Head and Neck Cancer

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Disclosure

• Employer: University of Pennsylvania
• Grant support: National Institutes of Health
• Speaker: Ion Beam Applications
• Consultant: Elekta
Learning Objectives

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

• Determine the best clinical and technical approaches for definitive and postoperative head and neck cancer radiotherapy treatment
Basic Anatomy: Neck levels
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
- Anterior to the posterior border of the sternocleidomastoid muscle
- Posterior to submandibular gland
- 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
- Anterior to the posterior border of the sternocleidomastoid muscle
- Posterior to submandibular gland
- 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
- Anterior to the posterior border of the sternocleidomastoid muscle
- Lateral to the medial margin of the common carotid/internal carotid
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
- Anterior to the posterior border of the sternocleidomastoid muscle
- Lateral to the medial margin of the common carotid/internal carotid
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.
- Anterior to the posterior border of the sternocleidomastoid muscle.
- Anterior and medial to an oblique line drawn through the posterior edge of the SCM and the posterolateral edge of the anterior scalene muscle.
- Lateral to the medial margin of the common carotid.
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
• Anterior to the posterior border of the sternocleidomastoid muscle
• Anterior and medial to an oblique line drawn through the posterior edge of the SCM and the posterolateral edge of the anterior scalene muscle
• Lateral to the medial margin of the common carotid
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: superior half, posterior to levels II and III
- Level Vb: inferior half, posterior to level IV
Basic Anatomy: Level V, Posterior triangle

- Posterior to the posterior edge of the SCM
- Anterior to the trapezius
- Level Va: superior half, posterior to levels II and III
- Level Vb: inferior half, 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
- Sits in between the anterior edges of the SCM
- 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
- Sits in between the anterior edges of the SCM
- 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
    - 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 / 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: $\chi^2_{197} = 179.8 \quad p < 0.0001$

$\chi^2_{2} = 26.60 \quad p < 0.0001$

LRT+CT better $\quad$ 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>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></td>
<td>LRT+CT</td>
<td>LRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Poly chemotherapy</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 [0.67;0.84]</td>
<td>p = 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 [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 [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 [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>
</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 [0.67;0.82]</td>
<td>p = 0.006</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 [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 [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 [0.78;0.86]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 1.69$ 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%

PFS

Log-rank $P=0.004$
HR=0.701
TPF 53%
PF 42%

- 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**

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

- **CRT**
  - Carboplatin (every week)
    - Daily RT (days 1-5) 7 weeks
  - 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
  • 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 during weekday, at least 6h after previous fraction
    • 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
Figure 5: Effect of overall treatment time on disease-specific survival and overall survival.

Figure 6: Early and late radiation-related morbidity. Acute and chronic morbidities in 1429 patients and actuarial probability of developing severe late reactions in 1149 patients.

Overgaard Lancet 2003; 362: 933
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)
    • Consider logistical obstacles
  • 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
    - Depends on disease status of primary echelon levels
    - 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 > 95%)

• Stage II-IVb
  • Concurrent chemoradiation + adjuvant chemotherapy

• Stage IVc (M1 disease)
  • Chemotherapy (palliative)
  • Reserve RT for focal therapy as clinically indicated
Concurrent Chemoradiation

