Controversies in Thyroid Cancer Therapy

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SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

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Disclosures

- Consultant to Jubilant Radiopharma
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- First Attendance Verification Code: 5220

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Learning Objectives

- Individuals attending this presentation will be able to:

- 1. Discuss the value of remnant ablation, and how much I-131 may be needed.
- 2. Discuss the use of dosimetry in the treatment of thyroid cancer and compare the use and value of administered activity versus absorbed dose.
- 3. Discuss the use of pre-therapy scans and post-therapy scans following RAI therapy
- 4. Discuss the difficulty of classifying radioiodine refractory disease.

First - Terminology and Definitions

- Differentiated thyroid cancer (DTC):
- Includes papillary and follicular thyroid cancers
- Also, Hurthle cell cancer, now called oncocytic carcinoma–was considered a category of follicular cancer, but is now a separate entity - reclassified by WHO in 2017
- Does not include medullary or anaplastic thyroid cancer
- Should DTC be called functioning thyroid cancer?
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Terminology and Definitions

- Activity vs. Dose
- Activity – dosage, administered activity or prescribed activity, mCi or MBq
- Dose – absorbed dose, rad/Gray (Gy), rem/Sievert (Sv)

- Remnant Ablation – Destruction or elimination of residual normal thyroid tissue.
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Theranostics

- Definition of Nuclear Theranostics:
- Theranostics is a portmanteau word derived from the terms *therapeutics* and *diagnostics.*
- Nuclear Theranostics is the pairing of diagnostic biomarkers and therapeutic agents that share the same or similar molecular structure and identify (diagnostic agent) and treat (therapeutic agent) the same molecular target.
- This commonality should improve patient selection, prediction of response and toxicity, prognosis, and ultimately, improve outcomes.
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Benefits of I-131 Therapy for DTC

- Solid evidence over many years of clear benefit from I-131 therapy.
- I-131 therapy has clearly shown disease-specific survival and overall survival.
- Refs: Jonklaas, et al. Thyroid. 2006(12):1229-1242
- Carhill, et al. J Clin Endocrinol Metab, Sept. 2015 NTCTCS
- Verburg, et al. JCEM 2014; 99:4487-4496
- Ruel, et al. JCEM 2015; 200:1529-1536
- Mazzaferri and Kloos. 2001;86(4):1447-1463
- I-131 therapy is clearly superior to external beam radiation.
- Ref: Yang, et al, Thyroid 2017: 27(7):944-952
- Courtesy of Anca Avram, MD

Mortality – I-131 Therapy vs. External Beam Therapy

- 11,832 pts (PTC: 91.24%, FTC: 8.76%)
- All cause mortality:
- PTC cohort:
- 5y mortality: 22.7% w/o RAI vs. 11.0% w adjuvant RAI
- 10y mortality: 25.5% w/o RAI vs. 14.0% w adjuvant RAI
- FTC cohort:
- 5yr mortality: 45.5% w/o RAI vs. 29.2% w adjuvant RAI
- 10yr mortality: 51% w/o RAI vs. 36.8% w adjuvant RAI

- Ref: Yang et al, Thyroid 2017; 27(7):944-952. Comparison of Survival Outcomes Following Postsurgical RAI Versus External Beam Radiation in Stage IV DTC

Standard of Care for Differentiated Thyroid Cancer

- First: Diagnosis
- Next: Subtotal/near total thyroidectomy
- Postoperative management: may vary between providers
- 1) Thyroglobulin Ag/Ab measurement,
- 2) Neck ultrasound,
- 3) Diagnostic whole-body scintigraphy (with I-131 or I-123) – assists in characterizing tumor I-131 avidity, identifies extent of disease.

