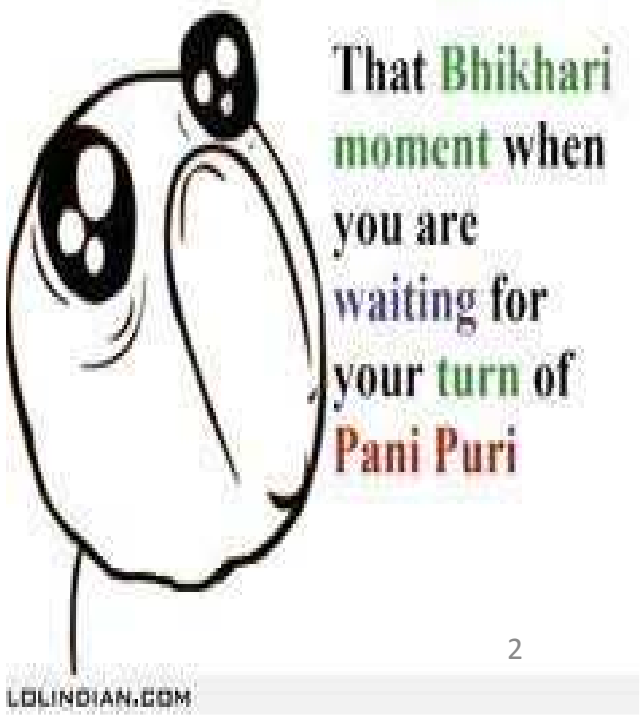
CLINICAL TRIALS
REDUCING
RADIATION INDUCED
XEROSTOMIA & DYSPHAGIA
IN HEAD & NECK CANCERS

Dr. KANHU CHARAN PATRO

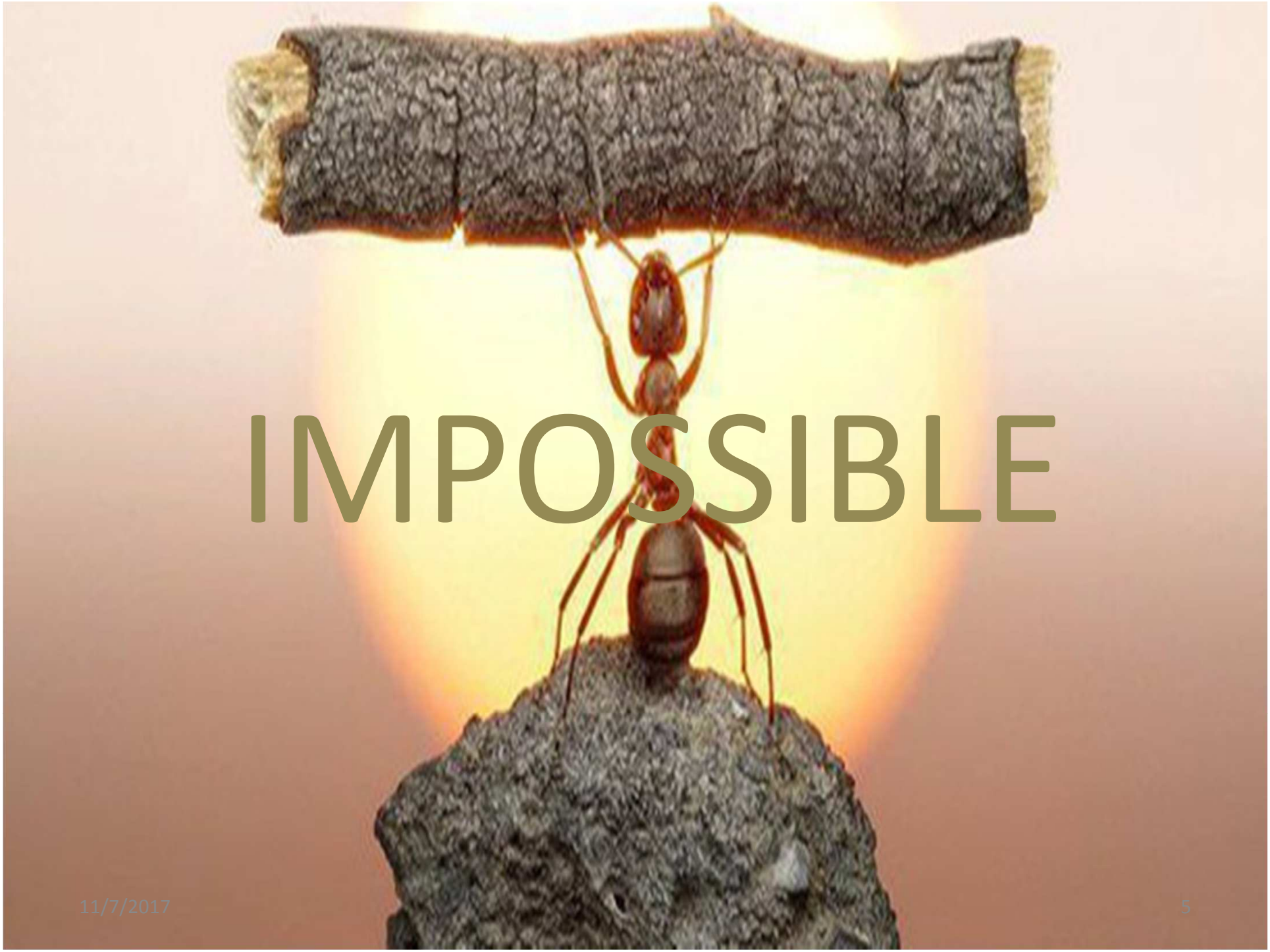
THAT PANIPURI MOMENT

DOCTOR : WHAT TRETMENT YOU HAVE GIVEN , I AM NOT ABLE TO EAT PANIPURI.



1. TRISMUS
2. DYSGUESIA
3. **XEROSTOMIA**
4. **DYSPHAGIA**

ZEROING THE XEROSTOMIA & DISCARDING THE DYSPHAGIA


IMPOSSIBLE

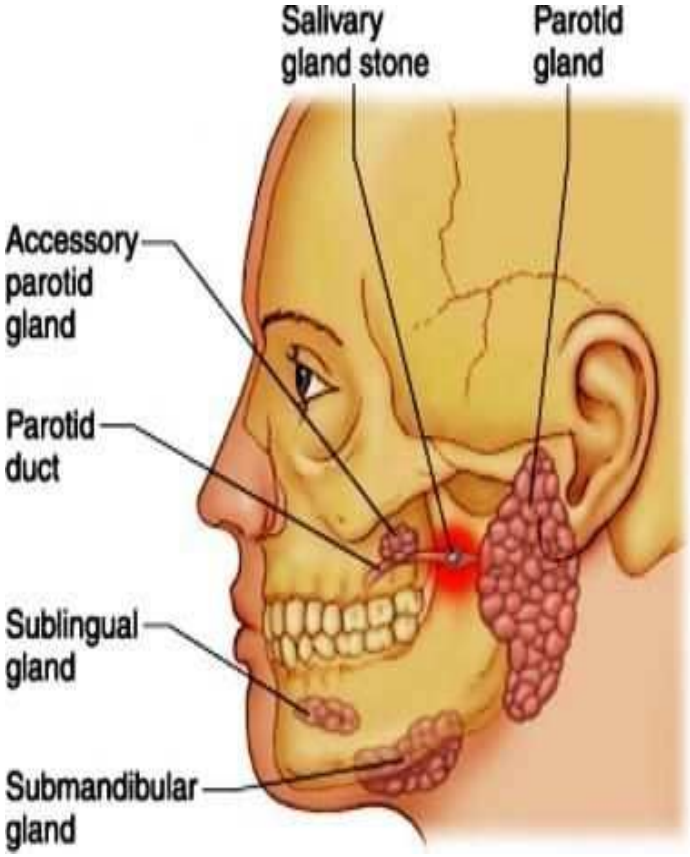
PARSPORT STUDY

~~PASSPORT~~

2011

THE LANCET Oncology

The source


Salivary gland stone
Parotid gland
Accessory parotid gland
Parotid duct
Sublingual gland
Submandibular gland

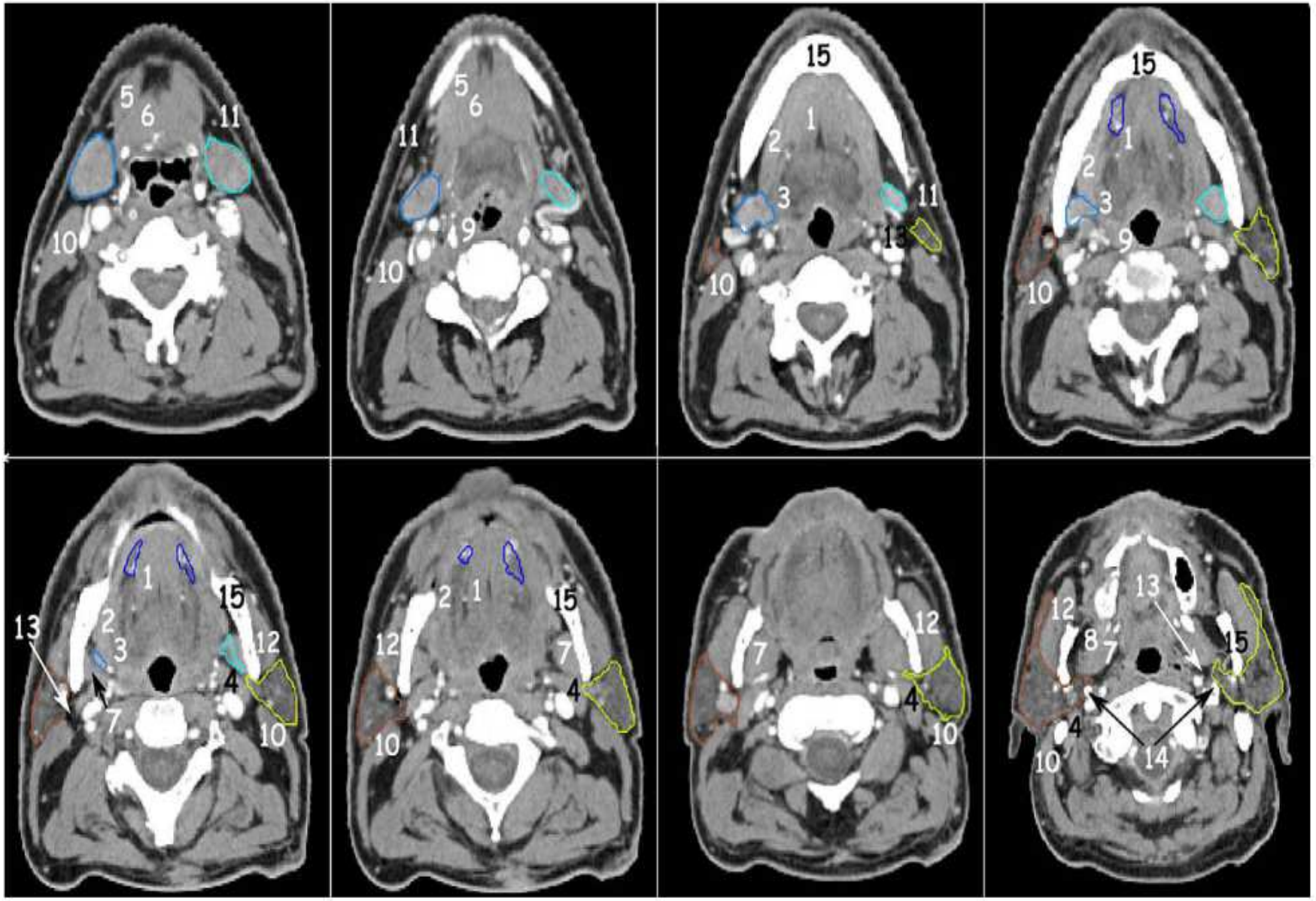


Fig. 2. Major salivary glands: the parotid glands are depicted in brown (left) and green (right), the submandibular glands are depicted in blue (the left one is brighter than the right one) and the sublingual glands are coloured dark blue (anterior part oral cavity). (1) Genioglossus m., (2) mylohyoid 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.

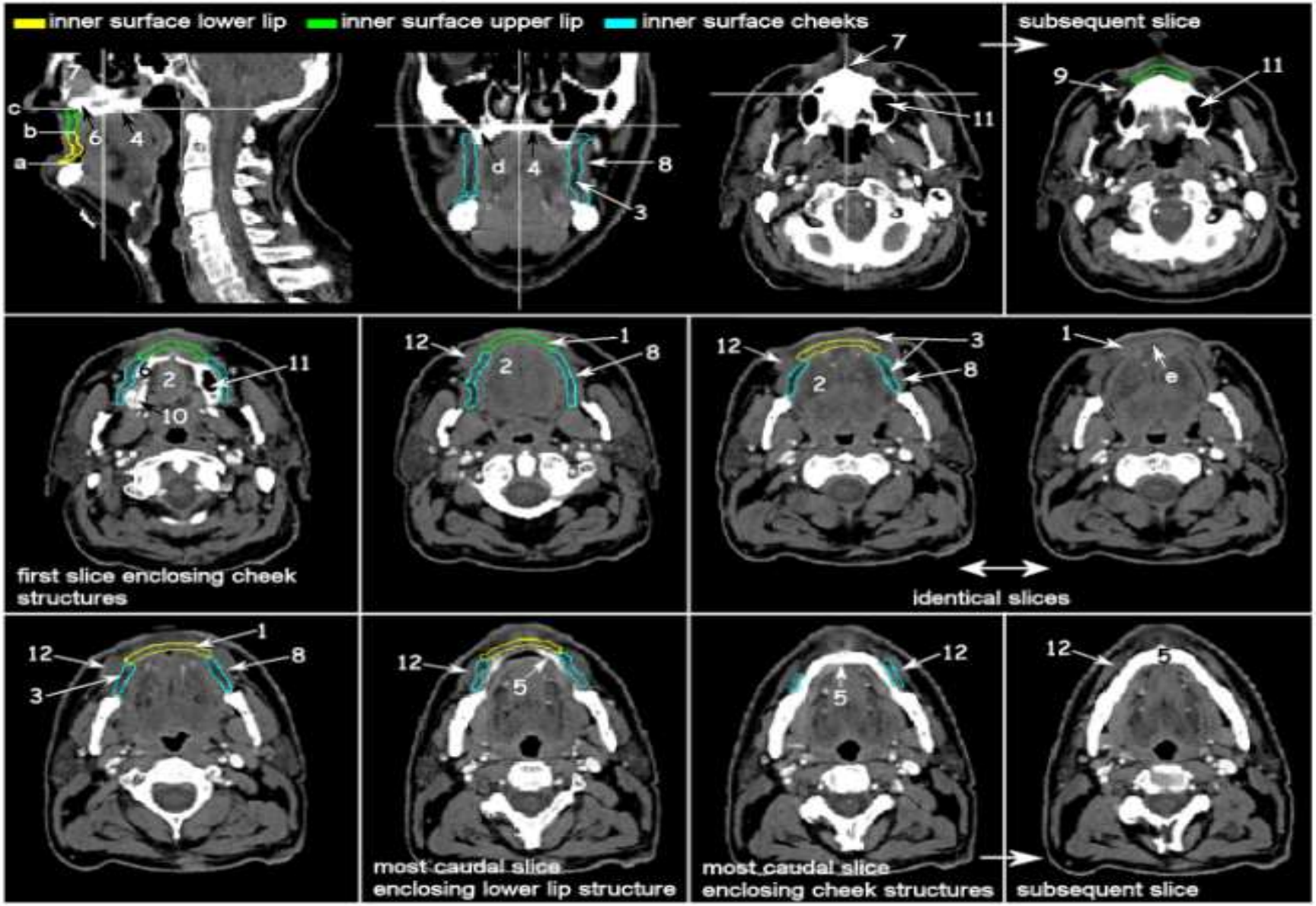


Fig. 5. Inner surface of the lower and upper lip plus cheek structure: (a) depicts the caudal border of the lower lip; (b) the cranial border of the lower lip and caudal border of the upper lip; (c) depicts the cranial border of the upper lip; (d) the upper edge of the inner surface cheek structure (transition between alveolar process maxilla – maxillary sinus); (e) the fatty tissue present posterior to the orbicularis oris muscle (m.). (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.

