SNMMI procedure standard/EANM practice guideline for nuclear medicine evaluation and therapy of differentiated thyroid cancer /2022

SNMMI PROCEDURE STANDARD/EANM PRACTICE GUIDELINE FOR NUCLEAR MEDICINE EVALUATION AND THERAPY OF DIFFERENTIATED THYROID CANCER

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Remember

- Certain cytologies are indeterminate, such as follicular neoplasm (or suspicious for follicular neoplasm) and the newly defined non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

- In such cases, FNA can be complemented by the assessment of specific molecular alterations (e.g. BRAF or TERT mutations, RET fusions) as well as molecular imaging with 99mTc-MIBI or 18F-fluorodeoxyglucose (FDG).

Remember

- Cervical lymph nodal metastases occur in 20–60% of patients with DTC and this nodal involvement varies from clinically relevant macrometastasis to seemingly clinically irrelevant micrometastases. (14, 15)

- Positron emission tomography/computed tomography (PET/CT) with 18F-FDG could be perfomed preoperatively in more aggressive DTC histotypes (i.e. poorly differentiated thyroid cancer or Hürthle cell carcinoma) and anaplastic thyroid cancer. (17)

Post-operative I131 therapy

- **The goal of therapeutic 131I:**

- - to eliminate normal thyroid tissue remnant in low-risk patients, thereby ensuring undetectable or minimal serum Tg levels (in the absence of neoplastic tissue), which facilitates follow-up (***remnant ablation***)

- - to irradiate suspected but unproven sites of neoplastic cells in low-intermediate and intermediate risk patients as determined by histopathologic features, thereby reducing the risk of disease recurrence (***adjuvant treatment***)

Post-operative I131 therapy

- - to treat persistent or recurrent disease in patients with demonstrated metastatic disease (***treatment of known disease***)

Table 1. Differentiated thyroid cancer: clinical and pathological characteristics. (5)

Histological subtypes	Morphology	Molecular markers	Pattern of Spread	RAI avidity
Papillary thyroid cancer (PTC)	Classical papillae Clear nuclei	BRAF V600E, RET/PTC fus	Lymph nodes	++++
PTC-Follicular variant (fvPTC)	Follicular structures Clear nuclei	BRAF K601E, RAS, PAX8/PPARγ	Lymph nodes	+++++
PTC-Aggressive variants*	Specific cell features and structural changes	BRAF V600E, 1q amp, TERT promoter	Lymph nodes Lung	+++
Follicular thyroid cancer (FTC)	Capsular invasion (MI) Vascular invasion (WI) Extrathyroidal invasion (WI)	RAS, PAX8/PPARγ, PTEN, TSHR, TERT promoter	Lung Bone	+++++

(*) tall, columnar, solid, hobnail variants.

Table 1. **Differentiated thyroid cancer: clinical and pathological characteristics**. (5)

Hurthle cell thyroid carcinoma	Hurthle cells	RAS, PAX8/PPARγ, PTEN, TSHR, chromosomal loss, mitochondrial DNA mutations, TERT promoter	Lung Bone	++
Poorly differentiated thyroid cancer (PDTC)	Invasion Mitoses >3 Necrosis Convoluted nuclei	RAS, TERT promoter, TP53, PIK3CA, PTEN, CTNNB1, AKT1, EIF1AX, ALK fus	Lymph nodes Lung Bone	+/-
Anaplastic thyroid cancer	Undifferentiated cells with immunoistochemical or ultrastructural features of epithelial origin but of morphological and immunophenotypic markers of thyroid origin	TP53, TERT promoter, PI3K/AKT/mTOR, SWI/SNF subunts, RAS, EIF1AX, BRAF	Local invasion Lung Bone Lymph nodes	-

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

Thyroglobulin

- Tg is subsequently metabolized in the liver with a mean elimination half-life (Tg t1/2) of 65.2 hours.(27)
- Correct timing of serum sampling for Tg measurement in regards to surgery is important, and measurements should not be performed sooner than 25 days after total thyroidectomy to allow for clearance of the post-surgical Tg peak (10 x Tg t1/2).(27)

- Tg levels must always be interpreted in the context of concomitant TSH level (unstimulated vs. stimulated Tg) and type of TSH stimulation (endogenous vs. exogenous). (28)

Tg Ab

- Thyroglobulin autoantibodies (TgAb) need to measured in conjunction with Tg in each serum sample provided for Tg testing.
- Every specimen needs TgAb testing to authenticate that the Tg measurement is not compromised by TgAb interference.
- When present, TgAb concentrations per se can be monitored as a surrogate tumor marker. (29)

- **Patient preparation for optimal 131I uptake by residual thyroid tissue and metastatic disease includes 1-2 weeks of low iodine diet (LID) and adequate TSH stimulation (TSH ≥ 30 mIU/L measured 1 - 3 days prior to 131I administration) by either thyroid hormone withdrawal (THW) or recombinant human TSH (rhTSH) stimulation.(30) (31).**

- However a recent paper showed that lower TSH levels may be sufficient for remnant ablation without influencing remnant ablation success rates. (32)

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32. Vrachimis A, Riemann B, Mader U, Reiners C, Verburg FA. Endogenous TSH levels at the time of (131)I ablation do not influence ablation success, recurrence-free survival or differentiated thyroid cancer-related mortality. Eur J Nucl Med Mol Imaging. 2016;43(2):224-31.

