Complications of Head and Neck Radiation

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None
Overview

- Basics of Radiation Oncology
- Acute Toxicity & Management
- Late Toxicity & Management
- Quality of Life
Basics of Radiation Oncology
Principles of Targeting

- **Gross Tumor Volume (GTV)**
  - Macroscopic disease

- **Clinical Tumor Volume (CTV)**
  - At risk for microscopic extension (CTV = GTV + Margin)
  - At risk for microscopic spread (i.e. elective neck)

- **Planning Treatment Volume (PTV = CTV + Margin)**
  - Account for daily setup error
  - Dependent on immobilization and on-board imaging
Principles of Targeting
Defining Normal Structures

- Brachial Plexus
- Brainstem
- Cochlea
- Esophagus
- Larynx
- Mandible
- Oral Cavity
- Parotid Glands
- Spinal Cord
- Submandibular Glands
DRR: Normal Structures

Isovalues (cGy)
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Radiation Therapy Techniques

- 2-Dimensional (2D)
- 3-Dimensional Conformal Radiation Therapy (3DCRT)
- Intensity Modulated Radiation Therapy (IMRT)
- Proton Beam Therapy (PBT)
3DCRT: Fields

Norm: Abs

Wedge ID: VW (20 deg)

Isovalues (cGy)
3DCRT: Fields

Norm: Abs

Wedge ID: VW (20 deg)

Isovaluss(cGy)

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3DCRT: Fields

Norm: Abs

Isovalues (cGy)
3DCRT vs. IMRT

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3DCRT vs. IMRT
3DCRT vs. IMRT
Acute Toxicity & Management
Team Management

Diagnosis

Pre-RT

During RT

ENT, Rad/Onc, Med/Onc

Dentist

Speech Therapy

IR or GI

Nurse

Rad/Onc, Med/Onc

Dietitian

IR or GI
Dental

- Do NOT recommend extraction of healthy or restorable teeth prior to RT.
- Rather, removal of non-salvageable teeth or retained root tips prior to RT will decrease risk of post-RT extraction and associated risk of osteoradionecrosis.
  - If required, should be performed 2 wks prior to RT.
- Prevention
  - Fluoride carriers with neutral 1.1% sodium fluoride gel (daily as tolerated during RT)
  - Amorphous calcium phosphate (ACP) rinse after fluoride treatments.
Post-RT, should have dental evaluation every 3 months
  - Fluoride varnish application three times per year

If extraction is required, removal of teeth one at a time will decrease risk of osteoradionecrosis
  - Alveoplasty as indicated
  - Antibiotics at least 1 day prior to procedure
  - Hyperbaric oxygen was initially thought to be of benefit based on a small RCT (Marx, J Am Dent Assoc, 1985), however has since been questioned (Wahl, IJROBP, 2006)
## Dental

- **Low Historical Rate of Osteoradionecrosis**

### Table 2. Overall incidence of ORN in radiation patients since 1997

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>ORN cases (n)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>151</td>
<td>3</td>
<td>Ang <em>et al.</em>, 2001 (3)</td>
</tr>
<tr>
<td>636</td>
<td>14</td>
<td>Babik <em>et al.</em>, 2000 (4)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>Berg <em>et al.</em>, 2000 (5)</td>
</tr>
<tr>
<td>334</td>
<td>5</td>
<td>Bernier <em>et al.</em>, 2004 (6)</td>
</tr>
<tr>
<td>116</td>
<td>2</td>
<td>Brizel <em>et al.</em>, 1998 (7)</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>Carl and Ikner, 1998 (8)</td>
</tr>
<tr>
<td>107</td>
<td>1</td>
<td>Chaux-Bodard <em>et al.</em>, 2004 (9)</td>
</tr>
<tr>
<td>35</td>
<td>4</td>
<td>Chavez and Adkinson, 2001 (10)</td>
</tr>
<tr>
<td>1,758</td>
<td>61</td>
<td>Cheng <em>et al.</em>, 2006 (11)</td>
</tr>
<tr>
<td>413</td>
<td>10</td>
<td>Cooper <em>et al.</em>, 2004 (12)</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>David <em>et al.</em>, 2001 (13)</td>
</tr>
<tr>
<td>918</td>
<td>9</td>
<td>Dische <em>et al.</em>, 1997 (14)</td>
</tr>
<tr>
<td>759</td>
<td>17</td>
<td>Fu <em>et al.</em>, 2000 (15)</td>
</tr>
<tr>
<td>83</td>
<td>1</td>
<td>Gwozdz <em>et al.</em>, 1997 (16)</td>
</tr>
<tr>
<td>47</td>
<td>0</td>
<td>Lambert <em>et al.</em>, 1997 (17)</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>Lozza <em>et al.</em>, 1997 (18)</td>
</tr>
<tr>
<td>1,495</td>
<td>27</td>
<td>Mendenhall, 2004 (19)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Németh <em>et al.</em>, 2000 (20)</td>
</tr>
<tr>
<td>81</td>
<td>4</td>
<td>Oh <em>et al.</em>, 2004 (21)</td>
</tr>
<tr>
<td>830</td>
<td>68</td>
<td>Reuther <em>et al.</em>, 2003 (22)</td>
</tr>
<tr>
<td>268</td>
<td>27</td>
<td>Studer <em>et al.</em>, 2004 (23)</td>
</tr>
<tr>
<td>1,194</td>
<td>11</td>
<td>Sulaiman <em>et al.</em>, 2003 (24)</td>
</tr>
<tr>
<td>193</td>
<td>9</td>
<td>Toljanić <em>et al.</em>, 1998 (25)</td>
</tr>
<tr>
<td>44</td>
<td>4</td>
<td>Tong <em>et al.</em>, 1999 (26)</td>
</tr>
<tr>
<td>36</td>
<td>2</td>
<td>Vudinjable <em>et al.</em>, 1999 (27)</td>
</tr>
</tbody>
</table>

