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Nuclear Imaging and Therapy of Thyroid Disorders

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Abstract: This chapter reviews the basics of molecular imaging in thyroid disease and special considerations in radioiodine therapy of benign diseases such as Graves' disease, autonomously functioning nodules, and toxic multinodular goiter. It also discusses the use of radioiodine therapy in the setting of differentiated thyroid carcinomas. A brief discussion of peptide receptor radionuclide therapy in medullary thyroid cancer is also included.

Keywords: hyperthyroidism; hypothyroidism; radioiodine treatment; thyroid cancer; thyroid nodules

INTRODUCTION

The most common benign thyroid diseases are hypothyroidism and hyperthyroidism. Hyperthyroid states include Graves' disease, toxic multinodular goiter, toxic adenoma, and destructive thyroiditis (e.g., amiodarone-induced thyroid dysfunction, and factitious hyperthyroidism). Ultrasound is used to determine the size and vascularity of the thyroid gland and to assess the location, size, number,

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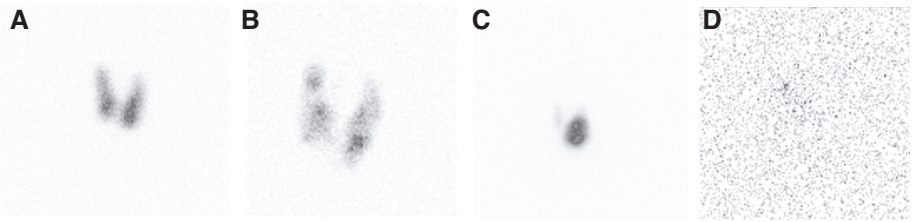

Figure 1. Distribution of RAI in different types of hyperthyroidism. A, Graves' disease; **B**, Toxic multinodular goiter; **C**, Autonomously functioning nodule; **D**, Thyroiditis.

and characteristics of thyroid nodules. Ultrasound and laboratory tests constitute the first-line diagnostic approach to distinguish different benign thyroid disorders (1). Nuclear imaging with radioiodine or ^{99m}Tc-pertechnetate can help assess the functional status of thyroid nodules (hyper or hypo- functioning). It is also useful for characterizing different forms of hyperthyroidism based on specific scintigraphic patterns (Figure 1) and for planning radioiodine therapy. The radioiodine uptake test using the thyroid uptake and probe system provides information for planning radioiodine therapy for hyperthyroidism. Scintigraphy with ^{99m}Tc-sestamibi allows differentiation of type 1 from type 2 amiodarone-induced hyperthyroidism.

THERAPIES FOR HYPERTHYROIDISM

Patients with hyperthyroidism have three options for therapy. Oral medications that decrease thyroid hormone, radioiodine (RAI) treatment, and surgery/thyroidectomy, which are reserved for patients who have obstructive symptoms. Oral medications tend to fail over time or patients may develop toxicities related to the medications, often demonstrated by elevated transaminases. At some point, many patients are sent for RAI therapy.

RAI therapy in hyperthyroidism

Prior to RAI therapy, an uptake and scan are needed to identify if the patient's hyperthyroidism is related to an etiology that takes up iodine. Some patients may have hyperthyroidism related to thyroiditis (multiple etiologies, Table 1) that will decrease in function over time or 'burn out'. Treatment for these patients is supportive, aimed at the etiology of their cause of thyroiditis, and radioiodine is not indicated. Patients who may be treated with RAI for benign causes fall into three groups: (i) hyperthyroidism related to Graves' disease; (ii) hyperfunctioning thyroid nodule, also called autonomously functioning nodule or toxic nodule; and (iii) toxic multinodular goiter. Optimal therapeutic dose can be achieved in different ways, although in general RAI dose is inversely related to the degree of thyroid uptake of radioiodine and the specific etiology of hyperthyroidism. For example, some institutions start with a dose of 8-15 mCi for Graves' disease, 25 mCi for an autonomously

TABLE 1 Causes of hyperthyroidism

Cause of Hyperthyroidism	Comments
Graves' disease	Usually causes high iodine uptake with a homogeneous distribution. Named after a physician from Ireland, does not mean patients will be in the grave soon as some patients fear.
Toxic or autonomously functioning nodule	Caused by a nodule that does not respond to the upstream messages from pituitary and continues to produce thyroid hormone in the absence of TSH.
Toxic multinodular goiter	Hyperfunctioning nodular goiter. Following uptake / scan, ensure that the patient has ultrasound to further assess areas of reduced iodine uptake which could represent possible malignancy; this should be done prior to possible RAIT.
Thyroiditis	This type of hyperthyroidism has multiple causes and does not have significant iodine uptake; resolves with time. Do not give RAIT.
Exogenous hyperthyroidism	Does not cause thyroid uptake of RAI; do not treat with RAIT. Multiple causes: Exogenous thyroid hormone ingestion (often called fictitious Struma ovarii Rare functional thyroid cancer metastases
Other causes	Iodine-induced hyperthyroidism Trophoblastic disease Germ cell tumors Effect of medication (e.g. epoprostenol)

functioning nodule, and 30 mCi for toxic multinodular goiter. A more individualized approach based on the patient's thyroid mass and uptake can also be calculated as in Figure 2 (2).

