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REVIEW

Radioiodine treatment of well-differentiated thyroid cancer

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Introduction

Radioiodine has been an essential and well-accepted therapy for patients with well-differentiated thyroid cancer (WDTC) ever since the first report in 1946 [1]. The following discussion of the use of radioiodine in the treatment of WDTC will first define the difference between "ablation" and "treatment," provide descriptions of disease staging, the indications for, and objectives of, ablation and treatment, the two principal methods for selection of a dosage of radioiodine for ablation and treatment and end with a review of the recommendations for the use of radioiodine for ablation and treatment from our professional organizations in Europe and the USA.

Definitions

Ablation refers to the first administration of radioiodine to a patient with WDTC. Usually, this dose is administered within 4–6 weeks after total thyroidectomy. Because some thyroid tissue is usually present in the neck even after total thyroidectomy, optimal follow-up is achieved following the ablation or destruction of this normal residual thyroid tissue. Other objectives of ablation are discussed below in the "Objectives of radioiodine ablation and treatment" section. The term "Treatment" applies subsequently, when there is evidence of residual and the distinction in the definitions aids in physician to physician communication of the therapeutic interventions. While most endocrinologists use the term "dosage" to apply to the amount of radioiodine administered, the more appropriate term is "activity". Rather, "dosage," should be used to express the amount of the radiation absorbed dose in rads or grays administered to the patient.

Staging

A large number of staging systems currently exist including the AMES (Age, Metastases, Extent of tumor, and Size of tumor), TNM (Tumor, Node, Metastases), Ohio state scoring system, AGES system (Age, Grade of histology, Extent, Size of tumor), MACIS system (Metastases, Age, Completeness of resection, Invasion, Size of tumor), and NTCTCS system (National Thyroid Cancer Treatment Cooperative Study). The TNM system was developed by the American Joint Commission on Cancer (AJCC) and is used by the American Thyroid Association (ATA) for the management guidelines for WDTC. The European Consensus did not use "stages" but used levels of risk, i.e., "very low," "low," and "high" which are defined below.

Approaches for the selection of radioiodine dosage (activity) for ablation or treatment

A dosage of radioiodine may be selected by one of two methods: empiric or dosimetric. Empiric therapy applies to the administration of a fixed dosage of radioiodine [2–7] based typically on the physician's experience and modified by that physician's weighting of various factors such as (1)

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whether the dose is for ablation versus treatment, (2) the extent and grade of tumor, (3) age of the patient, (4) the presence of distant metastases, and (5) whether the patient is a child or adult.

Empiric selection of a fixed dose has the advantages of (1) ease of dosage selection, (2) a long history of use, and (3) a reasonably acceptable frequency and severity of complications. Empiric dosage is much simpler and less costly in both time and expense, eliminating of the multiple venapunctures and blood counting and the diagnostic and/or dosimetric scans required by dosimetry. Note that the value of pre-ablation or pre-treatment scans before the administration of an empiric fixed dosages remains controversial [8–14]. In our view, the major weakness of the empiric approach is its failure to determine whether or not the dose administered will achieve a maximal therapeutic result as well as not exceeding the desirable radiation dose to a critical organ such as the lungs or bone marrow. When a given empiric dose is not sufficiently effective and one or more subsequent doses will be required, an additional potential limitation is that such multiple empiric fixed doses fractionated over time may not be equivalent to the same total dosimetrically determined radioiodine dosage of radioiodine given at one time. This is may be the case for two reasons. First, dose rates (rads/h) may be important. Fractionated dosages give lower dose rates. Second, previous non-lethal dosages may reduce the effectiveness of subsequent dosages. For example, two 100 mCi (3.7 GBq) doses administered 3 or 6 months apart may not deliver the same radiation absorbed dose as 200 mCi (11.1 GBq) administered as one single dosage because (1) the dose rate is lower by the former approach and (2) by only partially destroying the target lesion, the first 100-mCi-dosage may significantly reduce uptake of the second 100 mCi dose.