**Total:** 9,632  290  3.0%
Swallowing

- High level of **Pre-RT swallowing dysfunction** (Stenson, Arch Oto H&N Surg, 2000; n=79)
  - Baseline impairment in 67% (HPX > LX > OPX > OC)
  - Aspiration in 80% HPX, 67% LX, 30% OPX, 14% OC

- **Prophylactic PEG** (pPEG) is recommended for patients with significant functional decline
  - Significant weight loss (>5% over 1 mo or >10% over 6 mo)
  - Poor PO intake due to dysphagia, anorexia, or pain
  - Severe aspiration (or mild aspiration with compromised cardiopulmonary function)

- Even with pPEG, **must encourage PO intake** (however little) to prevent mucosal adhesions and muscle atrophy
## Swallowing

- University of California at Davis
  - No pPEG (n=50) vs. pPEG (n=70)

<table>
<thead>
<tr>
<th></th>
<th>Mean Weight Loss</th>
<th>Percentage Weight Loss</th>
<th>&gt;10% Weight Loss</th>
<th>&gt;20% Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pPEG</td>
<td>43 lbs</td>
<td>14%</td>
<td>74%</td>
<td>26%</td>
</tr>
<tr>
<td>pPEG</td>
<td>19 lbs</td>
<td>8%</td>
<td>27%</td>
<td>7%</td>
</tr>
<tr>
<td>P value</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>SS</td>
<td>SS</td>
</tr>
</tbody>
</table>

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Chen, IJROBP, 2010
Swallowing

- Despite **Reactive PEG (rPEG)** in 16/50 pts (38%), multiple differences in late toxicity

<table>
<thead>
<tr>
<th></th>
<th>G3+ Dysphagia</th>
<th>PEG Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 mo</td>
<td>6 mo</td>
</tr>
<tr>
<td>No pPEG</td>
<td>27%</td>
<td>5%</td>
</tr>
<tr>
<td>pPEG</td>
<td>46%</td>
<td>34%</td>
</tr>
<tr>
<td>P value</td>
<td>P=0.01</td>
<td>P=0.01</td>
</tr>
</tbody>
</table>

Devisetty

Chen, IJROBP, 2010
Speech Therapy

- Pre-RT speech therapy evaluation and swallowing exercises improve post-RT swallowing function

- Per videofluoroscopy (Carroll, Laryngoscope, 2008; n=18)

<table>
<thead>
<tr>
<th>Videofluoroscopy Measure</th>
<th>Pretreatment, Mean ± SD or % (n = 9)</th>
<th>Control, Mean ± SD or % (n = 9)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenbeck Aspiration Score</td>
<td>4.11 ± 2.84</td>
<td>3.88 ± 2.20</td>
<td>.86</td>
</tr>
<tr>
<td>Posterior tongue base position at rest</td>
<td>26.48 ± 4.28 mm</td>
<td>32.2 ± 7.99 mm</td>
<td>.071</td>
</tr>
<tr>
<td>Posterior tongue base position during swallow</td>
<td>15.2 ± 5.47 mm</td>
<td>22.0 ± 6.23 mm</td>
<td>.025</td>
</tr>
<tr>
<td>Posterior tongue base movement</td>
<td>11.28 ± 3.69 mm</td>
<td>10.29 ± 6.56 mm</td>
<td>.70</td>
</tr>
<tr>
<td>Vertical hyoid position at rest</td>
<td>43.73 ± 5.90 mm</td>
<td>42.8 ± 7.52 mm</td>
<td>.77</td>
</tr>
<tr>
<td>Vertical hyoid position during swallow</td>
<td>24.97 ± 6.26 mm</td>
<td>24.96 ± 5.59 mm</td>
<td>.99</td>
</tr>
<tr>
<td>Vertical hyoid movement</td>
<td>18.75 ± 4.21 mm</td>
<td>17.84 ± 8.19 mm</td>
<td>.77</td>
</tr>
<tr>
<td>Epiglottis inversion</td>
<td>89%</td>
<td>33%</td>
<td>.02</td>
</tr>
<tr>
<td>Cricopharyngeal opening</td>
<td>8.07 ± 3.86 mm</td>
<td>7.62 ± 3.95 mm</td>
<td>.81</td>
</tr>
<tr>
<td>PEG tube use 12 mo after CRT</td>
<td>33%</td>
<td>44%</td>
<td>.63</td>
</tr>
</tbody>
</table>

