



Alessandria, 23 marzo 2015

Radioterapia DARS/XRS sparing: vantaggi e warning

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Swallowing dysfunction

Underestimated symptom in HNC patients

(Feng et al IJROBP 2010)

Evaluating dysphagia is difficult given the lack of a uniform method for assessment

- **Baseline dysphagia**
- **Irradiated sites: base of tongue, posterior pharyngeal wall, larynx-ipopharynx**
- **Treatment intensity**
 - **Fractionation (bid)**
 - **Eventual CT**

RT –induced swallowing disfunction assessment

- **Multifactorial** (post-surgery scars, cyto/neurotoxic drugs, mucosal staminal depletion, xerostomia, mucositis, edentulous patients, post-RT fibrosis, atrophy from disuse)
- **Different assessments** of dysphagia in different series: aspiration and objective imaging, feeding tube dependency, patient-reported dysphagia, strictures, or observer-reported suchas RTOG, CTCAE, or PS Scale
- Different methods to delineate **OARs** (drawing the PCs anatomically, results in different mean doses compared with drawing only the posterior pharyngeal wall).

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Swallowing dysfunction in head and neck cancer patients treated by radiotherapy: Review and recommendations of the supportive task group of the Italian Association of Radiation Oncology

Elvio G. Russi^{a,*}, Renzo Corvò^b, Anna Merlotti^c, Daniela Alterio^d, Pierfrancesco Franco^e, Stefano Pergolizzi^f, Vitaliana De Sanctis^g, Maria Grazia Ruo Redda^h, Umberto Ricardiⁱ, Fabiola Paiar^l, Pierluigi Bonomo^k, Marco C. Merlano^l, Valeria Zurlo^m, Fausto Chiesaⁿ, Giuseppe Sanguineti^o, Jacques Bemier^o

Pre-treatment rate: 11-53%

Post-treatment rate: 11-62%

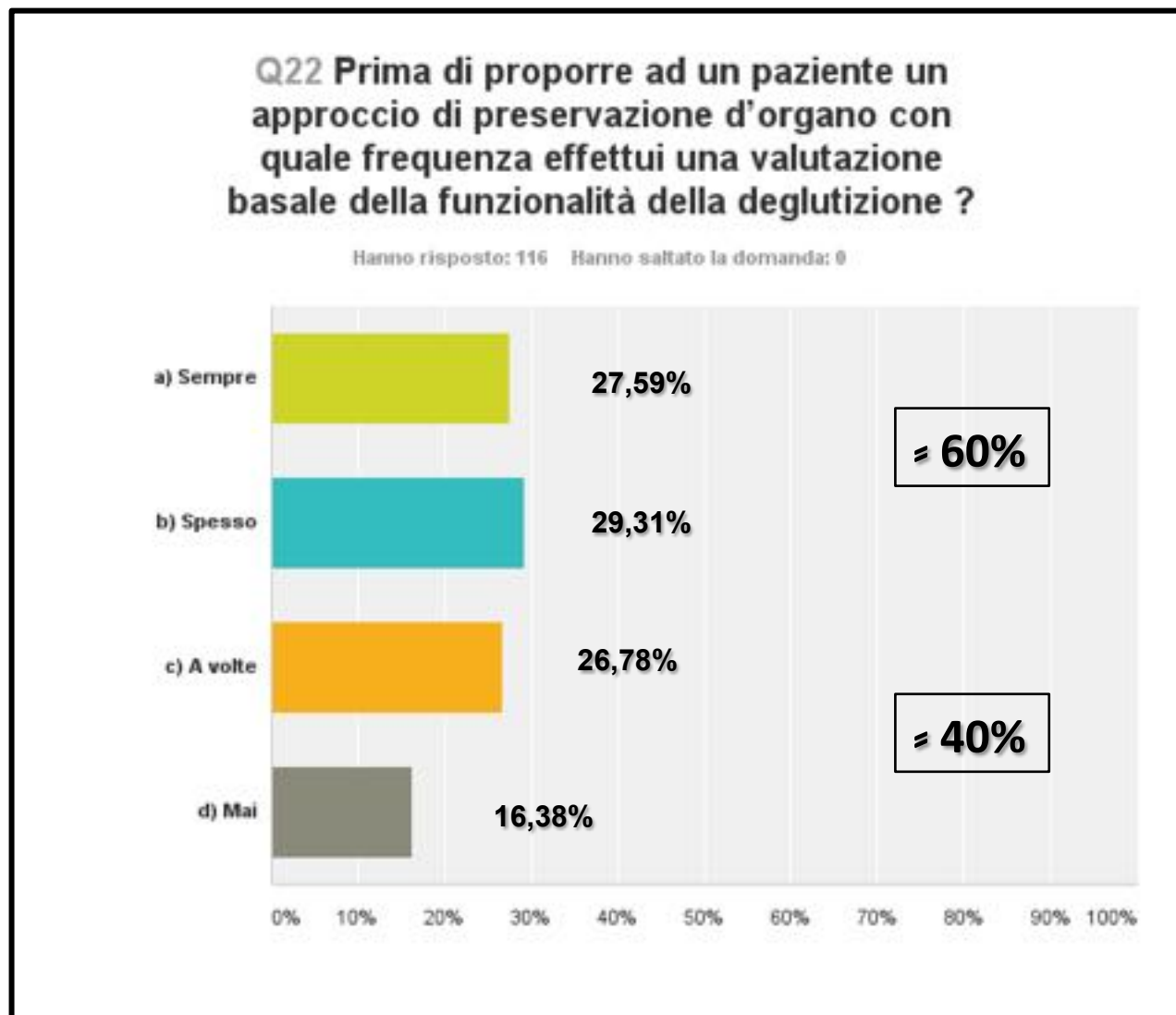
Authors	Year	Pts	Anatomical site	Stage	Aspiration at diagnosis [silent]	After [silent]*
Stenson et al. ⁴⁵	2000	79	Oral cavity Oropharynx Larynx	III-IV	43% (34/78) [†]	
Wu et al. ¹¹⁸	2000	31	Nasopharynx	Dysphagia		(93.5% (29/31)) [41.9% (13/31)] [22% (11/49)]
Hughes et al. ¹⁷⁹ Rowen et al. ¹⁷⁴	2000	49	Nasopharynx	Treated pts	43% (11/27) [18.5% (5/27)]	
Eisbruch et al. ²⁴	2002	22	Not specified	Non resectable	14% (3/22) [9% (2/22)]	62% (8/13) [38% (5/13)] [26% (5/19)]
Carrara-de Angelis et al. ¹⁷⁰	2003	19	Larynx Hypopharynx	II-IV		26% (5/19) [26% (5/19)]
Graver et al. ¹⁷⁸	2003	11	Oropharynx Larynx Hypopharynx	III-IV	18% (2/11)	54% (6/11)
Smith et al. ¹⁷⁷	2004	29	Oropharynx Hypopharynx	III-IV	n.r.	81% (13/16 → 74 Gy) 11% (1/9 → 60 Gy)
Kotz et al. ¹⁷⁶	2004	12	Oral cavity Oropharynx Larynx Unknown	III-IV	0%	41% (5/12)
Nguyen et al. ¹⁷⁹	2006	63	All [†]	II-IV	17% (10/63) [‡]	59% (37/63)
Langerman et al. ¹⁸⁰	2007	130	All [†] and unknown	II-IV	53% (33/62) (15% frank ^{††})	62% (81/130) (23.1% frank aspiration)
van der Molen et al. ²	2009	55	All [†]	III-IV	18% (10/55) [13% (7/55)]	
Dixit et al. ¹⁷⁷	2009	53	All [†]	III-IV	32.1% (17/53)	26.4% (14/53)
Feng et al. ¹⁸⁰	2010	73	Oropharynx	III-IV	11% (8/73)	26% (18/73) [60% (12/18)]

