Treatment strategies for locally advanced head and neck cancers

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The more intense RT-CT, the better?

Phase 3 randomised GORTEC 99-02 trial

Source = Randomized trials
EBM level 1

Other randomized trials
1. Integrating chemotherapy (CT) concomitant to radiotherapy (RT)

2. Altered fractionation

3. Hypoxic modifications

4. Induction chemotherapy with TPF

5. Integrating EGFR-targeting agents …

6. Optimizing RT
Update of MACH-NC Database

93 randomized trials

> 17,346 Patients (updated data)

Pignon, Radiother Oncol 2009
Overall, the meta-analysis included 93 trials with chemotherapy in 17346 patients.

**Updated of MACH-NC data base:**

Final gain in survival at 5 years of adding concomitant chemo = + 6.5%

**Concomitant chemotherapy**

- Survival (%)
  - Time from randomisation (Years)
  - 0 1 2 3 4 5 6 7 ≥ 8
  - 33.7%
  - 27.2%

**Induction chemotherapy**

- Survival (%)
  - Time from randomisation (Years)
  - 0 1 2 3 4 5 6 7 ≥ 8
  - 32.4%
  - 30.0%

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**Benefit of chemo**

- Pignon et al Radiother Oncol

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Meta-Analysis of Chemotherapy in Head & Neck Cancer
Which concomitant CT? : 100 mg/m² x 3 cycles

<table>
<thead>
<tr>
<th>Type of chemotherapy</th>
<th>No. Deaths / No. Entered</th>
<th>O-E Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
<th>p of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Poly chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5-FU and Platin</td>
<td>602 / 940</td>
<td>-92.2</td>
<td>0.75</td>
<td>[0.67;0.84]</td>
<td>p = 0.41</td>
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<tr>
<td>5-FU or Platin</td>
<td>495 / 743</td>
<td>-45.8</td>
<td>0.83</td>
<td>[0.74;0.94]</td>
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<tr>
<td>Neither 5-FU nor Platin</td>
<td>62 / 115</td>
<td>-11.1</td>
<td>0.73</td>
<td>[0.52;1.01]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (a)</td>
<td>1159 / 1798</td>
<td>-149.0</td>
<td>0.78</td>
<td>[0.72;0.85]</td>
<td></td>
</tr>
<tr>
<td>(b) Mono chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono Cisplatin</td>
<td>703 / 1151</td>
<td>-102.6</td>
<td>0.74</td>
<td>[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>0.89</td>
<td>[0.82;0.96]</td>
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<tr>
<td>Subtotal (b)</td>
<td>2012 / 3026</td>
<td>-177.4</td>
<td>0.84</td>
<td>[0.78;0.89]</td>
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</table>

Test for heterogeneity: $\chi^2_1 = 1.69$ p = 0.19
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<tr>
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<td>5-FU or Platin</td>
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<td>-92.2</td>
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<td>-102.6</td>
<td>341.8</td>
<td>0.74</td>
<td>[0.67;0.82]</td>
<td>p = 0.006</td>
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<tr>
<td>Mono Other</td>
<td>1309 / 1875</td>
<td>-74.8</td>
<td>643.3</td>
<td>0.89</td>
<td>[0.82;0.96]</td>
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<tr>
<td>Subtotal (b)</td>
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<td>-177.4</td>
<td>985.1</td>
<td>0.84</td>
<td>[0.78;0.89]</td>
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<td>p = 0.19</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Platin-5FU + RT : which benefit on tumor control ?

Meta-Analysis of Chemotherapy in Head & Neck Cancer

- Local failure: 63.2%
- Distant failure: 18.9%
- RT: 49.7%

Pignon et al Radiother Oncol 2009
Concomitant CT-RT: what is the price to pay ...
### Increased risk of treatment related-death by adding chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Chemotherapy</th>
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</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>0.5 %</td>
<td>1.3%</td>
</tr>
<tr>
<td>Induction</td>
<td>0.4 %</td>
<td>1.5%</td>
</tr>
<tr>
<td>Concomitant</td>
<td>0.9 %</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

+ 1% treatment related death
Increased late toxicity with CT-RT

RT-CT often used as … a « one shot » procedure …

Fig. 4. Five-year rate of Grade 3–4 late toxicity

F Denis et al 2004
Concomitant chemo-RT summary:

More efficient on tumor control / survival ...

with more side effects ...

