The Management of Head and Neck Cancers

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Disclosure

• Clinical trial research support: Genentech, Inc.
Learning Objectives

• Defend the use of IMRT in head and neck cancer.
• Describe 2 current controversies in the radiotherapy of oropharyngeal cancer.
• Evaluate the role of induction and concurrent chemotherapy in nasopharynx and larynx/hypopharynx cancers.
• State the common indications for postoperative radiation and chemoradiation.
Epidemiology of SCCHN

• Mucosally based squamous cell carcinomas of the head and neck in the U.S. in 2015:
  – 45,780 new cases (~3% of U.S. cancers)
  – 9\textsuperscript{th} most common cancer
  – 8,650 deaths (<2%); rate is declining!!

• Globally, these cancers result in:
  – 644,000 cases yearly, 2/3rds in developing world
  – Endemic areas of nasopharyngeal cancer and oral cavity cancer
  – 4-5% of world cancer deaths

American Cancer Society, Cancer Facts and Figures, 2015.
Survival

• The 5 year overall survival for mucosally based head and neck cancers remains about 60% for past few decades
  – Very dependent on site and stage
Survival and stage at diagnosis by site

Major etiology (smoking) is in decline in the U.S.
Smoking is synergistic with alcohol

- The combined effect is multiplicative of the individual effects
- ~75% of SCCHN can be attributed to their combined use
- Synergism:
  - EtOH acts as a solvent for tobacco hydrocarbon carcinogens
  - Smoking changes oral microflora increasing acetaldehyde concentrations
“New kid” on the block? HPV & HNSCC

• Association was difficult to establish due to heterogeneity & limited detection methods

• Syrjanen et al. 1983: some oral SCC morphologically and IHC features of HPV
HPV epidemiology

- Gillison et al, 2000 reported PCR detection of HPV DNA with oropharyngeal cancer
- Distinct clinical profile
  - Younger, Caucasian, non-tobacco smoking, male
  - Marijuana intake, multiple sex partners, oral sex
  - Tonsil and base of tongue with high predilection for nodal spread
  - Exceptionally responsive to all treatments
- ~70% of oropharynx cancers and incidence is rising unlike other HNSCC
Keratinizing SCC

Basaloid SCC

Courtesy of Richard Jordan
HPV detection methods

• Polymerase chain reaction (PCR):
  – Home made assays
  – Roche Linear Array and Amplicor

• In situ hybridization (ISH):
  – Dako GenPoint: HPV 16/18, 6/11
  – Ventana Inform HPV: “cocktail” containing HPV 16

• Immunohistochemistry (IHC):
  – HPV common antigens
  – p16 surrogate
p16 Immunohistochemistry

- Surrogate marker of HPV
- Correlates with HPV DNA integration into host
  - p16 inhibits CDK4 (which phosphorylates Rb, preventing cell cycle progression at G1/S phase)
  - Sensitivity 100%, specificity 80-100%
- ~7% of cases are p16+ but HPV16 –
- Differences due to non-HPV 16 strains, impaired pRb
## OPC survival differences by HPV-16 status

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th># Patients</th>
<th>TX type</th>
<th>Survival HPV + % (years)</th>
<th>Survival HPV - % (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lassen</td>
<td>2009</td>
<td>156</td>
<td>RT</td>
<td>62 (5)</td>
<td>26 (5)</td>
</tr>
<tr>
<td>Hafkamp</td>
<td>2008</td>
<td>77</td>
<td>NS</td>
<td>69 (5)</td>
<td>31 (5)</td>
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<tr>
<td>Reimers</td>
<td>2007</td>
<td>97</td>
<td>S, RT, CRT</td>
<td>73 (5)</td>
<td>63 (5)</td>
</tr>
<tr>
<td>Fakry</td>
<td>2008</td>
<td>62</td>
<td>CRT</td>
<td>78 (5)</td>
<td>50 (5)</td>
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<tr>
<td>Weinberger</td>
<td>2006</td>
<td>107</td>
<td>RT</td>
<td>79 (5)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Kumar</td>
<td>2008</td>
<td>50</td>
<td>CRT</td>
<td>80 (5)</td>
<td>40 (5)</td>
</tr>
<tr>
<td>Chung</td>
<td>2009</td>
<td>46</td>
<td>CRT</td>
<td>86 (5)</td>
<td>35 (5)</td>
</tr>
<tr>
<td>Nichols</td>
<td>2009</td>
<td>44</td>
<td>CRT</td>
<td>89 (3)</td>
<td>69 (3)</td>
</tr>
<tr>
<td>Ang</td>
<td>2010</td>
<td>323</td>
<td>CRT</td>
<td>82 (3)</td>
<td>57 (3)</td>
</tr>
<tr>
<td>Rischin</td>
<td>2010</td>
<td>185</td>
<td>CRT</td>
<td>91 (2)</td>
<td>74 (2)</td>
</tr>
<tr>
<td>Lassen</td>
<td>2011</td>
<td>794</td>
<td>RT, CRT</td>
<td>66 (5)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Posner</td>
<td>2011</td>
<td>111</td>
<td>CRT</td>
<td>82 (5)</td>
<td>35 (5)</td>
</tr>
</tbody>
</table>
Survival after recurrence

Kaplan-Meier estimates of overall survival after disease progression for patients with p16-positive and p16-negative oropharyngeal carcinoma (OPC) who had (A) locoregional progression, (B) distant metastases, (C) salvage surgery, and (D) no salvage surgery.

Carole Fakhry et al. JCO 2014;32:3365-3373
(Somewhat generally accepted) oropharynx cancer treatment options

- **T1-2 N0**, select T1-2N1 → single modality
  - RT alone
  - Surgery +/- postop RT
- **T1-2 N1-2b, T3N0-N2b** → double modality
  - Altered fractionation RT
  - Chemo-RT
  - Chemo-RT + brachytherapy
  - Surgery + postop RT +/- conc chemo
- **T4a-b or N2c-N3** → intensified therapy?
  - Chemo-RT
  - ?? Induction chemo → chemo-RT
Tonsillectomy

• Aulus Cornelius Celsus
• 1st Century BC
• “the tonsils are loosened by scraping around them [with a blunt hook] and then torn out” with a finger
• Vinegar and milk for postoperative hemostasis (Aetius de Amida recommended frog fat)
Figure Legend:
Robotic Equipment Positioning
Central position of the endoscope flanked by 2 robotic trocars is shown.
TLM or TORS, +/- RT +/- chemo

<table>
<thead>
<tr>
<th>Institution</th>
<th>#</th>
<th>T stage</th>
<th>N stage</th>
<th># PORT</th>
<th>LRC-5</th>
<th>OS-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo</td>
<td>69</td>
<td>T1-3</td>
<td>N0-2</td>
<td>None</td>
<td>70-90%</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>* 25 refused PORT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wash U</td>
<td>84</td>
<td>T1-2 74%</td>
<td>N0-3 76%</td>
<td>50</td>
<td>94%</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3-4 26%</td>
<td>N2 76%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univ of Paris</td>
<td>166</td>
<td>T1-3 87 T2</td>
<td>N0-3 85 N0</td>
<td>51</td>
<td>63-89%</td>
<td>82%</td>
</tr>
<tr>
<td>U Penn</td>
<td>47</td>
<td>T1-3 23 T2</td>
<td>N0-2c 24 N1</td>
<td>40</td>
<td>98% (2yrs)</td>
<td>82% (2yrs)</td>
</tr>
</tbody>
</table>
ECOG 3311 P16+ Trial – Low Risk OPSCC: Personalized Adjuvant Therapy Based on Pathologic Staging of Surgically Excised HPV+ Oropharynx Cancer

Assess Eligibility:
HPV (p16)^+ SCC oropharynx

Stage III-IV: cT1-3, N1-2b (no T1N1)
Baseline Functional/ QOL Assessment

LOW RISK: T1-T2N0-N1 negative margins

Radiation Therapy IMRT 50 Gy/25 Fx

INTERMEDIATE: Clear margins ≤ 1 mm ECS 2–3 metastatic LN PNI LVI

Radiation Therapy IMRT 60 Gy/30 Fx

HIGH RISK: Positive Margins > 1 mm ECS or ≥ 4 metastatic LN

Radiation Therapy IMRT 66 Gy/33 Fx + CDDP 40 mg/m^2 wkly

Evaluate for 2-yr PFS Local-Regional Recurrence, Functional Outcomes/QOL

Transoral Resection (any approach) with neck dissection

Observation

Randomize

Randomize

Courtesy of Robert Ferris
Postoperative Radiation Therapy: Unique Considerations after Surgery

• Postoperative status does not change the basic anatomy of elective coverage, but should try to reduce doses to avoid excessive fibrosis

• Risks of surgical intensification: palatal insufficiency, trismus, nerve pain, shoulder weakness, fibrosis

• Recently reported complication of nonhealing soft tissue necrosis in primary tumor bed with fraction size > 2Gy/day

RTOG 0022
- Small, early trial of IMRT feasibility
- For oropharyngeal cancer T1-T2, N0-N1
- Prescribed to 66 Gy at 2.2 Gy/fraction over 6 weeks with subclinical dose of 54-60 Gy
- Not selected for HPV or p16 status

- 2 year locoregional control 91% at 2 years
- All cases of LRF, metastasis, or second primary cancer occurred among patients who were current/former smokers
NCCN T1-T2 N0-N1 ALGORITHM

- Codifies the attempt to use single modality if possible for T1-T2 N0
- Note that concurrent systemic therapy is advised only for T2 N1 at a lower level of recommendation (2B)

