Current Pharmaceutical Design, 2020, *26*, 3812-3827

REVIEW ARTICLE

Radiotheragnostics Paradigm for Radioactive Iodine (Iodide) Management of Differentiated Thyroid Cancer

Einat Slonimsky[1] and Mark Tulchinsky[1,*]

[1]*Department of Radiology, Section of Nuclear Medicine, Penn State Health, the Milton S. Hershey Medical Center, Penn State University Hospital, Hershey, Pennsylvania 17033, USA*

Abstract: This review of radioactive iodide treatment (RAIT) extends from historical origins to its modern utilization in differentiated thyroid cancer (DTC). The principles embedded in the radiotheragnostics (RTGs) paradigm are detailed.

The diverse approaches in current practice are addressed, and this broad variability represents a major weakness that erodes our specialty's trust-based relationship with patients and referring physicians. The currently developing inter-specialty collaboration should be hailed as a positive change. It promises to clarify the target-based terminology for RAIT. It defines RAIT of post total thyroidectomy (PTT), presumably benign thyroid as 'remnant ablation' (RA). 'Adjuvant treatment' (AT) referrers to RAIT of suspected microscopic DTC that is inherently occult on diagnostic imaging. RAIT directed at DTC lesion(s) overtly seen on diagnostic imaging is termed 'treatment of known disease' (TKD).

It was recently recognized that a 'recurrent' DTC is actually occult residual DTC in the majority of cases. Thyroglobulin with remnant uptake concord (TRUC) method (aka Tulchinsky method) was developed to validate that a benign remnant in the post-thyroidectomy neck bed, as quantified by the RAI uptake, is concordant with a measured thyroglobulin (Tg) level at the time of the initial post-thyroidectomy evaluation. It allows recognition of occult residual DTC contribution to post-thyroidectomy Tg. Case examples demonstrate the application of the TRUC method for a logical selection of a specific RAIT category, using imaging-guided identification and management of RAI-avid versus RAI-nonavid residual DTC, i.e. the radiotheragnostics paradigm.

ARTICLE HISTORY

Received: January 17, 2020
Accepted: April 09, 2020

DOI:
10.2174/1381612826666200605121054

Keywords: Iodine Radioisotopes, therapeutic use; Iodine Radioisotopes, adverse effects/therapeutic use, thyroid neoplasms/th [therapy], Adenocarcinoma, Follicular, radiotherapy, Carcinoma, Papillary, radiotherapy, Thyroid Neoplasms/epidemiology, radiotherapy, Neoplasms, Radiation-Induced, epidemiology/etiology, Neoplasms, Second Primary, epidemiology/etiology.

1. INTRODUCTION

Radiotheragnostics (RTGs), a.k.a. theragnostics or theranostics, which is a therapeutic radiopharmaceutical-centered disease management paradigm where imaging with an identical or a biosimilar radiopharmaceutical plays the decision-making and treatment dosage modifying function for the therapeutic radiopharmaceutical. This therapy-centered paradigm integrates available patient and tumor characteristics from physical examination, laboratory analyses, and all available diagnostic imaging, thus comprehensively guiding through disease management continuum. RTG starts with holistic characterization, disease staging, and leading to optimizing therapeutic radiopharmaceutical administered activity and follow patients up with diagnostic radiopharmaceutical.

RTGs is the grammatically proper form and the most appropriate designation out of the listed synonyms as it most completely encompasses the term's meaning. The word is composed of 3 elements. The first element, radio-, originates from Latin word *radius*, meaning "beam." This denotes a relationship to isotopes that emit, i.e. beam out, a photon of energy. The second element, -thera-, is from the Modern Latin word *therapia*, in turn, originating from the Greek word *therapeia*. This element means literary "curing, healing, service done to the sick". The third element, -gnostics, is derived from a Proto-Indo-European root **gno*-, meaning "to know". It is one of the most commonly used roots in a plethora of modern words found in a vast array of languages with "diagnostic" being the most common examples among English medical terms.

*Address correspondence to this author at the Department of Radiology, Section of Nuclear Medicine, Penn State Health, the Milton S. Hershey Medical Center, Penn State University Hospital, 500 University Drive, Hershey, Pennsylvania 17033, USA; Tel: +001 717-531-3542;
E-mail: Mark.Tulchinsky@gmail.com

The concept of RTGs is rooted in the pioneering work conducted by Dr. Soul Hertz from the mid-1930s till the early 1940s, which led to the development of the first therapeutic indication for radioactive iodide (RAI) in Graves' hyperthyroidism [1]. Dr. Hertz administered the first therapeutic activity to a woman with Graves' disease on March 31st, 1941, meticulously documenting the patient's handling of the tracer dosage before administering the treatment activity, carefully monitoring the RAI excretion and the patient's response to the treatment by using contemporary radiation detectors, laboratory and clinical metrics. He particularly aspired to develop RAI therapy (RAIT) for the differentiated thyroid cancer (DTC) but his efforts were interrupted by the sudden thrust of the USA into World War II. Dr. Hertz volunteered for the US Army medical corps, entrusting his clinical practice and research to his colleagues. Only a few years later, Dr. Seidlin published the first successful application of RAIT for the treatment of DTC [2], building on the foundational concepts laid down by Dr. Hertz. Serendipitously, the first patient with DTC had a very rare form of highly functional metastatic disease that manifested not only in tumorous masses but also in clinically overt hyperthyroidism. The effect of RAIT was rather dramatic, causing obvious symptomatic improvement, followed by the patient's return to his healthy weight and functionality. While a highly skilled clinician, Dr. Seidlin was a novice to the field of radiation physics and had never dealt with RAI prior to this compassionate-use investigational treatment. His selection of the administered activity (AA) for the first RAIT was a rather lucky happenstance that was humorously chronicled by Dr. Marshal Brucer, a Nuclear Medicine luminary physician and a historian, in his witty collection of vignettes [3].

Our approach to RAIT for managing DTC is built on the principles of RTGs, a branch of 'targeted therapy' [4], and informed by the best of the current knowledge. The specific target for RAIT is

1873-4286/20 $65.00+.00

sodium-iodide symporter (NIS) located on the cellular membrane of targeted tissues. In one elegant study, *in vitro* identification of NIS on the excised DTC tissue predicted subsequent *in vivo* RAI uptake in remaining metastases [5]. The NIS is expressed on all normal thyrocytes but only some of DTC cells, which allows RAI binding to and retention in those normal and/or malignant cells, creating the opportunity for scintigraphic imaging of the benign thyroid and some DTC that is RAI-avid, as well as the treatment thereof. The density and functional integrity of NIS determine the RAI avidity of individual DTC cells, which is typically much lower than that of normal thyrocytes; hence, explaining DTC appearance as a "cold", i.e. hypo-concentrating NIS-targeting radiopharmaceutical focus on a diagnostic RAI or a biosimilar radiopharmaceutical, such as a ^{99m}Tc-pertechnetate scintigraphy. RAIT side-effects are also based on the physiologically NIS-rich tissues that determines RAI biodistribution, as well as on RAI excretory pathways.

RAI RTGs are enabled by surgical removal of the thyroid gland, which is necessary to 1) diagnose, characterize and remove the tumor bulk, 2) remove most of the original organ to ensure hypothyroidism, and 3) evaluate local/regional spread of the tumor. It is universally accepted that surgical removal of the clinically significant DTC from its origin is preferred to any other therapeutic alternative whenever technically possible. The overwhelming majority of experts also agree that regional extension of the tumor and metastatic lymphadenopathy should be surgically removed as long as the risks of surgical complications are within the patient-specified parameters, which have to be discussed and agreed upon *a priori* by a patient and her/his surgeon. The need for hypothyroidism via total or subtotal thyroidectomy was first recognized in 1948 by the group at the Memorial Sloan Kettering Cancer Center [6]. It is clear that a therapeutically meaningful RAI uptake (RAIU) in DTC typically requires high levels of the thyroid stimulating hormone (TSH). What remain unclear are the optimal TSH level(s) and duration of such stimulation prior to therapeutic RAI administration. Intrinsic TSH elevation can be predictably achieved by thyroid hormone withdrawal (THW). Administration of extrinsic TSH is an alternative approach, albeit shorter and less predictable.

2. FROM TRIAL-AND-ERROR TO WIDELY HETEROGENEOUS RADIOACTIVE IODIDE TREATMENT PRACTICES

The first patient with DTC was treated in 1943 with conservative amounts (small activities) of RAI, which were probably informed by RAIT for hyperthyroidism. It was administered multiple times and at various intervals. The effect of each treatment was meticulously evaluated for clinical response by collecting clinical variables and diagnostic testing of the era, as well as diagnostic RAI tracer studies by a hand-held Geiger counter, gathering information on collected radioactivity over various areas of the patient's body and plotting the Geiger counter readings over corresponding locations on a body diagram [2]. Given the lack of accurate diagnostic RAI scintigraphy (D-RAIS), i.e. scanning the radioisotope distribution in a patient with the intent to make a diagnosis and identify the distribution of the disease, and particularly the inability to reasonably estimate radiation absorbed doses in those early days, clinical investigators used relatively low (from as low as 2 mCi and up to about 50 mCi) administered activities that were followed by meticulous observation and recording of each individual patient's experience. This was a true "trial and error" approach with each treated patient presenting an opportunity to test various modifications of this emerging modality. The accumulated experience led to the following conclusions by mid-1949: 1) the best treatment of original disease site was surgery whenever possible, 2) RAI uptake in tumor metastases was possible and further enhanced when the majority of native thyroid was removed, 3) elevated TSH in thyroidectomized patients acted as the best stimulant of RAI avidity in DTC, 4) multiple administrations of small AAs can result in a fatal bone marrow suppression, and 5) multiple small AAs often led to a loss of RAI avidity by DTC that continued to grow even more aggressively. These realizations laid the foundation for the two key trends that offered conceptually different ways of solving the observed shortcomings. One trend was pioneered by the group at the Memorial Sloan Kettering Cancer Center where experts adopted administration of a single maximum tolerated activity (MTA) that was determined based on pre-treatment RAI imaging and cumbersome dosimetric assessment that required daily measurements of retained RAI in the whole body, the blood, and RAI excretion in patients' urine [7]. The approach included preparation of all patients with intense stimulation by either high intrinsic TSH levels by thyroid hormone withdrawal (THW) or, in rare instances, when inducing clinical hypothyroidism was medically or surgically risky and in some cases impossible, by injections with heterologous (bovine) TSH. The second trend was led by clinical investigators at the University of Michigan. They empirically set the minimum administered activity levels, intensifying it with increasing extent of DTC after confirming RAI-avid tumor on D-RAIS [8]. Those minimum levels of administered activity were 100, 150 and 175 mCi for patients whose D-RAIS showed uptake only in benign remnant within the thyroid bed, additional uptake in the cervical nodes, and the distant metastatic sites, respectively. Because the Memorial Sloan Kettering Cancer Center approach of MTA RAIT was by far more technically laborious and more challenging for patients, the historical empiric activity range (HEAR) approach developed by the University of Michigan group gained an overwhelming popularity in the USA and abroad. The highest HEAR activity for metastatic disease was later escalated to 200-250 mCi [8]. Others, however, de-escalated the HEAR approach by practicing a 'standard' one hundred millicurie activity (SOHMA) to all DTC patients until their post-treatment scan turned negative [9]. The relative therapeutic effectiveness of these various approaches remains unknown because evidence from adequately designed studies is lacking. Inadequacies in comparative studies were exemplified by the report that compared MTA practiced at Memorial Sloan Kettering Cancer Center with SOHMA practiced at a different institution and a different country [9], which evoked multiple critiques [10-13] detailing its shortcomings. The general challenges that remain difficult to overcome in such comparative research include unreliable pretreatment staging of the cohorts, lack of consistent standards in quantifying disease severity, no standard thyroglobulin measurements, no consensus on pretreatment stimulation and low iodine protocols to optimize RAI uptake by the target, and relatively short follow-up to assess outcomes.

Empirical practice or RAIT in the early days resulted in a broad range of RAI administered activities that were given to a variety of target lesions, which included lymph nodes (LN), pulmonary and bone metastases. Furthermore, all of those lesions displayed a significant variability in iodine-avidity as characterized by RAIU. Some clinical scientists sought to determine the absorbed radiation dose to the targeted lesions by using RAIU in those lesions, residence time of deposited activity, and their approximated mass. The two key groups among leading clinical investigators were from the University of Cincinnati Medical Center and the University of Michigan. Their pursuit of determining the killing radiation dose in the target using relatively primitive equipment of the era gave birth to the so-called 'lesional dosimetry' concept. This development that started in the 1970s produced fascinating results by the early 1980s as outlined by Maxon et al. [14, 15], but had to await improvements in imaging technology and three-dimensional dosimetry that is crystalizing only now for clinical applicability [16-19].

