Head and Neck Cancer: multi-modal therapeutic integration

P. Ponticelli, L. Lastrucci, R. De Majo, A. Rampini

U.O.C. Radioterapia

Ospedale S. Donato ASL 8 - AREZZO
Summary

• Biological considerations
• Clinical results of chemo-radiation in locally advanced H&N cancer
• Radiotherapy associated with cetuximab
• Role of neoadjuvant chemotherapy
• Possible integration between chemotherapy and cetuximab associated with radiotherapy
• Clinical results of chemo-radiation in larynx preservation programs
Rationale of radiation and chemotherapy association in head and neck cancer

- **Temporal modulation** enhances tumor response to fractionated RT through the 4 R’s of radiotherapy: repair, repopulation, reoxygenation, and redistribution
- **Biological cooperation** using different mechanism of cell killing
- **Cytotoxic enhancement** by modulating the induction or processing of intracellular damage

Bernier J, 2009
### HPV-associated head and neck cancer

<table>
<thead>
<tr>
<th></th>
<th>HPV-positive tumours</th>
<th>HPV-negative tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical site</td>
<td>Tonsil and base of tongue</td>
<td>All sites</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-keratinised</td>
<td>Keratinised</td>
</tr>
<tr>
<td>Age</td>
<td>Younger cohorts</td>
<td>Older cohorts</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>3:1 men</td>
<td>3:1 men</td>
</tr>
<tr>
<td>Stage</td>
<td>Tx, T1–2</td>
<td>Variable</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Sexual behaviour</td>
<td>Alcohol and tobacco</td>
</tr>
<tr>
<td>Incidence</td>
<td>Increasing</td>
<td>Decreasing</td>
</tr>
<tr>
<td>Survival</td>
<td>Improved</td>
<td>Unchanging</td>
</tr>
</tbody>
</table>

**Table 2: Differences between HPV-positive and HPV-negative head and neck squamous-cell carcinomas**
Human Papillomavirus as a Marker of the Natural History and Response to Therapy of Head and Neck Squamous Cell Carcinoma

Kie Kian Ang, MD, PhD,* and Erich M. Sturgis, MD†,‡

2012
Human Papillomavirus as a Marker of the Natural History and Response to Therapy of Head and Neck Squamous Cell Carcinoma

Kie Kian Ang, MD, PhD,* and Erich M. Sturgis, MD†,*
Clinical results of chemo-radiation in locally advanced head and neck cancer
Meta analysis

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

Jean-Pierre Pignon\textsuperscript{a,\ast}, Aurélie le Maître\textsuperscript{a}, Emilie Maillard\textsuperscript{a}, Jean Bourhis\textsuperscript{b}, on behalf of the MACH-NC Collaborative Group\textsuperscript{1}

\textsuperscript{a} Department of Biostatistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France
\textsuperscript{b} Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France
Platinum based chemotherapy

(a) Concomitant chemotherapy.

- Concomitant chemotherapy
- Control

Absolute difference at 5 years ± standard deviation:
- Concomitant chemotherapy: 6.5 ± 1.0 %
- Control: 27.2 %

(b) Induction chemotherapy

- Induction chemotherapy
- Control

Absolute difference at 5 years ± standard deviation:
- Induction chemotherapy: 2.4 ± 1.4 %
- Control: 30.0 %

Pignon JP et al, 2009
Hazard ratio of death by 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 difference at 5 years ± sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 50</td>
<td>803/1296</td>
<td>-107.6</td>
<td>386.9</td>
<td>9.8 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>1069/1645</td>
<td>-136.4</td>
<td>539.7</td>
<td>7.8 ± 1.8</td>
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</tr>
<tr>
<td>61-70</td>
<td>972/1368</td>
<td>-56.2</td>
<td>457.8</td>
<td>3.0 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>71 or over</td>
<td>273/356</td>
<td>-3.5</td>
<td>114.7</td>
<td>-0.7 ± 3.9</td>
<td></td>
</tr>
</tbody>
</table>

p_inter = 0.02
p_trend = 0.003

Pignon JP et al, 2009
Altered fractionation RT and chemotherapy
RTOG 0129 phase III trial: accelerated (AFX) vs standard RT (SFX) in combination with cisplatin 100 mg/m² for 2-3 cycles