Low Iodine Diet (LID)

- In preparation for 131I therapy the state of iodine deprivation induced by LID is considered ***adequate*** when spot urinary iodine < 100 mcg/L, and ***optimal*** when urinary iodine < 50 mcg/L (or I/Cr ratio < 50 mcg/g Cr). (38) (39)

- **A study of 101 patients comparing a 2-week vs. 4-week LID showed no significant difference in urinary iodine levels, both periods resulting in optimal I/Cr ratio for 131I therapeutic administration (i.e. < 50 mcg/g Cr).**

Table 2: Specific dietary instructions for preparatory low-iodine diet

Recommended Low-Iodine Diet Prior to Radioiodine Scintigraphy and Therapy (41)		
	ALLOWED	**RESTRICTED**
Baked goods, Pasta	Flour, oatmeal, wheat, macaroni, noodles, pancakes, spaghetti, homemade bread prepared with non-iodized salt	Cereals, rice, granola, popcorn; industrialized biscuits, breads, crackers
Meat, Poultry, Eggs	Beef, lamb, chicken, turkey, pork, veal; eggs-(max 2 eggs per week)	All seafood (fish, shrimp, oysters, clams, etc); processed, cured, smoked or breaded meats
Condiments	Salt-free margarine, vegetable oil, mayonnaise, sugar, jelly, honey	Iodized salt, pickles, white sauce, meat sauces, creamy sauces, soy sauces, agar-agar, unsalted nuts, vinegar or alginate additives, red colorants
Fruits, Juices	All raw fruits and homemade natural juices	Fruit cocktails, canned fruits, dried fruits
Beverages	Water, tea, coffee, wine, alcoholic drinks	Milk and all derivatives (yogurt, ice cream, cheese), soy beverages

Table 2: Specific dietary instructions for preparatory low-iodine diet

Desserts	Homemade cookies, homemade fruit pies, homemade cakes (prepared with non-iodized salt)	Chocolate, pudding, gelatin, ice cream, candies, industrialized desserts, foods with red colorants, molasses
Vegetables	Asparagus, beets, broccoli, cabbage, celery, carrots, cauliflower, corn, cucumber, lettuce, mushrooms, onions, peas, potatoes without peel, spinach, sweet potatoes (baked), tomatoes (fresh), zucchini	All canned vegetables, potatoes with peel, french fries, candied sweet potatoes, onion rings, beans
Combination Dishes	Homemade dishes prepared with allowed ingredients	Pizza, lasagna, macaroni and cheese, industrialized foods and foods with conservants
All dishes must be prepared with non-iodized salt. Avoid eating in restaurants.		

There are 2 major approaches for obtaining TSH stimulation:

- *Endogenous TSH stimulation :*

a) L-T4 (levothyroxine) withdrawal for 4 weeks; this interval is determined by T4 elimination half-life (T4 t1/2) of 7 days and the physiologic pituitary response to declining T4 concentrations.

- ❑ the TSH measurement of > 30 mIU/L in case of *metastatic disease* (43).

- ❑ Lower TSH levels may be sufficient for thyroid remnant ablation in *low-risk patients,* according to a single study which did not find any influence of TSH levels on post-operative 131I remnant ablation success (defined as stimulated Tg < 1 ng/mL).

- The study involved 1873 patients without distant metastases, majority (~80%) stage I-II disease (of which 15% had TSH < 30 mU/L and demonstrated higher median Tg levels, suggestive of larger volume of thyroid remnant tissue).

- **The area under the curve obtained by the TSH level plotted against time may achieve sufficient stimulation to result in the uptake of therapeutically effective 131I activities for ablation of thyroid tissue remnants which have high constitutive NIS expression and function (32).**

Notice

- However, the Guidelines Committee advises that this study findings cannot be extrapolated to high-risk patients and/or patients undergoing further 131I therapy for recurrent, persistent, or metastasized disease.

b) T4/T3 (levothyroxine/liothyronine) substitution

- for the first 2 weeks, followed by discontinuation of T3 for 2 weeks; this interval is based on T3 t1/2 of 0.75 days.
- In practice, T4 is stopped one day and T3 is started the next day in a typical dose of *25 mcg once or twice daily* (depending on patient's age and body weight).
- This regimen is well tolerated and has the advantage of minimizing hypothyroid symptoms. (44)

- For patients with limited pituitary functional reserve, it is advisable to proceed with administration of exogenous TSH stimulation (rhTSH injections) to avoid further delay in 131I therapy administration and limit hypothyroid symptoms (rhTSH augmentation protocol).

Exogenous TSH stimulation:

- **TSH elevation is obtained through administration of rhTSH (Thyrogen ® Stimulation Protocol): 0.9 mg rhTSH injection is administered intramuscularly on 2 consecutive days, followed by 131I therapy administration at 48-72 hours. (45)**

- When diagnostic 131I scan is performed as an integral part of 131I therapeutic protocol (*theragnostics*), the tracer 131I activity is administered after the 2nd rhTSH injection and WBS scan is obtained 24 hours later, followed by subsequent 131I therapy administration.

THW vs. rhTSH ?

- **The balance of the published data shows that for normal thyroid tissue (i.e. thyroid remnant ablation), rhTSH and THW stimulation are equivalent,**
- However, metastatic thyroid cancer has lesser density and poorer functionality of NIS, and therefore TSH elevation over time (area under the curve of TSH stimulation) is important to promote increased 131I uptake and retention in tumors. (46, 47).
- **In the setting of metastatic disease, it is possible to use rhTSH stimulation on an off-label basis.**

THW vs. rhTSH ?

- However, the combination of THW preparation and **dosimetry-guided 131I therapy** are favored when clinically safe and the necessary expertise for dosimetry is available. (45, 48, 49)
- However, tumor vs. critical organ (e.g., bone marrow, lung) radiation absorbed dose (Gy) after rhTSH vs. THW- stimulation protocols need further evaluation.
- Furthermore, no studies have yet been performed comparing rhTSH and THW in patients with distant metastases regarding patient-relevant outcome measures (i.e., survival).