Some patients may have rapid iodine turnover. An uptake done 4-6 hours after radioiodine and then again at 24 hours can easily identify these individuals. In this setting, multiple protocols have been published, ranging from the administration of a higher dose of RAI because of the shorter biological half-life/residence time (3) or pretreatment with methimazole to limit the dose of RAI needed (4). One should be aware that patients may have a worsening of their disease that could lead to a rare complication—thyroid storm. This is most common in patients with long-term untreated hyperthyroidism. Having patients withdraw from their antithyroid medication for a short time and then having them resume their medication 24 hours after treatment can help prevent this complication. A thyroid storm can be life-threatening with a mortality of up to 25%. Patients should be informed of possible symptoms including tachycardia, congestive heart failure, hyperpyrexia at temperatures 104-106 °F, agitation, anxiety, delirium, psychosis, stupor or coma. Patients can develop atrial fibrillation. Some patients may experience diarrhea, abdominal pain, or hepatic failure with jaundice. Patients should seek medical attention if they notice these signs. Management consists of evaluation of thyroid function, beta-blocker, intravenous fluids, anti-thyroid medication, and glucocorticoids. Patients are usually treated in an intensive care unit (5).

$$^{131}\text{I activity (mCi) dose} = \frac{0.2\text{mCi per gram of thyroid tissue} \times \text{target thyroid tissue mass}}{\text{RAIU}}$$

Figure 2. Hyperthyroid ^{131}I sodium iodide dose calculation (2).

Patient screening prior to therapy

Before setting up patients for treatment, some items need to be addressed. Uptake and scan should demonstrate a cause of hyperthyroidism that accumulates iodine. A review of medications is warranted, as some medications interfere with iodine uptake through the sodium iodide symporter (Table 2) (6). Patients should be screened for incontinence, living situation (including if there are pregnant individuals or young children at home) and occupational history (including working with pregnant individuals or children) as with other radionuclide therapies so that appropriate radiation safety instructions can be given. Pregnancy testing in accordance with local policies is recommended before treatment in individuals capable of childbearing as the fetal thyroid gland can begin to accumulate iodine early in pregnancy. Likewise, an inquiry about lactation is recommended to prevent a baby from receiving iodine that is excreted into breast milk. Patients should discontinue breastfeeding 6–12 weeks before therapy (7); 12 weeks is more conservative and can decrease the dose of radiation to the female breast, which is a particularly radiosensitive tissue. If necessary, bromocriptine can help decrease breast milk production (8) and is often overseen by an endocrinologist. Confirmation of cessation is recommended prior to RAI therapy.

Possible side effects / patient consent

Before any proposed treatment, there should be a discussion of the side effects and benefits of the treatment. The most common side effect of RAI treatment for hyperthyroidism is sore throat. This can be thought of as a 'sunburn' to the throat and is not accompanied by fever or other symptoms similar to upper respiratory infections. Patients should understand that there is a potential for a decrease in some blood counts after therapy, and patients may be more likely to catch an infection about 6-weeks after treatment. Vaccinations, if planned, should be performed before therapy to avoid possible blood count nadir times. Another issue to discuss with patients is radiation exposure. Some patients are concerned about the possibility of a future risk of malignancy; however, there have been multiple studies that have repeatedly found that future risk of malignancy following RAI for hyperthyroidism is similar to that of the general population (9, 10). Salivary gland uptake or pain is less likely to occur in this group of patients, as iodine is preferentially taken up by the thyroid gland (11). Patients can develop hypothyroidism after treatment. An individually calculated dose may help to reduce this but still can cause it. Patients should understand that they may require ongoing care from a primary care physician or endocrinologist and thyroid hormone supplementation for life (11). Patients can have worsening of their hyperthyroid symptoms, and discussion of the rare complication of thyroid storm along with warning signs on when to seek care should be discussed during the consent process. Restarting methimazole can help reduce risk.

TABLE 2 **Medications that interfere with iodine uptake and suggested withdrawal times (reference ACR practice guideline with some modifications from other references)**

MEDICATION	TIME
Methimazole	3-7 days
Propylthiouracil	3-7 days
Perchlorate	1 week
Thiocyanate	1 week
Iodine-containing cough medicines and vitamins	2-4 weeks
Iodine solution (Lugol's or SSKI*)	4-6 weeks
Iodine-containing topical agents	4 weeks
Kelp	4 weeks
Triiodothyronine (T_3)	2 weeks
Levothyroxine (T_4)	4 weeks
Thyroid extracts (desiccated thyroid extracts)	4 weeks
Intravenous iodinated contrast materials	1-2 months
Oil-based iodinated contrast materials	6-12 months

