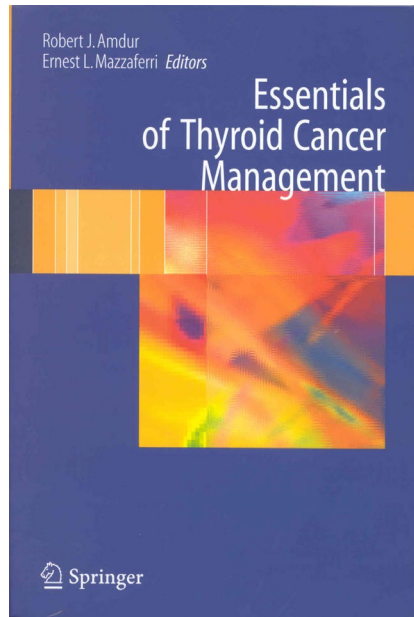
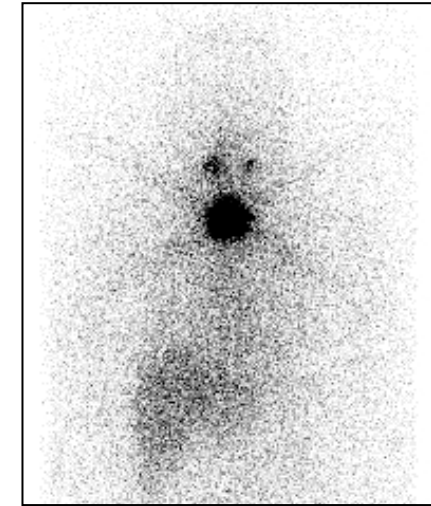


BASIC Principles of I-131 for Thyroid Cancer



CHAPTER 50

Perez and Brady

Thyroid Cancer

Robert J. Amdur and Roi Dagan

BASIC THYROID ANATOMY AND PHYSIOLOGY

Gross Anatomy

The thyroid gland is located in the central anterior neck at the cervical-thoracic junction (Figure 50.1). The bulk of the gland is located immediately anterior and inferior to the thyroid cartilage. It has two lateral lobes connected by a central isthmus. Approximately 50% of individuals have a pyramidal lobe that extends superiorly from the central aspect of the gland, which is a remnant of the gland's embryologic origin, the thyrogloss-

REVIEW ARTICLE

2019: PMID: 29727314

The University of Florida Department of Radiation Oncology Guidelines for Treatment of Differentiated Thyroid Cancer With I-131 or External-beam Radiotherapy

Robert J. Amdur, MD and Roi Dagan, MD†*

Abstract: The purpose of this paper is to summarize the University of Florida Department of Radiation Oncology guidelines for treatment of differentiated thyroid cancer with I-131 or external-beam radiotherapy. This article is not meant to compete with the many excellent book chapters and consensus guidelines that present comprehensive discussions of treatment options. This is a streamlined, "How we do it?" reference without substantial discussion of background or supporting data. To serve as a treatment reference, the great majority of the information is presented in topic-specific tables.

Key Words: differentiated thyroid cancer, radiotherapy, I-131, external beam
(*Am J Clin Oncol* 2019;42:92–98)

TABLE 1. Consensus Treatment Guidelines for Differentiated Thyroid Cancer

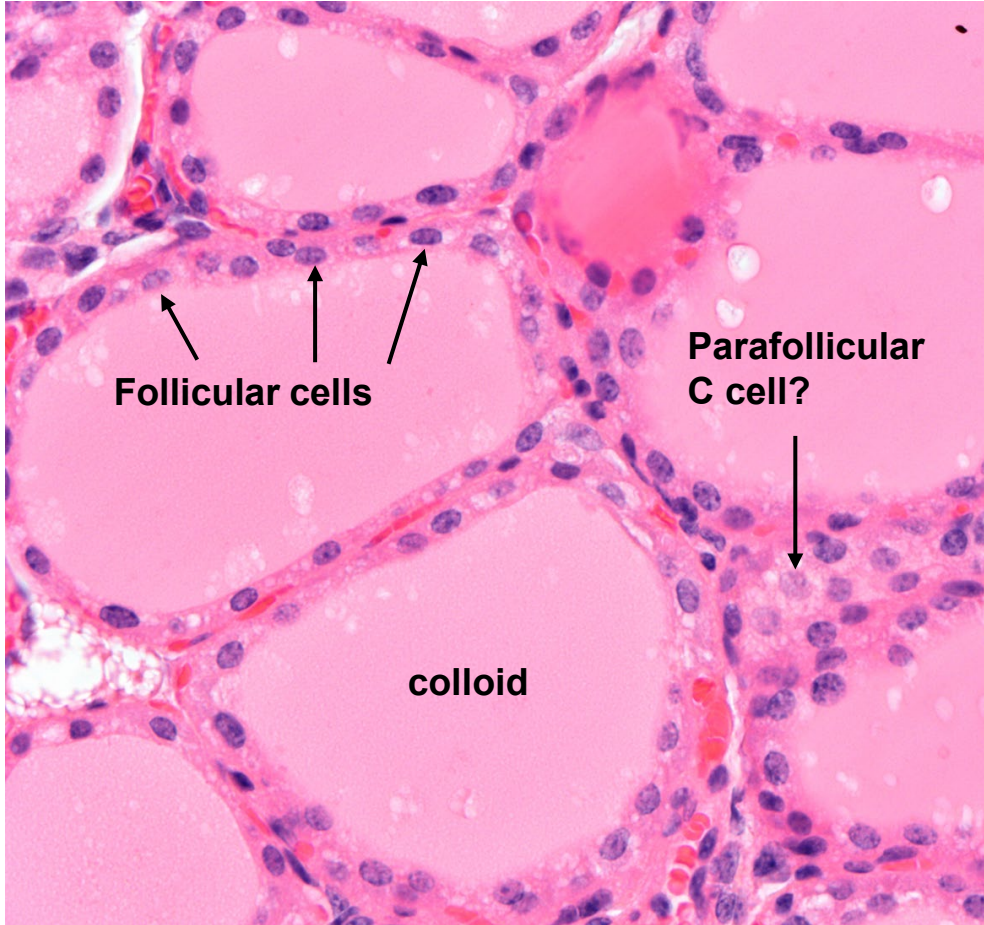
	References
NCCN	National Comprehensive Cancer Network ²
ATA: DTC in Adults	Haugen et al ³
ATA: DTC in Children	Francis et al ⁴
AHNS: EBRT for DTC	Kiess et al ⁵

AHNS indicates American Head and Neck Society; ATA, American Thyroid Association; DTC, well-differentiated thyroid cancer; EBRT, external-beam radiation therapy; NCCN, National Comprehensive Cancer Network.

