Perioperative Risk Stratification in Differentiated Thyroid Cancer:

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Risk Stratification in Thyroid Cancer

Traditional Risk Stratification
1990

Postoperative Risk Stratification
Primarily on a Basic Pathology Report
Gross tumor invasion
Distant metastasis

Predict Disease-Specific Mortality
Little Emphasis on Risk of Recurrence
Marginal Impact on Therapeutic Decision Making
One Size Fits All Management Approach

Tuttle, Alzahrani, Mini-review, JCEM March 2019

Risk Stratification in Thyroid Cancer

A dynamic, iterative, active process

Peri-Diagnostic Risk Assessment

Candidates for Minimalistic Management

Ideal

Appropriate  *Inappropriate*

Suspicious Nodule → Diagnosis → Thyroid Surgery → Adjuvant Therapy → Follow up

AJCC 8th Edition

Risk of death

Stage I, II, III, or IV

ATA Risk

Recurrent/Persistent Disease

Low, Intermediate, or High

Response to Therapy

Management recommendations

Excellent

Biochemical Incomplete  *Structural Incomplete*

Indeterminate

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Perioperative Risk Stratification

From detection until 4 months after initial surgery

Suspicious Nodule → **Diagnosis** → **Thyroid Surgery** → **Follow up**

Critical Management Decisions Are Made In The Perioperative Period

Extent of Pre-Operative Imaging
Extent of Surgery
Extent of Lymph Node Dissection
Diagnostic and Therapeutic Use of Radioactive Iodine
Extent of Early Postoperative Imaging
Initial TSH goals
Initial Follow-Up Strategy

Gulec et al. A joint statement form the American Thyroid Association, the European Association of Nuclear Medicine, The European Thyroid Association, The Society of Nuclear Medicine and Molecular Imaging on Current Diagnostic and Theranostic Approaches in the Management of Thyroid Cancer. Thyroid 31(7) 2021

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Preoperative Evaluations

Intraoperative Findings

Early Postoperative Testing

Integrate all of this information into staging systems and risk categories in order to improve predictions of disease-specific mortality and disease recurrence.

Guide early management recommendations

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Preoperative Evaluations

- History and Physical Examination
- Diagnostic Evaluation: Cytology, Molecular Findings
- Preoperative Imaging Findings

Guiec et al. Thyroid 31(7) 2021

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Intraoperative Findings

- Extent of thyroid and LN resection
- Gross Extrathyroidal Extension
- Specific Structures Grossly Invaded
- Completeness of Resection
- Interpret the Operative Report

Carty et al, Thyroid 2012 Baxi et al, European Endocrinology, 2017 Gulec et al. Thyroid 31(7) 2021

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Postoperative Findings

- Detailed Pathology Report
- Molecular Characterization
- Functional and Structural Postoperative Imaging
- Postoperative Thyroglobulin and Tg Antibodies

