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GUIDELINES

Guidelines for radioiodine therapy of differentiated thyroid cancer

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Abstract
Introduction The purpose of the present guidelines on the radioiodine therapy (RAIT) of differentiated thyroid cancer (DTC) formulated by the European Association of Nuclear Medicine (EANM) Therapy Committee is to provide advice to nuclear medicine clinicians and other members of the DTC-treating community on how to ablate thyroid remnant or treat inoperable advanced DTC or both employing large 131-iodine (^{131}I) activities.
Discussion For this purpose, recommendations have been formulated based on recent literature and expert opinion regarding the rationale, indications and contraindications for these procedures, as well as the radioiodine activities and the administration and patient preparation techniques to be used. Recommendations also are provided on pre-RAIT history and examinations, patient counselling and precautions that should be associated with ^{131}I iodine ablation and treatment. Furthermore, potential side effects of radioiodine therapy and alternate or additional treatments to this modality are reviewed. Appendices furnish information on dosimetry and post-therapy scintigraphy.

Keywords Radioiodine therapy · Thyroid remnant ablation · Radioiodine treatment · Guidelines

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Abbreviations

beta-hCG	beta human chorionic gonadotropin
Bq	Becquerel
Ci	Curie
CT	computed tomography
DTC	differentiated thyroid carcinoma
dxWBS	diagnostic whole-body scan
EANM	European Association of Nuclear Medicine
Gy	Gray
^{123}I	123-iodine
^{124}I	124-iodine
^{131}I	131-sodium or potassium iodide
LT3	triiodothyronine
LT4	levothyroxine
NIS	sodium iodine symporter
PET	positron emission tomography

QOL	quality-of-life
rhTSH	recombinant human thyroid-stimulating hormone
RAIT	radioiodine therapy
ROI	region of interest
rxWBS	post-therapy whole-body scan
SPECT	single photon emission computed tomography
Tg	serum thyroglobulin
THW	thyroid hormone withdrawal or withholding
TSH	thyroid-stimulating hormone
US	ultrasonography
WBS	whole-body scan
XRT	external beam radiotherapy

Introduction

Differentiated thyroid cancer (DTC) is defined as a carcinoma deriving from the follicular epithelium and retaining basic biological characteristics of healthy thyroid tissue, including expression of the sodium iodide symporter (NIS), the key cellular feature for specific iodine uptake. DTC is an uncommon disease clinically, but worldwide, its incidence shows a noticeable increase [1]. Consecutive autopsy studies have shown that papillary microcarcinoma is frequent in the general population. Improved detection of some of these subclinical tumours may account for at least part of the increase in DTC incidence [2].

When appropriate treatment is given, the prognosis of the disease is generally excellent. Although the 10-year survival rate in cases of distant metastasis is approximately 25–40% [3–5], the 10-year overall cause-specific survival for DTC patients as a whole is estimated at approximately 85% [6, 7]. However, the lifetime recurrence rate is relatively high, reaching 10–30% [7–10] in some series. Therefore, lifelong follow-up is needed in all DTC survivors and subsequent therapy in an appreciable number of patients. Because DTC survivors number approximately 250,000 in Europe alone [11], DTC management has notable patient quality-of-life (QOL) and pharmacoeconomic implications. This state of affairs has driven the elaboration of various national and international DTC management guidelines from diverse medical specialty organisations, reflecting the multi-disciplinary approach required for the care of DTC [12–19].

With the present paper, the European Association of Nuclear Medicine (EANM) seeks not simply to contribute to the series of publications but to focus on practical aspects of radioiodine therapy (RAIT) of DTC. Efforts have been made to harmonise our recommendations with those of the European Thyroid Association guidelines [12], and the lead author of those guidelines has critically reviewed this article. However, in the area of RAIT, the nuclear medicine specialty can offer unique experience and perspectives, and as a result, valuable advice to the clinician.

It should be noted that the level of evidence regarding therapy (as well as diagnosis and follow-up) of DTC patients is low in many instances, as has been documented in the 2006 American Thyroid Association guidelines [13]. The relatively low prevalence of the malignancy and the lengthy overall survival of most patients create the need for large sample sizes and very long-term follow-up to demonstrate outcome differences between interventions. This, in turn, hinders the execution of large-scale prospective studies, especially on new therapies. In light of this dilemma, in developing their recommendations, the authors have relied significantly on their clinical experience to supplement the observations reported in the literature. In the interests of simplicity, clarity and relevance to everyday practice, the authors have provided citations to key studies underlying their recommendations rather than formally classifying strength of evidence for proposed treatment strategies.

RAIT of DTC

Definition and goals

RAIT is defined as the systemic administration of 131-sodium or potassium iodide (^{131}I) for selective irradiation of thyroid remnants, microscopic DTC or other non-resectable or incompletely resectable DTC, or both purposes. Based on the primary goal of the RAIT, there are two main forms of the procedure.

The first form, radioiodine ablation, is a post-surgical adjuvant modality. It seeks to eliminate thyroid remnants to increase the sensitivity and specificity of follow-up testing for DTC persistence or recurrence, namely, of assays of serum thyroglobulin (Tg) as a tumour marker and of diagnostic whole-body scintigraphy (dxWBS). Ablation also allows sensitive "post-therapy" whole-body scintigraphy (rxWBS) that may detect previously occult metastases [15] and serves to treat any microscopic tumour deposits. Ablation, therefore, may reduce long-term morbidity and possibly, mortality [15, 20, 21]. Ablation success is evaluated 6–12 months after the ablation procedure with current definitions of such success including the following criteria:

- on follow-up dxWBS, negative thyroid bed uptake or thyroid bed uptake beneath an arbitrarily set, low threshold, e.g. 0.1%,
- absence of detectable thyroid-stimulating hormone-(TSH-) stimulated Tg antibodies has been excluded,
- absence of suspicious findings on neck ultrasonography (US) [22, 23].

The second form of RAIT, radioiodine treatment of non-resectable or incompletely resectable lesions, e.g. microscopic disease, macroscopic local tumour or lymph node or distant metastases, is performed as curative or palliative therapy either as a component of primary treatment of DTC or to address persistent or recurrent disease.

Rationale and indications

Ablation

Due to the generally favourable prognosis of DTC, the impact of radioiodine ablation on disease-specific mortality and relapse rate is hard to substantiate. Few randomised studies address this topic, and some of these studies are inconclusive. However, a recent meta-analysis documented the positive influence of RAIT as an adjunct to thyroidectomy, namely, in retrospective studies with follow-up of 10 years or more [20]. When thyroid surgery is performed in highly expert hands at selected tertiary referral centres, though, the positive influence of radioiodine ablation may not be apparent [24].

Radioiodine ablation after total or near-total thyroidectomy is a standard procedure in patients with DTC. The only exception is patients with unifocal papillary thyroid carcinoma ≤1 cm in diameter who lack:

- evidence of metastasis,
- thyroid capsule invasion,
- history of radiation exposure,
- unfavourable histology:
    - tall-cell, columnar cell or diffuse sclerosing subtypes.

In these cases without the above risk factors, completion thyroidectomy or RAIT of large remnants may be avoided. When such patients have been treated by total or near-total thyroidectomy, some centres refrain from radioiodine ablation under the rationale that this procedure would not materially improve an already excellent prognosis. Other centres consider radioiodine ablation as a means of improving follow-up and potentially decreasing relapse risk [25, 26]; potential risk factors for recurrence or mortality, such as family DTC history, tumour size, history of neck radiation exposure, histology, closeness of the tumour to the thyroid capsule, presence of vascular invasion and, in the future, thyroid cancer-related molecular genetic findings, should be considered when deciding whether to perform radioiodine ablation in these patients.

