Larynx preservation: How should we decide the best treatment?

Jean Louis Lefebvre
Lille, France
Disclosure

Advisory boards member and lecturer:
Merck-Serono
(Sanofi-Aventis)

Advisory boards member:
Boehringer Ingelheim
Sanofi-Pasteur MSD
Evolution of concepts in larynx and hypopharynx SCC management
Milestones in hypopharynx & larynx cancer management

The fundamentals

XIXème. 1900 1970s 1980s 1990s 2000s 2010s

surgery radiotherapy X-rays laser CT scan MRI

ASCO 1982

MACH NC MACH LP trials

Targeted therapies TPF PET chemotherapy, PF TORS
Looking at the fundamentals

Mid XIX\textsuperscript{th} century
   \textsuperscript{1st} partial laryngectomy

Late XIX\textsuperscript{th} century
   \textsuperscript{1st} total laryngectomy

Early XX\textsuperscript{th} century
   \textsuperscript{1st} radiation therapy for larynx cancer
Early-stage larynx/hypopharynx cancer

- Partial surgery (open/endoscopic)
- Radiation therapy

- No real consensus but
  - No survival impact
  - No difference in disease control

- But no functional impact
Advanced-stage larynx/hypopharynx cancer

radical surgery*
radiation therapy

no real consensus but
unknown survival impact
unknown difference in disease control

but functional impact

* partial surgery feasible in some moderately advanced cases
Total laryngectomy (± partial pharyngectomy)

498 cases, Centre Oscar Lambret (1974 - 1983): 5-yr results

loco-regional control (at last exam)

larynx cancer (254) 88 %
hypopharynx cancer (244) 84 %

Radiation therapy (literature)

local control

supraglottic cancer ≈ 60-70 %
glottic cancer ≈ 50-60 %
hypopharynx cancer ≈ 20-30 %
The missing trial:

Surgical and radiotherapeutic series were assessed and compared:

- retrospectively
- on different groups of patients/tumors
- during different periods of time

\[
\begin{align*}
\text{RANDOM} & \quad \text{total laryngectomy + postop RT} \\
& \quad \text{RT +/- salvage laryngectomy}
\end{align*}
\]
Milestones in hypopharynx & larynx cancer management

- **XIXème.**
- **1900**
- **1970s**
- **1980s**
- **1990s**
- **2000s**
- **2010s**

Research in surgery & radiation therapy

- Laser CT scan MRI
- ASCO 1982
- PET
- Targeted therapies
- TORS
- Chemotherapy, PF

LP trials
MARCH
MACH-NC

- Surgery
- Radiotherapy
- X-rays
Extending partial surgery

<table>
<thead>
<tr>
<th></th>
<th>#</th>
<th>5-yr results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>local ctrl.</td>
<td>survival</td>
</tr>
<tr>
<td>SCPL + CHP</td>
<td>424</td>
<td>94 %</td>
<td>79 %</td>
</tr>
<tr>
<td>SCPL + CHEP</td>
<td>560</td>
<td>93 %</td>
<td>87 %</td>
</tr>
<tr>
<td>HLP</td>
<td>452</td>
<td>89 %</td>
<td>47 %</td>
</tr>
</tbody>
</table>

But mostly T2 ("big T2")

SCPL: supra cricoid partial laryngectomy
CHP: crico hyoido pexy, CHEP: crico hyoido epiglottio pexy
HLP: hemi laryngo pharyngectomy

review of French literature
An option for more advanced cases?

**Lille experience:** 41 T3-T4 larynx treated by SCPL
- 5-yr local failure rate: 5 %
- 5-yr ultimate local control: 98 %
- 5-yr OS: 73 %

Lefebvre JL & Chevalier D, oral presentation Rio 2002

**Rio de Janeiro experience:** 43 T3-T4 larynx treated by SCPL
- 5-yr local failure rate: 7 %
- 5-yr specific S: 78 %
- 5-yr DFS: 83 %


⇒ An option but only in highly selected patients (and teams)
## Meta-analysis: trials on altered fractionation survival by site

