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Background:

I131 administration has been used to treat benign and malignant thyroid disorders since the 1940s and is of value for thyroid imaging. I have presented information on I131 for thyroid therapy within my prior episodes titled "Nuclear Medicine and the Thyroid Parts 1-3" with emphasis on thyroid treatment in part 3 (available online or study guides in The Radiology Review BOARD Exam Study Guide Episodes 1-101. However, I didn't cover the topic of I131 therapy in as much depth as I could have for the Core Exam, as well as Nuclear Medicine board exams, so I am diving into this topic further. This contains substantial new information in comparison to the prior episodes on this topic. I will also repeat some of the key questions from the prior episodes for completeness's sake. Questions regarding nuclear medicine thyroid therapies are commonly tested, from my experience, so I think this content will be helpful for many of you as you prepare for board exams.

Note this information is for educational purposes only. Variations do exist in diagnostic and therapeutic uses of radioactive iodine for thyroid imaging and therapy, so my intention is to provide a general overview of key concepts for board preparation purposes. Institutional and medical society guidelines must be referred to and strictly followed for any diagnostic or treatment decisions in clinical practice.

General Overview:

What are the most common thyroid disorders for which I131 therapy may be utilized?
Malignancies most commonly papillary and follicular thyroid cancer.
Benign disease such as hyperthyroidism from Grave's disease, solitary autonomous hyperfunctioning nodule, and toxic multinodular goiter, or benign non-toxic nodular goiter.

The therapeutic goal of treating various causes of hyperthyroidism is to achieve a euthyroid state which is typically most possible when treating a solitary hyperfunctioning nodule, or certain toxic multinodular goiters, or to induce hypothyroidism because of therapy that can subsequently be treated with oral levothyroxine to achieve a euthyroid state.

The therapeutic goal for treating a non-toxic nodular goiter (non-toxic means it is not causing hyperthyroidism) is simply reduction of thyroid size and volume to alleviate local compressive symptoms from the large goiter in the neck.

The therapeutic goal for treating thyroid malignancies is for curative intent in many scenarios, when combined with surgery and other appropriate care, or else to improve treatment outcomes and reduce morbidity and mortality for more advanced disease.

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What are the energies and half-lives of Iodine123 and Iodine131?
I131: 364 keV and 8-day half-life. Remember this is the beta emitter and therapeutic agent. This is reactor produced.

I123: 159 keV and 13-hour half-life. This provides overall superior image quality but cannot be used for therapy and is typically more expensive than I131. This is cyclotron produced.

What are common pharmaceuticals that block radioiodine uptake, and how long must one abstain from these prior to radioiodine administration?
Methimazole and propylthiouracil (3 days)
Synthroid or other thyroid hormone replacement (10-14 days)
Multivitamin with iodine (7-10 days)
Lugol's solution (saturated potassium iodide solution) (2-3 weeks)
Topical iodine for surgical skin preparation (2-3 weeks)
Iodinated contrast agents (if water soluble (most common) and normal renal function 6-8 weeks, more historical lipophilic iodinated contrast agents 1-6 months)
Amiodarone 3-6 months (some say even longer)

True or false? I131 therapy is always contraindicated in pregnant individuals.
True. The fetal thyroid gland can take up and concentrate iodine by 10 weeks, and I131 therapy would ablate the fetal thyroid which should always be avoided.

How long must one abstain from breast feeding after receiving Iodine 131?
After receiving I131, breast feeding must cease for that child. This is due both to the long half-life of I131 (8 days) as well as the risk to the child's thyroid of ablation and becoming hypothyroid as a result. I131 is contraindicated in pregnancy and in childhood. I131 therapy should furthermore be withheld until lactation ceases to minimize radiation exposure to the breast tissue itself. This generally requires waiting 4-6 weeks after breastfeeding stops. If there is a question of whether the breast tissue still is concentrating iodine following lactation cessation, breast uptake can be assessed at time of radioiodine uptake and scan.