Treatment

When radioiodine uptake is scintigraphically proven before therapy or after empiric RAIT, radioiodine treatment of non-resectable or incompletely resectable tumour, e.g. local recurrences, lymph node metastases or disseminated iodine-avid lung metastases or other distant lesions, has shown in various investigations to be effective in eradicating disease, slowing disease progression or providing symptomatic relief [4]. Indeed, outcome has been shown to be superior in patients with radioiodine-avid metastases compared to those with radioiodine-negative extra-thyroidal lesions [4]. Furthermore, a recently published study using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) suggests that FDG uptake in metastases, which typically reflects the presence of radioiodine non-avid disease, is itself a relevant independent unfavourable prognostic indicator [27]. In multivariate analysis, this study found that greater numbers of FDG-avid lesions or higher maximum standard uptake values in a patient's tumours on FDG-PET correlated significantly with overall mortality [27].

The results of RAIT are superior for microscopic or small macroscopic tumours than for larger lesions [4]. Therefore, the feasibility of partial or complete resection of macroscopic lesions should always be checked as a first treatment option.

Chart 1 provides indications and contraindications for radioiodine treatment. However, the decision on whether or not to give RAIT with the intention of cure or palliation should be individualised to the patient and should consider the following factors:

- Operability—except in cases of high risk of important surgical complications, excision is the preferred first-line treatment for persistent or recurrent DTC. This preference is based on the modality's high potential to improve survival, especially in cases of lesions limited to the thyroid bed or neck lymph nodes, or to palliate disease and improve QOL. However, RAIT should always be offered as an adjuvant to surgery of persistent or recurrent DTC, unless the disease has been confirmed to be iodine non-avid.
- Iodine avidity—RAIT exerts no benefit in the absence of iodine-avid tissue. However, lack of iodine avidity can only be confirmed through an rxWBS performed in the absence of iodine excess.
- Disease site—whilst lymph node, lung and most soft tissue metastases have high rates of cure by RAIT with or without surgery, cure of bone and brain metastases is relatively rare [4, 28].
- Tumour characteristics—patients with less differentiated tumour histotypes such as papillary tall-cell, columnar cell or diffuse sclerosing or follicular widely invasive, poorly differentiated or Hürthle cell have a greater risk of relapse and a reduced survival, yet despite diminished NIS expression, such tumour may respond well to RAIT [29]. Metastatic DTC has a highly variable rate of

progression, and in cases of asymptomatic stable disease, particularly when longstanding, a strategy of "watchful waiting" may be appropriate.

- Patient age—patients who are older, e.g. >45 years of age, at thyroid cancer diagnosis often present with more aggressive tumour and have a reduced age-adjusted disease-free and overall survival [7]; therefore, older age at diagnosis could be a factor favouring RAIT when the indication for this intervention is not definite.
- Patient health status—inability to tolerate surgery or other potential therapeutic interventions, e.g. chemotherapy, could make RAIT the preferred or the only therapeutic option; conversely, where use of recombinant human thyroid-stimulating hormone (rhTSH) is not economically feasible, inability to tolerate hypothyroidism could rule out RAIT (see the "Thyroid-stimulating hormone stimulation" section) [30].
- Potential risks of the procedure—whilst RAIT is generally well-tolerated, it is not without potential short- and long-term toxicity (Table 1), which includes second primary malignancy [31]. These potential risks should be weighed against the expected benefits of the intervention.

Contraindications

Absolute

1. Pregnancy
2. Breastfeeding

Relative

Before the potential RAIT, clinically relevant:

1. bone marrow depression, if administration of high ^{131}I activities is intended.
2. pulmonary function restriction, if a significant pulmonary ^{131}I accumulation is expected in lung metastases.
3. salivary gland function restriction, especially if ^{131}I accumulation in known lesions is questionable.
4. presence of neurological symptoms or damage when inflammation and local oedema caused by the RAIT of the metastases could generate severe compression effects.

Radioiodine activities and administration

As a matter of terminology, the amount of radioiodine given in a diagnostic or therapeutic procedure, expressed in Becquerels (Bq) or Curies (Ci), should be referred to as an "activity". The term "absorbed dose" or the shorter version, "dose", should be reserved to describe the radiation absorbed by an organ, tissue or body compartment, expressed in Gray (Gy).

RAIT activities are generally empirically determined and fixed by a given institution based on disease characteristics and patient age (see Appendix 1 for the discussion of dosimetry-based activities). The "optimal" activity for radioiodine ablation of post-surgical thyroid residues macroscopic disease is generally a single administration of 1–5 GBq, but within that range, remains controversial, with different centres advocating use of 1.11, 1.85 or 3.7 GBq [32]. A recent systematic review concluded that current evidence does not yet allow the determination whether ablation success rates are similar with ablation activities of 1.11 versus 3.7 GBq [32].

For radioiodine ablation in children, some centres adjust activity by body weight (e.g. to 1.85–7.4 MBq/kg) or surface area or by age (e.g. to 1/3 the adult activity in a 5-year-old, 1/2 the adult activity in a 10-year-old, or 5/6 the adult activity in a 15-year-old) [33]. Another approach, recommended in the German procedure guidelines for radioiodine therapy in paediatric DTC patients [16], is to adjust the ablation activity according to the 24-h thyroid bed uptake of a test activity of radioiodine as well as according to body weight: <5% uptake would warrant an activity of 50 MBq/kg, 5–10% uptake would warrant an activity of 25 MBq/kg and 10–20% uptake would warrant an activity of 15 MBq/kg. Because it maximises the degree of individualisation, flexible ablation dosing according to one or more individual patient body characteristics, i.e. weight, surface area, thyroid bed radioiodine uptake, appears to be a preferable strategy to fixed dosing or to flexible dosing based on age.

In general, the rationales for individualising radioiodine activities to a lower than adult level in paediatric patients are children's longer life expectancy, and hence, vulnerability to undesired treatment effects, and the greater absorbed dose to bone marrow and extra-thyroidal tissue in children, given their smaller body sizes and the increased cross-radiation due to shorter distances between organs [34].

In cases where ablation success criteria (see the "Definition and goals" section) are not met, one or more additional ablation activities may be considered. "Watchful waiting" is another alternative, especially in patients with small persistent residues, which appear to have no impact on clinical outcome. In patients with large persistent remnants, re-operation may be an option.

