Simultaneous Integrated Boost or Sequential Boost in the Setting of Standard Dose or Dose De-escalation for HPV-Associated Oropharyngeal Cancer

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Head and Neck/Cutaneous Service, Radiation Oncology
Overview

• Dose intensification
  – dose / fractionation / chemo

• HPV

• Dose de-intensification
  – Decreasing dose, decreasing chemo or no chemo
  – Early results
  – Recently closed trials
  – Currently accruing trials
  – What will we learn and when?

• Moffitt experience with de-intensification
  – 2 retrospective analyses
    • Sequential Boost Plans
    • Decreasing dose

• Where are we going?
Oral and Pharynx Cancer

• United States:
  – 49,670 estimated new cases in 2017
  – 2.9% of all new cases
  – 9,700 estimated deaths in 2017
  – 1.6% of all cancer deaths

• Twice as common in men as in women
• Equally common in blacks and whites
• New cases are declining slightly with women but have remained stable in men
• Average age of most people diagnosed is 62 with just over one-quarter being younger than 55
Oropharynx Anatomy

- Soft palate
- Base of Tongue
- Tonsils
- Pharyngeal Wall
Oropharynx Cancer / Etiology

- Tobacco
  - Cigarettes
  - Cigars
  - Pipes
- Human papillomavirus (HPV)
- Radiation
Oropharynx Cancer / Signs and Symptoms

- Persistent sore throat
- Earaches
- Hoarseness/Voice changes
- Enlarged lymph nodes
- Pain when swallowing
- Unexplained weight loss
Treatment Options for Oropharynx Cancer

- Radiation Therapy
- Surgery
- Chemotherapy
Must do more...
(tx intensification / rtog 9003)

• Fractionation Trial – Compared conventional fractionation to 3 different altered fractionation schemas
• Accrued 1113 patients between 1991 and 1997
• No chemotherapy
• Expected higher acute toxicities but lower late complications with accelerated fractionations
Tx Intensification / RTOG 9003

- **LRC** - significant improvement in LRC at 2 years with hyperfractionation (HFX) (54.4%) and accelerated fractionation with concomitant boost (AFX-C) (54.5%) compared to standard fractionation (SFX) (46.0%)
- **DFS** – trend toward improved DFS at 2 years with HFX (37.6%) and AFX-C (39.3%) compared to SFX (31.7%)
- **OS** – similar results
- **Acute toxicities** – higher for the altered fractionation arms
Tx Intensification / DAHANCA

- Compared 6 fx a week RT to 5 fx a week RT
  - No chemo
  - Did use Nimorazole
- 1992 to 1999
- 1485 patients
- 66 to 68 Gy (62 Gy T1 N0 Larynx)
- Primary endpoint LRC at 5 years

**Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial.**


1485 patients included

- accelerated radiotherapy 6 fractions per week
- conventional radiotherapy 5 fractions per week
Tx Intensification / DAHANCA

- 5 year LRC - significant for 6 fx 70% compared to 5 fx 60% (p=0.0005)
- 5 year DSS - significant for 6 fx 73% compared to 5 fx 66% (p=0.01)
- 5 year OS – similar
- Acute morbidity significantly higher in the accelerated fraction group
- Late morbidity similar
Tx Intensification / Head and Neck Intergroup

Tested the benefit of adding chemotherapy to radiation

Compared
- Standard fractionation
- Standard fractionation plus Cisplatin
- RT split course plus Cisplatin/5FU with surgery encouraged after the first course

Between 1992 and 1999 the study accrued 295 patients
- Closed early

An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer.

Adelstein DJ¹, L Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, Schuller DE, Forastiere AA.
Overall survival at 3 years:
- RT alone 23%
- RT w/ Cis 37% (p=0.014)
- RT split with Cis/5FU 27%

Disease free survival at 3 years:
- RT alone 33%
- RT w/ Cis 51% (p=0.01)
- RT split with Cis/5FU 41%

Greater toxicity but chemotherapy with radiation is better than radiation alone
Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients.


