Head and Neck Cancer Update

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Head and Neck Cancer in Australia in 2015

- New cases = 4,500
- M:F = 3:1
- 3.6% of all cancers
- Number of deaths = 1,000 (2% of all cancer deaths)
- Age-adjusted mortality rate is decreasing
- Chance of surviving at least 5 years is 68%

AIHW 2014
Current state of HNC Treatment

- Surgery + PORT
- Radiation therapy + systemic therapy
- Surgery/PORT - non functioning larynx
- Chemo-RT - functioning larynx
Topic Focus

- Mucosal Head and Neck Cancer
- Squamous cell carcinoma
- Predominantly oropharyngeal cancer
Head and Neck Cancer Update

- Evolution from 1990’s-current
- TNM staging in HPV associated OPC
- Hypoxia in HNC
- Immunosurveillance & Immunotherapy
mucosal Head and Neck Squamous Cell Carcinoma

EVOLUTION FROM 1990’S-CURRENT
Systemic Therapy

1990’s

- Induction chemotherapy
- Concurrent chemo-radiotherapy (platin-based)
- Targeted therapy - anti-EGFR (cetuximab)
- Induction chemotherapy (TPF)

2015-

- Immunotherapy
1990’s
- Emerging understanding of carcinogenesis - p53
- Traditional smoking, alcohol related HNC - 5yr OS of 50%
- Over-expression of EGFR
- Distinct clinical entity of HPV-associated OPC

2015-
- Human Genome Atlas - genomic differences between HPV+OPC and HPV-/non OPC s disease

*Hypoxia is a major determinant of RT treatment outcome
Treatment intensification

- Altered fractionated RT (1990’s)
- Concurrent chemo-RT
- Concurrent chemotherapy & altered fractionated RT
- Induction & concurrent chemotherapy-RT
- “Icarus Effect” (2015-)

Metro South Health
Toxicity, QoL & Patient Reported Outcomes

Standardization of treatment toxicity-acute & late (CTCAE)

Assessment of Quality of Life and Patient Reported Outcomes

De-escalation trials in the context of subset of favourable disease

Trial design with QoL & PRO as primary endpoint
Surgery

1990’s

- Surgery +/- post-operative RT
- Organ preservation in chemo-responsive disease (VA Study)
- De-escalation of surgery - MRND, laser
- Trans Oral Robotic Surgery (TORS)
- Elective ND improves overall survival in oral cavity cancer

2015–
Imaging

1990’s
- Contrast-enhanced CT

Magnetic Resonance Imaging

FDG-Positron Emission Tomography

PET-CT, PET-MRI

“Novel” PET tracers to biologically characterise tumours & response to tailor therapy

2015-
Advances in Head and Neck Cancer

• Recognition of HPV-associated OPC as a distinct entity & appropriate treatment de-escalation selection
• Significant technological advances in radiation therapy and surgery
• Emergence of functional imaging
• Improved understanding of the genomics of HNC
• Improved understanding of toxicity, QoL, PRO
• Emergence of targeted- & immuno-therapies
Ongoing controversies HNC

- Surgery/PORT vs chemo-RT
- High-dose cisplatin vs weekly cisplatin
- Role of cisplatin vs cetuximab
- Role of induction chemotherapy
- Optimal de-escalation treatment and selection of appropriate patients
- Role of hypoxic modifiers with RT
- Laser/TORS vs RT in early favourable disease
- Optimal supportive measures for long-term survivors
TNM STAGING & HPV-ASSOCIATED OPC
TNM Staging (AJCC/UICC 7th Edition)

- Developed for traditional HNC
- Does not reflect the outcomes of HPV-associated OPC
- Clinical dilemma where Stage IV HPV+ OPC may be misinterpreted as poor outcome-Stage IVa 40-50% 5yr OS
- Hinders appropriate trial design & treatment selection

KK Ang et al NEJM 2010 RTOG0129

Oropharyngeal Carcinoma (N=260)

- p16-positive (N=187)
  - ≤10 pack-years (94)
    - N0-2a (29)
    - N2b-3 (64)
    - T2-3 (9)
    - T4 (7)
  - >10 pack-years (93)
  - Intermediate-risk (N=73 or 28%) 3-Y OS: 67%
  - High-risk (N=64 or 25%) 3-Y OS: 42%
  - Low-risk (N=123 or 47%) 3-Y OS: 94%
- p16-negative (N=73)
  - ≤10 pack-years (16)
  - >10 pack-years (57)
TNM Staging

T1  Tumour <=2cm in greatest dimension
T2  Tumour >2 cm but not more than 4 cm in greatest dimension
T3  Tumour >4 cm in greatest dimension

