Combined Modality Therapy with Surgery and Radiation Therapy in Locally Advanced Head & Neck Cancers

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## Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV A</td>
<td>T4a</td>
<td>N0-N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-4a</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV B</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV C</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Locally Advanced Disease

• Stage III and Stage IV disease except dist mets

• Divided into resectable and unresectable subgroups

• Recent sub-grouping by UICC
### Definition of subgroups of HNSCC with different risk of treatment failure according to TNM-UICC AJCC classification [3]

<table>
<thead>
<tr>
<th>Prognostic subgroup</th>
<th>TNM features</th>
<th>Stage classification</th>
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</thead>
<tbody>
<tr>
<td>Low-risk subgroup</td>
<td>T1–T2 N0</td>
<td>I–II</td>
</tr>
<tr>
<td>Intermediate-risk subgroup</td>
<td>T3 N0</td>
<td>III</td>
</tr>
<tr>
<td>High-risk subgroup</td>
<td>T1–3 N1</td>
<td>IVA</td>
</tr>
<tr>
<td>Very high-risk subgroup</td>
<td>T4a N0–N1</td>
<td>IVB</td>
</tr>
<tr>
<td>Poor prognosis subgroup</td>
<td>T4b any N</td>
<td>IVC</td>
</tr>
<tr>
<td></td>
<td>Any T N3</td>
<td></td>
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<tr>
<td></td>
<td>Any T any N M1</td>
<td></td>
</tr>
</tbody>
</table>

Corvo R. Evidence based radiation oncology in HNSCC. Radiother Oncol 2007 (in press)
Treatment Modalities

• Three main modalities of treatment
  – Surgery
  – Radiation Therapy
  – Chemotherapy

• Optimal combination of above three modalities
Principles of Treatment

- Early Disease (Stage I, II) - Monotherapy
  - Surgery or Radio-therapy - Comparable results
  - 5 year survival stage I - 80 - 90%
  - 5 year survival stage II - 60 - 80%

- Choice depends –
  - Tumor factors - Site, Size, Type
  - Patient factors
  - Facilities available
Locally Advanced Disease

- Advanced disease (Stage III, IVA)
  Combination therapy
    Surgery + Post operative RT
    Concurrent Chemotherapy + RT
- 5 year survival stage III - 40-50%
- 5 year survival stage IVA - 20-30%

Why is combined treatment necessary?

• Advanced lesions (85% are stage III and IV cancers)

• Single modality of treatment gives unsatisfactory results

• Failure to control disease above clavicle (loco regional)
Historical evidence

• Strong (1969) observed failure rate of 70% in patients treated with surgery alone.

• Addition of post-operative RT resulted in improved NED status to about 50% (Vikram et al 1984)
Are two modalities of treatment competitive?

• The two modalities are complimentary

• Surgery to remove the gross tumour

• RT to eradicate the microscopic disease
Combined Modality Treatment: Possible regimes

- RT → Surgery (Pre-op RT)
- Surgery + RT (Intra-operative RT)
- Surgery → RT (Post-op RT)
- Radical RT → Salvage Surgery
RT \rightarrow Surgery (Pre-op RT)

- Not a common regime
- Borderline operable lesions
- Well oxygenated tumors
- Reduces the viability of tumor
- Improves resectability
- Delayed wound healing
- Have been used for RMT & PNS tumors
Pre-op RT

• Retrospective analysis: Preop RT vs Postop RT vs RT alone (10 vs 39 vs 15 pts)
• Pre-op RT: 30-55.2 Gy
• The 5-year DFS rates were 90% with preop RT, 63% with PORT, and 31% with RT alone
• Sample Size: small

Huang et al. Head Neck. 2001;23(9):758-63
Post-operative RT

• Takes care of microscopic disease after removal of gross disease.

