Adjuvant Treatment For Head & Neck Cancers

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Head & Neck Cancers

Paradigm shifts in management

- Multidisciplinary approach
- Advances in understanding Biology
- Exciting advances in radiotherapy delivery
- Newer chemotherapeutic agents

Intensification of treatment

Improvement in survival
Head & Neck Cancers

Single Modality Treatment
Definitive Radiotherapy

- Historically - only treatment for advanced unresectable cancers.
- Response and dose dependent on tumor volume/number of tumor clonogenic cells.
## Head & Neck Cancers

### Single Modality Treatment - Definitive Radiotherapy

<table>
<thead>
<tr>
<th>Author (Institute)</th>
<th>No. of patients (Year)</th>
<th>T-stage</th>
<th>Dose</th>
<th>Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellai.E (Univ. of Florence)</td>
<td>205 (1970-1985)</td>
<td>(Early Glottic Ca) T1a: 45 T1b: 110 T2: 50</td>
<td>61-64Gy</td>
<td>43(96%) 97(88%) 38(76%)</td>
</tr>
<tr>
<td>Chang (Univ. of Oregon)</td>
<td>74 (1971-1991)</td>
<td>(Pharyngeal Ca) T1:6 T2:27 T3:32 T4:9</td>
<td>60-70Gy</td>
<td>100% 55% 31% 29%</td>
</tr>
<tr>
<td>Overgaard (Danish Cancer Soc.)</td>
<td>478 (1963-1985)</td>
<td>T1larynx Glottic:358 Supra: 117 Sub: 3</td>
<td></td>
<td>81% 55%</td>
</tr>
<tr>
<td>Dinshaw (TMH)</td>
<td>568 (1990 - 1996)</td>
<td>All sites (except nasophx) All stages</td>
<td>60 - 70 Gy</td>
<td>53%</td>
</tr>
<tr>
<td>Author/Group</td>
<td>No. of pts.</td>
<td>Stage</td>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
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<td>------------------------</td>
<td>-------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Kokal et al (Virginia 1988)</td>
<td>46</td>
<td>III, IV</td>
<td>Rate of relapse was 37% Vs 68 % (P value- NS). 3 yr OS rate 58.5% and 46.5 %</td>
<td></td>
</tr>
<tr>
<td>(Randomised)</td>
<td>Sx (27) Sx + PORT (24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang et al (Virginia 1992)</td>
<td>125</td>
<td>LA</td>
<td>LRC - 59 Vs 31% ( P value- S) OS- 50 Vs 30% ( P value -S)</td>
<td></td>
</tr>
<tr>
<td>(High risk factors) Sx (71) Sx + PORT (54)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fletcher (M.D Anderson 1977)</td>
<td>169</td>
<td>IV</td>
<td>Rate of failure above the clavicles 24 Vs 13%</td>
<td></td>
</tr>
<tr>
<td>Badawi et al (1982)</td>
<td>328</td>
<td>III, IV</td>
<td>Rate of failure above the clavicles 48 Vs 16% and OS - 40 Vs 25%</td>
<td></td>
</tr>
<tr>
<td>Francheschi D MSKCC (1992)</td>
<td>297</td>
<td>Oral tongue cancer III ,IV</td>
<td>LRR 43 Vs 29% Neck rec. 29 Vs 13%</td>
<td></td>
</tr>
<tr>
<td>Mishra et al India 1996</td>
<td>140</td>
<td>LA Ca BM</td>
<td>DFS 68 % Vs 38 %. OS 94% Vs 84%</td>
<td></td>
</tr>
</tbody>
</table>
Head & Neck Cancers

Single Modality Treatment

- Radical radiotherapy & Surgery give consistent and reproducible results in early stage cancers
- Dismal results in advanced stage disease
- Complications & failures to RT related to: Stage, Total dose, Dose/ fr, Overall time
Head & Neck Cancers

Adjuvant Radiotherapy

- Why?- Rationale and evidence.
- What dose?- Rationale and evidence.
- When?- Rationale and evidence
Head & Neck Cancers