- Per MD Anderson Dysphagia Inventory (Kulbersh, Laryngoscope, 2006; n=37)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Pretreatment (n = 25), mean (95% CI)</th>
<th>Post-treatment only (n=12), mean (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global assessment</td>
<td>74.4 (64.5–84.3)</td>
<td>32.9 (17.0–48.7)</td>
<td>.0002</td>
</tr>
<tr>
<td>Emotional</td>
<td>72.1 (66.1–78.0)</td>
<td>53.9 (44.3–63.5)</td>
<td>.005</td>
</tr>
<tr>
<td>Functional</td>
<td>68.7 (62.4–75.1)</td>
<td>58.6 (48.5–68.8)</td>
<td>.114</td>
</tr>
<tr>
<td>Physical</td>
<td>66.4 (58.5–74.3)</td>
<td>43.2 (30.6–55.7)</td>
<td>.005</td>
</tr>
</tbody>
</table>
Taste

- Varying degrees of loss
  - Ageusia → complete loss of taste
  - Hypogeusia → partial loss of taste
  - Dysguesia → altered taste

- Alteration likely multi-factorial
  - Direct nerve damage leading to taste bud atrophy
  - Decrease number/density of taste buds
  - Cell membrane damage
  - Lack of salivation inhibits molecular transport

- Some patients have taste dysfunction prior to treatment (Mirza, Laryngoscope, 2008)
University of Pennsylvania

- 8 pts with H&N RT vs. 17 pts with non-H&N RT
- Prospectively tested taste (sweet, sour, bitter, salty) and performed video microscopy

- Majority of taste (except bitter) recovered by 7 mo post-treatment
Salivation

- **Anatomic/Temporal Contributions**
  - Parotid → main contributors during stimulation (i.e. mastication)
  - Submandibular → main contributor at baseline

- **Serous** producing cells more sensitive than **mucinous** producing cells
  - Net effect of mucinous and thick saliva during RT

- **During radiation, thick saliva causes:**
  - Alteration of taste
  - **Gagging sensation** associated with nausea or vomiting
  - **Mechanical inhibition** of swallowing solids
Parotid Glands

- Recovery is radiation dose and time dependent

Stimulated:

Resting:
Level 1 evidence (i.e. 5 RCT’s) that IMRT decreases parotid exposure and associated xerostomia without compromising loco-regional control or survival.

<table>
<thead>
<tr>
<th>Study</th>
<th>RT</th>
<th>Xerostomia grade 2-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months - 1 year</td>
</tr>
<tr>
<td>Pow et al. [16]</td>
<td>2D-RT</td>
<td>82.1</td>
</tr>
<tr>
<td></td>
<td>IMRT</td>
<td>39.3</td>
</tr>
<tr>
<td>Kam et al. [17]</td>
<td>2D-RT</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>IMRT</td>
<td>15</td>
</tr>
<tr>
<td>Nutting et al. [18]</td>
<td>3D-RT</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>IMRT</td>
<td>28.8</td>
</tr>
<tr>
<td>Gupta et al. [20]</td>
<td>2D-RT</td>
<td>57.4</td>
</tr>
<tr>
<td></td>
<td>IMRT</td>
<td>28.1</td>
</tr>
</tbody>
</table>
Salivation

- Submandibular Glands
  - Recovery is radiation dose dependent

Resting salivation rate is steeper & more dependent on RT dose
Chemoprevention may be effective, but lack of consistent results and high rates of adverse events has limited dissemination.

- **Amifostine**
  - Benefit with **RT alone** (Brizel, JCO, 2000)
  - No benefit with **chemoRT** (Buentzel, IJROBP, 2006; Haddad, Cancer, 2009)
  - Associated with high rates of nausea/vomiting and hypotension; no difference between IV and SQ (Bardet, JCO, 2011)

- **Pilocarpine (Salagen)** 5 mg tid
  - Benefit in RCT (Johnson, NEJM, 1993)
  - No benefit in RCT (Scarantino, J Support Oncol, 2006)

- **Cevimeline (Evoxac)** 30 mg tid
  - No benefit in RCT (Witsell, H&N, 2012)
**Mucositis**

- Nearly universal during RT
  - 91% with any grade of mucositis
  - 66% with G3-4 mucositis

- Degree is **site dependent** (OC/OPX > LX/HPX)

- Multiple **exacerbating factors**
  - Concurrent chemotherapy
  - High T stage
  - Altered fractionation

- Direct association with *pain levels* and *weight loss*
Erythematous mucosa (1-2 wks) \(\rightarrow\) white patchy ulcers, pseudomembranous lesions (3-4 wks) \(\rightarrow\) confluent pseudomembranes and ulceration (5-7 wks)
Erythematous mucosa (1-2 wks) → white patchy ulcers, pseudomembranous lesions (3-4 wks) → confluent pseudomembranes and ulceration (5-7 wks)
Mucositis

Not effective

- Non-absorbable antibiotics, e.g. polymyxin, tobramycin, bacitracin, clotrimazole, gentamicin (Stokman, BJC, 2003; El-Sayed, JCO, 2002)
- Sucralfate (Dodd, Cancer Invest, 2003)
- Chlorhexidine (Foote, JCO, 1994)
- Palifermin (Brizel, JCO, 2008)