## IMRT for oropharynx - outcomes

<table>
<thead>
<tr>
<th></th>
<th>UCSF</th>
<th>Stanford</th>
<th>Wash U</th>
<th>iowa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts</strong></td>
<td>71 definitive</td>
<td>85 definitive</td>
<td>31 definitive</td>
<td>56 opx pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 post-op</td>
<td>43 post-op</td>
<td>151 total HNSCC</td>
</tr>
<tr>
<td><strong>Chemo</strong></td>
<td>Concurrent platinum</td>
<td>Platinum 80%, cetuximab 7%</td>
<td>17 pts platinum</td>
<td>68 pts, platinum based</td>
</tr>
<tr>
<td><strong>F/U</strong></td>
<td>33 months</td>
<td>29 months</td>
<td>33 months</td>
<td>18 months</td>
</tr>
<tr>
<td><strong>LC</strong></td>
<td>3 yr 94%</td>
<td>-</td>
<td>-</td>
<td>2 yr 94% (all pts)</td>
</tr>
<tr>
<td><strong>LRC</strong></td>
<td>3 yr 90%</td>
<td>3 yr 92%</td>
<td>4 yr 87%</td>
<td>2 yr 98% (opx only)</td>
</tr>
<tr>
<td><strong>DFS</strong></td>
<td>3 yr 81%</td>
<td>3 yr 81%</td>
<td>4 yr 81%</td>
<td>-</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>3 yr 83%</td>
<td>3 yr 83%</td>
<td>4 yr 87%</td>
<td>3 yr 82% (all pts)</td>
</tr>
</tbody>
</table>

Huang, *Cancer* 113(3):497, 2008
Daly, *IJROBP* 2009
Chao, *IJROBP*, 59(1):43, 2004
Yao, *IJROBP*, 63(2):410, 2005
Rapid adoption of IMRT in the U.S.
Sites treated with IMRT in the U.S.
Justification for IMRT: NPC studies

• Kam et al. randomized NPC chemoRT study: observer-rated severe xerostomia was 82% in IMRT patients vs 39% in 2D patients at 1 year

• Pow et al. randomized study in early-stage NPC: improvements in stimulated saliva flow and quality of life at 1 year for IMRT vs 3D conformal radiation

Kam JCO 2007, Pow IJROBP 2006
Justification for IMRT: PARSPORT

- Pharyngeal SCC, T1-4 N0-3 at six UK centers
- Up to 24 months, benefits in recovery of saliva with IMRT
- Improved dry-mouth-specific and global quality of life scores
- At 24 mo, no differences in late toxicities, locoregional control, or overall survival

Justification for chemoradiation: GORTEC : XRT +/- carbo/5FU

- 226 pts
- stage III-IV OPX cancers
  - 86% had T3-T4 tumors
- RT 70 Gy in 35 fx +/- chemo
  - Carbo (70mg/m2/d x 4d) & 5FU (600 mg/m2/d CI x 4d) on days 1, 22, and 43 of RT

<table>
<thead>
<tr>
<th>RX</th>
<th>% G3-4 Muc</th>
<th>% LRC</th>
<th>% DFS-3</th>
<th>% OS-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>39</td>
<td>42</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>CRT</td>
<td>71</td>
<td>66</td>
<td>42</td>
<td>51</td>
</tr>
<tr>
<td>P-value</td>
<td>0.04</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Calais G, JNCI 91:2081-6, 1999
Oropharynx/Mixed Chemoradiation
Intergroup : XRT +/- CDDP

• 295/462 pts, stopped for slow accrual
• stage III-IV, 85% had T4 or N3 tumors

• Radiation: 70Gy/30fx
• ChemoRT: 70Gy + CDDP 100 mg/m2 in wk 1,4 and 7
• Split course chemoRT: 30Gy, break, 30-40 Gy + CDDP 75mg/m2 and 5-FU 1 g/m2 x 4 days q 3 wk
  – At break evaluate for resectability

Adelstein, JCO, 21(1):92, 2003
<table>
<thead>
<tr>
<th></th>
<th>GORTEC RT alone</th>
<th>GORTEC chemoRT</th>
<th>Intergroup RT alone</th>
<th>Intergroup chemoRT</th>
<th>Intergroup Split</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts</strong></td>
<td>113</td>
<td>109</td>
<td>95</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td>70 Gy 35 fx</td>
<td>70 Gy 35 fx</td>
<td>70 Gy 35 fx</td>
<td>70 Gy 35 fx</td>
<td>30 Gy break Surg v boost</td>
</tr>
<tr>
<td><strong>Chemo</strong></td>
<td>none</td>
<td>Carbo 70 5FU 600</td>
<td>none</td>
<td>Cisplatin 100</td>
<td>Cisplatin 75 5FU 1000</td>
</tr>
<tr>
<td><strong>F/U</strong></td>
<td>5.5 years</td>
<td>5.5 years</td>
<td>41 months</td>
<td>41 months</td>
<td>41 months</td>
</tr>
<tr>
<td><strong>LRC</strong></td>
<td>5 yr 25%</td>
<td>5 yr 48%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>DSS</strong></td>
<td>5 yr 15%</td>
<td>5 yr 27%</td>
<td>3 yr 33%</td>
<td>3 yr 51%</td>
<td>3 yr 41%</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>5 yr 16%</td>
<td>5 yr 22%</td>
<td>3 yr 23%</td>
<td>3 yr 37%</td>
<td>3 yr 27%</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>30% late</td>
<td>56% late</td>
<td>52% acute</td>
<td>89% acute</td>
<td>77% acute</td>
</tr>
</tbody>
</table>
## Impact of Therapeutic Sequence: MACH-NC Findings

<table>
<thead>
<tr>
<th>Design</th>
<th>(No. of Studies/No. of Subjects)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Chemotherapy Effect (P Value)</th>
<th>Absolute Benefit 2 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>1 (8/1854)</td>
<td>0.98 (0.85-1.19)</td>
<td>0.74</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>1 (31/5269)</td>
<td>0.95 (0.88-1.01)</td>
<td>0.10</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Concomitant</td>
<td>1 (26/3727)</td>
<td>0.81 (0.76-0.88)</td>
<td>&lt; 0.0001</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Total</td>
<td>1 (65/10,850)</td>
<td>0.90 (0.85-0.94)</td>
<td>&lt; 0.0001</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

MACH-NC = Meta-Analysis of Chemotherapy in Head and Neck Cancer; PF = cisplatin + fluorouracil.

Table 1 Indirect comparison of induction and concomitant chemotherapy in locally advanced head and neck squamous cell carcinoma

<table>
<thead>
<tr>
<th>Type of chemotherapy</th>
<th>LRT + concomitant chemotherapy versus LRT</th>
<th>LRT + induction chemotherapy versus LRT</th>
<th>Interaction test (P)</th>
<th>R^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platin + 5 fluorouracil</td>
<td>0.77 (0.69–0.85)</td>
<td>0.90 (0.82–0.99)</td>
<td>0.02</td>
<td>0.86</td>
</tr>
<tr>
<td>Other poly chemotherapy</td>
<td>0.80 (0.71–0.91)</td>
<td>1.01 (0.91–1.12)</td>
<td>0.004</td>
<td>0.80</td>
</tr>
<tr>
<td>Mono chemotherapy with platin</td>
<td>0.74 (0.67–0.82)</td>
<td>No trial</td>
<td>No trial</td>
<td>0.90</td>
</tr>
<tr>
<td>Other mono chemotherapy</td>
<td>0.89 (0.82–0.96)</td>
<td>0.99 (0.84–1.18)</td>
<td>0.24</td>
<td>0.90</td>
</tr>
<tr>
<td>Overall</td>
<td>0.81 (0.78–0.86)</td>
<td>0.96 (0.90–1.02)</td>
<td>0.0001</td>
<td>0.84</td>
</tr>
</tbody>
</table>

LRT, loco regional treatment.
^aRatio of the hazard ratio of the second column (LRT + concomitant chemotherapy versus LRT) divided by the hazard ratio of the third column (LRT + induction chemotherapy versus LRT); test for heterogeneity between R for the three chemotherapy categories. P = 0.06.

Improvements driven by use of platinum

ACUTE TOXICITY BURDEN OF CURRENT CHEMORADIATION APPROACH

Trotti A et al. Lancet Oncol 2007;
Phase III study:
“Dealer’s choice” RT +/- Cetuximab

- RT alone (213 pts)
  - 2 Gy qd to 70 Gy, 1.2 Gy bid to 72-76.8 Gy, or concomitant boost to 72 Gy

- RT + cetuximab (211 pts)
  - 400 mg/m2 one week prior to RT
  - 250 mg/m2 each week during RT

- Stage III/IV SCC of opx, hpx, lx
- Definitive tx, post-op pts excluded

Bonner, NEJM, 354:567, 2006
Kaplan–Meier Estimates of Locoregional Control and Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

Toxicity and QOL outcomes very similar between arms

RTOG 1016: PHASE III TRIAL OF RADIOTHERAPY PLUS CETUXIMAB VERSUS CHEMORADIOTherapy IN HPV-ASSOCIATED OROPHARYNX CANCER

CLOSED, 5 YEAR RESULTS NOT YET MATURE
(noninferiority design based on OS hazard)
Enlarged to 1000 patients, for analyzable 834 patients with 45 expected events
Profile that has achieved excellent outcomes in retrospective series and prospective trials
- P16+
- Oropharyngeal cancer
- Minimal smoking history ≤10 pack-years
- Non bulky primary and non extensive pattern of disease spread
RTOG 0129 PHASE III TRIAL: CONCOMITANT CRT WITH STANDARD VS ACCELERATED FRACTIONATION RT IN ADVANCED SCCHN

Stage III/IV (T2, N2-3, M0 or T3-4, any N, M0) SCCHN
- Oral cavity, oropharynx, hypopharynx, and larynx
- No prior RT to head and neck except radioactive iodine therapy
- No prior surgery to primary tumor or nodes except for diagnostic biopsy

Expected N=720

CRT

Cisplatin
(IV on d1, d22, d43)
Standard fractionation RT
(5 d/w for 7 wks)

Cisplatin
(IV on d1 and d22)
Accelerated fractionation RT
(5 d/wk for 3.5 wks; then bid, 5 d/w for 2.5 wks)

- 743 enrolled, 721 analyzable
- Primary endpoint = 25% increase in OS
RTOG 0129 RESULTS

