2014 ASTRO Refresher: Head and Neck Cancer

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Disclosures

- Research Funding
  - Genelux Inc.
  - Varian Medical Systems

- Special Thanks To:
  - Min Yao, M.D., Ph.D.
  - Steve Davis, M.D.
Introduction
Outline

**Will Cover**
- General Management Recs
- IMRT Techniques
  - Dose
  - Fractionation
  - Volume
  - Fields
- Level I Evidence (RCT, MA)
- Some Recent Advances
- Some Trials in Development

**Will Not Cover in Depth**
- Non-Randomized Studies (e.g. IMRT Case Series)
- Conventional Fields
- Anatomy
- Staging
- Most Side Effects / QOL
- Brachytherapy
- Proton / Particle Therapy
- Palliative Therapy
<table>
<thead>
<tr>
<th><strong>Outline</strong></th>
<th><strong>Primary RT or ChemoRT (SCC)</strong></th>
<th><strong>Primary Surgery</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregionally Advanced (Stage III-IVB)</td>
<td>- Oropharynx</td>
<td>- Hi-Risk Post-Op</td>
</tr>
<tr>
<td></td>
<td>- Hypopharynx</td>
<td>- Oral Cavity</td>
</tr>
<tr>
<td></td>
<td>- Larynx</td>
<td>- Paranasal Sinus</td>
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<tr>
<td>Nasopharynx</td>
<td></td>
<td>- Salivary Gland</td>
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<td>Early Stage (I-II)</td>
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<td>- Skin</td>
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<tr>
<td></td>
<td>- Oropharynx</td>
<td>- Sarcoma</td>
</tr>
<tr>
<td></td>
<td>- Hypopharynx</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>- Larynx</td>
<td>- Lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Radical Salvage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Palliative</td>
</tr>
</tbody>
</table>
Anatomy
Incidence by HPV-Relatedness

- SEER data 1973-2004
- HPV-related (OPX) 17,625
- HPV-unrelated (Oral Cavity) 28,144

Chaturvedi A K et al. JCO 2008;26:612-619
Human Papillomavirus (HPV)

- DNA virus
- >100 different sub-types
- Infects skin and mucosa
- Asymptomatic
- Benign growths – warts
- Oncogenic (cancer causing) types are mostly 16 and 18
HPV Virus Transforms Normal Cell Into Cancer Cell

Viral DNA enters nucleus
Virus “uncoats”

Viral DNA integrates into normal cell DNA

viral proteins E6 and E7

Disables TumorSuppressor Proteins

Uncontrolled cell growth

CA

Nucleus
HPV Biology

- E6 protein mediates p53 degradation
- E7 protein binds to pRb protein → E2F → cell cycle progression
- p16 IHC faster/cheaper, high concordance with direct HPV testing
- Both p16 and HPV testing prognostic
# HPV – Prognostic Marker

<table>
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<tr>
<th>Trial</th>
<th>Cases</th>
<th>Marker</th>
<th>Survival</th>
<th>First author, year</th>
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<tr>
<td>RTOG 0129</td>
<td>323</td>
<td>HPV</td>
<td>82% vs. 57% (3-year)</td>
<td>Ang, 2010</td>
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<tr>
<td>TROG 02.02</td>
<td>185</td>
<td>p16INK4A</td>
<td>91% vs. 74% (2-year)</td>
<td>Rischin, 2010</td>
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<tr>
<td>DAHANCA 6/7</td>
<td>794</td>
<td>p16INK4A</td>
<td>66% vs. 28% (5-year)</td>
<td>Lassen, 2011</td>
</tr>
<tr>
<td>TAX 324</td>
<td>111</td>
<td>HPV</td>
<td>82% vs. 35% (5-year)</td>
<td>Posner, 2011</td>
</tr>
</tbody>
</table>
Risk Classification for Overall Survival
by $p$-16, Smoking, & T-N Category

Ang et al. NEJM 2010
279 patients with untreated SCCHN
   • 80% w/history of smoking
   • 13% had HPV-positive tumors.

>30 sites of genetic alteration
15 esp. mutated genes similar to lung SQCA
   • CDKN2A
   • TP53
   • PIK3CA
   • NOTCH1
   • HRAS
   • NFE2L2

Patients with HPV+ SCCHN have:
   • Infrequent EGFR gene amplification
   • PIK3CA gene mutations activated in ~21%
   • TP53 alterations rare

4 groups based on genetic alterations:
   • Atypical—no amplification of EGFR, HPV+, high rate of PIK3CA
   • Classical—KEAP1 and NFE2L2 (also in lung)
   • Mesenchymal—mostly FGFR1 and FGFR2
   • Basal—highly associated with SOX2 amplifications

HPV- patients: EGFR and FGFR druggable
Management of Locoregionally Advanced Head and Neck Cancer
General Management

- Oropharynx
  - HPV (p16) +
  - HPV (p16) –
- Non-Oropharynx
  - Larynx
  - Hypopharynx
  - Oral Cavity
  - Other SCC

Ang et al. NEJM 2010
General Management

- HPV+ Oropharynx
  - Standard of Care = Concurrent RT + Cisplatin
  - Cisplatin 100 mg/m² Q 3 wks vs. 40 mg/m² weekly?
  - Induction Chemotherapy?
    - Probably Overtreatment
    - Randomized Trials Negative
  - RT + Cetuximab?
    - Directly being addressed by RTOG 1016
    - Good Choice if Cisplatin Contraindicated
  - RT Alone?
    - Supported by Single-Institution Data
General Management

- **HPV- Oropharynx / Non-Oropharynx**
  - Standard of Care = Concurrent RT + Cisplatin
  - Cisplatin 100 mg/m² Q 3 wks
  - Induction Chemotherapy?
    - Reasonable Option, Depending on Institutional Practice
      - TPF
    - Randomized Trials Negative
  - RT + Cetuximab?
    - Cisplatin Indicated → Supportable but Borderline
    - Cisplatin Contraindicated → Recommended
  - RT Alone?
    - Generally Regarded as Inferior Therapy
IMRT Techniques

- IMRT (SIB or Sequential)
  - Gross Disease = 70 Gy in 33-35 daily fractions
  - “High-Risk” = 59-63 Gy in 30-35 daily fractions
  - “Standard Risk” = 50-56 Gy in 25-35 daily fractions

- Altered Fractionation?
  - With Cisplatin ➔ Not Found Beneficial in RTOG 0129
  - With Cetuximab ➔ Beneficial on Subset Analysis of Bonner
  - With Neither ➔ Indicated Based on MACH-HN
    - Delayed Concomitant Boost (BID Field-in-Field)
    - Accelerated (e.g. 6-fractions / week per RTOG 1016)
    - Hyperfractionation (81.6 Gy in 1.2 Gy fractions BID)
Volumes: Primary & Bilateral Neck

- **CTV_Gross (2.00-2.12 Gy / fx)**
  - Primary GTV + 5-10 mm, trim out of bone
  - Nodal GTV + 5 mm

- **CTV_High (1.80-2.00 Gy / fx)**
  - Primary + ~10 mm, trim out of bone
  - Primary Draining Nodes (Nodal Fat Pad)
  - Neck Levels Adjacent to Involved Levels