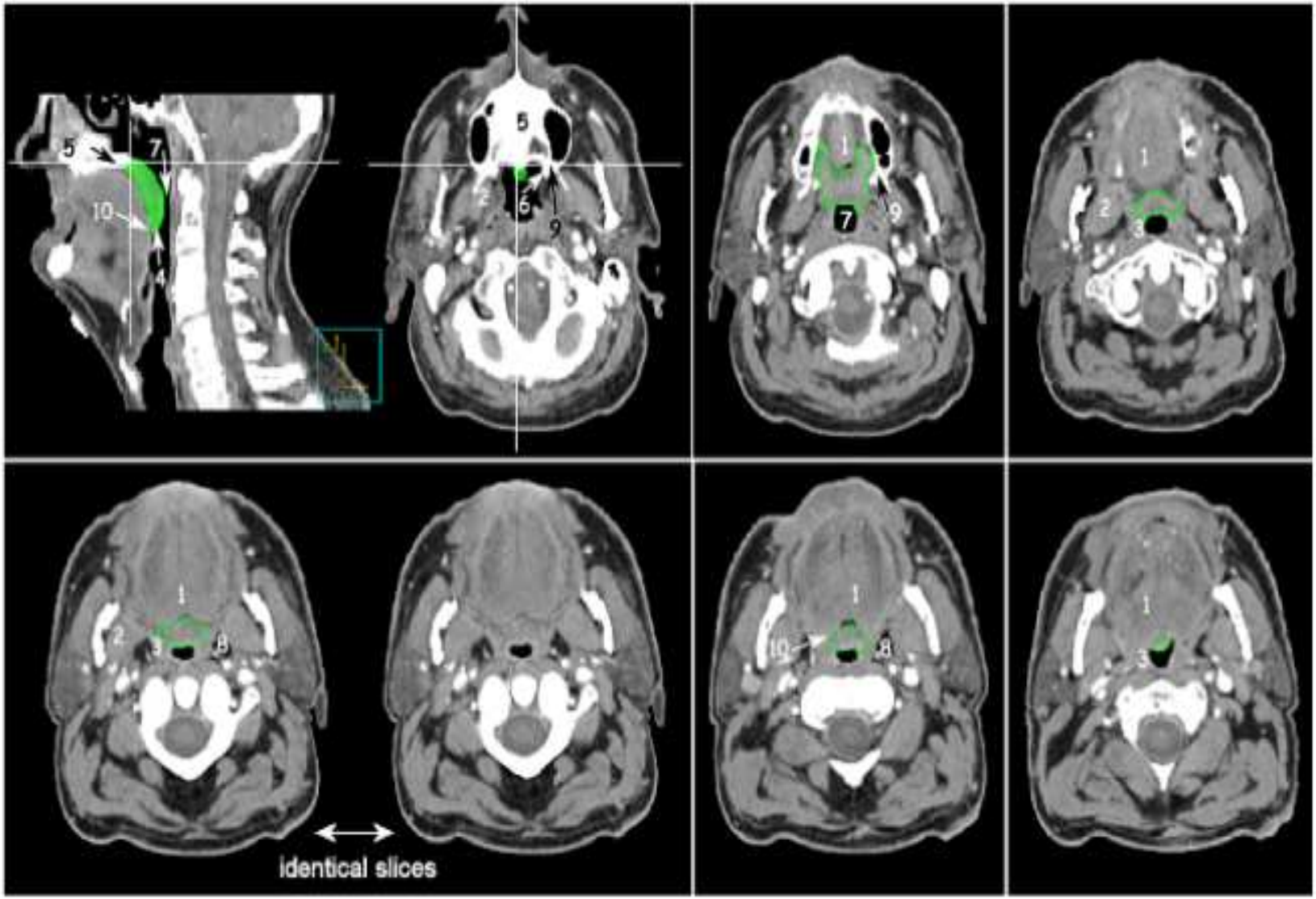
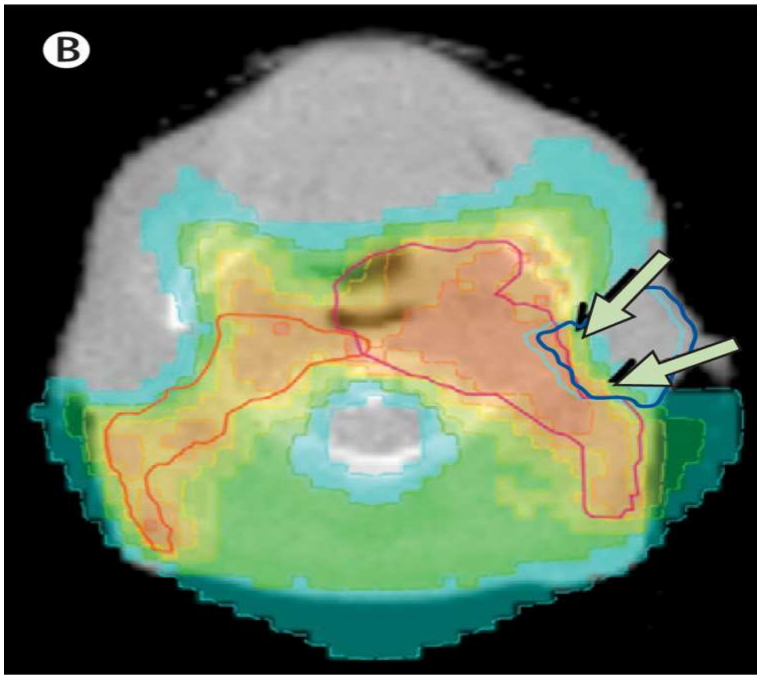
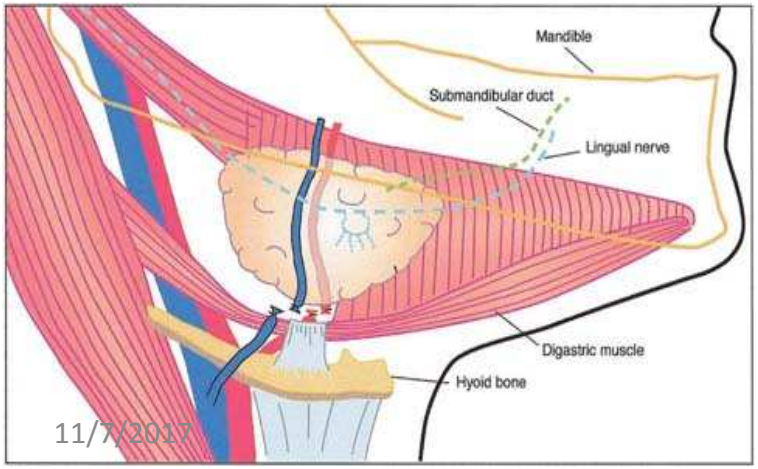


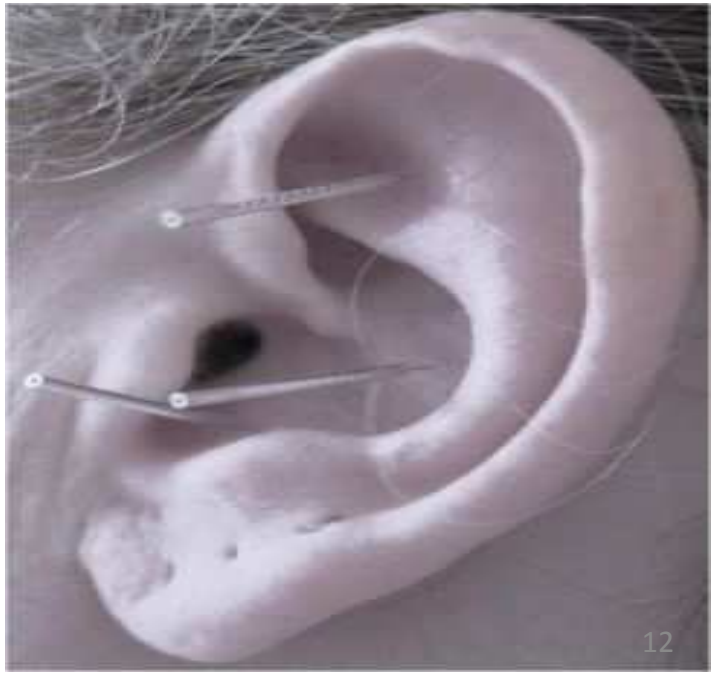
Fig. 4. Soft palate: the soft palate structure is depicted by the green contour. The sagittal view is depicted in the upper left corner, displaying the cranial border of the soft palate: the nasopharyngeal mucosal space/air lumen and the hard palate (see corresponding transversal plane). The two lower 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.

Organ at risk	Anatomic boundaries					
	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Parotid gland	External Auditory Canal Mastoid Process	Post. part Submandibular space	Masseter M., Post. border Mandibular bone, Medial and Lateral Pterygoid M.	Ant. belly Sternocleidomastoid M., Lat. side post. belly of the Digastric M. (posteriormedial)	Subcutaneous fat, Platysma	Post. belly of the Digastric M., Styloid process, Parapharyngeal space
Sub mandibular gland	Medial Pterygoid M, Mylohyoid M.	Fatty tissue	Lat. surface Mylohyoid M., Hyoglossus M.	Parapharyngeal space, Sternocleidomastoid M.	Med. surface Medial Pterygoid M., Med. surface Mandibular Bone, Platysma	Lat. surface Mylohyoid M., Hyoglossus M., Superior & Middle Pharyngeal Constrictor M., Anterior belly of the Digastric M.
Sub lingual gland	(Mucous membrane covering the floor of the mouth), crossing lingual septum – Intrinsic Tongue Muscles	Ant. part Mylohyoid M., Geniohyoid M.	Ant. part surface Mandibular bone Mylohyoid M.	Hyoglossus M.	Ant. part Med. surface Mandibular Bone, Mylohyoid M.	Genioglossus m.

Methods preventing xerostomia



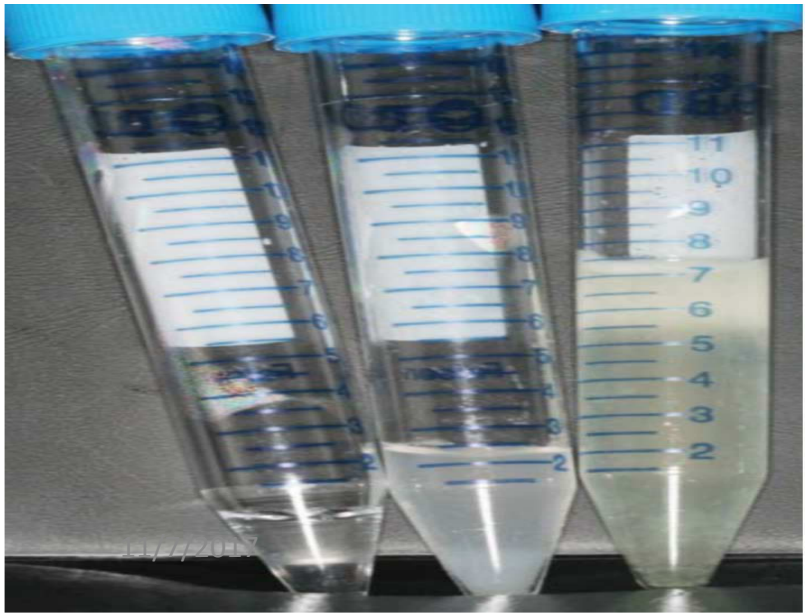




Unstimulated salivary flow

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

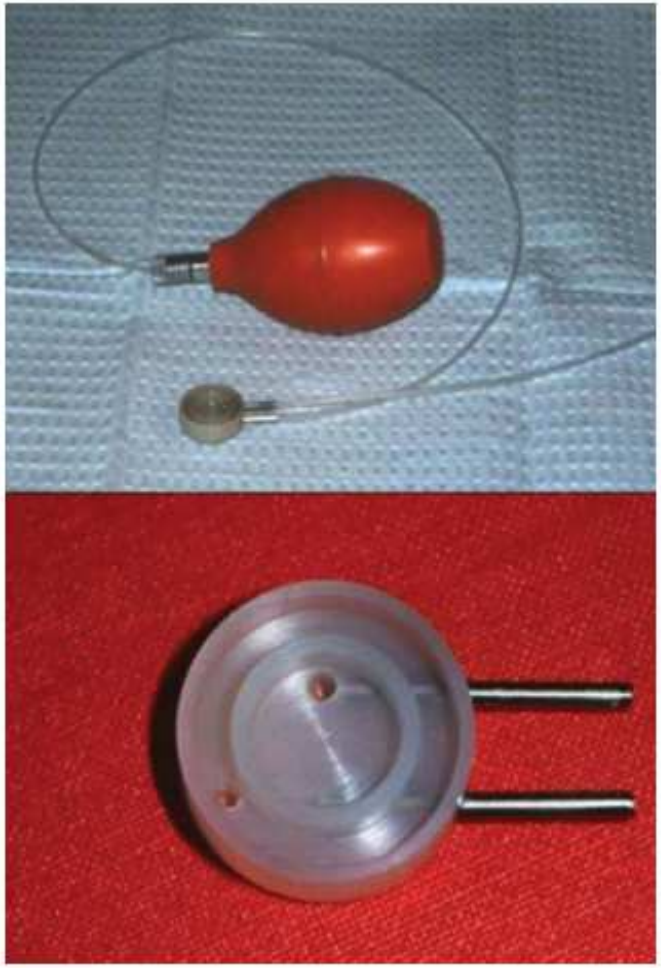


Figure 6. A modified Carlson-Crittenden device for collecting parotid gland saliva.

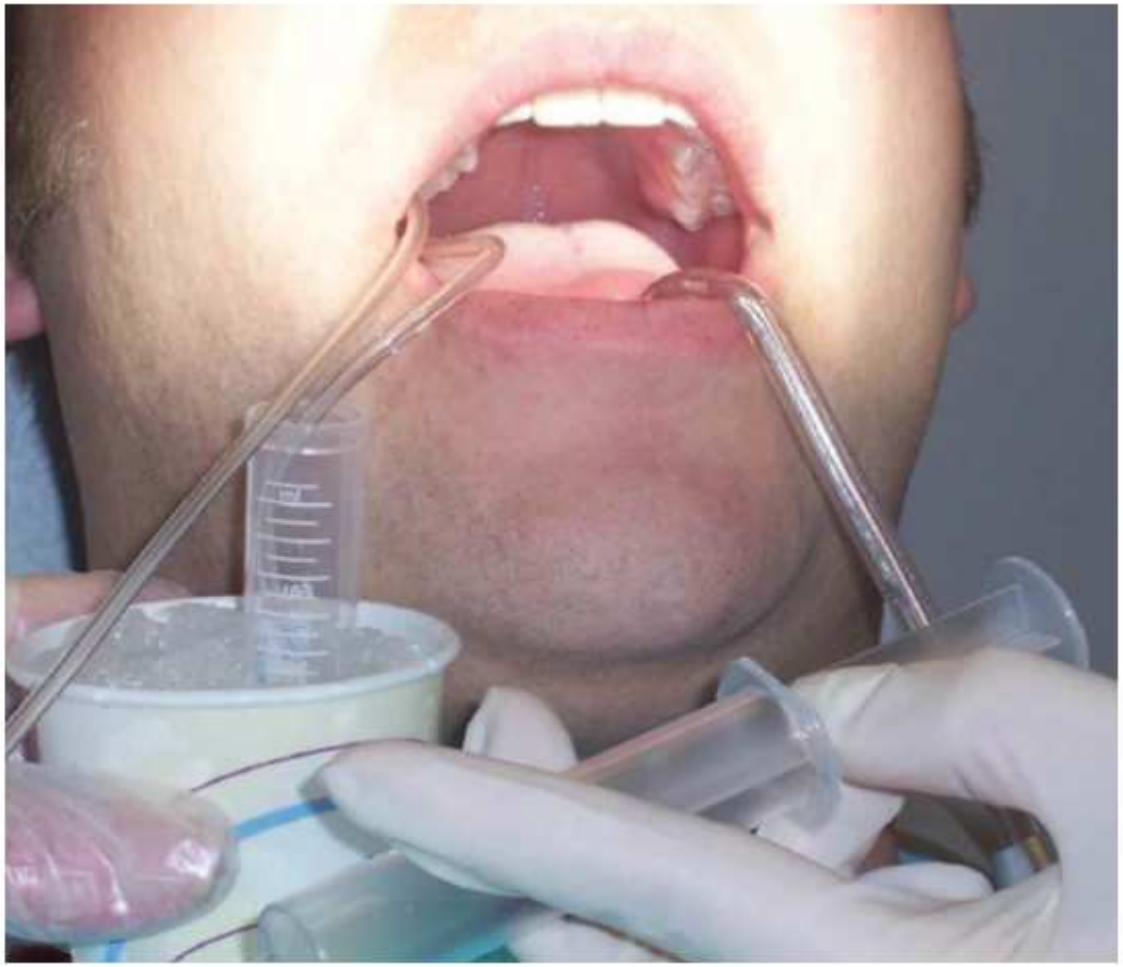
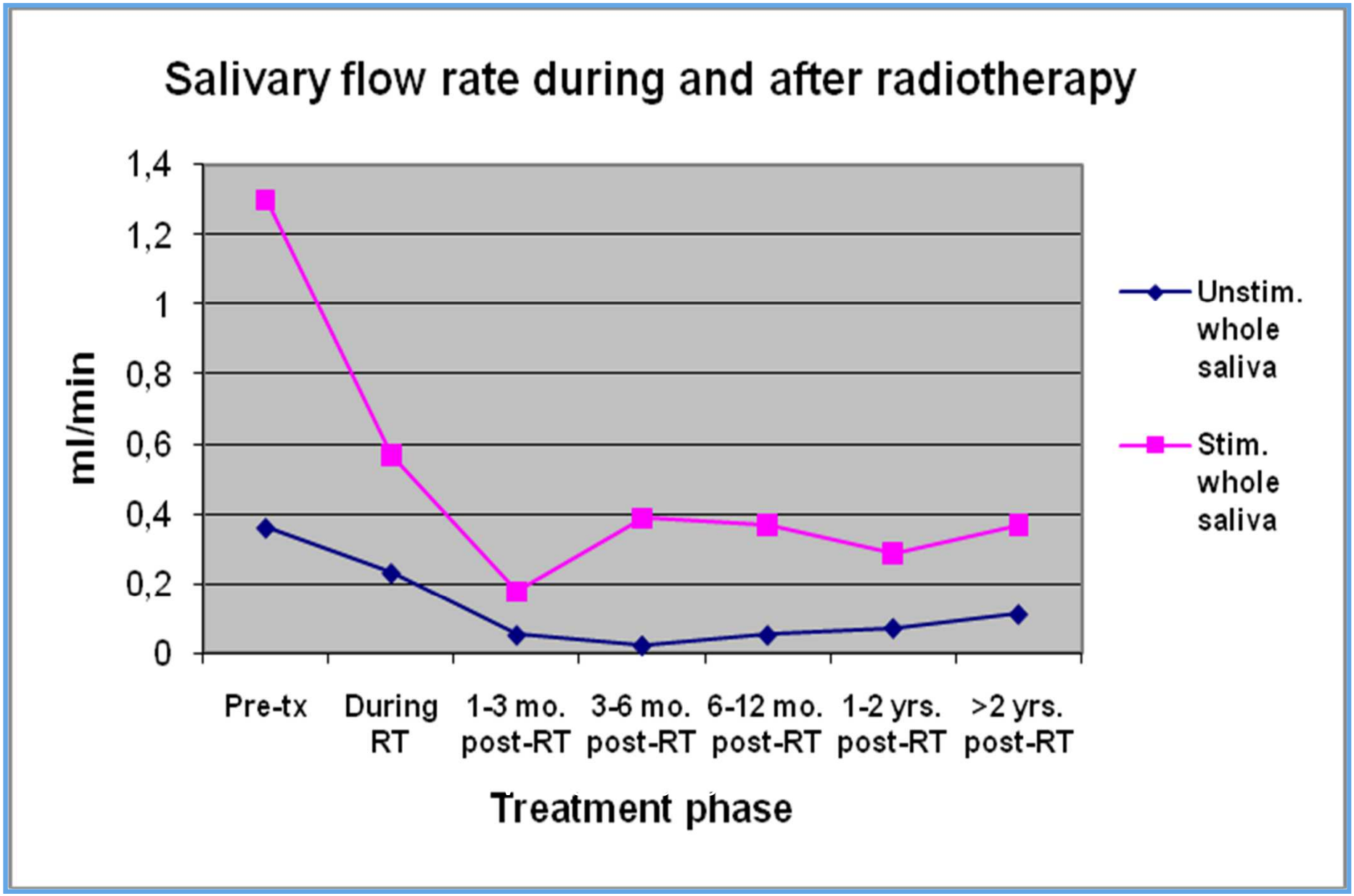


Figure 7. A custom-made Wolff saliva collector for submandibular and sublingual gland saliva collection.

SIALOMETRY

Table 1 Sialometry.