Robert Amdur, MD

**I do not have any financial
or nonfinancial interests in
any companies or products
that I will discuss during
this session**

The normal thyroid: “Follicle” is from the Latin word for “small sack”

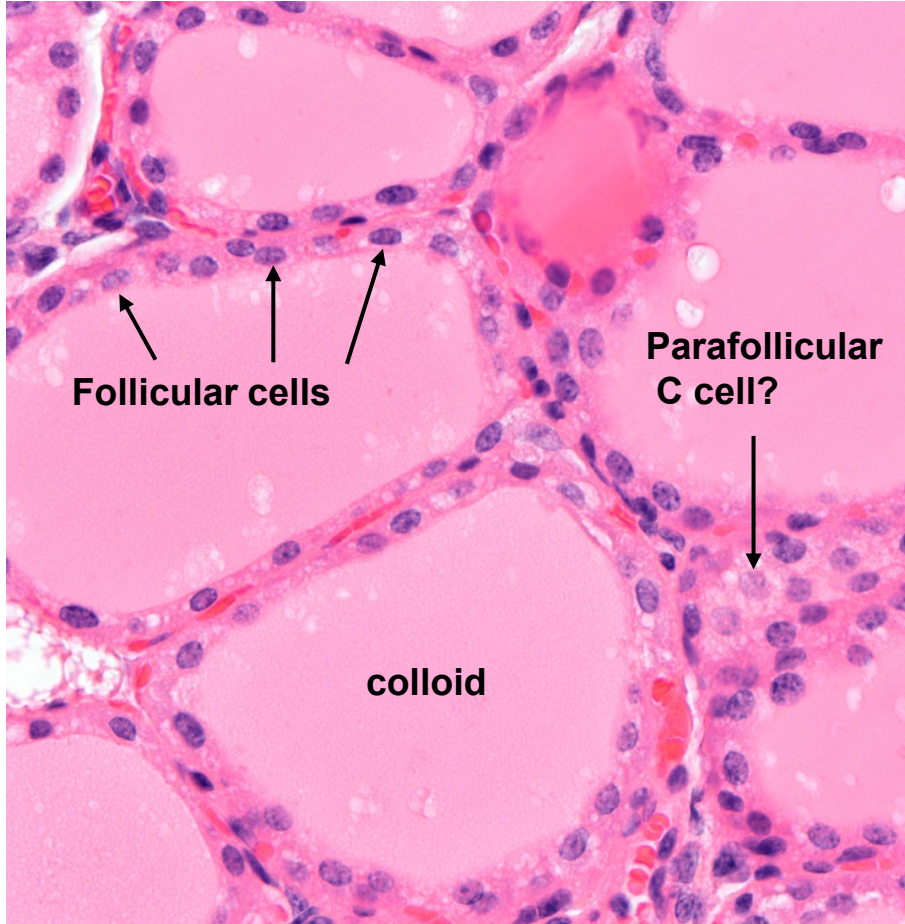


Parafollicular C cells make **CALCITONIN**

Follicular cells make **THYROID HORMONES**

- T3 (Triiodothyronine, Cytomel): used by tissues but not stable in blood
- T4 (Levothyroxine, Synthroid): stable in serum and converted to T3 in tissues

The normal thyroid:



Parafollicular C cell makes CALCITONIN

Follicular cell makes THYROID HORMONES

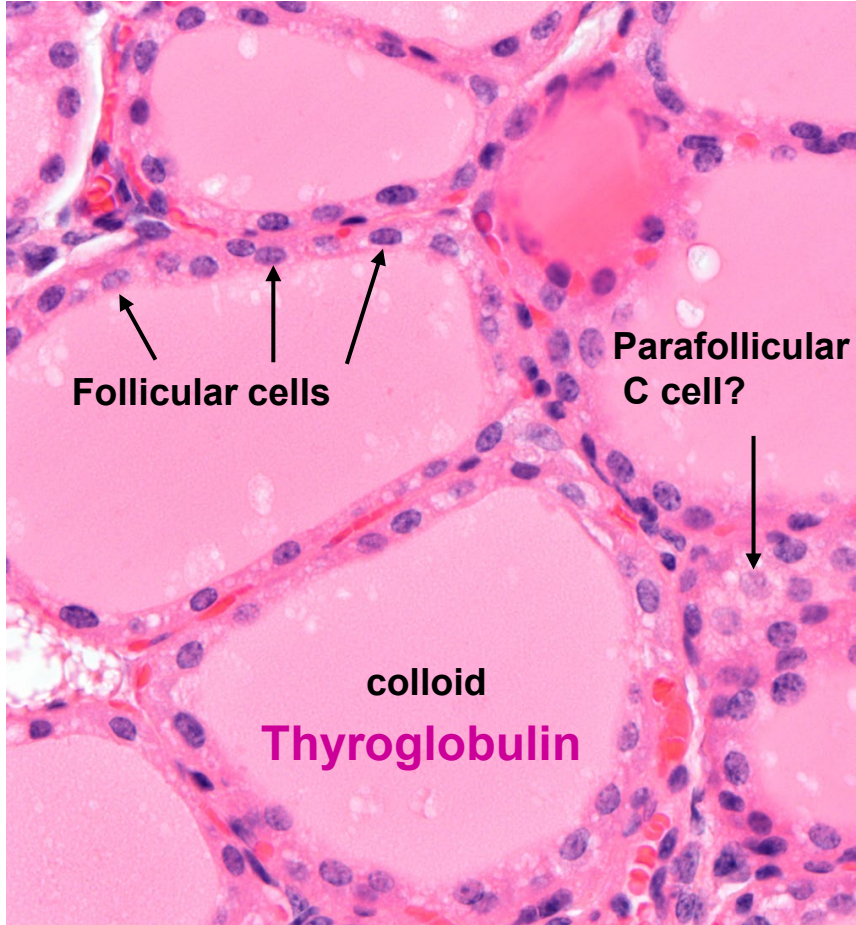
- T3 (Triiodothyronine, Cytomel): used by tissues but not stable in blood
- T4 (Levothyroxine, Synthroid): stable in serum and converted to T3 in tissues

Cancer of the Parafollicular C Cell is called
MEDULLARY carcinoma

Cancer of the Follicular cell called “Thyroid Carcinoma”
and is subclassified by Degree of Differentiation:

- **WELL Differentiated**: “Differentiated Thyroid Carcinoma” DTC
- **MODERATELY Differentiated**: “Insular Carcinoma”
- **POORLY Differentiated**: “Anaplastic” Carcinoma

The normal thyroid:



Cancer of the Parafollicular C Cell is called
MEDULLARY carcinoma

Cancer of the Follicular cell called “Thyroid Carcinoma”
and is subclassified by degree of differentiation:

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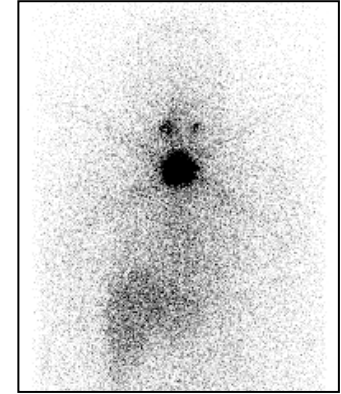
Colloid is Thyroglobulin (Tg): Glycoprotein storage of T3/4
Tg is 100% sensitive biomarker for normal follicular and DTC cells

Parafollicular C cell makes **CALCITONIN**

Follicular cell makes **THYROID HORMONES**

- T3 (Triiodothyronine, Cytomel): used by tissues but not stable in blood
- T4 (Levothyroxine, Synthroid): stable in serum and converted to T3 in tissues

I-131 Therapy for Thyroid Cancer



Cancer of Parafollicular C cell (Medullary Ca.)