**Why Adjuvant Radiotherapy?**

- Reduces local and locoregional recurrences.
- Scarce level I evidence but well studied in several retrospective studies.
<table>
<thead>
<tr>
<th>AUTHOR (Institute)</th>
<th>NO. OF PTS.</th>
<th>TREATMENT</th>
<th>RESULTS (Local cont.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang (Univ. of Virginia)</td>
<td>125 (1982-1988)</td>
<td>* 71(Surg alone)</td>
<td>Perinod.---31%(p=0.03) +ve C/M-- 41%(p=0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* 54(Surg+RT)</td>
<td>Perinod.---66% +ve C/M---68%</td>
</tr>
<tr>
<td>Zelefsky (MSKCC)</td>
<td>51 (1973-1985)</td>
<td>* Surg+RT</td>
<td>T2:84-100% T3:86-100% T4:84-50%</td>
</tr>
<tr>
<td>Dinshaw (TMH)</td>
<td>348 (1990-1996)</td>
<td>* Surg+RT</td>
<td>T2 - T4: 79%</td>
</tr>
</tbody>
</table>
Who should receive Adjuvant Radiotherapy?

- **High-risk features**
  - Microscopically +ve surgical margins
  - ECS
  - LVI
  - PNI
  - 2 involved neck nodes
  - > 1 positive nodal group,
  - Nodal diameter > 3 cm,
  - 6 week interval between surgery and radiation and
  - Oral cavity primary site.

- **Other important factors are advanced**
  - T stage
  - Recurrent disease
  - Tumor spillage
  - Multicentricity,
  - Invasion of bone, cartilage, skin or soft tissue of the neck.
  - Depth of tumor invasion

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>M.D. Anderson Cancer Center</th>
<th>University of Pennsylvania</th>
<th>UZ Amsterdam</th>
<th>EORTC/RTOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest risk</td>
<td>Margins</td>
<td>ECS; 2+ factors</td>
<td>ECS; margins; 2+ LNs</td>
<td>ECS; margins</td>
</tr>
<tr>
<td>Intermediate or high risk</td>
<td>2+ LNs; ECS</td>
<td>1 risk factor</td>
<td>1 risk factor</td>
<td>Perineural invasion; LN+ at levels 4-5 in oropharynx and oral cavity cancer patients; vascular embolisms; and stage III-IV</td>
</tr>
</tbody>
</table>
Several retrospective studies: 60-65Gy in 6-7 wks

No definite dose response relationship beyond 57.6Gy except for patients with extranodal extension (dose response till 63 Gy)

Hence, for patients with high risk features higher doses >60 Gy recommended.

Adjuvant Radiotherapy: Timing

- Not been studied sufficiently.

Bhadrasain et al. (1979) n=22

LRC - 70% (PORT within 7 weeks)
- 27% (PORT more than 7 weeks)

- Limited evidence and clinical experience suggests- within 6-8 wks post surgery or as soon as the wound heals.
Parsons et al showed that Irradiation should begin within about 6 weeks after surgery.*

Local control was better whose overall treatment time from date of Sx to RT completion was less than 100 days.*

Significant loss of local control was observed with prolongation**.

Short OTT of radiation was found to be associated with higher rates for LRC, DFS, and OS.***

LRC worsened by 9% with every week’s prolongation of OTT.***

* Parsons et al IJROBP Vol 39; 1;137-148;1997
** Fowler et al IJROBP 1992, Ang KK et al:
RT: The changing paradigm

Wide field radiation  Conformal radiation

Head & Neck Cancers

Clinical motivation for high-precision techniques
More conformality = Better sparing
But, What are the exact Target Volumes in Different Subsites and Stages?

There is no consensus worldwide on

– The ideal high risk CTV volumes in each subsite.
– Prophylactic treatment areas in the soft-tissue and ipsilateral neck.
– Treatment of the contralateral neck
– Dose prescriptions – conventional vs. integrated boost.
Post-Op CTV

• The entire operative bed should be covered, especially in case of ECE.
• If level II (IIa or IIb) pN+, include the retrostyloid space up to the base of skull.
• If level V pN+, include the SCF.
• When a pathological lymph node abuts or invades a muscle – include the muscle at least in the entire invaded level.
• In selected LN dissection with one or few (pN1) marginal nodes affected – include the adjacent level.
• In pharyngeal tumors with pN+, include the lateral retropharyngeal nodes.

