Head and Neck Reirradiation: Perils and Practice

David J. Sher, MD, MPH
Department of Radiation Oncology
Dana-Farber Cancer Institute/
Brigham and Women’s Hospital
Conflicts of Interest

• No conflicts of interest
Introduction

• Radiotherapy (RT) and chemoradiotherapy (CRT) have become established as standard treatment options in head and neck cancer

• Locoregional failure rates are still high
## Locoregional Failure Rates

<table>
<thead>
<tr>
<th>Trial</th>
<th>Site</th>
<th>Treatment</th>
<th>LRR Failure</th>
</tr>
</thead>
</table>
| RTOG 90-03    | All except NP   | Standard, Accelerated, Hyperfrac | 59.1% (5 y)
|               |                 |                            | 51.2% (5 y)          |
|               |                 |                            | 51.7% (5 y)          |
| RTOG 91-11    | Larynx          | PF → RT CRT                | 36% (2 y)            |
|               |                 |                            | 20% (2 y)            |
| RTOG 01-29    | All except NP   | CRT, A-CRT                 | 28%                  |
|               |                 |                            | 31%                  |
| TAX 324       | All except NP   | PF → CRT, TPF → CRT        | 38%                  |
|               |                 |                            | 30%                  |
| GORTEC 94-01  | Oropharynx      | RT CRT                     | 75% (5 y)            |
|               |                 |                            | 52% (5 y)            |
Fundamental Problem

TUMOR

TREATMENT
Risks of Reirradiation

- Acute and chronic dysphagia
- Osteoradionecrosis/soft tissue necrosis
- Trismus/fibrosis
- Carotid rupture
- 6-7 weeks of treatment plus 2-3 months of recovery
Not All Recurrences Are Equal

- Chemoradio-resistance
  - True recurrent (i.e. resistant) disease vs. second primary
  - In-field failure (i.e. resistant) vs. marginal/out-of-field miss

- Surgical resectability

- Performance status
Early Experience

- Institut Gustave-Roussy (De Crevoisier et al, 1993)
  - 169 patients with unresectable disease in irradiated field
  - 3 different RT regimens
    - Daily RT (2 Gy/fx) alone
    - Chicago protocol (4-7 weekly cycles)
    - BID RT with chemotherapy
Institut Gustave-Roussy

• Results
  – Median survival: 10 months
  – 2-year overall survival: 21%
  – 5-year overall survival: 9%
  – Patterns-of-failure
    • Local only: 53%
    • Nodal only: 20%
    • Metastatic only: 7%
    • Local and nodal: 8%
    • Locoregional and metastatic: 12%
Toxicity

• Acute
  – Grade 3 mucositis: 32%
  – Grade 4 mucositis: 14%

• Late
  – Grade 2/3 cervical fibrosis: 41%
  – Mucosal necrosis: 21%
  – Mild-severe trismus: 30%
  – Osteonecrosis: 8%
  – 5 deaths due to carotid hemorrhage
University of Chicago Data

• Salama et al, 2006
  – 115 reirradiated patients treated on serial phase I-II protocols between 1986 – 2001

  – Treatment paradigm
    • 5 days of chemoRT, 9 day break x 4-7 cycles
    • Chemotherapy: 5-FU, HU +/- 3rd agent
    • RT: daily (1.8 – 2 Gy/fx) or BID (1.5 Gy/fx)
Results

• Overall survival
  – Median 11 months
  – 3-year: 22%

• Patterns of failure
  – 42% any locoregional
  – 29% any metastatic
Toxicity

• 19 patients (17%) died of treatment-related toxicity
  – 9 during treatment
    • 4 sepsis
    • 3 respiratory arrest
    • 1 carotid blowout
    • 1 pulmonary embolism
  – 10 patients after treatment
    • 4 carotid blowout
    • 1 massive epistaxis
    • 1 soft tissue necrosis
Toxicity

- 13 patients (11%) required surgery for osteoradionecrosis
- 57% of patients dependent on gastrostomy
- 1 myelopathy
Prognostic Factors