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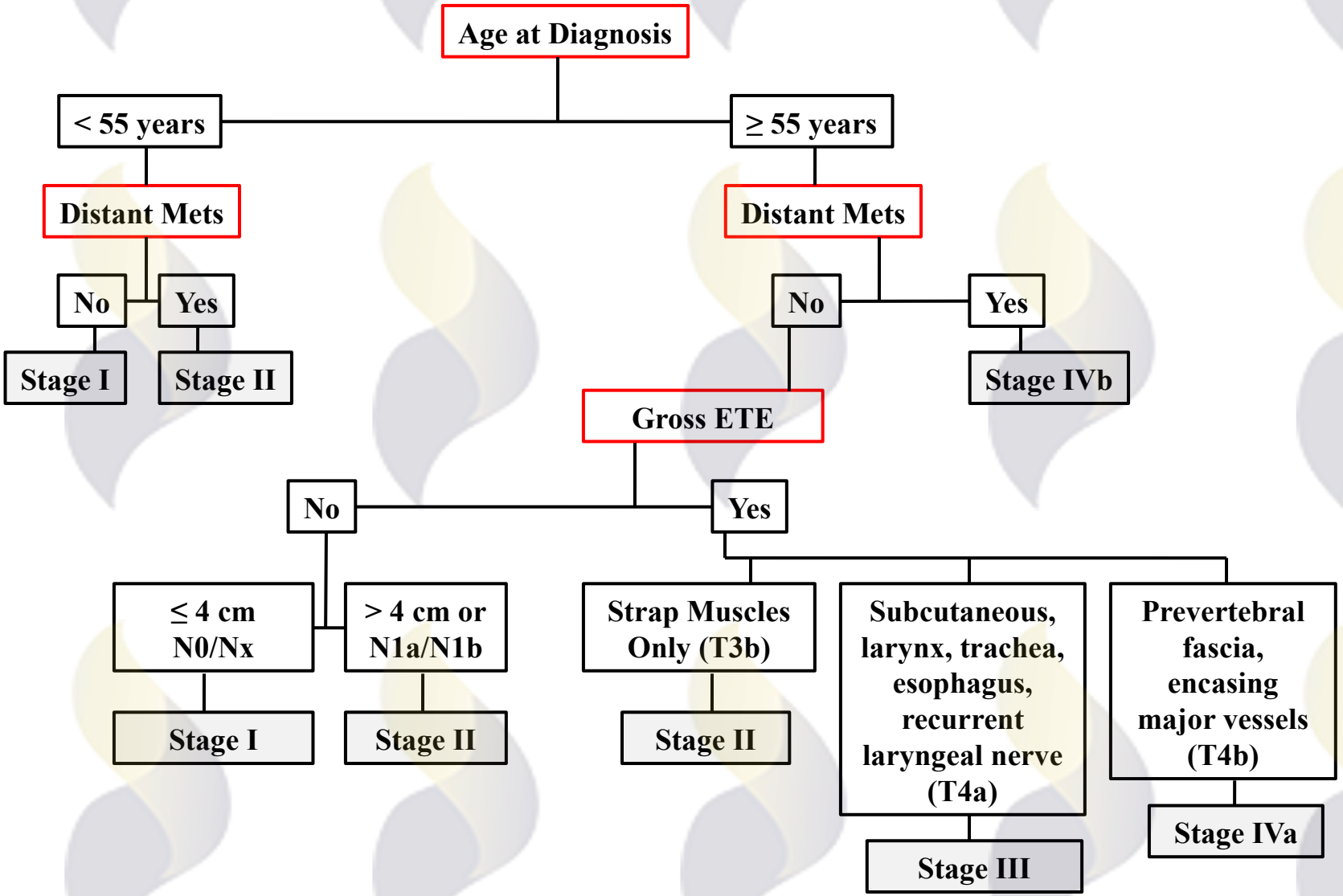
Differentiated Thyroid Cancer
8th Edition AJCC Staging



Tuttle, Haugen, Perrier. Thyroid 2017.

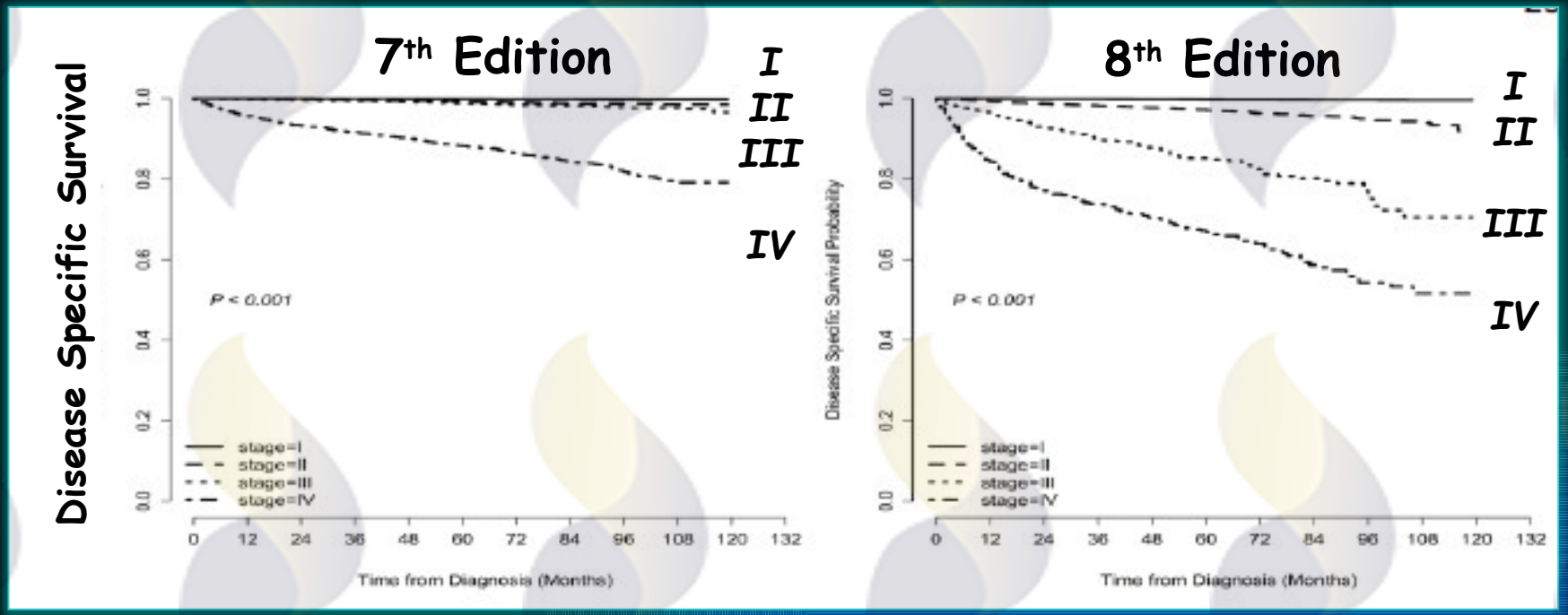
Perrier, Brierley, Tuttle. CA: A Cancer Journal for Clinicians, 2017

