Journal of Nuclear Medicine, published on August 19, 2021 as doi:10.2967/jnumed.121.262402

MANAGEMENT OF DIFFERENTIATED THYROID CANCER: THE STANDARD OF CARE

[1,2]Anca M. Avram, [3,4,5]Katherine Zukotynski, [6]Helen Ruth Nadel, [7,8]Luca Giovanella

[1]Division of Nuclear Medicine, Department of Radiology, and [2]Division of Endocrinology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI (USA)

[3]Departments of Medicine and Radiology, McMaster University, Hamilton, ON, [4]Department of Medical Imaging, Schulich School of Medicine & Dentistry, Western University, London, ON and [5] Department of Radiology, University of British Columbia, Vancouver, BC (Canada)

[6]Lucile Packard Children's Hospital at Stanford, Stanford University School of Medicine

[7]Clinic for Nuclear Medicine and Competence Center for Thyroid Diseases, Imaging Institute of Southern Switzerland, Bellinzona (Switzerland) and [8]Clinic for Nuclear Medicine, University Hospital and University of Zurich, Zurich (Switzerland)

Corresponding author:
Dr. Anca M. Avram
University of Michigan
1500 E. Medical Center Drive
Ann Arbor, MI. 48109-5028
Phone: 734 – 276 – 9155, Fax: 734 – 916 – 5096
E-mail: ancaa@umich.edu

Running title: Thyroid Cancer Standard of Care

ABSTRACT

In the past decade the management of differentiated thyroid cancer (DTC) underwent a paradigm shift towards the use of risk-stratification with the goal of maximizing benefit and minimizing morbidity of radioiodine (^{131}I) therapy. ^{131}I therapy is guided by information derived from surgical histopathology, molecular markers, postoperative diagnostic radioiodine scintigraphy and thyroglobulin (Tg) levels. ^{131}I is used for diagnostic imaging and therapy of DTC based on physiologic sodium-iodine symporter expression in normal and neoplastic thyroid tissue. We summarize the essential information at the core of multidisciplinary DTC management, which emphasizes individualization of ^{131}I therapy according to the patient's risk for tumor recurrence.

Key words: Differentiated Thyroid Cancer, State of the Art, Guidelines, Clinical Management

ABBREVIATIONS

CT, computed tomography

DTC, differentiated thyroid cancer

FDG, ^{18}F-fluorodeoxyglucose; **FNA**, fine-needle aspiration; **FTC**, follicular thyroid cancer

LID, low iodine diet

MTA, maximum tolerated ^{131}I activity

NIS, Na-I symporter

PET/CT, positron emission tomography/computed tomography

PTC, papillary thyroid cancer

SPECT/CT, single photon computed emission tomography/computed tomography

Tg, thyroglobulin; **TgAb**, anti-Tg antibodies;

TIRADS, Thyroid Imaging Reporting and Data System

THW, thyroid hormone withdrawal

TSH, thyrotropin, thyroid stimulating hormone; **rhTSH**, recombinant human TSH

US, ultrasound

WBS, whole body scan; **DxWBS**, diagnostic WBS; **PT-WBS**, post-therapy WBS

INTRODUCTION

Standard of care management for differentiated thyroid cancer (DTC) is risk-adapted and typically includes surgery, iodine-131 (^{131}I) therapy, and thyroid hormone therapy. In rare cases of radioiodine-refractory disease, external radiotherapy, radiofrequency ablation and multikinase or tyrosine kinase inhibitors (TKIs) may provide symptomatic relief and slow metastatic disease progression.

EPIDEMIOLOGY AND CLASSIFICATION

Thyroid neoplasms are the most common endocrine tumors (annual incidence 8-9 cases/100 000 people) and DTC accounts for more than 90% of cases. The rising DTC incidence in recent years may reflect a combination of increased imaging and a concomitant true rise in incidence. (1) DTC is biologically and functionally heterogeneous with different molecular pathways impacting cancer cell biology, in particular BRAF V600E mutation is associated with reduced expression of all thyroid specific genes involved in iodine metabolism resulting in variable decreased responsiveness to ^{131}I therapy. (2) Clinical, pathological and molecular characteristics of DTC are summarized in Supplemental Table 1. (3)

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). Sonomorphological nodule features are used to produce a standardized risk assessment for thyroid malignancy named the Thyroid Imaging Reporting and Data System (TI-RADS)**.** 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 TI-RADS score in the context of nodule size.

SURGICAL TREATMENT

Traditionally, (near-) total thyroidectomy was performed in most DTC patients, with lobectomy reserved for cytologically indeterminate nodules or patients with unifocal microcarcinoma (i.e., PTC $\leq$ 1 cm). Currently lobectomy is suggested for patients with unifocal intrathyroidal low-risk DTC up to 4 cm. in the absence of

additional risk factors (i.e. no clinical evidence of nodal metastases, cN0). (4) The management of low-risk DTC between 2 and 4 cm. remains a topic of debate and total thyroidectomy is still frequently advised. (5) Active surveillance is an alternative to lobectomy for unifocal micro-PTC with no extracapsular extension or lymph node metastases.(6) The decision for active surveillance is based primarily on age-related risk of progression, individual surgical risk factors and patient preference. (7)

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. (8, 9) 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 tumours (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. (10)

POST-OPERATIVE MANAGEMENT

Postoperative 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. Tumor biology information encrypted in the molecular profile may also help determine indications for ^{131}I treatment and modulate treatment intensity, however further studies are required before incorporating molecular profiling in clinical practice. 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. (11)

Post-operative ^{131}I therapy

The goal of ^{131}I therapy is determined upon integration of clinical-pathologic, laboratory and imaging information, using standardized definitions as follows: (12)

- *Remnant ablation* is intended to eliminate postoperative normal thyroid tissue remnants in low-risk DTC in order to achieve an undetectable serum thyroglobulin (Tg) level, facilitating follow-up and early detection of

relapse. Thyroid remnant ablation also enables high-sensitivity post-therapy whole body scan (PT-WBS) for diagnostic and localization of any residual disease after surgery, such as unsuspected regional cervical metastases or distant metastatic disease.

