Management of Recurrent Thyroid Cancer

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Recurrent Thyroid Carcinoma

Staging systems, such as MACIS, AGES, GAMES, and TNM/American Joint Committee on Cancer(AJCC) provides valuable insights with regard to disease-specific mortality, ***they fail to adequately predict the risk of disease recurrence.***

Baek SK, Jung KY, Kang SM, et al. Clinical risk factors associated with cervical lymph node recurrence in papillary thyroid carcinoma. Thyroid, 2010;20:147–152.

Orlov S, Orlov D, Shaytzag M, et al. Influence of age and primary tumor size on the risk for residual/recurrent well-differentiated thyroid carcinoma. Head Neck 2009;31:782–788.

Tuttle RM, Tala H, Shah J, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine

All papillary thyroid cancer is not the same

THYROID
Volume 28, Number 9, 2018

DOI: 10.1089/thy.2017.0483

Predictors of Neck Reoperation and Mortality After Initial Total Thyroidectomy for Differentiated Thyroid Cancer

Thomas J. Semrad,[1,2] Theresa H.M. Keegan,[2] Alison Semrad,[3] Ann Brunson,[2] and D. Gregory Farwell[4]

Reoperation rate has risen from 3.3% in 1991– 1999 to 6.1% in 2000–2008.

"Neck reoperation is becoming increasingly frequent and is strongly predictive of mortality."

Young S, Harari A, Smooke-Praw S, Ituarte PH, Yeh MW 2013 Effect of reoperation on outcomes in papillary thyroid cancer. Surgery 154:1354–1361; discussion 1361–1352.

Effect of reoperation on outcomes in papillary thyroid cancer

Stephanie Young, MPH,[a] Avital Harari, MD,[a] Stephanie Smooke-Praw, MD, MA,[b]
Philip H. G. Ituarte, PhD, MPH,[a] *and* Michael W. Yeh, MD,[a] *Los Angeles, CA*

Conclusion. “Reoperation is independently associated with mortality in PTC. Most reoperations are performed soon after initial thyroidectomy and likely reflect persistent rather than recurrent disease.”

(Surgery 2013;154:1354-62.)

Recurrent Thyroid Carcinoma

The value of identifying patients at risk for recurrence

in the pre- operative setting

Recurrent Thyroid Carcinoma

Preoperatively, identify patients at risk for recurrence.

1. Patients who present with metastatic disease
2. Aggressive variants
3. Select mutations, i.e. BRAF, TERT

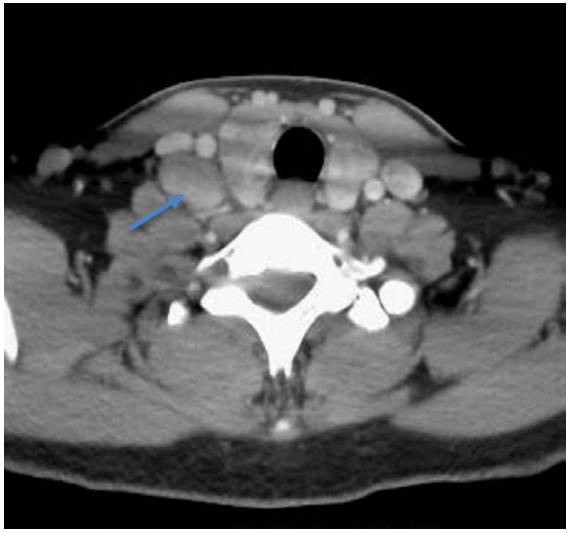
CEO Clinical and Experimental Otorhinolaryngology Vol. 11, No. 1: 58-64, March 2018
https://doi.org/10.21053/ceo.2017.00472
pISSN 1976-8710 eISSN 2005-0720

Original Article

Number of Metastatic Lymph Nodes and Ratio of Metastatic Lymph Nodes to Total Number of Retrieved Lymph Nodes Are Risk Factors for Recurrence in Patients With Clinically Node Negative Papillary Thyroid Carcinoma

Chuan-Ming Zheng[1,*] · Yong Bae Ji[2,*] · Chang Myeon Song[2] · Ming-Hua Ge[1] · Kyung Tae[2]

[1]*Department of Head and Neck Surgery, Zhejiang Cancer Hospital, Hangzhou, China;*
[2]*Department of Otolaryngology-Head and Neck Surgery, Hanyang University College of Medicine, Seoul, Korea*



Lymph Node Ratio of the Central Compartment is a Significant Predictor for Locoregional Recurrence After Prophylactic Central Neck Dissection in Patients with Thyroid Papillary Carcinoma

In Sun Ryu, MD[1], Chan Il Song, MD[1], Seung-Ho Choi, MD[1], Jong-Lyel Roh, MD[1], Soon Yuhl Nam, MD[1], and Sang Yoon Kim, MD[1,2]

[1]Department of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea;
[2]Biomedical Research Institute, Korea Institute of Science and Technology, Seoul, Korea

Ann Surg Oncol (2014) 21:277–283

The location of the nodal disease does not change the risk of eventual recurrence.

Recurrent Thyroid Carcinoma

Preoperatively, identify patients at risk for recurrence.

