Chemo-Radiation Therapy: Organ Conservation and Future strategies

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Radiation Therapy for:

• Conservation in locally advanced cancers

• Conservation in early cancers

• Improving outcomes in the near future...
Locally Advanced Cancers
Is there an alternative to:
Total Laryngectomy is morbid...
Modern surgical techniques have shown promising outcomes

- Single Centre
- Operator dependant
- Not tested in prospective RCT with standard comparators
- Not all studies have reported longer QOL
- Studies await longer follow up
The alternative must be equal or better than Laryngeectomy

**Outcome**
Locoregional control  
Disease free survival  
Overall survival

**Function**
(Is organ preservation possible?)

**Cosmesis**
Radiation for conservation: VA till now..

- VA study: IC (2+1 Cis-5FU) followed by RT after chemo selection versus total laryngectomy and post-operative RT.
- Non-partial responders received surgery after 2 IC

- 322 pts Pts with stage III and IV larynx cancer
- 2/3rd had supraglottic tumours
- 64% in IC arm had conserved larynx
- 30 patients received laryngectomy pre RT and 29 as salvage
- Decreased distant metastases with IC, more LR, similar OS
VA study: When was salvage laryngectomy required?

- Glottic vs. Supraglottic carcinoma (43% vs. 31%)
- Fixed vs. mobile vocal cords (41% vs. 29%)
- Gross cartilage involvement vs. no cartilage involvement (41% vs 35%)
- stage IV versus III cancers (44% vs 29%)
- T4 vs other T (56% vs 29%)
EORTC 24891- Hypopharynx

- T2 –T4 , No-N2 PFS, AEF
- Trial schema similar to VA (IC+RT vs S+RT)/ Salvage
- Dose of definitive RT standard 70GY (50Gy +20Gy)
- 58% of IC arm completed patients had conserved larynx at 5yrs
- DFS same (25 vs 27%) at 5 yrs; OS better for IC at 3yrs but similar at 5yrs and 10yrs (13.8 vs 13.1%)
- Fewer distant metastases with IC
- IC response related to T stage (T4-0%, T3-48%, T2 84%)
RTOG 91 11: Laryngeal Cancers (No hypopharyngeal cancers)

- T2-T4 (low volume and not going to more than 1cm in BOT)
- RT vs IC-RT vs CTRT
- Larynx Preservation at 10yrs (67.5% vs 63.8% vs 81%)
- DFS similar at 10yrs
- LC better (Larynx Preservation) with CTRT and lesser distant metastases with IC-RT
RTOG 91 11

- Established CTRT as the new standard for Laryngeal Sq CA

- Increased toxicity compared to RT

- CTRT- Trend towards poorer OS (extra non larynx cancer related death)

- Differentiated between larynx preservation and Laryngectomy free survival rates (Speech/swallowing)

- No difference in Laryngectomy free survival between IC-RT vs CTRT although both were better than M
EORTC 24954

• Clubbing Larynx and Hypopharynx together
• T2-4, No-2, who would otherwise need Laryngectomy

• 2 Cis/5FU IC + RT (70Gy) versus 4 Cis/5FU + RT as split course 3 phases 20Gy/10fr

• At 6.5yrs F/U- no difference in functional Larynx preservation

• Less acute toxicity in alternating arm (Dose related)
Challenges with RT to the Larynx
Image Guided radiotherapy

• What image guidance do we have now?

Isocentre check:
Good for 2D / 3D RT planning

2D images

Sup-Inf/ Lateral movements-

Matching on treatment
2D images (Portal Images) to Pre treatment (Digitally reconstructed radiographs)
Intensifying Induction chemotherapy: GORTEC 2000 01

• TPF versus PF as IC followed by RT (otherwise schema similar to the VA study)
• Larynx and Hypopharynx (n=223)
• But Functional preservation of Larynx was primary endpoint

• CR rates higher with TPF- 80% vs 50.2%
• 3yr Larynx preservation 70.3 vs 57.5%
• Functional preservation at 5 yrs 36 vs 28%
Smaller Studies

• GETTEC group: S+RT vs IC +RT
• Larynx Only
• Worse DFS and OS in IC group: ? IC detrimental
• Small Study (n=68) – underpowered to conclude as above

• TAX 324 subgroup- n=123 (TPF vs PF and Carbo RT)
• TPF improved PFS and larynx-function survival compared to PF.
• lower risk of death with TPF: median survival 71m vs 27m (non significant)
• Trial not designed for Larynx conservation (Early Larynx Cancers also)
TPF followed by CTRT

