XXV Congresso Nazionale AIRO
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La gestione degli effetti tardivi da radioterapia

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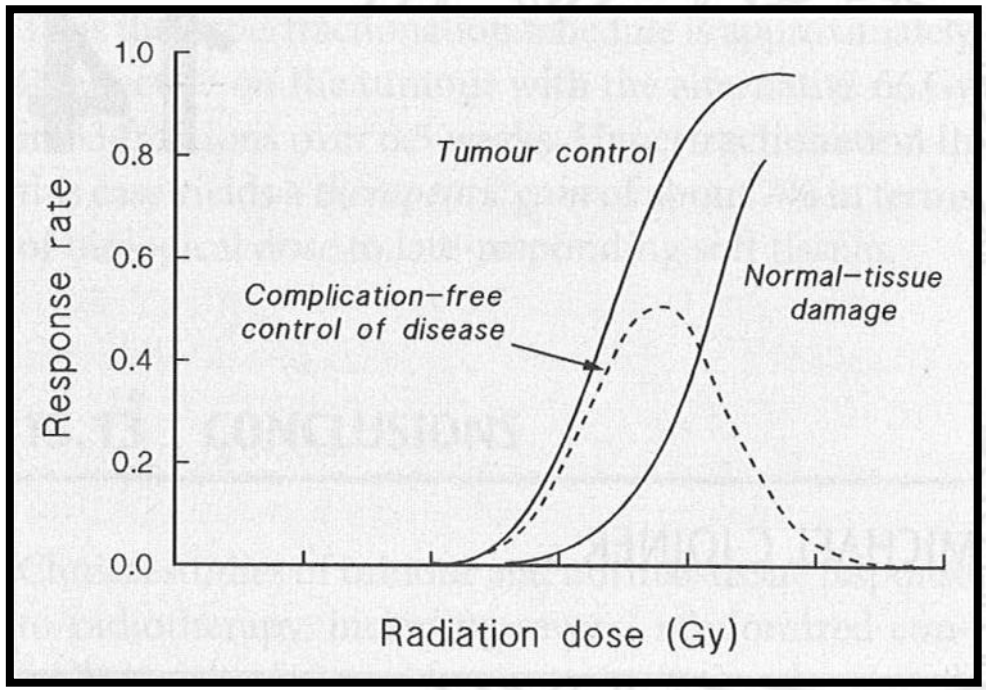
Oral cavity tumors

- ✓ Most of pts with oral cavity tumor have stage III-IVa disease
- ✓ Surgery ± radiotherapy ± chemotherapy for resectable disease
- ✓ Post-op RT-CT increases LRC, DFS for high-risk features pts (R1 and N+ with ECE +)
- ✓ RT-CT is a selected alternative for locally advanced disease

Uncomplicated local tumour control rate

as a bell-shaped curve



- ✓ **Increasing total dose: not only tumour control rates but also incidence/severity of normal-tissue damage rises**
- ✓ **ULTC probability initially increases with total dose but then falls because of normal-tissue toxicity**
- ✓ **Once the optimum, further improvements in ULTC rate needs shifts TCP to lower doses or NTCP to higher doses**

Cogent in head and neck cancer

Holthusen H, Strahlentherapie 1936

Acute toxicity

- ✓Occurring during or within few weeks after completion of RT
- ✓Involves tissues with high cell turnover rate (mucosal membranes, skin)
- ✓Usually transient
- ✓Has a high α/β ratio
- ✓Depends mainly on total nominal dose rather than dose per fraction

Late toxicity

- ✓Occurring after few months or year after RT
- ✓Involves tissues with slow cell turnover rate
- ✓Microenvironment, stroma and vessels
- ✓Has a low α/β ratio
- ✓Depends on fraction size
- ✓Usually persistent and progressive

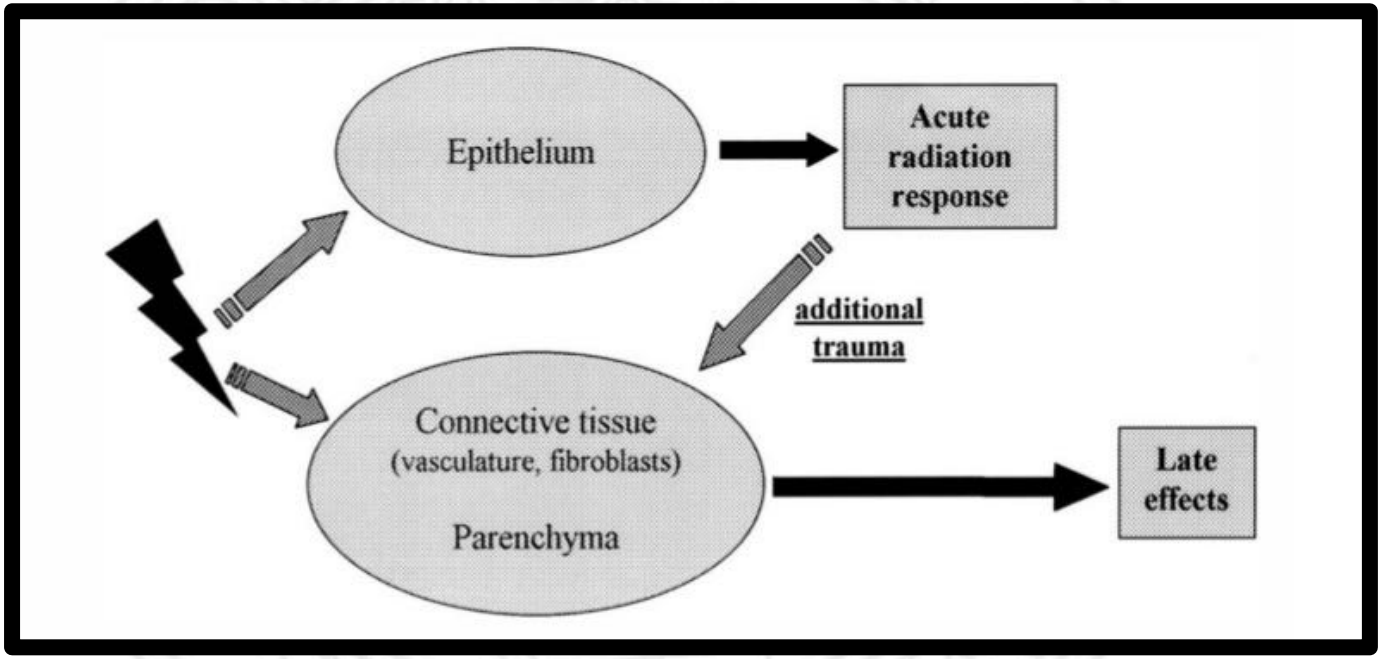
Challeges in defining late toxicity

- ✓Late effects are underscored and underreported
- ✓Selection of clinically relevant outcomes
- ✓Non uniform grading/scoring of late effects
- ✓Multi-modality treatment
- ✓Tumor and host factors may interact with therapy

Consequential late effects

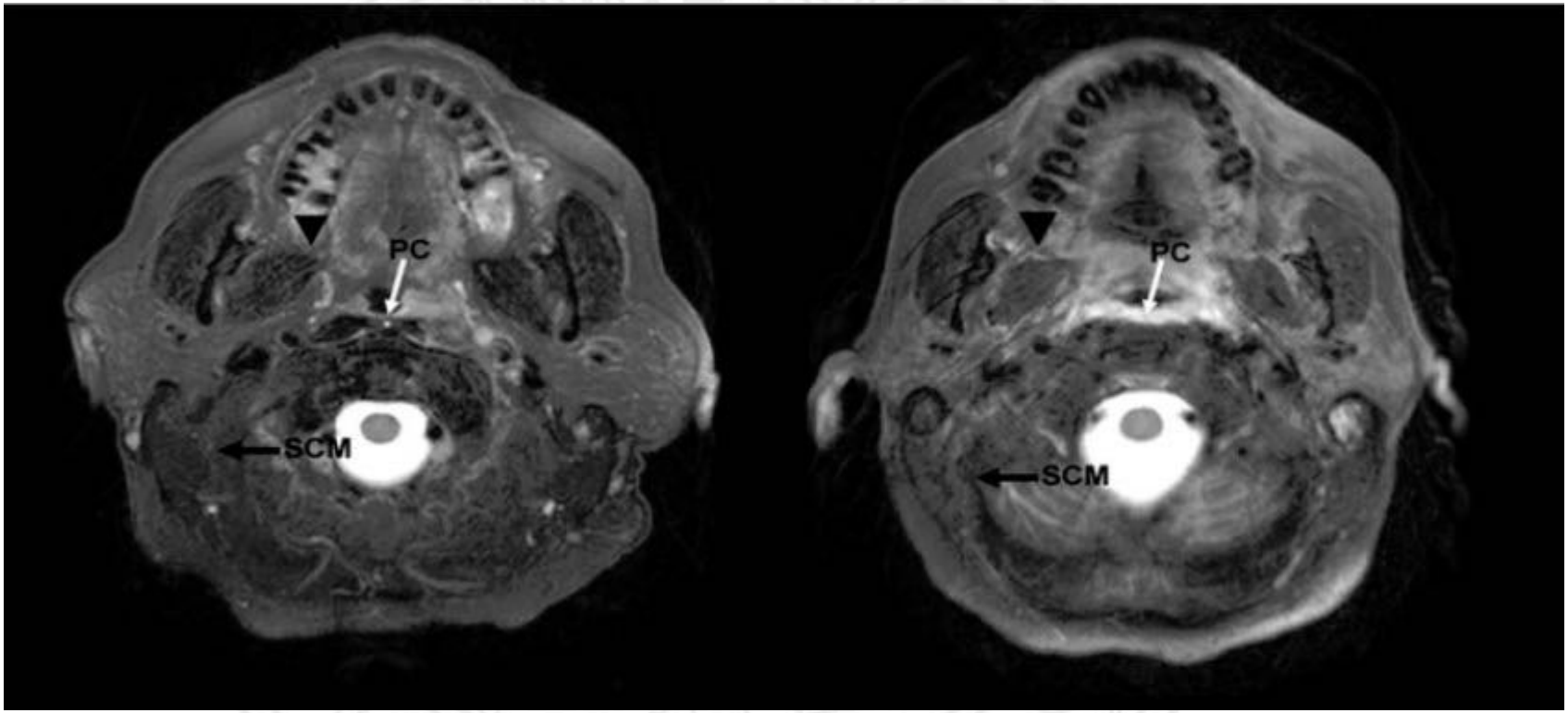
- ✓Severe early toxicity may be causally related to subsequent late effects
- ✓Both phases are manifestations of an ongoing sequence of events initiated immediately after injury
- ✓Autocrine, paracrine, endocrine messages resulting in dysregulation of tissue microenvironment

