La tossicità correlata al trattamento nei tumori del distretto cervico-cefalico:

Tra moderna radioterapia e terapie integrate di supporto

Rosario Mazzola, MD

Radiation Oncology Department
Sacro Cuore Don Calabria Hospital, Negrar-Verona, Italy

Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)

DICHIARAZIONE

Relatore: Rosario Mazzola

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

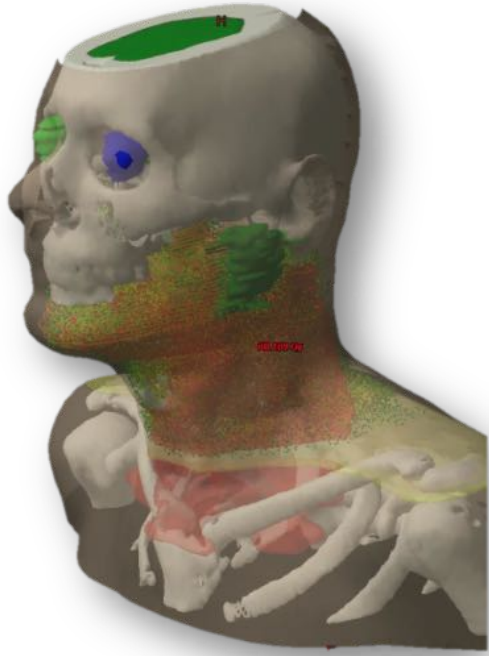
Topics

- Organ-sparing Radiotherapy in Head and Neck Cancer
- Which IMRT Technique?
- Image-guided Radiotherapy
- Predictive Factors of Toxicity (dosimetrics and clinics)
- Supportive Care
- Future Advances

Head and Neck Cancer RT:
Criticisms

Treatment for HNC is highly complex:

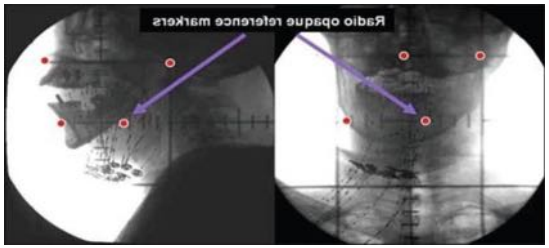
- **Variety of disease subsites**
- **Intricate anatomy**
- **Normal and tumoral structures often in close proximity**



***Xerostomia* and *Swallowing Disfunction* are the main causes of decreased quality of life after radiotherapy for head and neck cancer**

Head and Neck Cancer RT:

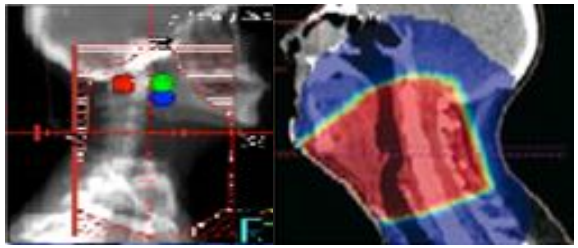
A continuous changing



2-Dimensional RT

Rx to Target defining
No accurate dose distribution
Set-up uncertainces(Rx)

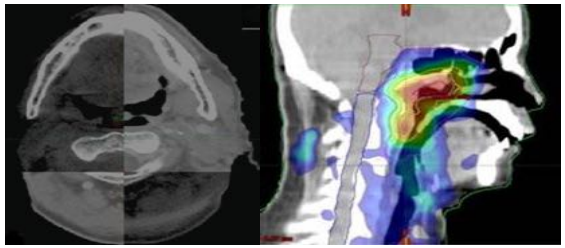
High toxicity (huge portals)



3D-conformal RT

3D conformal RT on CT slices
Possibility to > doses and LC
Better set-up checking (EPID)

< Toxicity (Field conformation)



IMRT
Inverse planning systems
"*concave shaped sculped*"
Possibility to > doses and LC
Better set-up checking (CBCT)

< Toxicity (ripid gradient of dose)

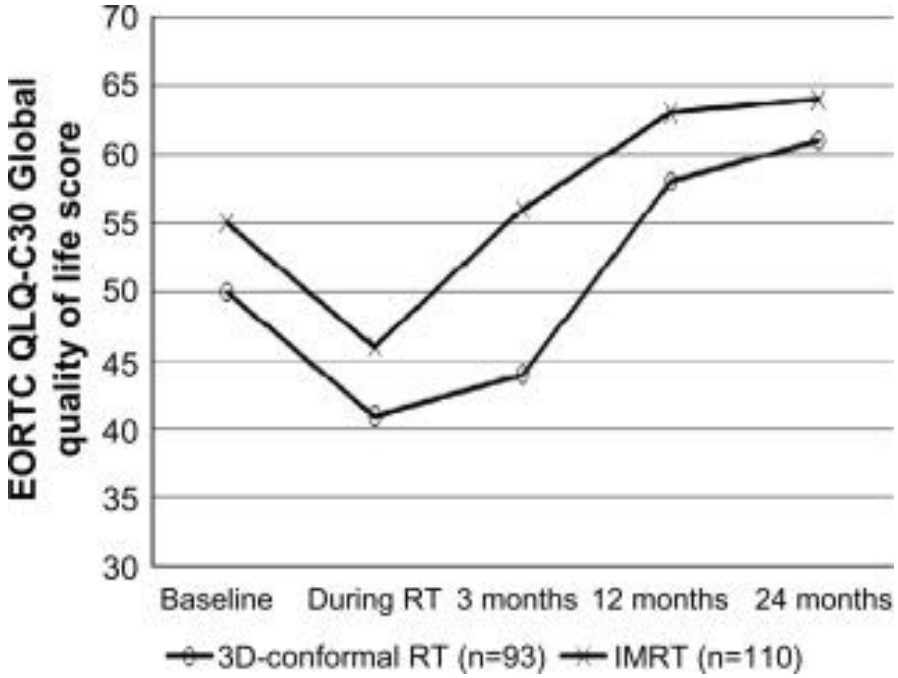
PREDICTIVE FACTORS OF TOXICITY

PERSONALIZED RADIATION ONCOLOGY IN HEAD AND NECK CANCER

Topics

- **Organ-sparing Radiotherapy in Head and Neck Cancer**
- Which IMRT Technique?
- Image-guided Radiotherapy
- Predictive Factors of Toxicity (dosimetrics and clinics)
- Supportive Care
- Future Advances

Organ-sparing Radiotherapy in Head and Neck Cancer



Reducing Radiation-Induced Morbidity Improves Health-Related Quality of Life

Vergeer et al. IJROBP, 2009

Organ-sparing Radiotherapy in Head and Neck Cancer:

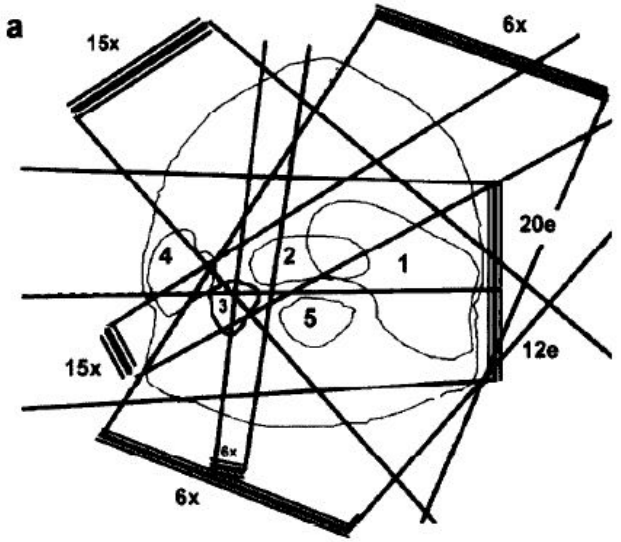
Parotid Glands

PAROTID GLAND SPARING IN PATIENTS UNDERGOING BILATERAL HEAD AND NECK IRRADIATION: TECHNIQUES AND EARLY RESULTS

AVRAHAM EISBRUCH, M.D.,* JONATHAN A. SHIP, D.M.D.,† MARY K. MARTEL, PH.D.,* RANDALL K. TEN HAKEN, PH.D.,* LON H. MARSH, C.M.D.,* GREGORY T. WOLF, M.D.,‡ RAMON M. ESCLAMADO, M.D.,‡ CAROL R. BRADFORD, M.D.,‡ JEFFREY E. TERRELL, M.D.,‡ STEPHEN S. GEBARSKI, M.D.§ AND ALLEN S. LICHTER, M.D.*

Departments of *Radiation Oncology, †Hospital Dentistry, ‡Otolaryngology–Head and Neck Surgery, and §Radiology, University of Michigan, Ann Arbor, MI

Conclusion: Partial parotid gland sparing is feasible by using three-dimensional planning in patients undergoing bilateral head and neck radiation. Approximately 50% of the saliva flow from the spared glands may be retained, and most patients thus treated have no or mild xerostomia in the early period after the completion of radiation. Whether tumor control and late complications are comparable to standard radiation will be assessed as more experience is gained.



Critical issues:

- Conformal dose distribution around the targets
- Plans with large dose inhomogeneities
- Very tedious and time-consuming process

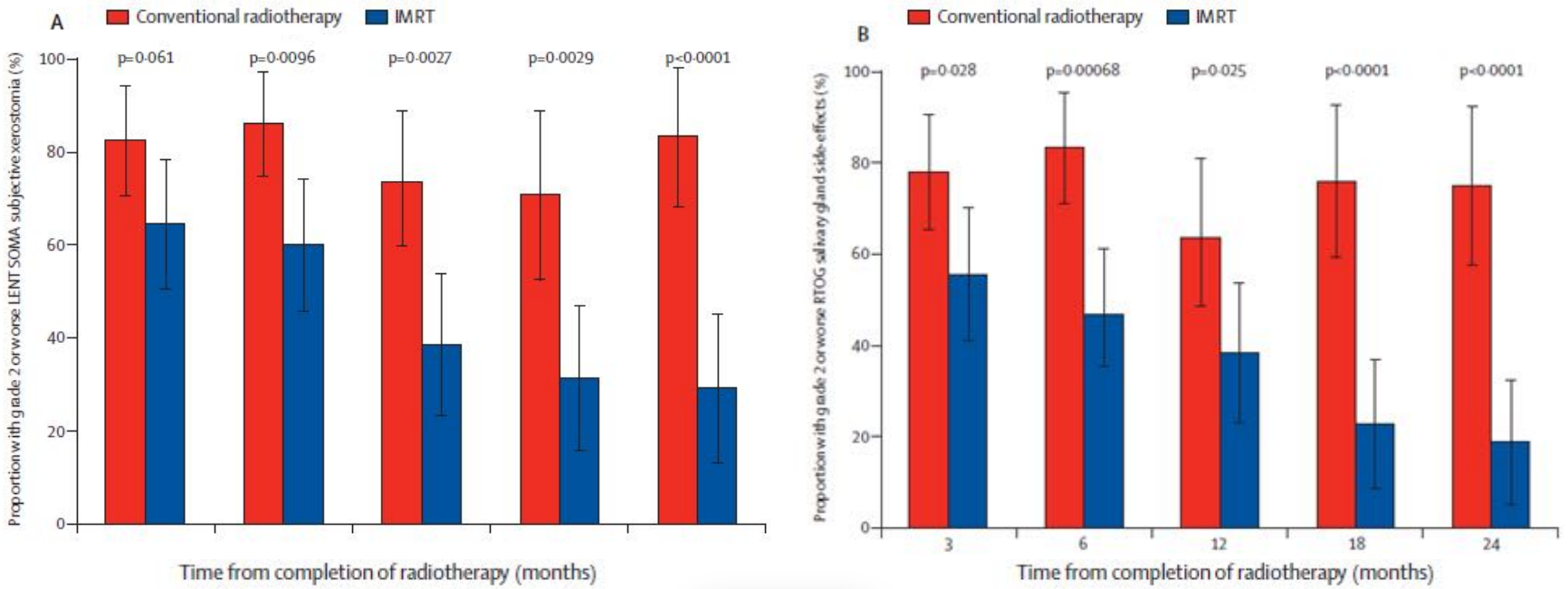
Eisbruch et al. IJROBP, 1996

Organ-sparing Radiotherapy in Head and Neck Cancer:

