Outline

• Historical data

• Toxicity as a result of non-surgical treatment

• Use of IMRT for oropharyngeal cancer

• Emergence of HPV related tumors
Oropharynx - Sites

Anterior View

Posterior View

- Soft Palate
- Base of Tongue
- Tonsil
- Pharyngeal wall
OROPHARYNX-Sites

- Base of tongue
- Soft palate
- Tonsillar fossa
- Anterior tonsillar pillars (palatoglossus muscle)
- Posterior tonsillar pillars (palatopharyngeal m.)
- Glosso-tonsillar sulci
- Uvula
- Posterior oropharyngeal wall
- Vallecula
MR staging also T3N0.
## Incidence of Lymph Node Metastases on Presentation

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base of Tongue</td>
<td>78%</td>
</tr>
<tr>
<td>Tonsil &amp; Tonsillar Fossa</td>
<td>76%</td>
</tr>
<tr>
<td>Oropharyngeal Wall</td>
<td>59%</td>
</tr>
<tr>
<td>Anterior Pillar</td>
<td>45%</td>
</tr>
<tr>
<td>Soft Palate</td>
<td>44%</td>
</tr>
</tbody>
</table>
**CA. OF THE OROPHARYNX**

**INCIDENCE OF CONTRALATERAL OR BILATERAL NODES**

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base of Tongue</td>
<td>30%</td>
</tr>
<tr>
<td>Soft Palate</td>
<td>16%</td>
</tr>
<tr>
<td>Tonsil &amp; Tonsillar Fossa</td>
<td>11%</td>
</tr>
<tr>
<td>Anterior Pillar</td>
<td>5%</td>
</tr>
</tbody>
</table>
## CA. OF THE OROPHARYNX
### INCIDENCE OF OCCULT NODES

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base of Tongue</td>
<td>50-60%</td>
</tr>
<tr>
<td>Tonsil &amp; Tonsillar Fossa</td>
<td>50-60%</td>
</tr>
<tr>
<td>Soft Palate</td>
<td>20-30%</td>
</tr>
<tr>
<td>Anterior Pillar</td>
<td>10-15%</td>
</tr>
</tbody>
</table>
Oropharyngeal CA: Treatment Volume
(Nathu et al. Univ of Florida, 2000)

- 1983-1985; N=114; T2-4 SCC Tonsil, BOT, Soft Palate
- Definitive RT+/- brachy; 12 pts had induction chemo
- Dose ranged from 50.4 to 81.6 Gy / 1.2 Gy BID +/- 10-15 Gy of brachy boost; 16 pts had QD RT with median dose of 70 Gy
- All had pretx CT scan to determine volume and subsequently underwent CT tx planning
- Multivariate analysis showed that local control rate correlated with T-stage but did not correlate with tumor volume within a given T-stage
Oropharyngeal CA: Treatment Volume
(Hermans et al. Belgium, 2001)

• Investigate the value of CT-derived tumor parameters as predictor of local and regional outcome of tonsillar squamous cell carcinoma treated by definitive RT
• N=112 from 1987-1998
• Median follow up was 33 months
• Primary volume did not predict local control within the T2, T3, and T4 category
• Total tumor volume was not significantly related to LC
• Multivariate analysis showed that T and N were the independent predictors of LC
RTOG 73-03
RT + Surgery for Head & Neck Carcinoma

STRATIFY

Oral Cavity
Oropharynx
Stage II-IV

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>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op RT</td>
<td>30%</td>
<td>p=0.81</td>
</tr>
<tr>
<td>(N=23/43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-op RT</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>(N=23/43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT Alone</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>(N=24/43)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RTOG 73-03 Oral Cavity and Oropharynx  
Local-Regional Control

<table>
<thead>
<tr>
<th>Treatment Control</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
Surgery and Adjuvant RT vs. CCRT in Stage III/IV Nonmetastatic SCC of head and neck: Randomized Comparison/Singapore, Soo et al.

**Stage III or IV of sq cell ca**
- Oral Cavity
- Oropharynx
- Larynx
- Hypopharynx
- Max Sinus

**Randomize**

**Surgery + RT**
- (60 Gy to 70 Gy)

**Chemo + RT**
- (CDDP+5FU x 2) and 66 Gy

**Medium F/U: 6 Years**
Surgery vs. Chemoradiotherapy


\[ P = 0.551 \]
\[ HR: 1.1 \ (95\% \ CI: \ 0.7 - 1.8) \]
Stage III/IV Head and Neck CA: Randomized Trial
Soo et al, Br J Cancer 2005

• No difference in 3-year disease-free survival rates (50% vs. 40%)