Adjuvant Therapy

- There is no clear data in literature allowing us to assess which of the two alternatives is better in the setting of adjuvant therapy separately from the setting of remnant ablation, especially with modern criteria for excellent response.
- **However, rhTSH is registered for use for initial post-operative 131I therapy in patients up to and including N1 M0 disease.**

Post-operative thyroglobulin measurement

- **Its predictive value is significantly influenced by a wide variety of factors, as follows:**

1 - the amount of residual thyroid cancer and/or thyroid remnants,

2 - the TSH level at the time of Tg measurement,

3 - the functional sensitivity of the Tg assay,

4 - the time elapsed since total thyroidectomy,

5 - the Tg cutoff used for analysis,

6 - and the individual risk of having radioiodine-avid loco- regional or distant metastasis. (50)

Tg interference by Tg Ab & Heterophile Ab

- Immunometric Tg assays may also be subject to **high-dose hook effect**, leading to inappropriately normal or low serum Tg values in sera with very high Tg concentrations, which require dilution for accurate measurement. (52)

In a retrospective study, Matrone et al.

505 low- to intermediate-risk DTC patients

No	Tg (Ng/mL)	Persistence or metastasis	%
150	<0.1	1	0.67
287	0.1<till<1	15	5.23
68	>1	11	16.2

Type of Disease

Persistence or metastasis	
1	Cervical Persistance
15	Nodal or distant metastasis
11	Neck metastasis

LT4 On

- This paper submits further evidence that basal Tg < 1 ng/mL cannot be used to rule out the presence of distant metastases; two of the four patients with distant metastases had Tg levels of 0.11 ng/mL and 0.12 ng/mL, respectively.

RADIOIODINE THERAPY PLANNING

There are two approaches to 131I therapy delivery:

- functional imaging-guided approach; *theragnostics* :

the approach integrating functional imaging information obtained with post-operative Dx radioiodine (123I, 131I or 124I) scans in the management algorithm,

- risk-adapted approach :

based on clinical- pathologic factors and institutional protocols

Management integrating functional diagnostic radioiodine imaging

- This *theragnostic* approach to 131I administration involves the acquisition of a postoperative Dx radioiodine (123I, 131I or 124I) scan for planning 131I therapy.

- **Dx whole body scans (WBS) are performed with the intent of identifying and localizing regional and distant metastatic disease, as well as evaluating the capacity of metastatic deposits to concentrate 131I.**

Theragnostic Approach

- Also, unnecessary ^{131}I therapy may be avoided if Dx WBS finds no evidence of residual thyroid tissue or metastatic disease and the stimulated Tg is <1 ng/mL in the absence of interfering TgAb. (59)

- A study comparing the diagnostic sensitivity for disease detection for Dx. 74-185 MBq (2–5 mCi) ^{123}I WBS versus 111–185 MBq (3–5 mCi) ^{131}I WBS (both performed after THW protocol) demonstrated that, although ^{123}I is adequate for imaging residual thyroid tissue, it appears to *be less sensitive* than ^{131}I for imaging thyroid cancer metastases: ^{123}I missed metastases shown by ^{131}I in the neck, mediastinum, lungs, and bone.
- No lesion was better seen with ^{123}I than with ^{131}I.

Theragnostic Approach

- Depending on the type of patient preparation, Dx. radioiodine (^{123}I or ^{131}I) activities such as 37 – 74 MBq (1-2 mCi) for THW protocols and 110-148 MBq (3-4 mCi) for rhTSH-stimulation protocols are frequently used. (39)

- **The higher tracer activity (3-4 mCi) employed for the rhTSH-stimulation protocols is to compensate for the competitive inhibition exerted by the iodine content of L-T4 (levothyroxine) on the uptake of radioiodine (^{131}I or ^{123}I) in thyroid tissue or metastatic lesions. (74)**

Theragnostic Approach

- For Preparation , LT4 replacement by LT3 , in rhTSH stimulation method ,strengthen radioiodine uptake in metastatic lesions.

- **Optimization of imaging acquisition parameters and current *SPECT/CT gamma camera technology* permit good quality visualization of distant metastatic disease using 37 MBq (1 mCi) ^{131}I Dx. activity. (71, 72, 77,78).**

post-therapy whole-body scan

- In all cases, ^{131}I therapy administration should be followed by a post-therapy whole-body scan (PT-WBS) to determine therapeutic ^{131}I localization which is routinely used to complete post-operative staging.

- ✓ However, the day to perform the PT-WBS after therapeutic ^{131}I administration remains controversial, ranging from *2–10 days*.

Early & Late PT-WBS

PT-WBS acquisition on two separate days may be valuable as demonstrated by Salvatori et al. in a group of 134 patients who underwent both early (at 3 days) and delayed (at 7 days) scans:

- 80.5% of detected lesions were oncordant on both early and delayed scans;
- however, 7.5% lesions were detected only on the early scans, while 12% lesions were detected only on the delayed scans.

(80)

Early & Late PT-WBS

- By performing both early (at 3 – 6 days) and delayed (at 10 – 11 days) PT-WBS, *Hung et al.* reported that 28% of nodal metastases, 17% of lung metastases and 16% of bone metastases were visible only on the early scans. (81)

Late PT-WBS

A. However, delayed PT-WBS acquisition provides the advantage of increased contrast resolution due to time-dependent ^{131}I clearance from normal tissues: *Chong et al.*

Hybrid imaging

- Hybrid imaging with *SPECT/CT* improves the accuracy of PT-WBS and should be done whenever possible.
- A systematic review of 14 original research articles describing the incremental value of ^{131}I *SPECT/CT* demonstrated significant clinical benefit in terms of staging, risk stratification, alteration of management and/or follow-up of DTC. (85)

Hybrid imaging

- Dx. WBS scintigraphy performed in follow-up evaluation after initial post-operative 131I administration is important to : 1) establish a new baseline after postoperative 131I therapy, (89)

  2) determine interval response to 131I treatment, and

  3) assess the patient's thyroid cancer status.