	Salivation at rest (ml/min)	Stimulated salivation (ml/min)
Hyposalivation	< 0.1	< 0.7
Low flow	0.1–0.25	0.7–1.0
Normal	0.25–0.35	1.0–3.0


Salivary flow rate during and after radiotherapy
1,4
1,2
1
0,8
0,6
0,4
0,2
0
ml/min
Pre-tx
During RT
1-3 mo. post-RT
3-6 mo. post-RT
6-12 mo. post-RT
1-2 yrs. post-RT
>2 yrs. post-RT
Treatment phase
Unstim. whole saliva
Stim. whole saliva

XEROSTOMIA QUESTIONNAIRE

Table 1. Xerostomia questionnaire (XQ)

Question	Score			
	1	2	3	4
	not at all	slightly	moderately	a lot
Communication	Frequency of taking water while eating			
Eating	Frequency of taking water while eating			
Normal times	Frequency of taking water at normal times			
Sleeping	Frequency of sleeping problems due to dryness			

	Patients, n	Site	Stage	Radiotherapy technique	Proposed constraint (mean dose)	Objective endpoint	Subjective endpoint	QoL endpoint	Patients without locoregional control, n*
Chao (2001)[16]	41	All	II–IV	3D/IMRT	≤32 Gy	SF	XQ	–	"
Eisbruch (2001)[17]	84	All	I–IV	3D/IMRT	≤26 Gy	SF	XQ	–	"
Henson (2001)[18]	20	All	II–IV	3D	≤26 Gy	SF	–	Yes	"
Maes (2002)[19]	39	All	I–IV	3D	≤20 Gy	SGS	VAS	–	28
Münter (2004)[15]	18	All	I–IV	IMRT	≤26 Gy	SGS	–	–	17
Parliament (2004)[20]	23	All	I–IV	IMRT	≤26 Gy	SF	XQ	Yes	21
Saarilahti (2005)[21]	17	OP/NP	II–IV	IMRT	≤25·5 Gy	SF	–	–	17
Blanco (2005)[22]	65	All	I–IV	3D/IMRT	≤25·8 Gy	SF	–	–	"
Scrimger (2007)[23]	47	All	I–IV	IMRT	≤26 Gy	SF	XQ	Yes	"

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*)

S16

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

QUANTITATIVE ANALYSES OF NORMAL TISSUE EFFECTS IN THE CLINIC (QUANTEC) DATA

LENT SOMA SCALE XEROSTOMIA

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

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective	Occasional dryness	Partial but persistent dryness	Complete dryness non-debilitating	Complete dryness debilitating
Objective		Scant saliva	Absence of moisture, sticky, viscous saliva	Absence of moisture, coated mucosa
Management		Occasional saliva substitute or water, sugarless candy or gum, sialogogues	Frequent saliva substitute or water, sugarless candy or gum, sialogogues	Needs saliva substitute or water in order to eat, sugarless candy or gum, sialogogues

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 Tanay, 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.

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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

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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.

Lancet Oncol 2011; 12: 127–36

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See Comment page 110

*Details given in the webappendix (p 2)

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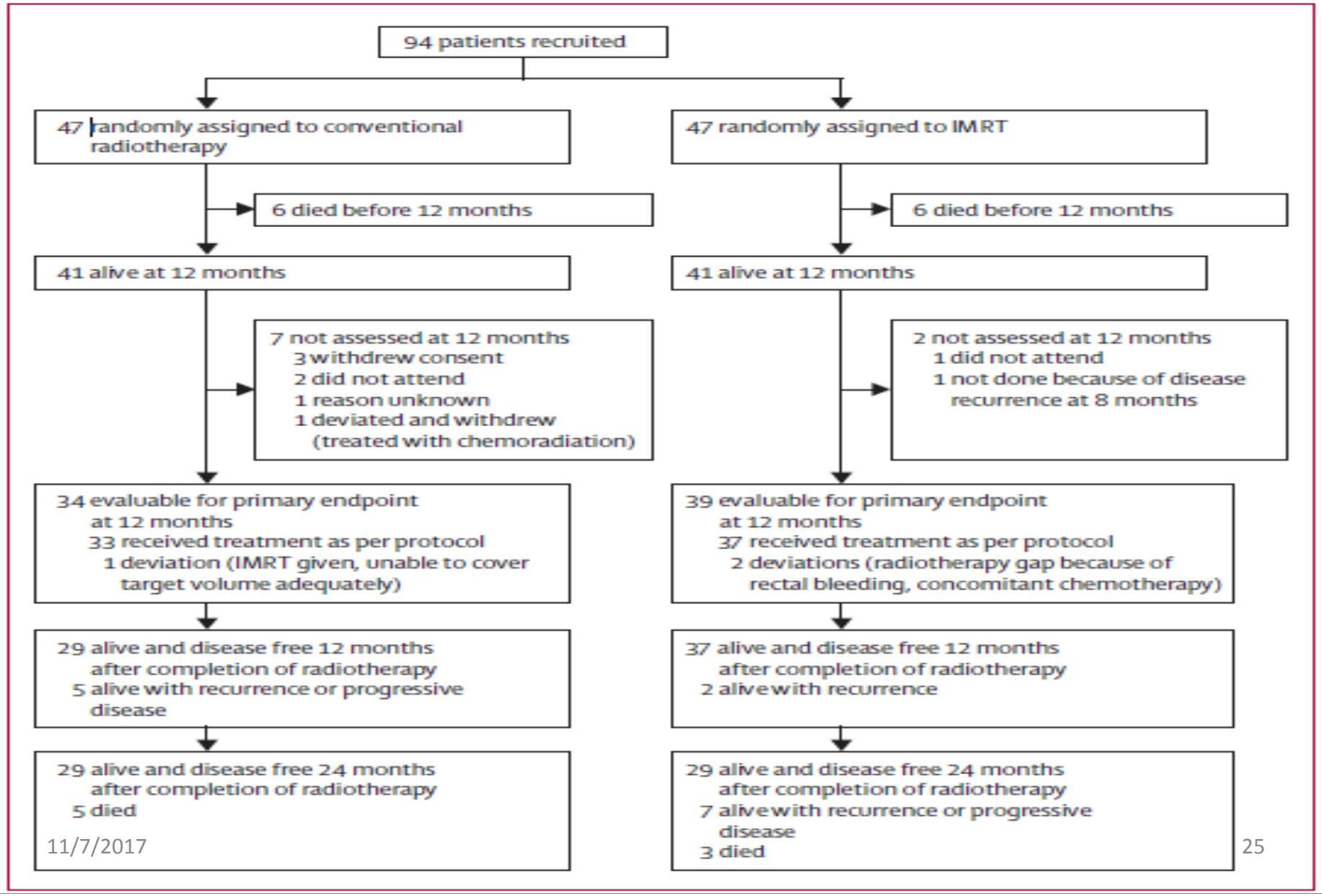
Study profile



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

Cont.

iv) <u>Elective Node</u> –

IMRT – 54 Gy in 25 fractions

Conventional – 50 Gy in 25 fractions

v) <u>Constraints</u> -

Spinal Cord - <50 Gy

Middle Ear & Inner Ear shielding

Parotid - <24 Gy to whole Contralateral Parotid (IMRT)

vi) <u>Acute Toxicity</u> –

Graded Weekly during RT upto 8 Weeks after treatment

NATIONAL CANCER INSTITUTE COMMON TOXICITY CRITERIA (VERSION 3)

vii) <u>Late Toxicities</u> –

At 3,6,12,18,24 months after RT

LENT SOMA & RTOG Scoring System

Cont.

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 1st year

2 monthly in 2nd year

3-6 monthly in 3rd 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

	Conventional radiotherapy (n=47)	IMRT (n=47)
Mean age at randomisation (years)	57·3 (10·2; 37·5–82·8)	59·5 (9·2; 44·1–77·1)
Number of women	12 (26%)	14 (30%)
WHO performance status		
0	42 (89%)	41 (87%)
1	5 (11%)	6 (13%)
Tumour site		
Oropharynx	40 (85%)	40 (85%)
[illegible]	[illegible]	[illegible]
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)
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)
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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%

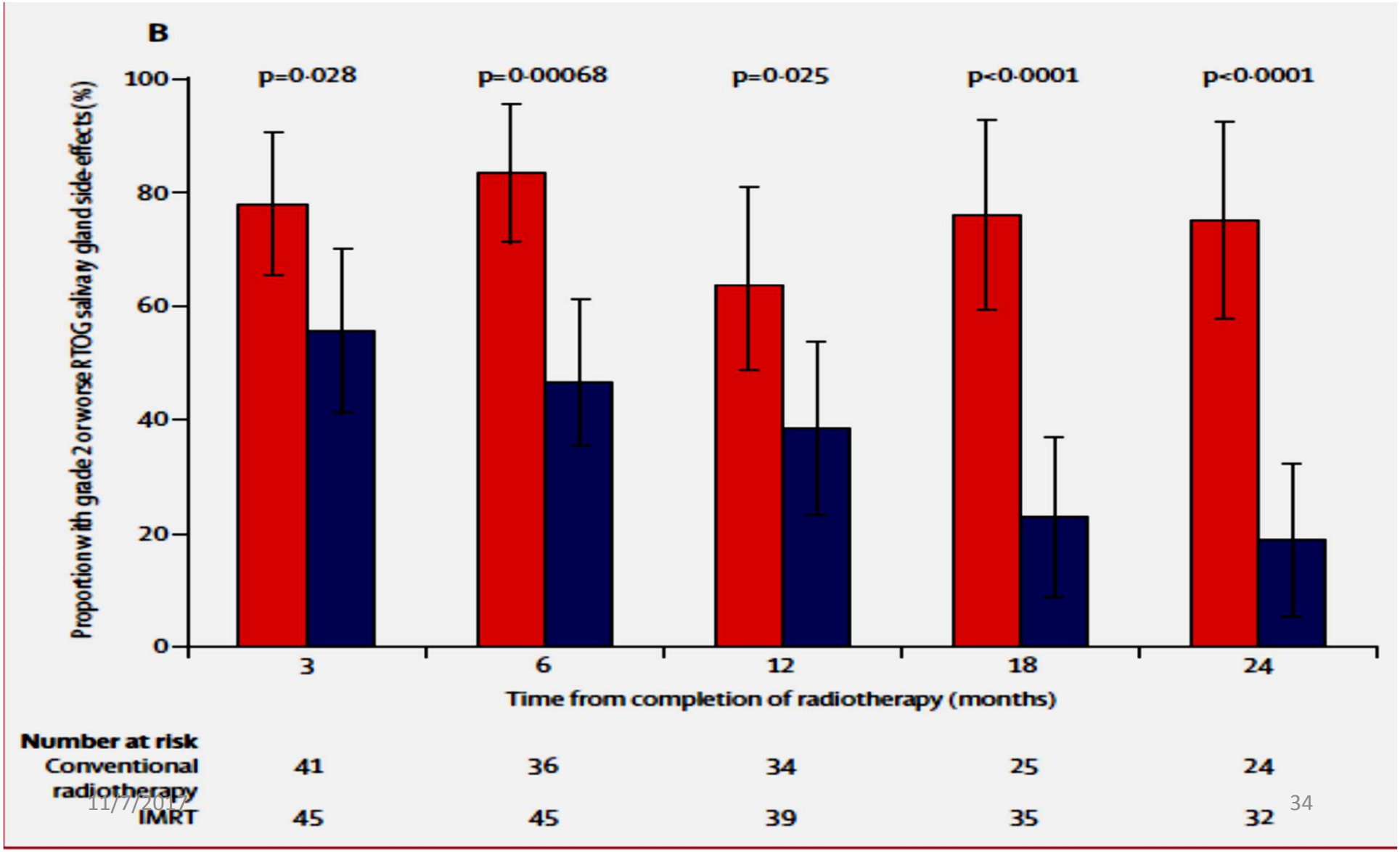
At 24 months: Conventional RT 20 (83%) of 24 patients.

IMRT 9(29%) of31 patients.

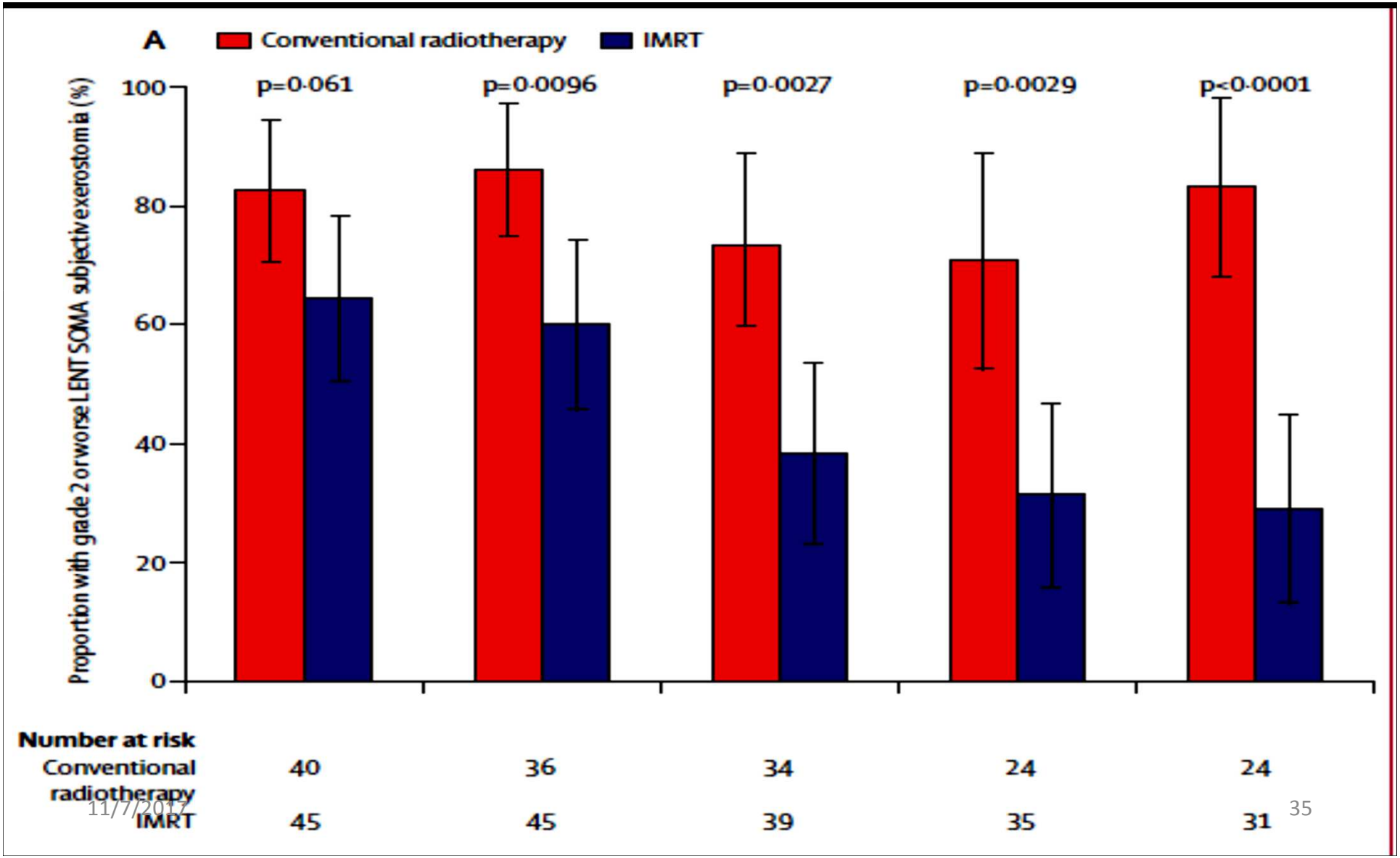
ORs 0.08, Absolute Reduction 54%

	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
Acute side-effects*												
Mucositis/stomatitis (clinical)	44	0	1 (2%)	16 (36%)	27 (61%)	0	46	1 (2%)	2 (4%)	14 (30%)	29 (63%)	0
Rash (dermatitis)†	44	0	3 (7%)	17 (39%)	24 (55%)	0	47	1 (2%)	9 (19%)	21 (45%)	15 (32%)	1 (2%)
Mucositis/stomatitis (functional/symptomatic)	39	1 (3%)	0	21 (54%)	17 (44%)	0	40	2 (5%)	3 (8%)	11 (28%)	24 (60%)	0
Dysphagia	44	0	1 (2%)	26 (59%)	17 (39%)	0	47	1 (2%)	6 (13%)	17 (36%)	23 (49%)	0
RTOG late side-effects§												
Salivary gland¶	42	1 (2%)	3 (7%)	26 (62%)	12 (29%)	0	46	0	12 (26%)	32 (70%)	2 (4%)	0
LENT SOMA late side-effects§												
Salivary gland‡,‖	41	0	3 (7%)	12 (29%)	14 (34%)	12 (29%)	46	0	8 (17%)	19 (41%)	15 (33%)	4 (9%)
(xerostomia‡)		0	3 (7%)	19 (46%)	14 (34%)	5 (12%)		0	8 (17%)	31 (67%)	4 (9%)	3 (7%)
LENT SOMA late side-effects§												
Salivary gland‡,‖	41	0	3 (7%)	12 (29%)	14 (34%)	12 (29%)	46	0	8 (17%)	19 (41%)	15 (33%)	4 (9%)
(xerostomia‡)		0	3 (7%)	19 (46%)	14 (34%)	5 (12%)		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)		20 (49%)	16 (39%)	3 (7%)	2 (5%)	0		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‖‖	41	19 (46%)	12 (29%)	7 (17%)	3 (7%)	0	46	27 (59%)	13 (28%)	6 (13%)	0	0

Rtog Garde 2 or worse



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.

	Conventional radiotherapy		IMRT	
	No measurable salivary flow* (n=25)	Measurable salivary flow (n=0)	No measurable salivary flow (n=18)	Measurable salivary flow (n=16)
Subjective xerostomia better than grade 2	6 (24%)	0	10 (56%)	12 (75%)
Subjective xerostomia grade 2 or worse	19 (76%)	0	8 (44%)	4 (25%)

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.