Cancer of the Follicular Cell

Well Differentiated (DTC)

Poorly Differentiated (Insular)

Undifferentiated (Anaplastic)

I-131 is only curative for Well Differentiated Thyroid Carcinoma because it's the only cancer subtype that retains the function of normal Follicular cells that concentrate Iodine a lot more than other tissues to make T3/4 where the 3 and 4 are the number of Iodine atoms per hormone molecule

The remainder of this presentation will be limited to treatment of DTC

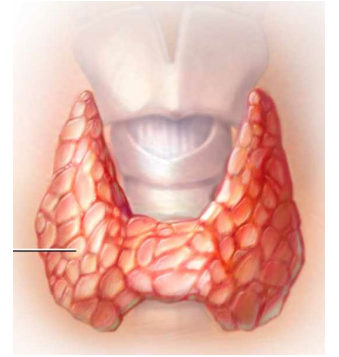
Subtypes of (Well) Differentiated Thyroid Carcinoma (DTC)

When is “capsular invasion” discussed and important?

The 2 main subtypes of DTC are:

- Papillary
- Follicular

Can both of these subtypes be diagnosed by Fine Needle Aspirate (FNA)?



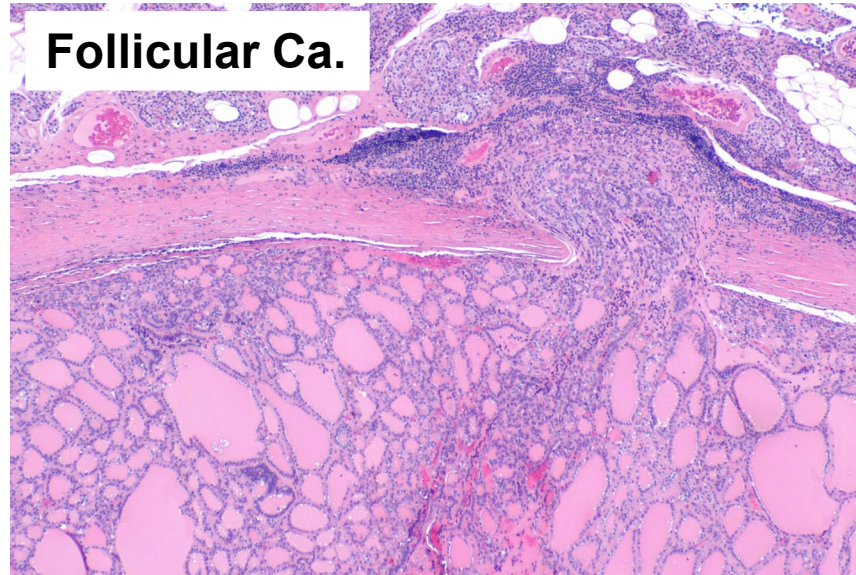
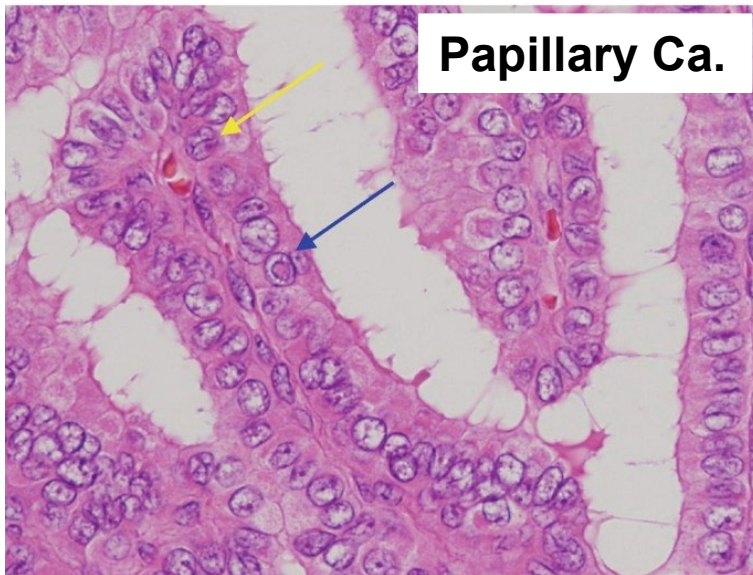
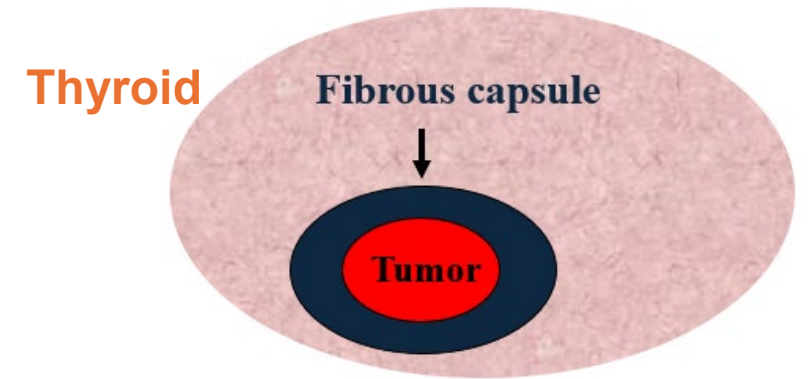
Thyroid gland does NOT have a well-defined capsule

But benign adenomas, and cancers, usually have a tumor capsule, within the thyroid

(Well) Differentiated Thyroid Carcinoma (DTC):

1. Papillary Carcinoma (Each cell is Ca so dxed by FNA)
2. Follicular Carcinoma

(Each cell is normal, must see invasion of tumor capsule to dx Ca vs Adenoma so can't dx by FNA. Must have at least hemi-thyroidectomy)



Confusing that “Follicular” is used 3 ways in classifying Thyroid Cancer

1. Cell of Origin of thyroid cancer: **Follicular Cell** vs Para Follicular C Cell (Medullary Ca)

2. Subtype of (Well) Differentiated Carcinoma of Follicle Cell origin

Papillary Carcinoma (PTC)

Follicular Carcinoma

3. Subtype of Papillary Thyroid Carcinoma (PTC)

Classic histology

Follicular Variant

Oncocytic Variant

Diffuse Sclerosing

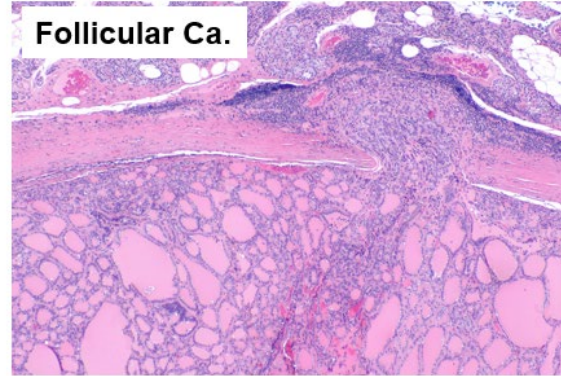
Tall Cell

Hobnail

} **Unfavorable Variants**

90% of Thyroid Cancer cases are Papillary or Follicular DTC

Does Papillary vs Follicular matter for treatment decisions?



It's reasonable to say NO

It doesn't change I-131 decisions

There's controversy about central node dissection

Does the subtype of Papillary DTC change I-131 decisions?