Standard of Care for Differentiated Thyroid Cancer

- 4) Post I-131 therapy whole body scintigraphy (utilizing the administered I-131 given for therapy). This scan assists in characterizing tumor I-131 avidity and identifies extent of disease.
- This scan is critically important for evaluation of disease status and determination of follow-up treatment, especially administered activity of I-131.
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Standard of Care of Differentiated Thyroid Cancer

- There are two main approaches to I-131 therapy:
- 1. Theranostic technique – utilizes the information derived from the postoperative whole body scan (WBS)
- 2. Risk-based or empiric approach based on clinical-pathologic factors and institutional protocols.
- Each of these techniques has strengths and limitations. However, I think the theranostic approach will ultimately prevail.
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Standard of Care for Differentiated Thyroid Cancer

- I-131 therapy (Overall term: **therapy**)
- Types of I-131 treatments are classified as follows:
    1. Remnant ablation
    2. Adjuvant treatment
    3. Treatment of known disease
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Types of I-131 Treatments

- Post diagnosis and post surgery I-131 treatment is classified as follows:
- **Remnant ablation –** eliminate normal thyroid tissue. Purpose: facilitates follow-up by improving subsequent detection of residual or recurrent disease.
- **Adjuvant treatment –** to irradiate suspected but unproven sites of malignancy. Purpose: reduce risk of recurrence and prolong survival.
- **Treatment of known disease** (persistent or recurrent, locoregional or metastatic)
- Diagnostic scan (including with SPECT/CT) – may be helpful
- Post therapy scan – essential/critically important – to assess presence and severity of metastatic disease, provides basis for subsequent ^{131}I therapy.
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Factors Determining Prescribed Therapeutic I-131

- Treatment objectives (cure, progression free survival, palliation)
- Time interval since previous I-131 treatment
- Amount of I-131 administered for the most recent treatment
- Response to the most recent treatment
- Total cumulative therapeutic activity of I-131
- Frequency and severity of side effects from previous I-131 treatments
- Take into account patient wishes and concerns
- Capabilities of the treating facility
- Regulations – Federal, State, Local

A Possible Risk-Based Strategy for RAI Therapy for DTC

- Activities listed below are one set of recommendations
- Remnant ablation – 30-150 mCi (1.11-5.55 GBq)
- Adjuvant treatment – 100-150 mCi (3.7-5.55 GBq)
- Small volume locoregional disease – 100-150 mCi (3.7-5.55 GBq)
- Advanced locoregional disease or small volume distant metastases – 150-200 mCi (5.55-7.4 GBq)
- Treatment of extensive distant metastatic disease- >200 mCi (>7.4 GBq), to maximum tolerated safe I-131 activity
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Risk Stratification – Risk of Structural Disease Recurrence

- Low risk – Intrathyroidal DTC, ≤5 LN (<0.2 cm)
- Intermediate risk – Aggressive histology, minor extrathyroidal extension, vascular invasion, >5 LN (0.2-3 cm)
- High risk – Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or LN >3 cm

- Accurate staging and risk assessment post surgery are essential for optimizing patient management.
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Remnant Ablation

- By definition, remnant ablation is the complete elimination (or destruction) of all normal thyroid tissue.
- Purpose: Since normal thyroid is more efficient at uptake of iodine, removing normal tissue will reduce serum thyroglobulin and facilitate detection of residual or recurrent tumor.
- Remnant ablation with I-131 is considered a safe and effective method for eliminating residual normal thyroid tissue.
- Ref: Bal CS and Padhy AK. World J Nucl Med. 2015; 14(3):144-155
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Remnant Ablation

- Remnant ablation is generally performed 4-6 weeks following subtotal/near total thyroidectomy.
- Substantial controversy regarding how much administered activity for remnant ablation.
- Some advocate 30-50 mCi.
- However, some NM physicians use 100 -150 mCi.

Remnant Ablation

- 30 mCi vs. 100 mCi.
- Post-surgical thyroid ablation with low or high radioiodine activities results in similar outcomes in intermediate risk DTC patients.
- Low = 30-50 mCi, High = 100 mCi or greater
- Conclusion: **In DTC patients at intermediate risk**, high RAI activities given for ablation have no major advantage over low activities.
- Ref: Castagna MG, et al, Eur J Endo. 2013; 169:23-29

- "30 mCi is equally as **effective** as 100 mCi"
- "30 mCi is equally as **ineffective** as 100 mCi"

Remnant Ablation

- However, the important consideration is absorbed dose, not how many mCi are given.
- Absorbed dose depends on administered activity, % uptake, and remnant mass.
- The absorbed dose necessary to provide remnant ablation is generally thought to be 300 Gray (Gy) = 30,000 rad.
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- Ref: Maxon, et al. NEJM. 1983; 309:937-941
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- Courtesy of D. Van Nostrand

Problematic Leboulleux, et al article in NEJM

- Leboulleux, et al, Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer
- Study evaluated thyroid cancer patients who were “low-risk”, one arm treated with 30 mCi (1.1GBq) vs. no RAI. Patients were followed for 3 years.
- Their conclusion: No radioiodine treatment is noninferior to any amount of radioiodine treatment for remnant ablation.
- **Several problems with this article**.
- N Engl J Med 2022; 386(10):923-932

2. "Absence of Evidence is Not Evidence of an Absence."