- *Adjuvant treatment* represents administration of ^{131}I therapy in patients with suspected microscopic 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, with the goal of improving recurrence-free survival.
- *Treatment of known disease* represents ^{131}I therapy administration in patients with known residual or metastatic disease with the goal of eliminating iodine-avid regional and/or distant metastases in order to achieve cure or remission, reduce persistent or recurrent disease, and improve overall prognosis.

Preparation for ^{131}I therapy

Evaluation with radioiodine scintigraphy and ^{131}I therapy is scheduled a minimum of 4 weeks after surgery, which allows time for patient preparation and to reach the necessary 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). (13) 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 Supplemental Table 2, and adequate TSH stimulation (TSH $\geq$ 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. (14) For childbearing females (age 12 - 50 year old) a negative pregnancy test is required within 72 hours of ^{131}I administration, or prior to the first rhTSH injection (if employed), unless the patient is status post hysterectomy or is postmenopausal.

There are 2 main 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 the 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 (thyroid hormone withdrawal, THW) has 2 variants: a) L-T4 (levothyroxine) withdrawal for 4 weeks; b) T4/T3 (levothyroxine/liothyronine) substitution for the first 2 weeks.
2) *exogenous TSH stimulation:* the patient continues T4 treatment and TSH elevation is obtained through administration of recombinant human TSH, rhTSH **(**Thyrogen ® Stimulation Protocol): 0.9 mg rhTSH administered intramuscularly on 2 consecutive days, followed by ^{131}I therapy administration at 48-72 hours.

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. (15, 16). In the setting of distant metastases THW preparation and dosimetry-guided ^{131}I therapy is favored, when clinically safe and feasible. (17-19)

^{131}I THERAPY

There are two approaches to ^{131}I therapy delivery: the theragnostic approach which integrates the information obtained with post-operative diagnostic (Dx) radioiodine (^{123}I or ^{131}I) scans in the management algorithm, and the risk-based approach based on clinical-pathologic factors and institutional protocols. Which of these two approaches is chosen depends on local factors, including the quality of surgery, the availability of, and expertise with various imaging modalities, and physician as well as patient preferences. Each approach has strengths and limitations, and no conclusive evidence regarding primary outcome measures is available for recommending one strategy over the other.

Management integrating functional diagnostic radioiodine imaging

This theragnostic approach to ^{131}I administration involves the acquisition of a postoperative Dx radioiodine (^{123}I, ^{131}I or ^{124}I) scan for planning ^{131}I therapy. Dx whole body scans (WBS) are performed for identifying and localizing regional and distant metastatic disease and for determining the capacity of metastatic deposits to concentrate ^{131}I. Depending on institutional protocols, the findings on Dx WBS may alter management, such as: 1) providing guidance for additional surgery; 2) altering the prescribed ^{131}I therapy, either by adjusting conventional ^{131}I activity, or performing dosimetry calculations for determining the maximum tolerated therapeutic ^{131}I activity (MTA) for treatment of distant metastases; 3) avoiding unnecessary ^{131}I therapy when 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 (note: the Tg cutoff should be adapted locally depending on the stimulation protocol and Tg assay). (17) Information acquired from the 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 the DxWBS). Wherever available, it is preferable for postoperative Dx scanning to be performed using integrated multimodality imaging (i.e. single photon computed emission tomography/computed tomography, SPECT/CT). SPECT/CT is relevant 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 (not appreciated on postoperative neck US). Scintigraphic evaluation with a Dx WBS can identify pulmonary micro-metastases (which are too small to be detected on routine chest x-ray and may remain undetected on CT) – see Figure 1, and bone metastases at an early stage (i.e. before cortical disruption is visible on bone x-rays or CT) – see Figure 2. 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.(20) (21) In a group of 320 thyroid cancer patients referred for postoperative ^{131}I therapy, Dx WBS with SPECT/CT detected regional metastases in 35% of patients, and distant metastases in 8% of patients. This scintigraphy information changed staging in 4% of younger, and 25% of older patients. (22) Clinical management was changed in 29% of patients when information from DxWBS and stimulated Tg was integrated into decision algorithm, as compared to a management strategy based on clinical

and histopathology information alone. (23) In 350 patients at intermediate and high risk of recurrence, a single ^{131}I therapeutic administration guided by postoperative Dx WBS information resulted in a complete response (CR) in 88% patients with local-regional disease and 42% patients with distant metastases (median follow-up of 3 years). (24) The information obtained with the Dx WBS reasonably predicts ^{131}I therapeutic localization and can be used for ^{131}I therapy planning in the paradigm of thyroid cancer radiotheragnostics.(22, 25, 26)

^{124}I is a positron emmitter isotope with 4.2-day half-life that has superior imaging characteristics compared with ^{123}I and ^{131}I scintigraphy. ^{124}I is expensive, with limited accessibility and is not widely available, however based on its PET imaging capability ^{124}I is the ideal agent for pre-therapy tumor and organ dosimetry calculations (27). A standardized protocol for ^{124}I PET/CT acquisition, analysis and quantification remains to be established.