Subtype of Papillary Thyroid Carcinoma (PTC)

Classic

Follicular Variant

Oncocytic Variant

Diffuse Sclerosing

Tall Cell Variant

Hobnail Variant

} Unfavorable Variants

No difference in management of Classic, Follicular, and Oncocytic

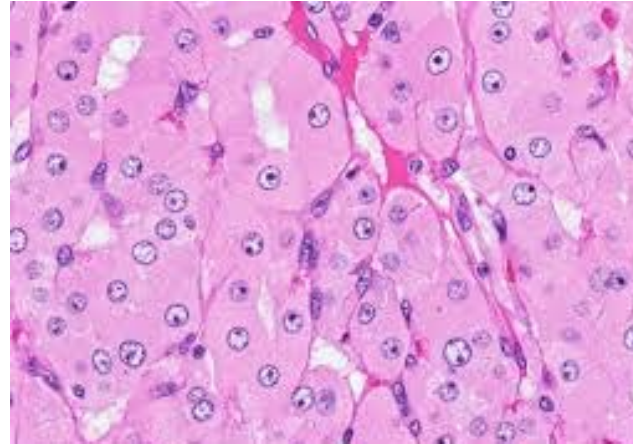
Most consider an UNFAVORABLE VARIANT an independent indication for I-131 and higher dose category regardless of stage

Where does Hurthle Cell Thyroid Cancer fit in these guidelines?

Hurthle Cell Thyroid Cancer



**Hurthle Cell
= Oncocyte**



Current debates are:

- Is Hurthle Cell Ca a subtype of Follicular Ca, or a unique entity?
- Does Hurthle Cell Ca have a worse prognosis than standard DTC?

ORIGINAL ARTICLE

2017 PMID 25730603

Favorable Outcome of Hurthle Cell Carcinoma of the Thyroid Treated With Total Thyroidectomy, Radioiodine, and Selective Use of External-Beam Radiotherapy

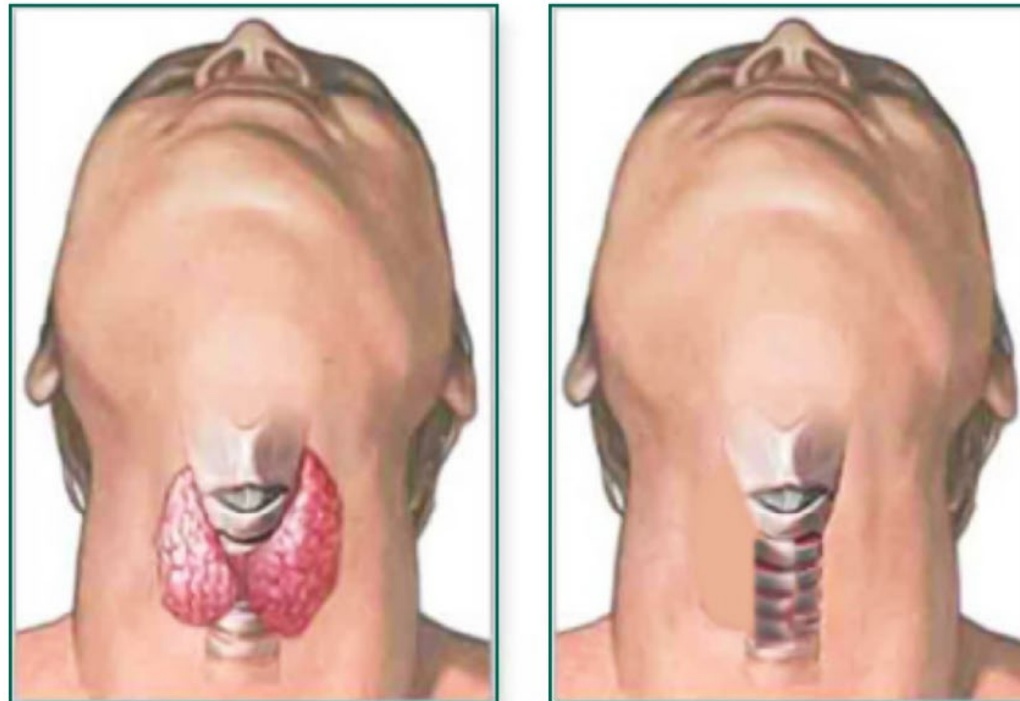
Peter Zavitsanos, MD, Robert J. Amdur, MD,* Peter A. Drew, MD,†
Kenneth Cusi, MD,‡ John W. Werning MD,§ and Christopher G. Morris, MS**

**I treat Hurthle Cell Carcinoma
like an Unfavorable Variant of DTC
with 100-200 mCi I-131 based on risk factors**

Is TOTAL Thyroidectomy required before considering adjuvant tx?

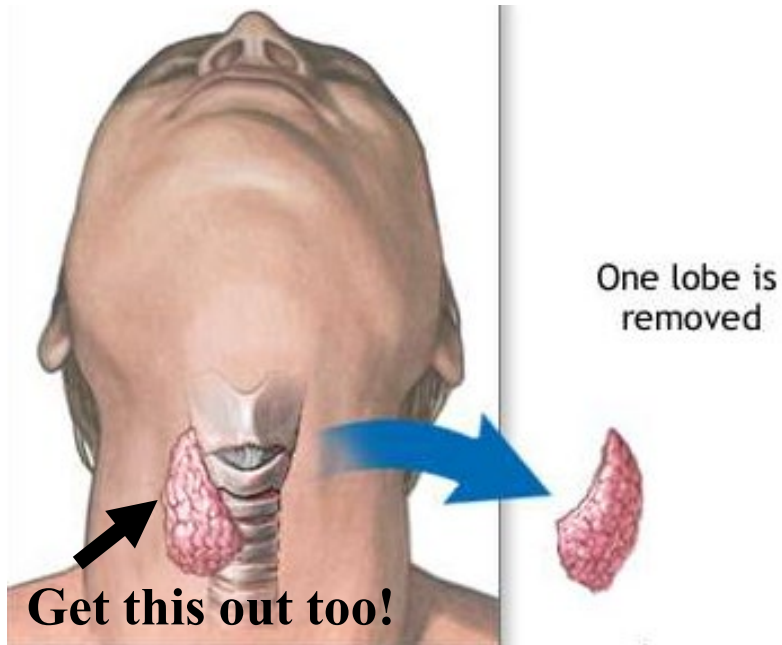
Total Thyroidectomy

The Removal of The Thyroid Gland



Total Thyroidectomy + Removal of all visible tumor and positive nodes, is required before considering adjuvant tx

Thyroid Cancer is PATHOLOGICALLY STAGED



I-131 less effective if $> 1\text{cc}$ of normal gland remaining due to the remnant concentrating most of the I-131

Risk of injury to esophagus, larynx, RLN is higher from I-131 with large thyroid remnant

Never want to treat gross dz with I-131 because cure rate is a lot higher if visible tumor removed surgically

Do we expect our surgical colleagues to ELECTIVELY DISSECT the lateral node stations (L2-4) as they would for other head and neck cancers?