- 60% oropharynx cancers
- 80-86% male
- Primary endpoint of 5y OS: 59% vs. 56% (p=0.18)
- 1 vs 3 cycles of cisplatin had significantly inferior OS (HR 2.1) and PFS (HR 1.8)
- SFX with 2 vs 3 cycles of cisplatin more likely to experience local-regional relapse (HR 1.7)
- RT given over 8-9 weeks vs. 6-7 weeks resulted in lower OS (HR 2.2)
- As a continuous variable, each day of RT delay decreased OS, PFS by 5%, 4% (p=0.001, 0.006)

Ang, JCO 28:15s, 2010 (suppl; abstr 5507); Ang NEJM 2010
RTOG 0129: HPV and p16 survival analyses

A. Overall Survival According to Tumor HPV Status

- HPV-positive
- HPV-negative

B. Progression-free Survival According to Tumor HPV Status

- HPV-positive
- HPV-negative

C. Overall Survival According to p16 Expression

- p16-positive
- p16-negative

D. Progression-free Survival According to p16 Expression

- p16-positive
- p16-negative
RTOG 0129: DEFINITION OF LOW RISK

266 Patients with oropharyngeal cancer, known tumor HPV status, and known number of pack-years of smoking

178 Had HPV-positive tumors

88 Had ≤10 pack-years

26 Had N0–N2a cancer

114 of 266 (42.9%) were at low risk

90 Had >10 pack-years

64 Had N2b–N3 cancer

79 of 266 (29.7%) were at intermediate risk

88 Had HPV-negative tumors

23 Had ≤10 pack-years

15 Had T2–T3 tumors

73 of 266 (27.4%) were at high risk

65 Had >10 pack-years

8 Had T4 tumors
RTOG 0129: SURVIVAL BY RISK CLASSIFICATION
E1308: A PHASE II TRIAL OF INDUCTION CHEMOTHERAPY FOLLOWED BY CETUXIMAB WITH LOW DOSE OR STANDARD DOSE IMRT IN PATIENTS WITH HPV-ASSOCIATED RESECTABLE SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX

**Induction Chemotherapy**

- **Key Eligibility**
  1. OPSCC
  2. HPV16 ISH + and / or p16+
  3. Resectable stage III, IVA

- **Cisplatin** 75mg/m² D1
- **Paclitaxel** 90mg/m² D1,8,15
- **Cetuximab** 250mg/m² D1,8,15

Q 21 days for 3 cycles

**Concurrent Chemoradiation**

- **CLINICAL CR**
  - Low dose IMRT 54Gy/27fx** + Cetuximab weekly

- **CLINICAL PR / SD**
  - Full dose IMRT 69.3Gy/33fx** + Cetuximab weekly

**Response Assessment**

- Direct visualization of primary
- Clinical exam of neck
- CT/MRI

N=90 patients, 80 analyzable

**Response**

**Uninvolved nodes get 51.3 Gy/27 fx**

*Courtesy of Barbara Burtness*
RESULTS: PFS IN STANDARD AND LOW DOSE RT ARMS

Progression-free Survival

- Low-dose (n=62)
- Std-dose (n=15)
- All evaluable pts (n=80)

# at risk
- All eval: 72, 69, 61
- Low dose: 57, 55, 48
- Std dose: 14, 13, 12

1-yr PFS 91%
1-yf PFS 87%
1-yr PFS 89%

1.0
0.8
0.6
0.4
0.2
0.0
0 5 10 15 20 25 30
0.0 0.2 0.4 0.6 0.8 1.0
Time in months
Probability

Courtesy of Barbara Burtness
ASCO 2012
For reduced-dose IMRT patients (78% of all patients), at 23 mo followup, PFS was 84%
- overall survival 95%
- primary site LC 94%
- nodal control 95%
- distant control 92%

Patients with <10yrs smoking, T1-3 and N0-2b disease achieved 96% PFS and OS

ECOG 1308: 2-YEAR PRIMARY ENDPOINT
### Results in Induction Chemotherapy + Cetux-54 Gy Arm at 2 Years

<table>
<thead>
<tr>
<th>Variable (n)</th>
<th>23mo PFS (90% CI)</th>
<th>24mo OS (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All reduced-dose pts (62)</td>
<td>0.84 (0.74, 0.90)</td>
<td>0.95 (0.87, 0.98)</td>
</tr>
<tr>
<td>T4A (7)</td>
<td>0.69 (0.29, 0.89)</td>
<td>0.86 (0.45, 0.97)</td>
</tr>
<tr>
<td>T1-T3 (55)</td>
<td>0.86 (0.75, 0.92)</td>
<td>0.96 (0.88, 0.99)</td>
</tr>
<tr>
<td>N2C (19)</td>
<td>0.77 (0.56, 0.89)</td>
<td>0.95 (0.76, 0.99)</td>
</tr>
<tr>
<td>N0-N2b (43)</td>
<td>0.87 (0.75, 0.94)</td>
<td>0.95 (0.85, 0.98)</td>
</tr>
<tr>
<td>Smoker &gt; 10 pkyr (21)</td>
<td>0.71 (0.48, 0.85)</td>
<td>0.90 (0.71, 0.97)</td>
</tr>
<tr>
<td>Smoker &lt;= 10 pkyr (40)</td>
<td>0.92 (0.81, 0.97)</td>
<td>0.97 (0.87, 0.995)</td>
</tr>
<tr>
<td>Smoker &lt;= 10 pkyr, &lt;T4, &lt;N2c (n=27)</td>
<td>0.96 (0.82, 0.99)</td>
<td>0.96 (0.82, 0.99)</td>
</tr>
<tr>
<td>All standard-dose pts (15)</td>
<td>0.64 (0.39, 0.81)</td>
<td>0.87 (0.63, 0.96)</td>
</tr>
</tbody>
</table>

ASCO 2014
Treatment of HPV positive HNSCC

Outcomes of HPV-related oropharyngeal cancer patients treated by radiotherapy alone using altered fractionation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3D-CRT</th>
<th>IMRT</th>
<th>HPV(+) I–IV (n = 148)</th>
<th>HPV(–) I–IV (n = 59)</th>
<th>Total (n = 207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 Gy/25 f/5 weeks, QD</td>
<td>Gross target</td>
<td>60 Gy/25f</td>
<td>60 Gy/25f</td>
<td>64 (43%)</td>
<td>22 (37%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>55.2 Gy/23f</td>
<td>56 Gy/25f</td>
<td>56 Gy/25f</td>
<td>53 (36%)</td>
<td>15 (25%)</td>
</tr>
<tr>
<td>Microscopic</td>
<td>43.2 Gy/18f</td>
<td>50 Gy/25f</td>
<td>50 Gy/25f</td>
<td>12 (8%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>64 Gy/40 f/4 weeks, BID</td>
<td>Gross target</td>
<td>64 Gy/40f</td>
<td>64 Gy/40f</td>
<td>53 (36%)</td>
<td>15 (25%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>57.6 Gy/36f</td>
<td>56 Gy/40f</td>
<td>56 Gy/40f</td>
<td>12 (8%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>Microscopic</td>
<td>44.8 Gy/28f</td>
<td>46 Gy/40f</td>
<td>46 Gy/40f</td>
<td>7 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>70 Gy/35 f/7 weeks, QD</td>
<td>Gross target</td>
<td>70 Gy/35f</td>
<td>70 Gy/35f</td>
<td>7 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>60 Gy/30f</td>
<td>63 Gy/35f</td>
<td>63 Gy/35f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic</td>
<td>50 Gy/25f</td>
<td>56 Gy/35f</td>
<td>56 Gy/35f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 Gy/35 f/6 weeks, QD, BID once per week</td>
<td>Gross target</td>
<td>70 Gy/35f</td>
<td>70 Gy/35f</td>
<td>7 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>60 Gy/30f</td>
<td>63 Gy/35f</td>
<td>63 Gy/35f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic</td>
<td>50 Gy/25f</td>
<td>56 Gy/35f</td>
<td>56 Gy/35f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td>12 (8%)</td>
<td>8 (14%)</td>
</tr>
</tbody>
</table>
PMH RADIOTHERAPY ALONE FOR P16+ AND <10 PY SMOKING: RT VS CRT

(a) Overall Survival
- RT-alone vs. CRT:
  - 3-year OS: 86% (70-94) vs. 88% (77-94)
  - Hazard Ratio: 0.71 (0.48-1.17), p=0.28
- No at Risk: RT-alone, 37, CRT, 67
- Years since diagnosis: RT-alone, 30, 23, 14; CRT, 58, 28, 7

(b) Local Control
- RT-alone vs. CRT:
  - 3-year LC: 95% (87-100) vs. 92% (86-99)
  - Hazard Ratio: 0.59 (0.12-2.99), p=0.512
- No at Risk: RT-alone, 37, CRT, 67
- Years since diagnosis: RT-alone, 27, 21, 14; CRT, 51, 25, 7

(c) Regional Control (RC)
- RT-alone vs. CRT:
  - 3-year RC: 97% (92-100) vs. 93% (86-99)
  - Hazard Ratio: 0.29 (0.03-2.48), p=0.219
- No at Risk: RT-alone, 37, CRT, 67
- Years since diagnosis: RT-alone, 27, 21, 14; CRT, 49, 25, 7

(d) Distant Control (DC)
- RT-alone vs. CRT:
  - 3-year DC: 92% (82-100) vs. 86% (77-95)
  - Hazard Ratio: 0.6 (0.19-1.88), p=0.365
- No at Risk: RT-alone, 37, CRT, 67
- Years since diagnosis: RT-alone, 28, 22, 14; CRT, 51, 25, 7
NRG HN002: A Randomized Phase II Trial for Patients with P16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer

Eligibility
- OP SCCA
- ≤10 pack-year
- T1-T2 N1-N2b
- T3 N0-N2b

44% of RTOG 1016 population eligible

Eligibility Criteria:
- Central review p16+ IHC

Stratification:
- Declare Intent
  - Unilat vs Bilat Neck XRT

Randomization:
- 60 Gy XRT (2 Gy/fx) in 6 weeks + cisplatin 40 mg/m² weekly x 6 cycles
- 60 Gy XRT (2 Gy/fx) at 6 fractions/week for 5 weeks
WHAT EVER HAPPENED TO INDUCTION ANYWAY?

