7 Radioiodine Theranostics of Differentiated Thyroid Carcinoma

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7.1 Introduction

DTC is a slow-growing tumor with a very low disease-specific mortality rate for local-regional disease (5-year survival 99.9% for localized disease, and 98.3% for regional metastatic disease), however, distant metastatic disease is associated with significantly worse prognosis (5-year survival 54.9%) [1]. Standard of care management for differentiated thyroid cancer (DTC) includes risk-adapted surgery, post-operative Iodine-131 (^{131}I) therapy, and thyroid hormone therapy. In uncommon cases of radioiodine-refractory tumors, additional therapy may include re-operative surgical intervention, external radiotherapy, and interventional radiology for the treatment of locoregional metastases, and multi-kinase or tyrosine kinase inhibitors for treatment of distant metastatic disease.

Current thyroid cancer guidelines emphasize a patient-individualized approach to therapeutic 131-I administration, recommending against 131-I ablation in low-risk tumors and selective use of 131-I therapy for medium-risk patients [2–4]. Defining the categories of low-, intermediate- and high-risk patients is important for clinical implementation of risk-adapted therapeutic 131-I administration and the 2015 American Thyroid Association (ATA) guidelines introduced the concept of continuum of risk based on estimated risk of structural disease recurrence according to surgical histopathology information [3]. Although referral for post-operative 131-I therapy is predicated on risk stratification based on surgical pathology information, post-operative diagnostic radioiodine (RAI) scintigraphy contributes to the completion of staging and risk stratification itself, thus having the potential to influence 131-I therapeutic strategy [5].

7.2 Diagnosis

The most common clinical presentation of DTC is as an incidental thyroid nodule. Neck ultrasound (US), serum thyroid stimulating hormone (TSH), and thyroid scintigraphy are used to select high-risk nodules for fine-needle aspiration (FNA). Sonographic features have been used to produce a standardized risk assessment for thyroid malignancy named Thyroid Imaging Reporting and Data System (TIRADS) [6, 7]. In the absence of suspicious cervical lymph nodes, FNA is discouraged for nodules less than 1 cm, and the decision to aspirate larger nodules is guided by the TIRADS score in the context of nodule size. The cytologic risk of malignancy is determined using the Bethesda System for Reporting Thyroid Cytopathology [8].

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L. Giovanella (ed.), *Integrated Diagnostics and Theranostics of Thyroid Diseases*,
https://doi.org/10.1007/978-3-031-35213-3_7

7.3 Surgical Treatment

Traditionally, (near-) total thyroidectomy was performed in most DTC patients, with lobectomy reserved for cytologically indeterminate nodules or patients with unifocal micro-PTC < 1 cm. Currently, lobectomy is sometimes suggested for patients with unifocal intrathyroidal low-risk DTC in the absence of additional risk factors (i.e., no clinical evidence of nodal metastases, cN0) [3]. The management of low-risk DTC between 2 and 4 cm is a topic of debate: While a lobectomy may be proposed, total thyroidectomy is still largely advised [9]. Active surveillance is an alternative to lobectomy for unifocal micro-PTC with no extracapsular extension or lymph node metastases [10]. The decision for active surveillance is based primarily on age-related risk of progression, individual surgical risk factors, and patient preference [11]. In all other cases, total thyroidectomy remains the preferred surgical approach [12].

Cervical lymph nodal metastases occur in 20–60% of patients with DTC and this nodal involvement varies from clinically relevant macrometastasis to seemingly clinically irrelevant micrometastases [13, 14]. When lymph nodal metastases are diagnosed pre-operatively, central and/or lateral neck compartment dissection reduces the risk of local-regional recurrence. Prophylactic central neck dissection may improve regional control for invasive tumors (T3–T4), but it is discouraged for low-risk DTC because potentially associated morbidities (i.e., hypoparathyroidism and recurrent laryngeal nerve damage) are not justified by a significant clinical benefit [15].

7.4 Staging and Risk Stratification for Differentiated Thyroid Cancer

The concept of oncologic staging is central for providing a baseline assessment and defining a management strategy in malignant diseases. Staging systems define the mortality risk in thyroid cancer using pTNM classification and the derived AJCC staging (summarized in Tables 7.1 and 7.2) [16].

Table 7.1 TNM classification for differentiated thyroid cancer. TNM UICC/AJCC 8th edition (2017) [16]

		TNM 2017
	Tx	Primary tumor cannot be assessed
T	T0	No evidence of primary tumor
	T1a	T ≤ 1 cm[a]
	T1b	T > 1 cm and ≤ 2 cm[a]
	T2	T > 2 cm and ≤ 4 cm[a]
	T3	T3a: Tumor more than 4 cm in greatest dimension, limited to the thyroid
T3b: Tumor of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles)		
	T4a	Tumor extends beyond the thyroid capsule and invades any of the following: Subcutaneous soft tissues, larynx, trachea, esophagus, and recurrent laryngeal nerve
	T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
N	Nx	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1a	Metastases in level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinum (level VII)[a]

Table 7.1 (Continued)

		TNM 2017
	N1b	Metastasis in other unilateral, bilateral, or contralateral cervical lymph nodes (levels I, II, III, IV, or V) or retropharyngeal
M	M0	No distant metastasis is found
	M1	Distant metastasis is present

