Appropriate Use Criteria for RAI Imaging and Treatment

Standard of Care

Remnant Ablation

Genomics and Molecular Considerations

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Disclosure

- Consultant to Jubilant Radiopharma

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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Appropriate Use Criteria (AUC)

- **Appropriate Use Criteria for Nuclear Medicine in the Evaluation and Treatment of Differentiated Thyroid Cancer**

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- Ref: J Nucl Med 2020; 61(3):375-396

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Why AUCs and why now?

- Beginning January 1, 2023, CMS will require referring physicians to document consulting AUCs via an approved Clinical Decision Support tool when ordering any Nuclear Medicine diagnostic imaging study.
- From CMS.gov:
- https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/appropriate-use-criteria-program

Program Timeline

Currently, the program is set to be fully implemented on January 1, 2023 which means AUC consultations with qualified CDSMs are required to occur along with reporting of consultation information on the furnishing professional and furnishing facility claim for the advanced diagnostic imaging service. Claims that fail to append this information will not be paid. Prior to this date the program will operate in an Education and Operations Testing Period starting January 1, 2020 during which claims will not be denied for failing to include proper AUC consultation information.

Post Diagnosis of Differentiated Thyroid Cancer (DTC) Scenarios

- "Appropriate":
- Initial staging for malignant iodine-avid (IA) thyroid tissue after thyroidectomy
- Assessing and quantifying residual IA remnant tissue
- Posttherapy I-131 localization performed 2-10 days after radioiodine therapy (3-5 and/or 5-7 days are optimal)
- Follow-up/diagnostic/restaging evaluation scan
- Follow-up/diagnostic/restaging eval scan to determine if a structural lesion is IA
- "May Be Appropriate":
- Follow-up/diagnostic/restaging scan with prior negative results of ^{131}I posttherapy images
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Dosage and Protocol Selection - DTC

- Diagnostic scan prior to I-131 therapy for thyroid cancer– I-131, 1-5 mCi
- 1-2 mCi of I-131 is best to avoid the rare complication of stunning.
- Diagnostic scan using I-123 – avg 275 microcuries
- Post therapy scan (use of the therapeutic administration for the scan - no additional administered activity is necessary). This scan is critically important for evaluation of disease status and determination of follow-up treatment, especially administered activity of ^{131}I.
- **Pregnancy and lactation are absolute contraindications to I-131 therapy**

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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AUC Scores :*Appropriate* I-131 treatment of DTC

TABLE 5
Clinical Scenarios for ^{131}I Therapy in Thyroid Cancer

Scenario no.	Description	Appropriateness	Score
1	Ablation of remnant tissue	Appropriate	8
2	Adjuvant ^{131}I treatment	Appropriate	8
3	Treatment of regional and distant metastatic disease	Appropriate	9
4	Treatment of patients with thyroid cancer who have had no prior thyroidectomy	Rarely appropriate	3
5	Thyroid cancer in patient with hemithyroidectomy and remaining residual functioning of thyroid lobe	May be appropriate	4
6	Abnormal Tg (or elevated anti-TgAb) level – no evidence of IA thyroid tissue on whole-body imaging with radioiodine	May be appropriate	5
7	Abnormal Tg (or elevated anti-TgAb) level in patients with no prior response to ^{131}I therapy	May be appropriate	4
8	Patient with history of DTC, uncharacterized new suspicious lesion	Rarely appropriate	2
9	Anaplastic thyroid carcinoma	Rarely appropriate	1
10	MTC	Rarely appropriate	1
11	^{18}F-FDG PET/CT shows ^{18}F-FDG-avid lesion	May be appropriate	5
12	Residual IA thyroid tissue documented with radioiodine imaging after total or near-total thyroidectomy in pregnant or lactating patients	Rarely appropriate	1
13	Pregnant or lactating patients	Rarely appropriate	1

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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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

Benefits of I-131 Therapy

- Strong evidence over many years of clinical benefit from I-131 therapy.
- I-131 therapy has shown disease-specific survival and overall survival.

- References:
- 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

Differentiated Thyroid Cancer

- Differentiated thyroid cancer (DTC):
- Includes papillary, follicular and Hurthle cell cancers
- Does not include medullary or anaplastic thyroid cancer

- Should DTC be called functioning thyroid cancer?

Standard of Care for Differentiated Thyroid Cancer

- First: Diagnosis
- Next: Subtotal/near total thyroidectomy
- Postoperative management:
- 1) thyroglobulin 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

- Postoperative I-131 therapy:
- Goal is determined largely by clinical and pathologic findings, laboratory values, and information from imaging.

- Refs:
- 1. Avram A, et al, 2022; J Nucl Med. 63(2):189-195.
- 2. Van Nostrand D, 2009; Thyroid. 19;1381-1391.