Transition from the 7th edition to the 8th edition

Shaha et al, MSKCC Surgical Database, Surgery 2019

Projecting Survival in Papillary Thyroid Cancer: A Comparison of the 7th and 8th Editions of the AJCC/UICC Staging Systems in Two Contemporary National Patient Cohorts

SEER
64,342 patients



Ponfus et al, Thyroid 2017

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ATA Risk Stratification

Predicting the risk of structural disease recurrence

Low Risk
Classic PTC
No local or distant mets
Complete resection
No tumor invasion
No vascular invasion
If given, no RAI uptake outside TB

Intermediate Risk
Microscopic ETE
Cervical LN mets
Aggressive Histology
Vascular invasion

High Risk
Macroscopic gross ETE
Incomplete tumor resection
Distant Mets
Inappropriate Tg elevation

Haugen et al, ATA Thyroid Cancer Guidelines, Thyroid 2016

Role of Diagnostic RAI Imaging in Initial Staging

TABLE 2. PRE-TX RADIOACTIVE IODINE IMAGING IN INTERMEDIATE RISK CATEGORY

	Technical considerations	*Biological considerations*
Sensitivity[a]	• RAI activity dependent • Higher activities are a concern for "stunning"	• Tumor biology dependent • Poor RAI avidity is not uncommon[b] • Higher yield with *RAS*-like tumors
Specificity[c]	• Equal with all RAI isotopes [$^{131}I = ^{123}I = ^{124}I$]	• Challenging for identification accuracy in cervical nodal disease[d]
Spatial resolution[e]	• PET/CT>SPECT/CT>PLANAR	• Same as sensitivity and specificity
	Clinical considerations	
Potential clinical benefit	• Upstaging from N0 to N1 and/or from M0 to M1[f] • The utility of the diagnostic RAI scan is firmly dependent on institutional treatment algorithms and strategies	

[a]Ability to identify RAI-avid foci.
[b]"Differentiated" thyroid cancers, particularly papillary type, most particularly those with BRAF mutations, express variable degrees of RAI avidity.
[c]Ability to distinguish cancer vs. tissues of physiological or nonmalignant tissue.
[d]Thyroid normal presumably, volume small very surgical remnants may be misinterpreted for nodal metastases, leading to false upstaging.
[e]Ability to discriminate areas of uptake as separate foci.
[f]N0 to N1 upstaging may not necessarily change the risk category, and thus may not translate into change in treatment strategy.
CT, computed tomography; PET, positron emission tomography; SPECT, single photon emission computer tomography.

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Role of Diagnostic RAI Imaging in Initial Staging

We support a selective use approach to diagnostic RAI scanning in ATA intermediate-risk patients rather than routine use or denial for all patients in this category.

