Panel 7: Anaplastic Thyroid Carcinoma

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M. Sara Rosenthal, Ph.D.
Eric Sherman, M.D.
Robert Smallridge, M.D.
Relevant Conflicts of Interests

- S. Sherman: None reported
- Cernea: None reported
- Foote: None reported
- Rosenthal: None reported
- E. Sherman: Bayer, BristolMeyerSquibb: consulting fees
- Smallridge: Daiichi Sankyo: research support
Topics to consider

• Prognosis
• Primary therapy with surgery, radiation, chemotherapy
• Adjuvant therapy
• Investigational therapy
• Palliative therapy
Poor prognosis for most patients

1 yr cause-specific survival: 19%

Kebebew, et al., Cancer 2005
Poor prognosis for most patients

1 yr cause-specific survival: 18%
Models of thyroid tumorigenesis

Haugen & Sherman, Endocr Rev 2013
Evidence for secondary mutations in genesis of ATC

PIK3CA mutation in both; BRAF mutation in both; BRAF mutation in both; PIK3CA in ATC only

Santarpia, et al., J Clin Endocrinol Metab 2008
2012 ATA guidelines

American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer


for the American Thyroid Association Anaplastic Thyroid Cancer Guidelines Taskforce

65 detailed evidence-based recommendations
<table>
<thead>
<tr>
<th>Treatment and care goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced care planning and goals of care</td>
</tr>
<tr>
<td>■ Recommendation 14</td>
</tr>
<tr>
<td>Decision-making capacity and informed consent</td>
</tr>
<tr>
<td>■ Recommendation 15</td>
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<tr>
<td>Surrogate decision making</td>
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<tr>
<td>■ Recommendation 16</td>
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<tr>
<td>Truth-telling, patient autonomy, and beneficent care</td>
</tr>
<tr>
<td>■ Recommendation 17</td>
</tr>
<tr>
<td>Advance directives, surrogate decision making, and code status</td>
</tr>
<tr>
<td>■ Recommendation 18</td>
</tr>
</tbody>
</table>
2012 ATA guidelines

**RECOMMENDATION 14**
Physicians involved with the management decisions in the care of the patient should consult with multidisciplinary specialists who may be involved in the care of the patient, either at the present time or in the future, before having “goals of care” discussions with patients.

**RECOMMENDATION 17**
In consultation with a multidisciplinary team, a candid meeting with the patient should be scheduled in which there is full disclosure of the potential risks and benefits of various treatment options, including how such options will impact the patient’s life. Treatment options discussed should include palliative care. Patient preferences should guide clinical management.
ThyCa patient handbook

Anaplastic
Thyroid Cancer

www.thyca.org
ThyCa: Thyroid Cancer Survivors’ Association, Inc.
Phone Toll Free 1-877-588-7904 • Fax 1-630-604-6078
E-mail: thyca@thyca.org

Download this handbook for FREE
Or ask ThyCa to mail it.
Share it with others!

2012 ATA guidelines

**RECOMMENDATION 15**
Patients must have decision-making capacity to consent to or make particular medical decisions. Concerns about diminished or impaired capacity may prompt a psychiatric consult or clinical ethics consult to assess barriers to capacity.

**RECOMMENDATION 18**
Patients should be encouraged to draft an advance directive in which they name a surrogate decision maker and list code status and other end-of-life preferences. Consider, in some cases, using “allow natural death” (AND) over “do not resuscitate” (DNR), which may be better understood by patients and families as an order that limits inappropriate aggressive care. Circumstances in which suspension of DNR or AND may occur must be discussed with the patient.
Case 1

- 7/03: 47 yo woman, “incidental” 6 cm R thyroid mass on neck ultrasound, no adenopathy
- Evaluated at “outside institution”
  - FNA: follicular neoplasm
  - Surgery?
Case 1

