EHNS-ESTRO multidisciplinary teaching course on H&N oncology Florence (Italy) June 26-29, 2016

MULTIDISCIPLINARY MANAGEMENT OF HEAD AND NECK ONCOLOGY

26 - 29 June 2016
Florence, Italy

MULTIMODAL CANCER TREATMENT
WHO?

TARGET GROUP

This multidisciplinary course organised as a collaboration between ESTRO and EHNS (European Head and neck Society) is meant for specialists and trainees with interest and expertise in head and neck surgery (head and neck surgeons, oto-rhino-laryngologists, maxillo-facial surgeons, reconstructive surgeons, etc.), radiation oncologists, medical oncologists and other medical specialties involved in the treatment of patients with head and neck cancer.

BACKGROUND

Over the last decade tremendous progress has been made in the biological understanding and management of patients with head and neck cancer. Significant progress has been made in tumour profiling and in the identification of relevant clinical characteristics, which rapidly led to the elaboration of tailored treatments. Functional imaging has emerged as a complementary modality to anatomic imaging methods for better staging, treatment response evaluation and optimal treatment targeting. Surgery has significantly improved, in particular with better reconstruction techniques reducing the limits of operability. Randomised studies have demonstrated the increasing role of combined modality approaches with chemotherapy and biological targeted therapies. New radiation techniques, expected to impact on survival and quality of life of head and neck patients, have taken off and are being validated.

COURSE AIM

The course aims to be interactive through integration of multidisciplinary lectures and more focused workshops. The faculty includes renowned European experts involved in the multidisciplinary treatment of head and neck cancer.

LEARNING OUTCOMES

By the end of this course participants should be able to:

- Understand the evolving concepts of head and neck epidemiology and tumour biology, with special focus on squamous cell histotype. Rare histotypes will be also included.
- Interpret complex head and neck imaging for the purpose of treatment decision making and therapy
- Make judgements regarding multidisciplinary reasoning and management of tumours in the light of alternative and sometime competing treatment options including surgery and the role of systemic and targeted therapies
- Make judgments about the availability of evidences for treatment recommendations
- Understand the challenges of supportive care
- Understand the principles and practice of modern radiotherapy.

COURSE CONTENT

- Anatomy (clinical and radiologic aspects) incidence, pathology, risk factors (including HPV) of head and neck tumours
- Clinical work-up for oral cavity and pharyngolaryngeal tumours, staging and follow up
- "Organ preservation" approach
- Rationale for unconventional radiotherapy fractionation, hypoxic sensitisers, concomitant chemo, EGFR inhibitors and new targeted agents
- Management of oral cavity tumours: medical oncology, surgery and radiotherapy (including brachytherapy)
- Management of nasopharyngeal carcinoma
- Management of oropharyngeal tumours: medical oncology, surgery and radiotherapy (including brachytherapy)
- Management of hypopharyngeal and laryngeal tumours: surgery, radiotherapy and medical oncology chemotherapy approach
- Management of nasal cavity and para-nasal sinus tumours: surgery, radiotherapy and medical oncology chemotherapy approach
- Management of the neck nodes
- Concepts behind selection and delineation of target volumes in radiotherapy
- Morbidity (acute and late) of treatment
- Supportive care during and after treatment
- Metastatic disease
- Management of recurrent tumours
- Second primary tumours.

PREREQUISITES

Before commencing this course, participants should have a medical degree with strong interest in head and neck tumour management from the radiation oncology, medical oncology or head and neck surgery point of view.

FACULTY

Course directors

Vincent Grégoire, *Radiation Oncologist, Cliniques Universitaires St-Luc, Brussels (BE)*
René Leemans, *Head and Neck Surgeon, VU University Medical Centre, Amsterdam (NL)*
Lisa Licitra, *Medical Oncologist, Istituto Tumori, Milan (IT)*

Teachers

Jesper Grau Eriksen, *Clinical Oncologist, Odense University Hospital, Odense (DK)*
Cai Grau, *Radiation Oncologist, Aarhus University Hospital, Aarhus (DK)*
Jean-Pascal Machiels, *Medical Oncologist, Cliniques Universitaires St-Luc, Brussels (BE)*
Piero Nicolai, *Oto-Rhino-Laryngologist and Head and Neck Surgeon, University of Brescia, Brescia (IT)*
Frank A. Pameijer, *Radiologist, University Medical Center Utrecht, Utrecht (NL)*

Local organisers

Lorenzo Livi, *Radiation Oncologist, University of Florence, Florence*
Pierluigi Bonomo, *Radiation Oncologist, University of Florence, Florence*

TEACHING METHODS

- 20 lecture hours
- 5 case discussion hours
- Delineation exercises.

METHODS OF ASSESSMENT

- MCQ
- Delineation exercise/s
- Evaluation form.

KEY WORDS

Multidisciplinary head and neck oncology, evidence based medicine.

FURTHER READING

Please consult the ESTRO website page of this course for further information.

ACCREDITATION

Application for CME recognition will be submitted to the European Accreditation Council for Continuing Medical Education (EACCME), an institution of the European Union of Medical Specialists (UEMS). EACCME credits are recognised by the American Medical Association towards the Physician's Recognition Award (PRA). Information on the status of the applications can be obtained from the ESTRO office.

Application for ESMO-MORA points is submitted to ESMO the European Society for Medical Oncology representing medical oncologists. Information on the status of the applications can be obtained from the ESTRO office.

EHNS www.ehns.org

This course is using the FALCON platform (Fellowship in Anatomic deLineation and CONtouring) for the contouring exercises

FALCON

Faculty

- J. Eriksen, Radiation Oncologist, Odense, Denmark
- C. Grau, Radiation Oncologist, Aarhus, Denmark
- V. Grégoire, Radiation Oncologist, Brussels, Belgium
- R. Leemans, H&N surgeons, Amsterdam, The Netherlands
- L. Licitra, Medical Oncologist, Milan, Italy
- J-P. Machiels, Medical Oncologist, Brussels, Belgium
- P. Nicolai, H&N surgeon, Brescia, Italy
- F. Pameijer, Radiology, Utrecht, The Netherlands

ESTRO Staff

- G. Axelsson, Brussels, Belgium

Local Organiser

- Prof. Dr. Lorenzo Livi, Radiation Oncologist, University of Florence
- Prof. Dr. Pierluigi Bonomo, Radiation Oncologist, University of Florence

House keeping announcement

- MCQ
- Evaluation
- …

Anatomy of the Head and Neck area

Clinical & radiological aspects

Frank Pameijer, MD, PhD

- Departments of Radiology and Radiation Oncology
- University Medical Center, Utrecht
- The Netherlands

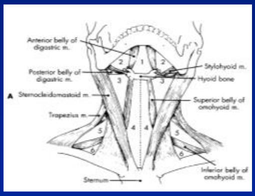
No disclosures

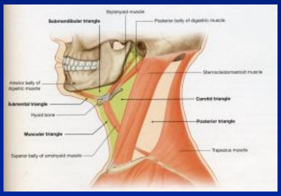
ESTRO School

Contents

- Fascial anatomy
- Spatial anatomy

Traditional Anatomy



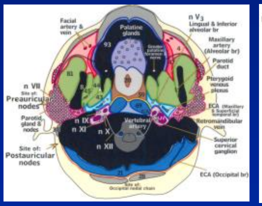


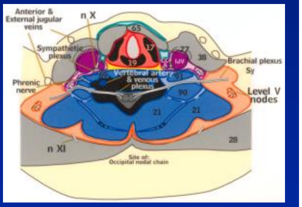
6 triangles divided by muscles

Usefull for surgeons

Fascial Anatomy

Spaces defined by layers of the Cervical Fascia





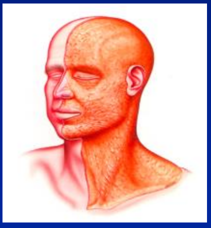
Usefull for imaging specialists

Fascial layers

- Superficial cervical fascia
- Deep cervical fascia

Superficial Cervical Fascia

- Loose connective tissue
- Platysma muscle
- Muscles of facial expression



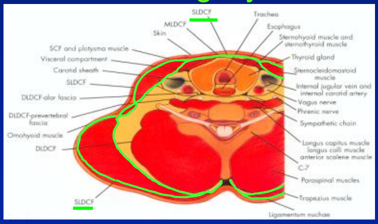
Deep Cervical fascia (DCF)

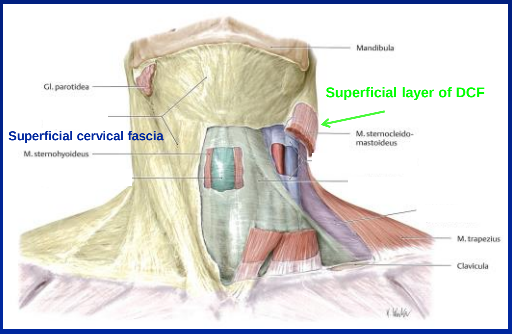
Three layers:

- Superficial layer (SLDCF)
- Middle layer (MLDCF)
- Deep layer (DLDCF)

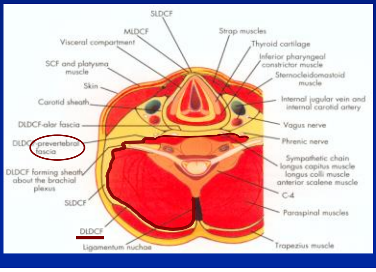
Superficial layer of DCF (SLDCF)

‘investing layer’



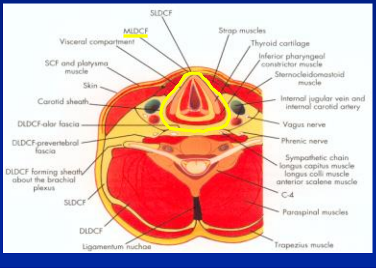


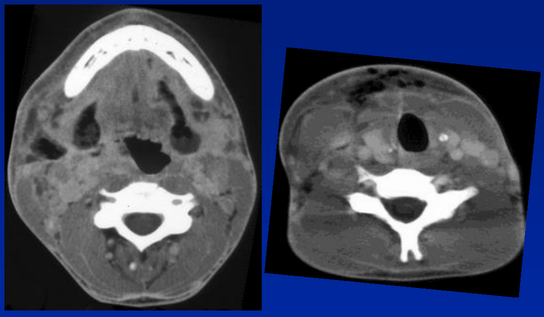
Deep layer of DCF (DLDCF)



Middle layer of DCF (MLDCF)

‘visceral layer’





