Organ at Risk Delineation & Radiation Tolerance

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Tata Memorial Hospital, India
• Radiation therapy is an integral component of treatment

• Increasing use of conformal therapy

• Emphasizes the need for consistent target and OAR delineation

• Outcomes are a function of dose delivered to target and OAR
Radiation Therapy in HN Cancers: Rationale

**INDICATION**
- Definitive
- Adjuvant
- Combined modality
- Palliation

**OUTCOME**
- Effective disease control
- Improves disease outcomes
- Effective organ preservation
- Improved QOL

Risk-benefit trade-off between toxicity and tumor control
Need for Guidelines

• OARs in head-neck have well defined dose-response relationships

• Widespread variation in definition and delineation of several OARs

• Inconsistent and non-congruent reporting of dose-volume parameters

• Resultant dose-volume effects may not be robust and completely reliable

• Rendering comparison of toxicity outcomes across studies difficult

To reduce variability & improve generalizability of NTCP models
3D Variation in delineation of head and neck organs at risk

Purpose:
- To investigate the magnitude of inter-observer variability of OARs with application of delineation Guidelines

Methods:
- IOV among five experienced RO, was studied in a set of 12 HNC patients for the spinal cord, parotid and submandibular glands, thyroid cartilage, and glottic larynx.
- For all OARs, three endpoints were calculated: the Intra-class Correlation Coefficient (ICC), the Concordance Index (CI) and a 3D measure of variation (3D SD).

Results:
- Largest IOV for the glottic larynx (ICC = 0.27, mean CI = 0.37 and 3D SD = 3.9 mm).
- Better agreement was observed for the other OARs (range, ICC = 0.32-0.83, mean CI = 0.64-0.71 and 3D SD = 0.9-2.6 mm).

Conclusions:
- Measures to reduce this variation can be: (1) guideline development, (2) joint delineation review sessions and (3) application of multimodality imaging.
Figure 3 Delineation variation of a parotid gland and a glottic larynx. Left parotid gland and glottic larynx delineations in a typical cranial (a and d), central (b and e) and caudal (c and f) transverse CT slice. Each colour corresponds to one observer.
Differences in delineation guidelines for head and neck cancer result in inconsistent reported dose and corresponding NTCP
Charlotte L. Brouwer *, Roel J.H.M. Steenbakkers, Elske Gort, Marije E. Kamphuis,

Purpose:
• To test the hypothesis that delineation of swallowing organs at risk (SWOARs) based on different guidelines results in differences in dose-volume parameters and subsequent NTCP values for dysphagia-related endpoints.

Materials and methods:
• Nine different SWOARs were delineated according to five different delineation guidelines in 29 patients.
• Concordance Index (CI), dosimetric as well as differences in the subsequent NTCPs were calculated.

Results:
• The median CI was 0.54 for the pharyngeal constrictor muscles, 0.56 for the laryngeal structures and 0.07 for the cricopharyngeal muscle and esophageal inlet muscle.
• The average difference in mean dose to the SWOARs between the guidelines with the largest difference (maxΔD) was 3.5 ± 3.2 Gy.
• A mean ΔNTCP of 2.3 ± 2.7% was found. For two patients, ΔNTCP exceeded 10%.

Conclusions: The majority of the patients showed little differences in NTCPs between the different delineation guidelines. However, large NTCP differences >10% were found in 7% of the patients. For correct use of NTCP models in individual patients, uniform delineation guidelines are of great importance.
Prerequisites for OAR delineation

• Imaging: Choice of optimal imaging

• Good Planning CT
  • Good Immobilization setup
  • Contrast imaging
  • 3mm slice thickness or smaller

• MRI fusion if required

• Optimal CT window settings [Centre (HU) and width (HU) values]:
  • Brain: C35, W100
  • Bone: C450, W1,600
  • H&N: C35, W350
  • Parotid: C840, W370
Contouring Guidelines

Swallowing Apparatus

• Piet Dirix et al.; International Journal of Radiation Oncology*Biology*Physics, Volume 75, Issue 2, October 2009, Pages 385-392

Optic Nerves and Chiasm

Xerostomia

Delineation guidelines for organs at risk involved in radiation-induced salivary dysfunction and xerostomia
Tara A. van de Watera, Henk P. Bijla, Henriëtte E. Westerlaab, Johannes A. Langendijka