[a] In this edition, minor extrathyroidal extension that involves perithyroidal adipose tissue, strap muscles, nerves, or small vascular structures, identified only by microscopy but not clinically appreciated (no gross invasion), is no longer used as a risk factor for staging; superior mediastinal (level VII) nodes are scored N1a

Table 7.2 AJCC prognostic grouping for differentiated thyroid cancer. TNM UICC/AJCC 8th edition (2017) [16]

	AJCC 8th edition (2017)	
	Stage < 55 years old	Stage ≥ 55 years old
Stage I	Any T, any N, M0	T1/T2, N0, M0
Stage II	Any T, any N, M1	T3a/T3b, N0, M0 T1/T2/T3, N1, M0
Stage III	–	T4a, any N, M0
Stage IVA	–	T4b, any N, M0
Stage IVB	–	Any T, any N, M1
Stage IVC	–	–

Table 7.3 Suggested framework for ^{131}I therapy

Strategy	Prescribed ^{131}I activity	Clinical/Pathological context
Risk-adapted ^{131}I therapy	1.11–1.85 GBq (30–50 mCi) ^{131}I[a]	Remnant ablation
Risk-adapted ^{131}I therapy	1.85–3.7 GBq (50–100 mCi) ^{131}I	Adjuvant treatment
Risk-adapted ^{131}I therapy	3.7–5.6 GBq (100–150 mCi) ^{131}I	Treatment of small volume local-regional disease
Risk-adapted ^{131}I therapy	5.6–7.4 GBq (150–200 mCi) ^{131}I	Treatment of advanced local-regional disease and/or small volume distant metastatic disease
Whole body/blood dosimetry	≥ 7.4 GBq (≥ 200 mCi) ^{131}I, maximum tolerable safe ^{131}I activity	Treatment of diffuse distant metastatic disease

[a]FDA approved the use of rhTSH in combination with 100 mCi ^{131}I for remnant ablation in December 2007 [1, 17]. Reproduced with permission from [18]

The risk of structural disease recurrence is defined by ATA as a continuum of risk for structural disease recurrence resulting in a 3-level system of risk stratification described as low-, intermediate-, or high-risk based on surgical pathology and clinical information (summarized in Table 7.3) [3]. Both staging and risk stratification play a crucial role in defining the initial management strategy and subsequent long-term surveillance for patients with thyroid cancer. Due to its indolent nature, thyroid cancer has a very low disease-specific mortality rate for local-regional disease after complete initial therapy (5-year survival 99.9% for localized disease, and 97.8% for regional metastatic disease), however, distant metastatic disease is associated with significantly worse prognosis (5-year survival 55.3%) [19] Therefore, in addition to staging which is used to predict disease-specific survival, secondary outcome variables such as rates of persistent disease, rates of recurrent disease, medico-economic issues, and quality of life outcomes, need to be considered when deciding 131-I therapeutic strategy [20].

7.5 Post-operative Management

Post-operative evaluation includes Tg measurement, neck US and diagnostic radioiodine (^{131}I or ^{123}I) whole-body scan (DxWBS) which is helpful to identify persistent disease and characterize tumor ^{131}I avidity. Institutional management protocols are established by multidisciplinary teams based on the local availability and expertise of the surgical, pathology, radiology, and laboratory components integral to the DTC treatment algorithm [21].

7.6 Post-operative ^{131}I Therapy

The goal of ^{131}I therapy is outlined based on standardized definitions as follows: *remnant ablation, adjuvant treatment, or treatment of known disease* [21, 22]. Upon integration of various parameters including clinical-pathologic, laboratory, and imaging information, ^{131}I therapy is administered for the following reasons:

- *Remnant ablation*, for elimination of the normal thyroid remnant tissue which achieves undetectable or minimal serum Tg levels (in the absence of neoplastic tissue) and facilitates follow-up.
- *Adjuvant treatment*, for elimination of suspected but unproven sites of neoplastic cells with the goal of reducing the risk of disease recurrence.
- *Treatment of known disease*, for treatment of persistent or recurrent metastatic disease.

