Combined Modality Treatment
For Head Neck Cancer:
Oropharynx, Larynx, Hypopharynx

Nancy Lee, M.D.
Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
Head and Neck Cancer

• Worldwide: > 680,000 cases per year

• ~ 5% of newly diagnosed cancers in adults

• U.S.A. per year: > 40,000 cases and 13,000 deaths
Head and Neck Cancer

- Majority present with locally or regionally advanced stages III or IV disease
- Mortality is high for locally advanced disease
- Those cured of disease experience long-term morbidity
History of Locally Advanced Head and Neck Cancer Treatment

Resectable Disease

- Surgery + radiotherapy
- Cosmetic and functional outcome can be devastating
- Improvement of surgical technique/reconstruction
- Perioperative/long-terms sequelae remain serious
- 5 year OS between 30-50%
• Traditional treatment involves radiation alone as single modality

• Results are suboptimal and **POOR** with control rates < 20%
Head and Neck Cancer

• How can we increase cure rates for locally advanced resectable and unresectable head and neck cancer?

• How can we decrease long-term morbidity from aggressive treatment modalities?
Can Local Control with RT Improve Survival?

• Wadsley (IJROBP, 2004): Establish the relationship between improvement in locoregional control and overall survival in 19 randomized trials

• A 10% improvement in the 2 year locoregional control is predicted to lead to a 6.7% 5 year increase in OS

• Limitation of RT in terms of dose escalation without causing excessive complications

• What about chemotherapy?
RATIONALE OF COMBINING RADIOTHERAPY AND CHEMOTHERAPY in H/N CA

Chemotherapy May:

• Perturb cell kinetics; Preferentially kill hypoxic cells
• Sensitize tumor cells to radiation; Inhibit tumor repopulation
• Enhance radiation induced apoptosis
• Inhibit repair of radiation damage
• Sterilize micrometastases outside the radiation field
• Decrease tumor mass leading to improved blood supply, reoxygenation, and increased radiosensitivity
RATIONALE OF COMBINING RADIOTHERAPY AND CHEMOTHERAPY in H/N CA

Radiotherapy May:

• Decrease tumor mass → improved blood supply → improved drug delivery and uptake
• Decrease tumor mass → increased cell proliferation → increased chemosensitivity
• Inhibit repair of drug damage
• Increase chemotherapy induced apoptosis
Outline

• Oropharynx Cancer: Historical data

• Use of IMRT for oropharyngeal cancer

• Emergence of HPV related tumors

• Describe organ preservation therapy approaches to larynx and hypolarynx cancer.
MR staging also T3N0.
RTOG 73-03
RT + Surgery for Head & Neck Carcinoma

**Oral Cavity**
- STRATIFY

**Oropharynx**
- STRATIFY

**Stage II-IV**
- STRATIFY

**Sex**
- T-Stage
- N-Stage

**Randomize**

- Pre-op RT (50 Gy) + surgery
- Surgery + Post-op RT (60 Gy)
- RT alone (65-70 Gy) ± surgical salvage
## RTOG 73-03 Oral Cavity And Oropharynx Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>4-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op RT (N=23/43)</td>
<td>30%</td>
</tr>
<tr>
<td>Post-op RT (N=23/43)</td>
<td>36%</td>
</tr>
<tr>
<td>RT Alone (N=24/43)</td>
<td>33%</td>
</tr>
</tbody>
</table>

\( p=0.81 \)
## RTOG 73-03 Oral Cavity and Oropharynx Local-Regional Control

<table>
<thead>
<tr>
<th>Treatment</th>
<th>4-Yr Local-Regional Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op RT (N=23/43)</td>
<td>43%</td>
</tr>
<tr>
<td>Post-op RT (N=23/43)</td>
<td>52%</td>
</tr>
<tr>
<td>RT Alone (N=23/43)</td>
<td>38%</td>
</tr>
</tbody>
</table>

\[ p = 0.42 \]
# SCC of Oropharynx

Parsons. Cancer. 2002

<table>
<thead>
<tr>
<th></th>
<th>Surgery+/-RT</th>
<th>RT +/- S</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BOT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>79%</td>
<td>76%</td>
</tr>
<tr>
<td>LRC</td>
<td>60%</td>
<td>69%</td>
</tr>
<tr>
<td>CSS</td>
<td>62%</td>
<td>63%</td>
</tr>
<tr>
<td>Cx(Fatal)</td>
<td>32% (3.5%)</td>
<td>3.8% (0.4%)</td>
</tr>
<tr>
<td><strong>Tonsil</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>70%</td>
<td>68%</td>
</tr>
<tr>
<td>LRC</td>
<td>65%</td>
<td>69%</td>
</tr>
<tr>
<td>CSS</td>
<td>57%</td>
<td>59%</td>
</tr>
<tr>
<td>Cx(Fatal)</td>
<td>23(3.2%)</td>
<td>6%(0.8%)</td>
</tr>
</tbody>
</table>
**Gortec French Study**
Denis et al, JCO, 2004