Delineation of organs at risk involved in swallowing for radiotherapy treatment planning
Miranda E.M.C. Christianena, Johannes A. Langendijka,b, Henriëtte E. Westerlaab, Tara A. van de Watera, Hendrik P. Bija

Recommendation for a contouring method and atlas of organs at risk in nasopharyngeal carcinoma patients receiving intensity-modulated radiotherapy
Ying Suna, Xiaoli Yua, Wei Luoa, Anne W.M. Leea,b, Joseph Tien Seng Weec,1, Nancy Lee

Organs at risk in the brain and their dose-constraints in adults and in children: A radiation oncologist’s guide for delineation in everyday practice
Silvia Scocciantia,a, Beatrice Dettia, Davide Gaddab, Daniela Gretoa, Ilaria Furfaroa, Fiammetta

CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines
Charlotte L. Brouwera,c, Roel J.H.M. Steenbakkera, Jean Bourhisa, Jean Bourhisb, Wilfried Budachc, Cai Graud, Vincent Grégoiree, Marcel van Herkf, Anne Lee, Philippe Maingonh, Chris Nuttingi, Brian O’Sullivani, Sandro V. Porcedduk, David I. Rosenthal, Nanna M. Sijtsema, Johannes A. Langendijka

2009
2011
2014
2015
CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines

Charlotte L. Brouwer a,a, Roel J.H.M. Steenbakkers a,1, Jean Bourhis b, Wilfried Budach c, Cai Grau d, Vincent Grégoire e, Marcel van Herk f, Anne Lee g, Philippe Maingon h, Chris Nutting i, Brian O'Sullivan j, Sandro V. Porceddu k, David I. Rosenthal l, Nanna M. Sijtsema a, Johannes A. Langendijk a

• This atlas is based mainly on CT scan and MRI used for clarifications

• MRI has a better resolution for soft tissue
  – Glands, muscles and other soft tissues should be contoured by referring to MRI

• CT can more reliably indicate bone boundaries and joint structures
  – TMJ, middle / inner ear and mandible, mainly defined by bone limit, contoured based on CT alone
OARs in Head and Neck Cancers

Consensus Guidelines 2015

25 OAR's
Lacrimal glands

• Lacrimal gland is located supero-lateral to the eye and lies within the pre-septal space

• The gland is moulded at its infero-medial aspect to the globe, giving it a concave outline

• It can be visualized on CT by its location partly encased in the bone and enveloped in low-density fat
Lacrimal Glands: superolateral portion of both orbits
**Optic apparatus: eyes, optic nerves and chiasm**

**Eyes**
Anterior segment: consists of the structures ventral from the vitreous humor, including the cornea, iris, ciliary body, and lens
Posterior segment: consists of the anterior hyaloid membrane and all of the posterior optical structures including the vitreous humor, retina, and choroid

**Optic nerves**
Optic nerve is usually 2–5 mm thick. It has to be contoured all the way from the posterior edge of the eyeball, through the bony optic canal to the optic chiasm.
MRI is recommended for a better delineation of the optic nerve, at least close to chiasm

**Chiasm**
The optic chiasm is located in the subarachnoid space of the suprasellar cistern.
Typically, it is located 1 cm superior to the pituitary gland in the sella turcica.
MRI is recommended for delineation of the optic chiasm. It is demarcated laterally by the internal carotid arteries and inferiorly to the third ventricle
Eyes, optic nerves, and optic chiasma
<table>
<thead>
<tr>
<th>Organ</th>
<th>Standard TPS name</th>
<th>Cranial</th>
<th>Caudal</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Lateral</th>
<th>Medial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal lobe</td>
<td>TemporalLobe⁹</td>
<td>Cranial edge of the sylvian fissure</td>
<td>Base of middle cranial fossa</td>
<td>Temporal bone and sylvian fissure, greater wing of sphenoid</td>
<td>Petrous part of temporal lobe, tentorium of cerebellum, incisura preoccpitalis</td>
<td>Temporal bone</td>
<td>Cavernous sinus, sphenoid sinus, sella turcica, and sylvian fissure including parahippocampal gyrus and hippocampus</td>
</tr>
</tbody>
</table>

Y. Sun et al. / Radiotherapy and Oncology 110 (2014) 390–397
<table>
<thead>
<tr>
<th>Organ</th>
<th>Standard TPS name [20]</th>
<th>Cranial edge of the sylvian fissure</th>
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</tr>
</tbody>
</table>

**Diagram:**
- **TemporalLobe_R:** Temporal lobe on the right side.
- **TemporalLobe_L:** Temporal lobe on the left side.
- **BrainStem:** The brainstem is highlighted in the center.