7.7 Benefits of 131-I Therapy in Thyroid Cancer

The impact of ^{131}I therapy on the clinical outcome of thyroid cancer patients has been demonstrated in several large data series. An analysis of 2936 DTC patients in the National Thyroid Cancer Therapy Cooperative Study Group (NTCTCS) reported improved overall survival and disease-specific survival in patients with advanced tumors and regional and/or distant metastatic disease who received post-operative ^{131}I therapy [23]. An updated analysis of 4941 patients in the NTCTCS study with a median follow-up of 6 years (range 0–25 years) confirmed improved overall survival in stages III and IV patients, and also demonstrated improved disease-free survival for stage II patients receiving ^{131}I therapy [24]. A meta-analysis of 31 patient-cohort studies regarding the effectiveness of ^{131}I therapeutic administration demonstrated a statistically significant effect on improving clinical outcomes at 10 years, with decreased risk for local-regional recurrence (RR 0.31; CI 0.2–0.49) and an absolute risk reduction of 3% for distant metastatic disease [25]. An analysis of the National Cancer Database comprising 21,870 intermediate-risk patients demonstrated that adjuvant ^{131}I treatment improved overall survival, both for the younger (<45 years) and for the older (≥65 years) subsets of patients. Adjuvant ^{131}I therapy was associated with a 29% reduction in the risk of death for all patients [26]. The beneficial effects of post-operative ^{131}I therapy are most evident in patients with local-regionally advanced and distant metastatic disease (stages IV-A, IV-B, and IV-C disease): an analysis of the National Cancer Database comprising 11,832 patients demonstrated that the administration of ^{131}I therapy was associated with significantly improved 5- and 10-year survival for both PTC and FTC patients, regardless of pathological sub-stage (Stage IV A, B, or C), as follows: mortality in the PTC cohort (n = 10,796) at 5 years at 10 years was 11% and 14%, respectively, in patients who received ^{131}I therapy, as compared to 22.7% and 25.5%, respectively, in patients who received none; mortality in the FTC cohort (n = 1036) at 5 years at 10 years was 29.2% and 36.8%, respectively, in patients who received ^{131}I therapy, as compared to 45.5% and 51%, respectively, in patients who received none [27].

7.8 Preparation for ^{131}I Therapy

Evaluation with radioiodine scintigraphy and ^{131}I therapy is scheduled at a minimum of 4 weeks after surgery, which allows time for patient preparation and for reaching post-operative Tg plateau levels, used as a marker for residual thyroid tissue and/or metastatic thyroid cancer after total thyroidectomy. Tg levels must always be interpreted in the context of concomitant TSH level (unstimulated vs. stimulated Tg) and type of TSH stimulation (endogenous vs. exogenous) [28]. Patient preparation for optimal ^{131}I uptake by residual thyroid tissue and metastatic disease includes 1–2 weeks of a low-iodine diet (LID)—see Table 7.2, and adequate TSH stimulation (TSH ≥ 30 mIU/L, measured 1–3 days prior to ^{131}I administration) by either a thyroid hormone

withdrawal (THW) or recombinant human TSH (rhTSH) stimulation [29]. For childbearing females (aged 12–50 years) a negative pregnancy test is required to be obtained within 72 h of ^{131}I administration, or prior to the first rhTSH injection (if employed), unless the patient is status post hysterectomy or postmenopausal.

There are two major approaches for obtaining TSH stimulation which is necessary for increasing Na-I symporter (NIS) expression and function in metastatic lesions (and residual thyroid tissue) with the goal of increasing diagnostic sensitivity of ^{131}I scintigraphy and radiation absorbed dose to target lesions

1. *Endogenous TSH stimulation* is obtained through thyroid hormone deprivation following total thyroidectomy, thus inducing a hypothyroid state: the hypothyroid stimulation protocol (THW) has 2 variants: a) L-T4 (levothyroxine) withdrawal for 4 weeks; this interval is determined by T4 elimination half-life (T4 $t_{1/2}$) of 7 days and the physiologic pituitary response to declining T4 concentrations. b) T4/T3 (levothyroxine/liothyronine) substitution for the first 2 weeks, followed by discontinuation of T3 for 2 weeks; this interval is based on T3 $t_{1/2}$ of 0.75 days.
2. *Exogenous TSH stimulation:* The patient continues T4 treatment and undergoes preparation with low-iodine diet. TSH elevation is obtained through administration of rhTSH (Thyrogen ® Stimulation Protocol): 0.9 mg rhTSH injection is administered intramuscularly on two consecutive days, followed by ^{131}I therapy administration at 48–72 h.

The choice of preparation method (THW vs. rhTSH) needs to be individualized for each patient. There is general agreement that for normal thyroid tissue (i.e., thyroid remnant), rhTSH and THW stimulation are equivalent, because normal thyroid tissue has constitutive high expression of highly functional NIS and does not require prolonged TSH stimulation for adequate ^{131}I uptake and retention. However, metastatic thyroid cancer has lesser density and poorer functionality of NIS, and therefore TSH elevation over time (area under the curve of TSH stimulation) is important to promote increased ^{131}I uptake and retention in tumors [30, 31]. In the setting of distant metastatic disease THW preparation and dosimetry-guided ^{131}I therapy is favored, when clinically safe and feasible [32–34].

7.9 ^{131}I Therapy Administration

There are two approaches to ^{131}I therapy delivery: the theranostic approach which integrates the information obtained with post-operative diagnostic (Dx) radioiodine (^{123}I, ^{131}I or ^{124}I) scans in the management algorithm, and the empirical approach based on clinical-pathologic factors and institutional protocols.