T4a  Tumour invades any of the following structures: larynx deep/extrinsic muscle of tongue, medial pterygoid, hard palate, and mandible
T4b  Tumour invades any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases the carotid artery
Staging groupings (7th Edition)

Anatomic Staging

Stage 0  TisN0M0
Stage I   T1N0M0
Stage II  T2N0M0
Stage III T3N0M0, T1/2/3N1M0
Stage IVA T4aN0/1, T1/2/3/4aN2M0
Stage IVB T4b Any N M0, Any T N3M0
Stage IVC Any T, Any N, M1
Refining American Joint Committee on Cancer/Union for International Cancer Control TNM Stage and Prognostic Groups for Human Papillomavirus–Related Oropharyngeal Carcinomas

Shao Hui Huang, Wei Xu, John Waldron, Lillian Siu, Xiaowei Shen, Li Tong, Jolie Ringash, Andrew Bayley, John Kim, Andrew Hope, John Cho, Meredith Giuliani, Aaron Hansen, Jonathan Irish, Ralph Gilbert, Patrick Gullane, Bayardo Perez-Ordonez, Ilan Weinreb, Fei-Fei Liu, and Brian O’Sullivan
Refining the TNM staging for HPV-associated OPC

- Single-institution study (PMH)
- Patients treated between 2000-2010
- Oropharyngeal cancer
  - HPV-associated = 573
  - HPV-unrelated = 237
- Treated with RT \pm chemotherapy
- Median FU 5.1 years
- Examined OS based on TNM 7\textsuperscript{th} edition group staging and HPV status
- For HPV+ OPC RPA used to derive a new staging classification which was compared to TNM 7\textsuperscript{th} edition

Huang S JCO 2015
Overall Survival based on TNM 7th Edition

HPV-associated OPC

HPV-unrelated OPC

Huang S JCO 2015
Proposed TNM for HPV-associated OPC (RPA) (n=573)

- **Stage I:** T1-T3N0-N2bM0 (n=335)
  - 5-year median OS, 82%;
  - 95% CI, 77% to 86%

- **Stage II:** T1-T3N2cM0 (n=91)
  - 5-year median OS, 76%;
  - 95% CI, 68% to 86%

- **Stage III:** T4 or N3M0 (n=147)
  - 5-year median OS, 54%;
  - 95% CI, 46% to 63%

*Stage IV = M1*

Huang S JCO 2015
International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S)

- Evaluation of the single-centre findings (*Discovery*)
- Multi-centre international cohort (*Validation*)
- New Staging Classification for HPV-associated OPC using RPA and Adjusted Hazard Ratio
- n= 1907 patient

*Unpublished Data*
ICON-S for HPV-associated OPC

- ICON-S
  - did not find a significant difference in OS between Stage I-IVa for current TNM staging (except IVb)
  - better defines survival outcomes for HPV-associated OPC
- Staging similar to Huang’s JCO publication
- Modification of T4 & N-staging
- Under consideration by UICC & AJCC for 8th Edition
- Consideration of extending ICON-S to include not only anatomic but non-anatomic factors into the TNM Matrix
- Findings soon to be published
HPV-associated OPC Survival based on TNM 7th Ed

<table>
<thead>
<tr>
<th>Stage</th>
<th>5yr OS</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>88</td>
<td>74-100</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>82</td>
<td>71-95</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>84</td>
<td>71-95</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>81</td>
<td>79-89</td>
<td>0.25</td>
</tr>
<tr>
<td>IVB</td>
<td>60</td>
<td>53-68</td>
<td>&lt;0.001</td>
</tr>
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</table>
Consideration by AJCC & UICC for 8th Edition

• Based on current TNM definitions
  – I: T1-2N0- N2b;
  – II: T1-2N2c or T3N0-N2c;
  – III: T4 or N3

• Based on proposed TNM definitions
  – I: T1-2N0-N1;
  – II: T1-2N2 or T3N0-N2;
  – III: T4 or N3.

– Metastatic disease (M1) is classified as ICON-S stage IV.
HYPOXIA IN HNC
Hypoxia determinant of outcome