**Annotations:**
- **Blue:** Represents the **TemporalLobe_R**.
- **Red:** Represents the **TemporalLobe_L**.
- **Green:** Represents the **BrainStem**.
Pituitary gland and Brainstem

Pituitary

The pituitary gland is a very small OAR, cannot be identified easily on CT. Alternatively, however, the inner part of the sella turcica can be used as surrogate anatomical bony structure. The borders of the pituitary gland can be defined best in the sagittal view.

Brainstem

The cranial border of the brainstem was defined as the bottom section of the lateral ventricles, the caudal border as the tip of the dens of C2 (cranial border of the spinal cord). MRI is recommended for delineation of the brainstem. The bottom section of the lateral ventricles is clearly visible on both CT and MRI.
### Anatomic boundaries of the temporal lobe, parotid gland, spinal cord, middle ear and inner ear in NPC.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Standard TPS name [20]</th>
<th>Cranial</th>
<th>Caudal</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Lateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>BrainStem</td>
<td>Bottom</td>
<td>Tip of dens</td>
<td>Post. edge of prepon.</td>
<td>Ant. edge of forth</td>
<td>Posterior cerebral</td>
</tr>
</tbody>
</table>

*Image of MRI showing pituitary and brainstem.*
Brainstem continues inferiorly as pons & medulla till C2 vertebra
Cochlea

- Embedded in the temporal bone
- Located anterior and lateral to the internal auditory canal
- Best identified on bone window setting

Adopted from Pacholka et al, AJCO 2005
Cochlea: use the bone window for delineation
Cochlea and internal auditory canal should be individually delineated and named.

Tympanic cavity, bony part of Eustachian tube should be individually delineated and named.
Spinal Cord (for head neck tumours)

• Delineated as the true spinal cord, not the spinal canal or thecal sac.
• Cranial border is defined at the tip of the dens C2 (the lower border of the brainstem), and the caudal border at the upper edge of T3.
• With inferiorly extending tumours (primary or lymph nodes) extend the spinal cord contours 5cm caudal to the lowest slice of the PTV.
• Contour is best verified on the mid-sagittal reformatted cuts
Extended oral cavity

For simplicity and consistency, the extended oral cavity structure was defined posterior to the internal arch of the mandible and maxilla.

Lips

The lip contour extends from the inferior margin of the nose to the superior edge of the mandibular body.

The mucosa anterior to mandible and maxilla is included in the lips.

Buccal mucosa

Delineated as oral mucosa that is located lateral to the mandible and maxilla.
# Extended Oral Cavity, Lips, Buccal Mucosa

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Remarks</th>
<th>Anatomic boundaries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cranial</td>
</tr>
<tr>
<td>Extended oral cavity</td>
<td>Posterior to mandible and maxilla, no inner surface of the lips</td>
<td>Hard palate mucosa and mucosal reflections near the maxilla</td>
</tr>
<tr>
<td>Lips</td>
<td></td>
<td>Hard palate (lateral), anterior nasal spine (at the midline)</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td></td>
<td>Bottom of maxillary sinus</td>
</tr>
</tbody>
</table>
Oral Mucosal Delineation
# Major Salivary Glands

Adopted from van de Water et al, Radiother Oncol 2009

<table>
<thead>
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<th>Anatomic boundaries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cranial</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>Include carotid artery, retromandibular vein and extracranial facial nerve.</td>
<td>External auditory canal, mastoid process</td>
</tr>
</tbody>
</table>
Parotid Gland
### Major Salivary Glands

| Submandibular gland | Med. pterygoid m., mylohyoid m. | Fatty tissue | Lat. Surface mylohyoid m., hyoglossus m. | Parapharyngeal space, sternocleidomastoid m. | Med. surface med. pterygoid m., med. surface mandibular bone, platysma | Lat. surface mylohyoid m., hyoglossus m., superior and middle pharyngeal constrictor m., anterior belly of the digastric m. |

