Organ and functional preservation strategies in head and neck cancers

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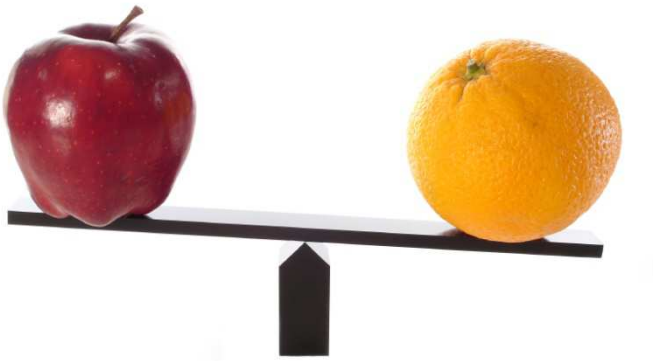
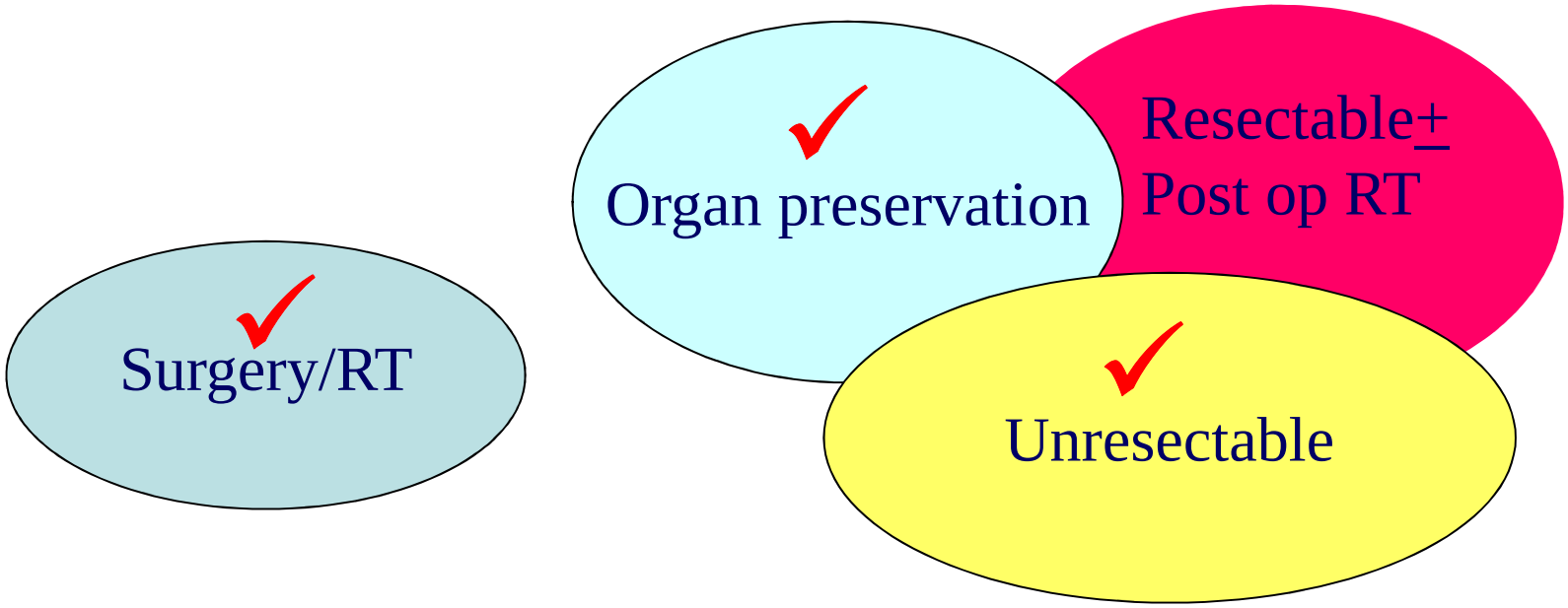
Overall results –surgery/RT

- Surgical series – 40-60%
- Radiotherapy series – 15-40%



So, if we wish to preserve the organ by radiotherapy, clearly there is a need for survival figures to match the surgical series (stage for stage)!

What are the subsets in which we can think of organ preservation?