1. Patients who present with metastatic disease
2. Aggressive variants
3. Select mutations, i.e. BRAF, TERT

Ann Surg Oncol (2012) 19:1874–1880
DOI 10.1245/s10434-011-2129-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Aggressive Variants of Papillary Thyroid Cancer: Incidence, Characteristics and Predictors of Survival among 43,738 Patients

Hadiza S. Kazaure, BSc, Sanziana A. Roman, MD, and Julie A. Sosa, MD, MA

Department of Surgery, Yale University School of Medicine, New Haven, CT

Aggressive variants were associated with higher rates of extrathyroidal extension, multifocality, and nodal and distant metastasis

Tall Cell Variant histology was associated with significantly reduced survival (5-year overall: 87.5% for diffuse sclerosing v, 80.6% tall cell variant vs. 93.5%

Recurrent Thyroid Carcinoma

Preoperatively, identify patients at risk for recurrence.

1. Patients who present with metastatic disease
2. Aggressive variants
3. Select mutations, i.e. BRAF, TERT

The *BRAF*^{V600E} Mutation Is an Independent, Poor Prognostic Factor for the Outcome of Patients with Low-Risk Intrathyroid Papillary Thyroid Carcinoma: Single-Institution Results from a Large Cohort Study

Rossella Elisei, David Viola, Liborio Torregrossa, Riccardo Giannini, Cristina Romei, Clara Ugolini, Eleonora Molinaro, Laura Agate, Agnese Biagini, Cristiana Lupi, Laura Valerio, Gabriele Materazzi, Paolo Miccoli, Paolo Piaggi, Aldo Pinchera, Paolo Vitti, and Fulvio Basolo

J Clin Endocrinol Metab, December 2012, 97(12):4390–4398

Analysis of 431 consecutive **low risk** PTC patients, we selected 319 patients with an intrathyroid tumor and no metastases (T1-T2, N0, M0).

The *BRAF*$_{V600E}$ mutation is a poor prognostic factor for the persistence of the disease independent from other clinical-pathological features in low-risk intrathyroid PTC patients.

Recurrent Thyroid Carcinoma

By identifying these patient is the preoperative setting, we consider our approach to therapy and counsel the patient and the family.

The value of identifying patients at risk for recurrence in the post- operative setting

Recurrent Thyroid Carcinoma

Postoperatively, identify patients at risk for recurrence.

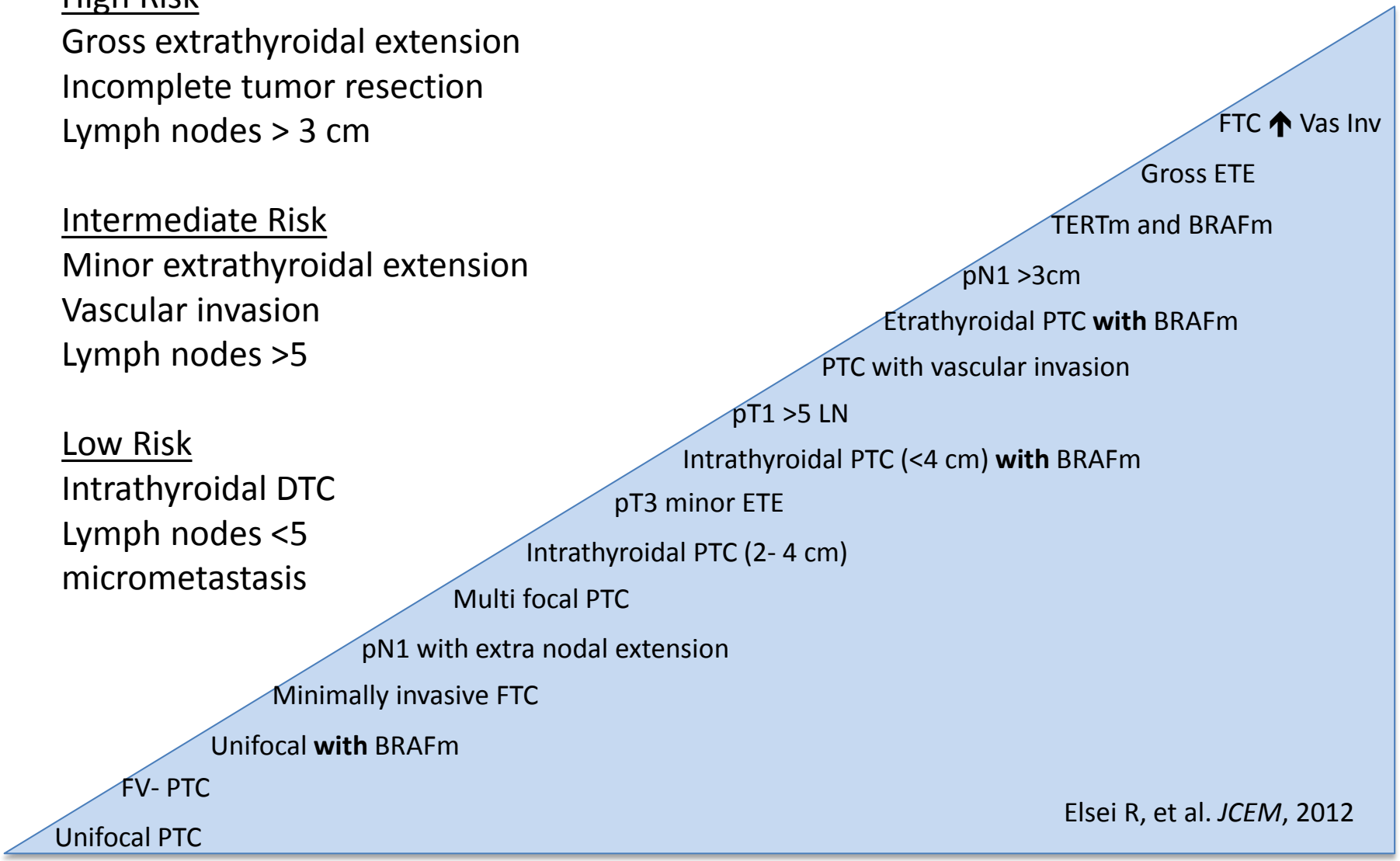
1. Gross extrathyroidal spread
2. Vascular invasion
3. Nodal disease >3 cm.

