Chemoradiotherapy of Laryngeal Cancers

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Development of Multimodal Therapy for Head & Neck Cancer


- Surgery
- Radiotherapy
- Chemotherapy
- Targeted Therapy
- Gene Therapy
Multimodal Treatment Combinations

- RT → Surg
- Surg → RT
- RT → Surg → RT
- Surg → RT → Chemo
- Chemo → Surg → RT (± Chemo)
- Chemo → RT (± Chemo)
- Concurrent Chemo & RT
- Intraarterial Chemo
- Brachytherapy
Development of Multimodal Therapy for Head and Neck Cancer

20th century

1960’s

Single modality treatments
Surgery – RT – Chemo Rx

Pre-operative radiotherapy

1970’s

Post-operative radiotherapy

1980’s

Induction chemotherapy with surgery + RT
Neoadjuvant chemo Rx

Organ preservation strategies
Concurrent chemo Rx & RT

1990’s

2002
Larynx: Protective sphincter at the inlet of air passage. Responsible for voice production.

Divided into:
Supraglottis – epiglottis, false cords, ventricle, arytenoids, aryepiglottic folds.
Glottis – true vocal cords, the ant. commisures.
Subglottis – below the vocal cords.
Situation and extent

• The larynx lies in the midline of the neck, extending from the root of the tongue to the trachea.

• In adult male it lies in front of the 3rd, 4th, 5th and 6th cervical vertebrae.

• In children and adult female it lies at a higher level.

• Length-44mm in males, 36mm in females
Fig. 54.1. Laryngeal framework.
Lymphatic drainage

- Supraglottis has a rich capillary lymphatic plexus.
- Pass through preepiglottic space and the thyrohyoid membrane and terminate mainly in the subdigastic nodes.
- Few drain to middle internal jugular nodes.
- Essentially no lymphatic capillary in the vocal cord.
- The subglottic area has few lymphatic capillaries.
- Lymphatic trunk pass through the cricothyroid membrane to the pretracheal (delphian) lymph node, some go to the paratracheal and inferior jugular nodes.
RADIOTHERAPY

- Primary treatment – typical dose 66Gy in 33 fractions over 6½ weeks
- Post-operative (adjuvant) – indications include close or involved resection margins, poorly differentiated tumours, extensive lymph node involvement
- Palliative e.g. bleeding, pain
Is there a survival benefit for combining CT with locoregional treatment of SCCHN?

- Meta-analysis of CT in head and neck cancer (MACH-NC)
- 87 trials: 17,858 patients

<table>
<thead>
<tr>
<th>Timing of CT</th>
<th>Absolute benefit after 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>-2%</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>2%</td>
</tr>
<tr>
<td>Concomitant CRT*</td>
<td><strong>8%</strong></td>
</tr>
<tr>
<td><strong>Total</strong>*</td>
<td><strong>5%</strong></td>
</tr>
</tbody>
</table>

*p<0.0001 for effect of CT + logoregional treatment vs logoregional treatment alone

Need for update of MACH-NC 2000

• The IPD meta-analysis (63 trials) showed that chemotherapy improved survival (4% at 5 years) in patients curatively treated for HNSCC with a higher benefit (8%) with concomitant chemotherapy.

• However the heterogeneity of the results limited the conclusions and prompted the group to confirm the results on a more complete database by adding the randomized trials conducted between 1994 and 2000.
Methods
(MACH-NC 2009, Pignon et al)

• The updated IPD meta-analysis included trials comparing loco-regional treatment to loco-regional treatment + chemotherapy in HNSCC patients and conducted between 1965 and 2000
• The log rank-test, stratified by trial, was used to compare treatments
• The hazard ratios of death or relapse were calculated
MACH-NC 2009: Results

• Absolute benefit of CT at 5 years: 6.5 %
• No difference between:
  - conventional vs. altered fractionation
  - Single agent vs. Multiple agent CT
• Decreasing effect of CT on survival with increasing age
Overall survival
Concomitant chemotherapy

<table>
<thead>
<tr>
<th>Survival (%)</th>
<th>Concomitant chemotherapy</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Absolute difference at 5 years ± standard deviation:
6.5 ± 1.0 %

Time from randomisation (Years)

Survival (%)

Concomitant chemotherapy
Control
Overall survival - Induction chemotherapy

Absolute difference at 5 years ± standard deviation: 2.4 ± 1.4 %
CCRT vs. Induction

Absolute difference at 5 years ± standard deviation:
- CCRT vs. Induction: 6.5 ± 1.0 %
- CCRT vs. Control: 2.4 ± 1.4 %
Overall survival - Adjuvant chemotherapy

Absolute difference at 5 years ± standard deviation: -1.0 ± 2.2 %
Overall Survival: All sequence of CT

Absolute difference at 5 years ± standard deviation: 4.5 ± 0.8%
### Death: CCRT vs. RT alone