Consequential late effects



Dorr et al; R&O 2001

Consequential late effects



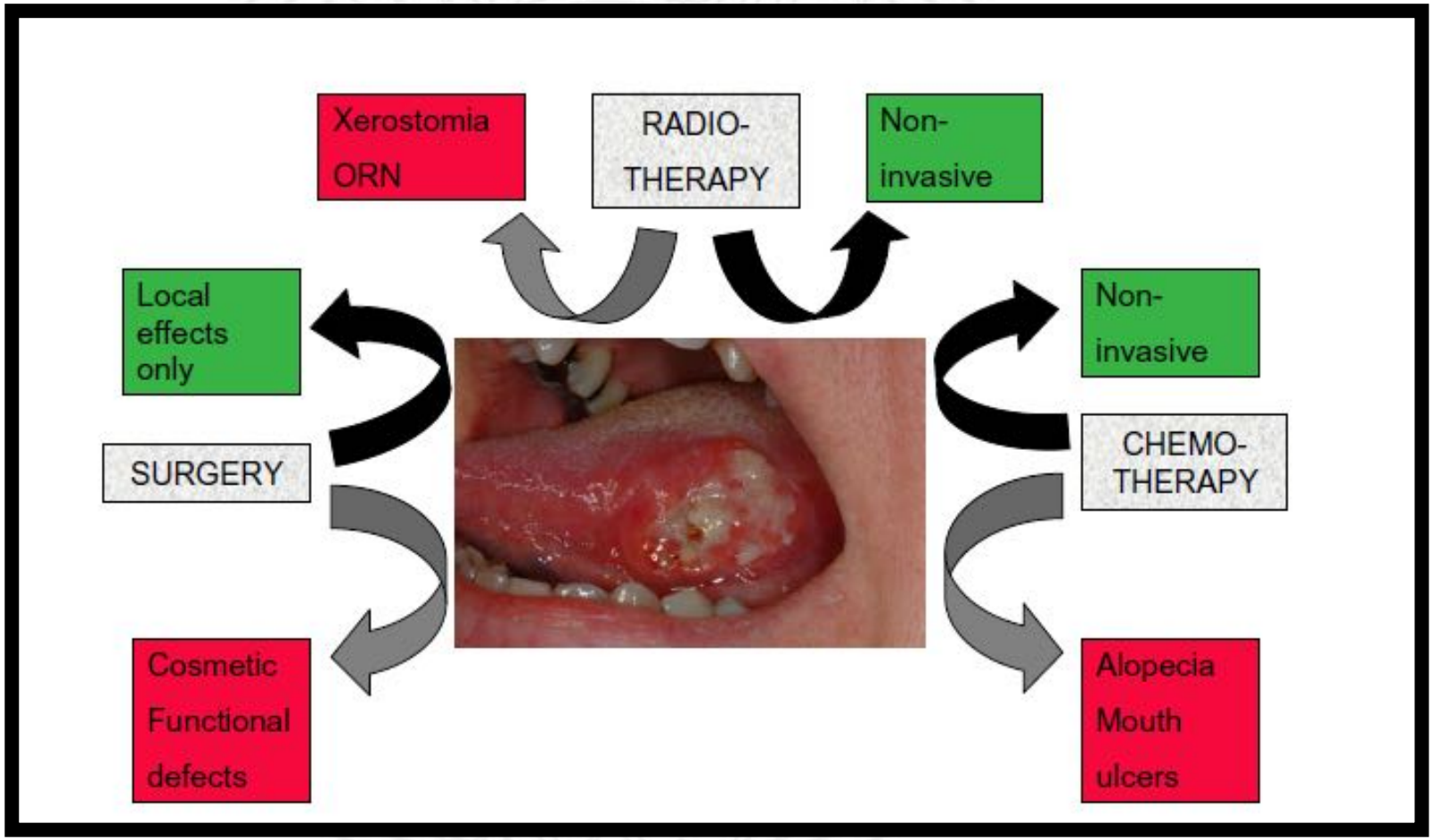
Severe acute mucositis is a surrogate risk-index for long-term dysphagia

Toxicity in oral cavity and oropharyngeal cancer

- ✓ Mucositis
- ✓ Xerostomia
- ✓ Dysphagia
- ✓ Osteradionecrosis
- ✓ Rampant caries/ dental disease
- ✓ Skin toxicity
- ✓ Burining and pain

Bernier J; Head and Neck Cacer: multimodality management

Combined modality treatment for oral cavity tumors



SURGERY

Oral and oropharyngeal surgery

- **Floor of the mouth resection** has impact on swallowing if:
  - ✓ **Geniohyoid or mylohyoid** muscles are resected (elevation and antero-pulsion of the larynx)
  - ✓ Type of reconstruction
    - ❖ **Primary closure** (less pharyngeal residue)
    - ❖ **Distal myocutaneous flap** (pectoralis major, latissimus dorsi, trapezius)
    - ❖ **Free microvascular flap** (fasciocutaneous forearm, lateral thigh, lateral arm, scapular

- ➢ Oropharyngeal swallowing is a pump: tongue is a piston and pharynx is a dinamic chamber
- ➢ Flaps are adynamic segments which reduce swallowing efficacy

Oral and oropharyngeal surgery

- **Oral tongue resection has impact on swallowing:**
  - ✓ Slows oral transit (worse with viscous bolus)
  - ✓ Aspiration rate increases with incresed % of resected tongue
  - ✓ In small resection (< 30%) of oral tongue or tongue base: primary closure
  - ✓ Wider resections: flaps

TORS

Oral and oropharyngeal surgery

❑ **Mandibular resection:**

- **Marginal resection: small impact on swallowing**
- **Mandibulotomy can damage:**
  - **Genioglossus muscles (sagittal mandibulotomy)**
  - **Inferior alveolar nerve (lateral mandibulotomy)**
  - **Occlusion (dysphagia due to loss of stability during swallowing and larynx elvation)**

Reconstruction of the mandible recommended if:

- ➢ **Large mandibular defects (> 5 cm)**
- ➢ **Large soft tissue deficit associated**
- ➢ **RT is planned**

Teeth and dentures

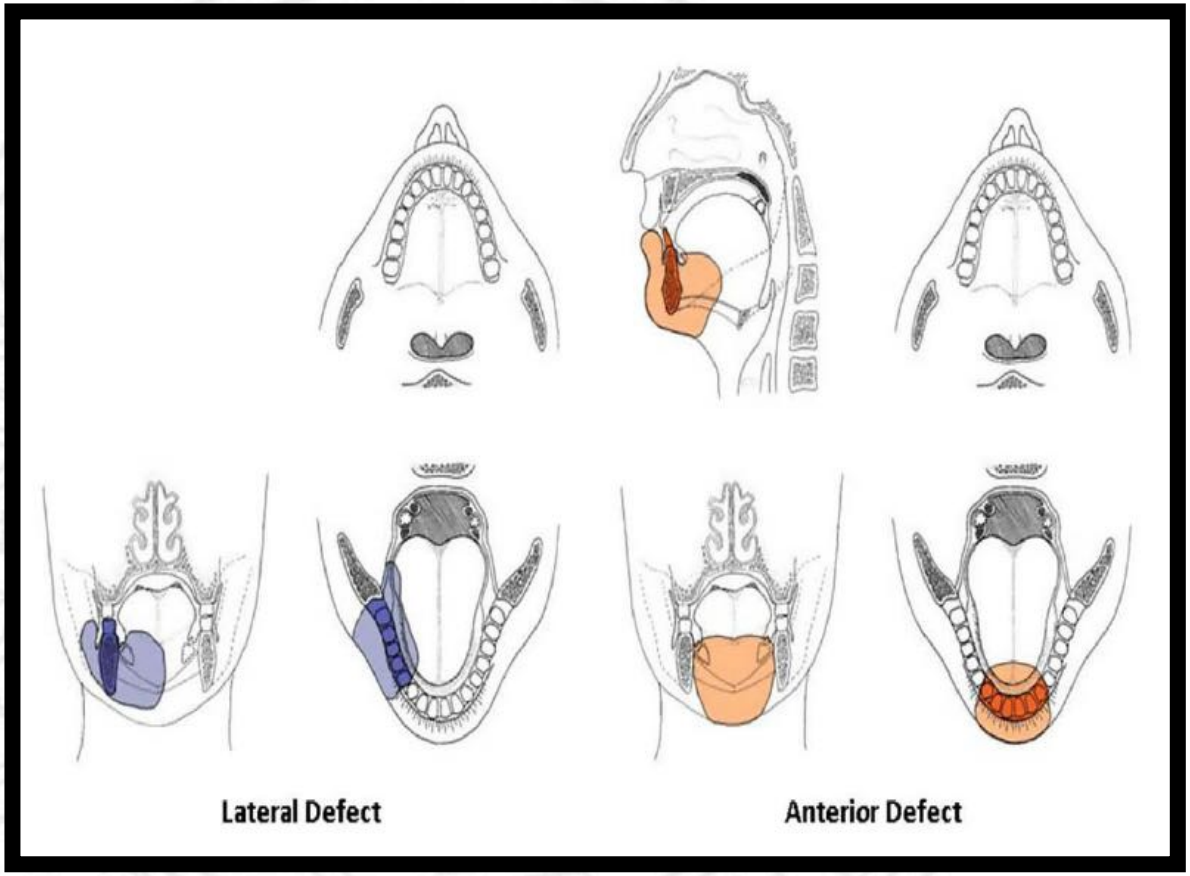
Important for

- **Jaw stabilization (posterior teeth occlusion)**
- **Suprahyoid muscles can pull forward and anterior the larynx**

Edentulus pts

- **Higher risk of laryngeal penetration (no apiration)**
- **Penetration 4 x risk of pneumonia**
- **Prostheses useful (after mucositis)**