Necrotizing fasciitis

DCF layers
Relevance

- 19th century; 3 layers of DCF described by anatomists
- 20th century; rediscovered by surgeons dissecting abscess pockets
  - Pathology tends to stay ´compartmental´

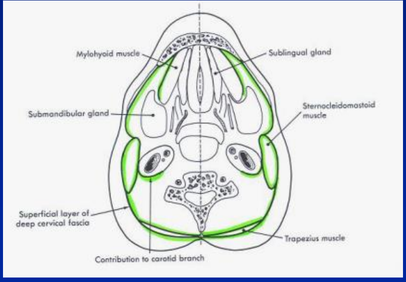
Contents

- Fascial anatomy
- Spatial anatomy

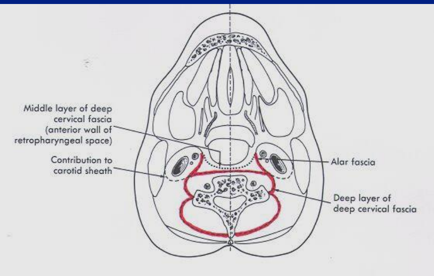
Anatomy of the head and neck
Spatial approach

- Deep Cervical Fascia (DCF): 3 layers
- These layers define ´spaces´

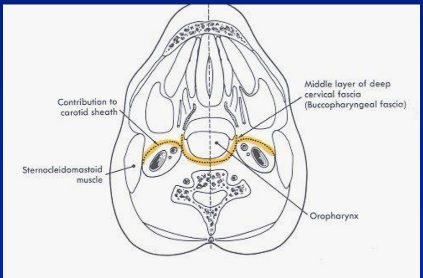
Superficial layer of DCF



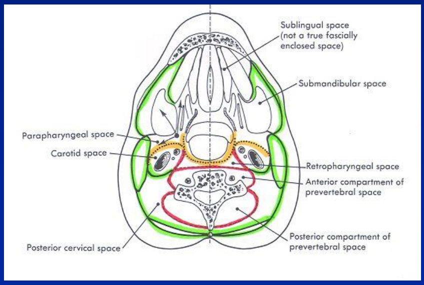
Deep layer of DCF



Middle layer of DCF



Three layers of DCF



Anatomy of the head and neck
Spatial approach

- Deep Cervical Fascia 3 layers
- These layers define ´spaces´
- Spaces are oriented in the axial plane

Anatomy of the head and neck
Spatial approach

- Deep Cervical Fascia 3 layers
- These layers define ´spaces´
- Spaces are oriented in the axial plane
- Useful for analyzing axial cross-sectional images (CT / MRI)

Spaces defined by DCF

- Parapharyngeal = Prestyloid PPS *
- Pharyngeal mucosal
- Masticator
- Parotid
- Carotid = Poststyloid PPS *
- Retropharyngeal / Danger
- Perivertebral

* Mukherji et al. Rad Clin of N Am 1998; 36; 761-780

Clinical suspicion of head & neck mass
What is expected of the radiologist?

- Correct identification of space of origin
  - normal spatial anatomy
  - radiographic pattern recognition
  - integration of clinical information
- Limited **space-specific** DD

Clinical suspicion of head & neck mass
What is expected of the radiologist?

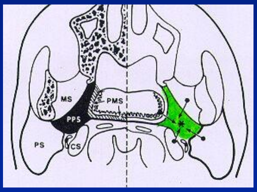
- Correct identification of space of origin
  - normal spatial anatomy
  - radiographic pattern recognition
  - integration of clinical information
- Limited space-specific DD
- Bottom-line: If you know the spaces, you don’t have to know the 3 layers of DCF (in detail)

Spaces defined by DCF

Parapharyngeal	PPS
Parotid	PS
Pharyngeal mucosal	PMS
Masticator	MS
Carotid	CS
Retropharyngeal / Danger	RPS / DS
Perivertebral	PVS

Parapharyngeal space (PPS)

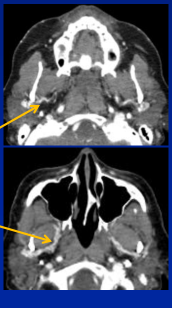
Central location



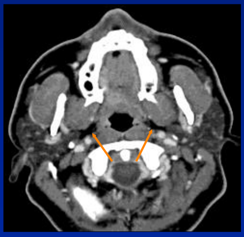
Parapharyngeal space (PPS)

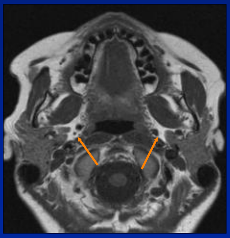
Contents

- **FAT**
  - easy to see on routine CT / MRI
- Vessels
  - internal maxillary / ascending pharyngeal art.
  - pharyngeal venous plexus



PPS

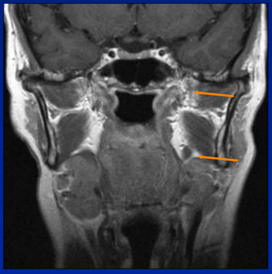


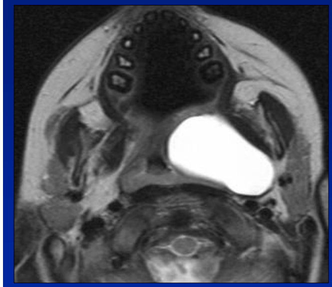


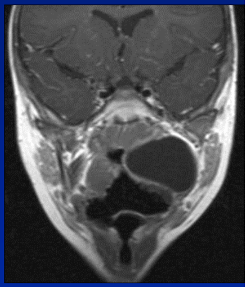
Fat easily recognized on CT / MR

PPS

- From skull base → submandibular gland
- Allows smooth motion during mastication
- Primary lesions PPS rare
  - Salivary gland remnants
  - Branchiogenic anomaly



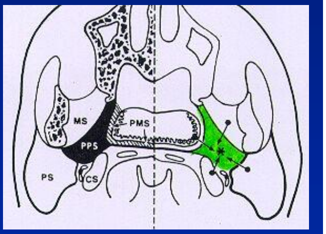




Branchial arch cyst

PPS: Strategic location

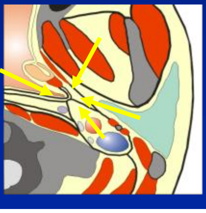
Lateral PS
Medial PMS
Anterior MS
Posterior CS



Head and neck lesions

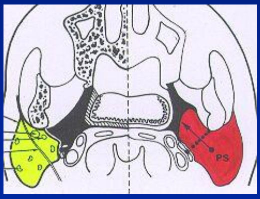
Rare: arise within PPS

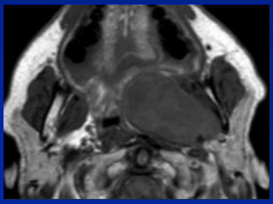
Frequent: invade or displace PPS



- Parotid space
- Pharyngeal mucosal space
- Masticator Space
- Carotid Space

Parotid space **Mass**

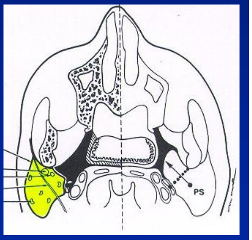




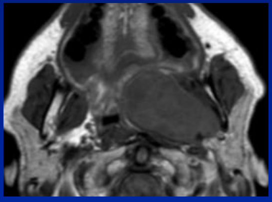
Parotid space (PS)

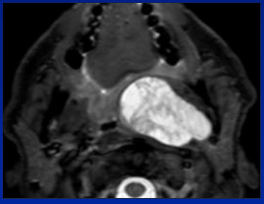
Contents

- Parotid gland
  - superficial / deep lobe
  - intra / peri-parotid lymph nodes
- Facial nerve (VII)
- Vessels
  - retromandibular vein (lateral)
  - external carotid artery (medial)



PS **Mass**

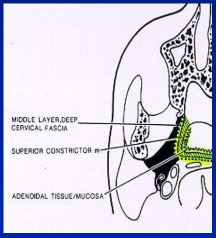




Pleomorphic adenoma

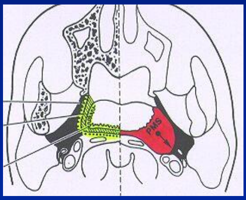
Pharyngeal mucosal space (PMS)

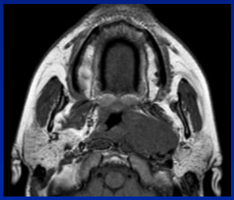
Contents



- **Mucosa** (SCCa !)
  - Lymphoid tissue
  - Minor salivary glands
- Pharyngobasilar fascia

PMS Mass

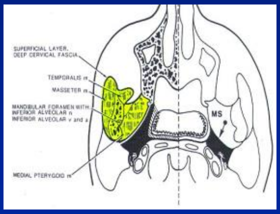




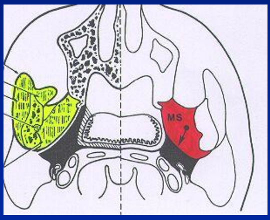
Nasopharyngeal carcinoma

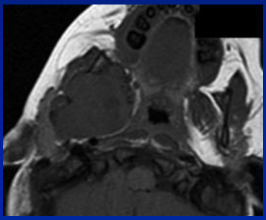
Masticator space (MS)

- Muscles of mastication
  - med. / lat. pterygoid, masseter, temporalis
- Nerves
  - V3 motor, V3 sensory (inf. alveolar nerve)
- Mandible
  - Ramus / posterior body



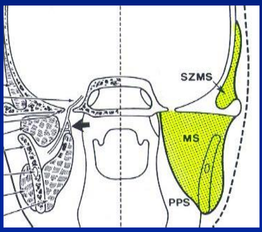
MS Mass





Juvenile fibromatosis

MS
Relationship to foramen ovale

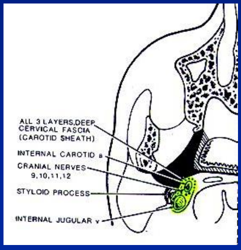


Perineural tumor spread along V3

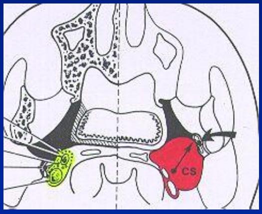
Carotid space (CS)
"Poststyloid Parapharyngeal space"