In late adolescents and adults, inoperable iodine-avid distant metastases are typically treated with multiple administrations, each 3.7–7.4 GBq or more, given every

Table 1 Potential early and late sequelae of RAIT

Sequelae	Approximate incidence	Comment	Potential intervention(s)
Early/short-term			
Radiation thyroiditis (clinically apparent swelling and pain or other discomfort)	10–20%	More frequent with larger remnants	Corticosteroids for several days after radioiodine administration
Tumour swelling	10–20%	May cause compressive symptoms, pain or both	Corticosteroids for several days after radioiodine administration
Sialadenitis [108]	30%		Liberal hydration, use of lemon juice, sour candy and chewing gum in the 24+ h after radioiodine administration [80, 81]
Gastritis	30%	Transient and self-limiting	Use of H2-blockers following radioiodine administration
Bone marrow depression (thrombocytopaenia/ leucocytopaenia)	Depends on the administered activity	Mostly transient decreases in cell counts; incidence of severe bone marrow depression increases with multiple bone metastases and large cumulative radioiodine activity	
Xerostomia/caries		Rare after a single radioiodine ablation procedure	
Abnormalities of taste and smell		Transient and self-limited	
Nausea/vomiting			Anti-emetics
Hypospermia [109, 110]		Usually transient	Gonadal radiation exposure can be minimised by liberal hydration and frequent urination; consider sperm banking in case of high activities
Late/long-term			
Radiation pulmonary fibrosis	<1% of patients with lung metastases	Affects patients with diffuse iodine-avid pulmonary metastases who receive multiple RAITs in a short time, who are treated with high activities, or both	Ensure appropriate interval between RAITs and consider their cumulative absorbed dose
Second primary malignancy (leukaemia and solid tumours)	<1%	Latency period of ≥5 years. Cases most frequently observed when cumulative radioiodine activities exceed 20–30 GBq [112–114]	Limit RAIT above these cumulative activities to patients in whom a clear therapeutic benefit may be expected
Permanent bone marrow depression	Rare		
Chronic hypospermia or azoospermia [109, 110]	Rare when cumulative activity <14 GBq [85]		Consider sperm banking in case of high activities
Early onset of menopause [84]			
Chronic sialadenitis with xerostomia, abnormalities of taste and smell	10–20% after radioiodine ablation, more frequent after multiple RAITs		Liberal hydration, use of lemon juice, sour candy and chewing gum in the 24+ h after radioiodine administration [80, 81]
Chronic dry eye	Rare		

4–8 months during the first 2 years following diagnosis of metastatic disease and at longer intervals thereafter [35–38]. In children, some clinicians use fixed activities of 1.1 to 11.0 GBq, whilst others use variable empirical activities ranging from 37.0 to 92.5 MBq/kg of body weight [16, 33]. In the paediatric radioiodine treatment setting, a fixed dosing scheme of similar activities to those used in adult patients appears to be preferable. Such a

strategy has the virtue of simplicity and may maximise the chances of complete response in a population in whom persistent tumour cells would have a particularly long time to progress to clinical recurrence or to de-differentiate. However, in using standard fixed activities in this setting, caution should be exercised to avoid inappropriately high absorbed doses to lung parenchyma (e.g. in patients with high lung radioiodine uptake) or bone marrow [39, 40].

As an alternative to the administration of fixed RAIT activities in adult or paediatric patients, pre-therapeutic dosimetry (see Appendix 1) may be used to calculate an individualised activity projected to deliver a desired amount of radioactivity to tumour or extra-thyroidal compartments, or both. The generally accepted absorbed dose thresholds providing high efficacy are ≥300 Gy to remnants or ≥80 Gy to tumour deposits [41]. The generally accepted surrogate dose threshold to avoid serious myelotoxicity is a blood absorbed dose ≤2 Gy [42]. Some centres combine the lesion- and blood-based dosimetric approaches [43]; however, larger patient series are warranted to further support this strategy. The EANM Dosimetry Committee recently published a standard operating procedure guideline on how to tailor the activity to be administered for systemic treatment of DTC so that the absorbed dose to blood does not exceed 2 Gy [44].

Whether giving radioiodine ablation or treatment, the clinician must bear in mind that severe renal failure abrogates whole-body radioiodine clearance [45, 46]. Absent renal dialysis, virtually all the administered activity will remain in the patient for a protracted time; therefore, in patients with renal failure, dialysis should be carried out within 24 h following radioiodine administration.

RAIT should continue until no evidence remains of iodine-avid disease, until intolerable toxicity develops or until the patient refuses this treatment modality. There is no maximum limit for the cumulative ^{131}I activity that can be given to patients with persistent iodine-avid disease. However, most remissions are obtained with cumulative activities ≤22 GBq [4]; above this threshold, continued RAITs should be considered on an individual basis. Post-RAIT transplantation of stem cells obtained autologously before RAIT appears to be a promising tool to allow continued RAIT resulting in high cumulative activities, e.g. 50 GBq, when such RAIT is the only treatment option. Outcomes of this strategy merit further investigation. In some patients with iodine-avid tumour who did not achieve a complete response to several RAITs but have clearly stable disease (e.g. no clinical signs of progression or increasing Tg levels), the intervals between RAITs may be increased, or RAIT may be halted in favour of "watchful waiting".

Because of the greater ease to the patient and the superior radiation protection for caregivers, ^{131}I generally should be administered orally as a capsule. Before administration, the actual therapeutic activity should be measured using an activimeter to confirm that it matches the planned activity.

Patient preparation

Thyroid-stimulating hormone stimulation

The effectiveness of RAIT depends on the patient's serum TSH level being sufficiently elevated. A TSH level of ≥30 mU/L is believed to increase NIS expression and thereby to optimise radioiodine uptake [13]. Such TSH elevation can be reached by waiting at least 3 weeks after thyroidectomy or 4–5 weeks after discontinuing treatment with levothyroxine (LT4). Triiodothyronine (LT3) may be substituted for LT4 until 2 weeks before RAIT in an attempt to decrease the duration of hypothyroidism; however, systematic data on the impact of interim LT3 medication are still lacking. When thyroid hormone is withheld, it should be initiated or resumed 2 days after radioiodine administration.

Nonetheless, traditional thyroid hormone witholding or withdrawal (THW) has the major drawback of causing weeks to months of hypothyroid symptoms in most patients [47–50]. Such physical and psychological morbidity may include fatigue, depression, impaired ability to concentrate, sleep disturbance, weight gain, constipation, dry skin, hoarseness, puffy face or hands, cardiovascular abnormalities, impaired renal function and exacerbation of dyslipidemia [48, 51–56]. These manifestations in turn frequently significantly decrease patient QOL, cause absenteeism from or impaired performance in work or study or lead to debilitating or even life-threatening worsening in psychological, cardiovascular, renal or other concomitant conditions [47–50, 57–61].

A few studies suggest that a shorter period of THW may effectively elevate TSH whilst mitigating hypothyroid disturbance in adults [62] or children [63]; however, this strategy has the disadvantages with respect to patient adherence and convenience and to health care costs of requiring multiple physician visits and TSH determinations. Additionally, a shorter THW fails to elevate TSH in an appreciable percentage (approximately 10%) of adults [62], and it is not always possible to predict which individuals will fail to respond to abbreviated THW.

An alternative to THW for attaining TSH elevation is rhTSH administration. In Europe and elsewhere, this drug has been approved for use in adults as preparation for serum Tg testing, dxWBS or both or for radioiodine ablation [22, 57, 58, 64]. Based on the regimen and patient characteristics in the pivotal phase 3 study [22], the European product labelling specifies an ablation activity

of 3.7 GBq ^{131}I and low-risk status for the patient. Lately, a nearly 400-patient retrospective analysis from Memorial Sloan-Kettering Cancer Center [65], which also used large activities but included a higher-risk study population than did the pivotal trial, found that, with a median 2.5 years of follow-up, rhTSH- and THW-aided ablation were associated with statistically similarly low rates of clinical recurrence or persistent thyroid bed scintigraphic uptake, as well as statistically similar time to recurrence. This study also found statistically similarly high ablation success rates for the two preparation modalities at 12–18 months.