Risk of Recurrence

<u>High Risk</u>
Gross extrathyroidal extension
Incomplete tumor resection
Lymph nodes > 3 cm

<u>Intermediate Risk</u>
Minor extrathyroidal extension
Vascular invasion
Lymph nodes >5

<u>Low Risk</u>
Intrathyroidal DTC
Lymph nodes <5
micrometastasis



How do we identify recurrence?

The 2015 ATA guidelines endorse a dynamic risk stratification system that uses a 4-tiered nomenclature to describe the response to therapy and clinical status at each follow-up visit

Excellent response

No clinical, biochemical, or structural evidence of disease

Biochemical incomplete response

Abnormal Tg or rising anti-Tg antibody levels in the absence of localizable disease.

Structural incomplete response

Persistent or newly identified loco-regional or distant metastases

Indeterminate response

nonspecific biochemical or structural findings that cannot be confidently classified

The Journal of Clinical Endocrinology & Metabolism; Copyright 2018 DOI: 10.1210/jc.2018-01383

Persistent and recurrent thyroid cancer outcome

Time to separate Persistent from Recurrent Differentiated Thyroid Cancer: different conditions with different outcomes

Giulia Sapuppo[1]MD, Martina Tavarelli[1]MD, Antonino Belfiore[1]MD, PhD, Riccardo Vigneri[1,2*] MD and Gabriella Pellegriti[3*]MD, PhD

In a cohort of 4292, 14.9% patients had disease events after initial treatment, (78%) with persistent disease and 22% with recurrent disease. In the group with persistent structured disease **distant metastases** were significantly more frequent (38.4% *vs* 17.0%).

In DTC patients not cured after initial treatment, persistent disease is more common and has a worse outcome than recurrent disease.

Recurrent disease is when disease events occur **after at least one year** of disease-free status

Persistent disease is the ascertained presence of disease within the first year after initial therapy

Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid : official journal of the American Thyroid Association 2016; 26:1-133

Identifying disease recurrence or disease progression

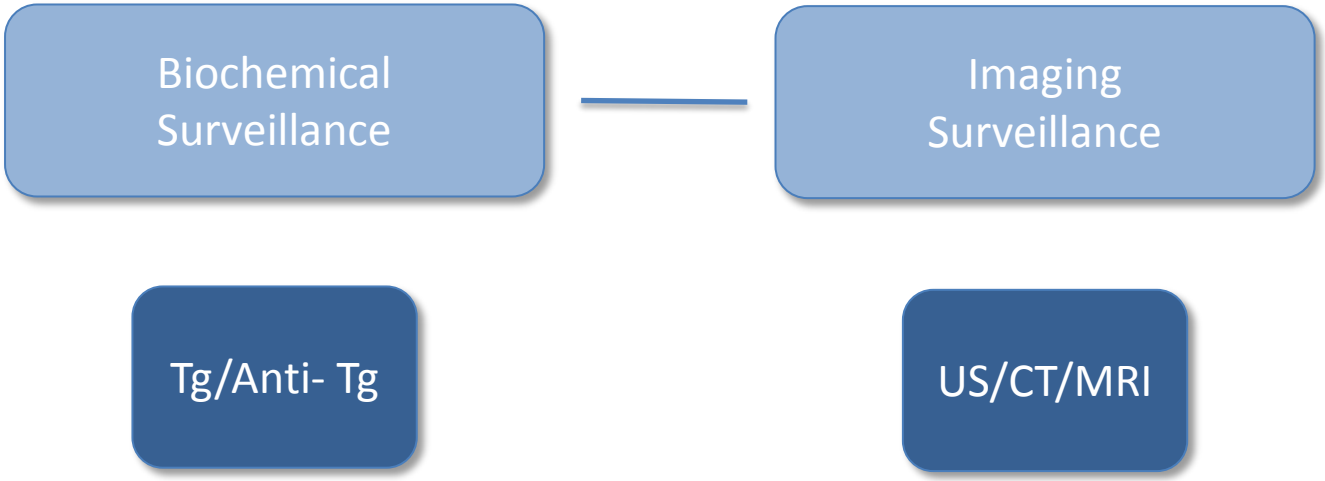


TABLE 1. Site of metastatic disease as a function of thyroglobulin level.

Tg level $<$10 ng/mL	Persistent/recurrent disease in neck
Tg level 20–500 ng/mL	Pulmonary metastases
Tg level in thousands	Bone metastases

Robbins RJ, Srivastava S, Shaha A, et al. Factors influencing the basal and recombinant human thyrotropin-stimulated serum thyroglobulin in patients with metastatic thyroid carcinoma. J Clin Endocrinol Metab 2004;89: 6010–6016.

