CLINICAL TRIALS
REDUCING
RADIATION INDUCED
XEROSTOMIA & DYSPHAGIA
IN HEAD & NECK CANCERS

Dr. KANHU CHARAN PATRO

11/7/2017
THAT PANIPURI MOMENT

DOCTOR: WHAT TREATMENT YOU HAVE GIVEN, I AM NOT ABLE TO EAT PANIPURI.
1. TRISMUS
2. DYSGUESIA
3. XEROSTOMIA
4. DYSPHAGIA
ZEROING THE XEROSTOMIA & DISCARDING THE DYSPHAGIA
PARSPORT STUDY

PASSPORT

2011

THE LANCET Oncology
The source
Fig. 2. Major salivary glands: the parotid glands are depicted in brown (left) and green (right), the submandibular glands are depicted in blue (the left one is brighter than the right one) and the sublingual glands are coloured dark blue (anterior part oral cavity). (1) Genioglossus m., (2) mylohyoid m., (3) hyoglossus m., (4) posterior belly digastric m., (5) anterior belly digastric m., (6) geniohyoid m., (7) medial pterygoid m., (8) lateral pterygoid m., (9) pharyngeal constrictor m., (10) sternocleidomastoid m., (11) platysma, (12) masseter m., (13) parapharyngeal space, (14) styloid process, (15) mandibular bone.
Fig. 5. Inner surface of the lower and upper lip plus cheek structure: (a) depicts the caudal border of the lower lip; (b) the cranial border of the lower lip and caudal border of the upper lip; (c) depicts the cranial border of the upper lip; (d) the upper edge of the inner surface cheek structure (transition between alveolar process maxilla – maxillary sinus); (e) the fatty tissue present posterior to the orbicularis oris muscle. (1) Orbicularis oris, (2) tongue, (3) fatty tissue, (4) hard palate, (5) mandibular body, (6) maxillary bone, (7) anterior nasal spine, (8) buccinator m., (9) levator anguli oris/risorius m., (10) alveolar process maxilla, (11) maxillary sinus and (12) depressor anguli oris muscle.
Fig. 4. Soft palate: the soft palate structure is depicted by the green contour. The sagittal view is depicted in the upper left corner, displaying the cranial border of the soft palate: the nasopharyngeal mucosal space/air lumen and the hard palate (see corresponding transversal plane). The two lower left pictures display the same axial CT-slice: one including and one not including the delineated soft palate structure. (1) Tongue, (2) medial pterygoid m., (3) superior pharyngeal constrictor m., (4) uvula, (5) hard palate, (6) medial pterygoid plate, (7) pharyngeal lumen, (8) parapharyngeal space, (9) pterygoid process and (10) level of the palatine tonsil.
<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Cranial</th>
<th>Caudal</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Lateral</th>
<th>Medial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Mastoid Process</strong></td>
<td></td>
<td>Medial and Lateral Pterygoid M.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sub mandibular gland</strong></td>
<td><strong>Medial Pterygoid M,</strong> Mylohyoid M.</td>
<td><strong>Fatty tissue</strong></td>
<td>Lat. surface Mylohyoid M., Hyoglossus M.</td>
<td>Parapharyngeal space, Med. surface Medial Pterygoid M., Med. surface Mandibular Bone, Platsma</td>
<td>Medial surface Mylohyoid M., Hyoglossus M., Superior &amp; Middle Pharyngeal Constrictor M., Anterior belly of the Digastric M.</td>
<td></td>
</tr>
<tr>
<td><strong>Sub lingual gland</strong></td>
<td><em>(Mucous membrane covering the floor of the mouth), crossing lingual septum – Intrinsic Tongue Muscles</em></td>
<td><strong>Ant. part Mylohyoid M,</strong> Geniohyoid M.</td>
<td>Ant. part surface Mandibular bone, Mylohyoid M.</td>
<td>Hyoglossus M.</td>
<td>Ant. part Med. surface Mandibular Bone, Mylohyoid M.</td>
<td>Genioglossus m.</td>
</tr>
</tbody>
</table>
Methods preventing xerostomia
Unstimulated salivary flow

To collect unstimulated whole saliva, the patient drools passively into the collection tube for five minutes.
Stimulated salivary flow
COLLECTION OF SALIVA FROM INDIVIDUAL GLANDS

Figure 6. A modified Carlson-Crittenden device for collecting parotid gland saliva.

Figure 7. A custom-made Wolff saliva collector for submandibular and sublingual gland saliva collection.
# SIALOMETRY

**Table 1. Sialometry.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Salivation at rest (ml/min)</th>
<th>Stimulated salivation (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyposalivation</td>
<td>&lt; 0.1</td>
<td>&lt; 0.7</td>
</tr>
<tr>
<td>Low flow</td>
<td>0.1–0.25</td>
<td>0.7–1.0</td>
</tr>
<tr>
<td>Normal</td>
<td>0.25–0.35</td>
<td>1.0–3.0</td>
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</tbody>
</table>
Unstimulated and stimulated whole saliva flow changes during and after radiotherapy in the head and neck region.

# XEROSTOMIA QUESTIONNAIRE

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Communication</td>
<td>1 not at all</td>
</tr>
<tr>
<td>Eating</td>
<td>2 slightly</td>
</tr>
<tr>
<td>Normal times</td>
<td>3 moderately</td>
</tr>
<tr>
<td>Sleeping</td>
<td>4 a lot</td>
</tr>
</tbody>
</table>

<p>| Frequency of taking water while eating |
| Frequency of taking water at normal times |
| Frequency of sleeping problems due to dryness |</p>
<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Site</th>
<th>Stage</th>
<th>Radiotherapy technique</th>
<th>Proposed constraint (mean dose)</th>
<th>Objective endpoint</th>
<th>Subjective endpoint</th>
<th>QoL endpoint</th>
<th>Patients without locoregional control, n*</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>All</td>
<td>II-IV</td>
<td>3D/IMRT</td>
<td>≤32 Gy</td>
<td>SF</td>
<td>XQ</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>84</td>
<td>All</td>
<td>II-IV</td>
<td>3D/IMRT</td>
<td>≤26 Gy</td>
<td>SF</td>
<td>XQ</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>All</td>
<td>II-IV</td>
<td>3D</td>
<td>≤26 Gy</td>
<td>SF</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>39</td>
<td>All</td>
<td>II-IV</td>
<td>3D</td>
<td>≤20 Gy</td>
<td>SGS</td>
<td>VAS</td>
<td>-</td>
<td>28</td>
</tr>
<tr>
<td>18</td>
<td>All</td>
<td>II-IV</td>
<td>IMRT</td>
<td>≤26 Gy</td>
<td>SGS</td>
<td>-</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>23</td>
<td>All</td>
<td>II-IV</td>
<td>IMRT</td>
<td>≤26 Gy</td>
<td>SF</td>
<td>XQ</td>
<td>Yes</td>
<td>21</td>
</tr>
<tr>
<td>17</td>
<td>OP/NP</td>
<td>II-IV</td>
<td>IMRT</td>
<td>≤25.5 Gy</td>
<td>SF</td>
<td>-</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>65</td>
<td>All</td>
<td>II-IV</td>
<td>3D/IMRT</td>
<td>≤25.8 Gy</td>
<td>SF</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>47</td>
<td>All</td>
<td>II-IV</td>
<td>IMRT</td>
<td>≤26 Gy</td>
<td>SF</td>
<td>XQ</td>
<td>Yes</td>
<td>-</td>
</tr>
</tbody>
</table>

3D=three-dimensional, IMRT=intensity-modulated radiotherapy, SF=salivary flow, XQ=xerostomia questionnaire, SGS=salivary gland scintigraphy, VAS=visual analogue scale, OP=oropharynx, NP=nasopharynx. All=all subsites. *At time of analysis. QoL=quality of life.