Effective

- Narcotics
- 2% Viscous Lidocaine
- “Haddad’s Maalox Mixture” (2% viscous lidocaine, diphenhydramine, Mg-Al hydroxide)
- Morphine sulfate mouthwash (Cerchietti, Cancer, 2002)
- Capsaicin lozenges (Berger, J Pain Symptom Manage, 1995)
- Tricyclic antidepressants (Ehrnrooth, Acta Oncol, 2001)
- MuGard (Allison, Cancer, 2014)
Other

- Skin erythema/desquamation
- Alopecia at base of skull
- Fatigue
- Hoarseness or loss of voice (low risk or non-LX/HPX)
Cumulative Effect

- During RT, challenge to maintain PO intake
  - Loss of taste (ageusia)
  - Painful swallowing (mucositis)
  - Difficult swallowing (thick salivary secretions)
  - Hyperstimulated gag reflex (thick salivary secretions)

- Team effort between physicians, nursing, dieticians, speech therapy, and social work required to get patients through treatment with minimal treatment breaks

- Most acute toxicities resolve in 1-3 months
Late Toxicity & Management
Team Management

Post-RT

PRN

ENT, Rad/Onc, Med/Onc

Dentist

Speech Therapy

Audiology

Prophylaxis

Extraction

Swallowing

Trismus

Lymphedema

Hearing Aid

Devisetty
Trismus

- Due to fibrosis of muscles of mastication
  - Restricted $\rightarrow$ Interincisor Distance $< 3.5$ cm
  - Severe $\rightarrow$ Interincisor Distance $< 1.8-2$ cm

- Historical rate (i.e. with 3DCRT) vary on location of primary
  - OPX $\rightarrow$ 16% (Teguh, H&N, 2008; n=56)
  - NPX $\rightarrow$ 5-16%

- Time course is most rapid during first year post-RT
  - Year 1 $\rightarrow$ 2.4% per month
  - Year 2 $\rightarrow$ 0.2% per month
  - Year 3-4 $\rightarrow$ 0.1% per month
Trismus

- **Old techniques** just used parallel opposed fields to treat, thus leading to high RT exposure to muscles of mastication.

- **New techniques** (i.e. IMRT) shape RT dose to spare parotid glands, which indirectly spares the muscles of mastication as well.

![Graph](image)

**FIGURE 4.** Dose–volume histogram for the left masseter muscle with and without a constraint in the left masseter muscle.
Trismus

- **IMRT** (Hsiung, BJR, 2008; n=17 with NPX)
  - 5 mo post-IMRT $\rightarrow$ 94% normalized MID
  - 12 mo post-IMRT $\rightarrow$ 98% normalized MID

![Graph showing normalized MID over time](image)
Trismus

- **Mechanical Treatment**
  - Tapered corks or stacked tongue blades
  - TheraBite

- **Pharmacologic Treatment**
  - Pentoxyifylline + Alpha-tocopherol (Delanian, JCO, 1999; Chua, AJCO, 2001)
  - Baclofen
  - Cyclobenzaprine
  - Tizanidine
  - Clonazepam
Larynx CA (Early Stage)

- **Early Stage** (i.e. clinical T1-2 N0)

- **RCT of Transoral Laser Surgery (TLS) vs. RT** (n=60)

  » No difference in 2-year cancer recurrence (10% vs. 12%)
After RT, voice quality improves over time and returns back to baseline in 50% of patients.

For those that do not return to baseline, primary risk factors are initial vocal cord stripping and continuation of smoking.

S = Speaker; P = Partner

Verdonck-de Leeuw, IJROBP, 1999
- Severe late toxicities are rare

- University of Florida (n=6 of 519, 1%)
  - 1 pt with severe mucositis
  - 1 pts with total laryngectomy for suspected local failure
  - 3 pts with tracheostomy due to laryngeal edema
  - 1 pt with pharyngocutaneous fistula after salvage laryngectomy
  - 5/6 pts had T2 N0

- Management of edema or cartilage necrosis
  - Steroids (e.g. dexamethasone)
  - Antibiotics
Larynx CA (Advanced Stage)

- **Advanced Stage** (i.e. clinical T3-4 N0-3)

- **VA Larynx Study (Surgery + RT vs. Chemo + RT)**

### Late Toxicity:

<table>
<thead>
<tr>
<th></th>
<th>Total, G3-4</th>
<th>2Y Speech Impairment</th>
<th>2Y Swallow Impairment</th>
<th>Tx Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo → RT</td>
<td>24%</td>
<td>3%</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>CCRT</td>
<td>30%</td>
<td>6%</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>RT alone</td>
<td>36%</td>
<td>8%</td>
<td>14%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Only 9/515 pts (2%, of which 2 pts were in CCRT arm) required laryngectomy for laryngeal dysfunction or necrosis* (Forastiere, H&N, 2010)
Locally Advanced (i.e. clinical T4 NX)

University of Chicago (n=32)
- Median f/u = 3.6 yrs
- N0 (14 pts), N1 (6 pts), N2 (10 pts), N3 (2 pts)

<table>
<thead>
<tr>
<th>Persistent tracheostomy and gastrostomy tube dependence at ≥1 year</th>
<th>All T4 (n = 20), %</th>
<th>Nonlarge-volume</th>
<th>Large-volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent tracheostomy</td>
<td>25</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Gastrostomy tube dependence</td>
<td>15</td>
<td>20</td>
<td>13</td>
</tr>
</tbody>
</table>

Speech outcome
- Normal speech: 30, 40, 27
- Hoarseness: 60, 60, 60
- Whisper only: 10, 0, 13
- No voice: 0, 0, 0
In non-LX/HPX primaries, RT dose to the larynx can increase risk for laryngeal edema and dysphonia.