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Adjuvant Radiotherapy

- Local failures-30-50%
- Distal failures- 25%
- 5 yr survival rate-30-35%
- Inspite of adjuvant radiation results are poor, esp. in patients with high risk features
  - Multiple nodal involvement.
  - Extranodal extension.
  - Perineural invasion.
  - Positive margins of resection.
  - Tumor thickness
- Hence, the need for Adjuvant chemoradiation
Head & Neck Cancers

Adjuvant Chemoradiotherapy

- Evaluated in patients with high risk features
- Initiated by Bachaud et al, later confirmed by 2 major trials (EORTC and RTOG trials)
## Prospective Trials on Adjuvant Chemoradiotherapy after Surgery

<table>
<thead>
<tr>
<th>Author / Group</th>
<th>Year</th>
<th>No. of pts</th>
<th>Standard arm</th>
<th>Experimental arm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bachaud</td>
<td>1991</td>
<td>88</td>
<td>RT</td>
<td>RT + Cisplatin</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Weissberg</td>
<td>1989</td>
<td>120</td>
<td>RT</td>
<td>RT + Mitomycin</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Haffty</td>
<td>1993</td>
<td>120</td>
<td>RT</td>
<td>RT + Mitomycin</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Weissler</td>
<td>1992</td>
<td>26</td>
<td>RT</td>
<td>RT + Cisplatin + 5 FU</td>
<td>NS</td>
</tr>
<tr>
<td>Smid</td>
<td>2003</td>
<td>114</td>
<td>RT</td>
<td>RT + Mito + Bleo</td>
<td>P&lt;0.037</td>
</tr>
<tr>
<td>Bernier</td>
<td>2004</td>
<td>334</td>
<td>RT</td>
<td>RT + Cisplatin</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td>Cooper</td>
<td>2004</td>
<td>459</td>
<td>RT</td>
<td>RT + Cisplatin</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

Jacques Bernier, M.D., Ph.D., Christian Domenge, M.D., Mahmut Ozsahin, M.D., Ph.D., Katarzyna Matuszewska, M.D., Jean-Louis Lefèbvre, M.D., Richard H. Greiner, M.D., Jordi Giralt, M.D., Philippe Maingon, M.D., Frédéric Rolland, M.D., Michel Bolla, M.D., Francesco Cognetti, M.D., Jean Bourhis, M.D., Anne Kirkpatrick, M.Sc., and Martine van Glabbeke, Jr., M.Sc., for the European Organization for Research and Treatment of Cancer Trial 22931
Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck

Jay S. Cooper, M.D., Thomas F. Pajak, Ph.D., Arlene A. Forastiere, M.D., John Jacobs, M.D., Bruce H. Campbell, M.D., Scott B. Saxman, M.D., Julie A. Kish, M.D., Harold E. Kim, M.D., Anthony J. Cmelak, M.D., Marvin Rotman, M.D., Mitchell Machty, M.D., John F. Ensley, M.D., K.S. Clifford Chao, M.D., Christopher J. Schultz, M.D., Nancy Lee, M.D., and Karen K. Fu, M.D.,
for the Radiation Therapy Oncology Group 9501/Intergroup
# Adjuvant Chemoradiotherapy Meta-Analysis

<table>
<thead>
<tr>
<th>Author/year, ref.</th>
<th>No. of pts.</th>
<th>Treatment arms</th>
<th>Point in time*</th>
<th>Locoregional recurrence</th>
<th>Progression-free survival</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
<th>Median survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernier et al, 2004(^\text{11})</td>
<td>167</td>
<td>CT/RT</td>
<td>5 y</td>
<td>18%</td>
<td>47%</td>
<td>NR</td>
<td>53%</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>167</td>
<td>RT</td>
<td></td>
<td>31%</td>
<td>36%</td>
<td>NR</td>
<td>40%</td>
<td>32</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Overall</td>
<td>NR</td>
<td>HR = 0.75, p = .04</td>
<td>NR</td>
<td>HR = 0.70, p = .02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooper et al, 2004(^\text{12})</td>
<td>206</td>
<td>CT/RT</td>
<td>3.8 y</td>
<td>19%</td>
<td>NR</td>
<td>40%</td>
<td>95% CI = 0.52-0.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>210</td>
<td>RT</td>
<td></td>
<td>30%</td>
<td>NR</td>
<td>30%</td>
<td>41%</td>
<td>32</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>NR</td>
<td>HR = 0.84, p = .19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachaud et al, 1996(^\text{13})</td>
<td>39</td>
<td>CT/RT</td>
<td>5 y</td>
<td>23%</td>
<td>NR</td>
<td>45%</td>
<td>36%(^\dagger)</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>RT</td>
<td></td>
<td>41%</td>
<td>NR</td>
<td>23%</td>
<td>13%</td>
<td>22</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>NR</td>
<td>HR = 0.61, p = .01</td>
<td>NR</td>
<td>HR = 0.61-0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Šmid et al, 2003(^\text{14})</td>
<td>59</td>
<td>CT/RT</td>
<td>2 y</td>
<td>14%</td>
<td>NR</td>
<td>78%(^\ddagger)</td>
<td>74%</td>
<td>&gt; 48(^\ddagger)</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>RT</td>
<td></td>
<td>31%</td>
<td>NR</td>
<td>60%</td>
<td>64%</td>
<td>32</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>NR</td>
<td>HR = 0.8, p &lt; .02</td>
<td>NR</td>
<td>HR = 0.65-1.09</td>
<td></td>
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</tr>
</tbody>
</table>