- **TAX 324: TPF vs PF**
  - Did not include direct comparison to concurrent CRT

- **PARADIGM**

- **DeCIDE**
TAX 324: Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU Sequential Therapy in Advanced SCCHN

**Chemotherapy- and RT-naïve stage III/IV SCCHN**
- Oral cavity, oropharynx, hypopharynx, larynx
  - N=501

**Randomization**

**ICT**
- Docetaxel (75 mg/m²)
- Cisplatin (100 mg/m²)
- 5-FU (1000 mg/m²/day, 96-hr C-I)
  - every 3 weeks, 3 cycles

**CRT**
- Carboplatin (AUC 1.5 weekly)
- Daily RT (5 days/week)

**Response**

<table>
<thead>
<tr>
<th>Response</th>
<th>TPF</th>
<th>PF</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (ICT)</td>
<td>72% (65.8-77.2)</td>
<td>64% (57.9-70.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>CR (ICT)</td>
<td>17% (12.1-21.6)</td>
<td>15% (10.8-20.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>ORR (ICT+CRT)</td>
<td>77% (70.8-81.5)</td>
<td>72% (65.5-77.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>CR (ICT+CRT)</td>
<td>35% (29.4-41.5)</td>
<td>28% (22.5-34.1)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

TAX 324: Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU Sequential Therapy in Advanced SCCHN: Results

- TPF significantly improves survival and PFS compared with PF in an ICT regimen followed by CRT

Paradigm: Phase III Sequential Therapy Trial in North America

**Paradigm**
Stage III/IV SCCHN
- Oral cavity, oropharynx, hypopharynx, larynx
- Expected N=330

**RANDOMIZE**

**ICT**
- Docetaxel
- Cisplatin
- 5-FU every 3 weeks, 3 cycles

**CRT**
- Carboplatin (every week)
  - Daily RT (days 1-5)
  - 7 weeks
- Docetaxel (every week for 4 wks)
  - Daily/twice-daily RT (days 1-5)
  - 6 weeks
- Cisplatin (weeks 1, 4)
  - Daily/twice-daily RT (days 1-5)
  - 6 weeks

PARADIGM

• Arm 1: TPF x 3 → weekly carboplatin or docetaxel with accelerated RT
• Arm 2: Cisplatin x 2 with accelerated RT
• Enrolled 145 pts: oropharynx: 80, larynx: 24, hypopharynx: 15, and oral cavity: 26
• Study terminated early due to low accrual
• 3y OS was 73% vs 78% (p=0.77)

Haddad et al., The PARADIGM trial: A phase III study comparing sequential therapy (ST) to concurrent chemoradiotherapy (CRT) in locally advanced head and neck cancer (LANHC). ASCO 2012. Abstract #5501.
Decide: Phase III Sequential Therapy Trial in North America

DeCIDE
Chemotherapy and RT-naïve SCCHN
- Expected N=400

RANDOMIZE

ICT
- Docetaxel (day 1)
- Cisplatin (day 1)
- 5-FU (days 1-5)
every 3 weeks, 2 cycles

CRT
- Docetaxel (day 1)
- 5-FU (days 0-4)
- Hydroxyurea (days 0-4)
- Twice-daily RT (days 1-5)
every 2 weeks, 5 cycles

Arm 1 (standard): 5 days of D 25 mg/m\textsuperscript{2}, F 600 mg/m\textsuperscript{2}, hydroxyurea 500 mg BID, and RT 150 cGy BID followed by a 9 day break

Arm 2 (induction): 2 induction cycles (D 75 mg/m\textsuperscript{2}, P 75 mg/m\textsuperscript{2}, F 750 mg/m\textsuperscript{2} day 1-5) → same CRT

Enrolled 280 patients

3y OS 73% vs 75% (p=0.70)

Cohen et al., DeCIDE: A phase III randomized trial of docetaxel (D), cisplatin (P), 5-fluorouracil (F) (TPF) induction chemotherapy (IC) in patients with N2/N3 locally advanced squamous cell carcinoma of the head and neck (SCCHN). ASCO 2012. Abstract #5501.
Defensible Induction Chemotherapy Scenarios

1. Need to optimize patient’s medical status
2. Very high potential for metastasis, or oligometastasis with plan to consolidate
3. Unavoidable delay in starting radiation
4. Impending local issue (airway, CNS) that is not well addressed with surgery
5. Markedly advanced neck disease (dermal infiltration, truly massive N3)
6. Markedly advanced primary disease (T4b)

* Consider 1-4% risk of mortality and effect on compliance with subsequent CRT

Adapted from: Haddad and Shin, NEJM 2008
Basic IMRT Delineation for OPC

• GTV = All gross disease on imaging or exam
• CTV1 = “Microscopic margin”: GTV + 5-10 mm margin (many use 7-8 mm)
• CTV2 = “High Risk” nodal volumes and mucosal sites
  – Not defined consistently
  – E.g. uninvolved level 3 nodes in base of tongue cancer with involved level 2 nodes
• CTV3 = “Elective” uninvolved nodal regions at risk for microscopic disease
  – E.g. uninvolved level 4 nodes in base of tongue cancer with involved level 2 nodes

• PTV = CTV + 2.5-5 mm (many use 3 mm)
  – Accounts for tumor motion and setup error
### Common standard dose schedules

<table>
<thead>
<tr>
<th></th>
<th>Chemo-RT</th>
<th>RT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 Fractions</td>
<td></td>
<td>30 Fractions</td>
</tr>
<tr>
<td>CTV1 = 70 Gy</td>
<td></td>
<td>CTV1 = 66 Gy</td>
</tr>
<tr>
<td>CTV2 = 59-63 Gy</td>
<td></td>
<td>CTV2 = 60 Gy</td>
</tr>
<tr>
<td>CTV3 = 54-57 Gy</td>
<td></td>
<td>CTV3 = 54 Gy</td>
</tr>
</tbody>
</table>
Tonsil cancer
start with CTV2 at pterygoid plates
include half of medial pterygoid

Medial vs lateral pterygoid muscle

High coverage not needed for tongue base cancers
Tonsil cancer
start RP nodes above jugular foramen
(put in intermediate dose if N+ neck)
Tonsil cancer
CTV1 should cover maxillary tuberosity
Tonsil cancer
cover retrostyloid nodes for N+ neck
Tonsil cancer include some tongue base/GP sulcus

Come out into neck at C2 transverse process

CTV stay outside bone
Tonsil cancer
CTV1 extends to just above hyoid

Make sure to cover vasculature

Follow lateral pharyngeal wall with CTV1
Tonsil cancer
CTV2 covers lateral pharyngeal wall to just above AE fold

Don’t go outside platysma

Can drop contralateral level 5 if limited adenopathy
Dose constraints

- Cord: 45Gy max dose (<40Gy, if achievable)
- Cord Expanded 5mm: 50Gy max dose if possible
- **Brainstem**: 54Gy max dose (typically <40 Gy) (try for <30 Gy to posterior portion to reduce nausea)
- Brain: Tight 54Gy gradient
- Parotid (contralateral): <26Gy mean dose
- Cochlea: <35Gy max dose (<30Gy, if possible)
- **Mandible**: <70Gy max dose, no hot spots >105%

Where is/what is the DVC (area postrema)?

- Area postrema lies within DVC, in the medulla oblongata between caudal aspect of pons and cranial aspect of the spinal cord
- Receives sympathetic and vagal innervation from GI tract: may serve as “vomiting relay” to CNS

Dose constraints

- Optic Chiasm & Optic Nerves: <54Gy max dose
- Oral cavity: ALARA, mean dose <40Gy or <34Gy
- Larynx: mean <35Gy (<25-30Gy preferred)
  - Strongly consider low neck split field approach which reduces dose to approximately 10 Gy
- Cervical Esophagus: ALARA, minimize 60Gy
- Posterior Neck: <35Gy (try to control the 30Gy to reduce hair loss and long term cramping)
- Lens <5Gy or <10Gy if close to the target
- Brachial plexus: <60 Gy max dose (LOW PRIORITY)

Contouring the plexus

• You can recognize BP on low-res CT
  – MR fusion not usually helpful
  – Practice will help

• How I do it
  – Identify C5, C6, C7 nerve roots above VB
  – Identify C8, T1 nerve roots below VB
  – Contour between ant and middle scalenes
  – 3-4 mm brush on axial cuts
  – Confirm using sagittal plane images
  – For postop cases, confirm using contralat neck
“Dose Dump” into Hot Spots

Think about this in advance and plan subvolumes accordingly.
1. Submandibular sparing? if contralateral level IIA uninvolved

submandibular gland may be bilobed and look like a node
Submandibular gland sparing

• Contribute 65-90% of unstimulated mucin-rich saliva and 95% of salivary flow during a 24-hour period
• Mean dose < 39 Gy improved salivary flow and correlated with improved patient- and observer-rated xerostomia
• Oral cavity and submandibular dose reduce xerostomia independently of parotid sparing

Little et al., IJROBP 2012, 83:1007-1014.
## SMG sparing IMRT for OPC

*Recurrences in oral cavity cases

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Definitive RT</th>
<th>Mean SMG dose</th>
<th>Disease control</th>
<th>Late xerostomia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gensheimer, U Washington</td>
<td>76</td>
<td>86%</td>
<td>30.7</td>
<td>No peri-SMG recurrence*</td>
<td>23% gr 2, no gr 3</td>
</tr>
<tr>
<td>Collan, Helsinki</td>
<td>50</td>
<td>49%</td>
<td>27.8</td>
<td>No peri-SMG recurrence</td>
<td>No perm gr 3</td>
</tr>
<tr>
<td>Doornaert, VU Netherlands</td>
<td>20</td>
<td>100%</td>
<td>34.1</td>
<td>No peri-SMG but 3 primary recur</td>
<td>--</td>
</tr>
<tr>
<td>Little, U Michigan</td>
<td>17</td>
<td>100%</td>
<td>43</td>
<td>No level I recurrence</td>
<td>No gr 3</td>
</tr>
<tr>
<td>Wang, Shanghai Jiao Tong U</td>
<td>17</td>
<td>12%</td>
<td>20</td>
<td>Two contralat level 2 recur</td>
<td>--</td>
</tr>
<tr>
<td>Chajon, Centre Eugene Marquis</td>
<td>8</td>
<td>100%</td>
<td>33.8</td>
<td>No peri-SMG recurrence</td>
<td>No gr 3</td>
</tr>
<tr>
<td>Robin, MSKCC-U Colorado</td>
<td>71</td>
<td>100%</td>
<td>33</td>
<td>One IIA recurrence</td>
<td>--</td>
</tr>
</tbody>
</table>
2. Reducing contralateral neck volumes