Ang K et al, ASCO, 2010

Prescribed radiation (RT) were 72 Gy/42 F/6 W and 70 Gy/35 F/7 W for AFX-C and SFX, and cisplatin doses were 100 mg/m² q3W for 2 and 3 cycles, respectively

<table>
<thead>
<tr>
<th></th>
<th>AFX</th>
<th>SFX</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>59%</td>
<td>56%</td>
<td>0.18</td>
</tr>
<tr>
<td>DFS</td>
<td>45%</td>
<td>44%</td>
<td>0.42</td>
</tr>
<tr>
<td>LRF</td>
<td>31%</td>
<td>28%</td>
<td>0.76</td>
</tr>
<tr>
<td>DM</td>
<td>18%</td>
<td>22%</td>
<td>0.06</td>
</tr>
<tr>
<td>G3-4 acute mucositis</td>
<td>33%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Worst G3-4 late toxicity</td>
<td>26%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Feeding tube pretreatment</td>
<td>22%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Feeding tube at therapy end</td>
<td>67%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Feeding tube at 1 year</td>
<td>28%</td>
<td>29%</td>
<td></td>
</tr>
</tbody>
</table>
Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial

Jean Bourhis, Christian Sire, Pierre Graff, Vincent Grégoire, Philippe Maingon, Gilles Calais, Bernard Geny, Laurent Martin, Marc Alfonsi, Patrick Desprez, Thierry Pignon, Etienne Bardet, Michel Rives, Lionel Geoffrois, Nicolas Daly-Schweitzer, Sak Sen, Claude Tuchais, Olivier Dupuis, Stéphane Guehré, Michel Lapeyre, Véronique Faure, Marc Hamoir, Antoine Lusinchi, Stéphane Temam, Antonella Pinne, Yun Gan Tao, Pierre Blanchard, Anne Aupérin

R

A. Conventional RT (70 Gy in 7 w) + concurrent Carbo-FU

B. Accelerated RT (70 Gy in 6 w; concomitant boost in the last 2 weeks) + concurrent Carbo-FU

C. Very accelerated RT: 64.8 Gy in 3.5 weeks (1.8 Gy x 2 /d) without CT

Analysis of 230 patients receiving CRT in 3 studies (RTOG 91-11, 97-03, 99-14)

- Any severe late toxicity: 43%
- Feeding-tube dependence > 2 yrs post-RT: 13%
- Pharyngeal dysfunction: 27%
- Laryngeal dysfunction: 12%
- Death: 10%

Macthay M et al, 2008
Intensity-Modulated Radiotherapy is Associated With Improved Global Quality of Life Among Long-term Survivors of Head-and-Neck Cancer

Allen M. Chen, M.D.,* D. Gregory Farwell, M.D.,† Quang Luu, M.D.,† Esther G. Vazquez, R.N.,* Derick H. Lau, M.D., Ph.D.,† and James A. Purdy, Ph.D.*
EGFR (epidermal growth factor receptor) is overexpressed in 90-100% of the HNSCC cases and is considered an unfavourable prognostic marker. EGFR constitutive activation is linked with HNSCC pathogenesis. **Cetuximab** is a monoclonal anti-EGFR antibody blocking the activation of the receptor and signal transduction.
Figure 2: Overall survival by treatment: 5-year update (median follow-up 60 months)

Stratified log-rank p=0.018

Bonner JA et al, 2010
### Table 4. Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Radiotherapy Alone (N = 212)</th>
<th>Radiotherapy plus Cetuximab (N = 208)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3–5</td>
<td>All Grades</td>
</tr>
<tr>
<td>Mucositis</td>
<td>94</td>
<td>52</td>
<td>93</td>
</tr>
<tr>
<td>Acneiform rash</td>
<td>10</td>
<td>1</td>
<td>87</td>
</tr>
<tr>
<td>Radiation dermatitis</td>
<td>90</td>
<td>18</td>
<td>86</td>
</tr>
<tr>
<td>Weight loss</td>
<td>72</td>
<td>7</td>
<td>84</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>71</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>63</td>
<td>30</td>
<td>65</td>
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<tr>
<td>Asthenia</td>
<td>49</td>
<td>5</td>
<td>56</td>
</tr>
<tr>
<td>Nausea</td>
<td>37</td>
<td>2</td>
<td>49</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>28</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Pain</td>
<td>28</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Anorexia</td>
<td>23</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>Fever</td>
<td>13</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>19</td>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td>Dehydration</td>
<td>19</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>22</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Coughing</td>
<td>19</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Voice alteration</td>
<td>22</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>&lt;1</td>
<td>19</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>2</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Increased sputum</td>
<td>15</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Infection</td>
<td>9</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Chills</td>
<td>5</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>
RT+cisplatin vs RT+cetuximab