G2+ Laryngeal Edema:

G0-1 Dysphonia on HN4:

* FACT-HN4 is self-reported and answers the question, “My voice has its usual quality and strength”
* The lower the score, the higher the toxicity

Devisetty

Sanguinetti, IJROBP, 2007
Sanguinetti, Clin Oncol, 2014
Auditory

- **External Ear**
  - Otitis Externa
  - Canal Stenosis

- **Middle Ear** (Conductive Hearing Loss, i.e. CHL)
  - Otitis Media
  - Mastoiditis
  - Tympanic Membrane Perforation
  - Chorda Tympani Dysfunction

- **Inner Ear** (Sensorineural Hearing Loss, i.e. SNHL)
  - Tinnitus
  - Vertigo
  - Labrynthitis
Auditory

- RT can induce CHL, SNHL, or mixed hearing loss that is often exacerbated by chemotherapy.
- Prospective study of hearing in RCT of RT vs. CCRT in NPX:

  Averaged 0.5-2 kHz:

  4 kHz:
Auditory

- Prospective study of high ipsilateral cochlea RT (mean 47 Gy) to low contralateral cochlea RT (mean 4 Gy) in all H&N sites
Auditory

- Ultimately, there are **competing risks** for hearing loss between RT and chemotherapy
Risk of hypothyroidism dependent on primary surgery (e.g. laryngectomy), neck dissection, thyroiditis, and RT dose

Rate dependent on presence/absence of surgery
- Laryngectomy + RT (Ho, H&N, 2008; n=147)
  - 3 yrs → 20%
  - 6 yrs → 39%
  - 10 yrs → 93%

- RT +/- Chemo (Mercado, Cancer, 2001; n=143)
  - 5 yrs → 48%
  - 8 yrs → 67%

- RT alone (Tell, IJROBP, 2004; n=308)
  - 5 yrs → 20%
  - 10 yrs → 27%
Thyroid

- Mean time to developing hypothyroidism for majority is 1-2 years, however due to late onset (i.e. 10-20 yrs), recommend to follow patients life-long

- RT dose to thyroid can guide risk assessment

Devisetty

Bhandare, IJROBP, 2007
Brachial Plexus

- Brachial plexopathy historically has not been well characterized in H&N patients (as opposed to breast cancer patients).

- Due to improved therapy and more favorable prognostic groups (i.e. HPV positive), longer life spans may increase observation and/or incidence of brachial plexus injury.

- University of California at Davis (n=352)
  - Prospective survey at median 3.3 yrs (range, 0.5 – 9.3)
  - 50% OPX, 15% OC, 15% LX, 8% CUP, 7% NPX, 6% HPX
  - 57% definitive RT, 43% adjuvant RT
  - 50% neck dissection
  - 63% concurrent chemotherapy

Devisetty, Chen, IJROBP, 2014
51/352 pts (14%) with symptoms of brachial plexopathy at median 1.8 yrs (range, 0.5 – 6.7)
- 50% ipsilateral pain
- 40% numbness or tingling
- 25% motor weakness and/or muscle atrophy

19/51 pts (57%) had electrophysiologic studies (e.g. nerve conduction analysis, EMG)
- 58% reduced sensory nerve conduction
- 53% differences in latency and amplitude between the affected and unaffected extremity
- 37% reduced motor nerve conduction velocity
- 26% prolonged F-wave latencies
Brachial Plexus

Freedom from Brachial Plexopathy:

<table>
<thead>
<tr>
<th></th>
<th>Survey (n=352)</th>
<th>Electrophysiologic (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year</td>
<td>86%</td>
<td>95%</td>
</tr>
<tr>
<td>5-year</td>
<td>81%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Survey:

- MVA
- N3: HR=3.17 (P<0.001)
- RT Dose: HR=1.11 (P=0.01)
Other

- Lhermitte’s Syndrome
- Lymphedema
- Skin Hyperpigmentation
- Skin Fibrosis
- Temporal Lobe Necrosis (only for NPX)
- Pituitary Dysfunction (only for NPX)
Quality of Life
Multifactorial

- **Radiation** related
  - 3DCRT vs. IMRT
  - Site dependent (LX/HPX vs. Other)
  - Volume dependent (e.g. Elective Neck)

- **Chemotherapy** related
  - Ototoxicity
  - Nephrotoxicity
  - Peripheral Neuropathy