Parotid Glands

Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial

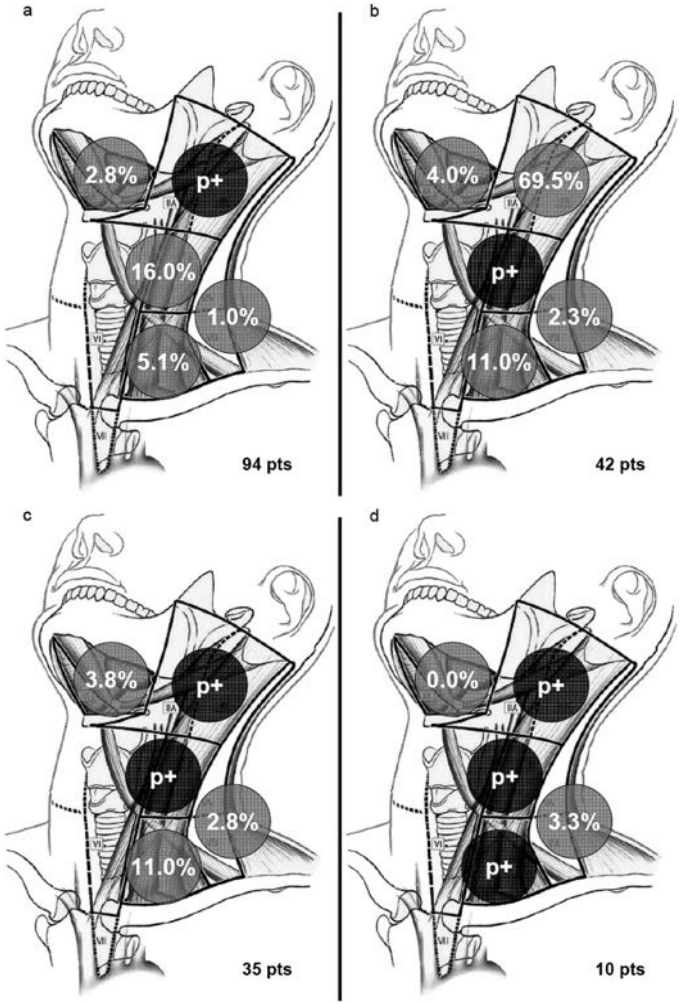
*Christopher M Nutting, James P Morden, Kevin J Harrington, Teresa Guerrero Urbano, Shreerang A Bhide, Catharine Clark, Elizabeth A Miles, Aisha B Miah, Kate Newbold, MaryAnne Tanay, Fawzi Adab, Sarah J Jefferies, Christopher Scrase, Beng K Yap, Roger P A'Hern, Mark A Sydenham, Marie Emson, Emma Hall,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



Nutting et al. Lancet Oncol, 2011

Organ-sparing Radiotherapy in Head and Neck Cancer:

Submandibular Glands



The risk of ipsilateral subclinical neck nodal involvement for early T-stage/node-positive oropharyngeal squamous cell carcinoma according to involvement of other levels: pathologic involvement of (a) Level II, (b) Level III, (c) Levels II and III, and (d) Levels II-IV

Levels IB and V are at very low (<5%) risk of involvement, even with ipsilateral to pathologically proven neck disease

Ospedale Sacro Cuore - Don Calabria Negrar (Verona)

Sanguineti G et al. IJROBP, 2009

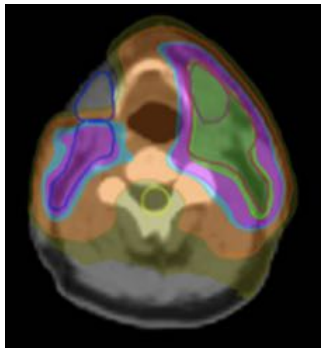
Organ-sparing Radiotherapy in Head and Neck Cancer:

Submandibular Glands

Safety of contralateral submandibular gland sparing in locally advanced oropharyngeal cancers: A multicenter review

Tyler P. Robin, MD, PhD,[1] Gregory N. Gan, MD, PhD,[1] Moses Tam, MD,[2] David Westerly, PhD,[1] Nadeem Riaz, MD,[3] Sana D. Karam, MD, PhD,[1] Nancy Lee, MD,[3] David Raben, MD[1]*

[1]Department of Radiation Oncology, University of Colorado Cancer Center, Aurora, Colorado, [2]New York University School of Medicine, New York, New York, [3]Department of Radiation Oncology, Memorial Sloan–Kettering Cancer Center, New York, New York.



Median follow-up	27.3 months
Mean dose to cSMG	3304cGy
Failures	# pts (% total pts)
Total	12 (16.9%)
Local	1 (1.4%)
Regional	6 (14.6%)
Distant	5 (7.0%)
Contralateral IB	0 (0%)

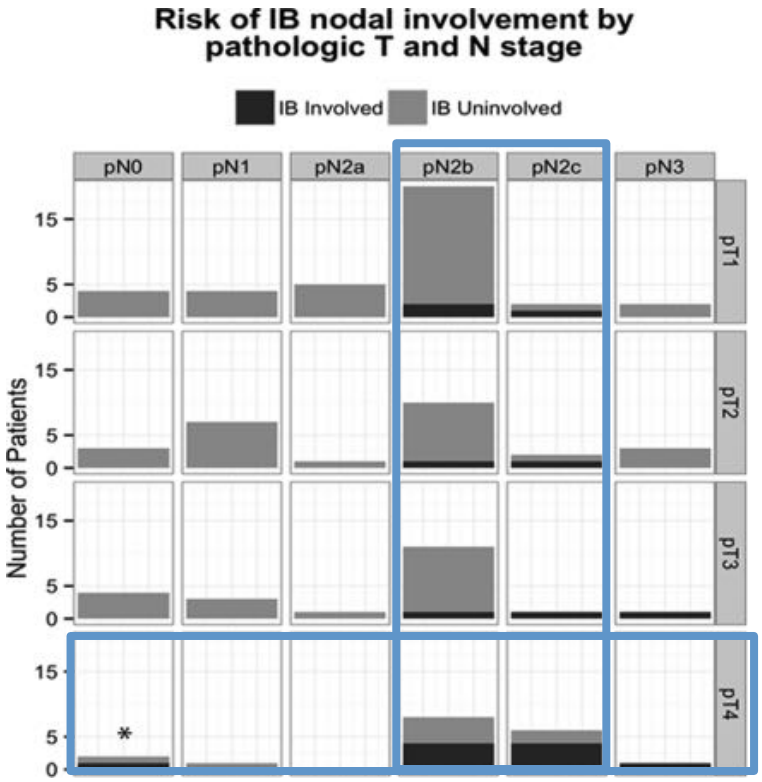
Conclusion. Xerostomia remains a significant morbidity despite parotid sparing and can be minimized further by contralateral submandibular gland sparing. These data provide important preliminary evidence that contralateral submandibular gland sparing is feasible and may be safe even in locally advanced cancers.

Robin et al. Head & Neck, 2015

Organ-sparing Radiotherapy in Head and Neck Cancer:

Submandibular Glands

Level IB nodal involvement in oropharyngeal carcinoma: Implications for submandibular gland-sparing intensity-modulated radiotherapy



Submandibular gland sparing IMRT can reasonably be offered to appropriately selected patients.

Yu et al. The Laryngoscope, 2015

Organ-sparing Radiotherapy in Head and Neck Cancer:

Submandibular Glands

Evidence-based organ-sparing radiotherapy in head and neck cancer

Piet Dirix, Sandra Nuyts

Although intuitively appealing, the available evidence regarding the safety and efficacy of submandibular gland-sparing radiotherapy is extremely limited. Moreover, meaningful reduction of the mean dose to the submandibular gland is potentially hazardous owing to its close proximity to the lower level II nodes, which require the full prescribed radiation dose to maximise regional tumour control.[54] Indeed, a planning study suggested that limiting the mean dose to the contralateral submandibular gland to 40 Gy requires reducing the dose coverage to the contralateral elective target volume from 95% to 90% of the prescribed dose.[55] At present, submandibular gland-sparing radiotherapy should not be undertaken outside clinical trials.

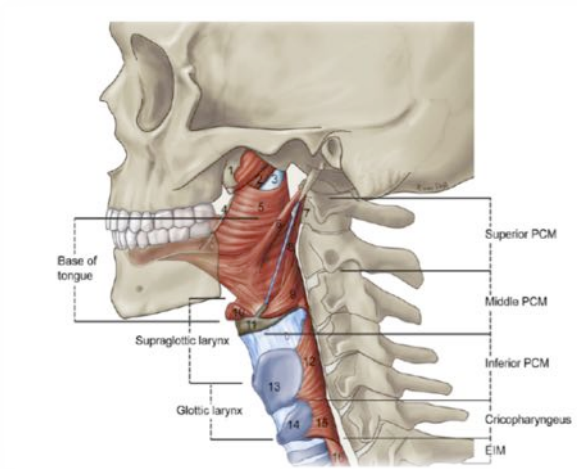
Dirix et al. Lancet Oncology, 2010

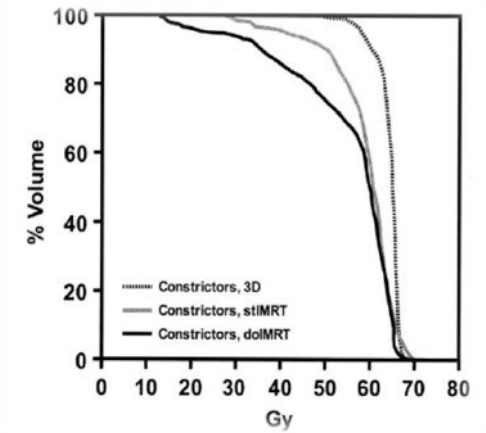
Organ-sparing Radiotherapy in Head and Neck Cancer:

Swallowing structures

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

Radiation damage to the *Pharyngeal Constrictors* and the glottic/supraglottic larynx were implicated in post-radiotherapy *dysphagia and aspiration*





IMRT can reduce the volumes of these structures receiving high doses

Eisbruch et al. IJROBP, 2004

Organ-sparing Radiotherapy in Head and Neck Cancer:

Swallowing structures

Studies assessing dose-volume analyses for late dysphagia

Author	Pts	Site	Dosimetric Factors correlated with late dysphagia	Limits	Anatomic Borders			
					SPC	MPC	IPC	Crico
Feng[34] (2007)	36	OP/NP	PCs (mean dose, V50, V60, V65)	Cranial	Caudal tips of pterygoid plates	Upper edge of hyoid bone	Below the hyoid bone	Not Mentioned
				Caudal	Upper edge hyoid bone	Lower edge of the hyoid bone	Inferior edge of cricoid	
Levendag[21] (2007)	56	OP	SPC, MPC (mean dose)	Cranial	Mild C2	Upper C3	Upper C5	Mild C6
				Caudal	Upper C3	Upper C4	Mid C6	First ring of trachea
Jensen[35] (2007)	25	PH	SL (mean dose, V60, V65)	Cranial	Lower part transverse process C2	Lower part transverse process C2	Lower part transverse process C2	Not Mentioned
				Caudal	Top of cricoid cartilage	Top of cricoid cartilage	Top of cricoid cartilage	
Caglar[29] (2008)	96	M	IPC (mean dose, V50, V60)	Cranial	Pterygoid plates	Upper edge of hyoid bone	Inferior edge hyoid bone	Not Mentioned
				Caudal	Upper edge ofthe hyoid bone	Lower edge of the hyoid bone	Lower edge cricoid	
Dirix[30] (2009)	53	M	MPC (mean dose,V50)	Cranial	Caudal tip of the pterygoid plates	Upper edge of hyoid bone	Inferior edge hyoid bone	Lower edge cricoid
				Caudal	Upper edge hyioid bone	Lower edge of the hyoid bone	Lower edge cricoid	Upper edge of trachea
Bhide[31] (2009)	37	M	No correlations	Cranial	Base of the skull	Superior end of hyoid bone	Inferior edge hyoid bone	Not Mentioned
				Caudal	Superior end hyoid bone	Caudal end of the cartilage cricoid	Lower edge cricoid	
Caudell[36] (2010)	83	M	IPC (V60, V65)	Cranial	Pterygoid plates	Upper edge of hyoid bone	Inferior edge hyoid bone	Not Mentioned
				Caudal	Upper edge of the hyoid bone	Lower edgem of the hyoid bone	Lower edge cricoid	
Mortensen[32] (2013)	65	M	SPC, MPC (mean dose)	Cranial	Caudal tip of the pterygoid plates	Upper edge of C3	First slice caudal to the lower edge of hyoid bone	First slice caudal to the arytenoid cartilages
				Caudal	Lower edge of C2	Lower edge of hyoid bone	Lower edge of the arythenoid cartilages	Lower edge of the cricoid cartilages

OP: Oropharynx NP: Nasopharynx PH: Pharynx M: Miscellaneous, PCs: All constrictors. C2: 2nd cervical vertebra, C3: 3th cervical vertebra, C4: 4th cervical vertebra, C5: 5th cervical vertebra, C6: 6th cervical vertebra

PCS: Pharyngeal constrictor muscle, SPC: Superior constrictor muscle, MPC: Middle constrictor muscle, SL: Supraglottic larynx, IPC: Inferior constrictor muscle,V50=volume of a structure receiving 50 Gy. V60=volume of a structure receiving 60 Gy. V65=volume of a structure receiving 65 Gy D60=minimum dose received by 60% of a structure. V70=volume of a structure receiving 70 Gy Dmax: Dose maximum

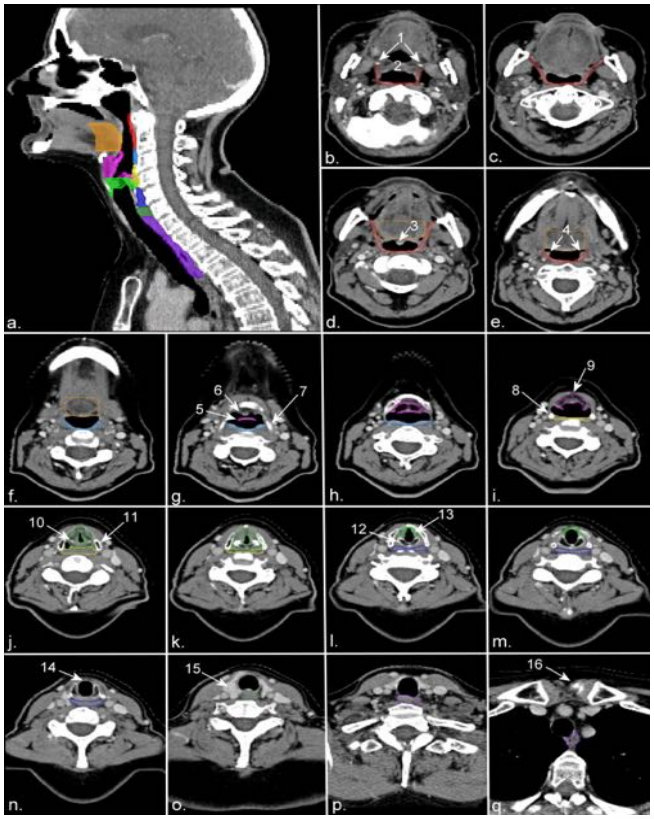
Mazzola R et al. BJR, 2014

Organ-sparing Radiotherapy in Head and Neck Cancer:

Swallowing structures

Delineation of organs at risk involved in swallowing for radiotherapy treatment planning

Miranda E.M.C. Christianen [a], Johannes A. Langendijk [a,*], Henriëtte E. Westerlaan [b], Tara A. van de Water [a], Hendrik P. Bijl [a]



- ✓ Superior Constrictor
- ✓ Middle Constrictor
- ✓ Inferior Constrictor
- ✓ Cricopharyngeus
- ✓ Esophagus inlet muscles
- ✓ Cervical esophagus
- ✓ Base of tongue
- ✓ Supraglottic
- ✓ Glottic larynx

Cristianen et al. Radiother Oncol, 2011

Organ-sparing Radiotherapy in Head and Neck Cancer:

Swallowing structures

VOLUME 28 · NUMBER 16 · JUNE 1 2010

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Intensity-Modulated Chemoradiotherapy Aiming to Reduce Dysphagia in Patients With Oropharyngeal Cancer: Clinical and Functional Results

Felix Y. Feng, Hyungjin M. Kim, Teresa H. Lyden, Marc J. Haxer, Francis P. Worden, Mary Feng, Jeffrey S. Moyer, Mark E. Prince, Thomas E. Carey, Gregory T. Wolf, Carol R. Bradford, Douglas B. Chepeha, and Avraham Eisbruch

Observer-Rated Dysphagia

Event Grade	Pre-therapy (n = 73)		3 (n = 72)		6 (n = 62)		12 (n = 68)		18 (n = 58)		24 (n = 51)	
	Time Period (months)											
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0	71	97	36	50	32	52	39	58	36	62	30	59
1	1	2	25	35	22	35	25	37	19	33	19	37
2	1	2	6	8	4	6	3	4	2	3	1	2
3	0	0	5	7	4	6	1	1	1	2	1	2

Videofluoroscopic-Measured Aspiration Rates and Summary Swallow Scores

Time, months	No. of Patients With VF Studies	Patients With VF-Based Aspiration (%)		Patients Who Aspirated After Therapy but Did Not Aspirate Before Therapy		VF Score*	
		No.	%	No.	%	Mean	SD
Pretherapy	72	8	11			2.9	1.5
3	68	22	32	18	26	4.3	1.1
12	66	16	24	13	20	4.1	0.9
24	44	10	22	7	16	4.2	0.9

Abbreviations: VF, videofluoroscopy; SD, standard deviation.
*VF scores reported on a scale of one to seven. Higher scores denoted worse function.

Limiting the radiation dose to the crucial swallowing structures is expected to decrease the incidence and severity of radiation-induced dysphagia

Organ-sparing Radiotherapy in Head and Neck Cancer:

Geographical Missing

RECURRENCES NEAR BASE OF SKULL AFTER IMRT FOR HEAD-AND-NECK CANCER: IMPLICATIONS FOR TARGET DELINEATION IN HIGH NECK AND FOR PAROTID GLAND SPARING

AVRAHAM EISBRUCH, M.D.,* LON H. MARSH, C.M.D.,* LAURA A. DAWSON, M.D.,* CAROL R. BRADFORD, M.D.,† THEODOROS N. TEKNOS, M.D.,† DOUGLAS B. CHEPEHA, M.D.,† FRANCIS P. WORDEN, M.D.,‡ SUSAN URBA, M.D.,‡ ALEXANDER LIN, M.D.,* MATTHEW J. SCHIPPER, M.SC.,§ AND GREGORY T. WOLF, M.D.†

Conclusion: These results suggest that when the contralateral node-negative side of the neck has a high risk of subclinical metastasis, it is adequate to include the SD nodes as the cranial-most Level II nodal target in non–nasopharyngeal head-and-neck cancer. In the node-positive side of the neck, this nodal level should be delineated more cranially. The RP nodal targets should be delineated bilaterally and should extend to the base of the skull, rather than to the top of C1. These guidelines allowed substantial sparing of the contralateral parotid gland. The results of this series validate a consensus for target delineation adopted recently by cooperative radiotherapy groups.

Organ-sparing Radiotherapy in Head and Neck Cancer:

Take Home Message

In HNC treated with IMRT it is important that all relevant normal structures at risk are delineated to predict potential complications and that the available radiation-dose constraints are possibly respected

Sparing the contralateral parotid gland should be attempted
Ipsilateral parotid gland has low priority, especially if level II lymph-node metastases are present

The submandibular glands play a role in the pathogenesis of xerostomia, but sparing them should not be undertaken outside clinical trials

To prevent late dysphagia, the best approach consists of reducing the doses to the pharyngeal constrictor muscles and the larynx as much as possible, although avoidance of target under-dosing remains the highest priority

Topics

- Organ-sparing Radiotherapy in Head and Neck Cancer
- **Which Intensity Modulated Technique?**
- Image-guided Radiotherapy
- Predictive Factors of Toxicity (dosimetrics and clinics)
- Supportive Care
- Future Advances

Which Intensity Modulated Technique?

PRO-IMRT

Radiotherapy and Oncology 101 (2011) 388–393

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Head and neck cancer radiotherapy

A comparison of several modulated radiotherapy techniques for head and neck cancer and dosimetric validation of VMAT

Florian Stieler*, Dirk Wolff, Heike Schmid, Grit Welzel, Frederik Wenz, Frank Lohr

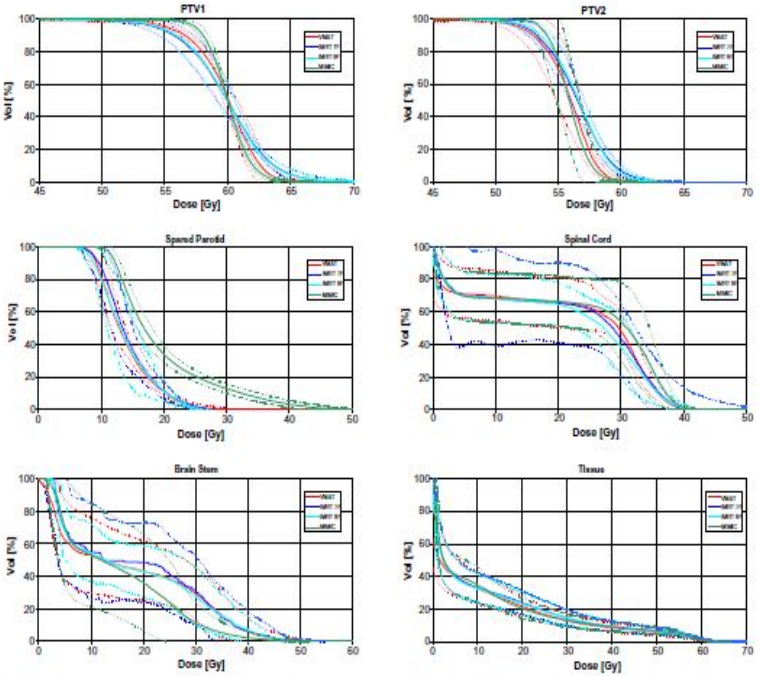


Fig. 2. DVHs with a 95% confidence interval (CINT) for all techniques and all PTVs and OARs.

