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EDITORIAL

Changes and open issues in the management of differentiated thyroid carcinoma: an overview

Markus Luster · Theresia Weber · Frederik A. Verburg

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Abstract Many of the topics briefly addressed in this article are discussed more extensively in this issue of *Clinical and Translational Molecular Imaging* by distinguished colleagues from all fields related to the care of differentiated thyroid cancer (DTC) patients. Several open issues in the management of DTC are fueled by the progress that has been made in the past decade, which is an indication of the liveliness of this scientific field. Aside from some remarkable results achieved in basic and clinical research, the greatest improvements and achievements in this field in recent years concern truly multidisciplinary research and patient-oriented guidelines. These should pave the way for future initiatives to build on the advances achieved in DTC care in the recent past.

Keywords Thyroid cancer · Radioiodine · Cancer management · Treatment · Follow-up

The incidence of differentiated thyroid cancer (DTC) has increased considerably over recent decades, a trend considered to be driven mainly by improved diagnosis (linked to the more frequent use and methodological improvements of neck ultrasound) [1]. Nowadays, smaller malignant lesions, representing earlier stages of differentiated papillary type (PTC) and—to a considerably lesser extent—follicular type (FTC) cancers, make up a much larger proportion of the total number of newly diagnosed DTC cases than they did in the past. These tumors frequently affect younger (under the age of 45), predominantly female, patients who, if treated adequately, mostly have a normal life expectancy [2, 3].

As a consequence, the great challenge today is to prevent "overdiagnosis" and potential "overtreatment" in a bid to reduce the risk of potential side effects of therapy, yet without overlooking more aggressive variants of the disease which require a more intensive follow-up and often need multidisciplinary management.

Globally, the age-standardized incidence rate of thyroid cancer is approximately 16 patients per 100,000 individuals in the general population. In contrast, the age-standardized mortality from thyroid cancer is <2 patients per 100,000 individuals.

Thus, the prognosis of DTC is excellent, with 10-year overall survival rates exceeding 90 % after up-to-date treatment (expert surgery often followed by adjuvant ^{131}I ablation). Even though relapse is a relatively rare occurrence after adequate treatment [4], it is certainly not unheard of and the fear of relapsing may have both medical implications and a considerable impact on patients' quality of life, in the sense that this fear will stop many patients from achieving the peace of mind they long for [5].

Questions regarding the appropriate surgical approach to adopt—lobectomy versus thyroidectomy and whether or not to perform central lymph node dissection—continue to be intensely debated in the literature [6]. The goal of prophylactic central neck dissection is to improve long-term regional disease control and/or survival. Whether the procedure achieves this goal is an unresolved issue on

M. Luster (✉)
Department of Nuclear Medicine, Ulm University Hospital, Albert-Einstein-Allee 23, 89081 Ulm, Germany
e-mail: Markus.luster@uniklinik-ulm.de

T. Weber
Department of Surgery, Ulm University Hospital, Ulm, Germany

F. A. Verburg
Department of Nuclear Medicine, Aachen University Hospital, Aachen, Germany

which thyroid surgeons are divided, as shown by the inconsistent recommendations in the published national and international guidelines [6, 7]. There does, however, appear to be a general consensus that modified radical neck dissection of the lateral compartment should be reserved for patients with known lymph node (LN) metastases.

Locoregionally metastasizing disease of variable extension is frequent, especially in patients with PTCs. Reported incidences range from 35 % to more than 70 % in different series and regional recurrence is comparatively common. Patient's age and the presence of grossly enlarged lateral cervical nodes appear to be determining factors for the risk of recurrence in this patient group. Detection of LN involvement may depend, among other contributing factors, on the extent of LN surgery, but it is also related to the size of the primary tumor [8, 9].

It has been shown that diagnostic or post-therapeutic ^{131}I SPECT/CT of the neck has a complementary value to planar imaging in the scanning of DTC patients [10].

As general recommendations, more "aggressive" procedures should be performed by "experienced hands" and potential complications of cervical LN dissection, e.g., temporary/permanent hypoparathyroidism and/or recurrent inferior laryngeal nerve injury, must be weighed up against the possible benefits.

Pre-therapeutic imaging after the application of a diagnostic activity of ^{131}I (i.e., exceeding 10–20 MBq) before radioiodine treatment may result in a reduced uptake of the subsequent therapeutic activity, a phenomenon that is also referred to as "stunning" [11, 12]. Therefore, the use of ^{123}I or the PET tracer ^{124}I should be preferred if pre-therapeutic scanning for assessment of iodine avidity and the extent of disease is required.

Since the first application of radioiodine for the treatment of differentiated thyroid cancer, post-surgical thyroid ablation has become a standard of care in most centers. The rationale for thyroid remnant ablation is mainly to eradicate microfoci of cancer tissue which might be a reservoir for future recurrences. However, after 70 years of practice, physicians have still not reached a consensus on the indications, the amount of radioiodine to be administered, or the method of preparation for ablation. The indications for radioiodine ablation have been reassessed in current guidelines and a general notion has evolved that candidates for adjuvant therapy should be selected on the basis of their individual risk of recurrence [6, 13, 14].