• Surgical complication rate: 27%

• Organ preservation rate overall is 45%

• Larynx/hypopharynx had higher organ preservation of 68% versus 30%
## 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>
### CA. OF THE TONSILLAR REGION
#### LOCAL CONTROL BY XRT

<table>
<thead>
<tr>
<th>Institution</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. D. Anderson</td>
<td>100%</td>
<td>90%</td>
<td>72%</td>
<td>38%</td>
</tr>
<tr>
<td>U. of Florida</td>
<td>87%</td>
<td>79%</td>
<td>71%</td>
<td>44%</td>
</tr>
<tr>
<td>M G H</td>
<td>81%</td>
<td>79%</td>
<td>60%</td>
<td>23%</td>
</tr>
<tr>
<td>U. of Michigan</td>
<td>92%</td>
<td>77%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Washington U.</td>
<td>92%</td>
<td>72%</td>
<td>57%</td>
<td>30%</td>
</tr>
</tbody>
</table>
## CA. OF THE TONSILLAR REGION
### SURVIVAL AFTER XRT

<table>
<thead>
<tr>
<th>Institution</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. D. Anderson</td>
<td>47.5% (5 yr. Determinate)</td>
</tr>
<tr>
<td>MGH</td>
<td>44% (3 yr. NED)</td>
</tr>
<tr>
<td>Princess Margaret Hospital</td>
<td>38% (5 yr. Actuarial)</td>
</tr>
<tr>
<td></td>
<td>54% (5 yr. Determinate)</td>
</tr>
<tr>
<td>Washington University</td>
<td>40% (5 yr. Absolute)</td>
</tr>
<tr>
<td>T-stage</td>
<td>Local Control</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td>T1</td>
<td>83%</td>
</tr>
<tr>
<td>T2</td>
<td>81%</td>
</tr>
<tr>
<td>T3</td>
<td>74%</td>
</tr>
<tr>
<td>T4</td>
<td>60%</td>
</tr>
<tr>
<td>Stage</td>
<td>5 Year Cause-Specific Survival</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Stage I</td>
<td>100%</td>
</tr>
<tr>
<td>Stage II</td>
<td>86%</td>
</tr>
<tr>
<td>Stage III</td>
<td>82%</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>83%</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>22%</td>
</tr>
</tbody>
</table>
Patient Selection Criteria

- Tumor stage or extent
- Growth pattern
- Histology
- Age
- General medical condition
- Availability of expertise and equipment
BASE OF TONGUE IMPLANTS

Contraindications

• Bone invasion
• Persistent otalgia (nerve invasion)
• Extension below the arytenoids
• Anesthetic risk
• Patient intolerance
# BASE OF TONGUE IMPLANTS

*Dose to the Primary*

<table>
<thead>
<tr>
<th>External Beam</th>
<th>50.4 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>20 Gy</td>
</tr>
<tr>
<td>T2</td>
<td>25 Gy</td>
</tr>
<tr>
<td>T3</td>
<td>30 - 35 Gy</td>
</tr>
<tr>
<td>T4</td>
<td>30 - 40 Gy</td>
</tr>
</tbody>
</table>
### BASE OF TONGUE IMPLANTS

**Dose to the Nodes**

<table>
<thead>
<tr>
<th>Node</th>
<th>Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>15</td>
</tr>
<tr>
<td>N2</td>
<td>20 - 30</td>
</tr>
<tr>
<td>N3</td>
<td>30 - 40</td>
</tr>
</tbody>
</table>

- **External Beam**: 50.4 Gy
- **Implant**:
Trans-Tasman Radiation Oncology
Poulsen et al. Radiotherapy Oncology. 2001

- N = 350
- Randomized trial
- 14 centers in New Zealand
- III/IV SCC of OC, oropharynx, hypopharynx, larynx
- Conventional vs ACC
- 70 Gy at 2 Gy per day versus 59.4 Gy at 1.8 Gy BID
- Median F/U 53 months
<table>
<thead>
<tr>
<th>5-year Results</th>
<th>AFx</th>
<th>CFx</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC</td>
<td>52%</td>
<td>47%</td>
<td>0.3</td>
</tr>
<tr>
<td>DFS</td>
<td>35%</td>
<td>41%</td>
<td>0.23</td>
</tr>
<tr>
<td>DSS</td>
<td>46%</td>
<td>40%</td>
<td>0.398</td>
</tr>
<tr>
<td>Confluent Mucositis</td>
<td>94%</td>
<td>71%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
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)
# RTOG 90-03