What are common precautions that patients must take before and following I131 therapy?
Prior to therapy, patients must discontinue use of iodide-containing medications as already discussed. A state of iodine deficiency is also desired for which a low-iodine diet for 7-14 days prior to therapy is often recommended. If there is concern whether a patient is in a true iodine deficient state (such as with somewhat recent iodinated contrast administration, or amiodarone use) a 24-hour urine iodine excretion test can be helpful.

For board exams, know that following I131 therapy a patient must isolate for 3 days including bathroom hygiene, sleeping alone, no exposure of others to bodily fluids including saliva and urine. Additionally, patients should stay well hydrated.

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Many additional recommendations exist which can vary between state and institution. Written instructions should be reviewed and provided to the patient/caregivers prior to I131 administration.

True or false? A patient can ingest non-iodinated salt without specific restriction prior to I131 therapy.
True. An iodine deficient diet does not equal a low-sodium diet, but the salt that is ingested should be non-iodinated to the maximal extent possible.

What is thyroid stunning?
Thyroid stunning is a reduction in I131 uptake of a therapeutic dose that is below predicted values following a low-dose diagnostic I131 scan. The thought is that either reduced cell function and/or cellular death following a diagnostic I131 scan (such as an I131 uptake study or whole-body search) can lead to reduced therapeutic I131 uptake due to "stunned" (or dead) thyroid cells secondary to the initial I131 low dose study. Whether thyroid stunning occurs in a clinically significant manner, especially with low dose I131 administrations (or even possibly I123 administration), is somewhat controversial. Nonetheless, I would understand the concept for radiology and nuclear medicine board examinations.

What are NRC guidelines for releasing a patient following I131 oral administration?
1. No individual of the public is likely to receive more than 5 mSv exposure from the patient treated with I131.
2. When a survey meter reading at 1 meter is less than 0.07 mSv/hour (7 mrem/hour)
3. When administered activity is 33 mCi or less. If administered activity is over this value, #1 and #2 above must be assured prior to releasing the patient.

Prior to release the authorized user should instruct the patient regarding best practices to minimize radiation exposure to others and written instruction describing recommended methods to limit radiation exposure to others is advised. Precautions include having the patient sleep alone, avoid pregnant individuals and children, avoid public transportation, follow strict bathroom hygiene, etc. Note also that I131 exposure is at high risk through bodily fluids but not through touching an object. For example, a family member need not worry if they touched a door handle that was recently touched by the person treated with I131.

Treatment of Thyroid Cancer:

What are common I131 doses for thyroid cancer without nodal or distant metastatic disease, thyroid cancer with local nodal metastases and thyroid cancer with distant metastases?
I131 for contained thyroid cancer post thyroidectomy with no nodal or distant spread: 50 to 100 mCi (some say 30-100 mCi)
I131 for thyroid cancer and local nodal disease in neck: 150-200 mCi

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I131 for thyroid cancer and distant disease: 200+ mCi (may require dosimetry, for example with lung metastases posing risk of post-radiation pulmonary fibrosis or for risk of marrow suppression)

The American Joint Committee on Cancer (AJCC) divides thyroid cancers into groups based on risk of recurrence and dying from thyroid cancer from very low to high risk. Can you describe what thyroid cancers have high risk per the AJCC?
High risk tumors include, for those under age 45, tumors that have distant metastases, extension to muscle, invasion of prevertebral fascia, subcutaneous soft tissues, larynx, trachea, esophagus, or the recurrent laryngeal nerve, encasement of the carotid artery or mediastinal vasculature.

For those over the age 45, high risk tumors include tumors that extend to muscle, invade subcutaneous soft tissue, the larynx, trachea, esophagus, or recurrent laryngeal nerve, prevertebral fascia, or encase carotid or mediastinal vasculature, any distant metastatic disease, as well as a follicular carcinoma larger than 4 cm.

What is the potential role of recombinant human TSH (i.e., Thyrogen) for patients undergoing I131 therapy for thyroid cancer?
When I131 is administered, you want thyroid cells to be primed to take up the I131 to promote effective therapeutic delivery. Thus, you want TSH levels to be high, so that the thyroid cells are stimulated to take up as much iodine as possible. For patients on thyroid hormone replacement, this can be achieved by thyroid hormone withdrawal, although symptoms of withdrawal and subsequent hypothyroidism can be unpleasant for the patient. Withdrawal periods of 10-14 days for T3 replacement and 3 weeks for T4 replacement are often necessary to achieve desired TSH elevation.

