Re-irradiation of Recurrent or Second Primary Head and Neck Cancer

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Outline

- Surgical Salvage
- Chemotherapy Alone
- Re-irradiation experience with:
  - EBRT/Concurrent Chemoradiotherapy
  - IMRT
  - Brachytherapy
  - SBRT
Recurrence

- Locoregional recurrence in H&N cancer patients treated with surgery and/or radiotherapy varies from 20-57%.
  - SEER analysis shows 15 year incidence of 2nd H&N CA 7.7% for those treated with RT and 10.5% for those treated without RT.
  - H&N chemoprevention trials show a 4%/year rate of second primary neoplasm.
- 50% of H&N CA patients who die from H&N cancer have local and/or regional as the sole site of failure.
- 90% of pts who develop DM also have locally persistent or recurrent disease.

Fig. 2. Percent incidence of second head and neck cancer (2ndHNCA) by treatment period comparing patients treated with and without radiotherapy (RT). (a) Patients treated from 1973 to 1997. (b) Patients treated from 1988 to 1997.
Surgical Salvage

- Retrospective analysis of 75 patients with locoregional recurrence after RT +/- chemo for H&N cancer.
  - 17 had salvage surgery
  - Median post-recurrence survival was 44 months for salvage surgery vs. 11 months for no surgery (p=0.001).

<table>
<thead>
<tr>
<th>Reasons for not undergoing salvage surgery</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable disease</td>
<td>25 (43%)</td>
</tr>
<tr>
<td>Poor health status/age</td>
<td>21 (30%)</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Metastasis and simultaneous local recurrence</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Rapid disease progression/intercurrent death</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Not clear</td>
<td>8 (11%)</td>
</tr>
</tbody>
</table>

Surgical Salvage

- Temam et al.
  - 16/69 recurrence of oropharyngeal cancer after RT had surgical salvage.
    - 3-year OS 20%, 5-year OS 11% for those with surgery
  - 23/26 LR Laryngeal cancer after RT for T1-2 SCC glottic larynx.
    - 59% had no recurrent cancer for at least 2 years after surgery.
- Parsons et al. IJROBP 1995.
  - 30/46 LR after RT for SCC of the SGL had salvage surgery.
    - 50% with no recurrence in first 2 years.
    - 5-year OS 20% for all LR, 29% for those with salvage surgery.
Surgical Salvage Summary

- Potentially curative option
- Surgical salvage favored in low volume disease recurrence.

However:
- Many patients with recurrent disease present with locally advanced disease where surgery would not be technically feasible.
- Many patients are medically inoperable or refuse surgery.
Chemotherapy

- Previously considered to be the standard treatment for unresectable recurrent H&N cancer.
- Cisplatin/5FU showed a better response rate (no difference in OS) compared to single agent chemotherapy.
- Cisplatin/5FU vs. Cisplatin/Taxol showed no survival difference in a phase III study.
- Pooled analysis of patients from ECOG trials with local disease only and previous irradiation who received salvage chemotherapy:
  - Response rate 10-35%
  - MS 5-8.7 months
  - 2-year OS 10.5%.
Re-irradiation

- Like surgery, a potentially curative option
- Thought to be high risk and considered experimental for some time, but gaining acceptance as a treatment option, especially in the IMRT era.
- Studies are highly variable and many are retrospective or single arm.
  - Patient selection varies widely.
  - Use of concurrent chemo varies, as do the agents used.
  - Timing, technique, and dose of radiation vary.
Two subsequent prospective trials were based on institutional data from the University of Chicago.

- 115 patients with locoregionally recurrent H&N cancer after irradiation.
  - 49 had surgical resection followed by CRT.
  - 66 treated with definitive CRT
  - Earlier protocols called for surgery only if complete R0 resection possible. Later protocols called for surgical cytoreduction.

Salama et al. IJROBP 2006.
Re-irradiation

- 2D and 3D techniques were used
- Treatment volume and doses varied.
- Lifetime spinal cord and brainstem dose max 50 Gy.
- No dose limits to soft tissue, bone, or major blood vessels.
- Treated 2Gy/day or 1.5 Gy BID (min 6 hours between).
- 96.5% of patients had recurrent tumor, 3.5% had second/third primary tumor.
Re-irradiation

- Outcomes
  - Median composite RT dose was 131 Gy
  - Median FU 67.4 months
  - Median OS 11 months, with 3-year OS 22%
  - 3-year LR control 51%

- Toxicity
  - 19 patients died of treatment related toxicity (median of 7 months after treatment).
  - 9 patients died during CRT and 10 died after completing treatment.

