Radiotherapy for the treatment of oropharyngeal cancer: state of the art

Renzo Corvò

S.C. Oncologia Radioterapica
Istituto Nazionale per la Ricerca sul Cancro
e Università degli Studi di Genova
Goals in the management of oropharyngeal SCC

• ? definitive cure for patients with **limited** disease

• ? survival in patients with **advanced** disease
  (improving loco-regional control, reducing probability of distant metastases)

• ? organ-function preservation in resectable and unresectable tumors

• ? therapeutic ratio (cure / toxicity ratio)

• ? metachronous tumor occurrence
ADJUVANT RADIOTHERAPY
post-operative setting

THE INCREASING ROLE OF RADIOTHERAPY
IN OROPHARYNX SCC

RADICAL CURE
in unresectable SCC

RADICAL CURE
WITH ORGAN FUNCTION PRESERVATION
in resectable SCC
Upfront treatment modalities in locally advanced oropharyngeal SCC

- Surgery in 20%
- Radiotherapy alone in 20%
- Chemo-radiotherapy in 50%
- Targeted-therapy plus (chemo) radiotherapy in 10%

IST Survey, Genoa 2008
Oropharyngeal SCC

A Challenge for The Radiation Oncologist

Tumor site

Total Dose Delivery Limited by Tolerance of Normal Structures (mucosa, spinal cord, brain stem, salivary gland, others)

• Dosimetric Challenges Due to Varying Contour/Tissue Heterogeneity

Tumor biology

- fast cell kinetics → repopulation
- Hypoxia → intrinsic radioresistance
- High burden of clonogenic cells in advanced disease → more dose
- New biological constraints (EGFR overexpression, Cox-2, others...)
Oropharyngeal SCC

A Challenge for The Radiation Oncologist

Tumor site → **ADVANCED TECHNOLOGY**

*Total Dose Delivery Limited by Tolerance of Normal Structures (mucosa, spinal cord, brain stem, salivary gland, others)*

• *Dosimetric Challenges Due to Varying Contour/Tissue Heterogeneity*

Tumor biology → **INTENSIFIED TREATMENT**

- Fast cell kinetics
- Hypoxia
- Intrinsic radioresistance
- High burden of clonogenic cells in advanced disease
- New biological constraints (EGFR overexpression, HPV -, others...)**
Radiotherapy for Oropharyngeal SCC

4 sites:
- Anterior wall
- Lateral wall
- Superior wall
- Posterior wall

7 subsites each with different local spread

STRATEGY AND TECHNIQUE DEPEND MAINLY ON PRIMARY TUMOR SUBSITE AND STAGE
Standard fractionation with sequential boost

70 Gy / 35 fr / 7 w
Radiotherapy is a treatment option in oropharynx with early-stage tumors

Body of Evidence

There are no randomized studies in which radiation therapy was compared with conservative surgery with respect to local control or survival. The recommendation to address this issue is based on evidence from prospective and retrospective cohort studies.
Outcome in oropharyngeal SCC after radiotherapy alone

- **Response according to clinical growth:**
  - Exophytic +++
    - (tonsillar wall, soft palate)
  - Infiltrative ++
    - (base of tongue, posterior wall)

- **Control according to tumor stage:**
  - **T1:** 80%-100%
  - **T2:** 70%
  - **T3:** 50%-60%
  - **T4:** < 30%

AIRO H&N Guidelines, 2007
Brachytherapy for Oropharyngeal SCC
GEC-ESTRO recommendations
Mazeron J et al, R&O 2009

- Brachytherapy alone is useful for exophytic tumors measuring 10 mm or less in diameter or recurrent lesion after radiotherapy.
- Brachytherapy may be useful as boost for SCC measuring < 50 mm arising in the base of tongue, the soft palate, the tonsillar fossa and the vallecula.
Brachytherapy for Oropharyngeal SCC
GEC-ESTRO recommendations
Mazeron J et al, R&O 2009

• Brachytherapy is usually delivered by Iridium LDR, HDR or PDR.
• After 45-50 Gy of external dose:
  • 30-35 Gy for base of tongue (macroscopic site should receive up to 80 Gy)
• Local control: base of tongue T1-T2: 80%
• Late necrosis of mucosa: up to 25%
Radiotherapy vs Surgery in limited disease

- The ultimate therapeutic choice depends on:
  - staging (T1 vs T2, N0 vs N1)
  - general physical condition
  - age, co-morbidity
  - expected functional, cosmetic and socio-economical results
  - emotional status
  - experience of the treating team
  - available treatment facilities

and why not ?....... patient preference!
Locally advanced disease
III-IV stages
(diagnosed in 60% of patients with SCC)