- Likelihood of failure in neck levels I and V is generally very low for OPC
- With high non-bulky jugulodigastric adenopathy, it is reasonable to treat contralateral levels II-IV only
  - Based on surgical dissection series
  - For limited-primary tonsil cancer, could also consider treating this unilaterally

Where is Level IB?
Sub-mandibular
Separation of levels IV and V

- **Va/b upper posterior triangle → Vc lower posterior triangle**
  - Separated by plane at inferior cricoid
  - Posterior border at anterior trapezius

- **IVa lower jugular → IVb medial supraclavicular**
  - IVa ends 2 cm above sternoclavicular joint, IVb ends at manubrium
  - Lateral aspect defined by plane of anterior scalene

Formerly “supraclav fossa” or “Ho’s triangle”

3. Ipsilateral radiation therapy for tonsil T1-2, N0-N2a ?maybe N2b?

The ultimate form of salivary gland sparing!
<table>
<thead>
<tr>
<th>Study</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>Total N</th>
<th>Contralat failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rusthoven, U Colorado</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>20</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Al-Mamgani, Rotterdam</td>
<td>43</td>
<td>50</td>
<td>0</td>
<td>93</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Jackson, British Columbia</td>
<td>54</td>
<td>7</td>
<td>16</td>
<td>77</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Chronowski, MDACC</td>
<td>23</td>
<td>43</td>
<td>0</td>
<td>66</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Cramer, Duke</td>
<td>1</td>
<td>22</td>
<td>0</td>
<td>23</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hwang, Wash U</td>
<td>6</td>
<td>35</td>
<td>0</td>
<td>41</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Kagei, Japan</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>10</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Koo, Korea</td>
<td>8</td>
<td>10</td>
<td>0</td>
<td>18</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lu, Peter MacCallum</td>
<td>14</td>
<td>14</td>
<td>5</td>
<td>33</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>O’Sullivan, PMH</td>
<td>56</td>
<td>36</td>
<td>3</td>
<td>95</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Mendenhall, Florida</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>64</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Vergeer, Netherlands</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>7 (14%)</td>
</tr>
</tbody>
</table>

*incl oral cavity
Caveats

• For primary site in contiguity with posterior pharyngeal wall or >1cm of soft palate or tongue base involvement, unilateral therapy is NOT advised
• Unilateral therapy for well lateralized tongue base tumors is extremely controversial – I would not recommend it
• With large size nodal burden or extracapsular extension in the neck, there is altered lymphatic flow to the contralateral side, not established whether this represents risk that will manifest but take this seriously
• Ipsilateral series with acceptable results represent highly selected patients treated at high volume centers
4. Sparing the larynx with split field

- Whenever possible, we match an upper IMRT plan at a monoisocentric plane set above the arytenoids
- Cheater block $\rightarrow$ cord block for initial 40 Gy then open up
- Generally this reduces larynx dose to 10 Gy versus 25-35 Gy with IMRT
- We will not split through any gross disease
4. Sparing the larynx with split field

- Whenever possible, we match an upper IMRT plan at a monoisocentric plane set above the arytenoids.
- Cheater block → cord block for initial 40 Gy then open up.
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4. Sparing the larynx with split field

- Whenever possible, we match an upper IMRT plan at a monoisocentric plane set above the arytenoids
- Cheater block $\rightarrow$ cord block for initial 40 Gy then open up
- Generally this reduces larynx dose to 10 Gy versus 25-35 Gy with IMRT
- We will not split through any gross disease
- Can block off cord completely if treating ipsilaterally
WHAT COULD THE FUTURE LOOK LIKE FOR “GOOD RISK” OPC? OPTIONS UNDER STUDY...

- Accelerated radiation (in its many artful forms)
- Radiation + systemic therapy (in its many artful forms)
- Surgery +/- radiation
- Surgery + radiation +/- systemic therapy
- Induction systemic therapy followed by radiation + systemic therapy
- Induction systemic therapy followed by de-escalated radiation-based treatment

Decision making will balance treating center’s expertise, therapeutic efficacy, long-term toxicity
Three patients with nasopharyngeal carcinoma

T4 skull base

T2 parapharyngeal

N2 neck nodes
Three patients with nasopharyngeal carcinoma

The same treatment will be recommended for all three
The search for better selection algorithms continues in NPC just as in other sites
NPC is fairly uncommon in Europe and the U.S. (2/100,000)

NPC is extremely common in southern China and Hong Kong (20-25/100,000) and accounts for up to 18% of all cancer diagnoses

NPC has been called “the Cantonese cancer”

NPC is also common in Taiwan, Singapore, Malaysia, Thailand, and Vietnam

NPC is seen in Africa, the Mediterranean, and among the Alaskan Inuit
## NPC Incidence in Chinese and White Males

<table>
<thead>
<tr>
<th>Area</th>
<th>Incidence* Chinese</th>
<th>Incidence* White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong 1965-1969</td>
<td>24.7</td>
<td>--</td>
</tr>
<tr>
<td>Singapore 1960-1964</td>
<td>20.2</td>
<td>--</td>
</tr>
<tr>
<td>San Francisco-Oakland 1969</td>
<td>17.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Hawaii 1960-1964</td>
<td>10.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* Incidence per 100,000 per year

Buell, Cancer Research 34:1189-1191, 1974
Nodal involvement is common, prognostic, and relates to type

• Nodal mets at presentation
  – 90% subclinically node +
  – 70% clinically node +
  – 50% bilateral node +

• Type of cancer impacts amount of lymph node spread
  – 73% node + if WHO type I (“keratinizing”)
  – 92% node + if WHO type IIA/IIB (endemic Chinese/Asian type)

• 40% of pts with N3 dz present with mets, 75% will ultimately have mets
Intergroup 0099 (RTOG 88-17)

AJCC 1992 stage III-IV M0

STRATIFY

T stage
N stage
Performance status
Histology

RANDOMIZE

RT alone (70 Gy)

RT (70 Gy) Cisplatin x3

Cisplatin + 5FU x3

N = early closure at 193 → 147
FU = 2.7 yrs

Al Sarraf, J Clin Oncol 1998; 16:1310-1317
## Intergroup 00-99

### Results

<table>
<thead>
<tr>
<th></th>
<th>RT only</th>
<th>CRT + adj chemo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr PFS</td>
<td>29%</td>
<td>58%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>5 yr DFS</td>
<td>46%</td>
<td>74%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>37%</td>
<td>67%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Closed early at first interim analysis (N=193)
Criticisms of Intergroup 00-99

- Possible overestimation of effects - due to early closure
- Ineligibility rate - high proportion (24%) not meeting criteria or with missing data
- Applicability - high proportion (22%) of WHO I, which has lower survival and may require more chemotherapy
- Low survival in RT-only arm compared to results in Asia. Did chemotherapy compensate for poor quality RT? Were RT results with the Western population worse than in Asia?
- Toxicity - only 63% completed concurrent chemo, 55% completed adjuvant chemo
- Design - did not distinguish benefit of concurrent vs. adjuvant vs. both
Taiwan – Taichung Veterans ph III: RT vs CRT

- 284 patients, stage III to IV (M0) NPC

- Arm 1: RT alone (70-74 Gy)
  vs

- Arm 2: RT (70-74 Gy) + Cisplatin 20 mg/m2/d and 5FU 400 mg/m2/d x 4 days, weeks 1 and 5
  (NO ADJUVANT)

Overall Survival

Radiation alone vs chemoRT

Intergroup 0099

Taichung Veterans Hospital

Al-Sarraff, JCO, 16(4):1310, 1998
Al-Sarraff, ASCO, Abs 905, 2001
RTOG 0225 phase II IMRT feasibility study

AJCC 2002
stage I-IVB
All WHO types
N=68

70 Gy to gross disease
59.4 to microscopic disease
All in 33 fractions with IMRT

Concurrent and adjuvant chemotherapy: ≥T2b and/or N+

Lee et al, JCO 2008
• 68 NPC patients, all WHO types
• T2b or N+ had concurrent cisplatin and adjuvant cisplatin-5FU

• 2-y local PFS 92.3%
• 2-y regional PFS 90.5%
• 2-y DM-free rate 85.7%

• Clinical outcomes improved compared to Intergroup 0099 due to IMRT
• Xerostomia scores were improved compared with previous RTOG trials
MAC-NPC metaanalysis: role of concurrent chemotherapy

- Individual patient data from 8 randomized trials
- OS benefit: 4% at 2 years, 6% at 5 years
- EFS benefit: 9% at 2 years, 10% at 5 years
- **Risk reduction from concurrent: 40%**
- **No discernible OS risk reduction from induction (1%) or adjuvant (3%)**
- NB: Intergroup 00-99 was classified in the concurrent group

Baujat, IJROBP, 2006 Jan 1;64(1):47-56
Sun Yat Sen Univ, Guangzhou trial

AJCC 1997
stage III-IV
M0
Excluded
T3-T4N0

N = 508

Randomize

RT (≥ 66 Gy)
Weekly cisplatin
40 mg/m²

Cisplatin + 5FU x3

Chen et al, Lancet Oncology 2011
Chen et al., Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial, Lancet 2012
NCCN 2.2013: response to SYS trial

T1, N1-3; T2-T4, any N →

Concurrent chemo/RT\textsuperscript{b,c} followed by adjuvant chemotherapy\textsuperscript{c,d}
or

Concurrent chemo/RT not followed by adjuvant chemotherapy (category 2B)\textsuperscript{b,c}

or

Induction chemotherapy (category 3)\textsuperscript{c,e} followed by chemo/RT\textsuperscript{b,c}

\textit{category 2A (previously category 1)}

Controversy over SYS trial

This trial did not have a statistically appropriate non-inferiority design.