= is considered in Europe and USA as the most common standard of care
Locally advanced HNC: EBM level 1

- Adaptive RT
- RT-CT
- Altered fractionation
- Induction CT
- Targeted therapy + RT
What gain in tumor control?

Adaptive RT

RT-CT

+ ? %

Altered fractionation

Induction CT

Targeted therapy + RT

+ 12%

+ 10%

+ ? % (7% ?)

+ 10%
What gain in tumor control?

Adaptive RT

RT-CT

Altered fractionation + 12%

Induction CT + 10%

Targeted therapy + RT
Cetuximab = + 10% benefit in locoregional control

HR=0.68 [95% CI: 0.52–0.89] p=0.005

3-year control rate

Bonner et al. NEJM 2006
Gain in tumor control probability

Adaptive RT

RT-CT

Altered fractionation + 12%

Induction CT

Targeted therapy + RT + 10%

?
Adding cetuximab to RT-CT?
RTOG H05-22 randomized trial (940 pts)

Stage III-IV

1) No improvement in LRC / PFS / OS.
2) More skin reactions …
What gain in tumor control?

- Adaptive RT
- RT-CT
- Induction CT
- Targeted therapy + RT

Altered fractionation

+ 10%
## Altered fractionation: tumor control

<table>
<thead>
<tr>
<th>Category/Study</th>
<th>No. Events / No. Entered</th>
<th>HR of local recurrence</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alt. fractionated RT</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alt. fractionated RT / Control</td>
<td></td>
<td></td>
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<tr>
<td>(a) Hyperfractionation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 22791</td>
<td>74/180</td>
<td>95/176</td>
<td>-16.5</td>
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<tr>
<td>PMH Toronto</td>
<td>77/172</td>
<td>94/164</td>
<td>-12.8</td>
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<tr>
<td>RTOG 9003 HF</td>
<td>97/276</td>
<td>110/279</td>
<td>-10.1</td>
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<tr>
<td>Subtotal (a)</td>
<td>248/628</td>
<td>299/619</td>
<td>-39.4</td>
</tr>
<tr>
<td>(b) Accelerated fractionation w/o total dose reduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 22851</td>
<td>82/257</td>
<td>108/255</td>
<td>-15.6</td>
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<tr>
<td>RTOG 9003 S</td>
<td>107/281</td>
<td>110/279</td>
<td>-4.6</td>
</tr>
<tr>
<td>RTOG 9003 B</td>
<td>89/277</td>
<td>110/279</td>
<td>-13.1</td>
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<tr>
<td>BCCA 9113</td>
<td>18/41</td>
<td>18/41</td>
<td>0.0</td>
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<td>DAHANCA</td>
<td>183/755</td>
<td>253/730</td>
<td>-40.4</td>
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<td>Oro 9301</td>
<td>36/65</td>
<td>38/63</td>
<td>0.4</td>
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<tr>
<td>CAIR</td>
<td>11/51</td>
<td>30/49</td>
<td>-13.1</td>
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<td>KBN PO 79</td>
<td>33/196</td>
<td>48/199</td>
<td>-7.1</td>
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<tr>
<td>Subtotal (b)</td>
<td>559/1923</td>
<td>715/1895</td>
<td>-93.4</td>
</tr>
<tr>
<td>(c) Accelerated fractionation with total dose reduction</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CHART</td>
<td>251/552</td>
<td>183/366</td>
<td>-11.2</td>
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<tr>
<td>Vienna</td>
<td>48/78</td>
<td>55/81</td>
<td>-4.0</td>
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<tr>
<td>GORTEC 9402</td>
<td>74/137</td>
<td>95/131</td>
<td>-16.8</td>
</tr>
<tr>
<td>Subtotal (c)</td>
<td>373/767</td>
<td>333/578</td>
<td>-32.0</td>
</tr>
<tr>
<td>Total (a ... c)</td>
<td>1180/3318</td>
<td>1347/3092</td>
<td>-164.8</td>
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<tr>
<td>Test for heterogeneity:</td>
<td>$\chi^2_{13} = 21.83$</td>
<td>$p = 0.06$</td>
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<tr>
<td>Test for interaction:</td>
<td>$\chi^2_{2} = 1.4$</td>
<td>$p = 0.5$</td>
<td></td>
</tr>
</tbody>
</table>