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Events / Total</th>
<th>Odds ratio and 95% CI</th>
<th>Odds ratio</th>
<th>Risk Reduction</th>
<th>NNT**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loco-regional control</td>
<td>1203 / 2406 1383 / 2399</td>
<td>0.71 (0.63-0.80)*</td>
<td>0.71*</td>
<td>8% (5-10%)*</td>
<td>13</td>
</tr>
<tr>
<td>Disease specific survival</td>
<td>1175 / 2335 1347 / 2329</td>
<td>0.73 (0.64-0.82)</td>
<td>0.73</td>
<td>7% (5-10%)*</td>
<td>14</td>
</tr>
<tr>
<td>Overall survival</td>
<td>1450 / 2312 1519 / 2305</td>
<td>0.87 (0.77-0.98)</td>
<td>0.87</td>
<td>3% (0-6%)</td>
<td>31</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>159 / 1427 179 / 1391</td>
<td>0.87 (0.69-1.09)</td>
<td>0.87</td>
<td>2% (-1-4%)</td>
<td>57</td>
</tr>
<tr>
<td>Radiotherapy complications</td>
<td>307 / 1864 297 / 1822</td>
<td>1.00 (0.82-1.23)</td>
<td>1.00</td>
<td>0% (-3-2%)</td>
<td>&gt;&gt;</td>
</tr>
</tbody>
</table>

** Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

- 95% CI.
- ** Numbers of patients Needed to Treat to achieve benefit in one patients.

Overgaard J. Radiother Oncol 2011
Overcoming Hypoxia

- Hypoxic cytotoxin eg Tirapazamine
- Hypoxic radiosensitizer eg Nimorazole
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

Stage III or IV H&N SCC

RANDOMISE

• Arm 1 – Intergroup Protocol
  radiation + cisplatin

• Arm 2 – TROG Protocol
  radiation + cisplatin + tirapazamine
Overall Survival TROG 02.02

Estimated percentage surviving

Years following randomisation

CIS

CIS/TPZ

Hazard ratio 95% CI

CIS/TPZ : CIS

Rischin D et al, J Clinic Oncol 2010
Failure Free Survival

Estimated percentage surviving and failure-free

Years following randomisation

CIS
CIS/TPZ

Hazard ratio 95% CI

CIS/TPZ : CIS

2P = 0.96

Locoregional Failure

Estimated percentage locoregional failure-free

Years following randomisation

CIS
CIS/TPZ

Hazard ratio 95% CI

CIS/TPZ : CIS

2P = 0.44

Rischin D et al, J Clinic Oncol 2010
• TROG Tirapazamine study did not stratify for HPV status

• Hypoxia is not a determinant of outcome in HPV-associated OPC

• Target (ie hypoxia) was not assessed

• Role of hypoxic cytotoxin unanswered in HPV-negative OPC and non-OPC HNC
P16 negative patients only

Overall Survival (%)

- p16+ (n = 106)
- p16- (n = 79)

HR = 0.36; P = .004
2-year OS: 91% & 74%

Locoregional Failure Free (%)

- CIS/TPZ (n = 41)
- CIS (n = 38)

HR = 0.33; P = .13
2-year OS: 92% & 81%

No. at risk

<table>
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<tr>
<th>Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>p16+</td>
<td>106</td>
<td>100</td>
<td>52</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>p16-</td>
<td>79</td>
<td>67</td>
<td>39</td>
<td>16</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CIS/TPZ</td>
<td>41</td>
<td>33</td>
<td>22</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CIS</td>
<td>38</td>
<td>29</td>
<td>16</td>
<td>7</td>
<td>0</td>
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</tr>
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</table>
A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85

Jens Overgaard\textsuperscript{a,}\textsuperscript{*}, Hanne Sand Hansen\textsuperscript{b}, Marie Overgaard\textsuperscript{c}, Lars Bastholt\textsuperscript{d}, Anne Berthelsen\textsuperscript{e}, Lena Specht\textsuperscript{e}, Birgit Lindeløv\textsuperscript{b}, Karsten Jørgensen\textsuperscript{f}
Figure 17.5 Results from the DAHANCA 5 study showing (a) actuarial estimated loco-regional tumour control and (b) disease-specific survival rate in patients randomized to receive nimorazole or placebo in conjunction with conventional radiotherapy for carcinoma of the pharynx and supraglottic larynx. From Overgaard et al. (1998), with permission.
A blind randomized multicenter study of accelerated fractionated chemo-radiotherapy with or without the hypoxic radiosensitizer nimorazole (Nimoral), using a 15 gene signature for hypoxia in the treatment of HPV/p16 negative squamous cell carcinoma of the head and neck.