- Non-inferiority studies are required.
- Power is to be a non-inferiority study and to reach statistical significance.
- Power means higher numbers of observations.
- No good non-inferiority studies.

Courtesy of D. Van Nostrand

Leboulleux, et al article in NEJM

- N Engl J Med 2022; 386(10):923-932
- Their conclusion that no radioiodine treatment is noninferior to any amount of radioiodine treatment for remnant ablation is not justified. Several issues:
- The article only addressed “low-risk” patients.
- They only evaluated 30 mCi. 30 mCi is likely insufficient in many patients.
- A follow-up of 3 years is insufficient.
  Probably need at least 10 years of follow up.

Whole-body Diagnostic Scintigraphy (WBS)

- Obtain postoperative/pretherapy whole body diagnostic scan with I-131 (or I-123 or I-124) to identify and localize regional and distant metastases and determine the RAI-avidity of these lesions. This information is used in planning subsequent I-131 treatment.
- **Warning** – these scans frequently do not detect all lesions.
- Management may be altered due to findings on the diagnostic whole body scan (findings may alter activity of administered I-131 or avoid unnecessary I-131 treatment).
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Diagnostic Pre-therapy Scan

- Diagnostic scan prior to I-131 therapy for thyroid cancer - 1-5 mCi
- 1-2 mCi of I-131 is best to avoid the rare complication of stunning.
- Diagnostic scan with I-123 – avg 275 microcuries

- **Pregnancy and lactation are absolute contraindications to I-131 therapy**

Whole-body Diagnostic Scintigraphy (WBS)

- Use of SPECT/CT with the postoperative diagnostic scan may provide additional useful information, such as:
  a. distinguishing thyroid remnant from nodal metastasis,
  b. detecting metastasis in normal-sized cervical lymph nodes,
  c. detecting pulmonary micrometastases or bone metastases.
  d. provide information for dosimetry.

Post Surgery Post Therapy Scan

- Post therapy scan (use of the therapeutic administration for the scan - no additional administered activity is necessary). This is critically important for evaluation of disease status and determination of follow-up treatment, especially administered activity of I-131.
- Remnant ablation enables high sensitivity post-therapy WBS for diagnosis and localization of residual tumor postoperatively.
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Whole-body Diagnostic Scintigraphy (WBS)

- Post therapy whole body diagnostic scans (WBS) with I-131 can be performed at 2-10 days post I-131 treatment. Optimal timing is 5-7 days post I-131 treatment.
- Post therapy scans are critically important for localization and evaluation of regional or distant metastases and planning for subsequent I-131 therapy.

I-131 Treatment

- Early identification of regional and/or distant metastases may allow for successful I-131 treatment which likely will improve outcomes.
- Postoperative whole body RAI scintigraphy (WBS) predicts localization of therapeutic I-131 and is important for planning for future I-131 therapy.

I-131 Treatment – Lesional Dosimetry

- Determination of minimal administered activity to achieve desired therapeutic outcome:
- Improved therapeutic response based on lesional dosimetry.
- At least 8,000 rad to prevent progression of metastases. (1)
- >2000 cGy (2000 rad) lesion dose improved response rate in advanced DTC (2)

- Ref: 1. Maxon, et al. NEJM. 1983; 309:937-941
- 2. Ho A, et al. N Engl J Med. 2013 Feb 14;368:623-632

Courtesy of D. Van Nostrand, MD

2 Main Approaches to I-131 Therapy

- 1) A. Dosimetric approach. Combines the information obtained from postoperative diagnostic RAI scans (using I-131 or I-123) in planning I-131 treatment. Warning – diagnostic scans have reduced sensitivity compared to post I-131 therapy scans.
- B. Maximum tolerated activity – maximum exposure to bone marrow.
- 2) Risk-based approach, which utilizes clinical-pathologic factors and institutional protocols to determine I-131 treatment.
- “Currently, no conclusive evidence as to which approach will result in better outcomes.” – **INCORRECT!!**
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I-131 Therapy

- "Currently, no conclusive evidence as to which approach will result in better outcomes" (i.e., survival). **- INCORRECT**
- However, there is published data that use of dosimetry can minimize side effects to bone marrow.