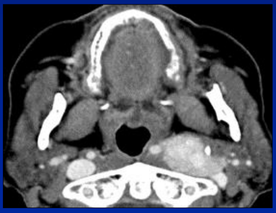
Contents

- Vessels
  - (I)CA, IJV
- Nerves
  - cranial nerves: IX, X, XI, XII
  - sympathetic plexus
- Lymph nodes
  - deep cervical chain (jugulodigastric)



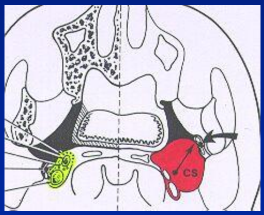
CS Mass

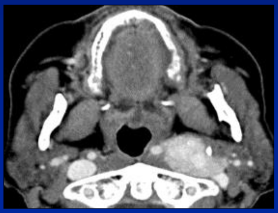




DD: neurogenic tumor / paraganglioma

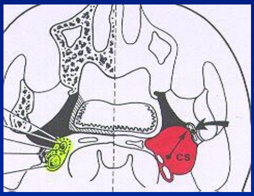
CS **Mass**

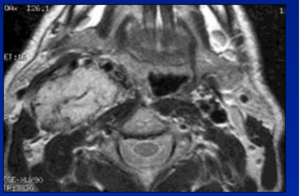




DD: neurogenic tumor / **paraganglioma**

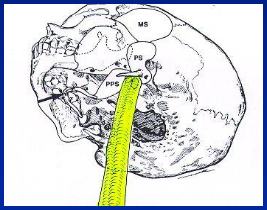
CS **Mass**

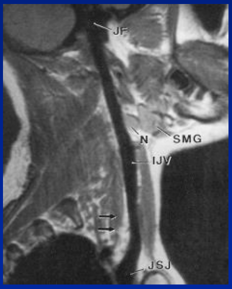




paraganglioma

CS: "elevator space"





Spaces defined by DCF

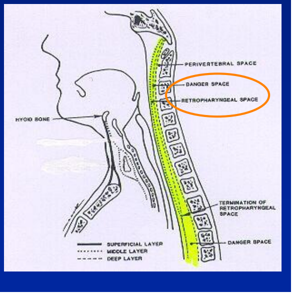
- **Parapharyngeal** **PPS**
- **Parotid** **PS**
- **Pharyngeal mucosal** **PMS**
- **Masticator** **MS**
- **Carotid** **CS**
- Retropharyngeal / Danger RPS / DS
- Perivertebral PVS

Retropharyngeal space (RPS)

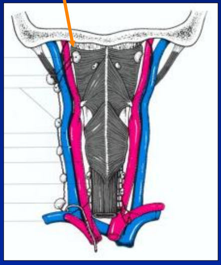
Contents

- Fat
- Lymph nodes
  - lateral retropharyngeal (Rouvière)

CT/MR cannot differentiate from "danger space"

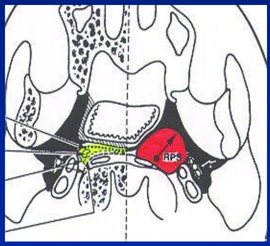


Retropharyngeal nodes



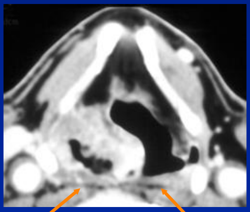
C1 – C3 level

RPS Mass

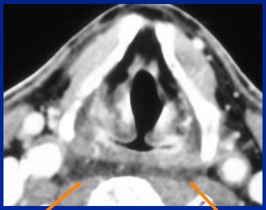


Lower RPS: virtual space

Pre-RT

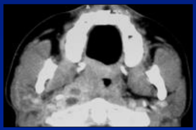


3 months post-RT

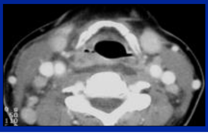


Post-RT edema

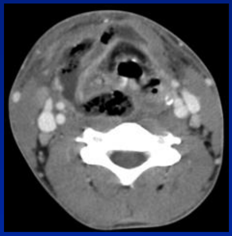
Retropharyngeal space / Danger space
‘Elevator space’

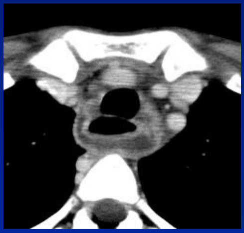


Tonsillitis + RP nodes



Retropharyngeal space / Danger space



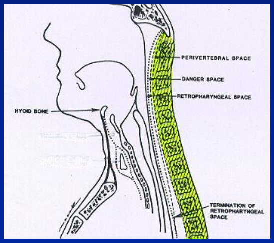


Neck abcess extending into mediastinum

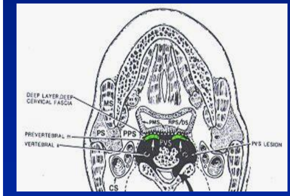
Perivertebral space (PVS)
Contents

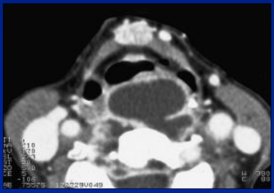
PVS: Prevertebral /
Paraspinal portion

- Muscles
  - scalene, prevertebral / paraspinal
- Nerves
  - brachial plexus, phrenic
- Vertebral artery / vein
- Vertebral body

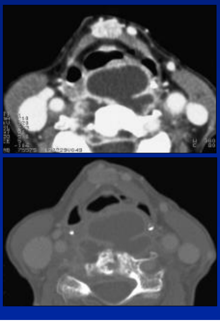


PVS **Mass**
prevertebral portion





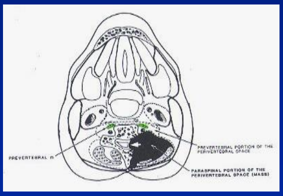
PVS Mass: Prevertebral portion

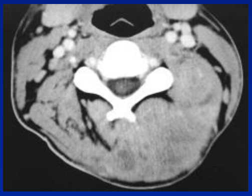


NHL C5 with prevertebral abcess extending in retropharyngeal space

PVS **Mass**

paraspinal portion

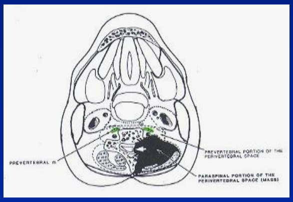




Sarcoma

PVS **Mass**

paraspinal portion

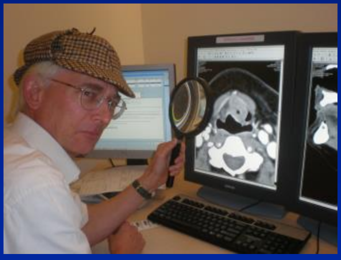


Lipoma

Contents

- Fascial anatomy
- Spatial anatomy

Head & Neck Anatomy is **Great**



Anatomy of the Head and Neck area

Clinical & radiological aspects

Frank Pameijer, MD, PhD

- Departments of Radiology and Radiation Oncology
- University Medical Center, Utrecht
- The Netherlands

No disclosures

ESTRO School

INCIDENCE, PATHOLOGY, RISK FACTORS (INCLUDING BUT NOT ONLY HPV) OF SCC

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

L. Licitra, MD

ESTRO School

INCIDENCE SCC

Surveillance of Rare Cancers in Europe

RARECARE

www.rarecare.eu

RARE CANCERS EUROPE

www.rarecancers.eu

EUROPEAN JOURNAL OF CANCER 48 (2012) 783–796

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ELSEVIER

EJC

Rare cancers of the head and neck area in Europe

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INCIDENCE SCC

RARECARE

Surveillance of Rare Cancers in Europe

The following list presents the number of cases reported by European Cancer Registries during the period 1995-2002 and the corresponding incidence rates. Both figures are derived from the data of 70 population-based cancer registries adhering to the RARECARE project

Rate: Incidence considered as number of cases / 100,000 persons / year

INCIDENCE SCC

Surveillance of Rare Cancers in Europe

RARECARE

Tumour	Rate	Patients
Epithelial Tumours of Oral Cavity and Lip	**4,79**	**38.537**
Squamous cell carcinoma with variants of oral cavity	3,28	26.422
Squamous cell carcinoma with variants of lip	1,22	9.854
Epithelial Tumours of Oropharynx	**2,75**	**22.104**
Squamous cell carcinoma with variants of oropharynx	2,58	20.795

Rate: Incidence considered as number of cases / 100,000 persons / year

INCIDENCE SCC

Surveillance of Rare Cancers in Europe

RARECARE

Tumour	Rate	Patients
Epithelial Tumours of Hypopharynx and Larynx	**6,26**	**50.360**
Squamous cell carcinoma with variants of **hypopharynx**	1,19	9.550
Squamous cell carcinoma with variants of **larynx**	4,64	37.330

Rate: Incidence considered as number of cases / 100,000 persons / year

INCIDENCE SCC

Surveillance of Rare Cancers in Europe

RARECARE

Tumour	Rate	Patients
Epithelial Tumours of Nasopharynx	**0,44**	**3.566**
Squamous cell carcinoma with variants of nasopharynx	0,33	2.630
Papillary adenocarcinoma of nasopharynx	<0.01	7
Epithelial Tumours of Nasal Cavity and Sinuses	**0,44**	**3.555**
Squamous cell carcinoma with variants of nasal cavity and sinuses	0,31	2.498
Lymphoepithelial carcinoma of nasal cavity and sinuses	<0.01	19
Undifferentiated carcinoma of nasal cavity and sinuses	0,02	139
Intestinal type adenocarcinoma of nasal cavity and sinuses	<0.01	20

Rate: Incidence considered as number of cases / 100,000 persons / year

POPULATION

- First and subsequent malignant H&N cancers diagnosed in adults up to the end of 2007 and followed up until 31st December 2008

- 238,608 cases were contributed by 86 population-based cancer registries (CRs) from 29 European countries

- Sites: tongue, lingual tonsil and oral cavity, oropharynx and tonsil, nasopharynx, hypopharynx and larynx; (nasal cavities, thyroid and salivary glands excluded)

Number of Head and neck cancers included in the study by country and European region. Proportion of cases ascertained by microscopic verification and cases codified as larynx not otherwise specified

