Head and Neck Cancer

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Disclosures

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• Speaker: Ion Beam Applications
• Consultant: Elekta
Learning Objectives

• Predict disease outcomes and survival for the major categories/subsites of head and neck cancer.

• Review and discuss new, high-impact, clinical evidence published in the past year that may impact treatment paradigms for head and neck cancer therapy.

• Determine the best clinical and technical approaches for definitive and postoperative head and neck cancer radiotherapy treatment.
Basic Anatomy: Neck levels

Som et al. AJR 2000
Basic Anatomy: Level Ia (submental)

- Below mylohyoid muscle
- Above caudal edge of hyoid bone
- Between the anterior bellies of the digastric muscle
Basic Anatomy: Level Ia (submental)

- Below mylohyoid muscle
- Above caudal edge of hyoid bone
- Between the anterior bellies of the digastric muscle
Basic Anatomy: Level Ia (submental)

- At risk from cancers of the:
  - Oral cavity
Basic Anatomy: Level Ib (submandibular)

- Below mylohyoid muscle
- Above caudal edge of hyoid bone
- Posterolateral to the anterior belly of the digastic muscles
Basic Anatomy: Level Ib (submandibular)

- Below mylohyoid muscle
- Above caudal edge of hyoid bone
- Posterolateral to the anterior belly of the digastic muscles
Basic Anatomy: Level Ib (submandibular)

- At risk from cancers of the:
  - Oral cavity
Basic Anatomy: Level II, Superior internal jugular (deep cervical) chain

- Extends from skull base superiorly to caudal edge of hyoid bone inferiorly
- Medial to the sternocleidomastoid
- Anterior border: posterior border of the submandibular gland
- Posterior border: posterior border of the sternocleidomastoid
- Posterior edge of jugular vein separates IIa from IIb
Basic Anatomy: Level II, Superior internal jugular (deep cervical) chain

- Extends from skull base superiorly to caudal edge of hyoid bone inferiorly
- Medial to the sternocleidomastoid
- Anterior border: posterior border of the submandibular gland
- Posterior border: posterior border of the sternocleidomastoid
- Posterior edge of jugular vein separates IIa from IIb
Basic Anatomy: Level II, Superior internal jugular (deep cervical) chain

• At risk from cancers of the:
  • Nasopharynx
  • Oral cavity
  • Oropharynx
  • Larynx/Hypopharynx
Basic Anatomy: Level III, Mid internal jugular (deep cervical) chain

- Extends from caudal edge of hyoid bone superiorly to caudal edge of cricoid cartilage inferiorly
- Medial to the sternocleidomastoid
- Anterior and posterior borders parallel the sternocleidomastoid
Basic Anatomy: Level III, Mid internal jugular (deep cervical) chain

- Extends from caudal edge of hyoid bone superiorly to caudal edge of cricoid cartilage inferiorly
- Medial to the sternocleidomastoid
- Anterior and posterior borders parallel the sternocleidomastoid
Basic Anatomy: Level III, Mid internal jugular (deep cervical) chain

- At risk from cancers of the:
  - Nasopharynx
  - Oral cavity
  - Oropharynx
  - Larynx/Hypopharynx
Basic Anatomy: Level IV, Low internal jugular (deep cervical) chain

- Extends from caudal edge of cricoid cartilage superiorly to the level of the clavicle inferiorly
- Medial to the sternocleidomastoid
- Anterior and posterior borders parallel the sternocleidomastoid
Basic Anatomy: Level IV, Low internal jugular (deep cervical) chain

- Extends from caudal edge of cricoid cartilage superiorly to the level of the clavicle inferiorly
- Medial to the sternocleidomastoid
- Anterior and posterior borders parallel the sternocleidomastoid
Basic Anatomy: Level IV, Low internal jugular (deep cervical) chain

- At risk from cancers of the:
  - Nasopharynx
  - Oropharynx
  - Larynx/Hypopharynx
Basic Anatomy: Level V, Posterior triangle

• Posterior to the posterior edge of the SCM
• Anterior to the trapezius
• Level Va: posterior to levels II and III
• Level Vb: posterior to level IV
Basic Anatomy: Level V, Posterior triangle

- Posterior to the posterior edge of the SCM
- Anterior to the trapezius
- Level Va: posterior to levels II and III
- Level Vb: posterior to level IV
Basic Anatomy: Level V, Posterior triangle

• At risk from cancers of the:
  • Nasopharynx
Basic Anatomy: Level VI, Prelaryngeal/Pretracheal

- Extends from caudal edge of hyoid superiorly to the manubrium of the sternum inferiorly
- Between the anterior edges of the sternocleidomastoid
- Anterior to levels III and IV
Basic Anatomy: Level VI, Prelaryngeal/Pretracheal

- Extends from caudal edge of hyoid superiorly to the manubrium of the sternum inferiorly
- Between the anterior edges of the sternocleidomastoid
- Anterior to levels III and IV
Basic Anatomy: Level VI, Prelaryngeal/Pretracheal

• At risk from cancers of the:
  • Thyroid
  • Larynx
    • Primary subglottic location or extension into subglottis
    • Extension through thyroid cartilage
  • Hypopharynx
    • Post-cricoid location
Basic Anatomy: Retropharyngeal

- Extends from base of skull superiorly to the cranial edge of the hyoid bone inferiorly
- Located medial to the carotid artery
Basic Anatomy: Retropharyngeal

- At risk from cancers of the:
  - Nasopharynx
  - Oropharynx
    - Posterior tonsillar pillar
    - Soft palate
    - Posterior pharyngeal wall
  - Hypopharynx
    - Posterior pharyngeal wall
Principles of RT and Combined Modality

• Concurrent chemotherapy

• Alternatives to standard chemotherapy
  • Induction chemotherapy
  • Cetuximab
  • Altered Fractionation

• Principles of RT technique/target delineation
The role of concurrent chemotherapy

For advanced stage (III, IVa, IVb)
Meta-analysis of randomized trials from 1965-2000 comparing RT alone vs CRT.