- Refs:
- 1. Kulkarni, et al. Thyroid 2006; 16:1019-1023
- 2. Esposito, et al. J Nucl Med 2006; 47:238P

I-131 Therapy

- Published data demonstrating improved clinical response of metastases using dosimetric approach.
- Metastases in dosimetric group were 70% less likely to progress. Advantage was specifically apparent in locoregionally advanced group.

- Ref: Klubo-Gwiezdzinska J, et al. Efficacy of dosimetric versus empiric prescribed activity of I-131 for therapy of differentiated thyroid cancer. J Clin Endocrinol Metab. 2011; 96(10):3217-3225
- Courtesy of D. Van Nostrand, MD

Dosimetry

- A fixed amount of administered activity can result in a wide range of absorbed dose of tumor
- Lesional dosimetry can result in improved outcomes

Dosimetry – Admin. Activity vs. absorbed dose

- Dewaraja found that with Lu-177 Dotatate, an administered activity of 3700 MBq (100 mCi) resulted in a range of mean absorbed dose to tumor of 6-18 Gy (600-1800 rad).
- An administered activity of 7400 MBq (200 mCi) resulted in a range of 2-77 Gy (200-7700 rad).
- The range depends on uptake, clearance rate and other factors.

- Dewaraja Y, et al. J Nucl Med. 2022; 63:1665-1672

Dosimetry – Admin. Activity vs. absorbed dose

- Richard Wahl found that in treating non-Hodgkin lymphoma with I-131 Tositumomab, the range of administered activity to deliver 75 cGy (75 rad) ranged from 48-200 mCi, 3 patients needed 200-300 mCi and one patient needed 250-300 mCi.
- Clearance rate ranged from 2.5 days – 5 days.

- Wahl R. J Nucl Med. 2005; 26:128S-140S.

Dosimetry

- Wide variation in tumor absorbed dose with standard dosage –
- According to Memorial Sloan-Kettering (MSK), dosimetry is routinely performed to determine the Maximum Tolerated Activity (MTA), generally 200 rad to blood/bone marrow. However, it is also important to identify the minimum effective dose for tumor treatment.

- Bodei L, et al. Eur J Nucl Med Mol Imaging. 2024; 51:325-329.
- Ho A, et al. N Engl J Med. 2013 Feb 14;368:623-632

Dosimetry

- According to Sunderland, patients treated with Lu-177 Dotatate and Lu-177 PSMA-617 are being underdosed with a standard administered activity (dosage) of 200 mCi.
- Routine use of dosimetry needed to adequately treat these patients.
- Need for accurate radioactivity measurement infrastructure.
- Need standardized SPECT quantitative imaging.
- Need standardized dosimetry practices.
- Need data on RPT dose-effect relationships for organs and tumors.
- Sunderland J. Towards Dosimetry as a Biomarker SNMMI Theranostics Mtg presentation Sept., 2023
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Dosimetry

- Need for accurate radioactivity measurement infrastructure.
- Need standardized SPECT quantitative imaging.
- Need standardized dosimetry practices.
- Need data on RPT dose-effect relationships for organs and tumors.
- Need to establish secondary standards calibration laboratories to support clinical trials and practice.
- Develop standard phantom based methodologies to calibrate SPECT/CT systems to support accurate and reproducible absorbed dose calculations.
- Sunderland J. Towards Dosimetry as a Biomarker SNMMI Theranostics Mtg presentation Sept., 2023
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Dosimetry - Conclusion

- With dosimetry, we can treat patients more effectively and safely.
- “In RPT we are currently operating in the late-stage disease space. Watch indications for RPT to migrate to earlier and earlier stages, where it will likely be MOST effective.” – John Sunderland 9/2023
- Quantitative imaging will become increasingly important for RPT
- We need to be able to do dosimetry accurately, which will require standardized dosimetry practices.