A recent prospective, randomised, controlled investigation [23] suggests that rhTSH-aided ablation with 1.85 GBq of ^{131}I may achieve a statistically non-inferior ablation success rate to that seen with rhTSH-aided ablation using 3.7 GBq, even in the presence of node metastases. Two prospective studies [66, 67], but not another [68], suggest equivalent ablation success rates with rhTSH- versus THW-aided ablation using 1.11 GBq. In the two positive trials, thyroid hormone was withheld for a few days before and after radioiodine administration [63, 64]. Further studies are desirable to increase the total number of patients and the duration of follow-up that have been reported for rhTSH-aided ablation, as well as the published experience with this modality using low ablation activities.

rhTSH has also been given "off-label" to aid RAIT of locally advanced or metastatic DTC or both in several hundred patients, predominantly adults and predominantly for palliative purposes, with some evident benefit of the rhTSH-aided treatment reported in retrospective series or anecdotally [69–71]. In a relatively large, retrospective multicenter series (N=90), rhTSH use appeared to be safe and effective in promoting Tg production, radioiodine uptake or both in patients ≤18 years old (Luster et al., personal communication, 25 June 2008).

The approved regimen of rhTSH is two consecutive daily intramuscular injections of 0.9 mg. Subcutaneous injection was successfully used in a small case series (N=5) of patients on oral anticoagulants and hence at risk of injection site haematoma [72]. Radioiodine is given 1 day and serum Tg testing is performed 3 or 4 days after the second rhTSH injection. When dxWBS is performed, it takes place 48–72 h after the radioiodine is applied; rxWBS is performed 2–7 days following radioiodine administration. rhTSH is typically well-tolerated with short-lived and generally mild nausea (approximately 10% incidence), headache (approximately 7% incidence) and asthaenia (approximately 3% incidence), the most common side effects.

In addition, very likely because of improved renal function and, as a consequence, more rapid excretion of peripheral ^{131}I under euthyroid versus hypothyroid conditions, rhTSH appears to decrease radiation exposure of extra-thyroidal tissues and blood after RAIT [73, 74]. This decreased exposure potentially may reduce length of stay under radioprotection conditions [75], the long-term risk of second primary malignancies, or both. rhTSH administration also provides more rapid and predictable TSH elevation than does THW.

For now, unless economically unfeasible, the use of rhTSH is generally the preferred TSH stimulation method before radioiodine ablation with medium–large activities (e.g. 1.85–3.7 GBq) of radioiodine. For ablation with smaller activities, either preparation method may be used.

The rationales for rhTSH use with higher activities are the statistically non-inferior, high ablation success rates [22, 65], the similarly low short-term relapse rate [65], the significantly decreased morbidity and the significantly improved QOL [22] of rhTSH preparation relative to THW stimulation that have been documented in two large well-conducted studies. The rationale for rhTSH use with medium activities is a prospective, randomised study showing non-inferior ablation success of 1.85 GBq versus 3.7 GBq under rhTSH stimulation [23].

In the absence to date of prospective studies demonstrating definitive clinical efficacy for rhTSH as an aid to curative RAIT of metastases, THW remains the preferred TSH stimulation method for treatment with a curative intent of metastatic disease. However, rhTSH is recommended in curative RAIT in patients who are unable to tolerate hypothyroidism, for example because of significant co-morbidities, or who are unable to raise endogenous TSH [69, 70]. For now, unless economically unfeasible, given the desirability of avoiding hypothyroid morbidity in this setting, the use of rhTSH is also the generally preferred stimulation method before radioiodine treatment of DTC lesions that has a solely palliative intent. If completion thyroidectomy is technically impossible or undesired in patients with large thyroid remnants, e.g. 5–10 ml, endogenous TSH levels <30 mU/L are acceptable before RAIT, but additional exogenous stimulation with rhTSH is a potentially useful, but as yet unproven means to increase the effectiveness of ablative RAIT.

Clinical caution and steroid co-administration are advised when using THW or rhTSH in patients with known or suspected tumour in confined anatomical spaces, especially in the central nervous system, lungs or bones. Such patients are susceptible to morbid complications of inflammatory tumour expansion or tumour growth under TSH elevation. Absolute and relative contraindications for glucocorticoids, such as diabetes mellitus, ulcus ventriculi or duodeni or electrolyte disorders must be taken into account when considering use of steroids.

Avoidance of iodine excess

To avoid competitive handling by NIS of non-radioactive iodine rather than radioiodine, with a resultant diminution in efficacy of RAIT, patients should be advised to avoid iodine-containing medications, e.g. iodinated contrast agents, antiseptics, eye drops or amiodarone, and iodine-containing foods, e.g. iodinated multivitamins or mineral supplements or seafood, for 4–6 weeks prior to RAIT. A low-iodine diet, when possible, <50 μg/day, starting 1–2 weeks prior to radioiodine administration is recommended optionally [76, 77]. A detailed discussion of low-iodine diets may be found in recent Dutch thyroid cancer management guidelines (http://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=554). Written instructions may be helpful in promoting patient adherence to iodine avoidance measures.

Before every RAIT, patients should be specifically questioned about ingestion of common iodine-containing medications or foods to rule out iodine excess. Urinary stable iodine excretion should be measured preferably routinely, but at a minimum, in doubtful cases. Urinary stable iodine excretion above an arbitrary institutional cut-off in the range of 150–200 μg/L is believed to reflect clinically relevant iodine excess and should lead to postponement of RAIT. After administration of lipophilic iodinated contrast agent (today rarely used) or after amiodarone medication, RAIT should be postponed for at least 3 months, and in other cases of iodine excess, RAIT should be postponed for 4–6 weeks.

The literature contains mixed findings as to whether the continued thyroid hormone ingestion permitted by rhTSH use leads to clinically relevant elevated iodine levels [22, 66]. Some clinicians favour a “mini-withdrawal” of thyroid hormone for a short period (e.g. 2 days each) before and after RAIT [67]. However, there is as yet no published evidence that “mini-withdrawal” improves ablation outcome.

Other

Abundant food intake may alter the resorption of orally administered radioiodine. Patients should fast or at a minimum, refrain from large meals 4 h prior to and 1 h after radioiodine administration.

Other procedural details

Physicians should ensure that national regulations for radioiodine administration, including those regarding radiation protection, are carefully observed. Special care should be exercised to ensure that patients living with young children are properly informed of radiation protection measures. During hospitalisation, residual whole-body ^{131}I activity should be quantified by measurement using, e.g. a gamma probe, at least upon discharge and preferably daily.