<table>
<thead>
<tr>
<th>Timing</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LRT+CT</td>
<td>LRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant</td>
<td>3171/4824</td>
<td>3389/4791</td>
<td>-326.4</td>
<td>1587.7</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[0.78;0.86]</td>
</tr>
<tr>
<td>Induction</td>
<td>1877/2740</td>
<td>1813/2571</td>
<td>-40.0</td>
<td>900.7</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[0.90;1.02]</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>631/1244</td>
<td>661/1323</td>
<td>17.9</td>
<td>317.4</td>
<td>1.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[0.95;1.18]</td>
</tr>
<tr>
<td>Total</td>
<td>5679/8808</td>
<td>5863/8685</td>
<td>-348.5</td>
<td>2805.8</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[0.85;0.92]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 179.8 \) \( p < 0.0001 \)

\( I^2 = 41\% \)

Test for interaction: \( \chi^2 = 26.60 \) \( p < 0.0001 \)

LRT+CT effect: \( p < 0.0001 \)
Recurrence: CCRT vs. RT alone

<table>
<thead>
<tr>
<th>Timing</th>
<th>No. Deaths/No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant</td>
<td>3447/4824</td>
<td>3735/4791</td>
<td>-401.7</td>
<td>1742.6</td>
<td>0.79 [0.76;0.83]</td>
</tr>
<tr>
<td>Induction</td>
<td>2036/2740</td>
<td>1924/2571</td>
<td>-13.3</td>
<td>956.7</td>
<td>0.99 [0.93;1.05]</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>703/1244</td>
<td>762/1323</td>
<td>-4.2</td>
<td>360.9</td>
<td>0.99 [0.89;1.10]</td>
</tr>
<tr>
<td>Total</td>
<td>6196/8908</td>
<td>6421/9696</td>
<td>-419.3</td>
<td>3060.2</td>
<td>0.87 [0.84;0.90]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 187.7$; $p < 0.0001$; $I^2 = 43\%$

Test for interaction: $\chi^2 = 35.40$; $p < 0.0001$

LRT+CT better vs. LRT better:

LRT+CT effect: $p < 0.0001$
Impact of CT on Cancer vs. Non-Cancer Deaths

Absolute difference at 5 years ± standard deviation:
-0.5 ± 1.9%

Concomitant chemotherapy

Control
## CT Drugs used: CCRT vs. RT alone

<table>
<thead>
<tr>
<th>Type of chemotherapy</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
<th>p of Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(a) Poly chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU and Platin</td>
<td>602/940</td>
<td>-92.2</td>
<td>317.6</td>
<td></td>
<td>0.75 [0.67;0.84]</td>
<td>p = 0.41</td>
</tr>
<tr>
<td>5-FU or Platin</td>
<td>495/743</td>
<td>-45.8</td>
<td>250.0</td>
<td></td>
<td>0.83 [0.74;0.94]</td>
<td></td>
</tr>
<tr>
<td>Neither 5-FU and Platin</td>
<td>62/115</td>
<td>-11.1</td>
<td>35.0</td>
<td></td>
<td>0.73 [0.52;1.01]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (a)</strong></td>
<td>1159/1798</td>
<td>-149.0</td>
<td>602.6</td>
<td></td>
<td>0.78 [0.72;0.85]</td>
<td></td>
</tr>
<tr>
<td><strong>(b) Mono chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono Platin</td>
<td>703/1151</td>
<td>-102.6</td>
<td>341.8</td>
<td></td>
<td>0.74 [0.67;0.82]</td>
<td>p = 0.006</td>
</tr>
<tr>
<td>Mono Other</td>
<td>1309/1875</td>
<td>-74.8</td>
<td>643.3</td>
<td></td>
<td>0.89 [0.82;0.96]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (b)</strong></td>
<td>2012/3026</td>
<td>-177.4</td>
<td>985.1</td>
<td></td>
<td>0.84 [0.78;0.89]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (a ... b)</strong></td>
<td>3171/4924</td>
<td>-326.4</td>
<td>1687.7</td>
<td></td>
<td>0.81 [0.78;0.86]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2_1 = 1.69 \quad p = 0.19 \quad \text{LRT+CT better} \quad \text{LRT better}$
### Patient Characteristics: CCRT vs. RT alone

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>LRT + CT</th>
<th>LRT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>Interaction and trend tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2635/3882</td>
<td>2807/3847</td>
<td>-259.2</td>
<td>1310.3</td>
<td></td>
<td></td>
<td>p_inter = 0.95</td>
</tr>
<tr>
<td>Female</td>
<td>483/788</td>
<td>508/788</td>
<td>-44.1</td>
<td>218.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>923/1667</td>
<td>1084/1696</td>
<td>-135.1</td>
<td>485.4</td>
<td></td>
<td></td>
<td>p_inter = 0.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1210/1080</td>
<td>1179/1538</td>
<td>-131.8</td>
<td>562.9</td>
<td></td>
<td></td>
<td>p_trend = 0.31</td>
</tr>
<tr>
<td>2 or 3</td>
<td>220/270</td>
<td>218/274</td>
<td>-15.8</td>
<td>00.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>133/251</td>
<td>155/286</td>
<td>-1.5</td>
<td>66.6</td>
<td></td>
<td></td>
<td>p_inter = 0.20</td>
</tr>
<tr>
<td>III</td>
<td>661/1140</td>
<td>699/1094</td>
<td>-83.7</td>
<td>319.9</td>
<td></td>
<td></td>
<td>p_trend = 0.60</td>
</tr>
<tr>
<td>IV</td>
<td>2268/3260</td>
<td>2430/3261</td>
<td>-240.9</td>
<td>1125.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p_inter = 0.16</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>060/997</td>
<td>754/1020</td>
<td>-72.8</td>
<td>327.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>1123/1723</td>
<td>1219/1681</td>
<td>-138.3</td>
<td>550.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>60/1013</td>
<td>644/1012</td>
<td>-64.0</td>
<td>294.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>546/760</td>
<td>563/757</td>
<td>-40.5</td>
<td>252.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>187/264</td>
<td>183/256</td>
<td>3.2</td>
<td>83.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LRT + CT better | LRT better
**Age: CCRT vs. RT alone**