❑ Along with basal and stimulated Tg testing and cross-sectional anatomic imaging, the results of follow-up Dx WBS contribute to dynamic risk restratification, which is usually performed at 6 – 12 months after initial treatment strategy

Hybrid imaging

- For patients with rising Tg levels, Dx WBS and PET/CT evaluation can be scheduled sequentially to asses for recurrent and/or metastatic disease and evaluate tumor biologic behavior for determining if the patient would benefit from additional 131I therapy. (73)

SEER database

- Importantly, a recent report examining the results of a large SEER database (28,220 patients diagnosed with DTC between 1998 and 2011) showed that follow-up Dx WBS performed after primary treatment of DTC are the only imaging studies associated with improved disease-specific survival, demonstrating the clinical benefit of ^{131}I theragnostics for DTC management (90).

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

- **Empiric activity selection is the most commonly used approach in advanced DTC, in which the nuclear medicine physician chooses an activity based on convention, availability, experience with various imaging modalities and patient-related parameters.**

- ✓ With this therapeutic approach patients are most commonly given activities of 1.1 GBq (30 mCi), 1.85 GBq (50 mCi), 3.7GBq (100 mCi), 5.6 GBq (150 mCi), or 7,4 GBq (200 mCi). (91)

Empiric Approach

i. Radioiodine-avid diffuse bilateral lung metastases were associated with a lowering of MTA to less than 9.25 GBq (250 mCi). (94)

I. In conclusion, caution should be exercised in applying an empiric approach with activities greater than 5.6 GBq (150 mCi), especially in the elderly, in patients with radioiodine-avid diffuse bilateral pulmonary metastases, and renal insufficiency. (93)

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Empiric Approach

- . However, it is essential to emphasize that maximum tolerated activity (MTA) can be exceeded in patients undergoing empiric ^{131}I therapy escalation for treatment of advanced DTC, which may cause acute dose-related toxicities.

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Empiric and Dosimetry-based prescribed activities of ^{131}I

- Klubo-Gwiezdzinska et al. :

  - Patients treated with the dosimetry-based strategy were 71% less likely to progress (odds ratio 0.29) and more likely to achieve complete response compared to those treated with empiric activities (odds ratio 8.2).

  - In the dosimetry-based group, there was a positive correlation between the complete response and percentage of MTA given as the first treatment of ^{131}I.

- Complete response was especially pronounced in patients with the locoregional disease treated according to dosimetric strategy (35.7 *vs.* 3.3% in empiric strategy group).

- The current evidence, although potentially biased, suggests that dosimetry-based high-activity ^{131}I therapy in patients with advanced DTC may be more effective in improving patients' outcomes and survival.(100, 101)

- Each ^{131}I therapy should be followed by post-therapeutic ^{131}I imaging (PT-WBS).

- There are distinct advantages offered by post-surgery ^{131}I activity administration for all risk stratification categories and irrespective of post-operative thyroglobulin levels, confirming the role of PT-WBS for early detection and treatment of local-regional and distant metastatic disease.

- A low stimulated Tg ≤ 2 ng/ml did not exclude the presence of distant metastases,
  - The body of published evidence regarding the outcome of postoperative ^{131}I ablation in low-risk patients (which in current terminology would encompass both remnant ablation and adjuvant treatment) demonstrates that these patients can be fully reassured by a complete treatment response and would not require Tg stimulation testing or periodic neck US examinations during long-term follow-up.(103)

- 572 - In fact, cohorts in which all patients, - including low-risk ones with non-metastasized, non-microcarcinoma disease, - received ^{131}I therapy after surgery, demonstrated that life expectancy is normal for > 85% of patients – only patients with stage IV disease at diagnosis have a reduction of life expectancy. (104, 105)

- 579 - Finally, early reassurance and more reliable follow-up are only possible when patients had received total thyroidectomy followed by postoperative ^{131}I therapy.

577 - In conclusion, as detailed above, post-operative Tg levels are helpful in identifying high-risk patients that require higher ^{131}I activity, but cannot be used for ruling-out ^{131}I therapy.

578 - Omission of the procedure exposes the patients to the risk of late diagnosis of residual disease.(106, 107)

DETERMINING THE PRESCRIBED THERAPEUTIC ^{131}I ACTIVITY

584 – 587 :

Current practice guidelines recommend routine ^{131}I adjuvant therapy for patients with intermediate to high risk of recurrence (although there are some differences concerning intermediate risk disease) and avoiding routine ^{131}I therapy for patients with a small (≤1 cm) intrathyroidal DTC and no evidence of locoregional or distant metastatic spread. (6, 91)

591 - 593

- Indeed, the ATA, the EANM, the SNMMI and the European Thyroid Association (ETA) recently published a joint statement acknowledging the absence of high-quality evidence either for or against the post-operative use of ^{131}I in low-risk patients. (20)

Table 3: Suggested framework for ^{131}I therapy

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

* FDA approved the used of rhTSH in combination with 100 mCi ^{131}I for remnant ablation in December, 2007. (146) (147)

606 - 610

- *Treatment of known disease* is performed with 3.7 - 5.6 GBq (100 – 150 mCi) for small volume local-regional disease, and 5.6-7.4 GBq (150-200 mCi) ^{131}I for treatment of advanced local-regional disease and/or small volume distant metastatic disease.