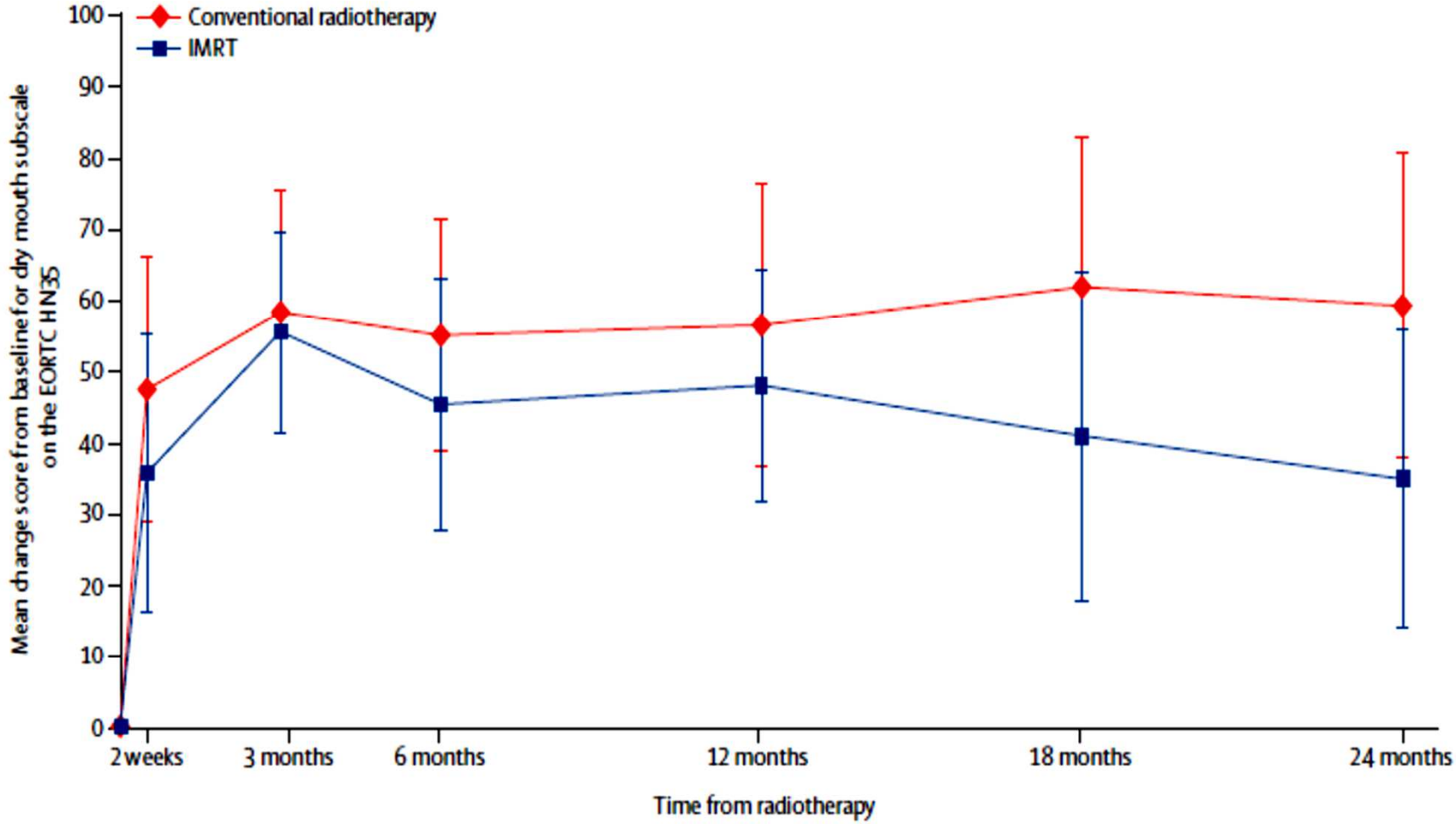
Table 3: Concordance between unstimulated contralateral saliva flow and LENT SOMA subjective xerostomia at 12 months

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:	Not at all	A little	Quite a bit	Very much
31. Have you had pain in your mouth?	1	2	3	4

Mean change score from baseline for dry mouth subscale-EORTC HN35



Conventional radiotherapy	26	24	23	23	21	18
IMRT	28	30	25	25	22	22
Difference in mean (99% CI)	11·7 (−14·4 to 37·8)	2·8 (−18·4 to 24·0)	9·7 (−13·5 to 32·9)	8·5 (−15·9 to 33·0)	21·0 (−8·9 to 50·9)	24·4 (−4·3 to 53·2)

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 : Convetional RT 2.8
IMRT 8.3

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

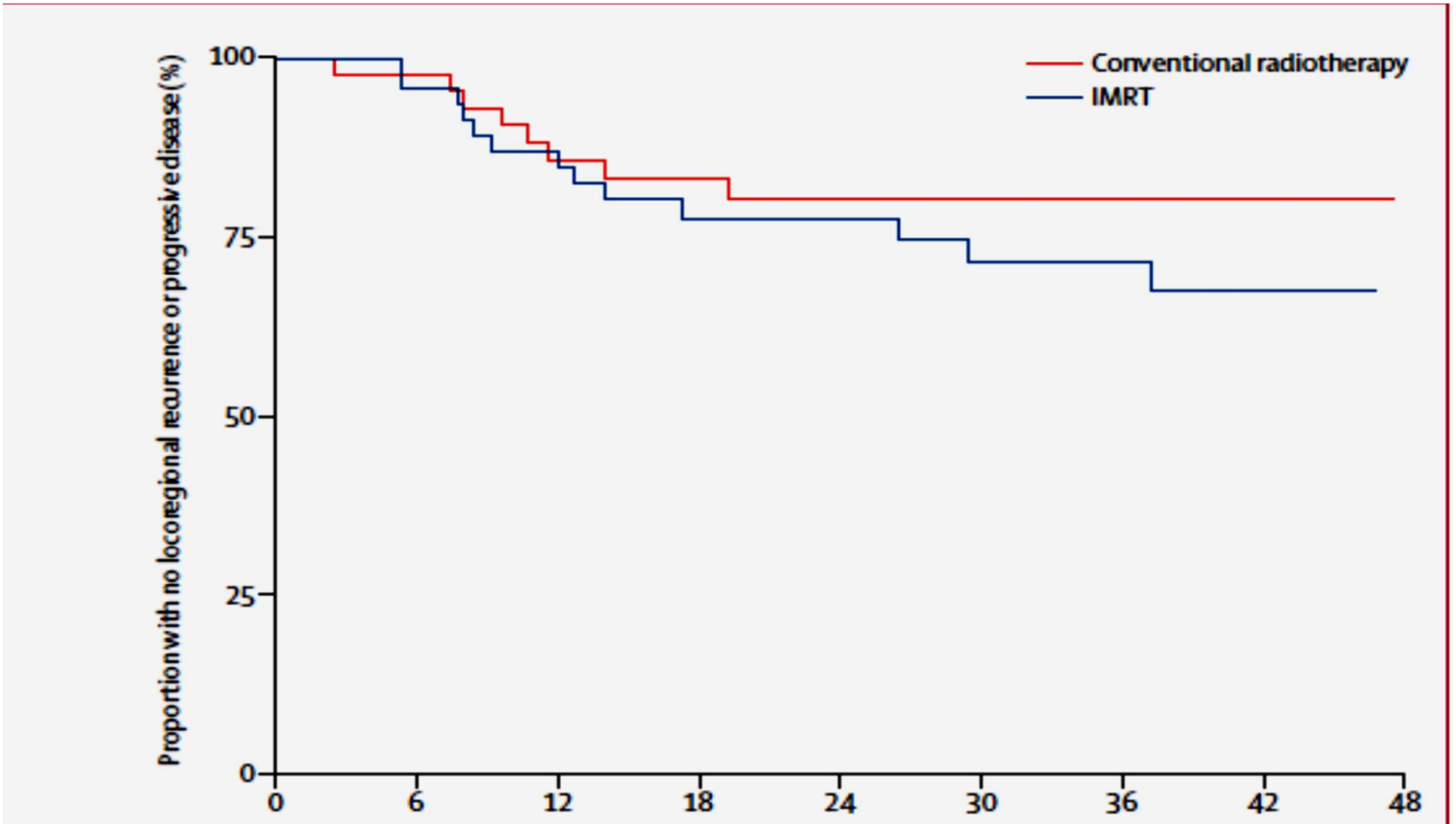
Results Cont.

4) LOCOREGIONAL PFS : PFS At 2 years

Conventional RT 80%
IMRT 75%

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

Conventional RT – 07 recurrances total
05 in high dose volume
02 in both high dose & electively irradiated region



Number of events/at risk									
Conventional radiotherapy	0/47	1/42	5/34	1/30	1/29	0/23	0/19	0/15	0/8
IMRT	0/47	2/44	4/39	4/31	0/28	2/22	0/18	1/15	0/11

***Figure 4*: Kaplan-Meier plot of locoregional progression-free survival by treatment group**

Results Cont.

4) <u>OVERALL SURVIVAL</u> :
(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 :

Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 4, pp. 981–991, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.06.013

CLINICAL INVESTIGATION **Head and Neck**

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.,*
MAY 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.

study and received IMRT or CRT. Stimulated whole (SWS) and parotid (SPS) saliva flow were measured and Medical Outcomes Short Form 36 (SF-36), European Organization for Research and Treatment of Cancer (EORTC) core quetionnaire, and EORTC head-and-neck module (QLQ-H&N35) were completed at baseline and 2, 6, and 12 months after radiotherapy.
Results: Forty-six patients (88%) were in disease remission 12 months after radiotherapy. At 12 months postradiotherapy, 12 (50.0%) and 20 patients (83.3%) in the IMRT group had recovered at least 25% of 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
BEYOND PAROTID SPARING

Sparing Parotids…./Beyond Parotids…

- **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.(****)**

*. Kam MK et al. Prospective randomized study of IMRT on salivary gland function in early-stage NPC patients. JCO, 2007;25:4873-4879.
. Pow et al. Xerostomia and quality of life after IMRT vs conventional RT for early NPC. IJROBP, 2006;66:981-991.
***Nutting CM et al. Parotid-sparing IMRT vs conventional RT in head neck cancer (PARSPORT). Lancet Oncol 2011;12:127-136.
****. Eisbruch A, et al. Xerostomia and its predictors following parotid-sparing RT of head-and-neck cancer. IJROBP, 2001;50:695-704.

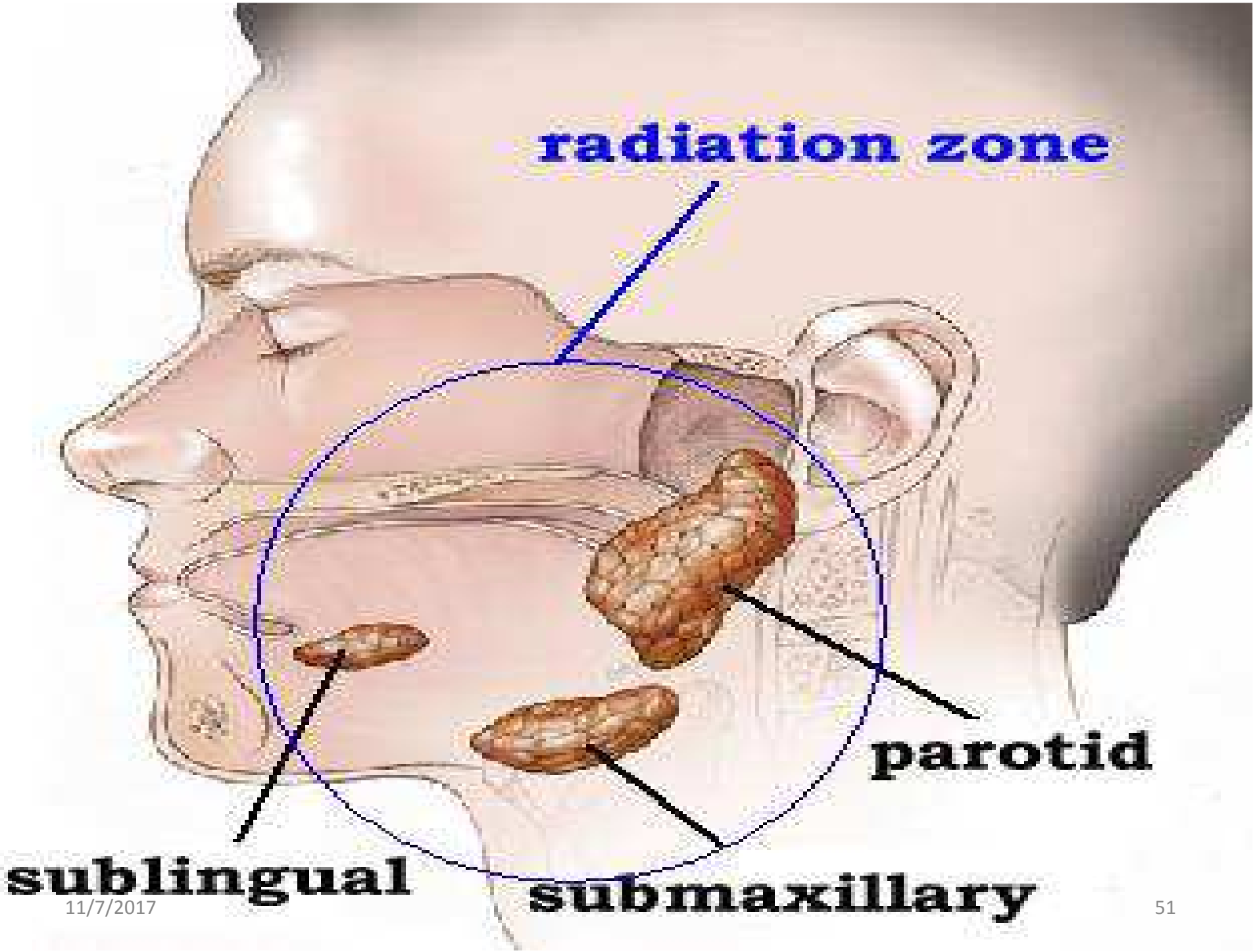
Discrepancy between preserved parotid function & patient-reported symptoms proves:

Parotid glands sparing alone is not sufficient

Role of the submandibular glands in:

Secreting saliva in the non-stimulated state

Rich in mucins


radiation zone
parotid
sublingual
submaxillary

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

Gland	Acinar Type	Viscosity	Percentage of Whole Unstimulated Daily Saliva
Parotid	Serous	Watery	25
Submandibular	Mixed	Seromucous	71
Sublingual	Mucous	Viscous	3-4
Minors	Mucous	Viscous	Trace

From Mandel ID. Sialochemistry in diseases and clinical situations affecting salivary glands. *Crit Rev Clin Lab Sci.* 1980;12:321.

Oral Oncology 50 (2014) 77–83

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

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

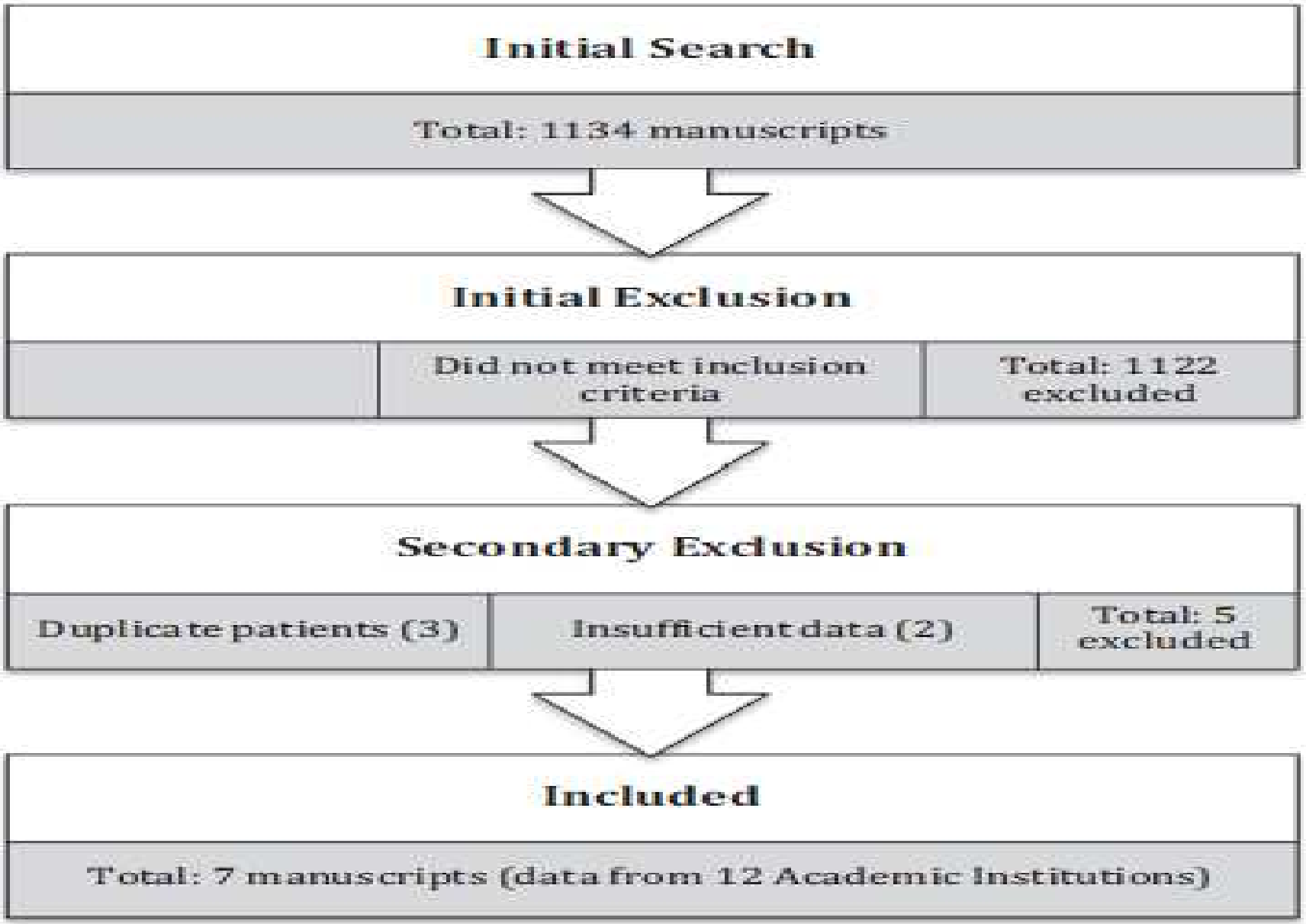


Figure 1. Algorithm of study selection.