- **CTV_Standard (1.64-1.80 Gy / fx)**
  - Level I if Oral Cavity / Level IB if Ipsilateral Level II Involved
  - Level V in most cases, esp. BOT, SP, FOM, NPX, HPX
  - Lateral Retropharyngeal Nodes; Medial RP if HPX, NPX
  - Regional Patterns of Spread (e.g. Parapharynx)

- **PTV = 3-5 mm expansion, trim out of skin**
Radiation Techniques

- Lateralized Primary?
  - May be OK to Omit Contralateral Neck (e.g. Tonsil)

- Conventional (e.g. 3-field)?
  - May be OK if good parotid sparing (e.g. larynx)
  - IMRT generally indicated to reduce xerostomia
  - IMRT spares other tissues (e.g. constrictors, OC)

- Arc Therapy?
  - Many studies support
IMRT Plan Evaluation

- Hot Spots < 115% & w/in target
- PTV coverage
  - V95 > 95% (97%)
  - D95 > 95% (97%)
  - V105 < 50%
  - V110 < 5%
- Cord max < 50 (45)
- Brainstem max < 54
- Parotid mean < 26 (contralateral)
- Spare mandible, oral cavity, lips, posterior pharynx AMAP
H&N IMRT Practice Heterogeneity

T2 N1 M0 Tonsil Cancer

P. Harari: Radiotherapy & Oncology 2012

Courtesy of Dr. Harari
Patient with T3N0 larynx cancer, received definitive IMRT
Only the larynx was included in IMRT
Poor Volume Definition

Patient recurred just inferior to the radiation field
Intensity-Modulated Radiotherapy
T3N2C Supraglottic cancer
Base of tongue Target Delineation

CTV 1 (Red)
Base of tongue Target Delineation

CTV2 (Blue)

CTV 3 (Yellow)
Base of Tongue Isodoses
Stage T2N0 Tonsil Cancer
Tonsil CTV 1

CTV 1
(Red)

Courtesy of Dr. Garden
Subclinical targets

CTV 1 (Red)
CTV2 (Blue)
CTV 3 (Yellow)

Courtesy of Dr. Garden
IMRT for Hypopharyngeal Cancer

- Include bilateral retropharyngeal lymph node to skull base
- Include level V
- Pay attention to the lower edge of the hypopharynx
## Ipsilateral tonsil radiation

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Patient number</th>
<th>% N0-1</th>
<th>% T1-2</th>
<th>Contralateral neck failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson, 1999</td>
<td>178</td>
<td>87%</td>
<td>65%</td>
<td>3% (N0-1)</td>
</tr>
<tr>
<td>Kagei, 2000</td>
<td>32</td>
<td>84%</td>
<td>56%</td>
<td>0%</td>
</tr>
<tr>
<td>O’ Sullivan, 2001</td>
<td>228</td>
<td>83%</td>
<td>84%</td>
<td>3%</td>
</tr>
<tr>
<td>Rusthoven, 2009</td>
<td>20</td>
<td>20%</td>
<td>90%</td>
<td>0%</td>
</tr>
<tr>
<td>Chronowski, 2012</td>
<td>102</td>
<td>56%</td>
<td>100%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Courtesy of Dr. Garden
Ipsilateral Radiation in Tonsil Cancer

• T1-T2, N0-N1 tumor
• <1.0 cm extension to soft palate
• No base of tongue involvement

ACR Appropriateness Criteria. Head Neck 2012;34:613-616
Patient Selection for Laryngeal Preservation

Not Eligible for RTOG 91-11

- T4 with tumor extending through thyroid cartilage into neck soft tissue
- Extending >1 cm into BOT
Patient Selection for Laryngeal Preservation

- T4 with tumor extending through the thyroid cartilage into neck soft tissue

Salvage Laryngectomy at the VA Trial

\[
\begin{array}{|c|c|c|}
\hline
\text{Stage} & \text{28\%} & \text{T4} \\
\hline
< T4 & 28\% & \text{56\%} \\
\hline
T4 & 56\% & p = 0.001 \\
\hline
\end{array}
\]
T4A Laryngeal Cancer
## Primary ChemoRT for T4 Laryngeal Cancer

<table>
<thead>
<tr>
<th>Institute</th>
<th>No</th>
<th>Treatment</th>
<th>OS</th>
<th>Larynx Preserved</th>
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</thead>
<tbody>
<tr>
<td>U Florida¹</td>
<td>43</td>
<td>XRT (bid)</td>
<td>37% (5y)</td>
<td>47% (5y)</td>
</tr>
<tr>
<td>U Chicago²</td>
<td>32</td>
<td>TFHX</td>
<td>53% (4y)</td>
<td>86% (f/u 43 mo.)</td>
</tr>
<tr>
<td>U Michigan³</td>
<td>36</td>
<td>ind/conXRT</td>
<td>78% (3y)</td>
<td>67% (f/u 69 mo.)</td>
</tr>
<tr>
<td>Case⁴</td>
<td>17</td>
<td>conXRT</td>
<td>64% (3y)</td>
<td>2 pt salvage</td>
</tr>
</tbody>
</table>

~20-25% patients need long term tracheostomy, PEG tube or salvage laryngectomy

4. 7th International Head and Neck Symposium 2008
Randomized Trials in Locoregionally Advanced Head/Neck Cancer
Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial

Christopher M Nutting, James P Morden, Kevin J Harrington, Teresa Guerrero Urbano, Shreerang A Bhide, Catharine Clark, Elizabeth A Miles, Aisha B Miah, Kate Newbold, MaryAnne Tanay, Fawzi Adab, Sarah J Jefferies, Christopher Scrace, Beng K Yap, Roger P A’Hern, Mark A Sydenham, Marie Emson, Emma Hall, on behalf of the PARSPORT trial management group.