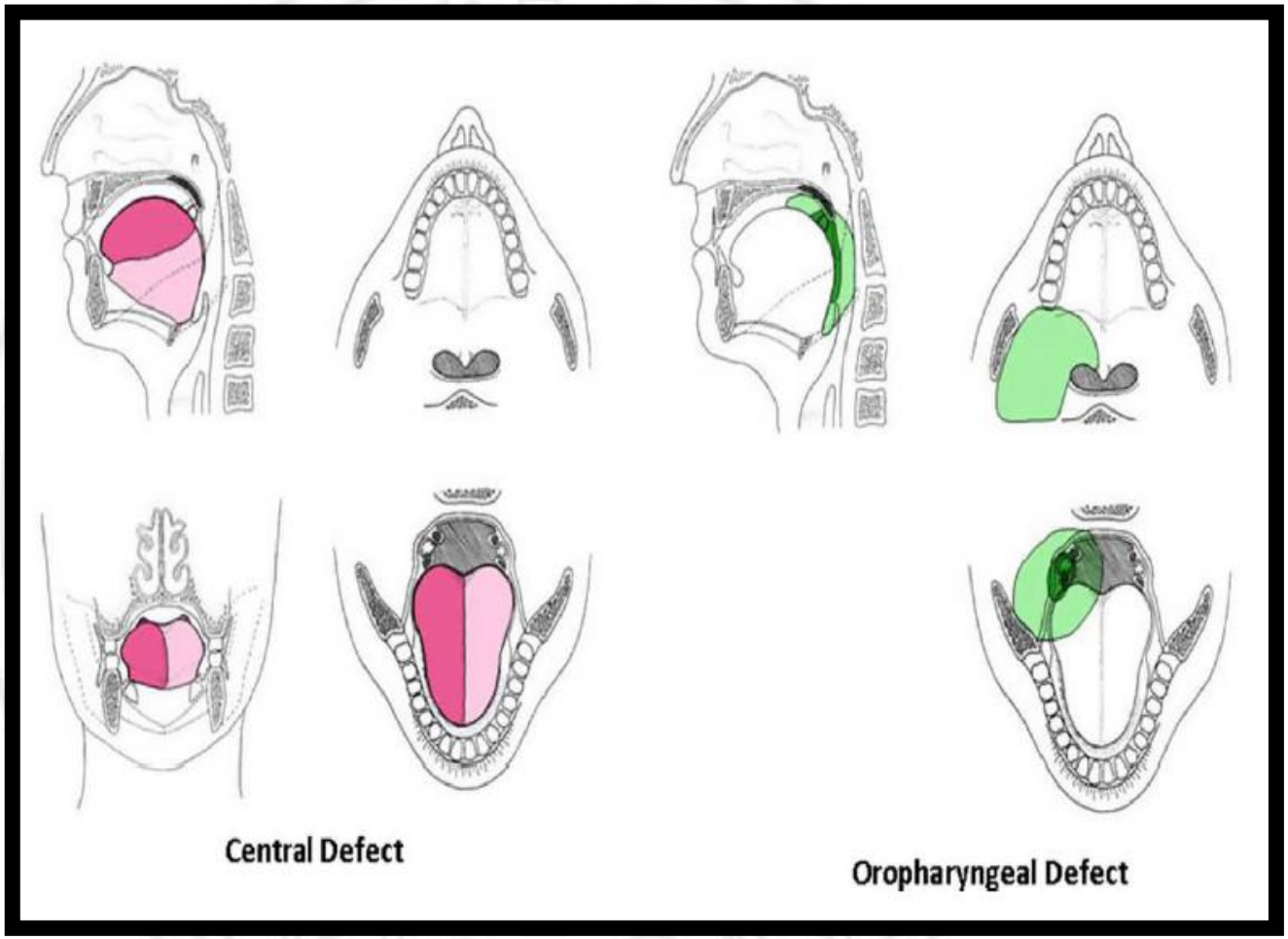
Oral cavity and oropharynx: 4 anatomical functional subsites



- **Lateral: lateral floor of the mouth; mandibular body; buccal cavity**
- **Anterior: anterior floor of the mouth; inter canine segment of the mandible; labial vestibule**

Kalavredzos et al; Oral Oncol 2010

Oral cavity and oropharynx: 4 anatomical functional subsites



- **Central: hemi- ot total tongue**
- **Oropharyngeal: retromolar trigone, soft palate and tonsillar fossa area**

Kalavredzos et al; Oral Oncol 2010

FOIS: Functional Oral Intake Score

FOIS GRADE	INTAKE DESCRIPTION
1	Nothing by mouth
2	Tube dependent with minimal attempts of food or liquid
3	Tube dependent with consistent oral intake of food or liquid
4	Total oral diet for a single consistency
5	Total oral diet with multiple consistencies, but requiring special
6	preparation, but with specific food limitations
7	Total oral diet with multiple consistencies without special preparation but with specific food limitations
	Total oral diet with no restrictions

Reconstruction: frequently with free tissue transfer rather than regional pedicled flaps

Dysphagia: extent and nature depends on

- **Tumor site and size rather than reconstruction used**
- **Post-operative treatment may damage swallowing more**
- **Central or anterior defects have worse swallowing outcomes at 4 months compared to lateral and oropharyngeal defects (more FOIS reduction compared to baseline)**

Schache et al; Oral Oncol 2009

CHEMOTHERAPY

"Sequential approach" improve outcomes?

May

ICT before a "lighter" CRT be better or more tolerable?

- **SWOG-0427** (III-IV Oropharynx): 1-3TPF → RT+3P vs RT+3P
- **DeCIDE** (N2-N3): 2TPF → HFRT+PFH vs HFRT+PFH
  - No difference OS
- **Paccagnella** (III-IV): RT+2PF vs 3 TPF → RT+2PF
  - CR rates: 21% vs 51%
  - Median PFS 19.7 vs 30.4; OS 33.3 vs 39.6
- **PARADIGM** (III-IV): 3TPF → RT+CBDCA weekly vs HFRT+2P
  - 3ys- OS: 73% vs 78%
- **INTERCEPTOR** (III-IV): 3TPF → RT + Cetuximab weekly vs RT+3P
- **GORTEC** (III-IV): 3TPF → RT + Cetuximab weekly vs RT+CBDCA-5FU

Benasso et al, Oral Oncol 2013


VOLUME 31 · NUMBER 6 · FEBRUARY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial of Induction Chemotherapy With Docetaxel, Cisplatin, and Fluorouracil Followed by Surgery Versus Up-Front Surgery in Locally Advanced Resectable Oral Squamous Cell Carcinoma

Lai-ping Zhong, Chen-ping Zhang, Guo-xin Ren, Wei Guo, William N. William Jr, Jian Sun, Han-guang Zhu, Wen-yong Tu, Jiang Li, Yi-li Cai, Li-zhen Wang, Xin-dong Fan, Zhong-he Wang, Yong-jie Hu, Tong Ji, Wen-jun Yang, Wei-min Ye, Jun Li, Yue He, Yan-an Wang, Li-qun Xu, Bo-song Wang, Merrill S. Kies, J. Jack Lee, Jeffrey N. Myers, and Zhi-yuan Zhang

- ✓ **Locally advanced resectable oral cavity tumors**
- ✓ **TPF x 2 cycles (DDP 75 mg/m^2 d1 + Docetaxel 75 mg/m^2 d1+ 5-FU 7500 mg/m^2 d1-5 infusion q 21) + surgery vs surgery upfront**
- ✓ **Post-operative RT if high-risk featured in both groups (54-66 Gy)**
- ✓ **Mean FU time: 30 months**
- ✓ **No advantage in OS and DFS**
- ✓ **Pts with favourable pathological response to ICT (≤ 10 vuable cells) had better OS**

Zong et al; JCO 2013

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Table 3. Adverse Events

Event	Experimental Arm						Control Arm					
	Grade 1		Grade 2		Grade 3		Grade 1		Grade 2		Grade 3	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Induction chemotherapy												
Hematologic toxicity	18	14.8	9	7.4	8	6.6	—	—	—	—	—	—
Diarrhea	11	9.0	6	4.9	1	0.8	—	—	—	—	—	—
Alopecia	83	68.0	3	2.5	0	0	—	—	—	—	—	—
Nausea and/or vomiting	66	54.1	2	1.6	0	0	—	—	—	—	—	—
Altered liver function tests	19	15.6	5	4.1	0	0	—	—	—	—	—	—
Febrile neutropenia	—	—	—	—	2	1.6	—	—	—	—	—	—
Postoperative radiotherapy												
Oral mucositis	38	34.2	44	39.6	7	6.3	41	36.3	43	38.1	7	6.2
Trismus	28	25.2	35	31.5	6	5.4	33	29.2	34	30.1	6	5.3
Dermatitis	31	27.9	41	36.9	5	4.5	29	25.7	38	33.6	4	3.5
Dysphagia and odynophagia	25	22.5	29	26.1	6	5.4	26	23.0	31	27.4	6	5.3

Zong et al; JCO 2013

original articles

Annals of Oncology

Annals of Oncology 25: 462–466, 2014
doi:10.1093/annonc/mdt555
Published online 8 January 2014

Preoperative chemotherapy in advanced resectable OCSCC: long-term results of a randomized phase III trial

P. Bossi[1], S. Lo Vullo[2], M. Guzzo[3], L. Mariani[2], R. Granata[1], E. Orlandi[4], L. Locati[1], G. Scaramellini[3], C. Fallai[4] & L. Licitra[1]

[1]*Head and Neck Cancer Medical Oncology Unit;* [2]*Clinical Epidemiology and Trial Organization Unit;* [3]*Otorhinolaryngology Unit;* [4]*Radiotherapy Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

- ✓ **Advanced resectable oral cavity tumors**
- ✓ **PF x 3 cycles (DDP 100 mg/m2 + 5-FU 1000 mg/m2 over 120 h infusion q 21) + surgery vs surgery upfront (T2-T4, N0-N2)**
- ✓ **Post-operative RT if high-risk featured in both groups**
- ✓ **Mean FU time: 11.5 years**
- ✓ **No advantage in loco-regional control, distant metastasis and death rate**
- ✓ **Pts with pCR had better OS**

Bossi et al; Ann Oncol 2014

original articles

Annals of Oncology

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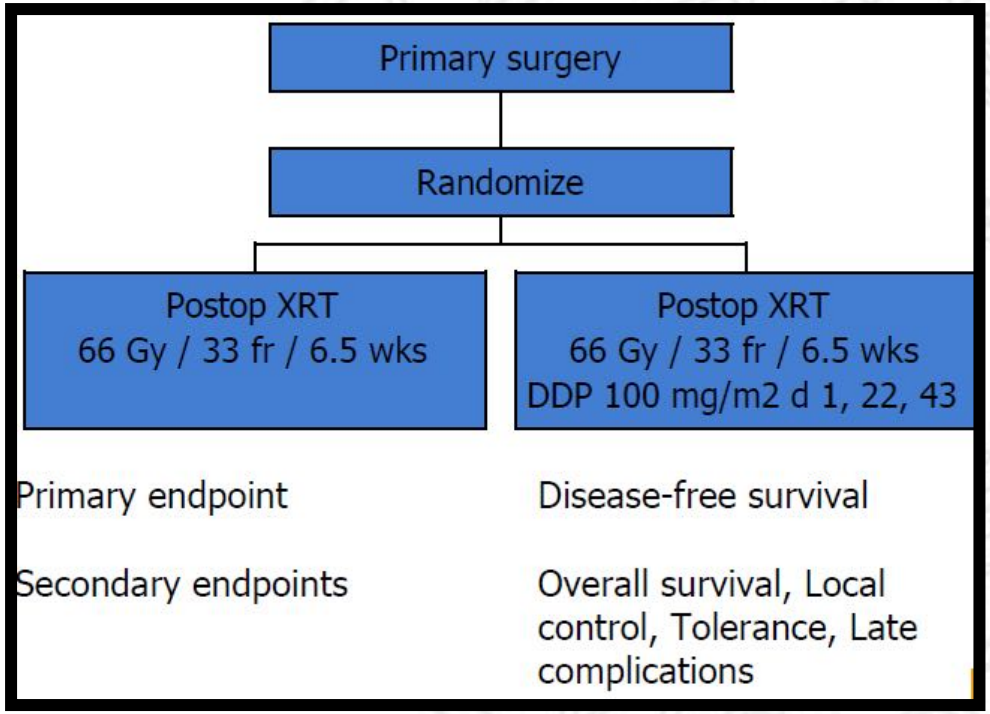
	Chemotherapy arm (%)		Control arm (%)	
	Grade 1	Grade 2	Grade 1	Grade 2
Dysphagia	29	5	29	14
Fibrosis	10	12	33	7
Xerostomia	5	/	5	/
Mucositis	2	/	/	/