*SSKI is supersaturated potassium iodide

Take-home instructions

The patient's take-home instructions are primarily for radiation protection of other individuals at home and are centered on time, distance and hygiene. The amount of time that patients need to follow the instructions technically has to do with the amount of uptake in the neck and the administered dose of radioiodine, although some centers may give instructions for a set time frame for all. Patients should be advised to limit their contact with others, increase their distance between themselves and others, including avoiding public transportation or other situations where they will have prolonged contact with others, sit while urinating (male or female), flush the toilet at least twice (the first flush is commonly held in a trap that is still leading to radiation exposure in the home, the second flush will move it out of the house), wash hands with soap and water (hand sanitizer will kill germs but spread around any radioactive contamination), avoid sharing body fluids (either with sharing glasses/utensils or intimacy). A possible timetable of these instructions is presented in Table 3. Relevant NRC (Nuclear Regulatory Commission) regulations impact the instructions given to patients (12). If patients are incontinent, they should be advised of the appropriate procedures for the disposal of contaminated diapers or pads. This or other contaminated garbage should be stored in the patient's home away from general living areas and disposed of within a couple of months (12). Patients should receive a written statement from the treating facility that the patient has been treated with medical radiation. If patients travel through airports, enter high-security buildings, or in

TABLE 3 Outpatient instructions for hyperthyroid RAI therapy from Emory University

General Recommendations

- Flush toilet 2x following each use. Use a separate toilet if possible or clean the toilet thoroughly if you will be sharing a toilet.
- Do not share food or utensils.
- Avoid open mouth kissing or sex.
- Avoid prolonged contact with infants, small children & pregnant women.
- Remain on a relatively low-iodine diet for 3 days

Instructions based on administered activity:	</= 15 mCi	16-20 mCi	21-30 mCi with </= 50% uptake	21-30 mCi with >50% uptake
Number of days to follow the above general recommendations:	3	5	7	7
Number of days to sleep alone in a bed that is >6 feet from another person, if possible in a separate room:	6	8	9	11
Number of days you need to sleep in a separate bed away from pregnant partners, infants, or children:	21	21	21	21
Number of days you need to stay home from work or work remotely (if working with adults):	1	2	3	5
Number of days you need to stay >3 feet away from adults:	1	2	3	5
Number of days to stay >6 feet from babies, children younger than 16 years old and pregnant women:	2	3	4	5
Number of days to avoid close contact with others in public places (movies, shopping, public transportation):	1	1	2	3
Number of days you need to stay away from school or daycare (including both teachers & students):	2	3	4	5
Other instructions if relevant to the patient:	• Do not become pregnant for at least 6 months. • Discontinue breastfeeding your current child 12 weeks prior to therapy if possible (you can breastfeed in the future if you have another child). • Do not eat for 1 hour before and after receiving your dose of radioiodine so nothing is competing for absorption. • Drink plenty of fluids. • Confirm instructions for restarting any anti-thyroid medications.			

other situations, their radiation could be detected. This written statement should include the name of the treatment facility and a way of efficiently getting in touch with the treatment team.

NUCLEAR MEDICINE AND THYROID CANCERS

Thyroid cancer is one of the most common endocrine cancers and accounts for about 1% of all cancers. Among the different subtypes of thyroid cancers, which include differentiated thyroid cancer (DTC), medullary thyroid cancer (MTC) and anaplastic thyroid cancer, DTC accounts for 80–85% of thyroid cancers with a favorable prognosis (13). There has been a significant increase in the incidence of DTC worldwide (14). This increase in incidence has been largely attributed to the detection of small papillary thyroid cancers (PTC), with evidence of an increase of all stages of DTC (14, 15). However, the mortality rate has only slightly increased from 0.4 to 0.5 per 100, 000 people per year since 1980 (14).

Molecular imaging of thyroid nodules

A thyroid nodule is defined as a discrete lesion within the thyroid gland (16), and the clinical evaluation of a thyroid nodule is to exclude thyroid cancer which occurs in about 7%-15% of cases (17, 18). Ultrasound (US) is the preferred and recommended first-line modality in the evaluation of thyroid nodules. The Thyroid Imaging Reporting and Data System (TIRADS) evaluates thyroid nodules based on the presence of suspicious US features (microcalcifications, hypoechogenecity, irregular margins, taller than wide shape and intra-nodular vascularity, etc.) and has the sensitivity and specificity of 0.79 and 0.71, respectively (19, 20). A serum thyroid stimulating hormone (TSH) should also be obtained to evaluate a thyroid nodule of >1 cm in diameter. If the serum TSH is subnormal, then a radionuclide thyroid scan should be obtained to assess whether the nodule is hyper-functioning (hot) or non-functioning (cold) (21). Thyroid scintigraphy is performed with sodium iodide symporter (NIS)-targeting radiotracers to detect focal and diffuse abnormalities of thyroid follicular cells. The radioiodine uptake test (RAIU) helps quantify global iodine metabolism within the thyroid gland (22, 23). Thyroid scintigraphy is performed using Tc-99m pertechnetate (TcO4) or sodium iodide (NaI-123 or NaI-131) which can help detect hyperfunctioning thyroid nodules and can exclude malignancy with a high negative predictive value of 96–99% (24). Molecular imaging using (99mTc) Tc-hexakis-(2-methoxy-2-isobutyl isonitrile (Tc-99m sestamibi) or Flourine-18 deoxyglucose (F-18 FDG) provides information on the biological behavior of cytologically indeterminate nodules and can help differentiate benign from malignant nodules (24–27).