Alternatively, you can give intramuscular injections of recombinant human TSH, which will artificially increase TSH levels in circulation, and prime thyroid cells to increase iodine uptake. Note that a minimum TSH value of 30 is often considered acceptable pre I131 ablation and a TSH value of 50 or higher may be considered ideal.

What subtypes of thyroid cancer classically may NOT take up I131?
Medullary thyroid cancer and anaplastic thyroid cancer classically may not take up I131 and therefore may not respond as well to I131 therapy compared to other types of thyroid cancer. Remember the commonly tested MEN 2A and 2B syndrome association with medullary thyroid carcinoma. Note that medullary thyroid cancer has neuroendocrine features and may have uptake on MIBG/octreotide/somatostatin receptor imaging studies. Papillary thyroid cancer is typically radioiodine avid.

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What other factors contribute to treatment resistance of thyroid cancer to I131 therapy?
Patients with prior I131 therapy are more likely to be resistant to I131 therapy in the future. So, if you are re-treating with I131 you often must significantly increase the I131 dose for subsequent therapies. Prior methimazole treatment is also thought to possibly contribute to resistance to I131 therapy. Poor patient preparation is also a cause of failure or poor response to I131 therapy.

True or false? The Hurthle cell variant of follicular carcinoma typically has worse prognosis than standard follicular carcinoma.
True.

True or False? For thyroid cancer therapy thyroidectomy typically precedes thyroid treatment with I131.
True. Thyroidectomy is first performed and I131 is subsequently given to ablate any residual thyroid tissue. Note that it is not possible, even with the most skilled surgeons, to remove all thyroid tissue at surgery so there will always be a thyroid remnant that can be ablated. As there can be variation in how much thyroid tissue remains post-thyroidectomy, one can perform a thyroid uptake test with I123/I131 and if thyroid uptake is something like 5% or greater in the neck, those patients may be at risk for thyroid pain following I131 therapy and may be considered for steroid treatment during I131 therapy to reduce symptoms or else, with significant residual thyroid tissue, return to the operating room to remove additional tissue.

How might a pre-therapy thyroid scan be helpful to guide I131 therapy for thyroid cancer in a patient after thyroidectomy has been completed?
First, in nearly all cases, not all thyroid tissue is removed at thyroidectomy, and estimating the degree of residual thyroid remnant is helpful. If significant thyroid tissue is present, this may indicate a need for a completion thyroidectomy as administration of I131 in high dose for a patient with significant residual thyroid tissue could have unacceptable risk of symptomatic radiation thyroiditis.

Additionally, the preablation scan may change the patient staging by indicating nodal or distant metastatic disease that was previously unknown, which would change the dose of administered I131 to higher dose levels compared to disease without local or distant metastases. Whether preablation imaging is performed by planar imaging, or also includes SPECT/CT imaging, may vary by institution. Note that information regarding potential local nodal metastatic disease in the neck could also be obtained on thyroid ultrasound, and ultrasound of the neck, as well as MRI or CT imaging.

True or false? I131 therapy can be considered for radioiodine avid brain metastases.
True. But this can vary depending on disease extent. Steroid treatment with I131 therapy will typically be considered to reduce degree of swelling in the confined intracranial space.

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What are some of the important potential side-effects of I131 therapy for cancer treatment?
Because I131 doses for cancer therapy are higher than those used for hyperthyroidism, more pronounced side effects may be seen. These include oral mucositis, sialadenitis, loss of taste, and painful thyroiditis. Painful thyroiditis is more common if there is significant remnant tissue following thyroidectomy and can have associated recurrent laryngeal nerve paralysis and neck swelling. If there is concern that painful thyroiditis or other more severe symptoms may occur, steroid treatment along with I131 therapy may be considered. To minimize side-effects robust hydration and frequent urination can be helpful. Some advocate for agents to stimulate flow of saliva such as sugar-free candy, though I've heard others say that increased salivary flow could theoretically increase dose to the salivary glands. In severe cases, and with higher administered doses, salivary gland damage and xerostomia can result. In cases of nausea, anti-emetics should be provided. In high-dose cases (150-200 mCi +) transient decreases in white blood cells and platelets may occur that in some instances require supportive care, but this is rare if pre-therapy blood counts are within normal limits.

