Advances in Radiotherapy

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Role of radiotherapy in HNC

- 75% HNC patients benefit from RT
  - Post-operative
  - Definitive
  - Palliative

Barton MB et al Radiother Oncol, 2014
Progress over 30 years

- Improved locoregional control & overall survival probability
  - LRC 27% to 80% over 30 years\(^1\)
- Reduction in long term adverse effects\(^2\)
- Superior QoL & patient reported outcomes\(^3\)
- Transition from primary surgery to function preserving RT (pharyngolaryngeal disease)\(^4\)

\(^1\) Overgaard J JAMA, 2014
\(^2\) Langendijk JA et al JCO, 2008
\(^3\) O’Sullivan B et al Clin Oncol, 2012
\(^4\) Gregoire V et al JCO, 2015
Advances

- Treatment intensification
- Treatment-related morbidity
- Radiotherapy delivery & image guidance
- Post-therapy assessment
- Biologic insights & de-escalation strategies
- Radiotherapy quality assurance
- Contouring consensus guidelines
Future advances

• Molecular imaging to identify tumour sub-volumes that may be targeted through dose escalation or targeted agent (dose painting)
• Adaption tracking of tumour or patient changes during treatment (MRI-Linac)
• Improved dose distribution (protons and heavy particle therapy)
• Concomitant immunotherapy
Role of radiotherapy in HNC

- Post-operative
- Definitive
- Palliative
TREATMENT
INTENSIFICATION
Meta-analysis conventional vs altered fractionation (MARCH)

• 15 randomised trials comparing conventional RT vs altered fractionation RT (6515 pts)

• Significant benefit in favour of altered fractionation at 5 years
  – Absolute survival benefit of 3.4%
  – Absolute locoregional control benefit of 6.4%

Conventional RT vs Hyperfractionation

Overall Survival

Progression Free Survival

MARCH; updated meta-analysis
Lacas B et al Lancet Oncol, 2017
Meta-analysis chemo-RT vs RT Phase III HNSCC Trials from 1965

<table>
<thead>
<tr>
<th>Therapy Modality</th>
<th>Absolute benefit at 5 years*</th>
<th>Risk Reduction*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N=17,493)</td>
<td>4.1 %</td>
<td>10 %</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>2.3 %</td>
<td>2 %</td>
<td>NS</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>2.2 %</td>
<td>5 %</td>
<td>NS</td>
</tr>
<tr>
<td>Concurrent</td>
<td>6.9 %</td>
<td>19 %</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Relative to Conventional Local-Regional Therapy

Pignon & Bourhis Lancet, 2000
Altered fractionation vs chemo-RT

MARCH; updated meta-analysis
Lacas B et al Lancet Oncol, 2017

<table>
<thead>
<tr>
<th>Study</th>
<th>Events (n)/patients (N)</th>
<th>Observed minus expected</th>
<th>Variance</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Altered fractionation radiotherapy</td>
<td>Concomitant chemoradiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INRC-HN-94</td>
<td>58/66</td>
<td>55/70</td>
<td>5.9</td>
<td>1.24 (0.85-1.79)</td>
</tr>
<tr>
<td>ORO 930135</td>
<td>50/65</td>
<td>42/64</td>
<td>6.2</td>
<td>1.32 (0.87-1.98)</td>
</tr>
<tr>
<td>EORTC 2296235</td>
<td>7/13</td>
<td>9/15</td>
<td>0.4</td>
<td>1.11 (0.40-3.03)</td>
</tr>
<tr>
<td>GORTEC 990236</td>
<td>207/281</td>
<td>196/279</td>
<td>147</td>
<td>1.16 (0.95-1.41)</td>
</tr>
<tr>
<td>TMH 111437</td>
<td>34/68</td>
<td>26/65</td>
<td>6.3</td>
<td>1.54 (0.92-2.56)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>356/493</td>
<td>328/493</td>
<td>33.6</td>
<td>1.22 (1.05-1.42)</td>
</tr>
</tbody>
</table>

χ² test for heterogeneity: p=0.87, I²=0%
Treatment effect: p=0.0098
Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

Bonner et al J NEJM, 2006
## Treatment Intensification

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>RT</th>
<th>CETUX-RT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRC median (mo)</td>
<td>14.9</td>
<td>24.4</td>
<td>0.005</td>
</tr>
<tr>
<td>PFS median (mo)</td>
<td>12.4</td>
<td>17.1</td>
<td>0.006</td>
</tr>
<tr>
<td>OS median (mo)</td>
<td>29.3</td>
<td>49.0</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Bonner et al J NEJM, 2006
Treatment Intensification