EORTC 1219 ROG-HNCG
TROG 14.03
Study Design

HPV/p16 negative
Stage III - IV (T1-4, N0-3)
Oropharynx
Larynx
Hypopharynx

RANDOMIZATION

Radiation therapy + cisplatin
+ placebo

Radiation therapy + cisplatin
+ nimorazole (oral tablet daily before RT)

Accrual Target 640 patients
1st primary objective:

- To evaluate in a randomized trial, whether the hypoxic cell radiosensitizer Nimorazole can improve the effect of primary curative accelerated fractionated concomitant chemo-radiotherapy with Cisplatin given to patients with locally advanced HPV/p16 negative HNSCC
2nd primary objective:

• To investigate if the patients who may have such benefit can be predicted by the use of a hypoxic gene profile, i.e. if the treatment benefit is larger and essentially restricted to the subset of patients who are hypoxic cell signature positive
1219 ROG-HNCG: accrual (cut-off date: 05/03/2015)

Accrual of study 1219

- Expected today: 30
- Observed today: 37
IMMUNOSURVEILLANCE AND IMMUNOTHERAPY
HNSCC is an immunosuppressive disease

- Lower absolute lymphocyte counts c/w healthy controls
- Impaired Natural killer (NK) cell activity
- Poor antigen presenting function
- Impairment of tumour-infiltrating T Lymphocytes
Immune system plays a key role in the development of HNSCC

- HNSCC evades the immune system through the manipulation of its
  - own immunogenicity (escaping immuno-surveillance)
  - production of immunosuppressive mediators
  - promotion of immunomodulatory cell types
Cancer Immunotherapy

2011 ipilimumab licensed for treatment of advanced melanoma

PD-1/ PD-L1 pathway in suppressing anti-tumor immunity

Pembrolizumab
Manipulation of APC & T-cell interaction

Checkpoint Inhibitors

When CTLA-4 binds to antigen presenting cells (APC) it switches “off” T-cell activity and downregulates the immune system

Ipilimumab=anti-CTLA-4

PD-L1 (found on tumour cells) binds to PD-1 and suppresses the immune system by inhibiting the activity of tumour-specific effector T-cells

Pembrolizumamb=anti-PD-1
PD-1 blockade
### Monoclonal Antibodies targeting PD-L1:PD-1

<table>
<thead>
<tr>
<th>mAb</th>
<th>Company</th>
<th>Target</th>
<th>Isotype</th>
<th>Clinical trial stage, Tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>MED14736</td>
<td>Medimmune</td>
<td>PD-L1</td>
<td>IgG1</td>
<td>Phase I, NSCLC, melanoma, GEC*, SCCHN, TNBC, CRC, pancreas.</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>Genentech/Roche</td>
<td>PD-L1</td>
<td>IgG1</td>
<td>Phase II, NSCLC, Phase I, melanoma, RCC, NSCLC, CRC, gastric, SCCHN</td>
</tr>
<tr>
<td>BMS-936659 (Nivolumab)</td>
<td>BMS</td>
<td>PD-1</td>
<td>IgG4</td>
<td>Phase III NSCLC, melanoma</td>
</tr>
<tr>
<td>MK-3475 (Pembrolizumab)</td>
<td>Merck</td>
<td>PD-1</td>
<td>IgG4</td>
<td>Phase III NSCLC, Phase II melanoma Phase I NSCLC, TNBC, Melanoma, SCCHN, urothelial tract cancer.</td>
</tr>
</tbody>
</table>
HNSCC Expansion Cohort of the KEYNOTE-012 Nonrandomized, Phase 1b Multi-Cohort Trial*

Patients:
- Recurrent or metastatic HNSCC, regardless of PD-L1 or HPV status
- Measurable disease based on RECIST 1.1
- ECOG 0 or 1

Response assessment: Every 8 weeks

Primary end points: ORR per modified RECIST v1.1 & safety

Secondary end points: PFS, OS, duration of response

- Treatment for 24 months†
- Documented disease progression‡
- Intolerable toxicity
Antitumor activity and safety of pembrolizumab in patients (pts) with advanced squamous cell carcinoma of the head and neck (SCCHN): Preliminary results from KEYNOTE-012 expansion cohort. *Tanguy Y. Seiwert, The University of Chicago, Chicago, IL*

**Methods**
Patients with advanced HNSCC irrespective of biomarker of HPV status. 200mg of pembrolizumab 3 weekly and evaluated every 8 weeks radiographically.

**Results**
99/132 were evaluable. Overall response rate 18.2% (95%CI; 11.1-27.2). >3AE 7.6% (any drug-related AE 47%); fatigue, appetite, pyrexia & rash. 58% had > 2 lines of therapy for recurrent disease. Biomarker evaluation ongoing.

**Conclusion**
Well tolerated with a meaningful ORR
Key messages

• A new TNM staging classification for HPV positive disease to better reflect outcomes, aid in treatment management & clinical trial design is required, with a large international collaboration soon to publish results of a new proposed staging classification

• Role of hypoxia modification with RT in non-HPV associated disease remains open and being tested in an Intergroup Study (EORTC/DAHANCA/TROG)

• HNSCC is an immunosuppressive condition with immunotherapy clinical trials underway or in development