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Thyroid Cancer Radiotheragnostics: the case for activity adjusted ^{131}I therapy

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Abstract

Radiotheragnostics represents the systematic integration of diagnostic imaging and therapeutics using radionuclides targeting specific characteristics of tumor biology. Radioiodine (^{131}I) is the classic radiotheragnostic agent used for the diagnosis and treatment of differentiated thyroid cancer (DTC) based on sodium-iodine symporter expression in normal and neoplastic thyroid tissue. Application of radiotheragnostics principles in thyroid cancer involves using pre-ablation diagnostic scans (Dx Scans) for detection of iodine-avid regional and distant metastatic disease and patient-individualized targeted ^{131}I therapy with goal of maximizing the benefits of the first therapeutic ^{131}I administration. Clinically available nuclear medicine imaging technology has significantly evolved over the past 10 years with the introduction of hybrid SPECT/CT and PET/CT systems, as well as advances in iterative image reconstruction with modeling of image degrading physical factors. This progress makes possible the acquisition of accurate diagnostic radioiodine scintigraphy capable of identifying regional and distant metastatic disease, which can be used for ^{131}I treatment planning and delivery of activity adjusted ^{131}I therapy for achieving intended treatment goals (e.g. *remnant ablation*, *adjuvant ^{131}I treatment* and *targeted ^{131}I treatment*). The overarching aim of thyroid cancer radiotheragnostics is to optimize the balance between ^{131}I therapeutic efficacy and potential side-effects on non-target tissues.

Keywords

Radiotheragnostics; theragnostics; diagnostic radioiodine scan; ^{131}I therapy; differentiated thyroid cancer; ^{131}I SPECT/CT

INTRODUCTION

For several decades the prevailing clinical practice paradigm for the management of differentiated thyroid cancer (DTC) was total thyroidectomy followed by empiric fixed ^{131}I

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activity administration for thyroid remnant ablation and subsequent post-treatment (post-Rx) ^{131}I scans for assessing therapeutic ^{131}I localization and identifying possible regional and distant metastases (1, 2) These post-Rx scans were typically performed at 3-10 days after ^{131}I therapy, and were used for guiding further steps in patient management, such as determining long-term surveillance strategy or planning repeated courses of ^{131}I treatment. (3) Although pre-ablation diagnostic scans (Dx Scans) had been historically done prior to ^{131}I therapy, (4) fixed dose ^{131}I ablation of residual thyroid tissue after thyroidectomy had become standard by the 1980's. (5, 6) However, 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. (7-9) A central issue for the clinical implementation of this concept is the definition of low-, intermediate- and high-risk categories which have been modified in the 2015 American Thyroid Association (ATA) guidelines (8). This most recent ATA risk stratification for DTC is based on recurrence risk estimations obtained on retrospective studies which have reported on the proportion of patients with no evidence of disease (NED) after total thyroidectomy and postoperative ^{131}I remnant ablation corresponding to each 2009 ATA Guidelines categories. (7) An estimated recurrence risk $< 10\%$ places a patient in the low-risk category managed without ablation for whom thyroid lobectomy is recommended, while an estimated recurrence risk $< 30\%$ results in intermediate-risk assignment and consideration for post-operative ^{131}I administration. A recommendation for ^{131}I therapy is endorsed for high-risk patients (locally invasive tumors with gross extra-thyroidal extension or extensive vascular invasion, nodal metastases $\geq 3\text{ cm}$, or distant metastases). (8) Although the risk stratification, which determines whether ^{131}I therapy is pursued, is predicated on surgical pathology information, postoperative diagnostic radioiodine (RAI) scintigraphy contributes to the completion of staging and risk stratification, thus having the potential to influence ^{131}I therapeutic strategy.