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

### FRACTIONATION SCHEMES

<table>
<thead>
<tr>
<th></th>
<th>Fractionation Scheme</th>
<th>T.D.</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Standard Fractionation</td>
<td>70.0 Gy/35 fx/7 wks</td>
<td>2.0 Gy/fx Q.D.</td>
</tr>
<tr>
<td>2</td>
<td>Hyperfractionation</td>
<td>81.6 Gy/68 fx/7 wks</td>
<td>1.2 Gy/fx B.I.D.</td>
</tr>
<tr>
<td>3</td>
<td>Accelerated Fractionation (Split Course)</td>
<td>67.2 Gy/42 fx/6 wks</td>
<td>2 wk split at 38.4 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.6 Gy/fx B.I.D.</td>
</tr>
<tr>
<td>4</td>
<td>Accelerated Fractionation (Concomitant Boost)</td>
<td>72.0 Gy/42 fx/6 wks</td>
<td>1.8 Gy/fx/d to large field + 1.5 Gy/fx/d to boost field X 12 fxs. in last 2.5 wks</td>
</tr>
</tbody>
</table>
CB:
33% Late Grade 3-4 Toxicity
RTOG 99-14
Phase II Trial of Concomitant Boost RT + Cisplatin for Advanced H&N Ca.

Zubrod Status: 0 or 1

TREATMENT

72 Gy/42 Fx/6 wks + Cisplatin 100 mg/m² on weeks 1 and 4
N=77
IV=83%
92% received RT within 5% of the protocol guideline
89% had both cycles of CDDP
Acute G3: 66%; G4: 25
Grade 3 mucositis: 51%; G4: 3%
4% died of sepsis or pneumonia
Dysphagia, BM suppression, N/V
Late toxicity 51%
Median F/U 1 year
2 year OS 72% and DFS 54%
2 year LRC 65% and DMFS 84%
RTOG 0129
Phase III Trial of Concurrent RT and CT for Advanced Head and Neck Cancer

**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

Arm 2: Concurrent 70 Gy + Cisplatin 100 mg/m²
I.V. on days 1, 22, 43.
Gortec French Study
Denis et al, JCO, 2004

**Arm 1:**
- Stage III/IV
- Oropharynx
- 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><strong>Med. Surv.</strong></td>
<td>20 mo</td>
<td>13 mo</td>
</tr>
<tr>
<td><strong>5 yr LRC</strong></td>
<td>48%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td><strong>5 yr DFS</strong></td>
<td>27%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td><strong>5 yr OS</strong></td>
<td>22%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td></td>
<td>0.05</td>
</tr>
</tbody>
</table>
Intergroup Trial
Adelstein. JCO 2003

- Randomized 3 arm Trial; n=295
- RT alone vs the Cleveland Clinic vs CDDP
- Invasive SCC of OC, ORO, Hypo, Layrnx
- Dose of RT 70 Gy
- Median F/U 41 months
- 3 year OS 23% vs. 27% vs 37%
- MS 12.6 mo vs. 13.8 mo vs. 19.1 mo
- Grade 3 Toxicity 52% vs. 77% vs. 89%
There is also 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 (3 yr.) 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</td>
<td>31% vs 51%</td>
</tr>
<tr>
<td>Staar</td>
<td>2001</td>
<td>178*</td>
<td>CpF</td>
<td>69.9</td>
<td>57% vs 68%</td>
</tr>
<tr>
<td>Bensadoun</td>
<td>2006</td>
<td>123*</td>
<td>PF</td>
<td>80.4</td>
<td>22% vs 41%</td>
</tr>
</tbody>
</table>

* planned subset analysis
Meta-Analysis: Chemo

(Pignon et al. Lancet, 2000)

• All randomized Head and Neck trials between 1965 and 1993
• CA of the oropharynx, oral cavity, larynx, or hypopharynx
• Total of 63 trials
• There was an absolute survival benefit of 4% at 2 and 5 years in favor of chemotherapy
• No significant effect of chemotherapy in adjuvant and neoadjuvant trials.
• There was a significant overall benefit of chemotherapy in concomitant trials and the absolute benefit was 8% at 5 years
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>Study</th>
<th>Year</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></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%</td>
<td>6%</td>
</tr>
<tr>
<td>Ang (RTOG)</td>
<td>2005</td>
<td>76</td>
<td>DDP</td>
<td>AF</td>
<td>84%</td>
<td>29%</td>
</tr>
<tr>
<td>Tsao (MDA)</td>
<td>2006</td>
<td>52</td>
<td>DDP/Doc</td>
<td>AF</td>
<td>79%</td>
<td>25%</td>
</tr>
<tr>
<td>Bensadoun(GORTEC)</td>
<td>2006</td>
<td>81</td>
<td>5FU/DDP</td>
<td>AF</td>
<td>100%</td>
<td>4%</td>
</tr>
<tr>
<td>Pfister (MSK)</td>
<td>2006</td>
<td>21</td>
<td>DDP/Cetux</td>
<td>AF</td>
<td>81%</td>
<td>0</td>
</tr>
</tbody>
</table>
German Trial
(Staar et al. IJROBP, 2001)

