The Nonsurgical Approach to Larynx Preservation: RT ± Chemotherapy

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IFHNOS 2018 World Tour
Outline

• Milestones in HNSCC management
• Role of induction chemotherapy
• First generation larynx preservation trials
• The importance of timing chemotherapy
• Second generation larynx preservation trials
• The design of future trials
• Conclusions
Milestones in Head and Neck Cancer Management

XIXème
1900
1950
1970s
1980s
1990s
2000s
2010
2014

Surgery
RT X-rays
CT Laser CT - scan MRI
ASCO 1982 PET Targeted therapies TORS IT

MARCH, meta-analysis of radiotherapy in squamous cell carcinomas of head and neck; MACH-NC, meta-analysis of chemotherapy in head and neck cancer; RT, radiotherapy; CT, chemotherapy; PET, positron emission tomography; TORS, Trans-oral robotic surgery; IT, immunotherapy

Modified from Jean-Louis Lefebvre (with permission)
Total laryngectomy (± partial pharyngectomy), Centre Oscar Lambret (1974 - 1983): 5-yr results

<table>
<thead>
<tr>
<th>site</th>
<th>#</th>
<th>control &gt; clavicles</th>
<th>survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>larynx *</td>
<td>254</td>
<td>88 %</td>
<td>48 %</td>
</tr>
<tr>
<td>hypopharynx **</td>
<td>244</td>
<td>84 %</td>
<td>35 %</td>
</tr>
</tbody>
</table>

NB: postop RT * 40 %, ** 100%

Courtesy of J.L. lefebvre
Milestones in Systemic Therapies (± RT) in Head and Neck Squamous Cell Cancer

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Rationale for 1st Generation LP Trials

- High response rates with induction chemotherapy (PF)
  - Response > 90%, complete response > 60%
    (Decker et al, Cancer 1983)

- Chemotherapy may predict radiosensitivity
  - 42/60 CR/PR → after RT, CRR 97%
  - 18/60 NC/PD → after RT, CRR 6%
    (Ensley et al, Cancer 1984)
The Concept of Larynx Preservation (LP)

- As good responders to induction PF seem to be good responders to subsequent radiotherapy (RT), it was an intriguing question whether patients who were candidates for total laryngectomy (TL) could be selected to undergo a non-surgical procedure and keep their larynx in place.

- As TL (with postop RT) provided good local control and survival, was this approach risky?

- Primary endpoint of these 1st generation LP trials was overall survival (OS).
## Induction Chemotherapy in Resectable SCCHN

Larynx preservation: 1st generation trials

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Tumor Size and stage</th>
<th>Treatment arms</th>
<th>No. of pts</th>
<th>Survival (at 5 &amp; 10 yrs)</th>
<th>LP</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Larynx</td>
<td>T1-T4, N2-3</td>
<td>TL + RND + RT</td>
<td>332</td>
<td>45% &amp; 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PFx3 → RT*</td>
<td></td>
<td>42% &amp; 25%</td>
<td>64%+</td>
</tr>
<tr>
<td>EORTC Hypopharynx</td>
<td>T2-T4, N0-3+</td>
<td>TL + RND + RT</td>
<td>202</td>
<td>33% &amp; 14%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PFx3 → RT*</td>
<td></td>
<td>38% &amp; 13%</td>
<td>62%</td>
</tr>
</tbody>
</table>

* non-responders → S + RT; *N2c was excluded (VA trial reported in 1992; EORTC 24891 trial in 1996 and 2012)

*64% is reported in the initial report, not reported in the updated results. **PF** = cisplatin 100 mg/m² d1, 5-FU 1000 mg/m²; d1-5
Duration of Survival

Hazard Ratio: 0.88 (95% CI: 0.65 - 1.19)
P-value for non-inferiority of LP: P=0.0015

Number of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>O</th>
<th>N</th>
<th>Surgery</th>
<th>Larynx preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>94</td>
<td>49</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>83</td>
<td>100</td>
<td>62</td>
<td>47</td>
<td>27</td>
</tr>
</tbody>
</table>

Treatment:
- Surgery
- LP (Larynx preservation)
Conclusions from VA Study and EORTC 24891

- There was no significant difference in survival.
- Around 60% of larynges could be preserved in the chemotherapy arm without a negative effect on survival:
  - Concept is validated for both larynx and hypopharynx cancer.
- Patients with T4 disease are not good candidates for this approach.
- Next trials should focus larynx preservation and the function of the larynx.
### Milestones in Systemic Therapies (± RT) in Head and Neck Squamous Cell Cancer

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Rationale for the 2\textsuperscript{nd} Generation LP trials

\textbf{MACH-NC Meta-analysis}

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Absolute benefit at 5 years</th>
<th>Risk reduction</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>1 %</td>
<td>2 %</td>
<td>NS</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>2 %</td>
<td>5 %</td>
<td>NS</td>
</tr>
<tr>
<td>- NACT with PF</td>
<td>5 %</td>
<td>12%</td>
<td>0.01</td>
</tr>
<tr>
<td>Concurrent</td>
<td>8 %</td>
<td>19%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