- Identification of iodine-avid diffuse metastatic disease may lead to escalation of prescribed therapeutic ^{131}I activity to ≥ 7.4 GBq (200 mCi) guided by dosimetry calculations. (73, 149, 150).

611 - 617

611. A special circumstance is presented by use of ^{131}I therapy (3.7 GBq [100 mCi]) for ablation of a remaining thyroid lobe after lobectomy/hemithyroidectomy as an alternative to completion thyroidectomy. (151-153).

- Current guidelines propose lobectomy for patients deemed as low-risk for recurrence; however, if the pathology demonstrates a higher risk tumor, then completion thyroidectomy with resection of the contralateral thyroid lobe is recommended with the goal of facilitating post-operative ^{131}I therapy and long- term surveillance.

❑ Therapeutic ^{131}I administration as a subsitute for completion thyroidectomy is not recommended routinely.

617 - 622

- However, it can be used to eliminate the residual thyroid lobe in highly selected cases, such as patients : who had experienced complications during initial surgery (e.g. recurrent laryngeal nerve paralysis), for whom completion thyroidectomy is contraindicated due to other comorbidities, or for patients who decline additional surgery.

- Therearelimiteddataregardingthelong-termoutcomes ofthisapproach.Thedatasuggestsimilarclinical outcomeswithaslightlyhigherproportionofpatients withpersistentlydetectableTg.

Successful ablation of the remaining lobe

- **In a randomized controlled equivalence trial of 136 low-risk DTC patients treated with lobectomy, which compared low- vs. high ^{131}I activities in achieving successful ablation of the remaining lobe, the remnant ablation success rate was significantly higher (75% success rate) using 3.7 GBq [100 mCi], as compared with 1.1 GBq [30 mCi] (54% ablation sucess rate);**

- ✓ mild to moderate short-term neck pain was more frequently reported in the high-activity group (66%) compared with the low-activity group (51%).

(622 – 627)

DOSIMETRY-GUIDED ^{131}I THERAPY

631 -633

- There are two approaches for individualization of ^{131}I therapy based on dosimetry calculations, as follows: (1) blood or bone-marrow dosimetry-based methods, primarily targeting *safety*, and (2) lesion dosimetry-based methods, primarily targeting *efficacy*.

The classic blood-based method

- Of these, the classic blood-based method is more widely used, and permits calculation of the maximum tolerated activity (MTA) that can be administered to an individual patient without the risk of severe hematopoietic toxicity.
- In this dosimetry -based regimen, the radiation absorbed dose to the blood is used as a surrogate for the absorbed dose to the red bone marrow, typically considered as the dose limiting critical organ in the majority of cases.
- An upper limit of 2 Gy to the blood is generally used as the threshold that minimizes serious bone marrow toxicity and pulmonary ^{131}I retention should not exceed 3 GBq (80 mCi) after 48h, , which is based on the findings of the original study of Benua et al. (155)

- To determine the blood activity, whole blood samples (5 ml heparinized aliquots) are collected at multiple time points (2, 24, 48, 72 and 96 hours) during the first week after administration of tracer amount (e.g. 15 - 74 MBq [0.4 - 2 mCi]) ^{131}I activity and measurements are performed in an accurately calibrated (for ^{131}I) well counter.

- To determine the whole-body activity, serial measurements are performed

  with either a dual head Gamma camera or a scintillation probe.

654 -659

- The therapeutic ^{131}I activity that can be safely administered while maintaining blood radiation absorbed dose ≤ 2 Gy) can then be determined based on this pre-therapy predicted radiation absorbed dose to the blood. (157)
- Further restrictions to MTA recommend that the administered therapeutic activity does not exceed 4.44 GBq (120 mCi) ^{131}I whole-body retention at 48 h, or 3 GBq (80 mCi) ^{131}I whole-body retention at 48 h if pulmonary metastases are present. (155)

lesion-based dosimetry

- The goal of lesion-based dosimetry is calculation of individualized ^{131}I therapeutic activity that would deliver sufficient radiation absorbed dose to target for achieving maximum therapeutic effect, while minimizing the risk for side effects on non-target tissues.

- . However, to date there is no validated method to determine the remnant or metastatic tissue mass, which gives high uncertainty to the lesion-dosimetry.

lesion-based dosimetry

- For instance, Maxon et al proposed a value of 300 Gy to thyroid remnants and 80 Gy to lymph nodal metastases,(158) Flux et al. a value of at least 49 Gy to thyroid remnants, (159) and Wierts et al. a value of 90 Gy to thyroid remnants and 40 Gy to lymph nodal metastases. (160)

RADIOIODINE TOXICITY : ACUTE AND CHRONIC SIDE EFFECTS OF RADIOIODINE THERAPY

674 - 683

- Oral ^{131}I is rapidly absorbed in the stomach and duodenum, and concentrated in the thyroid tissue, salivary and lacrimal glands, and in the breast tissue during pregnancy and lactation (estrogen-priming of transient NIS expression in ductal epithelial cells). This occurs through the action of the NIS,

- The emitted beta particles cause cellular damage which, if enough radiation enters the cell, will not be reparable.

Acute ^{131}I toxicity

- Numerous salivary glands concentrate ^{131}I rapidly, including : the paired submandibular, submaxillary, and parotid glands , as well as several hundred 1 - 2 mm diameter salivary glands in the buccal, labial, and lingual mucosa, hard palate, floor of the mouth, tongue, and throat.

- Because of the iodine-concentrating glands throughout the mouth, as well as from secreted radioactive saliva, *painful stomatitis and glossitis* may also occur in up to 20% of patients.

