Meta-Analysis in HNSCC
Cessal Thommachan Kainickal
Additional Professor, Head & Neck Oncology
RCC, Trivandrum

Contents
- Role of altered fractionation RT
- Role of Chemo along with RT
- Role of NACT prior to surgery
- Role of NACT prior to CCRT
- Adjuvant chemoRT in high risk patients
- Role of Chemotherapy in Ca Nasopharynx

March Meta Analysis

Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis

[Listing of authors and references]

15 Trials, 6500 Pts
Median FU 6 yrs
Local control

Altered fr Vs Con.

Hyper fr Vs Con.

(6.4%, p < 0.0001)

9.4%, p < 0.0001)

Over all survival

Altered fr Vs Con.

Hyper fr Vs Con.

p= (0.003).

(p < 0.0001)

Conclusions - Altered fractionation

- Al fr. superior to conventional RT - local control (6.4%) and OS (3.4%)
- Hyper Fr. Vs conventional RT – local control (9.4%) and OS (8.2%)
- Hyperfractionation Vs accelerated fractionation (8.2% vs 2% p= 0.02)
- Hyperfractionation and concurrent chemoradiation – similar results
- Limited data on head-to-head comparison
Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis

1. Altered fractionation superior to conventional radiotherapy (p=0.0023) - 5yr OS: benefit 3.1%
   - OS benefit restricted to the hyperfractionated group
   - OS benefit of 8.1% at 5 yrs and of 3.9% at 10 years

2. CCRT vs Altered fractionation - significantly worse with altered fr.

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Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: individual data

J-P Pignon, J Barthelemy, C Demange, J Duquet, on behalf of the MACH-NC Collaborative Group

<table>
<thead>
<tr>
<th>Trial category</th>
<th>Hazard ratio (95% CI)</th>
<th>Chemotherapy effect (p)</th>
<th>Heterogeneity</th>
<th>Absolute benefit At 2 years</th>
<th>Absolute benefit At 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>0.08 (0.05–1.19)</td>
<td>0.74</td>
<td>0.56</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>0.05 (0.02–1.21)</td>
<td>0.10</td>
<td>0.48</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Concurrent</td>
<td>0.81 (0.76–0.86)</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Total</td>
<td>0.90 (0.85–0.94)</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Lancet 2000; 355: 945–55

Radiotherapy and Oncology 92 (2009) 4–14

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon**, Auriol le Malier†, Emeline Maillard*, Jean Bouchet*, on behalf of the MACH-NC Collaborative Group*

*Departments of Otorhinolaryngology, Saint-Etienne University Hospital, Saint-Etienne, France
**Department of Otorhinolaryngology, Saint-Etienne University Hospital, Saint-Etienne, France
†Department of Radiation Oncology, Saint-Etienne University Hospital, Saint-Etienne, France

Editorial

Chemoradiotherapy of head and neck cancer – Can the bumble bee fly?

Jens Overgaard†

Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

HR for Recurrence

<table>
<thead>
<tr>
<th>Timing</th>
<th>HR Event Rate</th>
<th>HR Observed Rate</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent</td>
<td>2414/3590</td>
<td>2328/4376</td>
<td>45.7</td>
<td>1742.6</td>
<td>0.79 (0.69–0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>2088/3749</td>
<td>1634/2871</td>
<td>-13.3</td>
<td>905.7</td>
<td>0.61 (0.48–0.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunct</td>
<td>709/1384</td>
<td>702/1520</td>
<td>0.2</td>
<td>360.9</td>
<td>0.61 (0.48–0.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6186/10359</td>
<td>5424/5680</td>
<td>-13.1</td>
<td>3800.2</td>
<td>0.61 (0.48–0.79)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Radiotherapy and Oncology 92 (2009) 4–14

Meta-Analysis in HNSCC Dr. Cessal Thommachan Kainickal
Meta-Analysis in HNSCC Dr. Cessal Thommachan Kainickal
### Age