Russi EG et al; Cancer Treat Rev 2013

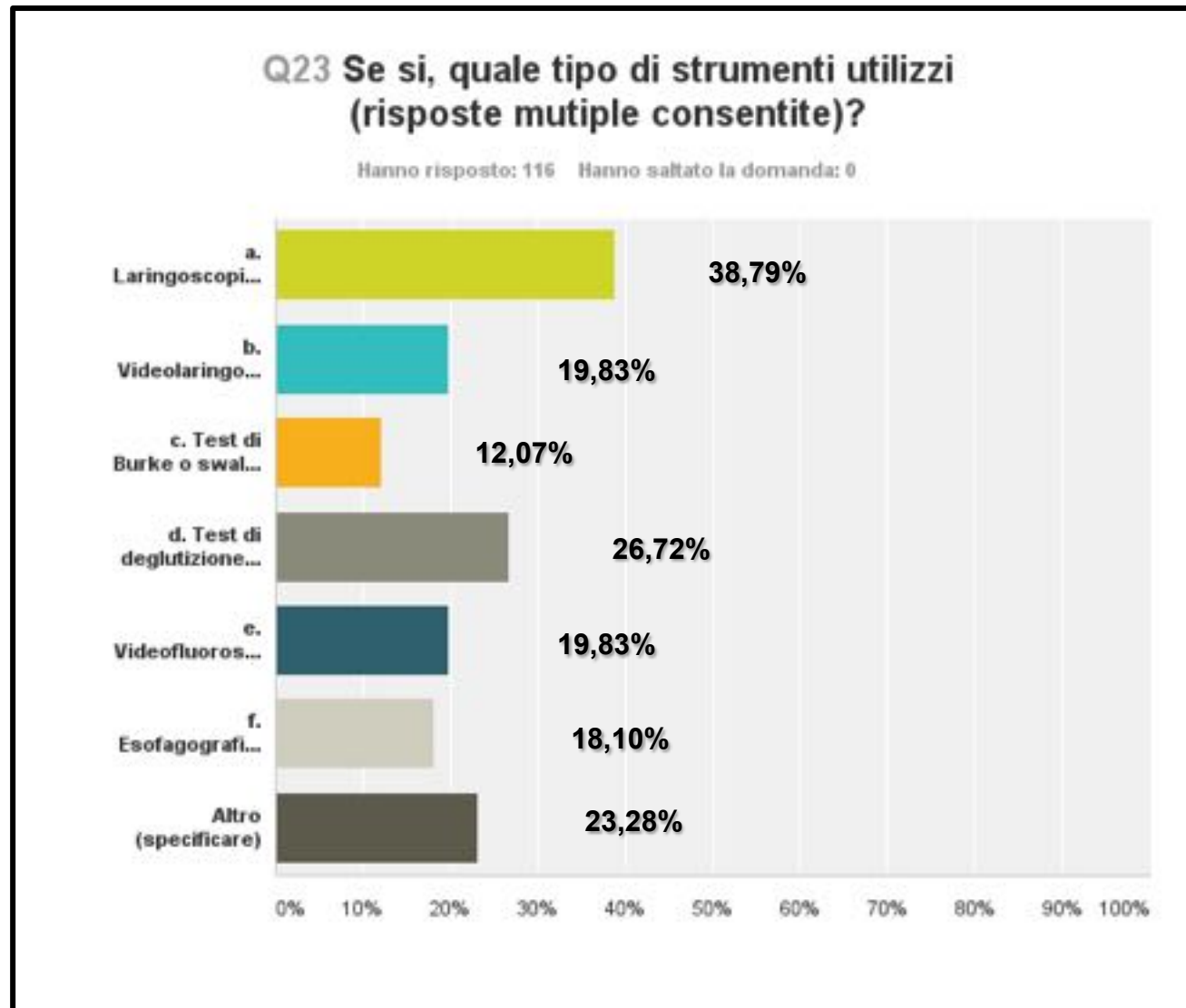
Swallowing disfunction leads to late sequelae

- ✓ Dysphagia
- ✓ Odyniphagia
- ✓ Reduced nutritional intake
- ✓ Increased risk of aspiration
- ✓ Extended duration of feeding tube dependency

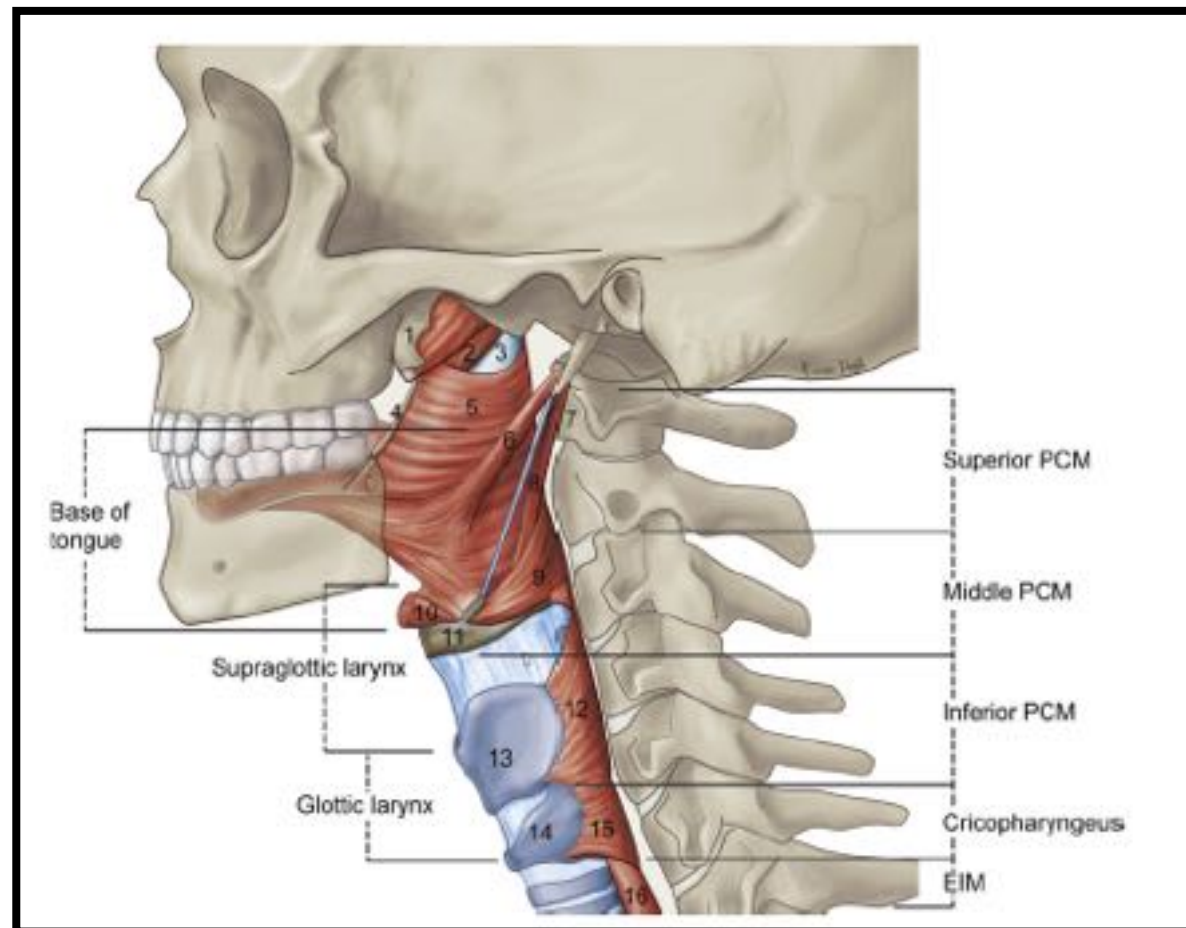
Survey AIRO-AIOM preservazione laringea d'organo



Survey AIRO-AIOM preservazione laringea d'organo



DARS



DARS: dysphagia/aspiration-related structures



- ✓ **26 pts receiving concurrent RT and gemcitabine**
- ✓ **Swallowing evaluation**
 - **videofluoroscopy (VF)**
 - **direct endoscopy**
 - **CT**

- ✓ **Anatomic structures causing VF abnormalities determined by literature**
- ✓ **Pre- and post-RT CT scans analyzed for post-RT damage**