Risk-adapted ^{131}I therapy followed by post-therapy ^{131}I scans with diagnostic intent

The conventional approach, in which the nuclear medicine physician chooses an ^{131}I activity based on local protocols, availability, experience with various imaging modalities and patient-related parameters, is widely used for thyroid remnant ablation, adjuvant treatment and curative therapy of known structural disease. With this therapeutic approach the prescribed ^{131}I activity depends on the goal of ^{131}I therapy as determined by the estimated risk for persistent/recurrent disease. *Thyroid remnant ablation* in low-risk patients is typically performed with low ^{131}I activity (i.e. 1.1 – 1.85 GBq [30 - 50 mCi]). *Adjuvant ^{131}I therapy* is performed with slightly higher activity (i.e. 1.85 - 3.7 GBq [50 - 100 mCi]), with some institutions extending this range to 5.55 GBq [150 mCi]). *Treatment of known disease* is performed by administration of high activity (i.e. 3.7 - 5.56 GBq [100-150 mCi] for therapy of advanced local-regional disease, and 5.6 -7.4 GBq [150-200 mCi] for treatment of distant metastatic disease. (28) However, when diagnostic scintigraphy demonstrates diffuse homogenous uptake throughout the lungs, simplified whole body dosimetry should be performed for adjusting the prescribed ^{131}I activity so that pulmonary ^{131}I retention should not exceed 3 GBq (80 mCi) after 48h, with the goal of minimizing the risk of radiation-induced lung toxicity. (29) Administration of therapeutic ^{131}I activities ≥

7.4 GBq [200 mCi] for treatment of diffuse distant metastatic disease requires full whole body/blood dosimetry calculations.(24) See Table 1 for a suggested ^{131}I therapy framework in DTC.

PT-WBS is obtained at 2-7 days after ^{131}I administration for ascertaining therapeutic ^{131}I localization and assessing for regional and distant metastatic disease. Campenni et al. reported in a cohort of 570 low- and low-intermediate risk DTC patients (pT1 - pT3) that PT-WBS 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. (30) Therefore, post-surgical nonstimulated Tg levels cannot be used independently in deciding whether to pursue therapeutic ^{131}I administration, mainly in patients assigned as low-risk based on surgical pathology alone.

THYROID HORMONE REPLACEMENT THERAPY

Following thyroidectomy, DTC patients require thyroid hormone (levothyroxine, L-T4) replacement. The TSH target for L-T4 therapy is based on dynamic risk classification, Tg level, Tg trend over time, anti-TgAb and potential adverse effects of TSH suppression. For patients with a structural incomplete response the serum TSH is suppressed <0.1 mU/L. In the excellent treatment response category, the serum TSH is maintained at 0.5–2 mUI/L for intermediate risk patients, and at 0.1-0.5 mUI/L for high-risk patients. For patients with biochemical indeterminate or incomplete responses, the recommended serum TSH target is 0.1-0.5 mU/L (6).

DTC MANAGEMENT IN CHILDREN

DTC represents 1.8% of all childhood cancer under 20 years of age. The incidence of pediatric thyroid cancer has increased in part due to better techniques for diagnosis. A 4.43% increase in all stage primarily papillary histology in boys and girls aged 10-19 in non-Hispanic whites, non-Hispanic blacks and Hispanics was reported in a study that included 39 US Cancer registries (31).

While 50% of adults over age 60 have thyroid nodules, only 5-7% of children and young adults are diagnosed with thyroid nodules. However, thyroid cancer is diagnosed in 25% of thyroid nodules in pediatric population (as compared to 10-15% of thyroid nodules in adults). TI-RADS assessment is not used in pediatric

patients as one study of 314 children under 18 years showed that 22% cancers would be missed (32). Children with thyroid cancer have an increased incidence of regional and distant metastatic disease at presentation as compared to adults, with cervical lymph nodal metastases diagnosed in 50%, and lung metastases in 20% of cases.

Recommended treatment for pediatric thyroid cancer is total thyroidectomy due to increased incidence of bilateral and multifocal disease (30% and 65%, respectively) and greater likelihood for regional and distant metastasis at presentation as compared to adults. (33) Central node dissection is recommended in the presence of locoregional cervical disease diagnosed by imaging and confirmed on FNA or identified during surgery. While some have approached disease in one lobe with lobectomy or phased approach, a recent study by Zong et al. suggested that due to large lesions often involving both thyroid lobes in the pediatric age group, there is increased morbidity in staged resection. (34) Lobectomy may be indicated in FTC with certain characteristics including size less than 4 cm with less than 3 vessel vascular invasion (minimally invasive FTC).

ATA pediatric guidelines identify three risk categories dependent on risk of persistent disease: *Low-risk*, disease confined to thyroid with few central nodes and no macroscopic metastases; *Medium-risk*, significant central and minimal lateral node involvement; *High-risk*, locally invasive tumor and extensive lateral neck lymph node involvement, and/or distant metastases. (33)

Postoperatively, the use of DxWBS imaging and 24-hour neck uptake performed at 6-12 weeks post-surgery and Tg testing is recommended. While the ATA guidelines suggest this for intermediate- and high- risk groups, many pediatric centers perform this in all risk groups. Apart from low-risk disease being less common, children have higher risk of recurrence of DTC. (35) DxWBS are now routinely performed with SPECT/CT (non-contrast CT) to evaluate for cervical, upper mediastinal, and pulmonary metastatic disease. Depending on the DxWBS findings, the child may be referred back to surgery for resection of unsuspected bulky residual nodal metastases in unexplored neck compartments, or proceed with ^{131}I therapy for remnant ablation or treatment of local-regional or pulmonary metastatic disease, if present.