7.9.1 Diagnostic and Post-therapy 131-I Scans with Diagnostic Intent

Historically, post-therapy 131-I imaging had the advantage of superior activity counts statistics (count density) and appeared to provide more diagnostic information than diagnostic 131-I scans. In addition, the issue of stunning by the diagnostic 131-I scan activity was raised (defined as a reduction of 131-I uptake seen on post-therapy scan as compared to the diagnostic scans and interpreted as potentially causing a decreased effect of the subsequent 131-I therapy dose when administered after diagnostic 131-I scans) [35–37]. However, other studies have questioned the clinical relevance of stunning demonstrating little or no clinical evidence of stunning [38–42]. Stunning appears not to be a problem when activities <2 mCi 131-I are utilized for diagnostic scintigraphy and when 131-I therapy is administered within 72 h of the diagnostic 131-I activity [43–45]. It is possible that stunning may be related to a true cytocidal effect of the high 131-I diagnostic activities (5–10 mCi 131-I) used in the past, and therefore an effort to decrease administered diagnostic 131-I activity and optimize the imaging technique to preserve diagnostic sensitivity for disease detection is

important [43]. Progress in gamma camera instrumentation over the past 10 years led to significant improvement in spatial and contrast resolution of modern gamma camera systems making possible the acquisition of high-quality diagnostic 131-I scintigraphic images highly concordant with the post-therapy 131-I scans. McDougall et al. reported in a cohort of 280 patients a 98% concordance rate between the findings obtained with 74 MBq (2 mCi) diagnostic 131-I scans and post-therapy scans obtained at 8 days after 131-I treatment [39]. Furthermore, Avram et al. reported a 92% concordance rate between the findings obtained with 37 MBq (1 mCi) diagnostic 131-I scans and post-therapy scans obtained at 2 days after 131-I treatment. In only 6% of patients, additional foci of activity were detected on post-therapy scans, however, the findings were clinically significant (i.e., upstaged the patient) in only 1.4% of cases [46]. Therefore, it is possible to use diagnostic 131-I scans for identification of regional and distant iodine-avid metastases and for planning activity-adjusted 131-I treatment. Diagnostic 131-I scans performed with modern gamma camera SPECT/CT technology and optimization of imaging protocols have been used post-operatively with good results for assessing the extent of metastatic disease and for guiding therapeutic 131-I administration [47, 48].

7.9.2 Integration of Histopathology, Laboratory, and Scintigraphy Information

Integration of diagnostic and/or post-therapy 131-I scintigraphy information and stimulated thyroglobulin (Tg) levels in the context of surgical pathology is of critical importance for determining disease status by completing initial staging and risk stratification and guiding management decisions. Tg is a glycoprotein exclusively produced by the follicular cells of the thyroid gland and metabolized in the liver. Tg levels can therefore be used as a thyroid cancer biomarker as it declines with a half-life ($t_{1/2}$) of approximately 65 h after total thyroidectomy. Tg levels can become significantly elevated immediately after surgery as compared to preoperative values due to surgical manipulation of thyroid resulting in enhanced wash-out of Tg into the circulation, and it takes approximately 25 days after surgery –10 $t_{1/2}$ for hepatic clearance) for Tg levels to become a reliable marker of residual thyroid tissue and/or metastatic disease [49]. Thyroglobulin autoantibodies (TgAb) are a marker of thyroid autoimmunity and are detected in approximately 20% of DTC patients. Presence of TgAb interferes with reliable measurement of Tg levels causing a falsely low/undetectable Tg. Therefore, every serum specimen for Tg testing needs concomitant TgAb testing to inform that Tg measurement is not compromised by TgAb interference [50]. Tg levels become undetectable in the absence of thyroid remnant and/or persisting disease after total thyroidectomy and 131-I therapy. On the other hand, an increased Tg trend is used as an indicator for residual or recurrent DTC [28].

7.10 Determining the Prescribed Therapeutic ^{131}I Activity

Current practice guidelines recommend routine ^{131}I adjuvant therapy for patients with intermediate to high risk of recurrence (although there are some differences concerning intermediate-risk disease) and avoiding routine ^{131}I therapy for patients with a small (≤1 cm) intrathyroidal DTC and no evidence of locoregional or distant metastatic spread [3, 51]. However, ^{131}I therapy for other low-risk DTC patients (i.e., pT1b-T2) remains controversial: the various iterations of the ATA guidelines advised against the systematic use of ^{131}I in these patients [3], while the 2008 European Association of Nuclear Medicine (EANM) suggests that ^{131}I therapy is helpful, citing the lack of prospective data showing that surveillance without ablation is non-inferior to ^{131}I administration [52].

The decision for ^{131}I therapy and the prescribed ^{131}I activity depends on the goal of ^{131}I therapy as determined by the estimated risk for persistent/recurrent disease. Please see Table 7.3

for suggested treatment ^{131}I activities in the context of therapeutic intent, as follows:

- *Thyroid remnant ablation* in low-risk patients is typically performed with low ^{131}I activity (e.g., 1.1–1.85 GBq; 30 mCi-50 mCi) based on the preponderance of published evidence demonstrating equal effectiveness as compared with higher 131-I activities, with lower rate of adverse events [53–89]. The Federal Drug Administration (FDA) approved the use of rhTSH (Thyrogen ®, Genzyme corporation) in combination with 3.7 GBq (100 mCi) ^{131}I for remnant ablation in December, 2007 [17, 90, 91].
- *Adjuvant ^{131}I therapy* is performed with 1.85–3.7 GBq (50–100 mCi), with some institutions extending this range to 5.6 GBq (150 mCi); there are no comparison data regarding the effectiveness of 3.7 GBq (100 mCi) vs. 5.6 GBq (150 mCi) for adjuvant treatment, while current guidelines advise that the risk for ^{131}I toxicity increases with therapeutic activity escalation [92].
- *Treatment of known disease* is performed with 3.7–5.6 GBq (100–150 mCi) for small volume local-regional disease, and 5.6–7.4 GBq (150–200 mCi) ^{131}I for treatment of advanced local-regional disease and/or small volume distant metastatic disease. Identification of iodine-avid diffuse metastatic disease may lead to escalation of prescribed therapeutic ^{131}I activity to ≥7.4 GBq (200 mCi) guided by dosimetry calculations [48, 93, 94].