Table 1: Overview of prospective phase 1-2 trials on parotid-sparing radiotherapy
Tolerance dose

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted) *(Continued)*

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume segmented</th>
<th>Irradiation type (partial organ unless otherwise stated)</th>
<th>Endpoint</th>
<th>Dose (Gy), or dose/volume parameters†</th>
<th>Rate (%)</th>
<th>Notes on dose/volume parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral whole parotid glands</td>
<td>3D-CRT</td>
<td>Long term parotid salivary function reduced to &lt;25% of pre-RT level</td>
<td>Mean dose &lt;39</td>
<td>&lt;50</td>
<td>For combined parotid glands (per Fig. 3 in paper)</td>
<td></td>
</tr>
<tr>
<td>Pariotid</td>
<td>Bilateral whole parotid glands</td>
<td>3D-CRT</td>
<td>Long term parotid salivary function reduced to &lt;25% of pre-RT level</td>
<td>Mean dose &lt;25</td>
<td>&lt;20</td>
<td>For combined parotid glands</td>
</tr>
<tr>
<td>Unilateral whole parotid gland</td>
<td>3D-CRT</td>
<td>Long term parotid salivary function reduced to &lt;25% of pre-RT level</td>
<td>Mean dose &lt;20</td>
<td>&lt;20</td>
<td>For single parotid gland. At least one parotid gland spared to &lt;20 Gy</td>
<td></td>
</tr>
</tbody>
</table>

QUANTITATIVE ANALYSES OF NORMAL TISSUE EFFECTS IN THE CLINIC (QUANTEC) DATA
# LENT SOMA SCALE XEROSTOMIA

**Table 2. LENT SOMA scale (LSS) for salivary glands**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Subjective</th>
<th>Objective</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Occasional dryness</td>
<td>Scant saliva</td>
<td>Occasional saliva substitute or water, sugarless candy or gum, sialogogues</td>
</tr>
<tr>
<td>2</td>
<td>Partial but persistent dryness</td>
<td>Absence of moisture, sticky, viscous saliva</td>
<td>Frequent saliva substitute or water, sugarless candy or gum, sialogogues</td>
</tr>
<tr>
<td>3</td>
<td>Complete dryness non-debilitating</td>
<td>Absence of moisture, coated mucosa</td>
<td>Needs saliva substitute or water in order to eat, sugarless candy or gum, sialogogues</td>
</tr>
<tr>
<td>4</td>
<td>Complete dryness debilitating</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial

Christopher M Nutting, James P Morden, Kevin J Harrington, Teresa Guerrero Urbano, Shreerang A Bhide, Catharine Clark, Elizabeth A Miles, Aisha B Miah, Kate Newbold, MaryAnne Taney, Fawzi Adab, Sarah J Jefferies, Christopher Scrase, Beng K Yap, Roger P A'Hern, Mark A Sydenham, Marie Emson, Emma Hall, on behalf of the PARSPORT trial management group

Summary

Background Xerostomia is the most common late side-effect of radiotherapy to the head and neck. Compared with conventional radiotherapy, intensity-modulated radiotherapy (IMRT) can reduce irradiation of the parotid glands. We assessed the hypothesis that parotid-sparing IMRT reduces the incidence of severe xerostomia.
Parotid Sparing IMRT versus Conventional RT in Head and Neck Cancer (PARSPORT): A phase 3 multicentric randomized controlled trial.
Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial

Christopher M Nutting, James PMorden, Kevin J Harrington, Teresa Guerrero Urbano, Shreerag A Bhide, Catherine Clark, Elizabeth A Miles, Aloha B Miah, Kate Newbold, Mary Anne Tanay, Fawzi Adab, Sarah J Jeffries, Christopher Sorace, Beng K Yap, Roger P A’Hern, Mark A Sydenham, Marie Emson, Emma Hall, on behalf of the PARSPORT trial management group

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Methods We undertook a randomised controlled trial between Jan 21, 2003, and Dec 7, 2007, that compared conventional radiotherapy (control) with parotid-sparing IMRT. We randomly assigned patients with histologically confirmed pharyngeal squamous-cell carcinoma (T1–4, N0–3, M0) at six UK radiotherapy centres between the two radiotherapy techniques (1:1 ratio). A dose of 60 or 65 Gy was prescribed in 30 daily fractions given Monday to Friday. Treatment was not masked. Randomisation was by computer-generated permuted blocks and was stratified by centre and tumour site. Our primary endpoint was the proportion of patients with grade 2 or worse xerostomia at 12 months, as assessed by the Late Effects of Normal Tissue (LENT SOMA) scale. Analyses were done on an intention-to-treat basis, with all patients who had assessments included. Long-term follow-up of patients is ongoing. This study is registered with the International Standard Randomised Controlled Trial register, number ISRCTN48243537.

Findings 47 patients were assigned to each treatment arm. Median follow-up was 44·0 months (IQR 30·0–59·7). Six patients from each group died before 12 months and seven patients from the conventional radiotherapy and two from the IMRT group were not assessed at 12 months. At 12 months xerostomia side-effects were reported in 73 of 82 alive patients, grade 2 or worse xerostomia at 12 months was significantly lower in the IMRT group than in the conventional radiotherapy group (25 [74%; 95% CI 56–87] of 34 patients given conventional radiotherapy vs 15 [38%; 23–55] of 39 given IMRT, p=0·0027). The only recorded acute adverse event of grade 2 or worse that differed significantly between the treatment groups was fatigue, which was more prevalent in the IMRT group (18 [41%; 99% CI 23–61] of 44 patients given conventional radiotherapy vs 35 [74%; 55–89] of 47 given IMRT, p=0·0015). At 24 months, grade 2 or worse xerostomia was significantly less common with IMRT than with conventional radiotherapy (20 [83%]; 95% CI 63–95) of 24 patients given conventional radiotherapy vs nine [29%; 14–48] of 31 given IMRT (p<0·0001). At 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional radiotherapy, as were clinically significant improvements in dry-mouth-specific and global quality of life scores. At 24 months, no significant differences were seen between randomised groups in non-xerostomia late toxicities, locoregional control, or overall survival.

Interpretation Sparing the parotid glands with IMRT significantly reduces the incidence of xerostomia and leads to recovery of saliva secretion and improvements in associated quality of life, and thus strongly supports a role for IMRT in squamous-cell carcinoma of the head and neck.
METHODS:

Multicentric Randomised phase 3 trial
UK based
Jan 2003 to Dec 2007

Inclusion criteria – Pharyngeal squamous cell carcinoma
(Oropharynx and Hypopharynx)
Any T , Any N, Non Metastatic
Both Primary and P/o
WHO PS- 0 or 1
No concomitant Chemotherapy
No Prophylactic Pilocarpine or Amifostine

Exclusion Criteria – Previous RT to Head & Neck
Previous Malignancy except non melanoma
Preexisting Salivary Gland disease
Tumour involving Parotid Gland
PROCEDURE:

1) STAGING INVESTIGATIONS: Physical Examination
   Biopsy
   CT / MRI Neck
   CXR
   Blood Count / Biochemistry

2) CT Scan Based Radiation Planning:
   a) 3D Conformal RT with Parallel opposed fields
   b) Parotid Sparing IMRT

3) DOSES:
   i) Primary Tumour & Involved Nodes – 65 Gy in 30 fractions
   ii) Post op – 60 Gy in 30 fractions
   iii) Post op gross residual – 65 Gy in 30 fractions
iv) **Elective Node** –
   IMRT – 54 Gy in 25 fractions
   Conventional – 50 Gy in 25 fractions

v) **Constraints** -
   Spinal Cord - <50 Gy
   Middle Ear & Inner Ear shielding
   Parotid - <24 Gy to whole Contralateral Parotid (IMRT)

vi) **Acute Toxicity** –
   Graded Weekly during RT upto 8 Weeks after treatment
   NATIONAL CANCER INSTITUTE COMMON TOXICITY CRITERIA (VERSION 3)

vii) **Late Toxicities** –
   At 3,6,12,18,24 months after RT
   LENT SOMA & RTOG Scoring System
vii) **Salivary Flow Measurements** –
   Before RT
   4 weeks of RT
   2 weeks after RT
   3, 6, 12, 18, 24 months after RT
   (Both Unstimulated and Sodium Citrate Stimulated Saliva from each Parotid duct and floor of mouth were collected)

viii) **Follow up** –
   Monthly in 1\textsuperscript{st} year
   2 monthly in 2\textsuperscript{nd} year
   3-6 monthly in 3\textsuperscript{rd} year
PRIMARY END POINT:

Proportion of patients with XEROSTOMIA of Grade 2 or worse assessed by LENT SOMA Scale 1 year after RT.