- Randomized, N=240
- III/IV SCC unresectable oropharyngeal and hypopharyngeal carcinoma; 96% IV
- 5FU(600)/Carbo(70) + concomitant boost RT to 69.9 Gy vs RT alone
  Median F/U of 22.3 months
- 1 yr LC 60% vs 40% (oropharyngeal ca)
- Greater Grade 3/4 mucositis 68% vs 52%; greater vomiting 8% vs 1.6%
- Late toxicity: 30% of the long-term survivors >/= 2 years remain dependent on a feeding tube
- 51% vs 25% with swallowing problems and continuous use of a feeding tube in the RCT arm than RT arm
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)*

  - Oral cavity: 14%
  - Oropharynx: 30%
  - Hypopharynx: 80%  \( P < .001 \)
  - Larynx: 67%

• Daggett et al demonstrated at least a minor degree of laryngeal penetration in 64% of normals over age 50.  
  *(Dysphagia 2006)*
Chemoradiotherapy: Late FT Dependence

Surgery

1. Obvious impact of primary site surgery

2. Machtay et al. (RTOG) reported that advanced age, higher T, larynx/hypopharynx primary site and a neck dissection were independently predictive of severe late swallowing dysfunction and/or feeding tube dependence.

(Proc ASCO 2007)
An example of patient with late effect

- 62 year old T3N2b SCC of the tonsil
- Concurrent CDDP chemotherapy with radiation to 72 Gy, COT 11/2003. Patient also underwent ND with no residual disease.
- Last follow-up 3/2010: NED by PE and imaging
- However, patient had severe secondary late effects: PEG-dependent, trach-dependent, severe pharyngeal stricture, respiratory obstruction, altered phonation.
An example of patient with late effect

- Patient was treated with delayed concomitant boost technique.
- Initial stage T3N2 disease
- Opposed lateral technique
- Neck dissection
Historical RT Dose Escalation

• In setting of chemotherapy: 2 randomized trials examined BID radiation versus QD radiation and found no difference in outcome

• GORTEC

• RTOG 0129
RTOG 0022
Phase I/II Study of Conformal and IMRT for Oropharyngeal Study

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
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 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

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

<table>
<thead>
<tr>
<th></th>
<th>OS: 3 years</th>
<th>DMFS: 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>84.9%</td>
<td>87.1%</td>
</tr>
<tr>
<td>5 years</td>
<td>78.7%</td>
<td>85.2%</td>
</tr>
</tbody>
</table>

#### Univariate (Logrank)

<table>
<thead>
<tr>
<th></th>
<th>T1/2 vs T3/4</th>
<th>N0/1 vs N2/3</th>
</tr>
</thead>
<tbody>
<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>

#### Multivariate (Cox)

<table>
<thead>
<tr>
<th></th>
<th>T1/2 vs T3/4</th>
<th>N0/1 vs N2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>p &lt; 0.0001</td>
<td>p = 0.009</td>
</tr>
<tr>
<td>LC</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RC</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DM</td>
<td>p = 0.01</td>
<td>p = 0.02</td>
</tr>
</tbody>
</table>

NS: Site, Age, Treatment Modality, Histology
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
  - 3mo: 27%
  - 6mo: 23%
  - 12mo: 13%
  - 24mo: 7%

• Dysphagia ≥ grade 3 in 3% of the patients

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

• Osteoradionecrosis occurred in 7 (2%) patients
IMRT for oropharynx: available data