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

AJCC Stage III or IV M0

T & N Stage
Performance Status
Histology

STRATIFY

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>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 JCO 21:631</td>
<td>III/IV</td>
<td>284</td>
<td>70-74Gy, 2D <strong>CDDP, 5FU (LD)</strong></td>
<td>54%</td>
<td>73%</td>
<td>53%</td>
</tr>
<tr>
<td>Chan, 2005 JNCI 97:536</td>
<td>II-IVB</td>
<td>350</td>
<td>66Gy, 2D <strong>CDDP weekly</strong></td>
<td>59%</td>
<td>NS</td>
<td>52%</td>
</tr>
<tr>
<td>Kwong, 2004 JCO 22:2643</td>
<td>II-IVB</td>
<td>219</td>
<td>62.5-68Gy, 2D <strong>Con: UFT; Adj CDDP, 5FU/VBM</strong></td>
<td>77%</td>
<td>72%</td>
<td>58%</td>
</tr>
<tr>
<td>Lee 2005 JCO 23:6966</td>
<td>III/IVB</td>
<td>348</td>
<td>&gt;66Gy, &gt;50% 3D <strong>Con: CDDP; Adj CDDP, 5FU</strong></td>
<td>78%</td>
<td>82%</td>
<td>61%</td>
</tr>
<tr>
<td>Wee, 2004 JCO 23:487</td>
<td>III-IVB</td>
<td>221</td>
<td>70Gy, 2D <strong>Con: CDDP; Adj CDDP, 5FU</strong></td>
<td>77%</td>
<td>NS</td>
<td>62%</td>
</tr>
<tr>
<td>Chen, 2011 JNCI 103:1761</td>
<td>Chinese Stage II (T2N0, T1-2N1)</td>
<td>230</td>
<td>70Gy, 2D <strong>Con: CDDP</strong></td>
<td>86%</td>
<td>NS</td>
<td>78%</td>
</tr>
</tbody>
</table>

**Notes:**
- **OS:** Overall Survival
- **LC:** Local Control
- **PFS/FFS:** Progression-Free Survival/Freedom from Second Primary
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

Chen Lancet Oncol 2012; 13: 163
Criticisms

• Statistical design: not appropriately powered for non-inferiority

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

• Over half of pts did not complete concurrent chemotherapy

• Close to 20% of pts randomized to adjuvant did not receive
EBV: Prognostic Marker

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
BiQSFp

All Pts
Receive Standard RT/cisplatin

Re-Assess EBV-DNA

"Detectable"

R
(Ph II)

Control:
Consolidation 5-FU/cisplatin X 3

Consolidation
Gemcitabine/
Paclitaxel X4

"Undetectable"

R
(Ph III)

Control:
Consolidation 5-FU/cisplatin X 3

Observation

Overall Sample Size: 924 patients, 27 pts/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, 7.7 yr

Quality of Life: FACT-NP, HHIE-S (audiometry), FACT-Taxane, EQ-5D
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 (Ib, if cervical nodes present): 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
Jugular Foramen
Clivus
Foramen ovale
Foramen spinosum
Carotid Canal
Foramen Lacerum
Foramen rotundum
Nasopharynx: Summary

• RT is only upfront definitive treatment
  • RT alone: stage I
  • CRT: stage II-IVb

• IMRT
  • High LC
  • Patterns of failure: largely systemic

• Methods to decrease systemic failure warranted
  • Adjuvant chemo?
    • Risk stratification via EBV
Clinical sections

• Nasopharynx

• Oral cavity

• Oropharynx

• Larynx/Hypopharynx
Oral cavity: Anatomy

- Lips
- Oral Tongue
- Floor of Mouth
- Retromolar Trigone
- Buccal Mucosa
- Hard Palate
- Gingiva/alveolar ridge
Treatment Approach

• Surgery as initial therapy whenever possible

• Reserve definitive RT for surgically unresectable or medically inoperable

• Indications for postop RT
  • Early stage (I/II)
    • Positive or close margins
    • LVI or PNI
  • Advanced stage
    • Concurrent chemotherapy if (+) margin or ECE
Role of therapeutic neck dissection (D’Cruz et al. NEJM 2015)

- RCT:
  - 596 pts, lateraled T1/2 oral cavity SCCA
  - Upfront (elective) vs salvage (therapeutic) neck dissection
Indications for postoperative chemoradiation (EORTC 22931 and RTOG 9501)
Oral cavity: Summary