There is controversy as to how the ^{131}I treatment activity is determined. Some suggest an empiric dosing for initial ^{131}I therapy in pediatrics, with dosimetry possibly relegated if follow-up ^{131}I therapy is needed. Weight

based dose as a multiplier of 70 kg adult, and 1-1.5 mCi/kg (37-56 MBq/kg) have been utilized (36). ATA guidelines do not specify recommended therapeutic ^{131}I activities. Parisi et al. presented this algorithm: low-risk disease 1.1-1.85 GBq (30-50 mCi); higher-risk local-regional disease 5.6-6.5 GBq (150-175 mCi), and in the presence of known or suspected pulmonary metastatic disease 6.5-7.4 GBq (175-200 mCi). All of these therapeutic ^{131}I activities are adjusted for body weight based on 70 kg adult weight, see Table 1. (35) As with adults, routine PT-WBS is performed at 5-7 days post-therapy.

The overall prognosis for pediatric DTC is good with greater than 98% 10-year survival rate (37). In the small subset of children with refractory disease or disease that is not responsive to ^{131}I treatment, newer molecular therapies that target the known genetic alterations and molecular mutations may be utilized. (38)

RESPONSE ASSESSMENT AFTER PRIMARY TREATMENT AND FOLLOW-UP

The combination of Tg measurement, neck US and follow-up DxWBS performed at 1 - 2 years after primary therapy is used to re-stratify the risk of recurrence according to the patient's response to initial therapy. This process of risk reassignment is called dynamic risk stratification and it is predictive of long-term clinical outcome. Treatment response evaluation criteria are summarized in Table 2. (4)

In patients with **excellent (complete) response** the risk of disease recurrence is 1 - 4%, which for *intermediate-risk patients* (whose initial recurrence risk is 36 - 43%) and for *high-risk patients* (whose initial recurrence risk is 68 - 70%) represents a major change in risk. The clinical outcome in patients with **biochemical incomplete response** is usually good: approximately 60% of patients have no evidence of disease over long-term follow-up; 20% of patients have persistently abnormal Tg without a structural correlate, and 20% of patients develop structurally identifiable disease over 5 - 10 years of follow-up. Patients with **biochemical indeterminate response** generally do well: in 80 - 90% of patients non-specific biochemical findings either remain stable or resolve over time with L-T4 suppression therapy alone; however, up to 20% of these patients will eventually develop functional, or structural evidence of disease progression and require additional therapy. Patients with **structural incomplete response** require multidisciplinary management tailored to their disease status (e.g.

regional vs. distant metastases; iodine-avid vs. non-iodine avid disease). (4); depending on the results of additional treatment patients are re-stratified according to the criteria above.

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). (39)

The prognosis of metastatic DTC is variable, with two distinct phenotypes identified - indolent and aggressive. (40) Patients with iodine-avid metastatic DTC tend to have more favorable prognosis with 10-year survival greater than 90%, while non-iodine avid metastatic DTC has a dire 10-year survival of 10%. (41) 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. (20) 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 - 4.5 years. (20, 42)

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. (43) ^{18}F-FDG-PET/CT is particularly useful for identification and localization of non iodine-avid metastastases and is used for evaluating patients with elevated Tg and negative DxWBS (i.e. Tg+/scan-). (44) 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. (45) In addition, ^{18}F-FDG PET/CT has shown a prognostic value in metastatic DTC predicting the course of disease as aggressive or indolent. (46) In radioiodine refractory meastatic DTC there is a survival disadvantage for patients with a positive PET as compared with those with a negative PET. (42)

Ablative treatment for local-regional disease control (i.e. resection, vertebroplasty, external beam radiation therapy and thermal ablation) can provide symptomatic relief and delay initiation of systemic therapy, while bisphosphonate or denosumab can delay time to skeletal related events. (47) In cases of confirmed radioiodine-resistant metastatic disease progression treatment with multikinase inhibitors (e.g. lenvatinib, sorafenib, vandetinib, cabozatinib, vemurafenib, dabrafenib/trametinib and others) may induce periods of progression-free survival (rarely remission) without evidence for increased cancer-specific survival and these drugs may be associated with side effects, such as hypertension, diarrhea, hand/foot skin reactions, rash, fatigue, mucositis, loss of appetite, and weight loss. (48) The optimal time to start therapy, especially in asymptomatic patients, is unclear as well as which patients are likely to benefit in terms of increased quality of adjusted life years. As a rule, molecular targeted therapies are started based on a multi-discplinary team discussion in patients with a negative DxWBS and symptoms that are not amenable to local therapy, and/or progression of measurable lesions, as defined by RECIST criteria over the previous 12 months, taking under consideration tumor burden and the risk of local complications. (49) The biological mechanisms implicated in radioiodine refractoriness involve gain-of-function mutations in the MAPK signaling pathway, resulting in reduced NIS and other iodine-metabolizing genes expression. Experimental data showed that MAPK signaling pathway inhibition using MEK or BRAF inhibitors restored radioiodine avidity. Subsequent clinical studies demonstrated that mutation-guided treatment using selective MEK inhibitors (selumetinib, trametinib), BRAF inhibitors (dabrafenib, vemurafenib), or a combination of BRAF inhibitor and MEK inhibitor, is feasible and represents a promising strategy to redifferentiate radioiodine refractory DTC, thereby permitting reapplication of ^{131}I therapy. Preliminary data obtained on a small clinical series of 13 patients demonstrated restoration of ^{131}I avidity in 62% of patients who subsequently received ^{131}I treatment [median activity 7.6 GBq (204.4 mCi), range 5.5 – 9.4 GBq (150 - 253 mCi)], resulting in durable disease control (median duration > 1 year) while not receiving chronic, expensive multikinase inhibitor therapy. (50) ^{131}I therapy remains the only known cure for metastatic radioidine-sensitive DTC and the use of a redifferentiating strategy to permit additional ^{131}I treatment for patients with radioiodine-refractory metastatic disease represents a promising therapeutic approach while minimizing exposure to kinase inhibitor therapy.

