Oropharyngeal carcinoma
State of the Art

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Institute Gustave Roussy
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- Among HNSCC what are the specificities of the oropharyngeal sub site?
  - Frequent among HNSCC
  - More HPV related carcinomas (up to 50-75%)
  - Importance of IMRT for parotid sparing

- Are the results obtained in the oropharynx different from the rest of HNSCC?

- Relative consensus on « general treatment guidelines »

Multidisciplinary approach in oropharynx carcinomas

T1-T2
Surgery (IM)RT (Uvula-tonsil) or non-infiltrating or HPV
Post-op RT +/- CDDP

T3-T4*
Surgery Inoperable (IM)RT-CT (IM)RT-erbitux

* Induction chemo revisited
How different are the oropharyngeal carcinomas as compared to the other HNSCC?

For altered fractionation …

Is the effect of altered fractionated RT any different in oropharynx sub site?

MARCH database of randomized trials (1970-1999)

Hyperfractionated or accelerated RT

Conventional RT
Meta-Analysis of Chemotherapy in Head & Neck Cancer

**Overall results (all sites)**

**Loco regional control**

<table>
<thead>
<tr>
<th>Risk of recurrence (%)</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperfractionation</td>
<td>62.9%</td>
<td>46.3%</td>
<td>38.1%</td>
<td>30.9%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Acceleration w/o total dose reduction</td>
<td>59.8%</td>
<td>52.9%</td>
<td>46.5%</td>
<td>40.2%</td>
<td>34.0%</td>
</tr>
</tbody>
</table>

**Time from randomisation (Years)**

- 0123456
- ≥7

**Risk of recurrence (%)**

- 20
- 40
- 60
- 80
- 100

<table>
<thead>
<tr>
<th>Time from randomisation (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>≥7</td>
</tr>
</tbody>
</table>

**Characteristics**

<table>
<thead>
<tr>
<th>Site of tumour</th>
<th>Altered fractionated RT</th>
<th>Conventional RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>Larynx</td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Others</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Altered fractionated RT</th>
<th>Conventional RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>II</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>III</td>
<td>28%</td>
<td>29%</td>
</tr>
<tr>
<td>IV</td>
<td>46%</td>
<td>45%</td>
</tr>
</tbody>
</table>

**Absolute difference at 5 years:**

- 6.4 ± 1.3%

Altered fractionated RT database (N > 6500 patients randomized)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Altered fractionated RT (n=3,650)</th>
<th>Conventional RT (n=3,423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>Larynx</td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Others</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site</th>
<th>Altered fractionated RT</th>
<th>Conventional RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>Larynx</td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Others</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Altered fractionated versus conventional RT : survival by site**

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths / No. Enrolled (Initial)</th>
<th>Deaths / No. Enrolled (Final)</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>Interaction term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50 or less</td>
<td>374/680</td>
<td>394/631</td>
<td>-45.5</td>
<td>184.5</td>
<td>p = 0.02</td>
</tr>
<tr>
<td></td>
<td>51-60</td>
<td>736/1172</td>
<td>719/1128</td>
<td>-19.4</td>
<td>355.5</td>
<td>p = 0.39</td>
</tr>
<tr>
<td></td>
<td>61-70</td>
<td>785/1221</td>
<td>736/1125</td>
<td>-29.3</td>
<td>371.4</td>
<td>p = 0.20</td>
</tr>
<tr>
<td></td>
<td>71 or over</td>
<td>408/561</td>
<td>376/524</td>
<td>14.2</td>
<td>191.0</td>
<td>p = 0.02</td>
</tr>
</tbody>
</table>

| Sex      | Male                            | 1916/3005                     | 1839/2777 | -93.6 | 924.9       |     p = 0.02    |
|          | Female                          | 388/630                       | 387/632   | -6.0  | 187.1       |     p = 0.02    |