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>LRT + CT</th>
<th>LRT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>Absolute difference at 5 years ± sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 50</td>
<td>803/1296</td>
<td>860/1288</td>
<td>-107.6</td>
<td>386.9</td>
<td>-</td>
<td>9.8 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>1069/1645</td>
<td>1198/1661</td>
<td>-136.4</td>
<td>539.7</td>
<td>-</td>
<td>7.8 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>61-70</td>
<td>972/1368</td>
<td>988/1330</td>
<td>-56.2</td>
<td>457.8</td>
<td>-</td>
<td>3.0 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>71 or over</td>
<td>273/356</td>
<td>260/336</td>
<td>-3.5</td>
<td>114.7</td>
<td>-</td>
<td>-0.7 ± 3.9</td>
<td></td>
</tr>
</tbody>
</table>

\[ p_{inter} = 0.02 \]
\[ p_{trend} = 0.003 \]
## End Points

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>NbDeaths/ NbExposed</th>
<th>Concurrent</th>
<th>Induction</th>
<th>CEValence</th>
<th>Hazard Ratio</th>
<th>HR[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes</td>
<td>36/430</td>
<td>36/431</td>
<td>-132</td>
<td>1788</td>
<td></td>
<td>0.90[0.77,1.04]</td>
</tr>
<tr>
<td>Benthic</td>
<td>228/340</td>
<td>397/347</td>
<td>-301</td>
<td>1438</td>
<td></td>
<td>0.81[0.69,0.95]</td>
</tr>
<tr>
<td>Locomotor</td>
<td>218/389</td>
<td>251/389</td>
<td>-304</td>
<td>1162</td>
<td></td>
<td>0.77[0.64,0.93]</td>
</tr>
</tbody>
</table>

Concurrent better | Induction better
Concurrent better: p=0.0001
Failure Rates: CCRT vs. Induction

Concomitant Chemotherapy
- Local failure: Absolute difference at 5 years ± sd: -9.3 ± 1.2%
- Distant failure: Absolute difference at 5 years ± sd: 19.3%

Induction Chemotherapy
- Local failure: Absolute difference at 5 years ± sd: 1 ± 1.7%
- Distant failure: Absolute difference at 5 years ± sd: 47.5%
Failure Rates: CCRT vs. Induction: 5FU + Platinum

- **Concomitant chemotherapy**
  - Local failure: 63.2%
  - Distant failure: 18.9%

- **Control**
  - Local failure: 60.2%
  - Distant failure: 16%

- **Induction chemotherapy**
  - Local failure: 50.9%
  - Distant failure: 15.6%

Absolute difference at 5 years ± sd:
- Local failure: -13.5 ± 2.8%
- Distant failure: -2.9 ± 2.7%
- Local failure: 1.8 ± 2.3%
- Distant failure: -3.5 ± 2.0%
Outlook

• This meta-analysis clearly demonstrates that Radiotherapy with PF chemotherapy can contribute substantial clinical benefit to the management of patients with locally advanced head and neck cancer.

• However, there remains considerable room for improvement, particularly in terms of long-term survival outcomes, treatment induced side effects /complications
Concurrent chemoradiotherapy
CONCURRENT CHEMOTHERAPY

• Most commonly single agent Cisplatin for 2–3 doses if given every 3 weekly
• Pignon meta-analysis showed an 8% absolute survival benefit when chemo added to RT
• Several randomised trials in unresectable disease show significant improvement in local control and survival
• Regarded by most clinicians as the best time to give chemotherapy
• Increased toxicity (especially mucositis) means only suitable for fit patients
Sanchiz F et al.

859 pts, HNSCC
stage III/IV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RR</th>
<th>10yr OS</th>
<th>10yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: RT</td>
<td>67.8%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>B: HFxRT</td>
<td>90%</td>
<td>40%</td>
<td>31%</td>
</tr>
<tr>
<td>C: CCRT (conventional RT)</td>
<td>96.3%</td>
<td>42%</td>
<td>37%</td>
</tr>
</tbody>
</table>

p < 0.01 (A v B)
< 0.01 (A v C)
< 0.01 (A v C)

Browman GP et al

175 pts, HNSCC
T3/T4

CCRT
Identical RT in both arms
RT: 60Gy/30fx, conventional
C/T: 5-FU 1200mg/m2/d, infusion
D1-D3, D22-D24