Alt. fractionated RT effect with $p < 0.0001$

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Bourhis Lancet 2006
Gain in tumor control probability?

- Post-op RT
- RT-CT
- Induction CT
- Altered fractionation
  - + 12%
  - + 10%

Targeted therapy + RT

?
N = 840 patients randomized with locally advanced HNSSC

Carbo-5-FU

70 Gy
7 weeks

70 Gy
6 weeks

64.8 Gy
3.5 weeks

Bourhis et al Lancet Oncol 2012
Conventional RT-CT versus Acc-RT CT

At risk

- Conventional RT + Carbo-5FU
- Acc RT + Carbo 5FU

At 3 years (95%CI)
- Arm A: Conv RT-CT
  - 37.6% (32-43)
- Arm B: Acc RT-CT
  - 34.1% (29-40)
- Arm C: Very acc RT
  - 32.2% (27-38)

B vs A p=0.88
B vs C p=0.060
A vs C p=0.041

Tests adjusted for T, N stage, tumor site

Conventional RT-CT versus Acc-RT CT

N = 840 randomized

p = NS

PFS

Bourhis et al Lancet Oncol 2012
Very accelerated RT, 64.8 Gy in 3.5 weeks

versus

CT-RT ?

Conventional RT-CT

Strongly intensified CT-RT

Moderately intensified CT-RT

949 patients randomized with locally advanced HNSCC
**Local control:** CT-RT better than very intense RT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events / Patients</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional RT-CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GORTEC 99-02a</td>
<td>111/278</td>
<td>126/280</td>
<td>0.76 [0.59;0.99]</td>
</tr>
<tr>
<td>Moderately intensified RT-CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GORTEC 99-02b</td>
<td>113/279</td>
<td>126/280</td>
<td>0.75 [0.58;0.97]</td>
</tr>
<tr>
<td>Very intensified RT-CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GORTEC 96-01</td>
<td>15/53</td>
<td>27/56</td>
<td>0.52 [0.27;0.996]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>239/610</strong></td>
<td><strong>279/616</strong></td>
<td>0.73 [0.61;0.87]</td>
</tr>
</tbody>
</table>

RT + conc CT better \| Very acc RT better

RT + conc CT effect: p = 0.0004
- Chemo-RT = better than very intense RT without chemo

- No need to dose intensify CT-RT
Gain in tumor control probability?

Adaptive RT

RT-CT

Induction CT

Targeted therapy + RT

Altered fractionation

+ 12%

+ 10%

+ ? (7% ?)

+ 10%
**Data available for 98% of the patients randomized**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Concomitant CT</th>
<th>n</th>
<th>Comparison</th>
<th>Data</th>
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<tbody>
<tr>
<td>SHNCG 1998</td>
<td>Yes</td>
<td>387</td>
<td>TPF vs. PF</td>
<td>IPD</td>
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<tr>
<td></td>
<td></td>
<td>(-5)</td>
<td></td>
<td></td>
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<tr>
<td>EORTC 24971</td>
<td>No</td>
<td>358</td>
<td>TPF vs. PF</td>
<td>IPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAX 324</td>
<td>Yes</td>
<td>539</td>
<td>TPF vs. PF</td>
<td>IPD</td>
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<tr>
<td></td>
<td></td>
<td>(-38)</td>
<td></td>
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<tr>
<td>GORTEC 2000-01</td>
<td>No</td>
<td>220</td>
<td>TPF vs. PF</td>
<td>IPD</td>
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<tr>
<td></td>
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<td>(-7 )</td>
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<tr>
<td>SHNCG 2002</td>
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<td>439</td>
<td>TPF vs. PF vs. none</td>
<td>IPD</td>
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<td>(-86)</td>
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<tr>
<td>GSTTC – XRP 6976</td>
<td>Yes</td>
<td>101</td>
<td>TPF vs. none</td>
<td>IPD</td>
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<tr>
<td></td>
<td></td>
<td>(-1 )</td>
<td></td>
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</tbody>
</table>
TPF > PF: less local failure