- ✓ **Pts with minum 60-month FU time**
- ✓ **Lower fibrosis rate (cumulative incidence: 22% vs 40%) and G2 dysphagia (cumulative incidence: 5% vs 14%)**

Bossi et al; Ann Oncol 2014

EORTC 22931



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

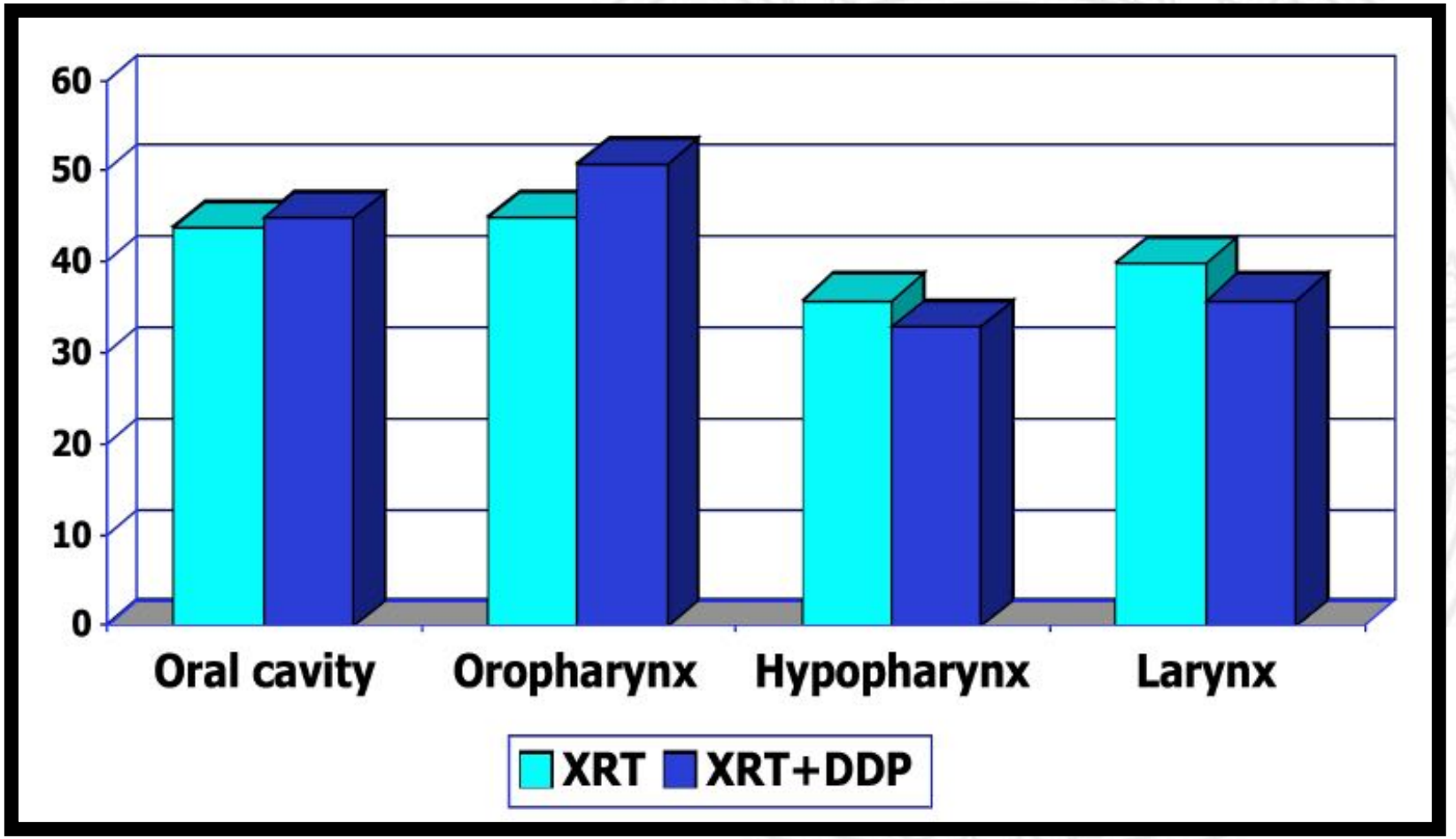
Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

Jacques Bernier, M.D., Ph.D., Christian Domenge, M.D., Mahmut Ozsahin, M.D., Ph.D., Katarzyna Matuszewska, M.D., Jean-Louis Lefèbvre, M.D., Richard H. Greiner, M.D., Jordi Giralt, M.D., Philippe Maingon, M.D., Frédéric Rolland, M.D., Michel Bolla, M.D., Francesco Cognetti, M.D., Jean Bourhis, M.D., Anne Kirkpatrick, M.Sc., and Martine van Glabbeke, Ir., M.Sc., for the European Organization for Research and Treatment of Cancer Trial 22931

- SCC
- Primary surgery performed with curative intent
- Oral cavity, oropharynx, hypopharynx and larynx
- pT3-T4 any N, pT1-T2 with pN2-N3 or pT1-T2 with pN0,N1 with high risk features
- Insufficient resection margins, ECE +, VI +, PNI +

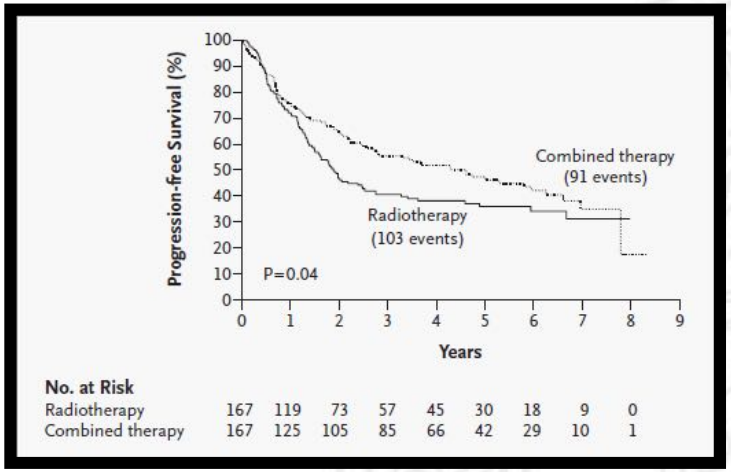
Bernier et al; NEJM 2004

EORTC 22931– Case Mix



Bernier et al; NEJM 2004

EORTC 22931 – Results



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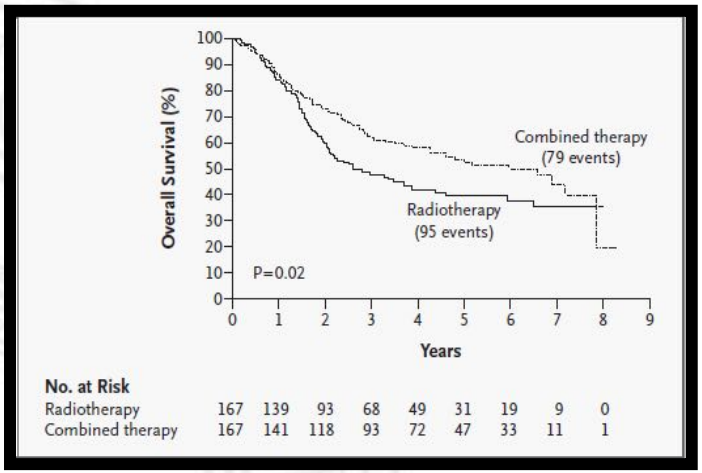
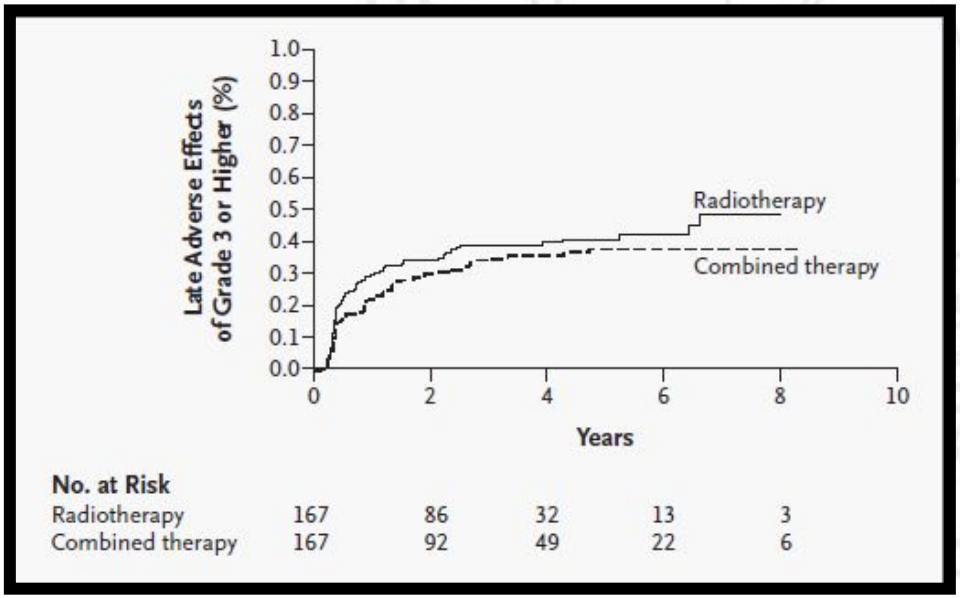


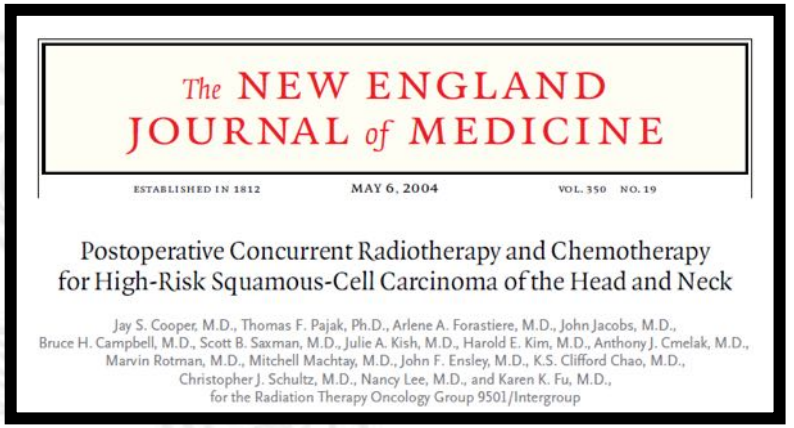
Cumulative incidence major late adverse effects