Higher absolute number of failures in the concurrent only arm and consistently lower than CRT+adjuvant

More followup needed to see DM?

54-59% quit concurrent weekly chemotherapy. 18% randomized to adjuvant arm did not get it.
A little-known recollection

I thought the ideal experimental arm would have been induction CT followed by concurrent cisplatin and RT…. However, some physicians were reluctant to treat tumors that had been “down-staged” with the then relatively new concept concurrent therapy (especially those tumors that had a complete clinical response). Also, induction CT precluded the head-to-head comparison of response rates and possible side effects. After considerable discussion, we decided that the experimental arm would consist of concurrent cisplatin [and RT] followed by the combination of [cisplatin-5FU]… for a total of three additional courses.

-- Muhyi Al-Sarraf, J Radiat Oncol 2012
## Phase III induction trial
### Hong Kong NPC-0501

Accrued 803 patients, stage III-IVB
Tested 3 questions: conventional vs accelerated RT, induction vs adjuvant PF, induction 5FU vs Xeloda
Endpoint: 5 year PFS

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
</table>
| Experimental: 1A  
Concurrent-Adjuvant CRT using P-PF regimen and conventional fractionation radiotherapy | Drug: Adjuvant chemotherapy using PF (5-Fluorouracil)  
Cisplatin 80 mg/m² IV + 5-Fluorouracil 1000 mg/m²/day IV infusion for 96 hr every 28 days for 3 cycles |
| Experimental: 1B  
Concurrent-Adjuvant CRT using P-PF regimen and accelerated fractionation radiotherapy | Drug: Adjuvant chemotherapy using PF (5-Fluorouracil)  
Cisplatin 80 mg/m² IV + 5-Fluorouracil 1000 mg/m²/day IV infusion for 96 hr every 28 days for 3 cycles |
| Experimental: 2A  
Induction-Concurrent CRT using PF-P regimen and conventional fractionation radiotherapy | Drug: Induction chemotherapy using PF (5-Fluorouracil)  
Cisplatin 100 mg/m² IV + 5-Fluorouracil 1000 mg/m²/day IV infusion for 120 hr every 21 days for 3 cycles |
| Experimental: 2B  
Induction-Concurrent CRT using PF-P regimen and accelerated fractionation radiotherapy | Drug: Induction chemotherapy using PF (5-Fluorouracil)  
Cisplatin 100 mg/m² IV + 5-Fluorouracil 1000 mg/m²/day IV infusion for 120 hr every 21 days for 3 cycles |
| Experimental: 3A  
Induction-Concurrent CRT using PX-P regimen and conventional fractionation radiotherapy | Drug: Capecitabine  
Dose: 1000 mg/m², BD, Day 1-Day 14 Interval: 21 days Cycles: 3 cycles  
Other Name: Xeloda |
| Experimental: 3B  
Induction-Concurrent CRT using PX-P regimen and accelerated fractionation radiotherapy | Drug: Capecitabine  
Dose: 1000 mg/m², BD, Day 1-Day 14 Interval: 21 days Cycles: 3 cycles  
Other Name: Xeloda |
Phase III induction trial
Hong Kong NPC-0501

- Changing the fractionation from conventional to accelerated did not achieve any benefit but incurred higher toxicities (acute mucositis and dehydration)

- Comparisons of induction PF versus adjuvant PF did not indicate a significant improvement

- Comparisons of induction PX versus induction PF revealed fewer toxicities (neutropenia and electrolyte disturbance)

Phase III induction trial
Singapore

Randomized phase II/III

216 patients

Arm 1: concurrent weekly cisplatin x 8 with IMRT 33 fractions

vs

Arm 2: induction gem/carlo/paclitaxel q21 days x 2, then same as arm 1

Endpoint: 5 year OS

ASTRO 2014: no difference, stopped early
Epstein-Barr Virus (EBV)

- Epstein-Barr Virus is a common virus
- 95 percent of people in the U.S. are exposed to EBV by 30–40 years of age
- The World Health Organization does not have preventative measures because it is so easily spread and is worldwide
- Very rarely does Epstein-Barr virus lead to cancer
High levels of Epstein Barr Virus in the blood predict the outcome of the treatment

Pretreatment

1 week after RT completion

Lin, NEJM 2004;350:2461
An International Collaboration to Harmonize the Quantitative Plasma Epstein-Barr Virus DNA Assay for Future Biomarker-Guided Trials in Nasopharyngeal Carcinoma

Quynh-Thu Le¹, Qiang Zhang², Hongbin Cao¹, Ann-Joy Cheng³, Benjamin A. Pinsky¹, Ruey-Long Hong⁴, Joseph T. Chang³, Chun-Wei Wang⁴, Kuo-Chien Tsao³, YM Dennis Lo⁶, Nancy Lee⁵, K. Kian Ang⁷, Anthony T.C. Chan⁶, and K.C. Allen Chan⁶

<table>
<thead>
<tr>
<th>Site</th>
<th>Pre-harmonization ICC (95% confidence interval)</th>
<th>Post-harmonization ICC (95% confidence interval)</th>
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</thead>
<tbody>
<tr>
<td>NTU vs. STF</td>
<td>0.62 (0.39–0.78)</td>
<td>0.83 (0.50–0.95)</td>
</tr>
<tr>
<td>CG vs. STF</td>
<td>0.70 (0.50–0.83)</td>
<td>0.72 (0.26–0.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.95 (0.83–0.99)</td>
</tr>
<tr>
<td>HK vs. STF</td>
<td>0.59 (0.35–0.76)</td>
<td>0.96 (0.86–0.99)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spike-in DNA Concentration</th>
<th>STF</th>
<th>NTU</th>
<th>CG</th>
<th>HK</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>600</td>
<td>720</td>
<td>336</td>
<td>335</td>
<td>519</td>
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<tr>
<td>6000</td>
<td>3445</td>
<td>4589</td>
<td>2830</td>
<td>6115</td>
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<tr>
<td>15000</td>
<td>13000</td>
<td>14493</td>
<td>11100</td>
<td>14087</td>
</tr>
<tr>
<td>Correlation</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
<td></td>
</tr>
<tr>
<td>Coefficienta</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.0058</td>
<td>0.0030</td>
<td>0.0034</td>
<td></td>
</tr>
</tbody>
</table>
**NRG HN001: Phase II/III Trial of Individualized Treatment for Nasopharynx CA, based on EBV DNA**

**Basic Eligibility:** Stage II-IVB NPC; detectable EBV-DNA pre-treatment

### Register and Stratify

- **N-stage**
  - N0-1 vs. N2-3

- **T-stage**
  - T1-2 vs. T3-4

- **PS**
  - 0 vs. 1

- **All Pts**
  - Receive Standard RT/cisplatin

- **Assess EBV-DNA BIQSFP**

### “Detectable”

- **Re-Assess EBV-DNA**

### “Undetectable”

- **Re-Assess EBV-DNA**

### Overall Sample Size

- 924 patients, 27 pts/mo

### Basic Statistical Design:

- **Phase IIIR sub-study (detectable EBV after chemo-RT):** 1-year PFS 55% vs. 40% superiority design. 120 analyzable pts, 4.2 yr
- **Phase III sub-study (undetectable EBV after chemo-RT):** 2-year OS 91% both arms noninferiority. 600 analyzable pts, 7.7 yr

### Quality of Life:

- FACT-NP, HHIE-S (audiometry), FACT-Taxane, EQ-5D

### Control:

- **Consolidation 5-FU/cisplatin X 3**
- **Consolidation Gemcitabine/Paclitaxel X 4**
- **Consolidation 5-FU/cisplatin X 3**
- **Observation**
Unique advantages of IMRT in NPC: CTVs curving around optics and temporal lobe

CTV2 (blue):
- Nasopharynx
- ½ for T1-2 vs entire sphenoid sinus for T3-4
- 1/3 max sinus
- Carotid canal, foramen ovale and spinosum
- Pterygoid plates
- Parapharyngeal space
- Ant ½ clivus
- Around nodes
In the right context, little clustered nodes should count ... especially for NPC

For NPC

- Cover bilateral level IB-5 and RP nodes in CTV2 (60 Gy) or CTV3 (54 Gy)
- May drop bilateral level 1B for N0 status
- Like OPC, may drop contralateral 1B if contralateral levels 1-2 are not involved

T1 FSE post gad

32 yo M with T3 N3b nasopharynx cancer

cover VB
Changes during Treatment Course

32 yo M
T3N3bM0 type IIB NPC

Prompted replanning at ~36 Gy

Locoregionally controlled, metastasized to the abdomen

Note coverage of upper mediastinum to aortic arch (cover level of innominate vein)
IMRT replanning before 25\textsuperscript{th} fraction improved QOL

- Prospective study of stages I-IV M0 NPC
- Chinese versions of EORTC QLQ-C30 and the EORTC QLQ-H&N35
- N=129: 43 refused replanning; 86 were replanned before 25\textsuperscript{th} fraction
- Replanning improved global QOL, functional QOL (role, social function), and symptoms e.g. dyspnea, appetite loss, constipation/diarrhea, speech problems, trouble with social contact, teeth, opening the mouth, dry mouth, and sticky saliva
Conclusions: Nasopharyngeal Carcinoma

- Concurrent chemoradiation + 3 adjuvant cycles is the accepted standard for \( \geq T2 \) and N+ stages.
- IMRT is uniquely able to provide excellent locoregional control and avoid toxicities for NPC.
- The necessity of adjuvant chemotherapy is in dispute given its high toxicity and recent data suggesting potential lack of additional benefit.
- Induction chemotherapy may be as effective as adjuvant chemotherapy but has not shown a benefit over concurrent CRT alone.
- Standardized EBV DNA as a biomarker to determine need for adjuvant chemotherapy is in clinical trials.
Laryngeal Cancers
Surgical Options T1 - Glottic