We like to believe that we have rid the patient of disease

THYROID
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DOI: 10.1089/thy.2017.0578

Intermediate-Risk Papillary Thyroid Cancer: Risk Factors for Early Recurrence in Patients with Excellent Response to Initial Therapy

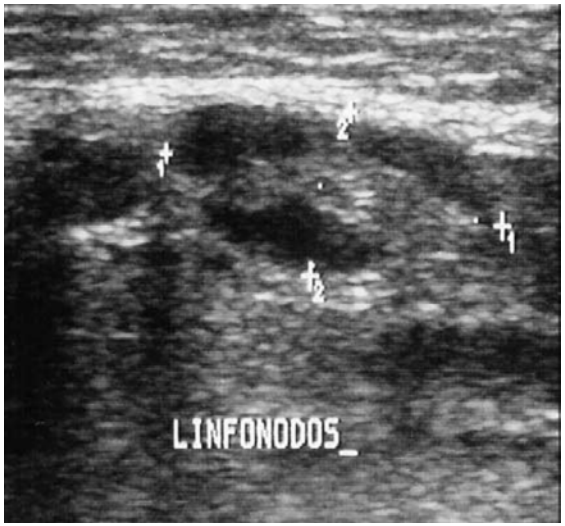
Augusto Enrique Llamas-Olier,[1] Diana Isabel Cuéllar,[2] and Giancarlo Buitrago[3]

The significant association that was found between recurrent disease and lateral neck lymph node metastasis, lateral neck I^{131} uptake in post-therapy whole-body scan, and preablation thyroglobulin levels >10 ng/mL indicates that early recurrence (<5 years) most likely indicates progression of micrometastatic disease already present at diagnosis and unsuccessfully eradicated with initial therapy.

*Approximately 95% of recurrent disease will occur in the **neck**.*

Cervical ultrasound is considered the first-line imaging study for assessing locoregional recurrence of thyroid cancer.

Recurrent structural disease that measures 8 to 10 mm or larger on anatomic imaging should be considered for cytology biopsy, Tg aspirate rinsing analysis, and revision surgery.



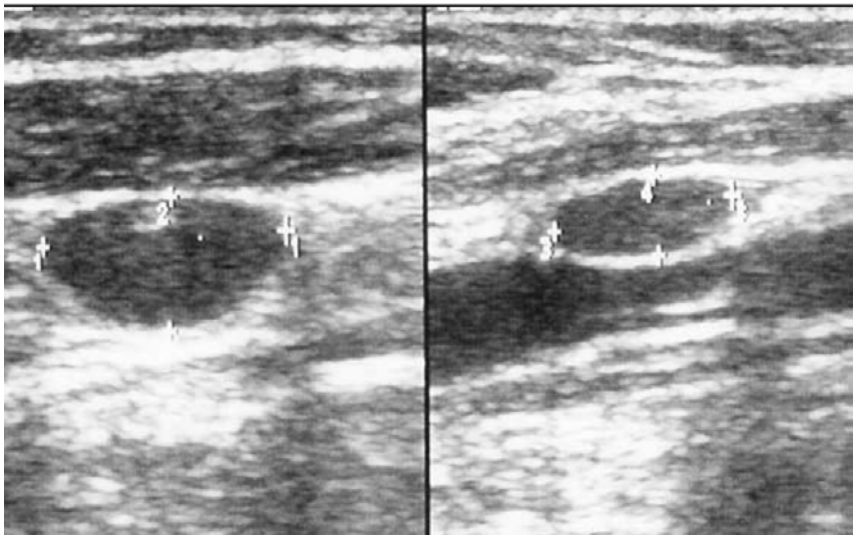


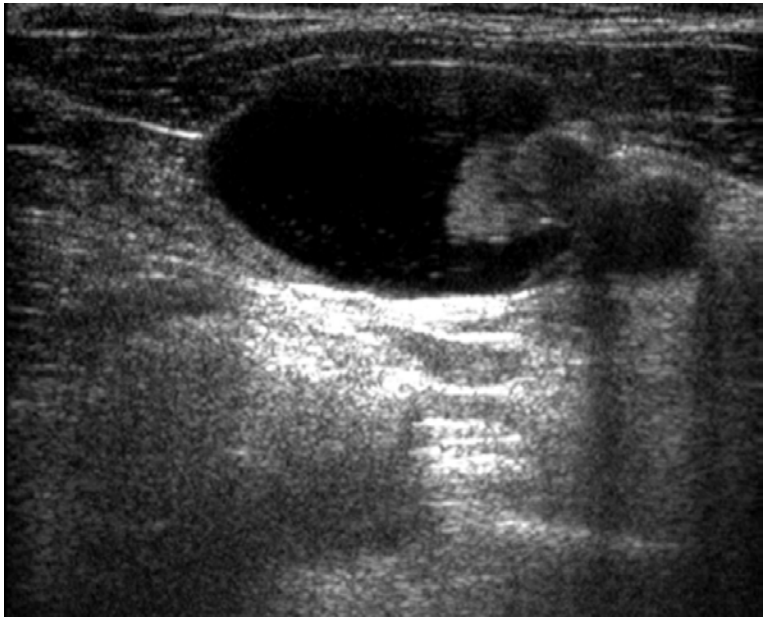
TABLE 2. Radiographic findings consistent with metastatic nodal disease.

Microcalcifications or macrocalcifications within lymph nodes on ultrasound or CT
Mixed echogenicity or cystic changes within lymph nodes on ultrasound or CT
Vascular flow that becomes chaotic or peripheral on ultrasound
Progressive lymph node enlargement on serial imaging

CYSTIC LYMPH NODES IN THE LATERAL NECK AS INDICATORS OF METASTATIC PAPILLARY THYROID CANCER

Christine S. Landry, MD[1]; Elizabeth G. Grubbs, MD[1]; Naifa L. Busaidy, MD[2]; Brett J. Monroe[5], MD; Gregg A. Staerkel, MD[3]; Nancy D. Perrier, MD[1]; Beth S. Edeiken-Monroe, MD[4]