RT alone

<table>
<thead>
<tr>
<th>Oral cavity</th>
<th>12%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx</td>
<td>42%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>14%</td>
</tr>
<tr>
<td>Larynx</td>
<td>27%</td>
</tr>
<tr>
<td>Other</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Complete response</th>
<th>3yr PFS</th>
<th>3yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT</td>
<td>68%</td>
<td>40%</td>
<td>58%</td>
</tr>
<tr>
<td>RT</td>
<td>56%</td>
<td>30%</td>
<td>42%</td>
</tr>
<tr>
<td>p value</td>
<td>0.04</td>
<td>0.057</td>
<td>0.08</td>
</tr>
</tbody>
</table>

More mucositis, weight loss, and skin toxicity in CCRT arm

*Journal of Clinical Oncology 1994; 12: 2648-2653*
Ardelstein DJ et al

100 pts, HNSCC stage III/IV

RT alone

CCRT

RT: 66-72Gy, conventional, 1.8-2Gy/fx
Cisplatin: 20mg/m2/d
5FU: 1000mg/m2/d
Infusion, D1-D4 D22-D25

Primary site resection +/- neck dissection

<table>
<thead>
<tr>
<th>Primary site</th>
<th>RT alone</th>
<th>CCRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Larynx</td>
<td>36%</td>
<td>36%</td>
</tr>
</tbody>
</table>

5yr OS | RFS | Dist. Mets-free survival | OS with primary site preserve | Local control without resection | p value |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>48%</td>
<td>51%</td>
<td>75%</td>
<td>34%</td>
<td>45%</td>
</tr>
<tr>
<td>CCRT</td>
<td>50%</td>
<td>62%</td>
<td>84%</td>
<td>42%</td>
<td>77%</td>
</tr>
<tr>
<td>p value</td>
<td>0.55</td>
<td>0.04</td>
<td>0.09</td>
<td>0.004</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Survival benefit from better local control

Cancer 2000; 88: 876-883
100 pts, HNSCC stage III/IV

**RT alone**
- RT: 66-72Gy, conventional, 1.8-2Gy/fx
- Cisplatin: 20mg/m2/d
- 5FU: 1000mg/m2/d
- Infusion, D1-D4, D22-D25

**CCRT**
- Residual dz or recurrence
- Primary site resection +/- neck dissection

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>RFS</th>
<th>Dist. Mets-free survival</th>
<th>OS with primary site preserve</th>
<th>Local control without resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>48%</td>
<td>51%</td>
<td>75%</td>
<td>34%</td>
<td>45%</td>
</tr>
<tr>
<td>CCRT</td>
<td>50%</td>
<td>62%</td>
<td>84%</td>
<td>42%</td>
<td>77%</td>
</tr>
<tr>
<td>p value</td>
<td>0.55</td>
<td>0.04</td>
<td>0.09</td>
<td>0.004</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Survival benefit from better local control

*Cancer* 2000; 88: 876-883
GORTEC

226 pts, oropharynx III/IV

RT alone

Identical RT in both arms
RT: 7000cGy/35fx, conventional

CCRT

Carbo 70mg/m2/d, D1-D4
5FU 600mg/m2/d, D1-D4
q3w, 3 cycles

Dose delivery

<table>
<thead>
<tr>
<th></th>
<th>RT dose</th>
</tr>
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<tbody>
<tr>
<td>RT</td>
<td>6920 cGy</td>
</tr>
<tr>
<td>CCRT</td>
<td>6960 cGy</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbo</td>
<td>98%</td>
<td>86%</td>
<td>66%</td>
</tr>
<tr>
<td>5FU</td>
<td>98%</td>
<td>88%</td>
<td>67%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>3yr</th>
<th>DFS</th>
<th>OS</th>
<th>Dist. mets</th>
<th>LR control</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT</td>
<td>31%</td>
<td>51%</td>
<td>11%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>20%</td>
<td>42%</td>
<td>11%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.04</td>
<td>0.02</td>
<td>NS</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Journal of National Cancer Institute 1999; 91:2081-2086
Jeremic B et al, Japan

130 pts, HNSCC stage III/IV

<table>
<thead>
<tr>
<th></th>
<th>CCRT (HFxRT)</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>5yr OS</th>
<th>5yr PFS</th>
<th>Local recur.-PFS</th>
<th>Dist. Mets-PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT</td>
<td>46%</td>
<td>41%</td>
<td>50%</td>
<td>86%</td>
</tr>
<tr>
<td>RT</td>
<td>25%</td>
<td>25%</td>
<td>36%</td>
<td>57%</td>
</tr>
</tbody>
</table>

p value: 
- 0.0075
- 0.0068
- 0.041
- 0.0013

Similar stomatitis, esophagitis in both arm, more leukopenia and thrombocytopenia in CCRT arm

Journal of Clinical Oncology 2000; 18: 1458-1464
ECOG RTOG

295 pts, HNSCC unresectable III/IV

A: RT alone
- RT: 7000cGy/35fx, conventional identical in three arms

B: CCRT
- Cisplatin 100mg/m2, D1, D22, D43

C: CCRT (RT 3000cGy)
- CR or unresectable
- CCRT (RT 3000cGy)
- PR
- surgery

Cisplatin 75mg/m2, D1
5FU 1000mg/m2/d x 4d
q4w x 3

Oral cavity 13%
Oropharynx 59%
Hypopharynx 19%
Larynx 9%

<table>
<thead>
<tr>
<th></th>
<th>3y OS</th>
<th>Dist. Mets as first site</th>
<th>Treatment compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>23%</td>
<td>17.9%</td>
<td>92.6%</td>
</tr>
<tr>
<td>B</td>
<td>37%</td>
<td>21.8%</td>
<td>85.1%</td>
</tr>
<tr>
<td>C</td>
<td>27%</td>
<td>19.1%</td>
<td>73%</td>
</tr>
<tr>
<td>p</td>
<td>0.014 (A vs B)</td>
<td>NS</td>
<td>0.001 (A vs C) 0.05 (B vs C)</td>
</tr>
</tbody>
</table>

