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EDITORIAL

Postoperative serum thyroglobulin and neck ultrasound to drive decisions about iodine-131 therapy in patients with differentiated thyroid carcinoma: an evidence-based strategy?

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Currently a trend towards "de-escalating" the role of adjuvant iodine-131 (^{131}I) in the treatment of differentiated thyroid cancer can be observed in the community of clinical thyroidology. This trend is however in many respects not based on hard facts but rather an overstretched interpretation of studies not performed with the intention of allowing the derivation of such statements as we and others previously underlined. Given the indolence of thyroid cancer, relative to some other malignancies, outcome measures can only be assessed in the long term. The benefits linked to avoiding adjuvant radioiodine (RAI) therapy in terms of cost or side-effects of treatment should be measured in the long-term considering potential benefits from dynamic re-stratification and reduced surveillance, early detection of residual disease or reduction in the risk of recurrence and associated costs [1]. Finally, different strategies need also to be compared as regards to their ability at providing early reassurance (or counseling) about long-term prognosis and to properly inform the follow-up's "intensity" [2, 3]. Measurement of serum thyroglobulin (Tg) and neck ultrasound (US) examination were recently proposed as yardsticks for postsurgical management of DTC patients with special emphasis on indications for RAI therapy [4]. The present paper was specifically undertaken to analyze the role and limits of serum Tg and neck US to assess DTC patients after surgery and inform decisions about post-operative RAI administration.

Postoperative thyroglobulin measurement

Although postoperative serum Tg measurement can provide valuable information with regard to the likelihood of achieving remission or having persistent or recurrent disease in response to an initial therapy, its predictive value (both negative and positive as regards residual disease) is significantly influenced by a wide variety of factors, as follows: the amount of residual thyroid cancer and/or thyroid remnants, the TSH level at the time of Tg measurement, the functional sensitivity of the Tg assay, the time elapsed since total thyroidectomy, the Tg cutoff used for analysis, and the individual risk of having radioiodine-avid loco-regional or distant metastasis [5, 6]. The fundamental role of Tg measurement in the monitoring of DTC implies the need for high-quality Tg assays. A major problem that still hampers accurate Tg measurement is the interference in the Tg assay by Tg antibodies (TgAb) and heterophile antibodies (HAb) resulting in either an under- or overestimation of the serum Tg concentration. Immunometric Tg assays may also be subject to high-dose hook effect, leading to inappropriately normal or low serum Tg values in sera with very high Tg concentrations, which require dilution for accurate measurement [5–7]. Additionally, undetectable serum Tg became detectable in a significant percentage of DTC patients by changing assays, suggesting that in some patients a decreased immunologic reactivity and/or structural changes of the Tg molecule caused the undetectable Tg levels

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[8]. In general, thyroid hormone withdrawal postoperative Tg values of about 10 ng/mL achieve the best balance of sensitivity and specificity for predicting recurrent or persistent disease over time and poorer survival [9, 10]. Notably, as such results were obtained in patients treated with RAI following thyroidectomy, they cannot be translated to those patients treated by surgery alone and used to decide for/against post-surgical radioiodine administration. Indeed, some studies not only excluded patients with anti-Tg autoantibodies from analysis, but also excluded patients showing evidence of extra-cervical metastases [11], introducing additional selection bias as regards translation of the data. Vaisman and colleagues proposed to skip radioiodine ablation in patients with low-risk DTC treated with selective central compartment neck dissection having serum rhTSH-stimulated Tg levels from <1 to 5 ng/mL measured 3 months after thyroidectomy with negative neck ultrasound and TgAb, respectively [12]. However, central neck dissection is not recommended in most DTC patients due to its not negligible morbidity. Moreover, the authors monitored their patients by repeating Tg measurement after stimulation with recombinant human thyrotroin (rhTSH) while costly rhTSH stimulations are no longer recommended in low to intermediate risk patients treated with RAI [5, 13].