ENDOCRINE PRACTICE Vol 17 No. 2 March/April 2011



Cystic Lymph node

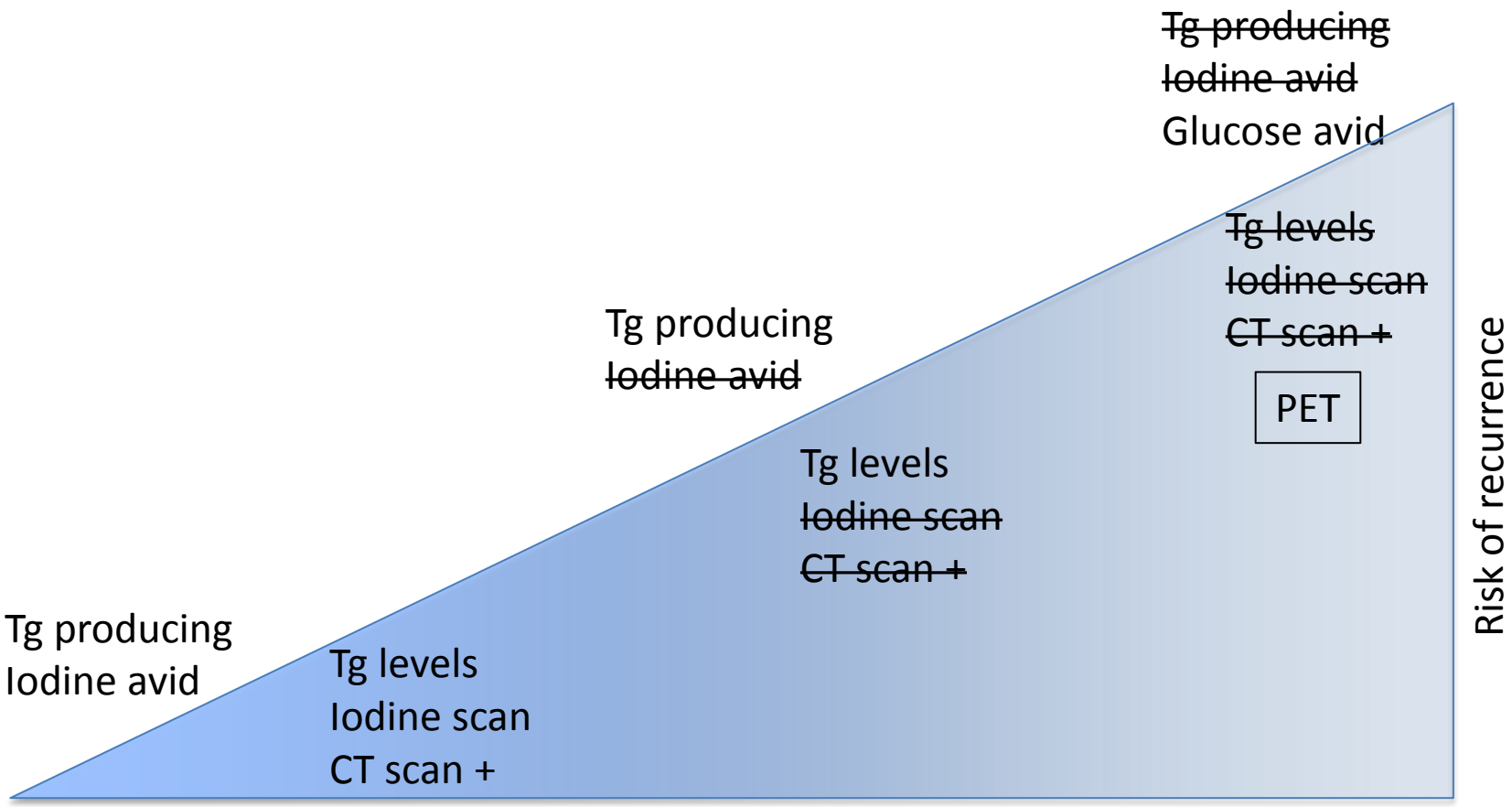
Aspiration of the wall

Thyroglobulin aspirate

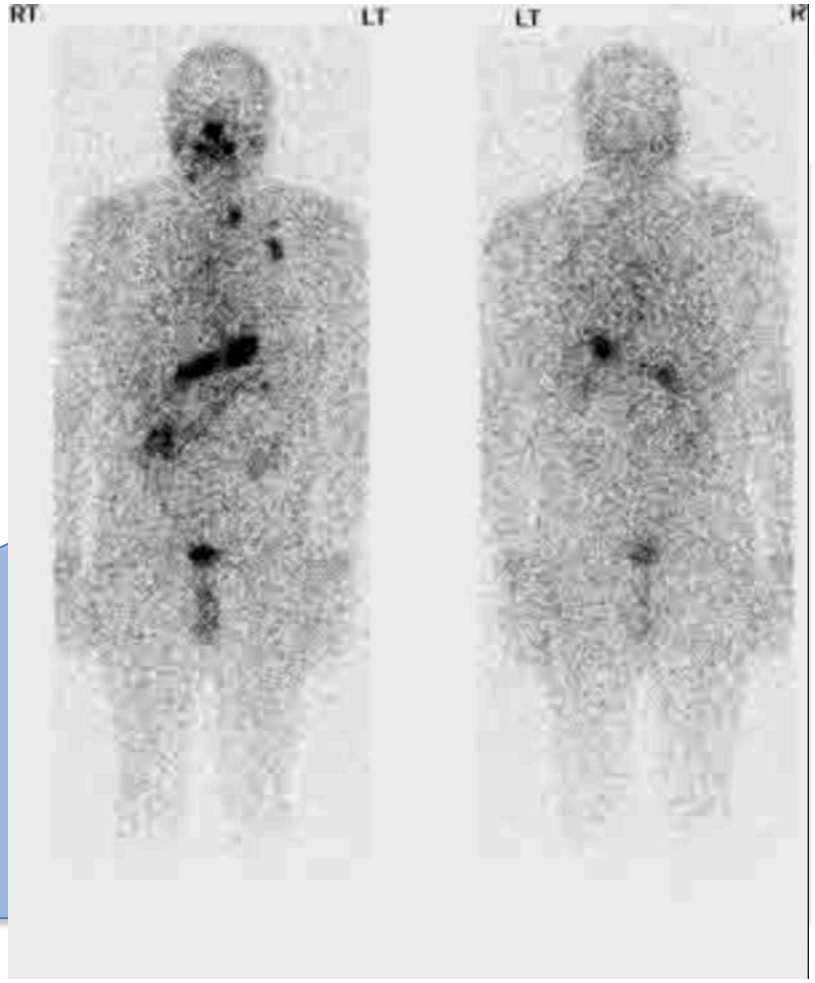
Don't fall in love with your diagnosis.