DIAGNOSTIC AND POST-THERAPY ^{131}I SCINTIGRAPHY

Historically, post-Rx imaging had the advantage of better count density and appeared to provide more diagnostic information than the pre-ablation Dx. scans. In addition, the issue of stunning by the diagnostic scan dose was raised (defined as a reduction of ^{131}I uptake seen on Post-Rx. as compared to Dx. scans, and interpreted as potentially causing a decreased effect of the subsequent ^{131}I therapy dose when administered after ^{131}I Dx. scans). (10-12) However, other investigators examining the issue have questioned this phenomenon with studies demonstrating little or no evidence of stunning. (13-17) Their view is that the clinical importance of stunning was overemphasized, that stunning appears not to be a problem at doses $< 2\text{ mCi }^{131}\text{I}$ when ^{131}I therapy is administered within 72 hours of the diagnostic ^{131}I activity, and that it may be related to a true cytotoxic effect of the high ^{131}I diagnostic activities (5 – 10 mCi ^{131}I) used in the past. (18-20) The main arguments against Dx. scans were that they provide unreliable information due to instances in which post-Rx scans identified distant metastatic disease not initially seen on Dx scans, (21-23) that they are inconvenient for patients, and ultimately unnecessary because all the information needed for patient management was obtained with Post-Rx. scans. (2) However, this treatment paradigm based on prescription of fixed ^{131}I activities followed by post-Rx scans

locked nuclear medicine therapeutics in the narrow confines of empiric ^{131}I activity prescription, based either on institutional protocols, or the individual experience and personal preferences of the prescribing physician. 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 scintigraphy images demonstrating high concordance rate with the post-therapy ^{131}I scans. Stanford University experience reported by McDougall et al. in a cohort of 280 patients showed a 98% concordance rate between the findings obtained with 74 MBq (2 mCi) Dx. scans and post-Rx scans obtained at 8 days after ^{131}I treatment. (14) Similarly, Avram et al. describing the University of Michigan experience reported a 92% concordance rate between the findings obtained with 37 MBq (1 mCi) Dx. scans and post-Rx scans obtained at 2 days after ^{131}I treatment. In only 6% of patients additional foci of activity were detected on post-Rx scans, however, in only 1.4% of cases the findings were clinically significant (i.e. upstaged the patient). (24) Therefore in our experience, using Dx. scans for planning the initial ^{131}I therapy is unlikely to underestimate the extent of metastatic disease.

There are distinct advantages offered by post-surgery ^{131}I activity administration for all risk stratification categories and irrespective of post-operative thyroglobulin levels, confirming the role of post-therapeutic ^{131}I imaging for early detection and treatment of local-regional and distant metastatic disease. Park et al. demonstrated in a large cohort of 824 DTC patients who underwent ^{131}I therapy after L-T4 withdrawal protocol that 52 patients (6.3%) had functioning metastases identified on post-Rx scans despite stimulated Tg 2 ng/ml in the absence of interfering anti-Tg antibodies. A low stimulated Tg 2 ng/ml did not exclude the presence of distant metastases, since in this group 7 patients (13.5%) had pulmonary and osseous metastases while the remainder 45 patients (86.5%) had cervical/mediastinal lymph nodal metastases. (25) In a recent study by Campenni et al. in 570 low- and low-intermediate risk DTC patients (pT1-pT3) post-Rx scans with SPECT/CT demonstrated metastases in 82 patients (14.4%), of which 73 patients (90.2%) had post-surgical nonstimulated Tg 1 ng/ml; furthermore, in 44 patients (54%) stimulated Tg remained 1 ng/ml, despite the presence of metastases on post-Rx scans. (26) Therefore, post-surgical nonstimulated Tg levels cannot be used in deciding whether to pursue therapeutic ^{131}I administration, mainly in the patients assigned as low-risk category based solely on surgical pathology information. The excellent results obtained with successful ablation in low risk patients show that these patients can be fully reassured and would not require thyroglobulin stimulation tests or periodic neck ultrasound examination during follow-up. (27) In conclusion, postoperative thyroglobulin levels are helpful in identifying high-risk patients that require higher ^{131}I activity, but cannot be used for ruling-out ^{131}I ablation. Omission of ablation exposes the patients to the risk of late diagnosis of residual disease. (28, 29) Finally, early reassurance and simplified follow-up are only possible when patients had received total thyroidectomy followed by therapeutic ^{131}I administration for remnant ablation and/or adjuvant treatment.