*Adopted from van de Water et al, Radiother Oncol 2009*
Submandibular Salivary Gland
<table>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Cranial</td>
</tr>
<tr>
<td>Supraglottic larynx</td>
<td>Tip of epiglottis</td>
<td>Cranial</td>
</tr>
<tr>
<td>Glottic area</td>
<td>Cranial edge of arytenoid cartilages</td>
<td>Caudal</td>
</tr>
<tr>
<td>Cricopharyngeal inlet</td>
<td>Caudal edge of arytenoid cartilages</td>
<td></td>
</tr>
<tr>
<td>Cervical esophagus</td>
<td>1 cm caudal to the lower edge of the cricoid cartilage</td>
<td>Caudal</td>
</tr>
<tr>
<td>Supraglottic larynx</td>
<td>Tip of epiglottis</td>
<td>Cranial edge of arytenoid cartilages</td>
</tr>
<tr>
<td>Glottis area</td>
<td>Cranial edge of arytenoid cartilages</td>
<td>Caudal edge of ant. part of thyroid cartilage</td>
</tr>
</tbody>
</table>
Cricopharyngeal Inlet

| Cricopharyngeal inlet | Caudal edge of arytenoid cartilages | 1 cm caudal to the lower edge of the cricoid cartilage | Tracheal lumen | Vertebral body |
Cervical Esophagus

Cervical esophagus

1 cm caudal to the lower edge of the cricoid cartilage

Caudal edge of C7
DYSPHAGIA AFTER CHEMORADIOOTHERAPY FOR HEAD-AND-NECK SQUAMOUS CELL CARCINOMA: DOSE-EFFECT RELATIONSHIPS FOR THE SWALLOWING STRUCTURES

PIET DIRIX, M.D.,† SARAH ABBEEL, M.D.,* BIANCA VANSTRAELEN,* ROBERT HERMANS, M.D. PH.D.,† AND SANDRA NUYTS, M.D. PH.D.*

Departments of *Radiation Oncology, and †Radiology, Leuven Kankerinstituut, University Hospitals Leuven, campus Gasthuisberg, Leuven, Belgium
Pharyngeal Constrictor Muscles (PCM)

- Variable guidelines for delineation are present in the literature
- PCM defined as a single OAR for simplicity and reproducibility
- Cranial border was defined as the caudal tip of pterygoid plates
- Caudal border as the lower edge of the cricoid cartilage
- A thickness of 3 mm was assumed for pragmatic reasons
- For research purposes, the PCM muscles may be subdivided further
Pharyngeal Constrictor Muscles
Mandible
Thyroid Gland

- Consists of two pyramidal lobes laterally connected by isthmus in midline
- Lies below the thyroid cartilage wrapping around the trachea
- Significant contrast uptake compared to surrounding soft tissues
Brachial Plexus: Literature

1. Identify and contour C5, T1, and T2.
2. Identify and contour the subclavian and axillary neurovascular bundle.
3. Identify and contour anterior and middle scalene muscles from C5 to insertion onto the first rib.
4. To contour the brachial plexus OAR use a 5-mm diameter paint tool.
5. Start at the neural foramina from C5 to T1; this should extend from the lateral aspect of the spinal canal to the small space between the anterior and middle scalene muscles.
6. For CT slices, where no neural foramen is present, contour only the space between the anterior and middle scalene muscles.
7. Continue to contour the space between the anterior and middle scalene muscles; eventually the middle scalene will end in the region of the subclavian neurovascular bundle.
8. Contour the brachial plexus as the posterior aspect of the neurovascular bundle inferiorly and laterally to one to two CT slices below the clavicular head.
9. The first and second ribs serve as the medial limit of the OAR contour.

Hall et al, IJROBP, 2008
<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial plexus</td>
<td>If the brachial plexus is wrapped around the vascular bundle on the most inferior slices, the vascular structure is included in the contour</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomic boundaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
</tr>
<tr>
<td>Cranial</td>
</tr>
</tbody>
</table>

![Image of anatomical structures](image-url)
RADIATION TOLERANCES
## Radiation effects on Normal tissue (tolerance): structural organization of the tissue/FSUs