3. RATIONAL FOR HOMOGENIZING PRACTICE WITH RADIOTHERAGNOSTICS

The most commonly utilized RAIT practice in DTC starts with total or near-total thyroidectomy (henceforth both surgical techniques are equated in this context and abbreviated as TTE), followed by the diagnostic RAI scans (D-RAIS) for differentiation of

residual tissue and/or possible regional and/or distant metastases for disease staging, culminating in empiric ^{131}I administration for 'ablation of functional thyroid tissue' without an explicit commitment to the specific target (i.e. benign or malignant RAI-avid focus that would be nebulously described as 'functional thyroid tissue'). It is unknown whether the target residual DTC, if present, is RAI-avid or not and not knowing where it happens to be located when its presence happened to be likely (such as in patients with elevated Tg). The closest to a target-specific formulation of this approach was stated by Mazzaferri *et al*. in 1994 [20], "Treatment with ^{131}I was considered to have been for ablation of remnant thyroid tissue if the scans disclosed no uptake of radioiodine outside the thyroid bed and the treating physicians, operative notes, and pathology reports made no mention of residual tumor." The term 'ablation' in his study was intended for the eradication of benign remnant thyroid. One limitation by our current standards is that patients who were treated between 1950 and 1993 had no Tg measurements (not yet routinely available) to assure that complete biochemical response had occurred. This study showed statistically significant benefits of ^{131}I 'ablation' for recurrence prevention, which by 30 years of follow-up reached the cumulative incidence of 38% in those who had not received *versus* 16% for those who had received ^{131}I 'ablation' ($p<0.001$) [20]. The 'ablation' also improved cancer mortality from 9% versus 3% ($p = 0.03$), respectively [20]. These results are arguably applicable to RA, as it is currently defined in the 2015 American Thyroid Association (ATA) guideline document. Curiously, the ATA document did not mention the study of Mazzaferri et al. in regards to RA. The study was mentioned briefly in the contexts related to some of its secondary findings, but not as far as the two main outcomes – the positive effect of RA on the disease-specific survival rate and recurrence rate.

Many studies before and after Mazzaferri's series used the term 'ablation' significantly more loosely, simply meaning the first RAIT after surgery irrespective of pretreatment likelihood of metastatic DTC; hence, those studies possibly including patients with residual regional and/or distant metastatic disease. As an example of the latter, it is instructive to consider the frequently cited study that explored RA using recombinant human TSH (rhTSH) in comparative analyses with the THW stimulation [21]. One of 30 selected patients recruited for 'ablation' under THW was unexpectedly shown to have lung metastases on post-treatment RAI scans (PT-RAIS) and authors had to exclude this patient from the final analysis. The PT-RAIS are now often performed for 2-10 days following the treatment and could occasionally reveal the presence of regional or distant metastatic disease that was not evident on D-RAIS. PT-RAIS by detecting additional disease could clarify staging and inform further treatment strategies and prognosis. Another study published in 1996 also addressed 'ablation' in a prospective randomized clinical trial (RCT) aimed at determining optimal administered activity (AA) to achieve 'ablation' in the thyroid bed [22]. D-RAIS was used to select the 155 patients for RA to exclude residual metastatic tumor. Patients were then assigned to one of 4 RAI activity ranges: 25-35 mCi, 35-64 mCi, 65-119 mCi, and 120-200 mC. All patients had PT-RAIS to improve the detection of unanticipated metastases, which disclosed 6 such patients (4 with regional nodal and 2 with pulmonary metastases, 3.9% of cohort). Again, those 6 patients were excluded from the final analysis. The successful ablation was achieved in 63%, 78%, 74%, and 77% in the activity ranges, respectively. The key practical finding was that increasing administered activity above 64 mCi achieved no additional benefit in this cohort undergoing empirical RA. The key academic finding was that it took about 300 Gy absorbed in the benign thyroid remnant to sterilize the target in the 35-64 mCi group, which was similar to that previously reported by Maxon *et al*. [15]. The approach of scaling administered activity to deposit a destructive radiation dose is conventionally called 'lesional dosimetry' even though the term 'lesion' in reference to benign thyroid remnant may not be appropriate. We find estimated sterilizing target radiation absorbed dose approach (ESTRADA) to be more meaningful and self-explanatory. While ESTRADA epitomizes RTGs, it is the most technically challenging method for guiding towards optimal RAI AA. It is available on a research basis in a very few facilities that have access to radiation physicists with the skill-set for either ^{123}I SPECT/CT [23, 24] and/or ^{124}I PET/CT [17, 19] dosimetry calculations. On the other hand, MTA could be more readily operationalized at any center that has a standard gamma-camera with high-energy collimator (a thyroid uptake probe is optional). At our center, the MTA dosimetry is executed entirely by our Nuclear Medicine technologists who follow our institutional protocol that was established and validated in 1995 by direct comparison with classic Benua *et al.* technique [7]. Our institutional protocol uses the absorbed radiation dose calculation by the schema developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine and Molecular Medicine. This formalism requires the total body time-activity curves exclusively; thus, no measurements are required of the activity in the blood nor in the urine, which were the obligatory parts of Benua's original protocol. The MIRD formalism allows dosimetry calculations for MTA RAIT easily implemented in any facility equipped with either gamma camera or the uptake probe – the latter successfully utilized at our facility for over 20 years. When ESTRADA becomes practicable, MTA will still be mandatory to determine. If the administered activity necessary to deliver sterilizing absorbed radiation dose to the metastatic target(s) exceeds the MTA, it would be unsafe to proceed with RAIT and alternatives would have to be explored. On the other hand, the ESTRADA may demonstrate in some patients that their specific goal requires the administered activity that could be significantly below those routinely used according to the HEAR.

3.1. Three-Tiered Categorization of Target-Based Treatment Paradigm

RAIT for DTC is practiced with a concerning level of heterogeneity to this day and, at least partly because of such diverging opinions, remains one of medicine's controversial topics. But some positive strides to homogenize definitions and practices of RAIT were initiated in 2017 and are gradually beginning to solidify consensus by harnessing endorsements from multiple specialty societies [25]. The following are the three most up-to-date target-based categories for RAIT that came to fruition through these multispecialty efforts [26]. The first is "remnant ablation" (RA) targeting post-surgical benign remnant thyroid. This is mainly intended to eliminate thyroglobulin (Tg) produced by that benign remnant thyroid, thus, making the Tg assay more specific for residual DTC and/or its recurrence. Some experts suggested that the reduction of recurrence risk is a reasonable additional goal for RA [27]. The logic behind the latter goal is that genetic mutation can occur in benign remnant thyroid tissue that may lead to *de novo* reoccurrence of DTC. It is conceivable that thyrocytes in affected patients are prone to such a mutation, as demonstrated by the fact of prior such event. Hence, decreasing thyrocyte population through RA should reduce the stochastic risk of their malignant transformation. RA is typically an option at the first post-thyroidectomy assessment of eligible patients. There are variable criteria for judging the success of RA. The second category is the "adjuvant treatment" (AT), which is aimed to destroy suspected microscopic DTC that cannot be demonstrated on imaging. It is given to patients with higher risk for recurrence/mortality according to one of many clinicopathologic stratification systems. RAIT for AT should hypothetically improve the disease-free survival, and it is administered with curative intent [26]. Finally, the third category is TKD, aimed at iodine-avid DTC, as demonstrated by either biochemical evidence or structural disease evident on physical examination and/or diagnostic imaging. It is not specified in the multispecialty statement whether this evidence has to be confirmed or not by tissue sampling. A therapeutic objective could be curative and/or palliative,

depending on the disease extent. While RA and AT terms are only applicable for the first post-thyroidectomy administration of RAIT, TKD can be used for as many treatments as necessary to treat recurrent/persistent presumably or demonstrably iodine-avid DTC.

The most impactful technical innovation in the initial staging of DTC came about with fusion Nuclear Medicine imaging, which combines tomographic scintigraphy, called Single Photon Emission Tomography (SPECT) and Positron Emission Tomography (PET) with anatomical tomographic imaging that is most commonly obtained with CT (now also offered with MRI alternative). The first step in RTGs management of DTC, D-RAIS, can be accomplished with either ^{131}I, ^{123}I or ^{124}I. The latter two isotopes have better physical properties for fusion Nuclear Medicine imaging – ^{123}I offering higher quality SPECT/CT imaging and ^{124}I enabling PET/CT with the best inherent resolution and imaging quality. While suboptimal for the D-RAIS with SPECT/CT, ^{131}I is well-suited for the second step of RTGs – the tumoricidal internal radiation therapy via its short-range beta emission that forms free radicals within the DTC cells where it accumulates as well as in a mean radius of 0.4 mm in soft tissue. Indeed, SPECT/CT markedly improved the specificity of our pre-therapy diagnostic evaluation with ^{131}I D-RAIS [28]. Thus, ^{131}I is not only the first isotope used for RTG management of cancer but remains the closest to an ideal singular-agent for RTGs in oncology [29]. There is excellent evidence that SPECT/CT correctly changes the risk stratification in up to 15% of patients when done prior to RAIT and changes administered activity for RAIT of DTC in about 30% of patients at the very first post-TTE evaluation [30]. In this study, all patients underwent whole body scintigraphy after 1 mCi of ^{131}I at 24 hours, routine SPECT/CT of the head, neck and upper chest (one field-of-view acquisition), and an additional SPECT/CT imaging for those who showed questionable findings outside of the routine SPECT/CT field-of-view. All patients who showed distant metastatic disease received MTA-based RAIT. This approach practiced at the University of Michigan since at least 2007 and summarized in the 2019 publication remains the closest to RTGs paradigm that can be and should be emulated by all and any modern facility today [31]. They achieved a complete response in 84.3%, incomplete biochemical response in 1.4%, indeterminate response in 2.3%, and structural incomplete response in 12%. Of the entire cohort of 350 patients, only 8 patients (2.3%) had persistent iodine-avid metastatic disease, which required repeated RAIT. Of 31 patients with iodine-avid distant metastases identified on Dx scans, 13 patients (42%) achieved complete response with a single RAIT session.

3.2. Specialty Biases Exacerbating Inhomogeneity in Practice and Guidelines

There are multiple guidelines [32-34] which present multiple specialties with their preferred approaches to RAIT for DTC. They all differ significantly in principles and specific recommendations, as born out of continuing debate about multiple specific practice variables that represent points of disagreement between communities of subspecialists. These debates fail to prove any proposed difference in RAIT approaches for DTC because of paucity in RCTs. This situation is known as 'clinical equipoise'. Generally, superiority of one approach over another is very hard to prove by comparative clinical research for a condition where patients' outcomes are relatively excellent even without any specific treatment and remain stable over extended periods of time [33]. Another characteristic obstacle to resolving a controversy by RCTs are long times it takes for the development of an adverse outcome in DTC, such as overt recurrence and/or death from the disease after RAIT. In such a circumstance, it stands best reasoning to adopt the most logical, evidence-supported approach and, when such evidence is not available, to follow at the very minimum what is evident from the established concepts in basic (patho)physiological knowledge. Several examples of the exact opposite approach are available from the 2015 ATA guideline document with the best one addressing the role of low iodine diet (LID) in patient preparation (recommendation 57). It states "A LID for approximately 1–2 weeks should be considered for patients undergoing RAI remnant ablation or treatment." This was qualified as "Weak recommendation, Low-quality evidence." The relevant text explains that "There are no studies examining whether the use of a LID in preparation for RAI remnant ablation or treatment impacts long-term disease related recurrence or mortality rates." Hence, to achieve a "Strong recommendation. High-quality evidence" it would follow from the above that the guideline would be looking for a study where patients would be randomly assigned to two arms – one group following strict LID and the other one not following LID. These two groups would need to be treated with otherwise identical protocol of RAIT and compared for the stated outcomes – the disease related recurrence or mortality rates. This is an obviously extreme and nonsensical requirement based on what we already know from basic physiology: 1) there is incontrovertible physiological evidence that low iodine levels in the body stimulate expression of NIS, 2) administration of the LID to all patients is absolutely benign and associated with no substantive risk under medical guidance. Hence, it should be evident from all that is known already that additional "high-quality evidence" by RCT is nonsensical. It is just as nonsensical as requiring RCT evidence before categorically recommending the use of a parachute by all members of airborne troop [35] and skydiving team.

One of the key goals of this review is to provide a practical outline of performing RAIT for DTC according to the available knowledge and practical principles of RTGs. Specifically, it is essential to understand the individual's risks from DTC based on the available literature, risks of applicable RAIT complications, as well as balancing these risks against the benefits of RAIT. It is appropriate to start with the comprehension of the relevant risks.

4. STAGING AND RISK STRATIFICATION

The pivotal decision of whether to proceed with RAIT or not is the balancing act of weighing the risks of unmitigated DTC versus the treatment [27, 36]. It is critical to recognize that DTC risks could be considered as likelihood of death *versus* survival, disease recurrence after apparently curative surgery *versus* sustained cure, and, importantly, reduced versus unchanged from baseline quality of life. The most consequential end-point, used in outcome studies is death, and, more specifically, death caused by DTC. Because this disease is commonly cured by surgery and in the few who have residual disease it is generally indolent in its behavior, this outcome metric is difficult to use in prospective investigations because, by definition, it would take a very large number of subjects and a very long time of follow-up to conduct a meaningful study. Thus, most of the data on mortality are derived from retrospective cohort studies that are easily tainted by inherent methodological challenges, including a preconceived bias. Both sides of the DTC equation are complex and, to unpack them, one should start with risk stratifications of DTC, which is compounded by the fact that DTC tumors are heterogeneous in histology and clinical behavior.

4.1. Risk-stratification Based on Survival and Mortality

The 'Tumor, Node, Metastasis' (TNM) system was developed by the American Joint Commission on Cancer (AJCC). Its core goal is to stratify patients into groups with distinct mortality outcomes, logically assigning a higher 'stage' to a group with incrementally more severe disease characteristics, as delineated in each of the TNM staging categories. The unique feature of staging DTC as compared to other cancers is the inclusion of age threshold for assigning survival grouping. The most recent update by AJCC is the 8th Edition (Table **1**) [37], which introduced significant improvements over the prior versions. The key improvements are its stronger predictive power for the overall and disease specific survival [37]. In addition, for the first time, the prognosis of papillary

Table 1. AJCC Staging System for DTC (8th Edition).