All that is cystic is not papillary thyroid carcinoma

A Disease Continuum



A Disease Continuum

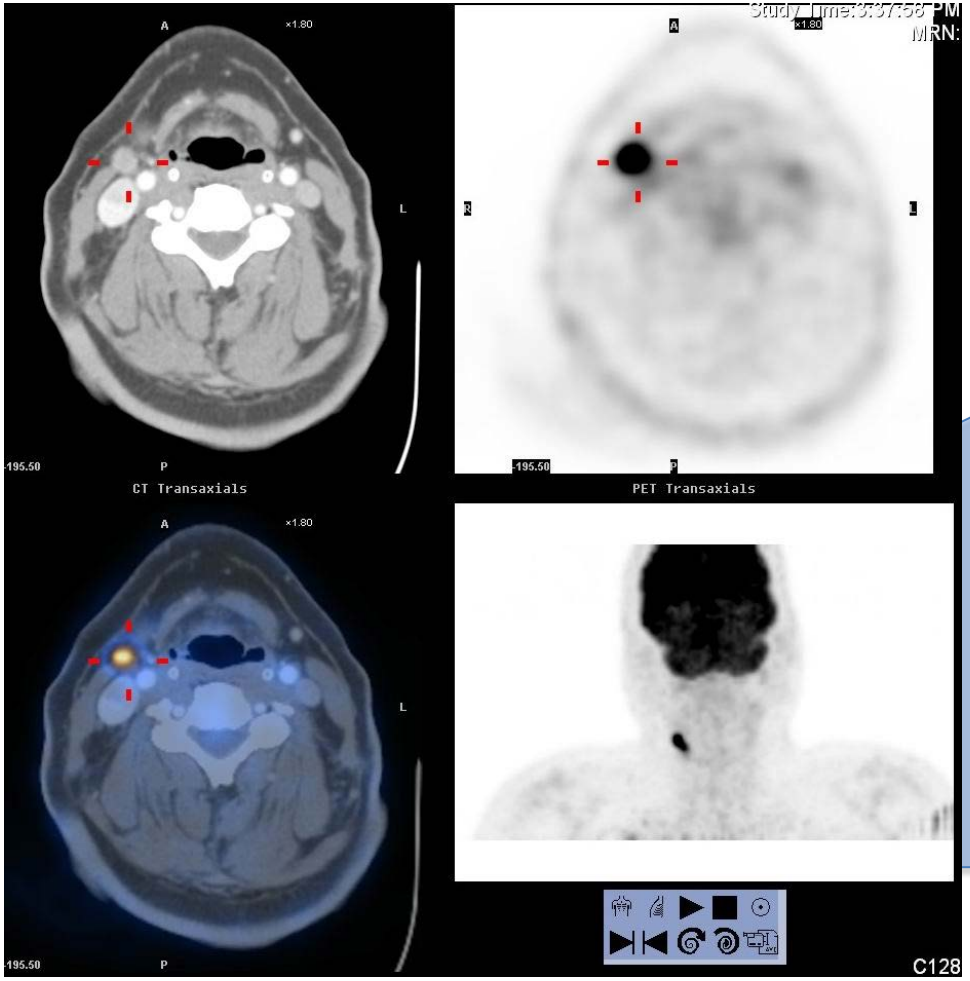


Tg producing
Iodine avid

Tg levels
Iodine scan
CT scan +

Risk of recurrence

A Disease Continuum



~~Tg producing~~
~~Iodine avid~~
Glucose avid

~~Tg levels~~
~~Iodine scan~~
~~CT scan +~~

PET

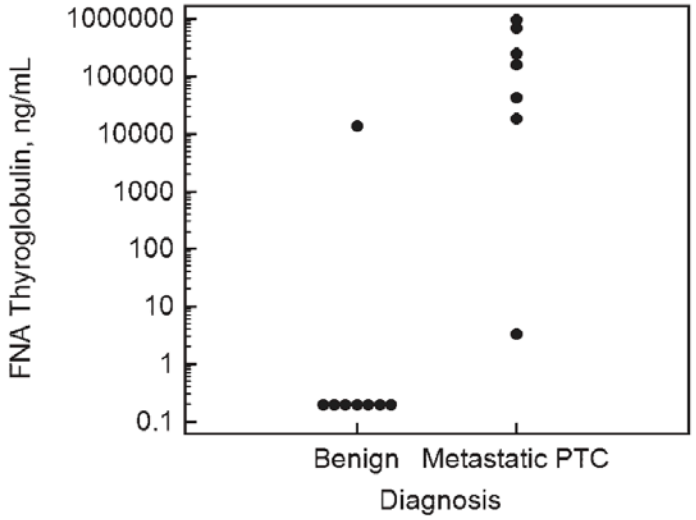
Risk of recurrence

The Role of Needle Aspiration
Thyroglobulin Assay

Measurement of Fine-Needle Aspiration Thyroglobulin Levels Increases the Detection of Metastatic Papillary Thyroid Carcinoma in Cystic Neck Lesions