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: the 2010 (7th edition) and 2017 (8th edition) versions of the pTNM classification and the derived AJCC staging systems are summarized in Tables 1 and 2. (30, 31) The risk of structural disease recurrence is defined by the American Thyroid Association (ATA) on a 3-level of risk and is stratified as low, intermediate or high based on surgical pathology information as summarized in Table 3. (8) 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%) (32) 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. (33)

BENEFITS OF ^{131}I THERAPY IN THYROID CANCER

Several observational studies in large cohorts of thyroid cancer patients reported long-term clinical outcomes in terms of recurrence rates and survival after ^{131}I treatment as compared with patients conservatively managed without postoperative ^{131}I administration. Collectively, these observational studies provide statistically significant findings in large patient cohorts, assessed as moderate-quality evidence for a therapeutic intervention as described by the formal methodological criteria for grading the strength of evidence of published literature (8). Large cohort retrospective studies with long term clinical follow-up (> 10 years) bring evidence regarding the impact of ^{131}I therapy for decreasing thyroid cancer mortality (34) and recurrence rates (34-36). 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 0.02-0.49) and an absolute risk reduction of 3% for distant metastatic disease (37), thus indicating that postoperative ^{131}I treatment has indeed an adjuvant effect contributory to long-term outcomes.

Both earlier and most recent analyses (max. n=4941) of patients in the American national thyroid cancer treatment cooperative study group (NTCTCS) reported improved overall and disease-specific survival in stages III and IV patients who received postoperative ^{131}I therapy (38). Furthermore, an improved disease-free survival for stage II patients receiving ^{131}I therapy was reported. (39) Of note, in the NTCTCS staging system distant metastatic disease is classified as stage III in young patients (age < 45 years) and stage IV in older patients (age ≥ 45 years). Additional details of NTCTCS staging are important for understanding the long-term outcomes of adjuvant ^{131}I treatment in thyroid cancer: for

patients 45 years, intrathyroidal tumors 1-4 cm, micro- or macroscopic multifocal tumors, or tumors with microscopic extrathyroidal invasion are considered stage II disease; while the presence of tumors > 4 cm., cervical lymph nodal metastases and macroscopic extrathyroidal extension upstages patients to stage III disease (38). In order to achieve this effect, the majority of patients (55%) received > 2.8 GBq (75 mCi) ^{131}I therapeutic activity, while only 5% of patients received 1.1-2.8 GBq (31-75 mCi) ^{131}I activity and 10% of patients received 1.1 GBq (30 mCi) ^{131}I activity. Considering the usual clinical practice patterns, it is highly probable that the lower activities have been prescribed for patients with low risk tumors, while patients with more advanced disease (stages III & IV) received higher prescribed ^{131}I activities (> 2.8 GBq). (4, 8, 40) While this cannot serve as definitive proof for a certain ^{131}I activity prescription required for therapeutic benefit, it can nonetheless be seen as an indicator of effectiveness. Similarly, concurrent results from a German thyroid cancer database showed that high risk patients without distant metastases had better disease specific survival with increasing ^{131}I therapeutic activities, with best results in patients receiving > 3 GBq (80 mCi) ^{131}I therapy.(41)

THE GOALS OF ^{131}I TREATMENT AND ^{131}I ACTIVITY PRESCRIBED

Historically, empiric fixed ^{131}I activities used for thyroid remnant ablation after total thyroidectomy have been based on multiples of 10 mCi ^{131}I activity (42, 43) and considerable controversy arose regarding what is the best single ^{131}I activity necessary for achieving successful thyroid remnant ablation, - e.g. high activity of 3.7 – 5.5 GBq (100 – 150 mCi), medium activity of 1.85 – 3.7 GBq (50 – 100 mCi), or low-activity of 1.1 – 1.85 GBq (30–50 mCi)?(44-51)