**Stage III/IV Oropharynx**

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

**Arm 2:**
70 Gy RT (QD)
French Trial: Oropharyngeal CA  
(Denis et al. JCO 2004)

• Randomized; N=226

• Invasive SCC of oropharynx, III and IV

• RT 70 Gy + 3 cycles of carbo (70) and 5FU (600) vs RT alone 70 Gy at 2 Gy

• No difference in Late toxicity

• Stage IV & Hg >/= 12.5 is most important prognostic factor--> survival and local control
# French Trial: Oropharyngeal CA

*(Denis et al, JCO, 2004)*

<table>
<thead>
<tr>
<th></th>
<th>Chemo + RT</th>
<th>RT Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med. Surv.</td>
<td>20 mo</td>
<td>13 mo</td>
</tr>
<tr>
<td>5 yr LRC</td>
<td>48%</td>
<td>25%</td>
</tr>
<tr>
<td>5 yr DFS</td>
<td>27%</td>
<td>15%</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>22%</td>
<td>16%</td>
</tr>
</tbody>
</table>

- 5 yr LRC comparison: *p*=.002
- 5 yr DFS comparison: *p*= 0.01
- 5 yr OS comparison: *p*=0.05
Other site-specific oropharynx cancer data that confirms a survival advantage for concurrent chemoradiotherapy:

<table>
<thead>
<tr>
<th>Year</th>
<th>No. pts.</th>
<th>Chemo</th>
<th>RT  (Gy)</th>
<th>Survival (RT vs. ChemoRT)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calais</td>
<td>1999</td>
<td>222</td>
<td>CpF</td>
<td>70 (3 yr.) 31% vs 51%</td>
<td>0.02</td>
</tr>
<tr>
<td>Staar</td>
<td>2001</td>
<td>178*</td>
<td>CpF</td>
<td>69.9 (1 yr.) 57% vs 68%</td>
<td>0.05</td>
</tr>
<tr>
<td>Bensadoun</td>
<td>2006</td>
<td>123*</td>
<td>PF</td>
<td>80.4 (2 yr.) 22% vs 41%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* planned subset analysis
Meta-Analysis: Chemo
(Pignon et al. Lancet, 2000; Bourhis et al., Radioth Oncol, 2011)

- All randomized Head and Neck trials between 1965 and 1993

- CA of the oropharynx, oral cavity, larynx, or hypopharynx

- Total of 63 trials

- 5 year absolute OS for the entire group with the addition of chemotherapy is 4%

- The 5-year absolute OS benefit at 5 years with concomitant chemotherapy was 8.95, 8.1%, 5.4%, and 4% for oral cavity, oropharynx, larynx, and hypopharynx.
Overall survival neoadjuvant trials

Courtesy of Jean Bourhis, M.D.

$p = NS$

**Difference : 2**

At risk

<table>
<thead>
<tr>
<th></th>
<th>2740</th>
<th>1848</th>
<th>1238</th>
<th>946</th>
<th>754</th>
<th>577</th>
<th>395</th>
<th>259</th>
<th>158</th>
<th>116</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Years

%
Overall survival adjuvant trials

At risk

Chemotherapy
- 1244
- 971
- 743
- 602
- 424
- 290
- 202
- 149
- 98
- 66
- 31

Control
- 1323
- 1049
- 799
- 640
- 454
- 301
- 212
- 155
- 104
- 62
- 29

p = NS

49%

Courtesy of Jean Bourhis, M.D.
Event Free Survival
Concomitant Trials

\[ p < 0.0001 \]

At risk

- **Chemotherapy**
  - 4824
  - 2617
  - 1892
  - 1493
  - 1177
  - 850
  - 614
  - 436
  - 330
  - 259
  - 205

- **Control**
  - 4791
  - 2255
  - 1507
  - 1118
  - 860
  - 655
  - 472
  - 345
  - 267
  - 217
  - 165

**Difference**: 8%

**At risk**: 31%

**At risk**: 23%

*Courtesy of Jean Bourhis, M.D.*
Overall Survival
Concomitant Trials (N=9615 patients)

At risk: 8%
P < 0.0001

Chemotherapy
Control

Difference: 8%
35%
27%

Years

0 1 2 3 4 5 6 7 8 9 10

At risk

4824 3180 2231 1715 1312 940 677 481 362 284 233
4791 2952 1908 1359 1016 746 531 394 304 246 186

Courtesy of Jean Bourhis, M.D.
RTOG 90-03

PHASE III STUDY OF ALTERED FRACTIONATION VS. STANDARD FRACTIONATION FOR H & N Ca.

**STRATIFY**
- Site
  - Oral Cavity
  - Oropharynx
  - Larynx
  - Hypopharynx
- Stage
  - N0 vs N+
- KPS
  - 90-100 vs 60-80

**RANDOMIZE**
1. Standard Fractionation
2. Hyperfractionation
3. Accelerated Fractionation (Split-Course)
4. Accelerated Fractionation (Concomitant Boost)
<table>
<thead>
<tr>
<th>Fractionation Scheme</th>
<th>Total Dose (T.D.)</th>
<th>Fraction (fx)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Fractionation</td>
<td>70.0 Gy</td>
<td>35 fx</td>
<td>7 weeks</td>
</tr>
<tr>
<td>Hyperfractionation</td>
<td>81.6 Gy</td>
<td>68 fx</td>
<td>7 weeks</td>
</tr>
<tr>
<td>Accelerated Fractionation (Split Course)</td>
<td>67.2 Gy</td>
<td>42 fx</td>
<td>6 weeks, split at 38.4 Gy</td>
</tr>
<tr>
<td>Accelerated Fractionation (Concomitant Boost)</td>
<td>72.0 Gy</td>
<td>42 fx</td>
<td>6 weeks, 1.8 Gy/fx/d to large field + 1.5 Gy/fx/d to boost field × 12 fxes. in last 2.5 wks</td>
</tr>
</tbody>
</table>
CB: 33% Late Grade 3-4 Toxicity
### Concurrent Chemoradiation with Altered Fx

- **Rationale springs from RTOG 90-03** where altered fx improves loco-regional control, disease-free survival when compared to standard fractionation.