	Number of cases	% Tumours microscopically verified	% Tumours C32.9
Northern Europe	19,919	99	30.3
Denmark	6747	99	30.5
Finland	3398	99	87.4
Iceland	161	100	29.3
Norway	3324	99	6.7
Sweden	6289	100	10.7
Ireland and UK	58,676	95	22.6
Ireland	2865	98	10.0
UK, England	44,214	95	25.6
UK, Northern Ireland	1464	95	19.2
UK, Scotland	7138	98	15.6
UK, Wales	2995	85	12.2
Central Europe	71,655	99	17.7
Austria	8687	99	47.2
Belgium	8368	99	19.5
France	9659	99	25.8
Germany	24,985	98	18.5
Switzerland	2915	99	15.0
The Netherlands	17,041	99	0.6
Southern Europe	48,759	96	35.1
Croatia	7647	87	71.8
Italy	22,683	96	29.3
Malta	356	97	11.6
Portugal	7799	99	51.8
Slovenia	3061	99	7.5
Spain	7213	99	11.6
Eastern Europe	39,599	96	36.7
Bulgaria	8517	96	35.5
Czech Republic	11,582	98	20.5
Estonia	1417	96	13.5
Latvia	2280	91	39.9
Lithuania	3350	95	51.2
Poland	5333	94	77.3
Slovakia	7120	97	8.4
Europe	$\boxed{238,608}$	97	27.8

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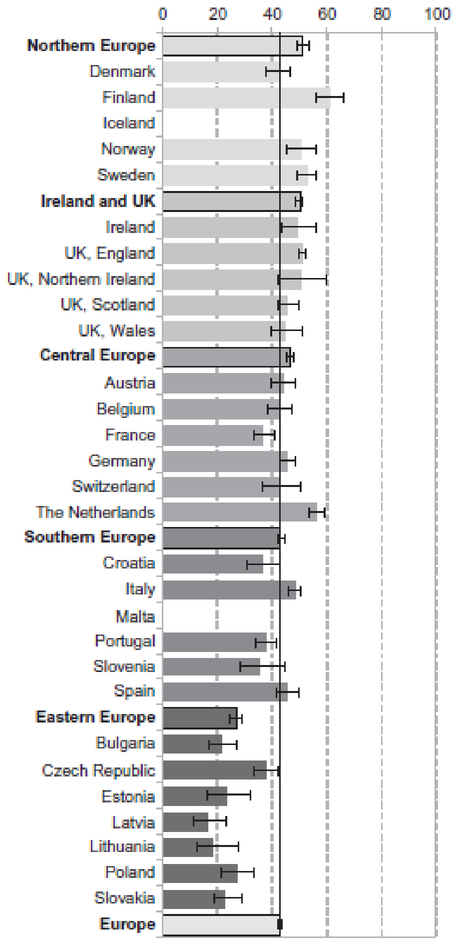
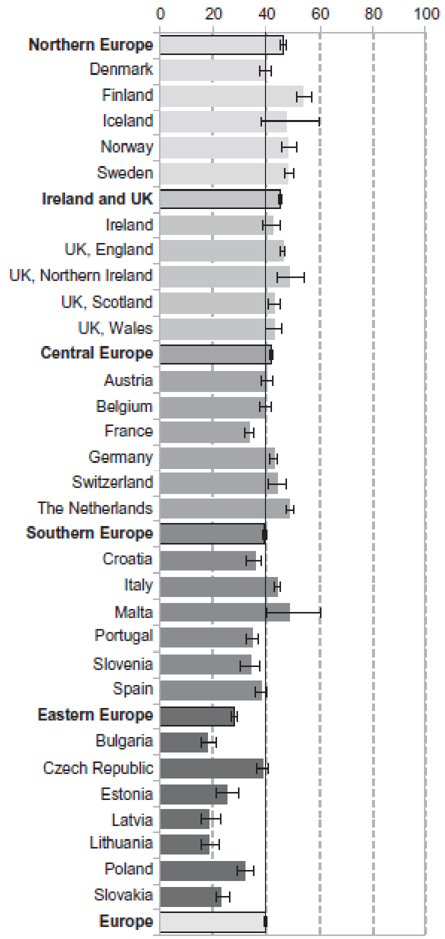
Age-specific and age-standardised 5Y relative survival for cases diagnosed in 2000–2007, by European region, country, gender and overall

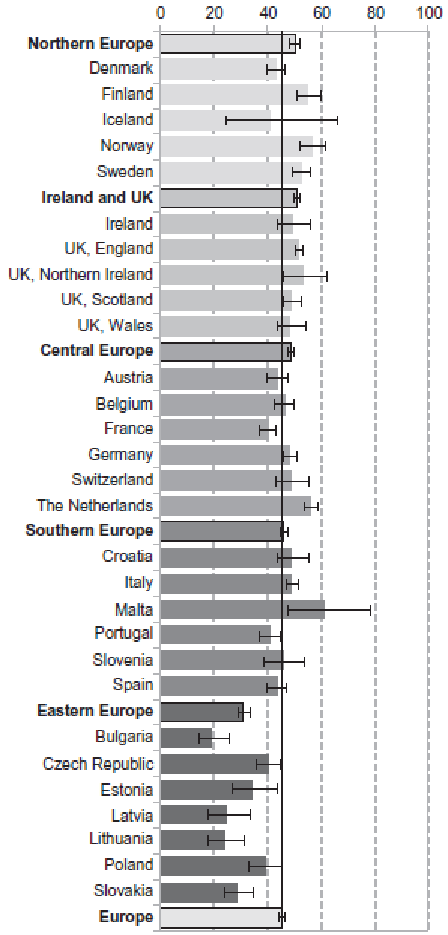
all cases combined (larynx excluded)



tongue and lingual tonsil cancer



oral cavity



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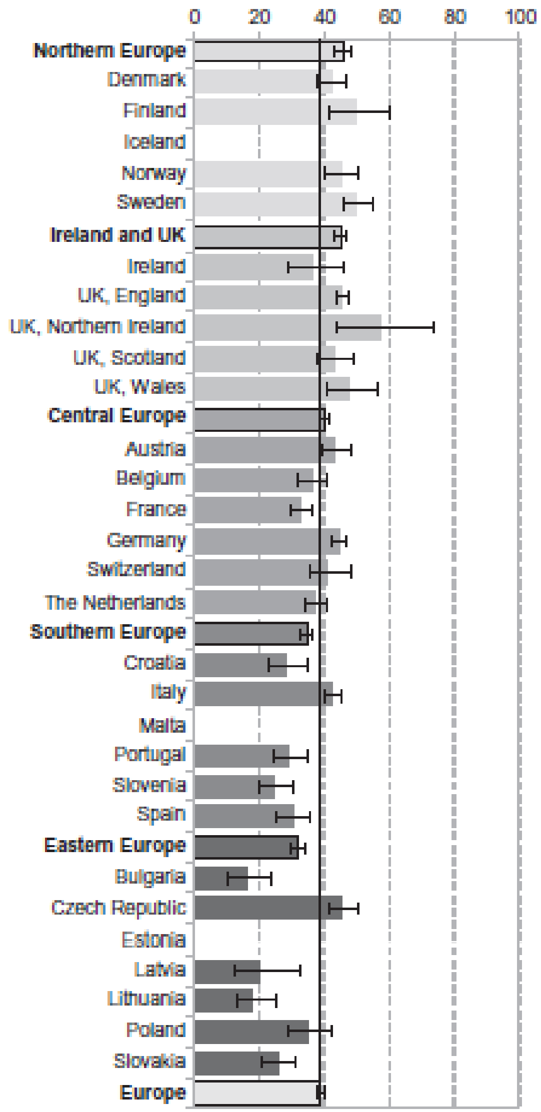
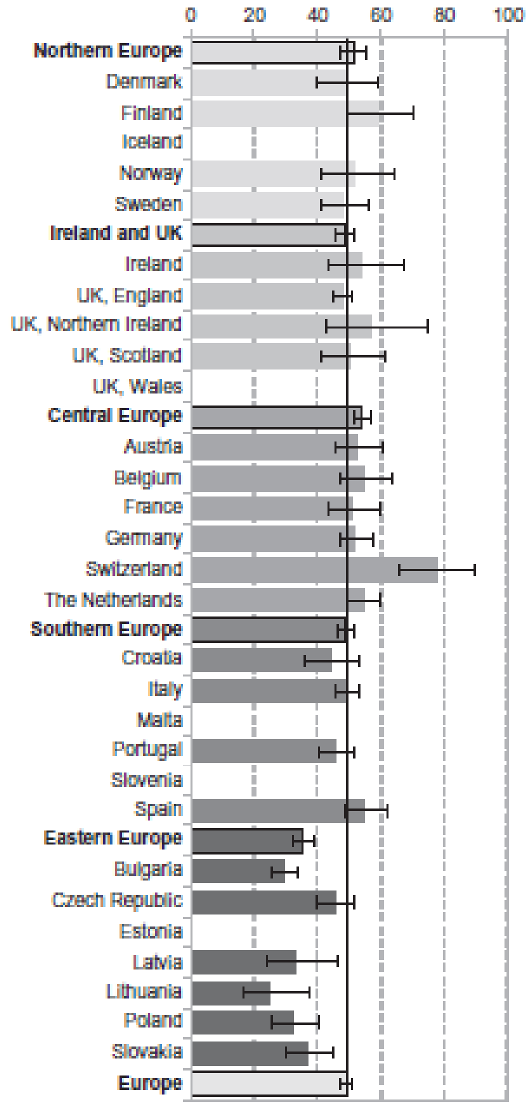
Age-specific and age-standardised 5Y relative survival for cases diagnosed in 2000–2007, by European region, country, gender and overall