Attempting to provide a definitive answer to the question of optimal prescribed ^{131}I activity for thyroid remnant ablation and to clarify the effect of endogenous (thyroid hormone withdrawal, THW) vs. exogenous (recombinant human TSH, rhTSH) TSH stimulation protocols, two large prospective randomized controlled trials (RCT) were conducted comparing the effectiveness of low (1.1 GBq/30 mCi) vs. high (3.7 GBq/100 mCi) ^{131}I activity for thyroid remnant ablation, each in combination with either rhTSH or THW. (52, 53) These studies demonstrated equivalent remnant ablation rates between high- and low ^{131}I prescribed activities, and between the THW vs. rhTSH-stimulation methods, with a reported overall ablation success of 92%, concluding that low ^{131}I activity (1.1 GBq/30 mCi) in conjunction with rhTSH stimulation protocol is sufficient for low-risk DTC. (52) However, a meta-analysis of 15 RCTs of low (1.1 GBq/30 mCi) versus high (3.7 GBq/100 mCi) ^{131}I activity for thyroid remnant ablation reported by Du et al. demonstrated a slight advantage of high-activity radioablation. (54) While low ^{131}I activity may achieve equivalent ablation success rate in patients with excellent surgical resection and minimal remnant tissue (neck ^{131}I uptake <5%) after total thyroidectomy, high-activity remnant ablation is required when surgery is less than optimal (neck ^{131}I uptake > 5 -10%) (55) Therefore it is reasonable to conclude that rather than a fixed dose, the ^{131}I activity prescribed for remnant ablation and adjuvant treatment needs to be selected based completeness of surgical intervention (i.e. thyroidectomy) as determined by the quantity of residual functional thyroid tissue remaining in the neck after surgery, the surgical pathology risk stratification and the results of post-operative imaging studies.

Generally, within the context of thyroid cancer management, the term “ablation” is used to describe the first ^{131}I therapeutic administration irrespective of patients’ risk stratification or other laboratory or imaging findings. While ablation success is important to establish a baseline for post-operative evaluation and long-term surveillance, however from the oncologic standpoint the relevant long-term patient outcome measures remain overall survival (OS), disease-specific survival (DSS) and disease-free survival (DFS).

For making a rational decision regarding the prescribed therapeutic ^{131}I activity, the primary goal of ^{131}I treatment needs to be determined before ^{131}I administration by considering each patient’s clinical presentation, surgical pathology information, post-operative thyroglobulin (Tg) levels and the pre- and post-operative imaging findings, such as neck ultrasonography or other imaging modalities. An understanding of the purpose of therapeutic ^{131}I administration is important, and the definitions proposed by Van Nostrand et al. (56) and adopted by the American Thyroid Association (ATA) Guidelines for thyroid cancer management (7, 8) clarify that *remnant ablation* is defined as the use of ^{131}I for elimination of normal residual functional thyroid tissue (thyroid remnant) for facilitating long-term follow-up and to maximize the therapeutic effect of any subsequent ^{131}I treatment; *adjuvant ^{131}I treatment* is defined as the use of ^{131}I for elimination of suspected but unproven metastatic disease based on histopathologic risk factors that predict tumor spread beyond thyroid gland, with the intention of irradiating and eliminating occult infra-radiologic residual disease in the neck or other occult micro metastases; and *targeted ^{131}I treatment* is defined as the use of ^{131}I for treatment of known local-regional and distant metastases. Depending on the quantity of thyroid remnant tissue and the extent of residual disease, it has been considered that a low therapeutic ^{131}I activity (e.g. 1.1 GBq/30 mCi) given solely for the purpose of remnant ablation and performing post-treatment whole-body imaging may not be sufficient to eradicate residual metastatic tumor if present.(7) Therefore, the selection of activity for ^{131}I therapy ideally needs to be balanced between optimizing treatment efficacy and minimizing potential side effects.

Several retrospective studies have compared dynamic risk stratification outcomes after radioablation in patients with intermediate-risk for recurrence who received *low ^{131}I activity* of 1.1 – 1.85 GBq (30-50 mCi), and < 2.8 GBq (< 75 mCi) vs. *high ^{131}I activity* of 3.7 GBq (100 mCi), and 2.8 GBq (75 mCi), concluding that the clinical outcomes in terms of complete response, biochemical incomplete response and structural disease recurrence were not statistically significant between the groups. (57, 58). Based on these data and considering that side effects of ^{131}I therapy are dose-related, these studies provided impetus for a trend to recommend that administration of low ^{131}I activities (i.e. 1.1 GBq/30 mCi) be generally favored for all patients, under the misinterpretation that “less prescribed ^{131}I activity is more,” in terms of achieving the same clinical outcomes while minimizing side effects of treatment. When no difference is shown, one may falsely conclude that lower ^{131}I activities are as effective as higher ^{131}I activities for adjuvant treatment. However, multiple confounding factors depending on the selected patients within each comparison group (eg. patients who have no residual disease, or patients who have non-iodine avid residual disease) can compound the interpretation of retrospective studies attempting a direct comparison at the effectiveness of lower vs higher ^{131}I activities.