691 - 696

- A*cute sialadenitis* characterized by pain and swelling of the salivary glands occurring within 48 hours of ^{131}I therapy has been reported in 13 - 50% of patients. (161, 162)
- The risk of salivary gland dysfunction increases with higher ^{131}I therapeutic activities (>3.7 GBq [100 mCi] for xerostomia; > 5.5 GBq [150 mCi] for sialadenitis). (148)

- However, the incidence of these salivary gland and oral adverse reactions can be ameliorated to as low as 1 - 5% by prolonged salivary stimulation and scheduled multiple efforts at washing out the mouth with water over several days.

- Protective measures to minimize acute salivary side effects consist of hydration, the use of lemon candies or lemon juice and salivary gland massage with the goal of stimulating salivary drainage and decreasing radiation absorbed dose to the salivary glands, however the optimal time to start, frequency and duration of salivary gland stimulation are not standardized. (148)

- Preparation by rhTSH stimulation results in lesser radiation absorbed doses to normal organs (including the salivary glands) due to faster ^{131}I clearance in euthyroid state as compared to hypothyroid state, therefore definitive conclusions about the salivary gland effects of lemon stimulation cannot be reached based on published ^{124}I salivary dosimetry data obtained in different patient groups.

- There is strong evidence that continuous sialagogues administration beginning shortly after ^{131}I therapy and continued through the first several days (and nights), significantly reduces the radiation absorbed dose to the salivary glands. (163, 170)

- *Dysgeusia* (taste dysfunction) results from damage of the small mucous salivary glands in the vicinity of the taste buds and is a temporary side effect of ^{131}I therapy lasting several weeks post-treatment. (171)

- *Radiation gastritis* and *enteritis* are not uncommon from radiation damage to the mucosa of the upper gastrointestinal tract, causing anorexia, nausea, and occasional emesis with an incidence as high as 30%.

❖If post-therapy *emesis* occurs just hours after ^{131}I ingestion, the treating physician does not know how much of the therapeutic activity was absorbed but cannot immediately retreat, as cumulative ^{131}I toxicity from the two administrations may occur.

- *Radiation thyroiditis* is a serious but uncommon complication following relatively large ^{131}I therapeutic activities, occurring when the patient's attempted total thyroidectomy has been inadequate to remove virtually the entire gland.

- This form of thyroiditis can be quite painful, and the residual tissue may swell significantly, rarely compromising the upper airway.

- This is another reason that post-operative diagnostic scintigraphy should be performed prior to therapeutic ^{131}I administration to exclude this possibility.

Chronic ^{131}I toxicity

- The threshold for the induction of permanent sterility in humans is 3.5 Gy for the testis and 2.5 Gy for the ovary.
- However, *male fertility* may be seriously reduced because highly radiosensitive sperm in the testes are exposed to significant radiation from the bladder after therapy, especially at activities in excess of 3.74 - 5.6 GBq (100 - 150 mCi).(175)

✓ In a series of 40 young men treated for DTC, sperm counts decreased by 3 months after therapeutic ^{131}I activity of 3.7 GBq (100 mCi), returning to normal by 13 months. (179).

- Based on this data it is recommended that for patients considered for high ^{131}I therapeutic activities $\geq$ 7.4 GBq ($\geq$ 200 mCi) and who anticipate fertility, sperm storage should be considered before ^{131}I therapy.

Chronic ^{131}I toxicity

- Aggressive hydration for several days following ^{131}I therapy (> 4 L [1 Gal] daily fluid intake) is recommended for diluting excreted ^{131}I in a large volume of urine and increasing urination frequency, with the goal of reducing scattered radiation from the bladder to adjacent gonads.

- *Chronic xerostomia* and *chronic painful sialadenitis* with sialolithiasis can result from salivary gland radiation in about 10% of patients. (163) (183)

Chronic ^{131}I toxicity

- *xerophthalmia.*
- *Epiphora* secondary to lacrimal system damage and subsequent local fibrosis
- High-activity ^{131}I therapy in patients with distant pulmonary metastatic disease carries a risk of *radiation-induced pneumonitis* and *lung fibrosis* when excessive ^{131}I activity is retained in the lungs.
- Progressive pulmonary fibrosis has been reported following repeated ^{131}I therapy in 7% of children with thyroid cancer metastatic to the lungs. (187)

Chronic ^{131}I toxicity

- *Bone marrow suppression* may be seen in pediatric thyroid cancer patients treated with 5.6 - 7.4 GBq (150 - 200 mCi) of ^{131}I, but usually with limited clinical significance.

- However, to avoid significant pancytopenia, especially in older patients with extensive metastatic thyroid cancer requiring larger ^{131}I therapeutic activities, *blooa dosimetry* becomes an important part of therapy planning to avoid radiation absorbed dose to blood (a surrogate of bone marrow dose) in excess of 2 Gy. (155, 157)

Chronic ^{131}I toxicity

- The lactating breast concentrates iodine : The time after receiving radioiodine therapy (and discontinuing lactation) required for the infant both to receive an effective dose < 1 mSv and thyroid dose < 10 mSv was calculated to be least **52 days**.