PARSPORT: ↓ Xerostomia with IMRT

PARSPORT: ↑ QOL with IMRT

Mean EORTC HN35 dry mouth score

# IMRT Meta-Analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IMRT Events</th>
<th>Conventional/Conformal Events</th>
<th>Total</th>
<th>O.E. Variance</th>
<th>Weight</th>
<th>Hazard Ratio (Exp[O.E./V]) Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peng 2012</td>
<td>306</td>
<td>178</td>
<td>108</td>
<td>-4.275</td>
<td>153.99</td>
<td>100.0%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>306</td>
<td></td>
<td>108</td>
<td></td>
<td></td>
<td>0.76 [0.65, 0.89]</td>
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<tr>
<td>Total events</td>
<td>88</td>
<td>178</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity:</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Test for overall</td>
<td>effect Z = 3.45 (P = 0.0008)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gupta 2012</td>
<td>32</td>
<td>23</td>
<td>55</td>
<td>-5.5</td>
<td>14</td>
<td>26.7%</td>
</tr>
<tr>
<td>Kam 2007</td>
<td>21</td>
<td>21</td>
<td>42</td>
<td>-6.26</td>
<td>14.93</td>
<td>26.5%</td>
</tr>
<tr>
<td>Nutting 2011</td>
<td>47</td>
<td>36</td>
<td>83</td>
<td>-10.87</td>
<td>22.5</td>
<td>44.6%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>107</td>
<td></td>
<td>103</td>
<td></td>
<td></td>
<td>0.65 [0.50, 0.85]</td>
</tr>
<tr>
<td>Total events</td>
<td>27</td>
<td>79</td>
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<tr>
<td>Heterogeneity:</td>
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<td>Test for overall</td>
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<td>2 years</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Gupta 2012</td>
<td>32</td>
<td>17</td>
<td>49</td>
<td>-6.37</td>
<td>14.93</td>
<td>38.9%</td>
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<td>Nutting 2011</td>
<td>47</td>
<td>39</td>
<td>86</td>
<td>-10.64</td>
<td>23.5</td>
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<td>75</td>
<td></td>
<td></td>
<td>0.66 [0.45, 0.90]</td>
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<td>56</td>
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<tr>
<td>Heterogeneity:</td>
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<td>Test for overall</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3 years</td>
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<td>Gupta 2012</td>
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<td>16</td>
<td>48</td>
<td>-5.12</td>
<td>14.93</td>
<td>7.2%</td>
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<td>28</td>
<td></td>
<td></td>
<td>0.71 [0.43, 1.16]</td>
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</tr>
<tr>
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<td></td>
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</tr>
<tr>
<td>5 years</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Peng 2012</td>
<td>306</td>
<td>92</td>
<td>398</td>
<td>-36.93</td>
<td>153.99</td>
<td>74.3%</td>
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<td>Subtotal (95% CI)</td>
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<td>310</td>
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<td>0.79 [0.68, 0.93]</td>
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<tr>
<td>Total events</td>
<td>29</td>
<td>92</td>
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<tr>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td></td>
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<tr>
<td>Test for overall</td>
<td>effect Z = 2.90 (P = 0.004)</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>413</td>
<td>170</td>
<td></td>
<td></td>
<td></td>
<td>0.76 [0.66, 0.87]</td>
</tr>
<tr>
<td>Total events</td>
<td>52</td>
<td>170</td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 1.39, df = 3 (P = 0.71); I² = 0%</td>
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<td>Test for overall</td>
<td>effect Z = 4.02 (P = 0.0001)</td>
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<td>Test for subgroup differences:</td>
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</tbody>
</table>

Marta et al. Radiother Oncol 2013
VA LARYNX TRIAL

Induction Chemotherapy: Cisplatin and 5-FU
VA LARYNX TRIAL

2 yr overall survival of 68% in both arms
64% patients in the induction chemo arm preserved their larynx
RTOG 91-11 LARYNX TRIAL

RANDOMIZE

CDDP/5FU

CR/PR \(\rightarrow\) CDDP/5FU \(\rightarrow\) XRT

No Response \(\rightarrow\) Surgery/XRT

RT plus concurrent cisplatin

RT alone
# RTOG 91-11 LARYNX TRIAL

**Median F/U 3.8 years**

<table>
<thead>
<tr>
<th></th>
<th>Induction</th>
<th>CCRT</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year Larynx preserved</td>
<td>75%</td>
<td>88%</td>
<td>70%</td>
</tr>
<tr>
<td>2 year LR control</td>
<td>61%</td>
<td>78%</td>
<td>56%</td>
</tr>
<tr>
<td>2 yr. DM</td>
<td>8%</td>
<td>9%</td>
<td>16%</td>
</tr>
<tr>
<td>5-yr. Survival</td>
<td>55%</td>
<td>54%</td>
<td>56%</td>
</tr>
</tbody>
</table>

* Estimated from survival curves

RTOG 91-11 LARYNX TRIAL


Median F/U 3.8 years

Radiotherapy with concurrent cisplatin 84%
Chemotherapy followed by radiotherapy 72%
Radiotherapy alone 67%
Long Term Update of RTOG 91-11

LARYNGEAL PRESERVATION

OVERALL SURVIVAL

Forastiere et al, JCO 2013
EORTC 24891 Laryngeal Preservation Trial

Induction Chemotherapy: Cisplatin and 5 FU

J.L. Lefebvre et al, JNCI 88:890-899, 1996
## EORTC 24891 Laryngeal Preservation Trial

<table>
<thead>
<tr>
<th></th>
<th>S + RT</th>
<th>CT+ RT± S</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median F/U:</strong> 10.5yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td><strong>10-yr. PFS</strong></td>
<td>8.5%</td>
<td>10.5%</td>
</tr>
<tr>
<td><strong>10-yr. Survival</strong></td>
<td>13.8%</td>
<td>13.1%</td>
</tr>
<tr>
<td><strong>Distant Mets.</strong></td>
<td>36%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>10 yr. Alive w/Larynx</strong></td>
<td>8.7%</td>
<td></td>
</tr>
</tbody>
</table>

J.L. Lefebvre et al, JNCI 88:890-899, 1996; Annals Oncology, 2012
RTOG 90-03: ALTERED FRACTIONATION (AFX) VS. STANDARD FRACTIONATION (SFX)

**STRATIFY**

- Sites
  - Oral Cavity
  - Oropharynx
  - Larynx
  - Hypopharynx
- Stage
  - N0 vs N+
- KPS
  - 90-100 vs. 60-80

**RANDOMIZE**

1. SFX
2. HFRT
3. AFX (Split-Course)
4. AFX (Concomitant Boost)
**RTOG 90-03**

**Standard fractionation**

- 7000 cGy/35 fx
- 7 weeks

**Hyperfractionation**

- 8160 cGy/68 fx
- 7 weeks (1.2 Gy Bid)

**Accelerated fractionation, split course**

- 6720 cGy/42 fx
- 6 weeks (1.6 Gy Bid)

**Accelerated fractionation, concomitant boost**

- 7200 cGy/42 fx
- 6 weeks
## RTOG 90-03

<table>
<thead>
<tr>
<th>Treatment Method</th>
<th>Grade 3+ acute</th>
<th>Grade 3+ late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard fractionation</td>
<td>35%</td>
<td>27%</td>
</tr>
<tr>
<td>Hyperfractionation</td>
<td>55%</td>
<td>28%</td>
</tr>
<tr>
<td>Accelerated/ split course</td>
<td>50%</td>
<td>28%</td>
</tr>
<tr>
<td>Accelerated/ concomitant boost</td>
<td>59%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Late effects defined at >90 days from treatment start.
>1400 patients

6 fractions per week
(Saturday or BID one weekday)
DAHANCA 6 & 7

- Locoregional control (%)

- Time after randomisation (months)

- 6 fractions per week
- 5 fractions per week

- Event: 6 fractions - 229, 5 fractions - 289
- All: 6 fractions - 750, 5 fractions - 726

- Odds ratio: 0.66 (0.54–0.82)

- p = 0.0005
DAHANCA 6 & 7

Disease-specific survival (%) over time after randomisation (months) for 6 fractions per week and 5 fractions per week, with a p-value of 0.01 and an odds ratio of 0.71 (0.56–0.88).