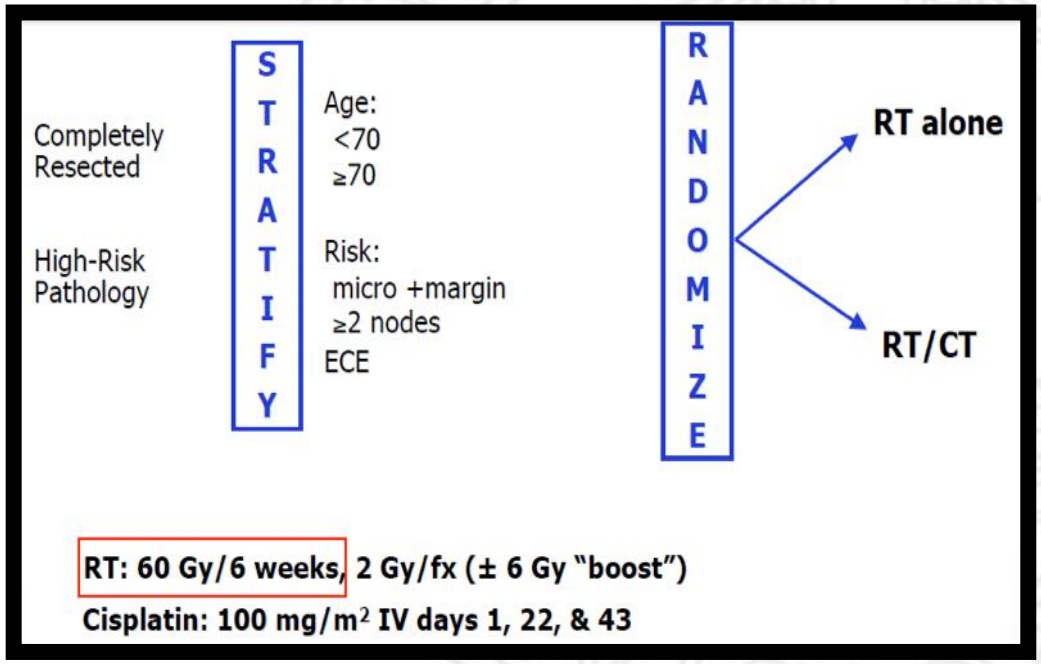


- Xerostomia
- Dysphagia
- Muscular fibrosis
- Shoulder syndrome
- Impairment of lymphatic drainage
- Laryngeal complications
- Bone complications
- Mucosal necrosis
- Skin/Soft tissue fibrosis

Bernier et al; NEJM 2004

RTOG 9501





- ❑ **SCC**
- ❑ **Macroscopically resected disease**
- ❑ **Oral cavity, oropharynx, hypopharynx and larynx**
- ❑ **High-risk features: ≥ 2 positive nodes, ECE +, R1 resection**

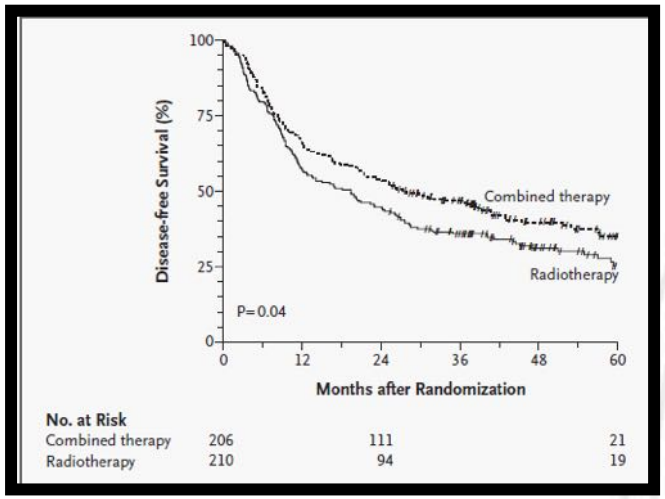
Cooper et al; NEJM 2004

RTOG 9501– Case Mix

Subsites	RT	RT-CT
Oral cavity	30%	24%
Oropharynx	37%	48%
Hypopharynx	12%	7%
Supraglottic larynx	15%	14%
Glottic larynx	5%	5%
Subglottic larynx	<1%	1%

Cooper et al; NEJM 2004

RTOG 9501 – Results



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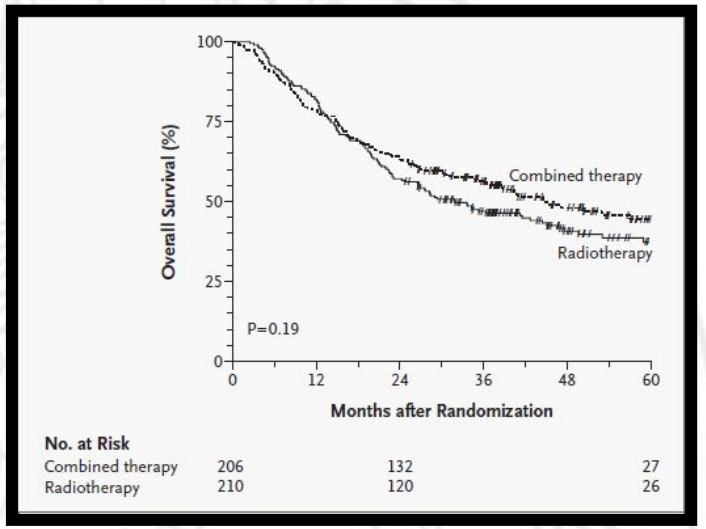
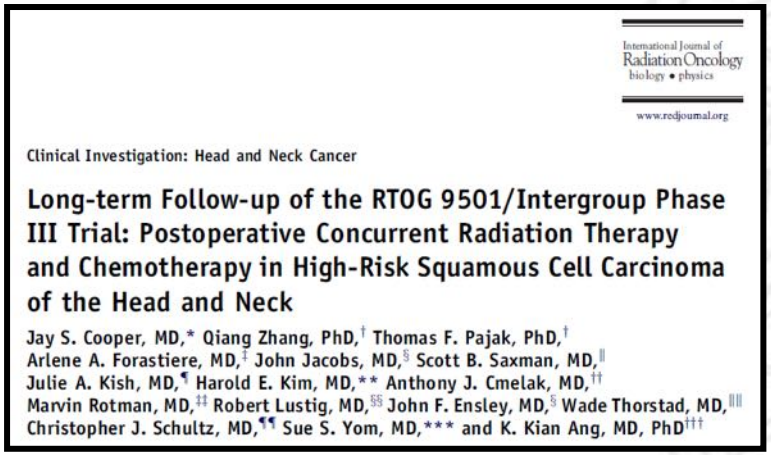


	RT Grade 2	RT Grade 3	RT Grade 4	RT + CT Grade 2	RT + CT Grade 3	RT + CT Grade 4
Acute in-field	65	4	0	77	8	0
other	--- N/A---			87	29	2
Late	29	6	0	28	10	2
Any time*	84	12	0	106	50	4
	40%	6%	0	51%	24%	2%

*significant difference, p < 0.0001
N/A = not assessed

Cooper et al; NEJM 2004

RTOG 9501 – Long term results



International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation: Head and Neck Cancer

Long-term Follow-up of the RTOG 9501/Intergroup Phase III Trial: Postoperative Concurrent Radiation Therapy and Chemotherapy in High-Risk Squamous Cell Carcinoma of the Head and Neck

Jay S. Cooper, MD,* Qiang Zhang, PhD,† Thomas F. Pajak, PhD,†
Arlene A. Forastiere, MD,‡ John Jacobs, MD,§ Scott B. Saxman, MD,‖
Julie A. Kish, MD,¶ Harold E. Kim, MD,** Anthony J. Cmelak, MD,††
Marvin Rotman, MD,‡‡ Robert Lustig, MD,§§ John F. Ensley, MD,§ Wade Thorstad, MD,‖‖
Christopher J. Schultz, MD,¶¶ Sue S. Yom, MD,*** and K. Kian Ang, MD, PhD†††

Table 4 Number of patients having late toxicity, by type and grade

	RT (n=205) Grade					RT + CT (n=193) Grade				
	1	2	3	4	5	1	2	3	4	5
Skin	72	17	2	0	0	67	20	2	4	0
Mucous membrane	48	17	4	2	0	50	24	2	2	0
Subcutaneous tissue	41	39	6	1	0	55	43	4	0	0
Salivary gland	50	61	6	0	0	34	77	8	0	0
Pharynx/esophagus	42	35	12	1	0	31	28	17	2	0
Larynx	36	6	3	2	0	46	8	6	0	1
Spinal cord	17	0	0	0	0	35	0	0	0	0
Bone	14	5	1	2	0	23	2	1	5	0
Joint	22	8	2	0	0	29	8	1	0	0
Brain	19	1	1	0	0	31	0	0	0	0
Other neurologic	20	4	2	0	0	29	9	4	0	0
Hematologic	26	5	1	1	0	39	12	4	0	0
Renal	17	0	0	0	0	32	3	2	0	0
Upper GI	19	3	1	0	0	31	3	3	0	0
Other	21	26	8	0	0	31	19	5	2	1

Cooper et al; IJROBP 2012

RADIOTHERAPY

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 4, pp. 1096–1103, 2009

0360-3016/09/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2008.05.024

CLINICAL INVESTIGATION **Head and Neck**

INTENSITY-MODULATED RADIOTHERAPY IN POSTOPERATIVE TREATMENT OF ORAL CAVITY CANCERS

DANIEL R. GOMEZ, M.D.,* JOANNE E. ZHUNG, B.A.,* JENNIFER GOMEZ, B.A.,* KELVIN CHAN, B.A.,* ABRAHAM J. WU, M.D.,* SUZANNE L. WOLDEN, M.D.,* DAVID G. PFISTER, M.D.,† ASHOK SHAHA, M.D.,‡ JATIN P. SHAH, M.D.,† DENNIS H. KRAUS, M.D.,‡ RICHARD J. WONG, M.D.,‡ AND NANCY Y. LEE, M.D.*

Departments of *Radiation Oncology, †Medical Oncology, and ‡Head and Neck Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

Disease subsite
- Oral tongue
- Floor of mouth
- Buccal mucosa
- Gingiva
- Hard palate
- Retromolar trigone

Variable	Dose (Gy)/fractions	Primary site	Nodal volume
Gross positive margins or gross residual disease	70/2.0	Gross PTV	—
Microscopic positive margins	66/2.0	Microscopic PTV	—
Negative margins, high-risk disease	60/2.0 or 59.4–63/1.8	High-risk PTV	High-risk PTV
Negative margins, low-risk/contralateral disease	54/1.8	Low-risk PTV	Low-risk PTV

	Grade (*n*)			
Toxicity	1	2	3	4
Dermatitis	0	0	0	0
Mucositis	1	2	1	0
Salivary gland	6	2	2	0
Mandible	3	3	0	0
Esophagus	2	1	3	0
Larynx	3	0	0	0
Trismus	3	3	0	0

Gomez et al; IJROBP 2009

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 Ricardi[i], Fabiola Paiar[j], Pierluigi Bonomo[k], Marco C. Merlano[l], Valeria Zurlo[m], Fausto Chiesa[m], Giuseppe Sanguineti[n], Jacques Bernier[o]