- **Bourhis et al. (Lancent 2006):** Meta-Analyses of 15 altered fx RT alone trials improves 5 year overall LC by 6.7% and survival by 3.4% (More pronounced with HFX than ACC FX)

- **Trials of CT combined with QD RT are positive**

- **Combining CT with altered fractionation should lead to further improvement of results**
Stage III or IV of sq cell ca

**RANDOMIZE**

- QD RT: 70 Gy / 7 weeks
  - Carbo/5FU (n=279)
- Acc RT: 70 Gy / 6 weeks
  - Carbo/5FU (n=280)
- Acc RT: 64.8 Gy / 3.5 weeks (n=281)

**GORTEC 99-02 trial**

Median F/U=5.2 years
• Accelerated chemoRT offered no PFS benefit compared with conventional chemoRT or accelerated RT alone.

• Conventional chemoRT improved PFS compared with accelerated RT. (p=0.041)

• The 3 year PFS was 37.6% with conventional chemoRT; 34.1% with accelerated chemoRT; 32.2% with very accelerated RT.

• More patients in the very accelerated RT group had RTOG grade 3-4 mucosal toxicity vs. accelerated chemoRT (76%) vs. conventional chemoRT (69%).

• Tube feeding highest among the very accelerated RT group (70%) vs. 64% in the accelerated chemoRT group vs. 60% in the conventional chemoRT group.
**RTOG 0129**

**Phase III Trial of Concurrent RT and CT for Advanced Head and Neck Cancer**

Ang, NEJM, 2010

---

**STRATIFY**

- **Zubrod PS**
  - 0 or 1

- **Site**: larynx vs none

- **Nodal Status**:
  - N0
  - N1 or N2a-b
  - N2c-N3

**RANDOMIZE**

- **Arm 1**: AFX-CB
  - 72 Gy/42 FXS/6 wks
  - plus CDDP 100 Mg/M2
  - days 1 and 22

  **No Difference in Outcomes**

- **Arm 2**: Concurrent 70 Gy + Cisplatin 100 mg/m²
  - I.V. on days 1, 22, 43.
RTOG 0129: HPV for Oropharynx
Ang et al. NEJM, 2010

• Median F/U 4.8 years
• 63.8% of oropharynx cancer patients were HPV+
• 3 year OS of 82.4% vs. 57.1% for HPV+ vs. HPV- patients
• After adjusting for age, race, T, N, tobacco exposure, treatment assignment, there was a 58% reduction in risk of death and the risk of death significantly increased with each additional pack year of tobacco smoking.

• Recursive-partitioning analysis was done and classified patients into low, intermediate, or high risk of death on basis of 4 factors:

• -HPV status, pack year of tobacco smoking, tumor/nodal stage
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: HPV for Oropharynx
Ang et al. NEJM, 2010

• Low risk group: 3-year OS was 93.0%
• Intermediate risk group: 3-year OS was 70.8%
• High risk group: 3-year OS was 46.2%
IMRT in the Treatment of Oropharyngeal Cancer: an Update of the Memorial Sloan-Kettering Cancer Center Experience.
Background

- IMRT in the treatment of OPC: widely investigated
- Missing long-term follow-up
- Previous studies: < ~100 patients

Purpose: Update our previous retrospective study [Fernando de Arruda] with longer follow-up and greater number of patients
Patients Population

**From 9/1998 to 4/2009 442 patient treated with IMRT for OPC (SCC, M0)**

**Site:**
- Tonsil 50%
- Base of Tongue 46%
- Soft Palate 2%
- Pharyngeal wall 2%

**Stage:**
- T2 42%, T3 18%, T4 14%
- N1 21%, N2 67%, N3 3%

*Stage III 19%, Stage IV 76%*
Treatment Modality

- Chemotherapy in 91%, CDDP based in 67%
- Definitive RT 93%, PORT 7%
- Neck dissection 21%
- Peg placed upfront 75%