Unstimulated salivary flow

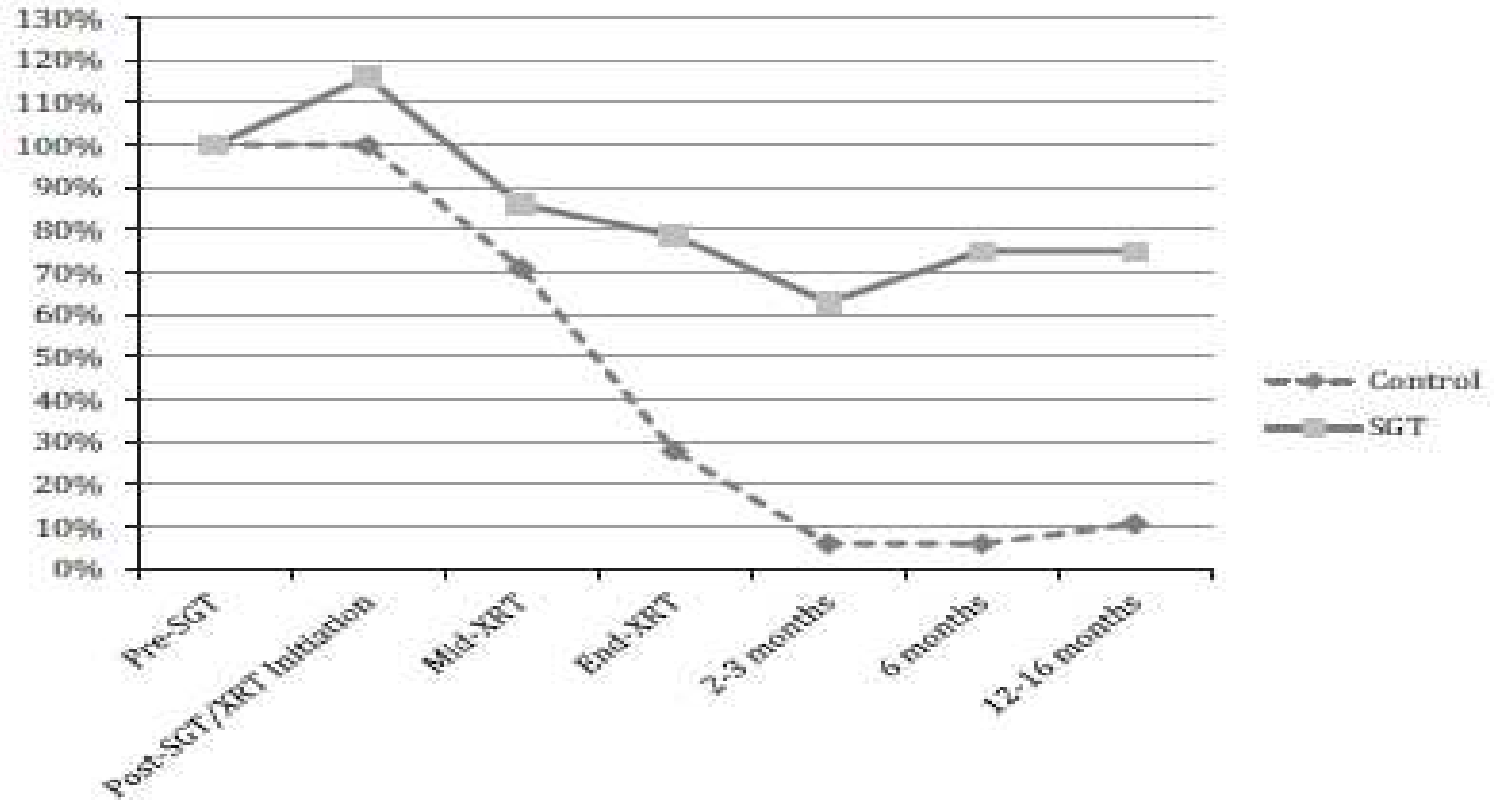


Figure 5. Salivary gland transfer (SGT) versus control, *unstimulated* salivary flow rates. Depicts mean change (%) from baseline before, during, and after radiation therapy (XRT).

Stimulated salivary flow

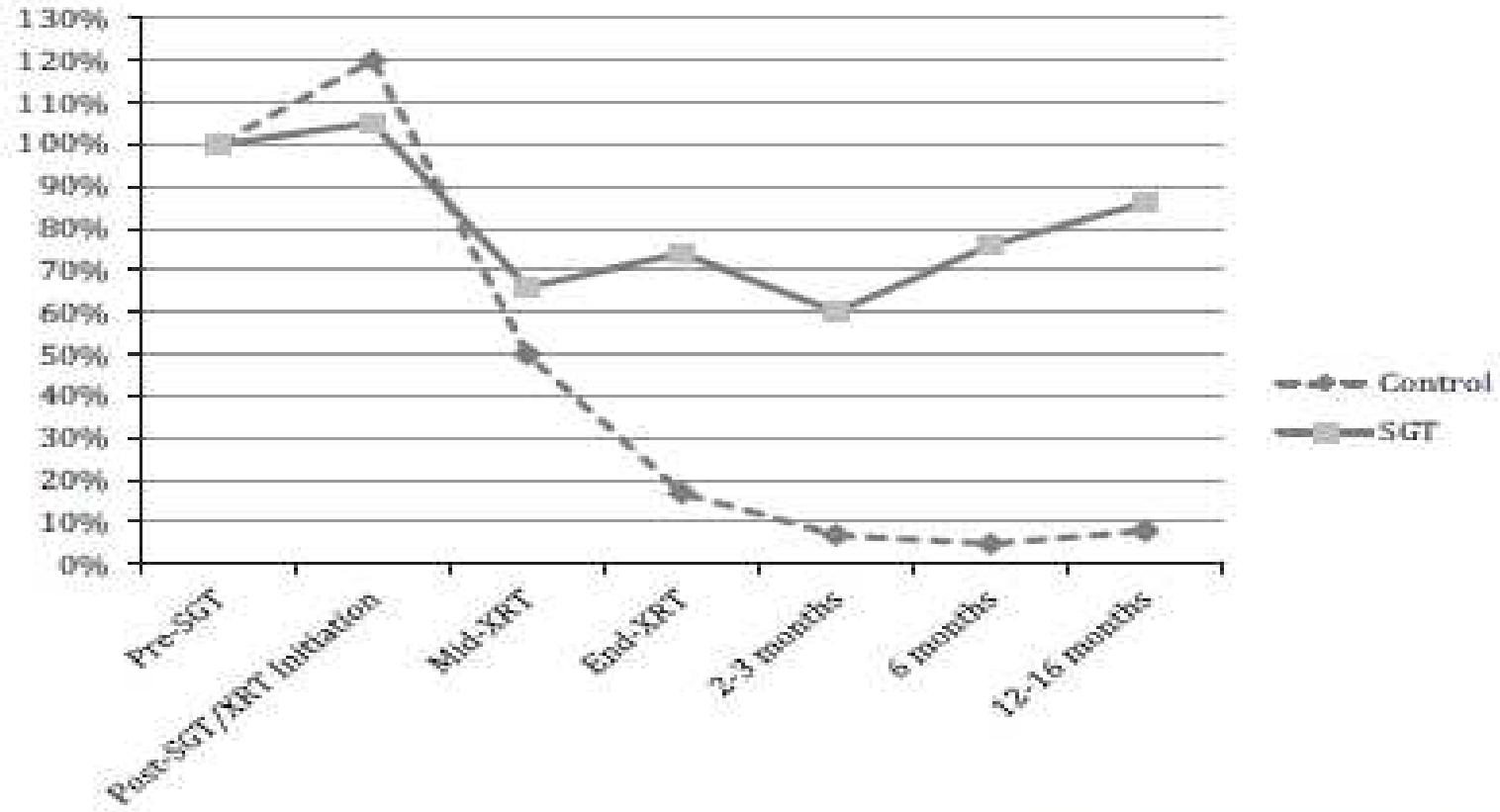


Figure 6. Salivary gland transfer (SGT) versus control, *stimulated* salivary flow rates. Depicts mean change (%) from baseline before, during, and after radiation therapy (XRT).

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

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 2, pp. 373–382, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.12.033

CLINICAL INVESTIGATION **Head and Neck**

DOSE-EFFECT RELATIONSHIPS FOR THE SUBMANDIBULAR SALIVARY GLANDS AND IMPLICATIONS FOR THEIR SPARING BY INTENSITY MODULATED RADIOTHERAPY

CAROL-ANNE MURDOCH-KINCH, D.D.S., PH.D.,* HYUGNJIN M. KIM, SC.D.,† KAREN A. VINEBERG, B.SC.,‡ JONATHAN A. SHIP, D.M.D.,* AND AVRAHAM EISBRUCH, M.D.‡

Departments of *Oral Medicine/Hospital Dentistry, †Biostatistics, and ‡Radiation Oncology, University of Michigan, Ann Arbor, MI

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.

Recurrence pattern

Chajon *et al. Radiation Oncology* 2013, **8**:132
http://www.ro-journal.com/content/8/1/132

RESEARCH Open Access

Salivary gland-sparing other than parotid-sparing in definitive head-and-neck intensity-modulated radiotherapy does not seem to jeopardize local control

Enrique Chajon[1*], Caroline Lafond[1,2,3], Guillaume Louvel[1], Joël Castelli[1], Danièle Williaume[1], Olivier Henry[1], Franck Jégoux[4], Elodie Vauléon[1], Jean-Pierre Manens[1], Elisabeth Le Prisé[1] and Renaud de Crevoisier[1,2,3]

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[a,*], Mauri Kouri[a], Juhani Collan[a], Aki Kangasmäki[a], Timo Atula[b], Heikki Joensuu[a], Mikko Tenhunen[a]

[a]*Department of Oncology, and* [b]*Department 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.

Acta Oncologica, 2012; 51: 735–742

informa
healthcare

ORIGINAL ARTICLE

Submandibular gland-sparing intensity modulated radiotherapy in the treatment of head and neck cancer: Sites of locoregional relapse and survival

JUHANI COLLAN[1], MIKA KAPANEN[1], ANTTI MÄKITIE[2], HEIDI NYMAN[1], HEIKKI JOENSUU[1], MIKKO TENHUNEN[1] & KAUKO SAARILAHTI[1]

[1]*Department of Oncology, Helsinki University Central Hospital, Finland, and* [2]*Department of Otorhinolaryngology – Head and Neck Surgery, Helsinki University Central Hospital, Finland*

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.**

*Eisbruch A. Reducing xerostomia by IMRT: what may, and may not, be achieved. J Clin Oncol 2007; 25: 4863–63.
** Houweling AC et al. Sparing the contralateral submandibular gland in oropharyngeal cancer patients: a planning study. Radiother Oncol 2008; 89: 64–70.

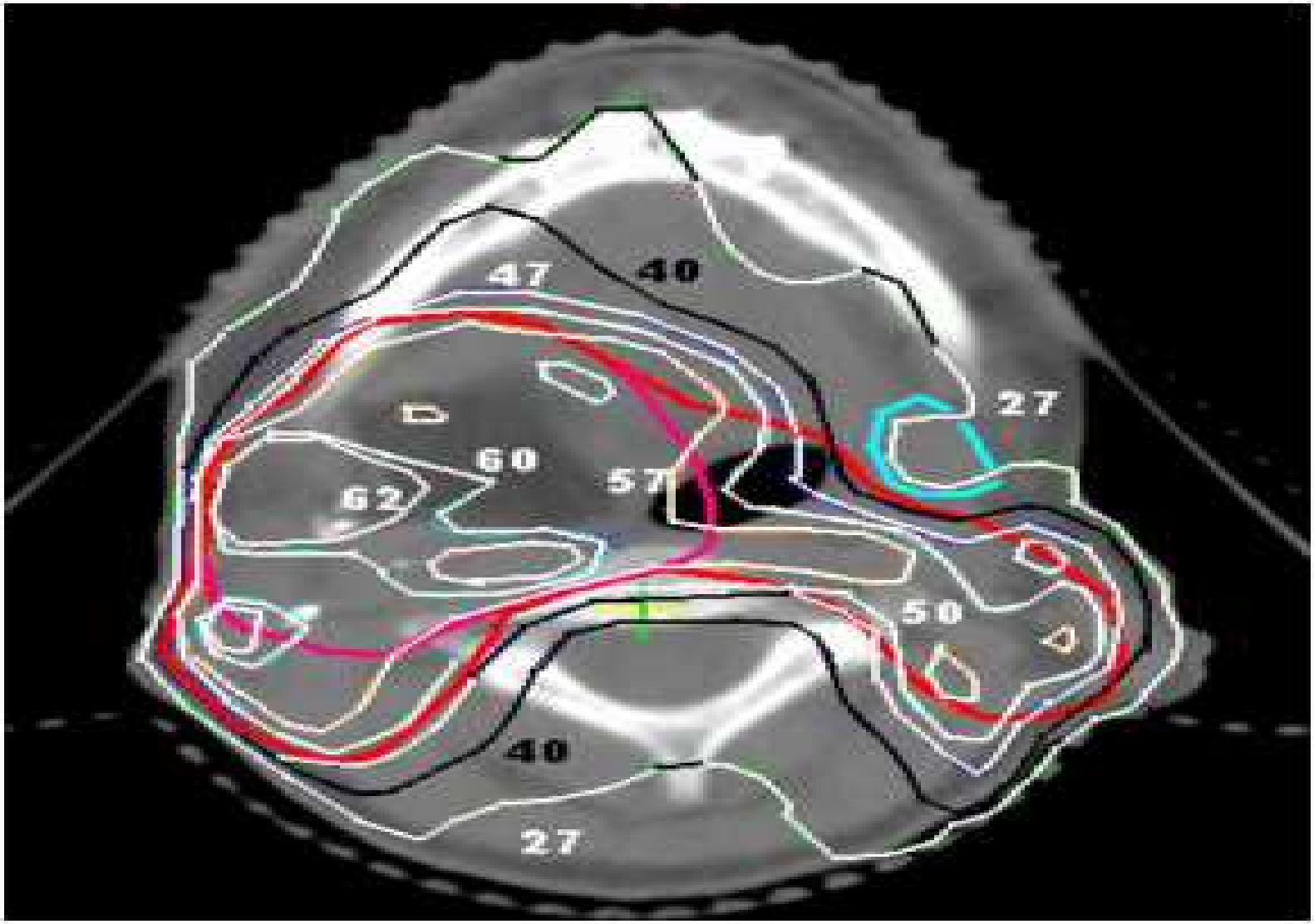


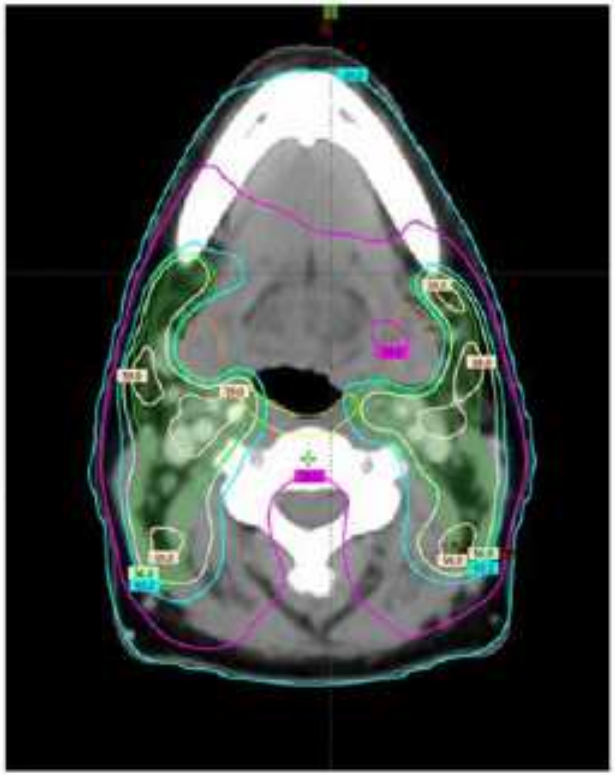
Fig. 2. An example of the cumulated dose distribution achieved by dose optimization. The outer red line: the CTV1 (the primary tumour site and the regional lymph nodes); the inner red line; the boosted volume (CTV2); the turquoise line: the contralateral submandibular gland.

SUBMANDIBULAR GLAND-SPARE OR SACRIFICE

TABLE I
REPORTED SUBMANDIBULAR GLAND INVOLVEMENT IN ORAL CAVITY SCC

Study	Pts (*n*)	SG inv (pts; *n*)	Spread (pts; *n*)
Byeon *et al.*[6]	44	2	2: contiguous
Chen *et al.*[7]	342	7	5: contiguous 1: adjacent lymph node 1: intraglandular lymph node
Junquera *et al.*[8]	31	0	None
Razfar *et al.*[9]	261	1	1: contiguous
Spiegel *et al.*[10]	169	9	3: adjacent lymph node 6: contiguous
Present	69	2	2: contiguous

SCC = squamous cell carcinoma; pts = patients; SG inv = submandibular gland involvement



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.

A K EBRAHIM/THE JOURNAL OF LARYNGOLOGY AND OTOLOGY/2011

16th MAY 2017 / HEAD & NECK

ONCOLOGY EDUCATIVE CARTOON/SLIDE -BY DR KANHU CHARAN PATRO, IMAGES & DATA- GOOGLE

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

*Murdoch-Kinch CA et al. Dose-effect relationships for the submandibular glands and implications for their sparing by IMRT IJROBP 2008; 72: 373–82.

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

Radiotherapy and Oncology 93 (2009) 545–552

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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 A, et al. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer.IJROBP 2001; 50: 695–704.
**Jellema AP et al, radiation dose to the salivary glands and oral cavity predict patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with curative radiotherapy? Radiother Oncol 2005;77: 164–71.
***Sciubba JJ, Goldenberg D. Oral complications of radiotherapy. Lancet Oncol 2006; 7: 175–83.

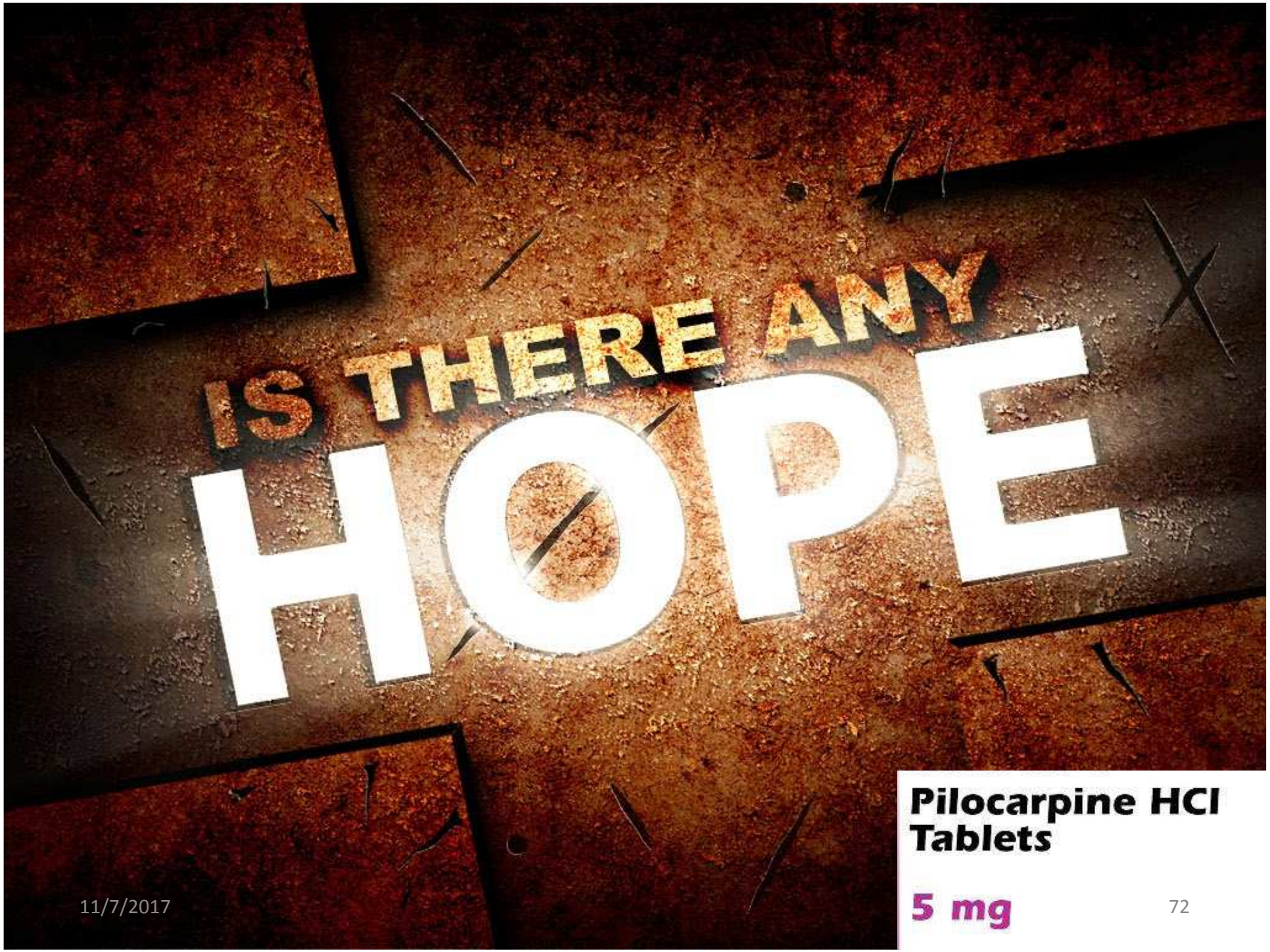
Doses for Oral Cavity

- 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.