• Favorable for OS, PFS, and LRC
  – Surgery
  – Increasing radiation dose
  – Triple-agent chemotherapy

• Favorable for OS and PFS
  – PS 0-1

• Favorable for DM
  – Triple-agent chemotherapy
Recent Series

- University of Michigan (Popovtzer et al, 2009)
  - 66 patients treated with 3D-CRT or IMRT
    - 54% daily, 46% BID
  - Median re-RT dose: 68 Gy
    - PTV margin: 5 mm on GTV
  - 71% received concurrent chemotherapy
Results

• Overall survival
  – 2-year: 40%
  – 5-year: 22%

• Locoregional progression-free survival
  – 2-year actuarial: 27%
  – 5-year actuarial: 19%
  – Total: 71% locoregional failure
Failure Patterns

- 46 patients (71%) had locoregional failure
  - 96% in-field (within 95% isodose line)
  - 4% out-of-field

- 18 patients (27%) had distant metastasis
  - 15 (83%) also had locoregional failure
Toxicity

- Late grade 3-5 complications: 19 patients (29%)
  - 12 patients (18%) long-term gastrostomy
  - 2 patients with stricture
  - 2 patients chrondronecrosis
  - 1 patient temporal lobe necrosis
  - 3 patients tracheostomy dependent
  - 2 carotid blowouts (neither lethal)
Moffitt Experience

- Tanvetyanon et al, 2009
  - 103 patients treated with reirradiation
  - Median reirradiation dose: 60 Gy
  - 46 patients underwent salvage surgery
  - 70% received concurrent chemotherapy

- Overall survival: median 19.3 months
  - 1-year: 64.8%
  - 2-year: 40.0%
Toxicity

• Acute: 43.7% developed at least 1 ≥ g3 toxicity (GI 40%)

• Late: 47.5% developed at least 1 ≥ g3 toxicity
Prognostic Factors

• Charlson comorbidity index
  – No comorbity: median survival 22.6 mo
  – $\geq$ 1 comorbidity: median survival 12.8 mo

• Organ dysfunction
  – Absent: median survival 30.7 mo
  – Present: median survival 11.3 mo

• Comorbidity and organ dysfunction
  – None: median survival 59.6 months
  – Both: median survival 16.5 months
Multivariable Analysis

- Favorable prognostic variables
  - Increased time since prior RT
  - No organ dysfunction
  - No comorbidity
  - Smaller T stage
  - Smaller tumor bulk after surgery
  - Reirradiation dose
Nomogram
Phase III Trial of Reirradiation

- **Institution:** GETTC and GORTEC
- **Eligibility**
  - Prior RT (at least 45 Gy)
  - Deep infiltration of tumor
  - KPS > 70
  - No severe sequelae after first RT
  - R0 or R1 salvage surgery without wound-healing complications
- **Treatment**
  - Observation versus chemoradiotherapy
Treatment Regimen

- 5 days in a row: 2 Gy RT per day with concurrent hydroxyurea and continuous infusion 5-FU
- 9 day break
- Total of 6 cycles
- Treatment summary:
  - 11 weeks
  - 60 Gy
Results

- 130 patients randomized between 1999 and 2005
### Table 3. Late Toxicity at 1 and 2 Years After Random Assignment

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>RT Arm (n = 42; 1 missing)</th>
<th>WS Arm (n = 33; 3 missing)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Toxicity at 12 and 12.5 months after random assignment, RTOG grade ≥ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Skin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subcutaneous tissues</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Larynx</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Trismus</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Pharyngeal stenosis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td><strong>11</strong></td>
<td><strong>26</strong></td>
</tr>
<tr>
<td>Toxicity at 24 months after random assignment, RTOG grade ≥ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Subcutaneous tissues</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Larynx</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Trismus</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Pharyngeal stenosis</td>
<td>1</td>
<td>5.5</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td><strong>7</strong></td>
<td><strong>39</strong></td>
</tr>
</tbody>
</table>

Abbreviations: RT, full-dose reirradiation combined with chemotherapy; WS, “wait and see” approach; RTOG, Radiation Therapy Oncology Group.