Tc-99m sestamibi

Tc-99m sestamibi is a lipophilic cation that passively penetrates the cell in response to negative plasma membrane and mitochondrial membrane potentials (28). The uptake of Tc-99m sestamibi depends on blood flow and tissue metabolism. The exact mechanism of uptake is not completely known. Cancer cells are known to be highly vascular and have increased metabolism, resulting

in increased accumulation of sestamibi in cancer cells compared to others (29). This can help characterize the biological behavior of indeterminate nodules (30). Reduced sestamibi uptake is associated with a high negative predictive value (NPV); however, the positive predictive value (PPV) is limited, as uptake could be seen in benign nodules such as follicular and oxyphilic adenomas (31, 32). A semi-quantitative approach evaluating the washout of radiotracer from the nodule (Washout Index) can help in the differential diagnosis of nodules with indeterminate cytology (33).

F-18 FDG PET-CT

F-18 FDG PET-CT imaging is widely performed for the evaluation of different types of cancers; however, FDG PET-CT is not recommended for the initial evaluation of thyroid nodules. Incidental focal or diffuse FDG uptake in thyroid gland can be seen. The focal increase in FDG uptake in a thyroid nodule warrants clinical evaluation, US and fine needle aspiration (FNA) are recommended for nodules ≥1 cm in size. Nodules <1 cm in size, which do not meet the FNA criteria, can be followed, such as thyroid nodules with high-risk sonographic patterns that do not meet the FNA criteria (34–36). FDG PET-CT can be performed in the preoperative staging of a high-risk or aggressive form of DTC with a high diagnostic accuracy for lateral lymph node metastases (37).

Thyroid cancer diagnosis

Routine measurement of serum thyroglobulin (Tg) is not recommended for initial evaluation of thyroid nodules, as serum Tg is elevated in most thyroid disorders and therefore is a nonspecific and insensitive test for thyroid cancer (38, 39). Ultrasound is considered the first-line imaging modality to evaluate palpable or incidentally detected thyroid nodules (17, 40), and suspicious-appearing nodules are subject to FNA. The main limitation of thyroid FNA is that about 30% of thyroid nodules undergoing FNA yield an indeterminate result and the rate of malignancy in indeterminate nodules ranges from 10 to 30%, which then requires a histological examination for the final diagnosis (41, 42). Molecular imaging can play a complementary role in refining the preoperative diagnosis of indeterminate thyroid nodules (25, 43). In 2015, the American Thyroid Association (ATA) revised the guidelines and recommendations for the management of thyroid nodules (36).

Radioiodine theranostics and the role of functional imaging

The management of DTC uses a risk stratified approach based on information from histopathology, molecular markers, postoperative Tg levels, and functional and anatomic imaging. Molecular imaging using radioiodine and other radiopharmaceuticals can help optimize personalized treatment decisions for patients with thyroid cancer. Molecular imaging using radioiodine (I-123, I-131) takes advantage of NIS, which helps to differentiate iodine avid versus non-iodine avid disease, and helps in localization and quantification of iodine avid post-operative thyroid remnant tissue (44).

Preparation for diagnostic RAI whole body scintigraphy (WBS)

The preparation for optimal I-131 uptake by residual thyroid tissue and metastatic disease requires 1-2 weeks of a low iodine diet and adequate TSH stimulation (TSH >30 mIU/L) before I-131 administration. Thyroid stimulating hormone (TSH) is used to improve the diagnostic sensitivity of RAI WBS and the radiation absorbed dose to the target lesions in RAI therapy. TSH is used to increase NIS expressions and function in metastatic lesions (45). This can be achieved through thyroid hormone withdrawal (THW) or through exogenous TSH stimulation. THW has two protocols, one protocol requires the withdrawal of levothyroxine (T4) for 4 weeks and the other protocol requires the substitution of levothyroxine/liothyronine, which means that T4 is stopped and replaced by T3 for the first 2 weeks followed by discontinuation of T3 for 2 weeks. This protocol appears to be better tolerated with the advantage of minimizing hypothyroid-related symptoms (46). For exogenous TSH stimulation, the patient continues to take hormone replacement therapy (levothyroxine), and TSH stimulation is achieved through the recombinant TSH (rhTSH) administration protocol, which is 0.9 mg rhTSH intramuscular injection on two consecutive days followed by I-131 or I-123 diagnostic dose after the second injection and imaging is usually performed 24-48 hours later (45, 47).