**Dose delivered**
- 70 Gy at 2.12 fr PTV1
- 59.4 Gy at 1.8 fr PTV2
- 54/ 50.4 Gy at 1.64/1.8 fr PTV3
Local Control

Median FU 36.8 months

3-year  94.4%
5-year  94.4%

Median FU 36.8 months
Regional Control

3-year  94.3%
5-year  94.3%
Local Failure versus T-stage

- T1-2 10 out of 303 3.3%
- T3-4 13 out of 139 9.4%

HR 2.89; P<0.01
### OS, DMFS and Statistics

**OS:**
- 3 years: 84.9%
- 5 years: 78.7%

**DMFS:**
- 3 years: 87.1%
- 5 years: 85.2%

<table>
<thead>
<tr>
<th></th>
<th>Univariate (Logrank)</th>
<th>Multivariate (Cox)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1/2 vs T3/4</td>
<td>N0/1 vs N2/3</td>
</tr>
<tr>
<td>OS</td>
<td>p &lt; 0.0001</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>LC</td>
<td>p = 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>RC</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DM</td>
<td>p = 0.01</td>
<td>p = 0.001</td>
</tr>
</tbody>
</table>

**NS:** Site, Age, Treatment Modality,
Kaplan-Meier curves of overall survival stratified by oropharyngeal pGTV

Log-rank Test P-value < 0.0001

pGTV = primary gross tumor volume
Cumulative incidence rates of local recurrence stratified by pGTV

Cumulative incidence rates of distant metastasis stratified by pGTV

pGTV = primary gross tumor volume
### Literature on oropharyngeal cancer pGTV and disease control

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>RT technique</th>
<th>Patients on CCRT</th>
<th>pGTV</th>
<th>p-value LC/LRC</th>
<th>p-value DMFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nathu et al.</td>
<td>2000</td>
<td>114</td>
<td>3DCRT</td>
<td>11%*</td>
<td></td>
<td>0.1</td>
<td>-</td>
</tr>
<tr>
<td>Mendenhall et al.</td>
<td>2003</td>
<td>190</td>
<td>3DCRT</td>
<td>4%</td>
<td></td>
<td>0.0892 - .9493</td>
<td>-</td>
</tr>
<tr>
<td>Keberle et al.</td>
<td>2003</td>
<td>80</td>
<td>3DCRT</td>
<td>†</td>
<td>0.19</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Been et al.</td>
<td>2008</td>
<td>79</td>
<td>3DCRT/IMRT</td>
<td>49%</td>
<td></td>
<td>0.6244</td>
<td>-</td>
</tr>
<tr>
<td>Hermans et al.</td>
<td>2001</td>
<td>112</td>
<td>3DCRT</td>
<td>†</td>
<td>0.047</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chao et al.</td>
<td>2004</td>
<td>31††</td>
<td>IMRT</td>
<td>55%</td>
<td>0.03</td>
<td>-</td>
<td>0.03</td>
</tr>
<tr>
<td>Struder et al.</td>
<td>2007</td>
<td>85††</td>
<td>IMRT</td>
<td>75%§</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Present study</td>
<td>2012</td>
<td>340</td>
<td>IMRT</td>
<td>95%</td>
<td>0.004</td>
<td>0.0008</td>
<td></td>
</tr>
</tbody>
</table>

CCRT = concurrent chemoradiotherapy, LC = local control, LRC = locoregional control, DMFS = distant metastasis free survival; *patients underwent induction chemotherapy; † not reported; †† subset of patients included in volumetric analysis; § CCRT rate is based on the total HNC cohort of 172
Toxicities: Acute

- **Mucositis**
  - grade 2: 26%
  - ≥ grade 3: 22%

- **Dermatitis**
  - grade 2: 35%
  - ≥ grade 3: 7%

- **Dysphagia**
  - grade 2: 39%
  - ≥ grade 3: 16%
Toxicities: Late

- *Xerostomia ≥ grade 2*
  
<table>
<thead>
<tr>
<th></th>
<th>3mo</th>
<th>6mo</th>
<th>12mo</th>
<th>24mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27%</td>
<td>23%</td>
<td>13%</td>
<td>7%</td>
</tr>
</tbody>
</table>

- Dysphagia ≥ grade 3 in 3% of the patients

- PEG dependence @ 12 months: 27 patients (6%)
  24 months: 11 patients (2.5%)

- Should we constrain the constrictor muscle?

- Osteoradionecrosis occurred in 7 (2%) patients
PEG Dependence: Pooled Data vs Haughey

- Median follow-up = 44 months

Haughey et al. 2009

![Graph showing PEG dependence over time with specified percentages at various time points.](image)
Pooled Data: PEG Dependence (N=2315)

SUBMITTED TO JCO, 2014
Mean Doses

Right Parotid  19.80 Gy
Left Parotid   24.94 Gy
Oral Cavity   33.6 Gy
Stage: T1 - T2, N0 - N1
Site: Tonsil, BOT, Soft Palate
Histology: SCC
No Chemo

Gross disease PTV: 66 Gy/30 FX
Subclinical disease PTV: 54-60 Gy/30 FX

Boost of 4-6 Gy in 2-3 FX to the gross disease PTV allowed

LRC: 93%
Larynx Cancer
VA LARYNGEAL CA. STUDY

Surgery → Radiation Therapy

CR or PR (3rd Cycle of Chemo) → Radiation Therapy

CR

Induction Chemotherapy (2 Cycles) < PR → Surgery

Induction Chemotherapy: Cisplatin and 5-FU

PR → Surgery

RANDOMIZE
<table>
<thead>
<tr>
<th></th>
<th>S + RT (N = 166)</th>
<th>CT + RT (N = 166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx preserved</td>
<td>20* (12%)</td>
<td>103 (62%)</td>
</tr>
<tr>
<td>Total laryngectomy</td>
<td>146 (88%)</td>
<td>63 (38%)</td>
</tr>
<tr>
<td>Patients alive</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 PRESERVATION STUDY

