Radioiodine Refractory Differentiated Thyroid Cancer:

Upd[illegible]he Classifications 2022

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Financial Disclosures

- **Jubilant Draximage** Consultant
- **Eisai** Consultant

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- **Rule #1: Reduce verbiage**
- **However, I will be violating rule #1.**
  - **Douglasvannostrand@gmail.com**
  - **Radioiodine refractory differentiated thyroid cancer: time to update the classifications. Thyroid. 2018;28:1083-93.**

Objectives:

1. Distill the classifications of radioiodine refractory DTC,

2. List the sources and literature supporting those classifications, and

3. Discuss the limitation of those classifications.

Objectives:

4. Propose next steps for revision of the classifications of radioiodine refractory DTC,

5. Submit potential approaches and caveats to help manage and minimize a patient from being excluded from an ^{131}I therapy that may have potential benefit, and

6. Discuss future areas of research.

Acknowledging:

The many individuals from many institutions and committees for their pioneering time and energy in the initial development of classifications to help determine better which patients with DTC are and are not radioiodine refractory

14th International Thyroid Congress

- September 2010
- Paris, France

Brose, et al. Regional approaches to the management of patients with advanced radioactive iodine-refractory differentiated thyroid carcinoma. Expert Rev Anticancer Therapy 12:1137-1147.

Panel of experts

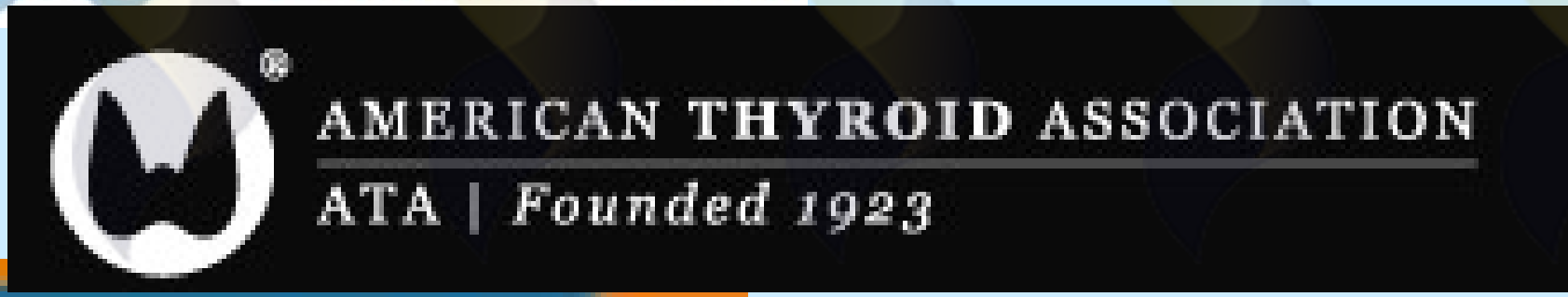
- 2012
- Pisa, Italy
- Sponsored by SciStrategy Comm
- Supported by Bayer HealthCare

Schlumberger, et al. 2014 Definition and management of radioactive iodine-refractory differentiated thyroid cancer: recommendations by an international expert panel. Lancet Endo 2:356. www.thelancet.com/diabetes-endocrinology .

Many more publications discussing classifications over the years:

- **Tuttle et al.** 2014 Defining RAI refractory thyroid cancer. When is RAI therapy unlikely to achieve a therapeutic response? Available at: www.thyroidmanager.org/chapter/s2-defining-rai-refractory-thyroid-cancer-whenis-rai-therapy-unlikely-to-achieve-a-therapeutic-response/(accessed December 6, 2017).
- **Sacks et al.** Endo Pract 2015;20:263-275
- **Haugen, et al.** American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26:1–133.

rtinique Working Group



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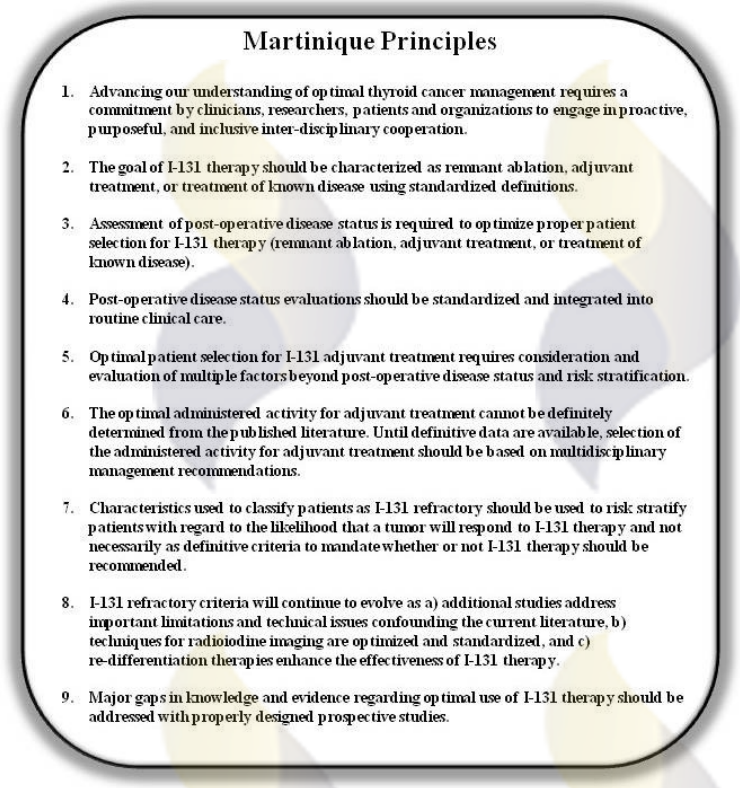