Eisbruch A et al; IJROBP 2004

DARS: dysphagia/aspiration-related structures

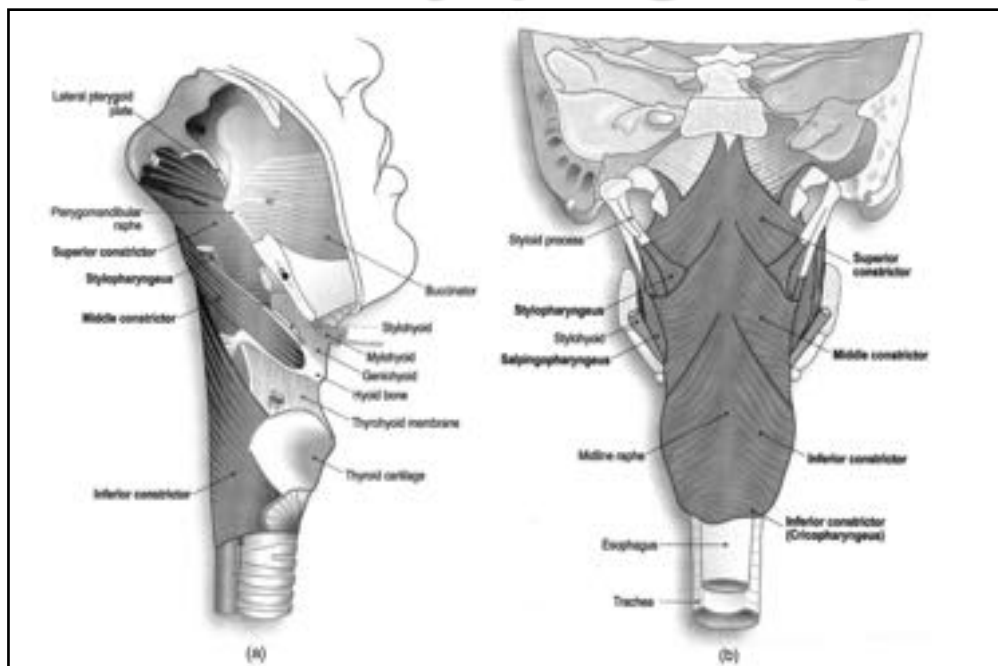
RT-induced VF abnormalities

- Weakness of the posterior motion of the base of tongue
- Prolonged pharyngeal transit time
- Lack of coordination between swallowing phases
- Reduced elevation of the larynx
- Reduced laryngeal closure and epiglottic inversion

High aspiration rate

Eisbruch A et al; IJROBP 2004

DARS: dysphagia/aspiration-related structures

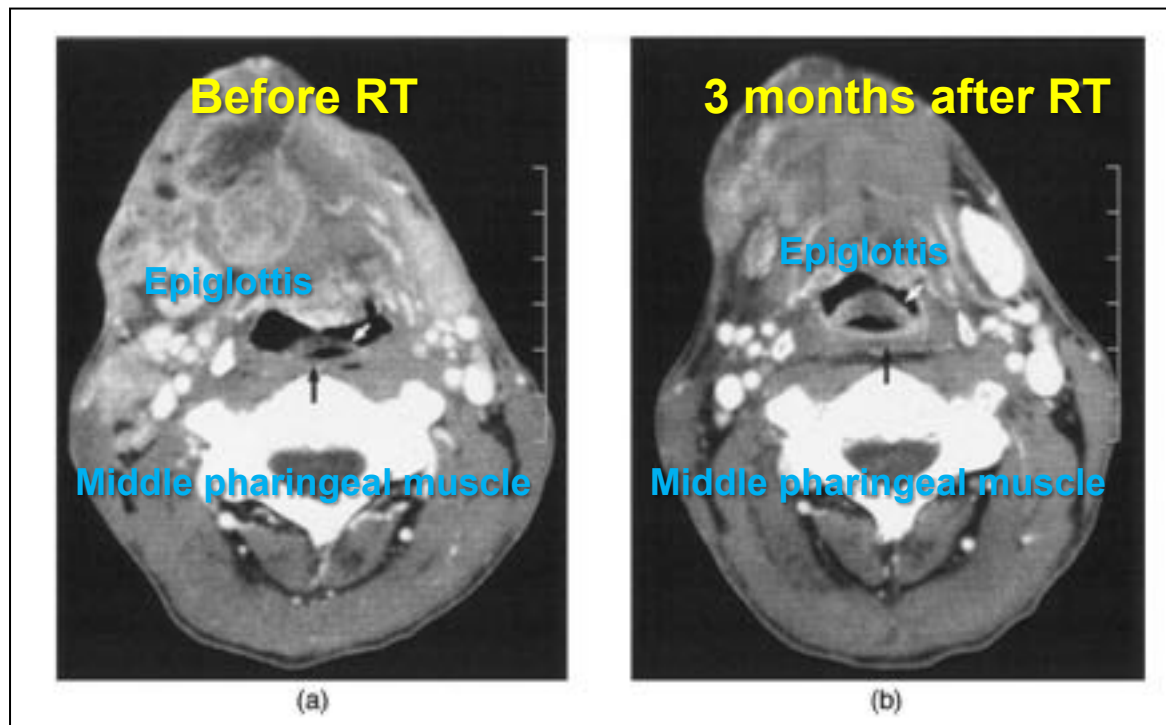


- **Constrictors muscles**
- PSCM**
- PMCM**
- PICM**
- **Supraglottic larynx**
- **Glottic larynx**

- **Suprahyoid muscles**
- Mylohyoid**
- Geniohyoid**
- Digastric**
- **Longitudinal pharyngeal muscles**
- Stylopharyngeus**
- Palatopharyngeus**
- Salpingopharyngeus**
- Proximal to their blending with pharyngeal constrictors**

Eisbruch A et al; IJROBP 2004

DARS: dysphagia/aspiration-related structures



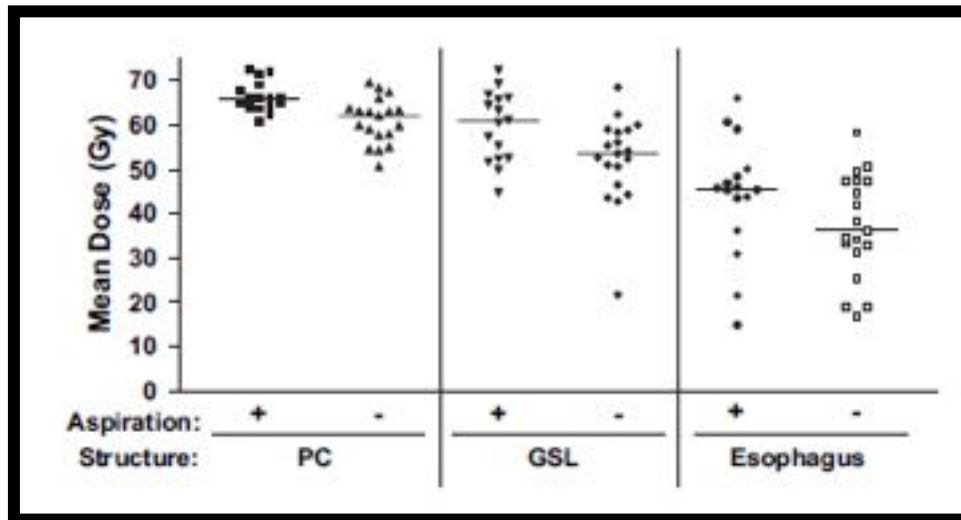
- Pharyngeal constrictors muscles (median midline thickness pre- vs post-RT: 2.5 mm vs 7 mm)
- Supraglottic larynx (median midline thickness pre- vs post-RT: 2 mm vs 4 mm)
- Glottic larynx and aryepiglottic folds (median midline thickness pre- vs post-RT: 2 mm vs 4 mm)

Eisbruch A et al; IJROBP 2004

INTENSITY-MODULATED RADIOTHERAPY OF HEAD AND NECK CANCER AIMING TO REDUCE DYSPHAGIA: EARLY DOSE-EFFECT RELATIONSHIPS FOR THE SWALLOWING STRUCTURES