A special circumstance is presented by use of ^{131}I therapy (3.7 GBq [100 mCi]) for ablation of a remaining thyroid lobe after lobectomy/hemithyroidectomy as an alternative to completion thyroidectomy [95–97]. Current guidelines propose lobectomy for patients deemed as low-risk for recurrence; however, if the pathology demonstrates a higher risk tumor, then completion thyroidectomy with resection of the contralateral thyroid lobe is recommended with the goal of facilitating post-operative ^{131}I therapy and long-term surveillance. Therapeutic ^{131}I administration as a substitute for completion thyroidectomy is not recommended routinely [3]. However, it can be used to eliminate the residual thyroid lobe in highly selected cases, such as patients who had experienced complications during initial surgery (e.g., recurrent laryngeal nerve paralysis), for whom completion thyroidectomy is contraindicated due to other comorbidities, or for patients who decline additional surgery.

7.11 The Role of Dosimetry for Thyroid Cancer Treatment

There are two approaches for individualization of 131-I treatment based on a pre-therapy study, as follows: (1) blood dosimetry- and (2) lesion dosimetry-based methods. Of these, the classic blood-based method is more widely used, and permits calculation of the maximum tolerated activity (MTA) that can be administered to an individual patient without the risk of severe hematopoietic toxicity. In this dosimetry schema the radiation absorbed dose to the blood is used as a surrogate for the absorbed dose to the red bone marrow, typically considered as the dose limiting critical organ (in some situations, such as extensive pulmonary metastatic disease, the lung could be the critical organ). An upper limit of 2 Gy to the blood is generally used as the threshold that avoids any serious bone marrow toxicity, which is based on the findings of the original study of Benua et al. [98]. Treatment individualization is based on determining the maximum 131-I activity that can be administered to each patient while keeping the absorbed dose to the blood at ≤2 Gy. Blood-based dosimetry is carried out by measuring activity counts in blood samples obtained at specified time points over a 4-day period after the administration of a tracer amount of 131-I as described in a document by the EANM Dosimetry Committee [99]. The contribution to the absorbed dose from beta radiation originating from the activity in the blood, as well as the contribution from gamma-ray emissions originating from the activity throughout the whole-body must be considered, although the latter component is usually <25%. To determine the blood activity, whole blood samples (5 ml hepa-

rinized aliquots) are collected at multiple time points (2, 24, 48, 72, and 96 h) during the first week after administration of tracer amount (e.g., 15–37 MBq [0.4–1 mCi]) 131-I activity and measurements are performed in an accurately calibrated (for 131-I) well counter. To determine the whole-body activity, serial measurements are performed with either a dual-head gamma camera or a scintillation probe. Once time-integrated activities (cumulated activities) for both blood and whole body are determined from the serial measurements, the absorbed dose to the blood per unit administered activity (i.e., Gy/GBq administered activity) can be determined using the S-value-based equations of the MIRD schema [99]. The therapeutic 131-I activity that can be safely administered while maintaining blood radiation absorbed dose ≤2 Gy) can then be determined based on this pre-therapy predicted radiation absorbed dose to the blood [100]. Further restrictions to MTA recommend that the administered therapeutic activity does not exceed 4.44 GBq (120 mCi) 131-I whole-body retention at 48 h, or 2.96 GBq (80 mCi) 131-I whole-body retention at 48 h if pulmonary metastases are present [101].

Maximizing therapeutic effectiveness is highly desirable for the treatment of distant metastatic disease, as the first 131-I treatment ("first strike") has the highest chance of being curative [102]. The lower response rates from fractionated empiric fixed activity treatments are a result of lower radiation absorbed dose rates and reduced radiation absorbed doses delivered by second and subsequent treatments because of decreased 131-I uptake in the metastatic lesions (likely related to elimination of most radiosensitive tumor cell populations with the first treatment and survival of more radio-resistant and less-iodine avid clonal cell lines) [103].