Conclusion: All treatment paradigms produced plans of excellent quality and dosimetric accuracy with IMRT providing best OAR sparing and VMAT being the most efficient treatment option in our comparison of treatment plans with high complexity.

Which Intensity Modulated Technique?

PRO-Rotational intensity modulated

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Technical notes

Static and rotational intensity modulated techniques for head-neck cancer radiotherapy: A planning comparison

Sara Broggi [a,*], Lucia Perna [a], Francesco Bonsignore [b], Giuseppe Rinaldin [a], Claudio Fiorino [a], Anna Chiara [c], Cristina Frigerio [b], Ivana Butti [b], Giulia Sangalli [b], Italo Dell'Oca [c], Nadia Di Muzio [c], Giovanni Mauro Cattaneo [a], Fausto Declich [b]

Results: Concerning PTV coverage, significantly better results were found for HT and RA. HT significantly improved the target coverage both compared to S-IMRT and VMAT. No significant differences were found between S-IMRT and volumetric techniques in terms of dose homogeneity. For OARs, all the techniques were able to satisfy all hard constraints; significantly better results were found for HT, especially in the intermediate dose range (15–30 Gy). S-IMRT reached a significantly better OARs sparing with respect to VMAT and RA. No significant differences were found for body mean dose, excepting higher values of V5–V10 for HT. A reduction of planned MUs and delivery treatment time was found with volumetric techniques.

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Negrar (Verona)

Broggi et al. Physica Medica, 2014

Which Intensity Modulated Technique?

PRO-Rotational intensity modulated

Holt *et al. Radiation Oncology* 2013, 8:26
http://www.ro-journal.com/content/8/1/26

RADIATION ONCOLOGY

RESEARCH Open Access

Multi-institutional comparison of volumetric modulated arc therapy vs. intensity-modulated radiation therapy for head-and-neck cancer: a planning study

Andrea Holt[1,7], Dirk Van Gestel[2], Mark P Arends[3], Erik W Korevaar[4], Danny Schuring[5], Martina C Kunze-Busch[6], Rob JW Louwe[6,8] and Corine van Vliet-Vroegindeweij[1*]

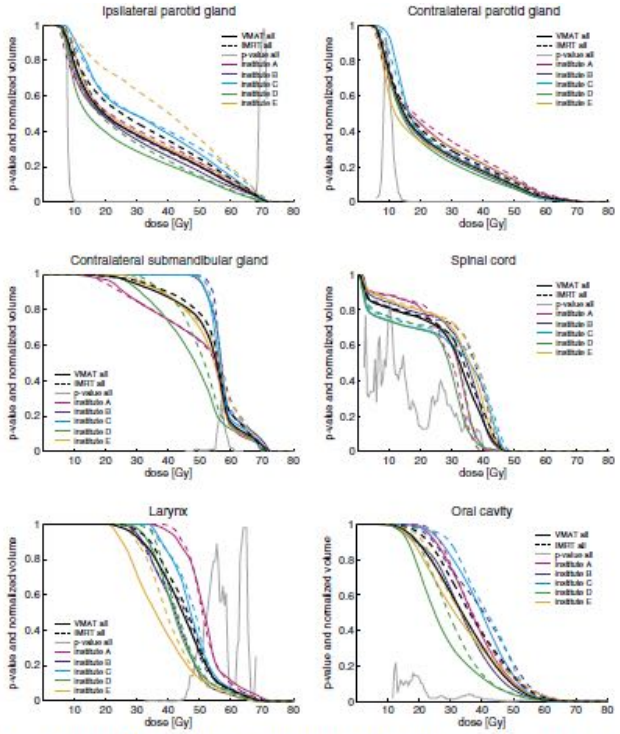


Figure 3 DVHs for different OARs for VMAT and IMRT and p-value for pooled data. DVHs for parotid and submandibular glands, spinal cord, larynx and oral cavity for VMAT (solid line) and IMRT (dashed line). DVHs are shown for pooled data of all institutes (black) and stratified by institute (colors see legend). The p-values shown were obtained for the pooled data using a paired two-sided Wilcoxon signed rank test.

Conclusions: Independently of institution-specific optimization strategies, the quality of the VMAT plans including double arcs was superior to step-and-shoot IMRT plans including 5–9 beam ports, while the effective treatment delivery time was shortened by ~50% with VMAT.

Which Intensity Modulated Technique?

Take Home Message

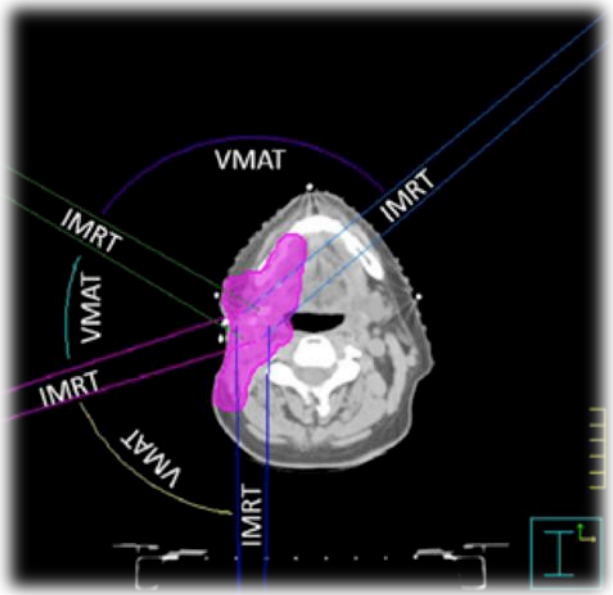
IMRT with its static beam directions might be advantageous in cases where steep dose gradients or highly intensity-modulated beam intensities are required in preferred directions

Rotational Techniques, particularly VMAT, has been rapidly adopted by the radiotherapy community due primarily to its delivery speed and monitor unit efficiency

Which Intensity Modulated Technique?

Take Home Message

Feasibility of a unified approach to intensity-modulated radiation therapy and volume-modulated arc therapy optimization and delivery



Conclusions: In this proof-of-concept work, a novel radiation therapy optimization and delivery technique that interlaces VMAT or IMRT delivery within the same arc has been demonstrated. Initial results show that unified VMAT/IMRT has the potential to be superior to either standard IMRT or VMAT. © *2015 American Association of Physicists in Medicine.*

Hoover et al. Medical Physics, 2015

Topics

- Organ-sparing Radiotherapy in Head and Neck Cancer
- Which IMRT Technique?
- Image-guided Radiotherapy
- Predictive Factors of Toxicity (dosimetrics and clinics)
- Supportive Care
- Future Advances

Image-Guided Radiotherapy

Background

Image-guided radiotherapy: rationale, benefits, and limitations

Laura A Dawson, Michael B Sharpe

Technological advances have greatly enhanced the specialty of radiation oncology by allowing more healthy tissue to be spared for the same or better tumour coverage. Developments in medical imaging are integral to radiation oncology, both for design of treatment plans and to localise the target for precise administration of radiation. At planning, definition of the tumour and healthy tissue is based on CT, augmented frequently with MRI and PET. At treatment, three-dimensional soft-tissue imaging can also be used to localise the target and tumour motion can be tracked with fluoroscopic imaging of radio-opaque markers implanted in or near the tumour. These developments allow changes in tumour position, size, and shape that take place during radiotherapy to be measured and accounted for to boost geometric accuracy and precision of radiation delivery. Image-guided treatment also enhances uniformity in doses administered in a population of patients, thus improving our ability to measure the effect of dosimetric and non-dosimetric factors on tumour and healthy tissue outcomes in clinical trials. Increased precision and accuracy of radiotherapy are expected to augment tumour control, reduce incidence and severity of toxic effects after radiotherapy, and facilitate development of more efficient shorter schedules than currently available.

Dawson et al. Lancet Oncology, 2010

Image-Guided Radiotherapy

Background

Radiotherapy and Oncology 115 (2015) 285–294

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy provide information to help?

Charlotte L. Brouwer, Roel J.H.M. Steenbakkers, Johannes A. Langendijk, Nanna M. Sijtsema *

Adaptive radiotherapy (ART) could be applied to reduce dose to OARs and eventually to improve quality of life.

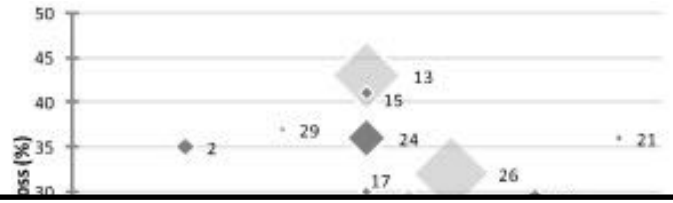
ART is a formal approach to correct for daily tumour and normal tissue variations through streamlined online or offline modification of original target volumes and plans.

Implementation of ART is challenging both from clinical and logistic points of view and generally requires many resources.

Clear guidelines are needed on the timing of rescanning and replanning

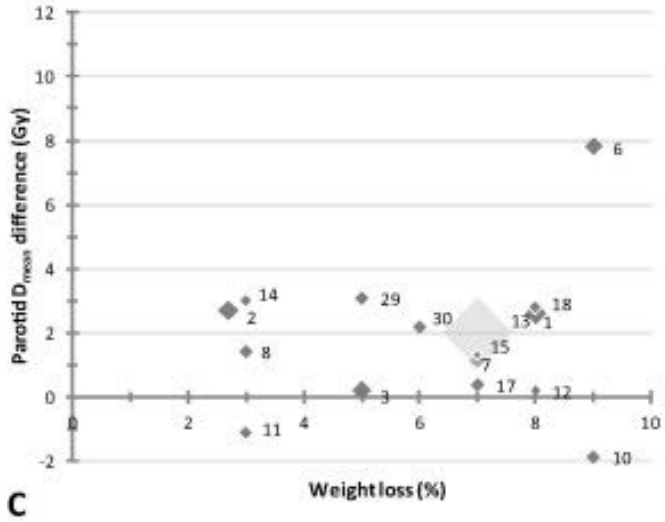
Image-Guided Radiotherapy

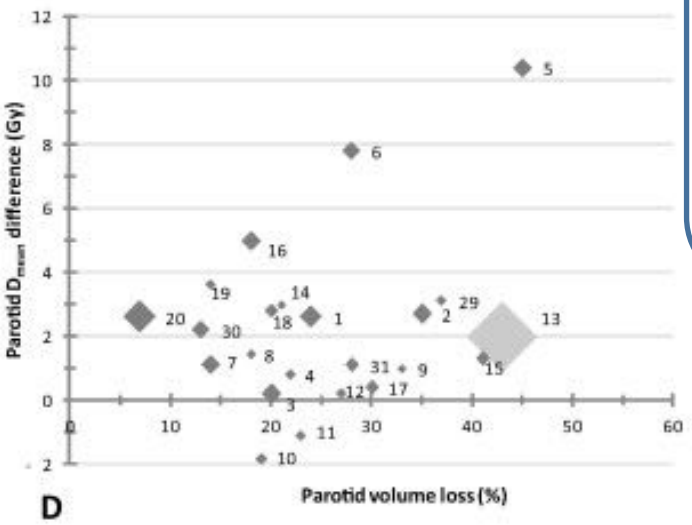
Parotid Glands and Xerostomia



Parotid volume loss vs. patient's weight loss (22 studies)
Parotid volume loss vs. planned parotid mean dose (20 studies)
Parotid mean dose increase (repeat CT – plan CT) vs. weight loss (16 studies)
Parotid mean dose increase (repeat CT – plan CT) vs. parotid volume loss (23 studies) during radiotherapy