- Timing: Induction, Concurrent, Adjuvant
- # agents: Mono- or polychemotherapy
(a) Hazard ratio of death.

<table>
<thead>
<tr>
<th>Timing</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant</td>
<td>3171/4824</td>
<td>-326.4</td>
<td>1587.7</td>
<td>0.81</td>
<td>[0.78; 0.86]</td>
</tr>
<tr>
<td>Induction</td>
<td>1877/2740</td>
<td>-40.0</td>
<td>900.7</td>
<td>0.96</td>
<td>[0.90; 1.02]</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>631/1244</td>
<td>17.9</td>
<td>317.4</td>
<td>1.06</td>
<td>[0.95; 1.18]</td>
</tr>
<tr>
<td>Total</td>
<td>5679/8808</td>
<td>-348.5</td>
<td>2805.8</td>
<td>0.88</td>
<td>[0.85; 0.92]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 179.8 \) \( p < 0.0001 \)

Test for interaction: \( \chi^2 = 26.60 \) \( p < 0.0001 \)

\( \bar{I}^2 = 41\% \)

LRT+CT better | LRT better
LRT+CT effect: \( p < 0.0001 \)
Suggests that main benefit of chemotherapy for HNC is from radiosensitization
<table>
<thead>
<tr>
<th>Type of chemotherapy</th>
<th>No. Deaths / No. Entered</th>
<th>LRT+CT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
<th>p of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Poly chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU and Platin</td>
<td>602/940</td>
<td>695/931</td>
<td>-92.2</td>
<td>317.6</td>
<td>0.75</td>
<td>[0.67;0.84]</td>
<td>0.41</td>
</tr>
<tr>
<td>5-FU or Platin</td>
<td>495/743</td>
<td>543/795</td>
<td>-45.8</td>
<td>250.0</td>
<td>0.83</td>
<td>[0.74;0.94]</td>
<td></td>
</tr>
<tr>
<td>Neither 5-FU nor Platin</td>
<td>62/115</td>
<td>85/129</td>
<td>-11.1</td>
<td>35.0</td>
<td>0.73</td>
<td>[0.52;1.01]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (a)</td>
<td>1159/1798</td>
<td>1323/1855</td>
<td>-149.0</td>
<td>602.6</td>
<td>0.78</td>
<td>[0.72;0.85]</td>
<td></td>
</tr>
<tr>
<td>(b) Mono chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono Platin</td>
<td>703/1151</td>
<td>739/1059</td>
<td>-102.6</td>
<td>341.8</td>
<td>0.74</td>
<td>[0.67;0.82]</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Mono Other</td>
<td>1309/1875</td>
<td>1327/1877</td>
<td>-74.8</td>
<td>643.3</td>
<td>0.89</td>
<td>[0.82;0.96]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (b)</td>
<td>2012/3026</td>
<td>2066/2936</td>
<td>-177.4</td>
<td>985.1</td>
<td>0.84</td>
<td>[0.78;0.89]</td>
<td></td>
</tr>
<tr>
<td>Total (a … b)</td>
<td>3171/4824</td>
<td>3389/4791</td>
<td>-326.4</td>
<td>1587.7</td>
<td>0.81</td>
<td>[0.78;0.86]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2_1 = 1.69 \quad p = 0.19 \)

LRT+CT better | LRT better
• Concurrent, mono-agent platinum-based chemotherapy is the optimal approach for patients undergoing concurrent chemoradiation.
  • Superior to induction and adjuvant

Why the enthusiasm for induction chemotherapy?
TAX 324: Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU Sequential Therapy in Advanced SCCHN

Chemotherapy- and RT-naïve stage III/IV SCCHN
- Oral cavity, oropharynx, hypopharynx, larynx
  N=501

Randomize

ICT
Docetaxel (75 mg/m²)
Cisplatin (100 mg/m²)
5-FU (1000 mg/m²/day, 96-hr C-I)
every 3 weeks, 3 cycles

CRT
Carboplatin (AUC 1.5 weekly)
Daily RT (5 days/week)
Cisplatin (100 mg/m²)
5-FU (1000 mg/m²/day, days 1-5)
every 3 weeks, C-I 3 cycles

<table>
<thead>
<tr>
<th>Response</th>
<th>TPF N=255 (95% CI)</th>
<th>PF N=246 (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (ICT)</td>
<td>72% (65.8-77.2)</td>
<td>64% (57.9-70.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>CR (ICT)</td>
<td>17% (12.1-21.6)</td>
<td>15% (10.8-20.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>ORR (ICT+CRT)</td>
<td>77% (70.8-81.5)</td>
<td>72% (65.5-77.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>CR (ICT+CRT)</td>
<td>35% (29.4-41.5)</td>
<td>28% (22.5-34.1)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

TAX 324: Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU Sequential Therapy in Advanced SCCHN: Results

Survival

Log-rank $P=0.0058$
HR=0.70

TPF 67%
PF 54%

TPF 62%
PF 48%

PFS

Log-rank $P=0.004$
HR=0.701

TPF 53%
PF 42%

TPF 49%
PF 37%

- TPF significantly improves survival and PFS compared with PF in an ICT regimen followed by CRT
Why Consider Induction Chemotherapy

• Pros:
  • Salvage subclinical M1 disease ➔ OS benefit?
  • Assessment of response
  • Reduce dose/volume of RT?