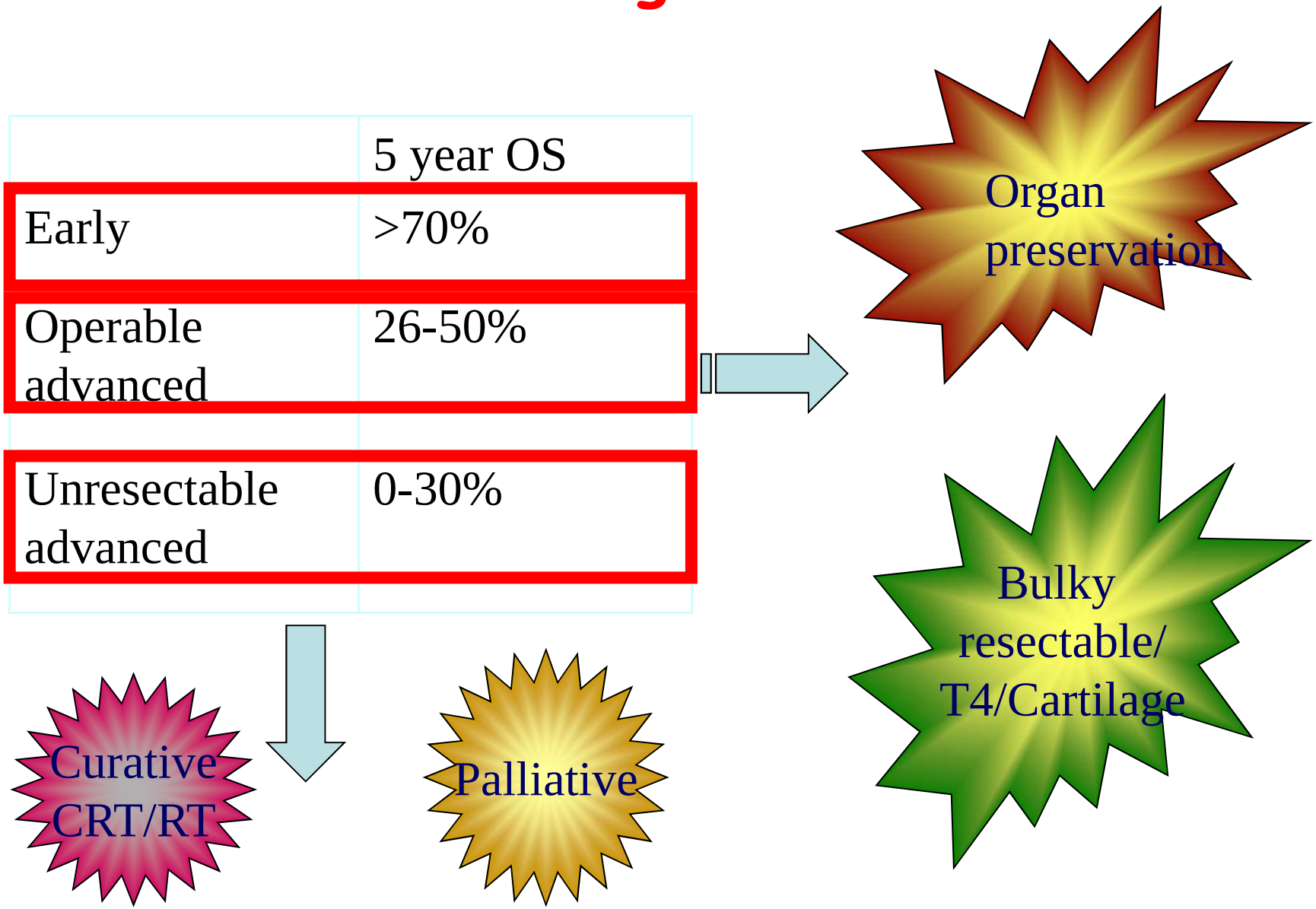


Early Disease

Locally advanced disease

Background

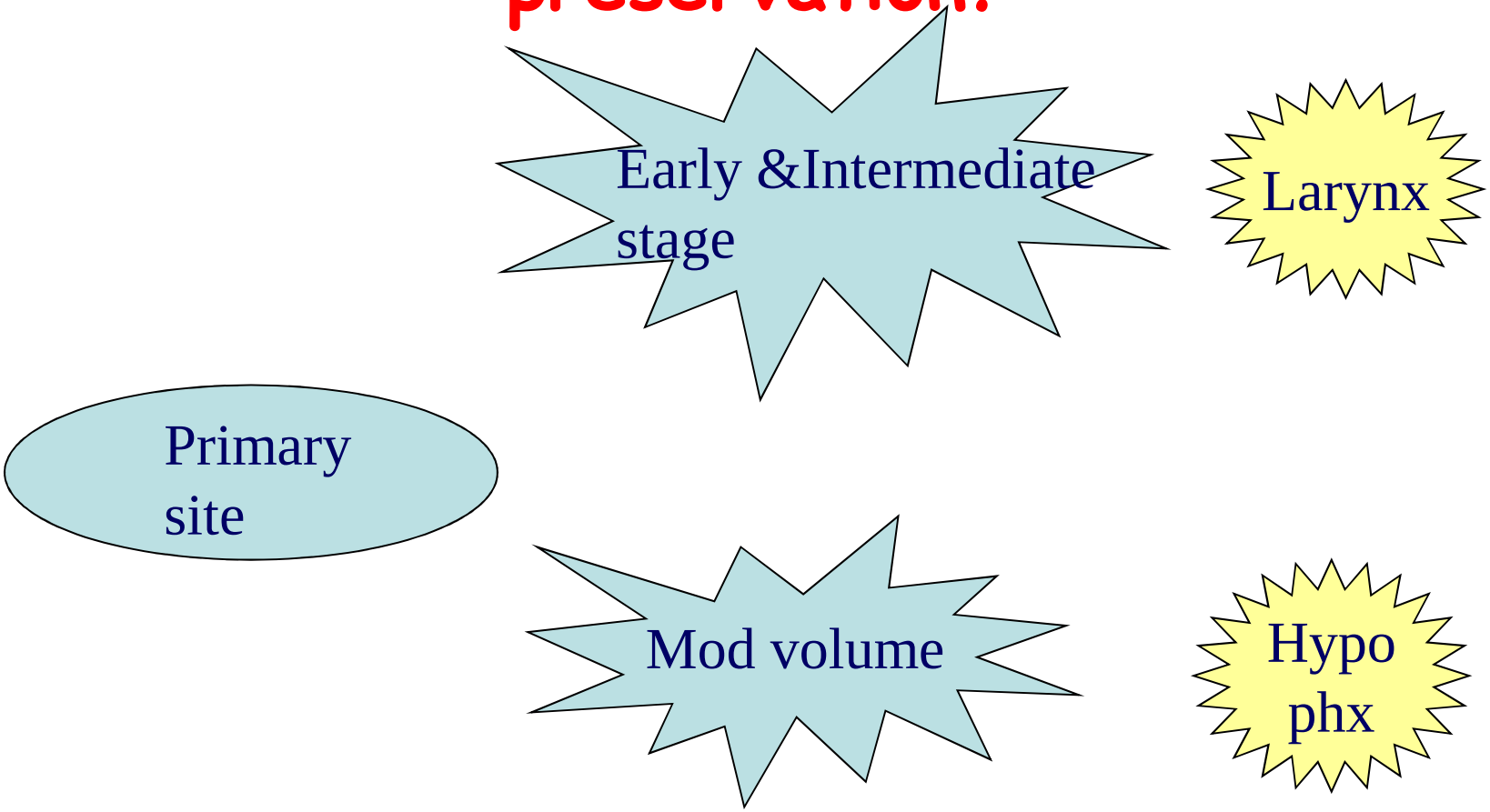
	5 year OS
Early	>70%
Operable advanced	26-50%
Unresectable advanced	0-30%



What is this so called resectable disease in Larynx?

T1	Tumor limited to the vocal cord(s)
T2	Tumor extends to supraglottis , subglottis, with impaired vocal cord mobility
T3	Tumor limited to larynx with vocal cord fixation, invades paraglottic space, minor thyroid cartilage erosion
T4a	Tumor invades the thyroid cartilage, invades tissues beyond the larynx (e.g. trachea, deep muscle of tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

What subsets are amenable to Organ preservation?



Who decides the operability?

Surgical member of the Joint clinic team

Bottomline is…

- Surgery is the gold standard.
- No head on comparison.
- If you can operate (i.e. resectable disease) you should. BUT…
- In resectable disease – if you can save the organ – you should.

Non surgical organ preserving strategy – Radiotherapy

May need intensification (select group) to match surgical results

So, What are the OP strategies?