• Considered when risk of loco regional failure > 20%

• Optimal timing and dose major considerations (4-6wks, Dose 60-64 Gy/30-32#/6-6.5 wks)

• Commonly done in stage III, IV tumors and selectively in early stages.
**Advantages:**
• Better information about the tumor pathology
• Knowledge of tumor spread
• Tailoring of radiation dose and volume

**Disadvantages:**
• Potential delay in starting RT
• Tumor hypoxia
• Wound healing
Preop vs. Postop RT

Preop RT

- ↓ viability of tumor, wound implantation
- Improves resectibility
- Postop RT superior to preop RT in H&N Cancer (RTOG, 73-03) trial, 1991
- Timing of postop RT critical-Within 3-6 weeks of surgery, >6 weeks delay detrimental (*Peters, IJROBP 26;3-11, 1993*)

Postop RT

- Pathologic information to modify dose or treatment portals
- Allows proper wound healing
- Allows delivery of ↑ dose of radiation
**Indications**

**Absolute Indications**
- Microscopically involved mucosal margins of resection
- Extra capsular extension

**Relative Indications**
- Close margins (<5mm)
- Multiple positive neck nodes (2 or more)
- pT3-T4 with negative margins (except pT3 larynx)
- Perineural spread or microvascular emboli

*Corvo R. Evidence based radiation oncology in HNSCC. Radiother Oncol 2007 (in press)*
## Postop RT: Literature

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Journal</th>
<th>Findings</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters et al MDAH</td>
<td>1993</td>
<td>Int J Rad Onc Bio Phy</td>
<td>Pri Failure Rate is significantly high $p=0.02$, when dose $&lt;54$ Gy vs $&gt;57.6$ Gy</td>
<td>Minimum 57.6 Gy to operative bed with boost up to 63 Gy and RT to be started asap</td>
</tr>
<tr>
<td>Ampil et al Lousiana State Univ</td>
<td>2003</td>
<td>J Oral Maxillofac Surgery</td>
<td>In close/positive margins LRFR 25% when dose $&lt;60$ Gy vs 8% when its $&gt;60$ Gy</td>
<td></td>
</tr>
<tr>
<td>Muriel et al Univ Hosp Spain</td>
<td>2001</td>
<td>Radiotherapy Oncology</td>
<td>OTT significant prognostic factor and time b/w Sx &amp; RT an independent predictor of failure</td>
<td></td>
</tr>
</tbody>
</table>
## Postop RT: Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Journal</th>
<th>Findings</th>
<th>Note</th>
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<tbody>
<tr>
<td>Ang et al</td>
<td>2001</td>
<td>IJROBP</td>
<td>In high risk pts, higher LRC and survival rates when PORT course reduced (5 vs 7wks) p=0.03</td>
<td>OTT had an impact</td>
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<tr>
<td>M D Anderson</td>
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<tr>
<td>Hospital</td>
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</tr>
<tr>
<td>Ampil et al</td>
<td>1993</td>
<td>J Oral Maxillofac Surgery</td>
<td>Local and regional recurrence rate 37% vs 20% when PORT delayed</td>
<td>Timely initiation of PORT important</td>
</tr>
<tr>
<td>Lousiana State</td>
<td></td>
<td></td>
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<tr>
<td>University</td>
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</tbody>
</table>
Technique of EBRT

- Treatment Unit: Co-60 or Linac 4-6 MV photons
- Volume of irradiation: Primary tumor +/- neck nodes
- Total Dose: 60-64 Gy
- No. of Fractions: 30-32
- Dose/fraction: 180-200 cGy
- Duration: 6-6.5 weeks
Postoperative IMRT in head and neck cancer: Rationale

- Despite high dose PORT in patients with locally advanced HNC with certain high risk factors, loco-regional recurrences rate is about 30%.

- IMRT has a potential to reduce the radiation accompaniments

- In Last 5 yrs, IMRT has been shown to be beneficial in head & neck cancer
Postoperative IMRT in head and neck cancer

- Studer* et al used Postop IMRT in HNC
- No of pts: 71
- Period of study: Jan 2002 - Aug 2006
- Sites: oral cavity, hypopharynx, larynx, PNS
- Mean Dose: 66.3 Gy (60–70), with 2–2.3 Gy/Fr
- Compared the results with historic series

*Studer et al. *Radiation Oncology* 2006, 1:40
Postoperative IMRT in head and neck cancer

- No grade IV toxicity
- All pts completed treatment without interruption
- Grade III xerostomia in 43 pts
- 2-year actuarial local control: 95%
- 2-year actuarial DFS: 90%
- Concluded that Postop IMRT resulted in high loco-regional tumor control rates compared with large prospective 3DCRT trials.
## Postoperative IMRT in head and neck cancer: literature