SECONDARY END POINT:

i) Proportion of patients with any measurable Salivary flow after RT.
ii) Acute and other late RT side effects.
iii) QUALITY OF LIFE – Included Xerostomia related (EORTC) & (Modified Xerostomia Questionnaire)
iv) PFS (RECIST)
v) OS
## Demography

<table>
<thead>
<tr>
<th></th>
<th>Conventional radiotherapy (n=47)</th>
<th>IMRT (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age at randomisation (years)</strong></td>
<td>57.3 (10.2; 37.5–82.8)</td>
<td>59.5 (9.2; 44.1–77.1)</td>
</tr>
<tr>
<td><strong>Number of women</strong></td>
<td>12 (26%)</td>
<td>14 (30%)</td>
</tr>
<tr>
<td><strong>WHO performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>42 (89%)</td>
<td>41 (87%)</td>
</tr>
<tr>
<td>1</td>
<td>5 (11%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td><strong>Tumour site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>40 (85%)</td>
<td>40 (85%)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Radiation dose (Gy)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median dose to primary tumour and involved nodes</td>
<td>65.0 (65.0–65.0; 44)</td>
<td>65.0 (65.0–65.0; 47)</td>
</tr>
<tr>
<td>Median dose to elective nodes</td>
<td>50.0 (50.0–50.1; 43)</td>
<td>54.0 (54.0–54.1; 47)</td>
</tr>
<tr>
<td>Mean contralateral parotid dose†</td>
<td>61.0 (54.6–63.8; 43)</td>
<td>25.4 (23.2–28.0; 46)</td>
</tr>
<tr>
<td>Mean ipsilateral parotid dose†</td>
<td>61.0 (57.0–64.4; 43)</td>
<td>47.6 (39.9–54.5; 46)</td>
</tr>
</tbody>
</table>

| **1 and 2**               | 8 (17%)                          | 15 (32%)    |
| **3 and 4**               | 39 (83%)                         | 32 (68%)    |
| **Neoadjuvant chemotherapy** |                                  |             |
| Yes                      | 19 (40%)                         | 20 (43%)    |
| No                       | 28 (60%)                         | 27 (57%)    |
| **Type of radiotherapy**  |                                  |             |
| Primary                  | 32 (68%)                         | 39 (83%)    |
| Postoperative            | 15 (32%)                         | 8 (17%)     |
| **Radiotherapy dose (Gy)**|                                  |             |
| Median dose to primary tumour and involved nodes | 65.0 (65.0–65.0; 44) | 65.0 (65.0–65.0; 47) |
| Median dose to elective nodes | 50.0 (50.0–50.1; 43) | 54.0 (54.0–54.1; 47) |
| Mean contralateral parotid dose† | 61.0 (54.6–63.8; 43) | 25.4 (23.2–28.0; 46) |
| Mean ipsilateral parotid dose† | 61.0 (57.0–64.4; 43) | 47.6 (39.9–54.5; 46) |

Data are mean (SD; range), n (%), or median (IQR; n). IMRT = intensity-modulated radiotherapy. *American Joint Committee on Cancer—groupings based on TNM staging data collected. †Mann-Whitney test p<0.0001.

**Table 1:** Baseline characteristics and treatment details
RESULTS:

1) XEROSTOMIA: Grade 2 or worse

At 3 months: 62 patients
   Conventional RT 33(87%) of 38 patients.
   IMRT 29(76%) of 38 patients.

At 12 months: Total no. decreased
   Conventional RT 25 (74%) of 34 patients.
   IMRT 15 (38%) of 39 patients.

ORs 0.23, Absolute Reduction 35%

At 24 months: Conventional RT 20 (83%) of 24 patients.
   IMRT 9(29%) of 31 patients.

ORs 0.08, Absolute Reduction 54%
<table>
<thead>
<tr>
<th>Acute side-effects*</th>
<th>Conventional radiotherapy</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Grade 0</td>
</tr>
<tr>
<td>Mucositis/stomatitis (clinical)</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Rash (dermatitis)†</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis/stomatitis (functional/symptomatic)</td>
<td>39</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>44</td>
<td>0</td>
</tr>
</tbody>
</table>

RTOG late side-effects§

<table>
<thead>
<tr>
<th>Salivary gland¶</th>
<th>Conventional radiotherapy</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Grade 0</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

LENT SOMA late side-effects§

| Salivary gland¶,|| (xerostomia†) | Conventional radiotherapy | IMRT |
|------------------|-----------------|---------------------------|------|
|                  | N  | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | N  | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|                  | 41 | 0 | 3 (7%) | 12 (29%) | 14 (34%) | 12 (29%) | 46 | 0 | 8 (17%) | 19 (41%) | 15 (33%) | 4 (9%) |
| (xerostomia†)    | 41 | 0 | 3 (7%) | 19 (46%) | 14 (34%) | 5 (12%) | 46 | 0 | 8 (17%) | 31 (67%) | 4 (9%) | 3 (7%) |
| Mucosa**         | 41 | 1 (2%) | 9 (22%) | 17 (41%) | 9 (22%) | 5 (12%) | 46 | 1 (2%) | 19 (41%) | 11 (24%) | 11 (24%) | 4 (9%) |
| Oesophagus††     | 41 | 15 (37%) | 15 (37%) | 4 (10%) | 5 (12%) | 2 (5%) | 46 | 20 (43%) | 16 (35%) | 4 (9%) | 4 (9%) | 2 (4%) |
| (dysphagia)      | 41 | 20 (49%) | 16 (39%) | 3 (7%) | 2 (5%) | 0 | 46 | 21 (46%) | 16 (35%) | 5 (11%) | 3 (7%) | 1 (2%) |
| Skin†            | 41 | 5 (12%) | 19 (46%) | 11 (27%) | 5 (12%) | 1 (2%) | 46 | 10 (22%) | 24 (52%) | 10 (22%) | 2 (4%) | 0 |
| Larynx§§         | 41 | 16 (39%) | 15 (37%) | 7 (17%) | 2 (5%) | 1 (2%) | 46 | 16 (35%) | 22 (48%) | 8 (17%) | 0 | 0 |
| Mandible¶¶       | 41 | 13 (32%) | 16 (39%) | 9 (22%) | 3 (7%) | 0 | 46 | 19 (41%) | 11 (24%) | 12 (26%) | 3 (7%) | 1 (2%) |
| Ear||| 11/7/2017 | 41 | 19 (46%) | 12 (29%) | 7 (17%) | 3 (7%) | 0 | 46 | 27 (59%) | 13 (28%) | 6 (13%) | 0 | 0 | 33 |
Rtog Garde 2 or worse

<table>
<thead>
<tr>
<th>Time from completion of radiotherapy (months)</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional radiotherapy</td>
<td>41</td>
<td>36</td>
<td>34</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>IMRT</td>
<td>45</td>
<td>45</td>
<td>39</td>
<td>35</td>
<td>32</td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th>Time</th>
<th>Conventional radiotherapy</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>39</td>
</tr>
<tr>
<td>18</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>24</td>
<td>24</td>
<td>32</td>
</tr>
</tbody>
</table>
Lent soma garde 2 -subjective
2) **SIALOMETRY** : Unstimulated Saliva Flow from Contralateral Parotid.

At 12 months: Conventional RT 0 (0%) of 25 patients.
IMRT 16 (47%) of 34 patients.

At 24 months: Conventional RT 0(0%) of 15 patients.
IMRT 7 (44%) of 16 patients.