Until now no one phase III trial was published

Retrospective analysis showed inconsistent results
Cetuximab Plus Radiotherapy Versus Cisplatin Plus Radiotherapy in Locally Advanced Head and Neck Cancer (CTXMAB+RT)

ClinicalTrials.gov Identifier: NCT01216020

Phase 2

**Arm A:** Radical radiotherapy (doses and volumes) concomitant with chemotherapy with Cisplatin (40 mg/m²/week)

**Arm B:** Radical radiotherapy (doses and volumes) concomitant with therapy with the monoclonal antibody Cetuximab (400 mg/m² ["loading dose"] and subsequently 250 mg /m²/week)

**PRIMARY OBJECTIVES:**
Evaluation and comparison of the compliance of the two treatments;

**SECONDARY OBJECTIVES:**
Evaluation and comparison of the grade and incidence of acute toxicity; Evaluation and comparison of local control; Evaluation and comparison of event free survival (both local control and distant metastases); Evaluation and comparison of cause specific and overall survival.
Cetuximab Plus Radiotherapy Versus Cisplatin Plus Radiotherapy in Locally Advanced Head and Neck Cancer (CTXMAB+RT)

Estimated Enrollment: 140
Study Start Date: October 2010
Estimated Study Completion Date: October 2016

Participating Centers

- Brescia
- Siena
- Genova
- Firenze
- Arezzo
- Prato
- Pistoia

Enrolled until now = 57 pts

September, 2013
RADIATION THERAPY ONCOLOGY GROUP  

RTOG 1016  

PHASE III TRIAL OF RADIOTHERAPY PLUS CETUXIMAB VERSUS CHEMORADIOTHERAPY IN HPV-ASSOCIATED OROPHARYNX CANCER  

Study Team (6/28/12)  

**SCHEMA**  

<table>
<thead>
<tr>
<th></th>
<th>T Stage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>S</td>
<td>1. T1-2</td>
</tr>
<tr>
<td>E</td>
<td>T</td>
<td>2. T3-4</td>
</tr>
<tr>
<td>G</td>
<td></td>
<td>Arm 1 (Control):</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td>Accelerated IMRT, 70 Gy for 6 weeks</td>
</tr>
<tr>
<td>S</td>
<td></td>
<td>+ high dose DDP (100 mg/m²) Days 1 and 22</td>
</tr>
<tr>
<td>T</td>
<td></td>
<td>(Total: 200 mg/m²)</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>Arm 2: Accelerated IMRT, 70 Gy for 6 weeks</td>
</tr>
<tr>
<td>R</td>
<td>Y</td>
<td>1. 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. 1</td>
</tr>
</tbody>
</table>

**Smoking History**  

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>≤ 10 pack-years</td>
</tr>
<tr>
<td>2.</td>
<td>&gt; 10 pack-years</td>
</tr>
</tbody>
</table>
Induction chemotherapy (IC) with TPF followed by radiotherapy (+/- concomitant CT)
### Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU Sequential Therapy in Advanced SCCHN: Randomized Phase III trials

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>INCLUSION CRITERIA</th>
<th>N° CYCLES OF ICT</th>
<th>RADIOTherAPy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 24971/TAX 323*</td>
<td>Unresectable stage III-IV</td>
<td>4</td>
<td>RT alone (CFRT or AFRT)</td>
</tr>
<tr>
<td>TAX 324**</td>
<td>Resectable or unresectable stage III-IV</td>
<td>3</td>
<td>CFRT + Carboplatin AUC 1.5 weekly</td>
</tr>
</tbody>
</table>

Figure 2. Effects of TPF and PF Therapy on Progression-free Survival (Panel A) and Overall Survival (Panel B).

TPF denotes docetaxel–cisplatin–fluorouracil, and PF cisplatin–fluorouracil.