<table>
<thead>
<tr>
<th>SERIAL ORGAN</th>
<th>PARALLEL ORGAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSUs are arranged in a series, like the links of a chain.</td>
<td>FSUs are arranged in a parallel manner</td>
</tr>
<tr>
<td>Integrity of each FSU is critical to organ function, and elimination of any one FSU results in a measurable probability of a complication.</td>
<td>Functional damage will not occur until a critical number of FSUs are inactivated by irradiation.</td>
</tr>
<tr>
<td>Radiation damage to such tissues show a binary response -- with a threshold dose below which there is normal function and above which there is loss of function.</td>
<td>Radiation damage to such tissues show a graded response—increasing severity of functional impairment with increasing dose</td>
</tr>
<tr>
<td>e.g. spinal cord</td>
<td>e.g. liver, kidney, lungs</td>
</tr>
</tbody>
</table>
Dose vs Complications - Volume effect

% Probability of Complications

Dose, (Gy)
“The Emami paper” (1991)

- Review of Committee of experts
- Known data, provide guidelines
- Some clinical data to suggest tissue tolerance
  - Comparatively poor ability to deliver dose
  - Poor ability to measure dose actually delivered
- Some laboratory data (cell cultures, etc.)
- Some data “made up” based upon best guess principles
Emami “Out of Date?”

- Move from 2D to 3D treatment planning
- Higher energy beams/better penetration
- Improved ability to measure dose
- Increased use combined chemo radiotherapy
- Numerous additional studies of tissue tolerance subsequently published

QUANTEC: Quantitative Analysis of Normal Tissue Effects in the Clinic

- Large committee of experts (n=57)
- Convened by ASTRO / AAPM
- Updated guidelines published in Red Journal supplement (vol 76, No. 3)
- 16 organ-specific papers
- Several “general principle” papers
Why QUANTEC?

- To provide the treatment planner information to predict the risk of a normal tissue injury for competing 3d dose distributions

- Modern techniques deliver near uniform doses to the target volume

- Dose distribution in the surrounding normal tissues is variable

AIM:

- To produce practical guidance allowing the clinician to reasonably (though not necessarily precisely) categorize toxicity risk based on dose–volume parameters or model results

The main paradigm shift → two dimensional to three dimensional planning
## Radiation Sensitivity/Tolerance Dose Of Skin

<table>
<thead>
<tr>
<th>Volume</th>
<th>10 cm²</th>
<th>30 cm²</th>
<th>100 cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD 5/5</td>
<td>-</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>TD 50/5</td>
<td>-</td>
<td>-</td>
<td>65</td>
</tr>
</tbody>
</table>

**End point telangiectasia:** Emami et al IJROBOP Vol 21 p 109-122

<table>
<thead>
<tr>
<th>Volume</th>
<th>10 cm²</th>
<th>30 cm²</th>
<th>100 cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD 5/5</td>
<td>70</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>TD 50/5</td>
<td>-</td>
<td>-</td>
<td>70</td>
</tr>
</tbody>
</table>

**End point necrosis:** Emami et al IJROBOP Vol 21 p 109-122

- Conventional doses of 60Gy are readily tolerated by the skin if they are spread out over 6-8 weeks.
### Radiation Sensitivity/Tolerance Dose Of Parotid

<table>
<thead>
<tr>
<th>Volume</th>
<th>TD 5/5</th>
<th>TD 50/5</th>
<th>TD 100/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>32</td>
<td>46</td>
<td>50</td>
</tr>
</tbody>
</table>

End point: xerostomia
Emami et al IJROBOP Vol 21 p 109-122

### Volume Dose Rate (%) Note

<table>
<thead>
<tr>
<th>Volume</th>
<th>Dose</th>
<th>Rate (%)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>B/L</td>
<td>Mean dose &lt; 25</td>
<td>&lt; 20</td>
<td>For combined parotids</td>
</tr>
<tr>
<td>U/L</td>
<td>Mean dose &lt; 20</td>
<td>&lt; 20</td>
<td>For single parotid</td>
</tr>
<tr>
<td>B/L</td>
<td>Mean dose &lt; 39</td>
<td>&lt; 50</td>
<td>For combined parotids</td>
</tr>
</tbody>
</table>

End point: Long term parotid salivary function reduced to <25% of pre-RT level -QUANTEC
Results:

• **Univariate analysis**: significant predictors of the XQ score → OC, PG, and SMG mean doses and the baseline XQ score, time since RT, and PG saliva flow rates.