<table>
<thead>
<tr>
<th>Performance status</th>
<th>Altered fractionated RT</th>
<th>Conventional RT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>Interaction term</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1017/1878</td>
<td>1030/1802</td>
<td>-64.2</td>
<td>507.0</td>
<td></td>
<td>p = 0.23</td>
</tr>
<tr>
<td>1</td>
<td>959/1348</td>
<td>900/1235</td>
<td>-8.4</td>
<td>454.6</td>
<td></td>
<td>p = 0.23</td>
</tr>
<tr>
<td>2 or 3</td>
<td>297/367</td>
<td>269/326</td>
<td>-14.0</td>
<td>124.2</td>
<td></td>
<td>p = 0.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site</th>
<th>Altered fractionated RT</th>
<th>Conventional RT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>Interaction term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>282/370</td>
<td>276/346</td>
<td>-15.7</td>
<td>134.9</td>
<td></td>
<td>p = 0.20</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>1359/2072</td>
<td>1363/1978</td>
<td>-5.6</td>
<td>327.2</td>
<td></td>
<td>p = 0.20</td>
</tr>
<tr>
<td>Larynx</td>
<td>586/1262</td>
<td>575/1142</td>
<td>-10.6</td>
<td>278.6</td>
<td></td>
<td>p = 0.20</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>235/397</td>
<td>232/384</td>
<td>-1.2</td>
<td>110.7</td>
<td></td>
<td>p = 0.20</td>
</tr>
<tr>
<td>Others</td>
<td>52/94</td>
<td>49/87</td>
<td>2.8</td>
<td>19.4</td>
<td></td>
<td>p = 0.20</td>
</tr>
</tbody>
</table>
MARCH:
Overall survival by age (incl. oropharynx)

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Events / No. Entered</th>
<th>Hazard ratio (Alt. fractionated RT/Control)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 or less</td>
<td>768 / 1 311</td>
<td></td>
<td>0.78 [0.65 - 0.94]</td>
</tr>
<tr>
<td>51-60</td>
<td>1 455 / 2 300</td>
<td></td>
<td>0.95 [0.83 - 1.09]</td>
</tr>
<tr>
<td>61-70</td>
<td>1 521 / 2 346</td>
<td></td>
<td>0.92 [0.81 - 1.06]</td>
</tr>
<tr>
<td>71 +</td>
<td>784 / 1 085</td>
<td></td>
<td>1.08 [0.89 - 1.30]</td>
</tr>
<tr>
<td>Total</td>
<td>4 528 / 7 042</td>
<td></td>
<td>0.92 [0.86 - 0.97]</td>
</tr>
</tbody>
</table>

Test of interaction: \( p = 0.02 \)
Test for trend: \( p = 0.007 \)

How different are the oropharyngeal carcinomas as compared to the other HNSCC?

For Chemo-RT …

A few pure oropharynx randomized trials …
Example of specific trial: RT-CT 94-01 trial

70 Gy / 7 weeks

N = 226
T3-T4 oropharynx
Non operated

70 Gy / 7 weeks + Carbo-5FU

GORTEC 94-01: oropharynx

LOCO-REGIONAL CONTROL

p = 0.002

- concomitant RT-CT
- RT alone

LR control rate (%)

months after randomization

48%
25%

OVERALL SURVIVAL

p (Mantel-Cox Logrank) = 0.06

7%
23%
16%

months after randomization
Concomitant chemo: the price to pay?

**GORTEC 94-01: oropharynx: Acute toxicity**

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RT+CT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucositis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patchy</td>
<td>32</td>
<td>57</td>
<td>.005</td>
</tr>
<tr>
<td>Confluent</td>
<td>7</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema . Dry desquamation</td>
<td>47</td>
<td>44</td>
<td>.02</td>
</tr>
<tr>
<td>Moist desquamation</td>
<td>12</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td><strong>Nutritional status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss &gt;10% of body mass</td>
<td>6</td>
<td>14</td>
<td>.04</td>
</tr>
<tr>
<td>Feeding tube</td>
<td>15</td>
<td>36</td>
<td>.02</td>
</tr>
<tr>
<td><strong>Haematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils &lt; 0.9</td>
<td>0</td>
<td>4</td>
<td>.04</td>
</tr>
<tr>
<td>Platelets &lt; 50</td>
<td>1</td>
<td>6</td>
<td>.04</td>
</tr>
<tr>
<td>Hemoglobin &lt; 8 g/100mL</td>
<td>0</td>
<td>3</td>
<td>.05</td>
</tr>
<tr>
<td>Toxic death</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**GORTEC 94-01: oropharynx: Late toxicity**

Fig. 4. Five-year rate of Grade 3-4 late toxicity for combined modality treatment (27 patients, RT+CT) vs. RT alone (17 patients, RT) assessed using three late toxicity scales simultaneously.
Is the effect of adding chemotherapy to RT any different in oropharynx sub site?