- ^{131}I administration needs to be postponed for several months for allowing physiological breast tissue involution after lactation. (190)

- ^{123}I scintigraphy can be performed to help confirm breast tissue involution and functional suppression of NIS expression in mammary glands by demonstrating lack of ^{123}I uptake within the breast. (191)

RISK OF SUBSEQUENT PRIMARY MALIGNANCIES AFTER ^{131}I THERAPY FOR DTC

2nd Malignancies after ^{131}I

- No definite threshold for administered ^{131}I activity as an etiology of a second primary malignancy has been identified at this time.
- Minimum follow-up for detection of radiogenic-induced malignancy should probably be at least 10 years. / Second primary malignancies identified prior to 4 years post ^{131}I therapy should be presumed to be co-incidental and not related to ^{131}I therapy. (192)
  - Several studies found no evidence of increased incidence of second primary malignancy (solid tumors or leukemia) in thyroid cancer patients treated with ^{131}I. (194-198)

2nd Malignancies after ^{131}I

- *Leukemia* - Several studies found no statistically significant increased risk of leukemia after ^{131}I therapy. (195, 196, 199, 200)
  - Rubino et al. evaluated three large cohorts of Swedish, French and Italian patients and found an excess of 3 cases of leukemia per 10,000 patients (0.03%; RR = 2.5). (201)
  - *Salivary gland cancers* - There is a small but apparently real increased incidence
  - *Breast cancer* Women with a history of thyroid carcinoma have a greater than expected risk of developing breast cancer, this risk being most pronounced in premenopausal white women. (198)
  - Premenopausal women (age 20 - 49 years) with an index DTC diagnosis have a significantly increased risk of developing subsequent breast carcinoma (RR= 1.42; P = 0.001), while women with index breast cancer do not have an increased risk for DTC. (205)

2nd Malignancies after ^{131}I

- In an extensive analysis performed in 2020 Reiners et al. concluded that ^{131}I therapy for thyroid cancer did not increase the risk of breast cancer. (202)

- ***Other solid tumors*** – After a mean follow up of 13 years Rubino et al. found a slight excess of 53 solid tumors per 10,000 patients over 10 years, per administered activity of 3.7 GBq (100 mCi). (201)

Overall, the incidence of salivary gland cancers and leukemia is small but real. Increased incidence of breast cancer from ^{131}I therapy for thyroid cancer has not been demonstrated. Increased incidence of other solid malignancies is seen in some studies but not in others. Verkooijen et al. suggests that there may be a common etiologic or genetic mechanism instead of a causal relationship. (197)

THYROID HORMONE THERAPY AND SURVEILLANCE STRATEGY

- **After 131I therapy patients receive levothyroxine (L-T4) therapy with the goal of TSH suppression depending on the patients' risk stratification (0.1 - 0.3 mU/L for patients with regional metastases and < 0.1mU/L for patients with distant metastases). (6)**

- European Thyroid Associations recommends that L-T4/L-T3 therapy should be considered under specific circumstances and for selected patients, especially hypothyroid patients without residual thyroid function and those with persistent symptoms of impaired well-being and cognitive dysfunction despite adequate L-T4 doses. (212)

Serum Tg measurement is employed for monitoring DTC status after primary therapy. However, the usefulness of following Tg is limited in patients who have anti-Tg antibodies (TgAb) because the serum Tg levels can be underestimated when using immunometric assays. (52) In these patients the trend of TgAb levels over time can serve as a surrogate tumor marker (29). Immune memory in patients with a background

levels should be interpreted with caution for at least 6 months after ^{131}I therapy. (51) During long-term surveillance the TSH-suppression target is adjusted taking into consideration the outcome of primary therapy according to dynamic risk restratification: in patients with a structural incomplete response serum TSH is maintained < 0.1 mIU/L indefinitely, while target values of 0.5 - 2 mIU/L and 0.1 - 0.5 mIU/L are adopted in low- to intermediate-risk, and high-risk patients with excellent response, respectively. Finally, TSH target

RESPONSE ASSESSMENT AFTER PRIMARY THERAPY

Accordingly, the use of US should be limited (particularly in low-risk DTC) and, in the absence of TgAb, reserved only for patients with unstimulated serum Tg levels ≥1 ng/mL. (103)

In combination with Tg measurement, follow-up DxWBS are helpful for therapy response evaluation and to identify patients with suspected non-iodine avid metastatic disease (based on elevated basal and/or stimulated Tg and negative WBS), which will prompt further investigation with ^{18}F-FDG PET/CT and/or diagnostic CT scan for localizing structural persistent disease. (73, 213, 214)

Table 4. Response to therapy in DTC patients: dynamic risk stratification criteria [modified from (6)]

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

- **excellent response** to therapy the risk of disease recurrence is 1 - 4%, which for *intermediate-risk patients* (whose initial risk for recurrence is estimated at 36 - 43%) and for *high-risk patients* (whose initial risk for recurrence is estimated at 68 - 70%) represents a major change in risk when complete response to therapy is achieved.

- The clinical outcomes in patients with **biochemical incomplete response** are usually good:approximately 60% have no evidence of disease over long-term follow-up; 20% patients continue to have persistently abnormal Tg values without structural correlate, and only 20% patients develop structurally identifiable disease over 5 - 10 years follow-up

Patients with **biochemical indeterminate response** do generally well: in 80 - 90% of patients the nonspecific biochemical findings either remain stable or resolve over time with L-T4 suppression therapy alone; however, up to 20% of these patients will eventually develop functional, or structural evidence of disease progression and require additional therapies.

- Patients with **structural incomplete response** require a multidisciplinary management tailored to their disease status (e.g. regional vs. distant metastases; iodine-avid vs. non-iodine avid disease). (6); depending on the results of such additional treatment patients may be re-stratified according to the criteria above.

- Importantly, the dynamic risk restratification has been validated only in patients treated with complete thyroid ablation (i.e. [near-] total thyroidectomy and post-operative ^{131}I therapy). Evidence is not available for patients treated with lobectomy alone, or with thyroidectomy without post-operative ^{131}I therapy. (215)

THERAPY OF ADVANCED DISEASE

- Younger patients and those with single-organ metastases and low disease burden have the best outcome. (60)

- About two-thirds of patients have radioiodine-avid distant metastases and more than 40% of the latter will achieve remission after ^{131}I treatments.(60) However, a minority of DTC cases loses the ability to concentrate iodine in sufficient quantities to allow therapeutically effective radiation absorbed doses to DTC lesions (i.e., radioiodine-refractory DTC).