• **Multivariate analyses** (after adjusting for PG/SMG doses): OC mean dose ($p < .0001$), interval from RT ($p < .0001$), and stimulated PG saliva ($p < .0025$) were significant predictors of the XQ scores.

• OC mean dose of $<40$Gy and contralateral SMG mean dose of $<50$Gy were associated with low xerostomia scores.

Conclusion:

• **These results support efforts to spare all the salivary glands by IMRT, beyond the PGs alone.**
Fig. 3. Plots of the ratios of submandibular salivary glands (SMG) saliva flow rates relative to pretherapy baseline flow rates vs. mean SMG doses at various post-radiotherapy time points (1, 3, 6, 12, 18, and 24 months). Note the logarithmic scale of the flow rate ratios; the horizontal line at 0 represents values near baseline. (A) Stimulated, (B) unstimulated salivary flow ratios.
Fig. 4. Mean submandibular salivary glands doses vs. Grade 4 toxicity at 12 months (salivary flow rate <25% of baseline pre-radiotherapy). (A) Stimulated, (B) unstimulated. The dots are the average observed toxicities of patients grouped in mean dose clusters at 10-Gy intervals. The bars represent 95% CI.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate model</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>p</td>
<td>Estimate</td>
</tr>
<tr>
<td>Baseline XQ score</td>
<td>0.37</td>
<td>0.17</td>
<td>.03</td>
<td>0.11</td>
</tr>
<tr>
<td>Oral cavity mean dose</td>
<td>1.3</td>
<td>0.20</td>
<td>&lt;.001</td>
<td>1.2</td>
</tr>
<tr>
<td>PG mean dose</td>
<td>0.77</td>
<td>0.29</td>
<td>.008</td>
<td>-0.27</td>
</tr>
<tr>
<td>SMG mean dose</td>
<td>0.72</td>
<td>0.21</td>
<td>&lt;.001</td>
<td>0.082</td>
</tr>
<tr>
<td>Stimulated parotid saliva rate</td>
<td>-18</td>
<td>4.7</td>
<td>&lt;.001</td>
<td>-16</td>
</tr>
<tr>
<td>Unstimulated parotid saliva rate</td>
<td>-37</td>
<td>18</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Stimulated SMG saliva rate</td>
<td>-11</td>
<td>21</td>
<td>.6</td>
<td></td>
</tr>
<tr>
<td>Unstimulated SMG saliva rate</td>
<td>-27</td>
<td>40</td>
<td>.5</td>
<td></td>
</tr>
<tr>
<td>AJCC stage III vs. IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>5.8</td>
<td>6.9</td>
<td>.4</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.20</td>
<td>0.28</td>
<td>.5</td>
<td></td>
</tr>
<tr>
<td>Time (categorical)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Purpose: Assess SMG dose–response relationships and implications for sparing these glands by IMRT.

Methods:

• 148 patients receiving IMRT underwent periodic salivary flow rate measurement from SMG starting before RT and up to 2 years after RT.
• Correlations of flow rates and mean SMG doses were modelled throughout all time points.

Results:

• Salivary flow rates decreased exponentially as mean dose increased up to 39Gy threshold, and then plateaued near zero.
• At mean doses <39Gy, but not higher, flow rates recovered over time.

SMG salivary flow rates depended on mean dose with recovery over time up to a threshold of 39Gy.
Dose distributions through oral mucosa need to be kept under control, preventing, where possible, oral mucosa $V_{9.5-V10}\text{ Gy/week}$ exceeding 50–60 cm$^3$, anterior oral cavity $V_{30}$ exceeding 65% and anterior oral cavity $V_{35}$ exceeding 35%.

In a partially overlapping patient population, it has been shown that OM weekly $V_{9.5}$ also predicts the need and the dependence on a PEG tube during exclusive IMRT for oropharyngeal carcinoma.
Eyes

• Eyes are a major dose limiting structure

• The lens is very sensitive to radiation
  • Cataract formation is major effect
    • Seen with doses as low as 2 Gy
    • Very likely at 4 gray

• Major side effect of RT to head and neck
Cataract:

- Radiation damages the germinative zone of lens epithelial cell DNA.
- Direct cytoplasmic effects like disruption of membrane channels.
- Protein cross-linking.
- Ion pump abnormalities.
- Abnormal cell of lens epithelium called as Wedl cell migrate posteriorly and form a posterior sub-capsular opacity.