CONCLUSIONS

DTC is the most common endocrine malignancy. While standard management including surgery and radioiodine therapy is successful in most cases, therapy should be tailored according to risk-stratification integrating the information from histopathology, molecular markers, post-operative Tg levels and imaging studies. Ultimately, local multidisciplinary teams consider the availability of surgical, pathological, nuclear medicine and laboratory expertise and take into account individual patient preferences to guide appropriate therapy.

Disclosure: the authors declare no conflics of interest.

Acknoledgement: the authors thank Ms. Vanessa Allen for composite figures preparation for this manuscript.

REFERENCES:

1. Davies L, Morris LG, Haymart M, Chen AY, Goldenberg D, Morris J, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: The Increasing Incidence of Thyroid Cancer. Endocr Pract. 2015;21(6):686-96.
2. Gulec SA, Ahuja S, Avram A, Bernet V, Bourguet P, Draganescu C, et al. A Joint Statement from the American Thyroid Association, the European Association of Nuclear Medicine, the European Thyroid Association, the Society of Nuclear Medicine and Molecular Imaging on Current Diagnostic and Theranostic Approaches in the Management of Thyroid Cancer. Thyroid. 2021.
3. Rossi E, Fadda G. Pathology and immunohistochemistry in thyroid tumors. (Ed) GL, editor: Springer International Publishing 2018.
4. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
5. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, et al. Extent of surgery affects survival for papillary thyroid cancer. Annals of surgery. 2007;246(3):375-81; discussion 81-4.
6. Ito Y, Miyauchi A, Oda H. Low-risk papillary microcarcinoma of the thyroid: A review of active surveillance trials. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2018;44(3):307-15.
7. Davies L, Roman BR, Fukushima M, Ito Y, Miyauchi A. Patient Experience of Thyroid Cancer Active Surveillance in Japan. JAMA Otolaryngol Head Neck Surg. 2019;145(4):363-70.
8. Miller JE, Al-Attar NC, Brown OH, Shaughness GG, Rosculet NP, Avram AM, et al. Location and Causation of Residual Lymph Node Metastasis After Surgical Treatment of Regionally Advanced Differentiated Thyroid Cancer. Thyroid. 2018;28(5):593-600.
9. Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Annals of surgery. 2007;245(4):604-10.
10. Barczynski M, Konturek A, Stopa M, Nowak W. Prophylactic central neck dissection for papillary thyroid cancer. Br J Surg. 2013;100(3):410-8.
11. Tuttle RM, Ahuja S, Avram AM, Bernet VJ, Bourguet P, Daniels GH, et al. Controversies, Consensus, and Collaboration in the Use of (131)I Therapy in Differentiated Thyroid Cancer: A Joint Statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association. Thyroid. 2019;29(4):461-70.
12. Van Nostrand D. The benefits and risks of I-131 therapy in patients with well-differentiated thyroid cancer. Thyroid. 2009;19(12):1381-91.
13. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab. 2001;86(4):1447-63.
14. Xiao J, Yun C, Cao J, Ding S, Shao C, Wang L, et al. A pre-ablative thyroid-stimulating hormone with 30-70 mIU/L achieves better response to initial radioiodine remnant ablation in differentiated thyroid carcinoma patients. Sci Rep. 2021;11(1):1348.
15. Potzi C, Moameni A, Karanikas G, Preitfellner J, Becherer A, Pirich C, et al. Comparison of iodine uptake in tumour and nontumour tissue under thyroid hormone deprivation and with recombinant human thyrotropin in thyroid cancer patients. Clin Endocrinol (Oxf). 2006;65(4):519-23.

16. Freudenberg LS, Jentzen W, Petrich T, Fromke C, Marlowe RJ, Heusner T, et al. Lesion dose in differentiated thyroid carcinoma metastases after rhTSH or thyroid hormone withdrawal: 124I PET/CT dosimetric comparisons. Eur J Nucl Med Mol Imaging. 2010;37(12):2267-76.
17. Giovanella L, Duntas LH. MANAGEMENT OF ENDOCRINE DISEASE: The role of rhTSH in the management of differentiated thyroid cancer: pros and cons. Eur J Endocrinol. 2019;181(4):R133-R45.
18. Zanotti-Fregonara P, Hindie E. On the effectiveness of recombinant human TSH as a stimulating agent for 131I treatment of metastatic differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2010;37(12):2264-6.
19. Plyku D, Hobbs RF, Huang K, Atkins F, Garcia C, Sgouros G, et al. Recombinant Human Thyroid-Stimulating Hormone Versus Thyroid Hormone Withdrawal in (124)I PET/CT-Based Dosimetry for (131)I Therapy of Metastatic Differentiated Thyroid Cancer. J Nucl Med. 2017;58(7):1146-54.
20. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006;91(8):2892-9.
21. Schmidt D, Linke R, Uder M, Kuwert T. Five months' follow-up of patients with and without iodine-positive lymph node metastases of thyroid carcinoma as disclosed by (131)I-SPECT/CT at the first radioablation. Eur J Nucl Med Mol Imaging. 2010;37(4):699-705.
22. Avram AM, Fig LM, Frey KA, Gross MD, Wong KK. Preablation 131-I scans with SPECT/CT in postoperative thyroid cancer patients: what is the impact on staging? J Clin Endocrinol Metab. 2013;98(3):1163-71.
23. Avram AM, Esfandiari NH, Wong KK. Preablation 131-I scans with SPECT/CT contribute to thyroid cancer risk stratification and 131-I therapy planning. J Clin Endocrinol Metab. 2015;100(5):1895-902.
24. Avram AM, Rosculet N, Esfandiari NH, Gauger PG, Miller BS, Cohen M, et al. Differentiated Thyroid Cancer Outcomes After Surgery and Activity-Adjusted 131I Theragnostics. Clin Nucl Med. 2019;44(1):11-20.
25. McDougall IR. 74 MBq radioiodine 131I does not prevent uptake of therapeutic doses of 131I (i.e. it does not cause stunning) in differentiated thyroid cancer. Nucl Med Commun. 1997;18(6):505-12.
26. Avram AM, Dewaraja YK. Thyroid Cancer Radiotheragnostics: the case for activity adjusted (131)I therapy. Clin Transl Imaging. 2018;6(5):335-46.
27. Jentzen W, Freudenberg L, Bockisch A. Quantitative imaging of (124)I with PET/ CT in pretherapy lesion dosimetry. Effects impairing image quantification and their corrections. The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the So. 2011;55(1):21-43.
28. Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJ, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2008;35(10):1941-59.
29. Sisson JC. Practical dosimetry of 131I in patients with thyroid carcinoma. Cancer biotherapy & radiopharmaceuticals. 2002;17(1):101-5.
30. Campenni A, Giovanella L, Pignata SA, Vento A, Alibrandi A, Sturiale L, et al. Undetectable or low (<1 ng/ml) postsurgical thyroglobulin values do not rule out metastases in early stage differentiated thyroid cancer patients. Oncotarget. 2018;9(25):17491-500.