Brittany J. Holmes, MD; Lori J. Sokoll, PhD; and Qing Kay Li, MD, PhD

Cancer Cytopathology July 2014



Surgical Intervention versus Active Surveillance

A complex Decision

Primary tumor- adverse histology

Rate of change of Tg levels

The rate of growth of the structural disease

Presence of extranodal extension critical structures

Iodine avidity

Thyroglobulin producing

Molecular markers for aggressive behavior

Patient comorbidities

The Role of Preoperative Imaging

THYROID
Volume 25, Number 1, 2015

DOI: 10.1089/thy.2014.0096

American Thyroid Association Statement on Preoperative Imaging for Thyroid Cancer Surgery

Michael W. Yeh,[1] Andrew J. Bauer,[2] Victor A. Bernet,[3] Robert L. Ferris,[4] Laurie A. Loevner,[5]
Susan J. Mandel,[5] Lisa A. Orloff,[6]

for the American Thyroid Associati

TABLE 3. FINDINGS THAT MAY PROMPT AXIAL IMAGING

- Hoarseness with vocal cord paresis/paralysis
- Progressive dysphagia or odynophagia
- Mass fixation to surrounding structures
- Respiratory symptoms, hemoptysis, stridor, or positional dyspnea
- Large size of tumor or mediastinal extension, incompletely imaged on ultrasound
- Rapid progression/enlargement
- Sonographic suspicion for significant extrathyroidal invasion (cT4)
- Bulky, posteriorly located, or inferiorly located lymph nodes incompletely imaged by ultrasound
- Ultrasound expertise not available

The Role of Preoperative Imaging

THYROID
Volume 25, Number 1, 2015

DOI: 10.1089/thy.2014.0096

SPECIAL ARTICLES

American Thyroid Association Statement on Preoperative Imaging for Thyroid Cancer Surgery

Michael W. Yeh,[1] Andrew J. Bauer,[2] Victor A. Bernet,[3] Robert L. Ferris,[4] Laurie A. Loevner,[5] Susan J. Mandel,[5] Lisa A. Orloff,[6,*] Gregory W. Randolph,[7] and David L. Steward[8]

for the American Thyroid Association Surgical Affairs Committee Writing Task Force

"The potential benefit of preoperative contrast CT scanning in enhancing disease localization supersedes concerns that administration of radioactive iodine will be delayed."

Surgery versus observation for small-volume disease

Disease recurrence is being found more frequently, at an earlier stage.

Detection of persistent or recurrent locoregional tumor engenders pressure to operate because surgery is the mainstay of thyroid cancer therapy.

Patient anxiety may prompt surgery

Concern for local invasion and progression

Medical legal concerns

Surgery versus observation for small-volume disease

Intervention requires careful consideration of the risks and the benefits.

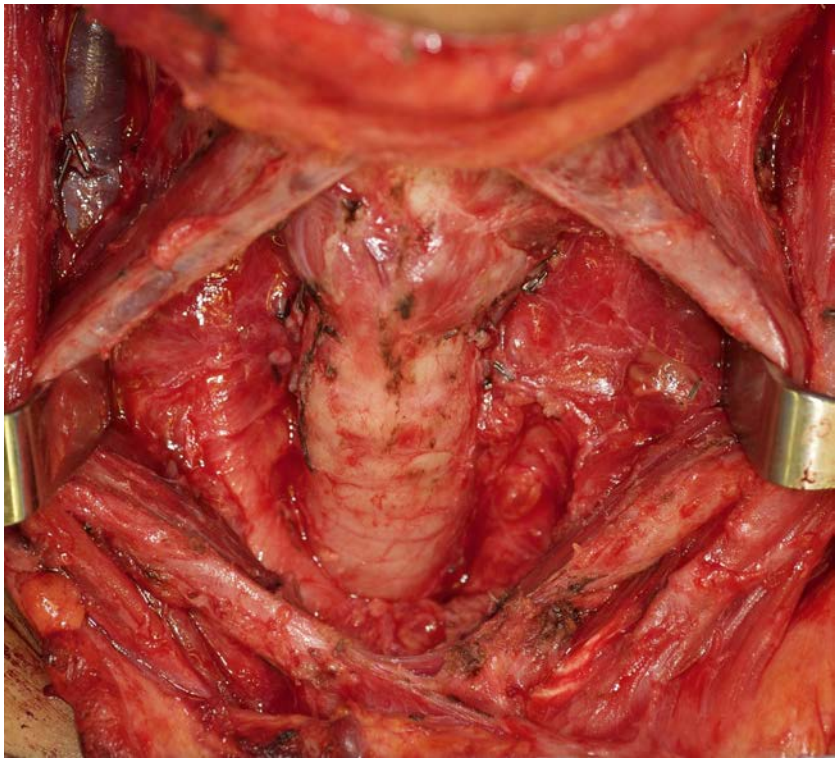
1) Careful prior operative and pathology note review to determine the compartments of the neck that were previously dissected
2) Status of the vocal cord function
3) Status of the parathyroid function
4) History of surgical complication that may complicate reoperation
5) The patient's motivation for therapy

