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.


All papillary thyroid cancer is not the same

“Neck reoperation is becoming increasingly frequent and is strongly predictive of mortality.”
Effect of reoperation on outcomes in papillary thyroid cancer

Stephanie Young, MPH, Avital Harari, MD, Stephanie Smooke-Praw, MD, MA, Philip H. G. Ituarte, PhD, MPH, and Michael W. Yeh, MD, 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
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

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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
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
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 patients in 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

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

Intermediate Risk
Minor extrathyroidal extension
Vascular invasion
Lymph nodes > 5

Low Risk
Intrathyroidal DTC
Lymph nodes < 5
Micrometastasis

Unifocal with BRAFm
Minimally invasive FTC
FV- PTC
Multi focal PTC
Intrathyroidal PTC (<4 cm) with BRAFm
pT3 minor ETE
Intrathyroidal PTC (2-4 cm)

Minimally invasive FTC
pN1 with extra nodal extension
Unifocal with BRAFm

Etrathyroidal PTC with BRAFm
pN1 >3 cm
ETE
PTC with vascular invasion
pT1 >5 LN

TERTm and BRAFm
Gross ETE
FTC with vascular invasion

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
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
Identifying disease recurrence or disease progression

**Biochemical Surveillance**

**Imaging Surveillance**

**Tg/Anti-Tg**

**US/CT/MRI**

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

<table>
<thead>
<tr>
<th>Thyroglobulin Level</th>
<th>Site of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg level &lt;10 ng/mL</td>
<td>Persistent/recurrent disease in neck</td>
</tr>
<tr>
<td>Tg level 20–500 ng/mL</td>
<td>Pulmonary metastases</td>
</tr>
<tr>
<td>Tg level in thousands</td>
<td>Bone metastases</td>
</tr>
</tbody>
</table>

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

The significant association that was found between recurrent disease and lateral neck lymph node metastasis, lateral neck ${}^{131}$I 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 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

- Tg producing
- Iodine avid
- Glucose avid

Risk of recurrence

- PET
- Tg levels
- Iodine scan
- CT scan +
- Tg producing
- Iodine avid
- Tg levels
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A Disease Continuum

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PET
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

American Thyroid Association Statement on Preoperative Imaging for Thyroid Cancer Surgery

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 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.

In high risk situations:
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.
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

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
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
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