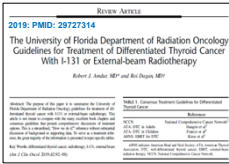
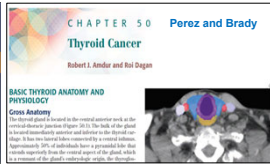
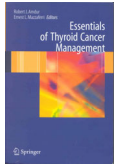
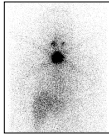


BASIC Principles of I-131 for Thyroid Cancer



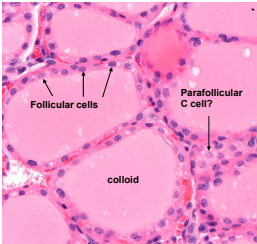
1

Robert Amdur, MD

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

2

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



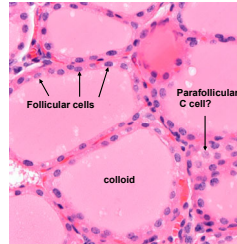
Parafollicular C cells make **CALCITONIN**

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

3

The normal thyroid:



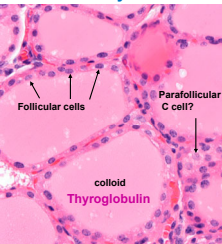
Parafollicular C cell makes **CALCITONIN**

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

4

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**

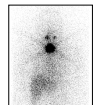
Cancer of the Follicular cell called "Thyroid Carcinoma" and is subclassified by degree of differentiation:

- WELL Differentiated: "Differentiated Thyroid Carcinoma" DTC
- MODERATELY Differentiated: "Insular Carcinoma"
- POORLY Differentiated: "Anaplastic" Carcinoma

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

5

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

6

Subtypes of (Well) Differentiated Thyroid Carcinoma (DTC)

When is “capsular invasion” discussed and important?

The 2 main subtypes of DTC are:

- Papillary
- Follicular

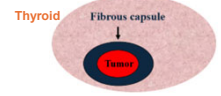
Can both of these subtypes be diagnosed by Fine Needle Aspirate (FNA)?



7

Thyroid gland does NOT have a well-defined capsule

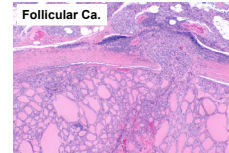
But benign adenomas, and cancers, usually have a tumor capsule, within the thyroid



(Well) Differentiated Thyroid Carcinoma (DTC):

1. Papillary Carcinoma (Each cell is Ca so dx'd 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)



8

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

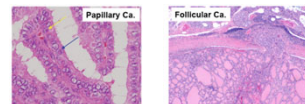
Tall Cell

Hobnail

} Unfavorable Variants

9

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

10

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

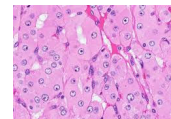
Where does Hurthle Cell Thyroid Cancer fit in these guidelines?

11

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 28730603
Favorable Outcome of Hurthle Cell Carcinoma of the Thyroid Treated With Total Thyroidectomy, Radioiodine, and Selective Use of External-Beam Radiotherapy
Peter G. Anderson, MD, PhD, Robert J. Andre, MD, PhD, Peter A. Dineen, MD, PhD, Kenneth C. Cote, MD, John W. Hwang, MD, and Christopher W. Ryan, MD

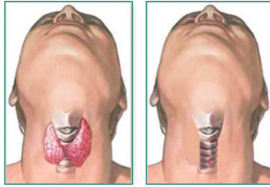
I treat Hurthle Cell Carcinoma like an Unfavorable Variant of DTC with 100-200 mCi I-131 based on risk factors

12

Is TOTAL Thyroidectomy required before considering adjuvant tx?