All in all, the reason to risk iatrogenic damage and to perform multiple rhTSH stimulations just to avoid RAI ablation is at least debatable in our opinion. Notably, RAI-avid tissue with a corresponding undetectable stimulated serum Tg is detected in up to 20% of DTC patients by post-treatment RAI whole body scan (WBS). Moreover, up to 6% of such patients had confirmed loco-regional or distant metastases in addition to thyroid tissue remnants [14]. In a retrospective study, Matrone and colleagues [4] reported on 505 low- to intermediate-risk DTC patients who had undergone total thyroidectomy and rhTSH–aided ablation with 1.1 GBq RAI. Just before ablation, a neck US was performed and Tg levels on thyroxine were measured using a high sensitive assay (i.e. functional sensitivity of 0.1 ng/mL). A planar post-treatment whole-body scan (PT-WBS) was performed and compared with pre-ablation basal Tg and US assessments. Among the main findings, 150 patients had Tg levels less than 0.1 ng/mL and 1 of 150 showed cervical persistence of disease; 287 patients had Tg levels between 0.1 and 1.0 ng/mL, 15 of whom had nodal or distant metastases; and 68 patients had Tg levels exceeding 1.0 ng/mL, 11 of whom had neck metastases. Notably, in the several patients with lung metastases the basal Tg was 0.11 ng/mL, 0.12 ng/mL, and 0.94 ng/mL, respectively, and basal Tg of 0.75 ng/mL was measured in one additional case of bone metastasis, the paper brings evidence that basal Tg < 1 ng/mL cannot be used to rule out the presence of distant metastases. Furthermore refering to patients with residual disease, the authors acknowledge that analyzing the basal Tg values in 27 DTC cases with structural disease; no significant differences between those with only LN and those with distant metastases were found. Finally, the authors contend radioiodine administration would be useless in patents with basal Tg < 0.1 ng/mL for which no "abnormal" uptake was identified on post-therapy scan. However, two of the four patients with distant metastases had Tg levels of 0.11 ng/mL and 0.12 ng/mL, respectively. Considering the 95% confidence interval that should have been attached to these results, the authors' confidence in making safe recommendations is debatable at best. Additionally, in order to have low postoperative Tg levels the importance of "more complete" thyroidectomy was underlined. However, dedicated endocrine surgeons know that small amounts of post-surgery thyroid remnant are often associated with delicate neck structures and, accordingly, a high-rate of surgery-related complications (7.9% permanent hypoparathyroidism and 1.4% permanent cord palsy) was observed in Matrone's series. Recently, Schlumberger et al. reported 5-year outcomes of ESTIMABL1, a randomised trial comparing four strategies of radioiodine (^{131}I) administration following thyroidectomy in low-risk thyroid cancer. In this study, the rate of patients with persistent structural disease at ablation was similar in the three subroups of stimulated Tg ranges (i.e. ≤1 ng/mL, >1 to ≤5 ng/mL and > 5 to <10 ng/mL, respectively) [15]. In summary, with regard to decision-making on the need for postoperative RAI administration, it appears that the serum Tg value will be more helpful in identifying patients for whom the administered activity should be high, rather than in identifying patients that do not require ablation.

Postoperative neck ultrasound

Neck ultrasound (US) is an established cornerstone in preoperative evaluation of DTC patients and their follow-up after treatment. However, it remains a highly operator-dependent imaging technique and no convincing inter-observer reproducibility studies have yet been reported. Accordingly, the overall accuracy of US after primary treatment is far from optimal [16]. Even more relevant, the early use of US after surgery, especially to inform RAI administration, is not clearly defined yet and should be balanced with a lack of strong evidence for any clinical benefit, yielding highly controversial results. First, the involvement of central nodes on pathological examination is a common feature associated with higher recurrence rate. However, preoperative neck US has limited sensitivity at predicting positivity of central nodes. Second, some locations such as the lower VI area, the mediastinum, and the retro-pharyngeal locations, escape the US field of view. Third, US has a rather low sensitivity in the early postoperative time, especially in the central compartment, precluding its reliable use before 3 to 6 months to decide if RAI is indicated or not in low/intermediate risk patients after surgery. Deferring the decision to treat at 6 to 12 months may be at risk