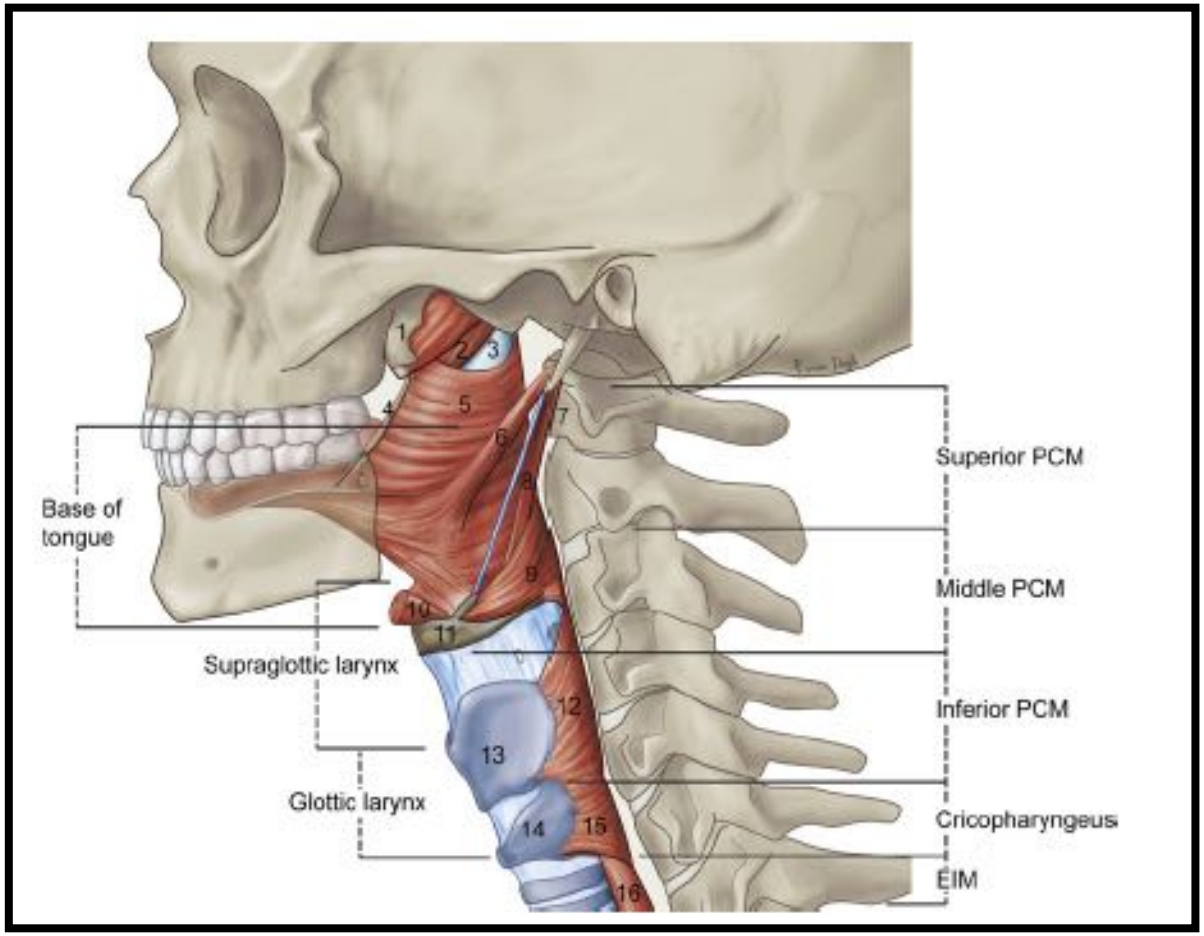
Pre-treatment rate: 11-53%

Post-treatment rate: 11-62%

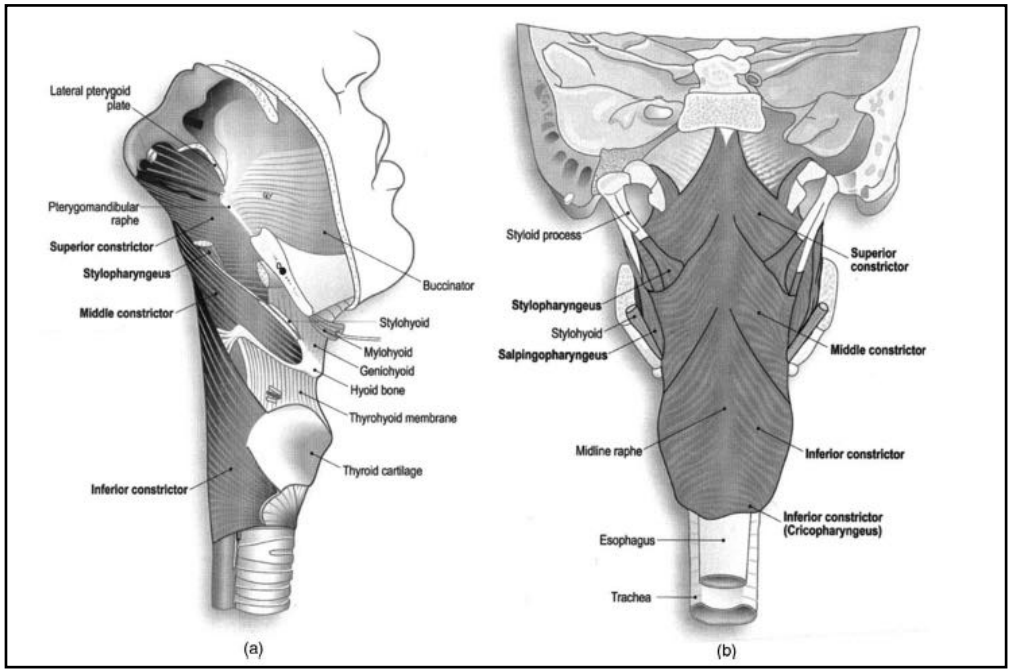
Authors	Year	Pts	Anatomical site	Stage	Aspiration at diagnosis [silent]	After [silent]*
Stenson et al.[45]	2000	79	Oral cavity Oropharynx Larynx Hypopharynx	III–IV	43% (34/78)†	
Wu et al.[118]	2000	31	Nasopharynx	Dysphagia		(93.5% (29/31) ***[41.9% (13/31)]***
Hughes et al.[173]	2000	49	Nasopharynx	Treated pts		***[22% [11/49)]***
Rosen et al.[174]	2001	27	Oral cavity Oropharynx Larynx Hypopharynx	III–IV	41% (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)]***
Carrara-de Angelis et al.[175]	2003	19	Larynx Hypopharynx	II–IV		26% (5/19) ***[26%(5/19)]***
Graner et al.[176]	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.[178]	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.[56]	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)]***	
Dirix et al.[57]	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

DARS


Base of tongue
Supraglottic larynx
Glottic larynx
Superior PCM
Middle PCM
Inferior PCM
Cricopharyngeus
EIM

DARS: dysphagia/aspiration-related structures



- **Constrictors muscles**

PSCM
PMCM
PICM

- **Supraglottic larynx**
- **Glottic larynx**

- **Suprahyoid muscles**

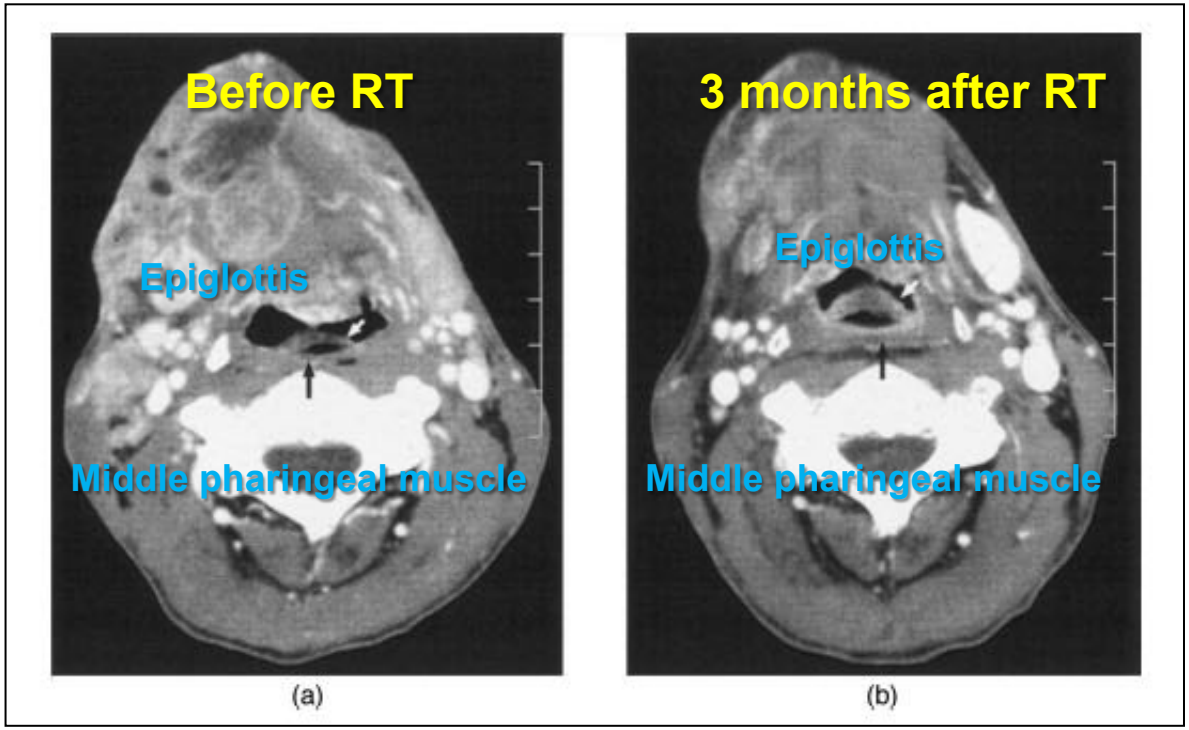
Mylohyoid
Geniohyoid
Digastric

- **Longitudinal pharyngeal muscles**

Stylopharyngeus
Palatopharyngeus
Salphyngopharyngeus
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

Floor of the mouth muscles

By elevating and anteriorly displacing the hyoid bone, an effective epiglottic tilt and negative pressure is generated allowing protection of the airway with entry of the food bolus into the upper esophagus