• Cons:
  • Prolongs treatment time/cost
  • Increases toxicity
  • No clinical benefit
Paradigm: Phase III Sequential Therapy Trial in North America

**Paradigm**
Stage III/IV SCCHN
- Oral cavity, oropharynx, hypopharynx, larynx
- Expected N=330

**Randomize**
- Docetaxel
- Cisplatin
- 5-FU
  - every 3 weeks, 3 cycles

**ICT**
- Carboplatin (every week)
  - Daily RT (days 1-5)
  - 7 weeks

**CRT**
- Docetaxel (every week for 4 wks)
  - Daily/twice-daily RT (days 1-5)
  - 6 weeks
- Cisplatin (weeks 1, 4)
  - Daily/twice-daily RT (days 1-5)
  - 6 weeks
• Study terminated early due to poor accrual (145 enrolled)

• Median f/u 49 mos

• 3-yr OS: (73% ICT vs 78% CRT, NS)

• Febrile neutropenia (23% ICT vs 1% CRT)

Decide: Phase III Sequential Therapy Trial in North America

DeCIDE
Chemotherapy and RT-naïve SCCHN
• Expected N=400

Randomize

ICT

Docetaxel (day 1)
Cisplatin (day 1)
5-FU (days 1-5)
every 3 weeks, 2 cycles

CRT

Docetaxel (day 1)
5-FU (days 0-4)
Hydroxyurea (days 0-4)
Twice-daily RT (days 1-5)
every 2 weeks, 5 cycles
• 285 Accrued (out of a planned 400)

• Adverse events more common with ICT
  • 47 vs. 28%, p = 0.002

• No differences in OS, DFFS, or RFS

Cohen JCO 2014; 32: 2735
Induction: Take home points

• Should not be considered standard therapy (outside of the nasopharynx---more on this later)
  • Greater toxicity, no improvement in outcomes

• Role?
  • High-risk patients
    • Bulky disease (T4b, N3)
    • Impending airway issue/unresectable disease
    • High-risk for M1 disease
    • Unavoidable delay to start of RT/need for rapid symptom palliation
    • Clinical trial: as a means of deintensification?
Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D., Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D., Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D., Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D., Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*
• Stage III, IV, OPX, hypopharynx, larynx

• Randomization
  • RT alone
  • RT + Cetuximab

• Cetuximab
  • 400 mg/m² loading dose
  • 250 mg/m² weekly

• RT
  • Once daily: 70 Gy, 35 fx
  • Twice daily: 1.2 Gy bid, 60-64 fx (72-76.8 Gy)
  • Concomitant Boost (72 Gy in 42 fx, 1.8 Gy daily x 3.6 wks, then 1.8 Gy AM dose, 1.5 Gy PM dose for last 2.5 wks)
**Figure 1.** Kaplan–Meier Estimates of Locoregional Control among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for locoregional progression or death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.68 (95 percent confidence interval, 0.52 to 0.89; P=0.003 by the log-rank test). The dotted lines indicate the median durations of locoregional control.

**Figure 2.** Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.74 (95 percent confidence interval, 0.57 to 0.97; P=0.03 by the log-rank test). The dotted lines indicate the median survival times.
• RT + Cetuximab superior to RT alone wrt LRC and OS for LA-HNSCC

• Valid therapeutic option, for pts CI to receive platinum-based chemotherapy

• Alternative to platinum?
  • Efficacy
  • Toxicity
  • Pending results (RTOG 1016)
Altered Fractionation RT
RTOG 90-03

- Locally advanced HNC, RT alone
- 4 arms
  - Standard (SFX): 2 Gy daily to 70 Gy (7 weeks)
  - Hyperfractionation (HFX): 1.2 Gy bid to 81.6 Gy (7 weeks)
  - Split course (AFX-S): 1.6 Gy bid to 67.2 Gy, with 2 week rest after 38.4 Gy (6 weeks)
  - Concomitant boost (AFX-C): 1.8 Gy daily, with 1.5 Gy boost as 2nd daily trt for last 12 days, 72 Gy (6 weeks)
• HFX improved OS compared to SFX

• 7 vs 6 wk trt
  • 6 wk trt: trend to increased grade 3-5 toxicity

• Worst toxicity per patient, by trt
  • AFX-C trended worse than SFX

Beitler *IJROBP* 2014; 89: 13
5 vs 6 fractions per week (DAHANCA)

- RCT of RT alone, 5 vs 6 fractions/week
  - DAHANCA 6 (RT alone): Glottic cancers
  - DAHANCA 7 (RT + nimorazole): Supraglottis, pharynx, oral cavity
  - 2 Gy per fraction, 62-68 Gy
  - 6th fraction given on weekend or weekday (> 6h after previous fx)
    - T1 glottis: 62 Gy
    - Primary or nodes < 4 cm: 66 Gy
    - Primary or nodes > 4 cm: 68 Gy
Figure 3: Effect of overall treatment time in T site and N site

Overgaard *Lancet* 2003; 362: 933
Figure 5: Effect of overall treatment time on disease-specific survival and overall survival

Overgaard *Lancet* 2003; 362: 933
Figure 6: Early and late radiation-related morbidity

Acute confluent mucositis in 1420 patients and actuarial probability of developing severe late reactions in 1249 patients.
Altered Fractionation: Summary

• Improves disease outcomes when compared to standard fractionation when treating with RT alone for advanced stage HNC