<table>
<thead>
<tr>
<th></th>
<th>Surgery → RT</th>
<th>CT → RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>166</td>
<td>166</td>
</tr>
<tr>
<td>Depression</td>
<td>28.0%</td>
<td>15.0%</td>
</tr>
<tr>
<td>HNQOL</td>
<td>Worse</td>
<td>Better</td>
</tr>
</tbody>
</table>

AOHNS 1998; 124:964*
<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>
GETTEC Trial - T3 Larynx Ca.
(J.M. Richard et al, 1998)

- **Induction Chemotherapy (3 Cycles)**
  - Induction Chemotherapy: Cisplatin and 5-FU

- **Randomize**
  - Surgery → Radiotherapy
    - ≥ 80% → RT
    - < 80% → Surgery → RT
## GETTEC Trial

*(J.M. Richard et al, 1998)*

<table>
<thead>
<tr>
<th></th>
<th>S + RT (N = 32)</th>
<th>CT+ RT+ S (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr. D-F Survival</td>
<td>62*%</td>
<td>32*%</td>
</tr>
<tr>
<td>5-yr. Survival</td>
<td>68*%</td>
<td>43*%</td>
</tr>
<tr>
<td>Site of 1st Recurrence:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local-Regional</td>
<td>12.5%</td>
<td>25%</td>
</tr>
<tr>
<td>Distant Mets.</td>
<td>3%</td>
<td>25%</td>
</tr>
<tr>
<td>2nd Primary</td>
<td>22%</td>
<td>11%</td>
</tr>
</tbody>
</table>

* Estimated from survival curves
Does Vocal Cord Fixation Preclude Nonsurgical Management of Laryngeal Cancer

Solares, et al. Laryngoscope 2009
Vocal Cord Fixation

- N = 23 where 14 patients were T3 disease
- SGL: 48% vs Glottic: 52%
- RT dose: 70 Gy concurrent with CDDP
- Median F/U: 68 months
- 5-year LC: 87% among those who had recovery of the vocal cord function vs 30% among those without recovery of vocal cord function
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

**Randomize**

**Arm 1:** Neoadjuvant CT + RT
- CR, PR → CP + 5-FU → RT
- X 1 Cycle
- CP + 5-FU X 2 Cycles
- NR → Surgery → RT

**Arm 2:** RT + CP

**Arm 3:** RT Alone
## RTOG 91-11

<table>
<thead>
<tr>
<th></th>
<th>Induction</th>
<th>CCRT</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year Laryng-free</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>

* Median F/U 3.8 years

* Estimated from survival curves
### RTOG 91-11

**Distant Metastases**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5 yr*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT→RT</td>
<td>15 %</td>
<td>NEJM 2003; 349:2091; JCO 2014</td>
</tr>
<tr>
<td>CT/RT</td>
<td>12 %</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>22 %</td>
<td></td>
</tr>
</tbody>
</table>

*P=0.03 CT/RT vs RT
Phase III Trial of Induction Chemotherapy with Cisplatin and 5FU+/-Docetaxel for Larynx Preservation

Stage III and IV SCC Larynx

Arm 1: TPF and 70 Gy

Arm 2: PF and 70 Gy

Pointreau et al. JNCI 2009
Phase III Trial of Induction Chemotherapy with Cisplatin and 5FU+/-Docetaxel for Larynx Preservation

- Median follow up was 36 months
- Overall response was 80% versus 59.2%
- 3 year larynx preservation rate was 70.3% versus 57.5% in favor of TPF (still inferior to CCRT→RTOG 91-11, 84%)

Pointreau et al. JNCI 2009
T4a: Thyroid Cartilage Invasion

What to consider when patients refuse upfront surgery?
Stage IV of squamous cell carcinoma
Stage III if BOT or hypopharynx

Carboplatin and Taxol weekly x 6
Taxol, 5FU, Hydroxyurea
BID XRT to 75 Gy

N=69, 96% stage IV
Induction Chemotherapy Followed By Concurrent Chemoradiotherapy

- Median Follow-up: 28 months
- Response to induction chemotherapy:
  - Partial: 52%
  - Complete: 35%
- 2-year local control: 94%
- 2-year distant control: 93%
- 2-year overall survival: 77%
- 3-year progression-free survival: 80%
- Five patients PEG dependent at 1 year
• N= 32 T4 disease including large volume T4
• Taxol, 5FU, Hydroxyurea with BID RT (75Gy)
• Median F/U=43 months
• 4-year LRC, DFS, OS, LFS was: 71%, 67%, 53%, 86%, respectively
• Results similar for those who had large volume T4
• Induction chemo improved 4 year LRC of 90% vs 46% and DFS 84% vs 42%
Hypopharynx
EORTC 24891 LARYNX PRESERVATION FOR HYPOPHARYNGEAL CA.

(J.L. Lefebvre et al, 1996)

- **Induction Chemotherapy** (3 Cycles)
- **Complete Responders*** → Radiation Therapy
- **Partial or Non-Responders** → Surgery RT
- **Surgery** → Radiation Therapy

Induction Chemotherapy: Cisplatin and 5-FU
EORTC 24891 LARYNX PRESERVATION FOR HYPOPHARYNGEAL CA.