Lesional or whole body dosimetry has been reviewed previously [15]. The method and rationale of lesional dosimetry was described by Maxon et al. [16, 17] and determines dosage to be administered based upon the radiation absorbed dose (rads or grays) required to destroy a metastasis. The advantages of lesional dosimetry are (1) potentially improving outcomes by selecting and administering higher radioiodine dosages that have a greater chance of having a tumoricidal effect, and (2) potentially selecting and administering lower and safer radioiodine dosages that will still have a tumoricidal effect while minimizing adverse effects.

The disadvantages of the dosimetric approach include (1) increased cost and inconvenience to perform the dosimetry and (2) the difficulty in performing lesional dosimetry for locoregional and distant metastases. Whole body dosimetry as described by Benua et al. [18] attempts to determine the maximum allowable activity (MTA) that would deliver a maximum tolerable dose (MTD) to a critical organ to prevent or minimize unacceptable side effects. The MTD is typically 200 rads (cGy) to the blood, which serves as a surrogate for the bone marrow. Using the medical internal radiation dose (MIRD) approach, 300 rads (cGy) to the blood has been proposed as the MTD [19, 20].

The advantages of whole body dosimetry are (1) the ability to determine in each patient the MTA of radioiodine based on a MTD, (2) the identification up to 20 % of patients whose MTA is less than the empiric fixed dosage that may have been given [21–23], (3) the assurance of the safety of the administration of a one-time higher radiation absorbed doses to metastases instead of multiple lower fractionated empiric dosages, (4) a long history of use, and (6) reasonable risk for frequency and severity of complications relative to the sites and the severity of the extent of distant metastatic disease. The limitations of the whole body dosimetric approach are (1) increased cost and inconvenience, (2) the possibility of failure to estimate the radiation dose to the metastasis, thereby administering the "MTA" but not having any therapeutic effect, (3) the potential for stunning from the diagnostic dosage of 131-I subsequently resulting in a reduced therapeutic radiation dose delivered to the metastasis, and (4) failure to measure MTD to organs other than the blood, such as the salivary glands.

Until recently, there have been no studies demonstrating improved outcomes with dosages of radioiodine determined by the dosimetric approach relative to empiric dosages. Klubo-Gwiezdzinska et al. [24] have demonstrated that dosimetric therapy in high risk patients provides much improved outcomes in patients with locoregional spread of disease with a similar safety profile to that seen with empiric dosage. As a result, they submit that empiric dosages should be used. On the other hand, there are no definitive studies evaluating outcomes of empiric dosages in the treatment of distant metastases.

Objectives of radioiodine ablation and treatment

Multiple objectives for radioiodine ablation have been proposed and include (1) ablating residual thyroid tissue thereby increasing the sensitivity of detecting metastatic disease on subsequent follow-up radioiodine whole body scans, (2) ablating residual thyroid tissue thereby facilitating the interpretation of follow-up serum thyroglobulin levels, (3) potentially treating residual post-operative microscopic tumor foci, (4) decreasing the rate of recurrence, (5) increasing survival, and (6) obtaining post-ablation whole body scans, which have higher sensitivity than diagnostic scans. The ATA guidelines state that the objectives of ablation are "… to eliminate the post surgical remnant in an effort to decrease the risk for recurrent locoregional disease and to facilitate long-term surveillance with whole body iodine scan and/or stimulated

thyroglobulin measurements."[8]. The objectives as noted by the European Consensus are "… (1) 131-treatment of residual postoperative microscopic tumor foci, [which] may decrease the recurrence rate and possibly the mortality rate, (2) 131-treatment of residual normal thyroid tissue [facilitating] the early detection of recurrence based on serum TG measurement and eventually on 131-I WBS, and (3) a high activity of 131-I permits a highly sensitive post-therapy WBS 2–5 days after the administration, and this may reveal previously undiagnosed tumors [9]." Evidence-based literature related to the success of radioiodine ablation for many of these objectives has been reviewed [25, 26]. Recent carefully done randomized prospective trials [27, 28] have demonstrated that comparable ablation is achieved in low risk DTC irrespective of whether 30 mCi (1.1 GBq) or 100 mCi (3.7 GBq) is administered and whether the patient is prepared for ablation by thyroid hormone withdrawal or by administration of recombinant human TSH. Moreover, a recent retrospective study has indicated that radioiodine ablation for low risk DTC did not have a salutary effect on survival [29] leading to the need for us to fully re-examine the role of ablation in these patients by a randomized controlled clinical trial [30].