After I131 therapy for thyroid cancer, when should a whole-body iodine scan be performed?
Typically, 3-7 days after I131 therapy a whole-body scan should be performed for staging purposes wherein you are imaging the distribution of the I131 that was administered and absorbed for therapy (i.e., does not require re-administration of I131 as it will still be on board). This scan will image with higher activities than are present on pre-treatment imaging, and the sensitivity for detection of metastatic disease will be higher. Remember that septal penetration artifact (star appearance) over the thyroid remnant is common, as is some degree of low-level salivary and GI activity.

What should you consider if thyroglobulin levels are rising in a patient who has completed thyroidectomy and I131 ablation for thyroid cancer and the thyroid I123/I131 scan is negative? What is the next best test to consider?
One must consider the possibility that the thyroid cancer is truly back, as suggested by the thyroglobulin levels, but has de-differentiated and therefore no longer takes up radioactive iodine. In this setting, one would want to perform an FDG-PET/CT study to show where the site(s) of recurrence are as de-differentiated thyroid cancer tends to be FDG avid.

What is the significance of antithyroglobulin antibodies?
Antithyroglobulin antibodies, if present, make thyroglobulin levels potentially false negative, and make thyroglobulin a potentially inaccurate test for monitoring of thyroid cancer recurrence. Essentially, thyroglobulin is only produced by thyroid cells, so in a patient post thyroidectomy and ablation, thyroglobulin levels should be nearly undetectable. Thyroglobulin levels should be assessed prior to I131 ablation (can be measured both with and without TSH stimulation) and can then be again measured post I131 ablation therapy, as a baseline measure. This lab value of thyroglobulin can thereafter be used as a biomarker (or in newer language a liquid biopsy test) to monitor for recurrence. If it rises, thyroid cells have recurred, and this is evidence of recurrent or worsening disease. If antithyroglobulin antibodies are present,

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however, the immune system can clear thyroglobulin from the body, and this is thereafter not a useful test as thyroid cancer could recur without any remaining thyroglobulin signal, due to immune clearance of the thyroglobulin precluding laboratory detection of rising levels. Therefore, testing for antithyroglobulin antibodies helps inform whether thyroglobulin is likely to be accurate for recurrence (in case of no antibodies) or not (antithyroglobulin antibodies positive).

Note also, that outside of the setting of thyroid cancer, antithyroglobulin antibodies can also be a sign of autoimmune thyroid damage, such as with thyroiditis from Graves', Hashimoto's, subacute thyroiditis, or with lupus or type 1 diabetes.

Treatment of Benign Thyroid Diseases:

What are general dose ranges for I131 therapy of Graves' disease, autonomous hyperfunctioning thyroid nodule and toxic multinodular goiter to keep in mind for board exam purposes?
Graves' disease is often treated with 5 to 15 mCi I131.
Autonomous hyperfunctioning thyroid nodule is often treated with 15-25 mCi I131.
Toxic multinodular goiter is often treated with 25-35 mCi I131.

Note that calculations do exist whereby doses may be calculated based on thyroid weight and radioiodine uptake values. However, these general ranges are something that may be beneficial to know for board exam purposes.

In what scenarios may a treating physician consider using somewhat higher doses than is standard for treatment of hyperthyroidism?
Patients with very large toxic diffuse goiters, patients with prior I131 treatment yielding insufficient response, and patients with rapid iodine turnover (4-hour uptake exceeds 24-hour uptake) may be considered for higher I131 doses than for standard cases.