Addition of chemotherapy to RT

Alteration of fractionation

Integration of both

Chemotherapy in what form …

Induction CT+RT

Concurrent CT+RT

Alternating CTRT

Adjuvant CT

3 issues one needs to consider…

- Locoregional control
- Metastatic spread (20%)
- Functional morbidity

CT will improve LRC

CT will ↓distant failure

CT may substitute pr. site Sx= OP

Induction chemotherapy

- Wayne State protocol- **Cisplatin+FU**
- Aim – to replace primary surgery with CT
- Reasons- better drug delivery
  - naïve pts- better tolerance
  - high dose- ↓ micrometastasis
  - Down sizing before IMRT
  - Waiting times
- Demerits – prolongs treatment
  - Repopulation of resistant cells

Bhide S, Br J Cancer,2008,99:57-62

Induction chemotherapy

- Rationale- downstages the tumor
- CR- 20-30; OR- 60-80%
- **Organ preservation**
- Act as a predictor for radiation response
- Act on distant micro metastasis

NACT trials

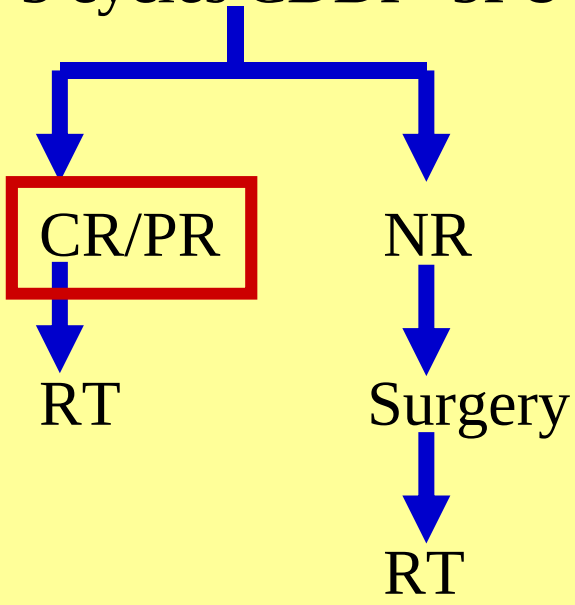
1991

Induction CT

(Evidence – Veterans trial- NEJM 1991)

- N=332
- Stage III/IV glottis and supraglottis primary

2-3 cycles CDDP+5FU



	Organ Preserv
After trt	78%
At 2 yrs	65%
At 5yrs	31%

Surgery + Post op RT

NACT trials- resectable gp

Veterans Trial

- OS similar 35%
- *What it answered?* Identified the subset that will respond to radiation
- Pathological response – Best predictor
- *What it didn't answer?* Was Radiotherapy equally good enough for organ preservation

NACT trials- resectable gp

2003

Is RT good enough for OP? - RTOG 91-11, Forestierre et al

- Resectable Stage III/IV larynx ca.
- 3 arm trial-
- NACT *versus* CTRT *versus* RT
- N=547

	Organ preserv	LRC at 2yrs	DMF rate	OS at 5yrs
NACT	75%	61%	91%	55%
RT	70%	56%	84%	54%
CTRT	88%	78%	92%	56%

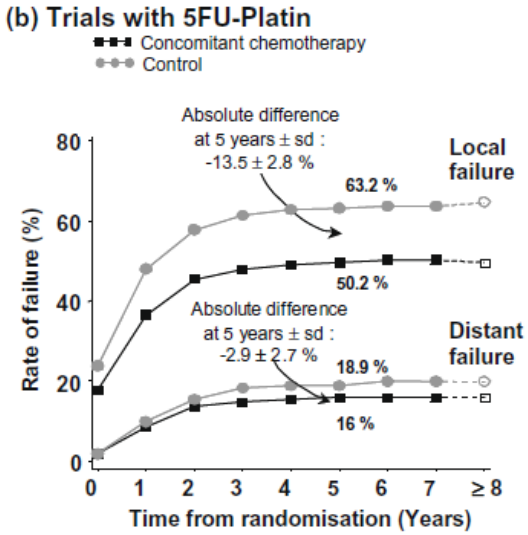
NEJM, 2003

Between 2000 to 2009

Concurrent CT-RT

Rationale

- Independent cell kill
- Radio potentiation
- Distant micro metastasis
- Cost and high toxicity !



8% survival benefit at 5 years

88% Organ preservation rate at 2 years

MACH NC meta analysis and update
RTOG 91-11, 2003

Conclusions of RTOG 91-11

- OP best with CTRT
- Addition of CT decreases distant metastasis rate
- Induction chemotherapy took a back seat

Good CTRT candidates
T2
T3
Low volume T4

Poor CTRT candidates
Significant BOT inv.
Gross Cartilage inv.

2009

Contents lists available at ScienceDirect

Radiotherapy and Oncology

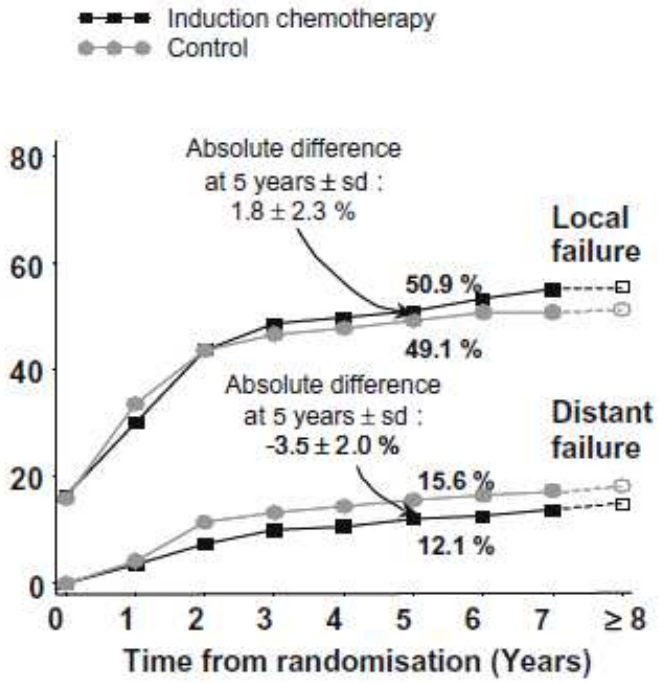
journal homepage: www.thegreenjournal.com

Meta analysis

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon [a,*], Aurélie le Maître [a], Emilie Maillard [a], Jean Bourhis [b], on behalf of the MACH-NC Collaborative Group [1]

[a] Department of Biostatistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France
[b] Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France



Induction CT (platin + FU) – OP and 5% survival benefit

Why NACT → CTRT?