Indications for radioiodine ablation

The ATA and the European Consensus have published their guidelines regarding the indications for ablation [8, 9]. The ATA recommendations are based upon the AJCC TNM staging system and are rated on the basis of the strength of the evidence. The European Consensus recommendations are based upon risk: very low, low, and high. The ATA and EC guidelines are currently under revision and the revised guidelines are likely to not recommend ablation for the majority of papillary microcarcinomata in stage I or in the very low risk group [31]. Stage I patients in whom it is deemed appropriate to forego ablation includes those patients lacking characteristics such as multi-focal disease, nodal metastases, extra-thyroidal or vascular invasive and/or more aggressive histology, or BRAF positivity. The very low risk group includes those patients who have had complete surgery (total thyroidectomy), favorable histology, unifocal $T < 1$ cm (microcarcinoma), N0, M0, and no extrathyroid extension.

Selecting a dosage of radioiodine for ablation and treatment

For the majority of patients with WDTC, the ATA guidelines [8] recommend that "The minimum activity (30–100 mCi) necessary to achieve successful remnant ablation should be chosen, particularly for low-risk patients." However, the ATA guidelines further suggest that "If residual microscopic disease is suspected or documented or if there is a more aggressive tumor histology (e.g., tall cell, insular, columnar cell carcinoma), then higher activities (100–200 mCi) may be given…." The European Association of Nuclear Medicine states, "For thyroid malignancy… for patients undergoing ablation of thyroid remnant, administered activities in the range of 100–150 mCi (3,700–5,500 MBq) are usually given" [32]. We believe that the recent studies [27, 28] cited above that demonstrated equivalent efficacy of an ablative dose of 30 mCi to that of 100 mCi will lead to a paradigm change in standard dosage recommendations. The trend has been already established to not treat very low risk tumors of 1.0 cm or less (T1a, N0, M0), and to do 131-I ablation only on a selective basis for low risk tumors of 1–2 cm. Now we will be even selectively treating those patients with moderate risk (T2, N1) tumors, and it will be primarily the high risk patients (T3, T4, M1) who will regularly be ablated.

Although these recommendations and guidelines are helpful, the selection of a dosage of radioiodine for ablation and treatment remains variable and problematic, with the dosage selected dependent upon the multiple factors as well as a subjective factor related to how each physician weighs each of those factors. As already discussed, good prospective controlled studies are needed that would compare the various empiric and dosimetric approaches, but such studies are not likely to be available in the foreseeable future.

Our approach

For those patients to be ablated with radioiodine, our facility could use either an empiric or a dosimetrically determined dosage depending upon the clinical circumstances. If there is no evidence of metastases before the 123-I pre-ablation scan, then the patient is treated with an empiric dosage of radioiodine. For adults, we typically use 75–150 mCi (2.78–5.55 GBq). The Reynolds' modification factors [33] are employed for pediatric patients (see Table 1). However, these empiric dosages for children or adults may be further modified on an individual basis. The adult dosage may also be modified by the thyroid bed uptake and the number and size of the area(s) of residual thyroid tissue seen on the diagnostic scan, and this has also been discussed in more detail elsewhere [25] (Figs. 1, 2).

If the patient had a pre-ablation scan that demonstrates the possibility of residual disease, then either the empiric dosage may be increased or whole body dosimetry may be performed, or the ablation or treatment may be postponed until further evaluation or treatment is performed. Further evaluation typically starts with imaging by ultrasound and/or MRI of the neck, CT of the chest, FDG-PET scanning, and fine needle aspiration for cytologic examination of any

Table 1 Reynold's modifications factors of prescribed activity for treatment for children [33]

Factor	Body weight (kg)	Body surface area (m^2)
0.2	10	0.4
0.4	25	0.8
0.6	40	1.2
0.8	55	1.4
1.0	77	1.7

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Body surface area $= 0.1 \times (\text{weight in kg})^{0.67}$

lesions imaged that appear suspicious. With positive cytology for cancer, additional surgical intervention would be likely to be recommended.

