Evidence for Best Management of Lacrimal Gland Tumors

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Financial Disclosure

- Hoffman-La Roche/Genentech: honorarium
- Merz Pharmaceutical: honorarium
Outline

- Epidemiology
- Treatment
  - Lymphoma: low dose RT
  - Malign Epithelial: Exenteration vs. Globe-sparing vs. Intra-arterial
- Targeted therapy
- Next step
Lacrimal Gland Tumor

Epithelial

Adenocystic carcinoma
(~25%)
  Malignant mixed
  (carcinoma ex pleomorphic)
  Adenocarcinoma
  Mucoepidermoid
  Squamous cell
  Malignant oncocytoma
  Acinic cell

Pleomorphic adenoma
(~50%)
  Oncocytoma
  Spindle cell myoepithelioma

Lymphoproliferative

Non-hogkin B-cell:
  MALT
    Follicular
    Diffuse Large cell
    Mantle cell
69 yo F with 2 mos of bulging eye
Question

What would you like to do next?
A. Excisional biopsy
B. Incisional biopsy
C. PET/CT
D. Bone marrow aspirate and biopsy
E. None of the above
DIAGNOSIS:
1. MASS, RIGHT LACRIMAL, BIOPSY (SP10-16292, A, 07/26/10, 1 H&E AND 5 UNSTAINED SLIDES):
   - CONSISTENT WITH MARGINAL ZONE LYMPHOMA
   - THE IMMUNOHISTOCHEMICAL STUDIES SHOW THAT THE LYMPHOID CELLS ARE POSITIVE FOR CD20 AND WEAKLY FOR BCL2; WHILE NEGATIVE FOR CD3 AND CD5. THE MIB-1 PROLIFERATION INDEX IS APPROXIMATELY 5%. THE FINDINGS SUPPORT THE ABOVE DIAGNOSIS.
What is the most appropriate next step?
A. Complete excision with capsule intact
B. Initiate induction chemotherapy
C. PET/CT
D. CSF for flow cytometry
E. None of the above
Orbital Lymphoma

- MALT 57%
- Follicular 11%
- Diffuse large B-cell 15%
- Mantle cell 8%
- NK-T cell*

Orbital Lymphoma

- Painless mass
- Bony erosion uncommon
- Bilateral 17%
- Accounts for 20% orbital mass
  - ~50% involves lacrimal gland
  - 30-50% systemic involvement
Ultra-low dose RT

- 4GY in 2 fractions
- Low-grade Bc (MALT/follicular) and Mantle cell
- Overall 100% response
  - 86% (19) CR
  - 14% (3) PR

53 yo F RUL swelling and headache x 3d
Diffuse Large B-cell Lymphoma

- Most common for systemic lymphoma
- Aggressive, rapidly growing
- Can be associated with visual loss and optic nerve compression

- Very chemo sensitive
  - CHOP = cyclophosphamide, doxorubicin, vincristin, pred
  - R-CHOP = plus rituximab
  - R-ICE = ifosfamide, carboplatin, etoposide, ritux
  - Cytarabine
  - Bendamustine
DLBCL with optic neuropathy
Lacrimal Gland Epithelial Tumor

- 50-50, malignant vs. benign
- Adenoid cystic
- Pleomorphic adenoma
Lacrimal Gland Epithelial Tumor

- 50-50, malignant vs. benign
- **Adenoid cystic**
  - 20-35% all lacrimal tumor
  - Early PNI
  - High recurrence and mortality 50%
  - Subtypes: cribriform, solid, sclerosing, comedocarcinomatous, tubular
- Pleomorphic adenoma
24F ptosis, intermittent sharp shooting

Photo courtesy Dr. Esmaeli
46F proptosis for 2 months

Photo courtesy Dr. Esmaeli
Lacrimal Gland Epithelial Tumor

- 50-50, malignant vs. benign
- Adenoid cystic

**Pleomorphic adenoma**
- 50% of all lacrimal epi tumor
- Risk of transformation 10% at 20 yrs, 20% at 30 years
- 5 year recurrence 3% complete excision vs. 32% incomplete
Pleomorphic Adenoma

Photo courtesy Dr. Esmaeli
Pleomorphic Adenoma
Survival 1972-2014

- 59% at 5-year
- 52% at 10-year

Ultrasound – Color Doppler

Non-Epithelial
- Lymphoma
  - Septa ($p<0.001$)
  - tree-shape vascularization ($p<0.05$)
  - Hypo echogenic ($p<0.001$)

Epithelial
- Cystic adenoid Ca
  - Resistance index $>0.7$ ($p<0.001$)
Clinicoradiologic Correlation

- Wedge sign
- Bony erosion vs excavation
- Calcification
- Moulding to globe

Which of the following treatment has been shown to improve survival?