TREMLIN

• Phase 2 (n=153/116)
• 3 IC cycles (TPF):
Pts with response <50% had surgery,
>50% were randomized to RT + P vs. RT
 +Cetuximab

No difference in functional larynx preservation
P-RT more toxic and more B-RT salvage possible

?? Is there a trend that salvage is difficult post
TOF and CTRT?
Molecular Markers

- HPV not beneficial for Laryngeal/Hypopharyngeal cancers
- ERCC$_1$
- Investigational
Oropharynx
RTOG 0129 OPC subgroup

- 433 (of 721 patients)-60%) OPC

- 266 of these patients had Smoking status documented
Biomarkers

- Smoking (Tobacco)
- HPV status
Which group of patients do we deal with?

**Demographics**
- Majority locally advanced
- Majority HPV negative

**Outcome of 100 CTRT patients**

<table>
<thead>
<tr>
<th>SITE</th>
<th>NUMBER (FREQUENCY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OROPHARYNX</td>
<td>52 (43.3 %)</td>
</tr>
<tr>
<td>HYPOPHARYNX</td>
<td>20 (16.7 %)</td>
</tr>
<tr>
<td>LARYNX</td>
<td>48 (40 %)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>120 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STAGE</th>
<th>NUMBER (FREQUENCY)</th>
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<tbody>
<tr>
<td>III</td>
<td>63 (52.5 %)</td>
</tr>
<tr>
<td>IVA</td>
<td>54 (45 %)</td>
</tr>
<tr>
<td>IVB</td>
<td>3 (2.5 %)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>120 (100%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SITE</th>
<th>OS %</th>
<th>DFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>OROPHARYNX</td>
<td>82.7</td>
<td>80.8</td>
</tr>
<tr>
<td>HYPOPHARYNX</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>LARYNX</td>
<td>81.3</td>
<td>89.6</td>
</tr>
<tr>
<td>OVERALL</td>
<td>82.5</td>
<td>86.7</td>
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</tbody>
</table>

TMC data unpublished
Strategies for escalation

• Will our patients accept escalation?

• Adding more chemotherapy? Will this help?

• Accelerating and Hypofractionating

• Brachytherapy Boost (? Unlikely to work in Laryngeal cancers)
The Future: Some Research and Development concepts.....
Radiobiological Comparison of the different plans: TCP

2phase vs. single phase vs. Tomotherapy

Chatterjee et al BJR 2010
Escalating Radiation Dose

• Is there a need

• What do Indian patients feel?
Inclusion criteria: (all of)

- Informed consent obtained
- Stage III/IV head and neck cancer patients - to be treated by CTRT
- Squamous cell carcinoma
- Non salivary gland primary

Exclusion Criteria: (any of)

- Previous radiotherapy
- Has had surgery first for the tumour
- Salivary gland tumour
- Is unable to read English, Bengali or Hindi.
- Patient is in such an emotional state that the treating oncologist feels taking part in the study will be detrimental to patient’s psychological health
What is the benefit that persuaded choosing CTRT versus RT?

<table>
<thead>
<tr>
<th>Difference in cure %</th>
<th>Before Trt (1) CTRT (%)</th>
<th>Completion of CTRT (2) CTRT (%)</th>
<th>3 months post CTRT (3) CTRT (%)</th>
<th>p-value 1-2</th>
<th>1-3</th>
<th>2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>60% vs 60%</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>65% vs 60%</td>
<td>83.3</td>
<td>16.7</td>
<td>30</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>70% vs 60%</td>
<td>96.6</td>
<td>3.4</td>
<td>76.6</td>
<td>S</td>
<td>S</td>
<td>NS</td>
</tr>
<tr>
<td>75% vs 60%</td>
<td>96.6</td>
<td>3.4</td>
<td>93.3</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
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</table>
What is the benefit that persuaded choosing CTRT versus RT?

<table>
<thead>
<tr>
<th>Difference in cure %</th>
<th>Before Trt (1)</th>
<th>Completion of CTRT (2)</th>
<th>3 months post CTRT (3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CTRT (%)</td>
<td>RT</td>
<td>CTRT (%)</td>
<td>RT</td>
</tr>
<tr>
<td>95% vs 95%</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>95% vs 90%</td>
<td>86.6</td>
<td>13.4</td>
<td>57.8</td>
<td>42.2</td>
</tr>
<tr>
<td>95% vs 85%</td>
<td>96.6</td>
<td>3.4</td>
<td>76.6</td>
<td>23.4</td>
</tr>
<tr>
<td>95% vs 80%</td>
<td>100</td>
<td>0</td>
<td>93.3</td>
<td>6.7</td>
</tr>
</tbody>
</table>
How important a factor was Nasogastric Tube placement to choose CTRT versus RT?