The utility of pre-ablation diagnostic scans has been previously described [12] and often demonstrate a significant number of findings that may suggest the need to alter the proposed management with the therapeutic dose of 131-I. For example, a surprisingly high uptake in the thyroid bed could suggest an inadequate total thyroidectomy. In such cases, and ultrasound is obtained, and if either a large residual thyroid mass or bulky lymphadenopathy is discovered, the patient is sent back to surgery. Another finding on a pre-therapy diagnostic scan that can be significant is breast uptake in young women, leading us to defer therapy until resolved. Appropriate uptake on the diagnostic scan also serves to rule out iodine contamination that would preclude a satisfactory result of the ablative therapy.

For patients with known metastases before the pre-ablation scan—or perhaps more appropriately, the first pre-treatment scan—or for follow-up of patients with elevated thyroglobulin levels, known or strongly suspected loco regional recurrence or distant metastatic disease, we will perform whole body dosimetry to help determine the maximum tolerated activity (MTA) that the patient could receive without exceeding the MTD—the calculated 200 rads (cGy) to the blood (bone marrow). We also use the guidelines of not exceeding 80 mCi (2.96 GBq) whole body retention at 48 h in patients with pulmonary metastases and 120 mCi (4.44 GBq) whole body retention at

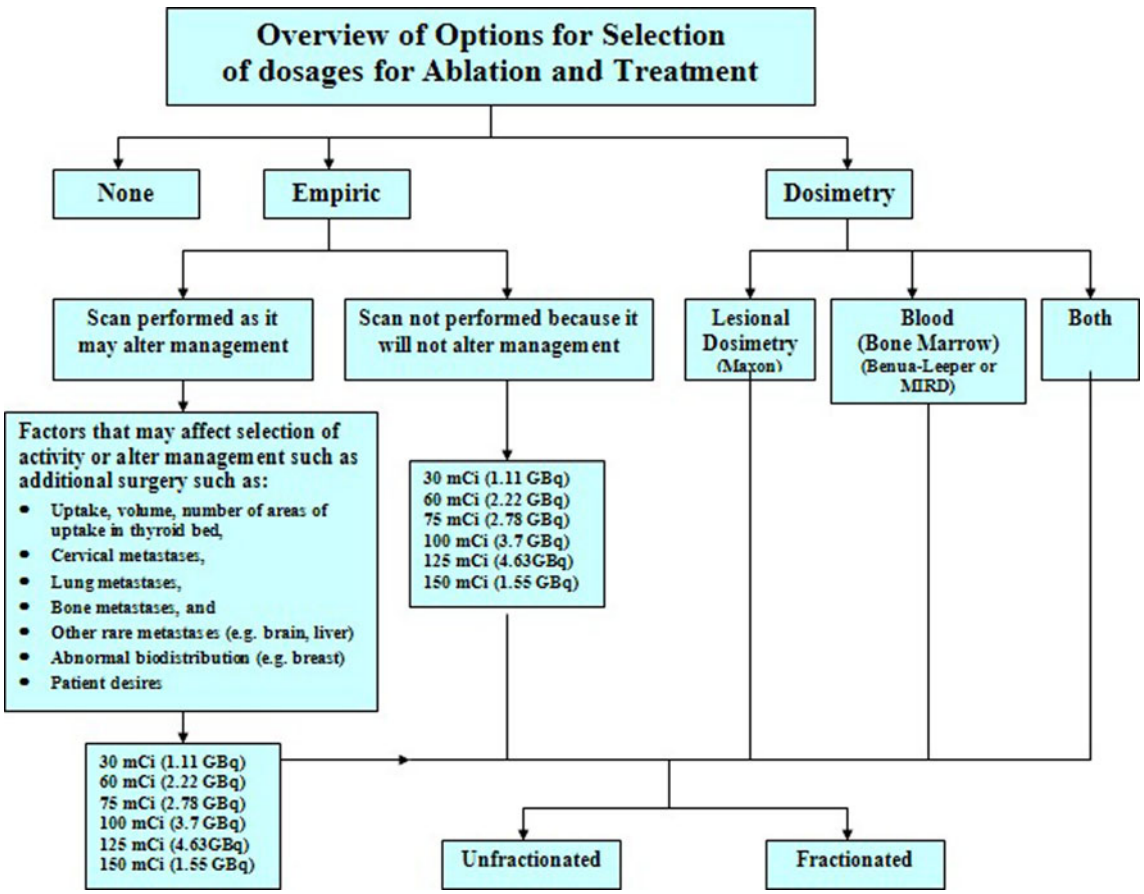

Fig. 1 An overview of various approaches for the selection of a dosage of radioiodine for ablation or treatment of patients with WDTC. This figure was reproduced with modifications with permission by Humana Press (Van Nostrand [25])