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 MARY FENG, M.D.,* FRANK P. WORDEN, M.D.,[§] DOUGLAS B. CHEPEHA, M.D.,^{||}
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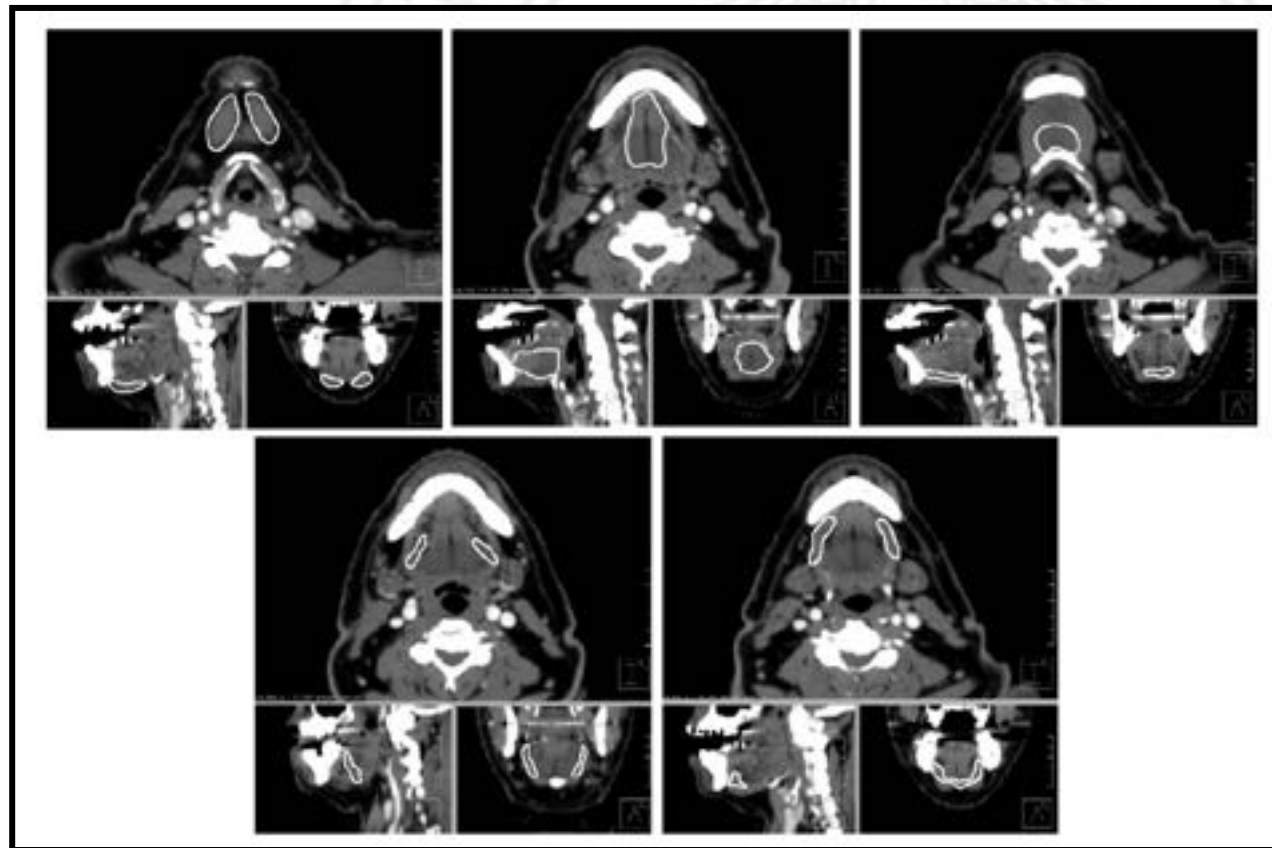


Dose-response and dose-volume relationships

Distribution of swallowing structures mean doses in aspirators versus non-aspirators

Felix F et al; IJROBP 2007

Floor of the mouth muscles



Extrinsic tongue muscles

- Anterior digastric
- Genioglossus

Suprahyoid muscles

- Geniohyoid
- Hyoglossus
- Mylohyoid

Kumar R et al; Oral Oncol 2014

Floor of the mouth muscles

Oral Oncology 50 (2014) 85–93

Contents lists available at ScienceDirect

Oral Oncology

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

Radiation dose to the floor of mouth muscles predicts swallowing complications following chemoradiation in oropharyngeal squamous cell carcinoma

Rachit Kumar^a, Sara Madanikia^a, Heather Starmer^b, Wuyang Yang^a, Emi Murano^b, Sara Alcorn^a, Todd McNutt^a, Yi Le^a, Harry Quon^{a,b,*}

Multivariate analysis comparing dosimetric characteristics. FoM – combined floor of mouth muscles. V40 – percent volume of muscle receiving a dose of 40 Gy or more.

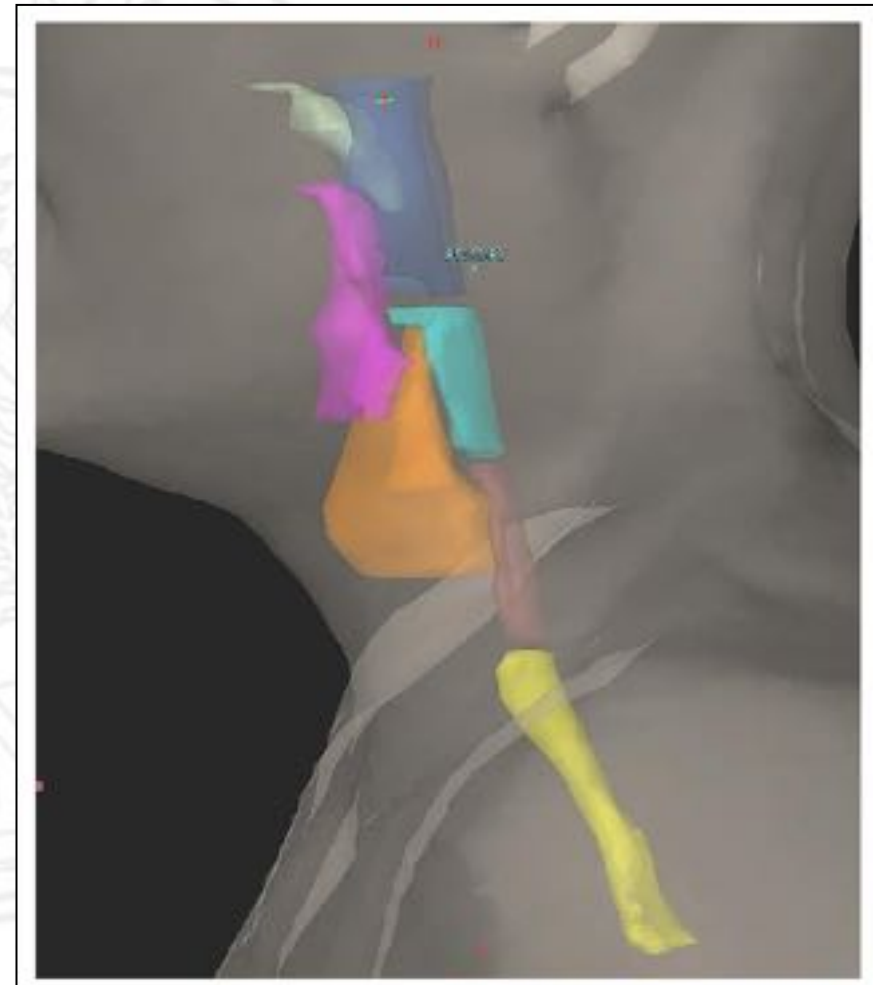
Variable	Estimate (Odds ratio)	p-Value	Confidence interval	VIF
T Stage	0.17	.061	[1.05, 58.29]	1.16
N Stage	12.40	.049*	[1.46, 256.95]	1.06
HPV Status	6.53	.145	[0.01, 1.62]	1.14
FoM Mean	0.54	.021*	[0.30, 0.86]	7.60
Genioglossus V40	1.16	.093	[1.00, 1.44]	2.18
Geniohyoid Minimum	1.30	.016*	[1.07, 1.68]	5.88

FoM meand dose correlates with VFS abnormalities

Kumar R et al; Oral Oncol 2014

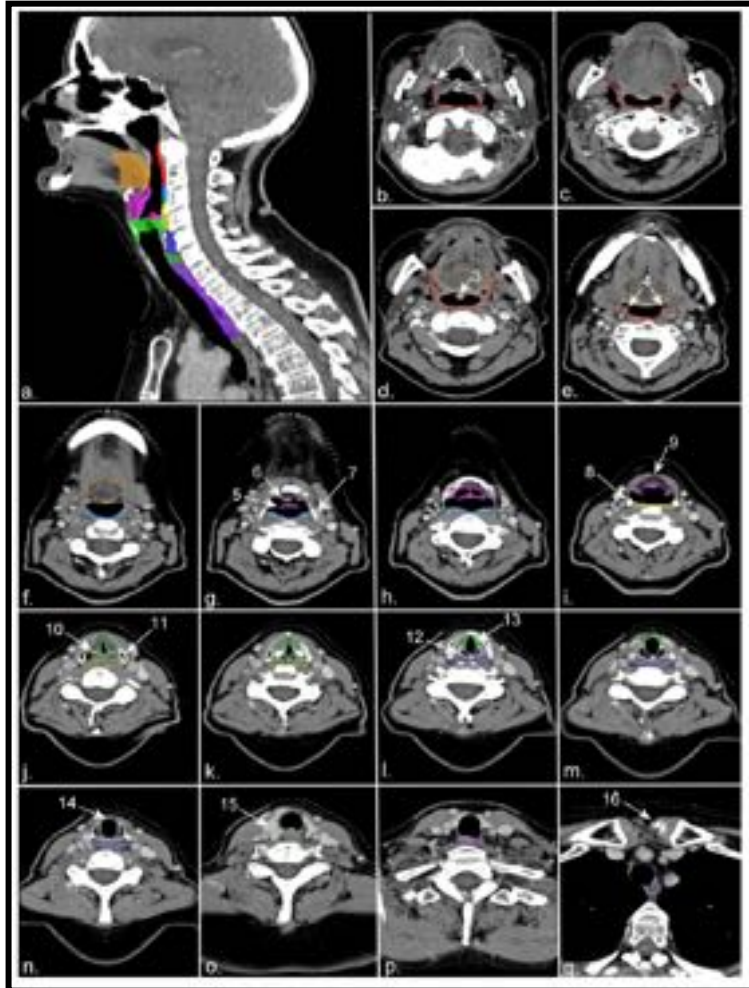
Swallowing structures

Soft palate
PSCM
PMCM
PICM
Base of tongue
Glottis
Supraglottic
Larynx
Oesophagus



Caudell JJ et al; IJROBP 2010

Swallowing structures



- Institutional guidelines for DARS delineation
- Standardization of contouring process
- Correct interpretation of relationship between anatomical structures and swallowing dysfunction in future trials