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>Interaction test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>282/370</td>
<td>-15.7</td>
<td>134.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>1150/1673</td>
<td>-53.9</td>
<td>561.2</td>
<td></td>
<td>p = 0.20</td>
</tr>
<tr>
<td>Larynx</td>
<td>586/1231</td>
<td>-19.9</td>
<td>276.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>235/297</td>
<td>-12.3</td>
<td>110.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>52/69</td>
<td>8.9</td>
<td>19.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DAHANCA 6 & 7, accelerated RT

1476 SCC of the oral cavity, larynx and pharynx
RT 66-68 Gy / 33-34 F + nimorazole*
⇒ random. 5 F / week vs 6 F / week

<table>
<thead>
<tr>
<th></th>
<th>6 F</th>
<th>5 F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr local control**</td>
<td>76 %</td>
<td>64 %</td>
<td>.0001</td>
</tr>
<tr>
<td>DFS***</td>
<td>73 %</td>
<td>66 %</td>
<td>.01</td>
</tr>
<tr>
<td>voice preservation (larynx)</td>
<td>80 %</td>
<td>68 %</td>
<td>.007</td>
</tr>
</tbody>
</table>

* if glottic SCC : 62 Gy, if glottic T1 no nimorazole
** no significant difference for regional control
*** no significant difference for OS

RT hyperfractionated and accelerated: CHART

918 pts (except T1N0), 404 larynx cancers:
random. 54 Gy/36 F/12 days vs 66 Gy/33 F/6,5 weeks

• overall group (919):
  no difference for local control or survival
  mucositis: CHART > conventional RT

• 404 larynx SCC: 3-yr local control

<table>
<thead>
<tr>
<th></th>
<th>RT conventional</th>
<th>CHART</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>all cases</td>
<td>67 %</td>
<td>79 %</td>
<td>.047</td>
</tr>
<tr>
<td>T1-2 (222)</td>
<td>76 %</td>
<td>78 %</td>
<td>.85</td>
</tr>
<tr>
<td>T3 (139)</td>
<td>47 %</td>
<td>70 %</td>
<td>.017</td>
</tr>
<tr>
<td>T4 (43)</td>
<td>38 %</td>
<td>78 %</td>
<td>.015</td>
</tr>
</tbody>
</table>

Milestones in hypopharynx & larynx cancer management

- XIXème.
- 1900
- 1970s
- 1980s
- 1990s
- 2000s
- 2010s

- surgery
- radiotherapy
- X-rays
- laser
- CT scan
- MRI
- ASCO 1982
- PET
- Targeted therapies
- chemotherapy, PF
- TPF
- TORS

Integration of systemic treatments
Chemotherapy for HNC: the “platinum revolution”

⇒ Induction chemotherapy (ICT)

• ICT with cisplatin and 5-FU provides impressive response rates
• responders to ICT with cisplatin do respond well to subsequent radiation therapy, non-responders don’t.


⇒ Concurrent chemoradiotherapy (CRT)

• CRT provides a significantly higher survival and locoregional control than ICT
• CRT with cisplatin provides the highest benefit

The 3 first RCTs for larynx preservation

3 trials:
VA (USA) larynx VALCSG. N Engl J Med 1991
GETTEC (F) T3 larynx Richard JM et al. Oral Oncol 1998
Metaanalysis (MACH-NC) of these 3 trials: carcinologic events

Conclusions from these 3 CRTs

- T4 and transglottic T3 were better controlled by upfront surgery
- Salvage surgery (after ICT or RT) was not compromised
- Meta-analysis (MACH-NC)
  Surgery arm: survival + 6 % non significant
  Chemotherapy arm: 56 % larynx preserved


The concept of ICT for selection to either RT or surgery was validated
TPF instead of PF: the GORTEC 2000-01 trial

1 trial: GORTEC 2000-01 larynx et hypopharynx

Pointreau Y et al. JNCI 2009
GORTEC 2000-01: TPF is significantly better than PF as ICT for organ preservation

- 213 patients with larynx/hypopharynx cancer requiring total laryngectomy randomized to receive TPF or PF; responders→(C)RT; non-responders→salvage surgery + (C)RT

TPF provided a significantly higher larynx preservation rate than PF

GORTEC, Oncology and Radiotherapy Group for Head and Neck Cancer; TPF, taxane, platinum, 5-FU