<table>
<thead>
<tr>
<th>Author, ref</th>
<th>(year)</th>
<th>n pIMRT (dIMRT)</th>
<th>HNC subsites</th>
<th>T3/4, rec, OCC</th>
<th>pIMRT dose</th>
<th>Chemotherapy</th>
<th>2-γ L(R)C</th>
<th>median FU</th>
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</thead>
<tbody>
<tr>
<td>Lee et al [15]</td>
<td>(2003)</td>
<td>43 (107)</td>
<td>all</td>
<td>53, 0, 2%</td>
<td>66 Gy</td>
<td>35% of pIMRT</td>
<td>83% LC</td>
<td>25 (6–78)</td>
</tr>
<tr>
<td>Chao et al [9]</td>
<td>(2004)</td>
<td>74 (52)</td>
<td>all</td>
<td>52, 0, 12%</td>
<td>~68 Gy (+/-4.7)</td>
<td>none of pIMRT</td>
<td>90% LRC</td>
<td>26 (12–55)</td>
</tr>
<tr>
<td>Feng et al [10]</td>
<td>(2005)</td>
<td>86 (72)</td>
<td>all but NPC/SNC</td>
<td>90 III/IV, 3, 23%</td>
<td>~70 Gy (66–76)</td>
<td>12% of all</td>
<td>~85% LRC</td>
<td>36 (6–127)</td>
</tr>
<tr>
<td>Yao et al [12]</td>
<td>(2005)</td>
<td>51 (100)</td>
<td>all</td>
<td>53, 0, 19%</td>
<td>64–66 Gy</td>
<td>none of pIMRT</td>
<td>~92% LC</td>
<td>18 (2–60)</td>
</tr>
<tr>
<td>Own</td>
<td>(2006)</td>
<td>71 (230)</td>
<td>all SCC</td>
<td>25, 18, 31%</td>
<td>~66 Gy (60–70)</td>
<td>83% of pIMRT</td>
<td>95% LC</td>
<td>17.6 (2–48)</td>
</tr>
</tbody>
</table>
Accelerated Post op RT

• Accelerated Treatment: 76 pts treated with 63 Gy in 5 wks

• Conventional Treatment: 75 pts treated with 63 Gy in 7 wks

• For high-risk patients, a trend toward higher LRC and survival rates was noted when PORT was given in 5 wks

• A 2-week reduction in the PORT duration did not increase the late treatment toxicity.

Accelerated Post op RT …contd…

- 226 pts with one or more high-risk features (pT4, positive resection margins, pN >1, perineural invasion, ECE) treated with accelerated PORT

- Two arms: 60Gy in 6 wks vs 64Gy in 5 wks

- 2-year locoregional control were 80% +/- 4% for CF and 78% +/- 5% for AF (p = 0.52)

- improved locoregional control with Accelerated RT for the pts who had a delay in starting RT

Sanguineti et al. IJROBP 2005; 61(3):762-71
## POSTOP CHEMORADIATION

Cooper et al. NEJM 2004; 350 : 1937-44.

n=459; surgery

<table>
<thead>
<tr>
<th></th>
<th>RT alone (60-66Gy)</th>
<th>RT+ CDDP (100mg/m² IV D1,22,43)</th>
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</thead>
<tbody>
<tr>
<td>Recurrence (FU 45.9 mo)</td>
<td>30%</td>
<td>19% (p=0.01)</td>
</tr>
<tr>
<td>2 year LC, RC</td>
<td>72%</td>
<td>82%</td>
</tr>
<tr>
<td>OS (Mo)</td>
<td>31.9</td>
<td>44.9 (p=0.19)</td>
</tr>
<tr>
<td>Gd 3,4 toxicity</td>
<td>34%</td>
<td>77% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>RT alone (66Gy)</td>
<td>RT+ CDDP (100mg/m² IV D1,22,43)</td>
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<tr>
<td>--------------------------</td>
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<td>----------------------------------</td>
</tr>
<tr>
<td>Locoregional failure (5 yr)</td>
<td>31%</td>
<td>18% (p=0.007)</td>
</tr>
<tr>
<td>5 year OS</td>
<td>40%</td>
<td>53% (p=0.02)</td>
</tr>
<tr>
<td>5 year PFS</td>
<td>36%</td>
<td>47% (p=0.04)</td>
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<tr>
<td>Gd 3,4 toxicity</td>
<td>21%</td>
<td>41% (p=0.001)</td>
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</table>
Intra-operative RT