31. Bernier MO, Withrow DR, Berrington de Gonzalez A, Lam CJK, Linet MS, Kitahara CM, et al. Trends in pediatric thyroid cancer incidence in the United States, 1998-2013. Cancer. 2019;125(14):2497-505.
32. Richman DM, Benson CB, Doubilet PM, Wassner AJ, Asch E, Cherella CE, et al. Assessment of American College of Radiology Thyroid Imaging Reporting and Data System (TI-RADS) for Pediatric Thyroid Nodules. Radiology. 2020;294(2):415-20.
33. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, et al. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015;25(7):716-59.
34. Zong Y, Li K, Dong K, Yao W, Liu G, Xiao X. The surgical choice for unilateral thyroid carcinoma in pediatrics: Lobectomy or total thyroidectomy? J Pediatr Surg. 2018;53(12):2449-53.
35. Parisi MT, Eslamy H, Mankoff D. Management of Differentiated Thyroid Cancer in Children: Focus on the American Thyroid Association Pediatric Guidelines. Semin Nucl Med. 2016;46(2):147-64.
36. Machac J. Thyroid Cancer in Pediatrics. Endocrinol Metab Clin North Am. 2016;45(2):359-404.
37. Sugino K, Nagahama M, Kitagawa W, Shibuya H, Ohkuwa K, Uruno T, et al. Papillary Thyroid Carcinoma in Children and Adolescents: Long-Term Follow-Up and Clinical Characteristics. World J Surg. 2015;39(9):2259-65.
38. Remiker AS, Chuang J, Corathers S, Rutter MM, Rutter MJ, Myer CMt, et al. Differentiated Thyroid Cancer in the Pediatric/Adolescent Population: Evolution of Treatment. Journal of pediatric hematology/oncology. 2019;41(7):532-6.
39. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet. 2016;388(10061):2783-95.
40. Ain KB. Papillary thyroid carcinoma. Etiology, assessment, and therapy. Endocrinol Metab Clin North Am. 1995;24(4):711-60.
41. Xing M, Haugen BR, Schlumberger M. Progress in molecular-based management of differentiated thyroid cancer. Lancet. 2013;381(9871):1058-69.
42. Robbins RJ, Wan Q, Grewal RK, Reibke R, Gonen M, Strauss HW, et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. J Clin Endocrinol Metab. 2006;91(2):498-505.
43. Giovanella L, van Nostrand D. Advanced differentiated thyroid cancer: when to stop radioiodine? The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the So. 2019;63(3):267-70.
44. Silberstein EB. The problem of the patient with thyroglobulin elevation but negative iodine scintigraphy: the TENIS syndrome. Semin Nucl Med. 2011;41(2):113-20.
45. Schleupner MC, Riemann B, Schafers M, Backhaus P, Vrachimis A. Impact of FDG-PET on therapy management and outcome of differentiated thyroid carcinoma patients with elevated thyroglobulin despite negative iodine scintigraphy. Nuklearmedizin. 2020;59(5):356-64.
46. Wang W, Larson SM, Fazzari M, Tickoo SK, Kolbert K, Sgouros G, et al. Prognostic value of [18F]fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J Clin Endocrinol Metab. 2000;85(3):1107-13.
47. Giovanella L, Scappaticcio L. Radioiodine therapy of advanced differentiated thyroid cancer: clinical considerations and multidisciplinary approach. The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the So. 2019;63(3):229-34.