Defining Characteristics for T, N, and M					
T1: T≤2 cm, without gross ETE					
T2: T>2 cm but ≤ 4 cm in greatest dimension without gross ETE					
T3a: T>4 cm in greatest dimension without gross ETE					
T3b: Any size T with gross ETE into strap muscles only					
T4a: Any size T, invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.					
T4b: Any size T, invading prevertebral fascia or encasing carotid artery or mediastinal vessels					
N0: No metastatic nodes					
N1a: Metastases to level VI (pretracheal, paratracheal and prelaryngeal/Delphian lymph nodes) and VII (superior mediastinal nodes).					
N1b: Metastases to unilateral, bilateral, or contralateral cervical (levels I, II III, IV, or V) or retropharyngeal lymph nodes.					
M0: No distant metastases.					
M1: Distant metastases.					
	Differentiated Thyroid Cancer TNM Staging		***10-y OS****		
	Age < 55 y	***Age ≥ 55 y***	***DTC***	***PTC***	***FTC***
Stage I	any T, any N, M0	T1-2, N0, M0	94.5%	95.5%	90.1%
Stage II	any T & N, M1	T1-2, N1, M0; T3a/b, any N, M0	71.7%	75.0%	64.5%
Stage III	N/A	T4a, any N, M0	33.2%	34.1%	N/A
Stage IVa	N/A	T4b, any N, M0	19.7%†	23.5%†	16.8%†
Stage IVb	N/A	any T, any N, M1			

Abbreviations: AJCC= American Joint Commission on Cancer; DTC = Differentiated Thyroid Carcinoma; Extrathyroidal Extension = ETE; M = Metastasis; N = Node; N/A = not applicable; OS = Overall Survival; T = Primary Tumor.

*Adopted from reference [37]

†10-year OS for stages IVa and IVb were combined

and follicular thyroid cancers (PTC and FTC) are about the same per each stage (previously FTC always had worse prognosis when compared to PTC per each stage) [37], which can be viewed as a more equitable system across all of the DTC sub-types. This edition uses 55 years of age as the threshold for upstaging (new since the prior edition that used age 45 years). The TNM system is somewhat cumbersome to apply but a web-based staging calculator (https://www.thyroid.org/professionals/calculators/thyroid-cancer-staging-calculator/) streamlines its clinical use. The quantitative expression of risk is also available but was based on the 6th edition of AJCC system and would need to be adopted to the 8th edition [38]. This quantitative score allows for a simpler three-tiered stratification (low, intermediate, and high risk groups) based on mortality risk. Other quantitatively expressed mortality risk based systems are the Metastases, Age, Completeness of resection, Invasion, and Size (MACIS) and Age, Metastases, Extent of disease, and Size (AMES), but their predictive values are limited to the PTC [39-42]. Comparisons of stratification/staging systems is available for interested readers [43-46].

Because the older editions of AJCC/TNM staging system did not adequately predict the risk of DTC recurrence/residual/ persistent disease, the 2009 version of the ATA thyroid cancer guidelines proposed a different three-tiered clinicopathologic risk stratification system that classified patients as having low-, intermediate-, or high-risk of 'recurrence' [32]. This brings up an important issue that majority of what was traditionally called 'recurrence' turns out to be a disease that was there all along right after TTE and before any post-TTE treatment administration. The recent report established that overwhelming majority of 'recurrences', 71 out of 74 (96%), are actually occult residual DTC that a healthcare team failed to identify prior to the first post-TTE treatment [47]. This distinction should be considered critically important but it is not broadly recognized among those with expertise in the management of DTC. It should compel the development of methods applicable as early as possible after TTE to guide the first RAIT and to help with identifying RAI-nonavid occult residual DTC (see sections 7-8).

4.2. Risk-stratification Systems Based on 'Recurrent' Disease

It is the risk of 'recurrence' (or more accurately, likelihood of post-TTE residual but occult DTC) that plays the pivotal role in deciding on whether or not to proceed with RAIT because it can be measured earlier and happens much more often than the cancer-related death. The 2015 ATA risk stratification approach (Table **2**) is the most recent system that offers significant refinements to the original 2009 ATA system. It incorporates adverse histopathologi-

Table 2. ATA 2015 Based Stratification on Risk for Recurrent/Persistent DTC*.

Risk	Histopathology and other Tumor Characteristics
Low	• PTC, classical histology, w/o local or distant mets, negative resection margins, w/o invasion into loco-regional tissues/structures, w/o aggressive histology, N0c or ≤5 N1p, no RAI-avid regional/distant M • PTC, follicular variant, encapsulated, any size, intrathyroidal • PTC, size ≤1 cm, solitary or multifocal, negative margins, intrathyroidal • FTC, ≤3 foci of vascular invasion, intrathyroidal
Intermediate	• Microscopic invasion of tumor into the perithyroidal soft tissues • PTC, classical histology with vascular invasion • PTC/FTC with aggressive histology • RAI-avid metastatic foci in the neck • N1c or >5 N1p, but no lymph nodes ≥2 cm in largest dimension • PTC, size ≤1 cm, multifocal with ETE and $BRAF^{V600E}$ mutated
High	• PTC/FTC w/ macroscopic invasion into perithyroidal soft tissues • PTC/FTC w/ positive resection margins • PTC/FTC w/ distant metastases • PTC/FTC w/ postoperative Tg above expected for neck RAIU@24hr • PTC, N1p ≥3 cm • FTC, >4 foci of vascular invasion

*Table inspired by Table **11** in reference [32].

Definitions and abbreviations: aggressive histology = tall cell variant, hobnail variant, columnar cell carcinoma; DTC = Differentiated Thyroid Carcinoma; ETE = Extrathyroidal Extension; FTC = follicular thyroid cancer; M = Metastasis; N = Node; Nc = clinically defined nodal involvement; Np = pathologically defined nodal involvement; N/A = not applicable; PTC = papillary thyroid cancer; RAIU@24hr = radioactive iodide uptake at 24 hours.

cal features, which include the more aggressive histologic sub-types (poorly differentiated, tall cell, Hürthle cell, hobnail, columnar and diffuse sclerosing variants), vascular invasion, microscopic and particularly the macroscopic extrathyroidal extension, extranodal extension, mutational status as well as number and size of nodal metastasis [32]. In the 2015 ATA classification (Table **2**), the low-risk patients include intrathyroidal PTC without vascular invasion, small-volume lymph node metastases (clinical N0 or <5 pathologic N1 micrometastases, <0.2cm in largest dimension), intrathyroidal encapsulated follicular variant of PTC, intrathyroidal well-differentiated follicular cancer with capsular or minor vascular invasion (<4 vessels involved), and intrathyroidal papillary microcarcinomas that are either BRAF wild-type or BRAF mutated. The intermediate-risk category includes patients with microscopic invasion of the tumor into perithyroidal soft tissues, vascular invasion, RAI uptake outside the thyroid bed at the time of remnant ablation, and adverse histopathological features. Lymph nodes involvement includes clinical N1 or >5 pathologic N1 with all involved lymph nodes <3cm in the largest dimension. Intermediate risk also includes multifocal papillary microcarcinoma with extrathyroidal extension and BRAF mutated (if known). The high risk category includes patients with macroscopic extrathyroidal extension, incomplete tumor resection, distant metastases, postoperative serum thyroglobulin suggestive of distant metastases, large-volume lymph node involvement (any metastatic lymph node >3cm in largest dimension), and FTC with extensive vascular invasion (>4 foci of vascular invasion or extracapsular vascular invasion). Based on 2015 ATA risk system that is essentially offering a range of recurrence risks continuum from <1% (in 'very low risk' patients) to >50% (in 'high-risk' patients), it is argued that individualized management recommendations should be based not only on the categorical risk of recurrence estimate but on a more individualized estimate of risk based on cluster of clinicopathologic features. The key hindrance to this concept is no clear requirement of detailed imaging confirmation of RAI-avidity prior to RAIT, no individualized algorithm of figuring out whether Tg is matching benign thyroid post-thyroidectomy remnant or not (*i.e.* excess Tg that likely is produced by remnant DTC). The ignored issue with 2015 ATA system is that to the best of our knowledge, the clinical application of this method was never tested prospectively nor has a known inter-observer reproducibility established. There is no evidence that if three independent experienced and qualified specialists evaluate the same individual and have access to the very same health information that they will come up with the same risk category. The worry should always be that they will come up with three different categories out of the three available choices unless proven otherwise. Using this system without putting it first through such an evaluation seems to be cavalier at best and some may consider it negligent.

5. RISKS OF RADIOACTIVE IODIDE THERAPY

The risks of RAIT can be subdivided into acute, moderately delayed, and late. This is an imperfect stratification because a number of specific complications may occur acutely and then recur later. There is much written about these complications, and general knowledge of possible side effects with common times to expect them is mandatory for any physician consulting a patient considering RAIT or managing such a patient after RAIT [48-50]. The most common early side effect is nausea that could develop into vomiting if unmitigated. We routinely pre-treat patients with antiemetic medication. The type, amount, and route of administration depend on administered activity for RAIT, prior history, a patient's weight, as many other confounders. This side effect is transient and resolves within 3-6 days. The next most common early side effect is acute sialadenitis. The basis of this side effect is acute obstruction of salivary ducts by inflamed and swollen ductal epithelium. The

pathophysiology is based on NIS mediated uptake in the ductal epithelium that causes radiation injury and acute swelling. There is conflicting evidence about prevention with sialagogues. We find that every report that found sialagogues not effective failed to recognize that the most important time to stimulate salivary glands is during the first evening and the following night [51]. Most patients who develop acute sialadenitis wake up with swollen glands after uninterrupted sleep through the first night following RAIT. Moreover, the greatest RAI uptake in the salivary glands happens exactly during the very same time [52]. Therefore, it is imperative to regularly wake up the patient after RAIT throughout the first night for salivary stimulation to prevent the accumulation of RAI in salivary glands. The results of one study with interrupted patient's sleep during the first night for salivary stimulation were much better than in any other historical cohort [53]. Our protocol starts intense stimulation with a table spoon of lemon juice every hour or half-hour if a patient can take it, starting 1.5-2 hours after the RAIT, continuing with this frequency for at least 36 hours in patients receiving 100-150 mCi of RAI. We increase duration proportionately for higher AAs or until the residual activity falls below 20-30 mCi. It is useful to have patients drink at least 3-4 sips of tap water with each lemon juice with swishing each sip in their mouth before swallowing it. Any patient who develops salivary gland swelling receives evaluation by a specialist skilled at sialendoscopy, which is the only effective therapy for it [54-57]. Administering sialagogues may help in temporizing the symptoms, but would usually lead to eventual worsening and loss of the respective glands. The same is true for lacrimal gland complications that are expressed in epiphora. Obstructed lacrimal ducts are effectively treated with external dacryocystorhinostomy with stent placement and other restorative procedures if patients are referred to ophthalmology. But even better management of sialadenitis is avoiding it altogether. To that end, the important observation in a survey study was that no patient who received <100 mCi reported any sialadenitis symptoms [58].

It is challenging to comprehensively address concerns about the late complications that all happen by chance (stochastic) and are known to induce a highly variable emotional response among patients. The extreme reaction is radiation phobia that precludes RTGs in some patients [59]. The most common concern discussed among referring physicians and patients is the risk of subsequent malignant neoplasms. The facts fail to show any clinically meaningful carcinogenesis at commonly administered activity ranges given for DTC [60]. Reports about RAIT-related carcinogenicity always ignore radiation hormesis effects that show in some studies to add benefits that outweigh the alleged carcinogenic harms of RAIT [36, 61].

6. PREPARATION FOR RADIOACTIVE IODIDE TREATMENT

At our institution, most of the patients with DTC are referred to Nuclear Medicine (NM) from departments of Endocrinology and (in minority of cases). After the surgery all of them had TTE. It is difficult to know how the decision not to send a patient to NM for consideration of RAIT is made since we never get to see or discuss such patients. But the patients referred to NM are always staged using TNM system (our hospital is part of the National Cancer Data Base and follows mandate from the Commission on Cancer) and risk-stratified by 2015 ATA guideline by their referring physician. In NM, we practice an individualized and holistic approach of practicable RTGs. We start with review the following materials: operative report, surgical pathology, all of the laboratory and diagnostic examinations, and particularly the baseline (4-6 weeks post-thyroidectomy) unstimulated Tg that is always measured together with TSH and Anti-Tg levels. These data usually are presented at our institutional meeting of specialists (usually in attendance are NM physicians, endocrinologists, surgeons and a pathologist who reviews the pathology slides with attendees), called the "Thyroid Unit" meeting. At this meeting, it is discussed whether the patient should undergo further diagnostic consideration of RAIT. After this decision is made, the patient is set up with standard preparation instructions for evaluation in NM. It is critical that all of the instructions and consultations are provided to patients as early as possible after the decision for NM evaluation is made because most will need weeks to make those required arrangements.