Recommended pre-RAIT history and examinations

To ensure that it is appropriate to perform RAIT and to optimise the preparation method, ^{131}I activity and other aspects of the procedure, the following information should be obtained and the following examinations should be conducted before each radioiodine ablation or treatment:

- Current patient age and age at DTC diagnosis and, if applicable, age at metastatic DTC diagnosis
- Tumour pathology:
  - staging based on the tumour-nodes-metastases system
  - focality, size(s) and diameter(s)
  - histology including differentiation
  - presence or absence of capsular invasion, involvement of surrounding tissues or both
  - sites and numbers of distant metastases
- Description of prior surgical procedure(s) for DTC, e.g. extent of thyroidectomy, number and localisation of resected lymph nodes including, if possible, assignment to cervical compartments
- History including:
  - medical and other radiation exposure
  - thyroid cancer in relatives
  - prior ^{131}I and other radiopharmaceuticals, including diagnostic administrations and therapies: number, activities, dates
  - toleration of thyroid hormone withholding or withdrawal
  - exposure to contrast agent or iodinated medication, and adherence to iodine avoidance recommendations or to any prescribed low-iodine diet
  - significant co-morbidity
- Menstrual history, pregnancy and breastfeeding status in post-pubertal females and family planning status in all patients
- Physical exam
- Laboratory tests:
  - TSH (if no adequate increase after THW, followed by free LT4 testing)
  - Tg including recovery test, quantification of anti-Tg antibodies or both
  - urinary stable iodine excretion if there is suspicion of iodine excess
  - creatinine
  - calcium
  - calcitonin (post-surgery, if medullary thyroid cancer has not been ruled out)

  - parathyroid hormone (post-surgery, especially in cases with low serum calcium)
  - complete blood count with differential
  - human chorionic gonadotropin-based pregnancy test (beta-hCG) in females of childbearing potential
- History of dxWBS: radioisotope, activity, date, results
- Results of prior rxWBS
- Results of neck US and of other imaging procedures, e.g. computed tomography (CT) without contrast or magnetic resonance imaging if applicable, including a rough estimate of thyroid remnant size
- Results of pulmonary function tests, if necessary
- Results of current laryngeal nerve function tests (post-surgery)

Precautions

To optimise the safety and efficacy and minimise the negative impact of each RAIT, the following precautions should be observed:

Avoidance of "stunning": Stunning is defined as diminution of RAIT uptake and efficacy due to suboptimal therapeutic effects, biological effects, or both, of prior diagnostic radioiodine administration. In cases where RAIT clearly will be necessary, pre-therapeutic ^{131}I dxWBS or thyroid bed uptake measurement should be avoided because their results will not modify the indication for RAIT and these procedures may induce stunning. To reduce the possibility of stunning when it is not yet known whether RAIT is indicated, thyroid bed uptake quantification or ^{131}I dxWBS performed before the potential RAIT should employ low radioiodine activities. Recommended quantities are approximately 3–10 MBq for uptake quantification and 10–185 MBq for WBS. Alternatively, use of 40–200 MBq of 123-iodine (^{123}I) for diagnostic imaging minimises the risk of stunning. However, the lower imaging sensitivity and higher cost of ^{123}I compared with ^{131}I are disadvantageous. ^{123}I WBS should employ a gamma camera with a large field of view and a medium-energy, high-resolution collimator. Thyroid scintigraphy with ^{99m}-technetium can give very useful information without the need for ^{123}I.

124-iodine (^{124}I) PET/CT is emerging as an attractive experimental modality in expert hands for pre-RAIT imaging and dosimetry [43, 78, 79]. The extent of stunning effects with ^{124}I is as yet unknown, but as a precaution, activities of this radioisotope should be kept to a minimum.

Minimisation of physiological radioiodine uptake and retention: In the 24 h following radioiodine administration, liberal oral hydration and use of lemon juice or sour candy or chewing gum increases salivary flow and reduces radiation exposure of the salivary glands [80, 81]. It is not evident whether lemon juice may be even more effective 24 h after than immediately after radioiodine administration [80].

Adjuvant medication with a mild laxative increases the colonic emptying rate, decreasing radiation exposure of the intestines and facilitating scan interpretation. This measure is especially important in cases of constipation. The stomach lining should be protected by liberal oral hydration, and use of medication, e.g. H2-blockers, also may be helpful. Liberal oral hydration and frequent urination may minimise radiation exposure of the urinary bladder and the gonads.

Management of and prophylaxis against neck compression symptoms: Ice packs should be applied and non-steroidal, anti-inflammatory medication should be administered if inflammatory reaction occurs in the lower neck. In cases of radioiodine ablation of larger thyroid remnants, glucocorticoids may be optionally given for some days as prophylaxis.

Pregnancy, breastfeeding and conception: Pregnancy must be excluded by a beta-hCG-based test within a few days before each RAIT. Adjunctive use of US to rule out pregnancy may also be considered. Routine urinary pregnancy tests might miss a late (midterm) pregnancy due to both a decreased production of beta-hCG and a decreased degree of sialinisation, which results in a shorter half-life of beta-hCG due to metabolisation in the liver [82, 83]. Patients should be advised to discontinue breastfeeding for 6–8 weeks before radioiodine administration. Conception should be avoided by means of effective contraception for 6 months after RAIT, an interval that allows the replacement of irradiated by non-irradiated spermatozoa and decreases risk of fetal abnormalities [83]. Avoidance of conception for 12 months has been shown to mitigate increased risk of miscarriage [84]. If RAIT is expected to involve high cumulative ^{131}I activities, e.g. ≥14 GBq, pre-RAIT sperm banking is recommended in men whose family planning is not yet completed [85]. Additionally, female patients should be advised that a modestly earlier onset of menopause has been reported after repeated courses of RAIT [84].

Potential side effects of RAIT

Whilst RAIT is generally well-tolerated if appropriate single and cumulative activities are used and precautions employed, the procedure does have a number of potential early and late sequelae. These sequelae and potential

prophylactic and treatment interventions are described in Table 1. Characterisation of the risks of RAIT remains ongoing; for example, an overview of the radiation absorbed dose to normal organs after RAIT was published recently [86].

Alternative or additional treatments

Besides surgery [87], treatments that may be used instead of or in addition to RAIT include cytotoxic chemotherapy, external beam radiotherapy (XRT), local interventions and so-called molecularly targeted therapies. The main settings for these treatments are late-stage, progressive DTC or symptomatic or progressive lesions that are unresectable and that have failed to respond to RAIT or are unlikely to do so.

Cytotoxic chemotherapy

Cytotoxic chemotherapy has no role in the routine management of DTC but rather should be restricted, preferably within controlled clinical trials, to symptomatic, progressive, end-stage disease uncontrolled by RAIT, surgery or XRT. Among chemotherapies studied to date, doxorubicin monotherapy still provides the best clinical results, even compared with combination regimens, but attains partial response rates of at most 10–20% and very rare durable responses [88, 89]. A recent small study [90] showed a 37% response rate (5/16) in patients with non-functioning lung metastases given the combination of carboplatin plus epirubicin under TSH stimulation (endogenous or rhTSH). The TSH elevation was applied to foster tumour cell division and, hence, vulnerability to chemotherapy; this strategy merits further study, though molecularly targeted therapies may be a more promising line of investigation.

XRT

The role of XRT of primary tumours, cervical metastases or both is still controversial: evidence is available only from retrospective reviews with sometimes poorly defined inclusion criteria, inconsistent treatment regimens or obsolete standards of radiotherapy [93]. Traditional indications for XRT in the DTC setting have been unresectable gross disease, gross tumours left behind after operation, gross evidence of local invasion or as post-operative adjuvant therapy.

When neck lesions accumulate ^{131}I, it may be useful to give RAIT and XRT in combination, since radioiodine may stop the tumour cells in phases (G2, M) in which the cells are especially sensitive to XRT [94]. Patients with tracheal invasion by DTC have a high local recurrence rate if they have undergone a "shave" excision of the tracheal cartilage; if "en bloc surgery" is not feasible, XRT is advocated in such patients even when only microscopic disease remains [95].

In addition, XRT should be considered in the management of painful bone metastases or of metastases in critical locations likely to result in fractures or neurological or compressive symptoms, if these lesions are not amenable to surgery [91, 96–98]. Use of RAIT in combination with XRT may increase the response, especially in painful bone lesions [98].