*Eisbruch A, et al. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. IJROBP 1999;45:577–87.

** Reducing Xerostomia After Chemo-IMRT for Head-and-Neck Cancer: Beyond Sparing the Parotid Glands.Little M. IJROPBP 2011;83.


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

2015/Cai-Qi Cheng/ journal of American Dental Association

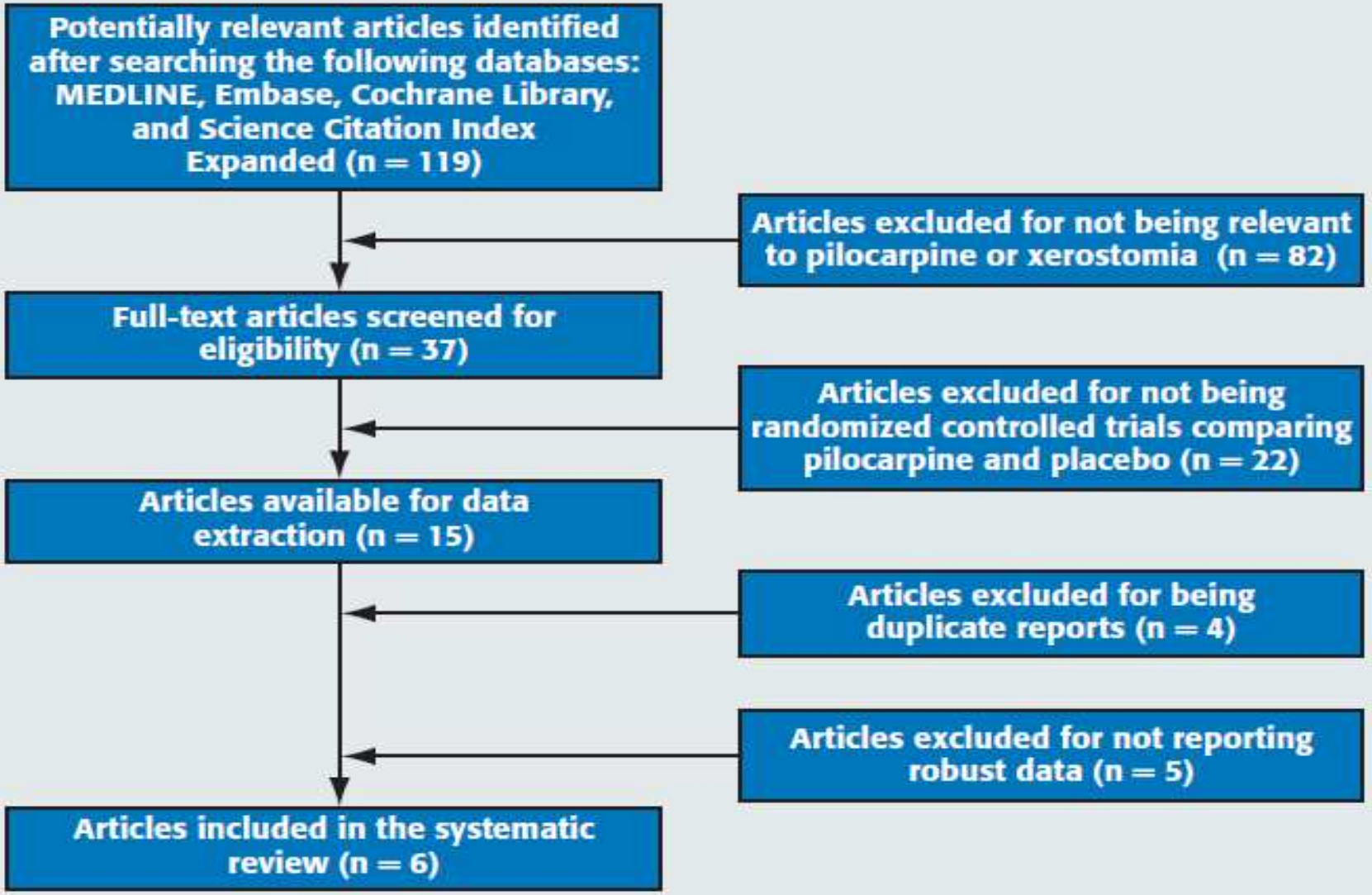


Figure 1. Flowchart of the selection process of related articles.

TABLE

Characteristics of included studies.

STUDY	DESIGN	PARTICIPANTS			DOSAGES AND DURATION	OUTCOME MEASURES
		Total	Pilocarpine	Placebo		
Johnson and Colleagues, 1993[22]	RCT*	138	73	65	5 milligrams 3 times per d for 12 wks	The number of study participants with > 25 millimeter changes in VAS† scores; whole and parotid saliva production
LeVeque and Colleagues, 1993[23]	RCT	162	75	87	2.5 mg for the first 4 wks, 5 mg for the second 4 wks, 10 mg the last wks	The number of study participants with > 25 mm changes in VAS scores; whole and parotid saliva production
Haddad and Karimi, 2002[24]	RCT	39	18	21	5 mg 3 times per d for 12 wks	VAS scores; LENT-SOMA‡ scale scores
Warde and Colleagues, 2002[25]	RCT	98	50	48	5 mg 3 times per d for 4 wks	VAS scores; quality of life (HNRQ§) scores; maximal toxicity scores
Nyarady and Colleagues, 2006[26]	RCT	66	33	33	5 mg 3 times per d for 12 wks	VAS scores; USF¶ rates
Scarantino and Colleagues, 2006[27]	RCT	249	124	125	5 mg 3 times per d for 13 wks	USF rates; SSF# rates; quality of life scores; acute mucositis toxicity scores

* 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

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Clinical Investigation

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

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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

Study or Subgroup	Pilocarpine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.1.1.At baseline								
Fisher 2003	1.8	1.1	110	2	1.1	115	2.4%	-0.20 [-0.49, 0.09]
Gornitsky 2004	2.7	0.97	29	2.4	0.97	29	0.8%	0.30 [-0.20, 0.80]
Nyarady 2006	0.69	0.26	33	0.7	0.25	33	13.2%	-0.01 [-0.13, 0.11]
Subtotal (95% CI)			**172**			**177**	**16.4%**	**-0.02 [-0.13, 0.09]**
Heterogeneity: $Chi^2 = 3.11$, df = 2 ($P = .21$); $I^2 = 36\%$								
Test for overall effect: Z = 0.41 ($P = .68$)								
3.1.2.After radiation therapy								
Fisher 2003	1.4	1.02	89	0.9	1.02	77	2.1%	0.50 [0.19, 0.81]
Gornitsky 2004	1	0.64	29	0.8	0.59	29	2.0%	0.20 [-0.12, 0.52]
Nyarady 2006	0.48	0.27	33	0.22	0.15	33	17.9%	0.26 [0.15, 0.37]
Subtotal (95% CI)			**151**			**139**	**22.0%**	**0.28 [0.18, 0.37]**
Heterogeneity: $Chi^2 = 2.30$, df = 2 ($P = .32$); $I^2 = 13\%$								
Test for overall effect: Z = 5.70 ($P < .00001$)								
3.1.3.At 5-6 week								
Gornitsky 2004	0.6	0.26	16	0.5	0.17	15	8.4%	0.10 [-0.05, 0.25]
Nyarady 2006	0.58	0.26	33	0.4	0.17	33	17.7%	0.18 [0.07, 0.29]
Subtotal (95% CI)			**49**			**48**	**26.2%**	**0.15 [0.07, 0.24]**
Heterogeneity: $Chi^2 = 0.71$, df = 1 ($P = .40$); $I^2 = 0\%$								
Test for overall effect: Z = 3.46 ($P = .0005$)								
3.1.4.At 3 month								
Fisher 2003	0.7	0.32	85	0.6	0.32	81	21.0%	0.10 [0.00, 0.20]
Subtotal (95% CI)			**85**			**81**	**21.0%**	**0.10 [0.00, 0.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.01 ($P = .04$)								
3.1.5.At 6 month								
Fisher 2003	0.6	0.35	68	0.5	0.35	69	14.5%	0.10 [-0.02, 0.22]
Subtotal (95% CI)			**68**			**69**	**14.5%**	**0.10 [-0.02, 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.67 ($P = .09$)								
Total (95% CI)			**525**			**514**	**100.0%**	**0.13 [0.09, 0.18]**
Heterogeneity: $Chi^2 = 23.54$, df = 9 ($P = .005$); $I^2 = 62\%$								
Test for overall effect: Z = 5.84 ($P < .00001$)								
Test for subgroup differences: $Chi^2 = 17.43$, df = 4 ($P = .002$), $I^2 = 77.1\%$								

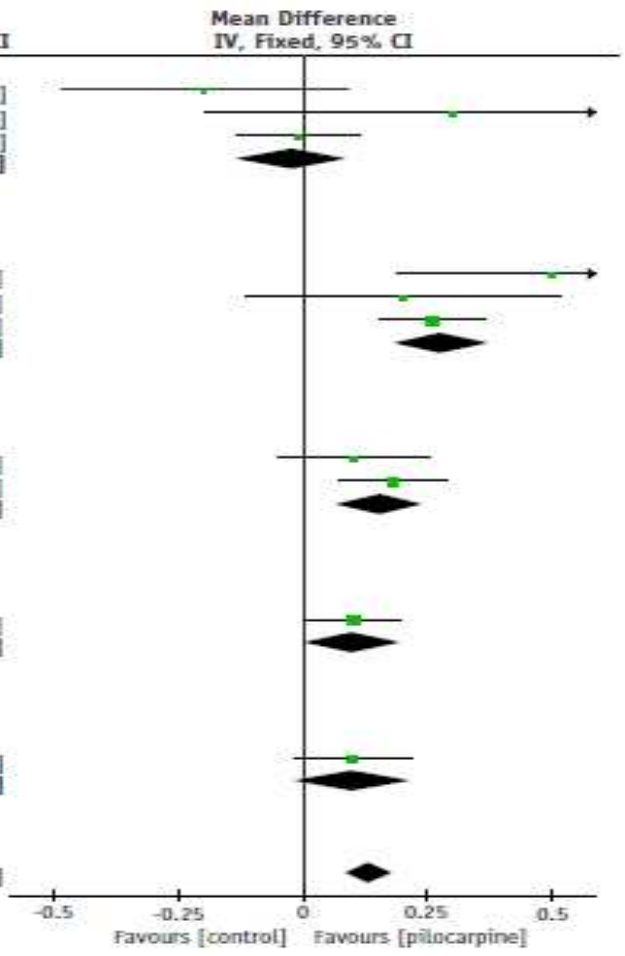
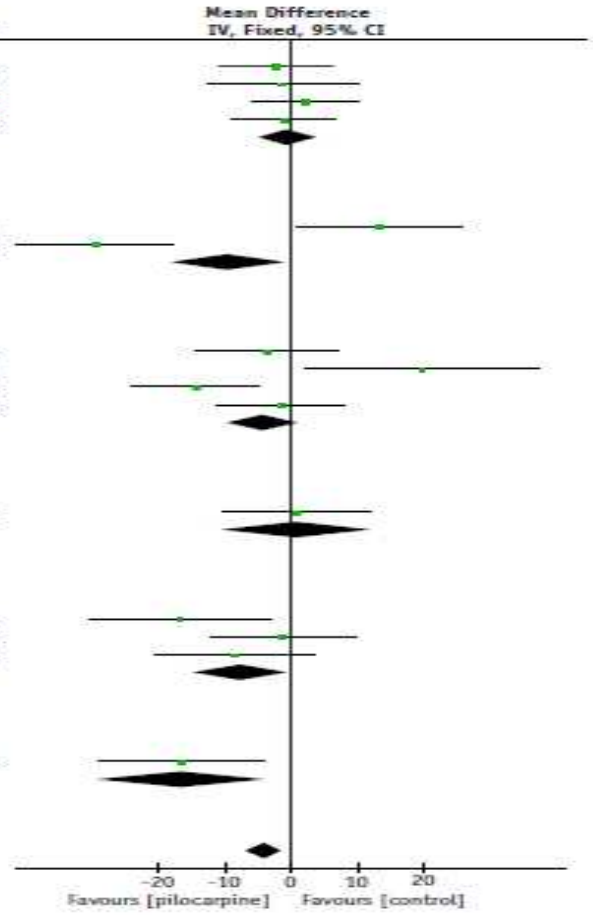


Fig. 3. Unstimulated salivary flow rates during and after course of radiation therapy. Depicts mean differences between the pilocarpine group and the control group. *Abbreviation:* CI = confidence interval.