Martinique Principles

1. Advancing our understanding of optimal thyroid cancer management requires a commitment by clinicians, researchers, patients and organizations to engage in proactive, purposeful, and inclusive inter-disciplinary cooperation.
2. The goal of I-131 therapy should be characterized as remnant ablation, adjuvant treatment, or treatment of known disease using standardized definitions.
3. Assessment of post-operative disease status is required to optimize proper patient selection for I-131 therapy (remnant ablation, adjuvant treatment, or treatment of known disease).
4. Post-operative disease status evaluations should be standardized and integrated into routine clinical care.
5. Optimal patient selection for I-131 adjuvant treatment requires consideration and evaluation of multiple factors beyond post-operative disease status and risk stratification.
6. The optimal administered activity for adjuvant treatment cannot be definitely determined from the published literature. Until definitive data are available, selection of the administered activity for adjuvant treatment should be based on multidisciplinary management recommendations.
7. Characteristics used to classify patients as I-131 refractory should be used to risk stratify patients with regard to the likelihood that a tumor will respond to I-131 therapy and not necessarily as definitive criteria to mandate whether or not I-131 therapy should be recommended.
8. I-131 refractory criteria will continue to evolve as a) additional studies address important limitations and technical issues confounding the current literature, b) techniques for radioiodine imaging are optimized and standardized, and c) re-differentiation therapies enhance the effectiveness of I-131 therapy.
9. Major gaps in knowledge and evidence regarding optimal use of I-131 therapy should be addressed with properly designed prospective studies.

Tuttle RM, et al. Thyroid. 2019 Mar 22. doi: 10.1089/thy.2018.0597 [Epub ahead of print].

Radioiodine-refractory DTC

2015 Final ATA Guidelines

Controversial

Radioiodine-refractory DTC

Radioiodine-refractory DTC

We all think we are doing the right thing;

But are we?

My objective is to inform you regarding some of the major limitations in categorizing a patient's differentiated thyroid cancer as radioiodine refractory.

Radioiodine-refractory DTC

2015 Final ATA Guidelines

Recommendation 91

When a patient with DTC is classified as refractory to radioiodine, there is no indication for further treatment. (Weak recommendation, low quality evidence)

Radioiodine-refractory DTC

"I agree with the statement that when a patient is *truly* radioiodine refractory, then that patient should not receive any further ^{131}I."

The operative word is "truly."

However, with the work of Dr. Fagin, Ho, Jaber, Rothenberg, and others, even this has changed.

Radioiodine-refractory DTC

The issues for me are:

First, the classification are frequently taken as definitions, sacrosanct, de facto, inviolable.
Second, the limitations are becoming less and less frequently discussed and less