One strategy for formulating XRT regimens is to take a similar approach to that used with other head and neck carcinomas. According to this strategy, total delivered absorbed doses should be 65–70 Gy to gross disease left behind, 60 Gy to adjacent target volume with risk of microscopic dissemination and 50 Gy to microscopic disease in a pre-operative setting. For DTC, a 2 Gy/fraction administered 5 days/week is most often used, but fractionation regimens have not been systematically evaluated. Another strategy for XRT regimen formulation is to choose the highest doses that are reasonably well-tolerated [92].

When possible, XRT of the neck should employ the three-dimensional conformational or intensity-modulated radiation therapy techniques, which provide better balance between anti-tumour efficacy and safety of normal adjoining structures than do traditional delivery methods [93]. Appropriate precautions should be taken to prevent radiation myelopathy. If possible, salivary glands on the least affected side should be excluded from the radiation target volume to prevent xerostomy.

XRT of distant metastases should follow similar practices to those employed with XRT of the neck, but with special consideration of the frequently slow progress of metastatic disease. A long expected survival together with a good performance status speak in favour of a lower fractionation dose (Gy/fraction) to potentially reduce late toxicity and in favour of a higher total absorbed dose to improve local control.

Local interventions

Local interventions to ameliorate symptoms or slow tumour progression include chemoembolisation, radiofrequency ablation or cement injection and, as a systemic therapy, bisphosphonate medication [10].

Molecularly targeted therapies

With improved understanding of the genetic and molecular bases of DTC, molecularly targeted therapies for the malignancy have emerged, particularly in the past decade, as the focus of considerable pre-clinical and clinical

research. Present molecularly targeted therapies can mostly be classified as (1) cell signalling or angiogenesis inhibitors or as (2) inducers of tumour cell re-differentiation and, hence, potentially, radioiodine uptake, retention or both [10].

A variety of compounds targeting vascular endothelial growth factor receptors, RET tyrosine kinase, BRAF kinase or membrane receptor kinases are currently in phase II clinical trials, have had preliminary results reported or both (reviewed in [10]). The preliminary results have included disease stabilisation or response. Some of the molecular targets of these compounds occur more frequently or exclusively in certain DTC histotypes, e.g. somatostatin receptor type 2 in Hürthle cell carcinoma; few, if any, of the targets are expressed in all DTC tumours [10, 100]. Hence, the future use of cell signalling agents or angiogenesis inhibitors is likely to entail pre-therapeutic pharmacogenomic testing to select patients in whom a given medication or combination of medications is likely to be efficacious.

The most widely investigated re-differentiation therapies have been the vitamin A analogues, the retinoids [10, 100–105], which by binding to their receptors, increase NIS expression and radioiodine uptake in tumour cells [103, 104]. However, de-differentiated DTC cells have numerous metabolic defects other than deficient NIS expression, and these defects may, for example, impair radioiodine retention, decreasing the tumour dose and RAIT efficacy [10]. This phenomenon may partially account for the relatively low response rates—20% to 30%—to retinoid re-differentiation therapy in clinical trials to date [10, 100]. Another explanation for the low response rates may be that studies till now have not screened patients for retinoid receptor expression; use of such screening might increase response rates even as it narrows the treated population [10, 100]. Of interest, a recent case report suggests that retinoids may exert therapeutic biological effects independent of enhancing RAIT [107].

Patient counselling

Before receiving RAIT, patients should be informed about:

- additional or alternative therapeutic and management options, as appropriate, including “watchful waiting”,
- potential benefits of RAIT,
- potential adverse effects and risks of RAIT (Table 1),
- advantages and disadvantages of THW and rhTSH and regulatory status of the latter,
- the need and methods to avoid iodine excess,
- the need for hospitalisation during RAIT,
- radiation protection recommendations during hospitalisation and after discharge,
- the need to avoid pregnancy and breastfeeding and the need for both female and male patients to use effective contraception for 6–12 months after RAIT,
- the need for lifelong, risk-adapted follow-up care for DTC patients and the importance of adherence to suppressive doses of LT4 in cases where such doses are indicated,
- local, regional and national support groups and other resources for DTC patients and their families.

It can be helpful to reiterate the above information in written handouts that patients and families can refer to at home. Clinicians should document the pre-RAIT counselling and should obtain written informed consent as required by institutional, regional or national regulations.

Post-therapy scintigraphy

Because of its high sensitivity for localising and characterising the extent of thyroid remnant and tumour and detecting previously occult lesions, whole-body gamma scintigraphy with spot imaging of regions of interest (ROIs) as applicable, should be performed following every RAIT. rxWBS should not take place sooner than 72 h after radioiodine administration during THW or sooner than 72 h after the second injection of rhTSH. Appendix 2 presents additional considerations for rxWBS.

Whenever available, single photon emission computed tomography (SPECT) or, preferably, SPECT/CT of the neck and other anatomical regions as appropriate and feasible, should be performed at the time of rxWBS. By providing a three-dimensional image of involved lymph nodes, SPECT is an excellent means of visualising DTC lymph node lesions, and SPECT/CT adds morphological information to the functional data furnished by SPECT alone [107].

Issues requiring clarification

- Role of outpatient RAIT.
- Optimal ^{131}I activities for safe and effective radioiodine ablation.
- Optimal definition of ablation success.
- Value of radioiodine therapy in patients with measurable or increasing Tg levels, e.g. >10 ng/ml under TSH stimulation, but no evidence of tumour in morphological or functional imaging, e.g. negative ^{131}I dxWBS.
- Optimal ^{131}I activities and number/schedule of therapies to treat incompletely or non-operable tumour.
- Impact on “stunning” of the length of the interval between a pre-RAIT ^{131}I dxWBS and the RAIT itself.
- Value of dosimetrically determined versus fixed empirical activities for RAIT.

- Role of rhTSH as preparation for RAIT to treat incompletely or non-resectable local recurrence or metastases, especially for RAIT with curative as opposed to palliative intent.
- Value of a low-iodine diet in light of an increasing alimentary iodine supply.
- Correlation between urinary stable iodine excretion values and extent of iodine interference with radioiodine uptake and efficacy; optimal cut-off urinary stable iodine excretion level predicting clinically relevant iodine interference.
- Role of pre-RAIT retinoids (vitamin A derivatives) for tumour cell re-differentiation and improvement of ^{131}I uptake into metastases.
- Role of re-differentiation therapy with peroxisome proliferator-activated receptor gamma agonists, an experimental modality that, in animal models, has been shown to induce tumour cell apoptosis and to slow tumour growth.
- Value of lithium therapy to improve radioiodine retention by tumour cells.