- NACT has pronounced effect on distant spread
- CTRT pronounced effect on LRC
- May complement each other

TPF protocol

- PF benefits but outcome < 50%
- Single agent Taxane activity seen

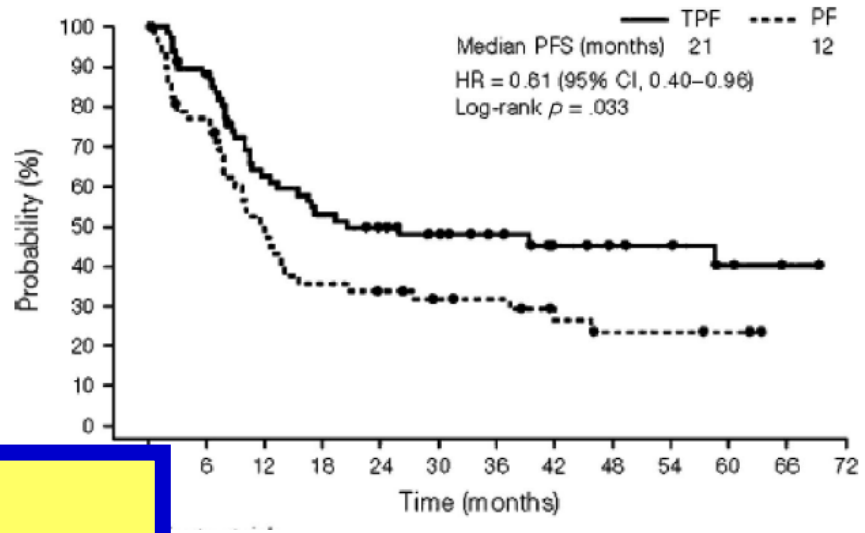
2007

TAX 323 & 324

Table 2. Results of phase III trials comparing OS, progression-free survival (PFS) and organ preservation for TPF and PF in curable patients

Study population	N	Primary end point	Regimen	Significant outcomes
Tax 32[illegible] inoperable [42]	358	PFS	PF/RT versus TPF/RT	TPF better, PFS and OS $P <$ 0.01
TAX 32[illegible] locally advanced [5, 4[illegible]]	501	OS	PF/CRT versus TPF/CRT	TPF better, 5-year PFS and OS $P = 0.01$; LFS $P < 0.03$
GORTEC 2000-01 resectable larynx/hypopharynx [9]	213	Larynx preservation (LP/FLFS)	PF/RT versus TPF/RT	TPF better, LP/FLFS $P < 0.04$

RT, radiotherapy.



Toxic schedule

NEJM, 2007

2011

TAX 324

Unresectable
TPF versus PF

40 versus 21 mo

Unresectable HN
or OP

OP
TPF versus PF

NR versus 42 mo

Holds promise in Organ preservation subset

Posner et al Lancet Oncol 2011;12(2): 153-9

Q – Does Sequential CTRT (TPF → CTRT) offer advantage over concurrent CTRT?

2013

Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial

Robert Haddad, Anne O'Neill, Guilherme Rabinowits, Roy Tishler, Fadlo Khuri, Douglas Adkins, Joseph Clark, Nicholas Sarlis, Jochen Lorch, Jonathan J Beitler, Sewanti Limaye, Sarah Riley, Marshall Posner

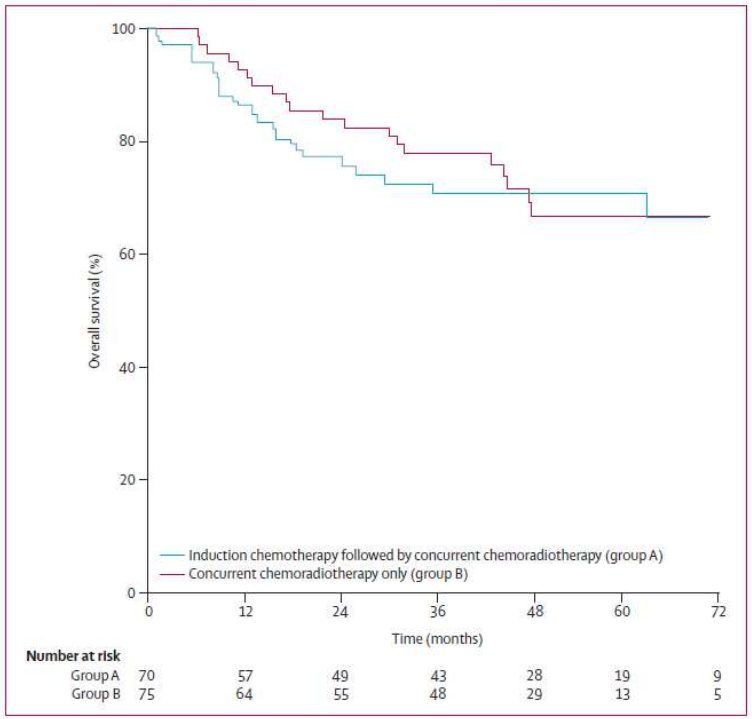


Figure 2: Kaplan-Meier estimates of overall survival

N=145; Median follow up -49 months

Poor accrual

Similar survival

Organ preservation not discussed

Conc CTRT is as good!

Haddad et al Lancet Oncol, 2013, 14(3):257-264

Which strategy to choose between – RT or NACT or CTRT?

-Stage

- Age

- Performance status

-Co-morbidities

-Tracheostomy

Nutritional support required before, during and after radiation treatment.