• For pts who cannot receive chemotherapy, consider:
  • Hyperfractionation (RTOG 9003): 1.2 Gy bid to 81.6 Gy (7 weeks)
  • 6 fractions per week, 2 Gy per fraction (DAHANCA)
Principles of RT technique/target delineation

• Simulation
  • Head extended
  • Supine
  • Arms down
  • IV contrast
  • 5-pt mask
  • Thin cut (2-3 mm)

• Technique: IMRT (except for early stage glottic cancer)

• Target delineation (elective nodes)
  • Primary echelon
    • Location/drainage of primary
    • Lateralized (ipsilateral) vs. midline (bilateral)
  • Secondary echelon
    • At risk if primary echelon contains bulky or high-volume disease
Doses/margins

• Gross disease (70 Gy)
  • GTV + CTV (0.5 – 1 cm) + PTV (3-5 mm)

• High-risk CTV elective regions (60 Gy)
  • Elective region around primary site (subclinical disease)
  • Primary echelon or involved nodal regions

• Low-risk CTV elective regions (50 Gy)
  • 2nd echelon regions

Daily IGRT, 3 mm PTV expansion
Clinical sections

• Nasopharynx

• Oral cavity

• Oropharynx

• Larynx/Hypopharynx
Clinical sections

- Nasopharynx
- Oral cavity
- Oropharynx
- Larynx/Hypopharynx
Nasopharynx: Anatomy
Treatment Approach

• Stage I
  • RT alone (10 yr LC and DSS > 90%)

• Stage II-IVb
  • Concurrent chemoradiation + adjuvant chemotherapy

• Stage IVc (M1 disease)
  • Chemotherapy
  • RT for symptom palliation
Concurrent Chemoradiation

PHASE III STUDY OF RADIOTHERAPY + CONCURRENT AND ADJUVANT CHEMOTHERAPY IN NASOPHARYNGEAL CANCER

STRATIFY

AJCC Stage III or IV M0

T & N Stage

Performance Status

Histology

RANDOMIZE

1. RT alone

2. RT + CT

CP 100 mg/m² D1, 22, 43 w. RT (63% completed)

CP 80 mg/m² & 5-FU 1000 mg/m² infusion for 96 h q. 4 weeks X 3 cycles (55% completed)

Al-Sarraf, J Clin Oncol 1998; 16: 1310
• LRF: 14 vs 41%
• DM: 13 vs 35%
• 3-y PFS: 69 vs 24%
• 3-y OS: 76 vs 46%

Toxicity: 63% completed CRT, 55% completed adjuvant chemo
Criticisms of the Intergroup Trial

• Non-endemic population
  • High proportion of WHO I (22%), for whom RT alone may not be acceptable
  • Applicable to endemic population?

• Design: did not address whether benefit from concurrent chemotherapy, adjuvant chemotherapy, or both.
<table>
<thead>
<tr>
<th>Study</th>
<th>AJCC 1988 Stage</th>
<th>N</th>
<th>Treatment</th>
<th>OS</th>
<th>LC</th>
<th>PFS/FFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin 2003</td>
<td>III/IV</td>
<td>284</td>
<td>70-74Gy, 2D CDDP, SFU (LD)</td>
<td>54%</td>
<td>73%</td>
<td>53%</td>
</tr>
<tr>
<td>Chan, 2005</td>
<td>II-IVB</td>
<td>350</td>
<td>66Gy, 2D CDDP weekly</td>
<td>59%</td>
<td>NS</td>
<td>52%</td>
</tr>
<tr>
<td>Kwong, 2004</td>
<td>II-IVB</td>
<td>219</td>
<td>62.5-68Gy, 2D Con: UFT; Adj CDDP, SFU/VBM</td>
<td>77%</td>
<td>72%</td>
<td>58%</td>
</tr>
<tr>
<td>Lee 2005</td>
<td>III/IVB, N2-3</td>
<td>348</td>
<td>&gt;66Gy, &gt;50% 3D Con: CDDP; Adj CDDP, 5FU</td>
<td>78%</td>
<td>82%</td>
<td>61%</td>
</tr>
<tr>
<td>Wee, 2004</td>
<td>III-IVB</td>
<td>221</td>
<td>70Gy, 2D Con: CDDP; Adj CDDP, 5FU</td>
<td>77%</td>
<td>NS</td>
<td>62%</td>
</tr>
<tr>
<td>Chen, 2011</td>
<td>Chinese Stage II (T2N0, T1-2N1)</td>
<td>230</td>
<td>70Gy, 2D Con: CDDP</td>
<td>86%</td>
<td>NS</td>
<td>78%</td>
</tr>
</tbody>
</table>
Meta-analysis

- 8 trials, 1753 pts
- CRT vs RT alone
- CRT: 6% OS benefit at 5y
- Survival benefit most pronounced for WHO Type I
- No impact on OS from induction or adjuvant chemotherapy

Baujat *IJROBP* 2006; 64: 47
Adjuvant chemo: RCT (Guangzhou)

• Stage III/IV
  • Excluded T3-T4N0

• CRT vs CRT + adjuvant
  • Concurrent: weekly cisplatin (40 mg/m2)
  • Adjuvant: Cisplatin + 5-FU x 3

Criticisms

• Design: not appropriately powered for non-inferiority

• Higher number of failures in the CRT arm (trend)

• >50% did not complete concurrent chemotherapy

• ~20% of pts randomized to receive adjuvant chemo did not receive it
EBV: Prognostic Marker