Similar Results were obtained in Stimulated Saliva Flow Results.
<table>
<thead>
<tr>
<th></th>
<th>Conventional radiotherapy</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No measurable salivary flow*</td>
<td>No measurable salivary flow</td>
</tr>
<tr>
<td></td>
<td>(n=25)</td>
<td>(n=18)</td>
</tr>
<tr>
<td>Subjective xerostomia better than grade 2</td>
<td>6 (24%)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td>Subjective xerostomia grade 2 or worse</td>
<td>19 (76%)</td>
<td>8 (44%)</td>
</tr>
</tbody>
</table>

Fisher's exact test for association (treatment groups combined) p=0.018. LENT SOMA=Late Effects of Normal Tissues Subjective-Objective Management Analytic.
IMRT=intensity-modulated radiotherapy. *Measurable salivary flow was defined as any saliva collected from the Lashley cup apparatus.

Table 3: Concordance between unstimulated contralateral saliva flow and LENT SOMA subjective xerostomia at 12 months
EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:

Have you had pain in your mouth?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Mean change score from baseline for dry mouth subscale-EORTC HN35
Results Cont.

3) **QUALITY OF LIFE**: EORTC Global Health Status Score  
   (Higher Score better QOL)

At 12 months: Conventional RT **1.1**  
IMRT **3**

At 24 months: Conventional RT **2.8**  
IMRT **8.3**

HN 35 Subscale Scores for Dry mouth, senses, Sticky Saliva shows similar Results in favor of IMRT.
Results Cont.

4) **LOCOREGIONAL PFS** : PFS At 2 years

Conventional RT 80%
IMRT 75%

IMRT – 12 recurrences total
  11 in high dose volume
  01 in electively irradiated nodal region

Conventional RT – 07 recurrences total
  05 in high dose volume
  02 in both high dose & electively irradiated region
Figure 4: Kaplan-Meier plot of locoregional progression-free survival by treatment group
Results Cont.

4) **OVERALL SURVIVAL**:  
   (32 Deaths in Total) 02 years OS

Conventional RT : 76%  
IMRT : 78%
DISCUSSION:

1) less Incidence of RT induced XEROSTOMIA in IMRT Arm.
2) Early Recovery of Saliva Flow in cases treated with IMRT.
3) Improved QOL in IMRT Arm.
4) Comparable PFS & OS in both Arms.
5) No significant effect of Neoadjuvant Chemotherapy on Incidence of Xerostomia.-not explained

Detailed Analysis of Dose Distribution to Salivary Glands including Parotid and its clinical correlation is Ongoing.

Initial Results suggest no correlation between salivary gland doses of RT and Xerostomia.
LIMITATIONS OF TRIAL:

Non Masking of treatment from either patients or clinicians due difference in treatment delivery technique.........
OTHER STUDIES SUPPORTING THE RESULTS:
XEROSTOMIA AND QUALITY OF LIFE AFTER INTENSITY-MODULATED RADIOThERAPY VS. CONVENTIONAL RadioThERAPY FOR EARLY-STAGE NASOPHARYNGEAL CARCINOMA: INITIAL REPORT ON A RANDOMIZED CONTROLLED CLINICAL TRIAL

Edmond H. N. Pow, M.D. S.,* Dora L. W. Kwong, M.B. B.S.,† Anne S. McMillan, Ph.D.,* Max C. M. Wong, Ph.D. ‡ Jonathan S. T. Sham, M.D.,† Lucullus H. T. Leung, Ph.D. †

preradiotherapy SWS and SPS flow respectively, compared with 1 (4.8%) and 2 patients (9.5%), respectively, in the CRT group. Global health scores showed continuous improvement in QoL after both treatments (p < 0.001). However, after 12 months subscale scores for role-physical, bodily pain, and physical function were significantly higher in the IMRT group, indicating a better condition (p < 0.05). Dry mouth and sticky saliva were problems in both groups 2 months after treatment. In the IMRT group, there was consistent improvement over time with xerostomia-related symptoms significantly less common than in the CRT group at 12 months postradiotherapy. Conclusions: IMRT was significantly better than CRT in terms of parotid sparing and improved QoL for early-stage disease. The findings support the case for assessment of health-related QoL in relation to head-and-neck cancer using a site-specific approach. © 2006 Elsevier Inc.
Reducing Xerostomia by sparing the parotid glands (*)

However, these achievements are relatively modest. (**)

Post-IMRT, Grade 2 or greater Xerostomia as high as 40% at 12 months. (***)

Thus, IMRT aiming to spare only the PGs, achieves partial gains in clinician rated and patient reported Xerostomia. (****)

Discrepancy between preserved parotid function & patient-reported symptoms proves:
   Parotid glands sparing alone is not sufficient

Role of the submandibular glands in:
   Secreting saliva in the non-stimulated state
   Rich in mucins
Submandibular gland can be surgically transferred to the submental space with its function preserved. The gland seems to continue functioning even after radiation therapy with the appropriate shielding.
<table>
<thead>
<tr>
<th>Gland</th>
<th>Acinar Type</th>
<th>Viscosity</th>
<th>Percentage of Whole Unstimulated Daily Saliva</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid</td>
<td>Serous</td>
<td>Watery</td>
<td>25</td>
</tr>
<tr>
<td>Submandibular</td>
<td>Mixed</td>
<td>Semiviscous</td>
<td>71</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Mucous</td>
<td>Viscous</td>
<td>3-4</td>
</tr>
<tr>
<td>Minors</td>
<td>Mucous</td>
<td>Viscous</td>
<td>Trace</td>
</tr>
</tbody>
</table>

Review

Salivary gland transfer to prevent radiation-induced xerostomia: A systematic review and meta-analysis

Amit J. Sood a, Nyssa F. Fox a, Brendan P. O’Connell a, Tiffany L. Lovelace b, Shaun A. Nguyen a, Anand K. Sharma c, Joshua D. Hornig a, Terry A. Day a,∗

a Department of Otolaryngology – Head and Neck Surgery, Medical University of South Carolina, United States
b College of Dental Medicine, Medical University of South Carolina, United States
c Department of Radiation Oncology, Medical University of South Carolina, United States
Figure 1. Algorithm of study selection.
Unstimulated salivary flow

Figure 5. Salivary gland transfer (SGT) versus control, unstimulated salivary flow rates. Depicts mean change (%) from baseline before, during, and after radiation therapy (XRT).
Figure 6. Salivary gland transfer (SGT) versus control, stimulated salivary flow rates. Depicts mean change (%) from baseline before, during, and after radiation therapy (XRT).
CONCLUSION

1. In comparison to control subjects twelve months after XRT, SGT subjects’ unstimulated (75% vs. 11%).
2. Stimulated (86% vs. 8%) salivary flow rates were drastically higher in SGT patients.
3. Salivary gland transfer appears to be highly effective in preventing the incidence of xerostomia in patients receiving definitive head and neck radiation therapy.
Feasibility of Sparing Submandibular Gland

Prospective non-randomised trial:

Submandibular gland-sparing feasible
Is there an evidence of salivary gland sparing other than parotid in definitive head and neck IMRT on local control??

Well the data is not robust......Few studies are published.... So lets see...
Dose response relationship

Conclusions: SMG salivary flow rates depended on mean dose with recovery over time up to a threshold of 39 Gy. Substantial SMG dose reduction to below this threshold and without target underdosing is feasible in some patients, at the expense of modestly higher doses to some other organs. © 2008 Elsevier Inc.
Salivary gland-sparing other than parotid-sparing in definitive head-and-neck intensity-modulated radiotherapy does not seem to jeopardize local control

Conclusion: Over 92% of LR failures occurred “in-field” within the high dose region when using IMRT with a whole salivary gland-sparing strategy. Sparing SMG and OC in addition to PG thus appears a safe strategy.
**Radiotherapy and Oncology 78 (2006) 270-275**

www.thegreenjournal.com

*Head and neck IMRT*

Sparing of the submandibular glands by intensity modulated radiotherapy in the treatment of head and neck cancer

Kauko Saarilahti*, Mauri Kouri, Juhani Collan, Aki Kangasmäki, Timo Atula, Heikki Joensuu, Mikko Tenhunen

*aDepartment of Oncology, and bDepartment of Otorhinolaryngology, Head and Neck Surgery, Helsinki University Central Hospital, Helsinki, Finland

**Results:** Twelve months following IMRT mean unstimulated saliva flow was 60% of the baseline value among patients who had one submandibular gland spared and 25% among those who did not (P = 0.006). Patients whose contralateral submandibular was spared reported less grade two or three xerostomia (4 vs. 11; P = 0.018), and used less saliva substitutes. No cancer recurrences were detected at the vicinity of the spared glands during a median follow-up time of 31 months.