• Q3 Will you accept for CTRT a 25% chance of short term feeding tube dependence v/s <5% chance of short term feeding tube dependence with RT alone?

<table>
<thead>
<tr>
<th>NG tube placement</th>
<th>Before Trt (1)</th>
<th>Completion of RT (2)</th>
<th>3 months post RT (3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (%) No</td>
<td>80 20</td>
<td>40 60</td>
<td>46.4 53.6</td>
<td>S S NS</td>
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</table>

<table>
<thead>
<tr>
<th>QN</th>
<th>Question</th>
<th>Response</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>What are your fears about NG tube feeding</td>
<td>No problems</td>
<td>60</td>
<td>6.6</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Afraid of tube and does not want CTRT</td>
<td>3.3</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not want Ryle’s tube</td>
<td>16.6</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Has to eat by any means</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Afraid of Ryles tube but will endure it</td>
<td>16.6</td>
<td>26.6</td>
<td></td>
</tr>
</tbody>
</table>
• Conclusion

• **Survival advantage 5-10%**: 20-36% patients regret deciding on CTRT

• **Survival advantage 5% (Baseline RT survival 60%)**: 50% regretted choosing CTRT at T2 BUT significant % reverted back to choosing CTRT at T3.

*(This group may choose dose escalation studies if such strategies provide a 10% extra benefit compared to RT)*
Strategies for dose escalation

- SIB IMRT
- Accelerating and Hypofractionating

- Brachytherapy Boost (? Unlikely to work in Laryngeal cancers)
# Fractionation: SIB IMRT vs Conventional

<table>
<thead>
<tr>
<th></th>
<th>PTV 1</th>
<th>PTV 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose level 1</strong></td>
<td>$63.0\text{Gy}$ 28# (2.25Gy)</td>
<td>$51.8\text{Gy}$ 28# (1.85Gy)</td>
</tr>
<tr>
<td></td>
<td>$\text{BED}<em>{10\text{Gy}}$ 66.6, $\text{BED}</em>{3\text{Gy}}$ 110.3</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Log cell kill $10.12$</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Conventional</strong></td>
<td>$70\text{Gy}$ 35# (2Gy)</td>
<td>$50\text{Gy}$ 25# (2Gy)</td>
</tr>
<tr>
<td><strong>70Gy 35#</strong></td>
<td>$\text{BED}<em>{10\text{Gy}}$ 74.1, $\text{BED}</em>{3\text{Gy}}$ 116.67</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Log cell kill $10.26$</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Fowler 2008: Work in progress

Slide: Courtesy Dr C Nutting
Dose escalation Hypopharynx and Larynx trial results

<table>
<thead>
<tr>
<th>28 fractions</th>
<th>Cohort 1 63Gy N=29 % (95% CI)</th>
<th>Cohort 2 67.2Gy N=31 % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loco-regional disease free survival</td>
<td>65% (48-82)</td>
<td>83% (68-98)</td>
</tr>
<tr>
<td>Disease specific survival</td>
<td>73% (58-88)</td>
<td>85% (71-99)</td>
</tr>
<tr>
<td>Laryngectomy free survival</td>
<td>84% (71-97)</td>
<td>92% (82-102)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>71% (54-88)</td>
<td>75% (59-91)</td>
</tr>
</tbody>
</table>

Guerrero Urbano et al Radiotherapy and Oncology 85 (2007) 36–41
Miah et al has also updated this
Vortigern:

Variation of radiotherapy target volume definition, dose to organs at risk (OAR) and clinical target volumes using anatomic (CT) vs. combined anatomic and molecular imaging (PET-CT): Intensity Modulated Radiotherapy delivered using a Tomotherapy Hi Art machine

**Inclusion criteria**

- Patients with tumours of oropharynx with involved or uninvolved neck nodes and who are being treated with IMRT will be included in the study.

**Objective**

**Primary Objectives**

1. To determine whether there is change in the tumour volumes used for radiotherapy planning from PET-CT images compared to CT images of head and neck cancers.

2. To estimate whether there is a difference in mean radiation dose received by organs at risk (parotid glands, larynx and spinal cord) when using PET-CT images rather than CT images to plan tomotherapy treatment.