- Practiced in very few centers
- Mainly for advanced/recurrent disease
- May be used in primary management of PNS/skull base tumors
- Mainly two methods: IOERT and IOHDR

*Limited experience at AIIMS*
IORT in Head and Neck Cancer

**IORT-Electron**
- Accessible lesion
- More homogenous and penetrating dose distribution

**IORT-HDR**
- Less accessible
- Heterogeneous dose (200% of prescribed dose at surface) & limited penetration
### Results of IOERT

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. of pts</th>
<th>LR control</th>
<th>2yr survival</th>
<th>Complications</th>
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<tbody>
<tr>
<td>Mayo Clinic (1994)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>S+IOERT</td>
<td>17</td>
<td>41%</td>
<td>25%</td>
<td>3%</td>
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<tr>
<td>S+IOERT+EBRT</td>
<td>14</td>
<td>64%</td>
<td>39%</td>
<td></td>
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<tr>
<td>UCSF (1994)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Primary</td>
<td>5</td>
<td>100%</td>
<td>70%</td>
<td>16%</td>
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<tr>
<td>Recurrence</td>
<td>25</td>
<td>60%</td>
<td>(overall)</td>
<td></td>
</tr>
<tr>
<td>Ohio State Univ (1997)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOERT+EBRT</td>
<td>28</td>
<td>79%</td>
<td>88%</td>
<td>15%</td>
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<tr>
<td>IOERT</td>
<td>12</td>
<td>50%</td>
<td>33%</td>
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<tr>
<td>Univ of Ryukyus (1992)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gross residual</td>
<td>7</td>
<td>0%</td>
<td>0%</td>
<td>33%</td>
</tr>
<tr>
<td>Microscopic</td>
<td>12</td>
<td>55%</td>
<td>33%</td>
<td></td>
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<tr>
<td>Close margins</td>
<td>11</td>
<td>82%</td>
<td>30%</td>
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</tr>
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</table>

*IORT: Technique & Results Gunderson, Humana Press 1999*
IOHDR for PNS Tumors

- Period of study: 1992 and 1998
- No. of patients: 34
- Dose of IOHDR: 10-12.5 Gy
- Dose of EBRT: 45-50 Gy
- 5-yr and 6-yr survival: 62%, and 44%

Definitive RT with salvage surgery v/s combined surgery and RT ….. AIIMS Data

- 119 pts of ca larynx T3N0M0
- Retrospective analysis
- Two arms Sx+RT and RT alone followed by Sx for salvage
- Non randomized, joint decision by Sx, RT team
- Actuarial 4-year DFS rates were significantly better with combined treatment (79.3 %) than with radical radiotherapy and surgical salvage (65.3 %) p value< 0.024

Definitive RT with salvage surgery v/s combined surgery and RT ..... AIIMS Data

- 195 pts of Ca Hypopharynx T3N0M0
- Retrospective analysis
- Two arms Sx+RT and RT alone followed by Sx for salvage
- Actuarial 2-yr DFS rates were better with Sx+RT than with RT with surgical salvage ($p = 0.0021$).

Combined therapy in advanced head and neck cancers: AIIMS Study

- 252 cases with stage III and IV resectable cancers of the head & neck
- treated by combined regime of pre- or post-operative RT and radical surgery
- 193 patients completed the treatment protocol
- 58 cases (33.5 per cent) who failed either at primary or regional sites or both
- Nine cases (five per cent) developed distant metastasis

Combined therapy in advanced head and neck cancers: AIIMS Study ….contd..

• Absolute and determinate four year disease-free survival was 55 per cent and 61 per cent respectively.

• Authors concluded that reduction in primary and regional failures correlates well with a combined therapy

Conclusions

• Locally advanced Head and neck cancer requires multimodal approach
• For operable lesions, most institutes practice surgery followed by PORT
• Addition of chemotherapy to PORT in pts with high risk factors: emerging role
• Newer techniques of RT like IMRT have shown encouraging results
Conclusions ...contd...

- Accelerated PORT for those where there is delay in starting RT

- Preop RT practiced in limited centers for selected sites

- Few institutes have studied role of Intra-operative RT in advanced head and neck cancer
Thank You