*(J.L. Lefebvre et al, JNCI 88:1685-90, 1996)*

<table>
<thead>
<tr>
<th></th>
<th>S + RT</th>
<th>CT+ RT± S</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>5-yr. D-F Survival</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td>5-yr. Survival</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>Distant Mets.</td>
<td>36%</td>
<td>25%</td>
</tr>
<tr>
<td>5-yr. Alive with Larynx</td>
<td>---</td>
<td>17%</td>
</tr>
</tbody>
</table>
# EORTC 24891 LARYNX PRESERVATION

## 10 year Results

*(J.L. Lefebvre et al, Annals Oncology, 2012)*

<table>
<thead>
<tr>
<th></th>
<th>S + RT</th>
<th>CT+ RT+ S</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median F/U: 10.5yrs</strong></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 yer. Alive with functional Larynx</strong></td>
<td>8.7%</td>
<td></td>
</tr>
</tbody>
</table>
Why shouldn’t we just treat all advanced squamous cell head and neck cancer patients with definitive chemoradiotherapy?

**Acute and late toxicity**

*Functional preservation (= organ preservation)*
Fig. 4. Five-year rate of Grade 3–4 late toxicity for combined modality treatment (27 patients, RT+CT) vs. RT alone (17 patients, RT) assessed using three late toxicity scales simultaneously.
## Chemoradiotherapy: Late FT Dependence

### Recent selected phase II-III reports

<table>
<thead>
<tr>
<th></th>
<th># pts</th>
<th>Chemo</th>
<th>RT FX</th>
<th>FT placed</th>
<th>Late (2-yr) FT depend.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staar</td>
<td>2001</td>
<td>113</td>
<td>5FU/Carb</td>
<td>AF</td>
<td>51%</td>
</tr>
<tr>
<td>Akst (CCF)</td>
<td>2004</td>
<td>196</td>
<td>5FU/DDP</td>
<td>CF/AF</td>
<td>76% 6%</td>
</tr>
<tr>
<td>Ang (RTOG)</td>
<td>2005</td>
<td>76</td>
<td>DDP</td>
<td>AF</td>
<td>84% 29%</td>
</tr>
<tr>
<td>Tsao (MDA)</td>
<td>2006</td>
<td>52</td>
<td>DDP/Doc</td>
<td>AF</td>
<td>79% 25%</td>
</tr>
<tr>
<td>Bensadoun(GORTEC)</td>
<td>2006</td>
<td>81</td>
<td>5FU/DDP</td>
<td>AF</td>
<td>100% 4%</td>
</tr>
<tr>
<td>Pfister (MSK)</td>
<td>2006</td>
<td>21</td>
<td>DDP/Cetux</td>
<td>AF</td>
<td>81% 0</td>
</tr>
</tbody>
</table>
### Pre-existing swallowing dysfunction

- **Stenson et al. (U.Chicago)** demonstrated aspiration in 44% of head and neck cancer patients prior to any treatment. *(Arch Otol H & N Surg 2000)*

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>14%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>30%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>80%</td>
</tr>
<tr>
<td>Larynx</td>
<td>67%</td>
</tr>
</tbody>
</table>

*P* < .001

- **Daggett et al** demonstrated at least a minor degree of laryngeal penetration in 64% of normals over age 50. *(Dysphagia 2006)*
Cetuximab Prolongs Survival in Patients with LA SCC of Head and Neck; Phase III Study of RT +/- Cetuximab

Bonner et al. NEJM, 2006

Stage III and IV SCC
Oropharynx
Larynx
Hypopharynx

Arm 1: RT (QD, BID, Conc Boost)
Arm 2: RT (QD, BID, Conc Boost)
Weekly C225
**RT +/- Weekly C225**

*Bonner et al., NEJM, 2006 [Update Lancet Oncology]*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RT (n = 213)</th>
<th>RT + C225 (n = 211)</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>28 mo</td>
<td>54 mo</td>
<td>0.02</td>
</tr>
<tr>
<td>2 year survival</td>
<td>55%</td>
<td>62%</td>
<td>0.02</td>
</tr>
<tr>
<td>3 year survival</td>
<td>44%</td>
<td>57%</td>
<td>0.02</td>
</tr>
<tr>
<td>G3/4 Mucositis</td>
<td>52%</td>
<td>55%</td>
<td>0.5</td>
</tr>
<tr>
<td>G3/4 skin reaction</td>
<td>18%</td>
<td>34%</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

**Improved survival for patient with more prominent cetuximab-induced rash, Bonner et al, ASTRO 2005**
Locoregional failure

![Graph showing time to local recurrence in months for Cetuximab and Cisplatin with a p-value of less than 0.0001.](image)
Disease-free Survival

- **Cetuximab**
- **Cisplatin**

$p < 0.0001$
Overall survival

- Cetuximab
- Cisplatin

\( p < 0.0001 \)

Overall survival table:

<table>
<thead>
<tr>
<th>Months</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
</tr>
<tr>
<td>24</td>
<td>0.2</td>
</tr>
<tr>
<td>30</td>
<td>0.0</td>
</tr>
<tr>
<td>36</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Significance level: \( p < 0.0001 \)
Multivariate analysis for survival outcomes

On multivariate analysis, treatment with CDDP/RT remained statistically significantly superior to C225/RT for locoregional control, disease-free survival, and overall survival (P <0.0001 for LRC and DFS; P = 0.01 for OS).
C225 vs. Cisplatin

• Caution should be used when routinely recommend C225 over cis-platin eligible patients

• MSKCC first hypothesis generating study, followed by Wash Univ. and now William Beaumont, Stanford [? Selection bias]

• Await results of RTOG 1016
Should Cetuximab Replace Cisplatin for Definitive Chemoradiotherapy in Locally Advanced Head and Neck Cancer?