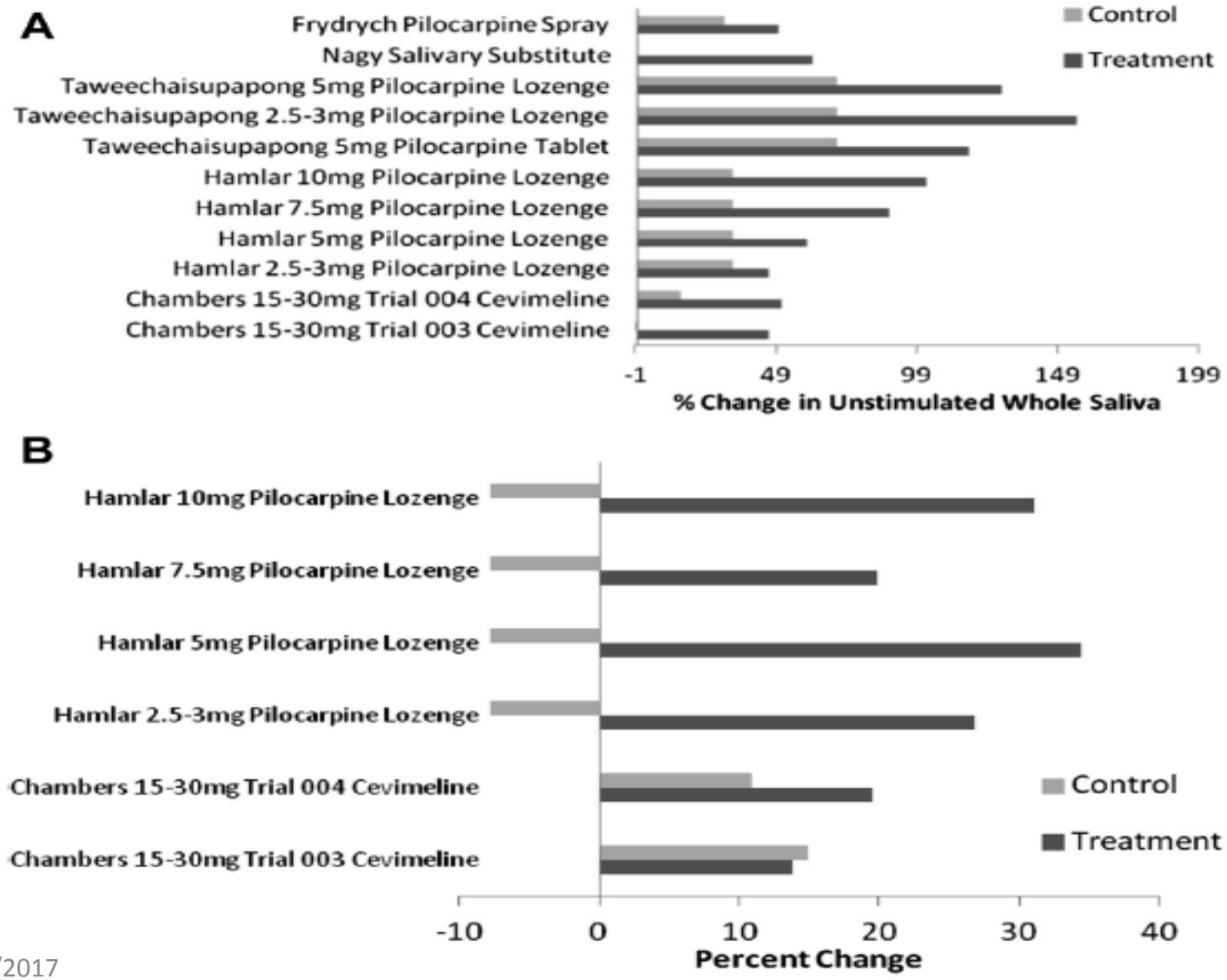
Subjective salivary flow



Study or Subgroup	Pilocarpine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
5.1.1 At baseline									
Warde 2002	19.8	24.2	63	22.1	23.5	64	10.6%	-2.30 [-10.60, 6.00]	2002
Gornitsky 2004	26.2	23.28	29	27.4	20.76	29	5.7%	-1.20 [-12.55, 10.15]	2004
Nyarady 2006	11.77	19.77	33	9.58	13.08	33	11.1%	2.19 [-5.90, 10.28]	2006
Burlage 2008	34.15	25.86	85	35.1	25.7	84	12.1%	-0.95 [-8.72, 6.82]	2008
Subtotal (95% CI)			**210**			**210**	**39.4%**	**-0.46 [-4.76, 3.84]**	
Heterogeneity: $Chi^2 = 0.63$, df = 3 ($P = .89$); $I^2 = 0\%$									
Test for overall effect: $Z = 0.21$ ($P = .83$)									
5.1.2 After radiation therapy									
Gornitsky 2004	65.5	24.78	29	52.2	23.89	29	4.6%	13.30 [0.77, 25.83]	2004
Nyarady 2006	35.88	24.78	33	65.22	23.89	33	5.3%	-29.34 [-41.08, -17.60]	2006
Subtotal (95% CI)			**62**			**62**	**9.9%**	**-9.40 [-17.96, -0.83]**	
Heterogeneity: $Chi^2 = 23.69$, df = 1 ($P < .00001$); $I^2 = 96\%$									
Test for overall effect: $Z = 2.15$ ($P = .03$)									
5.1.3 At 1 month									
Warde 2002	59.8	27.7	50	63.4	25.9	48	6.5%	-3.60 [-14.21, 7.01]	2002
Gornitsky 2004	72.3	22.89	16	52.7	26.53	15	2.4%	19.60 [2.11, 37.09]	2004
Nyarady 2006	13	11.88	33	27.4	25.13	33	8.1%	-14.40 [-23.88, -4.92]	2006
Burlage 2008	66.6	29.1	72	68.05	28.55	69	8.0%	-1.45 [-10.97, 8.07]	2008
Subtotal (95% CI)			**171**			**165**	**25.0%**	**-4.20 [-9.60, 1.20]**	
Heterogeneity: $Chi^2 = 11.89$, df = 3 ($P = .008$); $I^2 = 75\%$									
Test for overall effect: $Z = 1.52$ ($P = .13$)									
5.1.4 At 3 month									
Warde 2002	66.1	26.8	48	65.2	28.2	44	5.7%	0.90 [-10.37, 12.17]	2002
Subtotal (95% CI)			**48**			**44**	**5.7%**	**0.90 [-10.37, 12.17]**	
Heterogeneity: Not applicable									
Test for overall effect: $Z = 0.16$ ($P = .88$)									
5.1.5 At 6 month									
Haddad 2002	40.3	22	18	57	21.5	21	3.9%	-16.70 [-30.41, -2.99]	2002
Warde 2002	66.5	25.8	46	67.7	25.2	41	6.3%	-1.20 [-11.93, 9.53]	2002
Burlage 2008	61.6	32.64	59	70.2	35.4	65	5.1%	-8.60 [-20.58, 3.38]	2008
Subtotal (95% CI)			**123**			**127**	**15.3%**	**-7.59 [-14.49, -0.69]**	
Heterogeneity: $Chi^2 = 3.09$, df = 2 ($P = .21$); $I^2 = 35\%$									
Test for overall effect: $Z = 2.16$ ($P = .03$)									
5.1.6 At 12 month									
Burlage 2008	55.6	33.93	55	72.1	34.25	58	4.6%	-16.50 [-29.07, -3.93]	2008
Subtotal (95% CI)			**55**			**58**	**4.6%**	**-16.50 [-29.07, -3.93]**	
Heterogeneity: Not applicable									
Test for overall effect: $Z = 2.57$ ($P = .01$)									
Total (95% CI)			**669**			**666**	**100.0%**	**-4.03 [-6.73, -1.33]**	
Heterogeneity: $Chi^2 = 48.99$, df = 14 ($P < .00001$); $I^2 = 71\%$									
Test for overall effect: $Z = 2.93$ ($P = .003$)									
Test for subgroup differences: $Chi^2 = 9.69$, df = 5 ($P = .08$); $I^2 = 48.4\%$									

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 LOZENGE



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.

ISSO GUIDELINES-XEROSTOMIA

- 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).

ISSO GUIDELINES-XEROSTOMIA

- 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**

*Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, et al. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008; **26: 3770–76.**

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.(**)**

*Eisbruch A et al. Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head and neck cancer.IJROBP 2002; 53: 23–28.

** Nguyen N et al. Impact of dysphagia on QOL after treatment of head-and-neck cancer.IJROBP 2005; 61: 772–78.

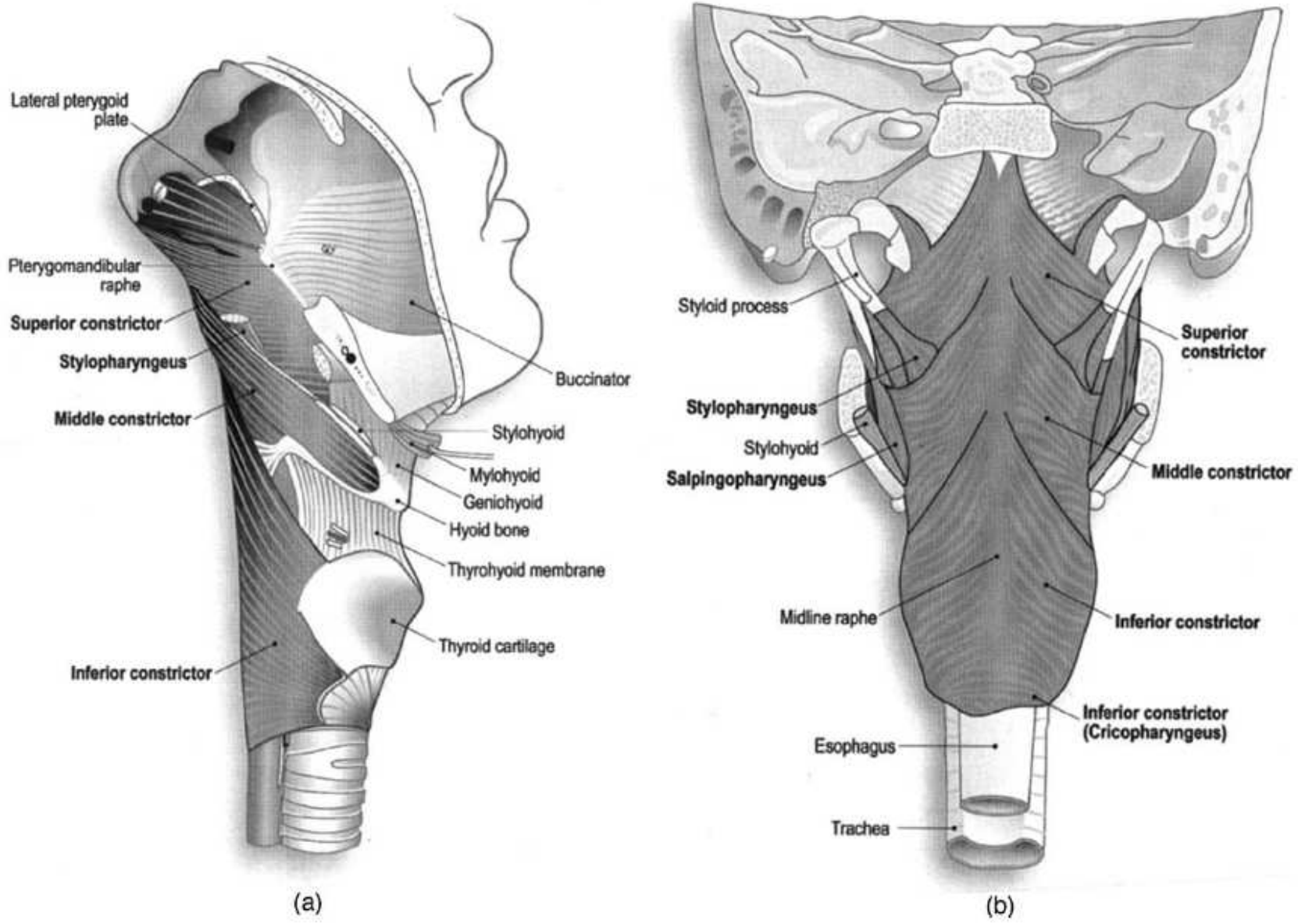


Fig. 1. Pharyngeal constrictor muscles and related structures. (a) Lateral, (b) posterior view. Circular constrictors and longitudinal muscles that blend distally with them in depicted in bold letters. After Gray's Anatomy (28).

DELINEATION GUIDELINES FOR DARS AS OAR

	Superior border	Inferior border	Anterior border	Posterior border
Superior pharyngeal constrictor muscle	Caudal tip of pterygoid plates (hamulus)	Upper edge of hyoid bone	Widest diameter of rhinopharynx, base of tongue, hyoid bone, and larynx	Cervical vertebra or prevertebral muscles
Middle pharyngeal constrictor muscle	Upper edge of hyoid bone	Lower edge of hyoid bone	..	..
Inferior pharyngeal constrictor muscle	Lower edge of hyoid bone	Lower edge of cricoid cartilage	..	..
Base of tongue	Below soft palate (uvula)	Upper edge of hyoid bone	Posterior third of the tongue	..
Supraglottic larynx (lumen excluded)	Top of piriform sinus and aryepiglottic fold	Upper edge of cricoid cartilage	Anterior tip of thyroid cartilage	Cornu of thyroid cartilage
Glottic larynx (lumen excluded)	At level of cricoid cartilage	..	..	..
Upper oesophageal sphincter including musculus cricopharyngeus	Lower edge of cricoid cartilage	Upper edge of trachea	Subglottic larynx	Cervical vertebra
Oesophagus	Upper edge of trachea	First 2 cm	Trachea	Cervical vertebra

Table 2: Proposed delineation guidelines for swallowing structures, by organ at risk

Swallowing assessment

Table 2 Functional measures and endpoints

Time point	Study	Domain	Endpoint
Baseline, 3, 6, 12, 18 and 24 months	MDADI	Swallowing related QoL	Composite (total), global, emotional, functional and physical subscale scores
Baseline, 3, 6, 12, 18 and 24 months	WST	Swallow Performance	Swallow capacity, Swallow volume
Baseline, 12 and 24 months	VF[a]	Airway protection	Penetration Aspiration Scale [52]
Baseline, 12 and 24 months	VF[a]	Physiology	MBSImp
Baseline, 12 and 24 months	VF[a]	Pharyngeal dysphagia grade	DIGEST grade [53]
Baseline, 3, 6, 12, 18 and 24 months	PSS-HN	Functional Performance Status	Normalcy of diet, eating in public, understandability of speech scores
Baseline, 3, 6, 12, 18 and 24 months	UW-QoL v.04	HR-QoL	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

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

[a]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.(*,)**

*Meirovitz A et al. Grading xerostomia by physicians or by patients after IMRT of head-and-neck cancer. IJROBP, 2006; **66: 445–53.**

Eisbruch A et al. How should we measure and report radiotherapy-induced xerostomia? Semin Radiat Oncol 2003; **13: 226–34.

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.[12] 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 DAR PARE DARS?

CAN THEY BE D 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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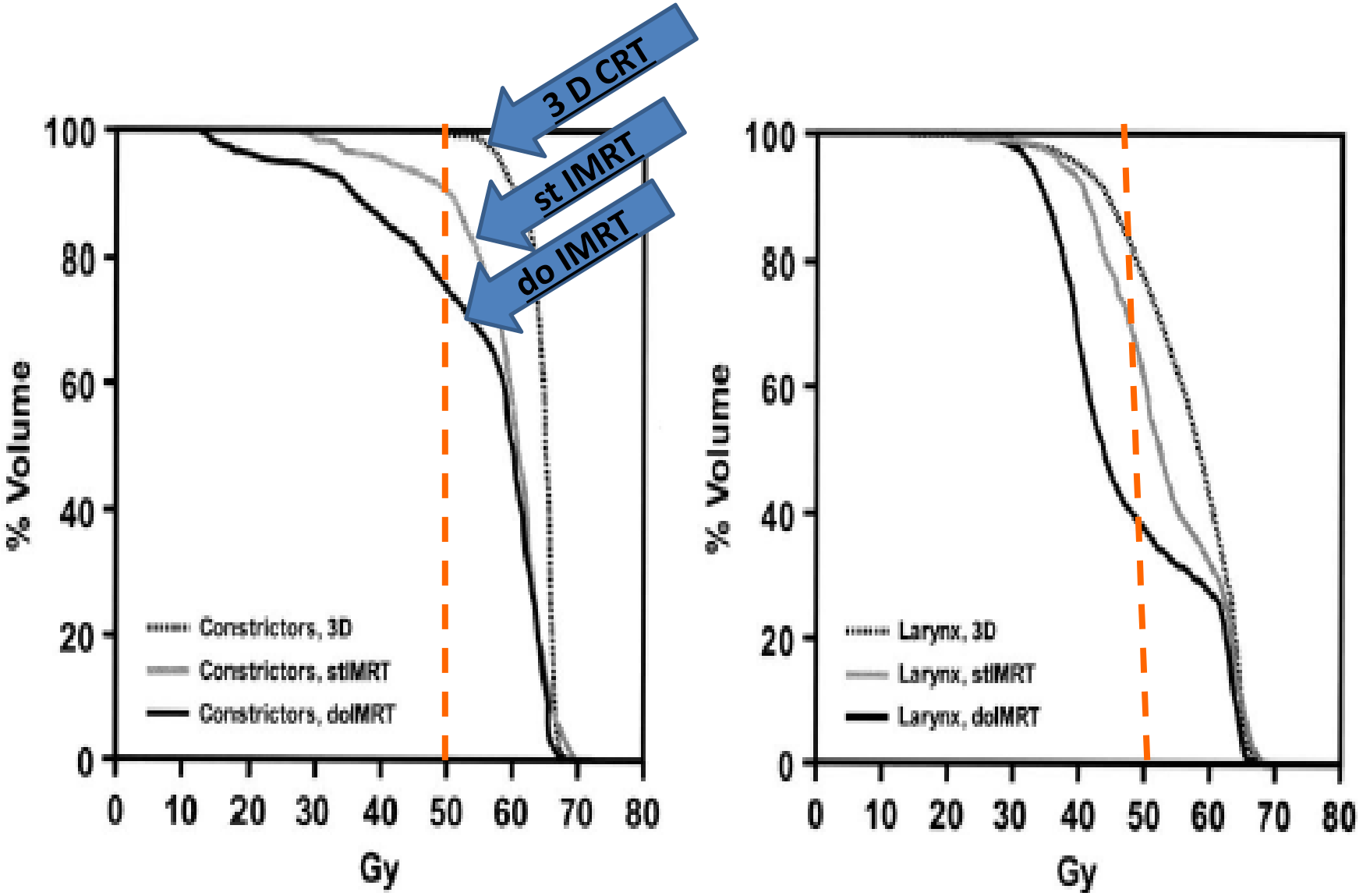
Table 2. Anatomic structures whose damage or malfunction were likely cause of videofluoroscopic abnormalities common to two intensive chemo-RT regimens

VF abnormality	Aspects of dysphagia/aspiration related to the VF abnormality	Anatomic structures whose damage or malfunction may cause the VF abnormality
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.
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)	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.
Incomplete or delay of glottic closure and reduced adduction of supraglottic larynx during swallow	Aspiration during swallow (34, 35)	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
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)	Stiffness of epiglottic walls due to edema and fibrosis (36) Malfunction of suprahyoid 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 timely opening of upper esophageal sphincter	Dysphagia and aspiration during swallow	Lack of relaxation of cricopharyngeal muscle (27, 41) Malfunction of suprahyoid muscles that pull larynx upward, forward, and away from posterior pharyngeal wall (42, 43)

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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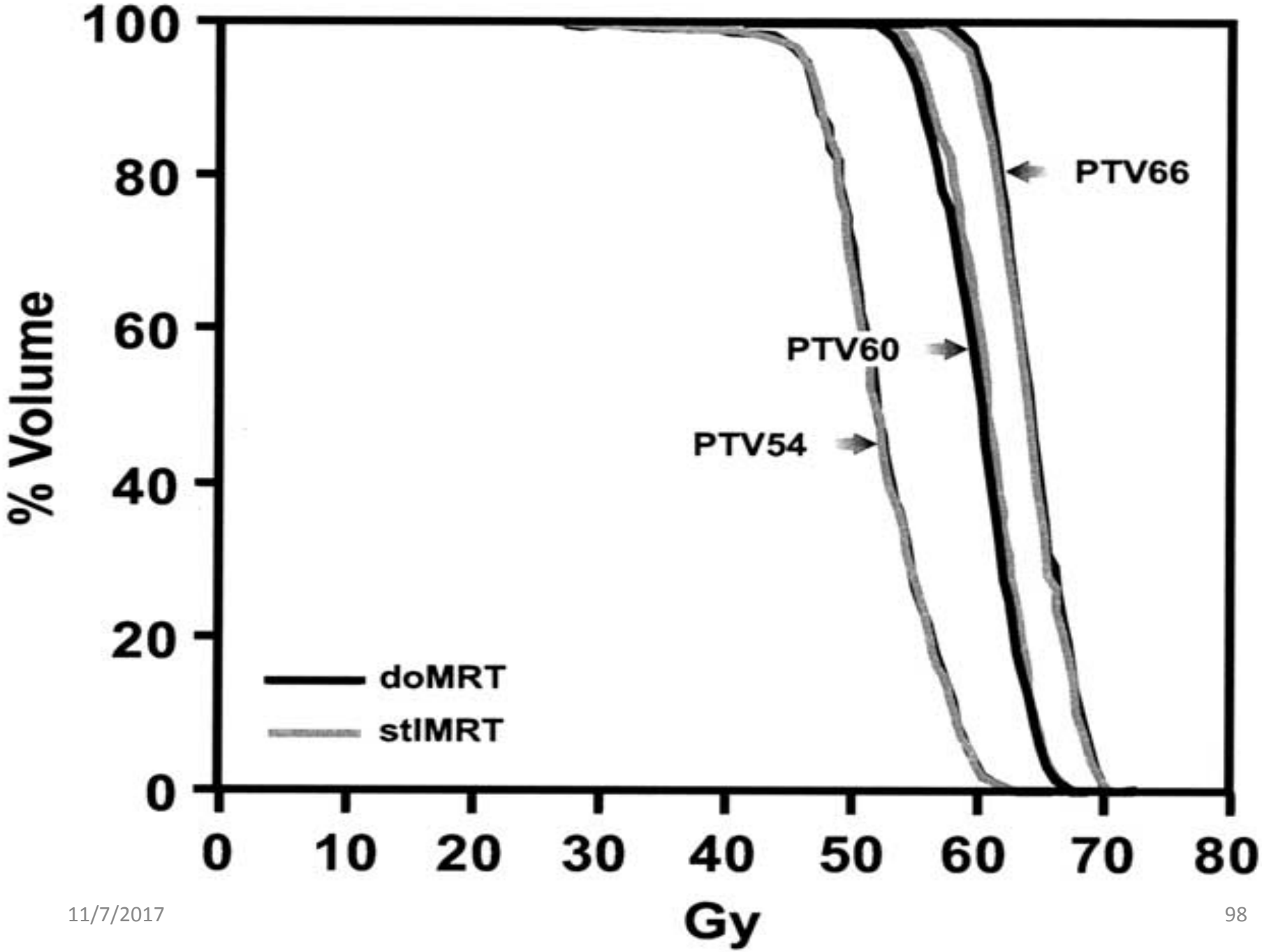
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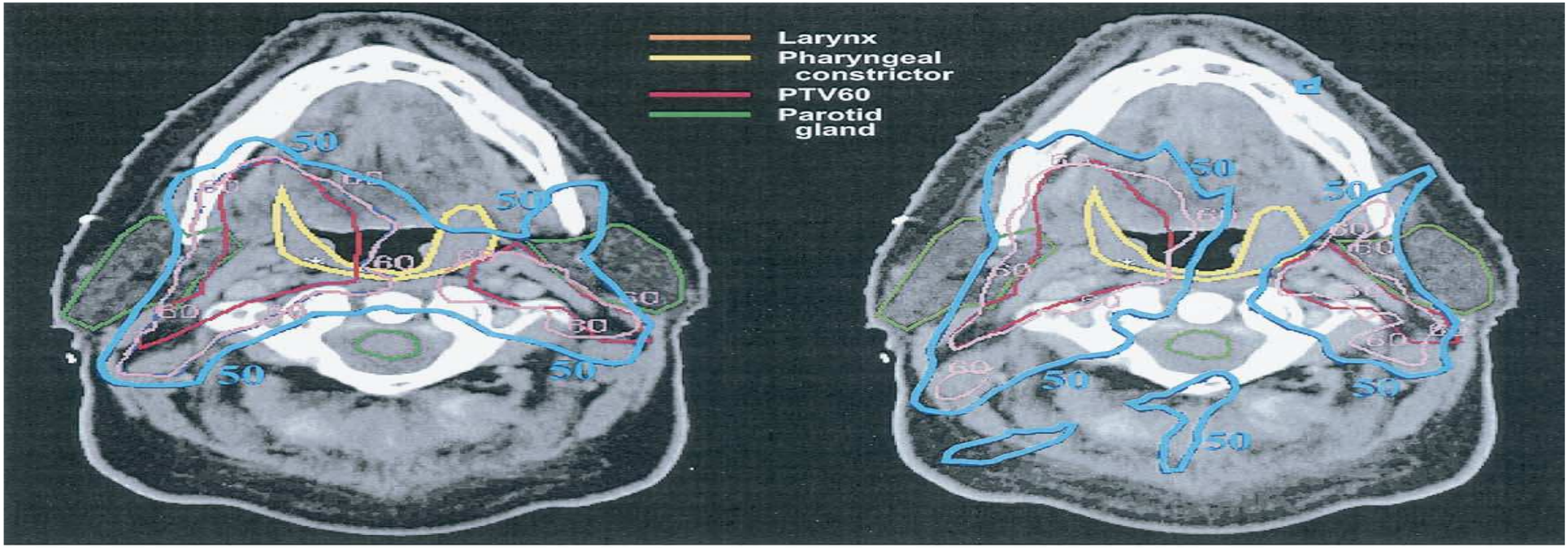
80
Gy
PTV66
PTV60
PTV54
doMRT
stIMRT