Latent period

- 2.5 – 6.5 Gy = average period = 8 years
- 6.5 – 11.5 Gy = average period = 4 years

<table>
<thead>
<tr>
<th>Duration of RT</th>
<th>TD 5/5</th>
<th>TD 50/5</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lens</td>
<td>10</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Retina</td>
<td>45</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>
### Optic Nerve/ Chiasm

**Technique** | **Dose** | **Rate (%)**
--- | --- | ---
3 D-CRT | Dmax < 55 | < 3
3 D-CRT | Dmax 55-60 | 3 – 7
3 D-CRT | Dmax > 60 | > 7 – 20
SRS | Dmax < 12 | < 10

**Emami et al:**
- No partial volume effect
- TD 5/5 - 50Gy
- TD 50/5 – 65Gy
- Partial volume tolerances not mentioned
- Emami et al. Value appears to be inaccurate

**QUANTEC**

**Issues:**
- Confounders in scoring toxicity
- Difficulty in defining volumes
- Unknown effect of comorbidities, concurrent chemotherapy and targeted therapy
Central Nervous System

• CNS is considered quite radio-resistant in adults.
  • Development continues to 12 years of age therefore whole brain dose can reduce development
  • Glial cells and vascular endothelium are the critical cells of interest.

• RT usually avoided in children.

• Increasing volume or dose increases the effects
  • Large volumes irradiated above 40 Gray lead to decreased function.
Threshold for radiation necrosis is 57.6 Gy with conventional fractionation. Leibel S A. 1991

Frequency depends upon fraction size larger than 2.2-2.5 Gy Aristizabal S et al IJROBP 1977
Spinal Cord

Radiation myelopathy changes

• **Type I** – involves only the white matter parenchyma or has only minor vascular changes assumed to be insufficient to produce symptoms.

• **Type II** – predominately vascular with any white matter damage secondary to it.

• **Type III** - both white matter parenchyma and vasculature damage.
Diagnostic criteria for radiation myelopathy

- Other causes must be ruled out – tumor progression, mets, trauma, central neurological deficits

- Presentation should be consistent with radiation myelopathy i.e. this eliminates cases with upper extremity symptoms in the absence of lower extremity symptoms

- The dose and time to expression of injury must be consistent with a spinal cord radiation injury. i.e. duration less than 6 months and dose less than 50Gy are not likely to be radiation myelopathy related unless there was any predisposing factors like chemotherapy, previous CNS damage, vascular changes.
## Radiation Sensitivity/Tolerance Dose Of Spinal Cord

<table>
<thead>
<tr>
<th>Distance (cm)</th>
<th>TD5/5</th>
<th>TD50/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>70</td>
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<tr>
<td>20</td>
<td>47</td>
<td>-</td>
</tr>
</tbody>
</table>

Emami et al, IJROBOP Vol 21 p 109-122

### Dose Parameter and Rate (%)

<table>
<thead>
<tr>
<th>Technique</th>
<th>Dose Parameter</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 D-CRT</td>
<td>Dmax = 50</td>
<td>0.2</td>
</tr>
<tr>
<td>3 D-CRT</td>
<td>Dmax = 60</td>
<td>6</td>
</tr>
<tr>
<td>3 D-CRT</td>
<td>Dmax = 69</td>
<td>50</td>
</tr>
<tr>
<td>SRS (single fraction)</td>
<td>Dmax = 13</td>
<td>1</td>
</tr>
<tr>
<td>SRS (hypofraction)</td>
<td>Dmax = 20</td>
<td>1</td>
</tr>
</tbody>
</table>

QUANTEC
Sensorineural hearing loss (SNHL) is defined as a clinically significant increase in bone conduction threshold (BCT) at the key human threshold frequency of 0.5 – 4.0 kHz as seen in Pure Tone Audiometry.

Precise mechanism is obscure and contributed also by the concurrent chemotherapy.

The recommendation to contour the cochlea and IAC individually is based on inner ear function.