Pre-RT

1 wk post-RT
NRG HN001: Phase II/III Trial of Individualized Treatment for Nasopharynx CA, based on EBV DNA

**Basic Eligibility:** Stage II-IVB NPC; detectable EBV-DNA pre-treatment

- **Register and Stratify**
  - **N-stage**
    - N0-1 vs. N2-3
  - **T-stage**
    - T1-2 vs. T3-4
  - **PS**
    - 0 vs. 1

- **Assess EBV-DNA**
  - BIQSPF

- **All Pts**
  - Receive Standard RT/cisplatin

- **Re-Assess EBV-DNA**

- **“Detectable”**
  - R (Ph II)
  - Control: Consolidation 5-FU/cisplatin X 3

- **“Undetectable”**
  - R (Ph III)
  - Consolidation Gemcitabine/ Paclitaxel X4
  - Control: Consolidation 5-FU/cisplatin X 3
  - Observation

**Overall Sample Size:** 924 patients, 27pts/mo

**Basic Statistical Design:**
- Phase II sub-study (detectable EBV after chemo-RT): 1-year PFS 55% vs. 40% superiority design. 120 analyzable pts, 4.2 yr
- Phase III sub-study (undetectable EBV after chemo-RT): 2-year OS 91% both arms noninferiority. 600 analyzable pts, 7.7yr

**Quality of Life:** FACT-NP, HHIE-S (audiometry), FACT-Taxane, EQ-5D
Insert slides on induction trial
Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial

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RT Treatment planning

- IMRT
  - LC > 90%

- Gross disease (primary + nodes): ~70 Gy

- High-risk CTV (bilateral RP, II-V, subclinical nasopharynx): 59-63 Gy

- Low-risk CTV: 56-59 Gy
Elective nasopharynx CTV

• Entire nasopharynx
  • Ant: posterior 1/3 of nasal cavity/maxillary sinuses (or greater if anterior extension)
  • Post: anterior 1/2 of clivus (entire clivus if involved)
  • Sup: Inferior 1/2 of sphenoid (entire if T3/4, including cavernous sinus)
  • Inf: Palate (or greater to ensure adequate inferior margin below GTV)

- Skull base (rotundum, ovale, lacerum)
- Pterygoid
- Parapharyngeal space
Pterygopalatine fossa

Foramen ovale

Clivus
Foramen Lacerum
Foramen rotundum
Nasopharynx: Summary

• RT is the curative modality
  • RT alone: stage I
  • CRT: stage II-IVb
  • IMRT: standard of care
    • High rates of local control (> 90%)
    • Failures predominantly systemic

• Approaches to address to systemic relapse warranted
  • EBV(+): Induction TPF → RT alone
    • OS benefit, drive by ↓ DM
  • Role of adjuvant chemotherapy?
    • Risk stratification via EBV, clinical study
Clinical sections

• Nasopharynx

• Oral cavity

• Oropharynx

• Larynx/Hypopharynx
Oral cavity: Anatomy

- Lips
- Oral Tongue (ant 2/3)
- Floor of Mouth
- Retromolar Trigone
- Buccal Mucosa
- Hard Palate
- Gingiva/alveolar ridge
Treatment Approach

- Initial surgery whenever possible

- Definitive RT: surgically unresectable or medically inoperable

- Postop RT
  - Early stage (I/II)
    - Positive/close margins
    - LVI or PNI
  - Advanced stage
    - Concurrent chemotherapy if (+) margin or ECE
Role of therapeutic neck dissection

- RCT:
  - 596 pts, lateralized T1/2 oral cavity SCCA
  - Upfront (elective) vs salvage (therapeutic) neck dissection

D’Cruz et al. NEJM 2015
Indications for postoperative chemoradiation (EORTC 22931 and RTOG 9501)

Overall Survival
Patients with positive margin and/or ECE

EORTC 22931

RTOG 9501

P = 0.019

P = 0.069

# at Risk
Year 0 2 5 0 2 5

RCT - 122 62 31 130 60 16

RT - 111 59 16 116 55 11

Overall Survival
Patients without positive margin and/or ECE

EORTC 22931

RTOG 9501

P = 0.33

P = 0.78

# at Risk
Year 0 2 5 0 2 5

RCT - 45 36 16 76 52 11

RT - 56 34 15 94 55 14
• Retrospective NCDB analysis of ~11,000 pts, stage III-IVb SCCA of the HN, treated with surgery + adjuvant RT or CRT.

• Excluding pts with ECE or positive surgical margins.

• Patterns of care: 47% pts received adjuvant CRT.
Oral cavity: Summary

• Initial surgery, whenever possible
  • Upfront, elective neck dissection

• Postop RT
  • Early stage: intermediate risk factors (PNI/LVI)
  • Advanced stage: all patients
    • Postop CRT for (+) margins and ECE
    • Intermediate risk factors in absence of (+) margins or ECE: RT alone vs CRT
RTOG 0920 for intermediate (NOT HIGH RISK) cancers

OC, larynx, OPX p16+/-

Intermediate risk factors:
cT2-3, N0-2 (minimal T4a)
Stage III-IVA
PNI
LVSI
Close <5mm >5mm deep

RT: 60 Gy in 30 fractions

RT: 60 Gy in 30 fractions
Cetuximab 400 mg/m2 loading, 250 mg/m2 x 10 cycles

Open and accruing, goal is 700+ pts
Clinical sections

• Nasopharynx

• Oral cavity

• Oropharynx

• Larynx/Hypopharynx
Palatine tonsil (if present)