Vermorken JB et al, NEJM, 2007
ASCO 2011
Posner MR et al., NEJM, 2007
Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial

Jochen H Lorch, Olga Goloubeva, Robert I Haddad, Kevin Cullen, Nicholas Saris, Roy Tishler, Ming Tan, John Fasciano, Daniel E Sammartino, Marshall R Posner, for the TAX 324 Study Group

Ext OS at 5 y 52% vs 42%
Functional imaging

Changes in functional imaging parameters following induction chemotherapy have important implications for individualised patient-based treatment regimens for advanced head and neck cancer

Ceri Powell a, Maria Schmidt a, Marco Borri a, Dow-Mu Koh a, Mike Partridge a, Angela Riddell a, Gary Cook d, Shreerang A. Bhide a,c, Christopher M. Nutting b, Kevin J. Harrington b,c, Katie L. Newbold a,*

a The Royal Marsden NHS Trust, Surrey; b The Royal Marsden NHS Trust, London; c The Institute of Cancer Research, London; and d Guys and St Thomas’ NHS Trust, London, United Kingdom
1. Evaluation by all managing physicians, especially radiation oncologist, before delivery of any IC is crucial for proper coordination of care and optimal RT planning.

2. Nutritional evaluation before beginning therapy, as well as ongoing nutritional support during treatment and recovery, is essential. The use of feeding tube support should be individualized; no specific feeding tube policy was recommended by Panel.

3. All dentulous patients should be evaluated by dentist before beginning cancer therapy to avoid delaying any component of therapy.

4. High-quality preinduction RT planning contrast-enhanced CT scan of head and neck should be obtained to generate reference anatomy for postinduction RT planning.

5. Although PET/CT in RT planning is being rapidly adopted, its precise role in target delineation is still in development; no clear guidance on PET/CT in RT planning can be given at this time.

6. RT should begin within 3–4 weeks from last dose of IC.

7. If patient underwent RT simulation before IC, in most cases, a new immobilization device should be created that approximates the anatomic position of pre-IC device as closely as possible.

8. Preinduction primary site and nodal GTVs should be used for RT planning. Post-IC targets should correspond as closely as possible to originally diseased tissue in all dimensions. All structures involved by tumor before IC should be included, even if not grossly involved after IC.

9. Fusion of preinduction CT simulation image with postinduction CT simulation image could be helpful.

10. Radiation doses should not be modified according to response to IC, even if complete response achieved.

**Abbreviations:** RT = radiotherapy; IC = induction chemotherapy; PET = positron emission tomography; CT = computed tomography; GTV = gross tumor volume.
IC with TPF followed by RT/CRT vs RT/CRT only
Argiris, 2013
**DeCIDE**

Patients
- Locally advanced SCCHN
- Karnofsky PS ≥70
- Previously untreated

**Randomize**

**Induction**
- TPF (n = 142)
- No induction regimen

**Definitive**
- TF+HU+RT
- TF+HU+RT (n = 138)

**Endpoints**
- OS
- Distant failure-free survival
- Failure pattern
- PFS
- QoL
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>IC arm (%)</th>
<th>CRT arm (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>75</td>
<td>73</td>
<td>0.7</td>
</tr>
<tr>
<td>DFS</td>
<td>69</td>
<td>64</td>
<td>0.39</td>
</tr>
<tr>
<td>RFS</td>
<td>67</td>
<td>59</td>
<td>0.18</td>
</tr>
<tr>
<td>DF</td>
<td>10</td>
<td>19</td>
<td>0.025</td>
</tr>
<tr>
<td>LRF</td>
<td>9</td>
<td>12</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Cohen EEW et al., ASCO 2012
The PARADIGM trial: A phase III study comparing sequential therapy (ST) to concurrent chemoradiotherapy (CRT) in locally advanced head and neck cancer (LANHC).

Arm A (70 pts): IC (TPFx3) followed by CRT

Arm B (75pts): RT + Cisplatin x2

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>3y OS</td>
<td>73%</td>
<td>78%</td>
<td>0.77</td>
</tr>
<tr>
<td>3y PFS</td>
<td>67%</td>
<td>73%</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Similar toxicity profiles. Febrile neutropenia more frequent in arm A

Haddad RI et al., ASCO 2012
Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial


Lancet Oncol 2013; 14: 257–64
Randomize

Induction

TPF

Cetuximab+RT

PF+RT

Definitive

Cetuximab+RT

PF+RT

Endpoints

OS (3 year)
PFS (3 year)
Response
Duration
Tolerability
Toxicity
Biomarkers
QoL

Paccagnella et al.
Patients†
Unresectable locally advanced SCCHN
Stage III/IV
ECOG PS 0-1
Previously untreated

No induction regimen
How do we integrate targeted therapies into chemoradiotherapy programs?
Efficacy and feasibility of induction chemotherapy and radiotherapy plus cetuximab in head and neck cancer.