- Meta-analysis of studies conducted between 1965 and 2000 to evaluate the benefit of chemotherapy
- Compared induction, concomitant, and adjuvant chemotherapy with loco-regional treatment alone
- Endpoint was overall survival
Chemotherapy adds a survival benefit of 4.5% at 5 years ($p<0.0001$).

Concomitant chemotherapy adds a survival benefit at 5 years of 6.5% — Greater than induction.

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The graphs illustrate the survival rates over time for different chemotherapy regimens: concomitant, induction, and adjuvant chemotherapy. Each graph compares survival rates between chemotherapy and control groups, showing the added benefit of chemotherapy over time. The survival rates are expressed as percentages and are compared at various time points, emphasizing the incremental survival benefit with chemotherapy.
Tx Intensification / RTOG 0129

Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity.


- Compared once a day RT with accelerated RT plus chemotherapy in locally advanced head and neck carcinoma
- Accrued 743 patients between 2002 and 2005
Tx Intensification / RTOG 0129

- No difference in tumor control or survival outcomes
- No increase in late toxicities
### Dose Intensification

<table>
<thead>
<tr>
<th>Study</th>
<th>Range</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 9003</td>
<td>1991 - 1997</td>
<td>Altered Fx better than SFx</td>
</tr>
<tr>
<td>DAHANCA</td>
<td>1992 – 1999</td>
<td>6 Fx better than 5 Fx</td>
</tr>
<tr>
<td>Head and Neck Intergroup</td>
<td>1992 – 1999</td>
<td>CRT is better than RT alone</td>
</tr>
<tr>
<td>MACH-NC</td>
<td>1965 – 2000</td>
<td>CRT is better than RT alone</td>
</tr>
<tr>
<td>RTOG 0129</td>
<td>2002 – 2005</td>
<td>Altered Fx + Chemo is the same as SFx + Chemo</td>
</tr>
</tbody>
</table>
OPx SCC caused by HPV
- Associated with favorable survival
- Independent prognostic significance of tumor HPV status remains unknown

Retrospective analysis of patients on the RTOG 0129 study

OPx = 323 patients
- 63.8% were HPV+ (206)

3 year OS
- 82.4% for HPV+ compared to 57.1% for HPV- (p=0.001)

HPV+ patients had a 58% reduction in risk of death after adjusting for age, race, tumor, nodal stage, tobacco exposure and treatment assignment.
• Retrospective analysis to determine influence of tumor HPV-status
• Larynx, pharynx, and oral cavity cancers treated with either 5 fx or 6 fx a week
• 66 – 68 Gy (2 Gy / fx)
  – T1 N0 Larynx – 62 Gy
• 794 patients with tissue for testing
  – 409 received 6 fx / wk
  – 385 received 5 fx / wk
DAHANCA 6&7 / 2011 cont.

LRC
Number of fx per week (794 patients)

LRC
p16-positive & p16-negative

LRC
Number of fx per week
p16-positive and p16-negative
p16

p16 is a cell cycle protein that is dysregulated by HPV

– Does not test for HPV directly
– Surrogate marker
– Advantage: agnostic to the HPV type
RTOG 9003

“It is also interesting that in successive RTOG randomized trials in head and neck cancer, the 2-year local-regional control rate has improved over time from 29% in the late 1970s to 40% in the late 1980s to 46% in the current trial.”

In contrast to historical comparisons 18; 19; 20; 21; 22, accelerated fractionation with split was not shown to improve local-regional control in this randomized trial. Any potential gain with accelerated fractionation may have been negated by the interruption of treatment during the split and a slightly lower total dose than standard fractionation. It is also interesting that in successive RTOG randomized trials in head and neck cancer, the 2-year local-regional control rate has improved over time from 29% in the late 1970s (4) to 40% in the late 1980s (13) to 46% in the current trial.
HPV Related Oropharynx

• How common is Oral HPV?
  – About 7% of people in the U.S. have oral HPV
  – About 1% have the type of oral HPV found in OPx cancers
  – 3 times more common in men than women