Christianen M et al; R&O 2011

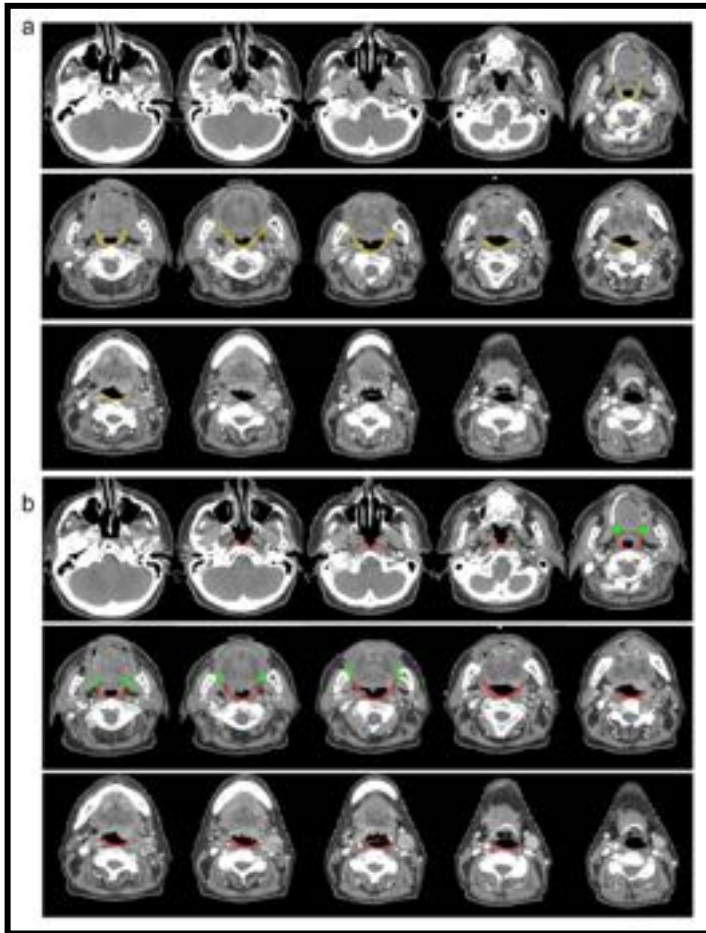
Swallowing structures

Author	Pharyngeal constrictor muscles			Cricopharynx	Esophagus inlet muscle	Cervical esophagus	Base of tongue	Larynx	
	Superior PCM	Middle PCM	Inferior PCM					Supraglottic	Glottic
White (2000) ¹	Cranial: base of the skull Caudal: superior end of the hyoid bone Posterior: pre-vertebral muscles Anterior: pharyngeal lumen (mucosa included)	Cranial: superior end of the hyoid bone Caudal: caudal end of the hyoid bone	Cranial: caudal end of the hyoid bone Caudal: caudal end of cricoid cartilage	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Çaglar (2008) ²	Cranial: pterygoid plates Caudal: upper edge of the hyoid bone	Cranial: upper edge of the hyoid bone Caudal: lower edge of the hyoid bone	Cranial: inferior edge of the hyoid bone Caudal: lower edge of the cricoid cartilage	Not mentioned	Not mentioned	Cranial: lower edge of the cricoid Caudal: caudal-most extent of the low-neck target	Not mentioned	Cranial: upper edge of the thyroid cartilage Caudal: upper edge of the cricoid	
Caselli (2010) ³	Cranial: pterygoid plates Caudal: superior portion of hyoid bone	Cranial: cranial portion of hyoid bone Caudal: inferior portion of hyoid bone	Cranial: inferior portion of hyoid bone Caudal: inferior edge of cricoid cartilage	Not mentioned	Not mentioned	Cranial: inferior edge of the cricoid cartilage Caudal: superior extent of the aortic arch	Cranial: intersection of a vertical plane projected from the posterior hard palate to the tongue Caudal: vallecula Lateral: glossopharyngeal sulcus	Cranial: epiglottis Caudal: vocal cords	
Dirix (2009)	Cranial: caudal tip of the pterygoid plates (hamulus) Caudal: upper edge of hyoid bone Posterior: cervical vertebra or prevertebral muscles Anterior: widest diameter of rhinopharynx, base of tongue, hyoid bone and larynx	Cranial: upper edge of hyoid bone Caudal: lower edge of hyoid bone	Cranial: lower edge of hyoid bone Caudal: lower edge of cricoid cartilage	Cranial: lower edge of cricoid cartilage Caudal: upper edge of trachea Posterior: cervical vertebra Anterior: subglottic larynx	Cranial: upper edge of trachea Caudal: first 2 cm Posterior: cervical vertebra Anterior: trachea	Cranial: below soft palate (uvula) Caudal: upper edge of hyoid bone Anterior: posterior third of tongue	Cranial: top of the piriform sinus and aryepiglottic fold Caudal: upper edge of the cricoid cartilage Posterior: cornu of thyroid cartilage Anterior: anterior tip of thyroid cartilage Lumen excluded	Level of the cricoid cartilage Lumen excluded	
Feng (2007) ⁴	Cranial: caudal tips of the pterygoid plates Caudal: upper edge of the hyoid bone	Cranial: upper edge of the hyoid bone Caudal: lower edge of the hyoid bone	Cranial: below the hyoid Caudal: inferior edge of the cricoid	Not mentioned	Not mentioned	Cranial: inferior border of the cricoid Caudal: caudal-most extent of the low-neck targets	Not mentioned	Contoured as a single structure	
Jensen (2007)	Cranial: lower part of transverse process of C2 Caudal: top of the cricoid cartilage Anterior: widest diameter of rhinopharynx, base of tongue, hyoid bone and larynx			Not mentioned	At the level of the cricoid cartilage Posterior: cervical vertebra Anterior: larynx	Not mentioned	Cranial: below soft palate Caudal: first slice with epiglottis Anterior: posterior 0.5-1.0 cm rim of the tongue	Cranial: top of the piriform sinus Caudal: top of the cricoid cartilage Anterior: cornu of hyoid bone / thyroid cartilage	Level of the cricoid cartilage Lumen excluded

MEAC: Christianen et al; Radiotherapy and Oncology; 101 (2011) 294-302

Christianen M et al; R&O 2011

DARS delineations: PCSM example



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Contouring of the Pharyngeal Superior Constrictor Muscle (PCSM). A cooperative study of the Italian Association of Radiation Oncology (AIRO) Head and Neck Group

Daniela Alterio ^{*,1}, Delia Ciardo ², Lorenzo Preda ³, Angela Argenone ⁴, Orietta Caspiani ⁵, Renato Micera ⁶, Maria G. Ruo Redda ⁷, Elvio G. Russi ⁸, Ernestina Bianchi ⁹, Ester Orlandi ¹⁰, Almalina Bacigalupo ¹¹, Mario Busetto ¹², Domenico Cante ¹³, Letizia Deantonio ¹⁴, Vitaliana De Sanctis ¹⁵, Pierfrancesco Franco ¹⁶, Luciana Lastrucci ¹⁷, Laura Marucci ¹⁸, Anna Merlotti ¹⁹, Marinella Molteni ²⁰, Fabiola Pajar ²¹, Monica Rampino ²², Luigi Santoro ²³, Annamaria Ferrari ²⁴, Federica Bazzani ²⁵, Mariangela Caputo ²⁶, Antonio Laudati ²⁷, Valentina Borzillo ²⁸, Sara Fallivene ²⁹, Nicola Simoni ³⁰, Federica Vigo ³¹, Eva Iannacone ³², Alessia Reali ³³, Alessio Bonanni ³⁴, Mariavittoria Leone ³⁵, Luca Giannello ³⁶, Riccardo Vigna Taglianti ³⁷, Roberto Orecchia ^{*,38}