Standard of Care for Differentiated Thyroid Cancer

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

Types of I-131 Treatments

- 1) **Remnant ablation**
- Process of eliminating residual (postoperative) normal thyroid tissue. Rationale: functioning tumor is less efficient than normal thyroid at organifying iodine and producing thyroid hormone.
- Goals: reduce serum thyroglobulin to an undetectable level, which will facilitate follow-up and early detection of recurrence
- Also enables high sensitivity post-therapy whole body scintigraphy for diagnosis and localization of residual tumor postoperatively.
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Types of I-131 Treatments

- 2) **Adjuvant treatment**
- Goal: Treat suspected microscopic but unproven sites of metastasis, based on histopathologic risk factors that predict tumor dissemination beyond the thyroid gland.
- Purpose: reduce risk of recurrence and prolong survival.

- There is commonly overlap of remnant ablation and adjuvant treatment
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Types of I-131 Treatments

- 3) **Treatment of known disease** (persistent or recurrent, locoregional or metastatic)
- Goal: Treatment of regional or distant metastatic disease to eliminate iodine-avid regional disease or distant metastasis to achieve cure or remission, reduce recurrent or persistent disease, and improve overall prognosis and survival.

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 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.
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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 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

Courtesy of D. Van Nostrand

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).
-

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.

Whole-body Diagnostic Scintigraphy (WBS)

- Postoperative diagnostic scan may not detect all or any lesions, and enhancement may be a useful next step.
- Postoperative diagnostic scan may provide information that would indicate additional functional metabolic imaging, such as F-18 FDG PET/CT when non-avid RAI metastatic disease is suspected.
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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.

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 showing 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

I-131 Treatment – Lesional Dosimetry

- Determination of minimal administered activity to achieve desired therapeutic outcome:
- At least 8,000 rad to prevent progression of metastases.
- Improved therapeutic response based on lesional dosimetry.

- Ref: Maxon, et al. NEJM. 1983; 309:937-941
- Plyku D, et al. Annals of Nuclear Medicine. 2022; 36(3):213-223

Courtesy of D. Van Nostrand, MD

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 I-131 therapy.
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I-131 Therapy

- Risk-based or risk-adapted approach
- Administered activity is chosen according to the goal of therapy and the estimated risk of persistent or recurrent malignancy.
- Based on several factors, including local protocols, experience and availability of patient-related parameters, and imaging modalities.

I-131 Treatment – Risk-Based Approach with Dosimetry

- Prescribed activities of I-131 treatment were listed previously
- In diffuse, homogeneous lung metastases, whole body dosimetry is required so that the prescribed administered activity of I-131 results in retention in the lungs of less than 80 mCi (3 GBq) at 48 hours to avoid the complication of pulmonary fibrosis (which can be a fatal complication)
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Response assessment after primary treatment

- WBS 1-2 years after primary treatment
- Used to re-stratify risk of recurrence
- Dynamic risk stratification – predictive of long-term clinical outcome
- Patients with an excellent (complete response) to I-131 treatment have a 1-4% chance of recurrence, a reduction of risk from 36-43% in intermediate risk patients, and from 68-70% in high-risk patients.

I-131 Treatment of advanced disease

- Distant metastases develop in approximately 10% of patients
- Prognosis is variable –
- In some patients, the disease is indolent;
- In some patients the disease is aggressive
- Patients with RAI-avid metastatic disease have a much better prognosis (>90% 10-year survival) than patients with non-iodine-avid metastases (10% 10-year survival).
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Use of genomics in Treatment of DTC

- Most common mutation of papillary thyroid CA is BRAF.
- BRAF mutations degrade ability of malignant thyroid tissue to take up RAI.
- Follicular thyroid CA more often has RAS mutations. These mutations degrade uptake of RAI by malignant thyroid cells less than BRAF tumors.

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.