• Oropharynx cancers:
  – About 70% of OPx cancers are HPV related
  – About 90% of HPV related OPx cancers are HPV16
  – 4 times more common in men than women
Oropharynx Cancers on the Rise

*Human papillomavirus and rising oropharyngeal cancer incidence in the United States.*

HPV+ Cancer

AJCC 8th Edition Cancer Staging System
• Starting January 2018
• International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S)
  – 7 centers, 1907 patients
  – Patients with HPV+ OPx cancer have remarkably higher overall survival than do those with HPV- disease
  – Many prognostic algorithms for OPx cancer incorporate HPV status as a stratification factor, rather than recognizing the uniqueness of HPV+ disease

Having a HPV-related OPx Cancer is prognostic not predictive:
• It doesn’t help us choose treatments
• It helps us tell patients that they will probably do well with treatments

ASTRO Guidelines / OPSCC
• February 2017
• Intended focus of the guidelines is the curative management of OPSCC
• Treatment recommendations are independent of HPV and smoking status
HPV+ Oropharynx Cancers

- Younger & healthier
- Present with larger nodes and smaller primaries
- Higher overall survival
- Radiotherapy can result in significant side effects
  - Mucositis
  - Dysguesia
  - Xerostomia
  - Skin Erythema
  - Dysphagia/Odynophagia
  - Hypothyroidism
  - Osteoradionecrosis
  - Aspiration Pneumonia
  - Soft Tissue Necrosis/Ulceration
  - Soft Tissue Fibrosis
- How do we reduce side effects of treatment without reducing the high likelihood of cure?
Back it down a notch…
De-Intensification / NC & UF

Radiation with weekly cisplatin followed by supra-selective neck dissection

Primary study endpoint: pathologic complete response (pCR)
- Bx / neck dissection after CRT
- Expected 87% pCR

43 patients

60 Gy / 6 weeks Weekly low-dose Cisplatin

Surgery – Bx primary site and dissection of the pretreatment positive lymph node regions
De-Intensification / NC & UF

- pCR 86%
  - 37 of 43 pts
- Early Sx?

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stage/site</th>
<th>HPV/p16 status</th>
<th>Smoking status</th>
<th>Treatment</th>
<th>Clinical response</th>
<th>Timing of surgery after CRT (wk)</th>
<th>Pathologic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>63 yoa WM</td>
<td>T2 N2c right base of tongue</td>
<td>HPV+/p16+</td>
<td>Never</td>
<td>60 Gy and 180 mg/m² cisplatinum</td>
<td>CR at primary and neck</td>
<td>7.7</td>
<td>&lt;1-mm focus in BOT and 1 lymph node. Subsequent TORS was negative</td>
</tr>
<tr>
<td>52 yoa WF</td>
<td>T2 N2b left tonsil</td>
<td>HPV-/p16+</td>
<td>Never</td>
<td>60 Gy and 180 mg/m² cisplatinum</td>
<td>CR in primary, PR in neck</td>
<td>8</td>
<td>&lt;1-mm focus in 1 lymph node</td>
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<tr>
<td>73 yoa WM</td>
<td>T1 N2b left base of tongue</td>
<td>HPV-/p16+</td>
<td>Never</td>
<td>60 Gy and 180 mg/m² cisplatinum</td>
<td>CR in primary, PR in neck</td>
<td>8.6</td>
<td>1-mm focus in 1 lymph node</td>
</tr>
<tr>
<td>54 yoa AAM</td>
<td>T3 N2b left tonsil</td>
<td>HPV-/p16+</td>
<td>1 pack-year</td>
<td>60 Gy and 60 mg/m² cisplatinum switched to carboplatin AUC 2</td>
<td>CR in primary, PR in neck</td>
<td>8.1</td>
<td>1-mm focus in 1 lymph node</td>
</tr>
<tr>
<td>56 yoa WM</td>
<td>T1 N2b left tonsil</td>
<td>HPV-/p16+</td>
<td>Never</td>
<td>60 Gy and 180 mg/m² cisplatinum</td>
<td>CR in primary, PR in neck</td>
<td>8.7</td>
<td>5 positive lymph nodes, largest focus 5 mm</td>
</tr>
<tr>
<td>69 yoa WF</td>
<td>T2 N2b left tonsil</td>
<td>HPV-/p16+</td>
<td>Never</td>
<td>60 Gy and 110 mg/m² cisplatinum</td>
<td>CR in primary, PR in neck</td>
<td>11</td>
<td>3-cm necrotic lymph node with 5% viable tumor</td>
</tr>
</tbody>
</table>
De-Intensification / UCLA & UCDavis