- Sunderland J. Towards Dosimetry as a Biomarker SNMMI Theranostics Mtg presentation Sept., 2023

Radioiodine Refractory DTC

- 4 criteria:
- 1. Malignant/metastatic tissue does not concentrate radioiodine. No uptake outside the thyroid bed at the first therapeutic WBS.
- 2. Tumor tissue loses its ability to concentrate RAI after previous evidence of RAI-avid disease (in the absence of stable iodine contamination).
- 3. Radioiodine is concentrated in some lesions but not in others.
- 4. Metastatic disease progresses despite significant concentration of radioiodine.

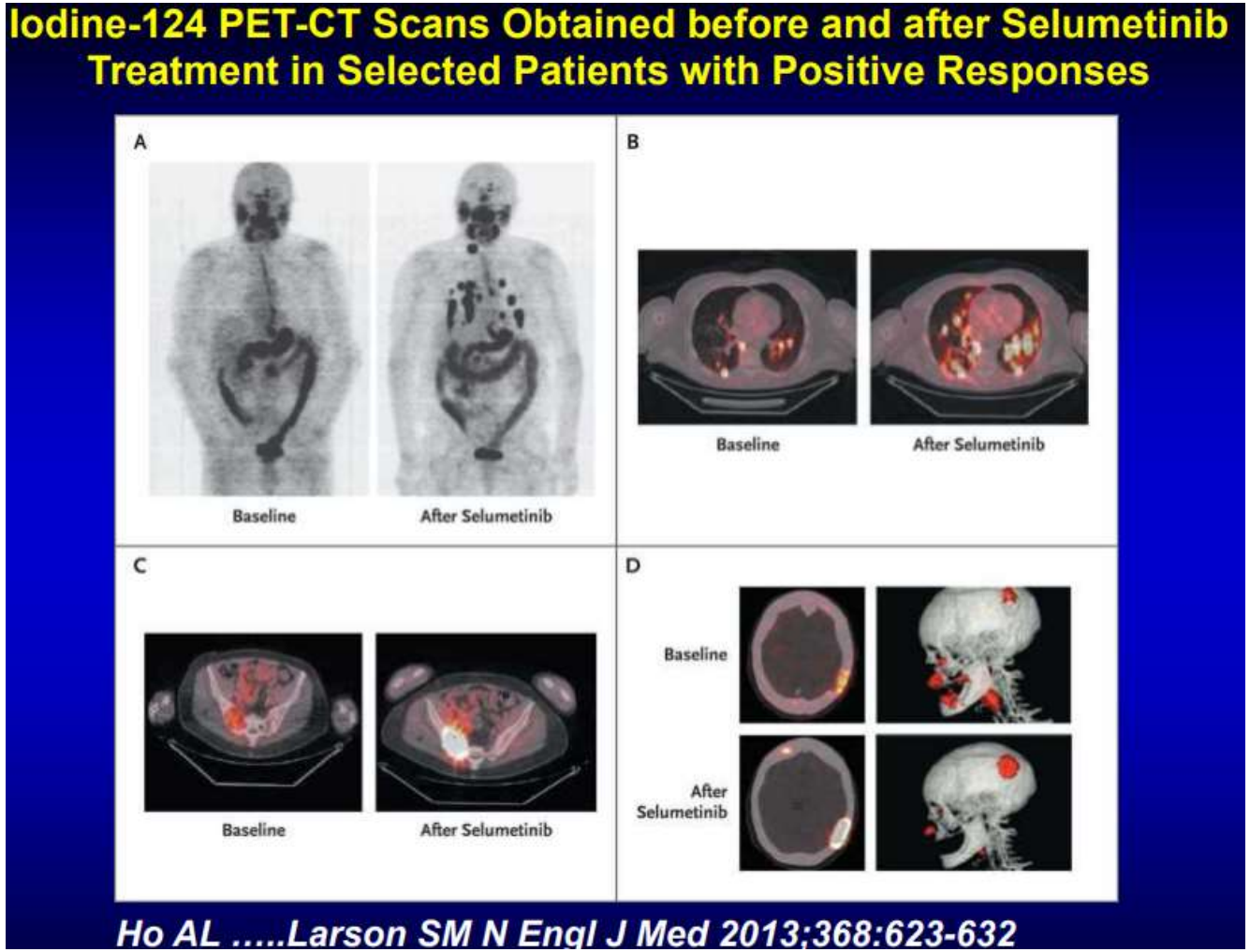
Radioiodine Refractory DTC

- 1. Malignant/metastatic tissue does not concentrate radioiodine. No uptake outside the thyroid bed at the first therapeutic WBS.
- If a patient with postoperative pre-therapy staging scan or post-therapy scan subsequently develops a lesion, is that lesion considered radioiodine refractory because it was not seen on the first pre-therapy scan.
- Possibly metastases were too small to see or occurred after the previous scan.