• 7/03: 47 yo woman, “incidental” 6 cm R thyroid mass on neck ultrasound, no adenopathy
  – FNA: follicular neoplasm
  – R hemithyroidectomy: FVPTC 7.8 cm with ETE, and multifocal microscopic ATC up to 6 mm confined to gland
    • ATC pT4am cN0 Mx
    • FVPTC pT3 cN0 Mx
  – What is the prognosis?
## Prognostic factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate $P$ value</th>
<th>Multivariate HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (&lt; 60 yrs)</strong></td>
<td>0.0009$^a$</td>
<td>0.482 (0.268–0.867)$^a$</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.0028$^a$</td>
<td>1.089 (0.746–1.590)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>0.0682</td>
<td>NA</td>
</tr>
<tr>
<td>First primary malignancy</td>
<td>0.7859</td>
<td>NA</td>
</tr>
<tr>
<td>Tumor size ($\geq 5$ cm)$^c$</td>
<td>0.0203$^a$</td>
<td>1.245 (0.854–1.816)</td>
</tr>
<tr>
<td>SEER stage</td>
<td>&lt; 0.0001$^a$</td>
<td></td>
</tr>
<tr>
<td><strong>Local</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Regional</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Distant</strong></td>
<td></td>
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</tr>
</tbody>
</table>

Kebebew, et al., *Cancer* 2005
Prognostic factors

• Improved outcomes associated with
  – Age <70
  – Absence of symptoms
  – Normal WBC
  – Tumor <5 cm
  – Intrathyroidal tumor (T4a N0 M0)

Case 1

- 7/03: 47 yo woman, “incidental” 6 cm R thyroid mass on neck ultrasound, no adenopathy
  - FNA: follicular neoplasm
  - R hemithyroidectomy: FVPTC 7.8 cm with ETE, and multifocal microscopic ATC up to 6 mm confined to gland
    - ATC \( pT4am \) cN0 Mx
    - FVPTC \( pT3 \) cN0 Mx
  - Completion? Why or why not?
Only complete resection associated with survival

Haigh, et al., Cancer 2001
Complete local resection improves survival in M0 patients

De Crevoisier et al, Int J Radiat Oncol Biol Phys 2004
2012 ATA guidelines

- **RECOMMENDATION 22**
- A total lobectomy or total or near-total thyroidectomy should be performed in most patients with an incidental area of ATC within a DTC. This is based primarily on treatment recommendations related to the non-anaplastic component of the malignancy.

Smallridge, *et al.*, *Thyroid* 2012
Case 1

7/03: 47 yo woman, “incidental” 6 cm R thyroid mass on neck ultrasound, no adenopathy
- FNA: follicular neoplasm
- R hemithyroidectomy: FVPTC 7.8 cm, with multifocal microscopic ATC up to 6 mm confined to gland
- Completion: no malignancy

8/03: initial MDACC evaluation
- TSH 93, Tg 105
- 24 hr RAIU: 2.3% confined to thyroid bed
- CT chest without contrast: no lesions
- Other tests?
Case 1

- 7/03: 47 yo woman, “incidental” 6 cm R thyroid mass on neck ultrasound, no adenopathy
  - FNA: follicular neoplasm
  - R hemithyroidectomy: FVPTC 7.8 cm, with multifocal microscopic ATC up to 6 mm confined to gland
  - Completion: no malignancy
- 8/03: initial MDACC evaluation
  - TSH 93, Tg 105
  - 24 hr RAIU: 2.3% confined to thyroid bed
  - CT chest without contrast: no lesions
  - Other tests?
2012 ATA guidelines

• RECOMMENDATION 6

• Adjunctive preoperative radiological tumor staging should not delay therapy and should make use of appropriate cross-sectional imaging including neck ultrasound, CT scans or MRI (for the neck and chest), and PET/CT fusion scans.