48. Porter A, Wong DJ. Perspectives on the Treatment of Advanced Thyroid Cancer: Approved Therapies, Resistance Mechanisms, and Future Directions. Front Oncol. 2020;10:592202.
49. Sabra MM, Sherman EJ, Tuttle RM. Tumor volume doubling time of pulmonary metastases predicts overall survival and can guide the initiation of multikinase inhibitor therapy in patients with metastatic, follicular cell-derived thyroid carcinoma. Cancer. 2017;123(15):2955-64.
50. Jaber T, Waguespack SG, Cabanillas ME, Elbanan M, Vu T, Dadu R, et al. Targeted Therapy in Advanced Thyroid Cancer to Resensitize Tumors to Radioactive Iodine. J Clin Endocrinol Metab. 2018;103(10):3698-705.
:

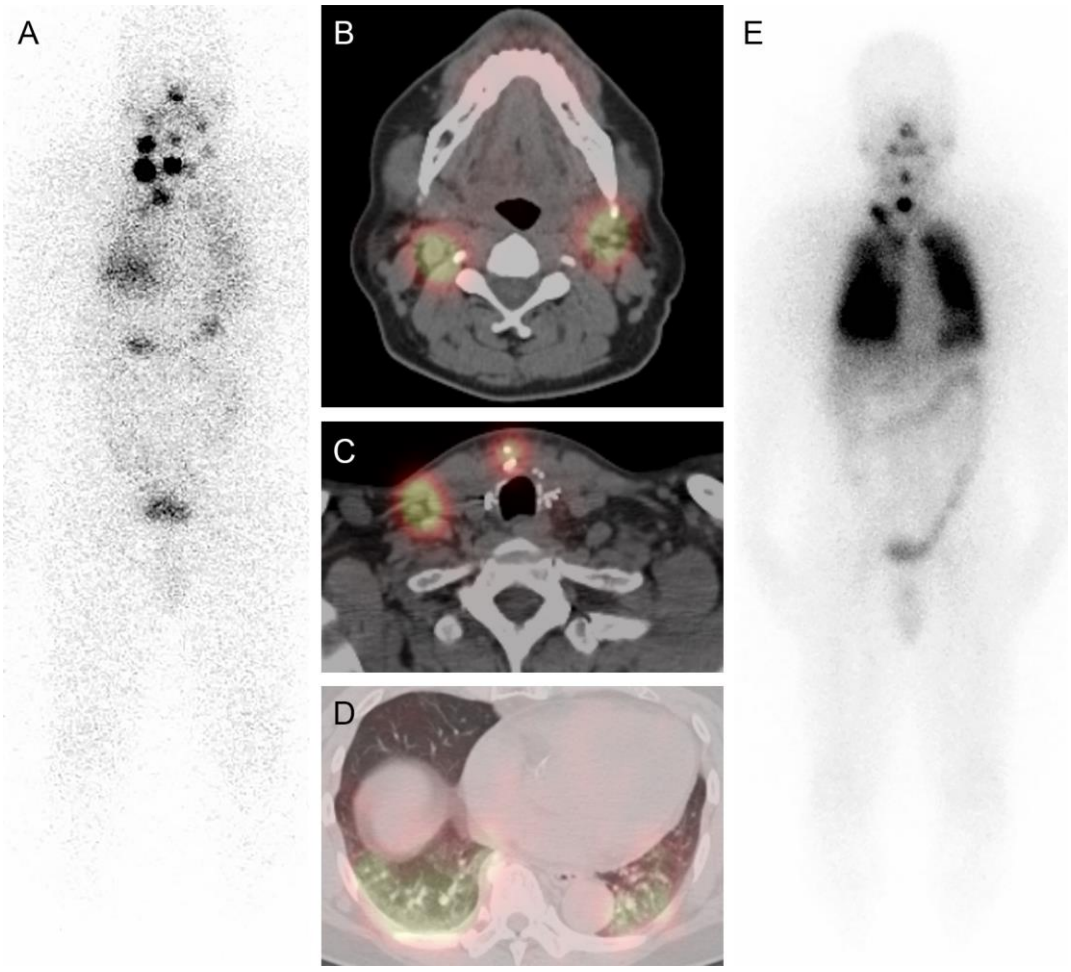

Fig. 1: Radioiodine theranostics for a 63 year-old-man with regionally advanced thryoid cancer: 2.2 cm. PTC, 11+/11 lymph nodes resected in the surgical specimen of total thyroidectomy. Diagnostic 1 mCi ^{131}I WBS, anterior projection (A) depicts multifocal neck activity and diffuse lung activity. Neck 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 milliary pulmonary metastatic disease.