- Single arm phase II study
- Induction chemo followed by response adapted radiotherapy plus chemo
- 44 patients enrolled between 2012 and 2015
- Primary endpoint was progression free survival at 2 years


44 patients received induction chemotherapy

- 24 patients achieved complete or partial response assigned 54 Gy + chemo
- 20 patients achieved minor response or stable disease and were assigned 60 Gy + chemo

44 patients included in analysis
55% patients with complete (11%) or partial (43%) responses to induction chemotherapy received 54 Gy radiation.

45% with less than partial responses received 60 Gy.

2-year progression-free survival was 92%.

2-year locoregional control was 95%.

2-year overall survival was 98%.
De-Intensification / RTOG 1016

PHASE III TRIAL OF RADIOTHERAPY PLUS CETUXIMAB VERSUS CHEMORADIOTHERAPY IN HPV-ASSOCIATED OROPHARYNX CANCER

- Accelerated RT with either cisplatin or cetuximab
- Study endpoint 5 year overall survival
- Accrued 987 patients
- Closed in 2014
- Have results in 2019?
• Reduced RT and reduced chemo vs. accelerated reduced RT and no chemo
• Primary objective is to select the arm(s) achieving a 2-year progression-free survival rate of ≥ 85% without unacceptable swallowing toxicity at 1 year
• Opened 2014
• Closed 2017
• Accrued 296 patients
• Results: 2019??
De-Intensification / ECOG 3311

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

- Transoral resection - risk adapted postop RT for intermediate risk
- Phase II
- Primary Objective: Assess 2-year progression-free survival (PFS) of intermediate-risk patients
- Target accrual 515
- Current accrual at 465
- Estimated closure: this year? the next?
- Estimated results: ~2 years after closure
## Dose De-Intensification

<table>
<thead>
<tr>
<th></th>
<th>Phase II / III</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC / UF</td>
<td>II</td>
<td>Reduced RT &amp; chemo With neck dissection surgery</td>
</tr>
<tr>
<td>UCLA &amp; UCDavis</td>
<td>II</td>
<td>Induction chemo followed by less RT &amp; chemo</td>
</tr>
<tr>
<td>RTOG 1016</td>
<td>III</td>
<td>Replacing cisplatin with cetuximab</td>
</tr>
<tr>
<td>NRG HN002</td>
<td>II</td>
<td>Reduced RT Reduced or eliminated chemo</td>
</tr>
<tr>
<td>E3311</td>
<td>II</td>
<td>Surgery with reduced RT for intermediate risk patients</td>
</tr>
</tbody>
</table>
While We Wait...

- Small reductions in dose
- Planning with sequential boost when possible
What’s the difference between Sequential Boost Plans and Simultaneous Integrated Boost?
Seq Compared to a SIB

Sequential Boost

• Base Plan
  – SIB
  – Single dose

• Boost Plan
  – SIB
  – Single dose

• Composite Plan

Simultaneous Integrated Boost

• One plan / Dose painting
Sequential

**Base Plan**
- 4600 cGy Gross Disease
- 200 cGy / fx
- 4140 cGy Elective Neck
- 180 cGy / fx

**Boost Plan**
- 2400 cGy Gross Disease
- 200 cGy / fx
(Elective Neck not treated)

**Composite Plan:**
- All in one -
  - 7000 cGy Gross Disease
  - 200 cGy / fx
  - 5600 cGy Elective Neck
  - 160 cGy / fx

SIB
Sequential Boost Planning
European Experience


**Sequentially delivered boost plans are superior to simultaneously delivered plans in head and neck cancer when the boost volume is located further away from the parotid glands.**

Lamers-Kuiper E¹, Heemsbergen W, van Mourik A, Rasch C.

