Persistent & Recurrent Differentiated Thyroid Cancer

Electron Kebebew
University of California, San Francisco
Department of Surgery

UCSF Postgraduate Course in General Surgery
March 19th, 2009

Objectives

• Risk factors for persistent & recurrent disease
• Causes of persistent & recurrent disease
• Risks of reoperation & perioperative management considerations

Thyroid Cancer

Histologic types of thyroid cancer
Follicular cell origin
- Papillary: ~ 80%
- Follicular/Hürthle: ~ 10 - 15%
- Anaplastic: <1%
- Parafollicular cell origin
- Medullary: ~ 3 - 7%

Pattern of metastasis
Lymph nodes:
- papillary & Hürthle (30-40%)
- medullary (80%)
Distant:
- anaplastic (>50%)
- follicular & Hürthle (40-70%)
- medullary (15%)

Thyroid Cancer

Histologic types of thyroid cancer
Follicular cell origin
- Papillary: ~ 80%
- Follicular/Hürthle: ~ 10 - 15%
- Anaplastic: <1%
- Parafollicular cell origin
- Medullary: ~ 3 - 7%

Pattern of metastasis
Lymph nodes:
- papillary & Hürthle (30-40%)
- medullary (80%)
Distant:
- anaplastic (>50%)
- follicular & Hürthle (40-70%)
- medullary (15%)
**Thyroid Cancer Epidemiology**

- **Risk Factors for Persistent & Recurrent DTC**
  - Low-risk vs. high-risk DTC
    - Older age
    - Extrathyroidal invasion
    - Distant metastasis
    - Tumor size > 4 cm
    - Lymph node metastasis

**Risk Factors for Persistent & Recurrent DTC**

- Low-risk vs. high-risk DTC
  - Older age
  - Extrathyroidal invasion
  - Distant metastasis
  - Tumor size ≥ 4 cm
  - Lymph node metastasis

*All patients are at risk of recurrent disease long term!*

---

**Predicting who is at risk for persistent & recurrent DTC**

*Jukkola A. et al. Endocrine-Related Cancer, 2004*
Predicting who is at risk for persistent & recurrent DTC

Mortality from DTC

Low Risk
High Risk

Risk classification systems in patients with thyroid cancer

BRAF V600E mutation is associated with aggressive tumor phenotype

BRAF testing to predict persistent & recurrent DTC

BRAF is a proto-oncogene that activates mitogen signaling

BRAF V600E mutation most common

Mutation has high prevalence in PTC

BRAF testing to predict persistent & recurrent DTC

BRAF is a proto-oncogene that activates mitogen signaling

BRAF V600E mutation most common

Mutation has high prevalence in PTC

BRAF V600E mutation is associated with aggressive tumor phenotype

- older age
- male gender
- extrathyroidal tumor invasion
- lymph node metastasis
- distant metastases
- higher tumor stage
Causes of persistent & recurrent DTC

Classification

- Inadequate initial operation
- Disease process vs. scrutiny
- Inadequate adjuvant therapy

Inadequate Initial Operation for Thyroid Cancer

Historical issues

- Total vs. hemithyroidectomy
  - All high-risk patients
  - Controversial in low-risk patients
  - Therapeutic lymph node dissection not "berry picking"

For disease that is more than T1N0M0
Loh et al., JCEM, 1997

Inadequate Initial Operation for Differentiated Thyroid Cancer?

- Detects additional disease not observed by PE
  - In 20% of patients with thyroid cancer lymph node metastasis: ½ in central neck & ½ in lateral neck nodes
  - Kouvaraki, Surgery 2003
  - In 31% of patients with thyroid cancer additional disease detected
    - lymph nodes
    - non-dominant tumors
  - Milas, Surgery 2005
  - one-third of cases the cancer is in the non-dominant nodule
  - Kunreuther, JCEM 2004
- Ultrasound allows for more complete initial surgical resection of DTC

Inadequate Initial Operation for Papillary Thyroid Cancer?

- "Prophylactic central and ipsilateral lateral neck dissection for PTC smaller than 2 cm facilitates the accurate selection of patients for 131I ablation and modifies the indication for 131I in 30% of patients with T1 tumors"

Caveats

- Low complications but in an experienced group
- Long-term outcome (mortality)?
  - Patients don’t die of positive Tg levels without detectable disease on imaging
  - From Bonnet et al. J Clin Endocrinol Metab December 30, 2008
Inadequate Initial Operation for Papillary Thyroid Cancer?