Event numbers: 192 for 6 fractions, 238 for 5 fractions, with a total of 750 and 726, respectively.
GORTEC French Trial: Oropharyngeal CA

Stage III/IV Oropharynx

N=226

Randomize

Arm 1:
5 FU + Carbo
70 Gy (QD)

Arm 2:
70 Gy RT (QD)

Denis et al. JCO, 2004
<table>
<thead>
<tr>
<th></th>
<th>Chemoradiation (ChemoRT)</th>
<th>RT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr LRC</td>
<td>48%</td>
<td>25%</td>
<td>p=0.002</td>
</tr>
<tr>
<td>5 yr DFS</td>
<td>27%</td>
<td>15%</td>
<td>p=0.01</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>22%</td>
<td>16%</td>
<td>p=0.05</td>
</tr>
</tbody>
</table>

Denis et al. JCO, 2004
HYPERFRACTIONATED IRRADIATION WITH OR WITHOUT CONCURRENT CHEMOTHERAPY FOR LOCALLY ADVANCED HEAD AND NECK CANCER

DAVID M. BRIZEL, M.D., MARY E. ALBERS, M.D., SAMUEL R. FISHER, M.D., RICHARD L. SCHER, M.D., WILLIAM J. RICHTSMIEER, M.D., PH.D., VERA HARS, M.S., STEPHEN L. GEORGE, PH.D., ANDREW T. HUANG, M.D., AND LEONARD R. PROSNITZ, M.D.

[Graphs showing survival and locoregional control of disease with hyperfractionation and combined treatment, with respective P-values indicated.]
The Lancet 2000; 355:949-955

DOI:10.1016/S0140-6736(00)90011-4

Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data*

JP Pignon, J Bourhis, C Domenge, and L Designé, on behalf of the MACH-NC Collaborative Group

Collaborators listed at end of paper

References 70 and 71 (see website) have WR Bezwoda as a co-author. One of Dr Bezwoda’s other studies has recently been audited negatively. References 70 and 71 contributed 58 and 27 patients to the meta-analysis. The authors have informed us that the overall hazard ratio in the meta-analysis is the same with or without these data. In the concomitant group, the hazard ratio changes from 0.81 to 0.83, but is anyway not statistically significant—Ed.
## MACH Meta-Analysis

<table>
<thead>
<tr>
<th>Trial category</th>
<th>Hazard ratio (95% CI)</th>
<th>Chemotherapy effect (p)</th>
<th>Heterogeneity (p)</th>
<th>Absolute benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At 2 years*</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>0.98 (0.85–1.19)</td>
<td>0.74</td>
<td>0.35</td>
<td>1%</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>0.95 (0.88–1.01)</td>
<td>0.10</td>
<td>0.38</td>
<td>2%</td>
</tr>
<tr>
<td>Concomitant</td>
<td>0.81 (0.76–0.88)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>7%</td>
</tr>
<tr>
<td>Total</td>
<td>0.90 (0.85–0.94)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Assuming survival rates of 50% at 2 years and 32% at 5 years in control groups.

• Individual patient data, trials from 1965-2000
• 87 trials; 16,485 patients
• Absolute OS benefit of chemo 4% when added to RT
• OS benefit 8% with concurrent chemoRT
• Magnitude of benefit higher with platinum (p < 0.01)
• No diff between concurrent poly-chemo and mono-chemo
• Benefit consistent across tumor locations

Pignon et al, Radiother Oncol 2009; Blanchard Radiother Oncol 2011)
### Table 1. Summary of the meta-analysis of the Meta-Analysis of Chemotherapy in Head and Neck Cancer collaborative group [8]: effect of chemotherapy on survival at 5 years

<table>
<thead>
<tr>
<th>Trial category</th>
<th>No. of trials</th>
<th>No. of patients</th>
<th>Difference (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td>65</td>
<td>10,850</td>
<td>+4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>8</td>
<td>1,854</td>
<td>+1</td>
<td>0.74</td>
</tr>
<tr>
<td>Induction</td>
<td>31</td>
<td>5,269</td>
<td>+2</td>
<td>0.10</td>
</tr>
<tr>
<td>Cisplatin + 5-fluorouracil</td>
<td>15</td>
<td>2,487</td>
<td>+5</td>
<td>0.01</td>
</tr>
<tr>
<td>Other chemotherapy</td>
<td>16</td>
<td>2,782</td>
<td>0</td>
<td>0.91</td>
</tr>
<tr>
<td>Concomitant</td>
<td>26</td>
<td>3,727</td>
<td>+8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
MARCH Meta-Analysis

Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis


- Meta-analysis of individual patient data
- Trials of altered vs. conventional fractionation
- Hypofractionation (>2.5 Gy/fraction) excluded
- Postop trials excluded
Figure 1: Hazard ratio of death with altered fractionated radiotherapy versus conventional radiotherapy.

The centre of each square is the hazard ratio (HR) for individual trials and corresponding horizontal line is the 95% CI. The area of the square is proportional to the number of deaths in each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95% CI. Open diamonds are the HR of different types of radiotherapy. BCCA = British Columbia Cancer Agency. CAIR = Continuous Accelerated Irradiation. CHART = Continuous Hyperfractionated Accelerated Radiation Therapy. DA HA NCA = Danish Head and Neck Cancer Study Group. EORTC = European Organisation for Research and Treatment of Cancer. GORTEC = Groupe d'Oncologie Radiothérapie Tête et Cou. KBN = Komitet Badan Naukowych (Committee for Scientific Research). O-E = observed minus expected. PMH-Toronto = Princess Margaret Hospital, Toronto. RT = radiotherapy. RTOG = Radiation Therapy Oncology Group. TROG = Trans-Tasman Radiation Oncology Group.
Figure 5: Hazard ratio of locoregional control with altered fractionated radiotherapy versus conventional radiotherapy.

The centre of each square is the hazard ratio (HR) for individual trials and the corresponding horizontal line is the 95% CI. The area of the square is proportional to the number of events from each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95% CI. Open diamonds are the HR of different types of radiotherapy. BCCA=British Columbia Cancer Agency. CAIR=Continuous Accelerated Irradiation. CHART=Continuous Hyperfractionated Accelerated Radiation Therapy. DA HANCA=Danish Head and Neck Cancer Study Group. EORTC=European Organisation for Research and Treatment of Cancer. GORTEC=Groupe d’Oncologie Radiothérapie Tête et Cou. KBN=Komitet Badan Naukowych (Committee for Scientific Research). O-E=observed minus expected. PMH-Toronto=Princess Margaret Hospital, Toronto. RT=radiotherapy. RTOG=Radiation Therapy Oncology Group. TROG=Trans-Tasman Radiation Oncology Group.
RADIATION THERAPY ONCOLOGY GROUP
RTOG 0129

A PHASE III TRIAL OF CONCURRENT RADIATION AND CHEMOTHERAPY (FOLLOWED BY SURGERY FOR RESIDUAL PRIMARY/N2-3 NODAL DISEASE) FOR ADVANCED HEAD AND NECK CARCINOMAS

R
A
M
N
D
O
I
Z
E

Arm 1:
Standard Fractionation (SFX): 70 Gy / 35 fx for 7 weeks
plus cisplatin: 100 mg/m² on days 1, 22, and 43

Arm 2:
Accelerated Fractionation by Concomitant Boost (AFX-CB): 72 Gy/42 fx for 6 weeks
plus cisplatin: 100 mg/m² on days 1 and 22
Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D., Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D., Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D., Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D., Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*

New England Journal of Medicine, 2006;354:567-78
RT vs. RT plus Cetuximab

Stage III-IVB HNSCC

Radiation alone

Radiation plus weekly Cetuximab

Bonner et al. NEJM 2006;354:567-578
Locoregional Control

LRF-FREE SURVIVAL

LOCOREGIONAL FAILURE

Figure 1. Conditional Probability of Locoregional Failure after Radiotherapy plus Cetuximab as Compared with Radiotherapy Alone.

Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.
Overall Survival

Bonner et al. NEJM 2006;354:567-578
Overall Survival – 5 Year Update

Bonner et al. Lancet Oncol 2010
A RANDOMIZED PHASE III TRIAL OF CONCURRENT ACCELERATED RADIATION AND CISPLATIN VERSUS CONCURRENT ACCELERATED RADIATION, CISPLATIN, AND CETUXIMAB (C225) [FOLLOWED BY SURGERY FOR SELECTED PATIENTS] FOR STAGE III AND IV HEAD AND NECK CARCINOMAS

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Accelerated Fractionation by Concomitant Boost (AFX-CB) or IMRT plus cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 2</td>
<td>Accelerated Fractionation by Concomitant Boost (AFX-CB) or IMRT plus cisplatin plus cetuximab</td>
</tr>
</tbody>
</table>

**Results**

Outcome by p16 Status and Treatment Regimen

- Oropharynx
  - p16-pos (N=235)
  - p16-neg (N=86)
  - No specimens (N=307)
- Non-oropharynx (N=267)
- All patients (N=895)

NB: p16 is a marker for HPV infection in HNC

www.OncologyEducation.ca
Induction Chemotherapy Followed by Either Chemoradiotherapy or Bioradiotherapy for Larynx Preservation: The TREMPLIN Randomized Phase II Study

Jean Louis Lefebvre, Yoann Poincare, Frederic Rolland, Marc Alfonsi, Alain Baudoux, Christian Sire, Dominique de Raucourt, Olivier Mahard, Marian Degardin, Claude Tuchais, Emmanuel Blot, Michel Rives, Emile Rey, Jean Marc Tourani, Lionel Geoffrois, Frederic Peyrade, Francois Guichard, Dominique Chevalier, Emmanuel Babin, Philippe Lang, Francois Janot, Gilles Calais, Pascal Garaud, and Etienne Bardet
Conclusions for Cetuximab

- Recommended for Locoregionally Advanced HNC Patients unfit for cisplatin therapy
- May be alternative to cisplatin in HPV+ OPX patients depending on results of RTOG 1016
- Not indicated in combination with cisplatin (RTOG 0522 negative study)
TAX324

TPF: Docetaxel 75D1 + Cisplatin 100D1 + 5-FU 1000 CI-D1-4 Q 3 weeks x3
PF: Cisplatin 100D1 + 5-FU 1000 CI-D1-5 Q 3 weeks x 3

Posner et al, NEJM 2007
TAX324

Posner et al, NEJM 2007
Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Eva Remenar, M.D., Carla van Herpen, M.D., Ph.D., Thierry Gorlia, M.Sc., Ricard Mesia, M.D., Marian Degardin, M.D., John S. Stewart, M.D., Svetislav Jelic, M.D., Jan Betka, M.D., Joachim H. Preiss, M.D., Ph.D., Danielle van den Weyngaert, M.D., Ahmad Awada, M.D., Ph.D., Didier Cupissol, M.D., Heinz R. Kienzer, M.D., Augustin Rey, M.D., Isabelle Desaunois, M.Sc., Jacques Bernier, M.D., Ph.D., and Jean-Louis Lefebvre, M.D., for the EORTC 24971/TAX 323 Study Group*
Figure 1. Enrollment and Outcomes.

- 358 Patients underwent randomization
  - 181 Were assigned to receive PF
    - 2 Did not receive PF
      - 1 Had incorrect diagnosis
      - 1 Received incorrect drug
    - 179 Started PF
  - 177 Were assigned to receive TPF
    - 4 Did not receive TPF
      - 1 Had physician-ordered change
      - 1 Declined to participate
      - 2 Received incorrect drug
    - 173 Started TPF
  - 10 Were lost to follow-up
    - 60 Discontinued chemotherapy for other reason
      - 13 Had progressive disease
      - 21 Had adverse event
      - 7 Declined to participate
      - 12 Died
      - 6 Had other reason
      - 1 Had unknown reason
    - 6 Discontinued radiotherapy for other reason
      - 2 Had progressive disease
      - 1 Declined to participate
      - 1 Died
      - 1 Withdrawn on physician's decision
      - 1 Had unknown reason
  - 9 Were lost to follow-up
    - 38 Discontinued chemotherapy for other reason
      - 13 Had progressive disease
      - 11 Had adverse event
      - 3 Declined to participate
      - 6 Died
      - 4 Had other reason
      - 1 Had unknown reason
    - 8 Discontinued radiotherapy for other reason
      - 3 Had adverse event
      - 1 Had administrative or technical reason
      - 3 Declined to participate
      - 1 Had unknown reason
  - 181 Were included in the intention-to-treat (efficacy) analysis
  - 179 Were included in the safety analysis during chemotherapy or chemoradiotherapy
  - 120 Were included in the safety analysis during radiotherapy
  - 177 Were included in the intention-to-treat (efficacy) analysis
  - 173 Were included in the safety analysis during chemotherapy or chemoradiotherapy
  - 129 Were included in the safety analysis during radiotherapy

Figure 2. Effects of TPF and PF Therapy on Progression-free Survival (Panel A) and Overall Survival (Panel B).
TPF denotes docetaxel–cisplatin–fluorouracil, and PF cisplatin–fluorouracil.
TAX323 / TAX324 - Critiques

• Control arm (PF → carbo/RT or RT) not standard of care
• High rates of grade 3-4 toxicity with induction TPF
• 1-4% risk of death during induction
• ~75% complete treatment per protocol

Posner et al, Vermorken et al, NEJM 2007
PARADIGM Trial: Phase III Trial of TPF/C-XRT vs P-ACBXRT

*T + ACB for Non-Responders
PARADIGM
(Haddad et al. Lancet Oncol 2013)
DeCIDE Trial

TPF: Docetaxel (75 mg/m²) + Cisplatin (75 mg/m²) + 5-FU (750 mg/m², 120 hours) Q3 weeks

DFHX: Docetaxel + Hydroxyurea + 5FU + Hyperfractionated RT
**DeCIDE (Cohen et al. ASCO 2012)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>IC arm (%)</th>
<th>CRT arm (%)</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>75</td>
<td>73</td>
<td>0.92</td>
<td>0.59-1.42</td>
<td>0.70</td>
</tr>
<tr>
<td>DF-free survival</td>
<td>69</td>
<td>64</td>
<td>0.84</td>
<td>0.56-1.26</td>
<td>0.39</td>
</tr>
<tr>
<td>RFS</td>
<td>67</td>
<td>59</td>
<td>0.76</td>
<td>0.52-1.13</td>
<td>0.18</td>
</tr>
<tr>
<td>Cumulative incidence of DF</td>
<td>10</td>
<td>19</td>
<td>0.46</td>
<td>0.23-0.92</td>
<td>0.025</td>
</tr>
<tr>
<td>Cumulative incidence of locoregional failure</td>
<td>9</td>
<td>12</td>
<td>0.79</td>
<td>0.37-1.68</td>
<td>0.55</td>
</tr>
</tbody>
</table>