6.1. General Information and Low Iodide Diet

The patient receives an informatio brochure about the upcoming evaluation that goes over their exact schedule for the visit to NM, general expectations for how long each appointment should last, and when to start and stop each part of the requisite preparations. Included is the general explanation letter for the need to follow the LID the detailed guidance booklet (https://www.thyca.org/ download/document/231/Cookbook.pdf). Patients start LID two weeks before their first visit to NM. All patients avoid excess iodide found in some medications (including the over-the-counter drugs) usually for at least two weeks and iodinated intravenous contrast agents for three months. Each patient who may need RAIT receives a bracelet at the first post-TTE visit to Endocrinology that helps to alert radiology about contrast avoidance. Special consideration must be given to several rare but recalcitrant to withdrawal drugs and contrast agents. Amiodarone is the most common among the former group that requires longer withdrawals. Among the latter, there are multiple oil-based iodinated radiographic contrast agents, some that are obsolete, such as iofendylate, but others still in use with most common being the ethiodized oil. It is used for hysterosalpingography, lymphography, and selective hepatic intr-arterial diagnostic and/or therapeutic (embolization) procedures. The oil-based iodinated contrast agents can leach out iodide for years to decades after a single administration. In cases exposed to recalcitrant to effective withdrawal agents, it is critical to check and monitor urinary iodide content.

Over 95% of all patients with DTC who get scheduled for NM evaluation in our practice are prepared with THW. Preparation with rhTSH is limited to the low-risk group of patients with DTC for D-RAIS and for RA. This policy took effect at our practice when rhTSH was approved by the US Food and Drug Administration on November 30, 1998 as an alternative for THW preparation prior to the D-RAIS or RA, but specifically for the 'low-risk' patients. In the initial package insert it clearly stated that rhTSH was indicated for low-risk patients who had no evidence of metastatic (including the regional) disease. This restriction was based on the two phase 3 studies that included 107 total THW-stimulated D-RAIS with 24 cases positive in the metastatic sites. In 7 of the 24 (29%) the paired rhTSH-stimulated D-RAIS was negative for uptake in the metastatic site. In the first year of use, we had one moderate-risk patient who was erroneously scheduled for rhTSH preparation prior to the D-RAIS. We recognized our mistake and offered the patient free of charge repeat of D-RAIS but under THW stimulation. The significantly better uptake after THW was compelling (Fig. **1A-D**). The uptake of RAI in the post-TTE thyroid bed was 40 times greater after THW when compared to rhTSH. This albeit anecdotal but compelling experience reinforced our prior restriction of rhTSH stimulation to low-risk group of patients. Over the years, there has been a number of publications in support of the fact that rhTSH preparation is inferior to THW in stimulating uptake in benign remnant thyroid and DTC metastases [62-66]. Of course, when THW is medically contraindicated (especially those with severe coronary disease or congestive heart failure, and particularly severe depression) we use rhTSH as the only other alternative. The data does not justify rhTSH stimulation to become the replacement for THW stimulation for anything other than RA and D-RAIS in low-risk patients. Hence, we strongly disagree with the 2015 ATA guidance [32] that enables rhTSH overuse by stating in recommendation 54(B) that "... rhTSH stimulation may be considered as an alternative to THW prior to adjuvant RAI treatment." The majority of the writing panel experts had claimed a financial relationship with the

rhTSH manufacturing company, which allows for a substantial bias in the formulation of this recommendation.

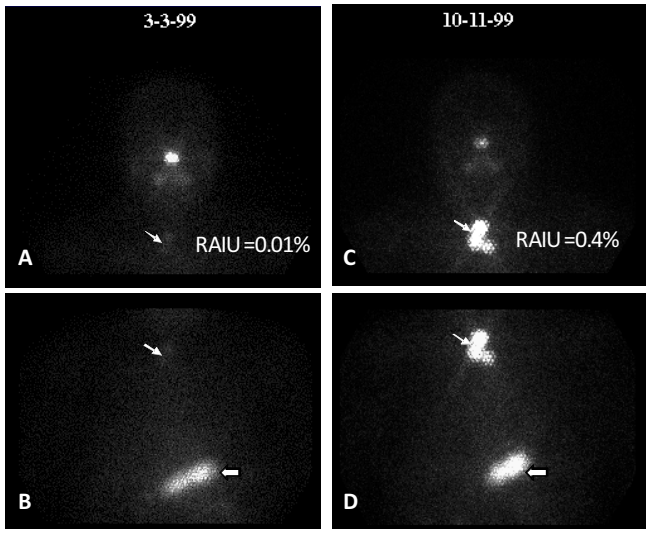

Fig. (1). (**A-D**) This is a case we encountered in 1999, shortly after commercial introduction of recombinant human thyrotropin. The indication for this new stimulating drug was exclusively for patients with low-risk disease at that time. The test was performed in March and showed a faint ^{131}I accumulation in the thyroid bed with calculated uptake of 0.01% at 48 hours after a 5 mCi ^{131}I activity. When it was realized during the test interpretation that the patient had high-risk disease, he was offered a repeat study under our traditional thyroid hormone withdrawal stimulation. The repeat scan showed a much better uptake of 0.4% in the thyroid bed, which was subsequently treated with radioactive iodide. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

6.2. Thyroid Hormone Withdrawal Protocol

It is important to make patients aware of the likely symptoms of hypothyroidism prior to initiation of the THW so that they could properly plan for it (take time off work, etc.). It is well established that during THW patients' attention, memory, and reaction time are significantly impaired. In fact, this can adversely impact these patients' ability to operate an automobile [67] or heavy equipment, which should be advised against to avoid significant accidental harm. Some patients may develop fluid retention and edema, therefore, they should not have any restricting accessories on their extremities. As an example, a tight finger ring could restrict blood flow with swelling. A patient is switched to a T3 preparation, liothyronine sodium, starting 48-hour after discontinuation of maintenance T4 preparation, usually levothyroxine sodium. The T3 daily dose should be equivalent in potency to that of T4. If the 48-h gap is not used, hyperthyroidism from overlap of the two may cause detrimental side-effects in sensitive cases (especially in those with coronary disease, congestive heart failure, history of dysrhythmias, and depression).

6.3. Radiation Hygiene Instructions

Patients must be adequately educated about the need to follow radiation hygiene instructions in order to minimize radiation exposure to public after they receive RAIT. Depending on the institutional, local and federal requirements, those instructions differ widely and will not be covered here in detail. It is most important to explain to patients that these instructions are prudent to follow because members of the public should not receive medically unnecessary and avoidable radiation exposure, but no less important is to avoid provoking excessive fear of radiation.

7. DIAGNOSTIC PREREQUISITES FOR RADIOACTIVE IODIDE THERAPY

The pre-TTE evaluation will not be addressed in this review. Here forth, we review the practice of RTGs in post-TTE patients and include specific prerequisites that must be ascertained before any decision can be made about the advisability of RAIT. The list of prerequisites starts with the key laboratory parameters – a TSH, Tg, and thyroglobulin antibody (TgAb). The first useful time-frame for these indexes is when a patient is on thyroid hormone replacement but after at least 4 weeks following TTE (allowing for the new baseline to be reached). These values help in general to survey the likelihood of residual DTC and, particularly, metastatic to distant sites, best used in combination with clinicopathologic variables. One critical point to recognize is the variability of the Tg that depends on level of TSH and also on the assay sensitivity. In order to use Tg most intelligently, one has to understand confounders on its variability and difference in the methodology used for various assays [68].

In one study notable for its prospective design [69] investigators selected low- and intermediate-risk patients with PTC who all had TTE that showed primary tumor size > 1 cm, no adverse histopathological features, negative post-TTE neck ultrasound (NUS), TSH < 2 μIU/mL, no interfering TgAb and Tg<0.3 ng/mL. These patients had no symptoms of possible distant involvement by DTC, such as skeletal pain or palpable masses. Patients with a higher risk of 'recurrence' based on one of the following characteristics were also excluded, extensive extrathyroid invasion (pT4), vascular invasion; LN metastases detected by preoperative US or during intraoperative inspection by the surgeon (i.e. clinical N1 (cN1)), >3 positive LN, LN >1.5 cm, or LN exhibiting macroscopic extranodal tumor invasion, as well as a combination of a tumor >4 cm, minimal extrathyroidal invasion, and cN1. The reason for collecting these carefully selected patients was to evaluate whether Tg <0.3 ng/mL could safely make 'ablation' unnecessary. The time of follow-up ranged from 15 to 102 months (median 62 months). Out of 222 prospectively enrolled patients, 5 had 'recurrences' at 30-60 months after TTE. These cases most likely were all occult residual DTC. As such, they presumably could have been identified applying the thyroglobulin with remnant uptake concord method (refer to 7.2) as early as after 6-10 weeks (time needed to heal the surgical incision and undergo THW) following TTE.

The second prerequisite includes D-RAIS performed with ^{131}I, RAIU at 24-hours measured over the thyroid bed, and SPECT/CT that covers at least one standard field-of-view (starting from just below the orbit and down). There are several options that could be as good as or better than ^{131}I, as outlined above (section 3). Another important component is the ability to perform whole body dosimetry to calculate MTA, if a high dosage becomes justified based on more extensive or distant metastatic disease revealed on D-RAIS with SPECT/CT.

7.1. Scenario of 'Cancer All Resected, Elsewhere Negative'

Our approach considers the following patient scenarios. The first and the most common scenario is a patient with surgical pathology and an operative report indicating no overt evidence for residual DTC. This implies that the surgical margins are clear of tumor and no obvious lymph nodes can be palpated nor known to be left in the neck (or anywhere else) based on the surgical report and pre- and post-TTE (if available) NUS, as well as any other anatomy-based diagnostic evaluation. This scenario can be briefly described as "cancer all resected, elsewhere negative". In our practice, the 'cancer all resected, elsewhere negative' scenario accounts for over 90% of all patients who are referred with the diagnosis of DTC for RAIT evaluation.

The individualized assessment of a patient that is critical to RTG approach pivots on reconciliation of stimulated Tg with the RAUI obtained at 24 hours (RAIU@24) over benign remnant thy-

roid in the neck. By definition, only the RAI activity in benign remnant thyroid contributes to this measurement in a 'cancer all resected, elsewhere negative' scenario. Of course, recognition of regional metastases in the neck could be encountered after they are revealed on the D-RAIS and clarified further on SPECT/CT. Indeed, during first post-TTE evaluation at the University of Michigan 38% and 8% of their patients revealed unsuspected metastatic regional lymph nodes and distant metastases, respectively [70]. The unexpected regional and distant metastases should be managed as structural disease, initiating TKD with RAIT. However, if the D-RAIS with SPECT/CT is negative for regional and/or distant metastases – i.e. confirmed 'cancer all resected, elsewhere negative' scenario – it is important to use Tg to further clarify presence or absence of RAI-avid and/or RAI-nonavid DTC that may be too small (microscopic) for imaging detection. In cases without such residual DTC, the Tg would be expected to stay below the maximum level produced by benign remnant thyroid under stimulation. This reconciliation is based on the empirical evidence that in patients without remnant DTC the Tg levels are proportional to the amount of benign remnant thyroid [71]. There is one provisional condition – levels of TSH stimulation must be reasonably consistent in a well standardized practice of THW protocol. This provision is important because a Tg level can vary significantly in the same patient under different levels of TSH, i.e. Tg secretion is TSH-dependent [72]. The other variable is the actual assay used to measure Tg. Hence, it is important to have a fixed protocol that provides stability to all of these variables.

7.2. Thyroglobulin with Remnant Uptake Concord (TRUC), aka Tulchinsky Method for Elucidating Occult Residual Disease in 'Cancer All Resected, Elsewhere Negative' Scenario

We postulated that in our low-risk patients with no positive lymph nodes at surgery, microscopic PTC (greatest diameter of the primary < 1cm), and negative PT-RAIS, the likelihood of residual DTC is negligible. Therefore, Dr. Tulchinsky embarked on a project to establish the correlation of RAIU@24 and measured Tg (the Immulite Tg assay, Siemens Inc., Deerfield, IL; catalog no. PIL2KTY, analytical sensitivity <0.2 ng/ml, in-house functional sensitivity 0.2 ng/ml minimum reported value 0.2 ng/ml) in patients pretreated with THW using our standard protocol. All patients with DTC at our institution from 2009-2012 were reviewed. Excluded were patients with: 1) positive regional metastatic disease at surgery, 2) positive scan or thyroglobulin at one year follow-up evaluation, 3) suspicious ultrasound findings or any other indication for residual disease at one year follow-up evaluation, and 4) Anti-Tg antibody titer ≥ 20 (L2KTG; Siemens; sensitivity 2.2 IU/mL, assay reportable range <20 to 3000 IU/mL, normal range <40 IU/mL, negative test <20 IU/mL). For the purposes of analysis, Tg less than 0.2 ng/mL was recorded as equal to 0.2. Linear regression analysis was performed comparing measured Tg with RAIU@24.

There were 43 patients (30:13, F:M) included in our study [73]. The cohort characteristics and results [mean ± standard deviation (range)] included age of 50.0 ± 15.0 (21-88), RAIU@24 of 7.12 ± 7.51 (0.1 - 32.7) %, and Tg of 5.87 ± 8.43 (0.2 - 47.8) ng/mL. The TSH ranged from 6.58 to >100 (<35 in 6 pts, ≥35 to 100 in 19 pts, and >100 in 18 pts) μIU/mL. The reason for relatively low TSH (e.g. 6.58 μIU/mL) were observed in patients with larger benign remnant thyroid (e.g. RAIU@24 of 32%) that was able to produce sufficient amount of thyroid hormone that did not allow a patient to become sufficiently hypothyroid (TSH > 35 ng/mL) with THW. The calculated linear regression equation was Tg (ng/mL) = 0.87 x RAIU@24 (%) - 0.32 (r^2 = 0.60, p < 0.0001).