RESULTS:
Eighty-one percent of patients had stage IV disease and 42% had hypopharyngeal and oral cavity primaries. The overall response rate was 81.8%, with 60.6% complete response and 33.3% partial response. Severe toxicities were febrile neutropenia (6%) during induction chemotherapy and dermatitis (48%), mucositis (33%) and dysphagia (12%) during the concurrent phase.

Rampino et al, Anticancer Res 2012
RTOG phase III 0522 trial

Stage III-IV SCC of:
- Oropharynx
- Hypopharynx
- Larynx

Statify:
- Larynx vs others
- N0-N1, 2a,2b vs N2c-3
- 3-D vs IMRT
- Pre-Rx PET (yes vs no)

Randomize:
- Accelerated Fx + CDDP 100 mg/m², q3wx2
- Accelerated Fx + CDDP 100 mg/m², q3wx2
  Cetuximab 400mg/m² pre-RT; then 250 mg/m²/wx7
From 2005 to 2009 enrolled 940 patients. Of 895 evaluable patients, 447 were randomized in arm A (Cetuximab), and 448 in arm B (Cisplatin). Median follow up = 2.4 years.

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>63%</td>
<td>64%</td>
<td>P=0.66</td>
</tr>
<tr>
<td>OS</td>
<td>83%</td>
<td>80%</td>
<td>P=0.17</td>
</tr>
<tr>
<td>Death within 30 days</td>
<td>2%</td>
<td>1.8%</td>
<td>P=0.81</td>
</tr>
<tr>
<td>g.3-5 adverse effects</td>
<td>92%</td>
<td>90%</td>
<td>P=0.30</td>
</tr>
<tr>
<td>g.3-4 mucositis</td>
<td>45%</td>
<td>35%</td>
<td>P=0.003</td>
</tr>
<tr>
<td>g.3.4 skin reaction</td>
<td>40%</td>
<td>17%</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>g.3-4 dysphagia</td>
<td>63%</td>
<td>66%</td>
<td>P=0.27</td>
</tr>
</tbody>
</table>

Ang K et al, 2011
Larynx preservation
VA Laryngeal Cancer Study Group (NEJM, 1991)

- 132 patients with stage III-IV laryngeal cancer

Cisplatin/5-FU x2

CR-PR

NR

Total laryngectomy

Surgery

Cisplatin/5-FU → RT

Surgery → PORT

Total laryngectomy → PORT

Response to induction CT = 85% (31% CR)

Estimated 2-year larynx preservation rate = 66%

No significant difference in OS after 10 years

Significant more local failure but decreased distant failure in CT arm
INT 91-11 trial to preserve the larynx
(Forastiere AA et al, NEJM, 2003)

A. Induction Cisplatin/5-FU

R → B. RT (70 Gy) + concomitant Cisplatin (100 mg/m² qg 1,22,43)

C. RT (70 Gy) only

547 patients with locally advanced laryngeal cancer
T3 =78%, N0-1= 70%
Planned neck dissection for N2N3 stage
<table>
<thead>
<tr>
<th>5 years</th>
<th>A (ind CT)</th>
<th>B (conc)</th>
<th>C (RT alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPR</td>
<td>75%</td>
<td><strong>88%</strong></td>
<td>70%</td>
</tr>
<tr>
<td>LRC</td>
<td>61%</td>
<td><strong>78%</strong></td>
<td>56%</td>
</tr>
<tr>
<td>High Grade Tox</td>
<td><strong>81%</strong></td>
<td><strong>82%</strong></td>
<td>61%</td>
</tr>
</tbody>
</table>

![Graphs showing Laryngeal Preservation and Local-Regional Control](image)
Long term results of RTOG 91-11

Forastiere AA et al, 2013
Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study.