\textit{Pignon et al, Lancet 335:949, 2000  (Pooled data from trials performed between 1965 and 1993)}

\textit{Monnerat et al, Ann Oncol 2002; 13: 995-1006}
## Sequential vs Concurrent (or Alternating) CRT

### Larynx preservation: 2nd generation trials

<table>
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<tr>
<th>Study Group</th>
<th>Tumor size and stage</th>
<th>Treatment arms</th>
<th>No. of pts</th>
<th>Survival 5 &amp; 10 yr</th>
<th>LP/SFL at 10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 91-11A</td>
<td>Glottic &amp; supragl. N0-1, N2, N3 T2, T3+, T3-, T4</td>
<td>PFx3 → RT</td>
<td>173</td>
<td>58% &amp; 39%</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCRT (CDDP)</td>
<td>172</td>
<td>55% &amp; 28%</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>173</td>
<td>54% &amp; 32%</td>
<td>64%</td>
</tr>
<tr>
<td>EORTC 24954B</td>
<td>Larynx &amp; Hypopharynx T2-T4, N0-N2</td>
<td>PF x 2-4 → RT</td>
<td>224</td>
<td>49% &amp; 34%</td>
<td>56%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PF alt. RT</td>
<td>286</td>
<td>52% &amp; 32%</td>
<td>56%*</td>
</tr>
</tbody>
</table>

*with fixed cord involvement; †without cord fixation; LP= larynx preservation; SFL= survival with functional larynx

**Forastiere A et al, NEJM2003, ASCO 2006, JCO 2012 (LP= larynx in place; function: voice quality, swallowing & Qol questionnaire)**

**Lefebvre JL et al, JNCI 2009, De Figueiredo et al EJC, 2016 (LP= larynx in place, no tumor, no tracheotomy, no feeding tube; function assessment: % of patients with intelligible voice, normal intake and normal breathing)**
**EORTC 24954**

Eligible pts. (previously untreated larynx /hypopharynx) amenable to TL

- **P** 100mg/m$^2$ d1- 5FU 1000mg/m$^2$ d1-5
- **P** 20 mg/m$^2$ d1-5 – 5FU 200mg/m$^2$ d1-5

### EORTC 24954: Global Results at 5 Yrs

<table>
<thead>
<tr>
<th></th>
<th>Sequential (N=224)</th>
<th></th>
<th>Alternating (N=226)</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>% without event</td>
<td>Events</td>
<td>% without event</td>
<td></td>
</tr>
<tr>
<td>Survival with functional larynx</td>
<td>160</td>
<td>30.5</td>
<td>154</td>
<td>36.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Larynx preservation</td>
<td>107</td>
<td>53.2</td>
<td>94</td>
<td>59.8</td>
<td>0.10</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>140</td>
<td>41.0</td>
<td>139</td>
<td>41.8</td>
<td>0.75</td>
</tr>
<tr>
<td>Overall survival</td>
<td>125</td>
<td>48.5</td>
<td>122</td>
<td>51.9</td>
<td>0.45</td>
</tr>
</tbody>
</table>

**Acute toxicity:** SEQ > ALT  
**Late toxicity:** SEQ = ALT

Organ Preservation in Advanced Laryngeal Cancer
RTOG 91-11

Patients
Stage III or IV
Glottic/supraglottic
SCC (excl. T1 and Large volume T4)

PF x 3 → RT (n=173)
CCRT (n=172)
RT (n=173)

PF = P 100 mg/m² (d1) and F 1000 mg/m d x 5
P during CCRT = 100 mg/m² d1, 22, 43
RT = 70 Gy, given in 35 fractions of 2 Gy over 7 weeks

Forastiere et al, 2003/2006/2012
Fig 2. (A) Laryngeal preservation, (B) laryngectomy-free survival, (C) overall survival, and (D) locoregional control according to treatment group. conc., concomitant; ind., induction; RT, radiation therapy.
RTOG 91-11 (10 years update) Phase III Trial of Larynx Preservation

Forastiere et al, November 26, 2012 as 10.1200/JCO.2012.43.6097. Exploratory analysis of death not caused by study cancer showed significant disadvantage for CCRT vs ICT→RT (52.8% vs 69.8%, respectively at 10 years; p=.03)
CCRT: Late Toxicity

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

MVA: significant variables correlating with severe late toxicity were: older age (OR, 1.05 per year; p=.001), advanced T-stage (OR, 3.07; p=.0036), larynx/hypopharynx primary site (OR, 4.17; p=.0041) and neck dissection (OR, 2.39; p=.018)

Milestones in Systemic Therapies (± RT) in Head and Neck Squamous Cell Cancer

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TPF: A Breakthrough in Induction Chemotherapy

- More efficacious (PFS, OS, larynx preservation)
  - Posner MR et al. with TAX 324 (NEJM 2007)
  - Vermorken JB et al with TAX 323 (NEJM 2007)
  - Pointreau Y, Janoray et al. with TAX 323 regimen (JNCI 2009, JNCI 2016)