- Vocal Cord Stripping – remove mucosa during direct laryngoscopy
- Laser Excision – appropriate for lesions involving middle third of cord
- Cordectomy – endoscopic or open
  - Contraindicated in large lesions involving entire cord or commissure
  - Voice compromise
- Total Laryngectomy may be required in 10% of patients
Surgical Options T2 - Glottic

• Vertical Partial Laryngectomy
• Contraindicated if lesion involves:
  – Epiglottis
  – Pre-epiglottic space
  – Subglottic extension
• Remove entire affected cord and <1/3 of contralateral cord
• Total Laryngectomy may be required in 55% of patients
Radiation Technique: Lateral opposed fields

- If there is anterior \(\frac{1}{2}\) cord involved and the patient has a thin neck, use 5 mm bolus
- Make sure there is always anterior flash on skin
- I recommended using CT based planning with real bolus placed on the field
- Do not over-wedge or you risk anterior failures; I try to use 15 degree wedges
Radiation Therapy for Larynx Cancer

• T1 Tumors
  – Local control 85-95%
  – Ultimate local control with surgical salvage about 95%

• T2 Tumors
  – Local control 65-85%
  – Ultimate local control with surgical salvage about 90%

• Surgical salvage most often with total laryngectomy
Voice Quality After Treatment of Early Vocal Cord Cancer: A Randomized Trial Comparing Laser Surgery With Radiation Therapy

Leena-Maija Aaltonen, MD, PhD,* Noora Rautiainen, MA, †
Jaana Sellman, PhD, † Kauko Saarilahti, MD, PhD, ‡ Antti Mäkitie, MD,*
Heikki Rihkanen, MD, PhD,* Jussi Laranne, MD, PhD, §
Leenamaija Kleemola, MD, PhD, † Tuija Wigren, MD, PhD, †
Eeva Sala, MD, PhD, † Paula Lindholm, MD, PhD, † Reidar Grenman, MD, †
and Heikki Joensuu, MD †

• Randomized trial of CO2 laser vs RT to 66 Gy
• 60 patients with T1a glottic SCCA in Helsinki
• At 6 and 24 months, compared voice quality, roughness, breathiness, asthenia, strain, videolaryngostroboscopic findings, self-rated voice quality and impact on daily life
• Overall voice quality was similar but RT patients showed improvement in breathiness over time, better glottal closure, and less inconvenience in their daily lives
• Conclusion: “Radiation therapy may be the treatment of choice when the requirements for voice quality are demanding.”
Possible Long Term Complications of RT

• Laryngeal edema 1-4%
• Webbing
• Stenosis
• Soft tissue or cartilage necrosis
• Long term dysphagia
• Very long term risk of second malignancy
T3 “Organ Preservation” Options

• Partial laryngectomy
  – Supracricoid
  – Supraglottic
  – Vertical hemilaryngectomy

• Partial laryngectomy followed by post-op radiation therapy for intermediate risk features or post-op chemoradiation for high risk features

• Chemotherapy → radiation

• Concurrent chemoradiation

How can we:
1. Avoid a stoma?
2. Maintain swallowing?
T3 supraglottic SCCA, s/p T1 FOM WLE and B neck dissection with left N2b with ECE

- GTV → 7 mm to CTV → 5 mm to PTV to account for motion
- Daily soft tissue based CBCT to align laryngeal tissues
- For oral cavity, cover levels 1A-1B-2-3, ipsi level 4 for N+, ipsi level 5 for N2b; bolus for ECE
- Cover bilateral 2-4 for larynx cancers, ipsi level 5 for N2b, and level 6 if he had subglottic or hypopharyngeal extension
- RPs if he had post pharyngeal wall or hypopharynx involvement
Organ Preservation

• Not a new debate

• Kernan JD. Malignancies of the larynx: shall we employ surgery or radiation therapy. Med Rec 1946 Jun; 159:351
What Spawned This Debate?

Patient reported quality of life/the morbidity of total laryngectomy

• The Toronto experience
  – 79% of T3 and T4 patients were working 9-15 months after RT compared to 44% of surgery patients
  – Survival was the same comparing radical radiation with surgery in reserve with primary surgery upfront
Stage III-IV excl T1N1

VA LARYNGEAL CA. STUDY

Induction Chemotherapy (2 Cycles)

Radiotherapy (3rd Cycle of Chemo)

CR or PR

Surgery

Radiation Therapy

< PR

< PR

Surgery

Radiation

CR

PR

Surgery

PR

Surgery

Induction Chemotherapy: Cisplatin and 5-FU
# VAH Laryngeal Carcinoma Study

*Patterns of First Failure – higher in CRT arm*

<table>
<thead>
<tr>
<th></th>
<th>S + RT (N = 166)</th>
<th>CT + RT (N = 166)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (4%)</td>
<td>15 (9%)</td>
<td>.042</td>
<td></td>
</tr>
<tr>
<td>Recurrent Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary only</td>
<td>0 (0%)</td>
<td>21 (13%)</td>
<td>.001</td>
</tr>
<tr>
<td>Nodes (± prim)</td>
<td>15 (9%)</td>
<td>27 (16%)</td>
<td>.001</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>30 (18%)</td>
<td>20 (12%)</td>
<td>.004</td>
</tr>
</tbody>
</table>
### VAH Laryngeal Carcinoma Study

**Cause of Death – similar in the end**

<table>
<thead>
<tr>
<th>Cause</th>
<th>S + RT (N = 166)</th>
<th>CT + RT (N = 166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local/Regional</td>
<td>20 (12%)</td>
<td>29 (17%)</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>22 (13%)</td>
<td>20 (12%)</td>
</tr>
<tr>
<td>Second Primary</td>
<td>4 ( 2%)</td>
<td>7 ( 4%)</td>
</tr>
<tr>
<td>Complications</td>
<td>6 ( 4%)</td>
<td>4 ( 2%)</td>
</tr>
<tr>
<td>Other causes</td>
<td>22 (14%)</td>
<td>17 (10%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 ( 3%)</td>
<td>10 ( 6%)</td>
</tr>
</tbody>
</table>

**Total**  
79 (48%)  
87 (52%)
### VAH Laryngeal Carcinoma Study

**at Four Years**

<table>
<thead>
<tr>
<th></th>
<th>S + RT (N = 166)</th>
<th>CT + RT (N = 166)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Larynx preserved</strong></td>
<td>20* (12%)</td>
<td>103 (62%)</td>
</tr>
<tr>
<td><strong>Total laryngectomy</strong></td>
<td>146 (88%)</td>
<td>63 (38%)</td>
</tr>
<tr>
<td><strong>Patients alive</strong></td>
<td>87 (52%)</td>
<td>79 (48%)</td>
</tr>
<tr>
<td>without larynx</td>
<td>79</td>
<td>27</td>
</tr>
<tr>
<td>with larynx</td>
<td>8 (5%)</td>
<td>52 (31%)</td>
</tr>
</tbody>
</table>

* Supraglottic Laryngectomy
VA larynx, long term QOL: significant differences in mental health and pain

Terrell Arch Otolaryngol 1998
### VAH Laryngeal Carcinoma Study

**Salvage Laryngectomy - Worse for T4**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>44%</td>
<td>0.048</td>
</tr>
<tr>
<td>&lt; T4</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>56%</td>
<td>0.001</td>
</tr>
</tbody>
</table>
RTOG 91-11 selection criteria

- Patient selection
  - T3
  - Limited T4

- Patient exclusions
  - Large volume T4a
    - Extending through thyroid cartilage
    - Greater than 1 cm extension into base of tongue
RTOG 91-11
Phase III Trial to Preserve the Larynx

Location:
- Glottic
- Supraglottic

T Stage:
- T2
- T3
- Early T4

N Stage:
- N0, N1
- N2, N3

Arm 1: Neoadjuvant CT + RT
CR, PR ➔ Cis + 5-FU ➔ RT x 1 Cycle

Arm 2: RT + cisplatin

Arm 3: RT Alone

Neck dissections for all pts with node > 3cm or multiple nodes, 8 weeks after RT

N = 547 stage III/IV
<table>
<thead>
<tr>
<th>Arm</th>
<th>LPR</th>
<th>LRC</th>
<th>OS</th>
<th>G3/4 (G5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadj CT</td>
<td>75%</td>
<td>61%</td>
<td>76%</td>
<td>66% (5)</td>
</tr>
<tr>
<td>Conc CT</td>
<td><strong>88%</strong></td>
<td>78%</td>
<td>74%</td>
<td><strong>77%</strong> (9)</td>
</tr>
<tr>
<td>RT alone</td>
<td>70%</td>
<td>56%</td>
<td>75%</td>
<td>47% (5)</td>
</tr>
</tbody>
</table>
RTOG 91-11 10 year update: CRT → highest rates of laryngeal preservation and LRC

Forastiere JCO 2013
RTOG 91-11 10 year update: IC→RT produced higher rates of LFS than RT alone

? Late “non-cancer related death” in CRT arm?