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>LRT + CT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>Absolute difference at 2 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 50</td>
<td>823/1236</td>
<td>968/1208</td>
<td>-167.4</td>
<td>388.9</td>
<td>9.8 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>1939/1642</td>
<td>1156/1651</td>
<td>-26.4</td>
<td>532.7</td>
<td>7.9 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>61-70</td>
<td>972/1336</td>
<td>968/1306</td>
<td>-6.2</td>
<td>457.8</td>
<td>3.0 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>71 or over</td>
<td>276/996</td>
<td>269/993</td>
<td>-3.5</td>
<td>114.7</td>
<td>-0.7 ± 0.9</td>
<td></td>
</tr>
</tbody>
</table>

Radiotherapy versus radiotherapy + chemotherapy

20,002 patients and 13,004 deaths (88%)

- Absolute difference at 3 years (95% CI): 4.2% (3.3% - 5.1%)
- Absolute difference at 5 years (95% CI): 2.2% (1.3% - 3.0%)

Bouchut J et al. ESMO 2016
Conclusions CCRT

- CCRT is superior to RT alone-OS&LCR
- Absolute benefit is 6.5 % at 5 yrs
- Induction chemo is not beneficial (Non taxane based)
- Maximum benefit of chemo in young pts
- Single agent is equivalent to combination
- Cisplatin is better than other agents
Sub site benefit

Timing of Chemotherapy

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Chemotherapy</th>
<th>5-year DFS (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>Adjunct</td>
<td>44 (66.6)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>Endosinfective</td>
<td>50 (79.5)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>Concurrent</td>
<td>37 (58.6)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>Adjunct</td>
<td>44 (66.6)</td>
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Meta-Analysis in HNSCC Dr. Cessal Thommachan Kainickal

Radiotherapy and Oncology 108 (2011) 35-49
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Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: Systematic review and meta-analysis

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MACH-NC subset analysis of the effects of chemotherapy on survival at 5 yrs

<table>
<thead>
<tr>
<th>Trial Category</th>
<th>No. of Trials</th>
<th>No. of Patients</th>
<th>Difference(%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td>95</td>
<td>10550</td>
<td>+4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>8</td>
<td>154</td>
<td>+1</td>
<td>0.74</td>
</tr>
<tr>
<td>Induction</td>
<td>31</td>
<td>5269</td>
<td>+2</td>
<td>0.10</td>
</tr>
<tr>
<td>PF</td>
<td>15</td>
<td>2487</td>
<td>+5</td>
<td>0.81*</td>
</tr>
<tr>
<td>Other Chemo</td>
<td>16</td>
<td>2782</td>
<td>0</td>
<td>0.91</td>
</tr>
<tr>
<td>Concurrent</td>
<td>26</td>
<td>3727</td>
<td>+8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Significance survival gain of 5% at 6 years in favour of PF
*No corroborative evidence obtained in a single large trial


Induction chemotherapy ⇔ ChemoRT

- 1. IC 3 Drug Vs 2drug ⇔ RT/CRT
- No CCRT arm
- To know the best induction chemo
- 2. CCRT Vs 3 Drug IC ⇔ CCRT
- To know best approach
- CCRT – control arm
Phase III Induction Chemotherapy – Taxanes

IC 3 Drug (TPF) Vs 2drug (PF) → RT/CRT

• TAX 323 :EORTC 24971 : Chemo → RT
• TAX 324 : Chemo → RT + Carboplatin q 1 week
• Madrid Study : Chemo → RT + Cisplatin q 3 weeks

Better OS & PFS
Induction chemotherapy → ChemoRT

1. IC 3 Drug Vs 2drug → RT/CRT
   - No CCRT arm
   - To know the best induction chemo

2. CCRT Vs 3 Drug IC → CCRT
   - To know best approach
   - CCRT – control arm

CCRT Vs 3 Drug IC → CCRT

- Hitt trial
- DeCIDE
- PARADIGM
  - No benefit
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Is there a survival benefit in patients with advanced squamous cell carcinoma of the head and neck under chemoradiotherapy or radiotherapy alone after surgery administration: A systematic review and meta-analysis.