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># of Pt</th>
<th>Median FU (mo)</th>
<th>Definitive (%)</th>
<th>Stage III-IV (%)</th>
<th>Chemo (%)</th>
<th>Local and/or Regional Control (years)</th>
<th>OS % (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chao</td>
<td>2004</td>
<td>74</td>
<td>33</td>
<td>42</td>
<td>93</td>
<td>27</td>
<td>LRC: 87 (4)</td>
<td>87 (4)</td>
</tr>
<tr>
<td>de Arruda</td>
<td>2006</td>
<td>50</td>
<td>18</td>
<td>96</td>
<td>92</td>
<td>86</td>
<td>LC: 98 RC: 88 (2)</td>
<td>98 (2)</td>
</tr>
<tr>
<td>Garden</td>
<td>2007</td>
<td>51</td>
<td>45</td>
<td>100</td>
<td>84</td>
<td>10</td>
<td>LRC: 93 (2)</td>
<td>94 (2)</td>
</tr>
<tr>
<td>Lawson</td>
<td>2008</td>
<td>34</td>
<td>20</td>
<td>100</td>
<td>94</td>
<td>100</td>
<td>LC: 92 RC: 97 (2)</td>
<td>90 (2)</td>
</tr>
<tr>
<td>Sanguineti</td>
<td>2008</td>
<td>50</td>
<td>33</td>
<td>100</td>
<td>88</td>
<td>0</td>
<td>LC: 94 RC: 85 (3)</td>
<td>NA</td>
</tr>
<tr>
<td>Huang</td>
<td>2008</td>
<td>71</td>
<td>33</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>LC: 94 RC: 94 (3)</td>
<td>83 (3)</td>
</tr>
<tr>
<td>Daly</td>
<td>2009</td>
<td>107</td>
<td>27</td>
<td>79</td>
<td>96</td>
<td>87</td>
<td>LRC: 92 (3)</td>
<td>83 (3)</td>
</tr>
<tr>
<td>Eisbruch*</td>
<td>2009</td>
<td>69</td>
<td>32</td>
<td>100</td>
<td>0*</td>
<td>0*</td>
<td>LRF: 9 (2)</td>
<td>NA</td>
</tr>
<tr>
<td>MSKCC</td>
<td>2010</td>
<td>442</td>
<td>35</td>
<td>93</td>
<td>95</td>
<td>91</td>
<td>LF: 5 RF: 6 (3)</td>
<td>85 (3)</td>
</tr>
</tbody>
</table>

Long-term PEG dependence 3%
RL/LL H&N + LAN: Dose Distribution

Levels in cGy:
- 7450.0
- 7000.0
- 6000.0
- 5400.0
- 4800.0
- 3000.0
- 1000.0
Mean Doses

- Right Parotid 19.80 Gy
- Left Parotid 24.94 Gy
- Oral Cavity 33.6 Gy
Levels in cGy.

- 7000.0
- 5940.0
- 4500.0
- 2600.0
DYSPHAGIA AND ASPIRATION AFTER CHEMORADIOThERAPY FOR HEAD-AND-NECK CANCER: WHICH ANATOMIC STRUCTURES ARE AFFECTED AND CAN THEY BE SPARED BY IMRT?

Avraham Eisbruch, M.D.,* Marco Schwartz, M.Sc.,† Coen Rasch, M.D.,†
Karen Vineberg, B.Sc.,* Eugene Damen, Ph.D.,† Corina J. Van As, Ph.D.,‡§
Robin Marsh, B.Sc.,* Frank A. Pameijer, M.D.,¶ and Alfons J. M. Balm, M.D.‡

*Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; Departments of †Radiation Oncology, ‡Otolaryngology-Head and Neck Surgery, and ¶Radiology, and §Section of Speech Therapy, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
IMRT vs Conventional RT

• 94 patients randomized from 6 UK centers

• Analysis on an intention to treat basis

• Primary Outcome
  – Incidence of subjective component of >G2 xerostomia 1 year after RT completed

• Secondary Outcomes
  – Survival, local control, QOL, saliva flow, acute and late radiation toxicity

Nutting et al. 2010
LENT SOM Subjective Xerostomia rates

No difference in locoregional control between 2 arms.
Phase III trial (GORTEC 2004-01)

Randomize

Stage II to IV of sq cell ca
Oral Cavity
Oropharynx

Conventional RT
70 Gy + CDDP

IMRT
75 Gy + CDDP

Endpoints: Xerostomia, Local Control
Conclusions

• RT preferred over Surgery for oropharyngeal carcinoma

• If RT alone: T1 (standard fractionation); T2-4 (altered fractionation-->RTOG 9003)

• If chemo is considered: use QD radiation with concurrent chemotherapy (CDDP)

• IMRT to decrease rate of xerostomia
Conclusions

• Excellent LRC is achieved with IMRT +/- chemotherapy

• Late PEG dependence is 2.5-3%

• What are methods we can use to further improve the therapeutic ratio?
Conclusions

• Careful selection of who needs prophylactic PEG placement.

• Efforts focus on using dysphagia-sparing IMRT

• All patients should be treated with once a day RT
Larynx Cancer
T1-2NO
Glottic Cancer
# T1 Ca of the Glottis

## Radiotherapy Dose Fractionation

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fraction Size</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>2 Gy/Fx/d</td>
<td>66 Gy</td>
</tr>
<tr>
<td></td>
<td>2.25 Gy/Fx/d</td>
<td>63 Gy</td>
</tr>
</tbody>
</table>
# T1 Carcinoma of the Glottis