Next step was finding the best-fit linear regression line that came the closest to including more than 90% of all Tg values in order to establish the top Tg per RAIU@24 that could be assigned to benign thyroid remnant origin, Tg_{max}. All values greater than this Tg_{max} would have to be explained by excess Tg coming from remnant DTC, Tg_{DTC}. We empirically tested several equations, finding the following two to be best fitting to achieve > 90% specificity. The first, Tg_{max1} = RAIU@24 x 2 + 1, rendered specificities (true negative for remnant DTC) of 95.3% (41 below the line out of the 43 patients without DTC). The second, Tg_{max2} = RAIU@24 x 2 + 2, enabled included 42 out of the 43 patients, i.e. specificity of 97.7%. The graphical representation is shown in Fig. (**2**). When patients are prepared using specific THW protocol, calculated Tg_{max2} establishes the maximal level that could be explained by benign remnant thyroid. In such cases the RA is the most rational objective and could be completed after such a patient accepts the risks and understands the benefits of RA RAIT.

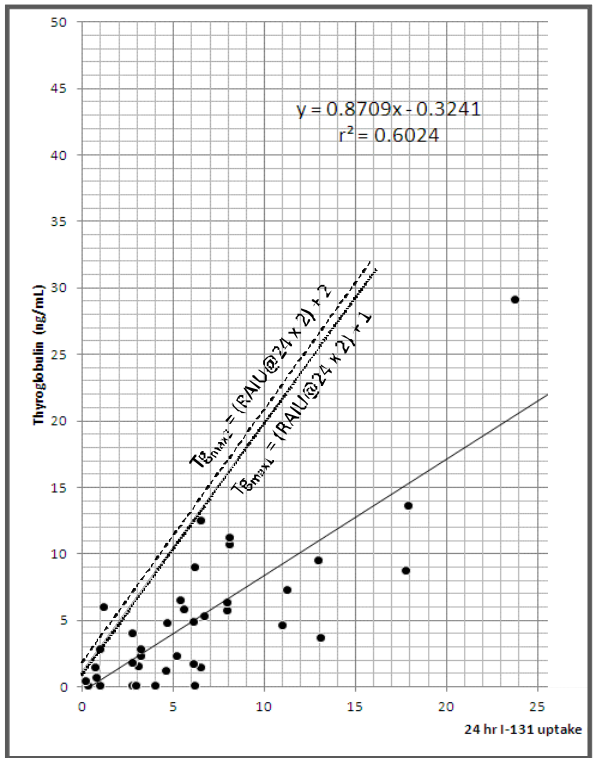

Fig. (2). Graphical representation for relationship between thyroglobulin and the radioactive iodide uptake at 24 hours (RAIU@24). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Note: The continuous line represents the linear regression line with the regression formula stated at the top of the plot. The dashed line represents linear equation for Tg_{max1}. The dotted line is linear representation of equation for Tg_{max2}.

If a patient's stimulated Tg is higher than Tg_{max2}, the excess is suspect to reflect production from an occult DTC source. This should intensify a search for the source on diagnostic imaging, including the whole-body D-RAIS (if DTC is RAI-avid) with SPECT/CT (can show RAI-avid but also RAI-nonavid as a mass on CT). If those tests are negative, microscopic DTC should be the suspect – tumor smaller than the test's spatial resolution. Such patients would be more appropriately treated with AT RAIT activities to address microscopic DTC. But the other option is RAI-nonavid DTC located outside of the SPECT/CT field-of-view. Therefore, these patients should have PET/CT with 2-[18F]-fluorodeoxyglucose (^{18}FDG) to search for ^{18}FDG-avid metastases [74-79] whenever possible. It has a sensitivity of 80-90% for tumor detection, depending on Tg level. In the U.S.A., ^{18}FDG PET/CT is often refused for payment by the third party (the medical insurance com-

panies), which limits our ability to best characterize such cases. When accessible, PET/CT enables to identify DTC as one of 5 categories: Type I (46%) is ^{18}FDG-positive/D-RAIS-negative, type II (15%) is ^{18}FDG-negative/D-RAIS-positive, type III (12%) is a mixed type (some metastasis are ^{18}FDG-positive/D-RAIS-negative and some are ^{18}FDG-negative/D-RAIS-positive), type IV (10%) is ^{18}FDG-positive/D-RAIS-positive, and type V (17%) is ^{18}FDG-negative/D-RAIS-negative [74].

At our institution, the second equation is used to reconcile stimulated Tg level with RAIU@24, as demonstrated in the examples (section 8). When applied to patients prepared with the above described THW protocol, this reconciliation (aka Tulchinsky) formula has following implications:

1. If the Tg level is below the Tg_{max2} then RA should be administered with 30-100 mCi range of activities, depending on several factors (section 3). The administered activity dosage should be guided by RAIU@24. Larger uptake increases chances for symptomatic radiation thyroiditis [80] and limiting it to 50-75 mCi would be reasonable when RAIU@24 >15%.
2. If the Tg level is above Tg_{max2} (i.e. excess production by probable occult residual DTC) then AT should be administered with 100-150 mCi range, depending on several factors. If RAIU@24 is above 15%, it may result in a painful local reaction. On the other hand, if Tg excess is > 10 ng/mL then it may be reasonable to favor PET/CT to localize occult residual DTC but a 150 mCi RAIT is also reasonable for the reason of targeting microscopic occult residual DTC.
3. If the Tg level is in excess of Tg_{max2} and the scan reveals structural RAI-avid regional metastatic DTC, then TKA can be administered with 150-200 mCi empirically or MTA-guided maximal but safe AA. We favor the latter option and use it in practice.
4. Some patients with Tg level in excess of Tg_{max2} have no RAI-avid regional or distant metastatic DTC on D-RAIS, but show pathological cervical/mediastinal nodes on localizing CT from the SPECT/CT. These patients are advised to receive RA (30-100 mCi) only and then proceed to treatment options for RAI-nonavid DTC when PT-RAIS confirms lack of RAI uptake in CT visualized lymphadenopathy. Resection of RAI-nonavid lesions is advised.
5. In some patients with excess Tg the localizing CT from SPECT/CT may disclose RAI-nonavid lung lesions suspicious for metastases. Such patients require tissue confirmation of lung nodules and managed with targeted molecular therapy in oncology. At this time, the option of re-differentiating these lesions to make them amenable to RAIT is investigational [81].
6. The PT-RAIS should be obtained in all treated patients in order to make sure that our presumptive diagnosis of RAI-nonavid DTC was true. Rarely, PT-RAIS could disclose a new lesion that was not appreciated on D-RAIS. This happens in those with either lesions smaller than D-RAIS resolution or when RAI avidity is too low for D-RAIS detection.
7. In all cases that show no RAI avid DTC lesions but excess Tg, ^{18}FDG PET/CT should be performed with the goal to localize and, if possible, remove RAI-nonavid DTC.

7.3. Follow-up and Surveillance Diagnostic Studies

The first follow up study post-RAIT is typically done with THW preparation 6-12 months later for all patients, and response to treatment is assessed by comparison of D-RAIS findings. In patients described in groups 1-3 above (section 7.2), there is usually a complete response to treatment since DTC was RAI-avid. In fact, a recent study showed that from the follow-up studies performed on DTC patients, performing RAIS was associated with mortality benefit [82]. None of the other diagnostic follow-up tests demonstrated an association with mortality benefit but resulted in increased use of invasive procedures, surgery, and RAIT benefit [82]. This fact is insufficiently emphasized, especially since the current trend in practice is showing decreasing utilization of D-RAIS. In type 4 cases, where the cancer is usually RAI-nonavid, and there are Tg levels in excess of RAIU@24, executing RAIT has not been shown to yield any clinical benefit. Discovery of isolated or oligometastatic disease on ^{18}FDG PET/CT could lead to cure through surgery and provide for a long disease free survival [83]. Management of more extensive RAI-nonavid DTC would be more reasonable with either surgical de-bulking and/or targeted molecular therapy (e.g. tyrosine kinase inhibitors) and/or external beam radiation therapy; thus, best referred to Oncology.

8. COMMON EXAMPLES

8.1. Benign Thyroid Remnant and No Evidence for Remaining Cancer (Fig. 3)

A 58-year-old male with Non-Hodgkin's lymphoma was found a mildly avid focus on surveillance ^{18}FDG PET/CT after successful therapy for lymphoma. NUS shortly after the finding demonstrated a single suspicious 1 cm cervical LN that was positive for PTC on biopsy as was also the thyroid nodule. She underwent total thyroidectomy on 8/20/13. The surgical pathology revealed multifocal papillary thyroid cancer, classical type. The tumor margins were not involved and there was no extrathyroidal extension. However, there was an extensive lymphvascular invasion. In addition, there were 3 positive lymph nodes out of 34 resected and one of them showed extranodal extension of the tumor. On 1/23/2014 evaluation was obtained under THW stimulation. The laboratory evaluation included TSH of 97.1 μIU/mL, thyroglobulin (Tg) of 9.9 ng/mL, and the negative TgAb. Contemporaneous D-RAIS with SPECT/CT (not shown as a figure) revealed two foci of activity in the surgical neck with RAIU@24 of 4%. Using the reconciliation formula the Tg_{max2} from the benign remnant thyroid was (4 x 2) + 2 = 10 IU/mL. Therefore, it was estimated that this patient's total Tg could be explained by benign remnant thyroid alone. The patient was explained the findings and he elected to proceed with 100 mCi RAIT with the goal of RA. The post-treatment scan (Fig. **3A**) obtained 7 days later showed two cervical foci of uptake in the identical position to D-RAIS, one was higher in the right neck (curved arrow) and the other one located more inferior and close to the midline (white thicker arrow). There was expected activity in the mouth (arrowhead). Finally, a small focus was seen in the head to the right of midline (straight thin arrow), which was in a typical pattern of activity accumulated in the blocked nasolacrimal gland that can be seen as a side effect of this therapy. This patient was referred for ophthalmology and successfully treated with dacryocystorhinostomy for the confirmed blockage. The long tubular activity seen on the chest/abdomen and abdomen/pelvis overlapping static views is in the typical located of the colon and seen commonly in these patients who experience constipation during hypothyroid period of THW. The SPECT/CT of the top focus (Fig. **3B**) showed activity in the typical location of thyroglossal duct (curved arrow) that retained functional thyroid tissue. The lower activity (Fig. **3C**) was in the tissue that had characteristic appearance of benign remnant thyroid in the left thyroid bed. There were no other findings. The patient returned one year later for THW D-RAIS (Fig. **3D**) that showed successful ablation. The contemporaneous laboratory values were TSH > 100 μIU/mL, Tg < 0.2 ng/mL (considered undetectable by the assay), and no TgAb.

8.2. Benign Thyroid Remnant and Probable Microscopic Remaining Cancer (Fig. 4)

A 37-year-old female with multifocal PTC was evaluated 3 months post-TTE on the THW stimulation. Her staging summary was pT1 pN1 MX, i.e. Stage I. However, her aggressive histopathology placed the patient into 2015 ATA intermediate-risk group

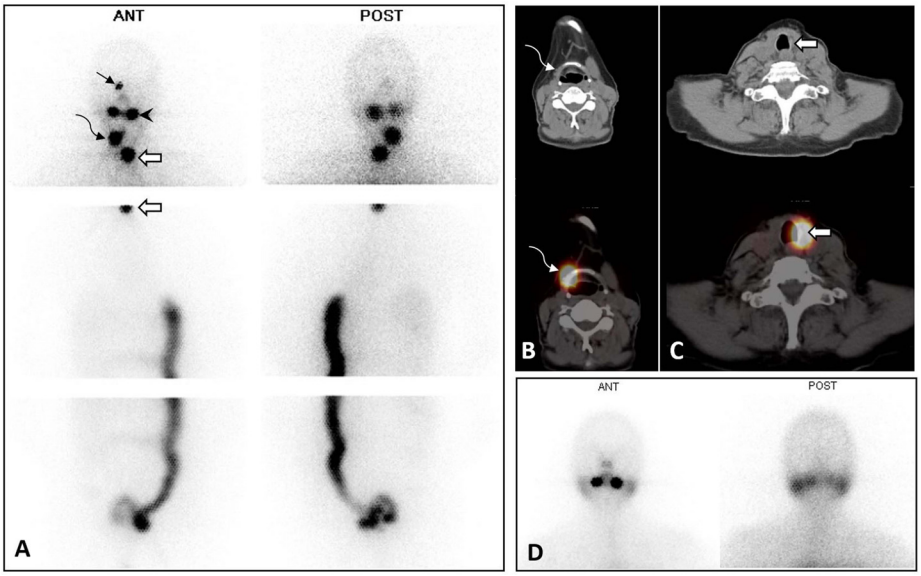

Fig. (3). Panel **A**: Shown are post therapy planar ^{131}I whole body images obtained in overlapping 3 static acquisitions in anterior and posterior projections. The treatment was given 7 days previously. There is an intense focus at the base of the neck (thick white arrow). Above and to the right is another intense focus (curved arrow). Some activity is seen in the mouth (arrowhead). A small focus of activity is seen in the position typical for a lacrimal glad location (confirmed on SPECT/CT but not shown here). Panel **B**: Shown are localizing CT (top image) and corresponding fusion image (bottom image) with only tiny focus of soft-tissue on CT (curved arrow) in the location corresponding to the intense focus seen on the fusion image (curved arrow). This represents a typical appearance of thyroglossal duct. Panel **C**: Shown are localizing CT (top image) with indiscrete small but slightly denser than nearby muscle soft-tissue on CT (thick white arrow) in the location corresponding to intense tracer activity (thick white arrow) on the fusion (bottom) image. Panel **D**: A single static image of the head, neck, and the upper chest in anterior and posterior projection are shown of the same patient one year after the therapeutic ^{131}I administration for remnant ablation. There is successful ablation of the previously seen remnant thyroid. There is no evidence for recurrent iodide avid cancer. There is also no uptake in the right lacrimal duct that was treated a year ago with dacryocystorhinostomy. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