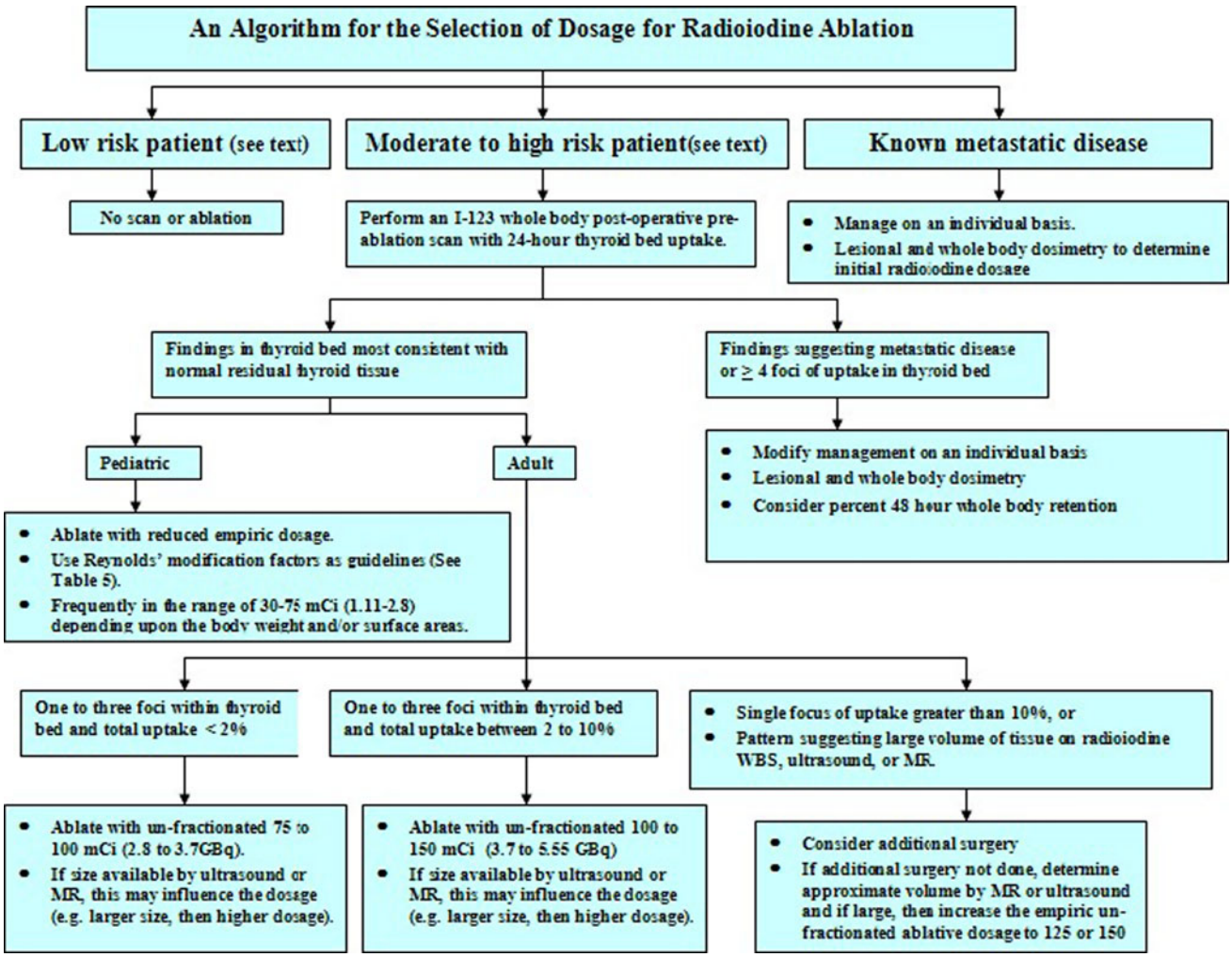

Fig. 2 An overview of the author's approach for the selection of a dosage of radioiodine for ablation or treatment of patients with WDTC at Washington Hospital Center. This figure was reproduced with modifications with permission by Humana Press (Van Nostrand [25])