Method	Margins			
	Superior	Inferior	Anterior	Posterior
"Literature-based"	Caudal tip of pterygoid plate (hamulus)	Hyoid bone at the lower edge of C2	Hamulus, widest diameter of pharyngeal lumen, posterior end of the mandibula, base of tongue	Prevertebral muscle, medial pterygoid muscle
"Optimized"	Base of skull	Hyoid bone	Hamulus, Pterygomandibular raphe base of tongue	Prevertebral muscle, medial pterygoid muscle

Alterio D et al; R&O 2014

DARS delineations: PCSM example

	Variability	Volume analysis	"Literature based" method	"Optimized" method	p-Value	Effect on the variability using the optimized method
PCSM	Intra-operator	Size	0.118	0.110	0.249	=
		Overlap	42.8%	45.3%	0.015	↓
	Inter-operator	Size	22.8%	12.8%	0.05	↓
		Overlap	48.4%	52.1%	<0.001	↓
Adherence to the MR-derived contour	Overlap	25.3%	30.7%	<0.001	↓	
Anterior sub-region-	Intra-operator	Size	0.132	0.141	0.389	=
		Overlap	49.7%	49.6%	0.94	=
	Inter-operator	Size	17.6%	9.6%	<0.001	↓
		Overlap	43.9%	42.5%	0.015	↑
Adherence to the MR-derived contour	Overlap	24.94%	23.55%	0.101	=	
Inferior sub-region	Intra-operator	Size	0.167	0.117	0.0017	↓
		Overlap	41.5%	38.3%	0.013	↓
	Inter-operator	Size	1.4%	1.4%	0.05	=
		Overlap	55.2%	58.4%	<0.001	↓
Adherence to the MR-derived contour	Overlap	28.98%	34.46%	<0.001	↓	
Superior sub-region	Intra-operator	Size	0.352	0.153	<0.001	↓
		Overlap	43.1%	43.5%	0.26	=
	Inter-operator	Size	18.7%	6.9%	0.05	↓
		Overlap	44.3%	53.1%	<0.001	↓
Adherence to the MR-derived contour	Overlap	14.20%	33.34%	<0.001	↓	



Alterio D et al; R&O 2014

Technical guidelines for head and neck cancer IMRT on behalf of the Italian association of radiation oncology - head and neck working group

Anna Merlotti^{1*}, Daniela Alterio^{2†}, Riccardo Vigna-Taglianti^{3†}, Alessandro Muraglia^{4†}, Luciana Lastrucci^{5†}, Roberto Manzo^{6†}, Giuseppina Garbaro^{7†}, Orietta Caspiani^{8†}, Francesco Micciché^{9†}, Francesco Deodato^{10†}, Stefano Pergolizzi^{11†}, Pierfrancesco Franco^{12†}, Renzo Corvo^{13†}, Elvio G. Rossi^{14†} and Giuseppe Sanguineti^{14†}

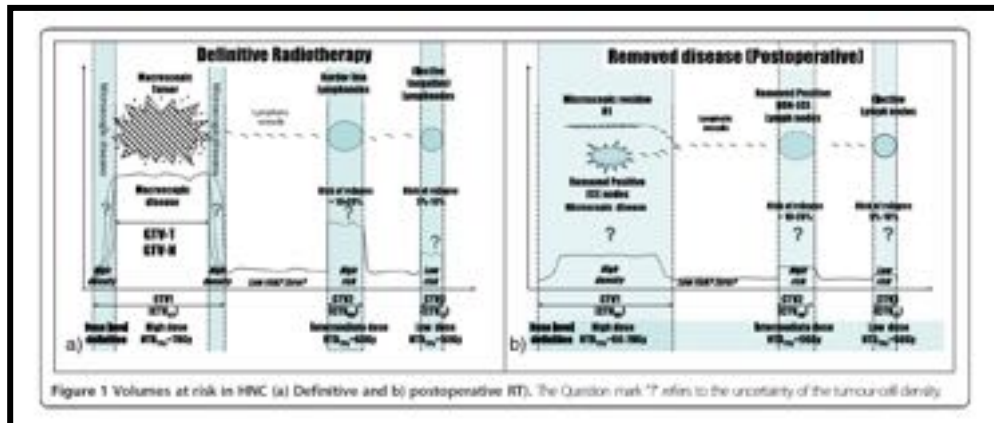
Optional OARS (usually unconstrained)

Submandibular glands

Masticatory spaces

Constrictor muscles

Cricopharyngeal muscles



OAR (R1)	Priority	Endpoint	Goal	Minor variation	Comment
Cord	PRM	0.1 cc	Dmax 5-44-45 Gy	Dmax 46 Gy	
Cord (PRV)	PRM	0.1 cc	Dmax 44-48 Gy	Dmax 48-50 Gy	
Brain	PRM	1 cc	Dmax 60 Gy	Dmax 63 Gy	
Temporal lobes	PRM	1 cc	Dmax 60 Gy	Dmax 65 Gy	
Brainstem (PRV)	PRM	0.1 cc	Dmax 54 Gy	Dmax 60 Gy	
Chiasm (PRV)	PRM	0.1 cc	Dmax 54 Gy	Dmax 60 Gy	
Optic nerve (PRV)	PRM	0.1 cc	Dmax 54 Gy	Dmax 60 Gy	
Larynx	PRM	1 cc	Dmax 73.5 Gy	Dmax 77 Gy	
Mandible	PRM	1 cc	Dmax 70-73.5 Gy	Dmax 75-77 Gy	
Inner ear	SEC	D mean	<50 Gy	<52.5 Gy	
Larynx (without cartilaginous framework)	SEC	V50	<25%	<30%	Oedema
Larynx (supraglottic)	SEC	Dmax	<66 Gy		Dysphonia
Larynx (whole organ)	SEC	Dmax	<50 Gy		Aspiration
Mandible	SEC	V55	<20%		
Esophagus	SEC	1 cc	Dmax 45 Gy	Dmax 55 Gy	
Parotid gland	SEC	V30	<50%	<60%	at least one
	SEC	Dmean	526 Gy		at least one
	SEC	V40	<33% (contrast)		
Upper GI mucosa (outside PTV)	SEC	1 cc	<30 Gy	<36 Gy	
Upper GI mucosa (whole volume)	SEC	V66.5	Dmax 64 Gy (<3%)	Dmax 70 Gy (<3%)	
Brachial plexus	PRM	0.1 cc	Dmax 60 Gy	Dmax 66 Gy	SEC in selected
Thyroid Gland	SEC	V45	<50%		
Submandibular gl	SEC	Dmean	<35 Gy		
Constrictor pharyngeal mm	SEC	Dmean	<50 Gy		
Lacrimal gland	PRM	Dmean	26 Gy		SEC in selected cases
Lens	PRM	Dmax	<4 Gy	<6 Gy	SEC in selected cases
Retina	PRM	0.1 cc	Dmax 54 Gy	Dmax 60 Gy	
Parotid gland	SEC	Dmax	<50 Gy		
TM joints	PRM	0.1 cc	<70Gy		

Merlotti et al. *Radiation Oncology* (2014) 9:264
 DOI 10.1186/s13014-014-0264-9

RADIATION ONCOLOGY

REVIEW Open Access

Technical guidelines for head and neck cancer IMRT on behalf of the Italian association of radiation oncology - head and neck working group

Anna Merlotti^{1*}, Daniela Alterio^{2†}, Riccardo Vigno-Tagliani^{3†}, Alessandro Muraglia^{4†}, Luciano Lestrucchi^{5†}, Roberto Manzoni^{6†}, Giuseppina Gambani^{7†}, Orietta Capiani^{8†}, Francesco Micciché^{9†}, Francesco Diiodato^{10†}, Stefano Pegolosi^{11†}, Pierfrancesco Franco^{12†}, Renzo Conio^{13†}, Elvio G Ruzi^{14†} and Giuseppe Sanguineti^{15†}