- Less toxic (less G3-4 PLT↓, nausea/vomiting, stomatitis, hearing loss and toxic death): European version

- Better quality of life
  - Van Herpen et al, BJC 2010; 103: 1173-1181

- Cost-effective
TPF vs PF for Larynx Preservation: GORTEC 2000-01

Arm A: Cisplatin (100 mg/m² on day 1)  
5-fluorouracil (1000 mg/m² by 24-h continuous infusion for 5 days)

< PR = Total Laryngectomy

> PR = Radiation therapy 70Gy

Arm B: Docetaxel (75 mg/m² on day 1), Cisplatin (75 mg/m² on day 1),  
5-fluorouracil (750 mg/m² by 24-h continuous infusion for 5 days)

< PR = Total Laryngectomy

> PR = Radiation therapy 70Gy

Eligible: Operable patients with untreated stage III or IV larynx or hypopharynx SCC, requiring total laryngectomy. Primary Endpoint: 13-year larynx-preservation rate. 213 patients included (103 in arm A, 110 in arm B)

At 3 years: LP 70.3% with TPF, 57.5% with PF (p=0.03)

A consensus panel summary

Recommendations were developed after reviewing results from completed phase III trials, meta-analyses, and published clinical reports available through November 2007.

Recommendations: the trial population should include patients with T2 or T3 laryngeal or hypopharyngeal SCCHN not considered for partial laryngectomy and exclude those with laryngeal dysfunction or age greater than 70 years. Functional assessments should include speech and swallowing. Voice should be routinely assessed with a simple, validated instrument. The primary endpoint should capture survival and function.

Lefebvre JL and Ang KK. Int J Radiat Oncol Biol Phys 2009
New Endpoints in Larynx Preservation Trials

• **Primary endpoint:**
  - laryngo-esophageal dysfunction-free survival
  - events are
    - death
    - local failure
    - laryngectomy
    - trach for ≥ 2 years
    - feeding tube ≥ 2 years

• **Secondary endpoints:**
  - overall survival
  - progression-free survival
  - locoregional control
  - time to tracheotomy
  - time to laryngectomy

Lefebvre JL and Ang KK. Int J Radiat Oncol Biol Phys 2009
GORTEC 2000-01: Updated Results

Larynx Preservation*

10-yr LP rate 70.3% (TPF) vs 57.5% (PF)

\[ p = 0.01 \]

Larynx DysFunction Free Survival

10-yr LDFFS rate 63.7% (TPF) vs 37.2% (PF)

\[ p = 0.001 \]

* Larynx in place, no tumor, no tracheotomy, no feeding tube

GORTEC 2000-01: Updated Results

Overall Survival

Disease Free Survival

How Aggressive Should We be For Larynx Preservation?

- **doublet ICT: PF followed by RT**
  - good tolerance/compliance to Tx
  - around 60% larynx preservation
  - no impact on survival

- **triplet ICT: TPF followed by RT**
  - still good tolerance/compliance to Tx
  - around 70% larynx preservation
  - no impact on survival

- **CCRT: RT + Px3**
  - substantial toxicity
  - around 80% larynx preservation
  - no impact on survival

- **SCRT: ICT followed by CCRT**
  - substantial toxicity
  - best protocol still unknown
  - place of biotherapies

*Courtesy of J-L Lefebvre*
Larynx Preservation Protocols: Recent Data

- Sequential designs with cytotoxic agents only
- Induction chemotherapy followed by CCRT
  - TPF vs PF→RT + weekly carbo: feasible¹
  - TPF→RT + cisplatin: difficult to tolerate² (better than TPF→RT)

- Sequential designs with integration of cetuximab
  - TPF→RT+ cetuximab: feasible² (better than TPF→RT?)
  - TPF→RT vs TPFE→RTE: not feasible³
  - TP→RT vs TPE→RTE: feasible³ (better than TPF→RT?)

SALTORL trial

Previously untreated T2-3, N0-2 larynx or hypopharynx SCC non eligible for partial surgery
440 pts

3 cycles TPF

\[ \begin{align*}
R < 50 \% & \quad TL + PORT \\
R \geq 50 \% & \quad RT \pm \text{salvage TL}
\end{align*} \]

RT + 3 cycles cisplatin ± salvage TL

Primary endpoint: laryngoesophageal dysfunction free survival

Secondary endpoints: overall survival, disease-free survival, locoregional control, feasibility of salvage surgery, quality of function
General Conclusions on Randomized Trials for Larynx Preservation

• Two validated options for LP as result of large RCTs
  - TPF followed by RT alone for larynx and hypopharynx ca.
  - RT + cisplatin (3 cycles) for larynx cancer

• Data on late toxicity induced by RT result from traditional irradiation techniques. Data of new RT techniques, such IMRT in LP are needed. In SALTORL, IMRT is mandatory

• The role of molecular targeted therapies remains to be determined.