Hearing loss:

• Grade – I = <10 db loss in one or more frequencies
• Grade – II = 10-15 db loss in one or more frequencies
• Grade – III = 15-20 db loss in one or more frequencies
• Grade – IV = >20 db loss in one or more frequencies
**Cochlea**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Dose</th>
<th>Rate (%)</th>
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</thead>
<tbody>
<tr>
<td>3 D-CRT</td>
<td>Mean dose &lt; 45</td>
<td>&lt;30</td>
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<tr>
<td>SRS</td>
<td>Prescription dose &lt; 14</td>
<td>&lt; 25</td>
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</table>

**QUANTEC**

<table>
<thead>
<tr>
<th>TD 5/5</th>
<th>TD 5/50</th>
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</thead>
<tbody>
<tr>
<td>60</td>
<td>70</td>
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</tbody>
</table>

Emami et al IJROBOP Vol 21 p 109-122

**QUANTEC recommendations** ➔ pre and post RT documentation, started 6 months after RT and then biannually thereafter, 4 frequencies BCTs should be used, higher frequencies are first affected.
<table>
<thead>
<tr>
<th>OAR</th>
<th>EMAMI</th>
<th>QUANTEC</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TD 5/5 Volume</td>
<td>TD 50/5 Volume</td>
</tr>
<tr>
<td></td>
<td>1/3 2/3 3/3</td>
<td>1/3 2/3 3/3</td>
</tr>
<tr>
<td>Brain</td>
<td>60 50 45     75 65</td>
<td>60</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>60 53 50 - - 65</td>
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<tr>
<td>Spinal Cord</td>
<td>50 50 47 70 70 70</td>
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<tr>
<td>Optic nerve / chiasm</td>
<td>- - 50 - - - 65</td>
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<tr>
<td>Cochlea</td>
<td>- - - - - - - - -</td>
<td>Mean dose &lt;45</td>
</tr>
<tr>
<td>OAR</td>
<td>TD 5/5 Volume</td>
<td>TD 50/5 Volume</td>
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<td>----------------------</td>
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<td>---------------</td>
</tr>
<tr>
<td></td>
<td>1/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Eye Lens</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
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<tr>
<td>Eye Retina</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear mid/external</td>
<td>55</td>
<td>55</td>
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</tbody>
</table>
Results:

• Significant correlations were observed between video fluoroscopy-based aspirations and the mean doses to the PC and GSL, as well as the partial volumes of these structures receiving 50–65Gy.

• All patients with aspirations received mean PC doses >60Gy or PC V65 >50%, and GSL V50 >50%.

• All 3 patients with strictures had PC V70 >50%.

• Worsening patient reported liquid swallowing was correlated with mean PC (p = 0.05) and oesophageal (p = 0.02) doses.

• Worsening patient-reported solid swallowing correlated with only mean PC doses (p = 0.04).

Conclusions: These dose-volume-effect relationships provide initial IMRT optimization goals and motivate further efforts to reduce swallowing structures doses to reduce dysphagia and aspiration.
<table>
<thead>
<tr>
<th>OAR</th>
<th>EMAMI</th>
<th>QUANTEC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TD 5/5 Volume</td>
<td>TD 50/5 Volume</td>
</tr>
<tr>
<td></td>
<td>1/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Parotid</td>
<td>-</td>
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<td>Pharynx</td>
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<td>Larynx</td>
<td>79</td>
<td>70</td>
</tr>
<tr>
<td>-</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>TMJ</td>
<td>65</td>
<td>60</td>
</tr>
</tbody>
</table>
Osteoradionecrosis (ORN)

- **Defined as** a condition in which irradiated bone becomes devascularized and exposed through the overlying skin or mucosa, persisting without healing for at least 3 months.

- **Ascribed to** radiation arteritis, which leads to the development of a hypo cellular, hypo vascular, and hypoxic environment.

- **Incidence** = 5% to 22% (mean, 10%–15%)

- Recent studies have shown a decrease in incidence to <5%.

- **Latent period** = Early ORN (latent period less than 2 years)

- Late-onset ORN develops several years after radiation.
Risk factors for development of ORN

• Dose more than 60Gy
• Dentulous patients who require tooth extraction after RT.
• More common after BRT than EBRT
• More common after trauma or surgery following RT.
• Male : Female = 1.6 : 1
• White population
• Tumor size, stage, proximity to bone.
• Continued smoking and alcohol consumption.

Take home message

- Guidelines available for most organs
- List of essential minimums lacking
- Good practice to delineate as many to report doses received vs outcomes

- Tolerance described: Need more clinical correlation
- Understand: Function of organ type, RT parameters
THANKYOU