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Chart 1. Indications and contraindications radioiodine treatment of DTC

A. Definite indications

1. Unresectable iodine-avid lymph node metastases where one or more of the following is true:
   - morphological imaging does not reveal location
   - surgery is high-risk or contraindicated
   - distant involvement is present that would indicate RAIT anyways
2. Iodine-avid pulmonary micrometastases, especially before they become visible on CT
3. Non-resectable or partially resectable iodine-avid pulmonary macrometastases
4. Non-resectable or partially resectable iodine-avid soft tissue metastases

B. Optional indications

1. Recurrent iodine-avid lymph node or distant metastases, as an adjuvant to surgery
2. Unresectable iodine-avid lymph node metastases where one or more of the following is true:
   - size is small
   - involvement includes numerous nodes or is widespread
3. Non-resectable or partially resectable iodine-avid bone metastases, especially when symptomatic or threatening vital structures
4. Known or suspected metastatic DTC where iodine avidity is not yet known, especially if Tg is detectable or increasing[a]
5. Anaplastic or poorly differentiated thyroid carcinomas that have (relevant) well-differentiated areas or express Tg, especially if symptomatic or progressive[b]

C. Non-indications

1. Iodine non-avid lymph node metastases
2. Iodine non-avid lung macrometastases
3. Iodine non-avid bone metastases

D. Contraindications

1. Pregnancy
2. Breastfeeding
3. Clinically relevant bone marrow depression when high-activity RAIT is planned (relative contraindication)
4. Clinically relevant pulmonary function restriction together with expected important accumulation in lung metastases (relative contraindication)
5. Clinically relevant salivary gland restriction, especially if ^{131}I accumulation in known lesions is questionable (relative contraindication)

Legend:

CT, computed tomography; DTC, differentiated thyroid carcinoma; ^{131}I, 131-iodine; RAIT, radioiodine therapy; Tg, thyroglobulin

Notes:

[a]These patients should receive an initial course of RAIT, and if the rxWBS is negative, RAIT should be discontinued.

[b]In these patients, the indication for XRT and the urgency of RAIT should be considered in the decision on whether to give RAIT.

Appendix 1. Pre-therapeutic dosimetry concepts for radioiodine therapy

Pre-therapeutic dosimetry for RAIT may take either or both of two forms: (1) remnant- and lesion-based dosimetry and (2) bone marrow (blood) dosimetry.

A. Remnant- and lesion-based dosimetry

1. Objective

The objective of remnant or lesion dosimetry, sometimes referred to as the "Maxon approach" in honour of one of its key developers, is to determine the individualised radioiodine activity that delivers the recommended doses of radiation to ablate thyroid remnant or to treat metastatic disease whilst minimising the risk to the patient. These absorbed doses are traditionally considered to be ≥300 Gy to ablate thyroid remnant and ≥80 Gy to successfully treat metastatic disease [115]. Individualising the RAIT activity may help avoid over- or under-treating the remnant, tumour or both, which is presumed to have efficacy or safety benefits, or both.

2. Procedures

To perform these calculations, it is necessary to measure the uptake and clearance of the ^{131}I from identifiable thyroid remnants, DTC metastases or both. To determine the ^{131}I concentration, one needs to know how much activity is contained in the lesion. One way to determine this is through an analysis of selected ROIs on conjugate view gamma camera images or on SPECT images [116].

These images are obtained at several time points following the administration of a tracer activity. Typically, these images would be acquired up to 96 h after tracer administration, but later time samples might be necessary if the uptake and clearance are delayed. In addition, transmission images, scatter images or both might be necessary to correct for attenuation or scatter or in the region of the lesion. Images of a standard for calibration purposes might also be needed [116]. A curve-fitting procedure then is used to determine the assumed single-exponential half-life value and to extrapolate the curve to time zero to determine the initial activity in the lesion.

Pre-therapeutic dosimetric assessments of the activity required to achieve a certain prescribed absorbed dose to a remnant or lesion are often based on adaptations of the generic MIRD equation for absorbed dose [117]:

$$\overline{D} = \frac{\widetilde{A} \times S \times m_{\mathrm{r}}}{m_{\mathrm{t}}}$$

where $\overline{D}$ denotes the mean absorbed dose to the remnant/lesion, $\widetilde{A}$, the cumulative activity (the integral of the activity–time curve), m_{r}, the reference mass of the thyroid (20.7 g), and m_{t} is the remnant/lesion mass. S is the MIRD-defined S value for thyroid self-irradiation (5.652×10^{-3} Gy MBq^{-1} h^{-1}, see MIRD Pamphlet 11 [117] or, for example, the guidelines of the German Society of Nuclear Medicine [118]).

3. Mass determination

The lesion mass is another variable needed in order to calculate the activity concentration delivering the required absorbed dose. For ablation therapies, remnant volumetry methods such as US or CT are unreliable, as it is impossible to differentiate thyroid tissue from haematoma on these modalities. Thus no thoroughly validated method yet exists to exactly determine the mass of thyroid remnants after surgery [73]. For this reason, one must be careful when reporting absorbed doses to the target tissue. For lesion dosimetry, higher spatial resolution images, such as those obtained with CT or US, can be used for attenuation correction and to determine the mass.

If the lesions are small, the nodule module of the OLINDA/EXM software might be useful to generate a spherical model of the remnant, tumour or both [119]. Furthermore, if the dimensions of the lesions are smaller than approximately 5 mm—assuming that this could be accurately determined—then the range of the beta particles can no longer be neglected in the dose calculation [120].

4. PET-based lesion dosimetry

The use of ^{124}I was proposed for quantifying in vivo tumour radioiodine concentration and biodistribution in DTC patients [78, 79, 121, 122]. Due to the complex decay process of ^{124}I, the quantification process cannot be performed in the same way as for the pure positron emitter FDG. Pentlow et al. [78] measured resolution, linearity and the ability to quantify the activity contents of imaged spheres of different sizes and activities in different background activities. It was shown that the ^{124}I quantification could reproduce the activities administered. ^{124}I PET was also successfully applied to the measurement of thyroid volume [121, 122]. Today's state-of-the-art ^{124}I PET-based DTC dosimetry protocol has been described in recent publications by Sgouros et al. [79]. Using the PET results as input to a fully three-dimensional dose planning programme, those investigators calculated spatial distributions of absorbed doses, isodose contours, dose–volume histograms and mean absorbed dose estimates for a total of 56 tumours. The mean tumour absorbed dose for each patient ranged widely, from 1.2 to 540 Gy. The absorbed dose distribution for individual tumour voxels was even more widely distributed, ranging from 0.3 to 4,000 Gy.

Findings similar to those of the Sgorous and coworkers study, of median per-patient tumour radiation absorbed doses between 1.3 and 368 Gy, were recently reported by de Keizer et al. [71] who performed tumour dosimetry after rhTSH-stimulated ^{131}I treatment. Dosimetric calculations were performed using tumour radioiodine uptake measurements from post-treatment ^{131}I scintigrams and tumour volume estimations were generated from radiological images.

5. Limitations

The main disadvantages of a lesion-based approach to RAIT dosimetry in DTC are:

- Absorbed lesion doses range widely even within a single patient.

- Contrary to assumptions inherent in dosimetry protocols, absorbed dose distributions vary within lesions, which could result in incomplete tumour destruction.
- A mono-exponential model may not accurately reflect lesional radioiodine kinetics.
- Unclearly defined correction factors must be applied for the initial phase of increasing uptake (up to approximately 24 h post-radioiodine administration).
- An accurate estimate of the lesion mass is not always possible, e.g. with disseminated iodine-avid lung metastases or irregularly shaped lesions.
- Low uptake in lesions and, therefore, low count rates may cause statistical errors in the measurements.
- The biological effectiveness of dosimetry-guided RAIT is not proven yet.
- Doses may be systematically underestimated for lesions <5 mm in diameter if no corrections are applied.

In addition, currently, when ^{131}I is used, relatively high diagnostic activities, i.e. at least 37 MBq, are necessary for quantitative imaging of the target thyroid tissue for dosimetry; these activities have the potential to induce "stunning" (see the "Precautions" section above), which is a particularly critical consideration in radioiodine treatment of metastatic disease [123].