Is it possible to predict which head and neck patients would benefit from sequential boost planning (Seq) compared to simultaneous integrated boost planning (SIB)?
Sequential Boost European Experience

- 50 patients
- Goal was to spare the parotid glands
- Seq –
  - 50 Gy followed by 20 Gy to the primary
    - 46 Gy to the elective neck
- SIB –
  - 70 Gy to the primary
    - 57.75 to the elective neck
Sequential Boost - European Experience

Conclusion:

Less dose to the parotid glands for most patients when using a sequential plan compared to SIB if the high dose region is more than 1 cm away.
SEQ Elective Neck Dose

Perspective:
- 4140 cGy
- 180 / fx
- 5600 cGy
- 160 / fx
Sequential Boost Planning
Sequential Boost Compared with Simultaneous Integrated Boost for Early Stage HPV Positive Oropharyngeal Cancer Patients
Sequential Boost Compared with Simultaneous Integrated Boost

• Why early stage?

• ICON Stage I
  – Primary site: $\leq 4$ cm / none
  – Unilateral lymphadenopathy: $\leq 6$ cm
Sequential Boost Compared with Simultaneous Integrated Boost

- Elective neck:
  - SEQ
    - 4140 – 5000 cGy
  - SIB
    - 5412 – 5600 cGy
Sequential Boost Compared with Simultaneous Integrated Boost

184 patients

- 32 patients
  sequential planning group (SEQ)

- 152 patients
  simultaneous integrated boost group (SIB)
Base Plan – 23 fx

- R BoT / R Neck 46 Gy
- Bilat elect neck 41.40 Gy
Boost Plan – 10 fx

- R BoT / R Neck 20 Gy
- Composite Plan – 33 fx
- R BoT / R Neck 66 Gy
- Bilat elect neck 41.40 Gy
Sequential Plan

- Normal tissue dose constraints met in all except right submandibular gland
- Global max hotspot 103%
  - (point dose)
Patients were reasonably similar

<table>
<thead>
<tr>
<th></th>
<th>SIB</th>
<th>SEQ</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>131</td>
<td>30</td>
<td>0.378</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>2</td>
<td></td>
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<tr>
<td><strong>Subsite</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BoT</td>
<td>72</td>
<td>13</td>
<td>0.4</td>
</tr>
<tr>
<td>Tonsil</td>
<td>79</td>
<td>13</td>
<td></td>
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<tr>
<td>Phx Wall</td>
<td>1</td>
<td>18</td>
<td></td>
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<tr>
<td><strong>T Stage (ICON)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>71</td>
<td>14</td>
<td>0.846</td>
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<tr>
<td>2</td>
<td>81</td>
<td>18</td>
<td></td>
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<tr>
<td><strong>N Stage (ICON)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13</td>
<td>5</td>
<td>0.321</td>
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<td>1</td>
<td>139</td>
<td>27</td>
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<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;70 Gy</td>
<td>7</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>≥70 Gy</td>
<td>145</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Concurrent Chemo</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>127</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

Exceptions - the SIB group was

- more likely to receive a higher total dose
- more likely to receive chemotherapy
Sequential Boost Compared with Simultaneous Integrated Boost

Total Dose
The SIB group was more likely to have received a higher total dose compared to the SEQ group, 95.4% to 15.6% respectively. (P=<0.001)

<table>
<thead>
<tr>
<th>DOSE</th>
<th>SEQ</th>
<th>SIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 Gy</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>≥70 Gy</td>
<td>5</td>
<td>145</td>
</tr>
</tbody>
</table>
Sequential Boost Compared with Simultaneous Integrated Boost

Chemotherapy
The SIB group was more likely to have received chemotherapy compared to the SEQ group, 83.6% to 43.8% respectively. (P=<0.001)