Jinbiao Shang, Jialei Gu, Qianbo Han, Yaping Xu, Xinmin Yu, Kejin Wang; Zhejiang Cancer Hospital, Hangzhou, China; Wenzhou Medical University, Zhejiang Cancer Hospital, Hangzhou, China

J Clin Oncol 32:5s, 2014 (suppl; abstr 6052)
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The Additional Value of Chemotherapy to Radiotherapy in Locally Advanced Nasopharyngeal Carcinoma: A Meta-Analysis of the Published Literature

J.A. Laperriere, C.L. Garmo, J. Breslow, J. Debord, and R.O. Stinson

Meta-Analysis in HNSCC Dr. Cessal Thommachan Kainickal
Meta-analysis in NPC
MAC-NPC Collaborative Group

- To assess the impact of adding chemotherapy to RT on survival
- 8 trials, 1753 pts
- HR for death=0.82 (95% CI 0.71-0.95)
- 6% absolute survival benefit at 5 years
- Greatest benefit from concurrent chemo
  HR=0.60 (concurrent)
  HR=0.97 (adjuvant)
  HR=0.99 (induction)

Baujat, IJROBP, 2006

Results

OS

EFS

P=0.006

p < (0.001)

Meta-Analysis in HNSCC Dr. Cessal Thommachan Kainickal
Results

### Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio</th>
<th>Weight</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2016</td>
<td>1.11</td>
<td>0.53</td>
<td>0.99 to 1.24</td>
<td>0.08</td>
</tr>
<tr>
<td>He 2014</td>
<td>0.86</td>
<td>0.58</td>
<td>0.78 to 0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>He 2017</td>
<td>0.90</td>
<td>0.64</td>
<td>0.82 to 1.00</td>
<td>0.056</td>
</tr>
<tr>
<td>Sun 2016</td>
<td>0.40</td>
<td>0.55</td>
<td>0.36 to 0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sun 2017</td>
<td>0.94</td>
<td>0.45</td>
<td>0.79 to 1.11</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Meta-Analysis in HNSCC Dr. Cessional Thommachan Kainickal
DFS

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>SE</th>
<th>Weight</th>
<th>HR, Random, WSS, CI</th>
<th>SE, Random, WSS, CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>0.84</td>
<td>0.214</td>
<td>34.0%</td>
<td>0.82 [0.72, 1.0]</td>
<td>0.24 [0.23, 0.26]</td>
</tr>
<tr>
<td>PostgreSQL</td>
<td>-0.16</td>
<td>0.205</td>
<td>14.4%</td>
<td>0.85 [0.60, 1.2]</td>
<td>0.24 [0.23, 0.26]</td>
</tr>
<tr>
<td>Twenty17</td>
<td>-0.25</td>
<td>0.05</td>
<td>6.0%</td>
<td>0.82 [0.64, 1.0]</td>
<td>0.09 [0.09, 0.10]</td>
</tr>
<tr>
<td>Han 2018</td>
<td>-0.45</td>
<td>0.205</td>
<td>4.8%</td>
<td>0.95 [0.68, 1.3]</td>
<td>0.24 [0.23, 0.26]</td>
</tr>
<tr>
<td>Sun 2018</td>
<td>-0.25</td>
<td>0.19</td>
<td>51.7%</td>
<td>0.82 [0.64, 1.0]</td>
<td>0.09 [0.09, 0.10]</td>
</tr>
<tr>
<td>Ten 2018</td>
<td>-0.35</td>
<td>0.20</td>
<td>14.4%</td>
<td>0.77 [0.54, 1.1]</td>
<td>0.09 [0.09, 0.10]</td>
</tr>
<tr>
<td>Total (50, 65)</td>
<td>14.0%</td>
<td>0.06</td>
<td></td>
<td>0.82 [0.64, 1.0]</td>
<td>0.09 [0.09, 0.10]</td>
</tr>
</tbody>
</table>

Heterogeneity: Test for overall effect: Z = 2.52 (P = 0.012) F = 0.0003

Test for overall effect: Z = 2.52 (P = 0.012) F = 0.0003

Thank you