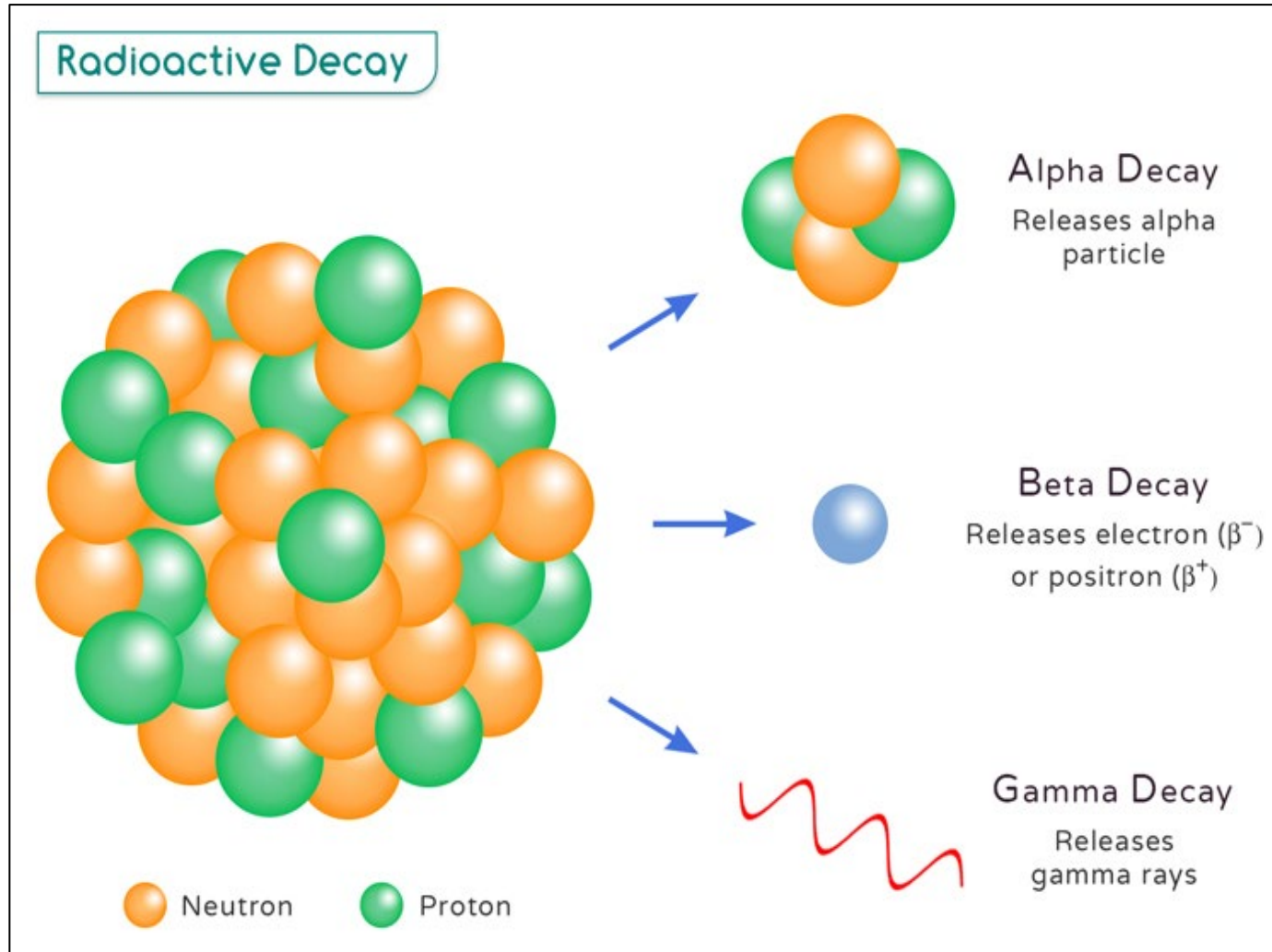
No.

With Thyroid Cancer, **Elective Neck Dissection is NOT done for L2,3,4,or 5** because I-131 is good at eliminating micro residual tumor.
(There's controversy about Elective Dissection of L6)



YES, dissect any neck station with **visible positive node**
by imaging preop or on inspection at the time of surgery

Radioiodine (RAI): I-131



Radioiodine (RAI): I-131



131

Mass number:

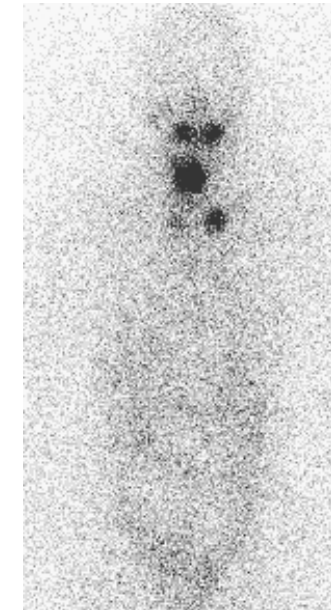
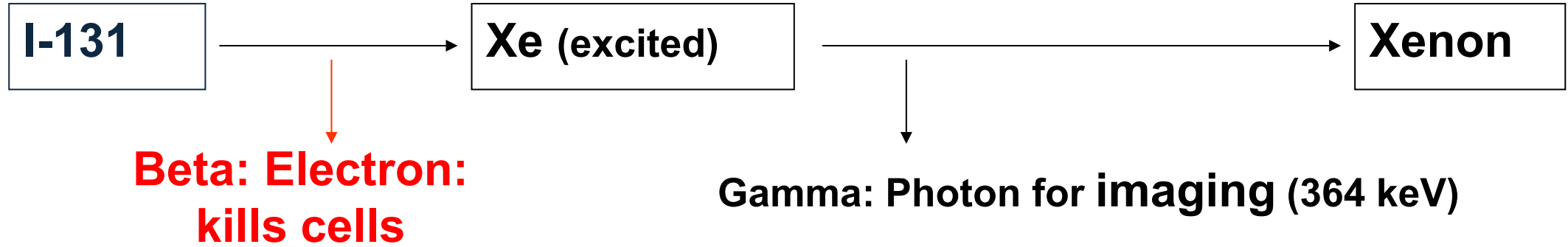
Protons + **Neutrons**
(isotopes)



53

Atomic number: # Protons

Radioactive Emissions of I-131





Maximizing the Effectiveness of I-131

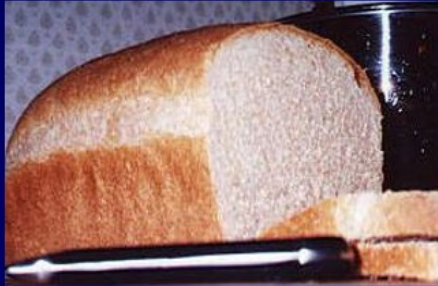
What are the two main things to do BEFORE I-131 administration that prepare the body to maximize the chance that I-131 will destroy target tissue (normal follicular and cancer cells)?

What is the minimum value for TSH elevation?

What are the two ways to get to this minimum TSH value and what are the potential negatives of each approach?

Two main things to do BEFORE I-131 administration that prepare the body to maximize the chance that I-131 will destroy target tissue (normal follicle and cancer cells) are:

**Low Iodine Diet for
≥ 14 days**



LOW-IODINE DIET

It is important that you follow a low-iodine diet for at least 2 weeks before receiving I-131. Continue the diet for two days after you receive I-131.

DO NOT EAT THESE FOODS:

Iodized salt and foods containing iodized salt: Do not eat iodized salt or sea salt. Non-iodized salt (such as Kosher salt) is OK.

Restaurant food: Avoid restaurant foods as most use iodized salt.

Processed food: Most commercially prepared food contain iodized salt

Seafood: Fish, shell fish, sea weed, and kelp are usually high in iodine

Dairy products: The milk from farm animals is high in iodine. Do not drink milk or eat ice cream, yogurt and butter or eat margarine because it usually contains iodized salt.

Commercial bakery products: Commercial bakery products like bread, cakes, muffins, and pastries often contain iodized salt or iodine dough conditioners. Homemade bread without iodized salt or iodine conditioners is OK.

Chocolate: Chocolate that contains milk is off limits. Milk-free chocolate is OK.

Egg yolk: Egg yolk contains iodine. Egg whites are OK on this diet.

The following additives contain iodine: Carrageen, agar, algin, alginates.