215 pts, HNSCC stage III/IV, unresectable

**RT 70Gy/35fx**

C/T → RT (A)

- Cisplatin 100mg/m², D1
- 5-FU 1000mg/m², D1-D5
- Q3w x 3

CCRT (B)

- Cisplatin 60mg/m², D1
- 5-FU 800mg/m², D1-D5
- Qw x 7

**Sinus** 1%

- Oral 32%
- Oropharynx 23%
- Nasopharynx 6%
- Hypopharynx 27%
- Larynx 11%

**LR recurrence**, **Dist Mets**, **3-yr OS**, **3-yr dz specific survival**

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR recurrence</td>
<td>55%</td>
<td>41%</td>
</tr>
<tr>
<td>Dist Mets</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>3-yr OS</td>
<td>36%</td>
<td>42%</td>
</tr>
<tr>
<td>3-yr dz specific survival</td>
<td>41%</td>
<td>55%</td>
</tr>
</tbody>
</table>

% Cisplatin 97% 88%

% 5-FU 97% 79%

% RT(>65Gy) 78% 81%

% RT delay No difference

Concurrent chemoradiotherapy

- Enhance locoregional control
- Minimal effect in distant metastasis
- Improve survival
  - Superior than sequential chemoradiotherapy
  - Disease nature: local recurrence predominant
- Enhance RT toxicity
  - Mucositis, skin toxicity, BW loss
  - Leukopenia depends on C/T type
Brockstein B et al

**PFLI**
- Cisplatin 100mg/m², D1
- 5FU 640mg/m²/d, CVI, D1-D5
- Leucovorin 100mg q4h po, D1-D6
- INF-α 2MU/m²/d, D1-D6

**Induction C/T x 3**

**CCRT**

**PFLI-FHX**
- 164 pts
- Induction C/T x 3

**CCRT**

- 5FU 800mg/m²/d x 5/wk
- Hydroxyurea 1000mg q12h, 11doses/wk
- RT 6000cGy/30fx

**(C/T)HF2X**
- 230 pts
- Intensified CCRT

- Cisplatin 100mg/m², D1
  or Paclitaxel 100mg/m², D1
  q3w x 3

- 5FU 800mg/m²/d x 5/wk
  + Hydroxyurea 1000mg q12h, 11doses/wk
  RT 6000cGy/30fx

*J Clin Oncol. 1995; 13: 876-83*

*Annals of Oncology 2004; 15: 1179-1186*
Distant failure

Locoregional failure

Overall survival

Progression-free survival

Yale 6557 protocol

42 pts, HN cancer, stage III/IV resectable/unresectable

C/T: 20mg/m2/d x 4d
5FU 800mg/m2/d x 4d
LV 500mg/m2/d x 4d
CCRT: RT: 70Gy/35fx
Cisplatin 100mg/m2, q3w

C/T x 2   CCRT

Non-responder
operation

Induction C/T: RR 76%
C/T → CCRT: 67% CR

5y PFS 5y OS 2y Local control 2yr Distant control
54% 52.4% 76.3% 79%

59 pts, HN cancer, resectable stage III/IV

SWOG

C/T: Cisplatin 100mg/m2
5FU 1000mg/m2/d x 5d

q3w

CCRT: RT: 72Gy/36fx
Cisplatin 100mg/m2, q3w

C/T x 2

CCRT

Non-responder

operation

Non-responder

operation

Hypopharynx 22 pts
Tongue base 37 pts

• Induction C/T: RR 78%
• C/T → CCRT: 54% CR

3y PFS 3y OS 3y PFS with Organ preservation

57% 64% 52%

Journal of Clinical Oncology 2005; 23: 88-95
Post-op CCRT
Risk factors of post-op recurrence

- Primary tumor
  - Positive or close margin
- Neck
  - Multiple LN: >2
  - Extracapsular extension
  - Perineural invasion
  - Vascular embolism
- Both locoregional and distant

Adjuvant RT

• For possible residual disease
  — Positive margin or close margin
  — Multiple neck LN

• Attempt to decrease local failure
  — Decrease subsequent distant failure

• CCRT better than RT?