- ✓ **Whole larynx: $D_{mean} < 50$ Gy, V_{60}**
- ✓ **Supraglottic larynx: $D_{max} < 66$ Gy**
- ✓ **Oesophagus: $D_{1cc} < 45$ Gy**
- ✓ **Parotid gland: $V_{30} < 50\%$**
 $D_{mean} < 26$ Gy

✓ **PCM:**
 $D_{mean}, V_{50}, V_{55}, V_{60}, V_{65}, V_{70}$

Merlotti A et al; Radiat Oncol 2014

IMRT - Definitions

Intensity Modulated RadioTherapy

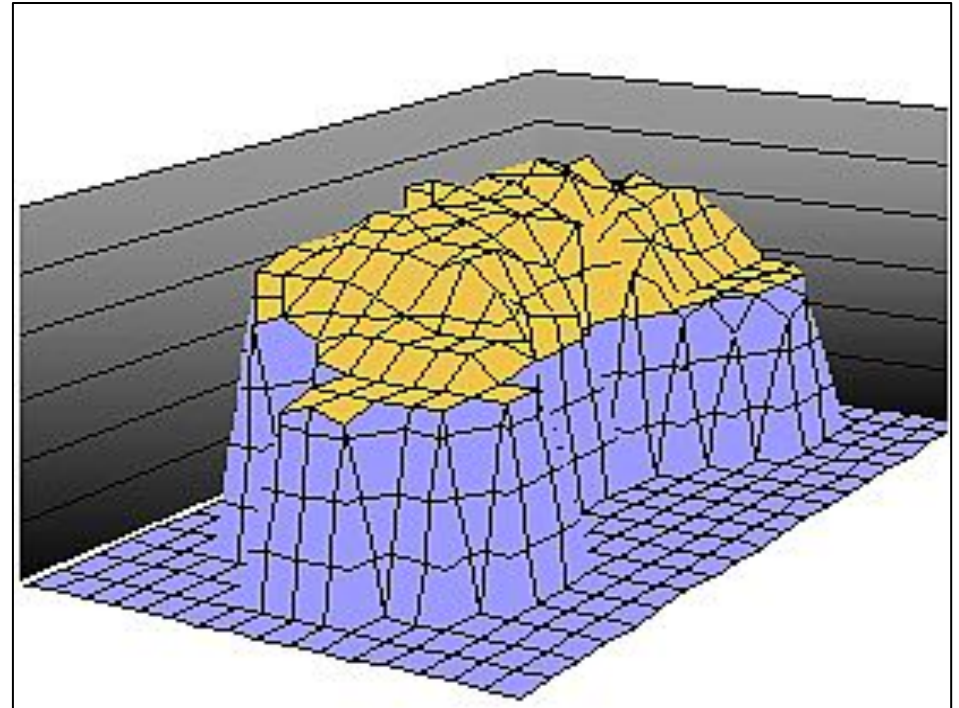
Conformal beam geometry

Changing dose intensity across the field thus NON FLAT (modulated) dose profile

Inverse "Backward" Planning

Setting of dose constraints for PTV and critical structures

Optimization of beam intensities to fulfill desired constraints



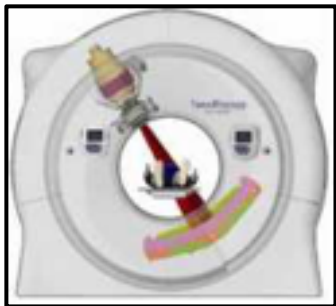
Intensity Modulated dose profile

IGRT

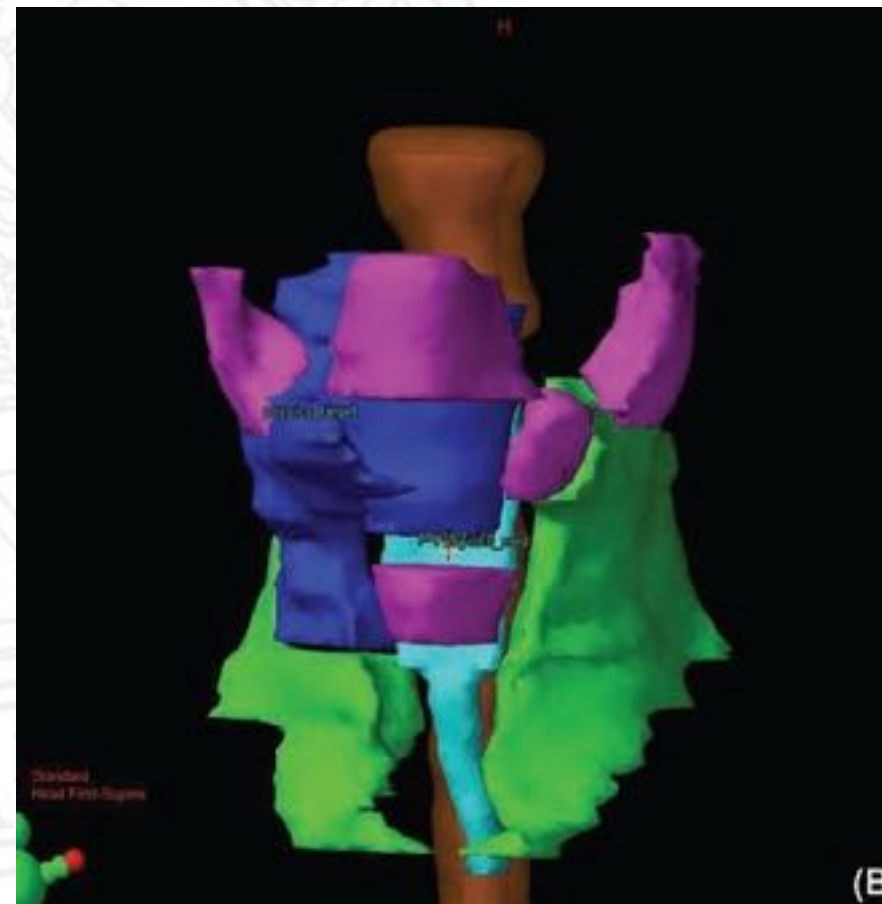
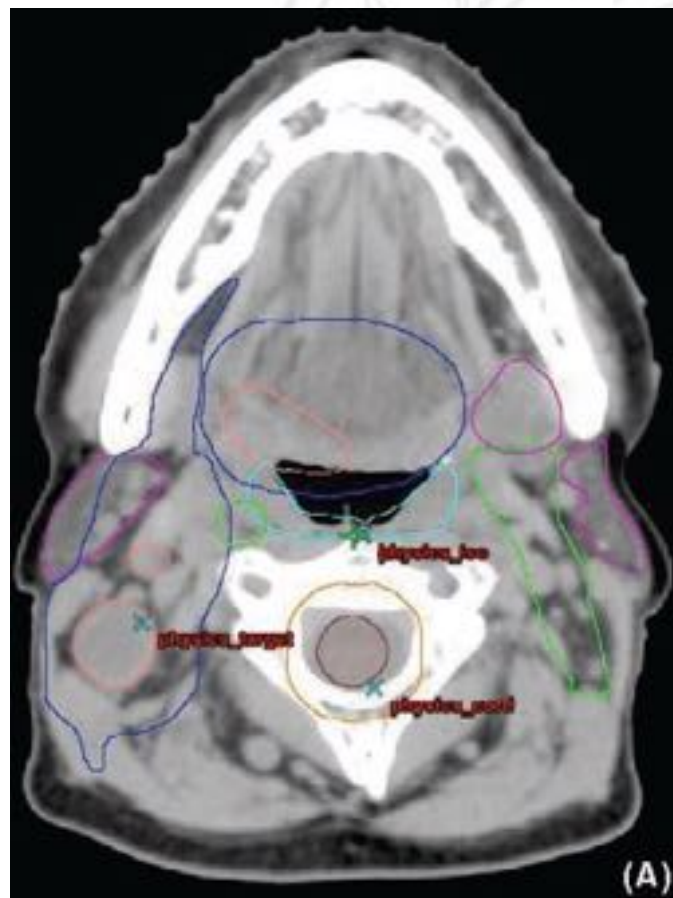