Smallridge, et al., Thyroid 2012
PET-CT provides better staging information than CT alone

- 38% of lesions only identified by PET-CT
- 16% of patients upstaged to IVC by PET-CT

Case 1

• 7/03: 47 yo woman
  – ATC pT4am cN0 M0 R0, stage IVA
  – FVPTC pT3 cN0 M0 R0, stage III

• 8/03: multidisciplinary conference, including palliative care
  – Radiotherapy? Radioiodine?
  – Chemotherapy? Chemoradiotherapy?
  – Observation? Other?
Treatment prognostic factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate P value</th>
<th>Multivariate HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical resection</td>
<td>&lt; 0.0001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.779 (0.312–1.946)</td>
</tr>
<tr>
<td>External beam radiation</td>
<td>0.0064&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.534 (0.147–1.940)</td>
</tr>
<tr>
<td>Combined surgical resection with external beam radiation</td>
<td>&lt; 0.0001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.722 (0.587–0.889)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Kebebew, et al., Cancer 2005
Treatment prognostic factors

• Improved outcomes associated with
  – Age <70
  – Absence of symptoms
  – Normal WBC
  – Tumor <5 cm
  – Intrathyroidal tumor (T4a N0 M0)
  – “Radical” surgery
  – EBRT ≥40 Gy (NOT stage IVA)
  – Chemotherapy (NOT stage IVA)

2012 ATA guidelines

• **RECOMMENDATION 23**
  
The data are inadequate to definitively recommend either for or against local or systemic adjuvant therapy for small, intrathyroidal ATCs. A majority of the authors would favor cautious observation with frequent anatomic imaging studies for at least the first year of follow-up, while a minority would recommend adjuvant therapy.

• **RECOMMENDATION 29**
  
Following an R0 or R1 resection (excluding an incidental intrathyroidal microscopic lesion), patients with good PS with no evidence of metastatic disease who wish an aggressive approach should be offered definitive radiation therapy (with or without concurrent chemotherapy).

Smallridge, et al., *Thyroid* 2012
Case 1

- **8/03:** $^{131}$I, 168 mCi
  - Posttreatment scan: no new lesions
  - Levothyroxine
- **9/03:** CT C-A-P, bone scan: no metastases
- **9/03:** initiate chemoradiation
  - Carboplatin, target AUC 1.5 weekly (low dose)
  - IMRT 60 Gy to target volume in 30 fractions
Case 1

• 11/03: completed therapy
  – “Grade 2 esophagitis, skin reaction”
  – Dysphagia requiring narcotic (somnolence)
  – Nausea/vomiting requiring ondansetron, dexamethasone (severe acne)
  – Weight loss 4 kg

• 1/04: restaging exams all negative, Tg <1

• 3/13: restaging exams all negative
Case 2

- **8/12**: 81 yo woman from Long Island, NY, c/o sore throat, L earache
  - PE unremarkable
  - Dx’d with viral URI
  - 11 subsequent physician visits during next 2 months for neck pain, sore throat

- **11/12**: vocal cord paralysis, L thyroid lesion
  - Ultrasound: L jugular thrombosis, 5 cm thyroid mass
  - Biopsy: Anaplastic thyroid carcinoma
Case 2

- 12/12: Initial MDACC multidisciplinary evaluation (only close family member lives in Houston)
  - “Young appearing”
  - Worsening sore throat, dysphagia, neck pain
  - Stable hoarseness
  - Eating soft foods and liquids only
  - Some shortness of breath while supine
  - ECOG PS 2
  - “Stable airway”
Case 2

- 12/12: 81 yo woman, PS 2
  - ATC T4b N1b M0, Stage IVB
- Treatment options:
  - Surgery?
  - Chemotherapy?
  - Radiotherapy?
  - Chemoradiotherapy?
  - Clinical trial?
  - Palliative care options?
  - Other?
Chemoradiation: MSKCC

Sherman, et al., Radiother Oncol 2011
Chemoradiation: MSKCC

Multivariate analysis of local regional progression-free survival (LR-PFS) and overall survival (OS).

