Management of The Neck After Primary Chemoradiation in Head and Neck Squamous Cell Carcinoma

Jason Y K Chan MBBS
Needs assessment

- The current regimen at GBMC is for planned neck dissection (ND) post primary chemoradiation (chemoXRT) for head and neck squamous cell cancer (HNSCC) with ≥N2 neck disease. However there is a body of evidence suggesting observation for those patients with a complete response
Learner objectives

- Examine the need for planned ND post primary chemoXRT for ≥ N2 neck disease with a complete response (cR)
- Evaluate the optimal timing of ND/imaging
- Examine the mode of monitoring response of the neck disease
Background

Post primary chemoXRT | Neck disease

Less than cR all N Stage
- cR N1
- cR ≥ N2
Background

Planned ND

• In ≥ N2 disease
• To reduce regional recurrence
• Historically low response rate to fractionated radiation therapy alone
• Salvage of neck failure is poor
• Ideally performed 4 to 12 weeks after chemoXRT
Background

Why do we perform planned ND?

- Lower radiation dose to uninvolved nodes in the neck
- Concern for micrometastases
Current Treatment paradigm

IMRT – 7000 to 7500 cGy to primary site.

IMRT – 6000 cGy to involved nodes

IMRT – 5000 cGy to uninvolved nodes

Concomitant cisplatin (30mg/m²) weekly for 6 to 7 cycles

Planned neck dissection
Planned Neck Dissections from 1999-2011

Number of patients (N=120)

ND < 12 weeks
ND > 12 weeks
Pathological findings in specimens for neck dissections depending on timing (N=120)

<table>
<thead>
<tr>
<th></th>
<th>ND &gt; 12 weeks (N=58)</th>
<th>ND &lt; 12 weeks (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>(19)</td>
<td>(23)</td>
</tr>
<tr>
<td>No viable Tumor</td>
<td>(21)</td>
<td>(21)</td>
</tr>
<tr>
<td>Positive</td>
<td>(18)</td>
<td>(18)</td>
</tr>
</tbody>
</table>
Patients pathological findings following a complete or partial response post chemoradiation

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Percentage</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative or no viable tumor</td>
<td>77%</td>
<td>103</td>
</tr>
<tr>
<td>Partial response</td>
<td>7%</td>
<td>17</td>
</tr>
<tr>
<td>Positive</td>
<td>26%</td>
<td>17</td>
</tr>
</tbody>
</table>

- Complete response (N=103)
- Partial response (N=17)
Pathological findings in specimens of patients with a complete response to chemoXRT (N=103)

<table>
<thead>
<tr>
<th></th>
<th>ND &gt; 12 weeks (N=52)</th>
<th>ND &lt; 12 weeks (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative and no viable tumor</td>
<td>(37)</td>
<td>(40)</td>
</tr>
<tr>
<td>Positive</td>
<td>(15)</td>
<td>(11)</td>
</tr>
</tbody>
</table>
Pathological findings in patients with a partial response to primary chemoXRT (N=17)
## Outcomes following complete versus partial response

<table>
<thead>
<tr>
<th></th>
<th>Complete Response</th>
<th>Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local Recurrence</strong></td>
<td>4 (3.9)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td><strong>Regional Recurrence</strong></td>
<td>4 (3.9)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td><strong>Second Primary</strong></td>
<td>12 (11.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Distant metastases</strong></td>
<td>12 (11.7)</td>
<td>5 (29.4)</td>
</tr>
</tbody>
</table>
Planned neck dissection

- Is there a need for planned neck dissection in $\geq N2$ disease?
### TROG 98.02 study

<table>
<thead>
<tr>
<th><strong>Aim</strong></th>
<th><strong>Radiation regimen</strong></th>
<th><strong>Concurrent chemotherapy</strong></th>
<th><strong>Monitoring</strong></th>
</tr>
</thead>
</table>
| • Prospective clinical trial  
• Identify incidence of isolated neck failure in patients with cR and ≥ N2 disease 12 weeks post treatment | • Radiation 7000cGy in 35 fractions over 7 weeks  
• Initial 5000 cGy encompassed gross clinical disease and suspected sites 7000cGy to macroscopic disease | • Cisplatin (75mg/m²) and Tirazepine (290 mg/m²) or  
• Cisplatin (50mg/m²) and 5FU (360mg/m²) | • Clinical and radiological assessment (CT) of treatment response at 12 weeks and 26 weeks post treatment |