Local Control with RT and Surgical Salvage

<table>
<thead>
<tr>
<th>1st Author</th>
<th>No. of Initial Local Salvage*</th>
<th>Surgical Local Control(%) (%)</th>
<th>Ultimate Preserv.</th>
<th>Larynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harwood</td>
<td>333</td>
<td>86</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Fletcher</td>
<td>332</td>
<td>89</td>
<td>31/36 (86%)</td>
<td>98</td>
</tr>
<tr>
<td>Mittal</td>
<td>177</td>
<td>83</td>
<td>23/30 (77%)</td>
<td>96</td>
</tr>
<tr>
<td>Amornmnarn</td>
<td>86</td>
<td>92</td>
<td>6/7 (86%)</td>
<td>99</td>
</tr>
<tr>
<td>Mendenhall</td>
<td>184</td>
<td>93</td>
<td>7/12 (58%)</td>
<td>97</td>
</tr>
<tr>
<td>Wang</td>
<td>723</td>
<td>90</td>
<td>46/59 (78%)</td>
<td>97</td>
</tr>
<tr>
<td>Johansen</td>
<td>358</td>
<td>83</td>
<td>40/55 (73%)</td>
<td>94</td>
</tr>
<tr>
<td>Le</td>
<td>315</td>
<td>83</td>
<td>42/52 (81%)</td>
<td>97</td>
</tr>
</tbody>
</table>

*No. of patients salvaged/No. of patients underwent salvage treatment.
LOCAL CONTROL OF T1 LESIONS
BY OVERALL TIME

Local Control (%)

Tumor Repopulation

Time from Treatment (Yr.)

≤ 43 D
> 50 D
44-50 D

p = 0.04
LOCAL CONTROL OF T1 LESIONS
BY FRACTION SIZE

Local Control (%)

Time from Treatment (Yr.)

≥ 2.25 Gy
2.0-2.24 Gy
1.8-1.99 Gy
<1.8 Gy
Radiotherapy Dose Fractionation

T2 Ca of the Glottis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fraction Size</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>2 Gy/Fx/d</td>
<td>70 Gy</td>
</tr>
<tr>
<td></td>
<td>2.25 Gy/Fx/d</td>
<td>65.25 Gy</td>
</tr>
</tbody>
</table>
### T2 Carcinoma of the Glottis
#### Local Control with RT and Surgical Salvage

<table>
<thead>
<tr>
<th>1st Author</th>
<th>No. of Pts.</th>
<th>Initial Local Control (%)</th>
<th>Surgical Salvage* (%)</th>
<th>Ultimate Local (%)</th>
<th>Larynx Preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harwood</td>
<td>244</td>
<td>69</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Fletcher</td>
<td>175</td>
<td>74</td>
<td>36/41 (88%)</td>
<td>94</td>
<td>--</td>
</tr>
<tr>
<td>Amornmarn</td>
<td>34</td>
<td>88</td>
<td>2/4 (50%)</td>
<td>94</td>
<td>88</td>
</tr>
<tr>
<td>Karim</td>
<td>156</td>
<td>81</td>
<td>20/25 (80%)</td>
<td>95</td>
<td>--</td>
</tr>
<tr>
<td>Mendenhall</td>
<td>120</td>
<td>75</td>
<td>20/26 (77%)</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Wang</td>
<td>173</td>
<td>69</td>
<td>28/43 (65%)</td>
<td>86</td>
<td>71</td>
</tr>
<tr>
<td>Howell-Burke</td>
<td>114</td>
<td>68</td>
<td>25/34 (74%)</td>
<td>94</td>
<td>74</td>
</tr>
<tr>
<td>Le</td>
<td>83</td>
<td>67</td>
<td>20/27 (74%)</td>
<td>92</td>
<td>72</td>
</tr>
</tbody>
</table>

*No. of patients salvaged/No. of patients underwent salvage treatment.
LOCAL CONTROL OF T2 LESIONS
BY OVERALL TIME

<table>
<thead>
<tr>
<th>Time from Treatment (Yr.)</th>
<th>Local Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>≤ 43 D</td>
<td></td>
</tr>
<tr>
<td>44-50 D</td>
<td></td>
</tr>
<tr>
<td>&gt; 50 D</td>
<td></td>
</tr>
</tbody>
</table>

- 100% at ≤ 43 D
- 70% at 44-50 D
- 66% at > 50 D
LOCAL CONTROL OF T2 LESIONS
BY FRACTION SIZE

- $\geq 2.25$ Gy
- 2.0-2.24 Gy
- 1.80-1.99 Gy
- $< 1.80$ Gy

Time from Treatment (Yr.)

Local Control (%)
LOCAL CONTROL FOR T2 LESIONS BY SUBGLOTTIC EXTENSION

SGE: Subglottic Extension

Local Control (%)

Time from Treatment (Yr.)