- 280 pts
OVERALL SURVIVAL

RECURRENCE-FREE SURVIVAL

DeCIDE
A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer


OVERALL SURVIVAL  PFS – PER PROTOCOL
Conclusion for Induction Chemotherapy

- Evidence does not support an advantage to using induction chemotherapy strategy
- Induction chemotherapy may compromise delivery of concurrent chemoXRT due to delay and/or side effects
- Use should be reserved for clinical trial settings
Management of Nasopharyngeal Carcinoma
NCCN Guidelines (V2.2011)

- **T1N0M0**: Definitive XRT to Nasopharynx and Elective XRT to neck
- **T1,N1-3, M0, T2-4, Any N**: Concurrent ChemoXRT Followed by adjuvant chemo
NPC: Techniques

- IMRT (SIB or Sequential)
  - Gross Disease = 70 Gy in 33-35 daily fractions
  - “High-Risk” = 59-63 Gy in 30-35 daily fractions
  - “Standard Risk” = 50-56 Gy in 25-35 daily fractions
### Table 2. 2-Year Estimates of Time-to-Event End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>All 2-Year Estimate</th>
<th>95% CI</th>
<th>Stages IIB to IVB 2-Year Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local progression-free interval</td>
<td>92.6</td>
<td>86.3 to 98.9</td>
<td>91.2</td>
<td>83.8 to 98.6</td>
</tr>
<tr>
<td>Regional progression-free interval</td>
<td>90.8</td>
<td>83.6 to 97.9</td>
<td>89.2</td>
<td>81.0 to 97.5</td>
</tr>
<tr>
<td>Locoregional progression-free interval</td>
<td>89.3</td>
<td>81.7 to 96.9</td>
<td>87.5</td>
<td>78.7 to 96.3</td>
</tr>
<tr>
<td>Distant metastases-free interval</td>
<td>84.7</td>
<td>75.9 to 93.5</td>
<td>82.1</td>
<td>72.0 to 92.3</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>72.7</td>
<td>61.9 to 83.5</td>
<td>68.0</td>
<td>55.7 to 80.2</td>
</tr>
<tr>
<td>Overall survival</td>
<td>80.2</td>
<td>70.5 to 89.8</td>
<td>76.7</td>
<td>65.6 to 87.8</td>
</tr>
</tbody>
</table>
NPC: Imaging
CTV2-P

Entire nasopharynx, posterior 4th or 3rd nasal cavity and maxillary sinus, anterior ½ to 2/3 clivus, laterally, parapharyngeal space.
CTV2-P

skull base, and inferior sphenoid sinus (entire sphenoid sinus in T3/4 disease)
CTV2-Node

Bilateral Upper deep jugular (junctional, parapharyngeal), Bilateral Level II, and level VA, Bilateral retropharyngeal nodes.
CTV2-Node
And also the lymphatic region adjacent to involved nodes
Max optic nerves 50 Gy

Max BS Dose: 50 Gy

Mean Oral Cavity 40 Gy
Late Complications

- Xerostomia
- Oral and dental complications
- Hearing loss (more with CCRT)
- Pituitary hypofunction
- Neural complications
- Soft and hard tissue necrosis
- Temporal Lobe Necrosis
IMRT Do’s & Don’ts

- MRI in virtually all cases
- PET/CT in most cases
- Bilateral Level V node coverage
- Retropharyngeal node coverage
- Adequate coverage of the clivus
- Adequate coverage of parapharynx
- Adequate soft tissue margin on primary
Clinical Trials in Nasopharyngeal Carcinoma
INTERGROUP 99 (RTOG 88-17)
Al-Sarraf et al. JCO 1998

AJCC (1992)
III or IV
M0

CONVENTIONAL RT
alone (70 Gy)

RT + CDDP x 3

CDDP + 5FU x 3

Al-Sarraf et al. JCO 1998
**INTERGROUP 99 (RTOG 88-17)**

Minimum 5 year follow up for all patients

<table>
<thead>
<tr>
<th></th>
<th>CT/RT</th>
<th>RT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year PFS</td>
<td>58%</td>
<td>29%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5 yr DFS</td>
<td>74%</td>
<td>46%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>67%</td>
<td>37%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
AJCC (1997)
III or IV
M0
WHO II/III

N = 221

Conventional RT (70 Gy)
RT + CDDP x 3
CDDP + 5 FU x 3

National Cancer Center-Singapore
Wee JCO 2005
### National Cancer Center-Singapore

Wee JCO 2005

---

**Median F/U 38 months**

<table>
<thead>
<tr>
<th></th>
<th>CT/RT</th>
<th>RT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 yr DFS</td>
<td>76%</td>
<td>59%</td>
<td>0.027</td>
</tr>
<tr>
<td>2 yr DM-Free</td>
<td>87%</td>
<td>70%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 yr OS</td>
<td>84%</td>
<td>77%</td>
<td>0.006</td>
</tr>
</tbody>
</table>
China – Chen et al. JNCI 2011

Chinese Stage II

230 Patients Med Follow-up 5 years

RANDOMIZE

RT (70 Gy)

RT (70 Gy)
Weekly CDDP (30mg/m2)
CCRT vs. RT alone for Stage II NPC

- 5 yr OS: 94.5% vs. 85.8%  p=0.007
- 5 yr PFS: 87.9% vs. 77.8%  p=0.17
- 5 yr DMFS: 94.8% vs. 83.9%  p=0.007

Chen et al. JNCI 2011
NPC: Summary

- CCRT followed by adjuvant chemotherapy remains the standard for stage II-IVB
- Stage II patients (esp. endemic) should be offered weekly cisplatin
- IMRT is treatment of choice to maximize target coverage and spare normal tissues
- EBV may be useful biomarker for monitoring and in future as selection tool
Stage I-II Oropharynx, Hypopharynx, Larynx
Early Stage: General Management

- RT Alone or Surgery Typically Provide Equivalent Oncologic Outcomes
- RT may be preferred for quality factors
  - Voice quality
  - Swallowing function
- High likelihood of needing postop RT if surgical approach taken
Early Stage Larynx Cancer

- **T1-T2 Glottic**
  - Larynx only, No nodal RT
  - 2.25 Gy daily fractions
  - 63 Gy for T1 disease
  - 65.25 Gy for T2 disease
  - Limit treatment course < 43 days

- **T1-T2 Supraglottic/Subglottic**
  - Larynx + level II-III nodes
## Risk of Lymph Node Metastasis

<table>
<thead>
<tr>
<th></th>
<th>Glottic Cancer</th>
<th>Supraglottic Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>&lt;2%</td>
<td>27 to 40%</td>
</tr>
<tr>
<td>T2</td>
<td>&lt;5%</td>
<td>27 to 40%</td>
</tr>
<tr>
<td>T3</td>
<td>15-18%</td>
<td>55 to 65%</td>
</tr>
<tr>
<td>T4</td>
<td>20-30%</td>
<td>55 to 65%</td>
</tr>
</tbody>
</table>