MACH-NC database of randomized trials (1965-2000)

MACH-NC Chemotherapy database (N=9615 pts randomized)

Effect of concomitant CT-RT versus RT (survival by site)

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Exposed</th>
<th>No. Treated</th>
<th>CHMIO</th>
<th>CONTROL</th>
<th>O-E Variance</th>
<th>Relative Risk &amp; 95% CI (CHMIO/CONTROL(SQ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>844/1806</td>
<td>674/812</td>
<td>-57.3</td>
<td>289.3</td>
<td></td>
<td>17% ± 5</td>
</tr>
<tr>
<td>Oral pharynx</td>
<td>1065/1686</td>
<td>1161/1681</td>
<td>-137.5</td>
<td>527.4</td>
<td></td>
<td>23% ± 4</td>
</tr>
<tr>
<td>Larynx</td>
<td>818/1918</td>
<td>832/1917</td>
<td>-81.6</td>
<td>245.5</td>
<td></td>
<td>22% ± 6</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>502/686</td>
<td>520/689</td>
<td>-40.4</td>
<td>232</td>
<td></td>
<td>16% ± 6</td>
</tr>
<tr>
<td>Others</td>
<td>179/240</td>
<td>185/251</td>
<td>-24.3</td>
<td>78.2</td>
<td></td>
<td>-3% ± 11</td>
</tr>
<tr>
<td>Total</td>
<td>2805/4507</td>
<td>2925/4614</td>
<td>-34.5</td>
<td>582.4</td>
<td></td>
<td>18% ± 2</td>
</tr>
</tbody>
</table>

Test for interaction: X²= 6.72, 2P < 0.05
Chemotherapy is more beneficial in younger patients (N = 9615 pts randomized)

<table>
<thead>
<tr>
<th>Age</th>
<th>Absolute survival benefit at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>12%</td>
</tr>
<tr>
<td>51-60</td>
<td>9%  p &lt; 0.001</td>
</tr>
<tr>
<td>61-70</td>
<td>4%</td>
</tr>
<tr>
<td>&gt; 71</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Platin-5FU: concomitant versus induction

<table>
<thead>
<tr>
<th>Time from randomisation (Years)</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>50%</td>
</tr>
<tr>
<td>6</td>
<td>40%</td>
</tr>
<tr>
<td>7</td>
<td>30%</td>
</tr>
<tr>
<td>8</td>
<td>20%</td>
</tr>
<tr>
<td>9</td>
<td>10%</td>
</tr>
<tr>
<td>10</td>
<td>0%</td>
</tr>
</tbody>
</table>

Local failure: 18.9%  Distant failure: 15.6%

Concomitant: Absolute difference at 5 years  Local failure: -13.5 ± 2.8%  Distant failure: -2.9 ± 2.7%

Neoadjuvant: Absolute difference at 5 years  Local failure: 1.8 ± 2.3%  Distant failure: -3.5 ± 2.0%

Taxotere-PF versus PF, Vermorken 2004
**TAX324 : Survival**

Log-Rank P = 0.005 Hazard Ratio = 0.70

**TPF** vs **PF**

**Survival Probability (%)**

- 50
- 60
- 70
- 80
- 90
- 100

**Survival Time (months)**

- 0
- 6
- 12
- 18
- 24
- 30
- 36
- 42
- 48
- 54
- 60
- 66
- 72

**Number of patients at risk**

TPF: 255 234 196 176 163 136 105 72 52 45 37 20 11
PF: 246 223 169 146 130 107 85 57 36 32 28 10 7


**Meta-Analysis of Chemotherapy in Head & Neck Cancer**

**MACH-NC**

**TPF**: a new standard for induction CT in HNSCC

- With no significant difference in toxicity...

**Combining TPF induction + concomitant...?**

- Efficacy? / toxicity?...
How different are the oropharyngeal carcinomas as compared to the other HNSCC?

For erbitux ...

**Erbitux + Radiotherapy**: a good ratio efficacy / toxicity in locally advanced HNSCC ...

**ERBITUX + RT in locally advanced HNSCC**: a phase III randomized study (the most important sub site was oropharyngeal cancer)

- Primary endpoint: Locoregional control

RT + cetuximab: local-regional control (more effect was seen in oropharynx... (subgroup ?))