**Conclusions:** Submandibular gland sparing with IMRT is safe in selected patients treated for head and neck cancer. It is effective in prevention of radiation-associated xerostomia.
**Conclusion.** In selected head and neck cancer patients who are estimated to have a low risk of cancer recurrence at the nodal levels I–II and who are treated with SMG-sparing IMRT the risk of cancer recurrence at the vicinity of the spared salivary glands is low.
Regarding the Safety and Efficacy of Submandibular Gland-sparing RT: Data Extremely Limited

- Reduction of the mean dose to the SG: Proximity to the lower level II nodes & underdosing of Jugulodiagastric lymph nodes(*). Might be hazardous.

- Mean dose to the contralateral SG to 39 Gy requires reducing the dose coverage to the contralateral elective target volume from 95% to 90% of the prescribed dose.(**)

**Hence, at present, submandibular gland-sparing RT should not be undertaken outside clinical trials.** If done then has to be very cautious.

---

Fig. 2. An example of the cumulated dose distribution achieved by dose optimization. The outer red line: the CTV1 (the primary tumour site and the regional lymph nodes); the inner red line; the boosted volume (CTV2); the turquoise line: the contralateral submandibular gland.
Patients with early stage oral cavity squamous carcinoma and with a pre-operative node stage zero neck may be candidates for preservation of submandibular gland during neck dissection.

Conclusion: Submandibular gland metastasis from head and neck primary squamous cell carcinoma is extremely rare. Preservation of the ipsilateral submandibular gland during neck dissection is oncologically safe, except in patients with prior surgery or radiotherapy, or a primary tumour in close relation to the gland.
Conclusion

- The dose–response relationships: Function Exponentially decrease if mean dose **threshold of 39 Gy**

- SMG function **recovery** is better: If mean dose < 39 Gy. (*)

- This threshold dose is much higher as compared to **Parotids** (Dose of 26 Gy.)

- Identification of a threshold dose of 39 Gy: SMG sparing feasibility more by reoptimization without compromising the PTV coverage

How to Contour the OAR’s Related to Radiation Induced Salivary Dysfunction and Xerostomia???

Xerostomia

Delineation guidelines for organs at risk involved in radiation-induced salivary dysfunction and xerostomia

Tara A. van de Water a,*, Henk P. Bijl a, Henriëtte E. Westerlaan b, Johannes A. Langendijk a

a Department of Radiation Oncology, University Medical Center Groningen/University of Groningen, The Netherlands; b Department of Radiology, University Medical Center Groningen/University of Groningen, The Netherlands

Results and conclusions: The provided OAR guidelines are accompanied by CT-based illustrations presenting examples of the delineated structures and their corresponding anatomic boundaries. The parts of the tongue bearing minor salivary glands could not be outlined. Difficulties and uncertainties in defining these minor salivary glands on CT remain to be resolved. Implementation of these guidelines in practice should lead to a reduction in inter- and intra-observer variability and therefore unambiguous reporting of possible dose-volume effect relationships.
Oral cavity and Minor salivary glands: Why???

- Minor salivary glands, dispersed throughout the oral cavity: > 10% of saliva production but **most of the total mucin**

- Mean RT dose to the oral cavity: **Independent predictor of xerostomia**, although there are **conflicting data.**(*),**(**

- Reducing dose to the oral cavity-Additional benefits in terms of **preventing taste dysfunction, as well as mucosal fibrosis and atrophy.***(****

- Therefore, the **uninvolved oral cavity** could be deemed an **OAR**, although with very **low priority**

---


Eisbruch et al.(*) observed a mean dose (TD50) for developing Xerostomia at 12 months of 26 Gy for a 75%- reduction of pre-t/t stimulated salivary flow.

Mean dose of <40 Gy to the whole OC can be kept as a constraint & dosimetric goal for IMRT optimization to achieve favourable patient and observer reported Xerostomia.


IS THERE ANY HOPE

Pilocarpine HCl Tablets

5 mg
Efficacy and safety of pilocarpine for radiation-induced xerostomia in patients with head and neck cancer

A systematic review and meta-analysis
Figure 1. Flowchart of the selection process of related articles.
<table>
<thead>
<tr>
<th>STUDY</th>
<th>DESIGN</th>
<th>PARTICIPANTS</th>
<th>DOSAGES AND DURATION</th>
<th>OUTCOME MEASURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson and Colleagues, 1993</td>
<td>RCT</td>
<td>138</td>
<td>73</td>
<td>65 5 milligrams 3 times per d for 12 wks</td>
</tr>
<tr>
<td>LeVeque and Colleagues, 1993</td>
<td>RCT</td>
<td>162</td>
<td>75</td>
<td>87 2.5 mg for the first 4 wks, 5 mg for the second 4 wks, 10 mg the last wks</td>
</tr>
<tr>
<td>Haddad and Karimi, 2002</td>
<td>RCT</td>
<td>39</td>
<td>18</td>
<td>21 5 mg 3 times per d for 12 wks</td>
</tr>
<tr>
<td>Warde and Colleagues, 2002</td>
<td>RCT</td>
<td>98</td>
<td>50</td>
<td>48 5 mg 3 times per d for 4 wks</td>
</tr>
<tr>
<td>Nyarady and Colleagues, 2006</td>
<td>RCT</td>
<td>66</td>
<td>33</td>
<td>33 5 mg 3 times per d for 12 wks</td>
</tr>
<tr>
<td>Scarantino and Colleagues, 2006</td>
<td>RCT</td>
<td>249</td>
<td>124</td>
<td>125 5 mg 3 times per d for 13 wks</td>
</tr>
</tbody>
</table>

* RCT: Randomized controlled trial.
† VAS: Visual analog scale.
‡ LENT-SOMA: Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic.
§ HNRQ: Head and Neck Radiotherapy Questionnaire.
‖ USF: Unstimulated saliva flow.
# SSF: Stimulated saliva flow.
Results. The authors identified 6 studies (including 752 patients in total). The results of a meta-analysis of 3 articles showed that pilocarpine was associated with a 12-point increase in VAS score (mean difference, 12.00; 95% confidence interval [CI], 1.93-22.08; \( P = .02 \)) and higher rates of adverse events compared with placebo in terms of sweating (odds ratio [OR], 3.71; 95% CI, 2.34-5.86; \( P < .00001 \)). There were no differences in rhinitis (OR, 1.21; 95% CI, 0.68-2.16; \( P = .52 \)) and nausea (OR, 1.44; 95% CI, 0.83-2.49; \( P = .19 \)).
Conclusions and Practical Implications. On the basis of the best available evidence, the results of this meta-analysis provide evidence that pilocarpine offers statistically significant clinical benefits for the symptomatic treatment of radiation-induced xerostomia in patients with head and neck cancer. However, the authors of this systematic review found the best available evidence in the meta-analysis in 3 studies, 1 of which showed no effect. The authors of this systematic review suggest that these patients take 5 milligrams of pilocarpine 3 times daily, and that there is need for further study.
Clinical Investigation

Is Pilocarpine Effective in Preventing Radiation-Induced Xerostomia? A Systematic Review and Meta-analysis

Wei-fa Yang, DDS,* Gui-qing Liao, DDS, PhD,* Samer G. Hakim, MD, DDS,† Dai-qiao Ouyang, DDS,* Jolie Ringash, MD,‡ and Yu-xiong Su, DDS, PhD§

*Department of Oral and Maxillofacial Surgery, Guanghua School of Stomatology, Guangdong Provincial Key Laboratory of Stomatology, Sun Yat-sen University, Guangzhou, China; †Department of Oral and Maxillofacial Surgery, University of Lübeck, Lübeck, Germany; ‡Department of Radiation Oncology, Princess Margaret Cancer Centre and the University of Toronto, Toronto, Ontario, Canada; and §Division of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Hong Kong, Hong Kong, China

11/7/2017

Received May 26, 2015, and in revised form Sep 29, 2015. Accepted for publication Nov 4, 2015.
**Purpose:** To evaluate the efficacy of concomitant administration of pilocarpine on radiation-induced xerostomia in patients with head and neck cancers.