VOLUME 31 · NUMBER 7 · MARCH 1 2013

JOURNAL OF CLINICAL ONCOLOGY

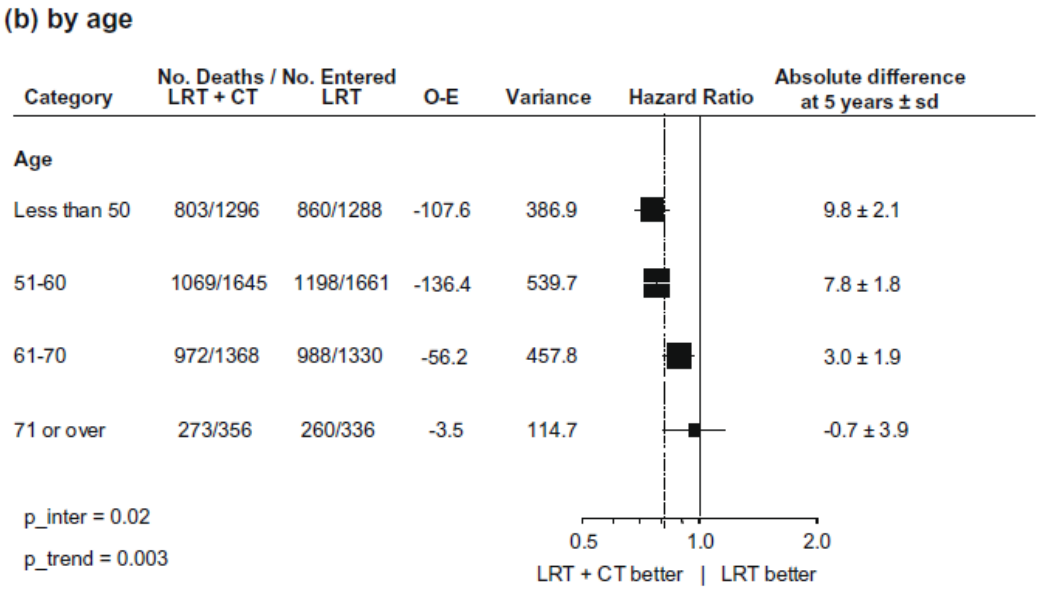
E D I T O R I A L

Competing Roads to Larynx Preservation

Everett E. Vokes, *University of Chicago Medical Center, Chicago, IL*

See accompanying articles on pages 845 and 853

No chemotherapy in elderly



Physiology

1.	Fat replaces muscle	Fat soluble drugs overstay in the body
2	Liver	↓ liver volume & blood flow
3	Kidney	Decline in renal function
4	Bone marrow	↓ marrow reserve → myelosuppression
5	GI tract	Change in gastric motility and absorbability; Prone to diarrhoea and dehydration

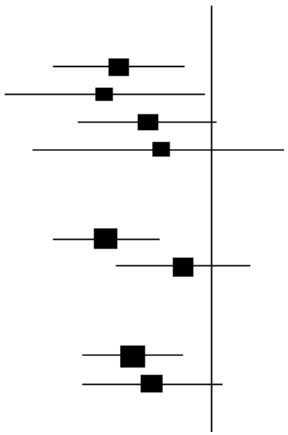
Altered fractionation for OP

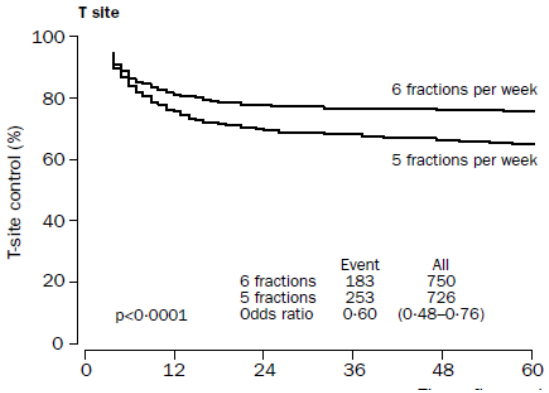
Articles

Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial

Jens Overgaard, Hanne Sand Hansen, Lena Specht, Marie Overgaard, Cai Grau, Elo Andersen, Jens Bentzen, Lars Bastholt, Olfred Hansen, Jørgen Johansen, Lisbeth Andersen, Jan F Evensen, on behalf of the Danish Head and Neck Cancer Study Group

	Fractions per week		Odds ratio (95% CI)
	Five	Six	
Tumour site			
Glottic	92/341	63/349	0·60 (0·42–0·86)
Supraglottic	48/101	39/117	0·55 (0·32–0·95)
Pharynx	109/222	86/213	0·70 (0·48–1·03)
Oral cavity	40/62	41/71	0·75 (0·38–1·51)
T classification			
T1–2	154/494	103/512	0·56 (0·42–0·74)
T3–4	132/232	126/238	0.85 (0·59–1·23)
Nodal status			
Node negative	164/504	129/542	0·65 (0·50–0·85)
Node positive	125/222	100/208	0·72 (0·49–1·05)