- Patients: 213 (RT), 211 (RT+C), 210 (RT)
- Events: 105, 90
- Median: 19 m, 36 m

Benefit also found with Erbitux + chemo in relapse / metastatic patients:
Extreme randomized study:

Log-rank: p = 0.03

Oropharyngeal carcinomas:
Importance of IMRT...
1) Better normal tissue protection (parotid)

2) Dose escalation to the tumor

Potentially interesting since:
- Most relapses in the GTV
- Dose effect relationship

IMRT in oropharynx carcinomas: carcinological results

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Primary Site</th>
<th>Preoperative</th>
<th>Median</th>
<th>Range</th>
<th>Metastatic</th>
<th>Regional</th>
<th>Internal Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheek et al.</td>
<td>12</td>
<td>OPC</td>
<td>64</td>
<td>26</td>
<td>12-16</td>
<td>28</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Lusk et al.</td>
<td>67</td>
<td>OPC</td>
<td>67</td>
<td>51</td>
<td>7.7</td>
<td>6</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>80</td>
<td>OPC</td>
<td>64</td>
<td>10</td>
<td>9.6</td>
<td>6</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Eason et al.</td>
<td>65</td>
<td>OPC</td>
<td>83</td>
<td>23</td>
<td>6.4</td>
<td>5</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>20</td>
<td>OPC</td>
<td>20</td>
<td>22</td>
<td>11.2</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Abbreviations: IMRT, intensity modulated radiotherapy; RT, radiotherapy; OPC, oropharynx; OPC, oropharynx.

*Percent stages I-IV: IBH to 20% 3-year intergroup difference radiotherapy was not before IMRT and IMRT thereafter.

Mendenhall W. JCO 2006
IMRT in oropharyngeal carcinomas: a multicentric prospective study of patients necessitating a bilateral IMRT

(M Lapeyre)

GORTEC: Loco-regional & survival (N=93)

Contrôle loco-régional
Survie globale
Recul moyen : 14 mois (3-37)

Late xerostomia (N=93)
(RTOG-EORTC scoring system)
Salivary toxicity at 1 year

**Grade 2-3**

**Controlateral parotid:**

- Dose moy < 30 Gy: 16 %
- Dose moy > 30 Gy: 43 %

\[ p=0.05 \]

QOL: 7 scores in favor of IMRT

<table>
<thead>
<tr>
<th>Scoring of symptoms</th>
<th>RTE conv</th>
<th>IMRT</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolor (HN)</td>
<td>33.5 [28.5]</td>
<td>21.5 [25.0]</td>
<td>0.01</td>
</tr>
<tr>
<td>Deglutition</td>
<td>35.1 [28.2]</td>
<td>23.0 [25.6]</td>
<td>0.01</td>
</tr>
<tr>
<td>Eating in public</td>
<td>38.2 [31.8]</td>
<td>26.9 [30.3]</td>
<td>0.03</td>
</tr>
<tr>
<td>Dental Pts</td>
<td>34.9 [40.0]</td>
<td>19.5 [30.6]</td>
<td>0.02</td>
</tr>
<tr>
<td>Opening mouth</td>
<td>48.3 [37.7]</td>
<td>28.8 [35.9]</td>
<td>0.001</td>
</tr>
<tr>
<td>Mouth dryness</td>
<td>83.1 [25.5]</td>
<td>57.2 [32.2]</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>Stick saliva</td>
<td>76.6 [30.1]</td>
<td>47.1 [34.7]</td>
<td>(&lt;0.0001)</td>
</tr>
</tbody>
</table>


Dose escalation with IMRT in oropharyngeal carcinomas?

**Hypothesis**: IMRT 75 Gy more efficient & less toxic?

N = 67 pts
IMRT in oropharynx carcinomas: summary

- Better conformality / 3D, & one of the tumor sites where it is increasingly used +++
- Steep dose gradient: need for clinical validation in locally advanced disease
- Promising & converging results (EBM 2-3):
  - Few LR recurrence
  - Less late toxicity
- Learning curve / Re-inforced QA needed ++

Radiotherapy for oropharyngeal carcinoma:

Importance of the RT-QA ...

Radiotherapy for oropharyngeal carcinoma:

Importance of the RT-QA …contouring
Importance of RT-QA: contouring; international survey: T2 Tonsil

Harari 2004

Samples: Elective CTV Designs

Harari 2004

Radiotherapy for oropharyngeal carcinomas:

Importance of the RT-QA ... RT plan verification
LR Failure according to RT plan deviations

yes / no (N= 820)  (Rishin, ASCO 2008)

![Graph showing LR Failure according to RT plan deviations]

IMRT: what’s next?