**Methods and Materials:** The PubMed, Web of Science, Cochrane Library, and ClinicalTrials were searched to identify randomized, controlled trials studying the effect of concomitant administration of pilocarpine for radiation-induced xerostomia. Included trials were systematically reviewed, and quantifiable outcomes were pooled for meta-analysis. Outcomes of interest included salivary flow, clinician-rated xerostomia grade, patient-reported xerostomia scoring, quality of life, and adverse effects.

**Results:** Six prospective, randomized, controlled trials in 8 articles were included in this systematic review. The total number of patients was 369 in the pilocarpine group and 367 in the control group. Concomitant administration of pilocarpine during radiation could increase the unstimulated salivary flow rate in a period of 3 to 6 months after treatment, and also reduce the clinician-rated xerostomia grade. Patient-reported xerostomia was not significantly impacted by pilocarpine in the initial 3 months but was superior at 6 months. No significant difference of stimulated salivary flow rate could be confirmed between the 2 arms. Adverse effects of pilocarpine were mild and tolerable.

**Conclusions:** The concomitant administration of pilocarpine during radiation increases unstimulated salivary flow rate and reduces clinician-rated xerostomia grade after
Unstimulated salivary flow rates during and after course of radiation therapy. Depicts mean differences between the pilocarpine group and the control group. Abbreviation: CI = confidence interval.
Subjective salivary flow

Fig. 5. Subjective xerostomia scores during and after course of radiation therapy. Depicts mean differences between the pilocarpine group and the control group. Abbreviation: CI = confidence interval.
Pilocarpine conclusion

1. Pilocarpine was most effective in patients with some residual salivary gland function, and even upon destruction of major salivary glands,
2. Pilocarpine has shown success due to action on minor salivary glands
3. Salivary gland stimulation ceases shortly after cessation of treatment with pilocarpine, and thus continued administration is required.
4. This may be problematic owing to the possible adverse effects associated with the muscarinic agonist.
5. Our meta-analysis found that treatment with systemic pilocarpine did not show significant improvement for subjective responders at less than 1 week after completion of treatment.
6. However, there was significant improvement in the number of responders for topical pilocarpine treatments.
7. Best response was noted with the pilocarpine lozenge, which also improved unstimulated and stimulated salivary flow rates the most.
8. The data also show that objective measures of systemic pilocarpine cause significant improvement up to 4 months after the cessation of therapy.
Management

- The panel recommends the use of parotid sparing IMRT for prevention of salivary gland hypofunction and xerostomia in head and neck cancer patients (Level of evidence II, recommendation grade A).

- No guideline possible for use of amifostine to prevent xerostomia during RT for head and neck cancer due to lack of consensus on the interpretation of existing evidence (Level of evidence II, recommendation grade C).

- The panel recommends the use of oral pilocarpine following radiation therapy in head and neck cancer patients for improvement of xerostomia. The improvement of salivary gland hypofunction may be limited (Level of evidence II, recommendation grade B).

- The panel cannot recommend the use of oral pilocarpine during radiotherapy in head and neck cancer patients for improvement of xerostomia as the results of the various randomized clinical trials were equivocal (Level of evidence II, recommendation grade C).
Management

- No guideline possible for use of gustatory and masticatory stimulation due to little evidence on which to base a guideline since this has been sparsely addressed specifically for patients suffering from xerostomia induced by cancer therapies (Level of evidence III, recommendation grade D).

- The panel recommends the use of oral mucosal lubricants/saliva substitutes for short-term improvement of xerostomia following radiation therapy in head and neck cancer patients (Level of evidence II, recommendation grade B).

- The panel suggests that the obtained level of sparing by submandibular salivary gland transfer might be of clinical significance (Level of evidence IV, recommendation grade B).

- The panel suggests the use of acupuncture to stimulate salivary gland secretion and to alleviate xerostomia (Level of evidence II, recommendation grade C).

- No guideline possible for hyperbaric oxygen treatment of xerostomia due to no evidence on which to base a guideline (Level of evidence IV, recommendation grade D).
BEYOND XEROSTOMIA
Why to Bother so much about Dysphagia? Just Bother about Xerostomia..

- Late Dysphagia is as important as permanent xerostomia. (*)

- Moreover, xerostomia can now be successfully avoided

- No comparable advances: Regarding prevention of dysphagia

- Shift of focus: Late dysphagia, rather than xerostomia, is the dose-limiting toxicity of CT-RT

Dysphagia Aspiration Related Structures (DARS)

- **Swallowing dysfunction** after RT: compromised QOL & can lead to life-threatening complications, such as aspiration pneumonia. (*)

- Aspiration pneumonia is an **under documented** complication of CT RT for head-and-neck cancer. (**) 


Fig. 1. Pharyngeal constrictor muscles and related structures. (a) Lateral, (b) posterior view. Circular constrictors and longitudinal muscles that blend distally with them are depicted in bold letters. After Gray's Anatomy (28).
<table>
<thead>
<tr>
<th>Superior pharyngeal constrictor muscle</th>
<th>Superior border</th>
<th>Inferior border</th>
<th>Anterior border</th>
<th>Posterior border</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudal tip of pterygoid plates (hamulus)</td>
<td>Upper edge of hyoid bone</td>
<td>Widest diameter of rhinopharynx, base of tongue, hyoid bone, and larynx</td>
<td>Cervical vertebra or prevertebral muscles</td>
<td></td>
</tr>
<tr>
<td>Middle pharyngeal constrictor muscle</td>
<td>Upper edge of hyoid bone</td>
<td>Lower edge of hyoid bone</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Inferior pharyngeal constrictor muscle</td>
<td>Lower edge of hyoid bone</td>
<td>Lower edge of cricoid cartilage</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Base of tongue</td>
<td>Below soft palate (uvula)</td>
<td>Upper edge of hyoid bone</td>
<td>Posterior third of the tongue</td>
<td>...</td>
</tr>
<tr>
<td>Supraglottic larynx (lumen excluded)</td>
<td>Top of piriform sinus and aryepiglottic fold</td>
<td>Upper edge of cricoid cartilage</td>
<td>Anterior tip of thyroid cartilage</td>
<td>Cornu of thyroid cartilage</td>
</tr>
<tr>
<td>Glottic larynx (lumen excluded)</td>
<td>At level of cricoid cartilage</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Upper oesophageal sphincter including musculus cricopharyngeus</td>
<td>Lower edge of cricoid cartilage</td>
<td>Upper edge of trachea</td>
<td>Subglottic larynx</td>
<td>Cervical vertebra</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Upper edge of trachea</td>
<td>First 2 cm</td>
<td>Trachea</td>
<td>Cervical vertebra</td>
</tr>
</tbody>
</table>

**Table 2**: Proposed delineation guidelines for swallowing structures, by organ at risk
# Swallowing assessment

<table>
<thead>
<tr>
<th>Time point</th>
<th>Study</th>
<th>Domain</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline; 3, 6, 12, 18 and 24 months</td>
<td>MDADI</td>
<td>Swallowing related QoL</td>
<td>Composite (total), global, emotional, functional and physical subscale scores</td>
</tr>
<tr>
<td>Baseline; 3, 6, 12, 18 and 24 months</td>
<td>WST</td>
<td>Swallow Performance</td>
<td>Swallow capacity, Swallow volume</td>
</tr>
<tr>
<td>Baseline, 12 and 24 months</td>
<td>VF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Airway protection</td>
<td>Penetration Aspiration Scale [52]</td>
</tr>
<tr>
<td>Baseline, 12 and 24 months</td>
<td>VF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Physiology</td>
<td>MBSimp</td>
</tr>
<tr>
<td>Baseline, 12 and 24 months</td>
<td>VF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pharyngeal dysphagia grade</td>
<td>DIGEST grade [53]</td>
</tr>
<tr>
<td>Baseline, 3, 6, 12, 18 and 24 months</td>
<td>PSS-HN</td>
<td>Functional Performance Status</td>
<td>Normalcy of diet, eating in public, understandability of speech scores</td>
</tr>
<tr>
<td>Baseline; 3, 6, 12, 18 and 24 months</td>
<td>UW-Qol v.04</td>
<td>HR-QoL</td>
<td>Composite scores of physical and social-emotional functioning are derived from 12 domains. Patients can also highlight up to 3 priority concerns from the previous 7 days</td>
</tr>
</tbody>
</table>