Author	Time point
1. Ahn et al. [31]	fx 11 (mean)
2. Bhide et al. [34]	end of tx
3. Capelle et al. [36]	fx 15
4. Castadot et al. [11]	fx 20-25
5. Chen et al. [15]	end of tx
6. Cheng et al. [16]	fx 25
7. Duma et al. [38]	fx 25
8. Duma et al. [13]	fx 16 (median)
9. Fung et al. [41]	fx 30-35
10. Hansen et al. [2]	fx 29 ± 9
11. Height et al. [42]	fx 20-25
12. Ho et al. [43]	fx 25-30
13. Jensen et al. [44]	fx 5-35
14. Lee et al. [46]	end of tx
15. Marzi et al. [48]	end of tx
16. Nishi et al. [4]	fx 10-20
17. Robar et al. [17]	end of tx
18. Wang et al. [59]	fx 18
19. Wu et al. [12]	fx 25-30
20. Zhao et al. [6]	fx <20
21. Ajani et al. [32]	fx 25-30
22. Barker et al. [33]	end of tx
23. Broggi et al. [35]	end of tx
24. Lu et al. [47]	fx 20
25. Richetti et al. [53]	fx 30-35
26. Sanguineti et al. [62]	fx 16(median)
27. Vasquez et al. [57]	fx 23
28. Wang et al. [60]	end of tx
29. Cozzolino et al. [66]	fx 25
30. Hunter et al. [65]	end of tx
31. Castelli et al. [63]	fx 25-30





Ospedale Sacro Cuore - Don Calabria Negrar (Verona)

Brouwer et al. Radiother Oncol, 2015

Image-Guided Radiotherapy

Take Home Message

There is a need for larger prospective studies including assessment of anatomic and dosimetric changes and to identify possible relationships between these changes and outcome

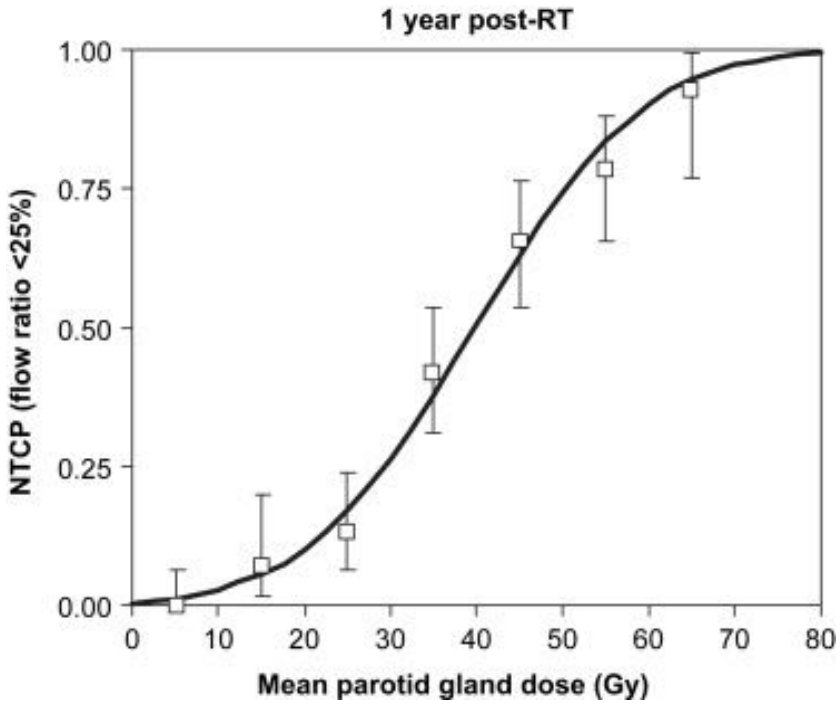
A number of potential selection criteria for anatomic and dosimetric changes were identified that could be included in well-designed and well-powered studies on anatomic and dosimetric changes during radiotherapy

Topics

- Organ-sparing Radiotherapy in Head and Neck Cancer
- Which IMRT Technique?
- Image-guided Radiotherapy
- **Predictive Factors of Toxicity (dosimetrics and clinics)**
- Supportive Care
- Future Advances

Predictive Factors of Toxicity:

Xerostomia



Mean parotid gland doses of 25–30 Gy correspond to 17–26% complication probability 1 year after RT

At a mean dose of 39.9 Gy, there is a 50% probability of parotid gland flow reduction to < 25% of the pre-RT flow rate

Ospedale Sacro Cuore - Don Calabria Negrar (Verona)

Dijkema et al. IJROBP, 2010

Predictive Factors of Toxicity:

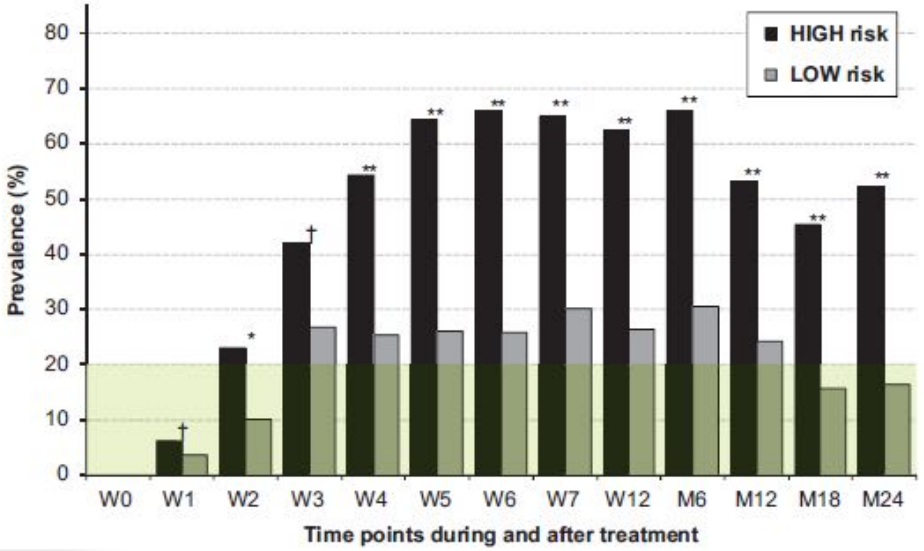
Xerostomia

Table II. Differences in baseline characteristics of the IMRT treated patients classified as low risk versus IMRT treated patients classified as high risk.

		LOW RISK		HIGH RISK			
Characteristics		n	%	n	%	P-value	DF
T-classification	T0-T2	25	44%	32	56%	p = 0.029	1
	T3-T4	19	24%	60	76%		
N-classification	N0	27	57%	20	43%	p < 0.001	1
	N-plus	17	19%	72	81%		
Tumour location	Oropharynx/oral cavity	11	18%	49	82%	p = 0.002	4
	Larynx	24	50%	24	50%		
	Hypopharynx	6	35%	11	65%		
	Nasopharynx/paranasal sinus	0	0%	8	100%		
	Miscelaneous	3	100%	0	0%		
Bilateral neck iradiation	No	6	100%	0	0%	p < 0.001	1
	Yes	38	29%	92	70%		

High risk group:
Positive lymph nodes
Oropharynx and Nasopharynx cancers
Bilateral Irradiation

- **High risk group more xerostomia**
- **Between 6 and 24 months after treatment, significant recovery was observed in both groups**
- **In low risk group, moderate-to-severe xerostomia after 12 months was less than 20%**

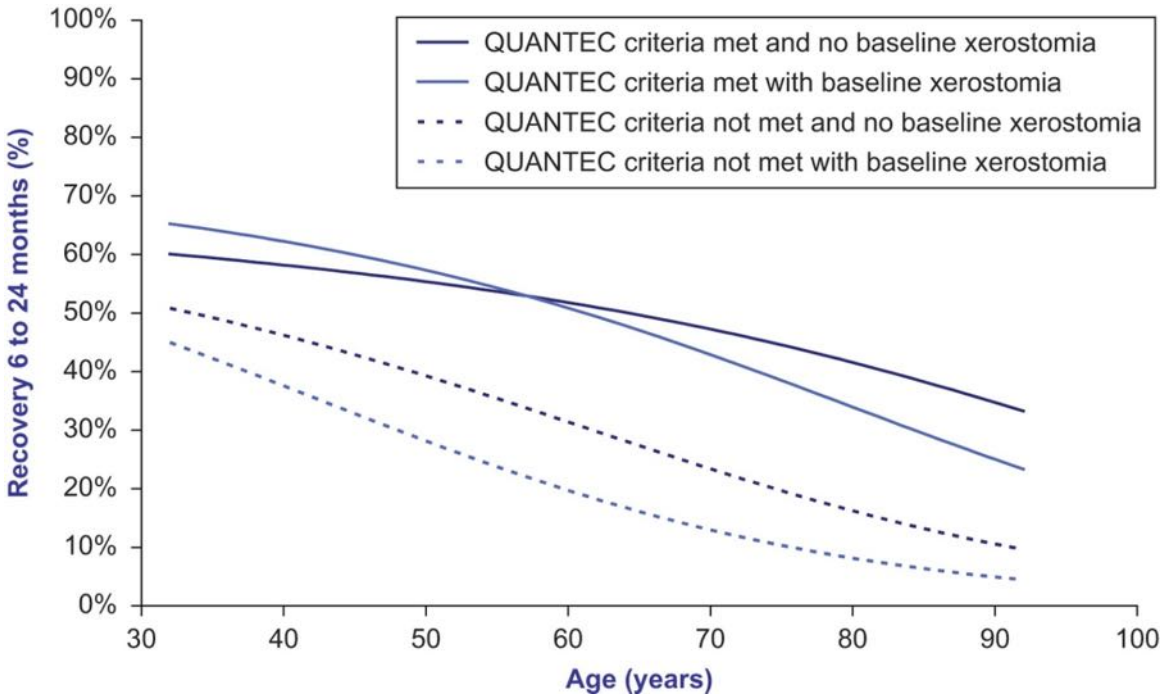


I. Beetz et al. Acta Oncologica, 2014

Predictive Factors of Toxicity:

Xerostomia

Influence of age on recovery of xerostomia



Elderly patients are more vulnerable to xerostomia due to their reduced secretory reserve

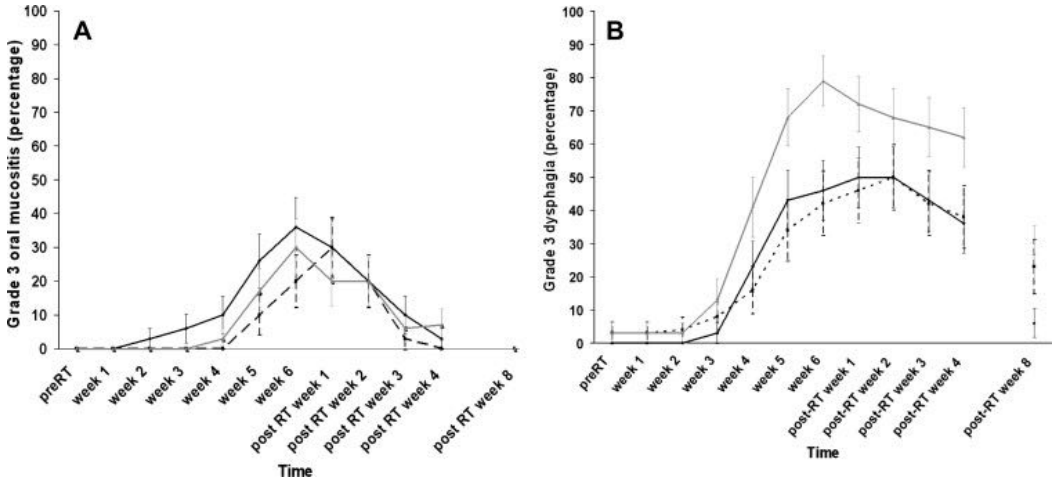
The probable cause is that radiation-induced salivary dysfunction results from the loss of parotid gland stem cells and that the number of stem cells decreases with age

I. Beetz et al. Acta Oncologica, 2014

Predictive Factors of Toxicity:

Mucositis

Prevalence of grade 3 oral mucositis (A) and grade 3 dysphagia (B) during and up to 8 weeks after Chemo-RT



Observer-assessed acute swallowing symptoms (such as burning, dysphagia, and pain) are surrogate of pharyngeal mucositis extension

Factors related to RT:

- Site of disease (especially Oral Cavity and Oropharynx)
- Treated volume
- Total dose and Fractionation
- Overall treatment time
- Chemotherapy

Bhide et al. Radiother Oncol, 2010

Predictive Factors of Toxicity:

Mucositis

MUCOSITIS VERSUS TUMOR CONTROL: THE THERAPEUTIC INDEX OF ADDING CHEMOTHERAPY TO IRRADIATION OF HEAD AND NECK CANCER

IRWIN H. LEE, M.D., PH.D., AND AVRAHAM EISBRUCH, M.D.