Total thyroidectomy versus Total thyroidectomy with prophylactic ipsilateral central neck dissection for PTC > 1 cm

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean no. of RAI (95% CI)</td>
<td>1.0 (1-1.3)</td>
<td>1.2 (1.0-1.3)</td>
<td>.51</td>
</tr>
<tr>
<td>Mean dose of I131 (95% CI)</td>
<td>5.2 (4.6-5.9)</td>
<td>4.8 (4.3-5.2)</td>
<td>.2</td>
</tr>
<tr>
<td>TG + antibodies patients (%)</td>
<td>5 (9)</td>
<td>43 (11)</td>
<td>.6</td>
</tr>
<tr>
<td>Mean serum TG level (95% CI)</td>
<td>0.41 (0-0.9)</td>
<td>9.3 (6.2-12)</td>
<td>.02</td>
</tr>
<tr>
<td>Serum TG undetectable (%)</td>
<td>40 (72)</td>
<td>168 (43)</td>
<td>.001</td>
</tr>
</tbody>
</table>

(Complication rate < 1.8% similar (permanent) but higher parathyroid autotransplantation and transient hypocalcemia in group A total + lymph node dissection) Data from Swayne et al. Surgery 2005

Inadequate Adjuvant Therapy for DTC

* Radioiodine in all high risk patients with differentiated thyroid cancer
* Thyroid hormone for TSH suppression

Disease scrutiny?
Overdiagnosis of persistent & recurrent DTC

* Serum thyroglobulin with & without TSH stimulation
* Neck Ultrasound

Reoperation for persistent & recurrent DTC

37 year old woman status post total thyroidectomy for papillary thyroid cancer and I-131 ablation with 102 mCi. At 2 years follow up she is found to have a 6 mm right central neck mass (“suspicious lymph node”).

72 year old man status post total thyroidectomy, bilateral central and lateral neck dissection for locally advanced papillary thyroid cancer is found to have a 8 mm left central neck and 1.2 cm level IV suspicious lymph node.
Risk of reoperative thyroid surgery

"The second most difficult decision in surgery is to advise operation, the most difficult decision, though, is the one to reoperate."

Organ

Risk factor of reoperation

- Dralle et al. Surgery, 2004
- N = 16,448 (29,998 nerves at risk)
- Three groups
- Higher rates of RLN injury:
  - reoperation OR = 4.7/6.7 (MNG/Cancer)
  - primary for cancer OR = 2.0
  - lobectomy OR = 1.8
  - No ID OR = 1.4
  - Low volume hospital OR = 1.4
  - Low volume surgeon OR = 1.2
- No difference between nerve probe and visual ID of nerve

Perioperative management for reoperative thyroid surgery

Where is the disease located?
Central versus lateral neck

Is there pre-existing morbidity?

Recurrent laryngeal nerve function - get a direct laryngoscopy

Hypoparathyroidism (review the pathology and operative reports)

Perioperative management for reoperative thyroid surgery

Thyroid cancer

*Get an ultrasound of the neck not to miss other disease

*Get a tissue diagnosis

*What is the thyroglobulin level?

N= 216 patients having reoperation
- 64% new nonpalpable disease detected in lateral neck and 28% in central neck
- Changed the operation in 43%
- FP=4%, FN=6%, PPV = 94%
Alternatives approaches and techniques for persistent & recurrent DTC

Alternative approaches
- Alcohol injection
- Radiofrequency ablation

Intraoperative techniques to localize tumor
- Ultrasound
- Hook needle
- Dye injection

Reoperation for persistent & recurrent DTC

37 year old woman status post total thyroidectomy for papillary thyroid cancer and I-131 ablation with 102 miCu. At 2 years follow up she is found to have a 6 mm right central neck mass (suspicious lymph node).

72 year old man status post total thyroidectomy, bilateral central and lateral neck dissection for locally advanced papillary thyroid cancer is found to have a 8 mm left central neck and 1.2 cm level IV suspicious lymph node at 1 years follow up.

Summary

- Risk factors for persistent and recurrent should guide adjuvant therapy and follow up
- Disease scrutiny accounts for some of the higher rates of persistent & disease
- Risks of reoperation: location, location, location....
- Indications for reoperation should be clear and likely to alter disease course & improve patient outcome
- Recurrent laryngeal nerve monitoring may be useful for reoperative cases
- Always try to do the definitive operation the first time and consider adjuvant therapy to avoid persistent/recurrent disease

Thank You!