Larynx Preservation - Non-surgical-radiation therapy

Sandro V Porceddu

Director, Radiation Oncology Research
Princess Alexandra Hospital, Brisbane, Australia
Professor of Medicine, University of Queensland
What do these animals have in common with the human larynx?

descended larynx for vocalisation
Laryngeal Cancer

- Billroth performed the first laryngectomy in 1873
- Röntgen discovered x-rays 1895 & Pierre and Marie Curie discovered radium in 1898
- Between 1920-1940 radiation therapy was the treatment of choice for his type of laryngeal cancer
Giacomo Puccini
1858-1924

- In 1924 Puccini diagnosed with laryngeal cancer while working on the opera *Turandot*
- Treated with the Columbia Apparatus – radium needles
Giacomo Puccini
1858-1924

“What an ordeal! God help me. This treatment will last no less than six weeks, it is terrible... I feel as though I have bayonets in my throat!”

Puccini died shortly after due to myocardial infarct brought on by a massive haemorrhage
External Beam Radiation Therapy

Standard Parallel Opposed

Highly Conformal

DEFINITIVE:
RT Alone
- Tis, N0: 60.75 Gy (2.25 Gy/fraction) to 66 Gy (2.0 Gy/fraction)
- T1, N0: 63 Gy (2.25 Gy/fraction) to 66 Gy (2.0 Gy/fraction)
- T2, N0: 65.25 (2.25 Gy/fraction) to 70 Gy (2.0 Gy/fraction)
Larynx preservation with radiotherapy

• Early laryngeal cancer

• Locally advanced laryngeal/hypopharyngeal cancer

• Case examples

• Radiotherapy contouring guidelines
EARLY LARYNGEAL CANCER
Early Laryngeal Cancer

- Spectrum of disease
  - T1 & T2
- Favourable disease
  - T2 glottis with extension onto supra- or subglottis, superficial & normal cord mobility
- Unfavourable disease
  - T2 glottis with deep extension and/or impaired mobility
Larynx Preservation Options

- Radiation Therapy
- Endoscopic Surgery
  - Trans Oral Laser microsurgery (TOLMS)
  - Trans Oral Robotic Surgery (TORS)
- Open partial laryngectomy
## Early Laryngeal Cancer

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy</th>
<th>Transoral Excision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5yr Local Control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>85-95%</td>
<td>T1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>83-93%</td>
</tr>
<tr>
<td>T2</td>
<td>68-80%</td>
<td>T2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73-89%</td>
</tr>
<tr>
<td><strong>5 yr DSS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>93-98%</td>
<td>T1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96-99%</td>
</tr>
<tr>
<td>T2</td>
<td>70-88%</td>
<td>T2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>83-97%</td>
</tr>
</tbody>
</table>

Feng Y et al (meta-analysis) ORL, 2011
Voice Quality Outcome

- Systematic review of functional outcome TOLM & RT
- 880pts; 448 TOLM, 442 RT
- Vocal outcomes (subjective analysis); 12 studies no difference, 3 superior RT
- Voice disability (patient perception); 5 studies no difference, 3 conflicting results
- Lack of uniformity of assessment of voice quality
- Neither modality clearly superior

Voice Quality Outcome

- Meta-analysis Voice Handicap Index (VHI) after treatment for T1 Glottic cancer with either RT or Laser (Laser=208, RT=91)

- No difference in VHI

- Regardless of treatment modality voice quality is dependant on initial disease extent and amount of tissue removed

Is RT obsolete in early glottic larynx cancer?

• Given the comparable outcomes
  – Cure rates
  – Voice Quality

• Not accounting for
  – Cost-effectiveness comparisons
  – Patient preference

• Accepting the convenience of endoscopic resection

• Endoscopic resection is the preferred choice
**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Is radiation therapy obsolete in early laryngeal cancer?

- Radiotherapy may no longer be the preferred initial choice
  - comparable outcomes both in local control & voice quality
  - relative low morbidity

- RT still has a role in selected cases
  - unfavourable anatomy
  - medically not suitable
  - widespread in-situ changes
  - deeply infiltrative
  - multiply failed laser procedures
  - patient preference
LOCALLY ADVANCED LARYNGEAL/HYPOPHARYNGEAL CANCER
Surgery/PORT vs chemo-radiotherapy

Guiding Principles in Management

• Functional outcome
  – Is it worth preserving?
  – What is the functional deficit

• Likelihood of clear macroscopic/microscopic margins

• Expected control rates & toxicities

• Aim to use the least number of modalities to obtain the required clinical outcome

• Biological characteristics of the tumour
  – chemo-responsive (to neoadjuvant)
  – recurrent disease
Larynx Preservation

- Early larynx preservation studies
  - VA study NEJM 1991
  - EORTC (Lefebvre JL et al) JNCI 1996
- Induction chemotherapy (Cisplatin/5FU)
  - Responders had definitive RT
  - Non-responders had surgery/PORT
- Larynx preservation rate 66% at 2 years
- No measure of functional outcomes
- No difference in survival
Eligibility