Due to the third-power relationship between the radius of a sphere and its volume ($\frac{4}{3}\pi r^3$):

a small reduction in margin yields a great reduction in volume



IG-IMRT



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

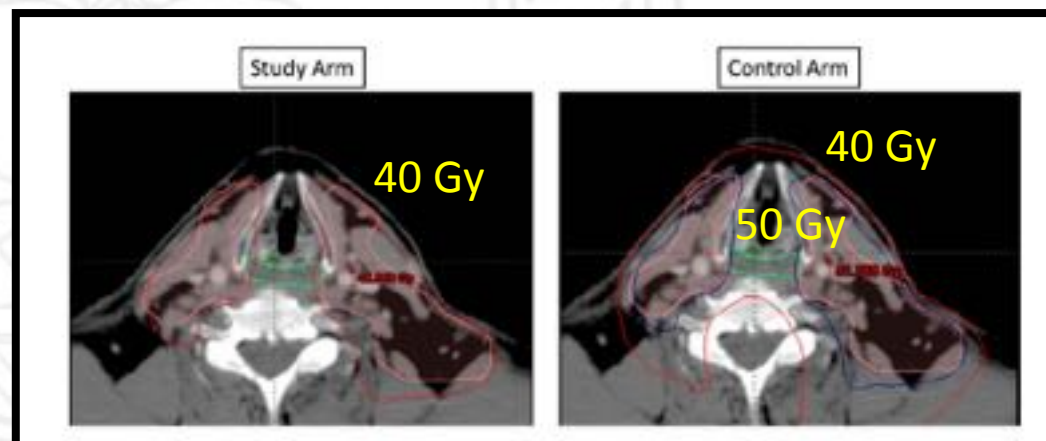
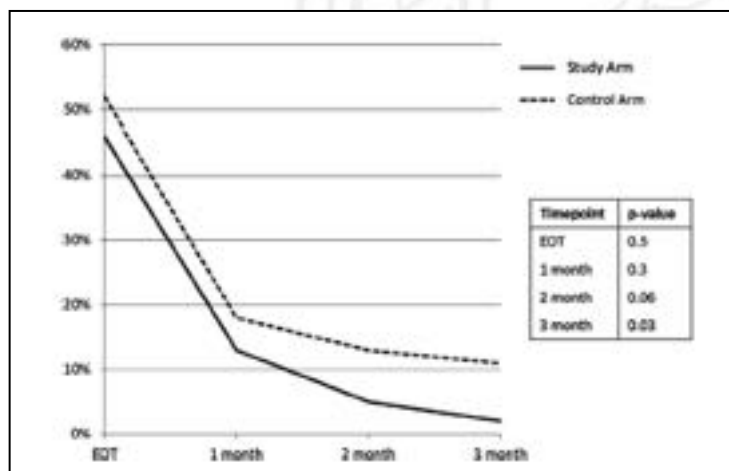
Phase III randomised trial

Reduction of the dose to the elective neck in head and neck squamous cell carcinoma, a randomized clinical trial using intensity modulated radiotherapy (IMRT). Dosimetrical analysis and effect on acute toxicity

Sandra Nuyts^{a,*}, Maarten Lambrecht^a, Frédéric Duprez^b, Jean-Francois Daisne^c, Dirk Van Gestel^b, Danielle Van den Weyngaert^{d,e}, Nele Platteaux^{a,f}, Yasmynne Geussens^a, Mia Voordeckers^g, Indira Madani^h, Wilfried De Neve^h

*Department of Experimental Radiotherapy ICI Leuven, Campus Gasthuisberg; ^aDepartment of Radiotherapy, Ghent University Hospital; ^bDepartment of Radiotherapy, Clinique de Médecine Séméiologique, Novor; ^cDepartment of Radiotherapy, Ziekenhuis Netwerk Antwerp; ^dUniversity of Antwerp; ^eDepartment of Radiation Oncology, ICI Brussel, Imp. Universitaire Brussel, Belgium; ^fDepartment of Radiotherapy, Ziekenhuis Netwerk Antwerpen and University of Antwerp, Antwerp, Belgium

- ✓ 200 HNCPs randomized
- ✓ 50 Gy vs 40 Gy prophylactic neck RT
- ✓ DARS possible : as low as possible



Severe dysphagia

Nuyts S et al; R&O 2013

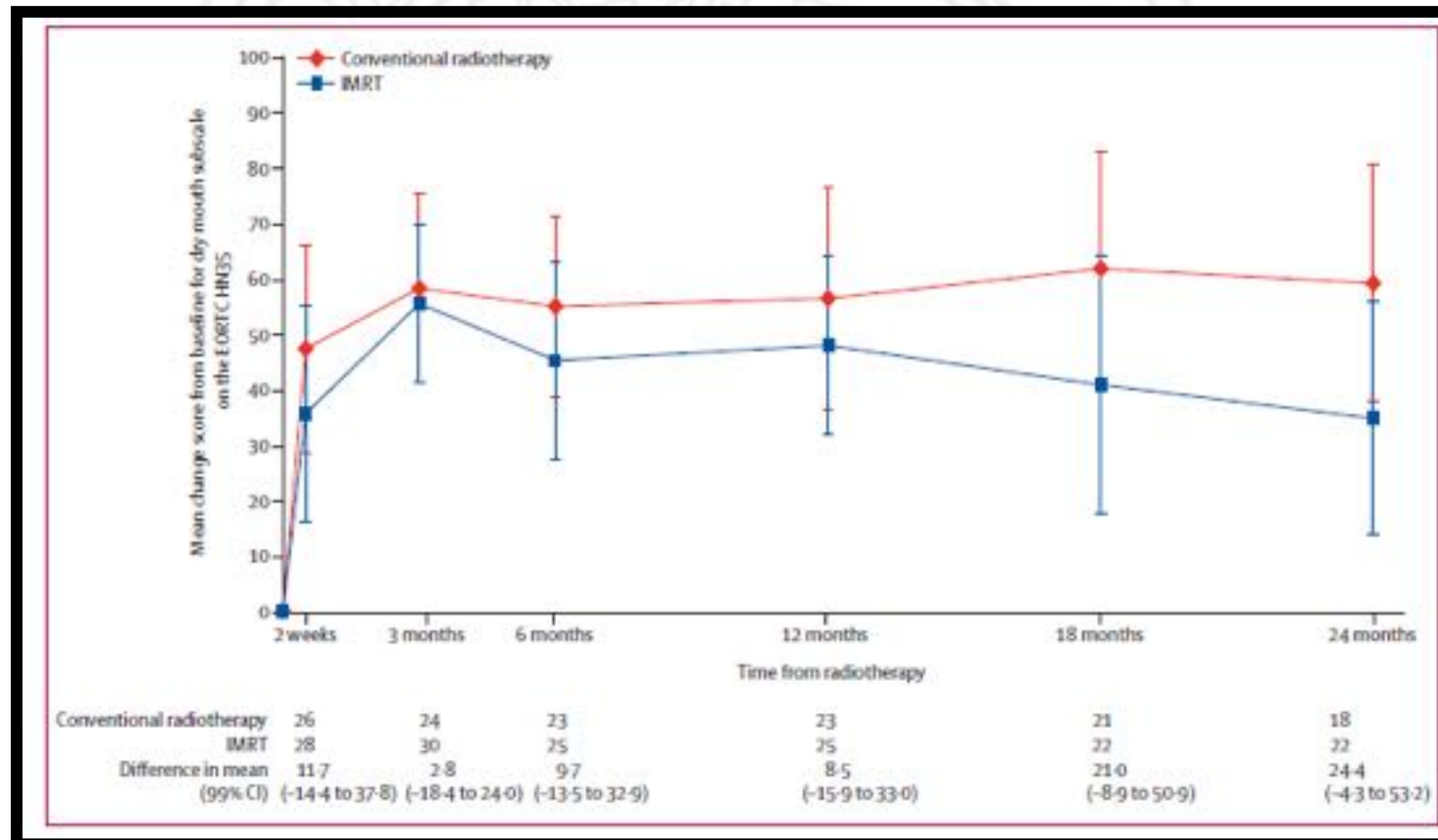
XRS: xerostomia-related structures

- **Parotid glands**
- **Submandibular glands**
- **Sublingual glands**
- **Minor salivary glands**
 - **Cheeks**
 - **Soft palate**
 - **Lips**

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 Menden, Eoin J Harrington, Trevor Gunnors, Maria D'Souza, A. Shuk, Catherine Clark, Elizabeth A Miles, Aashir M Malik, Kate Newbold, Margherita Tancig, Pascal A Adé, Sarah D Griffin, Christopher Sweeney, Roger F Foy, Roger P Kirkers, Mark A Symonds, Bruce Green, Emma Hall, on behalf of the PARSPORT trial management group*



Nutting et al; Lancet Oncol 2011

DARS-XRS

- **To be contoured**
- **To be included in treatment planning**
- **To be investigated with appropriate metric**

Prospective evaluation of oncological outcome

Pierfrancesco Franco

Grazie dell' attenzione



Mario Schifano – Indicazione - 1963