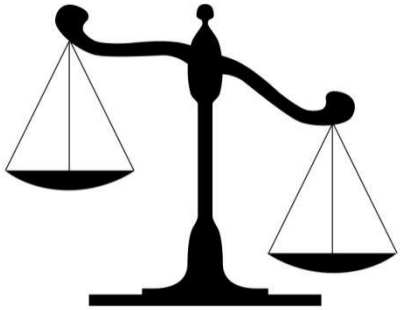


Organ preservation trials – realistic issues

Organ preservation ≠ Organ function

Multi disciplinary team

Patient Selection

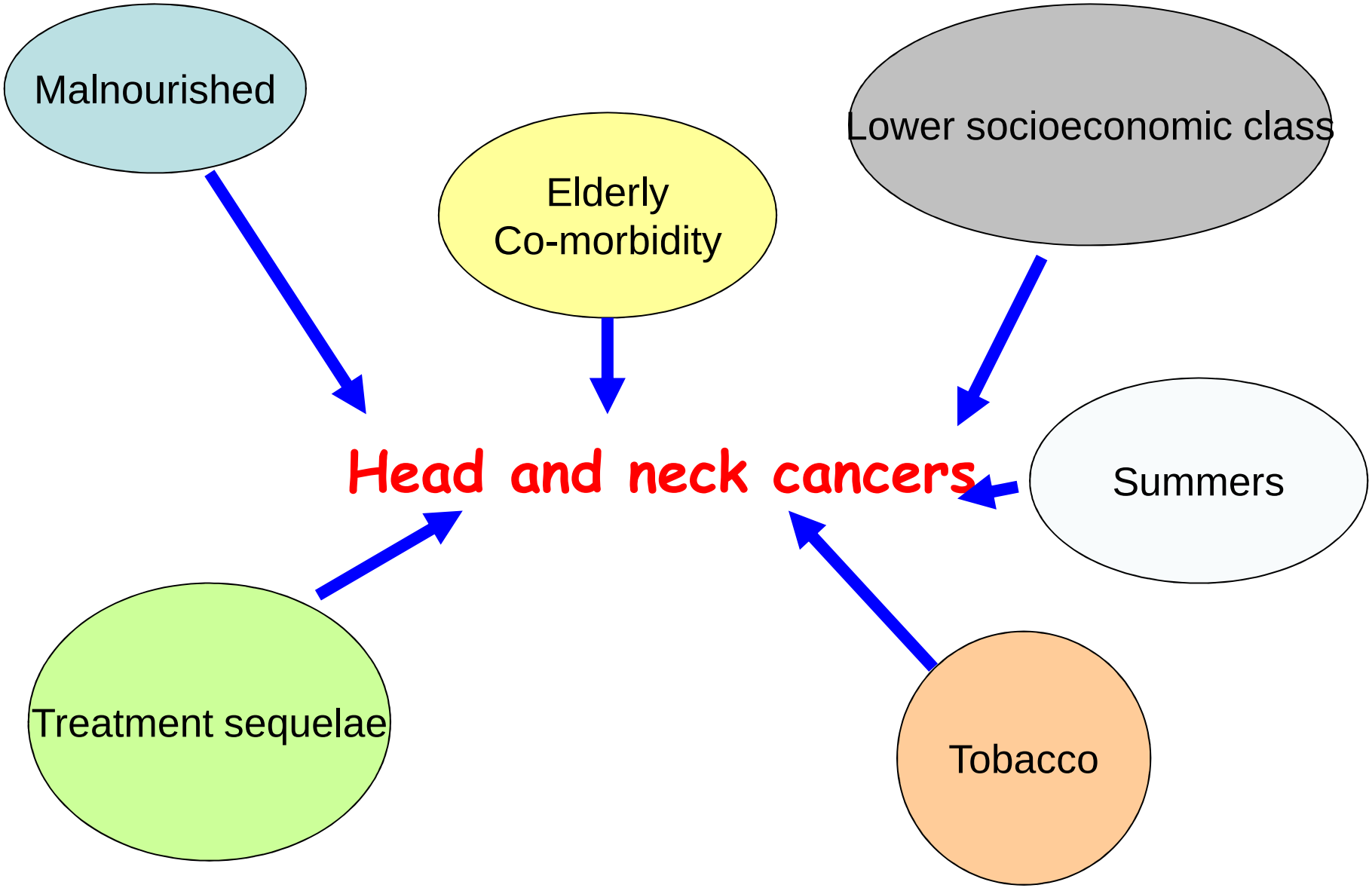


Functions that impact QOL

- Deglutition
- Aspiration
- Speech
- Breathing

Why did patients continue to loose wt, complain of dysphagia and develop pneumonia?

- Late toxicity observed in form of cervical and pharyngeal fibrosis and laryngeal dysfunction
  - swallowing dysfunction
  - aspiration
- The range of dysfunction
  - pharyngeal retention of food: 90%
  - silent aspiration : 40%
- Aspiration per se is often unrecognized: dysphagia is the commoner presentation
- Patients subconsciously reduce intake and hence continue to loose weight!


Malnourished
Elderly
Co-morbidity
Lower socioeconomic class
Head and neck cancers
Summers
Treatment sequelae
Tobacco

Mortality figures

	Resp	↓ TLC	Tox Deaths	3 yr OS
PF	54%	53%	4%	24%
TPF	68%	77%	8%	37%

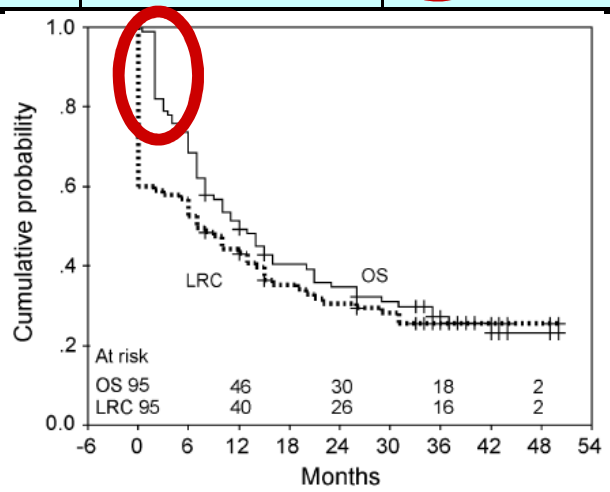


Fig. 1. Loco-regional control (LRC) and overall survival (OS).

If not carefully selected, patient may die of intense treatment.

Kumar et al Radiother Oncol, 2005

Reasons for toxicity related deaths

- Aspiration
- Septicemia
- Dyselectrolytemia & dehydration

	Induction chemotherapy followed by concurrent chemoradiotherapy (n=70)	Concurrent chemoradiotherapy only (n=75)
Mucositis		
Grade 1–2	29 (41%)	44 (59%)
Grade 3–4	33 (47%)	12 (16%)
Febrile neutropenia		
Grade 3–4	16 (23%)	1 (1%)

As you intensify treatment toxicity increases

Haddad et al Lancet Oncol, 2013, 14(3):257-264

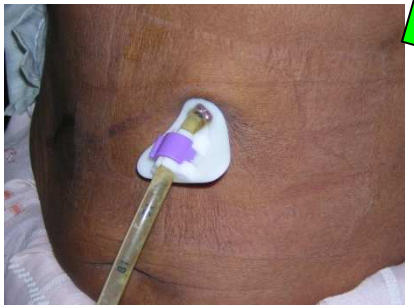
Long term problems following radiotherapy

Dryness of mouth

Speech
Taste
Dental caries
Swallowing

Swallowing difficulties

Malnutrition
Aspiration
Pneumonia
Failure to thrive
Death



20% aspiration rate in hypopharyngeal cancers

Lal P et al, South Asian J Cancer. 2014 Oct-Dec; 3(4): 209–212.

Relevance of toxicity with OP strategies

- Enhanced radiosensitization - synergistic effect
- Increased apoptosis
- Excessive fibrosis and xerostomia
- Speech and swallowing dysfunction

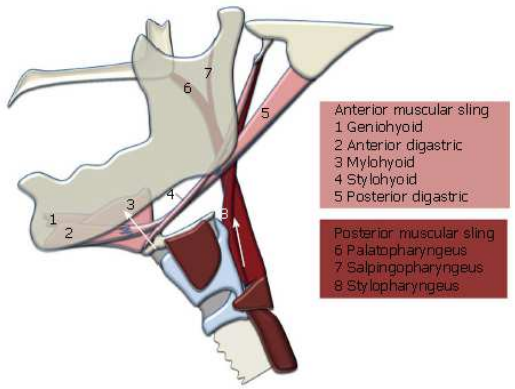
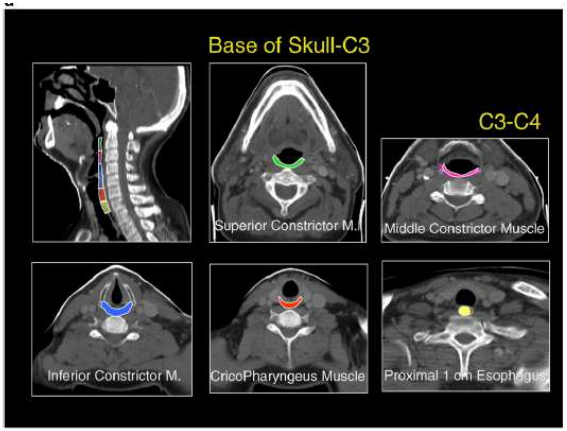


Figure 1 Two-sling mechanism for hyolaryngeal elevation in swallowing.