Theranostics

- **Theranostics** – direct linking of diagnostic information to therapy
- **Theranostic value** – potential of a diagnostic tool to influence therapy
- **Theranostic power** – clinical strength of a theranostic tool determined by biologic and technical factors
- **Theranostic technique** – Contribution of technical factors in enhancement of theranostic power
- **Theranostic performance** – Modifications in theranostic power via modulation of biologic and technical dynamics
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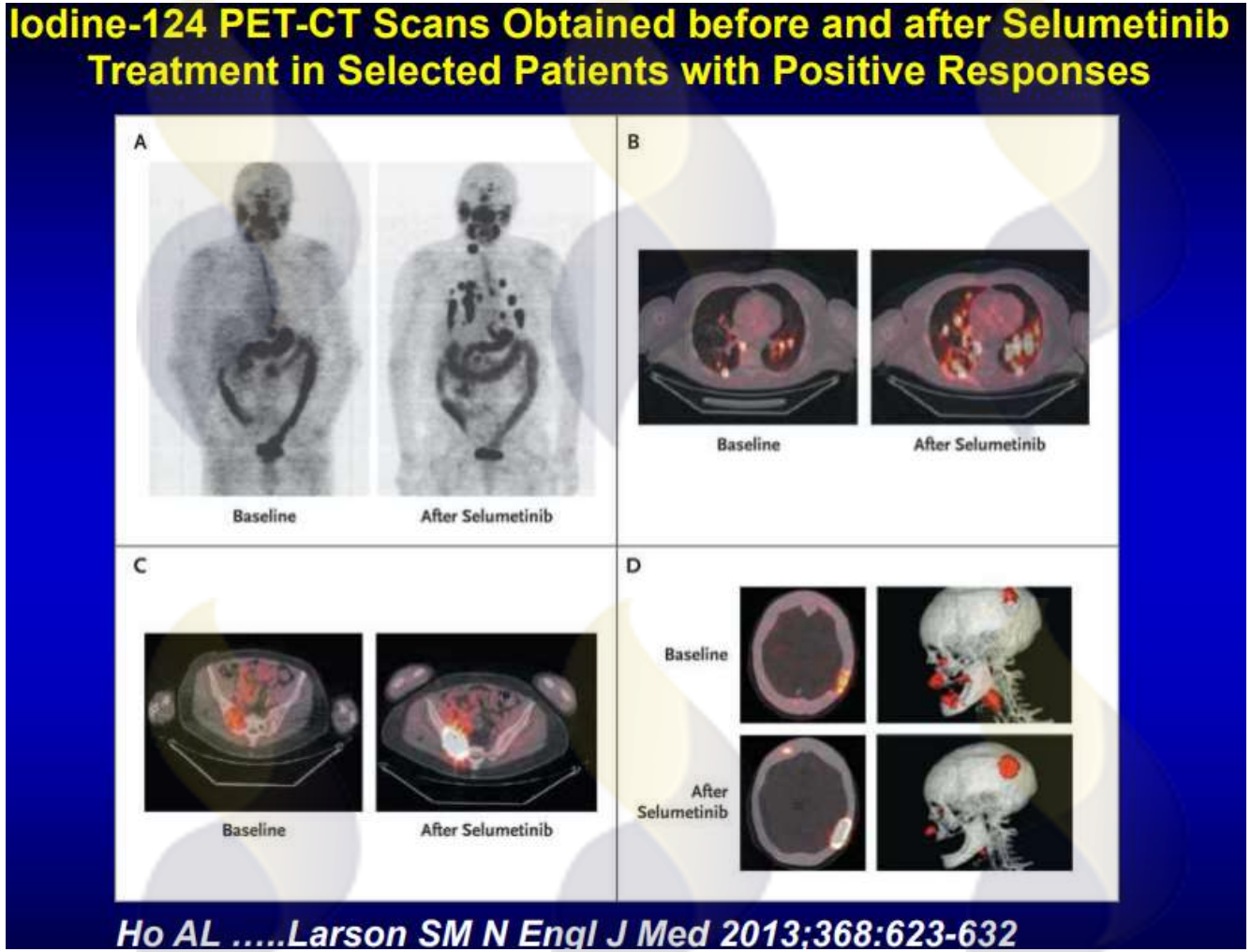
Enhancement of Theranostic Performance



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Courtesy of Richard Baum, MD

Theranostic performance with RAI can be enhanced

- Oncobiology of thyroid cancer decreases theranostic power of RAI
- Selumetinib enhances iodine incorporation in patients with I-131 refractory thyroid cancer and reverses I-131 resistance.
- Selumetinib effects upon iodine incorporation may be dependent on clinical factors and/or tumor genotype.
- Ref: Ho et al: N Engl J Med. 2013 Feb 14; 368(7):623-632. doi:10.1056/NEJMoa1209288

- Selumetinib, Trametinib – MEK inhibitor
- Dabrafenib, Vemurafenib - BRAF inhibitor
-

Thyroid Differentiation Score (TDS)

- TDS is a quantitative molecular measure of functional differentiation (or de-differentiation) of thyroid cancers.
- TDS influences theranostic power of RAI.
- Thyroid cancers with low TDS are “RAI-indifferent”.

Conclusions I - To Improve Outcomes:

- Understand the uses of nuclear theranostics, including theranostic value, theranostic power, theranostic technique and theranostic performance.
- Use of Thyroid Differentiation Score (TDS).
- Incorporation of information from genomics and use of lesional dosimetry will become critically important in the near future.
- Theranostic performance can and should be enhanced.
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Conclusions II - To Improve Outcomes:

- Remnant ablation with I-131 is considered a safe and effective method for eliminating residual normal thyroid tissue, since it facilitates follow-up by improving subsequent detection of residual or recurrent disease.
- Post therapy scans are critically important for localization and evaluation of regional or distant metastases and planning for subsequent I-131 therapy.
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- 1. Gomes MJF, et al. Theranostics in Nuclear Medicine: Emerging and Re-emerging Integrated Imaging and Therapies in the Era of Precision Oncology. Radiographics. 2020; 40(6):1715-1740
- 2. Greenspan BS and Jadvar H. Invited Commentary: Nuclear Theranostics – The Path Forward. Radiographics. 2020; 40:1741-1742
- 3. Donohoe KJ et al. Appropriate Use Criteria for Nuclear Medicine in the Evaluation and Treatment of Differentiated Thyroid Cancer. J Nucl Med 2020; 61(3):375-396
- 4. Avram A, et al. Management of Differentiated Thyroid Cancer: The Standard of Care. J Nucl Med. 2022;63:189-195
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- 8. Gulec, et al. A Joint Statement from ATA, EANM, ETA, and SNMMI. Thyroid. 2021; 31(7):1009-1019