Response at 12 weeks by nodal classification (N=102)

<table>
<thead>
<tr>
<th>Nodal Classification</th>
<th>cR</th>
<th>Not cR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2/3</td>
<td>60</td>
<td>42</td>
</tr>
<tr>
<td>N2</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>N3</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>
Patterns of failure in patients with ≥ N2 disease with primary and Nodal cR (N=53)

- Death without preceding failure: 4 patients
- Locoregional and distant failure (within 1 month): 3 patients
- Distant failure only: 15 patients
- Local and nodal failure: 1 patient
- Nodal failure only: 0 patients
- Local failure only: 2 patients
- None: 28 patients

Aim
• Assess the need for planned ND following cR after radiation
• Evaluate benefit of neck dissection in less than cR

Radiation Regimen
• Median dose to primary and nodes 7000cGy
• Conventional or altered (twice daily or concomitant boost) fractionation
• Dose was not limited in view of planned ND

Concurrent chemotherapy
• Regimen not documented

Monitoring
• Physical examination
• Contrast-enhanced CT 4-8 weeks after therapy

880 patients T1-4, N1-3

- cR 377
- Less than cR 503

ND 12
- Neck failure 1 (8%)

No ND 355
- Neck failure 26 (7%)
Planned Neck dissection

- Low rate of isolated neck failure
- Most failures either distant or primary site not neck
- With adequate irradiation of the neck if there is complete response in neck then there is no need for planned neck dissection in $\geq$ N2 disease.
Timing of ND

- Concerns regarding
  - Swallowing impairment
  - Prolonged feeding tube need
  - Shoulder dysfunction
  - Impaired wound healing
  - Radiation related fibrosis
### Timing of ND

<table>
<thead>
<tr>
<th>Complication Class</th>
<th>ND &lt; 12 weeks N=67 (%)</th>
<th>ND &gt; 12 weeks N=38 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 complication</td>
<td>24 (35.8)</td>
<td>5 (15.8)</td>
</tr>
<tr>
<td>Multiple complications</td>
<td>6 (9.0)</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>At least 1 wound</td>
<td>16 (23.9)</td>
<td>4 (10.5)</td>
</tr>
</tbody>
</table>

- No significant difference in overall survival or progression-free survival in ND < or > 12 weeks

Timing of ND

- Not worse if done > 12 weeks
- Important particularly with current disease monitoring, with imaging at ~12 weeks
Assessing response to treatment and need for Planned ND

- Clinical examination
- Ultrasound
- CT
- MRI
- PET/CT
### Aim
- Retrospective analysis
- Assess role of PET/CT in predicting early treatment response at primary site and neck after Chemo XRT

### Radiation Regimen
- Custom blocking and compensation or IMRT to primary site and neck 7000cGy

### Chemotherapy regimen
- Intrarterial cisplatin (150 mg/m²)

### Imaging
- PET/CT 6 weeks following completion of chemotherapy
## PET/CT neck in Pretreatment positive necks

<table>
<thead>
<tr>
<th></th>
<th>Positive Neck</th>
<th>Negative Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/CT Positive</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PET/CT Negative</td>
<td>1</td>
<td>17</td>
</tr>
</tbody>
</table>

- N = 21
- Sensitivity 75%
- Specificity 94%
- PPV 75%
- NPV 94%

### PET/CT

<table>
<thead>
<tr>
<th><strong>Aim</strong></th>
<th><strong>Radiation</strong></th>
<th><strong>Chemotherapy</strong></th>
<th><strong>PET/CT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Retrospective review of the utility of PET/CT in patients with ≥ N2 disease with cR prior to planned post treatment neck dissection</td>
<td>• Mean radiation dose 7042 cGy</td>
<td>• Concurrent cisplatin or, • Cisplatin and fluorouracil</td>
<td>• 8-11 weeks after chemoXRT • MRND at 11-12 weeks • Sensitivity 60% • Specificity 36% • PPV 30% • NPV 67%</td>
</tr>
</tbody>
</table>