and she was referred to NM for RAIT consideration. The laboratory evaluation revealed TSH of 42.11 μIU/mL, thyroglobulin (Tg) of 17.2 ng/mL without interfering TgAb. Planar imaging with ^{131}I (2 mCi administered) showed (Fig. **4A**) a focus of intense activity in thyroid bed (arrow), calculating RAIU@24 of 6%. The 6% uptake could be responsible for up to 14 ng/mL of the measured Tg, according to the TRUC (aka Tulchinsky) methodology. Unaccounted Tg (3.2 ng/mL) could have originated from microscopic or macroscopic remaining PTC. The CT portion (Fig. **4B**) of SPECT/CT (slice taken at the level indicated by dashed line on panel A) showed no anatomical evidence for pathologically enlarged lymph nodes and small amount of soft tissue remaining in the thyroid bed abutting the trachea (arrows) and surgical clips (arrowheads) on both sides of the trachea. The fusion image (Fig. **4C**), created by 50% blending of ^{131}I SPECT in yellow-to-red color scale with localizing CT showed that all of the thyroid iodine-avid tissue is in the normal post-surgical remnant (arrows). The patient was offered adjuvant therapy based on the intermediate-risk for 'recurrence' classification and elevated Tg in excess to the calculated Tg_{max2} value, which could be explained by microscopic remnant DTC production that contributed along with benign thyroid remnant production to the total Tg. The patient wished to proceed with the therapy after a detailed discussion of risks and benefits. She was given 100 mCi of ^{131}I and post-treatment scan showed no additional findings to suggest structural metastatic disease when compared to the D-RAIS. The repeat evaluation one year later showed undetectable THW-stimulated Tg and a negative ^{131}I D-RAIS. The patient remained on surveillance program using rhTSH-stimulated and suppressed Tg.

8.3. Benign Thyroid Remnant and Remaining Nodal RAI-Avid Cancer (Fig. 5)

A 63-year-old male with a 2.3 solitary PTC underwent thyroidectomy with lymph node sampling. Post-TTE staging was pT2 pN1aMx (5 out of 9 sampled nodes were positive for PTC). The patient was classified as high risk due to extrathyroidal on pathology. Post-operative TSH was 80.85 μIU/mL, thyroglobulin (Tg) was 39.2 ng/mL and negative TgAb. Planar imaging with ^{131}I (2 mCi administered) showed 3 foci of intense activity, two in the thyroid bed (Fig. **5A**, arrowhead) and one more laterally (arrow). The uptake was 4% of ^{131}I at 24 hours. The Tg_{max2} value was calculated at 10 ng/mL. The unaccounted Tg (39.2-10=29.2 ng/mL) could have originated from microscopic or macroscopic RAI-nonavid remaining PTC, according to the TRUC (aka Tulchinsky) methodology. SPECT/CT demonstrated uptake in laterally positioned focus showed on fusion slices (Fig. **5B**) and on small round lymph node in corresponding CT (Fig. **5C**) (white arrow), representing macroscopic disease. Two foci of uptake in thyroid bed were BENIGN THYROID REMNANT tissue seen on slice obtained through the more intense of the other two neck bed foci on fusion (Fig. **5D**) and on corresponding CT (Fig. **5E**). The patient was offered 150 mCi of ^{131}I for the treatment of known cervical LN disease. The post-treatment scan showed no additional disease in the neck or distant sites (not shown here). The patient on follow-up THW D-RAIS one year later showed no residual activity nor detectable Tg; thus, he was re-classified as no detectable disease.

8.4. Benign Thyroid Remnant and Remaining RAI-Nonavid Cancer (Fig. 6)

A 32-years-old female with complaints of a left thyroid lump revealed a large corresponding nodule and suspicious cervical lymph nodes on NUS. Subsequent biopsy established the diagnosis of PTC. She underwent total thyroidectomy and modified bilateral neck dissection. Surgical pathology revealed solitary left lobe papillary thyroid cancer with the greatest dimension of 5.3 cm with no extrathyroidal extension, margins clear of tumor, and no lymphovascular or perineural tumor invasion. Bilateral lymph node dissection resulted in 27 metastatic lymph nodes out of 61 excised

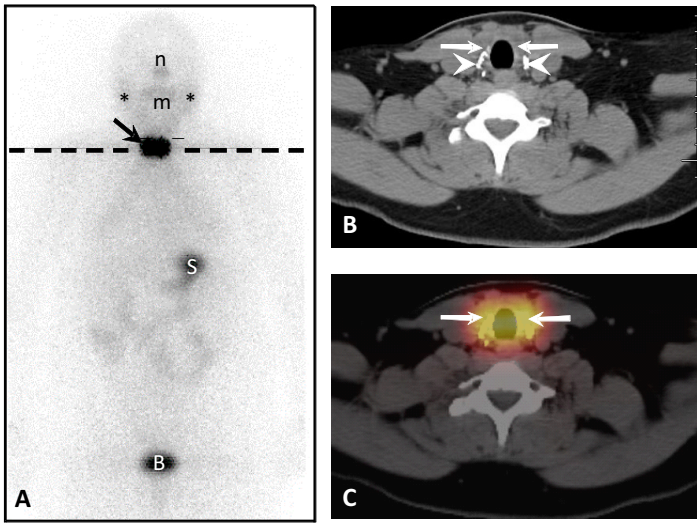

Fig. (4). Panel **A**: This is a standard whole body ^{131}I planar scan in the anterior view. The most intense focus of cervical tracer uptake is pointed at by the arrow. The dashed line indicates the level of separately displayed tomographic slices. The mild activity below letter "n" is the nasal uptake, above "m" is an activity in the mouth, faint activity in the parotid and submandibular glands is marked with apteryx and hollow circles, respectively. A greater activity in the abdomen, marked "S", represents stomach uptake with serpiginous activity below representing excreted activity into the small bowel. The excreted activity into the urinary bladder is marked with letter "B". Panel **B**: Displayed is one slice of localizing CT from the SPECT/CT examination performed on the same day. The white arrows show the location of indistinct thyroid remnant within the surgical bed bilaterally. The arrowheads point to the surgical clips. Panel **C**: Displayed is the fusion image with 50% blending of SPECT and CT. The white arrows show the intense 131I activity corresponding to the presumably benign remnant thyroid tissue. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

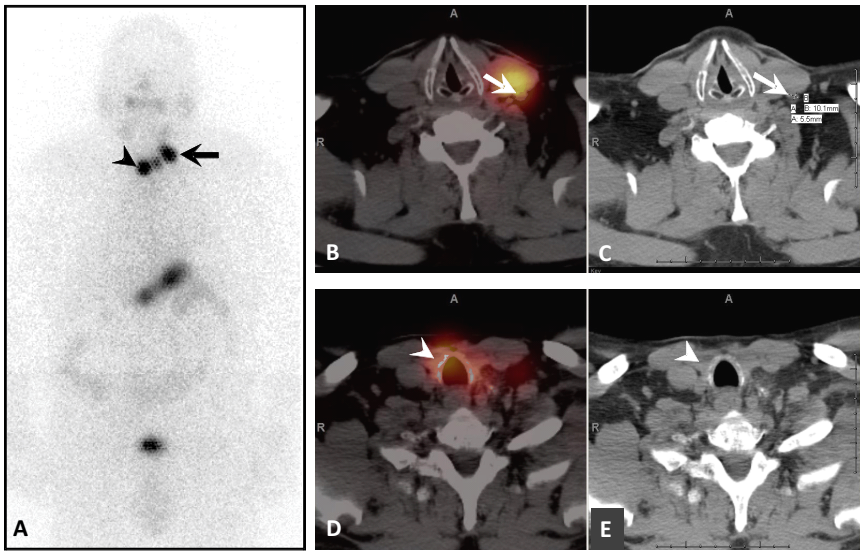

Fig. (5). Panel **A**: Shown is anterior view of the diagnostic whole-body ^{131}I planar scan. There are 3 foci of ^{131}I uptake in the neck. The one to the right of midline (arrowhead) is intense. Another very intense focus is on the left side in the lateral neck (arrow). There is a fainter focus of activity between the two intense foci. The rest of ^{131}I activity is in normal physiological distribution. Panel **B**: The fusion image shows a 50% blending of SPECT and CT, demonstrating an intense focus in the lateral neck compartment (arrow) at the level of thyroid cartilage. Panel **C**: Shown here is the corresponding localizing CT that better displays the lymph node tissue measuring 1.0 by 0.6 cm. Panel **D** and **E**: Shown are respectively the fusion and localizing CT images of the lower focus of activity in the right thyroid surgical bed, which is most consistent with remnant benign thyroid. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

(+27/61) with the largest measuring 3.5 cm and showing extranodal tumor extension. On the left side, dissection included levels 2A (0/8), 2B (0/4), 3 (+6/8) and 4 (+7/8). On the right side, dissection included levels 2A (0/11), 2B (0/2), 3 (0/2) and 4 (+8/10). The patient's ATA 2015 risk of 'recurrence' was high, based on positive cervical lymph node metastasis that was larger than 3 cm and demonstrated extranodal extension (≈ 40% risk of recurrence).

Two months after surgery, the patient underwent THW D-RAIS (Fig. **6A**). The residual thyroid uptake was 4.2% and localized to the thyroid bed in an elongated and lumpy pattern (Fig. **6A**, arrowheads). The SPECT/CT showed all of the activity localizing to barely discernable thin tissue in the thyroid bed (arrowheads), which is typical in location and imaging characteristics for benign remnant thyroid that resides in the bilateral thyroid beds, higher on the right and lower on the left (Fig. **6B**, top pair of coronal slices). The stimulated Tg level was elevated at 52 ng/mL, which cannot be explained by the benign remnant thyroid that could be responsible for Tg_{max2} of only 10.4 ng/mL, according to the TRCU (aka

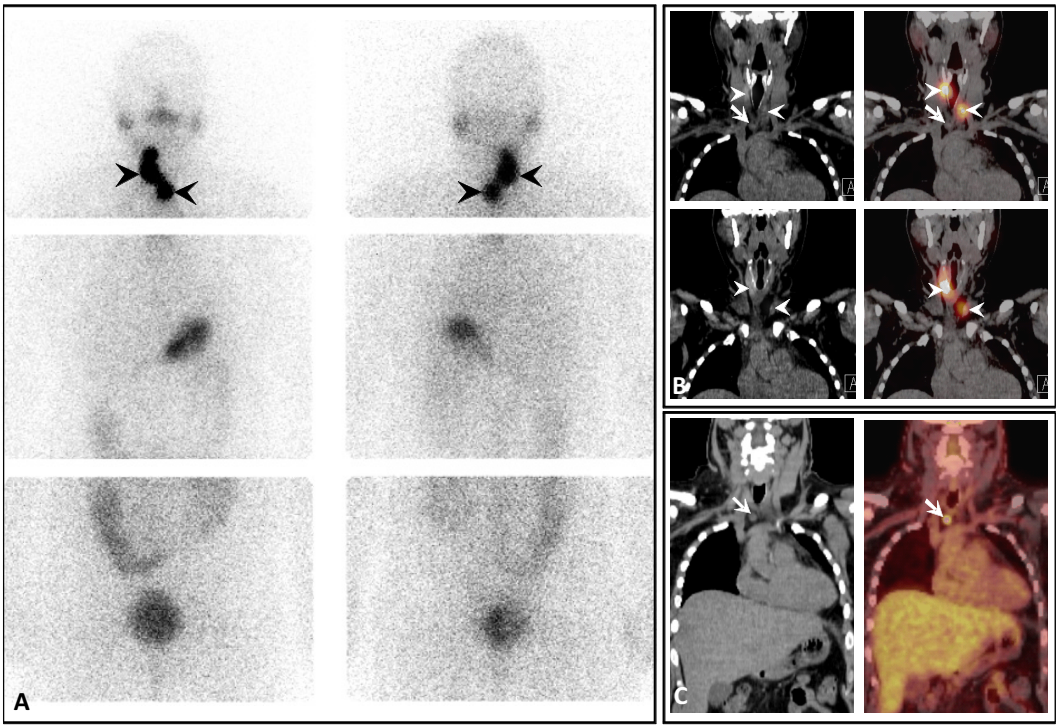

Fig. (6). A 32-years-old female with complaints of a left thyroid lump was diagnosed with papillary thyroid cancer by total thyroidectomy with the greatest dimension of 5.3 cm. The risk of 'recurrence' was high based on multiple positive cervical lymph node metastases with one that was larger than 3 cm and demonstrated extranodal extension (≈40% risk of 'recurrence'). The diagnostic whole-body ^{131}I planar scan (**A**) in anterior and posterior projections showed residual thyroid uptake of 4.2% in the thyroid bed in elongated and lumpy pattern (arrowheads). The SPECT/CT showed all of the activity localizing to barely discernable thin tissue (arrowheads) in the thyroid bed (**B**). SPECT/CT showed evidence of non-avid level 6 lymph node (arrow) measuring 1.0 x 1.5 cm (**B**). Further evaluation with ^{18}FDG PET/CT was obtained to try fully characterize and evaluate extent of metastatic DTC. The same level 6 lymph node was intensely FDG avid (**C**). The patient underwent modified neck dissection and the removed lymph node was a pathologically confirmed metastasis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Tulchinsky) method. The SPECT/CT showed round level 6 LN (white arrow), measuring 1.0 x 1.5 mm (Figure 6B, top pair of coronal slices). Due to suspected RAI-nonavid in the locoregional metastasis and no evidence for RAI-avid DTC, the top RA dosage of 100 mCi was proposed to the patient. Our goal was to achieve RA to allow better follow up with Tg in the future, document findings on PT-RAIS and in case of a remote chance of possible microscopic RAI-avid DTC we also intended to cover for AT.