4 cycles instead of 3: the EORTC 24954 trial

1 trial EORTC 24954  larynx et hypopharynx  Lefebvre JL et al. JNCI 2009
<table>
<thead>
<tr>
<th></th>
<th>Sequential (N=224)</th>
<th>Alternating (N=226)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>% without event</td>
<td>Events</td>
</tr>
<tr>
<td>Survival with functional larynx</td>
<td>160</td>
<td>30.5</td>
<td>154</td>
</tr>
<tr>
<td>Larynx preservation</td>
<td>107</td>
<td>53.2</td>
<td>94</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>140</td>
<td>41.0</td>
<td>139</td>
</tr>
<tr>
<td>Overall survival</td>
<td>125</td>
<td>48.5</td>
<td>122</td>
</tr>
</tbody>
</table>

**Acute toxicity:**  SEQ > ALT  
**Late toxicity:** SEQ = ALT  
More than 3 cycles of PF?

Adding taxotere to PF (3 cycles of TPF) increased larynx preservation but not survival.

Adding a forth cycle of PF did not modify survival nor larynx preservation.
RT + CT in the concurrent setting

RTOG 91-11 trial update

<table>
<thead>
<tr>
<th>Causes of Deaths</th>
<th>ICT</th>
<th>CRT</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx cancer</td>
<td>41</td>
<td>37</td>
<td>56</td>
</tr>
<tr>
<td>Other cancer</td>
<td>11</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Tx complic</td>
<td>8</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Other causes</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Non cancer-related</td>
<td>18</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Outcome</th>
<th>ICT</th>
<th>CRT</th>
<th>RT</th>
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<tbody>
<tr>
<td>LR failures</td>
<td>45</td>
<td>31</td>
<td>49</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>14</td>
<td>13</td>
<td>22</td>
</tr>
</tbody>
</table>

Forastiere AA et al. ASCO 2006
RTOG 91-11: Higher larynx preservation rate and locoregional control with CRT vs RT or ICT (PF)

Stage III or IV glottic or supraglottic SCCHN

- CRT significantly improved larynx preservation vs ICT/RT (p=0.005) and RT (p<0.001)
- However:
  - Deaths unrelated to larynx cancer or treatment were higher in the CRT arm vs other arms
  - PF may not be the optimal ICT choice in this setting

Conclusions for the RTOG 91-11 trial

CRT arm:
• larynx preservation 84% but acute and late toxicity (including deaths) +++
• no detailed information on function

- No difference in terms of OS or LFS* between ICT and CRT
- Both better than RT alone (update 2012)

* Laryngectomy free survival (primary endpoint)
Types of severe late toxicity after CRT

Data from RT-CT arms of 3 RTOG trials (91-11, 97-03 and 99-14):

Documented severe late toxicity 180 days after end of treatment chronic grade 3-4, pharynx and larynx*
SNG >= 2 yrs after registration treatment-related death within 3 yrs following treatment

Machtay et al. J Clin Oncol 2008
RT + CT in the alternating setting

4 cycles PF

R < 50%

(P)LT ± RT postop

R ≥ 50%

RT ± (P)LT de rattrapage

1 cycle PF

1 cycle PF

1 cycle PF

1 cycle PF

RT

RT

RT

RT

1 trial EORTC 24954

larynx et hypopharynx

Lefebvre JL et al. JNCI 2009
### EORTC 24954: global results at 5 yrs

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

TREMLIN: Cetuximab + RT or CRT after TPF induction?

Stage III–IV larynx/hypopharynx cancer (n=153)

Four early deaths

TPF (3 cycles, q3w), n=153

10 exclusions

PR (n=126)

<PR (n=23)

• Total laryngectomy + postoperative RT, n=16
• RT (surgery refused), n=7

58 started treatment

Cisplatin RT (70 Gy)

Cetuximab (weekly) RT (70 Gy)

56 started treatment

PR, partial response

TREMLIN: results

Stage III–IV larynx/hypopharynx cancer (n=153)

- **Primary endpoint***
  - Cetuximab + RT
  - Cisplatin + RT
  - No signal that one arm could be superior to the other one

- **Secondary endpoints**
  - Cetuximab + RT
  - Cisplatin + RT
  - No signal that one arm could be superior to TPF followed by RT alone