Post-operative diagnostic whole-body scintigraphy

WBS is performed with a diagnostic dose of I-131 or I-123. Postoperative diagnostic iodine whole-body scan can help improve risk stratification, staging, and decision making about the dose of subsequent radioactive iodine therapy (RAI-therapy) (48). Identification of iodine-avid metastatic disease in postoperative diagnostic WBS helps in risk re-stratification with potential adjustments in the prescribed dose of therapeutic radioactive iodine (RAI). There has been concern that that the diagnostic yield of postoperative WBS is relatively low compared to post-radioactive iodine treatment WBS; there is also a concern about 'stunning' effect when using I-131 for diagnostic imaging (49). Additional use of single-photon emission computed tomography with low-dose computed tomography (SPECT-CT) to postoperative diagnostic WBS can help improve sensitivity and specificity (44, 50). Postoperative Tg levels are helpful in disease monitoring and management. Elevated Tg levels/hyperthyroglobulinemia a few weeks after total thyroidectomy have been shown to be associated with persistent, recurrent, or metastatic DTC and survival (51, 52). Keeping this fact in mind, patients with negative RAI WBS with elevated Tg levels need to be further evaluated using other imaging, such as ultrasound of the neck, computed tomography (CT) of the neck and chest, and F-18 FDG PET-CT (36). Post-therapy WBS is performed routinely 5-10 days after radioactive iodine therapy to complete postoperative staging (53). The time interval of at least 5 days for posttherapy WBS helps improve contrast resolution due to time-dependent clearance of I-131 from normal tissues (54) (Figure 3).

FDG PET/CT has a role in the management of DTC in patients with elevated or rising Tg where ultrasound is negative or equivocal and negative diagnostic and post-therapy RAI scan. In these cases, FDG PET-CT has a reported pooled sensitivity and specificity of 80% and 90%, respectively (55, 56).

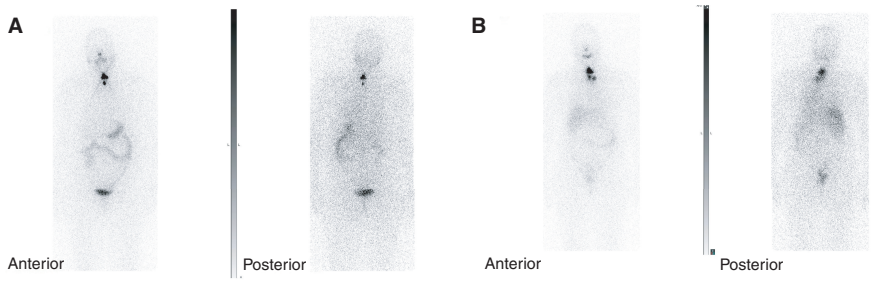

Figure 3. Examples of I-123 whole-body scans (A) and I-131 post-therapy scans (B).

DIFFERENTIATED THYROID CANCER

Patients with differentiated thyroid cancers are more likely to have iodine-avid disease, although this is most likely early in the course of the disease. Patients may require either pre-therapy imaging with iodine or pre-therapy imaging with FDG to best understand the biologic behavior of the individual patient's disease, and to guide dosing (Figure 4) (57).

RAI therapy for differentiated thyroid cancer

Patients with differentiated thyroid cancer can have either RAI ablation of the remaining thyroid tissue following surgery with no known additional disease or adjuvant therapy with RAI. Adjuvant therapy doses with RAI range from 30 mCi to 100 mCi, while adjuvant therapy doses are generally higher (58–60). Most treatment facilities use an empiric dosing method. According to Beierwaltes, RAI dosing is based on a pretherapy whole body scan (61). If bone lesions are identified, a dose of 200 mCi of sodium iodide ^{131}I is recommended, and generally a dose of 175 mCi is recommended for pulmonary metastases, although the maximum tolerated dose should be calculated first with dosimetry to avoid potential pulmonary fibrosis. If metastatic lymph nodes are detected or other known residual disease is present based on pathology findings, an empiric dose of 125–150 mCi is often used (58). Multiple dosimetric models are available, in particular the MIRD method, which also uses blood measurements of the RAI, the Maxon method, which will give lesional dosimetry, while other methods are also available (62–65). There is wide variability in practice across the globe due to the long-term survival of the majority of the patients with differentiated thyroid cancer. The Society of Nuclear Medicine and Molecular Imaging provides a comprehensive recommendation for the appropriate use of radioiodine therapy (53). Note that these recommendations differ from other guidelines, for example, the American Thyroid Association (36).