Survival (79% vs 27%; \( P < .001 \)) and OS (72% vs 25%; \( P < .001 \)) were worse in patients treated with C225.

To our knowledge, only two studies suggest equivalence between the two treatments. A retrospective study from the University of Alabama demonstrated similar outcomes between concurrent CDDP and C225.\(^6\) This study differed from ours because patients may have received additional agents besides CDDP and were treated with concurrent IMRT instead of definitive IMRT and radiation alone.

Nadeem Riaz, Eric J. Sherman, Matthew Fury, and Nancy Lee
Memorial Sloan-Kettering Cancer Center, New York, NY
Induction in Setting of CCRT
DeCIDE Schema
Primary Endpoint: Overall Survival at 3-yrs

N2/N3 HNSCC
N=400
↓ 46 mos
N=280

RANDOMIZE

TPF: Docetaxel + Cisplatin + 5-FU Q3 weeks X2
DFHX: Docetaxel + Hydroxyurea + FU + Hyperfractionated RT

PRESENTED BY: Ezra Cohen
DeCIDE

Overall Survival

Recurrence-Free Survival

Blue: IC->CRT

Red: CRT

$p=0.68$

$p=0.16$

PRESENTED BY: Ezra Cohen
Cumulative Incidence of Distant Recurrence without Prior Local/Regional Recurrence

PRESENTED BY: Ezra Cohen

Red: CRT
Blue: IC->CRT

\[ p = 0.043 \]
#5501: The PARADIGM Study: A phase III study comparing sequential therapy (ST) to concurrent chemoradiotherapy (CRT) in locally advanced head and neck cancer


PRESENTED BY: Robert Haddad
PARADIGM: Study Design
Primary Endpoint: Overall survival at 3 yrs

Stage III/IV SCC
- Oral cavity, oropharynx, hypopharynx, larynx
- Expected N=330

Randomize

IC

A

Non-CR

Docetaxel
Cisplatin
5-FU
every 3 wks X 3 cycles

CR

CRT

Docetaxel 20 mg/m² (wkly for 4 wks)
Accelerated Boost RT (d1-5) 6 wks

Carboplatin AUC 1.5 (every wk)
Daily RT (d1-5) 7 wks

Cisplatin 100 mg/m² (wks 1,4)
Accelerated Boost RT (d1-5) 6 wks

Accrual: 145 patients
08/’04 - 12/’08
Halted 12/08 for Poor Accrual

PRESENTED BY: Robert Haddad
PARADIGM

Overall Survival

Progression-Free Survival

No differences in patterns of Failure

PRESENTED BY: Robert Haddad
PARADIGM: Toxicities

- Acute toxicities
  - Febrile neutropenia
    - IC→CRT: 10 Pts Grade 3 and 6 Pts Grade 4
    - CRT alone: 1 Pt Grade 4
- No difference in mucositis, pain scores, xerostomia, PEG dependency

- Early Deaths
  - IC→CRT: Four patients died within the first year
    - Two died following CRT at 1 and 8 mo post-therapy
    - Two died during induction
  - CRT: One Patient died within the first year

PRESENTED BY: Robert Haddad
Conclusion

• DeCIDE and PARADIGM
  – Addition of TPF IC did not improve OS and RFS/PFS compared to CRT alone
  – Increased toxicities with TPF IC

• DeCIDE
  – IC improved cumulative incidence of distant failure but did not result in increased OS or RFS
Summary of HNC 2014

• Concurrent chemoradiation remains the standard of care

• Off trial, induction chemotherapy should not be routinely used except for select cases

• Cisplatin remains the most sensitive agent for head and neck cancer
IMRT

Head Neck Cancer
T3N2 Nasopharyngeal Carcinoma
Max optic nerves 50

Max BS Dose: 50 Gy

Mean Oral Cavity 40 Gy

Mean Whole Gland R & L Parotid: 30 Gy/29 Gy

Mean Superficial Lobes only: 23 Gy/22 Gy
When IMRT is not necessary
IMRT Head and Neck Cancer: What have we learned?

- IMRT allows preservation of salivary function: mean dose ≤ 26 Gy [3 randomized trials]

- More importantly, IMRT does not compromise loco-regional control [NPC: improved LRC, 1 randomized trial]

- Importance of knowing your treatment planning and delivery system
Mean Dose (whole gland):
L Parotid:  28 Gy
R Partoid:  30 Gy
Mean Dose (whole gland):
L Par: 23 Gy
R Par: 26 Gy
Cold spot

70 Gy,
59.4 Gy,
45 Gy
Where are the “hot spots”? 

Nerves, blood vessels & bone are embedded within the GTV

Nasopharynx tolerates hot spots better than oropharynx.