*3 months after end of treatment
**18 months after end of treatment
for patients who were randomized (n=116, 76%)
Notable TPF-induced toxicity, possibly compromising the subsequent combined therapy

Substantial overall toxicity of combined therapy but more manageable with Erbitux

No difference in survival or in larynx function preservation

Non significant trend for fewer local failures in the cisplatin arm but successful salvage surgery only in the Erbitux arm
Comparison of the clinical randomized trials on larynx preservation
### Summary of these trials: primary endpoints

<table>
<thead>
<tr>
<th>trial</th>
<th>Primary endpoint</th>
<th>First report results</th>
<th>Updated results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VALCSG</strong></td>
<td>Overall survival</td>
<td>2-yr OS: 68 % both arms</td>
<td>10 yrs: 30 % (surgery) vs 25 % (chemo) p = .34</td>
</tr>
<tr>
<td><strong>EORTC 24891</strong></td>
<td>Non-inferiority in OS in chemo arm (HR ≤ 1.43)</td>
<td>HR = .86 (chemo arm)</td>
<td>HR = .88 [.65-1.19]</td>
</tr>
<tr>
<td><strong>EORTC 24954</strong></td>
<td>Survival with functional larynx*</td>
<td>3-yr (5-yr) estimates</td>
<td>5-yr (10-yr) estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction: 39.5 % (32.5 %)</td>
<td>Induction: 31 % (19 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternating: 45.5 % (36 %)</td>
<td>Alternating: 35 % (18 %)</td>
</tr>
<tr>
<td><strong>RTOG 91-11</strong></td>
<td>Laryngectomy-free survival</td>
<td>2-yr (5-yr) estimates</td>
<td>5-yr (10-yr) estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction: 59 % (43%)</td>
<td>Induction: 44 % (29 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concomitant 66 % (45 %)</td>
<td>Concomitant 47 % (23.5 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT alone 53 % (38 %)</td>
<td>RT alone 34 % (17 %)</td>
</tr>
<tr>
<td><strong>GORTEC 2000-01</strong></td>
<td>3-yr larynx preservation*</td>
<td>3-yr estimates:</td>
<td>5-yr estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPF: 70 %</td>
<td>TPF: 60 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PF: 57.5 %</td>
<td>PF: 39 %</td>
</tr>
<tr>
<td><strong>GORTEC TREMPLIN</strong></td>
<td>3-mos larynx preservation *</td>
<td>CRT : 95 %</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRT : 93 %</td>
<td></td>
</tr>
</tbody>
</table>

* larynx in place, no tumor, no trach, no feeding tube
## Summary of these trials: larynx preservation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Definition</th>
<th>First report results</th>
<th>Updated results</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALCSG</td>
<td>Larynx in place</td>
<td>In the chemo arm 33-mo med survival: 64 %</td>
<td>NR</td>
</tr>
<tr>
<td>EORTC 24891</td>
<td>larynx in place, no tumor, no trach, no feeding tube</td>
<td>In the chemo arm 3.5-yr med survival: 57 %</td>
<td>in the chemo arm 10.5 med survival 37 % at last exam</td>
</tr>
<tr>
<td>EORTC 24954</td>
<td>larynx in place, no tumor, no trach, no feeding tube</td>
<td>5-yr estimates</td>
<td>NR</td>
</tr>
<tr>
<td>RTOG 91-11</td>
<td>larynx in place</td>
<td>Median f/u 3.8 yrs estimates</td>
<td>5-yr (10-yr) estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction 72 %</td>
<td>Induction 71 % (67.5 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternating 84 %</td>
<td>Concomitant 84 % (82 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT alone 67 %</td>
<td>RT alone 66 % (64 %)</td>
</tr>
<tr>
<td>GORTEC 2000-01</td>
<td>larynx in place, no tumor, no trach, no feeding tube</td>
<td>3-yr estimates</td>
<td>5-yr estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPF: 70 %</td>
<td>TPF: 60 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PF: 57.5 %</td>
<td>PF: 39 %</td>
</tr>
<tr>
<td>GORTEC TREMPLIN</td>
<td>3 months: larynx in place, no tumor 18 months: larynx in place, no tumor</td>
<td>3 mos: CRT: 95 % BRT: 93 % 18 mos: CRT: 87 % BRT: 82 % NB: in randomized patients only</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(76 % of initial population)</td>
<td></td>
</tr>
</tbody>
</table>
Summary of these trials: doses of systemic treatments, RT and overall treatment time