- Initial surgery, whenever possible
  - Neck dissection at time of surgery

- Postop RT
  - Early stage: intermediate risk factors
  - Advanced stage: all patients
    - Postop CRT for (+) margins and ECE
    - Intermediate risk factors (multiple nodes, neg margins, no ECE): RT alone or consider clinical trial
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)
Epiglottis

Palatopharyngeal arch

Base of Tongue

Pharyngoepiglottic fold

Glossoepiglottic fold

Vallecula

Base of Tongue (lingual tonsil)
Vallecula
Treatment approach

• Early stage: single modality
  • RT alone vs. surgery
    • RT
      • Unilateral neck: well-lateralized primary (tonsil)
      • Bilateral neck: central lesion (palate, BOT)
    • Surgery
      • Emergence of new, less invasive approaches: Transoral Robotic or 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
Age-adjusted incidence of head and neck squamous cell cancers between 1973 and 2006, stratified by age at diagnosis.
Classification of the Study Patients into Risk-of-Death Categories and Kaplan-Meier Estimates of Overall Survival According to Those Categories

A.

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

- 178 Had HPV-positive tumors
- 88 Had HPV-negative tumors

88 Had ≤10 pack-years
90 Had >10 pack-years
23 Had ≤10 pack-years
65 Had >10 pack-years

- 26 Had N0–N1a cancer
- 64 Had N2b–N3 tumors
- 15 Had T2–T3 tumors
- 8 Had T4 tumors

114 of 266 (42.9%) were at low risk
79 of 266 (29.7%) were at intermediate risk
73 of 266 (27.4%) were at high risk

B.

Overall Survival [%]

Years since Randomization

No. at Risk

Low risk
Intermediate risk
High risk

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O'Sullivan et al. JCO 2013;31:543-550
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 assist in patient selection
RTOG 1016: Phase III Trial of Radiotherapy Plus Cetuximab Versus Chemoradiotherapy in HPV-Associated Oropharynx Cancer

**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. ≤ 10 pack-years
2. > 10 pack-years

**Arm 1:**
Accelerated IMRT
70 Gy/6 weeks
plus cisplatin 100 mg/m² 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
REGISTER

Arm S
Transoral Resection with neck dissections

Step 2
REGISTER

Randomize

Low Risk
Arm A: (7 weeks) Observation

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

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

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

Long-term follow-up

Accrual: 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

REGISTER
- Central review
- p16+ IHC

STRATIFY
- 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

**Induction Chemotherapy**

N=90 patients, 80 analyzable

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

**Concurrent Chemoradiation**

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

**Response**

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

- **CLINICAL PR/SD**
  - Full dose IMRT 69.3Gy/33fx** +
  - Cetuximab weekly
Preliminary results (ASCO 2012)

- 90 pts enrolled, median f/u 23 mos
- 71% with clinical CR, 78% received reduced-dose RT
  - OS 95%
  - PFS 84%
  - LC 94%
  - NC 95%
  - DC 92%

- T4a, N2c, or > 10 p-y hx fared worse
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
    • 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
Arytenoids

Posterior commissure

Cricoid

First tracheal ring

Subglottis

Anterior commissure

TVOCs

Ventricle

False cord
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: should positioning
  - 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

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<td>2%</td>
<td>17%</td>
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<tr>
<td>Chemo→RT</td>
<td>12%</td>
<td>11%</td>
<td>68%</td>
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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
Patient selection/Patterns of care (Grover et al. IJROBP 2015)

• T4a disease
  • Poor outcomes in VA larynx
  • Largely excluded from RTOG 91-11
  • Concerns about organ preservation
    • Efficacy
    • Function

• NCDB
  • 969 pts trt for T4a larynx cancer from 2003-2006
  • Patterns of care/survival

• Results
  • 2/3 treated with OP, 1/3 with initial TL
Total laryngectomy MS: 60 months

Larynx Preservation: MS: 30 months

Chemoradiation

Surgical treatment

P < 0.001
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: prognostic, selection for omission of adjuvant chemo?
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