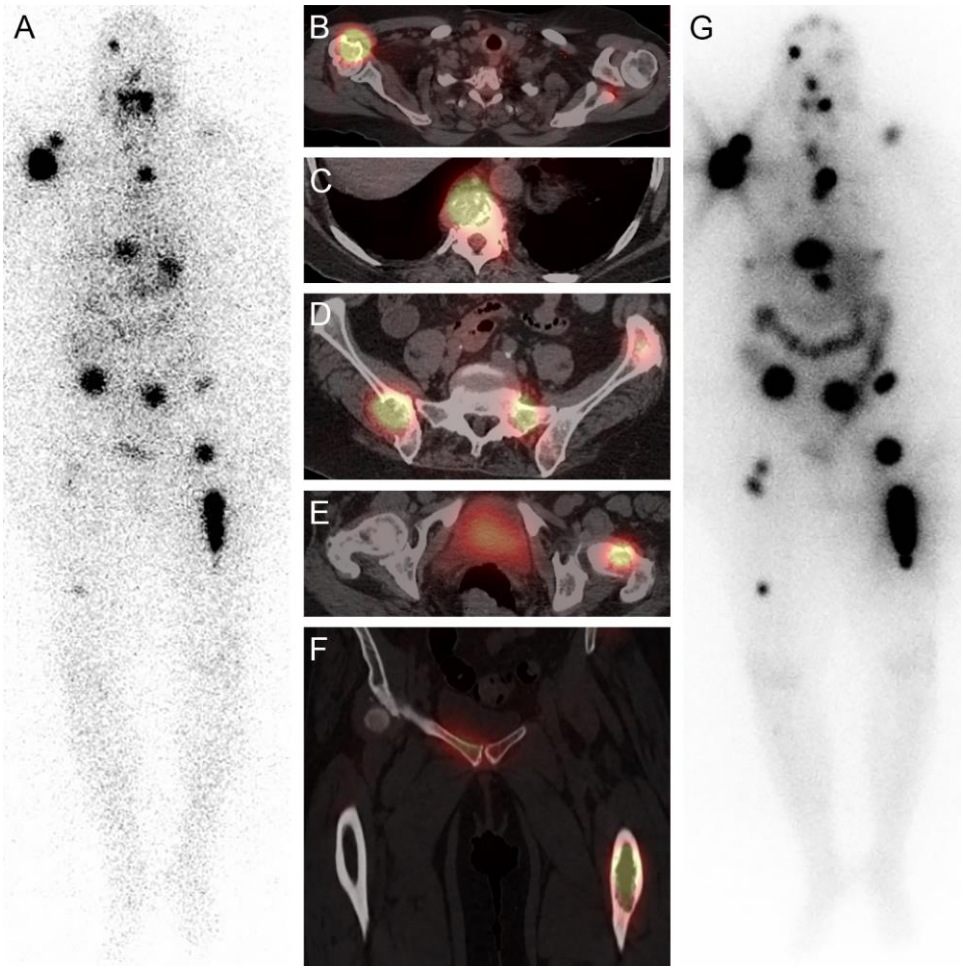

Fig. 2: Radioiodine theranostics for a 66 year-old-woman with 2.5 cm widely invasive FTC with osseous metastatic disease. Diagnostic 1 mCi ^{131}I WBS, anterior projection (A) depicts multifocal skeletal activity further characterized on SPECT/CT as iodine-avid lytic osseous metastases involving the right humerus (B), vertebrae (C), pelvis (D) left femoral neck (E) and left femoral diaphysis (F). The patient received dosimetry-guided 12 GBq (325 mCi) ^{131}I treatment and post-therapy WBS, anterior projection (G) obtained at 2 days demonstrates therapeutic ^{131}I targeting of extensive iodine-avid multifocal osseous metastatic disease involving the axial and proximal appendicular skeleton, with increased lesion conspicuity and numerous new foci detected as compared to the diagnostic scan.

Table 1: Suggested framework for ^{131}I therapy for DTC* [adapted from (28)]

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

* all pediatric therapeutic ^{131}I activities are adjusted as a multiplier based on 70 kg adult body weight

Table 2. Response to treatment in DTC patients: assessment criteria [modified from *(4)*]

▪ **Excellent (complete) response**: no clinical, biochemical or structural evidence of disease. Definition: negative imaging and *either* suppressed Tg <0.2 ng/mL *or* stimulated Tg <1 ng/mL.
▪ **Biochemical incomplete response**: abnormal Tg (suppressed Tg >1 ng/mL *or* stimulated Tg >10 ng/mL *or* rising anti-TgAb levels in the absence of localizable disease (i.e. negative imaging)).
▪ **Structural incomplete response**: persistent or new loco-regional or distant metastases (any Tg).
▪ **Indeterminate response**: nonspecific biochemical findings (suppressed Tg 0.2-1 ng/mL *or* stimulated Tg 1-10 ng/mL *or* stable/declining anti-TgAb levels) *or* structural findings that cannot be confidently classified as benign or malignant.

Supplemental Table 1. Thyroid cancer characteristics (3)

Histological subtypes	Morphology	Molecular markers	Pattern of Spread	RAI avidity
Papillary thyroid cancer (PTC)	Classical papillae Clear nuclei	BRAF V600E, RET/PTC fus	Lymph nodes	Yes
PTC-Follicular variant (fvPTC)	Follicular structures Clear nuclei	BRAF K601E, RAS, PAX8/PPARγ	Lymph nodes	Yes
PTC-Aggressive variants*	Specific cell features and structural changes	BRAF V600E, 1q amp, TERT promoter	Lymph nodes Lung	Yes
Follicular thyroid cancer (FTC)	Capsular invasion (MI) Vascular invasion (WI) Extrathyroidal invasion (WI)	RAS, PAX8/PPARγ, TSHR, TERT promoter, PTEN	Lung, Bone	Yes
Hurthle cell thyroid carcinoma	Hurthle cells	RAS, PAX8/PPARγ, TSHR, chromosomal loss, mitochondrial DNA mutations, TERT promoter, PTEN	Lung, Bone	Yes
Poorly differentiated thyroid cancer (PDTC)	Invasion Mitoses >3 Necrosis Convoluted nuclei	RAS, TERT promoter, TP53, PIK3CA, PTEN, CTNNB1, AKT1, EIF1AX, ALK fus	Lymph nodes Lung, Bone	Variably reduced
Anaplastic thyroid cancer	Undifferentiated cells with ultrastructural and immune-histochemical or features of epithelial origin but with morphological and immunophenotypic markers of thyroid origin	TP53, TERT promoter, PI3K/AKT/mTOR, SWI/SNF subunts, RAS, EIF1AX, BRAF	Local invasion Lung, Bone Lymph nodes	No

Legend: MI=minimally invasive; WI=widely invasive fus=fusion; *tall, columnar, solid, hobnail variants

Supplemental Table 2. Recommendations for reducing iodine intake (to be followed for 2 weeks)
.

• No iodized salt
• No dairy products or foods containing dairy products
• No foods from the sea
• No herbal supplements
• No vitamins or supplements containing iodine
• Limit grain products (i.e., noodles, pasta, and pastries) to 1 slice of bread, ½ cup of pasta daily
• Limit the amount of beef, chicken, and turkey