- Stage III-IV SCC glottic or supraglottic larynx
- Surgical treatment would require total laryngectomy
- T1 excluded
- Large-volume T4 disease defined as a tumor penetrating through the cartilage or extending more than 1 cm into the base of the tongue were excluded

Forestiere A et al NEJM, 2003
Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer
RTOG 91-11

3-arm randomised study \( (n=547) \)

2 year intact larynx

Induction cispatin/5FU
concurrent ChemoRT* 
88%

RT alone
70%

- *cisplatin 100mg/m² weeks 1, 4 & 7
- 70Gy over 7 weeks to gross disease

Overall survival no difference

Forestiere A et al NEJM, 2003
RTOG 91-11 10-year follow up

Primary Endpoint
LFS

<table>
<thead>
<tr>
<th></th>
<th>10 yr LFS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT + ICT</td>
<td>28.9</td>
<td>p=0.02</td>
</tr>
<tr>
<td>RT + cCT</td>
<td>23.5</td>
<td>p=0.03</td>
</tr>
<tr>
<td>RT</td>
<td>17.2</td>
<td></td>
</tr>
</tbody>
</table>

Forestiere A et al JCO, 2013
RTOG 91-11 10-year follow up

Larynx preservation (LP)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>10 yr LP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT + ICT</td>
<td>67.5</td>
<td></td>
</tr>
<tr>
<td>RT + cCT</td>
<td>81.7</td>
<td>p=0.02</td>
</tr>
<tr>
<td>RT</td>
<td>63.8</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

- No difference in survival
- No difference in late effects
- Deaths not attributed to larynx cancer or treatment were higher in the concomitant arm

Forestiere A et al JCO, 2013
Functional outcome

• Alive, disease free, retained larynx, over 2-5yrs

<table>
<thead>
<tr>
<th></th>
<th>RT - ICT</th>
<th>RT - cCT</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired speech/voice quality</td>
<td>3-9%</td>
<td>4-8.5%</td>
<td>5-8.5%</td>
</tr>
<tr>
<td>Soft foods only</td>
<td>13-14%</td>
<td>17-24%</td>
<td>10-17%</td>
</tr>
<tr>
<td>Liquids only</td>
<td>&lt;4%</td>
<td>&lt;4%</td>
<td>&lt;4%</td>
</tr>
<tr>
<td>Inability to swallow</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
</tr>
</tbody>
</table>

*no substantive differences in quality of function, but limited numbers

Forestiere A et al JCO, 2013
Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Larynx-preservation guidelines for laryngeal cancer

Larynx-preservation approaches for appropriately selected patients does not compromise survival

No LP approach offers survival advantage vs surgery/PORT

- T1-2
  - Larynx preservation Endoscopic resection or RT

- T3 (non-extensive) and T4
  - Larynx-preservation surgery, CRT or RT alone offer potential LP without survival detriment

- T3(extensive) and T4a & poor pretreatment laryngeal function
  - Better survival rates and QoL may be achieved with total laryngectomy

LP=larynx preservation

Forestiere A et al JCO, 2018
T3N0 Supraglottic SCC

Preservation

- No extension through laryngeal cartilage or into soft tissues
- Swallowing function intact
- At least one cord mobile
- Airway reasonable
- Voice worth preserving
- ECOG ≤2
- Lower threshold for offering CRT for supraglottic ca due to lower rate of long term swallowing issues and greater control rates
T4N2a hyopharyngeal SCC

Non-preservation

- Destroyed laryngeal cartilage/structures
- Extension through laryngeal cartilage and/or soft tissues
- Aspirating (Fluid/solids)
- Fixed bilateral cords
- Severe airway compromise
- Marked poor voice quality
- ECOG 3
- **Lower threshold for offering surgery for hypopharyngeal ca due to greater rate of long term swallowing issues and lower control rates**
Induction preservation case

T3N2b Hypopharyngeal SCC

- 46 year old man
- 60 pack years
- Bulky left neck mass
- No airway obstruction
- No dysphagia
- No weight loss
- ECOG 0
- Left level III 4x3cm nodal mass
- Mass involving left piriform sinus extending to base of tongue and immobile left cord

Induction chemotherapy - TPF

- Borderline organ preservation cRT
- High risk nodal N2c/N3

Haddad RI, Annals Oncol, 2018
T3N2bM0 Hypopharyngeal SCC

Post x2 cycles of TPF

Concurrent HD cisplatin/70Gy
Contouring guidelines
(Gregoire V et al Radiother Oncol 2018)

Primary Tumour CTV = 5mm + 5mm on GTV-p
- CTV1 = 5mm GTV-p
- CTV2 = 5mm + CTV1
- Cropping off anatomic boundaries/air cavities

Gross Tumour Volume (GTV)
Blue contour = 10mm isotropic expansion on GTV
Green contour = 10mm isotropic expansion on GTV with cropping = CTV2
Yellow contour = 5mm isotropic expansion on GTV with cropping = CTV1
Concluding remarks

• Radiotherapy still has a role in early laryngeal cancer
• Concomitant radiotherapy is superior to radiotherapy alone in preserving larynx
• Induction chemotherapy has a role in selected cases for larynx-preservation treatment
• Careful selection for larynx preservation based on disease extent and organ function warranted