Without SGE

With SGE

77%

58%

p = 0.02
LOCAL CONTROL FOR T2 LESIONS BY CORD MOBILITY

<table>
<thead>
<tr>
<th>Local Control (%)</th>
<th>Time from Treatment (Yr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>79%</td>
</tr>
<tr>
<td>Impaired</td>
<td>45%</td>
</tr>
</tbody>
</table>

p = 0.008
Randomized trial on RT fraction size and overall treatment time for T1 glottic cancer

Yamazaki et al. IJROBP 2006

1. Conventional Fractionation:
   2 Gy/fx/d to 66 Gy over 33 days

2. Hypofractionation:
   2.25 Gy/fx/d to 63 Gy over 28 days
Randomized trial on RT fraction size and overall treatment time for T1 glottic cancer

- 5-year local control was 77% vs. 92% (p=0.004) in favor of 2.25 Gy arm

- 5-year cause-specific rates, acute and chronic effects are similar

- Use of 2.25 Gy with a shorter overall treatment time showed superior local control compared with standard fractionation.

Yamazaki et al.  IJROBP 2006
RTOG 95-12

HYPERFRACTIONATION FOR
T2 VOCAL CORD CA. (Closed)

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 fx/6.5 wks

No Difference between the 2 arms
Meta-analysis of Impaired VC Mobility as a Prognostic Factor in T2 Glottic CA

- Identified 35 studies of which 21 met criteria.
- All studies retrospective
- 5-year LC for T2b versus T2a was significant 76% vs 64% (p<0.001)

McCoul et al.  Head Neck 2010
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 → 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
Phase III Trial to Preserve the Larynx

Chemotherapy

Arm 1: Cisplatin 100 mg/m² + 5-FU 1 gm/m²/hr infusion over 120 hours. 3 cycles, three weeks apart.

Arm 2: Cisplatin 100 mg/m² on days 1, 22, and 43 of RT.

Radiation Therapy

Arms 1, 2, and 3: 70 Gy/35 fx's/7 weeks. Treatment for Arm 1 will begin 3 weeks after the start of the third chemo cycle or 2-3 weeks after surgery as applicable.
## RTOG 91-11

<table>
<thead>
<tr>
<th></th>
<th>VA</th>
<th>CCRT</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year Laryng-FS</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>5-yr. D-F Survival</td>
<td>38%</td>
<td>36%</td>
<td>27%</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

Update 2006 abstract shows induction arm has better preservation rates than RT alone arm
T4a: Thyroid Cartilage Invasion

What to consider when patients refuse upfront surgery?
University of Chicago
Vokes et al. JCO, 2003

Stage IV of squamous cell ca

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
T3-4 Glottic/Supraglottic

Node – or +

Historical Overview:

RT alone data
### Stage T3 Carcinoma of the Glottis

#### Results of Radiotherapy and Surgical Salvage

<table>
<thead>
<tr>
<th>1st Author</th>
<th>No. of Pts.</th>
<th>% Local Control (with salvage)</th>
<th>5-yr. Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart</td>
<td>67</td>
<td>57 (69)</td>
<td>57 (determinate)</td>
</tr>
<tr>
<td>Harwood</td>
<td>112</td>
<td>51 (77)</td>
<td>74 (determinate)</td>
</tr>
<tr>
<td>Van den Bogaert</td>
<td>33</td>
<td>23 (37)</td>
<td>22 (actuarial)</td>
</tr>
<tr>
<td>Skolyszewski</td>
<td>91</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Mendenhall</td>
<td>75</td>
<td>63 (86)</td>
<td>53 (absolute)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>67 (determinate)</td>
</tr>
<tr>
<td>Wang</td>
<td>65</td>
<td>32 (57)</td>
<td>--</td>
</tr>
</tbody>
</table>
Stage T4 Carcinoma of the Glottis

Results of Radiotherapy

<table>
<thead>
<tr>
<th>1st Author</th>
<th>No. of Pts.</th>
<th>Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parsons</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Karim</td>
<td>38</td>
<td>24</td>
</tr>
<tr>
<td>Harwood</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>54 (63%)</td>
</tr>
</tbody>
</table>
Carcinoma of the Supraglottis
% Local Control with Radiotherapy (and Surgical Salvage)

<table>
<thead>
<tr>
<th>1st Author</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harwood</td>
<td>56</td>
<td>41-52</td>
</tr>
<tr>
<td>Wall</td>
<td>70</td>
<td>46</td>
</tr>
<tr>
<td>Mendenhall</td>
<td>61 (83)</td>
<td>33 (67)</td>
</tr>
<tr>
<td>Wang :</td>
<td>Q.D.</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>B.I.D.</td>
<td>71</td>
</tr>
<tr>
<td>Parsons</td>
<td>Q.D.</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>B.I.D.</td>
<td>67</td>
</tr>
</tbody>
</table>
T3-T4, N+ Glottic Surpагlottic
Combined Modality Treatment
VA LARYNGEAL CA. STUDY

