies.

Patients with DTC usually get periodic, often life-long reexaminations after the primary tumor therapy as this is done for any other oncologic entity aiming to detect as soon as possible non- or partial responders or early recurrences, but also to reassure their "disease-free state". In the case of DTC the great majority of patients have their remission confirmed.

The role of the diagnostic whole body radioiodine scintigraphy in the follow-up of DTC

There is no consensus about the indications for the routine use of the diagnostic whole body radioiodine scintigraphy

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(DxWBS) in the follow-up of DTC patients. Many studies demonstrated that the DxWBS usually is no longer necessary in low and intermediate risk patients with negative post-therapeutic radioiodine (RAI) scan, if complete response to therapy was achieved [8, 9]. In contrast, the DxWBS may have a role in the follow-up of patients with high or intermediate risk (and higher risk features) of persistent disease especially in the following clinical settings: 1. patients with abnormal uptake outside the thyroid bed on post-therapeutic WBS, 2. patients with poorly informative post-ablation RAI WBS due to extensive thyroid remnants, and 3. patients with anti-Tg antibodies, which put them at an increased risk of false-negative Tg measurements [5]. However, post-therapeutic RAI whole body hybrid imaging using SPECT/CT can already resolve many equivocal findings [10] reflecting the fact that this technique is superior in terms of diagnostic accuracy to planar imaging in DTC [11].

While ATA [5] and the British Thyroid Association [12] do not see a general role of DxWBS in the follow-up of most DTC patients, this is not the case in other countries, e.g. in Germany and Austria. In agreement with the national guidelines clinical practice includes a widespread use of DxWBS [13]. Of interest, Germany and Austria are among those countries in which nuclear medicine physicians are predominantly taking care of the management of thyroid cancer patients. With this regards the use and acceptance of DxWBS might reflect the adherence of nuclear medicine specialists to (diagnostic) techniques which they perform and interpret themselves.

The study of Gonzalez Carvalho et al. from Münster in Germany adds another piece of evidence to the debate on the follow-up of DTC patients studying retrospectively a large of cohort of 1420 subjects in all TNM risk categories [14]: Patients after total thyroidectomy and RAI ablation were followed up by sequential DxWBS performed as early as at 3 months after RAI ablation and in 1-year intervals up to four times thereafter adding up to more than 4000 DxWBS. The long follow-up period (up to 25 years) and the simultaneous assessment of basal and stimulated thyroglobulin levels were major strengths of this study. More than 580 DxWBS were done to document successful ablation of surgically cured patients, only. Out of 1420 patients, 31 exhibited a negative initial DxWBS, but developed a positive DxWBS later on, mostly due to LN or pulmonary metastasis. However, 64% of them achieved complete remission and disease specific mortality was very low. The authors concluded very prudently that follow-up DxWBS might be omitted if once WBS is negative and stimulated Tg is below the functional sensitivity in the absence of thyroglobulin antibodies. In summary, this study demonstrated that DxWBS i. is less accurate when performed 3 months as compared to 12 months after RAI ablation, ii. was mostly in agreement with the findings of basal (with a cut-off level of 2 ng/mL for the categorization normal/pathological) or stimulated Tg measurements, and iii. resulted infrequently in further RAI treatment.

Perspectives for the future

The era of precision medicine is linked to more individualised care of cancer patients. In TC genetic markers like BRAFV600E [15] and TERT promoter mutations [16] have improved our understanding of tumor biology and already been integrated clinically into risk stratification.

Surgical strategies, i.e. lobectomy or (near-)total thyroidectomy with or without prophylactic central lymph node dissection will be tailored to the individual risk and increasing patient demands with respect to low morbidity and complication rates, i.e. permanent hypoparathyroidism, shorter hospital stay and cosmetic outcome while maintaining high quality standards which are linked to surgical volume [17].

The indications for RAI ablation will be better defined in low-risk patients on the basis of ongoing prospective studies for the wide range of possible or probable indications as given in the ATA and EANM guidelines [5, 18].

The changes in thyroid cancer epidemiology with a predominance of small tumors and their effective surgical management suggest that the routine and repetitive use of DxWBS in the follow-up of DTC should be abandoned. A follow-up strategy restricted to neck sonography and measurement of (rhTSH) stimulated thyroglobulin seems to provide adequate care im terms of long-term survival for the great majority of DTC patients after successful surgery and radioiodine ablation avoiding numerous DxWBS.

In patients with structural disease after RAI ablation and/or high risk histological and molecular features setting them at persistently increased risk for recurrence after surgical intervention and radioiodine ablation early risk stratification using FDG PET/CT might yield more information for their future management [19].

Compliance with Ethical Standards

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Conflict of interest Christian Pirich and Gregor Schweighofer-Zwink declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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