oropharynx and tonsil

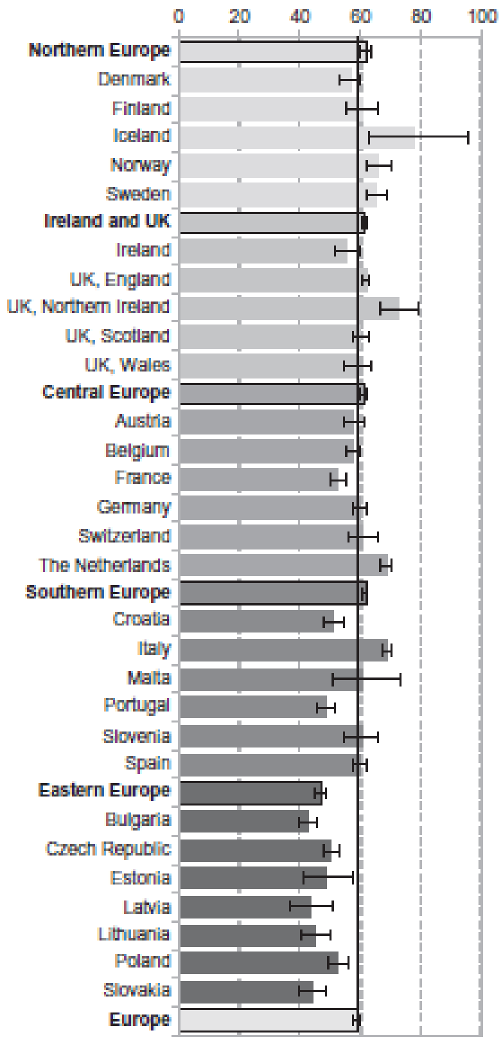


nasopharyngeal

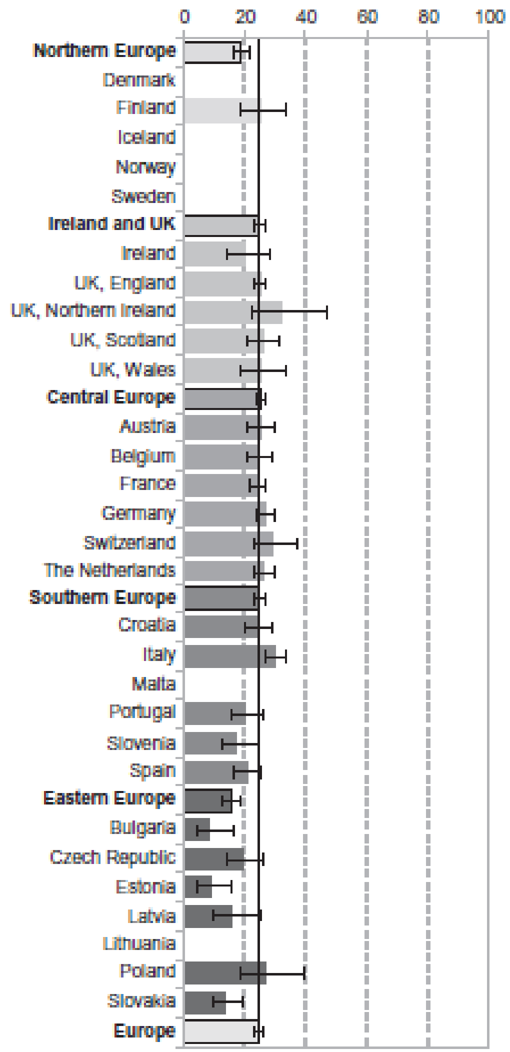


Age-specific and age-standardised 5Y relative survival for cases diagnosed in 2000–2007, by European region, country, gender and overall

laryngeal cancer



hypharyngeal



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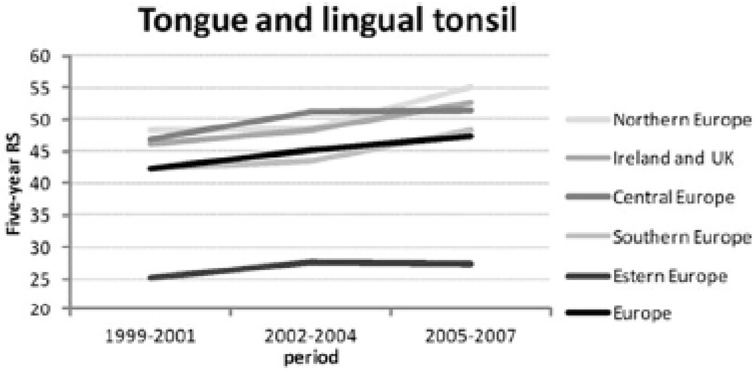
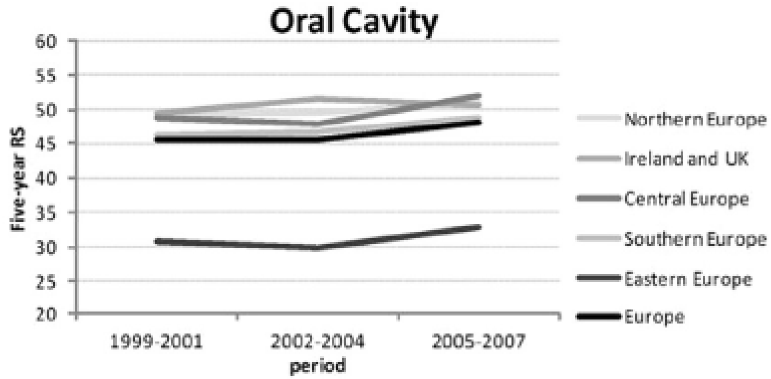
Time trend in age-standardised relative survival (RS, %) for head and neck cancer patients across European regions by site period 2005– 2007 versus period 1999–2001



	1999-2001	2002-2004	2005-2007	p-value[a]
Northern Europe	48.2	48.6	55.1	0.003
Ireland and UK	46.0	48.3	52.7	0.000
Central Europe	46.8	51.3	51.4	0.018
Southern Europe	42.1	43.4	48.4	0.020
Eastern Europe	25.2	27.7	27.4	0.209
Europe	42.3	45.2	47.4	0.000



	1999-2001	2002-2004	2005-2007	p-value[a]
Northern Europe	49.3	49.5	51.0	0.193
Ireland and UK	49.6	51.5	50.7	0.189
Central Europe	48.8	47.9	52.0	0.045
Southern Europe	46.2	46.8	48.7	0.181
Eastern Europe	30.8	29.8	32.9	0.216
Europe	45.6	45.5	48.1	0.012

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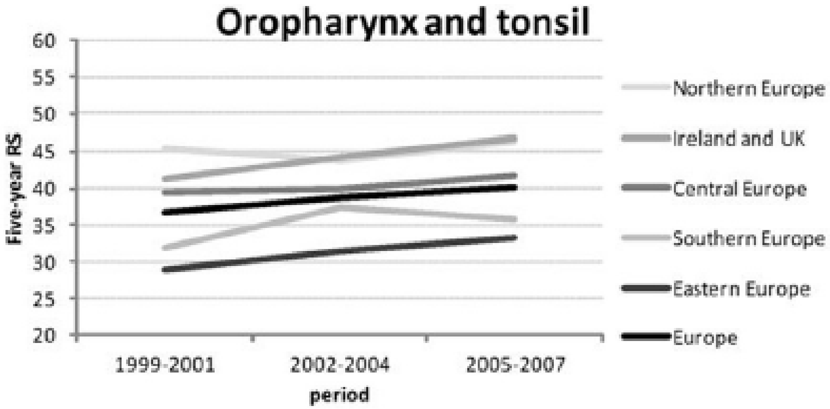
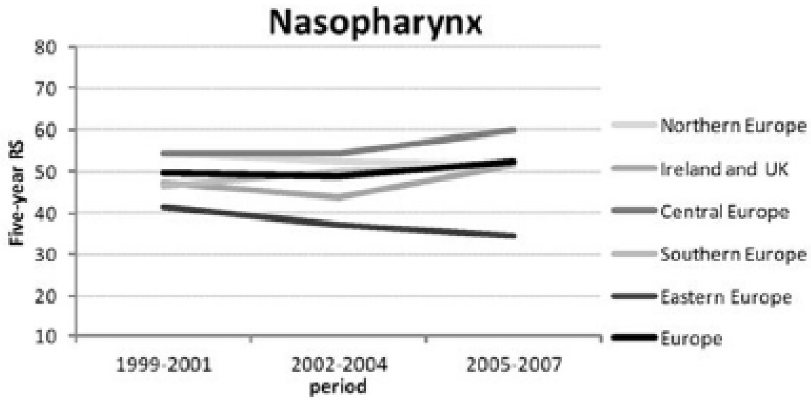
Time trend in age-standardised relative survival (RS, %) for head and neck cancer patients across European regions by site period 2005– 2007 versus period 1999–2001



	1999-2001	2002-2004	2005-2007	p-value[a]
Northern Europe	45.4	43.8	46.2	0.390
Ireland and UK	41.4	44.2	46.7	0.005
Central Europe	39.5	39.9	41.8	0.172
Southern Europe	32.0	37.3	35.8	0.108
Eastern Europe	28.9	31.5	33.4	0.056
Europe	36.7	38.8	40.1	0.006



	1999-2001	2002-2004	2005-2007	p-value[a]
Northern Europe	54.3	52.3	51.8	0.287
Ireland and UK	47.4	43.9	51.7	0.060
Central Europe	54.5	54.3	60.1	0.079
Southern Europe	46.7	50.0	51.8	0.129
Eastern Europe	41.4	37.3	34.4	0.023
Europe	49.6	49.0	52.5	0.080

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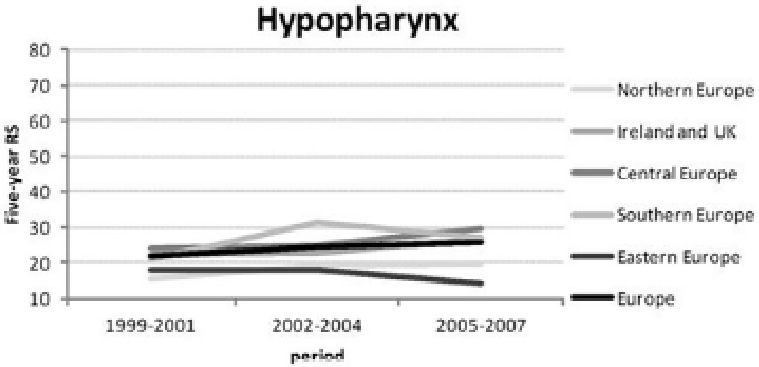
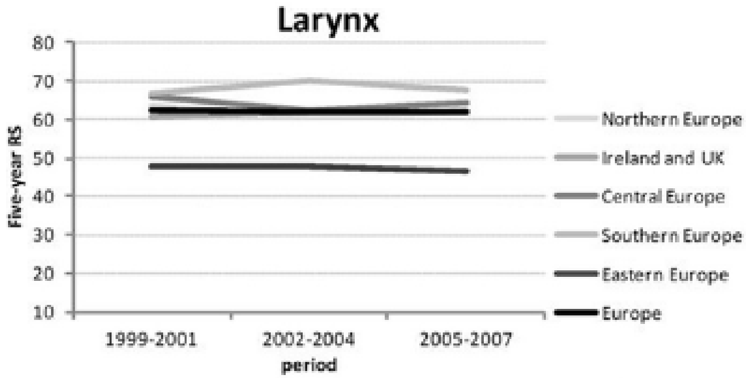
Time trend in age-standardised relative survival (RS, %) for head and neck cancer patients across European regions by site period 2005– 2007 versus period 1999–2001



	1999-2001	2002-2004	2005-2007	p-value[a]
Northern Europe	15.5	19.3	19.7	0.055
Ireland and UK	22.2	22.6	26.6	0.011
Central Europe	24.1	24.8	29.6	0.017
Southern Europe	21.2	31.1	26.9	0.053
Eastern Europe	18.0	18.1	14.3	0.112
Europe	21.7	24.6	25.6	0.004



	1999-2001	2002-2004	2005-2007	p-value[a]
Northern Europe	63.4	60.9	62.1	0.255
Ireland and UK	60.7	61.8	61.7	0.155
Central Europe	65.9	62.2	64.5	0.196
Southern Europe	66.8	70.1	67.6	0.327
Eastern Europe	47.7	48.0	46.8	0.299
Europe	62.4	61.8	62.0	0.307

Frequency distribution of stage (%) and 5-year relative survival (RS), by Head and neck (H&N) site, country and European region.