Floor of the mouth muscles

Oral Oncology 50 (2014) 65–70

Contents lists available at ScienceDirect

Oral Oncology

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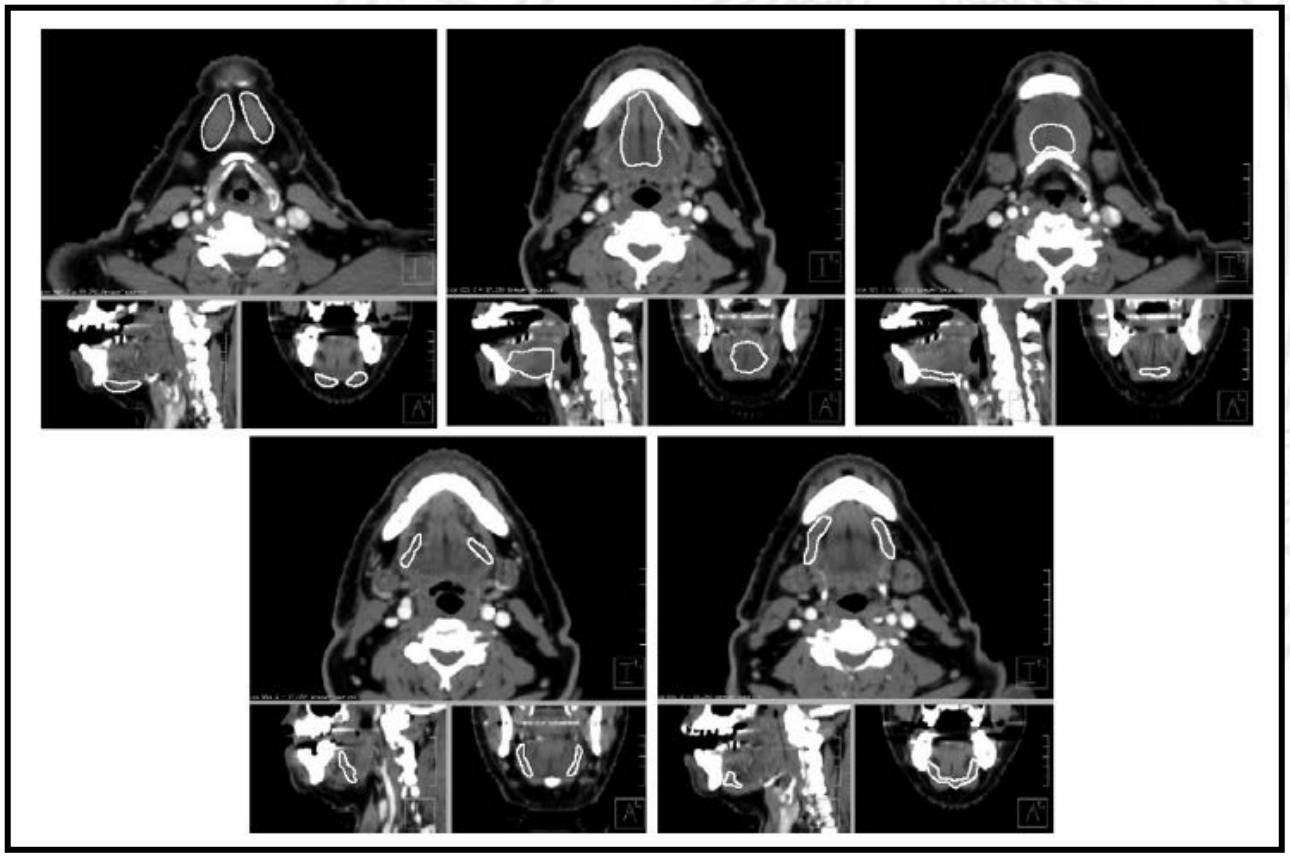
Radiation dose to the floor of mouth muscles predicts swallowing complications following chemoradiation in oropharyngeal squamous cell carcinoma

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,*]



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) 65–70

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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 mean dose correlates with VFS abnormalities

Kumar R et al; Oral Oncol 2014

Assessment methods of dysphagia

Subgroup		Assessment methods	Reference no.
Objective instrument evaluation		MBS examinations/VFSS	5,7,11,26–28,32
		FEES	12
		Transnasal esophagoscopy	12
Subjective evaluation	Patient-rated scales	MDADI	24,27,29,34
		PSS-HN	6,27,29
		SPSS	7,22
		EORTC H&N35	10,29
		UWQOL	12,24
		Swallowing Screening Questionnaire	34
		SF-36	34
		Head and Neck Radiotherapy Questionnaire	35
		The DAHANCA morbidity scoring system for dysphagia	6
		Swallowing scale of the AusToms	26
		Pharyngoesophageal stricture	28
		Percutaneous endoscopic gastrostomy PEG tube dependence at last follow-up visit	28
	Clinician-rated scales	CTCAE	5,23
		RTOG/EORTC Late Radiation Morbidity Scoring Criteria	5,10,29,31

Jiang et al; Head and Neck 2015

Predictors of late dysphagia after (chemo-) radiation


CLINICAL REVIEW

Risk factors for late dysphagia after (chemo)radiotherapy for head and neck cancer: A systematic methodological review

Evidence level	Predictors for dysphagia	No. of patients in high-quality studies	No. of patients in moderate-quality studies
Strong evidence	The use of CRT	714[24,28,31]	48[32]
	Hypopharyngeal carcinoma	1937[6,10,28]	407[22]
Moderate evidence	Advanced tumor stage	1990[6,31]	407[22]
	Base of tongue carcinoma	476[10,28]	
	Laryngeal carcinoma	476[10,28]	
	Nasopharyngeal carcinoma	591[6,31]	
	Mean RT dose to the middle PCM	404[5,10]	
	Mean RT dose to the superior PCM	354[10]	92[7,27]
	Mean RT dose to the inferior PCM		94[11,12]
	The presence of baseline dysphagia	1461[6]	53[29]
Limited evidence	A higher weight loss before RT	529[31]	
	A higher RT dose to supraglottic larynx	354[10]	
	A higher RT dose	167[24]	
	An increase in blood flow and volume in the PCM in the second week of RT	15[23]	
	A higher RT dose to cricoid pharyngeal inlet		39[12]
	Bilateral neck irradiation	529[31]	
	Dose-volume constraints (V30 <65%; V35 <35%) for anterior oral cavity		31[27]
	Dose-volume constraints (V55 <80%; V65 <30%) for high superior PCM		31[27]
	Women		407[22]
	Disease status at last follow-up (progression and dead)		47[25]
	Low SF-36 Mental Health Subscale Score		40[34]
	Poor pretreatment MDADI score	167[24]	
	Oral cavity carcinoma	354[10]	
	Pharyngeal wall cancer	122[28]	
	The history of speech pathology consultation		40[34]
	Prolonged nothing by mouth status		40[34]
	The use of 3D-CRT	354[10]	
Conflicting evidence	Younger age	643[10,24,28]	407[22]

Jiang et al; Head and Neck 2015

XRS: xerostomia-related structures

- Parotid glands
- Submanidibular glands
- Sublingual glands
- Minor salivary glands
  - Cheeks
  - Soft palate
  - Lips

Xerostomia

Sparing parotid glands

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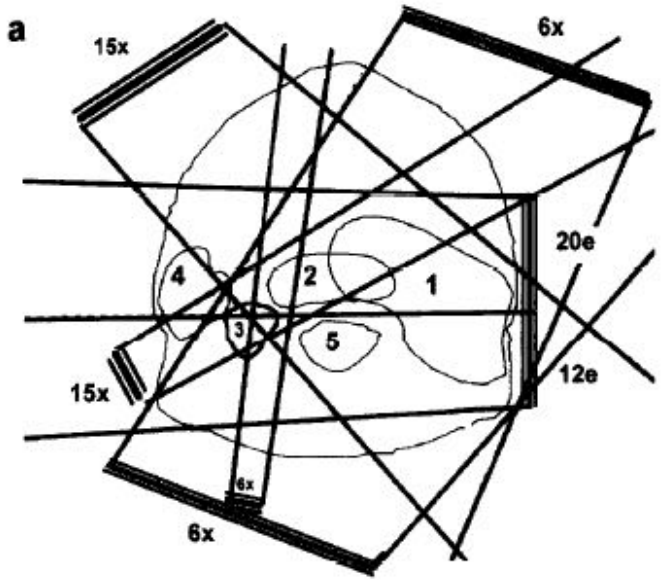
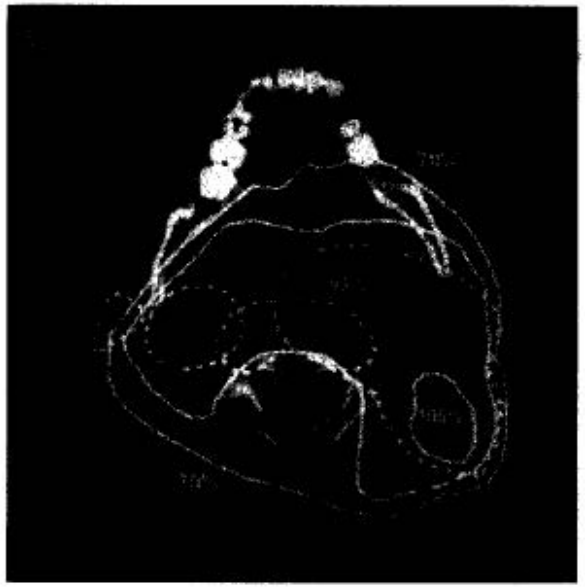
● *Technical Innovations and Notes*