Radioiodine-refractory DTC

Radioiodine-refractory DTC

I am not trying to tell you what to “drink” or to

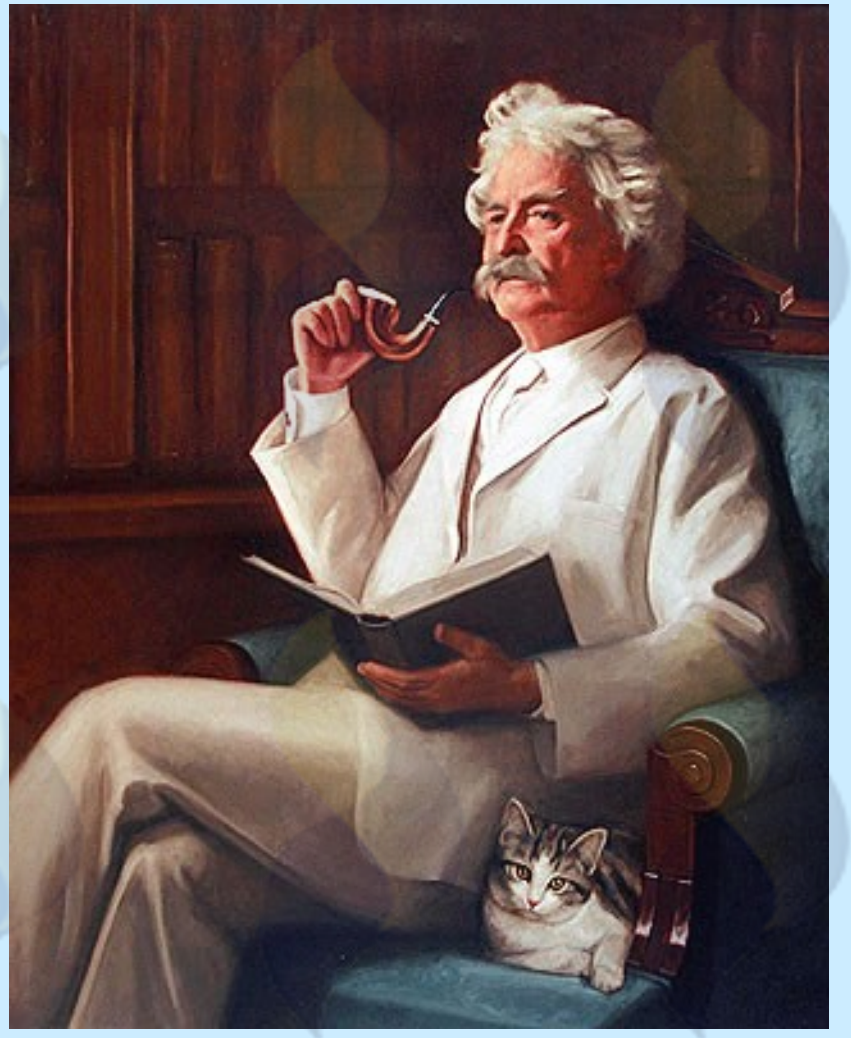
Radioiodine-refractory DTC

But guidelines, despite our disclaimers, are frequently

Radioiodine-refractory DTC

What I want to do is to inform about their

Radioiodine-refractory DTC



"It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so"

Mark Twain

Classification 1

Malignant/metastatic tissue does not concentrate radioiodine on a diagnostic radioiodine scan

Classification 1

Malignant/metastatic tissue does not concentrate radioiodine on a diagnostic radionuclide scan

Not a sacrosanct classification;

In fact, a weak classification.

Classification 1

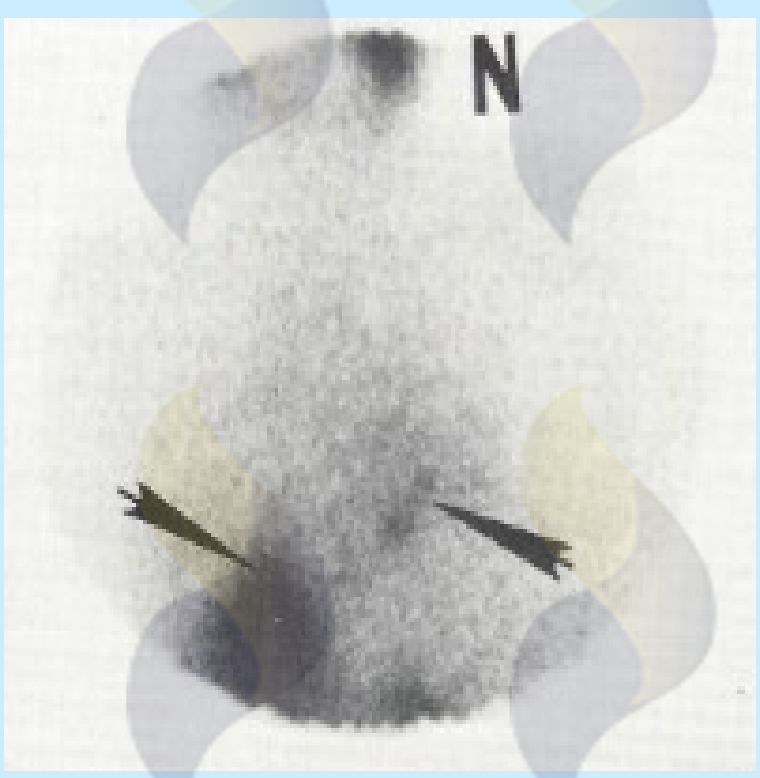
Limitation #1: Poor scan preparation

- No history for recent load of iodide
- No check of urine iodine levels
- For those that prepare patients with THW, no check of TSH