<table>
<thead>
<tr>
<th>trial</th>
<th>cisplatin</th>
<th>5FU</th>
<th>Tax.</th>
<th>Erb.</th>
<th>RT</th>
<th>OTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALCSG</td>
<td>300</td>
<td>15,000</td>
<td></td>
<td></td>
<td>66-76</td>
<td>20</td>
</tr>
<tr>
<td>EORTC 24891</td>
<td>300</td>
<td>15,000</td>
<td></td>
<td></td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>EORTC 24954</td>
<td>Induction: 400 Alternating: 400</td>
<td>Induction: 20,000 Alternating: 4,000</td>
<td>Induction: 70 Alternating: 60</td>
<td>23</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>RTOG 91-11</td>
<td>Induction: 300 Concomitant: 300 RT alone: 400</td>
<td>Induction: 15,000 Concomitant: 70 RT alone: 70</td>
<td>Induction: 70 Concomitant: 70 RT alone: 70</td>
<td>20</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>GORTEC 2000-01</td>
<td>225</td>
<td>11,250</td>
<td>225</td>
<td></td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>GORTEC TREMPLIN arm P</td>
<td>525</td>
<td>11,250</td>
<td>225</td>
<td></td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>GORTEC TREMPLIN arm E</td>
<td>225</td>
<td>11,250</td>
<td>225</td>
<td>1,900</td>
<td>70</td>
<td>20</td>
</tr>
</tbody>
</table>
**Question:** impact of the primary site?  
**Outcome by tumor location (table 1: %, table 2: HR)**  
**EORTC 24954 trial**

<table>
<thead>
<tr>
<th></th>
<th>hypopharynx</th>
<th>larynx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-yr OS</strong></td>
<td>59.4 %</td>
<td>68.0 %</td>
</tr>
<tr>
<td><strong>3-yr PFS</strong></td>
<td>47.2 %</td>
<td>53.5 %</td>
</tr>
<tr>
<td><strong>3-yr LFS</strong></td>
<td>40.9 %</td>
<td>44.3 %</td>
</tr>
<tr>
<td>SEQ</td>
<td>37.5 %</td>
<td>41.6 %</td>
</tr>
<tr>
<td>ALT</td>
<td>44.3 %</td>
<td>47.0 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>hypoph.</th>
<th>epilarynx</th>
<th>endolarynx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td>1</td>
<td>.88 (.66-1.18)</td>
<td>.69 (.49-.98)</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>1</td>
<td>1.01 (.77-1.33)</td>
<td>.80 (.58-1.10)</td>
</tr>
<tr>
<td><strong>LFS</strong></td>
<td>1</td>
<td>1.00 (.77-1.29)</td>
<td>.95 (.71-1.27)</td>
</tr>
</tbody>
</table>
Question 3: do patients requiring a TL for larynx preservation failure lose totally the function?

<table>
<thead>
<tr>
<th>EORTC 24954</th>
<th>Results in laryngectomees N (%)</th>
<th>Results in overall population N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngectomy in 138 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good voice rehabilitation</td>
<td>86 (62 %)</td>
<td>86 (19 %)</td>
</tr>
<tr>
<td>Normal diet</td>
<td>69 (50 %)</td>
<td>69 (15 %)</td>
</tr>
<tr>
<td>Normal breath</td>
<td>92 (67 %)</td>
<td>92 (20 %)</td>
</tr>
</tbody>
</table>

But 100 % permanent tracheostomy
The two on-going trials

- Induction or concurrent CRT?
  - the SALTO trial

- Role of molecular targeted therapies?
  - the DeLOS II trial
Previously untreated T2-3, N0-2 larynx or hypopharynx SCC non eligible for partial surgery
440 pts

Primary endpoint: laryngoesophageal dysfunction free survival

Secondary endpoints: overall survival, disease-free survival
locoregional control, feasibility of salvage surgery
quality of function
DeLOS II: Ongoing trial of ICT containing cetuximab in laryngeal/hypopharyngeal SCCHN