Patient screening before therapy

Before setting up patients for treatment, some items need to be addressed. According to Nuclear Regulatory Commission Part 35 in the United States, it is

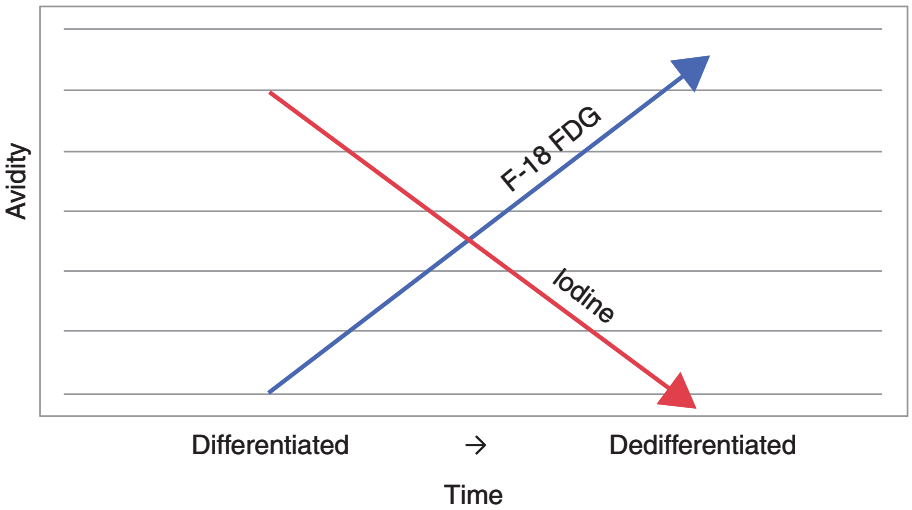

Figure 4. The biological behavior of differentiated thyroid cancers changes over time. Initially, the disease is avid for iodine but can become dedifferentiated or less likely to absorb iodine over time. FDG can be used for imaging in that setting. Some patients may have uptake with both imaging tracers depending on the biological behavior of the individual disease.

important to screen the patient to see if they are appropriate per their outpatient release criteria (12). This questionnaire is shown in Table 4. As with hyperthyroid therapy, careful screening is needed to understand the risks of radiation safety. A pregnancy test is performed according to institutional protocols; serum pregnancy tests are more sensitive. Pregnancy is a contraindication for treatment. Another contraindication is parenchymal lesions of the brain that, when treated can cause hemorrhagic transformation (66).

Possible side effects/patient consent

Before any proposed treatment, there should be a discussion of the side effects and benefits of the treatment. The side effects of patients with higher doses of radioiodine without much functional thyroid tissue (some pretherapy scans show neck uptake even <1%) are different compared to patients who have high thyroid uptake in the setting of hyperthyroidism. The most common side effect is salivary gland pain. This can be reduced by using sour candies at regular intervals, staying well hydrated, and performing a salivary gland massage. If pain develops, nonsteroidal anti-inflammatory medications can be used unless otherwise contraindicated for the patient (67).

As NIS is naturally expressed in the stomach mucosa, RAI therapy can cause nausea in some patients. Many practices choose to treat patients with anti-nausea medications prior to treating with RAI therapy. Ondansetron 4 mg orally is commonly administered before treatment with a few additional pills as needed.

TABLE 4 Pretherapy screening for I-131 therapy patients from Emory University

Screening Questions			
1. Are you breastfeeding?	N/A	Y	N
a. If yes, patient received written instructions on discontinuation		Y	N
2. Are you pregnant?	N/A	Y	N
a. If yes, Due date/LMP: _____			
3. Are you able to care yourself?		Y	N
4. Are you prone to stomach upset or nausea?		Y	N
5. Do you plan to, or is it possible for you to drive home alone after released?		Y	N
a. How long does it take to drive home? _____ hours			
6. Do you live alone? (if yes skip to question #12)		Y	N
7. Do you live in a nursing home or other communal living facility?		Y	N
8. Are there children living with you?		Y	N
a. Children ages _____			
9. Is there someone at your home who can care for the children for up to 7 days?		Y	N
10. Do you leave with a pregnant woman?		Y	N
11. Do you sleep alone or can you sleep for up to 7 days after therapy?		Y	N
12. Can you have sole use of a bathroom for up to 7 days after therapy?		Y	N
13. Can you avoid traveling by plane, bus, or train for up to 7 days after therapy?		Y	N
14. Will you be able to limit visits by family and friends for up to 7 days after therapy?		Y	N
15. Can you stop working or volunteering outside the home for up to 7 days after therapy?		Y	N
16. Do you require any type of special equipment for your health needs?		Y	N
17. Are you able to swallow a pill?		Y	N
18. Do you have complete bowel and bladder control?		Y	N
19. Has your neck wound completely healed?		Y	N

Table continued on following page

TABLE 4 Pretherapy screening for I-131 therapy patients from Emory University(*Continued*)

How do the questions relate to Occupancy Factor Choice:

Questions 3, 6, 13, 14, 15 are YES	=	occupancy factor of 0.125
Questions 9, 13, 14, 15 are YES	=	occupancy factor of 0.25
Question 10 is YES	=	occupancy factor of 0.75
Questions 4, 9, 11, 12, 13, 14 or 15 are NO	=	occupancy factor of 0.75

Patient Release Criteria

Use table if the thyroid uptake fraction is < 5% for thyroid cancer or < 80% for hyperthyroidism. Otherwise, contact the Radiation Safety Officer.