Total Thyroidectomy

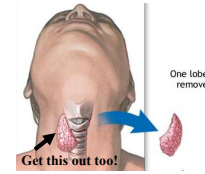
The Removal of The Thyroid Gland



13

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 > 1cc 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

14

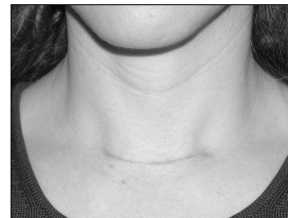
Do we expect our surgical colleagues to ELECTIVELY DISSECT the lateral node stations (L2-4) as they would for other head and neck cancers?



15

No.

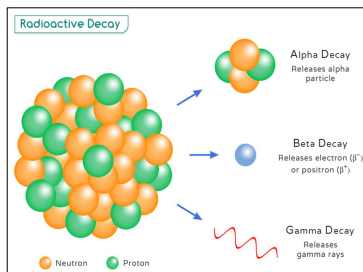
With Thyroid Cancer, **Elective Neck Dissection is NOT done for L2,3,4, or 5** because I-131 is good at eliminating micro residual tumor. (There's controversy about Elective Dissection of L6)



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

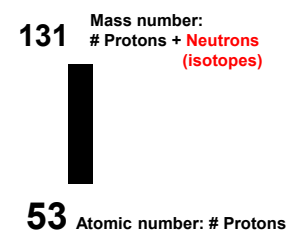
16

Radioiodine (RAI): I-131



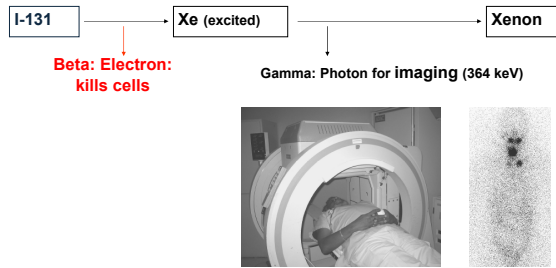
17

Radioiodine (RAI): I-131



18

Radioactive Emissions of I-131



19



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?

20

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

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:
 Seaweed and shellfish containing iodine salts (Do not eat iodized salt or sea salt).
 Processed foods: Many commercially prepared foods contain iodized salt.
 Seafood: Fish, shell fish, sea urchin, 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 use ingredients because it usually contains iodized salt.
 Commercial bakery products: Commercial bakery products like bread, rolls, muffins, and pastries often contain iodized salt or iodine through conventional processing.
 Household items: Many household items contain iodine.
 Eggs: Eggs contain iodine. Egg whites are OK on this diet.
 The following additional products contain iodine: Cereals, grains, legumes, corn, coconut oil, soybean oil, sunflower oil, canola oil, olive oil, vegetable oil, and many others.
 What can you eat? Unprocessed (fresh or frozen) fruits, vegetables, dry beans, and most grains that are not iodized. Eat these foods.
 Other foods that may contain iodine: Iodine-free salt, potassium-free products (e.g., soy sauce, soy milk, miso, nutmeg, nut butter, etc.), coconut flour, and many others. See your doctor for more information.

WHAT CAN YOU EAT? Unprocessed (fresh or frozen) fruits, vegetables, dry beans, and most grains that are not iodized. Eat these foods.
 Other foods that may contain iodine: Iodine-free salt, potassium-free products (e.g., soy sauce, soy milk, miso, nutmeg, nut butter, etc.), coconut flour, and many others. See your doctor for more information.

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

21

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

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:
 Seaweed and shellfish containing iodine salts (Do not eat iodized salt or sea salt).
 Processed foods: Many commercially prepared foods contain iodized salt.
 Seafood: Fish, shell fish, sea urchin, 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 use ingredients because it usually contains iodized salt.
 Commercial bakery products: Commercial bakery products like bread, rolls, muffins, and pastries often contain iodized salt or iodine through conventional processing.
 Household items: Many household items contain iodine.
 Eggs: Eggs contain iodine. Egg whites are OK on this diet.
 The following additional products contain iodine: Cereals, grains, legumes, corn, coconut oil, soybean oil, sunflower oil, canola oil, olive oil, vegetable oil, and many others.
 What can you eat? Unprocessed (fresh or frozen) fruits, vegetables, dry beans, and most grains that are not iodized. Eat these foods.
 Other foods that may contain iodine: Iodine-free salt, potassium-free products (e.g., soy sauce, soy milk, miso, nutmeg, nut butter, etc.), coconut flour, and many others. See your doctor for more information.