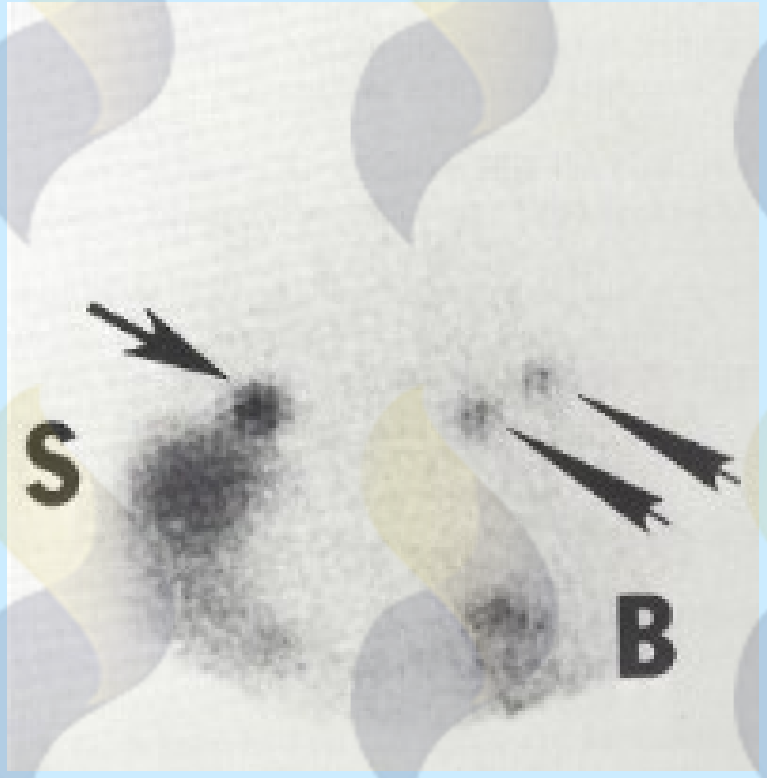
Classification 1

Limitation #2: “Not all scans are created equal”

Panel A



Panel B



Classification 1

Many enhancing techniques frequently not performed

- Spot parallel hole collimator image
- Spot pinhole collimator image
- Longer acquisition time
- Earlier or delayed initiation of images
- Alter contrast and brightness of display
- Additional imaging driven by patient specific history
- SPECT-CT

Thyroid 2019;29:901

Classification 1

Limitation #3: "Many diagnostic scans are negative but post-therapy scans are positive"

Author	% positive postTxWBS
deKeizer	69%
Fatourechi	25%
Kabasakal	63%
Koh	43%
Mazzaferri	80%
Pachucki	64%
Pacini '87	94%
Pacini '01	72%
Pineda	94%
Ronga	64%
Saghari	54%
van Tol	50%
Wells	64%

Classification 1

Malignant/metastatic tissue does not concentrate radioiodine on a diagnostic radioiodine scan

Not a reliable classification even with "appropriate" imaging technique.

Classification 2

Malignant tissue does not concentrate radioiodine on a post-^{131}I therapy scan.

Classification 2

Malignant tissue does not concentrate radioiodine on a post-^{131}I therapy scan.

This is one of the better classifications.

However. . .

Classification 2

Post-therapy scans are not sacrosanct either.

Classification 2

Salvatori, 2013 Nucl Med Com **34**:900-908.

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3 Days	7 Days	Lesions detected
+	+	80.5% (108/134)

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+	-	7.5% (10/134)

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Classification 2

Salvatori, 2013 Nucl Med Com **34**:900-908.

3 Days	7 Days	Lesions detected
+	+	80.5% (108/134)
+	-	7.5% (10/134)
-	+	12% (16/134)

Classification 2

Salvatori, 2013 Nucl Med Com **34**:900-908.

Not the only study

Many other similar studies have been published.

Reference	Total number	Positive only on early scan	Positive only on late scan
Salvatori [36]	134 patients	7.5% (10/134) on 3 day	12% (16/134) on 7 day
Hung [37]	122 lesions	28% (18/63) of lymph nodes, 17% (7/41) of lung mets &16% (3/18) of bone mets 5 % of remnant tissues On 3-6 day	10-11 day scan
Lee[38]	81 patients		5% (4/81) of patients had 5 additional lesions
Chong [39]	52 patients	3 day scan	22% (10/45) lung metastasis and 33% (5/15) bone metastasis on the 7 day
Kodani[40]	24 patients	3 day scan	29% (2/7) lung metastasis and 20% (1/5) bone metastasis on the 7-9day scan

Classification 2

Malignant tissue does not concentrate radioiodine on a post-^{131}I therapy scan.

A good but not a sacrosanct classification, so know the limitations.

Classification 2

But how do I handle this?

- **Perform a scan at 3 and 7 days — not going to happen.**
- **Perform a scan at 3-4 days, and if negative and “high” suspicion for metastases, repeat at 6-8 days.**

Classification 2

Malignant tissue does not concentrate radioiodine on a post-^{131}I therapy scan.

A good but not a sacrosanct classification, so know the limitations.

Classification 3

The tumor tissue loses the ability to concentrate radioiodine after previous evidence of radioiodine-avid disease.

Exactly the same concerns as previously discussed.

Classification 4

Radioiodine is concentrated in some lesions but not in others.

This should not be a classification.

Classification 4

Radioiodine is concentrated in some lesions but not in others.

- So, I have 4 bone lesions that take up radioiodine but one lesion doesn't.

- Does that characterize that patient's disease as radioiodine refractory?