- **Surgically** related
  - Neck Dissection
University of California at Davis

- Retrospective comparison of 3DCRT (n=71) vs. IMRT (n=84) with either definitive (53%) or adjuvant RT (47%) +/- chemotherapy (47%)
- University of Washington Quality of Life inventory performed at 6 mo, 1 yr, and 2 yr after treatment
- Only included pts with no disease and at least 2 yrs of follow-up, but excluded laryngectomy history

## Table 2

<table>
<thead>
<tr>
<th>UW-QOL Score</th>
<th>1 year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMRT</td>
<td>3D CRT</td>
</tr>
<tr>
<td>Pain</td>
<td>75.4</td>
<td>77.1</td>
</tr>
<tr>
<td>Appearance</td>
<td>76.5</td>
<td>75.2</td>
</tr>
<tr>
<td>Activity</td>
<td>82.9</td>
<td>84.0</td>
</tr>
<tr>
<td>Recreation</td>
<td>74.4</td>
<td>72.8</td>
</tr>
<tr>
<td>Swallowing</td>
<td>63.5</td>
<td>60.5</td>
</tr>
<tr>
<td>Chewing</td>
<td>62.3</td>
<td>58.9</td>
</tr>
<tr>
<td>Speech</td>
<td>80.1</td>
<td>82.3</td>
</tr>
<tr>
<td>Shoulder</td>
<td>66.6</td>
<td>68.5</td>
</tr>
<tr>
<td>Taste</td>
<td>70.0</td>
<td>71.8</td>
</tr>
<tr>
<td>Saliva</td>
<td>70.5</td>
<td>50.6</td>
</tr>
<tr>
<td>Mood</td>
<td>72.9</td>
<td>70.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>62.1</td>
<td>65.6</td>
</tr>
</tbody>
</table>

Devisetty

Chen, IJROBP, 2012
# 3DCRT vs. IMRT

## Health Related QOL:

<table>
<thead>
<tr>
<th></th>
<th>1-year</th>
<th>2-year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMRT</td>
<td>3DCRT</td>
</tr>
<tr>
<td><strong>Current</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Much better”</td>
<td>67%</td>
<td>56%</td>
</tr>
<tr>
<td>“Somewhat better”</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Outstanding”</td>
<td>60%</td>
<td>42%</td>
</tr>
<tr>
<td>“Very good”</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean Scores</strong></td>
<td>62.0</td>
<td>50.9</td>
</tr>
</tbody>
</table>

* Current = QOL compared to 1 month before the development of cancer
** Recent = QOL during the past 7 days
### 3DCRT vs. IMRT

**Global QOL:**

<table>
<thead>
<tr>
<th></th>
<th>1-year</th>
<th>2-year</th>
<th>P value</th>
<th>1-year</th>
<th>2-year</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMRT</strong></td>
<td>51%</td>
<td>41%</td>
<td>P=0.11</td>
<td>73%</td>
<td>49%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>3DCRT</strong></td>
<td>41%</td>
<td>49%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Outstanding&quot; or &quot;Very good&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean Scores</strong></td>
<td>67.5</td>
<td>55.4</td>
<td>P=0.2</td>
<td>80.1</td>
<td>57.0</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Devisetty Chen, IJROBP, 2012
University of Michigan

- 40 pts with stage III/IV OPX (98% HPV positive) without posterior pharyngeal wall involvement or recurrence treated with definitive swallowing & salivary sparing IMRT on prospective clinical trials from 2003-2011
  - Median follow-up 6.5 yrs
  - 98% with follow-up >3 yrs, 75% with follow-up >5 yrs

- Health-related QOL assessment at pre-treatment and 1, 3, 6, 12, 18, 24 months:
  - Head and Neck QOL (HNQOL) questionnaire
  - University of Washington QOL (UWQOL) questionnaire
  - Xerostomia Questionnaire (XQ)

- Long term assessment after 2 years:
  - Short Form-36 (SF-36) questionnaire
  - Head and Neck QOL (HNQOL) questionnaire
  - University of Washington QOL (UWQOL) questionnaire
# Swallowing & Salivary Sparing IMRT