Radiology 1970; 95: 185-188
Clinical Otolaryngology 1982; 7: 185-192
Head and Neck Surgery 1984; 6: 720-723
Head and Neck Surgery 1987; 10: 19-30
EORTC 22931

Cisplatin 100mg/m², D1, D22, D43
XRT 54Gy/27fx, Boost 12Gy/6fx

167 pts, HNSCC
stage III/IV

Surgery
Surgery

Cisplatin + XRT
XRT

pT3/T4 + any N
pT1/T2 + N2/N3
pT1/T2 + N0/N1 + unfavorable patho

<table>
<thead>
<tr>
<th>Margin</th>
<th>Margin Perineural invasion Extracapsular spread Vascular embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>28% 13% 57% 20%</td>
</tr>
<tr>
<td>Negative</td>
<td>71% 85% 43% 80%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1% 2%</td>
</tr>
</tbody>
</table>

EORTC 22931

<table>
<thead>
<tr>
<th></th>
<th>C/T on time without delay</th>
<th>5yr PFS</th>
<th>5yr OS</th>
<th>LRR</th>
<th>Dist Mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>88%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>66%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>49%</td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>CCRT</th>
<th>RT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5yr PFS</td>
<td>47%</td>
<td>36%</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>5yr OS</td>
<td>53%</td>
<td>40%</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>LRR</td>
<td>18%</td>
<td>31%</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Dist Mets</td>
<td>21%</td>
<td>25%</td>
<td>0.61</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Acute mucosa reaction</th>
<th>Mucosa fibrosis</th>
<th>Xerostomia</th>
<th>Severe leukopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT</td>
<td>41%</td>
<td>10%</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>RT</td>
<td>21%</td>
<td>5%</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>p value</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*N Eng J Med 2004; 350: 1945-1952*
RTOG 9501

Cisplatin 100mg/m², D1, D22, D43
XRT 60Gy/30fx, Boost 6Gy/3fx

416 pts, HNSCC, high risk of recurrence

Surgery → Cisplatin + XRT
Surgery → XRT

Positive margin 17%
LN>2 or extracapsular extension 83%

Oral cavity 27%
Oropharynx 42%
Hypopharynx 10%
Larynx 21%

### DFS OS LRR Dist Mets as 1st event

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>OS</th>
<th>LRR</th>
<th>Dist Mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT</td>
<td>40%</td>
<td>52.5%</td>
<td>19%</td>
<td>23%</td>
</tr>
<tr>
<td>RT</td>
<td>30%</td>
<td>45%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>p value</td>
<td>0.01</td>
<td>0.19</td>
<td>0.01</td>
<td>0.46</td>
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</table>

### Acute adverse effect Late adverse effect

<table>
<thead>
<tr>
<th></th>
<th>Acute adverse effect</th>
<th>Late adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT</td>
<td>77%</td>
<td>21%</td>
</tr>
<tr>
<td>RT</td>
<td>34%</td>
<td>17%</td>
</tr>
<tr>
<td>p value</td>
<td>0.001</td>
<td>0.29</td>
</tr>
</tbody>
</table>

hematological, mucosa, GI tract

*N Eng J Med 2004; 350: 1937-1944*
Post-op adjuvant CCRT

• Decrease locoregional recurrence
• Not affect distant metastasis
  – Though systemic side-effect
  – Insufficient dose delivery?
  – Single agent not enough?

• Actually improve survival
  – Locoregional recurrence dominant in HNSCC
Organ preservation
Organ Preservation

- Laryngeal cancer as an example
  - Supraglottic
  - Subglottic
    - T1: limited, not extend to glottis
    - T2: extend to glottis, but normal cord mobility
    - T3/T4: cord fixation, invade adjacent tissue
  - Glottic
    - T1a/b: limited to one/both sides, no cord fixation
    - T2: impair cord motility, to supra- or subglottis
    - T3/T4: cord fixation, invade adjacent tissue/organ
Laryngeal cancer

- Historically
  - Early: T1, T2
    - RT alone, surgical salvage, or
    - Surgical → adjuvant RT
    - Larynx usually preserved
  - Advance: T3, T4
    - RT alone not sufficient
    - Surgical resection, usually total laryngectomy
Veterans Affairs Laryngeal Cancer Study Group

332 pts, laryngeal SCC stage III/IV

Surgery

C/T x 2 → Adjuvant RT

RT: 5000cGy/25fx

C/T x 1 → Definitive RT

RT: 6600-7600cGy

Surgery +/- RT

Residual disease

Cisplatin 100mg/m2, D1
5FU 1000mg/m2/d x 5d q3w

T1/T2 9%
T3 65%
T4 26%

Glottis 37%
Supraglottis 63%

<table>
<thead>
<tr>
<th>2yr</th>
<th>DFS</th>
<th>OS</th>
<th>Recur at primary</th>
<th>Recur at regional</th>
<th>Distant mets</th>
<th>Laryngectomy-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>75%</td>
<td>68%</td>
<td>2%</td>
<td>5%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>C/T →RT</td>
<td>65%</td>
<td>68%</td>
<td>12%</td>
<td>8%</td>
<td>11%</td>
<td>39%</td>
</tr>
</tbody>
</table>

p value

0.12 0.98 0.001 NS 0.001

VALSG study

- Patients requiring total laryngectomy: 36%
- Laryngeal preservation rate: 64%
- Estimated 2-year survival: 68% (p=0.9846)
- Tumor response to CT (after 2 cycles): 85%

- 2-year and 10-year follow up show significant difference in survival
- More local recurrences (p=0.0005) but fewer distant metastases (p=0.0016) in experimental arm