Classification 4

Radioiodine is concentrated in some lesions but not in others.

- Why not treat the non-avid ^{131}I bony lesion with focally directed treatment (e.g. surgery, XRT, etc.), and administer ^{131}I to treat the other 4 bony lesions?

Classification 4

Radioiodine is concentrated in some lesions but not in others.

This should not be a classification.

Classification 5

Metastatic disease progresses despite significant concentration of radioiodine.

- **In my opinion, this is one of the most important classifications.**

However, ...

Classification 5

Metastatic disease progresses despite significant concentration of radioiodine.

The term, “progresses,” needs more specific criteria than just the fact that the patient is “progressing.”

Classification 5

Metastatic disease progresses despite significant concentration of radioiodine.

- If the patient is progressing after a therapy with an activity of 100 mCi of ^{131}I, why is that considered “radioiodine refractory disease”?

- Why isn’t that considered a “radioiodine refractory physician”?

Classification 5

Metastatic disease progresses despite significant concentration of radioiodine.

Likewise

If the patient is progression free, let's say for 14 months after an ^{131}I therapy, why is that considered good for daily administrations of Lenvatinib and refractory for one administration of ^{131}I that was given 14 months earlier?

Classification 5

Metastatic disease progresses despite significant concentration of radioiodine.

The key is the word “progresses,” which needs to be further categorized.

Classification 5

Metastatic disease progresses despite significant concentration of radioiodine.

Why not give another ^{131}I therapy?

Classification 5

Metastatic disease progresses despite significant concentration of radioiodine.

The latter part of this presentation will discuss in more detail "progression."

Classification 6

The patient has received a total of 600 mCi of ^{131}I.

“This should not be a classification”

Classification 6

The patient has received a total of 600 mCi of ^{131}I.

Why 600 mCi?

This threshold was based on reports such as:

- **Durante et al. (JCEM 2006; 91:2892–9)**
- **Huang et al. (Clin Endo 2012;76:439–47)**

that it was unlikely that the patient would benefit with ^{131}I activity above 600 mCi.

Classification 6

The patient has received a total of 600 mCi of ^{131}I.

Why 600 mCi?

However, with cumulative activities of >22 GBq (>600 mCi

- **Durante et al. reported 4% of patients had a response.**
- **Huang et al. reported 12% of patients had a response.**

Classification 6

The patient has received a total of 600 mCi of ^{131}I.

- If they have had more than 600 mCi and " responded," than consider them for another ^{131}I therapy.
- If they have had less than 600 mCi and did not " respond," than consider them potentially radioiodine refractory--

Classification 6

The patient has received a total of 600 mCi of ^{131}I.

"This should not be a classification"

Classification 6

The patient has received a total of 600 mCi of ^{131}I.

“Progression” with specific criteria is a better classification.

posed next steps for of radioiodi actory differentiated thyroid can

A multi-specialty international team has been established to update the classifications of radioiodine refractory differentiated thyroid cancer with extensive discussions of limitations.

oposed next steps for of radioiod actory differentiated thyroid can

This team includes representatives from

- ATA,
- EANM,
- ETA,
- SNMMI,
- ALASBIMN
- CSNM
- SNM India,
- Thyca, and
- Multiple additional individuals.

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In place of implementing "cookbook definitions," recommend:

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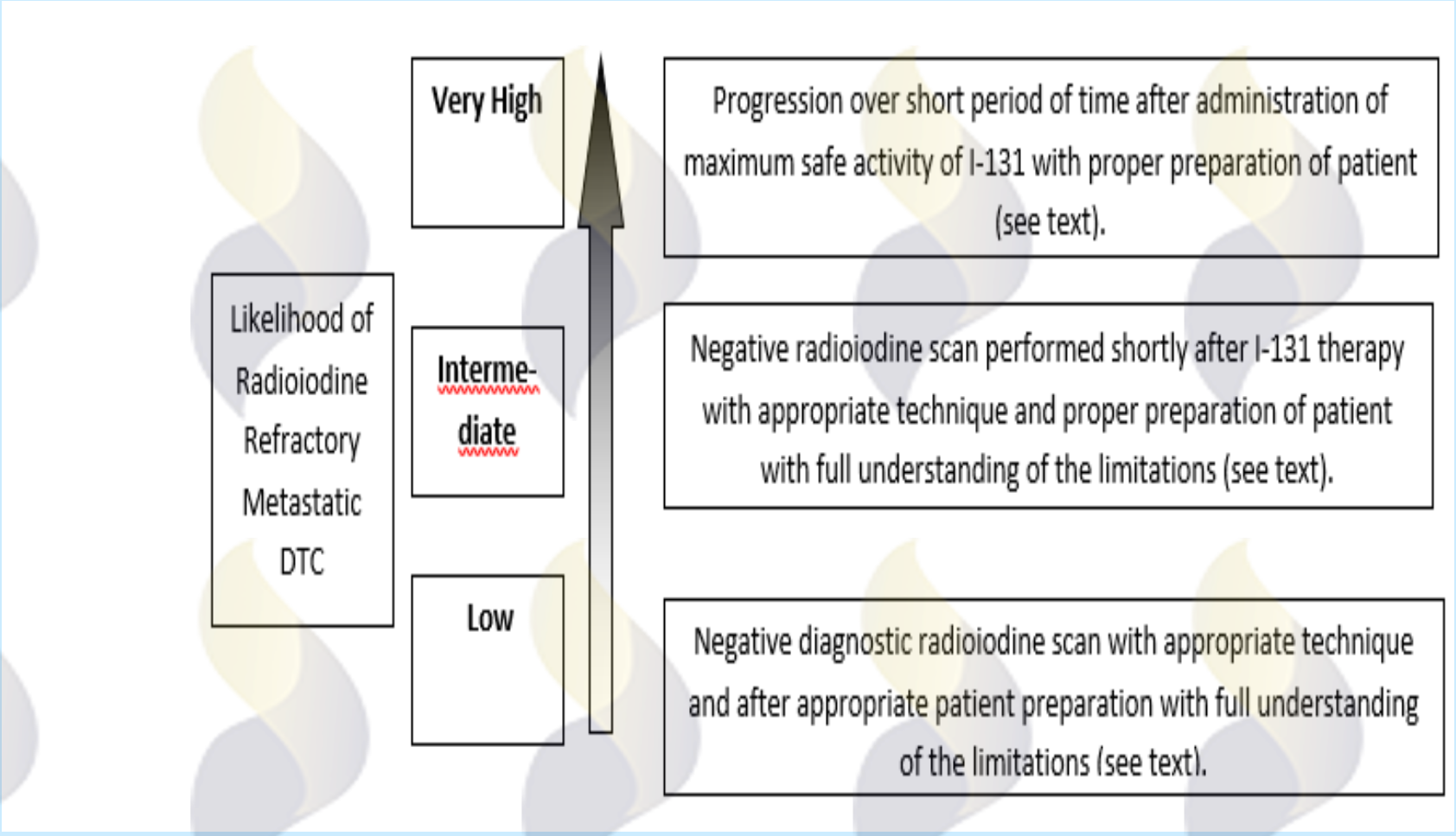

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1. **Consider referring the patient,**
2. **Do not consider a DTC patient to be radioiodine refractory just because the patient's diagnostic radioiodine scan is negative,**
3. **Do not consider a patient's DTC as being radioiodine responsive just because the patient's radioiodine diagnostic or post-^{131}I therapy scan is positive,**
4. **Remember, "Not all scans are**

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5. Assess the quality of the diagnostic and post-^{131}I therapy scan.

- Measure spot urine ,
- Evaluate TSH,
- Assess time of diagnostic imaging after administration of radioiodine ,
- Assure appropriate technique for radioiodine imaging:
  - Not just whole-body imaging but including spot images, pin-hole images, SPECT-CT,
  - Duration of imaging acquisition, time of imaging acquisition, delayed imaging,.

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6. A pre-determined cumulated prescribed activity of ^{131}I should not be a sacrosanct definition of radioiodine refractory disease.

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7.The patient's response to the prior ^{131}I therapy is one of the best classifications—but consider multiple additional factors.

8.Do not use the criterion of just "progression."

9.Assess the character and duration of the response to the

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Warning about next slide

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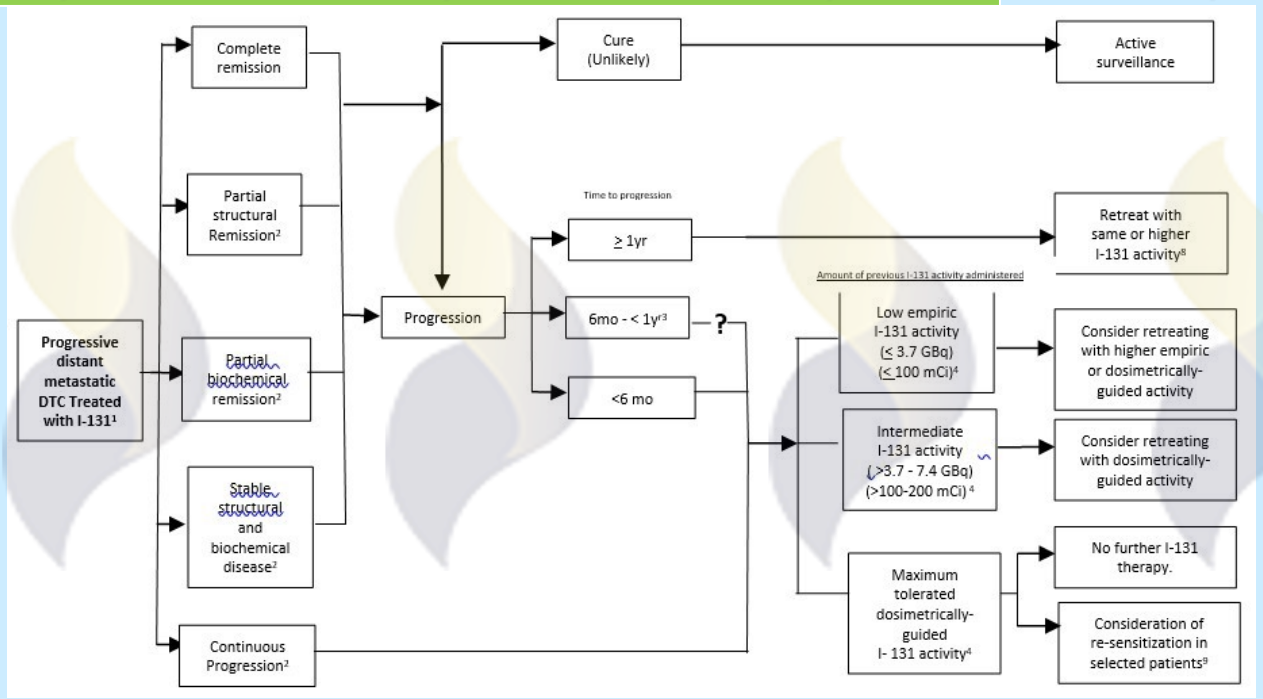