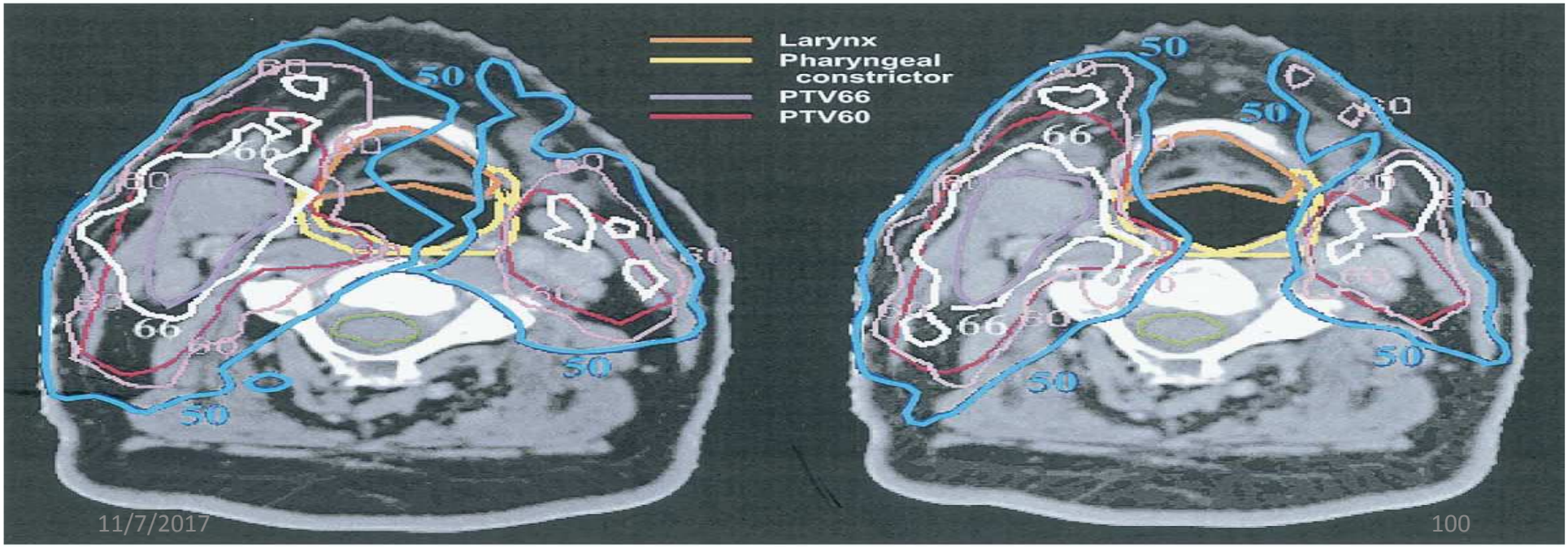
IMRT for DARS – Goals

- 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%

*Eisbruch et al, Dysphagia and Aspiration after CTRT for Head & Neck cancer :IJROBP,Vol.60, N0 5,PP-1439-1239,20014


Larynx
Pharyngeal constrictor
PTV60
Parotid gland
50
60

(a)


Larynx
Pharyngeal constrictor
PTV66
PTV60
50
60
66

(b)

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.

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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.

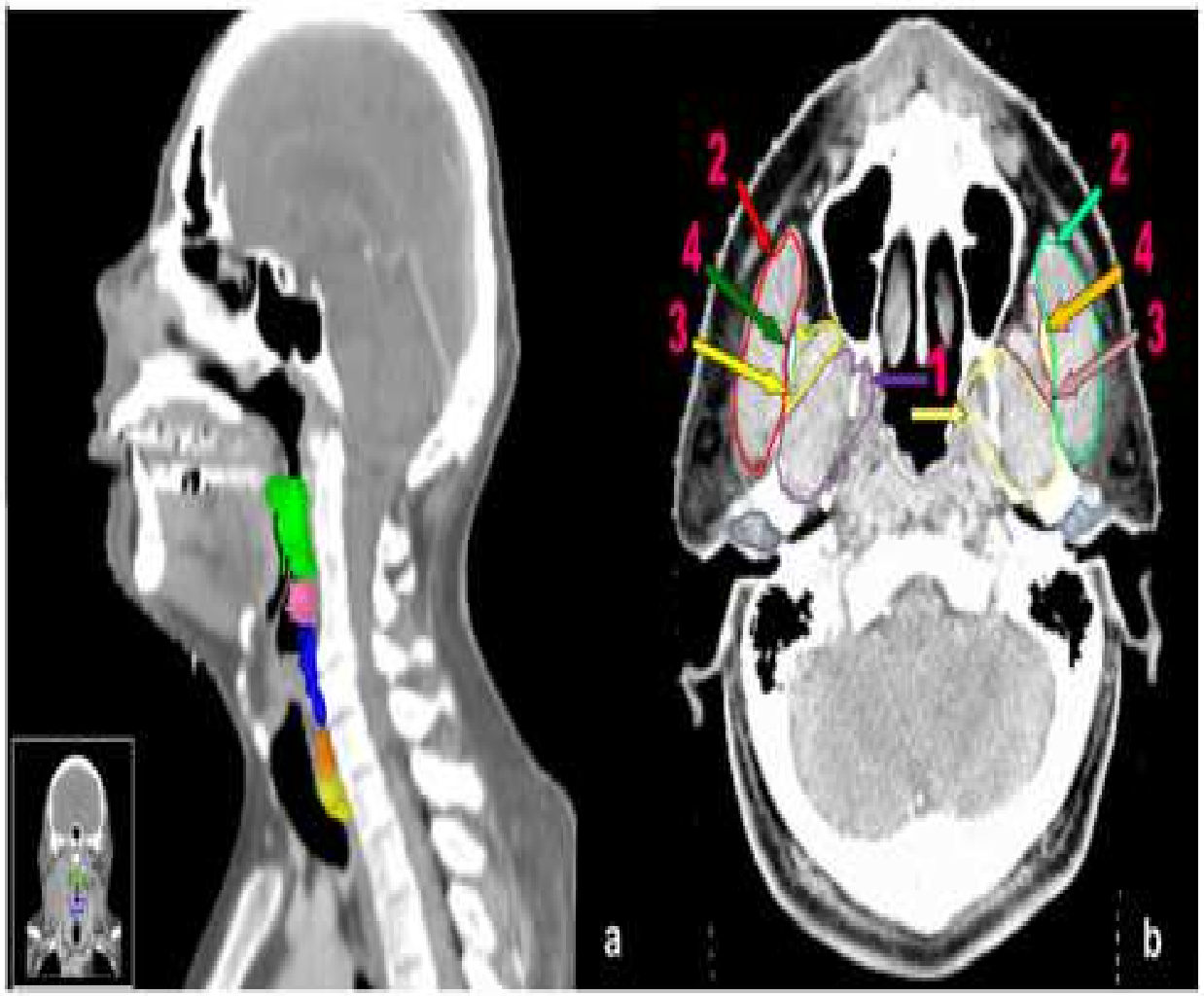


Fig. 1. Delineated structures. (a) Three-dimensional example of swallowing structures contoured: Green; superior constrictor muscle, Pink; middle constrictor muscle, Blue; inferior constrictor muscle, (Orange; cricopharyngeal muscle, Yellow; proximal esophagus). (b) Two-dimensional example of mastication 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 $\geqslant 60$ 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.

 Radiotherapy and Oncology 106 (2013) 364–369

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.(##)

*Feng FY, et al. IIMRT of head and neck cancer aiming to reduce dysphagia: early-dose eff ect relationships for the swallowing structures. Int J Radi2007; 68: 1289–98.
** Levendag PC, et al. Dysphagia disorders in patients with cancer of the oropharynx are signifi cantly aff ected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-eff ect relationship. Radiother Oncol 2007; 85: 64–73.
# Jensen K, et al. Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: frequency, intensity and correlation with dose and volume parameters. Radiother Oncol 2007; 85: 74–82.
Teguh DN et al. Treatment techniques and site considerations regarding dysphagia-related QOL in cancer of the oropharynx and nasopharynx. Int J Radiat 2008; 72: 1119–27.

DARS STUDY-ONGOING

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)

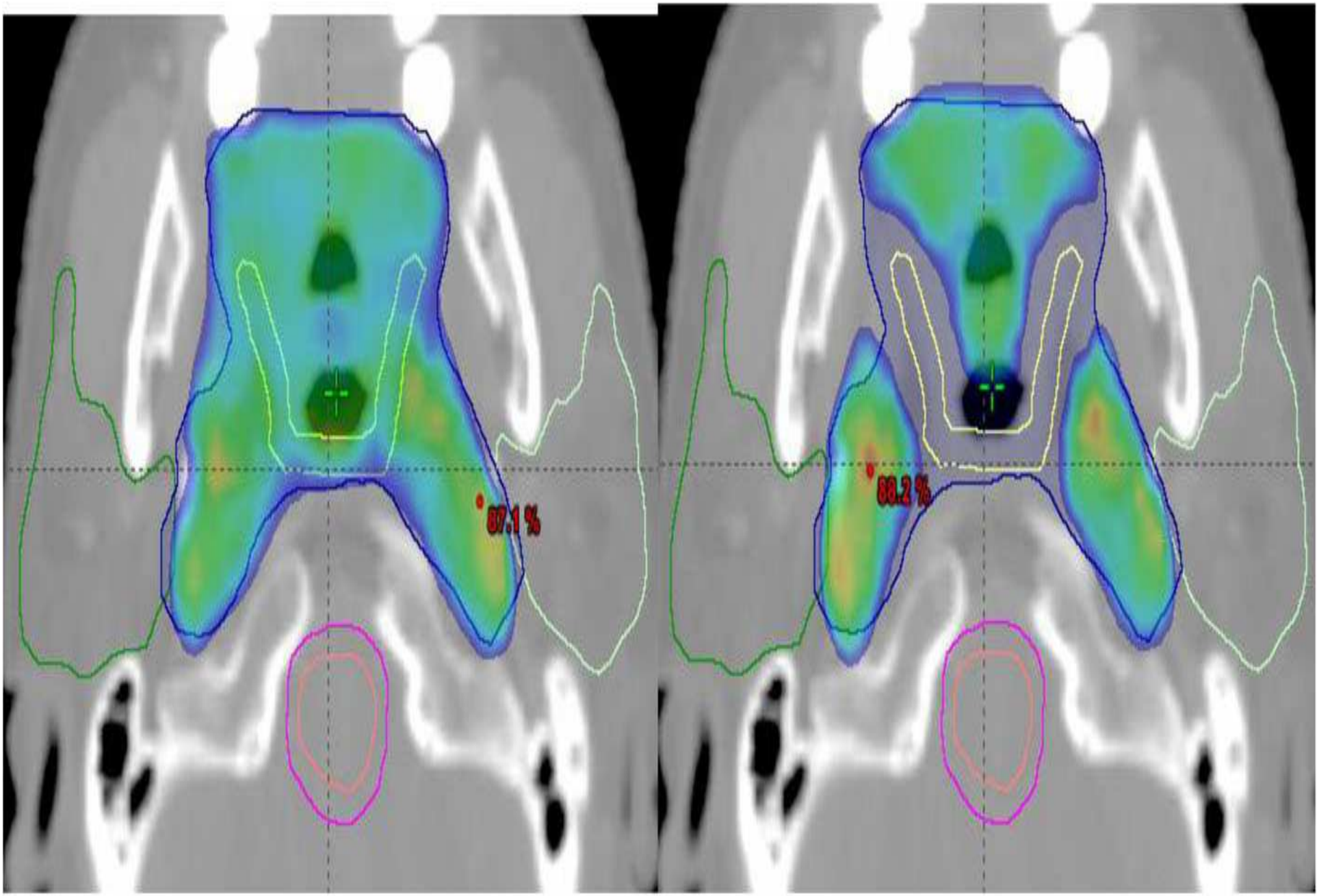
DO-IMRT

Do-IMRT

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.



(a) (b)

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

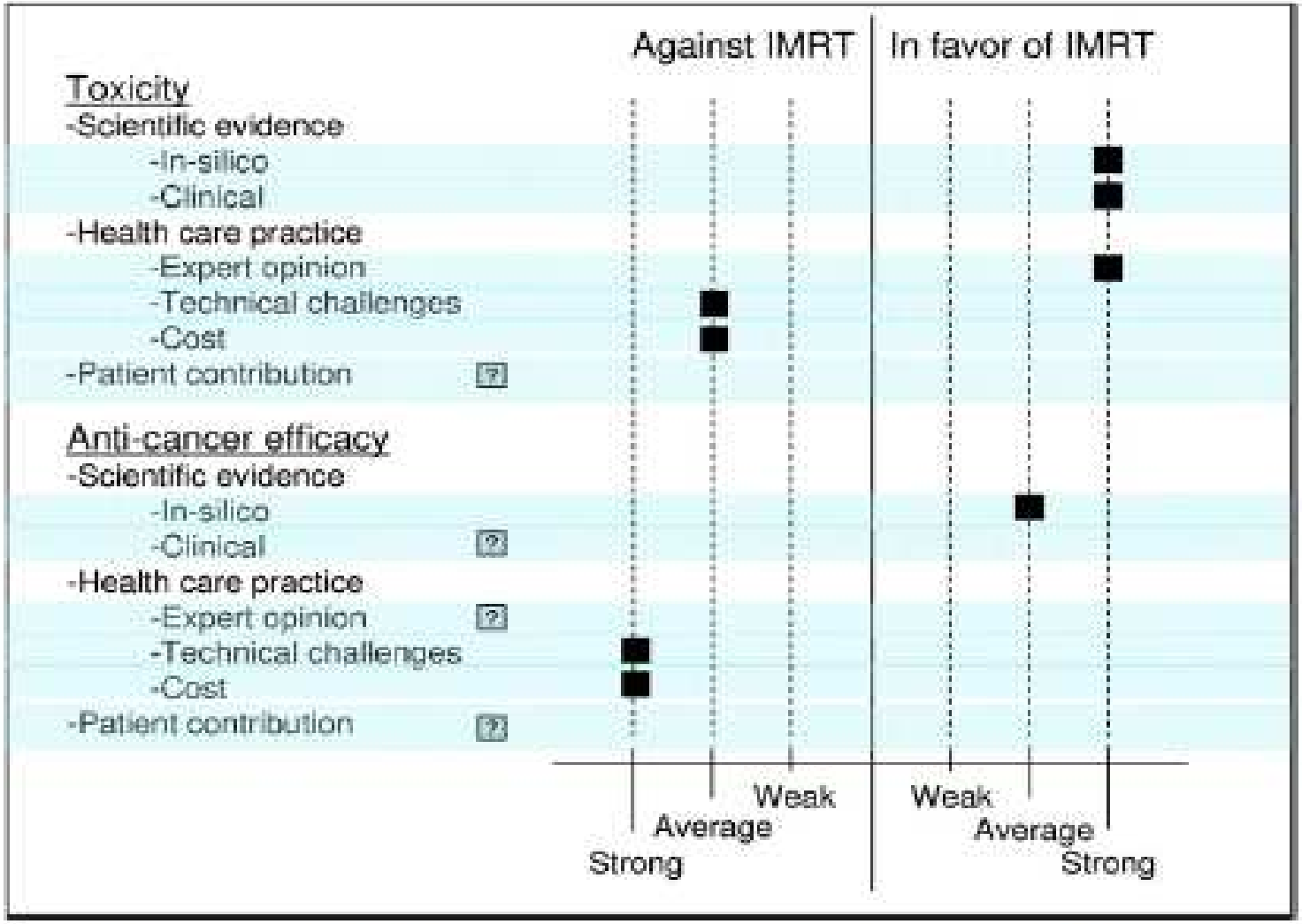


Figure 1 Factors in favor or against IMRT are represented by a rectangle on the right or on the left of the vertical solid line, respectively. A question mark inside a rectangle indicates too much uncertainty for using the factor in the graph.

De Neve W et al, Semin Radiat Oncol 2012

Conclusion

- T/t by IMRT or 3 D 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 bench mark for further studies

TRAIN YOUR BRAIN TO DECREASE THE DOSES TO XEROSTOMIA & DARS STRACTURES BUT NOT AT THE COST OF PTV

RESTRAIN YOURSELF FROM GIVING MORE CONSTRAIN OTHERWISE TUMOR WILL SUSTAIN.