for some patients, which is not acceptable considering that US is also suboptimal to identify disease persistence [17]. Fourth, neck US identifies three classes of results, quoted as normal, suspicious and indeterminate. Both the second and third results will generate additional imaging, biochemical testing and fine needle cytology/Tg washout determinations, cause of concern for the patients and additional costs for the health care system. Indeed, when measured, the false positive results of early post-surgery US are extremely high, often >50%, especially in low risk patients [18]. On the other hand, suspicious cervical nodes detected after surgery do not resolve spontaneously in most cases, justifying long-term follow-up with US [19], while RAI ablation would have solved the problem in the short term, offering rapid and precise risk stratification, thus reducing the need for follow-up examinations. All in all, the average costs for the surveillance were recently reported to be of 1225 $ (low risk) and 1760 $ (intermediate risk), respectively, for a 3-year follow-up period [20]. Indeed, the relationships between the US mapping and the Tg detectability are far from simple, especially for cervical persistent/recurrent disease. Clearly, small nodules mapped using post-surgery US may be normal tissue remnants or persistent nodes, with no significant change in Tg values because persistent nodal involvement often represents a small tumor burden. For instance, mean LT4-Tg levels were found to be not significantly different in patients with suspicious versus indeterminate lesions at post-surgery US, suggesting that this association had limited additional value to help decision making [21]. Overall, because US is unable to detect residual small or poorly located lymph node metastases, a higher rate of postoperative recurrent/persistent disease is expected, especially when surgery is not extensive, a rather routine risky practice as compared to the RAI related hazards, which are negligible using low activities in low-risk patients.

RAI offers distinct advantages

The application of RAI which encapsulates the integration of diagnostics and therapeutics (i.e. theranostics) enables individualized management of thyroid cancer patients. Depending on risk-groups, postoperative RAI therapy has different objectives: remnant ablation (i.e. elimination of postoperative normal thyroid tissue), adjuvant RAI therapy (i.e. elimination of infra-radiologic residual disease in the neck or other occult micro metastases predicted by histopathologic risk factors) or RAI treatment (i.e. elimination of known iodine-avid regional and/or distant metastases). In some instances, a preablation diagnostic scintigraphy can be proposed for guiding the optimal RAI activity to be delivered. The information obtained from diagnostic WBS and SPECT/CT regarding the presence of iodine-avid regional and/or distant metastases can be very useful to properly inform RAI treatment and to plan it. Diagnostic WBS and SPECT/CT imaging can identify bulky regional metastatic disease in unexplored neck compartments which can lead toward reoperation before RAI therapy. Additionally, the integration of diagnostic WBS with SPECT/CT imaging prior to RAI administration is able to identify regional and distant metastases [22]. This information in conjunction with the results of stimulated Tg levels led to a change in management for 31% of patients, as compared to proposed management predicated on histopathology findings alone [23]. Finally, identification of iodine-avid distant metastases on diagnostic WBS scans can guide prescription of high RAI activity, usually ≥7.4 GBq, based on clinical dosimetry protocols which determines maximum tolerated activity (MTA) delivering blood radiation absorbed dose ≤2Gy [24]. Regarless of how RAI therapy is performed, it allows early diagnosis and treatment of residual disease and reduces the risk of recurrence. Importantly, when patients had received RAI ablation with no signs of persistent disease, they could be fully reassured and not require thyroglobulin stimulation tests or periodic neck ultrasound examination during follow-up [2].

Conclusions

Basing on above reported data the current fashion of obviating RAI based on a negative post-operative US and low serum Tg value is not yet supported by the literature and should be investigated using well designed prospective studies with clear-cut endpoints. In our opinion, the evolution of thyroid cancer management cannot pass through a substitution of RAI by serum Tg measurement and neck US but by an appropriate use of radioiodine theranostics. This will also need to develop basic and clinical research programs that bring together physicians from various specialties.

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Compliance with ethical standards

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