48 h in all other patients. A low diagnostic dosage of 131-I in the range of 1–2 mCi (37–74 MBq) is used to avoid or minimize stunning. The final treatment dosage of 131-I to be administered is selected to not exceed either the MTA or the above guidelines for whole body retention.

Use of recombinant human TSH for radioiodine ablation or therapy

As described above, virtually all traditional methods and approaches for radioiodine ablation or therapy require patients to be hypothyroid with elevated endogenous TSH levels either after thyroidectomy or after withdrawal from levothyroxine therapy. As a consequence, they undergo a period of hypothyroidism ranging from 3 to 6 weeks with many unpleasant symptoms associated with thyroid hormone deficiency. With the development of human recombinant TSH (thyrotropin alfa for injection) and its approval by both the EMEA and the FDA, patients now had an alternative option for surveillance monitoring for residual or recurrent disease [34]. Use of rhTSH has improved cancer diagnostic sensitivity by the measurements of thyroglobulin (Tg) to detect residual cancer, as well as rhTSH-stimulated radioiodine scans which were found to be comparable to the diagnostic utility of thyroxine withdrawal scans [35]. Consequently, use of rhTSH has become a safe and effective alternative to thyroid hormone withdrawal in the detection of recurrent or residual thyroid cancer.

The typical protocol for rhTSH testing is to monitor the serum Tg before and after rhTSH and perform a radioiodine scan after rhTSH. We routinely also confirm that the patient is on optimal levothyroxine dosage before rhTSH by the measurement of baseline TSH, and rule out the presence of interfering anti-Tg antibodies by the measurement of the latter by RIA. By protocol, the radioiodine dosage used for the scan is 4 mCi, a dose that has been

shown to provide a scan comparable to that achieved by withdrawal of thyroxine (28). After drawing a basal blood for Tg, rhTSH is administered by i.m. injection on that day and again the following day. The 4 mCi dose of radioactive iodine is given 24 h later and the patient is scanned and a second blood drawn for Tg measurement 48 h later. The most common procedure is as follows:

Monday	Blood drawn for Tg Thyrogen® injection 0.9 mg
Tuesday	Thyrogen® injection 0.9 mg
Wednesday	4 mCi dose of radioactive iodine
Thursday	No procedures
Friday	Blood drawn for Tg Whole body scan

Essentially all of the initial studies with rhTSH have been in the context of diagnosis, and it was inevitable that its use would be extended to examine the efficacy of rhTSH as an alternative to thyroxine withdrawal for preparation before radioiodine treatment for either or both the initial ablation and for subsequent therapies for persistent disease.

Remnant ablation after rhTSH preparation

Apart from the findings of the recent studies [27, 28] indicating that low doses of radioiodine will be sufficient for low risk disease, the usual method [36] is to administer 0.9 mg rhTSH on two consecutive days before dosing with a mean activity of 110 mCi (range 30–250 mCi). Ablation is deemed successful when the complete absence of visible thyroid bed uptake is seen on a follow-up diagnostic scan, and was seen 5–13 months later in 10/10 patients [36]. That rhTSH preparation might be equally effective for therapy as for initial ablation was indicated by the observation that two of their patients had uptake outside the thyroid bed thought to be lymph node metastases that was not seen on the follow-up diagnostic whole body scans. Long-term studies have confirmed the efficacy of rhTSH preparation for ablation [37, 38]. As an alternative to a repeat post-ablation scan, failure of serum Tg to rise after rhTSH also may be taken to reflect successful ablation.