VOLUME 31 · NUMBER 7 · MARCH 1 2013

JOURNAL OF CLINICAL ONCOLOGY

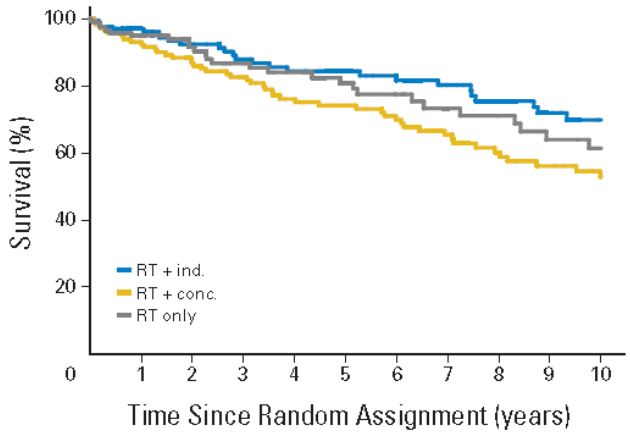
ORIGINAL REPORT

Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients With Locally Advanced Larynx Cancer

Arlene A. Forastiere, Qiang Zhang, Randal S. Weber, Moshe H. Maor, Helmuth Goepfert, Thomas F. Pajak, William Morrison, Bonnie Glisson, Andy Trotti, John A. Ridge, Wade Thorstad, Henry Wagner, John F. Ensley, and Jay S. Cooper

RT was not better than treatment with RT alone (HR, 1.26; 95% CI, 0.88 to 1.82; $P = .35$). No difference in late effects was detected, but deaths not attributed to larynx cancer or treatment were higher with concomitant chemotherapy (30.8% *v* 20.8% with induction chemotherapy and 16.9% with RT alone).

B



No. at risk											
RT + ind.	174	117	88	76	70	66	60	52	46	38	30
RT + conc.	174	124	107	91	79	73	64	54	45	38	30
RT only	172	102	78	66	59	49	42	34	31	26	24

VOLUME 26 · NUMBER 22 · AUGUST 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of Late Treatment-Related Toxicity on Quality of Life Among Patients With Head and Neck Cancer Treated With Radiotherapy

Johannes A. Langendijk, Patricia Doornaert, Irma M. Verdonck-de Leeuw, Charles R. Leemans, Neil K. Aaronson, and Ben J. Slotman

Conclusion

Late radiation-induced toxicity, particularly $RTOG_{swallowing}$ and $RTOG_{xerostomia}$, has a significant impact on the more general dimensions of HRQoL. These findings suggest that the development of new radiation-induced delivery techniques should not only focus on reduction of the dose to the salivary glands, but also on anatomic structures that are involved in swallowing.

Factors affecting

Original Articles

Risk Factors for Severe Dysphagia after Concurrent Chemoradiotherapy for Head and Neck Cancers

Keiichiro Koiwai, Naoto Shikama, Shigeru Sasaki, Atsunori Shinoda and Masumi Kadoya

Department of Radiology, Shinshu University School of Medicine, Matsumoto, Nagano, Japan

Received January 20, 2009; accepted March 15, 2009; published online April 20, 2009

Conclusions: Larger radiation portal field was associated with severe dysphagia induced by chemoradiotherapy.

Jpn J Clin Oncol, 2009

Site, stage & treatment modality? do not impact the course of dysphagia

Nguyen NP, Anticancer research, 2009; 29: 3299-3304

What are the solutions?

Proper selection of patients & treatment strategy

Mini Symposium: Head and Neck

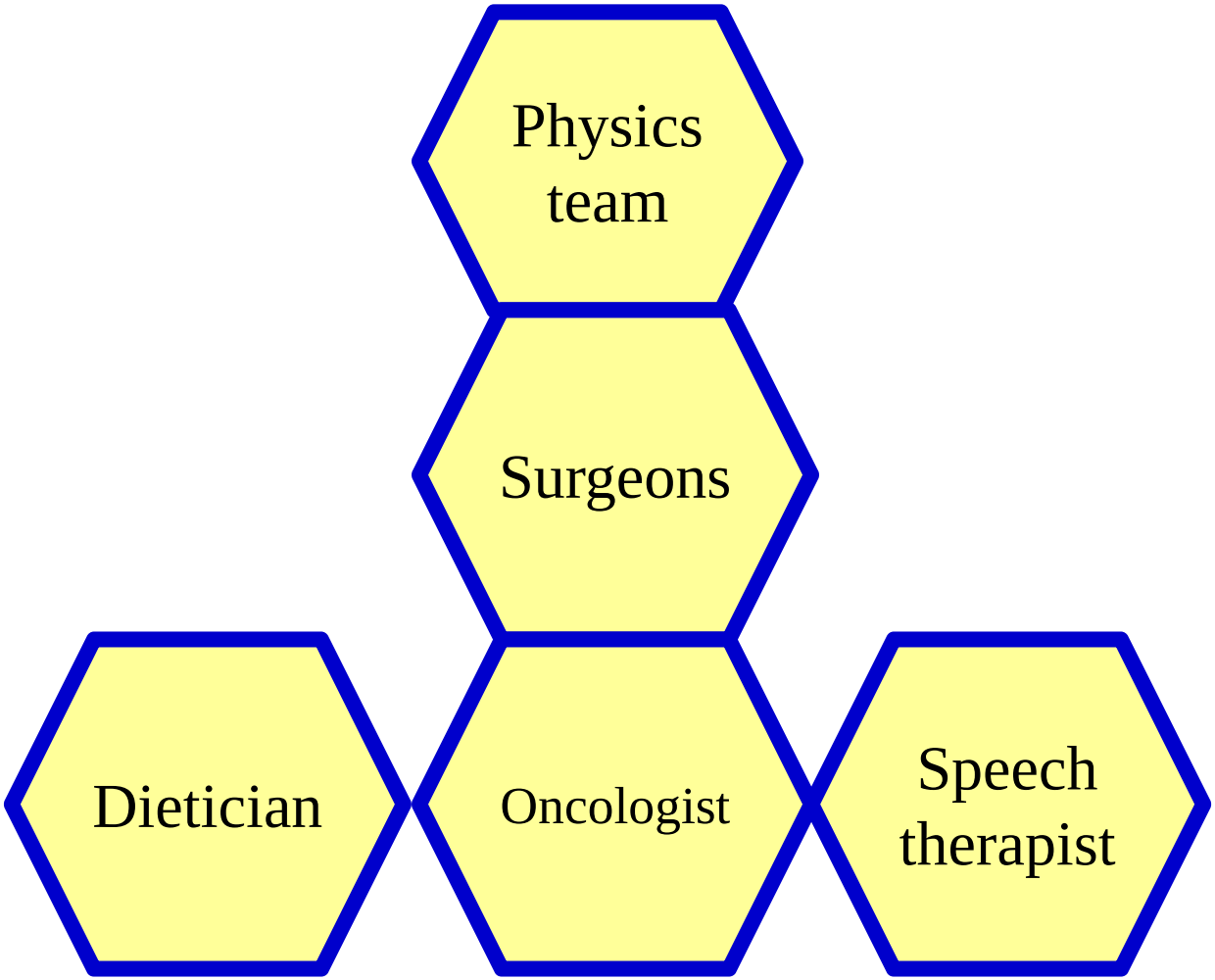
Feasibility of organ-preservation strategies in head and neck cancer in developing countries