Decreasing the ^{131}I activity prescribed for all patients runs the risk of delivering an ineffective treatment since lesion dosimetry studies have demonstrated a relationship between tumor radiation absorbed dose and treatment response. Thresholds of lesional radiation absorbed dose necessary for achieving a complete therapeutic response have been established for small (< 1.0 cm) pulmonary metastases (60 – 70 Gy), metastatic lymph nodes (85 – 100 Gy), and osseous metastases (350 – 650 Gy). (59-63) Based on radiation therapy principles, decreasing prescribed ^{131}I activity would ultimately result in lesser radiation absorbed dose to target lesions. From the viewpoint of efficacy, radiation therapy principles dictate that higher administered ^{131}I activities will on average lead to higher delivered radiation absorbed doses to target metastatic lesions and consequently be more effective therapeutically. On the same note, the radiation absorbed dose to non-target tissue such as e.g. the salivary glands will also be greater, thus leading to a higher incidence of adverse effects such as a sialadenitis. Herein are the great challenge and also the opportunity for ^{131}I radiotheragnostics guided on dosimetry principles for delivering patient-individualized treatment that balances the risks and benefits of therapeutic ^{131}I administration.

THE ROLE OF DOSIMETRY FOR THYROID CANCER TREATMENT

There are two approaches for individualization of the radioiodine treatment based on a pre-therapy study, as follows: (1) blood dosimetry-based and (2) lesion dosimetry-based methods. Of these, the classic blood-based method is more widely used. Here the 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. (64) The individualization of the treatment involves 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 relatively easy to carry out after the administration of a tracer amount of ^{131}I and the procedure is well described in a document by the EANM Dosimetry Committee. (65) 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 are collected at multiple time points during the first week 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 per GBq) can be determined using the S-value based equations of the MIRD schema. (65) 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 absorbed dose to the blood.

The limitation of the blood-dosimetry based approach of treating to the maximum tolerated activity (MTA) is the lack of information regarding the radiation absorbed dose to the

targeted metastatic lesions, which can lead to over- or under treatment. The time integrated activity from serial quantitative imaging using a tracer amount of ^{131}I can be used with the MIRD schema to determine the predicted lesion absorbed dose per unit administered activity considering only the dominant self-irradiation component of the total absorbed dose. Lesion dosimetry using this approach is detailed in a guidelines document by the EANM Therapy committee.(66) Alternatively, quantitative SPECT/CT can be coupled with Dose Point Kernel or Monte-Carlo radiation transport-based voxel-level calculations to predict the total absorbed dose accounting for both self-irradiation and cross irradiation.(67) The pre-therapy prediction can be used to determine the activity that must be administered for successful treatment, generally considered to be an absorbed dose of 80 Gy for metastatic lesions and

300 Gy for thyroid remnant, based on the report of Maxon et al.(68) Challenges for lesion dosimetry include the difficulty of accurately estimating lesion mass for the MIRD based calculation or lesion segmentation for the voxel-level calculation. However, there has been considerable improvement in quantitative SPECT imaging of ^{131}I with the availability of hybrid SPECT/CT and iterative reconstruction with resolution recovery. (69) Because of the superior resolution of PET imaging, ^{124}I PET has been used as a surrogate imaging agent for pre-therapy lesion dosimetry (70), however dosimetry estimates for small (diameter less than 2–3 times the system spatial resolution) lesions should be used with caution. In a study by Jentzen et al, because the lower volume limit of determinability of their PET-based lesion segmentation method was 0.8 mL, for smaller lesions the estimated quantity was the minimum absorbed dose determined using a fixed sphere volume of 0.8 mL. (62) Another consideration in lesion dosimetry-based individualized treatment is that typically multiple lesions are treated and the uptake and consequently the radiation absorbed doses to the different lesions in the same patient can vary considerably.