Palatoglossal arch

Tonsillar Fossa

Palatopharyngeal arch
Soft Palate

BOT Tonsil
Treatment approach

• Early stage: single modality
  • RT alone vs. surgery
    • RT
      • Unilateral neck: well-lateralized primary (tonsil)
      • Bilateral neck: central lesion (palate, BOT)
    • Surgery
      • New, less invasive approaches: Transoral Robotic/Laser
      • Best for well-lateralized lesion (Tonsil, well-lateralized BOT)

• Advanced stage: combined modality
  • Organ preservation (CRT)
  • Surgery + adjuvant RT (+/- chemo)
Oropharyngeal SCCA

- Traditionally associated with smoking/drinking
- Increasing incidence of tumors associated with HPV (~ 85%)
- Males account for at least 80% of cases, generally younger
- Patients present with prominent neck adenopathy and relatively small primary tumors

Chaturvedi, JCO 2011
266 Patients with oropharyngeal cancer, known tumor HPV status, and known number of pack-years of smoking

178 Had HPV-positive tumors
- 88 Had ≤10 pack-years
- 90 Had >10 pack-years

88 Had HPV-negative tumors
- 23 Had ≤10 pack-years
- 65 Had >10 pack-years

26 Had N0–N2a cancer
- 114 of 266 (42.9%) were at low risk

64 Had N2b–N3 cancer
- 79 of 266 (29.7%) were at intermediate risk

15 Had T2–T3 tumors
- 73 of 266 (27.4%) were at high risk

Kaplan-Meier Estimates of Overall Survival According to Those Categories

No. at Risk
- Low risk: 114, 111, 106, 102, 95, 46
- Intermediate risk: 79, 70, 64, 54, 44, 24
- High risk: 73, 52, 43, 33, 28, 8

O'Sullivan et al. JCO 2013;31:543-550

- OPC (N = 505)
  - HPV positive (n = 382)
    - 3-year DC: 90% (95% CI, 86 to 92)
      - N0-N2c (n = 349)
        - 3-year DC: 90% (95% CI, 86 to 93)
          - T1-T3 (n = 286)
            - 3-year DC: 93% (95% CI, 89 to 95)
              - HPV positive low risk (n = 286)
                - 3-year DC: 93% (95% CI, 89 to 95)
                - 3-year LRC: 95% (95% CI, 91 to 97)
          - HPV positive high risk (n = 96)
            - 3-year DC: 76% (95% CI, 65 to 84)
            - 3-year LRC: 82% (95% CI, 72 to 89)
  - HPV negative (n = 123)
    - 3-year DC: 86% (95% CI, 78 to 91)
      - N0-N2c (n = 115)
        - 3-year DC: 83% (95% CI, 72 to 89)
          - T1-T2 (n = 56)
            - 3-year DC: 93% (95% CI, 79 to 98)
              - HPV negative low risk (n = 56)
                - 3-year DC: 93% (95% CI, 79 to 98)
                - 3-year LRC: 76% (95% CI, 62 to 86)
          - HPV negative high risk (n = 67)
            - 3-year DC: 72% (95% CI, 56 to 82)
            - 3-year LRC: 62% (95% CI, 46 to 74)
      - N3 (n = 8)
        - 3-year DC: 73% (95% CI, 28 to 93)
Rationale for toxicity mitigation based on HPV status

- Disease outcomes excellent
- Treatment is morbid (acute and chronic)
- Approaches:
  - Chemotherapy: alternative agents (cetuximab) or omit
  - RT
    - Dose
    - Volume
  - Surgery: pathologic data to risk stratify
RTOG 1016: PHASE III TRIAL OF RADIOThERAPY PLUS CETUXIMAB VERSUS CHEMORADIOThERAPY IN HPV-ASSOCIATED OROPHARYNX CANCER

**Stratify**

**Tumor Stage**
1. T1-2
2. T3-4

**Nodal Stage**
1. N0-2a
2. N2b-3

**Zubrod Performance Status**
1. 0
2. 1

**Smoking history**
1. \( \leq 10 \text{ pack-years} \)
2. > 10 pack-years

**Randomize**

**Arm 1:**
Accelerated IMRT
70 Gy/6 weeks plus cisplatin 100 mg/m\(^2\) on days 1, 22

**Arm 2:**
Accelerated IMRT
70 Gy/6 weeks plus cetuximab 8 doses

CLOSED, 5 YEAR RESULTS NOT YET MATURE
(noninferiority design based on OS hazard)
Enlarged to 1000 patients, for analyzable 834 patients with 45 expected events
ECOG 3311

Schema

Step 1

Step 2

Register

Randomize

Low Risk

Arm A: (7 weeks)
Observation

Arm B: (5-7 weeks)
Radiotherapy
IMRT 50 Gy/25 Fx

Intermediate Risk

Stratify:
- 10 pk-yr vs.
- > 10 pk-yr

Arm C: (5-7 weeks)
Radiotherapy
IMRT 60 Gy/30 Fx

Unknown Risk

Arm D: (5-7 weeks)
Radiotherapy
IMRT 66 Gy/33 Fx + CDDP 40 mg/m² weekly

High Risk

LONG TERM FOLLOW-UP

Acclual: 377
NRG HN002: A Randomized Phase II Trial for Patients with P16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer

Eligibility

- OP SCCA
- ≤10 pack-year
- T1-T2 N1-N2b
- T3 N0-N2b

44% of RTOG 1016 population eligible

Stratify

Central review p16+ IHC

Declare

Intent

Unilat vs Bilat Neck XRT

Randomize

60 Gy XRT (2 Gy/fx) in 6 weeks + cisplatin 40 mg/m2 weekly x 6 cycles

60 Gy XRT (2 Gy/fx) at 6 fractions/week for 5 weeks
ECOG 1308: Phase II trial of IC followed by cetuximab with low or standard dose IMRT in pts with HPV-associated resectable oropharyngeal SCCA