# PET/CT

**Aim**
- Retrospective review of PET/CT imaging surveillance of post chemoXRT advanced HNSCC

**Radiation**
- IMRT mean 6970 cGy to neck

**Chemotherapy**
- Unknown regimen

**PET/CT**
- Median 11.8 weeks post treatment (range 3.7 - 29.4)

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*Rabalais et al. (2009) Laryngoscope. 119:1120-1124*
PET/CT

52 Patients with Advanced HNSCC

Negative PET/CT 42
- Neck dissections 5 (All negative pathology)

Positive PET/CT 10
- Neck dissections 3 (1 negative pathology)

- Sensitivity 100%
- Specificity 87.5%
- PPV 40%
- NPV 100%

- No significant difference if PET obtained before or after 8 weeks
### PET/CT

<table>
<thead>
<tr>
<th>Aim</th>
<th>Radiation</th>
<th>Chemotherapy regimen</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Observational study to determine PET/CT use in deferring planned neck dissection for patients with advanced HNSCC</td>
<td>• Mean radiation dose 6410 cGy</td>
<td>• Taxane or, • Platinum agent or, • Both</td>
<td>• Obtained every 3-4 months</td>
</tr>
</tbody>
</table>

Nayak et al. (2007) Laryngoscope 117:2129-2134
PET/CT

43 patients with Stage IV >N2 disease

- PET/CT Positive in 10
  - Positive pathology in 7
  - Negative pathology in 3
- PET/CT Negative in 33
  - Recurrence in 1
  - No recurrence in 32

- Sensitivity 88%
- Specificity 91%
- PPV 70%
- NPV 97%
- In cohort 75% spared ND

Nayak et al. (2007) Laryngoscope 117:2129-2134
PET/CT

- PPV is variable possibly related to timing of PET/CT
- Has a high NPV
**PET/CT**

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<th>Chemotherapy</th>
<th>PET/CT</th>
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</thead>
</table>
| • Prospective Study in omitting ND in all PET-negative nodes after definitive chemoXRT regardless of the presence or size of residual nodal abnormalities on contrast CT | • Concomitant boost or fractionated RT  
• 5000 cGy to elective sites  
• 7000 cGy to known sites of disease | • Concurrent Cisplatin (100 mg/m²) | • PET within 3 weeks of commencing RT and 12 weeks post therapy.  
• Diagnostic CT contemperously |

Porceddu et al. (2011) Head Neck
Pretreatment assessment: Clinical examination, Diagnostic CT and/or MRI, PET-CT

Definitive chemoXRT

6 weeks post-therapy clinical assessment

12 week re-staging CT(and/or MRI) + PET/CT

- **PET neck negative**: Observe
- **PET neck equivocal**: Repeat at 4-6 weeks
- **PET neck positive**: Neck dissection
PET/CT

<table>
<thead>
<tr>
<th></th>
<th>PET Alone (95% CI)</th>
<th>CT Alone (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</td>
<td>77.8 (40.0 – 97.2)</td>
<td>14.0 (5.8-26.7)</td>
</tr>
<tr>
<td>NPV</td>
<td>98.1 (93.2-99.8)</td>
<td>96.8 (88.8-99.6)</td>
</tr>
</tbody>
</table>

- Similar values in p16 positive group.

Porceddu et al. (2011) Head Neck
Response outcome in N2 patients (N=82)

<table>
<thead>
<tr>
<th>Pathology positive</th>
<th>Pathology negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET positive</td>
<td>3</td>
</tr>
<tr>
<td>PET negative</td>
<td>1</td>
</tr>
</tbody>
</table>

- PPV 60%
- NPV 98.7%
### Response outcome in N3 patients (N=14)

<table>
<thead>
<tr>
<th></th>
<th>Positive Pathology</th>
<th>Negative Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET positive</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PET negative</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>

- PPV 100%
- NPV 100%
PET/CT

- Optimal timing for PET/CT inconclusive but generally around 12 weeks
- Cost effectiveness remains to be evaluated compared to ND
- No current SUV cutoff used that conclusively improves monitoring
Conclusions

- Planned neck dissection following complete response to primary chemoXRT has no significant added benefit in the adequately irradiated neck for neck control
- Response monitored clinically and with PET/CT
- Delaying ND after 12 weeks has no significant consequence
- Need further to evaluate in HPV population