Shared decision- making is critical

The goal of reoperation

- Remove the remaining thyroid tissue and the remaining nodal tissue

- Failure to be complete will lead to future recurrence and reoperation

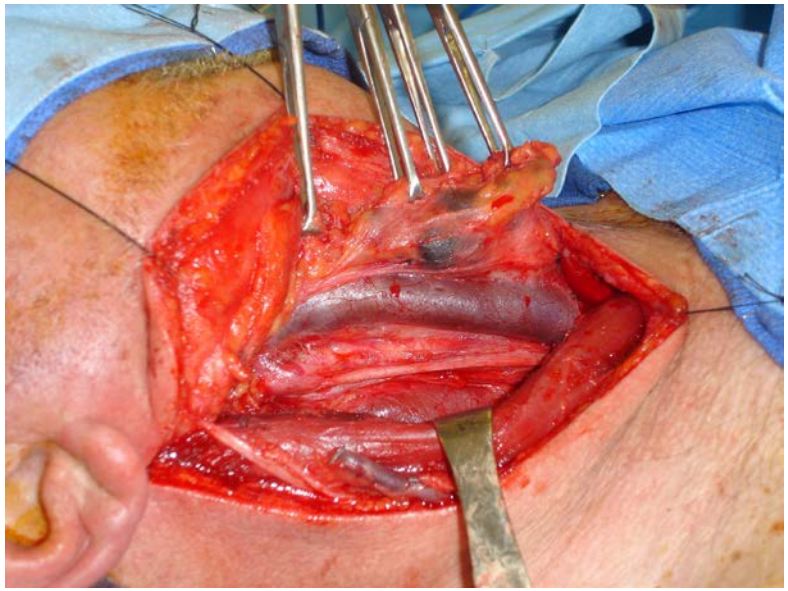


The goal of reoperation

In the face of bilateral paratracheal disease, contralateral central compartment dissection may be staged

<u>In high risk situations</u>:

The targeted resection of specific sites of disease, without a formal node dissection, may be an appropriate strategy



Surgical Technique

- Nerve monitoring
- PTH monitoring

1. Identify the carotid artery
2. Identify the recurrent laryngeal nerve- start low
3. Spot the parathyroid glands-

Surgery for Advanced Disease

Sharply “shaving” cancer from the cricoid cartilage, thyroid cartilage, and trachea are accepted approaches when the tumor does not enter the airway lumen.

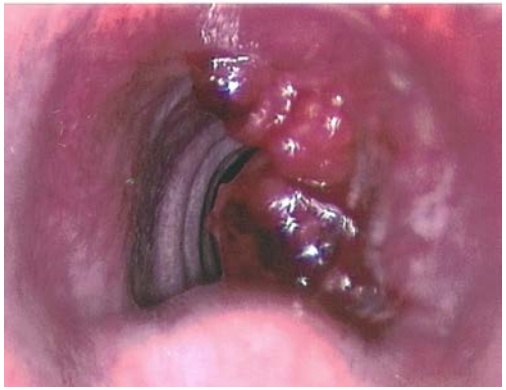
THYROID
Volume 26, Number 2, 2016

DOI: 10.1089/thy.2015.0433

Treatment Outcomes and Risk Factors for Recurrence After Definitive Surgery of Locally Invasive Well-Differentiated Papillary Thyroid Carcinoma

Ji Won Kim,[1] Jong-Lyel Roh,[1] Gyungyup Gong,[2] Kyung-Ja Cho,[2] Seung-Ho Choi,[1] Soon Yuhl Nam,[1] and Sang Yoon Kim[1]

Disease extent, surgical extent, and involving nerve preservation did not associate with recurrence or overall survival outcomes. The post-ablation stimulated thyroglobulin level may be an independent predictor for recurrence.



Tracheal resection, or even laryngectomy may be indicated for select cases.

The Role of external Beam Radiotherapy

AHNS CONSENSUS STATEMENT

Management of invasive well-differentiated thyroid cancer: An American Head and Neck Society Consensus Statement

AHNS Consensus Statement

Maisie L. Shindo, MD,[1*] Salvatore M. Caruana, MD,[2] Emad Kandil, MD,[3] Judith C. McCaffrey, MD,[4] Lisa A. Orloff, MD,[5] John R. Porterfield, MD,[6] Ashok Shaha, MD,[7] Jennifer Shin, MD,[8] David Terris, MD,[9] Gregory Randolph, MD[10]

External beam radiation therapy is considered postoperatively:

1. In cases in which DTC has high-grade histology
2. In cases in which there is unresectable gross disease

Shindo ML, Caruana SM, Kandil E, et al. Management of invasive well differentiated thyroid cancer: an American Head and Neck Society consensus statement. AHNS consensus statement. Head Neck 2014;36:1379–1390.

Failure to localize structural recurrence

- Biochemically persistent disease (elevated serum Tg levels) but no structural disease

- Biochemically persistent disease does not necessarily lead to the discovery of structural recurrence later

THYROID
Volume 22, Number 8, 2012

DOI: 10.1089/thy.2011.0522

THYROID CANCER AND NODULES

Even Without Additional Therapy, Serum Thyroglobulin Concentrations Often Decline for Years After Total Thyroidectomy and Radioactive Remnant Ablation in Patients with Differentiated Thyroid Cancer

Rosália P. Padovani,[1] Eyal Robenshtok,[2] Matvey Brokhin,[3] and R. Michael Tuttle[2]

Closing points

- Persistent disease must be separated from recurrent disease
- Indolent disease must be separated from progressive disease
- Don’t chase ghosts- Surgery is rarely indicated in the absence of structural disease

“We don’t want to hurt a patient trying to save them for a disease that will never hurt them”

Michael Tuttle, MD