In order to make sure our presumptive diagnosis of RAI-nonavid DTC was true, PT-RAIS was obtained seven days after RAIT. There was no evidence of additional RAI uptake to suggest regional or metastatic disease, and therefore the only remaining concern was for RAI-nonavid DTC. Further evaluation with PET/CT was obtained a few days after PT-RAIS to better map out the RAI-nonavid DTC. The same level 6 lymph node (white arrow) demonstrated intense ^{18}FDG uptake (Fig. **6C**) consistent with metastatic RAI-nonavid DTC without other significant findings. We concluded that this patient had oligometastatic RAI-nonavid DTC and referred her for surgical management of level 6 lymph node, which was later removed and pathologically confirmed as a solitary PTC metastasis with few other negative LN also excised at surgery.

CONCLUSION

The described approach to radiotheragnostic management of DTC with RAI is accessible to most facilities that are currently offering Nuclear Medicine services. It is logical and offers patients personalized care based entirely on their individual findings on physical examination, laboratory assessment, diagnostic imaging, and most importantly, the modern D-RAIS with SPECT/CT. The use of maximum tolerated RAI activity is favored in our practice for those demonstrating RAI-avid metastatic DTC. The goal of RAIT should always be stated using the three-tiered terminology for clarity, and that should facilitate an open discussion of risks and benefits with patients. Reconciliation methodology of Tg with RAIU@24 helps greatly in navigating these three options with greater certainty. Using RTGs paradigm has documented high success rate that was recently reported [31, 84] and our practice confirms those results.

GLOSSARY

AJCC	=	American Joint Commission on Cancer
AJCC	=	American Joint Commission on Cancer
AT	=	Adjuvant treatment
ATA	=	American Thyroid Association
D-RAIS	=	Diagnostic RAI scintigraphy
DTC	=	Differentiated thyroid cancer
ESTRADA	=	Estimated sterilizing target radiation absorbed dose approach
FTC	=	Follicular thyroid cancer
HEAR	=	Historical empiric activity range
LID	=	Low iodine diet
LN	=	Lymph nodes
MTA	=	Maximum tolerated activity
NIS	=	Sodium-iodide symporter
NM	=	Nuclear Medicine
NUS	=	Neck ultrasound

PTC	=	Papillary thyroid cancer
PT-RAIS	=	Post-treatment RAI scans
RA	=	Remnant ablation
RAI	=	Radioactive iodide
RAIT	=	RAI treatment
RAIU@24	=	RAI uptake at 24 hours
RCT	=	Randomized controlled trial
rhTSH	=	Recombinant human TSH
SOHMA	=	'Standard' one hundred millicurie activity
SPECT	=	Single photon emission computed tomography
SPECT/CT	=	Single photon emission computed tomography–computed tomography
Tg	=	Thyroglobulin
TgAb	=	Thyroglobulin antibody
THW	=	Thyroid hormone withdrawal
TKD	=	Treatment of known disease
TRUC method	=	Thyroglobulin with remnant uptake concord (aka Tulchinsky) method
TSH	=	Thyroid stimulating hormone
TTE	=	Total or near-total thyroidectomy

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Fahey FH, Grant FD, Thrall JH. Saul Hertz, MD, and the birth of radionuclide therapy. EJNMMI Phys 2017; 4(1): 15. http://dx.doi.org/10.1186/s40658-017-0182-7 PMID: 28451906

[2] Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. J Am Med Assoc 1946; 132(14): 838-47. http://dx.doi.org/10.1001/jama.1946.02870490016004 PMID: 20274882

[3] Brucer M. From Surgery without a Knife to the Atomic Cocktail.Vignettes in Nuclear Medicine I. St. Louis, Missouri: Mallinckrodt Chemical Works 1969; pp. 1-11.

[4] NCI. Targeted therapy. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/targeted-therapy

[5] Min JJ, Chung JK, Lee Y, *et al.* Relationship between expression of the sodium/iodide symporter and (131)I uptake in recurrent lesions of differentiated thyroid carcinoma. Eur J Nucl Med 2001; 28(5): 639-45. http://dx.doi.org/10.1007/s002590100509 PMID: 24633540

[6] Rawson RW, Marinelli LD, *et al.* The effect of total thyroidectomy on the function of metastatic thyroid cancer. J Clin Endocrinol Metab 1948; 8(10): 826-41. http://dx.doi.org/10.1210/jcem-8-10-826 PMID: 18890104

[7] Benua RS, Cicale NR, Sonenberg M, Rawson RW. The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. Am J Roentgenol Radium Ther Nucl Med 1962; 87: 171-82. PMID: 13867399

[8] Beierwaltes WH, Rabbani R, Dmuchowski C, Lloyd RV, Eyre P, Mallette S. An analysis of "ablation of thyroid remnants" with I-131 in 511 patients from 1947-1984: experience at University of Michigan. J Nucl Med 1984; 25(12): 1287-93. PMID: 6502251

[9] Deandreis D, Rubino C, Tala H, Leboulleux S, Terroir M, Baudin E, *et al.* Comparison Of Empiric Versus Whole Body/Blood Clearance Dosimetry-Based Approach To Radioactive Iodine Treatment In Patients With Metastases From Differentiated Thyroid Cancer. J Nucl Med 2016. PMID: 27738010

[10] Flux GD, Verburg FA, Chiesa C, *et al.* Comparison of Empiric Versus Dosimetry-Guided Radioiodine Therapy: The Devil Is in the Details. J Nucl Med 2017; 58(5): 862. DOI: 10.2967/jnumed.116.186643 http://dx.doi.org/10.2967/jnumed.116.186643 PMID: 28183989

[11] Jentzen W, Nahum AE, Bockisch A, Binse I, Tulchinsky M. Fixed 3.7-GBq ^{131}I Activity for Metastatic Thyroid Cancer Therapy Ignores Science and History. J Nucl Med 2017; 58(9): 1530. http://dx.doi.org/10.2967/jnumed.117.192872 PMID: 28385792

[12] Tulchinsky M, Gross LJ. Comparison of Empiric Versus Dosimetry-Guided Radioiodine Therapy: The Devil Is in the Details. J Nucl Med 2017; 58(5): 863. DOI: 10.2967/jnumed.117.190199 http://dx.doi.org/10.2967/jnumed.117.190199 PMID: 28232615

[13] Van Nostrand D. Prescribed Activity of ^{131}I Therapy in Differentiated Thyroid Cancer. J Nucl Med 2017; 58(5): 697-9. http://dx.doi.org/10.2967/jnumed.116.188862 PMID: 28209908

[14] Maxon HR, Thomas SR, Hertzberg VS, *et al.* Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. N Engl J Med 1983; 309(16): 937-41. http://dx.doi.org/10.1056/NEJM198310203091601 PMID: 6621620

[15] Maxon HR III, Englaro EE, Thomas SR, *et al.* Radioiodine-131 therapy for well-differentiated thyroid cancer-a quantitative radiation dosimetric approach: outcome and validation in 85 patients. J Nucl Med 1992; 33(6): 1132-6. PMID: 1597728

[16] Sgouros G, Kolbert KS, Sheikh A, *et al.* Patient-specific dosimetry for 131I thyroid cancer therapy using 124I PET and 3-dimensional-internal dosimetry (3D-ID) software. J Nucl Med 2004; 45(8): 1366-72. PMID: 15299063

[17] Jentzen W, Hoppenbrouwers J, van Leeuwen P, *et al.* Assessment of lesion response in the initial radioiodine treatment of differentiated thyroid cancer using 124I PET imaging. J Nucl Med 2014; 55(11): 1759-65. http://dx.doi.org/10.2967/jnumed.114.144089 PMID: 25332440

[18] Jentzen W, Bockisch A, Ruhlmann M. Assessment of Simplified Blood Dose Protocols for the Estimation of the Maximum Tolerable Activity in Thyroid Cancer Patients Undergoing Radioiodine Therapy Using 124I. J Nucl Med 2015; 56(6): 832-8. http://dx.doi.org/10.2967/jnumed.114.153031 PMID: 25858042

[19] Jentzen W, Verschure F, van Zon A, *et al.* 124I PET Assessment of Response of Bone Metastases to Initial Radioiodine Treatment of Differentiated Thyroid Cancer. J Nucl Med 2016; 57(10): 1499-504. http://dx.doi.org/10.2967/jnumed.115.170571 PMID: 27199362

[20] Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994; 97(5): 418-28. http://dx.doi.org/10.1016/0002-9343(94)90321-2 PMID: 7977430

[21] Pacini F, Ladenson PW, Schlumberger M, *et al.* Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. J Clin Endocrinol Metab 2006; 91(3): 926-32. http://dx.doi.org/10.1210/jc.2005-1651 PMID: 16384850

[22] Bal C, Padhy AK, Jana S, Pant GS, Basu AK. Prospective randomized clinical trial to evaluate the optimal dose of 131 I for remnant ablation in patients with differentiated thyroid carcinoma. Cancer 1996; 77(12): 2574-80. http://dx.doi.org/10.1002/(SICI)1097-0142(19960615)77:12<2574::AID-CNCR22>3.0.CO;2-O PMID: 8640708

[23] Brown SR, Hall A, Buckley HL, *et al.* Investigating the potential clinical benefit of Selumetinib in resensitising advanced iodine re-

fractory differentiated thyroid cancer to radioiodine therapy (SEL-I-METRY): protocol for a multicentre UK single arm phase II trial. BMC Cancer 2019; 19(1): 582.
http://dx.doi.org/10.1186/s12885-019-5541-4 PMID: 31200667

[24] Wadsley J, Gregory R, Flux G, *et al.* SELIMETRY-a multicentre I-131 dosimetry trial: a clinical perspective. Br J Radiol 2017; 90(1073)20160637
http://dx.doi.org/10.1259/bjr.20160637 PMID: 28291381

[25] Van Nostrand D. Radioiodine Theranostics: Increasing Dialogue and Collaboration. J Nucl Med 2017; 58(10): 19N-20N.
PMID: 28970353

[26] Tuttle RM, Ahuja S, Avram AM, *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.
http://dx.doi.org/10.1089/thy.2018.0597 PMID: 30900516

[27] Rosenthal MS, Angelos P, Bible K, Fassler CA, Finder S, Wissner Greene L, *et al.* Informed consent for low-risk thyroid cancer. Int J Endocr Oncol 2016; 3(2): 131-42.
http://dx.doi.org/10.2217/ije-2015-0010

[28] Avram AM. Radioiodine scintigraphy with SPECT/CT: an important diagnostic tool for thyroid cancer staging and risk stratification. J Nucl Med 2012; 53(5): 754-64.
PMID: 22550280

[29] Dizdarevic S, Tulchinsky M, McCready VR, *et al*. The World Association of Radiopharmaceutical and Molecular Therapy position statement on the initial radioiodine therapy for differentiated thyroid carcinoma. World J Nucl Med 2019; 18(2): 123-6.
http://dx.doi.org/10.4103/wjnm.WJNM_117_18 PMID: 31040741

[30] 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.
http://dx.doi.org/10.1210/jc.2014-4043 PMID: 25734251

[31] Avram AM, Rosculet N, Esfandiari NH, *et al.* Differentiated Thyroid Cancer Outcomes After Surgery and Activity-Adjusted 131I Theragnostics. Clin Nucl Med 2019; 44(1): 11-20.
http://dx.doi.org/10.1097/RLU.0000000000002321 PMID: 30371575

[32] Haugen BR, Alexander EK, Bible KC, *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.
http://dx.doi.org/10.1089/thy.2015.0020 PMID: 26462967

[33] Luster M, Aktolun C, Amendoeira I, Barczynski M, Bible KC, Duntas LH, *et al.* European perspective on the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer Proceedings of an interactive international symposium Thyroid.

[34] Silberstein EB, Alavi A, Balon HR, *et al.* The SNMMI practice guideline for therapy of thyroid disease with 131I 3.0. J Nucl Med 2012; 53(10): 1633-51.
http://dx.doi.org/10.2967/jnumed.112.105148 PMID: 22787108

[35] Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ 2003; 327(7429): 1459-61.
http://dx.doi.org/10.1136/bmj.327.7429.1459 PMID: 14684649

[36] Tulchinsky M, Baum RP, Bennet KG, *et al.* Well-Founded Recommendations for Radioactive Iodine Treatment of Differentiated Thyroid Cancer Require Balanced Study of Benefits and Harms. J Clin Oncol 2018; 36(18): 1887-8.
http://dx.doi.org/10.1200/JCO.2018.78.5972 PMID: 29723091

[37] van Velsen EFS, Stegenga MT, van Kemenade FJ, Kam BLR, van Ginhoven TM, Visser WE, *et al.* Comparing the Prognostic Value of the Eighth Edition of the American Joint Committee on Cancer/Tumor Node Metastasis Staging System Between Papillary and Follicular Thyroid CancerThyroid. 2018; 28: pp. (8)976-81.