Cured, corned or spicy meats, including most meat cold cuts: Bacon, ham, sausage, salami, lox, corned beef, etc. contain salt with iodine. Fresh meat is OK.

Vitamins and food supplements: Most vitamin preparations contain iodine. Check the label and ingredients and do not take vitamins or supplements that contain iodine.

Red, orange or brown food, pills, and capsules: Many red, red-orange, and brown food dyes contain iodine. FD&C Red Dye #3 contains iodine.

Other foods that may contain iodine dyes and preservatives: Soy products (soy sauce, tofu, soy milk), molasses, instant coffee and tea, canned fruits and vegetables often contain additives with iodine. Avoid these foods.

WHAT CAN YOU EAT? Unprocessed (fresh or frozen) fruits, vegetables, egg whites, and meat (other than seafood) are OK. Non Iodized or Kosher salt, unsalted nuts, unsalted peanut butter, and bread made without salt or iodine are OK. Fresh ground (not instant) coffee or tea is OK. Beer, wine, and hard liquors are OK. More information and specific menus and recipes are listed on the web at <http://www.thyca.org/ThyCa%20Cookbook%20011804.pdf>

Elevate serum TSH > 30 mIU/mL (nl 0 < 4.0)

T4 deprivation (hypothyroid):

T4 has long half-life so need ~6 weeks off T4 to get TSH >30

In older adults, Hypo T4 is morbid and dangerous



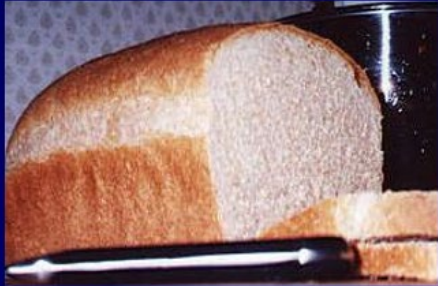
Two rhTSH (Thyrogen) injections (day -2 and -1):

- Not FDA approved in minors
- Need insurance or pay ~\$1500
- Some experts say less effective than T4 deprivation for high-risk situations

I use rhTSH prep in all risk cases in an adult with insurance coverage

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I-131 Indications and dose



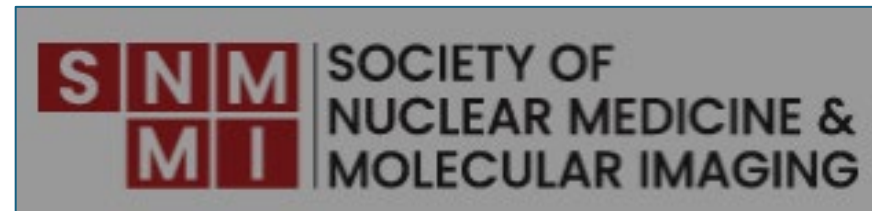
Indications for different doses of I-131 vary between published guidelines



National Comprehensive
Cancer Network®

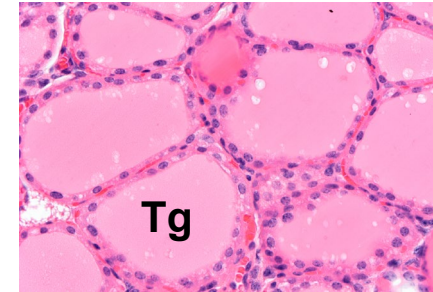


AMERICAN **THYROID** ASSOCIATION®
ATA® | *Guidelines*



The policies that I use are permitted by at least one organizational guideline

Postop serum Thyroglobulin (Tg) is now a factor in deciding I-131 dose in most guidelines:



Is it useful to use postop Tg to determine I-131 dose if a substantial portion of normal thyroid remains?

No. Normal follicular cells make Tg, which is why detectable Tg at any level after I-131 means residual cancer

What is the minimum number of weeks postop before checking Tg? 6 weeks because Tg has long half life in serum

What is the threshold value of Tg that makes a decision about I-131 dose? < 1.0 vs ≥ 1.0

What does “suppressed” mean regarding postop Tg?

Suppressed means TSH is low, say < 1.0

Current NCCN does not specify what TSH must be to invoke the < 1.0 postop Tg value as low risk of recurrence

Where does the level of Anti-Thyroglobulin Antibodies (TgAb) fit in the decision about I-131 dose?

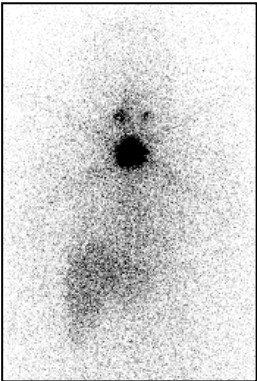
First, TgAbs block measurement of Tg by usual method so can't trust low Tg level if TgAb present

Second, TgAb have the same meaning as Tg for tumor presence

I-131 Dose Selection: FIXED by risk category or DOSIMETRIC

Fixed Dose: Same dose for all patients in a given risk category based on path findings

Dosimetric: Test Iodine uptake in the patient to determine best dose for individual physiology



THE RELATION OF RADIOIODINE DOSIMETRY TO
RESULTS AND COMPLICATIONS IN THE TREAT-
MENT OF METASTATIC THYROID CANCER*
By RICHARD S. BENUA, M.D., NORMA R. CICALA, MARTIN SONENBERG, M.D., Ph.D.,
and RULON W. RAWSON, M.D.
NEW YORK, NEW YORK

Absence of Bone Marrow Toxicity in Elderly Patients Treated
With Recombinant Human Thyroid-stimulating Hormone
and Empirically Dosed Radioiodine for Thyroid Cancer
Robert J. Amdur, MD, Tu Dan, MD,* and Ernest Mazzaferri, MD†*

Bottom Line:

In most situations, at most institutions, I-131 is prescribed with the **FIXED DOSE** approach

Very Low Risk:	no I-131
Low Risk:	30 or 50 mCi
Intermediate Risk:	100 or 150 mCi
High Risk:	200 or 250 mCi

2019: PMID: 29727314

The University of Florida Department of Radiation Oncology
Guidelines for Treatment of Differentiated Thyroid Cancer
With I-131 or External-beam Radiotherapy

Robert J. Amdur, MD* and Roi Dogan, MD†

TABLE 4. University of Florida Department of Radiation Oncology I-131 Dose Guidelines for DTC*†‡

Adjuvant soon after initial thyroidectomy

No prior I-131 treatment and no visible residual tumor

Active surveillance§ (No I-131 treatment)

zero mCi

All must be present:

pT1-2, pN0-1a, M0

~~≤ 3 positive nodes~~ ≤ 1 positive node

No ENE

Negative margin

Postoperative Tg < 1.0 ng/mL||

30 mCi

All other scenarios

~~150 mCi~~**100 mCi**

If any are present:

pT3b **Stap muscle invasion**~~≥ 4 positive nodes~~ ≥ 5 positive nodes

ENE that is not extensive¶

Positive margin and postoperative Tg⁵ ≥ 1.0 ng/mL~~200 mCi~~**150-200 mCi**

If any are present:

pT4 **Invasion of RLN, Trachea, Esophagus**

Extensive ENE¶

M1 (with the exception of large-volume disease)

**Biochemical Recurrence
(Tg or TgAB)**

Biochemical recurrence

Recurrent tumor based only on serum thyroglobulin level with no visible disease following at least one prior I-131 treatment

Active surveillance without additional I-131 treatment is always a reasonable option