Key Eligibility
1. OPSCC
2. HPV16 ISH + and / or p16+
3. Resectable stage III, IVA

Induction Chemotherapy

Cisplatin 75mg/m² D1
Paclitaxel 90mg/m² D1,8,15
Cetuximab 250mg/m² D1,8,15
Q 21 days for 3 cycles

R*

Concurrent Chemoradiation

CLINICAL CR
Low dose IMRT 54Gy/27fx** + Cetuximab weekly

CLINICAL PR / SD
Full dose IMRT 69.3Gy/33fx** + Cetuximab weekly

N=90 patients, 80 analyzable
<table>
<thead>
<tr>
<th>Patients registered (N = 90)</th>
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<tbody>
<tr>
<td>Patients found eligible (n = 80)</td>
</tr>
<tr>
<td>Patients started on IC per protocol (n = 80)</td>
</tr>
<tr>
<td>Patients who received all three cycles of IC (n = 77)</td>
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<tr>
<td>Infusion reaction to cetuximab (n = 1)</td>
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<tr>
<td>Parathyroidectomy (n = 1)</td>
</tr>
<tr>
<td>Received cycle 1, developed grade 4 infection, treated off protocol (n = 1)</td>
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</table>

### Clinical response at primary to IC:

- **cCR** (n = 56, including five patients with postbaseline biopsy and site-reported cCR) (n = 7)
- **PR** (n = 11)
- **SD** (n = 6)*

*Biopsy done after baseline measurements of primary, and site-reported non-cCR (n = 2)
Tonsillar primary had tonsillectomy after baseline measurement (n = 1)
Received D1 cycle 1 of IC, later off protocol received paclitaxel and carboplatin (n = 1)
No follow-up assessment (n = 1)
Postbaseline tonsillectomy (with positive deep margin) and no follow-up assessment (n = 1)

### Radiation dose by primary site IC response:

- **cCR (n = 56)**
  - 54 Gy (n = 49), 52 Gy (n = 1), 40 Gy (n = 1), 69.3 Gy (n = 5)
- **PR (n = 7)**
  - 54 Gy (n = 2), 69.3 Gy (n = 5)
- **SD (n = 11)**
  - 40 Gy (n = 1), 54 Gy (n = 5), 66.1 Gy (n = 1), 69.3 Gy (n = 4)
- **UE (n = 6)**
  - treated off protocol (n = 3), 54 Gy (n = 3)

---

Marur et al. JCO 2016
Progression-Free Survival (probability)

1-year PFS: 96% (95% CI, 76% to 99%)
2-year PFS: 96% (95% CI, 76% to 99%)

Overall Survival (probability)

1-year OS: 96% (95% CI, 76% to 99%)
2-year OS: 96% (95% CI, 76% to 99%)

No. at risk: 27 27 24 23 21 19 10
0 6 12 18 24 30 36 Time (months)

Marur et al. JCO 2016
• **Benefits:**
  - Pts receiving low dose RT had improved 12 mo dysphagia.
  - Excellent results (96% 2yr PFS and OS)

• **Concerns:**
  - Of 80 pts, only 46 eligible for dose reduction to both primary site and nodes (70% achieved primary site cCR, 58% nodal cCR)
  - Toxicity:
    - 3 pts could not finish induction
    - 3 pts could not complete RT
    - 21%: changed from cis-carboplatin during IC
    - 28%: dose modification of cetuximab during IC or RT
  - Pts who had T4 disease, N2c disease, and ≥ 10 p-y tobacco did worse (2 yr PFS of 71% vs 96%)
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  - Pts who had T4 disease, N2c disease, and $> 10$ p-y tobacco did worse (2 yr PFS of 71% vs 96%)

• If pts clinical characteristics are more or equally predictive of outcome as response to IC, question whether IC is needed to select pts for de-intensification
Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study

Prof Brian O'Sullivan, MD, Shao Hui Huang, MD, Jie Su, MSc, Prof Adam S Garden, MD, Prof Erich M Sturgis, MD, Kristina Dahlstrom, PhD, Prof Nancy Lee, MD, Nadeem Riaz, MD, Xin Pei, PhD, Shlomo A Koyfman, MD, Prof David Adelstein, MD, Prof Brian B Burkey, MD, Jeppe Friborg, MD, Claus A Kristensen, MD, Anita B Gothelf, MD, Frank Hoebers, MD, Bernd Kremer, MD, Prof Ernst-Jan Speel, PhD, Daniel W Bowles, MD, Prof David Raben, MD, Sana D Karam, MD, Eugene Yu, MD, Wei Xu, PhD

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DOI: 10.1016/S1470-2045(15)00560-4
<table>
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<th>ICON-S stage classification</th>
<th>T1</th>
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<th>T3</th>
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<td>N0</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
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<td>II</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>N3</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
</tbody>
</table>
Oropharynx: Summary

• Early stage disease: single modality (RT or surgery alone)

• Advanced stage: Combined modality approach

• Demographics changing (HPV)
  • Improved disease outcomes
  • Methods for toxicity mitigation are warranted for low-risk patients
    • Await results from clinical trials
Clinical sections

• Nasopharynx

• Oral cavity

• Oropharynx

• Larynx/Hypopharynx
Anatomy

- **Supraglottis**
  - Epiglottis
  - Arytenoids
  - AE folds
  - False cords
  - Ventricles