New tools for radiation delivery:

- Image guided RT
- Adaptive RT
- Dose Guided RT

Adaptive Radiotherapy - Anatomic and set-up Changes

19 CT Scans over 47 Days

Patient Immobilized with Acquaplast Mask

Barker et al. JUROBP 59:960-970, 2004 (MDACC); Lei Dong et al. (MDACC)
Dose distribution in Superior Constrictor Muscle from Brachytherapy in Tonsillar Fossa (<50%)

Cyberknife boost

Brachytherapy boost

New generation of trials in locally advanced oropharyngeal carcinomas?

Most of them do integrate concomitant CT-RT (CDDP-RT)
New generation of trials for oropharynx carcinomas:

- Concomitant CT-RT
- Modifying the radiotherapy

GORTEC 99-02 randomized trial

- Conventional RT + Carbo/5FU
- Stage III/IV
- Accelerated RT + Carbo/5FU
- Very accelerated RT

N = 840 pts randomized, 2/3 of oropharynx

<table>
<thead>
<tr>
<th>Year</th>
<th>At risk</th>
<th>A (RTconv-CT)</th>
<th>B (RTacc-CT)</th>
<th>C (Very-Acc-RT)</th>
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<tr>
<td>0</td>
<td>-279</td>
<td>162</td>
<td>102</td>
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<td>151</td>
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<td>5</td>
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</tbody>
</table>

**Progression Free Survival**

- A vs. B vs. C p = 0.07
- A vs. B, p = 0.61
- A vs. C, p = 0.03

Ajusté sur T, N et localisation
New generation of trials in locally advanced oropharyngeal carcinomas?

- Concomitant CDDP-RT
- Adding a new drug

**RTOG H05-22: Phase III**

- Stage III-IV HNSCC
- Randomize
- Accelerated FX CDDP
- CDDP Erbitux

Future directions: multiple targeting?
Example: ZD6474: a Dual EGFR-VEGFR TKI

Multiple - better than single-targeting? several ongoing trials in HNSCC ...

Phase I (Localy advanced HNC) Brisol, 2007

- RT-CDDP + Erlotinib
- RT-CDDP + Avastin
- RT-CDDP + Erlotinib + Avastin

New GORTEC trial (> 2/3 oropharynx)

- Erbitux - RT

R

- Erbitux - RT + Carbo-5FU (best arm 99-02)

T2-T4 N0-N1

New generation of trials in localy advanced oropharyngeal carcinomas?

concomitant CT-RT & testing induction CT
6 ongoing randomized trials
(Decide, Paradigm, Paccagnella etc…)

RT-CT

TPF  RT-CT

Other Strategy tested: a new GORTEC trial

TPF  Erbitux - RT

RT-CT (best arm 99-02)

T2-T4
N2b-N3

New generation of trials in locally advanced oropharyngeal carcinomas?

Replacing CDDP concomitant to RT by a molecular targeted drug (erbitux)?
Replacing chemo by a molecular targeted drug? 
**larynx preservation randomized trial** 
(GORTEC-GETTEC)

TPF  CDDP-RT

TPF  +  Erbitux-RT

Decreasing the dose intensity of the treatment: 
a relevant question for HPV+ oropharyngeal carcinomas?

**Other directions in oropharyngeal carcinoma ...**

Specific treatments for HPV related tumors?...

- HPV found in 20-25% of HNSCC (and 30% benign biopsies of oropharynx)
- Up to 50% in oropharynx carcinomas (some series: 90%): 
  - 85-90% HPV16 (De Souza, NEJM 2007)
- HPV+ tumors associated with:
  - Better survival (Richties 2003)
  - Better survival in surgically treated tumors (Lattira JCO 2006)
  - More radiosensitivity (Lindel 2007)
  - More response to induction chemo (Worden JCO 2008)
  - Cellular marker of prognostic value: p16 (Lassen JCO 2009)
    survival 62% versus 26% with conventional RT)
Do we need different therapeutic approaches for HPV associated oropharyngeal tumors?

- De-escalation?
- Value of EGFr targeting instead of concomitant chemo?
- Other specific anti-viral strategies?

Antiviral agent Cidofovir + irradiation in HPV+ SC carcinoma xenografts (ongoing phase I)

Oropharyngeal carcinoma

- Conclusions -

- High proportion of HNSCC (about 50%)
- The effect of chemotherapy and/or altered fractionation or EGFr targeting = not different from the other HNSCC ... EBM level 1a
- Importance of IMRT / IGRT / RT-QA ... for normal tissue sparing in this particular sub-site
- Question: more HPV related carcinomas (specific targeting? Treatment Desescaletion)