Courtesy of A. Eisbruch
RTOG 0022  A case of osteoradionecrosis  Dr G. Sanguineti, UTMB

Gomez et al.  ASTRO 2008
Now: Orfit System

2-3mm accuracy 
Mechalakos et al.
J App Med Phys 2007
In Press

Future: Maskless System
Patient Neck Skin Problem
Present: Faceless mask
Use real time on machine monitoring system
RT aligned system; pre and post KV imaging

Future: no mask system
Dose Prescription for IMRT HNC

- MSKCC and UCSF: 70 Gy over 33 days. (BED = CB)
  
  - GTV: 2.12 Gy per day
  - \( \text{CTV}_{\text{high risk}} \): 1.8 Gy per day = 59.4 Gy
  - \( \text{CTV}_{\text{low risk}} \): 1.64 per day = 54 Gy

- NYP, MDACC, Wash Univ.: 70 Gy over 35 Days (BED = SF)
  
  - GTV: 2 Gy per day
  - \( \text{CTV}_{\text{high risk}} \): 1.8 Gy per day = 63 Gy
  - \( \text{CTV}_{\text{low risk}} \): 1.6 per day = 56 Gy
CT vs. MRI vs. PET volume

Thiagarajan A. et al. IJROBP 2012

Final GTV

Importance of Physical Examination
**GTV\textsubscript{70} to PTV\textsubscript{70}**

**GTV:** Gross tumor based on imaging, PE

**GTV is also known as CTV\textsubscript{70}**

**PTV\textsubscript{70}:** GTV + 3-5mm (based on your comfort level)
Primary and nodal $\text{GTV}_{70}$

$\text{PTV}_{70} : \text{GTV}_{70} + 3\text{mm Margin}$

$\text{T2N2C BOT}$
Oropharynx (Primary) 
CTV\textsubscript{59.4} Delineation

- Should probably have at least 1cm circumferential margin except near bony region, especially there are no good salvage options for failure

- Base of tongue cancer to include pre-epiglottic fat and entire base of tongue (but can be in the next lower dose region)

- Tonsil cancer, should include the pterygoid plate (ensuring good coverage superiorly of pterygoid mandibular raphe).
Ensuring Coverage of Pre-epiglottic space
Look at the growth pattern of your cases to determine $CTV_{59.4}$ coverage.

Need to Include Pterygoid Plate
Oropharynx (Nodal): 
CTV_{59.4} Delineation

- Node+: levels IB-V

- Can consider shrinking volume, just treat levels Ib-IV or II-IV in node positive cases

- Node negative: levels II-IV

- At MSKCC, we no longer perform routine planned neck dissection. IMRT with precise targeting of the gross neck nodes has changed practice
CTV low neck
For oropharynx CA

Not treating level V
Base of Tongue CA

PTV_{70}

CTV_{59.4}

PTV_{59.4}

PTV_{59.4}
Example Stage IVB oropharynx CA

Superior to Inferior slices

Treat Bilateral Retrostyloid Spaces
No actively trying to spare Constrictor muscles

Distance from GTV To PTV59.4 is at least 1.3 cm
Coverage of pre-epiglottic fat but spare larynx

Even with N+, level V not included
Node-: $CTV_{54}$ Delineation

- Levels II-IV

- Coverage of the retropharyngeal region.

- For oropharyngeal CA, when posterior belly of digastric just crosses IJ, can omit treating high level II, i.e., only target subdigastric nodes. (Omitting the retrostyloid space)

- $CTV_{54} + 3\text{mm} = PTV_{54}$
N- Neck Typically around C2

Omit high levels IIA/IIB
N- Contralateral Neck Can Spare the high IIA/IIB nodes
Base of Skull Coverage

(Eisbruch et al, IJROBP 59:1, 2004)

- N=133
- All non-nasopharyngeal sites
- Retropharyngeal nodal regions delineated to level of C1
- 2 marginal failures, both cranial to C1

- Recommend bilateral delineation of retropharyngeal nodal regions to the base of skull
Retropharyngeal Space

N+

N−
Contour at RP nodal level for bilateral N+ neck

Univ Michigan

MSKCC
Can We further Dose Paint?

Even a lower risk microscopic region!
Perhaps we should have $\text{CTV}_{50}$

Apisarnthanarax S, IJROBP 64(3);678-83, 2006
PTV_{50}

BED calculation is 57.6 for tumoricidal effect.

BED for 44 Gy at 2 Gy per fraction: 52.8

BED for 50 Gy at 2 Gy per fraction: 60
Decrease Toxicity

Additional Contouring?

Concerns of Late effects?
Brachial Plexus
The pharyngeal constrictors
“Standard IMRT”

“Dysphagia/aspiration-specific IMRT”

Eisbruch et al, IJROBP 2004
Mean Dose 35-40 Gy

Eisbruch et al, IJROBP 2001

Mean dose < 39 Gy
IMRT Summary

• We should be cautious with our physician contours to ensure no marginal failure.

• Questions?