No increase in in-field toxicity

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy (N=212)</th>
<th>Radiotherapy plus cetuximab (N=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Skin reaction*</td>
<td>200 (94.3%)</td>
<td>45 (21.2%)</td>
</tr>
<tr>
<td>Mucositis/stomatitis†</td>
<td>199 (93.9%)</td>
<td>110 (51.9%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>134 (63.2%)</td>
<td>63 (29.7%)</td>
</tr>
<tr>
<td>Xerostomia‡</td>
<td>150 (70.8%)</td>
<td>6 (2.8%)</td>
</tr>
<tr>
<td>Acneiform rash§</td>
<td>21 (9.9%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Infusion reaction¶</td>
<td>4 (1.9%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Table 2: Most common adverse events

Bonner et al J NEJM, 2006
TREATMENT-RELATED ADVERSE EFFECTS
Treatment related adverse effects

Figure from Trotti 2007

RTOG 1016 will utilize accelerated radiation in both arms (70 Gy in ... treated with the same regimen (accelerated fractionation with concurrent cisplatin, but non-IMRT) on RTOG 0129 (2.8%).
Treatment related adverse effects

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

- Any severe late toxicity: 43%
- Feeding-tube dependence >2 yrs post-RT: 13%
- Pharyngeal dysfunction: 27%
- Laryngeal dysfunction: 12%
- Death: 10%

Treatment related adverse effects

T4N2M0 Nasopharyngeal carcinoma (2008)  
Concurrent chemotherapy + IMRT (70Gy)
RADIOTHERAPY DELIVERY & IMAGE GUIDANCE
Radiotherapy delivery

- 2 Dimensional
Radiotherapy delivery

3D CT

IMRT

Dynamic IMRT
Dose Volume Histogram

Oral Cavity

VMAT
IMRT
3D CT
Conventional radiotherapy (CRT) Head and neck cancer patients at risk of radiation induced xerostomia (oropharynx/hypopharynx)

Randomisation 1:1

Conventional radiotherapy (CRT)

65Gy/30 fractions in 6 weeks - radical and post-operative R1/R2
60Gy/30 fractions in 6 weeks - post-operative R0

Parotid-sparing IMRT (Contralateral Parotid Mean dose <24Gy)

Nutting CM et al Lancet Oncol, 2011
LENT SOMA Subjective Xerostomia rates

Percentage ≥G2

<table>
<thead>
<tr>
<th>Months post treatment</th>
<th>CRT</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>83</td>
<td>62</td>
</tr>
<tr>
<td>n=40</td>
<td></td>
<td>n=45</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>60</td>
</tr>
<tr>
<td>n=36</td>
<td></td>
<td>n=45</td>
</tr>
<tr>
<td>12</td>
<td>74</td>
<td>39</td>
</tr>
<tr>
<td>n=34</td>
<td></td>
<td>n=38</td>
</tr>
<tr>
<td>18</td>
<td>71</td>
<td>29</td>
</tr>
<tr>
<td>n=21</td>
<td></td>
<td>n=31</td>
</tr>
</tbody>
</table>

p = 0.04, p = 0.01, p = 0.004, p = 0.003

Nutting CM et al Lancet Oncol, 2011
Improved tumour delineation

Molecular imaging (FDG PET) - structural imaging (CT/MRI)
Image guided radiotherapy

Cone beam CT (CBCT)

- Efficient in-room 3D treatment verification
- Assess and account for translation and rotation
- Ability to match to predefined region and correct around a point of interest
- Monitoring of anatomical change during treatment
- Use for adaptive radiotherapy

Volumetric Modulated Arc Therapy Delivery

Week 5 CBCT image
POST-THERAPY ASSESSMENT
**PET in the post-therapy assessment of residual nodes**

**Negative Predictive Value**
12-16 week restaging PET  
95-97%

_Yao et al IJROBP 2005_  
_Porceddu SV et al HN 2005_

**Brisbane PET Protocol Study**
Post-therapy PET guided management of the neck
  - regardless of the presence of _residual nodal_ abnormality

2 year total nodal failures 3.5%
  - median residual node 1.5cm (1.0-4.0cm)

Safe to observe neck if residual nodal abnormality is PET negative

_Porceddu SV et al Head Neck 2011_
PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer

for the PET-NECK Trial Management Group*
Overall survival

No difference in locoregional control or overall survival in patients undergoing PET-directed management vs planned neck dissection following chemo-RT

Mehanna H et al NEJM, 2016
CONTOURING CONSENSUS GUIDELINES
Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines ☆

Vincent Grégoire a,*, Kian Ang b, Wilfried Budach c, Cai Grau d, Marc Hamoir e, Johannes A. Langendijk f, Anne Lee g, Quynh-Thu Le h, i, Philippe Maingon j, Chris Nutting k, Brian O'Sullivan l, Sandro V. Porceddu m, Benoit Lengele n
CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines

Charlotte L. Brouwer a,*,1, Roel J.H.M. Steenbakkers a,1, Jean Bourhis b, Wilfried Budach c, Cai Grau d, Vincent Grégoire e, Marcel van Herk f, Anne Lee g, Philippe Maingon h, Chris Nutting i, Brian O’Sullivan j, Sandro V. Porceddu k, David I. Rosenthal l, Nanna M. Sijtsema a, Johannes A. Langendijk a
Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines

Vincent Grégoire, Mererid Evans, Quynh-Thu Le, Jean Bourhis, Volker Budach, Amy Chen, Abraham Eisbruch, Mei Feng, Jordi Giralt, Tejpal Gupta, Marc Hamoir, Juliana K. Helito, Chaosu Hu, Keith Hunter, Jørgen Johansen, Johannes Kaanders, Sarbani Ghosh Laskar, Anne Lee, Philippe Maingon, Antti Mäkitie, Francesco Micciche, Piero Nicolai, Brian O’Sullivan, Adela Poitevin, Sandro Porceddu, Krzysztof Składowski, Silke Tribius, John Waldron, Joseph Wee, Min Yao, Sue S. Yom, Frank Zimmermann, Cai Grau
BIOLOGIC INSIGHTS & DE-ESCALATION STRATEGIES
Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

Radiation Therapy Oncology Group 0129

No difference in OS or PFS

- Oropharyngeal 433
Survival outcomes by HPV status

Overall Survival (%)

HPV Positive

5-year difference 29%, 12-45

HPV Negative

log-rank p<0.001

Patients at risk

Years after Randomization

HPV Pos. 206
HPV Neg. 117

89 193 180 163 119 34 9

Gillison M. ASCO 2009, Orlando, abstract # 6003
RTOG 0129

Oropharyngeal Carcinoma (N=260)

- **p16-positive (N=187)**
  - ≤10 pack-years (94)
    - N0-2a (29)
      - Low-risk (N=123 or 47%) 3-Y OS: 94%
  - >10 pack-years (93)
    - N2b-3 (64)
      - Intermediate-risk (N=73 or 28%) 3-Y OS: 67%

- **p16-negative (N=73)**
  - ≤10 pack-years (16)
    - T2-3 (9)
      - High-risk (N=64 or 25%) 3-Y OS: 42%
  - >10 pack-years (57)
    - T4 (7)

KK Ang et al NEJM, 2010
Biologic differences OPC based on HPV status

Adapted from Dillon & Harrington JCO, 2015
Rising incidence of HPV+ OPC

Larsen P Radiother Oncol, 2010
De-escalation strategies

• Substitute biologic agent for cytotoxic chemotherapy
• Omit or reduce chemotherapy
• Reduce radiation dose
• Use induction chemotherapy to select responders and then reduce radiation dose
• Surgical excision and stratify further treatment based on pathologic findings

Pending de-escalation studies
RADIOTherapy quality assurance
Tirapazamine, Cisplatin, and Radiation Versus Cisplatin and Radiation for Advanced Squamous Cell Carcinoma of the Head and Neck (TROG 02.02, HeadSTART): A Phase III Trial of the Trans-Tasman Radiation Oncology Group

Overall Survival TROG 02.02

Rischin D et al J Clinic Oncol, 2010
Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

Survival based on RT Quality

20% survival difference

Peters LJ et al JCO, 2010
HEAVY PARTICLE RADIATION THERAPY

PROTON THERAPY
Proton Therapy Unit

- Heavy-particle radiation therapy
- Differing physical properties to photons

Clinical implications
- Less integral dose
- Negligible dose beyond the Bragg Peak

Re-treatment following previous RT
Salivary gland tumours
<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible</th>
<th>Drug</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JAVELIN 100</strong> (Pfizer)</td>
<td>Locally advanced head and neck cancer</td>
<td>Avelumab</td>
<td>Avelumab + Cisplatin chemoradiation</td>
<td>Placebo + Cisplatin chemoradiation</td>
<td>PFS</td>
</tr>
<tr>
<td><strong>KEYNOTE 412</strong> (Merck)</td>
<td>Locally advanced head and neck cancer</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab + Cisplatin chemoradiation</td>
<td>Placebo + Cisplatin chemoradiation</td>
<td>EFS</td>
</tr>
<tr>
<td><strong>NCT03349710</strong> (Bristol-MyersSquibb)</td>
<td>Locally advanced head and neck cancer</td>
<td>Nivolumab</td>
<td>Nivolumab + Cetuximab/Cisplatin + radiation</td>
<td>Placebo + Cetuximab/Cisplatin + radiation</td>
<td>EFS</td>
</tr>
<tr>
<td><strong>NCT03452137</strong> (Roche)</td>
<td>Locally advanced head and neck cancer</td>
<td>Atezolizumab</td>
<td>Standard definitive local therapy (multi-modality) followed by adjuvant atezolizumab</td>
<td>Standard definitive local therapy (multi-modality) followed by placebo</td>
<td>EFS</td>
</tr>
</tbody>
</table>
Concluding remarks

• Substantial improvement in locoregional control, modest improvement in survival & an overall reduction in toxicity with radiotherapy due to
  
  – role of concomitant chemotherapy
  – improved technologies & techniques (IMRT)
  – improved quality assurance of planning & delivery
  – image guidecancer
  – universally accepted contouring guidelines