Abbreviations: WST Water Swallowing Test, DIGEST Dynamic Imaging Grade of Swallowing Toxicity, MBSimp Modified Barium Swallow Impairment Profile

<sup>a</sup>Subset of centres only
Endpoint of dysphagia: Not clear (Both Subjective & Objective)

- **Objective assessment:**
  - Video fluoroscopy
  - CT Scans,
  - Direct endoscopic evaluation

- **Subjective Assessment:**
  - Validated questionnaires: EORTC QLQ-H&N35 or swallowing subscale (HNSW), consisting of four questions regarding swallowing of liquid, pureed food, swallowing of solid & aspiration when swallowing.

Patient-reported endpoints preferable.(*,**)


MD Anderson Dysphagia Inventory (MDADI)

The MDADI was administered by written questionnaire at the time of arrival for MBS studies. The MDADI is a 20-item self-administered questionnaire that quantifies swallowing-related quality of life. The MDADI has been validated with regard to content, criterion and construct validity and is considered reliable based on test-retest correlations (0.69-0.88) and overall Cronbach’s coefficient = .96. Each item is scored on a 5 point Likert scale (strongly disagree, disagree, no opinion, agree, strongly agree). The MDADI quantifies an individual’s global (G), physical (P), emotional (E), and functional (F) perceptions of their swallowing ability. Two summary scores can be obtained from the MDADI: 1) global and 2) composite. The global scale is a single question, scored individually, to assess the overall impact that swallowing abilities have on quality of life (“my swallowing impacts my day-to-day life”). The composite MDADI score summarizes overall performance on remaining 19-items of the MDADI, as a weighted average of the physical, emotional, and functional subscale questions. Global, composite, and emotional subscales assess domain-specific performance. Summary and subscale MDADI scores are normalized to range from 20 (extremely low functioning) to 100 (high functioning). The composite MDADI score was chosen as the primary endpoint for this analysis because it reflects overall performance on 19-items. Only one MDADI questionnaire was analyzed per subject; the MDADI was taken from the first eligible MBS study in cases where multiple were completed during the review period.
CAN WE DARE TO SPARE DARS?
CAN THEY BE SPARED BY IMRT?

**CLINICAL INVESTIGATION**

**Head and Neck**

**DYSPHAGIA AND ASPIRATION AFTER CHEMORADIOThERAPY FOR HEAD-AND-NECK CANCER: WHICH ANATOMIC STRUCTURES ARE AFFECTED AND CAN THEY BE SPARED BY IMRT?**

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<table>
<thead>
<tr>
<th>VF abnormality</th>
<th>Aspects of dysphagia/aspiration related to the VF abnormality</th>
<th>Anatomic structures whose damage or malfunction may cause the VF abnormality</th>
</tr>
</thead>
</table>
| Reduced peristalsis and lack of synchronization among pharyngeal contraction wave, opening of upper esophageal sphincter, and closure of larynx | Dysphagia  
Food residue in oropharynx and hypopharynx at completion of swallowing, increasing risk of aspiration after swallow | Pharyngeal musculature (23–27, 35), including circular constrictors (superior, middle, and inferior) and longitudinal muscles (stylopharyngeus, salpingopharyngeus, and palatopharyngeus) that blend distally with circular constrictors (28) (Fig. 1).  
Nerve supply: pharyngeal plexus, supplied by n. V, IX, and X.  
Contraction of mylohyoid muscle (Fig. 1) causes this movement (32).  
Mucosal and submucosal fibrosis at base of tongue or at its attachment to pharyngeal musculature  
Nerve supply: XII.  
Glottic adductor muscles (thyroarytenoid, lateral cricoarytenoid, and transverse arytenoid) and supraglottic adductors (oblique arytenoids and aryepiglottic muscles) (29).  
Stiffness of laryngeal walls due to edema and fibrosis (36)  
Nerve supply: superior laryngeal and recurrent laryngeal (X), and sympathetic.  
Stiffness of epiglottic walls due to edema and fibrosis (36)  
Malfunction of suprathyroid muscles (geniohyoid, mylohyoid, and digastric) that pull hyolaryngeal complex superiorly and anteriorly, and with it pull epiglottis to horizontal plane (30, 33, 34, 37–40)  
Nerve supply: VII.  
Lack of relaxation of cricopharyngeal muscle (27, 41).  
Malfunction of suprathyroid muscles that pull larynx upward, forward, and away from posterior pharyngeal wall (42, 43) |
| Reduced, or lack of, posterior movement of base of tongue toward posterior pharyngeal wall | Movement required to push bolus downward and prevent residue in vallecula that may be aspirated after swallow (31) | |
| Incomplete or delay of glottic closure and reduced adduction of supraglottic larynx during swallow | Aspiration during swallow (34, 35) | |
| Lack of superior motion of hyoid and larynx and lack of inversion of epiglottis | Reduced airway protection during swallow (as larynx elevates, epiglottis tilts horizontally and arytenoids tilt anteriorly toward base of epiglottis, closing entrance to airway) (23)  
Increased dysphagia (laryngeal elevation required for opening of upper esophageal sphincter by pulling larynx away from posterior pharyngeal wall and creating continuous passage) (27) | |
| Lack of timely opening of upper esophageal sphincter | Dysphagia and aspiration during swallow | |

*Abbreviation: VF = videofluoroscopy.*
Table 1. Dose specifications and constraints used for two IMRT strategies

1. stIMRT
   
   **Targets**
   - PTV66: gross disease; prescribed dose 66 Gy in 30 fractions
   - PTV60: subclinical disease at high risk (adjacent to GTVs or first-echelon nodal levels); prescribed dose 60 Gy in 30 fractions
   - PTV54: subclinical disease at lower risk (other nodal levels at risk); prescribed dose 54 Gy in 30 fractions
   
   Prescribed dose encompassed ≥95% of PTVs
   ≤1% of PTVs received <93% prescribed dose
   <20% of PTVs received >110% prescribed dose
   
   **Noninvolved tissues and organs**
   - Glottic larynx: 2/3 should receive <50 Gy
   - Brainstem: maximal dose 54 Gy
   - Spinal cord: maximal dose 45 Gy
   - Mandible: maximal dose 70 Gy
   - Nonspecified tissue outside PTVs: <1% to receive >110% of PTV66 dose
   - Parotid glands: in at least one gland, mean dose ≤26 Gy or ≥50% receive ≤30 Gy
   
   Reduce dose to esophagus as much as possible*

2. doIMRT
   
   Same dose specifications and constraints as stIMRT.
   
   In addition, minimize volumes of DARS receiving ≥50 Gy
IMRT for DARS – Goals

- Eisbruch et al (*) assigned V50 as an endpoint for t/t planning & evaluation for DARS.