<table>
<thead>
<tr>
<th>Table 7. Grade 4–5 complications*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complication</td>
</tr>
<tr>
<td>Carotid hemorrhage</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
</tr>
<tr>
<td>Brain necrosis</td>
</tr>
<tr>
<td>Myelopathy</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
</tr>
</tbody>
</table>

* Using common terminology criteria for adverse events.
RTOG 96-10

- 86 patients (81 assessable)
  - Second primary tumor or recurrence > 6 months after definitive RT to > 45 Gy
  - 4 weekly cycles of RT separated by 1 week rest
    - 1.5 Gy BID x 5 days per cycle (6 hour separation)
    - 1.5 g hydroxyurea given 2hr and 300mg/m² of 5FU given 30 minutes before 2nd daily fraction.

Re-irradiation

- RTOG 96-10

Table 5. Survival estimates

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Total (n)</th>
<th>Dead (n)</th>
<th>Median (mo)</th>
<th>% 1-Year (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
<td>81</td>
<td>66</td>
<td>8.2</td>
<td>41.7 (30.6–52.8)</td>
</tr>
<tr>
<td>Recurrence†</td>
<td>61</td>
<td>53</td>
<td>7.7</td>
<td>38.4 (25.8–50.9)</td>
</tr>
<tr>
<td>Second primary†</td>
<td>18</td>
<td>12</td>
<td>19.8</td>
<td>54.2 (30.6–77.7)</td>
</tr>
</tbody>
</table>

\[
p = 0.0833
\]

\[
<3 \text{ yr from prior RT}‡ \quad 45 \quad 41 \quad 7.0 \quad 35.4 (21.0–49.7)
\]

\[
>3 \text{ yr from prior RT}‡ \quad 32 \quad 23 \quad 10.2 \quad 48.1 (30.4–65.9)
\]

\[
p = 0.0172
\]

* Median follow-up time for living patients was 16.3 months (range 2.1–36.5).
† Excludes 2 patients for whom type of recurrence was pending.
‡ Time from end of prior RT to registration in RTOG 96-10 (excludes 4 patients for whom the date of the end of prior RT was unknown).

Table 4. Toxicities (n = 81)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>3</td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>11</td>
</tr>
<tr>
<td>Pharynx/esophagus</td>
<td>16</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>6</td>
</tr>
<tr>
<td>Hematologic</td>
<td>11</td>
</tr>
</tbody>
</table>

Fatal tumor hemorrhage, 2 patients.
RTOG 99-11

- Phase II multi-institutional study; similar eligibility to RTOG 96-10
- 1.5 Gy BID x 5d every 2 weeks x 4 to 60 Gy with concurrent Cisplatin 15 mg/m2 daily and Taxol 20 mg/m2 daily during radiotherapy. IMRT allowed, but numbers receiving it not defined.
- 105 patients (23% second primary, 40% oropharynx). Median prior RT 65.4 Gy, median time from prior RT 40 months.

**Re-irradiation**

- **RTOG 99-11 results**
  - Median f/u 23.6 months
  - Median Survival 12.1 months
  - 2-year OS 25.9%

- **Toxicity**
  - Grade >= 4 toxicity 28%
    - Delayed osteoradionecrosis 4%
    - 8 fatal Grade 5 toxicities (5 acute and 3 late – 2 carotid blowout).

**Fig 1.** Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) for Radiation Therapy Oncology Group protocol 9911.
Re-irradiation

- Phase II data with re-irradiation and concurrent chemotherapy appeared more promising than chemotherapy alone.
- RTOG 04-21 was a phase III trial evaluating treatment per RTOG 99-11 vs. standard chemotherapy.
  - Closed due to poor accrual.
Phase III study of patients previously receiving RT of at least 45 Gy with at least 65% overlap of previous and new fields, deep infiltration of tumor, no DM, and KPS 80-100. At least 6 months since initial RT, no severe effects of initial RT, macroscopic CR, and able to start RT within 8 weeks.

- 130 patients randomized to:
  - CRT 60 Gy in 12 weeks (2 Gy/day x 5 days with 9 day rest periods) with 5FU and hydroxyurea (2D or 3D)
  - Observation

Janot et al. JCO 2008.
Post-op Re-irradiation

- **Results**
  - Significant difference in locoregional control in favor of the RT arm (HR 2.73 p < 0.001).
  - Significant difference in DFS in favor of RT arm on MVA (HR 1.68 p = 0.01).
  - No significant difference in OS.