*Percentiles reflect the point in time that outcomes were measured; overall data reflect hazard ratios from Kaplan-Meier curves.
†Survival corrected by deaths of intercurrent disease was 47% with chemoradiotherapy and 32% for radiotherapy alone.
\daggerData extracted from survival curves by reviewer.

Abbreviations: pts., patients; CT/RT, chemotherapy plus radiotherapy; RT, radiotherapy; NR, not reported; HR, hazard ratio; CI, confidence interval; NS, not statistically significant; Y, years.
Head & Neck Cancer

Adjuvant Chemoradiotherapy Meta-Analysis

Overall Survival

12.5% absolute improvement in OS (NNT=8)

Grade III/IV mucositis- 70% vs. 34%

Treatment related deaths-1-2%
Adjuvant Chemoradiotherapy Meta-Analysis

Conclusions:

• Chemoradiotherapy beneficial for high risk factors:
  Extranodal extension
  Positive Cut margins

• Beneficial < 70 years of age

• Significant toxicity

• Need for intense supportive care
Head & Neck Cancers

Adjuvant Chemoradiotherapy: TMH EXPERIENCE
Oral Cavity Adjuvant Therapy - HN / 04/008/R
(Initiated in June 2005, Ongoing
498 pts accrued so far)

- Phase III Study, 3 arms

- For High Risk, Locally Advanced, Stage III & IVA, Resectable Squamous Cell Carcinoma of Oral Cavity

- Target Accrual: 750 patients over 3 years

SURGERY

RANDOMIZATION

Adjuvant Conventional External Radiotherapy v/s
Adjuvant Accelerated Radiotherapy (6 fr/ week) v/s
Adjuvant Concurrent Chemoradiotherapy
Adjuvant Chemoradiotherapy

- Postoperative chemoradiation - intensify treatment for resectable tumors to improve upon existing control rates.

- Existing evidence - adjuvant chemoradiation in patients with high risk features (Intergroup 0034 trial).

- High incidence of treatment related toxicity –need for intense supportive measures.
Head & Neck Cancers
Optimization of Radiotherapy Response

Biological optimization

- Altered fractionation
- Biological response modifiers
- Targeted therapies
• 226 patients.
• Median follow-up 30.6 mths
• Two arms CF RT 60Gy/30#/6wk or AF(biphasic concomitant boost with boost delivered during first and last weeks of treatment, to deliver 64 Gy in 5 week
• 2-yr LRC- CF 80% and AF 78%  (p=0.52)
• 2-yr OS - CF 67% and AF 64%  (p=0.84)
• Patients who had a delay in starting RT showed improved LRC with AF compared with those with a similar delay but who were treated with CF
Agents being tested in various clinical trials are:
- Cetuximab (RTOG0234, RTOG0522)
- Lapatinib
- Nimotuzumab
Toxicity to Multimodality Treatment

Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Mucositis incidence (% of patients)</th>
<th>Grade 3–4 mucositis (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>6181</td>
<td>80</td>
<td>39</td>
</tr>
<tr>
<td>RT-C</td>
<td>2875</td>
<td>97</td>
<td>34</td>
</tr>
<tr>
<td>RT-AF</td>
<td>1096</td>
<td>100</td>
<td>57</td>
</tr>
<tr>
<td>RT + CT</td>
<td>1505</td>
<td>89</td>
<td>43</td>
</tr>
<tr>
<td>CT only</td>
<td>318</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

Oral Pain- 69%
Opioid Use- 53%

Overall Incidence of- Hospitalization: 16%
Feeding Tube Insertion: 19%
Mean Wt. Loss: 6-12% of BW (34% lost wt)
Dysphagia: 56%

Affecting their overall QOL
Head & Neck Cancers

Conclusions

- Appropriate Institution of Multidisciplinary approach
- Adjuvant radiotherapy is an essential component
- Adjuvant chemoradiotherapy is still investigational and reserved for high risk cases
- IMRT and other conformal techniques improve the therapeutic gain
- Targeted therapies are still investigational
- Intensive supportive care is essential for success