*At 24 months after random assignment, n = 16 (three missing) for RT arm and n = 19 for WS arm.
Conclusions

- In patients who undergo salvage surgery, repeat CRT have substantially reduced locoregional failure.
- Does not translate into survival benefit.
- Associated with significant toxicity.
  BUT morbidity of recurrence not considered.
DFCI Experience

• Retrospective study of patients treated at Dana-Farber Cancer Institute with IMRT-based reirradiation

• Eligibility
  – History of definitive or adjuvant RT for squamous cell carcinoma of the head and neck
  – Diagnosis of recurrent or second primary squamous cell carcinoma
  – Treated at DFCI with IMRT with radical intent between August 2004 and December 2008
    • Analyzed October 2009

• 35 patients met criteria
# Recurrence Characteristics

<table>
<thead>
<tr>
<th>Age at recurrence (median, IQR)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>57 years (51-63 years)</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG Performance Status</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18 (51%)</td>
</tr>
<tr>
<td>1</td>
<td>16 (46%)</td>
</tr>
<tr>
<td>2</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior disease-free interval (median, IQR)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 years (1.2-9.7 years)</td>
<td>13 (37%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharynx</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Larynx/hypopharynx</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>Neck failure only</td>
<td>9 (26%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>III</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>IV</td>
<td>22 (63%)</td>
</tr>
</tbody>
</table>
# Treatment Characteristics

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery plus CRT</td>
<td>17 (49%)</td>
</tr>
<tr>
<td>Definitive CRT</td>
<td>8 (23%)</td>
</tr>
<tr>
<td>Induction chemotherapy plus CRT</td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Concurrent chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Platinum alone</td>
<td>10 (29%)</td>
</tr>
<tr>
<td>Platinum/taxane</td>
<td>10 (29%)</td>
</tr>
<tr>
<td>Platinum/cetuximab</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Platinum/taxane/cetuximab</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Cetuximab alone</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Radiation PTV dose (median, IQR)</td>
<td>60 Gy (60-64 Gy)</td>
</tr>
<tr>
<td>- No prophylactic nodal RT</td>
<td></td>
</tr>
</tbody>
</table>
Survival

- Median F/U: 2.3 years (IQR 1.6-3.6 years)
  - Minimum F/U 9 months
- **Overall survival**
  - 1-year: 59%
  - 2-year: 48%
  - Median: 1.9 years
- **Locoregional progression-free survival**
  - 1-year: 67%
  - 2-year: 67%
- **Distant metastasis-free survival**
  - 1-year: 85%
  - 2-year: 73%
Patterns-of-Failure

• 14 total recurrences

• 7 (50%) first developed locoregional recurrence

• 4 (29%) first developed distant metastasis

• 3 (21%) developed simultaneous locoregional and distant failure
Local Recurrence Patterns

- 11 patients developed locoregional recurrence
  - 8 (73%) in-field
  - 2 (18%) out-of-field
  - 1 (9%) both in- and out-of-field
  - All 3 out-of-field failures occurred in nodal basins

- Out of entire population
  - 26% developed in-field recurrence
Acute Toxicity

• 91% developed at least one grade 3 or 4 toxicity
  – 15 (43%) grade 3 or 4 mucositis
  – 11 (32%) grade 3 or 4 dermatitis
  – 1 emergent tracheostomy

• 5 (14%) developed acute grade 4 toxicity

• 14 patients (40%) developed more than 1 grade 3 or 4 toxicity

• 31 (91%) patients had gastrostomy
Late Toxicity

- 16 patients (46%) developed grade 3 or higher late toxicity
  - Necrosis: 4 (12%)
  - Respiratory: 5 (15%)
  - Skin: 4 (12%)
  - Trismus: 4 (11%)

- 9 patients (26%) developed more than one grade 3 or 4 late toxicity
Treatment-Related Mortality

• Four deaths in patients with no evidence of disease

• 1 clearly related to treatment
  – 1 fatal oropharyngeal hemorrhage (10 months)

• 3 possibly related to treatment
  – 2 aspiration events (8 months and 2.6 years)
  – 1 persistent infection leading to debilitation and hospice (6 months)
Gastrostomy Tube Outcomes

- 55% (17/31) of patients had PEG removed at median 3 months after RT (IQR, 1.7-12 months)
- Of all patients surviving 1 year, 78% (16/18) were free from PEG-dependence
- Of all patients surviving 2 years, 89% (8/9) were free from PEG-dependence
Treatment Paradigm

• Question #1
  – Can this be surgically resected with a functionally-acceptable outcome?