<table>
<thead>
<tr>
<th>Variables</th>
<th>$P$ value</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LRP-FS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age $&lt;70$ years</td>
<td>0.037</td>
<td>0.28</td>
<td>0.09–0.92</td>
</tr>
<tr>
<td>RT $\geq 50$ Gy</td>
<td>0.012</td>
<td>0.25</td>
<td>0.08–0.73</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin $\geq 5$ weeks</td>
<td>0.012</td>
<td>0.31</td>
<td>0.13–0.77</td>
</tr>
<tr>
<td>Age $&lt;70$ years</td>
<td>0.013</td>
<td>0.32</td>
<td>0.13–0.78</td>
</tr>
<tr>
<td>RT $\geq 50$ Gy</td>
<td>0.049</td>
<td>0.39</td>
<td>0.15–0.995</td>
</tr>
</tbody>
</table>

RT, radiotherapy.

Sherman, et al., Radiother Oncol 2011
Chemoradiation: Mayo

Foote, et al., Thyroid 2011
Pazopanib + Paclitaxel

Isham, et al., Sci Transl Med 2013
RTOG 0912: Randomized Phase II Study of Concurrent IMRT, Paclitaxel, and Pazopanib vs. Placebo

Arm 1
- Paclitaxel/pazopanib 2-3 wks
- IMRT, 66 Gy in 33 fxr + Paclitaxel/pazopanib
- Adjuvant paclitaxel/pazopanib

Arm 2
- Paclitaxel 2-3 wks
- IMRT, 66 Gy in 33 fxr + Paclitaxel
- Adjuvant paclitaxel

88 pts with ATC
Path centrally rvwd

• Primary endpoint = 1Y OS

Provided by L. Wirth
2012 ATA guidelines

- **RECOMMENDATION 32**
  - Patients who have undergone R2 resection or have unresected disease with good performance status and who wish an aggressive approach should be offered definitive radiation (with or without concurrent chemotherapy).

- **RECOMMENDATION 34**
  - Patients with local symptoms and poor performance status should be offered palliative radiotherapy.

- **RECOMMENDATION 35**
  - Patients who are to receive radiation for unresectable thyroid cancer or in the postoperative setting should, where available, be treated with IMRT; however, treatment should not be delayed because of lack of availability of IMRT.

Smallridge, *et al.*, *Thyroid* 2012
Case 3

- 9/12: 21 yo woman noted painful thyroid lump; hoarse and visible 2 wks later
  - U/S: 3.5 cm R mass with microcalcifications, vascular flow, ill-defined borders suspicious for PTC
  - Clinical DDx: lymphoma vs PTC
Case 3

- FNA: atypia of undetermined significance
  - Negative: TTF-1, Tg, calcitonin, CD130, CD45
  - Positive: PTH
- Core Bx: atypical parathyroid lesion
- Calcium, serum PTH normal
- R TVC weak
- CT angiogram: 40% right carotid stenosis

What to do?
Case 3

- 10/12: excisional wedge biopsy
  “The tumor appeared white and soft, easily extruding from the capsule, much like fish flesh, the common appearance of thyroid lymphoma.”

- Path: anaplastic carcinoma
Case 3

- 11/7/12
- 11/12/12
9/12/2012 and 11/7/2012 CT neck
Case 3

- 21 yo woman, PS 0
  - ATC T4b N1b M1 Rx, stage IVC

- Treatment options:
  - Surgery?
  - Chemotherapy?
  - Radiotherapy?
  - Chemoradiotherapy?
  - Clinical trial?
  - Supportive care?
  - Other?
Chemotherapy

- Doxorubicin - <20% response

- Paclitaxel 96hr continuous infusion every 1-3 weeks
  - 53% response (disease control rate)
  - Median survival 32 weeks for responders, 7 weeks for non-responders
  - No long-term survivors

Ain et al., Thyroid 2000
Vascular disrupting agent versus antiangiogenic agent
Novel therapeutics: Fosbretabulin

Clayton Twigg died June, 2012
Fosbretabulin for anaplastic carcinoma

- Phase II study, fosbratabulin 45 mg/m$^2$ days 1, 8, 15 of 28 day cycles
- N = 26 pts, median age 59
- Toxicity: 10 grade 3/4 AE’s
- CR or PR = 0
- 3 mo “event free survival”: 23%
- Median survival: 4.7 months