We recommend active surveillance when life expectancy is <5 y or when the risk of additional I-131 treatment is high due to renal insufficiency, peripheral blood count deficiency, or substantial dry eye from prior I-131 treatment

100 mCi~~150 mCi~~ is our standard dose for biochemical recurrence (no visible tumor)**Visible Dx****150-200 mCi**Visible residual recurrent tumor following ≥ 1 I-131 treatments **Or high risk of micro residual dz following salvage surgery**

Visible tumor on ultrasound, CT, MRI, or PET, following salvage surgery if applicable

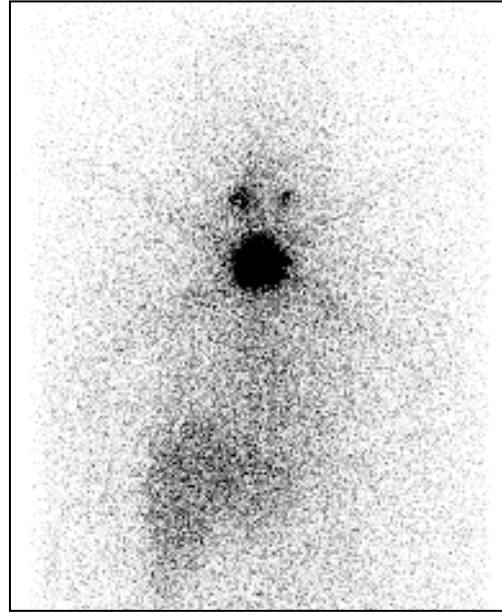
The range of scenarios in the category is large and includes distant metastasis, unresectable disease in the neck, no visible residual disease following salvage neck surgery but pathologic findings suggesting a high risk of recurrence (positive margin, multiple positive nodes, extranodal extension)

We do not retreat with I-131 when the risk of another I-131 treatment is high (serious renal insufficiency, peripheral blood count deficiency, or dry eye problems)

200 mCi is our standard dose when treating visible recurrent tumor - 150 mCi for high risk of micro residual dz following salvage surgery

**High Risk of micro residual
dz after salvage surgery**

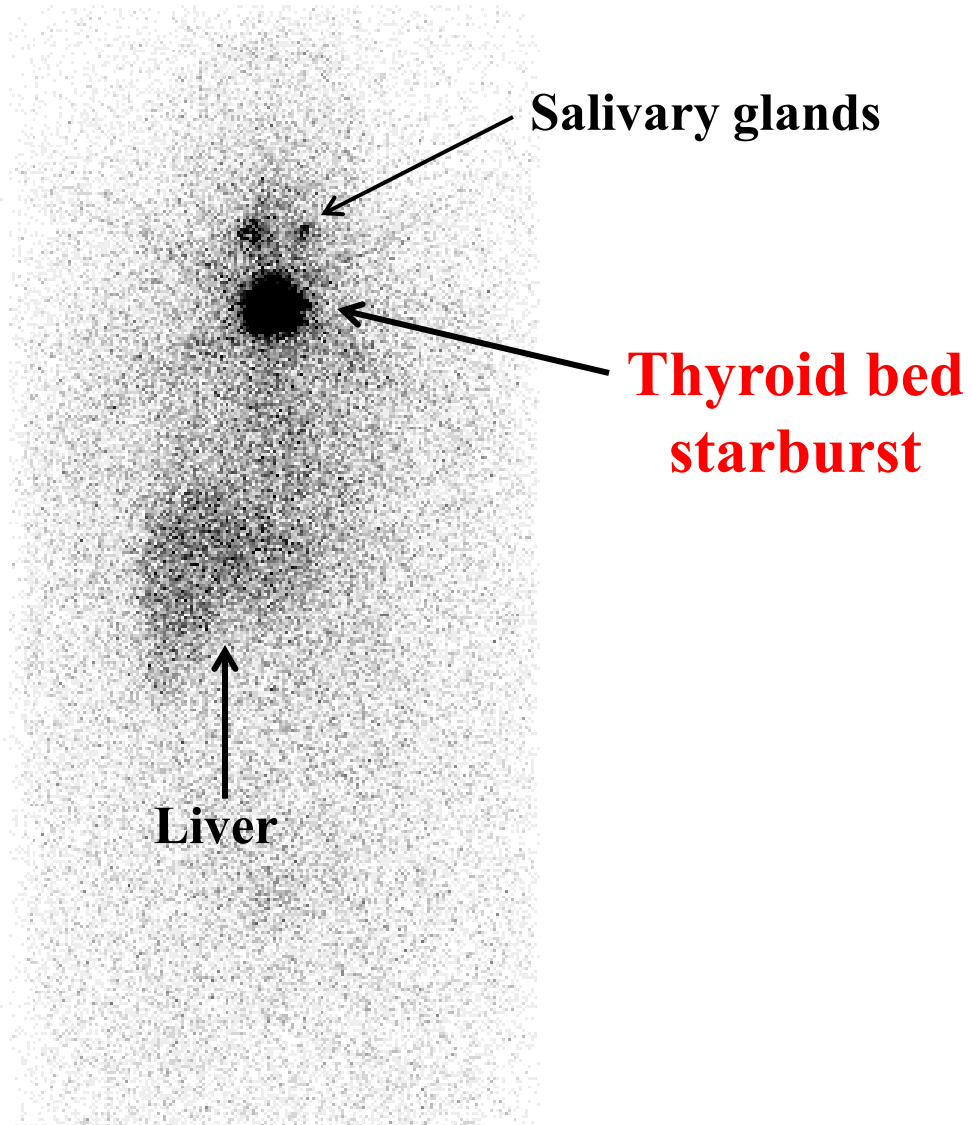
Good Luck with I-131 for Thyroid Cancer



Questions?

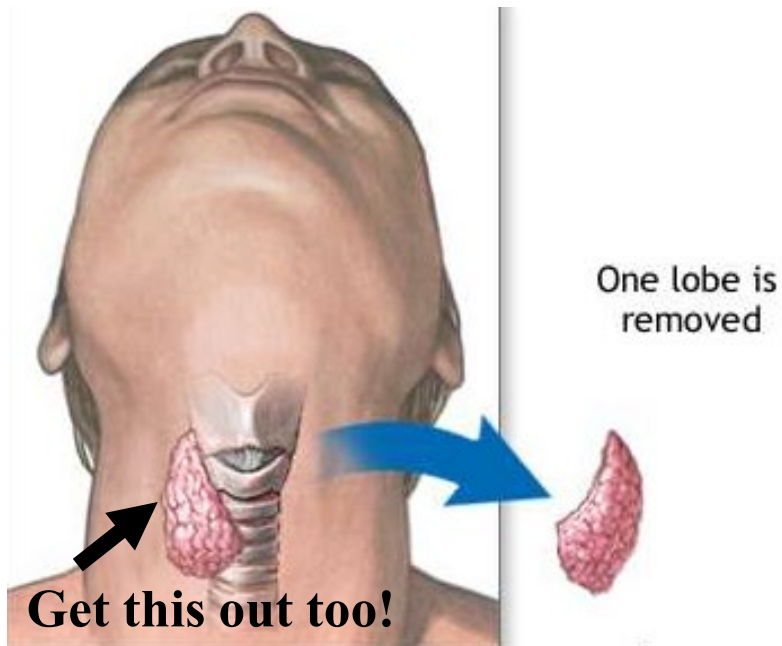
The best “total thyroidectomy” is really a **NEAR TOTAL**