## Table 2  Patient-reported quality of life after organ-sparing chemo—intensity modulated radiation therapy

<table>
<thead>
<tr>
<th>Measure</th>
<th>Before treatment*</th>
<th>24 mo*</th>
<th>Long term*</th>
<th>Δ Long term vs 24 mo†</th>
<th>Δ Long term vs before treatment†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HNQOL instrument</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary score</td>
<td>15.1 (11.2-19.0)</td>
<td>9.5 (6.3-12.6)</td>
<td>11.9 (6.9-16.9)</td>
<td>+1.0 (−2.2 to 4.2)</td>
<td>−3.2 (−8.1 to 1.7) (P=.20)</td>
</tr>
<tr>
<td>Eating</td>
<td>9.4 (4.8-13.9)</td>
<td>15.8 (10.7-20.9)</td>
<td>15.5 (10.1-20.9)</td>
<td>−1.4 (−5.3 to 2.4)</td>
<td>+6.2 (0.1-12.3) (P=.05)</td>
</tr>
<tr>
<td>Pain</td>
<td>17.3 (12.5-22.1)</td>
<td>9.3 (5.0-13.6)</td>
<td>15.2 (8.5-21.8)</td>
<td>+5.1 (−0.9 to 11.1)</td>
<td>−2.1 (−8.6 to 4.3) (P=.51)</td>
</tr>
<tr>
<td>Communication</td>
<td>8.3 (3.9-12.7)</td>
<td>4.6 (2.1-7.1)</td>
<td>7.3 (2.8-11.9)</td>
<td>+1.3 (−2.4 to 5.0)</td>
<td>−0.9 (−6.7 to 4.9) (P=.75)</td>
</tr>
<tr>
<td>Emotion</td>
<td>21.3 (15.5-27.1)</td>
<td>5.9 (2.4-9.3)</td>
<td>8.5 (3.2-13.8)</td>
<td>+1.2 (−2.4 to 4.9)</td>
<td>−12.8 (−18.3 to −7.2) (P&lt;.001)</td>
</tr>
<tr>
<td>Overall Bother</td>
<td>32.1 (23.3-40.8)</td>
<td>10.8 (5.6-16.0)</td>
<td>16.3 (9.1-23.4)</td>
<td>+4.2 (−0.7 to 9.0)</td>
<td>−15.4 (−24.0 to −6.7) (P&lt;.001)</td>
</tr>
<tr>
<td><strong>UWQOL instrument</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary score</td>
<td>10.0 (6.6-13.4)</td>
<td>15.2 (11.3-19.0)</td>
<td>16.5 (11.9-21.1)</td>
<td>+0.5 (−2.4 to 3.4)</td>
<td>+6.5 (1.6-11.4) (P=.01)</td>
</tr>
<tr>
<td>Swallowing</td>
<td>6.3 (1.5-11.0)</td>
<td>9.7 (5.1-14.4)</td>
<td>13.1 (7.7-18.6)</td>
<td>+2.1 (−2.1 to 6.3)</td>
<td>+6.9 (−0.1 to 13.9) (P=.05)</td>
</tr>
<tr>
<td>XQ summary score</td>
<td>6.4 (2.2-10.6)</td>
<td>29.0 (20.4-37.7)</td>
<td>29.9 (21.2-38.5)</td>
<td>−0.8 (−5.7 to 4.1)</td>
<td>+23.4 (14.8-32.1) (P&lt;.001)</td>
</tr>
</tbody>
</table>

* Normalized on a linear 100-point scale, with 0 = no toxicity and 100 = maximum toxicity

* Clinically meaningful is ≥10 point change (Osoba, JCO, 1998)
Compared to pre-treatment, long-term HNQOL and UWQOL summary scores corresponding to “moderate” or greater severity were reported by only 5% and 2.5% of patients, respectively.

On the SF-36, long-term overall physical and mental health mean scores for the cohort were comparable in each HRQOL domain to the US population norms [not shown]
Compared to pre-treatment, 12-14 pts (30-35%) with decreased swallowing function, but only 2 pts (5%) had ≥ “moderate” severity.

After 2 years, 5 pts (14%) had worsening swallowing, of which only 1 pt had “moderate” severity eventually requiring PEG.

Freedom from PEG dependence beyond 2 yrs = 98%
## VA Larynx Study

- **(Laryngectomy + RT) vs. (Chemo + RT)**
  - Surveyed 46/65 (71%) long term survivors
  - Mean follow-up = 10.4 yrs (range, 8.5-12.7)

- **Health related QOL:**
  - Short Form-36 (SF-36) questionnaire
  - Head and Neck QOL (HNQOL) questionnaire
  - Beck Depression Inventory (BDI)

### Table 2. Baseline Demographics and Clinical Characteristics of Patients by Randomization*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Surgery + RT</th>
<th>CT + RT</th>
<th>No Laryngectomy</th>
<th>Laryngectomy</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>55.7</td>
<td>61.2†</td>
<td>56.5</td>
<td>58.9</td>
<td>58.3</td>
</tr>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>21</td>
<td>13</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>2</td>
<td>3 (12)</td>
<td>1 (5)</td>
<td>1 (8)</td>
<td>3 (9)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>3</td>
<td>13 (52)</td>
<td>15 (71)</td>
<td>11 (85)</td>
<td>17 (52)</td>
<td>28 (61)</td>
</tr>
<tr>
<td>4</td>
<td>8 (32)</td>
<td>5 (24)</td>
<td>1 (8)</td>
<td>12 (36)</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Node stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13 (52)</td>
<td>12 (57)</td>
<td>5 (38)</td>
<td>20 (61)</td>
<td>25 (54)</td>
</tr>
<tr>
<td>1</td>
<td>5 (20)</td>
<td>3 (14)</td>
<td>4 (31)</td>
<td>4 (12)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>2</td>
<td>5 (20)</td>
<td>4 (19)</td>
<td>3 (23)</td>
<td>6 (18)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>3</td>
<td>2 (8)</td>
<td>2 (10)</td>
<td>1 (8)</td>
<td>3 (9)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>11 (44)</td>
<td>12 (57)</td>
<td>8 (62)</td>
<td>15 (45)</td>
<td>23 (50)</td>
</tr>
<tr>
<td>IV</td>
<td>14 (56)</td>
<td>9 (43)</td>
<td>5 (38)</td>
<td>18 (55)</td>
<td>23 (50)</td>
</tr>
</tbody>
</table>
Surgery vs. Organ Preservation