A. Exenteration (cranio-orbital resection)
B. No prior biopsy
C. Predominant basaloid histology
D. Adjuvant chemotherapy
E. None of the above
Overall Survival (1972-2014)

Factors for Overall Survival

- Residual tumor
  - Ro/1 100% (p=0.149)
  - R2 53.6%

- Intracranial extension
  - No 91.7% (0.0117)
  - Yes 50%

- Basaloid subtype (p=0.002)

- Not significant: ≤T2 vs. ≥T3

Ro = no microscopic residual
R1 = no gross residual but microscopic residual on path
R2 = gross residual

Goal of Innovation

1. Improve mortality
2. Preserve sight
3. Better QOL
Globe-sparing

- Complete en bloc excision
- Adjuvant RT in 31/37 (most common IMPT)
- Median age 43 years
- DFS worse with $\geq T_3$

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<th>N</th>
<th>Local recurrence</th>
<th>Death</th>
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<tr>
<td>Gross residual</td>
<td>7</td>
<td>71.4%</td>
<td>3</td>
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<tr>
<td>No/micro residual</td>
<td>12</td>
<td>16.7%</td>
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Globe-sparing

- Overall 87.4%
- DFS 72.9%
- *RFS 44.8%

- FU 53 months
- >90% eye preservation

RT and the Globe

- **Dry eye**: 59%
  - 7 punctal occlusion
  - 2 therapeutic CL
- **Retinopathy**: 38%
- **Cataracts**: 16%
- **Enucleation**: 3/37

- **Final VA >20/40**: 68%

- **Corneal perforation**: 9/67 (13%)
  - Median 10.4 months
- Acute keratoconjunctivitis 76%
  - 6-8 weeks
  - ALL significant PEE
- Filamentary keratitis 15/67 (22%)
- Therapeutic CL: 22%
- Chronic epi defect: 54%
- Tarsorrhaphy: 7/67
Intra-arterial Chemotherapy

- IA 2 cycles 3 weeks apart: cisplatin x1
  - Concurrent IV doxorubicin daily x 3
- Optional 3rd cycle (surgeon decision)

- Orbital exenteration 3-4 weeks later
- ChemoRT (55-60Gy) with weekly cisplatin, 2-4 weeks later
- Adjuvant cisplatin/doxorubicin x 6 cycles
Intra-arterial Chemotherapy

<table>
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<th>Group 1</th>
<th>Group 2</th>
<th>Overall</th>
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<tr>
<td>N</td>
<td>8</td>
<td>11</td>
<td>19</td>
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<tr>
<td>Median FU</td>
<td>11 years</td>
<td>7.25 years</td>
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<tr>
<td>DFS</td>
<td>8</td>
<td>7</td>
<td>15 (78.9%)</td>
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<td>DOD</td>
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<td>AWD</td>
<td>-</td>
<td>1</td>
<td>1 (5.3%)</td>
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<tr>
<td>Overall Survival</td>
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<td></td>
<td>84.2%</td>
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Intra-arterial Chemotherapy

Median DFS 10 years

IACC as designed

IACC as designed versus
IACC protocol deviation (p=0.035)
Conventional BPEI (p<0.001)
IACC protocol deviation versus
Conventional BPEI (p=0.044)

Median DFS 7 years

Cumulative proportion without recurrence
What about personalized medicine?
Lacrimal gland epithelial tumors show the same genetic profile as salivary and parotid gland?

A. True
B. False
Variable miRNA Expression

Upregulated:
- miR-455-5p
- miR-181d-5p
- miR-181a-2-3p
- miR-93-3p
- miR-106b-3p
- miR-1307-5p
- miR-181a-5p
- miR-93-5p

Genomics LG ACC

Myo Clinic
- 12 ACC
  - Fish analysis for MYB rearrangement in 7/12 (58.3%)

MD Anderson
- 16 ACC
  - MAIDI-ROF mass array
    - 168 common point mutation in 40 genes:
      - 5/16 KRAS
      - 1/16 MET
      - 1/16 NRAS

Bascom Palmer
- 14 ACC
  - Whole exome sequencing:
    - 5/14 NOTCH

- FGFR (dovitinib)
- HDAC (Vorinostata)
- NFIB

- (KRAS)
- RAF-MAPK, PI3K

- Gamma-secretase inhibitors (GSI)

Chen TY et al. Eye 2017;31.
Genomics LG ACC

~50 LG ACC

Fish Fusion Analysis MYB-NFIB

Fusion/Rearrangement

MSK IMPACT NextGen 468 genes

Gene mutation

Whole exome

MicroRNA/mRNA Expression

Phenotype Genotype Correlation
Summary

- Low grade lymphoma and Mantle cell can be treated with low dose (4Gy) radiation

- Exenteration does not increase survival for LGMT

- Globe-sparing + RT = IA + exent + chemo
Summary

- miRNA expression distinct for LG tumors
- Kras, Myb and Notch implicated for LGACC
- STAT3 possible marker for differentiating LGET
Thank You

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