- In regard to various proposed classifications of radioiodine refractory disease, the criterion with the best predictive value that a patient has radioiodine refractory disease and will not response to another ^{131}I treatment is the patient progressing after a short time interval after the administration of a maximum safe ^{131}I therapeutic activity

Table 7. Additional Options prior to radioiodine refractory classification

- Consider a "blind" ^{131}I therapy (see text)
- Refer the patient to a site that performs dosimetry
- Refer the patient to a site that routinely manages metastatic DTC
- Consider exploring the patient's eligibility for participating in a study that offers "re-sensitizing" or "redifferentiating" agents to see if radioiodine uptake can be re-established or increased for a potential ^{131}I therapy

- In cases of confirmed systemic progression of radioiodine refractory disease, intravenous chemotherapy with doxorubicin was traditionally used, but a partial response was obtained only in a small minority of patients

- More recently “targeted” therapies, including the multikinase inhibitors (MKI) (e.g., sorafenib and lenvatinib) have been approved by the US Food and Drug Administration and European Medicines Agency for patients with advanced radioiodine refractory DTC. These drugs have been shown to induce periods of progression-free survival (rarely remission). However, they do not increase cancer-specific survival and may be associated with significant side effects, such as hypertension, diarrhea, hand/foot skin reactions, rash, fatigue, mucositis, loss of appetite, and weight loss. (218)

- It remains unclear which patients will benefit from MKI in terms of an increase in quality adjusted life years and the optimal time to start therapy, especially in asymptomatic patients

Advanced Disease

- Focally-targeted treatment (i.e., resection, vertebroplasty, external beam radiation therapy and thermal ablation) can provide local control, provide symptomatic relief and delay initiation of systemic therapy.

- Treatment with bisphosphonates or denosumab can delay time to skeletal related events. (233)

- Experimental data showed that MAPK signaling pathway inhibition using MEK or BRAF inhibitors may restore radioiodine avidity.

Advanced Disease

- selective MEK inhibitors (selumetinib, trametinib),
- BRAF inhibitors (dabrafenib, vemurafenib),

18F-FDG PET/CT IMAGING FOR THYROID CANCER

“flip - flop” phenomenon

- ***Type I pattern*** is characterized by *negative* 131I /*positive FDG uptake* and it is the most commonly encountered pattern **.(** **Tg+/scan-** **)** = 46%

- ***Type II pattern*** is characterized by *positive* 131I /*negative FDG uptake* and it represents the most favorable context for therapeutic radioiodine.
- ***Type III pattern*** consists of a combination of type I and II patterns recognized in different metastatic lesions within the same patient due to varying biological behavior in metastatic foci.
- ***Type IV pattern*** is characterized by uptake of both 131I and for 18FDG within same metastatic lesions. (236, 237)

- The most common application of PET/CT imaging in DTC is for evaluation of patients with elevated thyroglobulin and negative DxWBS (i.e.Tg+/scan-). (239)

MANAGEMENT ALGORITHM FOR PATIENTS WITH ELEVATED TG AND NEGATIVE DX WBS (TG+/SCAN-)

TENIS syndrome, i.e. thyroglobulin elevation, negative iodine scintigraphy

Step 1: Rule out false negative DxWBS and false positive Tg levels

Step 2: Perform dynamic risk restratification

Step 3: Obtain non-radioiodine imaging

Step 4: Customize management to the location and number of the metastases

Step 3: Obtain non-radioiodine imaging

- The primary tier includes: 1) neck US, 2) ^{18}F-FDG PET/CT imaging, and/or 3) CT of the neck, chest, abdomen and pelvis.
- The secondary tier includes: 1) brain MRI; 2) bone scanning (using ^{99m}Tc methylene disphosphonate [^{99m}Tc MDP] or ^{18}F Sodium fluoride PET-CT [^{18}F-NaF-PET-CT]), and 3) mitochondrial imaging (e.g., ^{99m}Tc-sestamibi, ^{201} Thallium, or ^{99m}Tc-tetrofosmin).
- The tertiary tier includes : somatostatin receptor (SSR) imaging with radiolabeled somatostatin analogs (e.g., ^{99m}Tc-depreotide, 99mTc -EDDA/HYNIC-Tyr3-Octreotide [Tektrotyd], ^{111}In-octreotide and ^{68}Ga-DOTATATE/TOC/NOC). (e.g. Hürthle cell, tall cell, insular variants)

Step 4: Customize management to the location and number of the metastases

- Focally directed therapy needs to be considered for management of unifocal or oligometastatic disease :

  (e.g. surgical resection, external beam radiation therapy, alcohol injection, radiofrequency ablation, cryotherapy, embolization, and/or radioisotope embolization).

18F-FDG PET/CT IMAGING FOR PROGNOSIS OF METASTATIC DTC

- Patients with iodine-avid metastatic DTC tend to have more favorable prognosis with 10-year survival greater than 90%, while non-iodine avid metastatic DTC has a dire 10-year survival of 10%. (251)

- Thyroglobulin doubling time (Tg-DT) has been identified as a prognostic factor, with Tg-DT < 1 year portending poor prognosis and Tg-DT > 2 years signifying good prognosis. (255)

- Robbins et al. demonstrated that in patients with metastatic DTC a positive ^{18}F-FDG-PET/CT scan result predicted a 7 fold increased risk of mortality as compared with patients who had a negative FDG scan. (248)

CONCLUSIONS

- . Early identification of residual nodal and/or distant metastases is particularly relevant for successful ^{131}I therapy of metastatic disease, since patients who achieve a complete response have considerably higher survival rates than patients with structural incomplete responses.
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