WHAT CAN YOU EAT? Unprocessed (fresh or frozen) fruits, vegetables, dry beans, and most grains that are not iodized. Eat these foods.
 Other foods that may contain iodine: Iodine-free salt, potassium-free products (e.g., soy sauce, soy milk, miso, nutmeg, nut butter, etc.), coconut flour, and many others. See your doctor for more information.

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

22

I-131 Indications and dose



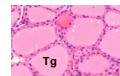
Indications for different doses of I-131 vary between published guidelines



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

23

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

24

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 TREATMENT OF METASTATIC THYROID CANCER*
 By: RICHARD S. MENON, M.D., NARAYAN S. CHOLE, M.D., MARTIN ROSENBERG, M.D., Ph.D., and ROBERT A. HANAUER, M.D.
 JCO 1994; 12:155-160

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

Bottom Line:

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

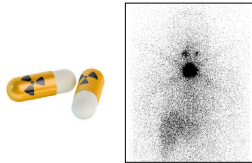
Very Low Risk:	no I-131
Low Risk:	30 or 50 mCi
Intermediate Risk:	100 or 150 mCi
High Risk:	200 or 250 mCi

25

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	All must be present: pT1-2, pN0-1a, M0 ≤5 positive nodes No DNE Negative margin Postoperative Tg < 1.0 ng/mL
zero mCi	All other scenarios
30 mCi	If any are present: pT3b, S1ap muscle invasion ≤4 positive nodes ≤5 positive nodes INE that is not extensive† Positive margin and postoperative Tg [§] ≥ 1.0 ng/mL
100 mCi	If any are present: pT4 Invasion of RLN, Trachea, Esophagus Extensive INE‡ MI (with the exception of large volume disease)
150-200 mCi	
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 <5y 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	
Visible Dx 150-200 mCi	
High Risk of micro residual dz after salvage surgery	
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 metastases, 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, extracapsular extension) We do not retreat with I-131 when the risk of another I-131 treatment is high (severe 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	

26

Good Luck with I-131 for Thyroid Cancer

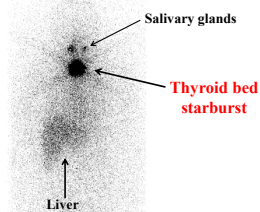


Questions?

27

The best "total thyroidectomy" is really a **NEAR TOTAL**

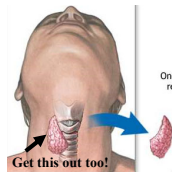
Total body scan 7 days after 150 mCi I-131



28

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 > 1cc 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?

29

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

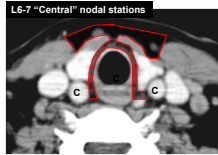
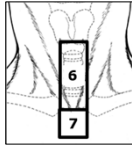
Are Thyroid Cancer N stages similar to HN Scca?

30

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

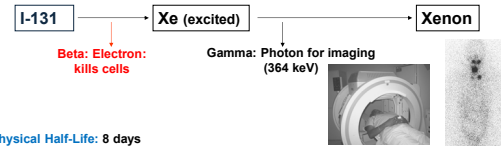
8th Edition AJCC: Thyroid Cancer (all histologies)

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



31

Radioactive Emissions of I-131

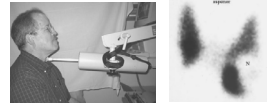


I-131 Physical Half-Life: 8 days

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

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



32