Lesion dosimetry-based individualized treatment needs to be accompanied by blood-dosimetry calculations to ensure that the 2 Gy limit of radiation absorbed dose to blood is observed. Further studies on the relationship between lesion absorbed dose and outcome are also needed because the 80 Gy limit is based on studies performed with the available imaging technology over 25 ago. Furthermore, the agreement between predicted and delivered lesion absorbed doses need to be carefully investigated, especially because the potential and origins of the ‘stunning’ phenomenon are yet to be fully understood.

RADIOTHERAGNOSTICS CLINICAL APPLICATIONS: ACTIVITY ADJUSTED

^{131}I THERAPY

The University of Michigan Nuclear Medicine Therapy Clinic has traditionally employed an individualized approach to therapeutic ^{131}I administration for patients with local-regionally advanced and metastatic thyroid cancer, by integration of diagnostic ^{131}I scintigraphy information and stimulated Tg levels in the context of surgical pathology results. (71) The University of Michigan experience has demonstrated that post-operative diagnostic ^{131}I scans with SPECT/CT (Dx scan) contribute to thyroid cancer staging and risk stratification. (72, 73) and changed clinical management in approximately 30% of cases as compared to a management strategy based on clinical and surgical pathology information alone.(40) Our management strategy includes post-operative Dx scan evaluation in all patients referred for

¹³¹I treatment, and individualized ¹³¹I therapy guided by Dx scan findings in addition to surgical pathology and post-operative stimulated Tg levels. Post-Rx ¹³¹I scans are obtained at 2 – 5 days to determine therapeutic ¹³¹I localization and compared with Dx scans to assess for concordance. In a group of 320 thyroid cancer patients referred to our center for postoperative therapeutic ¹³¹I administration, Dx scans detected regional metastases in 35% of patients, and distant metastases in 8% of patients. (24) Information acquired with Dx scans changed staging in 4% of younger (age < 45 years), and 25% of older (age ≥ 45 years) patients. (24) Both imaging data and stimulated Tg levels acquired at the time of Dx scans are consequential for ¹³¹I therapy planning, providing information that changes risk stratification in 15% of patients and clinical management in approximately 30% of patients as compared to recurrence risk estimation and management strategy based on clinical and surgical pathology information alone. (40) Identification of unsuspected regional and distant metastases on Dx scans confirms their capacity to concentrate ¹³¹I and therefore their potential to respond to ¹³¹I therapy. Defining the target of ¹³¹I therapy permits adjustment of prescribed ¹³¹I activity, by either adjusting empiric “ablative” ¹³¹I activities or performing dosimetry calculations. (72, 74) Avoiding unnecessary ¹³¹I therapy is equally important for patients in whom residual and/or metastatic disease has been excluded. SPECT/CT improves characterization of focal central neck activity as benign thyroid remnant when pathology review demonstrates no evidence of extra-thyroidal tumor extension and negative surgical excision margins, justifying administration of low ¹³¹I activity (e.g. 1.1 GBq/30 mCi) or even omission of ¹³¹I ablation in patients with minimal thyroid remnant tissue and very low or undetectable postoperative Tg levels (71). SPECT/CT imaging applied to Dx scans is important not only for accurate anatomic localization, but also for measuring the size of metastatic lesions: this information is essential in deciding if ¹³¹I therapy vs surgical resection is recommended, since ¹³¹I therapy is most effective for smaller (< 1.0 cm) metastatic deposits, (75, 76) whereas surgical resection before ¹³¹I therapy is recommended for large metastatic lesions. Re-operative neck dissection prior to ¹³¹I therapy was performed in 6.6% of patients in our series diagnosed with unsuspected residual nodal metastases identified on Dx scans in cervical compartments not explored at initial surgical intervention. In these instances, the findings of Dx scans guided subsequent surgery for removing these metastatic deposits and maximizing the chance of complete response with a single postoperative ¹³¹I therapy. (77)