The choice of empiric vs. dosimetry-guided 131-I therapy remains controversial, as there is no definitive published data to show the superiority of one approach versus the other. Although Deandreis et al. showed no survival advantage in metastatic DTC patients who received dosimetry-guided treatments vs. patients treated with repeated courses of empiric 131-I activity [104], the study has significant limitations due to the imperfect matching of patient cohorts in regard to age and preparation method (rhTSH stimulation vs. L-T4 withdrawal protocols) [105]. Klubo et al. also compared clinical outcomes for two patient cohorts treated either with empirically selected vs. dosimetry-determined 131-I activities and found that the rates of partial response, stable disease, and progression-free survival, as well as frequency of side effects, were not significantly different between the two groups. However, based on multivariate analysis, the dosimetry-guided treatment group was 70% less likely to progress (odds ratio 0.29; 95% CI 0.087–1.02; $p < 0.052$) and more likely to obtain a complete response (odds ratio 8.2; 95% CI 1.2–53.5; $p < 0.029$) [106]. Taking into consideration the limitations of retrospective studies, the advantages and disadvantages of empiric fixed activity versus dosimetry-guided treatments, the radiobiological principles, and thyroid cancer prognosis in the context of disease stage, this author considers that empiric fixed activity methods are adequate for the selection of 131-I activity for remnant ablation and adjuvant treatment, however, dosimetry-guided treatments may offer a distinct advantage for treatment of known metastatic disease. Scintigraphic identification of distant metastatic disease and therapeutic 131-I administration are the most important factors associated with significant improvement in survival and prolonged disease-free time interval [107–110].

7.12 Radioiodine Theranostics

The theranostic approach to ^{131}I administration involves the acquisition of a post-operative Dx radioiodine (^{123}I, ^{131}I, or ^{124}I) scan for planning ^{131}I therapy. Figure 7.1 presents the central role of radioiodine theragnostics in the management of thyroid cancer.

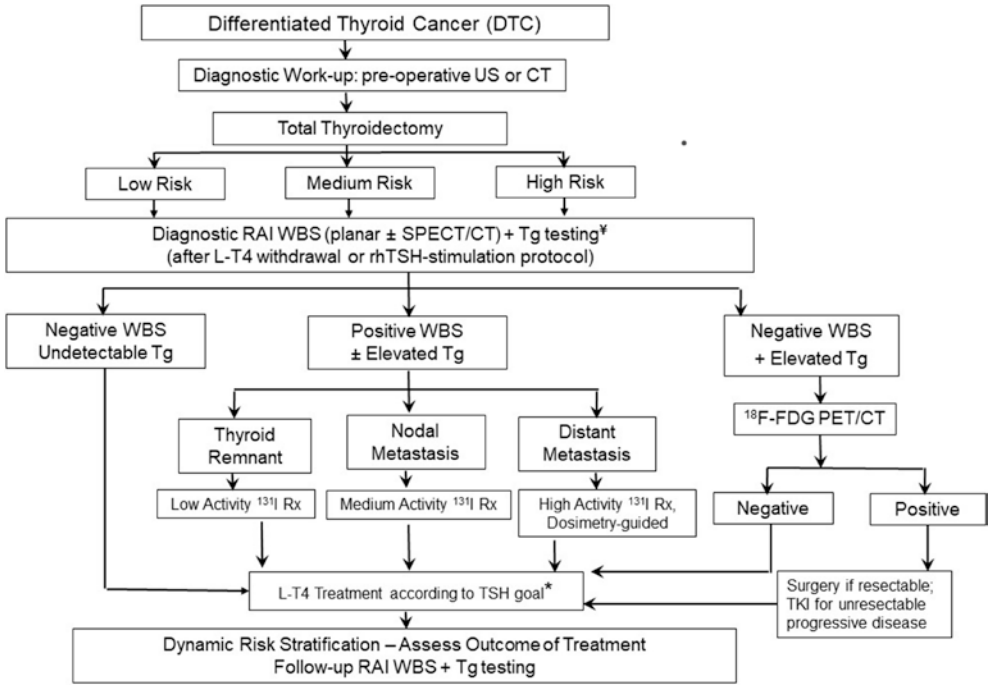

Fig. 7.1 Algorithm for radioiodine theragnostics for thyroid cancer management

Dx whole-body scans (WBS) are performed with the intent of identifying and localizing regional and distant metastatic disease, as well as evaluating the capacity of metastatic deposits to concentrate ^{131}I. Depending on institutional protocols, the findings on Dx WBS may alter management, such as providing guidance for additional surgery or altering the prescribed ^{131}I therapy, either by adjusting empiric ^{131}I activity, or performing dosimetry calculations for determining the maximum tolerated therapeutic ^{131}I activity (MTA) for therapy of distant metastatic disease. Also, unnecessary ^{131}I treatment may be avoided if Dx WBS finds no evidence of residual thyroid tissue or metastatic disease and the stimulated Tg is <1 ng/mL in the absence of interfering anti-Tg antibodies. Information acquired from DxWBS may also lead to additional functional metabolic imaging with ^{18}F-FDG PET/CT when non-iodine avid metastatic disease is suspected (based on Tg elevation out of proportion to the findings on DxWBS). Wherever available, it is preferable for post-operative Dx scanning to be performed using integrated multimodality imaging (i.e., single photon computed emission tomography/computed tomography (SPECT/CT). SPECT/CT imaging is particularly important for assessing focal radioiodine uptake in the neck and differentiating thyroid remnant versus nodal metastasis and for detecting metastases in normal-size cervical lymph nodes (that would not be visible on post-operative neck ultrasonography). Scintigraphic evaluation with Dx WBS can identify pulmonary micrometastases (which are too small to be detected on routine chest X-ray and may remain undetected on computer tomography) and can diagnose bone metastases at an early stage before cortical disruption is visible on bone X-rays or CT. Most importantly, since ^{131}I therapy is most effective for smaller metastatic deposits, early identification of regional