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





Eisbruch et al; IJROBP 1996

Xerostomia

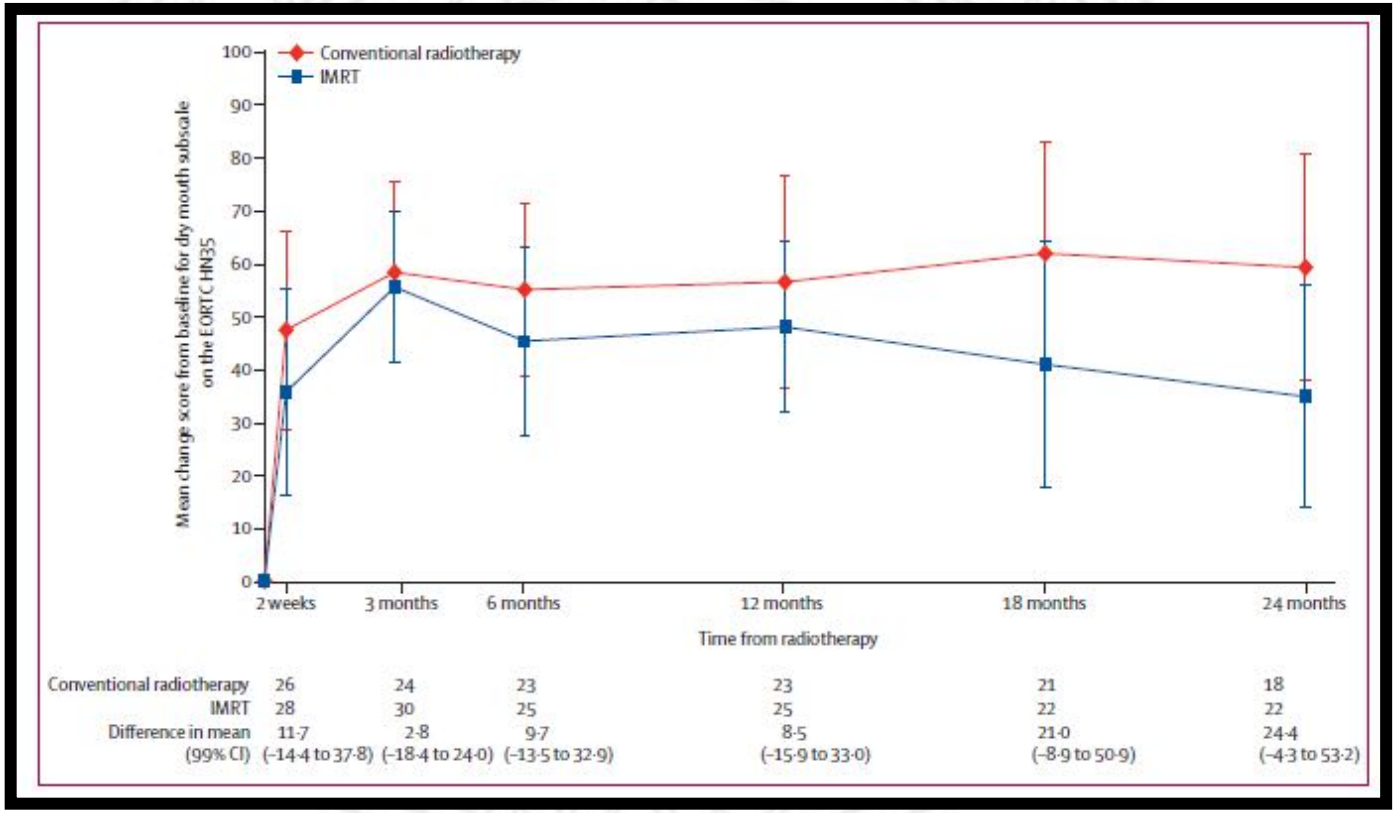
Sparing parotid glands

Investigator	Patients (n)/follow-up (mo)	Total prescribed target dose (Gy)*	"Functional" endpoints assessed	Dose–volume parameters	
				Unstimulated	Stimulated
Blanco *et al.* (6), 2005	55/6; 29/12	50–71†	Stimulated saliva flow‡		Mean dose <25.8 Gy§
Eisbruch *et al.* (7), 1999	88/1–12	58–72	Saliva flow, stimulated and unstimulated	Mean dose ≤22–25 Gy¶	Mean dose ≤25–26 Gy‖
				V_{15} <66%	V_{15} <67%
				V_{30} <43%	V_{30} <45%
				V_{45} <26%	V_{45} <24%
Li *et al.* (9), 2007	142/1–24	60–75	Saliva flow; stimulated and unstimulated#	Mean dose <25–30 Gy	Mean dose <25–30 Gy
Maes *et al.* (8), 2002	39/1–4	66–70**	SEF††; stimulated flow, ^{99m}Tc-pertechnetate scintigraphy		Mean dose ≤20 Gy‡‡

Deasy et al; IJROBP 2010

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*

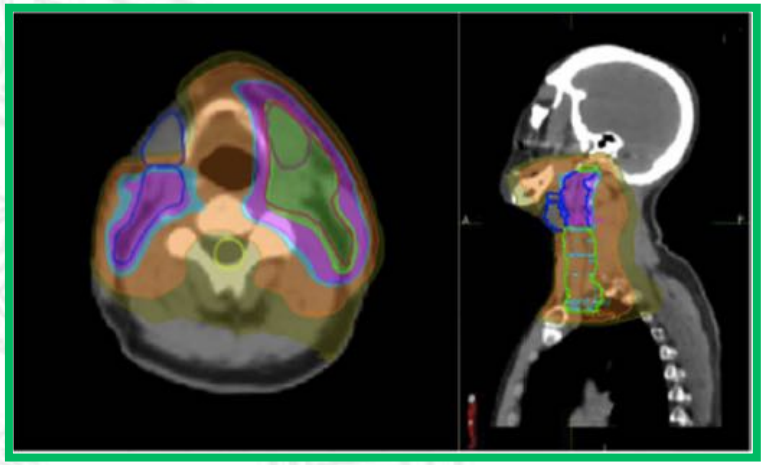


Conventional radiotherapy	26	24	23	23	21	18
IMRT	28	30	25	25	22	22
Difference in mean (99% CI)	11·7 (−14·4 to 37·8)	2·8 (−18·4 to 24·0)	9·7 (−13·5 to 32·9)	8·5 (−15·9 to 33·0)	21·0 (−8·9 to 50·9)	24·4 (−4·3 to 53·2)

Nutting et al; Lancet Oncol 2011

Xerostomia

Submandibular glands



ORIGINAL ARTICLE

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.

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TABLE 3. Patterns of treatment failure in patients treated with contralateral submandibular gland-sparing radiation therapy.

Number	Primary site	T classification	N classification	Overall stage	Location of failure	Time to failure, mo
1	BOT	1	2b	IVa	BOT	24.2
2	Tonsil	3	1	III	Ipsilateral level 2	Persistent disease
3	Tonsil	2	2b	IVa	Ipsilateral levels 2/3	29.3
4	Tonsil	2	2b	IVa	Ipsilateral level 2	8.8
5	Tonsil	2	2c	IVa	Ipsilateral level 2	2.8
6	Tonsil	2	2b	IVa	Ipsilateral levels 2/3/4	3.9
7	Tonsil	1	3	IVb	Contralateral level 2A*	15.5
8	Tonsil	2	2b	IVa	Distant metastases	4.5
9	BOT	1	2b	IVa	Distant metastases	6.7
10	Tonsil	2	2b	IVa	Distant metastases	26.6
11	Tonsil	4a	2b	IVa	Distant metastases	12.8
12	Tonsil	2	2b	IVa	Distant metastases	4.5

Robin et al; Head and Neck 1996

Adaptive radiotherapy

Sanguineti *et al. Radiation Oncology* (2015) 10:19
DOI 10.1186/s13014-015-0331-x

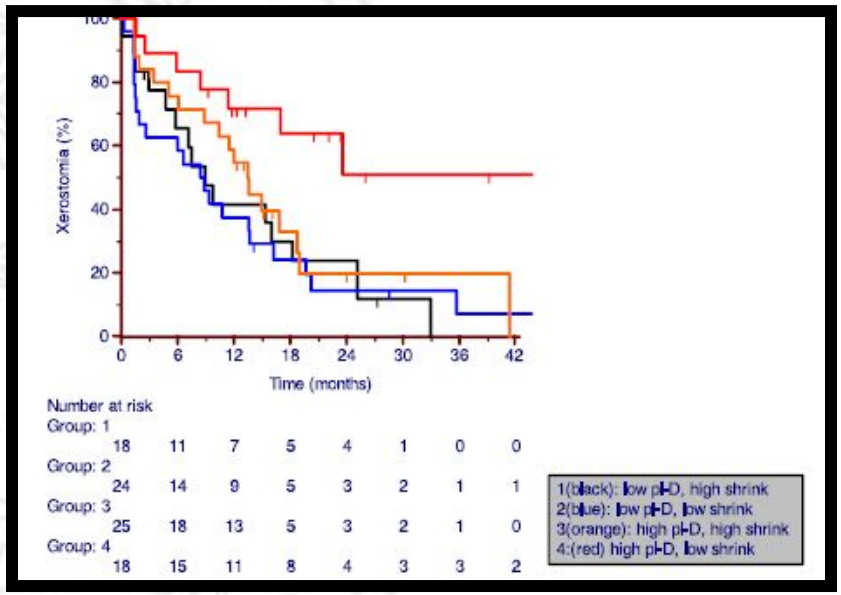
RADIATION ONCOLOGY

RESEARCH Open Access

Parotid gland shrinkage during IMRT predicts the time to Xerostomia resolution

Giuseppe Sanguineti[1,2], Francesco Ricchetti[1,2], Binbin Wu[1,2], Todd McNutt[1,2] and Claudio Fiorino[3*]

Covariate	HR	95%CI		p value
		Lower	Upper	
Body Mass Index	0.932	0.875	0.992	0.027
% PG Shrinkage at mid-tmt	1.034	1.004	1.064	0.024
WA mean PG pl-D	0.927	0.886	0.971	0.001



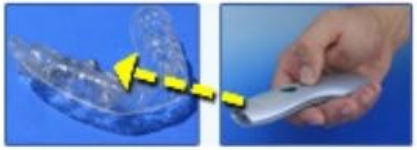
Sanguineti et al; Radiat Oncol 2015

Limited Success in Relieving Xerostomia









2012 International Federation of Head and Neck Oncologic Societies

Skin effects

- **Risk factors:**
  - **Pt related:**
    - **poor nutritional status**
    - **diabetes**
    - **vasculopathy**
    - **connective tissue disease**
  - **Treatment related:**
    - **large fields**
    - **electron beam RT**
    - **post- op RT**
    - **concurrent CT**
    - **thin epidermis (face, neck)**

Susceptibles sites:

- **Skin folds, lips, ear lobes, incision lines or wounds, peristomal skin**

Skin effects

- **Treatment:**
  - **General skin care (cleaning, moisturizing)**
  - **Avoidance of sun exposure**
  - **Steroid creams ± antibacterial ointments**
  - **Silvadene ointments**
  - **Pain killers**

Late skin effects:

- **Thining, teleangiectasia, hair loss in irradiated area, loss of sweat and sebaceous glandular function, hyper/hypopigmentation**

Osteoradionecrosis

Bone within the radiation field becomes devitalized and exposed through the overlying skin or mucosa, persisting as a non-healing wound for 3 months or more

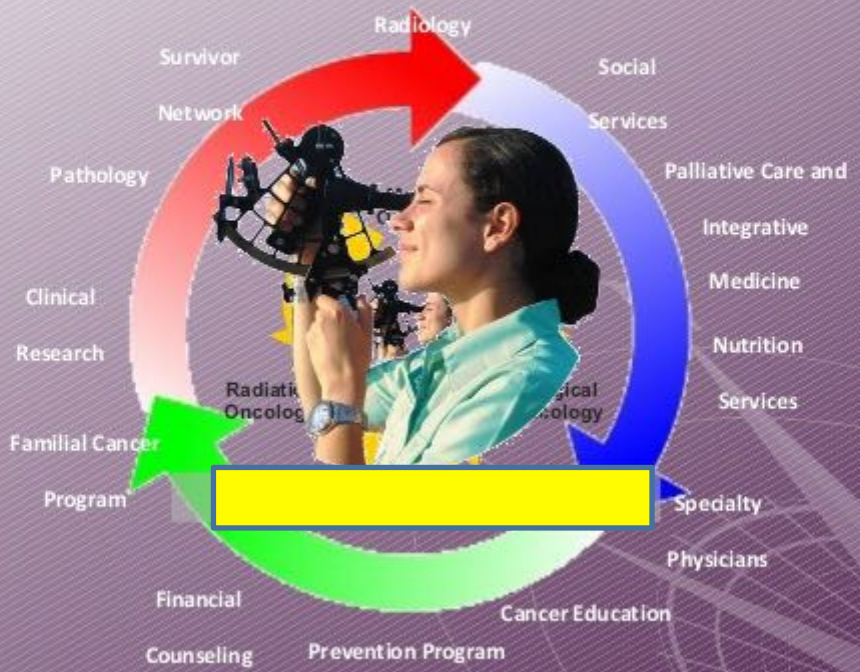
Osteoradionecrosis

- Most frequently noted in the first few years after completion of treatment (70-94%)
- 'Early onset' ORN (< 2 yrs): related to RT doses > 70 Gy or surgical trauma
- 'Late onset' ORN: thought to arise from trauma in a chronically hypoxic tissue environment

Osteoradionecrosis

- Risk factors: alcohol, smoking (during RT)
- Poor dental care; no evaluation prior RT
- Dosimetric parameters: Dmax > 70 Gy
- Treatment:
  - Pentoxyfilline
  - Clodronate
  - Hyperbaric oxygen (no useful in a systematic review)

Multidisciplinary Team Approach



Pierfrancesco Franco

Grazie dell' attenzione

Mario Schifano – Indicazione - 1963