	Local			Regional			Metastatic			Unknown		
	%	RS	95% CI[c]	%	RS	95% CI	%	RS	95% CI	%	RS	95% CI
Tongue and lingual tonsil	36.0	64.9	62.9–66.9	52.0	33.4	31.9–34.9	3.0	9.1	5.4–14.0	9.0	39.4	35.4–43.3
Oral cavity	39.0	69	67.3–70.7	47.0	33.6	32.2–35.0	3.0	8.8	5.8–12.7	11.0	50.8	47.6–54.0
Oropharynx and tonsil	19.0	57.6	55.0–60.2	69.0	38.2	36.9–39.5	4.0	12.4	9.3–16.0	8.0	33.1	29.2–37.0
Hypopharynx	14.0	41.8	38.0–45.6	72.0	23.6	22.3–25.0	7.0	3.9	2.0–6.6	7.0	20.2	16.3–24.4
Larynx	56.0	74.4	73.1–75.6	31.0	37.8	36.3–39.4	2.0	7.2	4.5–10.7	11.0	61.4	58.6–64.1
All H&N	36.0	68.7	67.9–69.5	50.0	33.7	33.0–34.3	4.0	8.2	6.9–9.8	10.0	47.3	45.7–48.9
Northern Europe												
Norway	34.3	74.4	70.3–78.0	42.2	41.7	38.4–44.9	4.4	12.8	7.2–19.9	19.1	59.8	54.6–64.7
Central Europe	37.7	73.0	72.0–73.9	47.7	38.8	38.0–39.7	3.5	9.5	7.7–11.5	11.1	49.0	47.2–50.9
Austria	29.7	69.5	67.1–71.9	52.5	39.8	38.0–41.5	4.8	10.9	7.6–15.0	13.0	37.4	33.8–40.9
Germany[a]	30.0	70.2	68.5–71.9	49.0	37.7	36.5–39.0	4.0	11.0	8.2–14.2	17.0	51.0	48.7–53.4
The Netherlands	50.0	75.2	73.8–76.6	43.8	38.2	36.8–39.6	2.3	4.5	2.2–8.0	3.9	55.1	50.1–59.9
Southern Europe												
Slovenia	31.7	70.80	66.5–74.7	65.2	31.7	29.2–34.3	2.1	2.8	0.3–11.4	1.0	13.40	2.7–32.7
Eastern Europe	34.2	53.50	51.6–55.3	56.9	20.70	19.6–21.8	4.0	5.00	3.0–7.6	5.0	28.70	24.6–32.8
Estonia	49.3	50.20	45.1–55.1	45.9	21.8	18.0–25.8	3.6	N.A	N.A	1.2	32.70	9.2–59.2
Lithuania	36.5	48.90	45.3–52.4	45.8	16.4	14.3–18.7	3.4	0.0	N.A	14.4	29.00	24.3–34.0
Poland[b]	65.1	56.30	50.0–62.1	27.7	26.7	19.4–34.5	7.2	6.6	1.3–18.3	0.0		
Slovakia	27.8	56.40	53.7–59.0	66.0	21.6	20.3–22.9	4.0	6.2	3.6–9.7	2.1	27.00	19.7–34.8

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Relative excess risks (RERs) of death by country for all mouth-pharynx sites by age and sex (Model 1) and by age, sex and sub-site (Model 2) compared with UK, England

	Model 1		Model 2	
(A) Country	RER of death	95% CI[b]	RER of death	95% CI[b]
Northern Europe				
Norway	0.88	0.83–0.95	0.89	0.84–0.96
Sweden	0.86	0.81–0.90	0.87	0.83–0.91
Ireland and UK				
Ireland	1.04	0.96–1.11	0.99	0.92–1.07
UK, England	**1 (reference)**		**1 (reference)**	
UK, Northern Ireland	0.96	0.87–1.07	0.93	0.84–1.03
UK, Scotland	1.02	0.97–1.07	0.99	0.95–1.04
UK, Wales	1.00	0.93–1.07	1.00	0.93–1.07
Central Europe				
Belgium[a]	1.12	1.08–1.17	1.07	1.03–1.12
France[a]	1.20	1.15–1.25	1.08	1.04–1.12
Germany[a]	1.02	0.99–1.05	0.92	0.89–0.94
Switzerland[a]	0.98	0.90–1.06	0.91	0.84–0.98
The Netherlands	0.92	0.89–0.95	0.91	0.88–0.94
Southern Europe				
Italy[a]	0.95	0.91–0.99	0.90	0.86–0.94
Slovenia	1.34	1.27–1.43	1.24	1.17–1.31
Spain[a]	1.15	1.09–1.22	1.06	1.00–1.12
Eastern Europe				
Bulgaria	2.76	2.65–2.88	2.68	2.57–2.79
Czech Republic	1.37	1.32–1.42	1.32	1.27–1.37
Latvia	2.43	2.27–2.60	2.08	1.94–2.22
Slovakia	1.94	1.87–2.02	1.79	1.72–1.85
Poland[a]	1.67	1.57–1.79	1.63	1.53–1.75

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RERs of death by sub-site relative to base of tongue plus vallecula plus lingual tonsil with age, sex and country as covariates.

(B) Sub-site	ICD-O-3[c] code	%	RER of death	95% CI[b]
Base of tongue, vallecula and lingual tonsil	C01.9, C02.4, C02.8, C10.0	11.2	1 (reference)	
Tongue, other parts	C02.0–C02.3, C02.9	16.8	0.73	0.70–0.75
Gum	C03.0–C03.9	5.5	0.75	0.72–0.79
Floor of mouth	C04.0–C04.9	11.7	0.83	0.80–0.86
Palate	C05.0–C05.9	6.4	0.67	0.64–0.70
Cheek and vestibule of mouth	C06.0–C06.1	3.2	0.61	0.58–0.65
Retro-molar area	C06.2	2.4	0.73	0.69–0.78
Mouth, NOS[d]	C06.8–C06.9	2.5	0.88	0.83–0.93
Tonsil	C09.0–C09.9	16.4	0.73	0.71–0.75
Anterior surface of epiglottitis	C10.1	0.4	0.72	0.62–0.83
Lateral wall of oropharynx	C10.2, C10.8	2.5	1.30	1.23–1.37
Posterior wall of oropharynx	C10.3	0.6	1.24	1.12–1.37
Oropharynx and pharynx, NOS[d]	C10.9, C14.0, C14.8	6.0	1.53	1.47–1.59
Pyriform sinus and posterior wall of hypopharynx	C12.9, C13.2	7.6	1.26	1.22–1.31
Aryepiglottic fold	C13.1	0.7	0.87	0.79–0.97
Postcricoid region	C13.0	0.8	1.62	1.49–1.76
Hypopharynx, NOS[d]	C13.8–C13.9	5.4	1.52	1.46–1.58

G. Gatta et al. / European Journal of Cancer 51 (2015) 2130–2143

RISK FACTORS

Rare cancers of the head and neck area in Europe

EUROPEAN JOURNAL OF CANCER 48 (2012) 783–796

B.A.C. Van Dijk [a,], G. Gatta [b], R. Capocaccia [c], D. Pierannunzio [c], P. Strojan [d], L. Licitra [b],*
The RARECARE Working Group

Worldwide, more than 500,000 cases of squamous cell carcinoma of the head and neck (SCCHN) were estimated in 2008[1.] In Europe alone, estimates reached 130,000 cases of oral cavity, pharyngeal, and laryngeal cancers, and over 60,000 deaths[2].

1. Ferlay J, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010
2. Ferlay J, et al. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010

ESTRO School

RISK FACTORS

Most important risk factors for H&N SCC are:

√ **tobacco use**
√ **alcohol intake**

proportion of the incidence due to tobacco and alcohol use: **<u>72%</u>**

of which **4%** due to alcohol alone,
33% due to tobacco alone
35% due to tobacco and alcohol combined.

RISK FACTORS

Other risk factors…

- Oral hygiene
- Leukoplakia / Erythroplakia
- Irritation from dentures
- Immuno suppression (Transplant, AIDS, GVHD)
- Malnutrition (VitA deficency, high consumption of salted meat or fish)
- Exposure to sunlight - UV (for lip and conjunctival cancers)

RISK FACTORS

- Bile – gastric reflux
- Genetic susceptibility
  - ✓ Alcohol metabolism (polymorphisms of aldehyde dehydrogenase)
  - ✓ CYP2E1
  - ✓ DNA repair / Cell cycle control
- Genetic syndrome (Fanconi's aniemia / Dyskeratosi congenita)
- Batel quid and gutka

HPV (see below)

NPC risk factors

√ Ethnicity (Asian > Caucasian)