<table>
<thead>
<tr>
<th></th>
<th>SEQ</th>
<th>SIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>no chemo</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>chemo</td>
<td>14</td>
<td>127</td>
</tr>
</tbody>
</table>
Sequential Boost Compared with Simultaneous Integrated Boost

- Median follow up was 29 months
- There were no significant differences in outcomes between the SEQ and SIB groups.
  - LRC  $p=0.774$
  - DFS  $p=0.592$
  - OS  $p=0.611$
Sequential Boost Compared with Simultaneous Integrated Boost

Locoregional Control

Overall Survival

$p = 0.774$

$p = 0.611$
Sequential Boost Compared with Simultaneous Integrated Boost

When stratifying by prescription dose, there were no significant differences in outcomes between the low dose or high dose groups.
Sequential Boost Compared with Simultaneous Integrated Boost

When stratifying by the use of chemotherapy, there were no significant differences in outcomes whether the patient had chemotherapy or not.
Sequential Boost Compared with Simultaneous Integrated Boost

Patients in the SEQ group were significantly less likely to receive a reactive gastrostomy tube (PEG) \( (p=0.003) \).

<table>
<thead>
<tr>
<th>Reactive PEG Tubes</th>
<th>No PEG</th>
<th>PEG Placed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIB</td>
<td>83</td>
<td>30</td>
<td>113</td>
</tr>
<tr>
<td>SEQ</td>
<td>32</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>115</td>
<td>30</td>
<td>145</td>
</tr>
</tbody>
</table>

While there was no difference in late grade 3 or greater toxicity between the groups \( (p=0.354) \), of note all \( (n=8) \) occurred in the SIB group.
Sequential Boost Compared with Simultaneous Integrated Boost

Reactive Peg Tubes

- ICON stage I, II, and III
- Chemo: ~58% (prognostic for PEG)
- No Prophylactic PEG: 68%
- Reactive PEG: 44% of those
- At 1 year: 6.4% of reactive
Sequential Boost Compared with Simultaneous Integrated Boost

Reactive Peg Tubes

ICON stage I
Combined SEQ & SIB patients:
- Chemo: 76.6% (prognostic for PEG)
- No Prophylactic PEG: 78.8%
- Reactive PEG: 20.7% of those
- At 1 year: 0% of reactive
  (1 patient lost to follow-up)

ICON stage I
SEQ patients:
- Chemo: 43.8% (prognostic for PEG)
- No Prophylactic PEG: 100%
- Reactive PEG: 0% of those
- At 1 year: 0% of reactive
Sequential Boost Compared with Simultaneous Integrated Boost

Conclusions

• SEQ plans, while logistically more complicated, appear to provide similar LRC, DFS, and OS for early (ICON stage I) HPV positive oropharyngeal cancer patients.

• SEQ plans is associated with a lower likelihood of reactive PEG placement.
Small Reductions in Dose are Effective for HPV Positive Oropharyngeal Cancer Patients
Small Reductions in Dose

- 66 Gy
  - gross disease is less than 4 cm
- 68 Gy
  - gross disease is greater than 4 cm
Small Reductions in Dose

306 patients – ICON stage I, II, and III

• 43 patients in the low dose group
  – Median dose of 66 Gy
    • Range 62 – 68 Gy

• 263 patients in the high dose group
  – Median dose of 70 Gy
    • Range 70 – 75.2 Gy
Small Reductions in Dose

Reasonably similar

<table>
<thead>
<tr>
<th></th>
<th>Low Dose Group</th>
<th>High Dose Group</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>42</td>
<td>232</td>
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<td></td>
<td>Phx Wall</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Smoking History</td>
<td>&lt; 10 pack year</td>
<td>27</td>
<td>147</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 pack year</td>
<td>16</td>
<td>116</td>
</tr>
<tr>
<td>ICON Stage</td>
<td>I</td>
<td>35</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>5</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Concurrent Chemo</td>
<td>No</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>25</td>
<td>232</td>
</tr>
</tbody>
</table>