While not the subject of this review, the question often arises as how to provide optimal surveillance for residual or recurrent disease when radioiodine ablation has not been performed in patients with low to moderate risk disease. This topic was elegantly discussed by Durante and Filetti [39] recently with emphasis on the use of ultrasonography coupled with measurements of serum thyroglobulin.

The MSKCC group subsequently reported a comparison of the efficacy of rhTSH ablation in 45 patients versus ablation after thyroxine withdrawal in 42 patients [40]. The results were comparable with 84 % after rhTSH and 81 % after thyroid hormone withdrawal achieving resolution of visible thyroid bed uptake on the 1 year follow-up whole body diagnostic RAI scan. Mean administered 131-I activity following thyroid hormone withdrawal was 129 ± 74 mCi (range 30–300 mCi) compared to 110 ± 65 mCi (range 30–330 mCi) following rhTSH preparation.

Pacini et al. [41] found that satisfactory ablation was not achieved with a dose of 30 mCi of 131-I following rhTSH in contrast to that achieved after withdrawal, but their conclusion is flawed by having their administered ablative dose of RAI 48 h (rather than 24 h) after the second injection of rhTSH. A better result was demonstrated by Barbaro et al. [42] with administration of the ablative dose of 30 mCi 131-I 24 h after the second injection of rhTSH. No visible uptake was seen in the thyroid bed at the 1-year follow-up diagnostic whole body scan in 88 % (14/18) of patients prepared with rhTSH compared to 75 % (18/24) of patients prepared by thyroid hormone withdrawal. If the additional parameter of thyroglobulin measurement is included to assess efficacy of ablation, no significant difference was seen in their series with a success rate of 81 % with rhTSH versus 75 % with withdrawal.

Other results from a multicenter prospective, randomized trial compared traditional thyroid hormone withdrawal with rhTSH stimulation in low risk differentiated thyroid cancer patients [43]. Patients received 3.7 GBq (100 mCi) and all patients had <0.1 % uptake in the thyroid bed at the follow-up diagnostic rhTSH whole body scan 1 year later. Comparable results have been seen in the USA since the approval by the FDA of the use of rhTSH for ablation in 2007. Ablation with rhTSH was approved earlier as an alternative to withdrawal by the European Consensus [9], who employ a fixed dose of 3,700 MBq (100 mCi) in low risk patients. The protocol is similar to that described above with 0.9 mg rhTSH given i.m. on two consecutive days with the radioiodine given 24 h after the second injection.

Radioiodine treatment after rhTSH preparation

Use of rhTSH preparation in lieu of thyroxine withdrawal for subsequent therapy of residual or metastatic thyroid cancer represents an "off label" use in the USA and very few studies have been published to support such use. The ATA guidelines indicate that insufficient outcome data exist to recommend this practice although rhTSH use might be justified in selected patients with co-morbidities making withdrawal and the attendant symptoms of hypothyroidism of significant risk to the patient. Another indication for rhTSH would be in the rare circumstance of a patient with coincidental hypopituitarism who cannot raise their endogenous TSH after withdrawal, or the patient with such extensive metastatic disease that endogenous thyroid

hormone production from the tumor continues to suppress pituitary secretion of TSH after withdrawal of thyroxine therapy. Use of rhTSH in these latter circumstances is also recommended by the European Consensus [9]. Studies showing comparable efficacy of treatment of metastatic disease after preparation with rhTSH have been encouraging, although it may be that uptake of radioiodine as either 131-I or 124-I is significantly better after withdrawal than after preparation with rhTSH [44]. Nevertheless, the only studies published to date do demonstrate equivalent benefit although the studies are retrospective [45, 46]. And of course, rhTSH stimulation of radioiodine uptake has been effectively employed as well in the non-surgical treatment of benign nodular goiter [47].

Radioiodine ablation and treatment remain indispensable components in the armamentarium for the management of patients with WDTC, whether the dosages of radioiodine are selected on the basis of either empiric or dosimetric approaches. With a thorough understanding of the various empiric and dosimetric approaches along with thoughtful consideration of the many factors that may alter the dosage of radioiodine, we believe that a team that is composed of a nuclear medicine physician (or nuclear radiologist) and an endocrinologist may select an appropriate dosage of radioiodine that is individualized for that patient's specific situation.

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