- Proper Patient Selection
- Risk of Adverse Outcomes
- Likelihood of RAI Avidity
- Impact of Early vs Late RAI Therapy on Outcomes
- Optimization of RAI Diagnostic Scanning

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Expanding the Definition of ATA Low Risk

Papillary thyroid cancer (with all of the following):

- No local or distant metastases
- All macroscopic tumor has been resected
- No tumor invasion of loco-regional tissues or structures
- The tumor does not have aggressive histology
- If 131I is given, there are no metastatic foci outside thyroid bed
- No vascular invasion
- Clinical N0 or ≤ 5 pathologic N1 micrometastases (<0.2 cm in largest dimension)
- Intrathyroidal, encapsulated FVPTC
- Intrathyroidal, well differentiated FTC with capsular invasion and no or minimal (<4 foci) vascular invasion
- Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAFV600E mutated (if known)

Haugen et al, ATA Guidelines, Thyroid 2016

Risk of Structural Disease Recurrence

(In patients without structurally identifiable disease after initial therapy)

High Risk

- FTC, extensive vascular invasion (≈ 30-55%)
- pT4a gross ETE (≈ 30-40%)
- pN1 with extranodal extension, >3 LN involved (≈ 40%)
- PTC, > 1 cm, TERT mutated ± BRAF mutated* (>40%)
- pN1, any LN > 3 cm (≈ 30%)
- PTC, extrathyroidal, BRAF mutated*(≈ 10-40%)

Intermediate Risk

- PTC, vascular invasion (≈ 15-30%)
- Clinical N1 (≈20%)
- pN1, > 5 LN involved (≈20%)
- Intrathyroidal PTC, < 4 cm, BRAF mutated* (≈10%)
- pT3 minor ETE (≈ 3-8%)
- pN1, all LN < 0.2 cm (≈5%)
- pN1, ≤ 5 LN involved (≈5%)
- Intrathyroidal PTC, 2-4 cm (≈ 5%)
- Multifocal PMC (≈ 4-6%)
- pN1 with extranodal extension, ≤ 3 LN involved (2%)
- Minimally invasive FTC (≈ 2-3%)

Low Risk

- Intrathyroidal, < 4 cm, BRAF wild type* (≈ 1-2%)
- Intrathyroidal unifocal PMC, BRAF mutated*, (≈ 1-2%)
- Intrathyroidal, encapsulated, FV-PTC (≈ 1-2%)
- Unifocal PMC (≈ 1-2 %)

*While analysis of BRAF and or TERT status is not routinely recommended for initial risk stratification, we have included these findings to assist clinicians in proper risk stratification in cases where this information is available.

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Initial Static Risk Assessments
Guide initial treatment and early follow-up recommendations

Dynamic Risk Stratification
Continually modify those risk estimates as new data becomes available

Re-evaluate Management Plans
Stay the course
Testing strategy
Interventions

Focus of Yeh

Momesso, Tuttle. Endo Metab Clinic NA. 2014

Response To Therapy Definitions

Excellent Response

No clinical, biochemical, or structural evidence of disease

Biochemical Incomplete Response

Abnormal Tg values or rising Tg Ab levels in the absence of localizable disease

Structural Incomplete Response

Persistent or newly identified loco-regional or distant metastases

Indeterminate Response

Non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant

Haugen, Thyroid 2015. Tuttle, Thyroid 2010 .Vaisman, Clin Endo 2012 . Momesso End Met NA 2014

Using Response to Therapy to Guide Clinical Management

Response	Expected Outcomes	Clinical Implications
Excellent	1-4% recurrence <1% death	Decrease intensity and frequency of follow up and degree of TSH suppression. Use US sparingly.
Biochemical Incomplete	>30% spontaneously resolve 20% develop structural disease <1% death	Observation with stable/decreasing Tg and TgAb. Rising Tg or TgAb should prompt additional investigations.
Structural Incomplete	50-85% will have persistent disease despite additional treatments Nearly all deaths arise from this group	Some require additional treatments. Some can be followed with observation depending on the specifics of the individual case.
Indeterminate	20% develop structural disease <1% death	Continued observation with mild TSH suppression.

Castagna et al. Eur J Endo 2010; Cooper et al. Thyroid 2010; Vaisman et al. Clin Endo 2012
Pitoia et al. Thyroid, 2013 Additional references will be provided in the 2015 ATA thyroid cancer guidelines.

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