- **Toxicity**
  - 28% of RT arm experienced Grade 3-4 acute toxicity
  - 3 early and 2 late treatment related deaths.
  - Late Grade 2-3 toxicity
    - At 12 months: 26% in RT vs. 9% in WS (p = 0.06)
    - At 24 months: 39% in RT arm vs. 10% in WS arm (p = 0.06)
Retrospective, single-institution review of 105 patients with recurrent H&N cancer after RT

- 75 had chemo with reirradiation
- Median initial RT dose 62 Gy, median reirradiation dose 59.4 Gy
- 70% of reirradiation plans used IMRT
- 2-year locoregional PFS 42%; 2-year OS 37%

Lee et al. IJROBP 2007.
# Re-irradiation: IMRT

## Grade 3 complications
- Neck fibrosis

## Common (mostly due to first course of RT)
- Cranial neuropathy: 1
- Hearing loss: 3
- Dysphagia: 3
- Stricture: 1
- Temporal-lobe necrosis: 1
- Trismus: 3

## Grade 4 complications
- Unilateral blindness: 1
- Temporal-lobe necrosis: 3
Re-irradiation: IMRT

- Inherent advantages in the re-irradiation setting.
- Data are heterogeneous and retrospective.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>RT Regimen (Chemotherapy)</th>
<th>Median OS (Median Follow-Up)</th>
<th>1-Year Survival (%)</th>
<th>Toxicity, % (Number of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulman et al</td>
<td>78</td>
<td>Median RT dose 60 Gy (49% CT)</td>
<td>28 (NR)</td>
<td>75</td>
<td>Acute + late: 20 (15) grade 3-5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deaths: 1 (1) unspecified</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute Gr 3 (3) 23 (24)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Late Gr ≥3: 11 (12)</td>
</tr>
<tr>
<td>Lee et al</td>
<td>105 (74 IMRT)</td>
<td>Median RT dose 59.4 Gy (74% CT)</td>
<td>25 (35)</td>
<td>56</td>
<td>Acute ≥3: 6 (4); 2 deaths</td>
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<td></td>
<td>Late ≥3: 29 (19)</td>
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<td>Acute: 6 (2) grade 4</td>
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<td></td>
<td></td>
<td>Late: 21 (8) grade 0-3</td>
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<td></td>
<td></td>
<td></td>
<td>Deaths: 0</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Acute: 91 (32) grade 3-4 and 14 (5) grade 4</td>
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<td>Late: 46 (16) grade 3-5</td>
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<td>Deaths: 11 (4) -1 fatal bleed</td>
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<td></td>
<td></td>
<td></td>
<td>Acute + late, grade 3 or 4: 68 (28)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Deaths: 0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cumulative toxicity: NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deaths: 0</td>
</tr>
<tr>
<td>Popovtzer</td>
<td>66</td>
<td>Median RT dose 64 Gy (71% CT)</td>
<td>(42)</td>
<td>40%: 2-year OS</td>
<td></td>
</tr>
<tr>
<td>Zwicker et al</td>
<td>38</td>
<td>Median RT dose 49 Gy (50% concurrent CT)</td>
<td>17 (NR)</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Sher et al</td>
<td>35</td>
<td>Median RT dose 60 Gy</td>
<td>23 (28)</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Goldstein et al</td>
<td>41</td>
<td>Median RT dose 61.1 Gy (curative) 54.5 Gy (palliative)</td>
<td>10.2 (NR)</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al</td>
<td>21</td>
<td>Median RT dose 66 Gy</td>
<td>NR (20)</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

Wang et al. Seminars in Radiation Oncology 2012.
Retrospective study of 60 patients with recurrent or second primary H&N cancer.

- All received IMRT to 70 Gy in 35 fractions or 69.12 Gy in 32 fractions.
  - Spinal cord dose constraint:
    - D50 < (45 Gy – ½ previous dose)
    - V(50 Gy – ½ previous dose) < 5%
- Median f/u in living patients 18.5 months.
- Actuarial 1, 2, and 5y locoregional control was 64%, 48%, and 32%.
- Median OS 9.6 months, median DFS 6.7 months.
- Actuarial 1, 2, and 5y OS was 44%, 32%, and 22%.
- Still high rate of Grade 3-5 toxicity (four pts Grade 5).

A potential serious complication of re-irradiation.

