Neoadjuvant chemo therapy in Larynx and Hypopharynx cancers

Faye Johnson MD, PhD

Associate Professor
Thoracic/Head and Neck Medical Oncology

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Objectives

• Understand the role of neo-adjuvant chemotherapy for cancers of the larynx and hypopharynx.
Conflict of Interest

• No relevant COI
• Research funding from PIQUR pharmaceuticals for unrelated lab based research.
The problem: Advanced Stage Larynx Cancer

• About 40% die within 5 years
  – About half of those die from cancer.

• Quality of life (QOL) often severely affected.
  – Communication
  – Swallowing
  – QOL better with a preserved larynx.
Advanced T stage: Larynx

- **T3** – Limited to larynx.
  - Vocal cord fixation or invasion into post cricoid, pre-epiglottic, or para-epiglottic spaces.

- **T4a** – tumor invades
  - Thyroid/cricoid cartilage, trachea, soft tissue neck, deep muscles of the tongue, thyroid, esophagus.

- **T4b** – tumor invades
  - Prevertebral space, encases carotid, mediastinum
Advanced T stage: Hypopharynx

• **T3**
  - Tumor >4 cm or fixation hemilarynx or extend to esophagus.

• **T4a**
  - Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, central compartment sift tissue

• **T4b**
  - Tumor invades prevertebral fascia, encases carotid, mediastinum
Hypopharynx

• Poorer prognosis than larynx.
• Poor ability for surgical salvage.
• Higher risk of pharyngeal dysfunction.
• Extrapolation from larynx data may not be applicable.
• Paucity of randomized data.
The Landmark VA study

2 cycles
cisplatin +
5 FU

CR (31%)
PR (54%)
SD/PD (15%)

± 3rd Cycle (83%)
XRT (66-76 Gy)

Stage III
Stage IV
Larynx
SCC

n=166

Total Laryngectomy

n=166

XRT (50.4 6y)

VA Laryngeal Study Group, NEJM 1991
The landmark VA study

- After 10 years – no difference in survival.
  - Salvage laryngectomy for those who progressed after radiotherapy.
- 62% in LP had a retained larynx.

<table>
<thead>
<tr>
<th>Site of recurrence</th>
<th>Surgery (N = 166)</th>
<th>Chemotherapy (N=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>4 (2%)</td>
<td>20 (12%)</td>
</tr>
<tr>
<td>Regional</td>
<td>9 (5%)</td>
<td>14 (8%)</td>
</tr>
<tr>
<td>Distant</td>
<td>29 (17%)</td>
<td>18 (11%)</td>
</tr>
<tr>
<td>All</td>
<td>42 (25%)</td>
<td>52 (31%)</td>
</tr>
</tbody>
</table>

No difference in rate of recurrence, significant difference in site of recurrence, significant difference in development of a 2nd primary CA (surg 6%, chemo 2%)

RTOG 91-11
Phase III Trial of Larynx Preservation

547 pts
Stage III/IV glottic, supraglottic intermediated stage

RANDOMIZE

A XRT → ± Surgery
B XRT → ± Surgery
C P F → XRT → Surgery

Forastiere, NEJM, 2003
Forastiere AA, et al. ASCO 2006. Abstract 5517
RTOG / Intergroup 91-11

Stage III
Stage IV
Larynx
SCC

n=169
3 cycles
cisplatin +
5 Fu

PD
Surgery

SD, PR

Cisplatin + XRT (70 6y)

n=173

n=169
XRT (70 6y)

Salvage Laryngectomy if needed

Forastiere, et. al. JCO 2013
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.
EORTC 24891: Hypopharynx

T2-T4
NO-N2B
Piriform Sinus or Hypopharyngeal aspect of the aryepiglottic fold
SCC

Surgery -

3 cycles Cisplatin + 5Fu

PR

XRT

Lefebure, et.al., Annals of Oncology 2012
Figure 3. Overall survival. $o$ is the number of events; $n$ is the number of patients.

Figure 4. Progression-free survival (time to locoregional or distant recurrence, second cancer or death of any cause). $o$ is the number of events; $n$ is the number of patients.
• Stage III or IV larynx or hypopharynx invasive squamous cell carcinoma.

• Non-responders to the induction chemotherapy underwent laryngectomy followed by radiotherapy.

• Responders received radiotherapy +/- chemotherapy.

• The primary endpoint was three-year larynx preservation rate.
GORTEC 2000-01: TPF regimen was superior to the PF regimen in terms of organ preservation and preservation of functionality of the larynx.

**A**  
Larynx preservation rate, %  
Time since random assignment, y  

- **TPF**:  
  - 110  
  - 56  
  - 36  
  - 28  
  - 13  

- **PF**:  
  - 103  
  - 39  
  - 26  
  - 16  
  - 5  

**B**  
Larynx dysfunction-free survival, %  
Time since random assignment, y  

- **TPF**:  
  - 110  
  - 54  
  - 35  
  - 27  
  - 12  

- **PF**:  
  - 103  
  - 33  
  - 23  
  - 15  
  - 5  

*P = .01*  
*P = .001*
GORTEC 2000-01: No difference in OS or DFS

\[ P = .28 \]

\[ P = .18 \]

\[ P = .21 \]
TREMPLIN: Induction Chemotherapy Followed by Either Chemoradiotherapy or Bioradiotherapy for Larynx Preservation

- Stage III to IV larynx hypopharynx squamous cell carcinoma.
- Induction with 3 cycles TPF (5FU+docetaxel + cisplatin).
- Concurrent cisplatin 100 mg/m² q 3 weeks of RT vs. concurrent weekly cetuximab.

Lefebvre, et al JCO 2013

Only 116/153 (76%) assigned to randomization
**TREMPLIN: Induction Chemotherapy Followed by Either Chemoradiotherapy or Bioradiotherapy for Larynx Preservation**

- First study of induction followed by concurrent.
- Concurrent difficult to deliver after TPF.
- Fewer local failures in cisplatin arm.
- Similar results to GORTEC 2000-01 trial.

**Fig 2.** Overall survival (intent to treat) for the subgroup of patients who were responding to induction chemotherapy.
Notes

• Not eligible for larynx preservation.
  – T4 with invasion through cartilage.
  – Poor function at baseline (airway compromise or PEG).

• Many trials used 2 dimensional radiotherapy treatment plans.

• Definition of larynx preservation not standardized.
Conclusions and Future

• No single approach that is accepted worldwide.
  – Induction (TPF) followed by radiotherapy.
  – Concurrent.

• Whole landscape may change with immunotherapy that is being tested as neoadjuvant, adjuvant, and concurrent.

• Smoking cessation could prevent most of these cases.