Exceptions - the higher dose group was more likely:
- to be a higher ICON stage
- to receive chemotherapy
Small Reductions in Dose

Low Dose Group

- ICON stage
  - stage 1: 81%
  - stage 2: 7%
  - stage 3: 12%

High Dose Group

- ICON stage
  - stage 1: 58%
  - stage 2: 27%
  - stage 3: 15%

High dose group

- More likely to be a higher ICON stage
- 42% vs 19%
- p=0.013
Higher dose group more likely to receive chemotherapy

- 88.2% compared to 58.1%
- p=<0.001
Small Reductions in Dose

- There were no significant differences in outcomes between the low or high dose groups.
  - LRC ($p = 0.748$), DFS ($p = 0.741$), or OS ($p = 0.709$)

**Locoregional Control:**

**Overall Survival:**
Small Reductions in Dose

When stratifying by ICON stage or the use of chemotherapy, there were no significant differences in outcomes between the low dose or high dose groups.
Small Reductions in Dose

Patients in the low dose group were significantly less likely to receive a reactive gastrostomy tube (PEG) (p=0.002).

<table>
<thead>
<tr>
<th>Reactive PEG Tubes</th>
<th>No PEG</th>
<th>PEG Placed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose Group</td>
<td>35</td>
<td>4</td>
<td>39</td>
</tr>
<tr>
<td>High Dose Group</td>
<td>115</td>
<td>90</td>
<td>205</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>94</td>
<td>244</td>
</tr>
</tbody>
</table>

- There was no difference in late grade 3 or greater toxicity between the groups (p=0.053)
  - of note - all (n=22) occurred in the high dose group
Small Reductions in Dose

Patients in the low dose group are associated with a lower likelihood of reactive PEG placement.

---

**ICON stage I, II, and III**

- Combined low dose & high dose patients:
  - Chemo: 84.0% (prognostic for PEG)
  - No Prophylactic PEG: 77.9%
  - Reactive PEG: 36.9% of those
  - At 1 year: 0.8% of reactive
    (1 patient lost to follow-up)

**Low Dose Patients:**

- Chemo: 58.1% (prognostic for PEG)
- No Prophylactic PEG: 90.7%
- Reactive PEG: 10.3% of those
- At 1 year: 0% of reactive

---

**A multi-institution pooled analysis of gastrostomy tube dependence in patients with oropharyngeal cancer treated with definitive intensity-modulated radiotherapy.**


Small Reductions in Dose

Conclusions

• Mild dose de-escalation on the order of ~3-6% appears to provide similar LRC, DFS, and OS for HPV positive oropharyngeal cancer patients.

• Patients receiving less than 70Gy were less likely to receive reactive PEG tubes during or after radiotherapy.
Where are we going?

- Immunotherapy
- Personalized RT
- Adaptive Therapy
- Smaller Volumes
- Decreasing the elective neck volume
Where are we going?

Immunotherapy

There doesn’t seem to be much of a response rate for HPV for immunotherapy. But it is currently entering into the curative setting in clinical trials for patients not eligible cisplatin or for patients with high risk disease in combination with cisplatin.
Where are we going?

Personalized RT -> RSI/GARD

- Radiosensitivity Index
  - A surrogate for surviving fraction of cells after 2 Gy.
- Genomically Adjusted Radiation Dose
  - A mathematical transformation of RSI based on the linear quadratic equation to give a sense of the effective dose.
- Currently planning clinical trials to use RSI/GARD to personalize dose in H&N cancer.
Where are we going?

Adaptive Therapy

Planned re-plan during the course of treatment to take advantage of smaller tumor volumes
  – Decrease normal tissue dose
  – Ensuring tumor coverage
  – Improve setup accuracy
Where are we going?

Smaller volumes

- CTV
- PTV
Where are we going?

Decreasing the elective neck volume

- Reduce the nodal eschelons treated
- Unilateral vs. contralateral neck
Thank you

Cassidy, Daughter Extraordinaire

Vladimir Feygelman, PhD

Jimmy Caudell, MD, PhD
Hope to see you!

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