SF-36 Domains:

- **Table 1. Domains of the Short-Form 36 General Health Measure**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Meaning of Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>Limitations in performing various physical activities</td>
</tr>
<tr>
<td>Role physical (RP)</td>
<td>Problems with work or other daily activities as a result of physical health</td>
</tr>
<tr>
<td>Bodily pain (BP)</td>
<td>Extent of pain or limitations due to pain</td>
</tr>
<tr>
<td>General health (GH)</td>
<td>Perception of personal health</td>
</tr>
<tr>
<td>Vitality (VT)</td>
<td>Level of energy</td>
</tr>
<tr>
<td>Social functioning (SF)</td>
<td>Extent and frequency of interference with social activities due to physical and emotional problems</td>
</tr>
<tr>
<td>Role emotional (RE)</td>
<td>Problems with work or other activities due to emotional problems</td>
</tr>
<tr>
<td>Mental health (MH)</td>
<td>Feelings of nervousness and depression</td>
</tr>
</tbody>
</table>

(S + RT) vs. (Chemo + RT):

- Per SF-36, organ preservation scored higher in all domains, but only significant for mental health \((p<0.05)\)

- Per HNQOL, organ preservation scored higher in pain domain \((p<0.05)\), and suggested improvement in eating and emotion domains [not shown]
Neck Dissection

- **RTOG (pre-IMRT)**
  - 230 pts from RTOG 9111, 9703, 9914
  - 99 pts (43%) with severe late toxicity, 131 pts (57%) as controls

- **Severe Late Toxicity:**
  - Grade 3-4 pharyngeal/laryngeal toxicity
  - Feeding tube ≥ 2 years after registration
  - Treatment related death within 3 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>91-11</th>
<th>97-03</th>
<th>99-14</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding tube dependence &gt; 2 years post-radiation therapy</td>
<td>—</td>
<td>29*</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>RTOG late toxicity criteria, grade 3+</td>
<td></td>
<td></td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>Pharyngeal dysfunction</td>
<td>16</td>
<td>28</td>
<td>19</td>
<td>63</td>
</tr>
<tr>
<td>Laryngeal dysfunction</td>
<td>22</td>
<td>6</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Death</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Other (e.g., infection, fistula)</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Any</td>
<td>38†</td>
<td>40†</td>
<td>21†</td>
<td>99†</td>
</tr>
<tr>
<td>No severe late toxicity event (controls)</td>
<td>50</td>
<td>62</td>
<td>19</td>
<td>13</td>
</tr>
</tbody>
</table>
Severe Late Toxicity:
Neck Dissection = 55%
No Neck Dissection = 40%

**Multivariate Analysis:**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LX/HPX Primary</td>
<td>4.17</td>
<td>0.0041</td>
</tr>
<tr>
<td>T3-4</td>
<td>3.07</td>
<td>0.0036</td>
</tr>
<tr>
<td>Neck Dissection</td>
<td>2.39</td>
<td>0.018</td>
</tr>
<tr>
<td>Old Age</td>
<td>1.05</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*C* patients who Experienced Treatment Failure

**Machtay, JCO, 2008**
Neck Dissection

Head and Neck Cancers

PRINCIPLES OF SURGERY
(POST CHEMORADIATION OR RT NECK EVALUATION)¹

1. **Persistent disease or progression**
   - **If diagnosis confirmed or progression**
     - **No lymph node or node <1 cm; PET/CT negative³** → **Observe**
     - **Lymph node <1 cm; PET/CT positive⁴** → **Observe or Neck dissection**
     - **Lymph node >1 cm; PET/CT negative³** → **Observe**
     - **Lymph node >1 cm; PET/CT positive⁴** → **Neck dissection**

2. **After chemo/RT or RT**
   - **4-8 weeks clinical assessment as appropriate**
     - **If response**
       - **PET/CT² (including CT + IV contrast) at minimum 12 weeks**
         - **Imaging positive**
           - **Neck dissection or Consider PET imaging at 12 weeks**
         - **Imaging negative** → **Observe**
     - **or**
       - **CT and/or MRI with contrast at 8-12 weeks**
         - **Imaging positive**
           - **Neck dissection or Consider PET imaging at 12 weeks**
         - **Imaging negative** → **Observe**

¹ NCCN Guidelines Index
Head and Neck Table of Contents
Discussion

Devisetty
There are significant acute toxicities with chemoradiotherapy, however with a team effort, supportive strategies can facilitate continuous and timely treatment.

Late toxicities are not uncommon, but through the appropriate use of treatment technology (e.g. IMRT, protons) and close surveillance, they can be minimized and well managed.

Despite the potential acute and late toxicities, long term quality of life returns close to pre-treatment levels for most domains when using modern treatment technologies.

Organ preservation (i.e. no laryngectomy, no neck dissection) is associated with improved quality of life and late toxicity profile.
Questions?

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