VALSG study

• Laryngeal preservation achieved in 64% of patients in the CT arm

• Fewer distant metastases in the CT arm

• Overall survival rates for the two groups were similar, suggesting that chemotherapy could be used effectively for organ preservation without compromising overall survival.
QOL assessment

- Veterans Affairs Laryngeal Cancer Study Group

- C/T → RT vs. Surgery → RT
  - “pain”, “mental health”, “bother”

- Laryngectomy vs. Laryngeal preserve
  - “pain”, “mental health”, “bother”
  - “role physical”, “social function”, “emotion”, “response”

- No difference in speech and eating

EORTC

194 pts, hypopharynx SCC stage II/III/IV

Surgery

Adjuvant RT

RT: 5000cGy/25fx

C/T x 2

C/T x 1

Definitive RT

RT: 7000cGy

Residual disease

Poor respond

Surgery +/- RT

T2 20%

T3 75%

T4 5%

Cisplatin 100mg/m², D1 5FU 1000mg/m²/d x 5d

q3w

5yr DFS OS Recur at local Recur at regional Distant mets Larynectomy-free survival

Surgery 32% 35% 17% 23% 36%

C/T → RT 25% 30% 12% 19% 25% 35%

p value NS NS NS NS 0.041

Pyriform sinus 78%

Aryepiglottic fold 22%

Journal of National Cancer Institute 1996; 8: 890-899
GETTEC, French

68 pts, laryngeal SCC all T3

Surgery → Adjuvant RT
RT: 5000cGy/25fx
C/T x 3 → Definitive RT
RT: 7000cGy

Cisplatin 100mg/m2, D1
5FU 1000mg/m2/d x 5d q3w

Supraglottis 31%
Glottis 41%
Unknown 28%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2yr DFS</th>
<th>2yr OS</th>
<th>8yr Laryngectomy-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>78%</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>C/T → RT</td>
<td>62%</td>
<td>69%</td>
<td>42%</td>
</tr>
<tr>
<td>p value</td>
<td>0.02</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

Inferior outcome !!

Oral Oncology 1998; 34: 224-228
RTOG 91-11

518 pts, laryngeal SCC III/IV

RT alone

CCRT

C/T x 2

C/T x 1

RT

CCRT:
RT 7000cGy/35fx
Cisplatin 100mg/m², q3w

Residual disease

Cisplatin 100mg/m², D1
5FU 1000mg/m²/d x 5d
q3w

Poor respond

Surgery +/- RT

<table>
<thead>
<tr>
<th>T2</th>
<th>12%</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>78%</td>
</tr>
<tr>
<td>T4</td>
<td>10%</td>
</tr>
</tbody>
</table>

Supraglottis 69%
Glottis 31%

Speech/swallow: similar

<table>
<thead>
<tr>
<th></th>
<th>A: RT</th>
<th>B: CCRT</th>
<th>C: C/T→RT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02(C v A)</td>
<td>27%</td>
<td>36%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>0.006(B v A)</td>
<td>56%</td>
<td>54%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>0.005(B v C)</td>
<td>70%</td>
<td>88%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>0.001(B v A)</td>
<td>56%</td>
<td>78%</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>0.001(B v C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.004(B v C)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0.03(B v A)</td>
<td></td>
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</tbody>
</table>

Distant mets:
A: RT 22%
B: CCRT 12%
C: C/T→RT 15%

Laryngeal preservation

• Chemoradiotherapy becomes standard
  – No negative survival impact, at most series
• Organ preserved, but function?
  – Fibrosis, choking, difficult speech
  – Reconstructed organ followed by rehabilitation
    • Function may be better
    • Loss of organ, psychological stress

• ASCO guideline
  – CRT for T3/T4 to preserve larynx (Aug. 2006)
CCRT, H&N, SJH*

PROTOCOL

- **Arm I (Control)** Radiotherapy alone
- **Arm II** RT+CDDP 70mg/m² D1&21
- **Arm III** RT+CDDP 100mg/m² D1&21
- **Arm IV** RT+CDDP 30mg/m² D1,8,15,21,28
- **Arm V** RT+CDDP 70mg/m² D1&21
  + 5FU 1000mg/m² D1,2,3 &21,22,23

*Kumar T Bhowmik, N Das, Rajiv Sharma, JS Bhatia, Daulat Singh, Shantanu Sharma, Vikas Madhola, Surbhi Gupta, A Safaya, VP Venkatachal, Jyotsna Pandey et. al. 2000*
CCRT, H&N, SJH

PROTOCOL

• Radiotherapy
  Cobalt 60, 80 cm SSD
  Tumor dose 60-65Gy in 30-32 #
  Portals reduced at 44Gy