B. Bone marrow (blood) dosimetry

1. Overview

The method originally reported by Benua et al. [42] and Leeper [124] allows the estimation of the radiation dose that will be delivered to the haematopoietic system from each GBq administered to any patient. The method involves measurement of radiation counts of serial blood samples and serial calibrated probe measurements of the patient's whole-body activity over the course of 4 or more days after ^{131}I tracer administration. The original Benua et al. study [42] determined that the subgroup of patients who received ≤2 Gy to the blood avoided serious myelosuppression; this dose has become the principal traditionally accepted safety threshold for RAIT. In addition, the whole-body retention at 48 h after radioiodine administration should not exceed 4.44 GBq (120 mCi) in the absence of iodine-avid diffuse lung metastases or 2.96 GBq (80 mCi) in the presence of such lesions [39].

2. More recent developments

In the classic Benua approach, the blood is considered the critical organ that is irradiated either by the particles emitted from activity in the blood itself or by the emissions originating from activity dispersed throughout the remainder of the body. Recently, in the framework of international multi-centre studies of radioiodine biokinetics after rhTSH administration [125], the absorbed dose to the blood was calculated with a modified method derived from a procedure originally described by Thomas et al. [126]. Refinements to this model have been introduced to account for:

- the contribution to the blood dose of penetrating radiation from activity in distant blood,
- the mass dependency of the S value representing the radiation from the total body to the blood,
- a mean value, $S_{\text{blood}\leftarrow\text{blood}}$, representing an average for blood circulating in vessels of varying diameters and s values [44].

The recent studies show that the results of pre-therapeutic blood-based dosimetry agree well with measured post-therapeutic absorbed doses. Therefore, the pre-therapeutic data can reliably project therapeutic absorbed doses to blood.

For blood-based dosimetry, only two compartments need be monitored for radioactivity: the blood and the gamma ray absorbed doses to the whole body. The activity in the blood is determined by measuring periodic heparinised blood samples. The activity in the whole body, i.e. remaining in the patient, can be monitored redundantly using independent techniques: 24-h urine collections, whole-body counting with a probe using a fixed geometry and, if applicable, conjugate views of a WBS obtained with a dual-headed gamma camera.

Details regarding the sampling times, measurements and calculations can be found in the EANM Dosimetry Committee Series on Standard Operational Procedures for Pre-Therapeutic Dosimetry (I. Blood and Bone Marrow Dosimetry in Differentiated Thyroid Cancer Therapy) [44].

The recommended equation for the absorbed dose to the blood per unit of administered activity [44] is:

$$\frac{D_{\text{blood}}}{A_0}\left[\frac{\text{Gy}}{\text{GBq}}\right] = 108 \times \tau_{\text{ml of blood}}[\text{h}] + \frac{0.0188}{(\text{wt}[\text{kg}])^{2/vlldelimiterspace3}} \times \tau_{\text{total body}}[\text{h}]$$

$\tau_{\text{total body}}$ [h] and $\tau_{\text{ml of blood}}$ [h] stand for the residence time in a source organ, representing the integral of the time–activity curve in that organ (cumulative activity) divided by the administered activity A_0; wt represents the patient's weight. In addition, the EANM Dosimetry Committee guidelines give a formula for the assessment of the absorbed dose to the bone marrow [44].

The tracer activity necessary for a reliable assessment of the whole-body residence time depends on the equipment used (see Section 3.3 in [44]). The potential risk of the diagnostic absorbed dose dramatically changing the iodine kinetics in target tissue limits the administered activity to amounts much lower than 74 MBq ^{131}I [123]. Under all circumstances, one should avoid administering activities which lead to total absorbed doses to iodine-avid tissue of >5 Gy [127].

An activity of 10–15 MBq of ^{131}I should suffice for a pre-therapeutic blood-based dosimetry assessment. Based on experience to date, this range of activities will provide sufficient count statistics whilst most probably not causing any changes between pre- and post-therapeutic biokinetics of ^{131}I.

3. Strengths and limitations

The strengths of the blood-based approach are:

- determination of the maximal safe activity of radioiodine for each RAIT in each individual,
- identification of patients for whom empiric fixed activities are not safe [128],
- the potential to administer higher activities once instead of lower activities multiple times in a "fractionated" therapy to avoid changes in lesion biokinetics after multiple therapies that have been observed, e.g. by Samuel et al. [129],
- a long history of use in several institutions,
- an expected increase in the probability of curing patients in advanced stage of the disease with fewer courses of therapy.

Limitations that need to be mentioned are:

- a benefit of the strategy is plausible, but no valid clinical data yet exist on improved response or outcome rates;
- the absorbed dose to the tumour is not known: higher activities might be administered without achieving a better therapeutic effect when using this methodology;
- the current debate regarding the issue of "stunning" argues that diagnostic administrations of ^{131}I could alter lesion biokinetics and, consequently, the absorbed dose in a subsequent RAIT;
- increased cost and inconvenience, although this may be outweighed by rendering further treatments unnecessary.

Patient-specific blood-based dosimetry is easy to perform both pre-therapeutically and peri-therapeutically and allows the RAIT activity for selected patients to be increased without risk of severe side effects. In addition, simplified protocols have not been tested yet.

Appendix 2. Additional considerations in rxWBS

A. Purpose of rxWBS

Detection and localisation or exclusion of one or more of functioning thyroid remnants, persistent or recurrent local disease or metastases in patients with DTC.

B. Image acquisition

^{131}I rxWBS should employ a gamma camera with a large field of view and a high-energy collimator. Preferably, a camera with a thick, e.g. 2.5 cm, sodium iodide crystal should be used to increase the sensitivity of the scan.

The patient should lie supine on an imaging table with moderate head reclination. Anterior and posterior images should show the whole body. Spot images should be obtained for at least 5–10 min per view. If images are obtained with a whole-body scanner, the scan speed should be adjusted so that whole-body imaging takes at least 20–30 min per view. Longer imaging times may be helpful for images obtained more than 3 days after radioiodine administration.

C. Interpretation and quantification

rxWBS images should be interpreted visually for location of functional tissue. The quantification of radioiodine uptake in functioning tissue by a ROI technique and by comparison with a calibrated ^{131}I activity can be helpful for post-therapeutic dosimetry and for follow-up data.

D. Reporting and documentation

The report should include the location, size and intensity of any areas of uptake that correspond to any functioning tissue. Description of comparisons with prior images is useful. The results of Tg assays and TSH are helpful for the interpretation of the scintigraphic findings.

Documentation (radiographic films or paper prints or computer files) should include:

- patient's name for identification,
- radiopharmaceutical administered,
- activity administered in MBq,
- timing of the images in relation to radiopharmaceutical administration,
- acquisition time in minutes and counts acquired,
- in the case of functioning tissue, imaging of ROIs of the hot spot, of background activity and of calibrated activity (for dosimetry purposes).

E. Quality control

Many national nuclear medicine societies have written guidelines to promote the cost-effective use of high-quality nuclear medicine procedures. Relevant parameters of quality control for gamma cameras are, e.g. background activity, energy window, homogeneity, spatial resolution and linearity.

F. Error: potential sources and avoidance

Potential sources of error in rxWBS interpretation include:

- local contamination (clothing, skin, hair, collimator, crystal),
- oesophageal activity,
- asymmetrical salivary gland uptake,
- non-specific uptake, e.g. in pulmonary infections, oedema, the breast, kidney cysts and the thymus.

To avoid artefacts caused by cutaneous contamination with radioiodine, the patient should shower and change underwear before rxWBS.

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