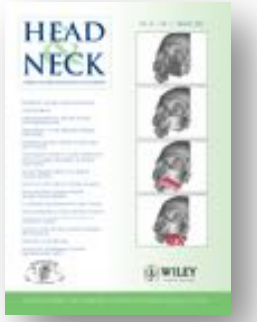
Department of Radiation Oncology, University of Michigan, Ann Arbor, MI

CONCLUSIONS

We estimate that the addition of concurrent chemotherapy to radiation for HNSCC increases the BED for mucositis by 8 Gy_{10}, corresponding to three or four additional 2-Gy fractions. This estimate is strongly dependent on the assumed relationship between BED and mucositis, but within the range

Predictive Factors of Toxicity:

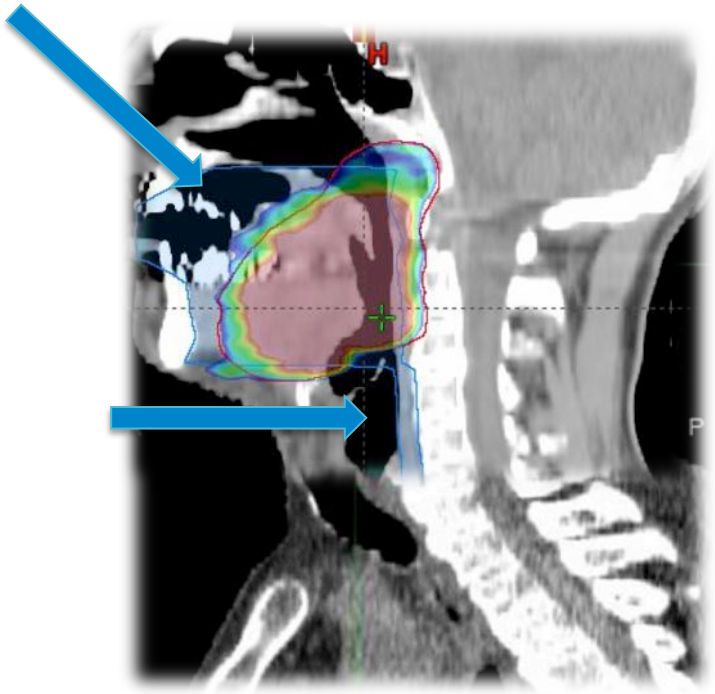
Mucositis



Predictors of mucositis in oropharyngeal and oral cavity cancer in patients treated with volumetric modulated radiation treatment: A dose–volume analysis

Rosario Mazzola, MD[1,2] Francesco Ricchetti, MD[1] Sergio Fersino, MD[1] Alba Fiorentino, MD[1] Niccolò Giaj Levra, MD[1] Gioacchino Di Paola, MS[3] Ruggero Ruggieri, PhD[1] Filippo Alongi, MD[1]*

[1]Department of Radiation Oncology, Sacro Cuore Don Calabria Hospital, Negrar-Verona, Italy, [2]Department of Radiation Oncology School, University of Palermo, Palermo, Italy, [3]Statistic Sciences Faculty, University of Palermo, Palermo, Italy.



Mucosa-sparing dose constraints Predictors of Mucositis ≥ G2 (RTOG/EORTC)

	Dose constraints
Total oral mucosa	Mean dose ≥50 D_{max}* >65
Oral mucosa minus target PTVs	V45 Gy >40% V50 Gy >30% V55 Gy >20%

Abbreviations: PTVs, planning target volumes; Vx, structure volume receiving at least the dose x.
* Maximum dose received in 1 cm^3;

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Mazzola R et al. Head Neck, 2015

Predictive Factors of Toxicity:

Mucositis

Risk of grade ≥ 2 Mucositis according to EORTC/RTOG scale

Variable	P-value	(95% CI)	Odds Ratio	% Risk
Concomitant Chemotherapy	0.006	0.1 - 1.2	5	**50 %**
Total OM: *Dmean ≥ 50 and Dmax ≥ 65*	0.02 - 0.04	0.1 - 1.3	3.75	38 - 40%
Ratio total OM/ OM out of PTVs: ≥ 2.5	0.03	0.8 - 1.8	2.6	**35%**
OM out of PTVs: *V45 > 40, V50 > 30, V55>20*	0.04 - 0.009 - 0.003	0.5 - 2.3	4.85	8 -22%

Abbreviations: OM=Oral Mucosa; CI=confidence interval; PTVs=planning target volumes; Dmean=mean dose; Dmax=maximum dose;V45=volume % of oral mucosa exposed to at least 45 Gy; V50=volume % of oral mucosa exposed to at least 50 Gy; V55=volume % of oral mucosa exposed to at least 55 Gy

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Mazzola R et al. Head Neck, 2015

Predictive Factors of Toxicity:

Late swallowing disorders

Contents lists available at ScienceDirect

Radiotherapy and Oncology

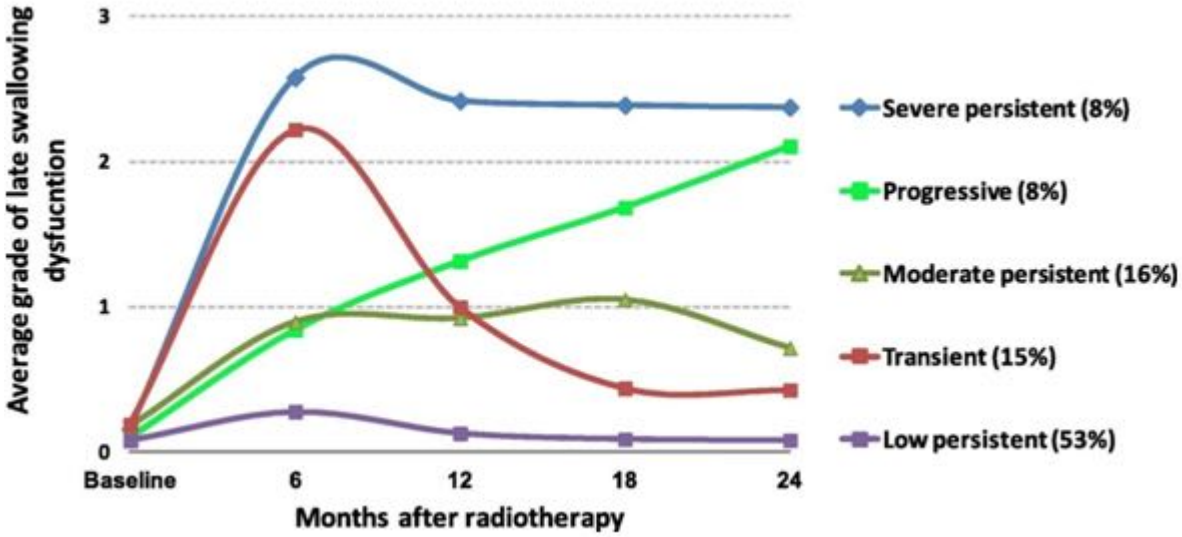
journal homepage: www.thegreenjournal.com

Swallowing dysfunction

Patterns of long-term swallowing dysfunction after definitive radiotherapy or chemoradiation

Miranda E.M.C. Christianen [a], Irma M. Verdonck-de Leeuw [b], Patricia Doornaert [c], Olga Chouvalova [a], Roel J.H.M. Steenbakkers [a], Phil W. Koken [c], C. René Leemans [b], Sjoukje F. Oosting [d], Jan L.N. Roodenburg [e], Bernard F.A.M. van der Laan [f], Ben J. Slotman [c], Hendrik P. Bijl [a], Johannes A. Langendijk [a,*]

[a] *Department of Radiation Oncology, University of Groningen, University Medical Center Groningen;* [b] *Department of Otolaryngology-Head and Neck Surgery;* [c] *Department of Radiation Oncology, VU University Medical Center Amsterdam;* [d] *Department of Medical Oncology;* [e] *Department of Oral and Maxillofacial Surgery; and* [f] *Department of Otolaryngology-Head and Neck Surgery, University of Groningen, University Medical Center Groningen, The Netherlands*



Cristianen et al. Radiother Oncol, 2015

Predictive Factors of Toxicity:

Late swallowing disorders

Pattern	Superior PCM	Base of tongue	Middle PCM	Inferior PCM	Cricopharyngeal muscle	Esophagus inlet muscle	Cervical esophagus	Supraglottic larynx	Glottic larynx	Parotid glands	Submandibular glands
Low persistent	32,0	34,5	46,7	59,8	52,0	32,1	22,3	57,7	60,8	19,9	40,1
Intermediate persistent	46,8	49,2	57,4	58,9	50,0	36,5	29,3	61,2	57,8	32,7	52,7
Severe persistent	66,1	66,9	68,1	59,9	47,7	39,3	32,6	66,6	56,3	47,6	67,6
Transient	51,2	53,5	62,1	60,8	51,6	43,0	32,5	64,6	58,6	34,8	57,2
Progressive	53,2	56,0	55,1	51,2	42,2	28,3	23,2	56,4	48,2	36,3	55,9
	Upper pharyngeal region			Lower pharyngeal region				Laryngeal region		Salivary glands	

✓ **Severe persistent swallowing dysfunction (Grade ≥ 2; 6-24 months): high dose to the upper pharyngeal, laryngeal and lower pharyngeal region**

✓ **Transient (Grade ≥ 2; recovering during follow up): high dose to the laryngeal and lower pharyngeal regions**

✓ **Progressive pattern (Grade < 2; progressing during follow up): after moderate dose to the upper pharyngeal region**

Cristianen et al. Radiother Oncol, 2015

Predictive Factors of Toxicity:

Take Home Message

It is crucial to identify patients at risk of toxicity that could benefit promptly of appropriate Supportive Care

Topics

- Organ-sparing Radiotherapy in Head and Neck Cancer
- Which IMRT Technique?
- Image-guided Radiotherapy
- Predictive Factors of Toxicity (dosimetrics and clinics)
- **Supportive Care**
- Future Advances