Pooled analysis of re-irradiation data

- Significantly higher incidence of carotid blowout in patients receiving accelerated (1.5 Gy BID) or delayed concomitant boost techniques vs. those with standard fractionation or hyperfractionation (1.2 Gy BID): 4.5% vs. 1.3% (p=0.002).
- 76% of cases of carotid blowout were fatal.
- A clear dose constraint has not been established.

McDonald et al. IJROBP 2012.
Retrospective study of 220 patients with prior RT and recurrent or new primary H&N CA.

- Treated with LDR Ir-192 interstitial implant
  - Median initial dose 57 Gy (range 39-74 Gy)
  - Median re-irradiation dose 53 Gy (range 46-60 Gy)
- Local control 77% (f/u varied)
- Toxicity
  - 36% toxicity


<table>
<thead>
<tr>
<th>Type</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue necrosis</td>
<td>28</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>17</td>
</tr>
<tr>
<td>Orocutaneous fistulae</td>
<td>3</td>
</tr>
<tr>
<td>“Woody” fibrosis</td>
<td>7</td>
</tr>
<tr>
<td>Carotid “blowout”</td>
<td>4</td>
</tr>
<tr>
<td>Tongue atrophy</td>
<td>6</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>8</td>
</tr>
<tr>
<td>Severe trismus</td>
<td>4</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>80* / 220 (36%)</td>
</tr>
</tbody>
</table>

* Twenty patients experienced more than one complication.
Retrospective study of 30 patients with recurrent H&N cancer after previous RT

- Treated with HDR interstitial radiotherapy
  - Mean dose 34 Gy at 3-4 Gy/fx
  - Median fractions 9.3 (range 3-12) with 2 fractions/day
- Local control: 69%
- Complications: 16.7%

Hepel et al. IJROBP 2005.
Given significant numbers of local recurrences after re-irradiation, SBRT is attractive.
Again, data are heterogeneous and retrospective.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Treatment Mean Dose (Range)</th>
<th>Median OS, Months (Median Follow-up)</th>
<th>1-Year Survival (%)</th>
<th>Toxicity, % (Number of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roh et al(^{21})</td>
<td>36</td>
<td>30 Gy (18-40), 3-5 fractions; Median GTV 22.6 cm³</td>
<td>16.2</td>
<td>61</td>
<td>Acute: 66 (24) grade 1-3 Late: 8 (3), grade NR Deaths: 3 (1) soft tissue, skull-base necrosis</td>
</tr>
<tr>
<td>Unger et al(^{22})</td>
<td>65</td>
<td>30 Gy (21-35), 5 fractions</td>
<td>12 (16)</td>
<td>70</td>
<td>Acute: 19 (12) grade 1-3 Late: 9 (6) grade 4 Death: 1.5 (1) unknown</td>
</tr>
<tr>
<td>Cengiz et al(^{23})</td>
<td>46</td>
<td>30 Gy (18-35)</td>
<td>12 (NR)</td>
<td>47</td>
<td>Acute: 4 (2)-grade 3 Late: 13 (6) grade 2-3 Deaths: 19 (9)-bleeding</td>
</tr>
<tr>
<td>Heron et al(^{24})</td>
<td>35 SBRT alone, 35 SBRT + cetuximab</td>
<td>40 Gy (20-44 Gy), 5 fractions</td>
<td>21 (25)-SBRT alone 53 SBRT alone</td>
<td>53</td>
<td>Acute: 0 grade 4 or 5; 4 (3/70) grade 3 Late: 0 grade 3 and 4 Deaths: 0</td>
</tr>
</tbody>
</table>

Wang et al. Seminars in Radiation Oncology 2012.
Surgery is first option for recurrent H+N CA or second primary in previously irradiated field
Surgical debulking may have a role
Adjuvant CRT after surgical resection has a PFS advantage but no survival advantage over no further treatment in a phase III study.
Toxicity with CRT is significant, but it does offer a small chance of prolonged PFS.
Patient selection for reirradiation is very important.

- Second primary > Recurrent tumors
- Surgical debulking improves outcome
- Higher doses improve outcome
- Longer time interval to recurrence is better
  - In-field radio-resistant tumor-clones?
- Patients with better performance status have better outcomes.
- Patients with better recovery from initial radiotherapy have better outcomes.
- Laryngeal and Nasopharyngeal tumors tend to have better outcome compared to other H+N sites
- Neck recurrences < Primary site recurrence
- Many questions remain unanswered.