and distant metastases is important for successful therapy [111, 112]. In a group of 320 thyroid cancer patients referred for post-operative ^{131}I therapy, Dx WBS with SPECT/CT imaging detected regional metastases in 35% of patients, and distant metastases in 8% of patients. This information acquired changed staging in 4% of younger, and 25% of older patients [46]. Both imaging data and stimulated thyroglobulin levels acquired at the time of Dx WBS are consequential for ^{131}I therapy planning, providing information that changed clinical management in 29% of patients as compared to a management strategy based on clinical and surgical pathology information alone [5]. The benefits of integrating Dx WBS in the management algorithm of intermediate- and high-risk thyroid cancer for guiding ^{131}I therapeutic administration have been demonstrated in a group of 350 patients who were evaluated to assess treatment response with a median follow-up of 3 years after primary treatment (surgery and post-operative ^{131}I therapy): complete response (CR) to treatment was achieved in 88% patients with local-regional disease, and in 42% patients with distant metastases after a single ^{131}I therapeutic administration [48].

In all cases, ^{131}I administration should be followed by a post-treatment whole-body scan (PT-WBS) to determine therapeutic ^{131}I localization which is routinely used to complete post-operative staging. Hybrid imaging with SPECT/CT improves the accuracy of PT-WBS and should be done whenever possible, most importantly when DxWBS was not performed or when PT-WBS shows additional foci of activity as compared to Dx WBS [113]. A high level of concordance between Dx WBS and PT-WBS findings has been demonstrated in 2 large data series from Stanford University (98% concordance in a group of 280 patients) and the University of Michigan (92% concordance in a group of 303 patients) [39, 46]. Therefore, the information obtained with Dx WBS reasonably predicts ^{131}I therapeutic localization and can be used for ^{131}I therapy planning in the paradigm of thyroid cancer radiotheragnostics [114]. The theragnostic approach for the management of metastatic DTC is illustrated in Fig. 7.2.

Treatment response evaluation is integral to radiotheranostics, and the detection of elevated basal and/or stimulated Tg in the context of negative diagnostic radioiodine scan requires further evaluation with 18F-FDG PET/CT for early identification of non-iodine avid metastatic disease, which is unlikely to respond to repeated 131-I treatments [116]. In a study by Avram et al., only a minority of patients had iodine-avid structural incomplete response (8 patients, 2.3% of the entire cohort) and required repeated 131-I treatments. Meticulous follow-up and comprehensive imaging evaluation for patients with biochemical evidence of residual disease explain the low number of cases categorized as indeterminate (2.3%) and biochemically incomplete (1.4%) treatment responses in this study [48].

Integration of diagnostic radioiodine scintigraphy in the management algorithm of patients with thyroid cancer is feasible and advantageous because it permits 131-I therapy planning according to radiotheragnostic principles. The cost of diagnostic radioiodine scintigraphy is reasonable and approximately equal to or significantly less than the cost of most other imaging studies. According to a cost analysis by Van Nostrand et al., as of December 2013, the cost of a 131-I diagnostic whole-body scan was US $308, and compared favorably with Chest CT scan $411, Neck MRI $726, Neck PET-CT $1043, two rhTSH injections $2424. Neck US study is the least expensive study ($102), and in many instances needs to be supplemented by a US-guided FNA biopsy ($175) for definitive characterization of US study findings [117].