Induction Chemotherapy: Cisplatin and 5-FU

randomize

Surgery  →  Radiation Therapy

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

< PR  →  Surgery  →  Radiation Therapy

PR  →  Surgery

CR
### VAH Laryngeal Carcinoma Study

#### Larynx Preservation 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>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 $\rightarrow$ RT</th>
<th>CT $\rightarrow$ 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
## VAH Laryngeal Carcinoma Study

### Salvage Laryngectomy

<table>
<thead>
<tr>
<th>Stage</th>
<th>29%</th>
<th>44%</th>
<th>&lt; T4</th>
<th>29%</th>
<th>T4</th>
<th>56%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; T4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$p = 0.048$  

$p = 0.001$
GETTEC Trial - T3 Larynx Ca.
(J.M. Richard et al, 1998)

Induction Chemotherapy (3 Cycles)

- Surgery
- Radiotherapy

≥ 80% → RT

< 80% → Surgery → RT

Induction Chemotherapy: Cisplatin and 5-FU
# 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*% P = 0.02</td>
</tr>
<tr>
<td>5-yr. Survival</td>
<td>68*%</td>
<td>43*% P = 0.006</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

**STRATIFY**

- 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
Phase III Trial to Preserve the Larynx

Chemotherapy

Arm 1: Cisplatin 100 mg/m² + 5-FU 1 gm/m²/hr infusion over 120 hours. 3 cycles, three weeks apart.

Arm 2: Cisplatin 100 mg/m² on days 1, 22, and 43 of RT.

Radiation Therapy

Arms 1, 2 and 3: 70 Gy/35 fx's/7 weeks.

Treatment for Arm 1 will begin 3 weeks after the start of the third chemo cycle or 2-3 weeks after surgery as applicable.
## 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>
</tr>
</thead>
<tbody>
<tr>
<td>CT→RT</td>
<td>15 %</td>
</tr>
<tr>
<td>CT/ RT</td>
<td>12 %</td>
</tr>
<tr>
<td>RT</td>
<td>22 %</td>
</tr>
</tbody>
</table>

*P=0.03 CT/RT vs RT
**Squamous Cell Head and Neck Cancer**

**RTOG 91 - 11**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Preserved LFS (5 yr.)</th>
<th>Loco-reg. Larynx (5 yr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (5 yr.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction CT</td>
<td>173</td>
<td>45%</td>
<td>71% 55%</td>
</tr>
<tr>
<td>RT / DDP</td>
<td>171</td>
<td>47%</td>
<td>84% 69%</td>
</tr>
<tr>
<td>RT</td>
<td>171</td>
<td>34%</td>
<td>66% 51%</td>
</tr>
</tbody>
</table>

Survival equivalent for all three arms
Distant metastases decreased in chemotherapy arms
(p=.06)

Forastiere et al. Proc. ASCO 2006
T4a N+ Glottic Surpaglottic Treatment?
Functional Organ Preservation with Definitive Chemoradiotherapy for T4 Laryngeal SCC

Knab et al. (U Chicago) Annals Oncol 2008

- 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%
For T4a tumors:

BID fractionation?

Induction chemotherapy?
What is the best RT Fractionation in setting of chemotherapy?
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
GORTEC 99-02 trial

Stage III or IV of sq cell ca

Randomize

QD RT: 70 Gy / 7 weeks
Carbo/5FU x 3 cycles

Acc RT: 70 Gy / 6 weeks
Carbo/5FU x 2 cycles

Acc RT : 64.8 Gy / 3.5 weeks

No difference in outcome between the two chemotherapy arms

Both chemo arms were superior to accRT alone

ASTRO 2008
Bourhis et al.
Chemoradiotherapy

- In the setting of chemotherapy, conventional fractionation offers equal results with less toxicity than altered fractionation.

- If treating T4a disease and patient not a candidate for surgery and refuses induction chemotherapy, recommend CCRT using QD fractionation.
Hypopharynx
EORTC 24891 LARYNX PRESERVATION FOR HYPOPHARYNGEAL CA.

(J.L. Lefebvre et al, 1996)

Surgery $\rightarrow$ Radiation Therapy

Complete Responders* $\rightarrow$ Radiation Therapy

Induction Chemotherapy (3 Cycles)

Partial or Non-Responders $\rightarrow$ Surgery $\rightarrow$ 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>
Hypopharynx

Levels in cGy:
- Red: 7400.0
- Purple: 7000.0
- Green: 5940.0
- Blue: 2600.0
Concurrent Chemoradiotherapy

70 Gy + 3 cycles of CDDP

Be aware of stricture formation!