- V50: Lowest dose delivered to most of the constrictors involved in a stricture

- Dose (V50) reduction of constrictors:
  - 3D CRT vs. standard (st)IMRT: 10% on average
  - st IMRT vs. dysphagia optimized (do) IMRT: additional 10%
  - No difference in D max (due to overlap with PTV)

- Dose reduction of larynx (glottic & supraglottic; V50): (larynx or vallecula not involved)
  - 3D CRT vs. st IMRT: 7% (p-0.054)
  - st IMRT vs. do IMRT: additional 11%

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*Eisbruch et al, Dysphagia and Aspiration after CTRT for Head & Neck cancer: IJROBP, Vol. 60, No 5, PP-1439-1239, 20014
CONCLUSION

This study represents the first step in a systematic evaluation of the utility of IMRT in reducing dysphagia and aspiration after intensive chemo-RT. We determined the anatomic structures whose damage possibly caused the swallowing abnormalities observed after two different intensive regimens. IMRT can reduce the volumes of these structures receiving high doses, and incorporating the goal of sparing these structures into the optimization cost function can achieve significant additional benefit. Target delineation rules that maximize the relative sparing of the DARS by IMRT were identified. Clinical validation is required to determine whether the dosimetric benefits translate into clinical ones.
Dysphagia after chemoradiotherapy

Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures

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• Dose–effect relationships for swallowing and mastication structures
• 55 patients before, 10-weeks (N = 49) and 1-year post-treatment.
• Calculation of dose–volume parameters for swallowing (inferior (IC), middle (MC), & superior constrictors (SC)), and mastication structures (e.g. masseter)
• Investigation of relationships between dose-parameters and endpoints for swallowing problems
• Videofluoroscopy-based laryngeal Penetration-Aspiration Scale (PAS).
• Study-specific structured questionnaire) and limited mouth-opening (measurements and questionnaire), taking into account baseline scores
Conclusions

The present study shows that dose relationships between dysphagia and trismus measures and the radiation doses to the critical swallowing-, and mastication structures exist. However, since dose relationships seem to vary at different measurement points, a strict multidimensional assessment protocol, including objective and subjective assessment, is mandatory. No thresholds were found, but delineation of organs at risk, especially the masseter muscle, for treatment planning is essential to reduce potentially damaging radiation doses to these structures.
Fig. 1. Delineated structures. (a) Three-dimensional example of swallowing structures contoured: Green; superior constrictor muscle, Pink; middle constrictor muscle, Blue; inferior constrictor muscle, (Orange; cricopharyngeal muscle, Yellow; proximal esophagus). (b) Two-dimensional example of mastication structures contoured: 1. right and left lateral medial pterygoid muscles, 2. right and left masseter muscle, 3. right and left temporalis muscle, 4. right and left mandibular condyle.
ABSTRACT

Background and purpose: Prospective assessment of dysphagia and trismus in chemo-IMRT head and neck cancer patients in relation to dose-parameters of structures involved in swallowing and mastication.

Material and methods: Assessment of 55 patients before, 10-weeks (N = 49) and 1-year post-treatment (N = 37). Calculation of dose–volume parameters for swallowing (inferior (IC), middle (MC), and superior constrictors (SC)), and mastication structures (e.g. masseter). Investigation of relationships between dose-parameters and endpoints for swallowing problems (videofluoroscopy-based laryngeal Penetration-Aspiration Scale (PAS), and study-specific structured questionnaire) and limited mouth-opening (measurements and questionnaire), taking into account baseline scores.

Results: At 10-weeks, volume of IC receiving ≥60 Gy (V60) and mean dose IC were significant predictors for PAS. One-year post-treatment, reported problems with swallowing solids were significantly related to masseter dose-parameters (mean, V20, V40 and V60) and an inverse relationship (lower dose related to a higher probability) was observed for V60 of the IC. Dose-parameters of masseter and pterygoid muscles were significant predictors of trismus at 10-weeks (mean, V20, and V40). At 1-year, dose-parameters of all mastication structures were strong predictors for subjective mouth-opening problems (mean, max, V20, V40, and V60).

Conclusions: Dose–effect relationships exist for dysphagia and trismus. Therefore treatment plans should be optimized to avoid these side effects.
Dose constraint for DARS

- Sparing these structures could prevent late dysphagia. (#)
- No clear dose or volume constraints available
- Mean dose to DARS: < 50 Gy.
- Beyond 50–60 Gy: Occurrence of late dysphagia. (*, **) 
- Best approach: Keep RT dose to these structures as low as possible. (##)

** Levendag PC, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. Radiother Oncol 2007; 85: 64–73.
Abstract

Background: Persistent dysphagia following primary chemoradiation (CRT) for head and neck cancers can have a devastating impact on patients’ quality of life. Single arm studies have shown that the dosimetric sparing of critical swallowing structures such as the pharyngeal constrictor muscle and supraglottic larynx can translate to better functional outcomes. However, there are no current randomised studies to confirm the benefits of such swallow sparing strategies. The aim of Dysphagia/Aspiration at risk structures (DARS) trial is to determine whether reducing the dose to the pharyngeal constrictors with dysphagia-optimised intensity-modulated radiotherapy (Do-IMRT) will lead to an improvement in long-term swallowing function without having any detrimental impact on disease-specific survival outcomes.

Methods/design: The DARS trial (CRUK/14/014) is a phase III multicentre randomised controlled trial (RCT) for patients undergoing primary (chemo) radiotherapy for T1-4, N0-3, M0 pharyngeal cancers. Patients will be randomised (1:1 ratio) to either standard IMRT (S-IMRT) or Do-IMRT. Radiotherapy doses will be the same in both groups; however, in patients allocated to Do-IMRT, irradiation of the pharyngeal musculature will be reduced by delivering IMRT identifying the pharyngeal muscles as organs at risk. The primary endpoint of the trial is the difference in the mean MD Anderson Dysphagia Inventory (MDADI) composite score, a patient-reported outcome, measured at 12 months post radiotherapy. Secondary endpoints include prospective and longitudinal evaluation of swallow outcomes incorporating a range of subjective and objective assessments, quality of life measures, loco-regional control and overall survival. Patients and speech and language therapists (SLTs) will both be blinded to treatment allocation arm to minimise outcome-reporting bias.

Discussion: DARS is the first RCT investigating the effect of swallow sparing strategies on improving long-term swallowing outcomes in pharyngeal cancers. An integral part of the study is the multidimensional approach to swallowing assessment, providing robust data for the standardisation of future swallow outcome measures. A translational sub-study, which may lead to the development of future predictive and prognostic biomarkers, is also planned.

(Continued on next page)
The experimental Do-IMRT technique aims to spare the PCM lying outside the high dose CTV. For oropharyngeal primaries, mandatory mean dose constraints of <50 Gy to the volume of SMPCM lying outside CTV_6500 (PlanSMPCM) together with an optimal mean dose constraint of <20 Gy to the volume of IPCM lying outside CTV_6500 (PlanIPCM) have been defined. Likewise, for hypopharyngeal tumours, mandatory and optimal mean dose constraints of <50 Gy and <40 Gy have been set for PlanIPCM and PlanSMPCM respectively.

Crucially, it is important to note that although the PCM will overlap with the PTVs, there will be no sparing of the constrictor muscles that lie within the PTV_6500.

Planning objectives will be prioritised in the following order: critical organ constraints (spinal cord and brainstem); PTV_6500 coverage; constrictor constraints; PTV_5400 coverage; parotid gland constraints and other non-specified normal tissue.
Why IMRT in Head and Neck Cancer?

- 2 Most common late sequelae of RT for HNC are:
  - Xerostomia
  - Dysphagia

- IMRT aims to reduce these sequelae.

- Reducing these sequelae improves QOL.
Factors influencing the rational use of IMRT for head-and-neck cancer

Figure 1 Factors in favor or against IMRT are represented by a rectangle on the right or on the left of the vertical solid line, respectively. A question mark inside a rectangle indicates too much uncertainty for using the factor in the graph.
Conclusion

- T/t by IMRT or 3D CRT: Important to delineate the relevant OAR’s to predict potential complications.

- Submandibular gland sparing should be done with utmost caution.

- Late dysphagia prevention: Reduce dose to the pharyngeal constrictors & larynx.

- PTV coverage should remain the highest priority.

- QOL endpoints should be the benchmark for further studies.
TRAIN YOUR BRAIN TO DECREASE THE DOSES TO XEROSTOMIA & DARS STRUCTURES BUT NOT AT THE COST OF PTV
RESTRAIN YOURSELF FROM GIVING MORE CONSTRAIN OTHERWISE TUMOR WILL SUSTAIN.