It is commonly accepted that patients at high risk of recurrence or thyroid cancer-related death will benefit from radioiodine treatment; whereas so-called low-risk patients (i.e., with tumors $\leq$1 cm and without lymphatic or distant metastatic spread) should definitely be spared this modality. Instead, the value of radioiodine treatment in patients falling in between these two groups (i.e., in those at intermediate risk) has not been unequivocally established; however, many of these patients may benefit from radioiodine therapy, whereas others would probably do (equally) well without adjuvant therapy after surgery. In 2008, Sawka et al. [15] demonstrated in their meta-analysis that ^{131}I remnant ablation is significantly important in avoiding recurrence and later metastatic disease.

The quantity of ^{131}I to use is another open issue. Until recently, fixed activities of 3.7 GBq or more were routinely administered, but there is growing evidence that lower amounts of the radioactive compound can, alternatively, be used in certain subgroups; this suggestion is based on the finding that short-term results of radioiodine therapy with lower activities appear to be equivalent to those obtained using higher activities [16, 17].

Similarly, the concept that thyroid ablation should be performed after thyroid hormone withdrawal (THW) has been questioned in favor of the use of exogenous stimulation with recombinant human TSH (rhTSH), which in several studies has been found to be equivalent to THW both when using high and low radioiodine activities [16–19].

In radioiodine therapy for persistent or metastatic disease, the activity actually administered is chosen on the basis of a physician or institution's estimation of the amount of radioiodine needed to deliver the highest safe radiation dose (to neoplastic foci), taking into account the patient's tumor burden, amount of remnant tissue, age, etc.

Chiesa et al. [20] described important changes in tumor/lesion biokinetics in patients undergoing multiple courses of treatment for persistent disease accompanied by a loss of therapeutic efficacy along the sequence of fixed activity administrations.

The rationale underlying individual dosimetry is to calculate the amount of ^{131}I to use and the resulting absorbed dose to iodine-avid thyroid tissue, which must be maximized for each patient while avoiding bone marrow toxicity, pulmonary fibrosis, and other potential side effects [21]. An alternative approach for treating the advanced stages of DTC is to establish and use the activity that is as high as safely administrable (AHASA), i.e., that delivers an absorbed dose of 2 Gy to the organ at risk, i.e., the bone marrow; in practice, the blood dose is used as a surrogate parameter [22].

Finally, the most frequent permanent side effect of (repeated) radioiodine therapy is xerostomia due to chronic sialadenitis, sometimes leading to a loss of taste and an increased risk of caries. The value of salivary gland stimulation, using lemon juice or sour drops for example, remains unclear, as does the optimal timing of such "interventions" [23, 24].

The definition of "iodine refractory thyroid cancers" is becoming increasingly relevant since the recent advent of new therapeutic agents for patients suffering from

advanced PTC or FTC, or poorly differentiated cancers that are unresponsive to radioiodine treatment [25]. The estimated incidence of local recurrent or metastatic DTC is 4,000 patients per year in Europe, and it usually carries a poor prognosis. No conventional chemotherapies have shown long-term success, prompting an intensive search for novel options for this demanding subgroup of patients. A minority of patients with a mixed response to ^{131}I, who may have developed resistant clones over time, also require a different therapeutic intervention. The loss of sodium/iodide symporter (NIS) expression (an essential biological function) is correlated with tumor aggressiveness and often mirrored by increased glucose consumption, as demonstrated in FDG PET/CT scanning [26, 27].

Redifferentiating agents have been tested in multiple trials, but none of these compounds has entered clinical routine [28], although the novel agent selumetinib was recently shown to re-induce therapeutically meaningful ^{131}I uptake in 40 % (8/20) of patients [29]. Most of the new drugs being developed for the treatment of ^{131}I-refractory DTC are agents targeted to molecular pathways thought to be critical for tumor growth [30]. In nearly all cases of PTC, genetic defects involving the RET, RAS, and RAF protein kinase signaling cascade are identified; however, the genetic mechanisms underlying FTC are less clear [31].

Questions related to patient selection, patient-relevant endpoints, and the potential duration of treatment with these many new therapeutic compounds are still open and should be the prime considerations in designing new trials.

Many of the topics briefly addressed above are discussed more extensively in this issue of *Clinical and Translational Molecular Imaging* by distinguished colleagues from all fields related to the care of DTC patients. Several open issues in the management of DTC are fueled by the progress that has been made in the past decade, which is an indication of the liveliness of this scientific field. Aside from some remarkable results achieved in basic and clinical research, the greatest improvements and achievements in this field in recent years concern truly multidisciplinary research and patient-oriented guidelines. These should pave the way for future initiatives to build on the advances achieved in DTC care in the recent past.

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