Demonstrates importance of two factors

1. Amount of administered activity of ^{131}I

11. What are the criteria for a response from the prior ^{131}I therapy that warrants consideration of another ^{131}I therapy?

For example:

- **What structural response?**
  - **RECIST criteria**
  - **Modified RECIST criteria**
- **What thyroglobulin response?**
- **What duration of response?**

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12. What additional factors should be considered that may or may not suggest another ^{131}I therapy?

For example:

i. **Amount of ^{131}I activity administered for prior therapy,**

ii. **The frequency and severity of side effects from prior ^{131}I therapies.**

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13. What additional factors should be considered that may or may not suggest another ^{131}I therapy?

For example:

iii. Is the patient a minimalist or maximalist?*

iv. Are you a minimalist or maximalist and how should that affect your patient?

*Your Medical Mind: How to Decide What is

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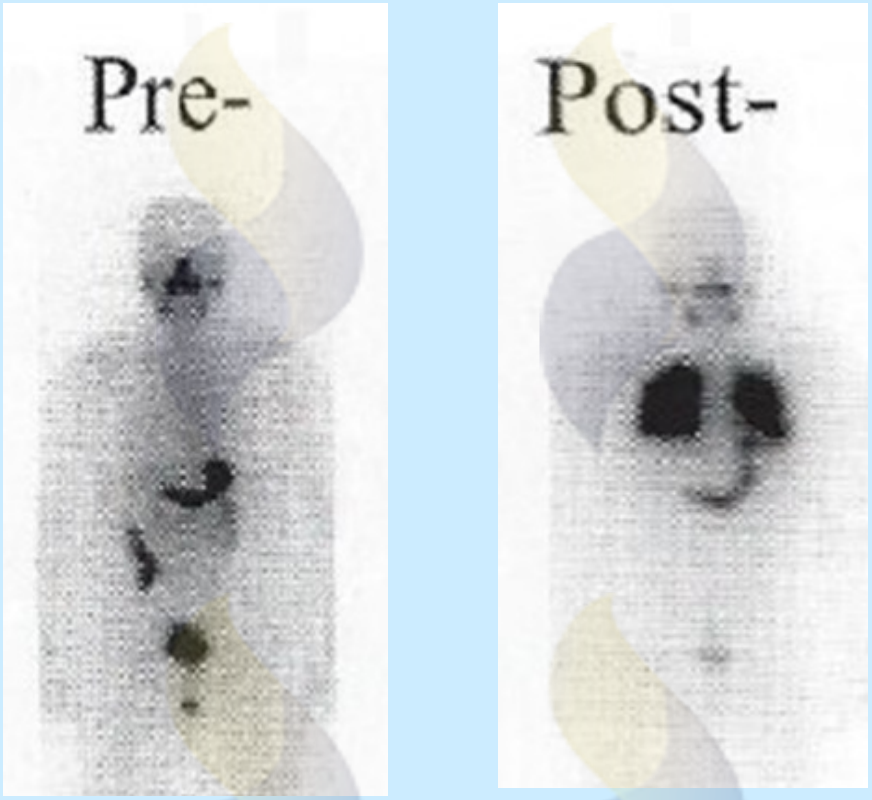
14. Consider referring the patient for clinical trials using trametinib, dabrafenib, and/or other agents.