CC Wang. Radiation Therapy for Head and Neck Neoplasms
Radiation Technique for Early Stage Glottic Cancer
Randomized Trial on T1 Glottic Cancer

Conventional Fractionation
2 Gy/Fx

Hypofractionation
2.25 Gy/Fx

Tumor < 2/3 of glottis
60 Gy/30 Fx

Tumor ≥ 2/3 of glottis
66 Gy/33 Fx

Tumor < 2/3 of glottis
56.25 Gy/25 Fx

Tumor < 2/3 of glottis
63 Gy/28 Fx

Yamazaki. IJROBP 2006;64:77-82
Local Control Rate Between Arm A and Arm B

Yamazaki. IJROBP 2006;64:77-82
RTOG 95-12: HFRT FOR T2 GLOTTIC

Stage
1. T2a
2. T2b

1. Conventional Fractionation:
   2 Gy/fx/d to 70 Gy/35 fx/7 wks

2. Hyperfractionation:
   1.2 Gy/fx BID to 79.2 Gy/66 fxs/6.5 wks

No Difference between the 2 arms
Radiation Treatment Outcomes

Early Stage OPX / HPX Cancer

- T1-T2 Tonsil / Pharyngeal Wall
  - Primary and ipsilateral levels II-IV
  - Surgical staging of neck an option
- T1-T2 BOT/ Soft Palate
  - Primary and bilateral neck levels II-V
  - Lateral retropharyngeal nodes
- T1-T2 HPX
  - Primary and bilateral neck levels II-V
  - Medial retropharyngeal nodes
Postoperative Radiotherapy
Postop RT: General Management

- Surgical resection if feasible
  - Surgical staging / prognostic information
  - Reserve RT for salvage
  - Limited morbidity
- Tailored adjuvant RT based on risk factors
- Instances where RT Alone may be reasonable option (for cosmesis, elderly, e.g.)
Postop RT: General Management

- Oral Cavity
  - Floor of Mouth
  - Oral Tongue
  - Hard Palate
  - Buccal Mucosa
  - Lip
  - Gingiva
  - Retromolar Trigone

- Paranasal Sinus
  - Ethmoid
  - Maxillary
  - Frontal
  - Sphenoid
  - Salivary Gland
  - Skin
Postop RT: Indications

- Multiple lymph nodes involved
- Extracapsular extension (ECE)
- Positive/close surgical margins
- Perineural invasion
- Lymphovascular invasion
- Deep (>5mm) invasion
Postop RT: General Management

- May deliver RT as soon as the wound is healed
- Ideally initiate within 6 weeks after surgery
- Intermediate Risk: 60 Gy / 30 fractions
- High Risk (Positive margin / ECE): 66 Gy / 33 fx
- Concurrent systemic therapy in high risk patients
Post-Op RT: General Management

- Review **Pre-operative Info** including exam and images to identify extent of disease
- Read **Op Note** and talk to surgeon to find out the areas of concern
- Read **Path Report**, talk to pathologist if necessary
- **Registration** of Pre-Op images to sim CT
- If unsure, ask **Surgeon to Assist** with delineation
<table>
<thead>
<tr>
<th>CTV1</th>
<th>Tumor bed (tumor and involved nodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV2</td>
<td>CTV1 + high risk surrounding tissue</td>
</tr>
<tr>
<td></td>
<td>High risk lymphatic areas (hemi-neck)</td>
</tr>
<tr>
<td>CTV3</td>
<td>Intermediate risk lymphatic areas</td>
</tr>
<tr>
<td></td>
<td>(lymphatic areas not included in CTV2)</td>
</tr>
</tbody>
</table>
Postop Target Delineation

- Oral Tongue/FOM - Cover the entire OC
- Cover the postop bed
- Cover the flap
- Wire scars & cover
- Usually, bilateral neck level I-IV (FOM – V)
- Cover skull base if neck involved
- Cover nerve tracks if PNI
T3N1 oral tongue cancer. Post-op IMRT included only ipsilateral oral cavity and ipsilateral upper neck.
Contralateral Level 2 Failure

T2N1 oral tongue cancer, postoperative radiation

Courtesy of Dr. Nancy Lee

Ipsilateral Level 3 Failure

T2N1 oral tongue cancer, postoperative radiation

Courtesy of Dr. Nancy Lee

Submental Failure

Patient with T4AN3 oral tongue cancer with FOM involvement. Level 1A was not included in the IMRT treatment.

Courtesy of Dr. Nancy Lee

Make sure to cover level 1A and the submental skin well. Placement of Bolus in your planning.

SCC of FOM extending into mandible
T4AN2C Buccal Mucosa Cancer, Recurred at skull base before PORT
Oral Tongue Cancer with Extensive Perineural Involvement and Skull Base Extension
Postoperative IMRT for Laryngeal Cancer

Stoma ≥ 60 Gy
Clinical Trials in Postoperative Radiotherapy
RTOG 73-03: RT + Surgery for Head & Neck Carcinoma

Pre-op RT (50 Gy) + surgery
Surgery + Post-op RT (60 Gy)
RT alone (65-70 Gy) + salvage

Pre-op RT (50 Gy) + surgery
Surgery + Post-op RT (60 Gy)

• 1973-1979, 320 pts, median f/u 60 mos
• All pts pooled

<table>
<thead>
<tr>
<th></th>
<th>LRC</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative XRT</td>
<td>48%</td>
<td>33%</td>
</tr>
<tr>
<td>Postoperative XRT</td>
<td>65%</td>
<td>38%</td>
</tr>
</tbody>
</table>

p=0.04  p=0.10

PORT in Head and Neck Cancer
Phase III Randomized Study to Determine the Optimal Dose

Pathology adverse Features
- ECE
- Margin +
- ≥2 N+
- T stage
- PNI
- Oral cavity primary

Randomize

Low Risk
Dose A
57.6 Gy/32 fx

High Risk
Dose B
63 Gy/35 fx
Dose C
68.4 Gy/38 fx

Peters, et al. IJROBP 1993;26:3
Local Regional Control by Risk Factors

Peters, et al. IJROBP 1993;26:3
Registered (8/91 - 8/97): 288 Patients

**Low Risk**
- LR (n=31):
  - No PoRT

**Intermediate Risk**
- IR (n=31):
  - 57.6 Gy/6.5 W

**High Risk**
- HR (n=151):
  - Randomize
  - 63 Gy/5 wk (n=76)
  - 63 Gy/7 wk (n=75)

Ineligible for PoRT (n=30)

Elected to receive PoRT closer to hometown or declined randomization (n=45)

Ang et al. IJROBP 2001;51:571-578
Accelerated PORT may improve LRC and OS for high risk patients, particularly when prolonged interval between surgery and RT.
Local Regional Control and Survival by Risk Factors