Forastiere JCO 2013
Putting the induction issue in perspective

• The induction→RT arm vs RT:
  – IC→RT was better for composite endpoint of laryngectomy free survival
  – No statistical difference for LP, LRC, or OS

• The induction→RT arm vs CRT:
  – IC→RT was worse for larynx preservation and local control
  – No statistical difference in other endpoints
Unanswered “real-life” dilemmas

• Should induction-RT be an option along with concurrent chemoradiation?
• Should “induction” mean TPF or PF?
• Should induction be followed by chemoradiation instead of RT, in keeping with original TPF vs PF protocol?
• Which T3 cancers should have surgery and would they do better with partial laryngectomy?
• Should “minimal” T4 cancers be considered for organ preservation?
GORTEC Phase III Trial: Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU ICT for Organ Preservation in Hypopharynx and Larynx Cancer

Treatment-naïve resectable larynx or hypopharynx cancer
- Requiring total (pharyngo) laryngectomy
  N=210

Randomize

ICT

Docetaxel (75 mg/m², day 1)
Cisplatin (75 mg/m², day 1)
5-FU (750 mg/m², days 1-5 C-I)
every 3 weeks, 3 cycles
(N=112)

Cisplatin (100 mg/m², day 1)
5-FU (1000 mg/m², days 1-5)
every 3 weeks, 3 cycles
(N=108)

Surgery
Post-op RT (54-66 Gy)

No response= tumor regression <50% and/or persistent larynx fixation

Response= tumor regression >50% and larynx recovering normally

Pointreau, JNCI 2009
GORTEC: Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU ICT for Organ Preservation in Hypopharynx and Larynx Cancer: Results

- DFS and OS trends favor TPF but are not statistically significant

*European definition.
T4 larynx cancers

• T4: outer cortex of thyroid cartilage
  – Full thickness destruction of the thyroid cartilage
    → total laryngectomy
  – These patients will do poorly with failure of CRT requiring salvage laryngectomy

• T4: extralaryngeal extension
  – Consider pre-existing function (patient’s age)
  – Consider volume of tumor e.g. >12cc is concerning
Long-Term Outcomes for T4 Larynx Cancer

However, many of the patients treated with an LP approach experienced functional impairments, as evidenced by an observed 5-year and 10-year (LED)-free survival rate of 32% and 13%, respectively. Thus, even in our heavily screened institutional cohort, only approximately one-third of patients receiving LP strategies for T4 larynx cancer were alive with a functional larynx and free of a gastrostomy feeding tube at 5 years after diagnosis.

Accelerated fractionation in the absence of concurrent chemotherapy: long term update of RTOG 9003

- If CRT is not an option, and surgery not possible or not desired, consider hyperfractionation or accelerated fractionation for oropharynx, larynx, hypopharynx cancers

Beitler et al IJROBP 2014
Conclusions: Larynx Preservation Trials

- Organ preservation does not compromise survival IF patients are appropriately selected and treated.
- T4 tumors with extensive/complete cartilage invasion should have primary laryngectomy.
- For bulky T4 tumors, surgical salvage is less successful after concurrent chemoradiation; also, chemo and RT prior to TL decrease quality of life and increase feeding tube dependence.
- The highest rates of organ preservation are seen with CRT but there is non-cancer related late death and late toxicities increase over time.
- This is a very challenging area requiring careful multidisciplinary evaluation and patient counseling.
Postoperative Radiation: Clinical Indications

- Tumor at or close to surgical margin
- Perineural Invasion
- Cartilage invasion
- Invasion of bone or soft tissues of the neck
- Emergent Tracheostomy

- Lymph-vascular Invasion
- Multiple (> 2) lymph node metastasis
- Extra capsular extension
Historical PORT results

• Locoregional control 69-72%
• 5-year survival 30-40%
Radiation Dose
MD Anderson randomized dose-finding study

N=240

Stratification

- Oral Cavity
- Larynx
- Hypopharynx
- Larynx

Low risk -> no radiation

Int Risk*

Dose A 57 Gy/32 Fx
Dose B 63 Gy/35 Fx
Dose C 68.4 Gy/38 Fx

High Risk

- Based on T- & N-stage, margin, PNI
- Raised midway from 52.2-54 Gy/29-30 Fx

MD Anderson randomized dose-finding study
MDA dose finding results

• <54 Gy had significantly higher failure rate
• ECE needed at least 63 Gy
• 2-3 negative factors increased LR recurrence risk:
  – oral cavity
  – close/pos margins
  – perineural
  – >2 involved nodes
  – node >3 cm
  – treatment delay >6 wks
  – Zubrod performance status >2
4+ negative factors $\rightarrow$ locoregional recurrence risk similar to ECE

Table 9. Crude recurrence rates by ECE status and number of other adverse factors

<table>
<thead>
<tr>
<th>Number of adverse factors</th>
<th>ECE+ (%)</th>
<th>ECE− (%)</th>
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<tbody>
<tr>
<td>0–1</td>
<td>2/5</td>
<td>2/41 (5)</td>
</tr>
<tr>
<td>2–3</td>
<td>8/37 (22)</td>
<td>4/32 (13)</td>
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<tr>
<td>4–5</td>
<td>16/58 (28)</td>
<td>6/16 (38)</td>
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<tr>
<td>$\geq 6$</td>
<td>3/10 (30)</td>
<td>—</td>
</tr>
</tbody>
</table>

Peters, IJROBP, 1993, 26:3-11
Radiation Timing
Pathologic T stage was T3–4 in 129 (61%) and N2–3 in 123 (58%) patients.

Ang KK, IJROBP 2001, 51:571
LRC & OS by package time (date of surgery to PORT completion) – for high risk pts
LRC and OS based on interval from surgery to PORT

median = 31d
Chemotherapy
Randomized trials of RT vs chemoRT: EORTC 22931 & RTOG 9501

EORTC versus RTOG Eligibility

- Stage III-IV
- OP, OC with level 4 or 5 LN
- Perineural Disease
- Vascular Embolisms
- Margins + ECE
- 2+ pos. nodes

NEJM 2004; 350:1945-1952
EORTC vs RTOG – LRC 11-13% improvement

EORTC

RTOG
EORTC vs RTOG – OS 10-11% improvement

EORTC

RTOG

NOT STATISTICALLY SIGNIFICANT
EORTC & RTOG - Combined data

Overall Survival
Patients with positive margin and/or ECE

EORTC 22931

P = 0.019

RTOG 9501

P = 0.063

30% reduction in risk of death

<table>
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<tr>
<th># at Risk</th>
<th>Year</th>
<th>0</th>
<th>2</th>
<th>5</th>
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<tr>
<td>RCT</td>
<td></td>
<td>122</td>
<td>82</td>
<td>31</td>
</tr>
<tr>
<td>RT</td>
<td></td>
<td>111</td>
<td>59</td>
<td>16</td>
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<th>Year</th>
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<tr>
<td>RCT</td>
<td></td>
<td>130</td>
<td>80</td>
<td>16</td>
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<tr>
<td>RT</td>
<td></td>
<td>116</td>
<td>55</td>
<td>11</td>
</tr>
</tbody>
</table>
RTOG 9501: 10 year followup

• No overall benefit for LRC or OS from postop chemoradiation at 10 years
  – LRC still better for ECE or pos margins

• Multiple nodes without ECE or pos margin: shows no LRC benefit from postop CRT
  – Analysis of patients with up to 6 involved nodes

• Conclusion: Multiple nodes is not an indicator in itself for postoperative CRT
  – Faint suggestion of unexplained non-cancer related deaths in patients who received chemo in absence of ECE/+marg
RTOG 1216: Phase II-III Randomized Trial of Surgery Followed by Chemoradiation for High Risk SCCHN

Register:
p16 and EGFR

Stratify by:
Tumor Site
Zubrod
EGFR level

High Risk:
Positive margins
Extranodal extension

N=475

60-66 Gy/6 wks
CDDP 40mg/m² wkly

60-66 Gy/6 wks
Docetaxel 15mg/m² wkly

60-66 Gy/6 wks
wkly Cetuximab
wkly Docetaxel
Intermediate Risk: Using Targeted Therapy
RTOG 0920 for intermediate (NOT HIGH RISK) cancers

OC, larynx, OPX p16+/-

Intermediate risk factors:
  cT2-3, N0-2 (minimal T4a)
  Stage III-IVA
  PNI
  LVSI
  Close <5mm >5mm deep

Randomize

RT: 60 Gy in 30 fractions

RT: 60 Gy in 30 fractions
  Cetuximab 400 mg/m2
  loading, 250 mg/m2 x 10 cycles

Open and accruing, goal is 700+ pts
CTVs for T3N0 oral tongue with close inferior margin at FOM

- Refused chemotherapy
- 66 Gy (red) at area of inferior close margin
- 60 Gy (blue) to remainder of postop bed and flap
- Bilateral necks radiated electively given midline tumor location including level 1A and bilateral 1B
- No PNI, so did NOT cover V3 to base of skull
For oral cavity cases, assess status of:
1) lingual nerve, 2) hypoglossal nerve and 
3) inferior alveolar nerve
Inferior alveolar nerve (V3) foramen infiltration into mandible

T1-weighted MRI
V3 invasion easily travels to skull base – for major PNI, cover pathway along masticator space to foramen ovale

- Alveolar ridge SCCA
- Invading inferior alveolar nerve
- Traveling on V3 in the masticator space
- Invading through foramen ovale to cavernous sinus
Very pragmatic problem: Review imaging carefully after surgery

- T4a (extrinsic tongue muscle) N2b (right neck) tongue SCCA
- Postop chemo-RT
- Early regrowth detected at the margin of the flap → 66 Gy
- Bilateral neck irradiated 60 Gy levels 1-3 and 54 Gy level 4
Very pragmatic problem: Do not assume surgery removes all nodes (or tumor)

Water T2 IDEAL

s/p supraomohyoid neck dissection

s/p total parotidectomy

Check postsurgical bed! If questions, order diagnostic scan.
Conclusions: Postoperative Radiation

• Postoperative not preoperative radiation is standard.
• Accelerated fractionation may benefit patients with a delayed RT/chemo-RT start.
• Total treatment package time is highly prognostic for high risk patients.
• Patients with ≥2 LN, ECE, +margins are at the highest risk for recurrence.
• 4+ intermediate factors have prognosis similar to ECE.
• Postop chemo-RT is beneficial for patients with involved margins or ECE or both.
• Current trials incorporate targeted therapies; immune-based therapy is a future possibility.
Learning Objectives

• IMRT is ideal for HN cancer treatment and its adoption is near-universal, but delineation requires greater understanding of anatomical and nodal spread patterns.

• OPC is undergoing a series of major revolutions due to the etiology of HPV; strategies at present can be radiation-, surgery-, and chemotherapy-based.

• Induction chemotherapy does not have a clear role at present in the standard management of OPC or NPC; it may be part of future development of larynx preservation strategies.

• Postoperative RT is given for intermediate risk factors and postop CRT is advised for high risk patients; high risk patients are being investigated for further intensification.