Total body scan 7 days
after 150 mCi I-131



Total Thyroidectomy + Removal of all visible tumor and positive nodes, is required before considering adjuvant tx

Thyroid Cancer is PATHOLOGICALLY STAGED



I-131 less effective if $> 1\text{cc}$ of normal gland remaining due to the remnant concentrating most of the I-131

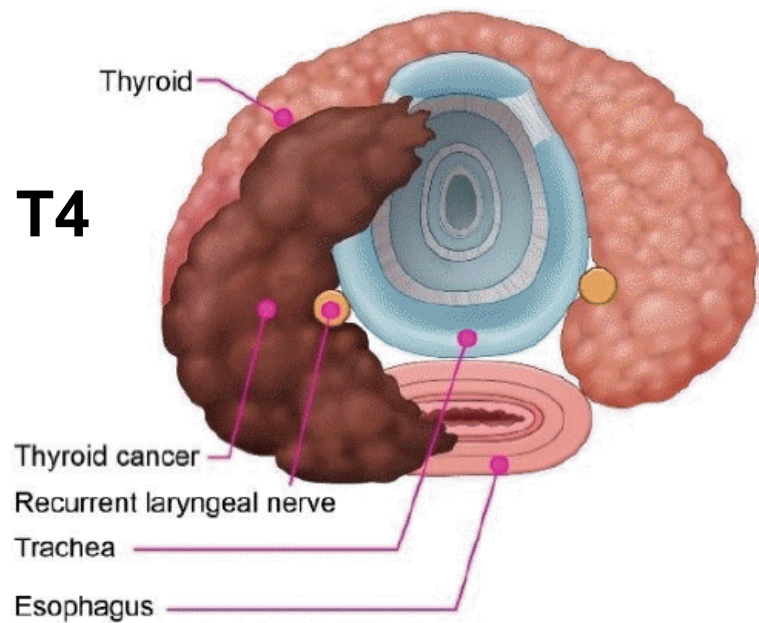
Risk of injury to esophagus, larynx, RLN is higher from I-131 with large thyroid remnant

Never want to treat gross dz with I-131 because cure rate is a lot higher if visible tumor removed surgically

What makes a case stage T3 or T4?

AJCC 8th Edition

Stage T3 and T4 Thyroid Cancer

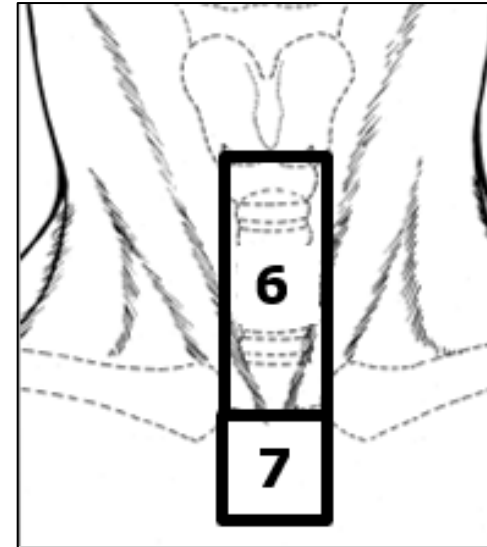


8 th Edition AJCC: Thyroid Cancer (all histologies)	
T1	≤ 2cm limited to thyroid
T2	> 2 but ≤ cm limited to thyroid
T3	4cm or GROSS extra-thyroid extension only to STRAP m.
T4	Extra-thyroid extension to major structures: - Trachea - Esophagus - Recurrent Laryngeal Nerve
Are Thyroid Cancer N stages similar to HN Scca?	

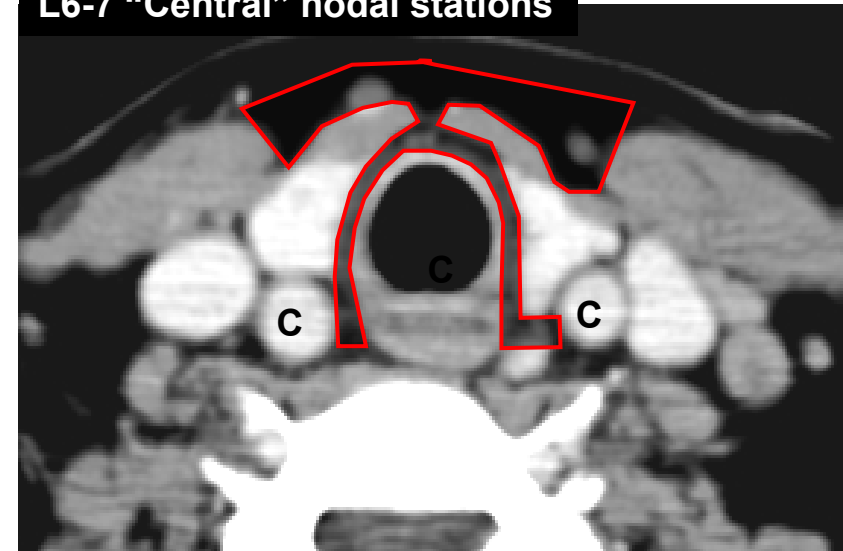
N-staging for Thyroid Cancer is very different from other HN tumors!

8th Edition AJCC: Thyroid Cancer (all histologies)

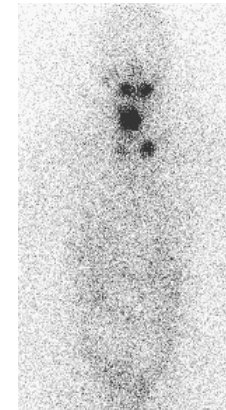
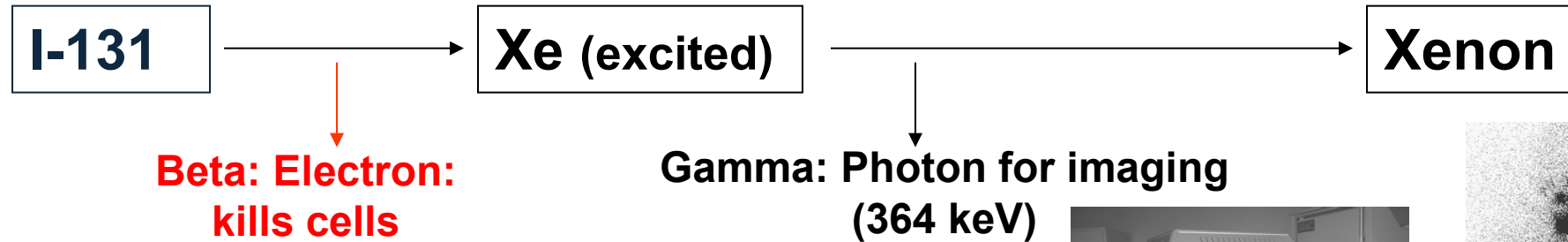
N1a	Positive in Level 6 or 7 uni or bilateral
N1b	Positive in a lateral neck station (L1-5) uni or bilateral



L6-7 “Central” nodal stations



Radioactive Emissions of I-131



I-131 Physical Half-Life: 8 days

Thyroid Uptake study (RAIU %): I-131 (3 mCi) or I-123 (~300 μ Ci)

**I-123: pure photon emitter used only for thyroid uptake %
(Almost no absorbed ionizing radiation in the body)**

Half-Life only 13 hours so difficult to use and expensive