Risk of recurrence (%) vs Time from randomisation (Years)

at 5 years ± SD: -7.3 ± 3.22 p=0.003
Meta-Analysis of Chemotherapy in Head & Neck Cancer

TPF > PF: less distant failure

At 5 years
\[ \pm SD: -5 \pm 2.7 \; p=0.02 \]
Gain in tumor control probability?

Adaptive RT

RT-CT

Induction CT

Targeted therapy + RT

Altered fractionation

+ 12%

+ ? % (<7%)

?
TPF before CT-RT … ?

TPF may compromise the RT-CT phase.

Compliance to concomitant cisplatin after TPF x 3 cycles = only 43% in the TREMLIN randomised study (JCO Lefebvre 2013)
A randomized trial of
Cetuximab + RT *versus* CDDP + RT

TPF X 3

RT (70 Gy) Cisplatin

RT (70 Gy) Erbitux (weekly)

larynx/hypopharynx suitable for total laryngectomy (n=153)

Lefebvre et al. JCO 2013
Erbitux + RT versus Cisplatin-RT: compliance

Patients completing RT after induction therapy (%)

- CRT: 43%
- Erbitux + RT: 71%

Lefebvre et al. JCO 2013
Overall survival ($N = 153$ patients randomized)

Hazard Ratio (0 to 18 months) = 1.015 - I.C. 95% [0.359; 2.868]

Hazard Ratio (0 to 36 months) = 1.038 - I.C. 95% [0.406; 2.654]

$p$ (Logrank - 0 to 36 months) = 0.437

Lefebvre JCO 2013
DeCIDE randomized trial: overall survival

E. E. W. Cohen et al., ASCO 2012, Abs 5500
PARADIGM randomized trial: overall survival

Log Rank Test $p=0.77$

Survival (Mois)

TPF
CRT
Cisplatine + RT

R. I. Haddah et al., ASCO 2012, Abs 5501
Gain in tumor control probability?

Adaptive RT

RT-CT

Altered fractionation

Induction CT

Targeted therapy + RT

Based on randomized trials then the benefit are not cumulative … there is a need to choose the most appropriate treatment …
How to choose? how to personalize medical practice?

Patients characteristics

Tumor Characteristics

Clinical

Biological
How to choose? how to personalize medical practice?

Patients characteristics

Tumor Characteristics
  - Clinical
  - Biological
Concomitant chemo: the benefit *decreases* with age ...

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

p of interaction = 0.02  
p of trend = 0.003

Hazard Ratio  
LRT + CT better | LRT better
Cetuximab also may have limited effect for $\geq 65$ years

*Bonner, et al. Lancet Oncology, 2010*
Another patient characteristic that may help to predict the outcome after RT-cetuximab is the grade of acne/rash.


ERBITUX + RT

Grade 2-4 Acne/Rash

Median 25.6 68.8+ p=0.002 HR (CI)= 0.49 (0.34 – 0.72)

ERBITUX + RT

Grade 0-1 Acne/Rash

Median 25.6 68.8+ p=0.002 HR (CI)= 0.49 (0.34 – 0.72)
How to choose? How to personalize medical practice?