• Question #2
  – Is this resistant disease?
  – Evidence
    • Time since completion of RT
    • In-field vs. marginal or out-of-field miss
Treatment Paradigm

• Question #3
  – What are the complications of reirradiation?
    • Swallowing
    • Hemorrhage
    • Myelitis
    • Osteonecrosis
Balance

Treatment-related toxicity

Tumor-related morbidity
Clinical Example

• 68 yo woman who developed 2 cm soft palate mass in October 2008

• Past Medical History
  – HTN, T2DM, COPD, h/o ARDS, prosthetic aortic valve

• Treatment
  – 68.4 Gy with weekly carboplatin
Follow-Up

- Restaging PET-CT in May 2008 disclosed enlarged JD node

- Clinical exam also showed right soft palate lesion

- Palate biopsy: undifferentiated carcinoma
Three Questions

• Question #1: Surgically resectable?
  – Answer: Yes

• June 2009: Transoral resection plus right modified radical neck dissection

• Pathology
  – Palate: 5 mm grade 2 SqCC, ~4 mm margin
  – Neck: 2.4 cm mass in level 2 with ECE
    • 1 additional node in level 2
Is Reirradiation Feasible?

• Question 2: Is this resistant disease?
  – Answer: Yes
    • Reason 1: Recurrence presented ~ 4 months from treatment
    • Reason 2: In-field failure
      – Always look at original plan
Prior RT Plan

Soft Palate Absolute
7100.0 cGy
7000.0 cGy
6840.0 cGy
6500.0 cGy
6000.0 cGy
5500.0 cGy
5000.0 cGy
4700.0 cGy

Slice 81: Z = -0.700 Hodge\^Lillian\^F

Slice 93: Z = 0.800 Hodge\^Lillian\^F
Recommendation

• Question 3: Complications of reirradiation
  – Answer: Potentially severe
    • Carotid blowout (prior surgery, prior dose)
    • Oropharyngeal hemorrhage
    • Permanent dysphagia

• Recommendation:
  – Best supportive care
Clinical Example

• 74 yo man who developed T4N2b left base-of-tongue SqCC in 1996

• Past Medical History
  – Atrial fibrillation, HTN, hyperlipidemia

• Treatment
  – TPFL induction chemotherapy
  – 72 Gy to primary and bilateral neck
Recurrence

• March 2009: coughing with food

• Clinical examination:
  – Cratered tumor with large, hard margins, extending towards vallecula

• Biopsy of tongue and pharyngeal wall
  – Squamous cell carcinoma, HPV-negative
Imaging
Three Questions

• Question #1: Surgically resectable?
  – Answer: Not without profound functional compromise
    • Patient refused

• Question #2: Is this resistant disease?
  – Answer: No
    • Original treatment 13 years ago!
Recommendation

• Question 3: Complications of reirradiation
  – Answer: Modest
    • Oropharyngeal hemorrhage
    • Permanent dysphagia
  – Complications of tumor progression?
    • Certain oropharyngeal hemorrhage
    • Certain permanent dysphagia

• Recommendation: chemoradiotherapy
  – Concurrent carboplatin, paclitaxel, cetuximab
Radiotherapy Plan

PTV 66

PTV 54

66 Gy
Follow-Up

- NED 8 months following reirradiation
- Persistent PEG-dependence
- No other significant grade 3 toxicities
Conclusions

• There is a non-trivial cohort of patients with recurrence who can be salvaged

• Trimodality therapy is associated with optimal outcomes

• Reirradiation is associated with substantial acute and late toxicity

• Must carefully balance risks and benefits of treatment and inaction
Questions?

• Contact information
  – 617-632-3591
  – dsher@partners.org