	Hyperthyroidism		Thyroid cancer	
Occupancy factor	Immediate	Inpatient therapy	Immediate	Inpatient therapy
0.125	101 mCi	27.4 mrem/hr	303 mCi	172.8 mrem/hr
0.25	56.6 mCi	13.7 mrem/hr	220 mCi	86.4 mrem/hr
0.75	20.4 mCi	4.6 mCi	105 mCi	28.8 mrem/hr
Effective half-life extrathyroid, T_1	0.32 days		0.32 days	
Effective half-life thyroid, T_2	5.2 days		7.3 days	
Uptake fraction extrathyroid, F_1	0.2		0.95	
Uptake fraction, thyroid, F_2	0.8		0.05	

Check the applicable statement based on the table above:

- The prescribed dose is less than the activity listed above for the patient's occupancy factor. The patient may be released after treatment as long as the patient does not suffering any ill effects.
- The patient must be admitted for therapy. The patient may be released after an overnight stay if the patient's dose rate at one meter is less than that listed for the occupancy factor.
- The patient must be admitted for therapy. The patient may not be released until the patient's dose is less than 5 mR/hr at one meter.*

* Please note that the release criteria may be different in other states. NRC release criteria is 7 mR/hr for NRC states.

Other side effects are less common (67):

i. Change in taste and smell:
   - Alleviated by hydration and sour candies.

ii. Radiation cystitis:
   - Managed by frequent drinking of fluids and frequent urination.

iii. Bone marrow suppression:
- Uncommon
- If extensive, a dosimetric evaluation for osseous metastatic disease can be performed to understand the maximum dose tolerated dose to the red marrow.
- If there are effects on bone marrow, it will be about 6 weeks following treatment.
- Some practices will get relevant laboratory analysis if there is concern based on biodistribution or in older individuals, such as complete blood count with differential, etc.

iv. Effects on fertility:
- Overall, there is no long-term ill-effect on fertility.
- Although transient, ovarian failure can be seen at higher therapy doses which may cause missing menses.
- Miscarriage rate is higher in the first year after RAI therapy.
- Most practices recommend avoiding pregnancy for up to 12 months after RAI therapy.
- No significant increase in congenital anomalies. Some articles have recommended pretreatment ova or sperm banking (68, 69).

The risk of future malignancy in response to treatment has been a topic of discussion. Some studies suggest that the incidence is similar to the general population (70), while other studies suggest that there may be a somewhat higher risk of malignancy (71) or leukemia (72) in patients treated with more than 100 mCi. According to radiobiology data, the expected time to develop such a disease related to radiation exposure would be approximately 10 years and other solid organ malignancies approximately 20 years (12). In addition, the age of the individual can have an impact on radiation exposure (73). Overall, pediatric patients are more radiosensitive than adult patients and careful consideration of dose should be taken.

Take-home instruction for patients is primarily focused on radiation protection of other individuals in the home. Table 5 provides an overview of the recommended instructions (12).

Follow-up in differentiated thyroid cancers

After RAI therapy, patients are generally followed up by endocrinology. Another component of thyroid cancer patient therapy is synthetic thyroid hormone replacement; endocrinology generally gives a goal TSH depending on the risk of the patient. Patients need to understand that this is an important part of their therapy even though it can be challenging to remember to take medication(s) daily. Periodically, at least 6 months to 1 year after treatment, patients generally follow up with imaging, either with ultrasound and/or whole-body iodine imaging determined by considering individual risk. At the time of follow-up, thyroglobulin levels and anti-thyroglobulin antibodies are also evaluated. A suggested follow-up decision tree is shown in Figure 5.

TABLE 5 Thyroid cancer outpatient instructions from Emory University

General Recommendations

- Take care not to contaminate others with urine, saliva, or sweat.
- Do not become pregnant for at least 12 months.
- Discontinue breastfeeding your current child; children of future pregnancies can be breastfed.
- Remain on a low-iodine diet for 3 days after therapy.
- Drink extra fluids and use the bathroom frequently, especially during the first 48 hours.
- Sucking on hard candies can help prevent injury to your salivary glands.
- Gentle brushing of the entire mouth with a soft toothbrush 6 times a day.
- Do not share food, dishes or utensils. Use the dishwasher or wash your dishes separately.
- Wash hands before eating or wear disposable gloves if you prepare food for others; if you can avoid this, that may be better.
- Flush toilet at least 2x following each use. Use a separate toilet if possible or thoroughly clean the toilet if you will be sharing a toilet.
- Wash your hands frequently with soap and water and shower daily.
- Wash your laundry separately and use an extra rinse cycle.
- Avoid open mouth kissing or sex.