**Secondary Objective**

To develop tools for dose escalation within tumour, tumour sub-regions and nodal areas according to quantitative images of CT and PET tracer distribution.
Variation in radiotherapy target volume definition, dose to organs at risk and clinical target volumes using anatomic (computed tomography) versus combined anatomic and molecular imaging (positron emission tomography/computed tomography): intensity-modulated radiotherapy delivered using a tomotherapy Hi Art machine: final results of the VortigERN study.


Feasibility of PET-CT based hypofractionated accelerated dose escalation in oropharyngeal cancers: Final dosimetric results of the VORTIGERN study. (Secondary endpoint of UK NCRI portfolio: MREC No: 08/H0907/127, UKCRN ID 7341)
Intensifying radiation treatment in advanced/poor prognosis laryngeal, hypopharyngeal (LH) and oropharyngeal cancers (OPC) using PET–CT based dose escalation strategies. (INTELHOPE)
Studies of RT Dose escalation

<table>
<thead>
<tr>
<th>Arm of Treatment</th>
<th>N</th>
<th>Overall Time (weeks)</th>
<th>d</th>
<th>a/b</th>
<th>BED</th>
<th>Kappa</th>
<th>D-28</th>
<th>BED loss</th>
<th>Total effective BED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Int CTV1</td>
<td>30</td>
<td>6</td>
<td>2.1</td>
<td>10</td>
<td>76.23</td>
<td>0.9</td>
<td>14</td>
<td>12.6</td>
<td>63.63</td>
</tr>
<tr>
<td>BTV</td>
<td>30</td>
<td>6</td>
<td>2.45</td>
<td>10</td>
<td>91.51</td>
<td>0.9</td>
<td>14</td>
<td>12.6</td>
<td>78.90</td>
</tr>
<tr>
<td>Std CTV1</td>
<td>30</td>
<td>6</td>
<td>2.2</td>
<td>10</td>
<td>80.52</td>
<td>0.9</td>
<td>14</td>
<td>12.6</td>
<td>67.92</td>
</tr>
<tr>
<td>CTV2</td>
<td>30</td>
<td>6</td>
<td>1.8</td>
<td>10</td>
<td>63.72</td>
<td>0.9</td>
<td>14</td>
<td>12.6</td>
<td>51.12</td>
</tr>
</tbody>
</table>

Radiobiology of doses used in other International studies:

<table>
<thead>
<tr>
<th>Study name</th>
<th>N</th>
<th>Overall Time (weeks)</th>
<th>d</th>
<th>a/b</th>
<th>BED</th>
<th>Kappa</th>
<th>D-28</th>
<th>BED loss</th>
<th>Total effective BED</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAHANCA (7)</td>
<td>34</td>
<td>5.5</td>
<td>2</td>
<td>10</td>
<td>81.6</td>
<td>0.9</td>
<td>10</td>
<td>9</td>
<td>72.60</td>
</tr>
<tr>
<td>ART DECO (8)</td>
<td>28</td>
<td>5.5</td>
<td>2.4</td>
<td>10</td>
<td>83.328</td>
<td>0.9</td>
<td>10</td>
<td>9</td>
<td>74.32</td>
</tr>
<tr>
<td>RTOG (8)</td>
<td>30</td>
<td>6</td>
<td>2.4</td>
<td>10</td>
<td>89.28</td>
<td>0.9</td>
<td>14</td>
<td>12.6</td>
<td>76.68</td>
</tr>
<tr>
<td>ARTFORCE (9)</td>
<td>35</td>
<td>6</td>
<td>2.2</td>
<td>10</td>
<td>93.94</td>
<td>0.9</td>
<td>14</td>
<td>12.6</td>
<td>81.34</td>
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<tr>
<td>Leclerc et al (10)</td>
<td>30</td>
<td>6</td>
<td>2.5</td>
<td>10</td>
<td>93.95</td>
<td>0.9</td>
<td>14</td>
<td>12.6</td>
<td>81.15</td>
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<td>Proposed study</td>
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<td>6</td>
<td>2.45</td>
<td>10</td>
<td>91.51</td>
<td>0.9</td>
<td>14</td>
<td>12.6</td>
<td>78.90</td>
</tr>
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*Intensifying radiation treatment in advanced/ poor prognosis laryngeal, hypopharyngeal (LH) and oropharyngeal cancers (OPC) using PET-CT based dose escalation strategies. (INTELHOPE)*

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**TATA MEDICAL CENTER**

**Trial Protocol**
Escalating Radiation Dose

• Will OUR patients accept dose escalation?
  Yes

• Can we escalate dose?
  Yes

• Is it safe?
  Await results
Thank You