How long after I131 treatment for hyperthyroidism does it commonly take for a patient to become hypothyroid?
It often takes 2-3 months following therapy for a hyperthyroid patient to become clinically hypothyroid. Therefore, laboratory monitoring is required after treatment, and thyroid replacement with levothyroxine or similar should be started when TSH becomes elevated and may need to be subsequently titrated to ensure the patient is euthyroid and symptom-free.

What are classic severe toxicities that can result from treatment of hyperthyroidism with methimazole or propylthiouracil?
The side effects I would most be aware of for board exams are potential hepatotoxicity and agranulocytosis.

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What is the so called "thyroid storm" that can result after I131 therapy of hyperthyroidism?
As I131 destroys thyroid cells, they can release stored thyroid hormone into circulation which can worsen symptoms of hyperthyroidism or, in extreme cases, cause thyroid storm where severe symptoms can result from sudden release of thyroid hormone. Risk factors for thyroid storm include patients with a large thyroid gland that is highly I131 avid and who receive high activities of I131. Patients with rapid turnover of iodine are also at increased risk, meaning patients for whom the 4-hour I131 uptake exceeds that measured at 24 hours (thus they are rapidly taking up and thereafter rapidly processing the administered I131). For those with risk factors of thyroid storm, pre-treatment with methimazole or propylthiouracil can be considered to deplete thyroid hormone stores but must be discontinued at least 3 days prior to I131 therapy. Treatment with beta blockers can also be helpful for symptomatic control.

True or false? Beta blockers need to be discontinued prior to I131 therapy.
False.

What are other potential side effects/symptoms patients may experience after I131 therapy for hyperthyroidism?
Beyond initial possible transient worsening of hyperthyroid symptoms, including possible worsening of Graves ophthalmopathy, these include a mildly painful radiation thyroiditis, dysgeusia (altered sense of taste), and recurrent laryngeal nerve palsy. For patients with a large goiter causing compressive symptoms within the neck, these symptoms may initially become worse as the thyroid may initially swell following I131 administration, and this requires close clinical follow-up and consideration of supportive treatment to include possible use of corticosteroids if swelling becomes severe.

Is De Quervain's thyroiditis treated with radioactive iodine?
No. This is a self-limiting disease, and one would not want to ablate the thyroid that is expected to recover on its own. Also, the hyperthyroidism is transient and self-resolving with De Quervain's thyroiditis and thus does not require radioiodine ablation.

What laboratory and imaging information should be reviewed prior to I131 administration for treatment of hyperthyroidism?
For patients with history of diabetes or renal disease, renal function tests should be obtained to ensure kidneys will adequately clear unbound I131 from the circulation. Results of thyroid hormone levels and TSH should be reviewed. A negative pregnancy test, for individuals capable of pregnancy, should be assured, ideally within 24 hours of treatment. Iodine uptake from either I123 or I131 should be reviewed. A thyroid scan or a stimulating TSH receptor antibody study should be obtained to distinguish between Graves disease, toxic multinodular goiter, or uninodular adenoma, and to exclude silent thyroiditis and factitious thyrotoxicosis. Note that I131 uptake values but not a thyroid scan may be appropriate for patients with classic clinical presentation of Graves' disease that includes elevated anti-TSH receptor antibody, pretibial myxedema, and classic orbitopathy.

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Is hypothyroidism common in patients with toxic multinodular goiter following I131 therapy?
No. In toxic multinodular goiter the radioactive iodine preferentially is taken up into the toxic nodule(s) and the remainder of the gland has suppressed uptake and is therefore not ablated. Note that many of these patients with toxic multinodular goiter will become euthyroid following I131 treatment. The same principle would also hold true for a hyperfunctioning thyroid nodule—the background thyroid is suppressed, and the radioactive iodine is preferentially taken up within and preferentially ablates the hyperfunctioning nodule, sparing the normal thyroid parenchyma, and potentially resulting in a euthyroid state.

Want more information on this topic?
Refer to the SNMMI I131 therapy practice parameters: https://s3.amazonaws.com/rdcms-snmmi/files/production/public/docs/I-131_V3.0_JNM_pub_version.pdf