Patients characteristics

Tumor Characteristics

Clinical

Biological
## Concomitant chemo: effect by tumor stage

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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CHIMIO</td>
<td>CONTROL</td>
<td>(CHIMIO:CONTROL) (±SD)</td>
<td></td>
</tr>
<tr>
<td>T1-T2</td>
<td>537/973 649/1029</td>
<td>20% ± 5</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>2494/3649 2616/3587</td>
<td>20% ± 3</td>
<td></td>
</tr>
</tbody>
</table>

**Total**

| Total | 3031/4622 3265/4616 | −330.7 | 1501.4 | 20% ± 2 |

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**Test for Interaction:** $X^2 = 0.01, 2P = 0.92$
### Benefit of concomitant chemo by tumor site

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Oral Cavity</td>
<td>633/906</td>
<td>673/912</td>
<td>-57.3</td>
<td>299.3</td>
<td>17% ± 5</td>
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<tr>
<td>Oropharynx</td>
<td>1058/1596</td>
<td>1151/1551</td>
<td>-137.3</td>
<td>527.4</td>
<td>23% ± 4</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>516/859</td>
<td>532/817</td>
<td>-61.9</td>
<td>245.5</td>
<td>22% ± 6</td>
<td></td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>502/706</td>
<td>509/689</td>
<td>-40.4</td>
<td>232</td>
<td>16% ± 6</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>179/240</td>
<td>161/215</td>
<td>2.4</td>
<td>78.2</td>
<td>-3% ± 11</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2888/4307</td>
<td>3026/4184</td>
<td>-294.5</td>
<td>1382.4</td>
<td>19% ± 2</td>
<td></td>
</tr>
</tbody>
</table>

Test for interaction: \( X^2 = 6.72 \) 2P = 0.15

**CHIMIO better** | **CONTROL better**
---|---
0.0 | 0.5 | 1.0 | 1.5 | 2.0

CHIMIO effect 2P < 0.0001
How much induction TPF changed the scenario?
TPF better than PF: distant failure

Absolute difference at 5 years ± SD: -5 ± 2.7 p=0.02

Absolute benefit at 5 years = +8% N2-N3
= +4% N0-N1

Blanchard et al JCO 2013
Induction TPF *before* concomitant CT-RT?

<table>
<thead>
<tr>
<th>Group</th>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTCC (Sp)</td>
<td>TPF (or PF) x 3 → CRT</td>
<td>Restricted to N2-N3</td>
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<tr>
<td></td>
<td>CRT (cisplatin)</td>
<td>ASCO 2012</td>
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<tr>
<td>Paradigm (US)</td>
<td>TPF x 3 → CRT</td>
<td>Benefit of induction CT only on Metastase</td>
</tr>
<tr>
<td></td>
<td>CT-RT (cisplatin)</td>
<td></td>
</tr>
<tr>
<td>DeCIDE (US)</td>
<td>TPF x 2 → THFX</td>
<td></td>
</tr>
<tr>
<td>245 pts</td>
<td>THFX</td>
<td></td>
</tr>
<tr>
<td>GCTCC (It)</td>
<td>TPF x 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>XRT (cetuximab)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>XRT (PF)</td>
<td></td>
</tr>
</tbody>
</table>
How to choose? How to personalize medical practice?

Patients characteristics

Tumor Characteristics

Clinical

Biological
1) Biomarkers with strong prognostic value:

- HPV
- EGFr
- Hypoxia

2) Other prognostic / predictive biomarkers?
1) Biomarkers with strong prognostic value

- HPV
  - EGFr
  - Hypoxia

2) Other prognostic / predictive biomarkers ?
HPV(+) vs. HPV(-): two different diseases

(N=505 patients)

Cancer-specific Survival

Local Control

Distant Control

B O’Sullivan, PMH
Can we safely reduce the dose in HPV + & non smoking patients?