With conventional-one-a-day fractionation RT:

→ local recurrence up to 50%-60% at 2 years
→ metastatic disease up to 15%-20%
→ overall survival at 5 years < 30%
Intrinsic Radioresistance

Accelerated RT chemoradiation repopulation

Chemoradiation Escalating RT dose (hyperfractionation, brachytherapy, IMRT)

RADIOBIOLOGY

Hypoxia • Radiosensitizer
EGF-R + • Targeted Therapy
Effect of HPV-Associated p16<sup>INK4A</sup> Expression on Response to Radiotherapy and Survival in Squamous Cell Carcinoma of the Head and Neck

Bertille Lessem, Jesper G. Broesen, Stephen Hamilton-Dutoit, Trine Tronvik, Jan Albrecht, and Jens Overgaard
EGFR Expression vs Radiation Response

Overall Survival

- EGFR ≤ Median
- EGFR > Median

n=155

p=0.0006

Local-Regional Relapse

- EGFR > Median*
- EGFR ≤ Median

n=155

* >80% tumor cells +

p=0.003

HNSCC - Ang et al., Cancer Res 62: 7350, 2002 (Zymed antibody)
Improving Efficacy of Irradiation. Hypothesis: improving LRC \(\rightarrow\) better OS

- Dose escalation (Brachytherapy Boost, IMRT-SIB)
- Altered Fractionation Schemes
- Chemo-radiotherapy
- Biological Therapy and Molecular Targeting + Radiotherapy
Phase III trials and meta-analyses
(pts with oropharynx SCC: near to 50%)

• CT-RT > conventional RT (level 1)

• Hyperfractionated or accelerated radiotherapy > conventional RT
  (RTOG/ EORTC trials - level 1)
Overall survival

MARCH
Meta-analysis

8% benefit
<table>
<thead>
<tr>
<th>Chemo-radiotherapy trials META-ANALYSES</th>
<th>No of Trials</th>
<th>No of patients</th>
<th>Benefit in overall survival</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Chemoradiotherapy vs RT MACH-NC- Pignon et al, 2000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall results</td>
<td>63</td>
<td>10741</td>
<td>4% at 5 years</td>
<td>0.0001</td>
</tr>
<tr>
<td>-Neoadjuvant chemotherapy</td>
<td>31</td>
<td>5269</td>
<td>2% at 5 years</td>
<td>0.10</td>
</tr>
<tr>
<td>-Concomitant chemoradiotherapy</td>
<td>26</td>
<td>3727</td>
<td>8% at 5 years</td>
<td>0.0001</td>
</tr>
<tr>
<td>-Adjuvant chemotherapy</td>
<td>8</td>
<td>1054</td>
<td>1% at 5 years</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>2. Chemoradiotherapy vs RT Updated MACH-NC- 2004</strong></td>
<td>87</td>
<td>16000</td>
<td>5% at 5 years</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Evidence-based Radiation Oncology in locally advanced OROPHARYNX SCC

→ *Improved loco-regional control* (with respect to conventional RT)

- hyperfractionation with increased total dose
- accelerated RT (without total dose reduction)
- concurrent chemo-radiotherapy
- radiosensitizer (?) – radiotherapy
- EGFR-inhibitors + radiotherapy

- Reduced rate of distant metastases? chemohradiotherapy (doubtful evidence)
Evidence-based Radiation Oncology in locally advanced OROPHARYNX SCC

\[ \text{Improved overall survival} \]
(with respect to conventional RT)

- concurrent chemo-radiotherapy *
- hyperfractionated RT with ? total dose *
- accelerated RT (at lower level of evidence)
- EGFR-inhibitors –RT (at lower level of evidence)

* benefit of 8% at 5 yrs in meta-analyses
HYPERFRACTIONATION OR ACCELERATED RADIOTHERAPY

CHEMO-RADIOTHERAPY
Potential indications for altered fractionation radiotherapy in oropharyngeal SCC

- Good performance status
- Age < 70 yrs
- Intermediate stage:
  - Stage III: T1 N1- T2 N1 – T3 N0- T3 N1

→ chemotherapy-induced toxicity may be avoided!
Adjuvant (chemo) radiotherapy in oropharyngeal SCC
Post-operative score of failure risk after surgery

- **Low-risk:**
  pT1-pT2 N0 with clear margins

- **Intermediate risk:**
  pT3-pT4 pN0 with clear margins
  pN+ (without ECE)
  close margins (not involved)