Supportive Care:

Multidisciplinary Management

CRITICAL REVIEWS IN
Oncology Hematology
Incorporating Geriatric Oncology
www.elsevier.com/locate/critrevonc

Dysphagia in head and neck cancer patients treated with radiotherapy and systemic therapies: Literature review and consensus

Antonio Schindler[a], Nerina Denaro[b], Elvio G. Russi[c,*], Nicole Pizzorni[a], Paolo Bossi[d], Anna Merlotti[e], Massimo Spadola Bissetti[f], Gianmauro Numico[g], Alessandro Gava[h], Ester Orlandi[i], Orietta Caspiani[j], Michela Buglione[k], Daniela Alterio[l], Almalina Bacigalupo[m], Vitaliana De Sanctis[n], Giovanni Pavanato[o], Carla Ripamonti[p], Marco C. Merlano[b], Lisa Licitra[e], Giuseppe Sanguineti[q], Johannes A. Langendijk[r], Barbara Murphy[s]

	Before RT	During RT				Follow up period
Timeline	Baseline	1st w	2nd w	Other w	Last week	
PRO-SCALE	Yes	Yes	Yes	Yes	Yes	Yes at each visit
ORO-SCALE	Yes	Yes	Yes	Yes	Yes	Yes at each visit
Searching for Sign and Symptoms	Yes	Yes	Yes	Yes	Yes	Yes at each visit
Nutritionist evaluation	Yes	On demand	On demand	On demand	On demand	Yes at 1st visit, then on demand
Deglutologist evaluation	Yes	On demand	On demand	On demand	On demand	Yes at 1st visit, then on demand
Instrumental evaluation	On demand	No	No	No	No	On demand
Radiotherapeutic precautions	Yes	--	--	--	--	--
Swallowing exercises	Yes	Yes	Yes	Yes		Yes
Pain assessment and control	Yes	Yes	Yes	Yes	Yes	Yes

Supportive Care:

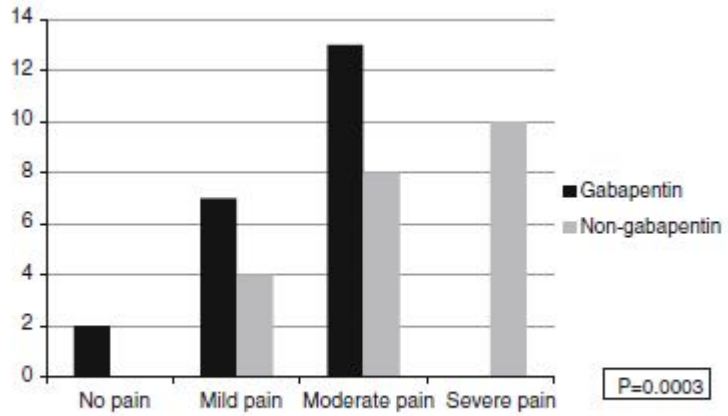
Painful Mucositis

Dysphagia (2014) 29:396–402
DOI 10.1007/s00455-014-9521-1

ORIGINAL ARTICLE

Effect of Gabapentin on Swallowing During and After Chemoradiation for Oropharyngeal Squamous Cell Cancer

Heather M. Starmer · WuYang Yang · Raju Raval · Christine G. Gourin · Marian Richardson · Rachit Kumar · Bronwyn Jones · Todd McNutt · Sierra Cheng · Harry Quon



Pain scores by gabapentin

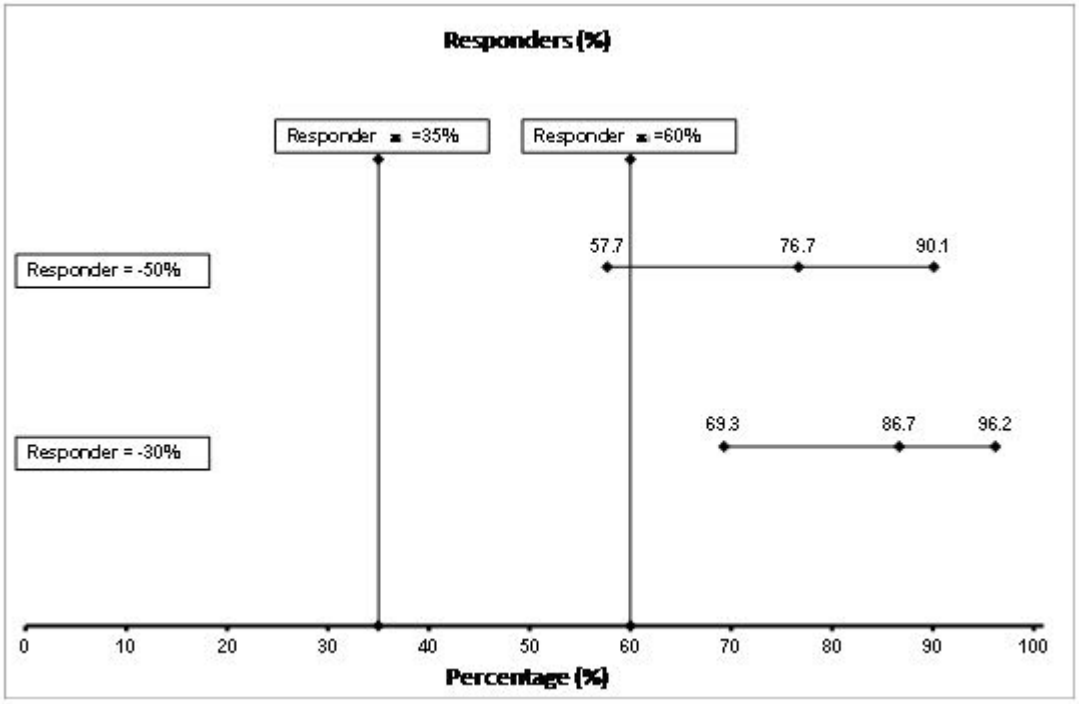
Supportive Care:
Painful Mucositis

Tapentadol Prolonged Release

Responders 30%: 86.7%
Responders 50%: 76.7%

NRS Scale:
Basal: 4.8 ± 1.21
Final: 1.33 ± 2.07 (P<0.01)

Average daily pain intensity (NRS scale)



Mazzola R. et al. Under Review

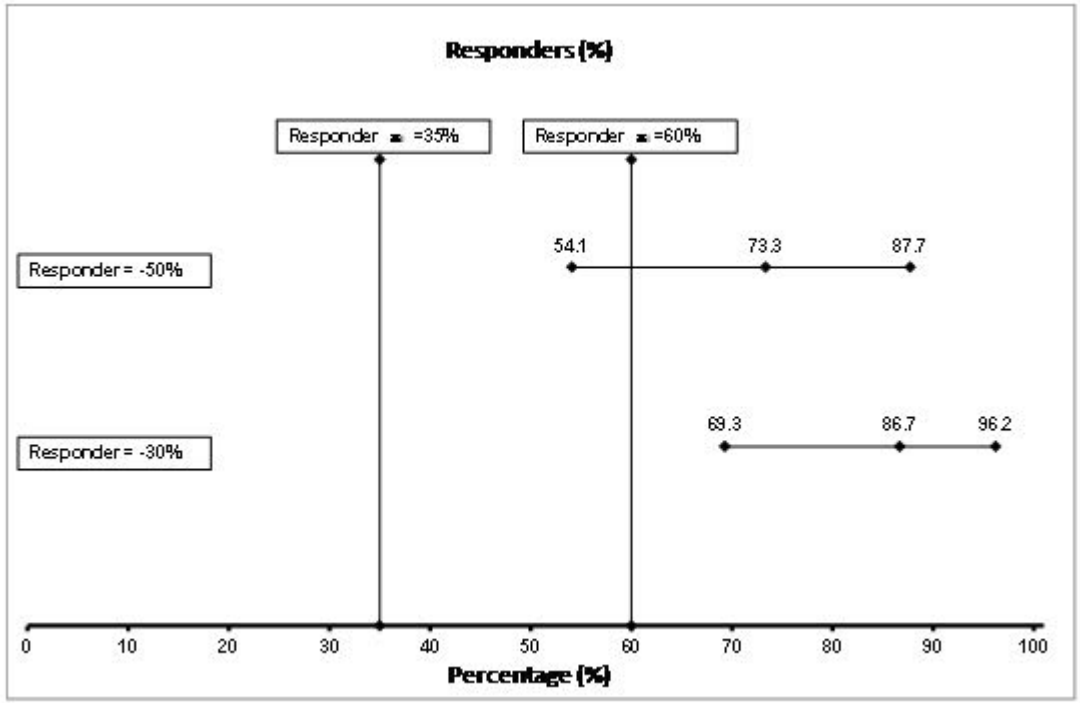
Supportive Care:
Painful Mucositis

Tapentadol Prolonged Release

Responders 30%: 86.7%
Responders 50%: 73.3%

NRS Scale:
Basal: 4.77 ± 1.36
Final: 1.33 ± 2.02 (P<0.01)

Pain during swallowing (NRS scale)



Mazzola R. et al. Under Review

Topics

- Organ-sparing Radiotherapy in Head and Neck Cancer
- Which IMRT Technique?
- Image-guided Radiotherapy
- Predictive Factors of Toxicity (dosimetrics and clinics)
- Supportive Care
- Future Advances

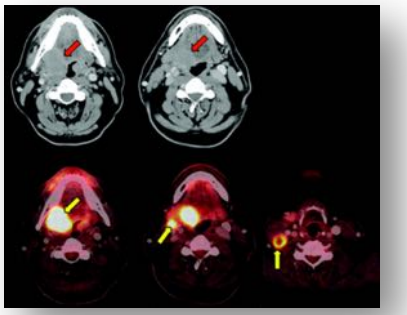
Future Advances:

A New Era?

JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Advances in Radiotherapy for Head and Neck Cancer

Vincent Grégoire, Jan A. Langendijk, and Sandra Nuyts



Gregoire et al. J Clin Oncol. 2015

Future Advances:

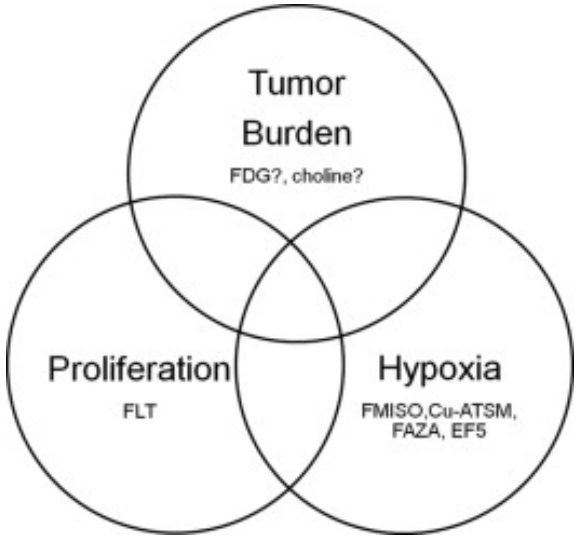
New Tracers?