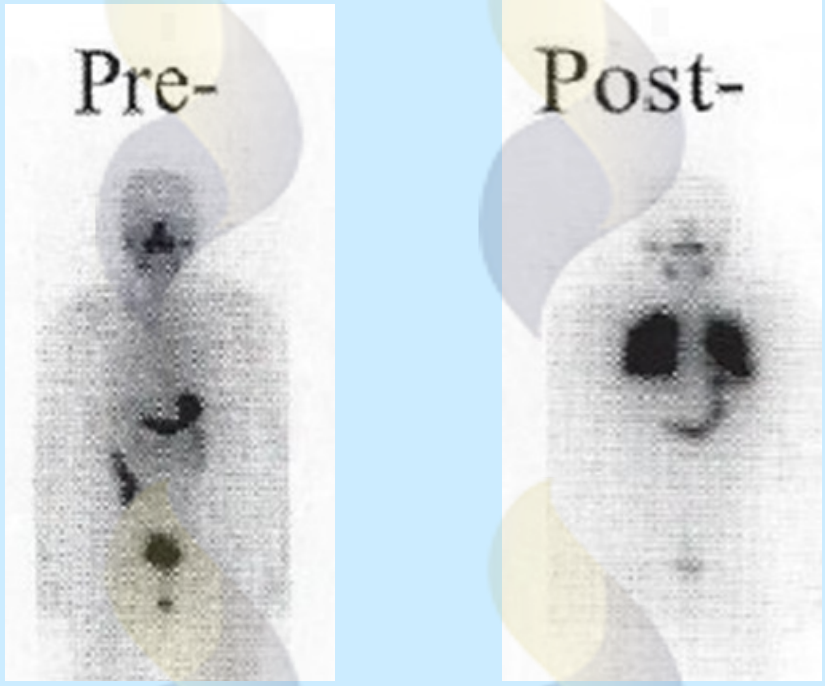
“Things to Come”



Jaber T, J Clin Endocrinol Metab. 103(10):3698-705.

~~"Things to Come"~~

"This is already here"



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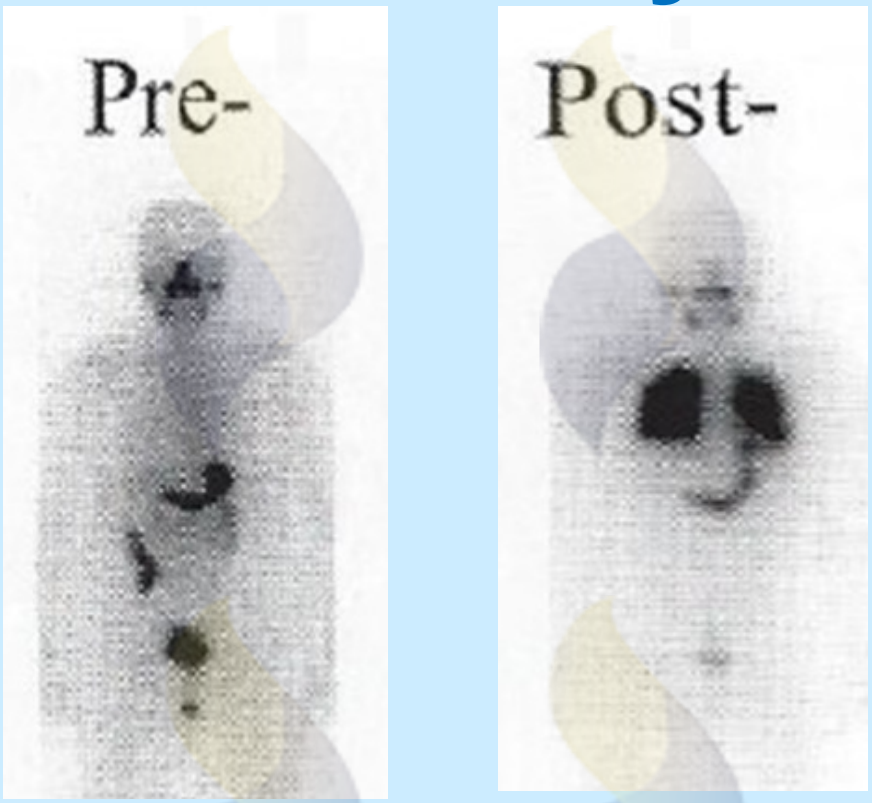

This completely changes the paradigm and classifications of "radioiodine refractory disease."

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14. **Consider a "blind" ^{131}I therapy with either an empiric or dosimetrically-guided prescribed activity of ^{131}I.**

15. **Consider a "30 mCi 'probe" scan.**

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Conclusion

- The various authors who developed and upgraded the classifications are complimented for their pioneering time and efforts.

- The classifications of radioiodine-refractory DTC are not sacrosanct.

- One should know the limitations of the classifications, and

- It is again time to update the classifications.

Remember this image

I am not trying to tell you what to “drink” or to

Remember this image

I hope I have at least informed you regarding the

And also this image.

Special thanks to my past staff of the MedStar Washington Hospital Center Division of Nuclear Medicine

Special thanks to my MedStar Health research staff

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