- **High risk:** extracapsular invasion
  involved margins
Post-operative score of failure risk after surgery

- **Low-risk:** → no radiotherapy
  pT1-pT2 N0 with clear margins
- **Intermediate risk:** → radiotherapy alone?
  pT3-pT4 pN0 with clear margins
  pN+ (without ECE)
  close margins (not involved)
- **High risk:** extracapsular invasion
  involved margins → chemo-RT
How to reduce toxicity?
Evidence-based therapeutic ratio

Evolving Strategies in HNSCC

1980  1990  2000  2010 yrs

- low
- high

- conventional radiotherapy (early-stage)
- targeted-therapy radiotherapy
- IMRT
- altered fractionation
- radiosensitizer + radiotherapy
- chemo- (altered) radiotherapy
### Concerns with 3-D RT: OARs

<table>
<thead>
<tr>
<th>OARs</th>
<th>Incidence/ prevalence of severe effects with 3-D RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>mucosa</td>
<td>mucositis 3+ up to 70%</td>
</tr>
<tr>
<td>parotid gland</td>
<td>severe xerostomia up to 82%</td>
</tr>
<tr>
<td></td>
<td>? stimulated parotid flow rate</td>
</tr>
<tr>
<td>larynx</td>
<td>hoarseness up to 30%</td>
</tr>
<tr>
<td>pharynx constrictor muscles</td>
<td>chronic disphagia / aspiration: 35-76%</td>
</tr>
<tr>
<td>cochlea</td>
<td>sensor-neural hearing loss up to 68% with doses &gt; 45 Gy</td>
</tr>
</tbody>
</table>
UNILATERAL 3-D RADIOTHERAPY for oropharynx SCC

Contralateral parotid may be fully preserved.

Contralateral nodal progression:
- Up to 21% if midline is involved
- < 3% if not involved

Jensen K. et al, R&O 2007
IST- Genoa, Tumori 2004
→ LEVEL OF EVIDENCE IN 2009: IMRT offers effective local control with lower late toxicity rates than historical data.
<table>
<thead>
<tr>
<th>Prognostic subgroup &amp; 5-yr survival estimation</th>
<th>TNM features</th>
<th>Stage classification 2002 6th edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk subgroup 75%-90%</td>
<td>T1- T2 N0</td>
<td>I-II</td>
</tr>
<tr>
<td>Intermediate-risk subgroup 60%</td>
<td>T3 N0</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>T1-3 N1</td>
<td></td>
</tr>
<tr>
<td>High-risk subgroup 32%</td>
<td>T4a N0-N1</td>
<td>IVA</td>
</tr>
<tr>
<td></td>
<td>T1-T4 N2</td>
<td></td>
</tr>
<tr>
<td>Very-high risk 25%</td>
<td>T4b any N</td>
<td>IVB</td>
</tr>
<tr>
<td></td>
<td>Any T N3</td>
<td></td>
</tr>
</tbody>
</table>
Radiotherapy for oropharyngeal SCC: old and new investigations

- Conventional radiotherapy
- Brachytherapy alone
- External RT plus brachytherapy
- Hyperfractionation/accelerated RT
- Concurrent chemo-radiotherapy
- Concurrent radiotherapy with cetuximab
- **Induction CT → concurrent CT-RT**
- **Intensified Radiotherapy (SIB-IMRT) +/-CT**
Practice recommendation

for the population with locally advanced oropharyngeal SCC disease participation in clinical trials is emphasized as a preferred or recommended treatment option”

Head & Neck Cancer Practical Guidelines – v.1-2008
National Comprehensive Cancer Network- NCCT
Radiotherapy for Oropharyngeal SCC

- Multi-modality Strategy
- Team expertise-based Strategy
- Technology-based Strategy
## Radiotherapy: guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>NCCN</th>
<th>recommendation</th>
<th>PDQ-NCI</th>
<th>recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>RT</td>
<td>2B ++</td>
<td>RT for tongue base and tonsil</td>
<td>2A ++</td>
</tr>
<tr>
<td>II</td>
<td>RT</td>
<td>2B ++</td>
<td>RT for tongue base and tonsil</td>
<td>2A ++</td>
</tr>
</tbody>
</table>
| III early (T2N1) | CT-RT     | 3 +           | HF-RT (tonsil) | 1iiA ++++
| III-IVA     | Concurrent CT-RT | 1 +++       | HF-RT (tonsil) | 1iiA ++++
|             | Induction CT → CT-RT | 3 +        | Concurrent CT-RT | 1iiA ++
|             |           |               | Induction CT → CT-RT | 2A ++         |