[38] Onitilo AA, Engel JM, Lundgren CI, Hall P, Thalib L, Doi SA. Simplifying the TNM system for clinical use in differentiated thyroid cancer. J Clin Oncol 2009; 27(11): 1872-8.
http://dx.doi.org/10.1200/JCO.2008.20.2382 PMID: 19273697

[39] Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery 1987; 102(6): 1088-95.
PMID: 3686348

[40] Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery 1988; 104(6): 947-53.
http://dx.doi.org/10.1016/S0039-6060(98)70034-0 PMID: 3194846

[41] Pasieka JL, Zedenius J, Auer G, *et al.* Addition of nuclear DNA content to the AMES risk-group classification for papillary thyroid cancer. Surgery 1992; 112(6): 1154-9.
PMID: 1455318

[42] Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993; 114(6): 1050-7.
PMID: 8256208

[43] Lang BH, Lo CY, Chan WF, Lam KY, Wan KY. Staging systems for follicular thyroid carcinoma: application to 171 consecutive patients treated in a tertiary referral centre. Endocr Relat Cancer 2007; 14(1): 29-42.
http://dx.doi.org/10.1677/erc.1.01284 PMID: 17395973

[44] Momesso DP, Tuttle RM. Update on differentiated thyroid cancer staging. Endocrinol Metab Clin North Am 2014; 43(2): 401-21.
http://dx.doi.org/10.1016/j.ecl.2014.02.010 PMID: 24891169

[45] Pitoia F, Jerkovich F, Urciuoli C, *et al.* Implementing the Modified 2009 American Thyroid Association Risk Stratification System in Thyroid Cancer Patients with Low and Intermediate Risk of Recurrence. Thyroid 2015; 25(11): 1235-42.
http://dx.doi.org/10.1089/thy.2015.0121 PMID: 26132983

[46] Domínguez JM, Martínez MT, Massardo JM, *et al.* [Risk of recurrence in differentiated thyroid cancer]. Rev Med Chil 2018; 146(3): 282-9. [Risk of recurrence in differentiated thyroid cancer].
PMID: 29999097

[47] Bates MF, Lamas MR, Randle RW, *et al.* Back so soon? Is early recurrence of papillary thyroid cancer really just persistent disease? Surgery 2018; 163(1): 118-23.
http://dx.doi.org/10.1016/j.surg.2017.05.028 PMID: 29128176

[48] Albano D, Bertagna F, Panarotto MB, Giubbini R. Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer. Pediatr Blood Cancer 2017; 64(11)
http://dx.doi.org/10.1002/pbc.26595 PMID: 28436606

[49] Clement SC, Peeters RP, Ronckers CM, *et al.* Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma-a systematic review. Cancer Treat Rev 2015; 41(10): 925-34.
http://dx.doi.org/10.1016/j.ctrv.2015.09.001 PMID: 26421813

[50] Fard-Esfahani A, Emami-Ardekani A, Fallahi B, *et al.* Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. Nucl Med Commun 2014; 35(8): 808-17.
http://dx.doi.org/10.1097/MNM.0000000000000132 PMID: 24751702

[51] Nakada K, Ishibashi T, Takei T, *et al.* Does lemon candy decrease salivary gland damage after radioiodine therapy for thyroid cancer? J Nucl Med 2005; 46(2): 261-6.
PMID: 15695785

[52] Liu B, Kuang A, Huang R, *et al.* Influence of vitamin C on salivary absorbed dose of 131I in thyroid cancer patients: a prospective, randomized, single-blind, controlled trial. J Nucl Med 2010; 51(4): 618-23.
http://dx.doi.org/10.2967/jnumed.109.071449 PMID: 20237029

[53] Silberstein EB. Reducing the incidence of 131I-induced sialadenitis: the role of pilocarpine. J Nucl Med 2008; 49(4): 546-9.
http://dx.doi.org/10.2967/jnumed.107.049411 PMID: 18344428

[54] Atienza G, López-Cedrún JL. Management of obstructive salivary disorders by sialendoscopy: a systematic review. Br J Oral Maxillofac Surg 2015; 53(6): 507-19.
http://dx.doi.org/10.1016/j.bjoms.2015.02.024 PMID: 25823614

[55] Bhayani MK, Acharya V, Kongkiatkamon S, *et al.* Sialendoscopy for Patients with Radioiodine-Induced Sialadenitis and Xerostomia. Thyroid 2015; 25(7): 834-8.
http://dx.doi.org/10.1089/thy.2014.0572 PMID: 25860842

[56] Kim YM, Choi JS, Hong SB, Hyun IY, Lim JY. Salivary gland function after sialendoscopy for treatment of chronic radioiodine-induced sialadenitis. Head Neck 2016; 38(1): 51-8. http://dx.doi.org/10.1002/hed.23844 PMID: 24995941

[57] Wu CB, Xi H, Zhou Q, Zhang LM. Sialendoscopy-assisted treatment for radioiodine-induced sialadenitis. J Oral Maxillofac Surg 2015; 73(3): 475-81. http://dx.doi.org/10.1016/j.joms.2014.09.025 PMID: 25544300

[58] Dingle IF, Mishoe AE, Nguyen SA, Overton LJ, Gillespie MB. Salivary morbidity and quality of life following radioactive iodine for well-differentiated thyroid cancer. Otolaryngol Head Neck Surg 2013; 148(5): 746-52. http://dx.doi.org/10.1177/0194599813479777 PMID: 23462656

[59] Angelidis G, Tsougos I, Valotassiou V, Georgoulias P. Low-dose radiation cancer risk hypothesis may lead to 'radiophobia'-driven imaging avoidance? J Nucl Cardiol 2018. http://dx.doi.org/10.1007/s12350-018-1354-0

[60] Yu CY, Saeed O, Goldberg AS, *et al.* A Systematic Review and Meta-Analysis of Subsequent Malignant Neoplasm Risk After Radioactive Iodine Treatment of Thyroid Cancer. Thyroid 2018; 28(12): 1662-73. http://dx.doi.org/10.1089/thy.2018.0244 PMID: 30370820

[61] Molenaar RJ, Sidana S, Radivoyevitch T, Advani AS, Gerds AT, Carraway HE, *et al.* Risk of Hematologic Malignancies After Radioiodine Treatment of Well-Differentiated Thyroid Cancer. J Clin Oncol 2017; 7(50): 232. PMID: 29252123

[62] Vaiano A, Claudio Traino A, Boni G, *et al.* Comparison between remnant and red-marrow absorbed dose in thyroid cancer patients submitted to 131I ablative therapy after rh-TSH stimulation versus hypothyroidism induced by L-thyroxine withdrawal. Nucl Med Commun 2007; 28(3): 215-23. http://dx.doi.org/10.1097/MNM.0b013e328014a0f6 PMID: 17264781

[63] Hung GU, Ho M, Kao CH. Faster radioiodine washout in the treatment of pulmonary metastases of papillary thyroid cancer prepared with recombinant human thyroid-stimulating hormone. Clin Nucl Med 2009; 34(5): 316-7. http://dx.doi.org/10.1097/RLU.0b013e31819e5108 PMID: 19387216

[64] Freudenberg LS, Jentzen W, Petrich 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. http://dx.doi.org/10.1007/s00259-010-1565-3 PMID: 20661558

[65] Zanotti-Fregonara P, Hindié 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. http://dx.doi.org/10.1007/s00259-010-1608-9 PMID: 20821206

[66] Van Nostrand D, Khorjekar GR, O'Neil J, *et al.* Recombinant human thyroid-stimulating hormone versus thyroid hormone withdrawal in the identification of metastasis in differentiated thyroid cancer with 131I planar whole-body imaging and 124I PET. J Nucl Med 2012; 53(3): 359-62. http://dx.doi.org/10.2967/jnumed.111.096016 PMID: 22315442

[67] Smith CD, Grondin R, LeMaster W, Martin B, Gold BT, Ain KB. Reversible cognitive, motor, and driving impairments in severe hypothyroidism. Thyroid 2015; 25(1): 28-36. http://dx.doi.org/10.1089/thy.2014.0371 PMID: 25381990

[68] Giovanella L, Castellana M, Trimboli P. Unstimulated high-sensitive thyroglobulin is a powerful prognostic predictor in patients with thyroid cancer. Clin Chem Lab Med 2019; 58(1): 130-7. http://dx.doi.org/10.1515/cclm-2019-0654 PMID: 31444962

[69] Mourão GF, Rosario PW, Calsolari MR. Low postoperative non-stimulated thyroglobulin as a criterion to spare radioiodine ablation. Endocr Relat Cancer 2016; 23(1): 47-52. http://dx.doi.org/10.1530/ERC-15-0458 PMID: 26503963

[70] 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. http://dx.doi.org/10.1210/jc.2012-3630 PMID: 23430789

[71] Verkooijen RB, Rietbergen D, Smit JW, Romijn JA, Stokkel MP. A new functional parameter measured at the time of ablation that can be used to predict differentiated thyroid cancer recurrence during follow-up. Eur J Endocrinol 2007; 156(1): 41-7. http://dx.doi.org/10.1530/eje.1.02322 PMID: 17218724

[72] Clark P, Franklyn J. Can we interpret serum thyroglobulin results? Ann Clin Biochem 2012; 49(Pt 4): 313-22. http://dx.doi.org/10.1258/acb.2011.011248 PMID: 22589360

[73] Thomas N, Gent ML, Tulchinsky M. Thyroglobulin Levels Relative to the 24 Hour Radioiodine Uptake in the Thyroid Bed May Help Identify Residual Disease Post-Thyroidectomy in Differentiated Thyroid Carcinoma Washington. DC: Endocrine Society 2015. Available at: https://endo.confex.com/endo/2015endo/webprogram/Paper21538.html

[74] Feine U, Lietzenmayer R, Hanke JP, Held J, Wöhrle H, Müller-Schauenburg W. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. J Nucl Med 1996; 37(9): 1468-72. PMID: 8790195

[75] Nahas Z, Goldenberg D, Fakhry C, *et al.* The role of positron emission tomography/computed tomography in the management of recurrent papillary thyroid carcinoma. Laryngoscope 2005; 115(2): 237-43. http://dx.doi.org/10.1097/01.mlg.0000154725.00787.00 PMID: 15689742

[76] Lee JW, Min HS, Lee SM, Kwon HW, Chung JK. Relations Between Pathological Markers and Radioiodine Scan and (18)F-FDG PET/CT Findings in Papillary Thyroid Cancer Patients With Recurrent Cervical Nodal Metastases. Nucl Med Mol Imaging 2015; 49(2): 127-34. http://dx.doi.org/10.1007/s13139-015-0324-6 PMID: 26085858

[77] Wiebel JL, Esfandiari NH, Papaleontiou M, Worden FP, Haymart MR. Evaluating Positron Emission Tomography Use in Differentiated Thyroid Cancer. Thyroid 2015; 25(9): 1026-32. http://dx.doi.org/10.1089/thy.2015.0062 PMID: 26133765

[78] Caetano R, Bastos CR, de Oliveira IA, *et al.* Accuracy of positron emission tomography and positron emission tomography-CT in the detection of differentiated thyroid cancer recurrence with negative (131) I whole-body scan results: A meta-analysis. Head Neck 2016; 38(2): 316-27. http://dx.doi.org/10.1002/hed.23881 PMID: 25251544

[79] Haslerud T, Brauckhoff K, Reisæter L, *et al.* F18-FDG-PET for recurrent differentiated thyroid cancer: a systematic meta-analysis. Acta Radiol 2016; 57(10): 1193-200. http://dx.doi.org/10.1177/0284185115594645 PMID: 26163534

[80] Cherk MH, Kalff V, Yap KS, Bailey M, Topliss D, Kelly MJ. Incidence of radiation thyroiditis and thyroid remnant ablation success rates following 1110 MBq (30 mCi) and 3700 MBq (100 mCi) post-surgical 131I ablation therapy for differentiated thyroid carcinoma. Clin Endocrinol (Oxf) 2008; 69(6): 957-62. http://dx.doi.org/10.1111/j.1365-2265.2008.03276.x PMID: 18419785

[81] Ho AL, Grewal RK, Leboeuf R, *et al.* Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med 2013; 368(7): 623-32. http://dx.doi.org/10.1056/NEJMoa1209288 PMID: 23406027

[82] Banerjee M, Wiebel JL, Guo C, Gay B, Haymart MR. Use of imaging tests after primary treatment of thyroid cancer in the United States: population based retrospective cohort study evaluating death and recurrence. BMJ 2016; 354: i3839. http://dx.doi.org/10.1136/bmj.i3839 PMID: 27443325

[83] Kaul S, Tulchinsky M, Campbell DB, Crist HS, Manni A. Isolated cardiac metastasis from papillary thyroid cancer: prolonged survival with late diagnosis related to inadequate positron emission tomography preparation. Thyroid 2012; 22(4): 443-4. http://dx.doi.org/10.1089/thy.2011.0295 PMID: 22376168

[84] Avram AM, Dewaraja YK. Thyroid Cancer Radiotheragnostics: the case for activity adjusted ^{131}I therapy. Clin Transl Imaging 2018; 6(5): 335-46. http://dx.doi.org/10.1007/s40336-018-0291-x PMID: 30911535