The decision for ¹³¹I therapy and the prescribed ¹³¹I activity is determined based on all available information (histopathology, stimulated Tg, and Dx scan findings). Per our institutional protocol, thyroid remnant ablation in low risk patients is performed with low ¹³¹I activity of 1.1GBq (30 mCi). Adjuvant ¹³¹I treatment is performed with 1.8 – 3.7 GBq (50 – 100 mCi) activity for patients with histopathologic risk factors and normal thyroid remnant tissue demonstrated on Dx scan, with the intent of eliminating suspected microscopic foci of residual disease. Identification of iodine-avid cervical lymph nodal metastases on Dx scans leads to administration of medium ¹³¹I activity of 5.5 GBq (150 mCi). Identification of iodine-avid distant metastases on Dx scans leads to prescription of high ¹³¹I activity, usually 7.4 GBq (200 mCi) based clinical dosimetry protocols which determine maximum tolerated activity (MTA) delivering blood radiation absorbed dose 2Gy. (65) Dosimetry calculations are performed based on thyroid uptake probe whole body

counts measurements (whole body dosimetry protocol) and blood activity counts quantification in heparinized blood samples (blood dosimetry protocol) obtained at 1, 24, 48, and 72 hours using the tracer 1 mCi (37 MBq) ^{131}I activity administered for Dx scan.(78-80) The actual administered ^{131}I activity for these patients was the calculated maximum releasable activity to deliver $< 5 \text{ mSv}$ (500 mrem) to any member of the public, in accord with the Nuclear Regulatory Commission criteria. The equation used for this calculation is presented in Supplemental Figure 1. Input factors in this calculation are: patient's % neck uptake measured at 24h; the calculated effective half-life of ^{131}I within the patient; the patient's specific living circumstances (e.g. occupancy factor and contact time with family members for the first 8 hours after treatment administration). An example for the calculation of maximum releasable ^{131}I activity for a patient with distant metastatic disease is presented in Supplemental Figure 2.

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 or significantly less than 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 WBS was US \$308, and compared favorably with Chest CT scan \$411, Neck MRI \$726, Neck PET-CT \$1,043, two rhTSH injections \$2,424. 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. (81)

FUTURE DIRECTIONS

It is known from prior dosimetry studies that a single prescribed ^{131}I activity is associated with a high variability in resultant radiation absorbed dose to blood (as a measure of the bioavailability of ^{131}I), as well as to great intra- and inter-individual differences in radiation absorbed doses to target and non-target tissues (82). Clinical experience has shown that low ^{131}I activities (1.1 GBq) successfully ablate benign thyroid remnant tissue (52) (53). Effective treatment of iodine-avid regional and distant metastatic disease will however, on average require higher ^{131}I activities, as demonstrated by ^{131}I and ^{124}I lesion dosimetry studies (59-61) (62, 63, 83, 84). Therefore an effort at identification of residual nodal and/or distant metastatic foci for successful ^{131}I treatment of metastatic disease is particularly relevant, since patients who achieve a complete response have considerably higher survival rates than patients with structural incomplete responses. (28, 75, 85, 86)

Any 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. The role of both pre-therapeutic and post-therapeutic dosimetry for determining the optimal prescribed ^{131}I activity for different patient populations and for achieving specific therapeutic objectives needs to be determined. Dosimetry studies in thyroid cancer need to determine the correlation between tracer-predicted and therapy-delivered radiation absorbed dose to metastatic tumors. Devising dosimetry protocols for routine implementation in clinical practice remains a top priority. Determining the objective and the target of ^{131}I therapy is essential for performing dosimetry and for assessing the outcome of treatment,

providing new compelling reasons for pre-therapeutic diagnostic scintigraphic imaging with low activities of ^{131}I or ^{124}I . Due to its short half-life, diagnostic ^{123}I scanning is considered less suited to provide reliable diagnostic data. Future dosimetry-based prospective multicenter studies devised to determine the relevant outcomes of post-operative ^{131}I treatment, including disease-specific survival and disease free survival, as well as the incidence of side effects of ^{131}I therapy, would be able to provide more definitive answers to the current controversies regarding optimal protocols for delivering ^{131}I treatment for thyroid cancer. Until the results of such studies become available, the therapeutic ^{131}I activity to be prescribed for thyroid cancer treatment remains a question best answered on an individual basis based on radiotheragnostic principles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS LIST:

Anti-Tg Ab	anti-thyroglobulin antibody
ATA	American Thyroid Association
DTC	differentiated thyroid cancer
Dx Scan	diagnostic ^{131}I scan with single-photon emission computer tomography (SPECT) with inline computed tomography (CT) SPECT/CT
ETE	extra-thyroidal extension
L-T4	levothyroxine
Post-Rx Scan	post-therapy ^{131}I scan
PTC	papillary thyroid cancer
Tg	thyroglobulin
THW	thyroid hormone withdrawal

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Table 1.

TNM Classification for differentiated thyroid cancer TNM UICC/AJCC 7th (2010)²⁵ versus 8th edition (2017)²⁶

		TNM 2010	TNM 2017
	Tx	Primary tumor cannot be assessed	Primary tumor cannot be assessed
T	T0	No evidence of primary tumor	No evidence of primary tumor
	T1a	Tumor ≤ 1 cm, limited to the thyroid	T ≤ 1 cm *
	T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension, limited to the thyroid	T > 1 cm and ≤ 2 cm *
	T2	Tumor size > 2 cm but ≤ 4 cm, limited to the thyroid.	T > 2 cm and ≤ 4 cm *
	T3	Tumor size > 4 cm, limited to the thyroid or any tumor with macroscopic or microscopic minimal extrathyroidal extension (e.g., extension to strap muscles or perithyroidal adipose tissue)	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 of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve	Tumor extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve.
	T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessel	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
N	Nx	Regional lymph nodes cannot be assessed**	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis	No regional lymph node metastasis
	N1a	Metastasis in level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)	Metastases in level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinum (level VII) *
	N1b	Metastasis to unilateral, bilateral, or contralateral cervical (levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII)	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	No distant metastasis is found
	M1	Distant metastasis is present	Distant metastasis is present

* 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 2.

AJCC prognostic grouping for differentiated thyroid cancer TNM UICC/AJCC 7th (2010)²⁵ *versus* 8th edition (2017)²⁶

AJCC 7th edition (2010)			AJCC 8th edition (2017)	
	Stage < 45 years old	Stage 45 years old	Stage < 55 years old	Stage ≥ 55 years old
Stage I	Any T, any N, M0	T1, N0, M0	Any T, any N, M0	T1/T2, N0, M0
Stage II	Any T, any N, M1	T2, N0, M0	Any T, any N, M1	T3a/T3b, N0, M0 T1/T2/T3, N1, M0
Stage III	-	T3, N0, M0	-	T4a, any N, M0
Stage IVA	-	T1/T2/T3, N1a, M0 T4a, N1b, M0	-	T4b, any N, M0
Stage IVB	-	T4b, any N, M0	-	Any T, any N, M1
Stage IVC	-	Any T, any N, M1	-	-

Table 3:American Thyroid Association 2015 Risk Stratification System⁸

Low risk	<p>Papillary thyroid cancer (with all of the following):</p> <ul style="list-style-type: none"> • No local or distant metastases; • All macroscopic tumor has been resected • No tumor invasion of loco-regional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • If 131I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first post treatment whole-body RAI scan • No vascular invasion • Clinical N0 or ≤ 5 pathologic N1 micrometastases (<0.2 cm in largest dimension) Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer <p>Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion</p> <p>Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAF-V600E mutated (if known)</p>
Intermediate risk	<p>Microscopic invasion of tumor into the perithyroidal soft tissues</p> <p>RAI-avid metastatic foci in the neck on the first post-treatment whole-body RAI scan</p> <p>Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma)</p> <p>Papillary thyroid cancer with vascular invasion</p> <p>Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension</p> <p>Multifocal papillary microcarcinoma with ETE and BRAFV600E mutated (if known)</p>
High risk	<p>Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE)</p> <p>Incomplete tumor resection</p> <p>Distant metastases</p> <p>Postoperative serum thyroglobulin suggestive of distant metastases</p> <p>Pathologic N1 with any metastatic lymph node >3 cm in largest dimension</p> <p>Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)</p>