Ang et al. IJROBP 2001;51:571-578
RTOG 9501/EORTC 22931

Surgery

Patients with high risk pathology features

**RANDOMIZE**

Arm 1:
60-66 Gy

Arm 2:
60-66 Gy plus Cisplatin X3
Overall Survival Results

EORTC 22931

Combined therapy (79 events)
Radiotherapy (95 events)

P=0.02

Years

Radiotherapy

P=0.19

Months after Randomization

RTOG 9501

Combined therapy
Radiotherapy

Bernier. NEJM 2004; 350:1945
Cooper. NEJM 2004; 350:1937
Combined RTOG/EORTC Analysis

EORTC versus RTOG Eligibility

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

Bernier, Cooper. Head Neck 2005;27:843
Combined RTOG/EORTC Analysis
Overall Survival for Patients WITH Positive Margin and/or ECE

Bernier, Cooper. Head Neck 2005;27:843
Combined RTOG/EORTC Analysis
Overall Survival for Patients **WITHOUT** Positive Margin and/or ECE

Bernier, Cooper. Head Neck 2005;27:843
Long Term Follow Up of RTOG 9501 Patients with Positive Margin and/or ECE

Cooper et al. IJROBP 2012
Skin Cancer with Metastasis to Neck

**Figure 1.** Survival based on adequacy of excision.

**Figure 2.** Survival based on the state of the immune system.

**Figure 3.** Survival based on the presence of extracapsular spread.

**Figure 4.** Survival based on treatment.

Oddone et al. Cancer 2009
Skin Cancer – ITEM Score

- Immuno-suppression
- Treatment
- ECE
- Margins

Oddone et al. Cancer 2009
Skin Cancer with Metastasis to Neck

Kim et al. Head Neck 2009
Eligibility

- Recurrent or 2\textsuperscript{nd} Primary
- Previous RT \(\geq\) 45 Gy
- Underwent Salvage Surgery
- Field Intersection \(>\) 65%
- No Distant Metastasis
- KPS \(\geq\) 80

<table>
<thead>
<tr>
<th>Arm 1:</th>
<th>Arm 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 Gy / 2 Gy daily Conc. 5FU/ HU WOWO</td>
<td>Wait &amp; See</td>
</tr>
</tbody>
</table>
GORTEC Re-Irradiation Trial

Fig 2. Locoregional control. Large tick marks represent the 95% CI of the point estimates. Chemoradiation, reirradiation plus concomitant chemotherapy.

Fig 4. Overall survival. Large tick marks represent the 95% CI of the point estimates. Chemoradiation, reirradiation plus concomitant chemotherapy.
Clinical Trials

(Recent) Past
Present
Future
ECOG 1308

**ELIGIBILITY**
- Stage III, IVA, B
- Resectable
- HPV + Oropharynx

N=83

**INDUCTION**
(3 cycles)
- Weekly Paclitaxel
- Cetuximab

**CONCURRENT**
IMRT 54Gy/27 fxs
- Cetuximab 250mg/m2 qwk

CR

**CONCURRENT**
IMRT 69.3Gy/33fxs
- Cetuximab 250mg/m2 qwk

<CR

Cetuximab loading dose = 400mg/m2 on Day1 of Cycle1 with Induction
RTOG 1016 - Cetuximab-RT vs ChemoRT

Eligibility

Oropharynx

P16 pos

• T1-2, N2a-3
• T3-4 any N

T-stage

T 1,2
T 3,4

N-stage

N0-2A
N2B-C

Smoking

<10 PY
>10 PY

Zubrod

1
2

N=700
3.8 yrs to enroll
~8 yr to analysis

IMRT 6 fractions per week

IMRT 70 Gy in 6 wks
cisplatin x 2

IMRT 70 Gy in 6 wks
cetuximab for 8 wks
RTOG 0920 Phase III Intermediate Risk PORT

Eligibility

- Perineural invasion;
- Lymphovascular invasion;
- T1, N1-2 or T2-4a, N0-2,
- no extracapsular extension
- Close margin (≤ 5 mm)
- T2 oral cavity cancer with > 5 mm depth of invasion.

Arm 1:
60 Gy

Arm 2:
60 Gy plus Cetuximab X 11
RTOG 1216 Phase II/III High Risk PORT

**Eligibility**

- Stage III or IV HNSCC
- Extracapsular extension
- $\leq$ 3 mm surgical margin

**Randomize**

Arm 1: 60-66 Gy cisplatin X 6

Arm 2: 60-66 Gy docetaxel X 6

Arm 2: 60-66 Gy docetaxel and Cetuximab
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
Transoral Resection (any approach) with neck dissection
Observation

INTERMEDIATE:
Clear margins ≤ 1 mm ECS
2–3 metastatic LN PNI LVI
Radiation Therapy IMRT 50Gy/25Fx

HIGH RISK:
Positive Margins > 1 mm ECS or ≥ 4 metastatic LN
Radiation Therapy IMRT 60 Gy/30Fx

LOW RISK: T1-T2N0-N1 negative margins
Transoral Resection (any approach) with neck dissection
Radiation Therapy IMRT 66 Gy/33Fx + CDDP 40 mg/m² wkly
Evaluate for 2-yr PFS Local-Regional Recurrence, Functional Outcomes/QOL

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
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LOW RISK: T1-T2N0-N1 negative margins
Transoral Resection (any approach) with neck dissection
Radiation Therapy IMRT 66 Gy/33Fx + CDDP 40 mg/m² wkly
Evaluate for 2-yr PFS Local-Regional Recurrence, Functional Outcomes/QOL
RTOG 1221 & ECOG E3311
Risk Based Therapy for Oropharynx Cancer

Assess Eligibility:
HPV (p16) negative SCC oropharynx
Stage III-IV: cT1-3, N0-2b
Baseline Functional/QOL Assessment

IMRT 70 Gy +/- chemotherapy
TORS / TLM and Neck dissection
Risk-based PORT +/- chemotherapy
RTOG 1305: NPC Phase II-III

**REGISTRATION**

- T ≥2 or N+
- WHO I-III

**Therapy Details**

- IMRT (70 Gy) + Weekly CDDP 40mg/m²
- CDD(80) + 5FU(1000)x3
- Gem (1000) Paclitaxel (80) x 4

**Outcomes**

- Detectable EBV DNA
  - R
  - Observe
  - N=154 (Ph 2R)

- Undetectable EBV DNA
  - R
  - Observe
  - N=770 (Ph 3)

N=770 (Ph 3)

N=154 (Ph 2R)
ECOG Trial Schema

- **T1-4a, N1-3**
- **HPV+ OPSCC**
- **Amenable to TORS**
- **n = 46-54**

**Induction Chemo**
- **3 cycles**
- **Cisplatin 75 mg/m²/q3wk**
- **Paclitaxel 90 mg/m²/week**
- **BYL719 daily**

**TOR**
- **TORS, SLND**

**Risk-Stratified IMRT**
- **Arm 1**
  - pCR or pT1-2 N0-1
  - (-) margin, no ECE
  - Observe
- **Arm 2**
  - Close margin, ≥pN2, or PNI/LVI
  - 60 Gy IMRT
- **Arm 3**
  - (+) margin, ECE
  - 66 Gy IMRT + Weekly Cisplatin

**FDG/PET-CT scan**
DONE!