Lefebvre JR et al, JCO, 2013

Stage III-IV larynx/hypopharynx SCC received 3 cycles of TPF

Poor responders (<50%) → salvage surgery

Responders (>=50%) →

Arm A: RT (70Gy) + conc. cisplatin 100 mg/mq 1,2,2,43

Arm B: RT (70 Gy) + conc. Cetuximab 400 mg/mq loading dose and 250 mg/mq per week

Primary end point: larynx preservation (LP) at 3 months
Secondary end points: larynx function preservation (LFP) and overall survival (OS) at 18 months
Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study.

<table>
<thead>
<tr>
<th></th>
<th>LP at 3 mo</th>
<th>LFP at 18 mo</th>
<th>OS at 18 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>95%</td>
<td>87%</td>
<td>92%</td>
</tr>
<tr>
<td>Arm B</td>
<td>93%</td>
<td>82%</td>
<td>89%</td>
</tr>
</tbody>
</table>

Treatment compliance was higher in arm B

Lefebvre JL et al, 2013
III-IV stage laryngeal cancer patients

One cycle of chemotherapy (Cisplatin 100 mg/mq + 5FU 1000 mg/mq gg 1-5)

PR < 50%

laryngectomy

CR or PR>50%

Radiation therapy with concomitant Cisplatin 100 mg/mq days 1,22,43
University of Michigan Study - Results

Of 97 eligible patients, 73 (75%) achieved more than 50% response and received chemoradiotherapy. A total of 29 patients (30%) had salvage surgery; 19 patients (20%) had early salvage surgery after the single cycle of induction chemotherapy, three patients (3%) had late salvage surgery after chemoradiotherapy, six patients (6%) eventually had salvage surgery for recurrence, and one patient had laryngectomy for chondroradionecrosis. The median follow-up time was 41.9 months. The overall survival rate at 3 years is 85%. The cause-specific survival rate was 87%. Larynx preservation was achieved in 69 patients (70%).

(Urba S et al, JCO, 2006)
LARYNX PRESERVATION CLINICAL TRIAL DESIGN: KEY ISSUES AND RECOMMENDATIONS - A CONSENSUS PANEL SUMMARY

Lefebvre JL, Ang KK on behalf of the Larynx Preservation Consensus Panel

IJROBP, 2009
Main recommendations

• The trial population should include patients with T2 or T3 laryngeal or hypopharyngeal carcinoma *not considered for partial laryngectomy* and exclude those with laryngo-esophageal dysfunction or age over 70 years.
• The panel favored a new composite endpoint: "laryngo-esophageal dysfunction-free survival"
• Desired secondary endpoints are: OS, PFS, LRC, time to tracheotomy, time to laryngectomy, time to discontinuation of feeding tube, QoL
• Correlative biomarker studies for near-term trials should include: EGFR, ERCC-1, etc

Lefebvre JL, Ang KK on behalf of the Larynx Preservation Consensus Panel, 2009
Locally advanced H&N Cancer- Conclusions 1

• Concomitant cisplatin-based chemotherapy improves the probability of survival in comparison with radiotherapy alone with a significant increase in severe late toxicity. AFRT doesn’t improve the clinical results in comparison with SFRT in chemoradiation (CTRT) setting.

• Radiotherapy and cetuximab increases the probability of survival in comparison with radiotherapy alone. Phase II and phase III clinical trials comparing CTRT and RT+Cetuximab are now ongoing.

• IC with TPF increases OS in comparison with IC with PF.
Locally advanced H&N Cancer- Conclusions 2

- No one clinical phase III trial until now showed the superiority of IC followed by CTRT, in comparison with CTRT alone
- RTOG 0522 trial failed to show better results adding cetuximab to the standard cisplatin based CTRT
- In larynx preservation trials, RT associated with CT (IC and/or concomitant) obtained the same OS than laryngectomy, with an high proportion of laryngectomy free survival, but with significant toxicity. The primary endpoint of these trials must be not only the laryngectomy free survival but the “laryngo-esophageal dysphunction-free survival”
Locally advanced H&N Cancer- Conclusions 3

• Our porpose must be to optimize the multi-modal therapeutic integration by improving the RT technique (e.g. IMRT) and by reducing the toxicity of the drugs (targeted therapy and/or chemotherapy)

Brizel & Vokes, 2009
Thank you for your attention!!