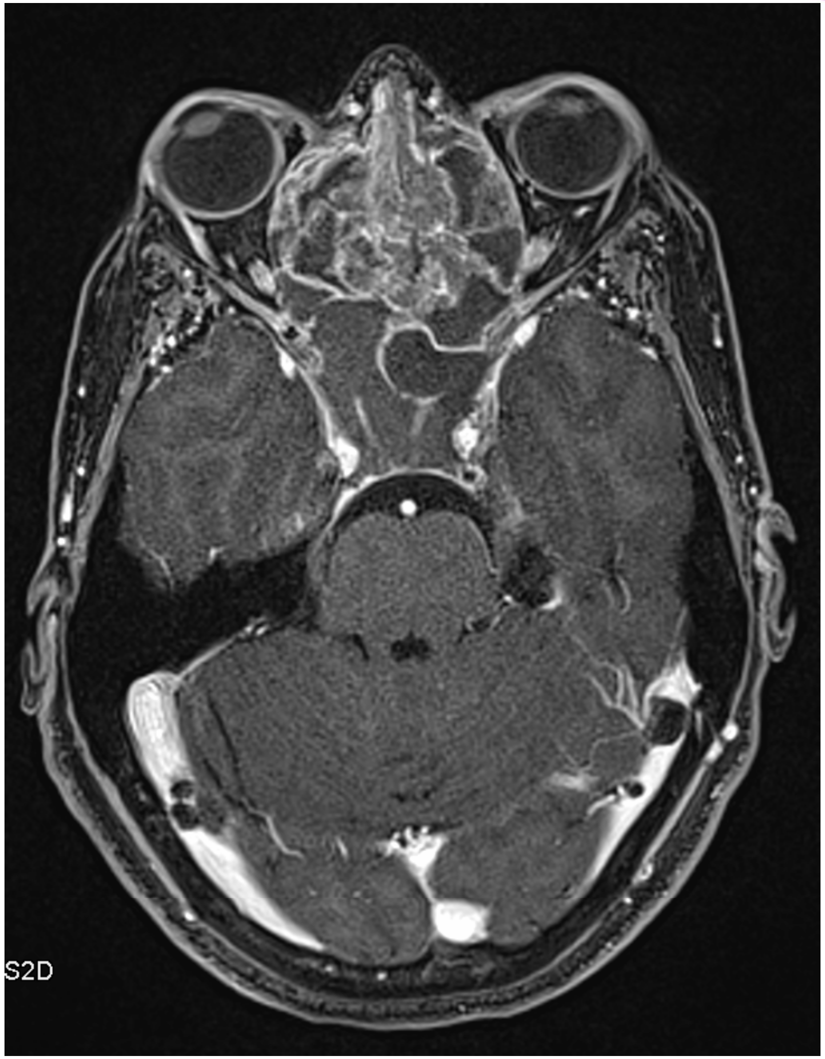
√ Epstein–Barr Virus (EBV) for nasopharyngeal cancer

√ Tabacco use (keratinizing type)

√ Genetics factor and family history

√ Gender (Male > Female)

SINONASAL CANCER



2005 WHO Classification of Sinonasal Tumor

- Squamous cell carcinoma (SCC)
- Lymphoepithelial carcinoma
- Adenocarcinoma

  ITAC, non ITAC (tubulopapillary LG)
- Salivary gland type carcinomas
- Neuroendocrine tumours

  carcinoid, small cell neuroendocrine type
- Sinonasal undifferentiated carcinoma (SNUC)

  (HPV 10% - El-Mofty Am J Surg Pathol 2005)

Differential diagnosis of Sinonasal Tumor

Feature	ENB	SNUC	SNEC
Prognosis	variable	poor	favorable
Necrosis	+	+++	-
Nuclear anaplasia	+	+++	-
Mitoses	variable	+++	variable
Vascular invasion	++	+++	NR
Secretory granules	+++	+	+++
Keratin	+	+++	++
S100	++	-	++
NSE	+++	variable	+++

Frierson Am J Surg Pathol 1986
Ejaz Adv Anat Pathol 2005

Sinonasal Tumor

TABLE 1. Selective immunohistochemical reactivity of sinonasal malignancies[2]

	CK	NSE	CG	SYN	S100	HMB	LCA	CD56	CD99	VIM	DES	Myf-4
SCC	+	−	−	−	−	−	−	−	−	−	−	−
SNUC	+	v	−	−	−	−	−	−	−	−	−	−
Esth	−	+	v	v	+*	−	−	−	−	−	−	−
SCUNC	+	+	+	+	+	−	−	−	−	−	−	−
MMM	−	−	−	−	+	+	−	−	−	+		−
T/NK ML	−	−	−	−	−	−	−	+	−	v	−	−
RMS	−	−	−	−	−	−	−	−	−	+	+	+

Abbreviations: CD99, Ewing marker; CG, chromogranin; CK, cytokeratin; DES, desmin; Esth, esthesioneuroblastoma; HMB (includes HMB-45 and Melan-A), melanocytic marker; LCA, leukocyte common antigen; MMM, mucosal malignant melanoma; NSE, neuron-specific enolase; RMS, rhabdomyosarcoma; SCC, squamous cell carcinoma; SCUNC, small cell undifferentiated neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; SYN, synaptophysin; S100, S100 protein; T/NK ML, nasal-type natural killer/ T cell lymphoma; v, variably positive; VIM, vimentin; +, positive; −, negative.
*Positive in the peripherally situated sustentacular cells.

Risk Factors for Sinonasal Tumor

- Workplace exposures
  - Wood dusts from carpentry (such as furniture and cabinet builders), sawmills, and other wood-related industries
  - Dusts from textiles (textile plants)
  - Leather dusts (shoemaking)
  - Flour (baking and flour milling)
  - Nickel and chromium dust
  - Mustard gas (a poison used in chemical warfare)
  - Radium (a radioactive element rarely used today)

  - Glues
  - Formaldehyde
  - Organic solvents

- Tabacco
- Human papilloma virus infection

Sinonasal Tumor - HPV

Syrjänen K, Hum Pathol. 2013

Detection of human papillomavirus in sinonasal carcinoma: systematic review and meta-analysis.

- 492 cases
- 133 (27.0%) cases tested HPV-positive

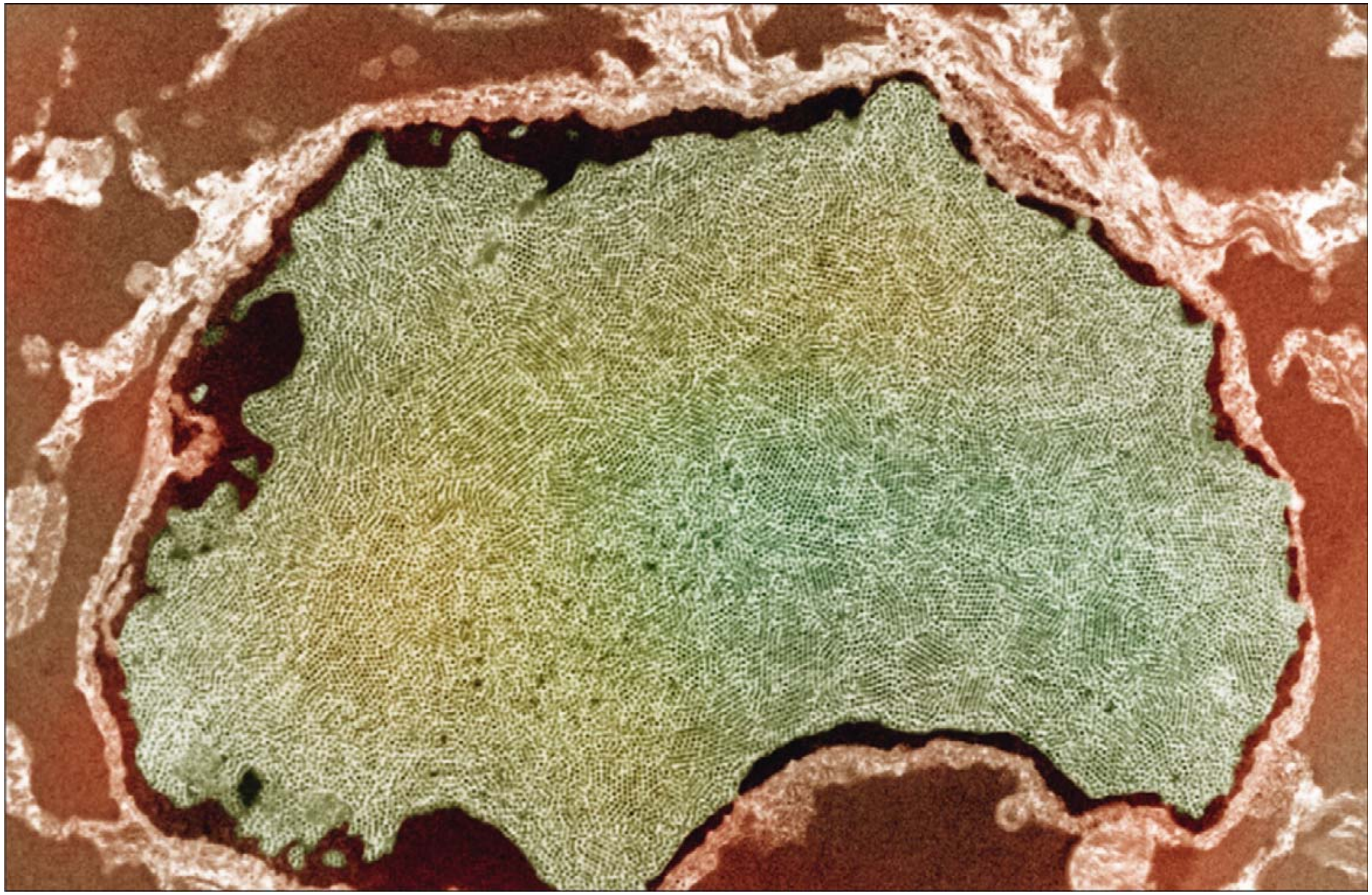
Sinonasal Tumor - HPV

Bishop JA; Am J Surg Pathol. 2013

Human papillomavirus-related carcinomas of the sinonasal tract

- 161 sinonasal carcinomas
- 34 (21%) HPV Pos (28 SCC and variants)
- 59 (37%) p16 IHC positive
- p16 expression strongly correlate with HPV DNA presence :
- A trend toward improved survival was observed in the HPV-positive group

HPV



HPV: IARC 2009

Group 1 agent	Cancers for which there is sufficient evidence in humans	Other sites with limited evidence in humans	Established mechanistic events
Epstein-Barr virus (EBV)	Nasopharyngeal carcinoma, Burkitt's lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin's lymphoma	Gastric carcinoma,* lympho-epithelioma-like carcinoma*	Cell proliferation, inhibition of apoptosis, genomic instability, cell migration
Hepatitis B virus (HBV)	Hepatocellular carcinoma	Cholangiocarcinoma,* non-Hodgkin lymphoma*	Inflammation, liver cirrhosis, chronic hepatitis
Hepatitis C virus (HCV)	Hepatocellular carcinoma, non-Hodgkin lymphoma*	Cholangiocarcinoma*	Inflammation, liver cirrhosis, liver fibrosis
Kaposi's sarcoma herpes virus (KSHV)	Kaposi's sarcoma,* primary effusion lymphoma*	multicentric Castleman's disease*	Cell proliferation, inhibition of apoptosis, genomic instability, cell migration
Human immunodeficiency virus, type 1 (HIV-1)	Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin's lymphoma,* cancer of the cervix,* anus,* conjunctiva*	Cancer of the vulva,* vagina,* penis,* non-melanoma skin cancer,* hepatocellular carcinoma*	Immunosuppression (indirect action)
Human papillomavirus type 16 (HPV-16)†	Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil	Cancer of the larynx	Immortalisation, genomic instability, inhibition of DNA damage response, anti-apoptotic activity
Human T-cell lymphotrophic virus, type-1 (HTLV-1)	Adult T-cell leukaemia and lymphoma	..	Immortalisation and transformation of T cells
Helicobacter pylori	Non-cardia gastric carcinoma, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma*	..	Inflammation, oxidative stress, altered cellular turn-over and gene expression, methylation, mutation
Clonorchis sinensis	Cholangiocarcinoma*	..	..
Opisthorchis viverrini	Cholangiocarcinoma	..	Inflammation, oxidative stress, cell proliferation
Schistosoma haematobium	Urinary bladder cancer	..	Inflammation, oxidative stress

*Newly identified link between virus and cancer. †For other types, see table 2.