Instructions based on administered activity:	</= 50 mCi	50-124 mCi	125-174 mCi	175+ mCi
Number of days to follow the above general recommendations:	3	5	7	7
Number of days to sleep alone in a bed that is >6 feet from another person, if possible in a separate room:	1	3	5	7
Number of days you need to sleep in a separate bed away from pregnant partners, infants or children:	7	7	7	7
Number of days you need to stay home from work or work remotely (if working with adults):	1	3	5	7
Number of days you need to stay >3 feet away from adults:	1	3	5	7
Number of days you need to stay >6 feet away from babies, children under 18 years old and pregnant women:	7	7	7	7
Number of days you need to avoid close contact with others in public places (movies, shopping, etc.).	1	3	5	7
Number of days you need to stay away from school or daycare (including both teachers and students):	7	7	7	7

Please note that these are standard recommendations based on an average patient but may be modified by information in your individual imaging findings.

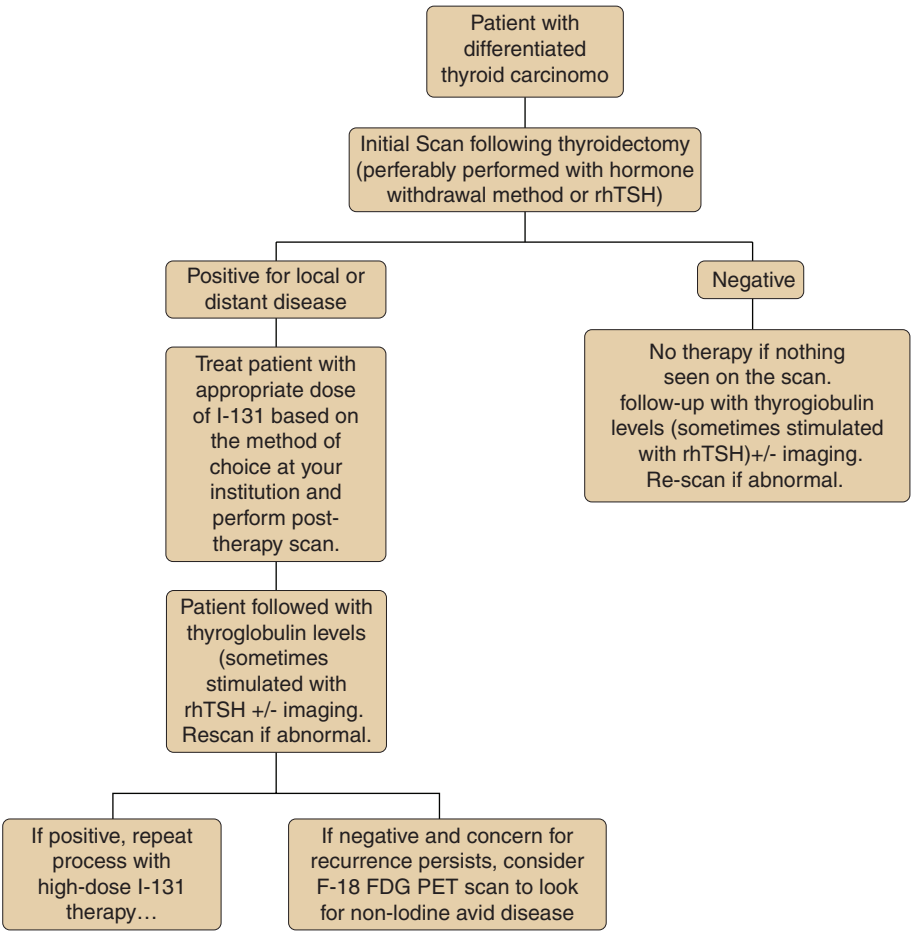

Figure 5. Suggested management in nuclear medicine and follow-up of differentiated thyroid cancer patients. Multidisciplinary management is preferred.

TREATMENT FOR DEDIFFERENTIATED THYROID CANCERS

^{131}I-sodium iodide may not be effective in the setting of anaplastic or dedifferentiated thyroid cancer as iodine uptake may not be present. There has been proposal of reactivating the sodium-iodide symporters in some dedifferentiated thyroid cancers with digitalis-like compounds (74, 75). More work in this area is ongoing and may hold promise for additional use of ^{131}I-sodium iodide in some dedifferentiated thyroid cancers in the future.

MEDULLARY THYROID CANCER THERAPY

NaI-131 is not administered in the setting of medullary thyroid cancer, as this is not differentiated thyroid cancer. Given the status of the receptor in these cells, imaging with somatostatin transmembrane receptor analogs such as -In-111 Octreoscan or DOTATATE, DOTATOC, and similar PET agents can be used. When there is uptake at the site of the disease, intravenous -Lu-177-DOTATATE peptide receptor radionuclide therapy (PRRT) can be used in patients with metastatic medullary thyroid cancer (76, 77). See the neuroendocrine chapter (Chapter 8) for more information on this therapeutic agent.

CONCLUSION

RAI has played a long-standing role in the imaging and therapy of differentiated thyroid cancers. PRRT has an emerging and promising role in the treatment of medullary thyroid cancers. It is important for the nuclear medicine professional to know the appropriate radiation safety instructions for patients and their families to help minimize unintended radiation exposure.

Conflict of Interest: The authors declare that they have no potential conflict of interest with respect to the research, authorship, and/or publication of this chapter.

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