- **Glottis**
  - True vocal cords

- **Subglottis**
  - 5mm below glottis to bottom of cricoid
Base of Tongue (lingual tonsil)

Epiglottis

Vallecula

Hyoid

Vallecula

Epiglottis
Aryepiglottic fold
Epiglottis
Arytenoids
Pyriform sinuses
AE fold
Pyriform sinuses
Pyriform sinuses
AE fold
Post-cricoid area
Posterior Pharyngeal Wall
Pyriform sinuses
Treatment Approach

• Glottic, early stage: single modality
  • RT: limited field
  • Surgery: partial laryngectomy, cordectomy, laser

• Supraglottic, early stage: single modality
  • RT: include regional nodes (bilateral levels II-IV)
  • Surgery: partial laryngectomy + neck dissection

• Advanced stage: combined modality
  • Organ preservation (concurrent chemoradiation): VA larynx, RTOG 91-11
  • Surgery + adjuvant RT (+/- chemo)
    • Selection: need to consider disease and patient characteristics
RT technique: T1 glottis

• Superior: thyroid notch
• Inferior: bottom of cricoid
• Anterior: flash skin
• Posterior: anterior to vertebral body

• Field arrangements
  • Opposed laterals
    • Risk: shooting through shoulders, underdosing the target
    • Alternatives: obliques (superior or anterior)
Dose and fractionation: T1 glottis (Yamazaki et al. IJROBP 2006)

- Prospective, Randomized Trial, 1993-2001
- 180 pts with T1N0 Glottic Cancers
- Randomized to
  A) 2.00 Gy/fraction
     1) 60 Gy in 30 fractions (<2/3 VC)
     2) 66 Gy in 33 fractions (>2/3 VC)
  B) 2.25 Gy/fraction
     1) 56.25 Gy in 25 fractions (<2/3 VC)
     2) 63 Gy in 28 fractions (>2/3 VC)

- No significant increase in acute or chronic toxicity

Conclusion: Use 225 cGy per fraction to 63 Gy for T1 Glottic Ca
VA Larynx Study (NEJM 1991)

• Randomized, Prospective Phase 3, 1985-1989.
  • 332 patients, Stage III or IV (excluding T1N1) laryngeal cancer

• Arm 1) **Total laryngectomy + Postop RT**

• Arm 2) **Induction Chemo + Definitive RT**
  • Induction Chemo: Cisplatin 100mg/m2 + 5FU 1000mg/m2 Q3W x 3c
    • Clinical Evaluation after cycle 2
      • If PR (54%) or CR (31%) → proceed with cycle 3 → RT
      • If < PR (15%) → TL + PORT
• Larynx Preservation Rate: 64%

• No difference in 2-yr OS

• Patterns of Failure:
  • Higher LF with Chemo→RT
  • Higher DM with TL+PORT

<table>
<thead>
<tr>
<th>2-yr</th>
<th>LF</th>
<th>DM</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td>TL+PORT</td>
<td>2%</td>
<td>17%</td>
<td>68%</td>
</tr>
<tr>
<td>Chemo→RT</td>
<td>12%</td>
<td>11%</td>
<td>68%</td>
</tr>
</tbody>
</table>

Established larynx preservation as a viable option

T4: 56% required salvage laryngectomy (excluded from RTOG 91-11)
RTOG 91-11 (Forastiere et al. NEJM 2003)

• Rationale: What about concurrent chemoRT instead of induction chemo?

• RTOG 91-11: Randomized, Prospective Phase 3, 1992-2000
  • 547 patients, Stage III/IV Laryngeal Cancer requiring TL
    • Excluded large volume T4 (>1cm into BOT or penetration through thyroid cartilage)
    • only 10% of pts ended up being T4

• Arm 1) Induction Chemo → RT (same as VA Larynx study)
• Arm 2) Concurrent ChemoRT (cisplatin 100mg/m2 Q3wk)
• Arm 3) RT alone

• Primary endpoint: larynx preservation
Long-term results (Forastiere et al. JCO 2012)

• Median f/u 10.8 yrs:
  • Concurrent ChemoRT improved larynx preservation rate and LRC compared to induction chemo + RT and RT alone
  • No difference in laryngectomy-free survival or overall survival

Conclusions:
- Concurrent CRT standard of care for larynx preservation
- Long-term disease outcomes poor
- Novel approaches are needed
Larynx: Summary

• Early stage disease
  • Unimodality therapy: RT or surgery
  • Disease limited to glottis: use > 2 Gy daily (2.25 Gy)

• Advanced-stage disease
  • Organ preservation vs surgery + PORT
  • Patient selection: consider disease extent and function
Learning objectives

• HNC is a complex disease site where trt decisions/modalities often depend on multiple factors (site, stage, epidemiology).
• RT is a well-established modality of tx (definitive/postop)
• Knowledge of anatomy (visual inspection, CT) and patterns of spread are critical to proper trt/target delineation.
• Nasopharynx: CRT is standard (except for stage I)
  • IMRT: very high LC
  • EBV(+)
    • Consider IC (TPF) → RT
      • OS benefit via ↓DM vs. upfront CRT
Learning Objectives

• Oral cavity: surgery is initial trt of choice
  • RT used in adjuvant setting

• Oropharynx:
  • HPV has changed disease outcomes (disparate outcomes HPV (+) vs (-) despite similar staging)
  • Future directions: improving therapeutic ratio via toxicity mitigation (clinical trials)

• Larynx: need to improve outcomes
  • Organ preservation for advanced stage is a valid, standard option
    • Consider patient, organ, and disease factors
Questions