Oropharyngeal cancer (n=266)

HPV-positive (n=178)
- ≤10 pack-years (n=88)
  - N0-N2a (n=26)
    - 42.9% at low risk
      3 year OS = 93.0%
  - N2b-N3 (n=62)
HPV-negative (n=88)
- >10 pack-years (n=90)
  - ≤10 pack-years (n=23)
    - T2-T3 (n=15)
  - >10 pack-years (n=65)
    - T4 (n=8)

Ang et al. NEJM 2010
HPV(+) de-intensification?

(a) **Overall Survival**
- RT-alone vs. CRT:
  - 3-year OS: 86% (70-94) vs. 88% (77-94)
  - Hazard Ratio: 0.71 (0.28 – 1.75), p=0.45

(b) **Local Control**
- RT-alone vs. CRT:
  - 3-year LC: 95% (87-100) vs. 92% (86-99)
  - Hazard Ratio: 0.59 (0.12-2.99), p=0.512

(c) **Regional Control (RC)**
- RT-alone vs. CRT:
  - 3-year RC: 97% (92-100) vs. 93% (86-99)
  - Hazard Ratio: 0.29 (0.03-2.48), p=0.219

(d) **Distant Control (DC)**
- RT-alone vs. CRT:
  - 3-year DC: 92% (82-100) vs. 86% (77-95)
  - Hazard Ratio: 0.6 (0.19-1.88), p=0.365

RT-alone: mostly altered fractionated
HPV(+) not all suitable for de-intensification
Oropharyngeal cancer (n=266)

HPV-positive (n=178)
- ≤10 pack-years (n=88)
  - N0-N2a (n=26) 42.9% at low risk, 3 year OS = 93.0%
  - N2b-N3 (n=64)
- >10 pack-years (n=90)

HPV-negative (n=88)
- ≤10 pack-years (n=23)
  - T2-T3 (n=15) 29.7% at intermediate risk, 3 year OS = 70.8%
  - T4 (n=8) 27.4% at high risk, 3 year OS = 46.2%
- >10 pack-years (n=65)

RT-CT versus RT-CT + TG4001, HPV vaccine

42.9% at low risk, 3 year OS = 93.0%
29.7% at intermediate risk, 3 year OS = 70.8%
27.4% at high risk, 3 year OS = 46.2%
1) Biomarkers with strong prognostic value

- HPV
- EGFr
- Hypoxia

2) Other prognostic / predictive biomarkers?
EGFr expression
In the GORTEC 99-02 Randomized trial

EGFR Negative

EGFR 2+ (Mosaic)

EGFR 3+ (Diffuse)
EGFr prognostic value for survival

RT-CT arms

- EGFR negative
- EGFR positive

At risk: 247, 175, 127, 105, 85, 59, 18

Years: 0, 1, 2, 3, 4, 5, 6

p = 0.77

RT alone arm

- EGFR negative
- EGFR positive

At risk: 35, 24, 19, 15, 10, 8, 3

Years: 0, 1, 2, 3, 4, 5, 6

p = 0.010

Interaction test p=0.008

Bourhis et al ICHNO 2013
1) Biomarkers with strong prognostic value

- HPV
- EGFr
- Hypoxia

2) Other prognostic / predictive biomarkers?
Impact of hypoxia on local failure
(N = 122 patients randomized)
(Rishin et al, JCO)
- Importance of radiotherapy techniques and quality assurance for RT -
Importance of quality assurance of RT: impact of major deviation (Rishin, JCO, 2010)

Patients who had received at least 60 Gy of RT to PTV2

% locoregional failure-free

Compliant/No mod
Compliant/Mod
Non-compliant/No TCP dev
Non-compliant/TCP dev

P < 0.001
Conventional 3D RT

= 1489 cc
= 879 cc
Tomotherapy

Less side effects
+++
So far, concomitant chemo-RT remains a standard treatment in locally advanced HNSCC

- More efficient on tumor control / survival
- More side effects …

- Larynx preservation : induction TPF

- Pending questions :
  - Induction TPF before CT-RT ?
  - Specific treatment according to HPV status ?
  - New molecular targeted agents … ex : GA 201
  - New induction : TPE / TPA …
  - Predictive factors ? etc…
Obrigado !