Trivedi NP, Kekatpure VD, Trivedi NN, Kuriakose MA, Shetkar G, Manjula BV
Department of Head and Neck Oncology, Mazumdar-Shaw Cancer Center, Narayana Hrudayalaya, Bangalore, India

- Results from developed world cannot be copied in the developing country
- An Indian survey of 100 head and neck physicians
- 40% cobalt unit
- **1/3 MDT and 1/3 adequate set up**
- **>2/3 need dose modification**

Trivedi, IJC, 2012,vol 49; 15-20

Need for a multidisciplinary team



Role of exercise –before & after

JAMA Otolaryngol Head Neck Surg. 2013 November ; 139(11): 1127–1134. doi:10.1001/jamaoto.2013.4715.

USE IT OR LOSE IT: EAT AND EXERCISE DURING RADIOTHERAPY OR CHEMORADIOTHERAPY FOR PHARYNGEAL CANCERS

Katherine A. Hutcheson, PhD, Mihir K. Bhayani, MD, Beth M. Beadle, MD, PhD, Kathryn A. Gold, MD, Eileen H. Shinn, PhD, Stephen Y. Lai, MD, PhD*, and Jan Lewin, PhD*

Retèl *et al. BMC Cancer* 2011, **11**:475
http://www.biomedcentral.com/1471 2407/11/475

BMC Cancer

RESEARCH ARTICLE Open Access

A cost-effectiveness analysis of a preventive exercise program for patients with advanced head and neck cancer treated with concomitant chemo-radiotherapy

Newer techniques -IMRT

VOLUME 28 · NUMBER 16 · JUNE 1 2010

JOURNAL OF CLINICAL ONCOLOGY

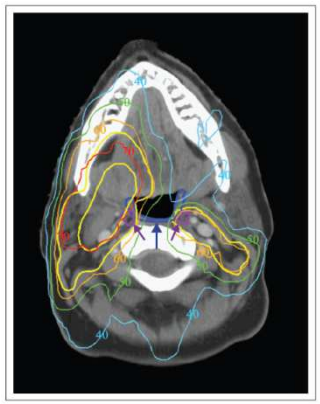
ORIGINAL REPORT

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

Conclusion

Chemoradiotherapy with IMRT aiming to reduce dysphagia can be performed safely for OPC and has high locoregional tumor control rates. On average, long-term patient-reported, observer-rated, and objective measures of swallowing were only slightly worse than pretherapy measures, representing potential improvement compared with previous studies.



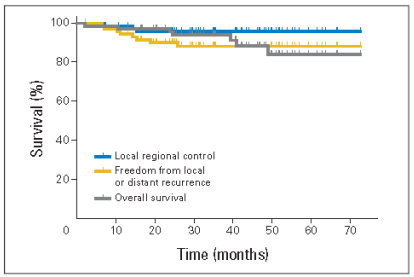
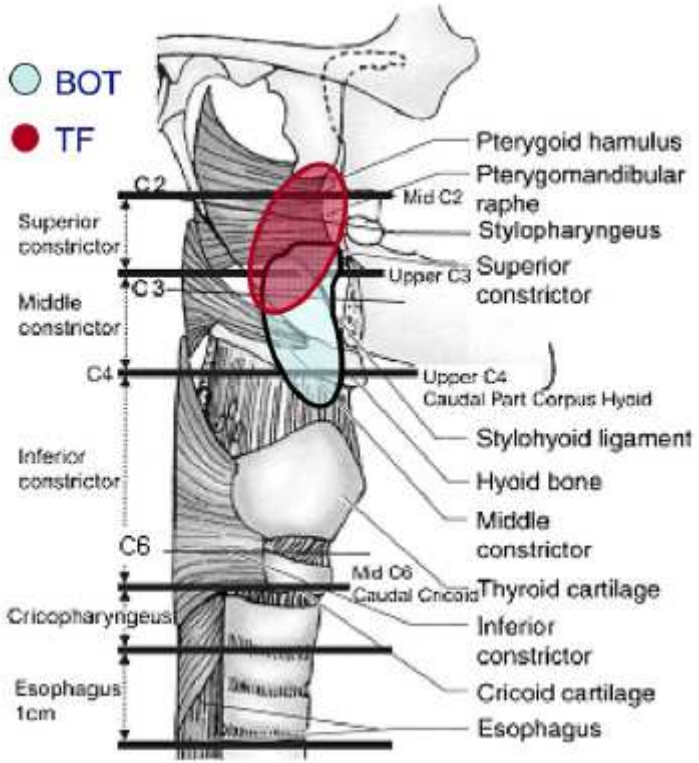


Fig 2. Kaplan-Meier estimates of overall survival, freedom from recurrence, and locoregional control.

Summary

Successful treatment of dysphagia requires interdisciplinary collaboration, accurate diagnostic workup, effective therapeutic strategies, and consideration of unique patient characteristics.

Thank you


BOT
TF
C2
Mid C2
Superior constrictor
Upper C3
C3
Middle constrictor
C4
Upper C4
Caudal Part Corpus Hyoid
Inferior constrictor
C6
Mid C6
Caudal Cricoid
Cricopharyngeus
Esophagus 1cm
Pterygoid hamulus
Pterygomandibular raphe
Stylopharyngeus
Superior constrictor
Stylohyoid ligament
Hyoid bone
Middle constrictor
Thyroid cartilage
Inferior constrictor
Cricoid cartilage
Esophagus