Radioiodine Refractory DTC

- 1. Patients should not be considered refractory based on no uptake outside the thyroid bed on the first therapeutic WBS.
- Also, considering the development of re-differentiation agents, absence of uptake on a post-therapy scan may not indicate radioiodine refractory disease.

Enhancement of Theranostic Performance



Courtesy of Richard Baum, MD

Radioiodine Refractory DTC

- 2. Tumor tissue loses its ability to concentrate RAI after previous evidence of RAI-avid disease.
- If RAI uptake was seen earlier on a diagnostic scan but is now not seen on a diagnostic scan, the patient should not necessarily be classified as radioiodine refractory. The likelihood increases, but 20-64% of patients have a positive post I-131 therapy scan after treatment despite the diagnostic scan being negative.
- Also, consider use of a re-differentiation agent.

Radioiodine Refractory DTC

- 3. Radioiodine is concentrated in some lesions but not in others.
- These patients are not necessarily radioiodine refractory, as some lesions could be treated with I-131, and other lesions could be treated with one or more of a variety of methods such as radiofrequency therapy, cryotherapy, embolization, and external radiation therapy.
- Again, consider use of a re-differentiation agent.
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Radioiodine Refractory DTC

- 4. Metastatic disease progresses despite significant concentration of radioiodine.
- Problematic for 2 reasons:
- 1) Progressive disease may have been treated with insufficient prescribed activity of I-131, rather than being refractory.
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Radioiodine Refractory DTC

- 4. Metastatic disease progresses despite significant concentration of radioiodine.
- 2) If metastatic disease progresses despite significant concentration of I-131 but metastases responded for a significant time after the last I-131 therapy, consider another therapeutic administration of I-131.
- Progression after a single therapy should not necessarily be considered a failure without consideration of whether or not there was a response, the significance of that response, and the duration of that response.
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Summary/Conclusions

- Discuss the value of remnant ablation, and how much I-131 may be needed.

- Remnant ablation with I-131 is considered a safe and effective method for eliminating residual normal thyroid tissue. Remnant ablation facilitates detection of residual or recurrent disease.
- Optimal administered activity is currently not settled.
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Summary/Conclusions

- Discuss the use of dosimetry in the treatment of thyroid cancer and compare the use and value of administered activity versus absorbed dose.
- Use of lesional dosimetry can improve therapeutic response – prevent progression or metastases, reduce side effects to bone marrow, and hopefully reduce recurrence rates and improve survival.
- Currently, administered activity can be measured very precisely, but absorbed dose cannot. I think this will change in the near future.
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Summary/Conclusions

- Discuss the use of pre-therapy scans and post-therapy scans following RAI therapy.
- Pre-I-131 therapy: These scans may identify and localize regional and distant metastases and determine the RAI-avidity of these lesions. **Warning** – these scans frequently do not detect all lesions.

- Post-I-131 therapy: These scans are critically important for evaluation of disease status and determination of follow-up treatment, especially administered activity of I-131.

Summary/Conclusions

- Discuss the difficulty of classifying radioiodine refractory disease.
- 1. No uptake on a WBS does not necessarily indicate refractory disease.
- 2. Tumor tissue that loses its ability to concentrate RAI after previous evidence of RAI-avid disease may not be radioiodine refractory.
- 3. Radioiodine is concentrated in some lesions but not in others does not necessarily indicate radioiodine refractory disease.
- 4. Metastatic disease progresses despite significant concentration of radioiodine- Not necessarily, need to consider previous response.

Verification Code

- Second Attendance Verification Code: 5225

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- 8. Gulec, et al. A Joint Statement from ATA, EANM, ETA, and SNMMI. Thyroid. 2021; 31(7):1009-1019
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References

- These references include information on activity versus dose:

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