• Chemotherapy
  Cisplatin after adequate hydration and antiemetic therapy
  5FU in a 4hour infusion
## PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>RT+CDDP70 D1,21</th>
<th>RT+CDDP100 D1,21</th>
<th>RT+CDDP30 D1,8,15,21,28</th>
<th>RT+CDDP +5FU</th>
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<tbody>
<tr>
<td><strong>ENROLLED</strong></td>
<td>1800</td>
<td>749</td>
<td>350</td>
<td>498</td>
<td>528</td>
</tr>
<tr>
<td><strong>EVALUABLE</strong></td>
<td>1640</td>
<td>528</td>
<td>276</td>
<td>369</td>
<td>425</td>
</tr>
<tr>
<td><strong>MALE</strong></td>
<td>1476</td>
<td>475</td>
<td>248</td>
<td>332</td>
<td>386</td>
</tr>
<tr>
<td><strong>FEMALE</strong></td>
<td>164</td>
<td>53</td>
<td>28</td>
<td>67</td>
<td>39</td>
</tr>
<tr>
<td><strong>MEAN AGE</strong></td>
<td>52</td>
<td>54</td>
<td>51</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>SITE OF LESION</td>
<td>CONTROL</td>
<td>RT+CDDP70</td>
<td>RT+CDDP100</td>
<td>RT+CDDP30</td>
<td>RT+CDDP +5FU</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>ORAL CAVITY</td>
<td>391</td>
<td>186</td>
<td>89</td>
<td>96</td>
<td>122</td>
</tr>
<tr>
<td>OROPHARYNX</td>
<td>429</td>
<td>197</td>
<td>104</td>
<td>162</td>
<td>171</td>
</tr>
<tr>
<td>LARYNX</td>
<td>436</td>
<td>195</td>
<td>106</td>
<td>159</td>
<td>158</td>
</tr>
<tr>
<td>HYPOPHARYNX</td>
<td>384</td>
<td>171</td>
<td>51</td>
<td>81</td>
<td>77</td>
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</table>
## RESULTS

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>RT+CDDP70 D1,21</th>
<th>RT+CDDP100 D1,21</th>
<th>RT+CDDP30 D1,8,15,21,28</th>
<th>RT+CDDP +5FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>1640</td>
<td>528</td>
<td>276</td>
<td>369</td>
<td>425</td>
</tr>
<tr>
<td>C.R.</td>
<td>161 (10%)</td>
<td>132 (25%)</td>
<td>71 (26%)</td>
<td>114 (31%)</td>
<td>127 (30%)</td>
</tr>
<tr>
<td>P.R.</td>
<td>246 (15%)</td>
<td>153 (29%)</td>
<td>93 (34%)</td>
<td>132 (36%)</td>
<td>148 (35%)</td>
</tr>
<tr>
<td>N.C.</td>
<td>230 (14%)</td>
<td>105 (20%)</td>
<td>55 (20%)</td>
<td>55 (15%)</td>
<td>63 (15%)</td>
</tr>
<tr>
<td>P.D.</td>
<td>1003 (61%)</td>
<td>138 (26%)</td>
<td>57 (20%)</td>
<td>68 (18%)</td>
<td>87 (20%)</td>
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</tbody>
</table>
### RESULTS Contd.

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>RT+CDDP70 D1,21</th>
<th>RT+CDDP100 D1,21</th>
<th>RT+CDDP30 D1,8,15,21,28</th>
<th>RT+CDDP +5FU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Locoregional Control(%)</strong> (at 1 year)</td>
<td>42</td>
<td>55</td>
<td>62</td>
<td>73</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>P=0.05</td>
<td>P=0.01</td>
<td>P=0.005</td>
<td>P=0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Progression Free Survival(mo)</strong></td>
<td>8.2</td>
<td>11.6</td>
<td>13.4</td>
<td>18.3</td>
<td>21.8</td>
</tr>
<tr>
<td></td>
<td>P=0.01</td>
<td>P=0.01</td>
<td>P=0.005</td>
<td>P=0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Actuarial Survival (2 years)</strong></td>
<td>25%</td>
<td>40%</td>
<td>45%</td>
<td>60%</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>P=0.01</td>
<td>P=0.005</td>
<td>P=0.001</td>
<td>P=0.001</td>
<td></td>
</tr>
</tbody>
</table>
## TOXICITIES (Grade III & IV)

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>RT+CDDP70 D1,21</th>
<th>RT+CDDP100 D1,21</th>
<th>RT+CDDP30 D1,8,15,21,28</th>
<th>RT+CDDP +5FU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MUCOSITIS</strong></td>
<td>820(50%)</td>
<td>316(60%)</td>
<td>179(65%)</td>
<td>258(70%)</td>
<td>297(70%)</td>
</tr>
<tr>
<td><strong>NEUTROPENIA</strong></td>
<td>33(2%)</td>
<td>53(10%)</td>
<td>41(15%)</td>
<td>73(20%)</td>
<td>106(25%)</td>
</tr>
<tr>
<td><strong>NEPHROTOXICITY</strong></td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>18(5%)</td>
<td>42(10%)</td>
</tr>
<tr>
<td><strong>TRT.INTURRPT. 0-7 DAYS</strong></td>
<td>156(9%)</td>
<td>26(5%)</td>
<td>14(5%)</td>
<td>37(10%)</td>
<td>64(15%)</td>
</tr>
<tr>
<td></td>
<td>82(5%)</td>
<td>11(2%)</td>
<td>5(2%)</td>
<td>55(15%)</td>
<td>65(15%)</td>
</tr>
</tbody>
</table>
Conclusions

• Carcinoma of larynx has a very good control rates

• Both radiotherapy and surgery gives good results in early stages

• Combined modality treatment gives optimum results in advanced stages

• Presently the focus is on use of modalities with best cure rates and organ preservation
Thank You