170 patients with only laryngectomy-operative laryngeal/hypopharyngeal SCCHN

TP: Docetaxel + cisplatin; (F), 5-FU until Feb 2009

Primary endpoint: Survival with a functional larynx at 2 years

ASCO 2014, A. Dietz et al., abstract 6016
## Results – toxicity profiles

<table>
<thead>
<tr>
<th></th>
<th>TPF/TP (%)</th>
<th>TPF/TP + Erbitux (%)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>40</td>
<td>30</td>
<td>0,25</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>33</td>
<td>38</td>
<td>0,70</td>
</tr>
<tr>
<td>Pain</td>
<td>15</td>
<td>10</td>
<td>0,57</td>
</tr>
<tr>
<td>Rash/RT</td>
<td>26</td>
<td>20</td>
<td>0,51</td>
</tr>
<tr>
<td>Rash/Erbitux</td>
<td>0</td>
<td>5</td>
<td>0,25</td>
</tr>
</tbody>
</table>

ASCO 2014, A. Dietz et al., abstract 6016
Results – Survival with functional larynx (6 months) Kaplan-Meier analyses

ASCO 2014, A. Dietz et al., abstract6016

![Survival Kaplan-Meier curve](image)

**ITT population, n = 174**

<table>
<thead>
<tr>
<th></th>
<th>Min(^1)</th>
<th>Max(^1)</th>
<th>Endpoint reached n (%)</th>
<th>HR</th>
<th>95% CI (HR)</th>
<th>p-value(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPF / TP, n = 86</td>
<td>0.4</td>
<td>5.9</td>
<td>27 (31.4)</td>
<td>0.502</td>
<td>0.267–0.944</td>
<td>0.0289</td>
</tr>
<tr>
<td>TPF / TP + cetuximab, n = 88</td>
<td>0.5</td>
<td>5.5</td>
<td>15 (17.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Patients, who reached the endpoint (loss of functional larynx due to laryngectomy, recurrent disease, tumor progression, death).

\(^2\) log-rank test (2-sided, alpha = 0.05).
Results – Survival with functional larynx (6 months) Kaplan-Meier analyses

ASCO 2014, A. Dietz et al., abstract 6016

ITT population, n = 174

\( p = 0.0734 \)
How to assess a CRT on larynx preservation
Question: which endpoint?

Larynx preservation?
   no laryngectomy

Larynx function preservation?
   no laryngectomy, no long-term trach and/or feeding tube

Laryngectomy-free survival?
   alive, no laryngectomy

Survival with functional larynx?
   alive, no laryngectomy, no long-term trach and/or feeding tube

What are the respective weights of these parameters when considering the final benefit for the patients?
"Survival seems to be of paramount importance to both patient and nonpatient groups, overshadowing associated toxicities and potential dysfunction"
Laryngoesophageal dysfunction-free survival

Events:
- Death
- Local failure
- Total or partial laryngectomy
- Tracheotomy or feeding tube at 2 yrs or later

How to select the most appropriate strategy for larynx preservation?
General conclusion for randomized trials on larynx preservation

• Two validated options
  ➢ TPF followed by RT
  ➢ RT+ cisplatin (3 cycles)

• Their results cannot be compared adequately (different larynx preservation concepts)

• They still need to be compared in a phase III (SALTO trial)

• The role of molecular targeted therapies is to be determined (DeLOS II trial)
Conclusions: management of previously untreated larynx and hypopharynx SCC

⇒ Aiming at preserving function
- early larynx/hypopharynx SCC (T1, T2)
  Partial surgery (endoscopic or open) or radiation therapy
- moderately advanced larynx/hypopharynx SCC (large T2 and T3)
  Partial surgery whenever technically feasible
- advanced larynx/hypopharynx (T3 non eligible for partial surgery)
  Organ preservation protocols (ICT+RT or CRT, both ± salvage TL)

⇒ Aiming at insuring disease control and survival
- advanced larynx/hypopharynx SCC (T4)
  Total laryngectomy + postop RT (± CT)
Larynx preservation: How should we decide the best treatment?

1) Multidisciplinary tumor board for decision making

2) Enroll patient in well designed clinical randomized trials