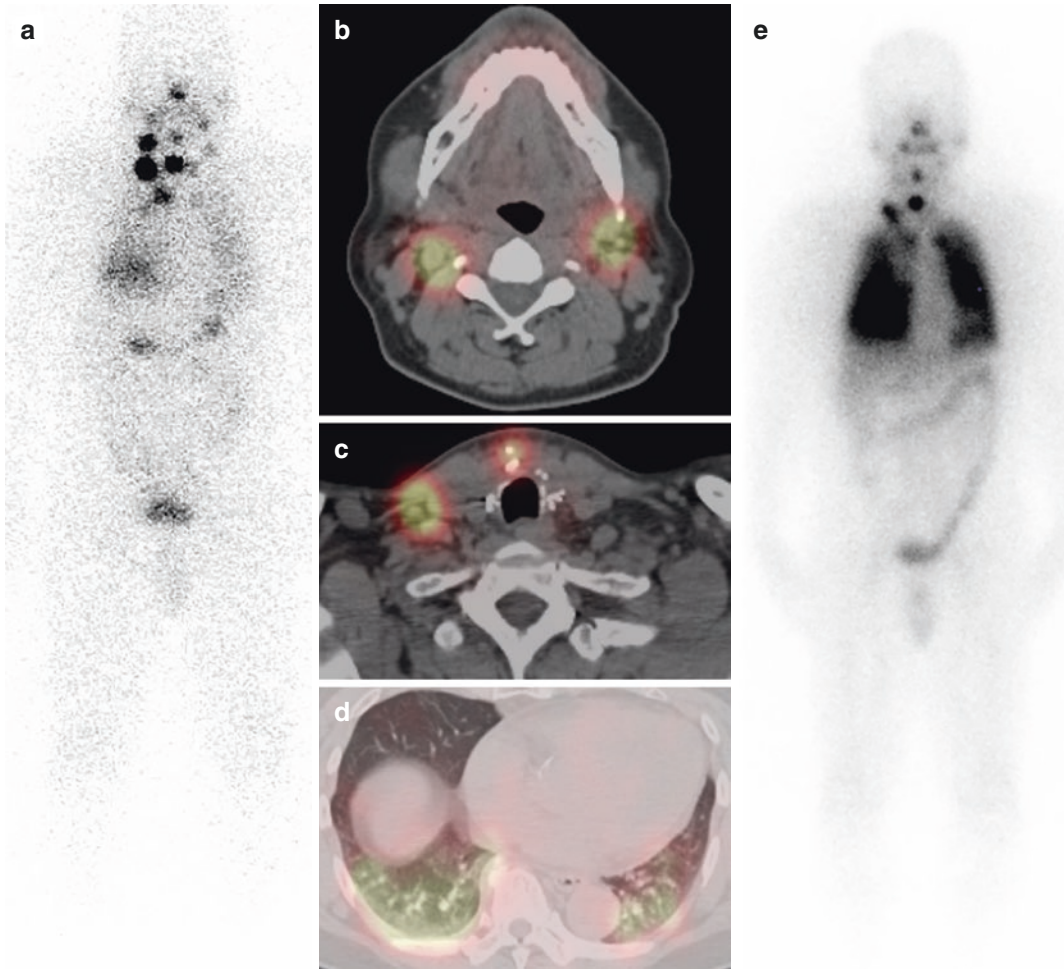

Fig. 7.2 Radioiodine theranostics for a 63-year-old man with regionally advanced thyroid cancer: 2.2 cm. PTC, 11+/11 lymph nodes resected in the surgical specimen of total thyroidectomy. Diagnostic 1 mCi ^{131}I WBS, anterior projection (**a**) depicts multifocal neck activity and diffuse lung activity. Neck SPECT/CT (**b**, **c**) demonstrates iodine-avid soft tissue nodules consistent with cervical nodal metastases. Chest SPECT/CT (**d**) demonstrates diffuse lung activity and branching pulmonary vasculature without definite lung nodules identified. The patient received dosimetry-guided 12.6 GBq (340 mCi) ^{131}I treatment and post-therapy WBS, anterior projection (**e**) obtained at 3 days demonstrates therapeutic ^{131}I localization to cervical lymph nodal metastases and diffuse miliary pulmonary metastatic disease. Reproduced with permission from [115]

7.13 Treatment of Advanced Disease

Distant metastases develop in about 10% of DTC patients, commonly in the lungs, bone, brain, liver and skin, and are the main cause of death (i.e., overall mortality 65% at 5 years and 75% at 10 years) [118].

The prognosis of metastatic DTC is variable, with two distinct phenotypes identified—indolent and aggressive [119]. Patients with iodine-avid metastatic DTC tend to have a more favorable prognosis with 10-year survival greater than 90%, while non-iodine avid metastatic DTC has a dire 10-year survival of 10% [120]. Younger patients and those with single-organ metastases and low disease burden have the best outcome. The mainstay of treatment is TSH suppression and ^{131}I therapy as long as the disease remains radioiodine avid. About two-thirds of patients

have radioiodine-avid distant metastases and one-third of them will achieve remission after multiple radioiodine treatments [111]. Approximately 15–20% of patients with metastatic DTC and most patients with Hurthle cell thyroid cancer are refractory to radioiodine (i.e., radioiodine-refractory) and overall survival for these patients ranges between 2.5 and 4.5 years [111, 121].

Determining when a patient no longer responds to ^{131}I can be challenging. Factors impacting the specific clinical situation such as age, tumor histology, stage, residual radioiodine avidity, and FDG avidity should be evaluated [122]. ^{18}F-FDG-PET/CT is particularly useful for the identification and localization of non-iodine avid metastastases and is used for evaluating patients with elevated Tg and negative DxWBS (i.e., Tg+/scan-) [123]. In this setting, having already established the lack of ^{131}I uptake on a DxWBS, a positive ^{18}F-FDG-PET/CT strongly supports the suspicion of ^{131}I negative/refractory disease, leading to changes in management by identifying patients unlikely to benefit from additional ^{131}I therapy and instead qualify for alternative therapy [124]. In addition, ^{18}F-FDG PET/CT has shown a prognostic value in metastatic DTC predicting the course of disease as aggressive or indolent [125]. In radioiodine refractory metastatic DTC there is a survival disadvantage for patients with a positive PET as compared with those with a negative PET [121].

7.14 Future Perspectives

Future studies addressing the benefits and limits of 131-I therapy in thyroid cancer must optimize the balance between 131-I treatment efficacy and minimization of potential side effects. Determining the objective and the target of 131-I therapy is essential for performing dosimetry and for assessing treatment the outcome, providing new compelling reasons for pre-therapeutic diagnostic scintigraphic imaging with low activities of 131-I or 124-I. ^{131}I therapy remains the only known cure for metastatic radioiodine-sensitive DTC and the use of redifferentiating strategies to permit additional ^{131}I treatment for patients with radioiodine-refractory metastatic disease represents a promising therapeutic approach that remains yet to be fully explored in future clinical trials.

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