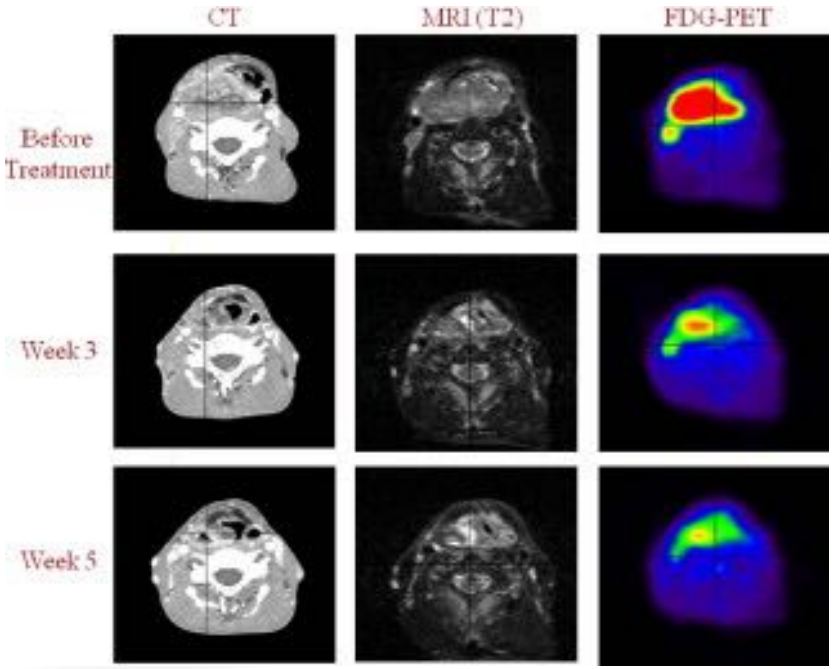
ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Molecular Imaging–Based Dose Painting: A Novel Paradigm for Radiation Therapy Prescription

Søren M. Bentzen, PhD, DSc,*,† and Vincent Gregoire, MD, PhD, FRCR*,†

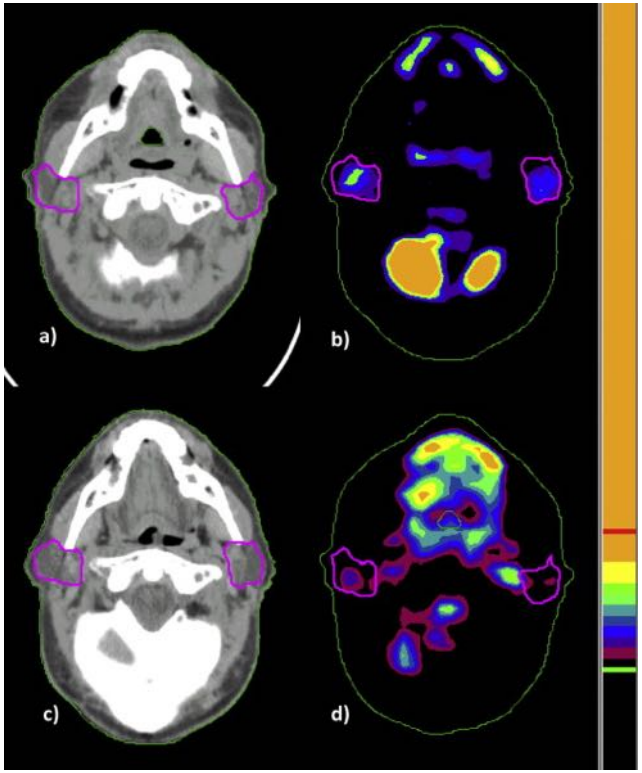




Bentzen et al, 2011

Future Advances:

Imaging?



Deformably aligned parotid contours overlaid onto baseline (a) CT, (b) PET images and post-treatment (c) CT, (d) PET images.

Baseline CT and PET images

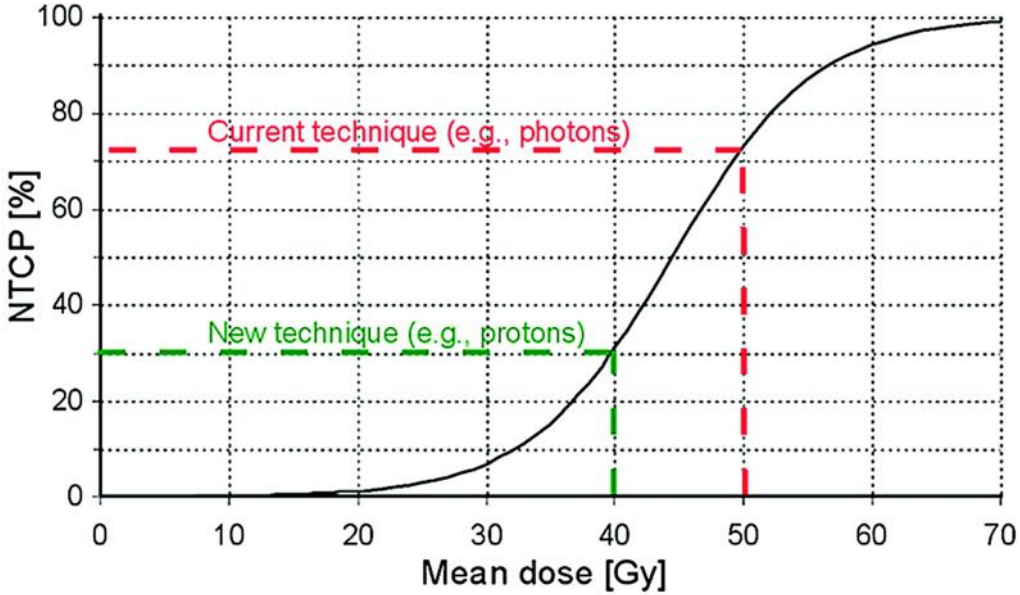
Post-RT CT and PET images

Cannon et al. IJROBP, 2012

Future Advances:

Protons?

Example of a possible normal tissue complication probability (NTCP) model with the risk of a given complication (NTCP in %) as a function of radiation dose (in this case the mean dose)



The Oncologist

Example of a possible normal tissue complication probability (NTCP) model with the risk of a given complication (NTCP in %) as a function of radiation dose (in this case the mean dose). NTCP models can be used to estimate the risk for a certain complication as a function of dose and thus also to translate differences in dose into differences in the risk for side effects. In this example, the lower dose that can be obtained with the new technique (−10 Gy) translates into a −42% lower risk. Note that in the case of a dose reduction from 30 to 20 Gy, the benefit in terms of the risk reduction will be much less

Van de Water et al. The Oncologist, 2011

Future Advances:

Gene Profile?

RESEARCH ARTICLE

Estimate of the accelerated proliferation by protein tyrosine phosphatase (PTEN) over expression in postoperative radiotherapy of head and neck squamous cell carcinoma

P. Pedicini · A. Fiorentino · G. Improta · A. Nappi · M. Salvatore · G. Storto

Conclusion

Radiation therapy has a central role in the local control of H&N tumors despite being the new technology it has risk of side effects also. These effects could be reduced by stratifying patients into groups according to their specific cellular characteristics. This has been already demonstrated for the EGFr which is a predictive factor when the H&N radiotherapy is accelerated because of its influence on the cellular proliferation rate and on the activation of specifically tumorigenic subpopulations of stem cells during the continuing radiotherapy.

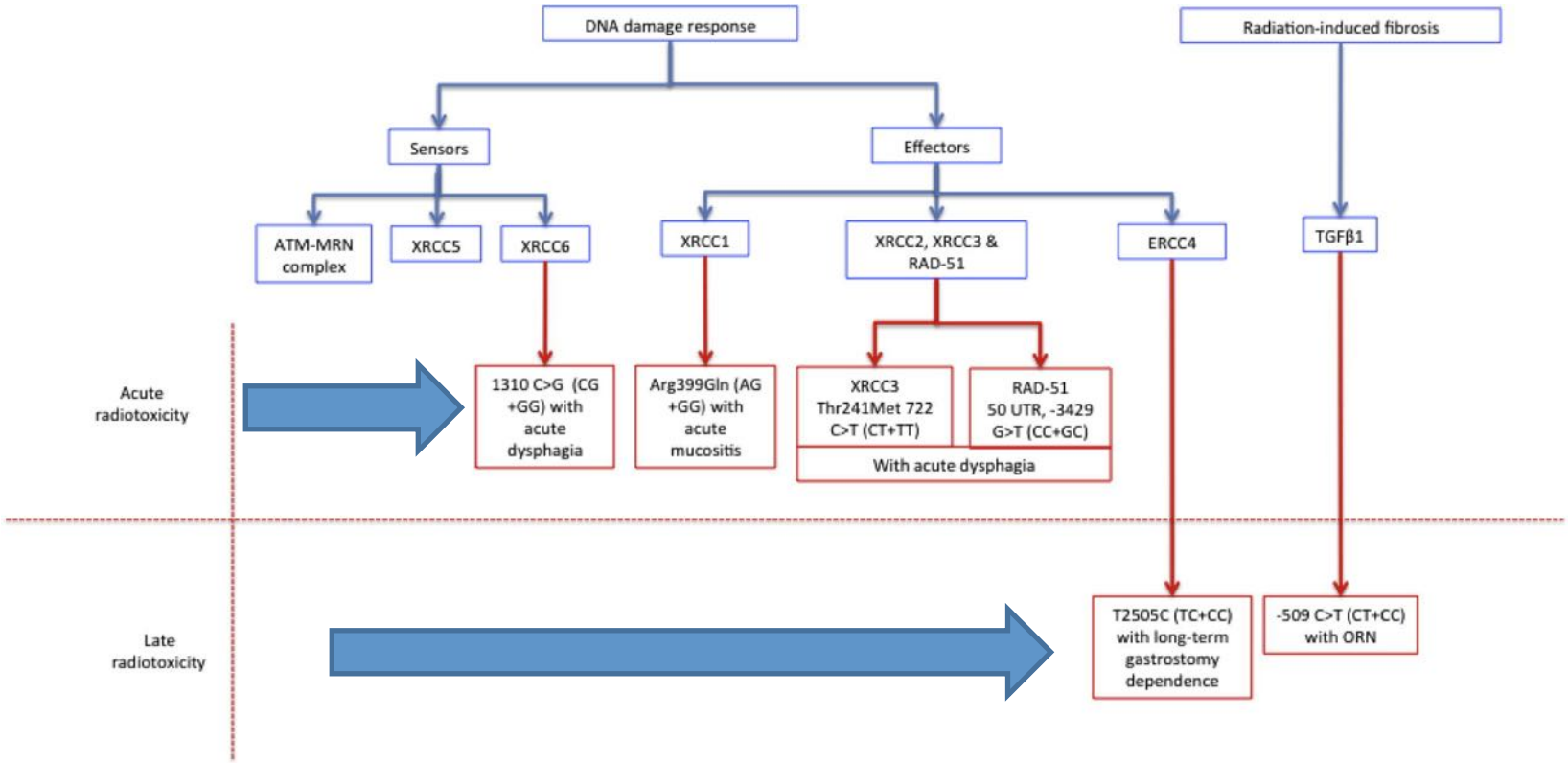
However, to our knowledge, there are no similar data in the literature about the role of PTEN expression on the local control for H&N patients treated with standard or accelerated radiotherapy. Therefore, our results could have clinical implication in the treatment choice for H&N cancer patients, much more tailored based on molecular knowledge: high-PTEN expression patients would benefit from the accelerated radiotherapy achievable with a hypo-fractionation, while the low-PTEN group would benefit from the less toxic no accelerated hyper-fractionation schedule. This conclusion is far to be clinically demonstrated and more data and trials are need.

Ospedale Sacro Cuore - Don Calabria Negrar (Verona)

Pedicini et al, Clin Transl Oncol 2013

Future Advances:

Gene Profile?



Ghazali et al. Oral Oncology, 2012

Conclusion

Waiting for new horizons to follow…

THANKS FOR ATTENTION!