Mooney, et al., Thyroid 2009
Phase III carbo/paclitaxel/fosbretabulin vs. carbo/paclitaxel

180 pts w metastatic ATC
Central path rvw

2:1 ratio

• Primary endpoint = OS

Provided by L. Wirth
Fosbretabulin for anaplastic carcinoma

<table>
<thead>
<tr>
<th></th>
<th>CA4P+C/P (n=55)</th>
<th>C/P (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (%95 CI)</td>
<td>5.1 (3.1, 9.2)</td>
<td>4.1 (2.8, 8.9)</td>
</tr>
<tr>
<td>Hazard Ratio:</td>
<td>0.71 (0.42, 1.22)</td>
<td></td>
</tr>
<tr>
<td>Reduction in Risk:</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>6 month survival</td>
<td>48%</td>
<td>37%</td>
</tr>
<tr>
<td>1 year survival</td>
<td><strong>23%</strong></td>
<td><strong>9%</strong></td>
</tr>
</tbody>
</table>

Sosa, et al., Thyroid 2013

![Graph of survival rates](image)
Fosbretabulin for anaplastic carcinoma: age ≤60

Survival Time (months)

K-M Overall Survival Estimate (% of Patients)

<table>
<thead>
<tr>
<th>Survival Time (months)</th>
<th>CA4P+C/P (n=24)</th>
<th>C/P (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>80</td>
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<tr>
<td>9</td>
<td>70</td>
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<td>12</td>
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<td>15</td>
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<td>24</td>
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<tr>
<td>27</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median (%95 CI)

- CA4P+C/P: 10.9 (3.1: 11.1)
- C/P: 3.1 (1.7, 9.5)

Hazard Ratio: 0.38 (0.16, 0.88)

Reduction in Risk: 62%

Sosa, et al., Thyroid 2013
Subgroup: Surgery before chemotherapy

K-M Estimate of Overall Survival

Survival Time (Months)

CA4P+C/P (N=30)
C/P (N=14)

<table>
<thead>
<tr>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% CI)</td>
<td>8.2 (3.0, 13.7)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI):</td>
<td>0.66 (0.33, 1.32)</td>
</tr>
<tr>
<td>Reduction in Risk:</td>
<td>34%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Months</td>
<td>0.567</td>
<td>0.310</td>
</tr>
<tr>
<td>1 Year</td>
<td>0.333</td>
<td>0.077</td>
</tr>
</tbody>
</table>

Sosa, et al., Surgery 2012
Phase II Imatinib

6mon estimate = 45.5%, 95%CI = (16.7%, 70.7%)
12mon estimate = 36.4%, 95%CI = (11.2%, 62.7%)
18mon estimate = 27.3%, 95%CI = (6.5%, 53.9%)

Ha, et al, Thyroid 2010
Phase II Pazopanib

Bible, et al., J Clin Endocrinol Metab 2012
Phase II Sorafenib

Savvides, et al., Thyroid 2013

PR: 10%
PR+SD: 35%
PFS: 1.9 mo
OS: 3.9 mo
PPAR gamma agonist + paclitaxel blocks growth

Copland, et al, Oncogene 2006
Phase I Efatutazone/paclitaxel

Smallridge, et al, J Clin Endocrinol Metab 2013
BRAF inhibitor neoadjuvant therapy

A

![Graph showing tumor volume at 25 days (mm³)]

- Sham Surgery + Vehicle
- Sham Surgery + PLX4720
- Thyroidectomy + PLX4720

* = p<0.001

B

![Graph showing tumor volume at 50 days (mm³)]

- Sham Surgery + PLX4720
- Thyroidectomy + PLX4720

* = p<0.05

Number of lung metastases per whole mount lung section

- Sham Surgery + Vehicle
- Sham Surgery + PLX4720
- Thyroidectomy + PLX4720

* p<0.01
** p<0.001

Nehs, et al, Surgery 2011
Case: vemurafenib in BRAF mutant

Other agents of interest

- Everolimus
- Crilobulin
- ????