Table 1: Biological agents assessed by the IARC Monograph Working Group

HPV: IARC 2009

Group	HPV types	Comments
Alpha HPV types		
1	16	Most potent HPV type, known to cause cancer at several sites
1	18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Sufficient evidence for cervical cancer
2A	68	Limited evidence in humans and strong mechanistic evidence for cervical cancer
2B	26, 53, 66, 67, 70, 73, 82	Limited evidence in humans for cervical cancer
2B	30, 34, 69, 85, 97	Classified by phylogenetic analogy to HPV types with sufficient or limited evidence in humans
3	6, 11	..
Beta HPV types		
2B	5 and 8	Limited evidence for skin cancer in patients with epidermodysplasia verruciformis
3	Other beta and gamma types	..

Table 2: Human papillomavirus (HPV) types assessed by the IARC Monograph Working Group

ESTRO School

HPV: Gene Expression

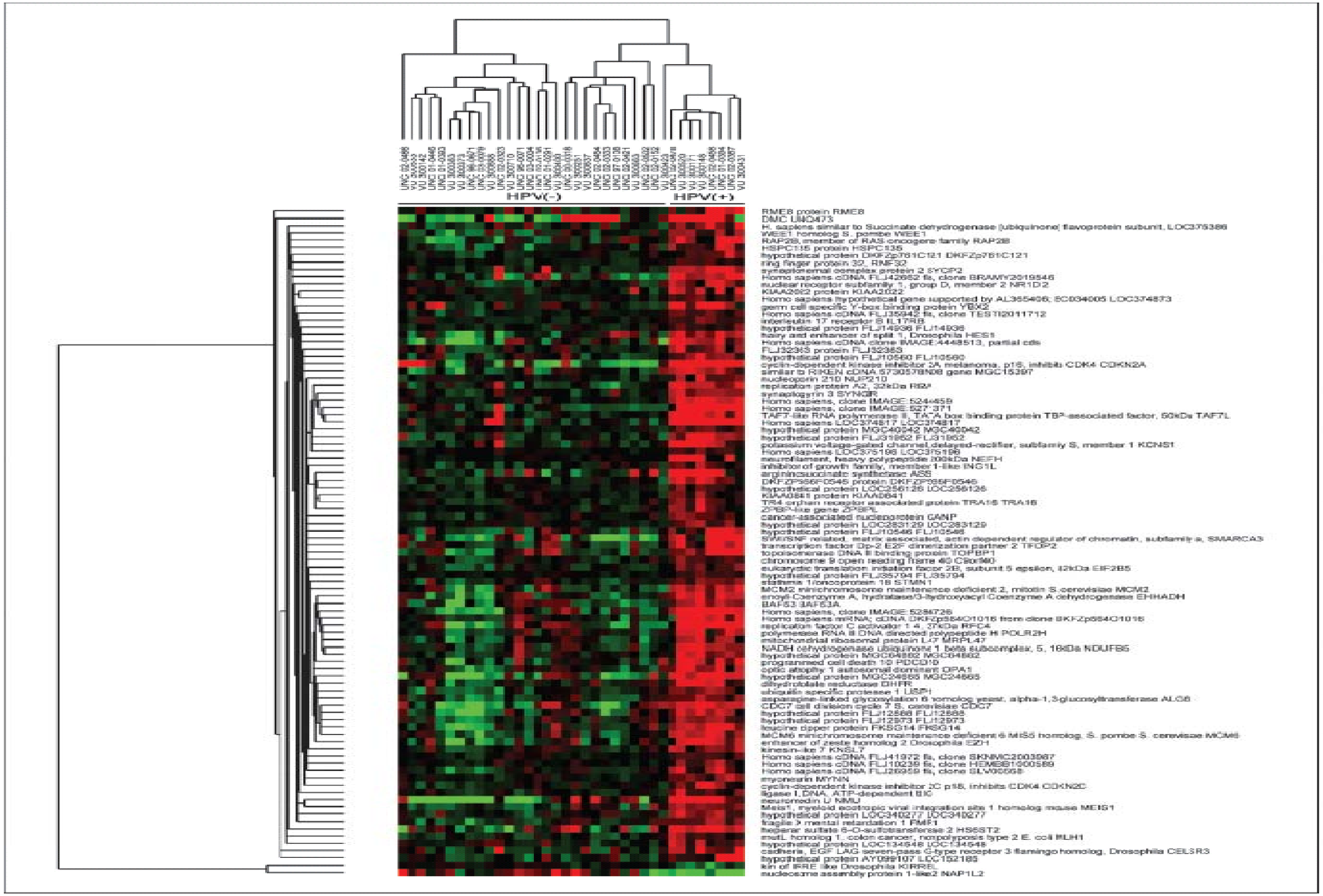


Fig. 2. Cluster diagram of 91 genes that are differentially expressed between HPV^{+} and HPV^{-} HNSCC tumors. HPV^{+} tumors form a separate cluster (*right*).

Slebos JR Clin Cancer Res 2006

HPV: Gene Expression

Table 2. Named genes from the 91 top classifiers for HPV status by Significance Analysis of Microarrays

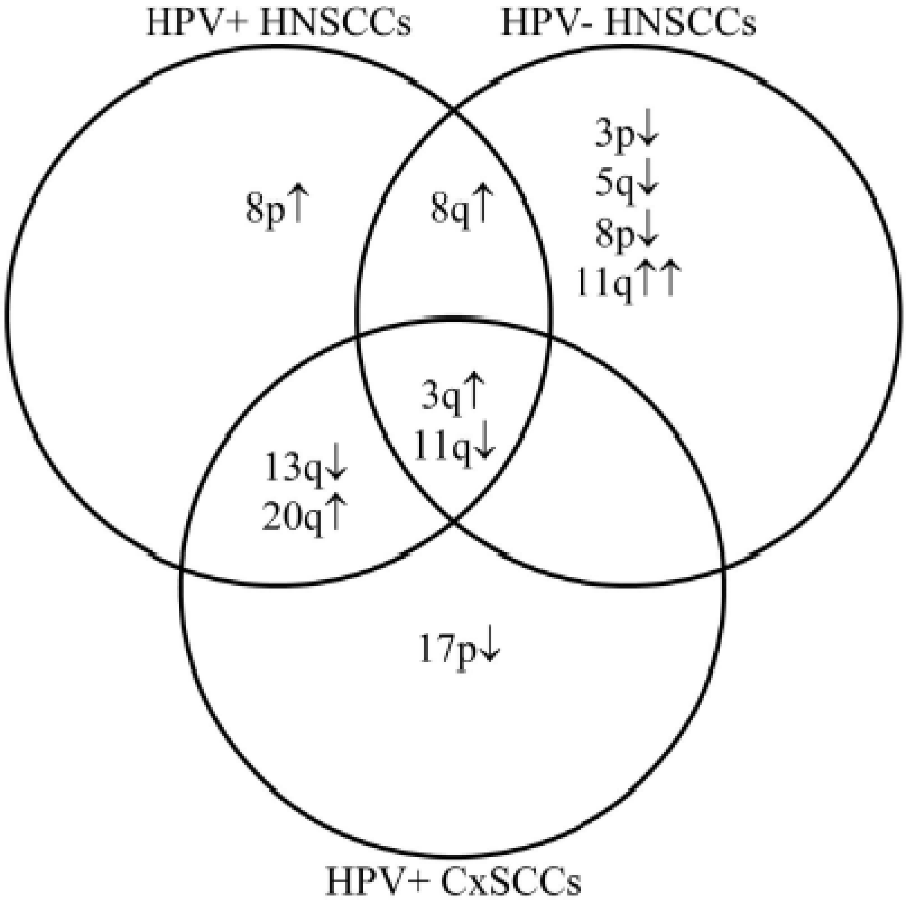
Genes with higher expression in HPV$^+$ tumors than HPV$^-$ tumors

Significance Analysis of Microarrays Rank	HUGO ID	Chromosome	Description
1	*TCAM1*	17q22	Testicular cell adhesion molecule 1
2	*AL833646*	2q21	Unknown protein
3	*TAF7L*	5q31	TAF7-like RNA polymerase II
4	*SYNGR3*	16p13	Synaptogyrin
5	*CDKN2A*	9p21	Cyclin-dependent kinase inhibitor 2A (p16^{INK4A})
6	*FLJ39749*	3q29	Unknown protein
7	*FLJ37881*	16	Unknown protein
8	*RPA2*	1p35	Replication protein A2
9	*MYNN*	3q26	Myoneurin
10	*FLJ31952*	17q21	Unknown protein
11	*RIBC2*	22q13	RIB43A domain with coiled-coils 2
12	*FLJ4628*	22q13	Unknown protein
13	*BF055370*	7	Unknown protein
14	*MCM6*	2q21	Minichromosome maintenance deficient 6
15	*FLJ42662*	X	Unknown protein
16	*RFC4*	3q27	Replication factor C4
17	*NR1D2*	3p24	Nuclear receptor subfamily 1, group D2
18	*MGC24665*	16p13	Unknown protein
19	*EHHADH*	3q26	Enoyl-CoA, hydratase
20	*FKSG14*	5p15	Leucine zipper protein
Genes with lower expression in HPV$^+$ tumors than HPV$^-$ tumors			
1	*NAP1L2*	Xq	Nucleosome assembly protein 1-like 2
2	*KIRREL*	1q21-25	Kin of IRRE-like (nephrin related)

Slebos JR Clin Cancer Res 2006

ESTRO School

HPV: Gene Expression

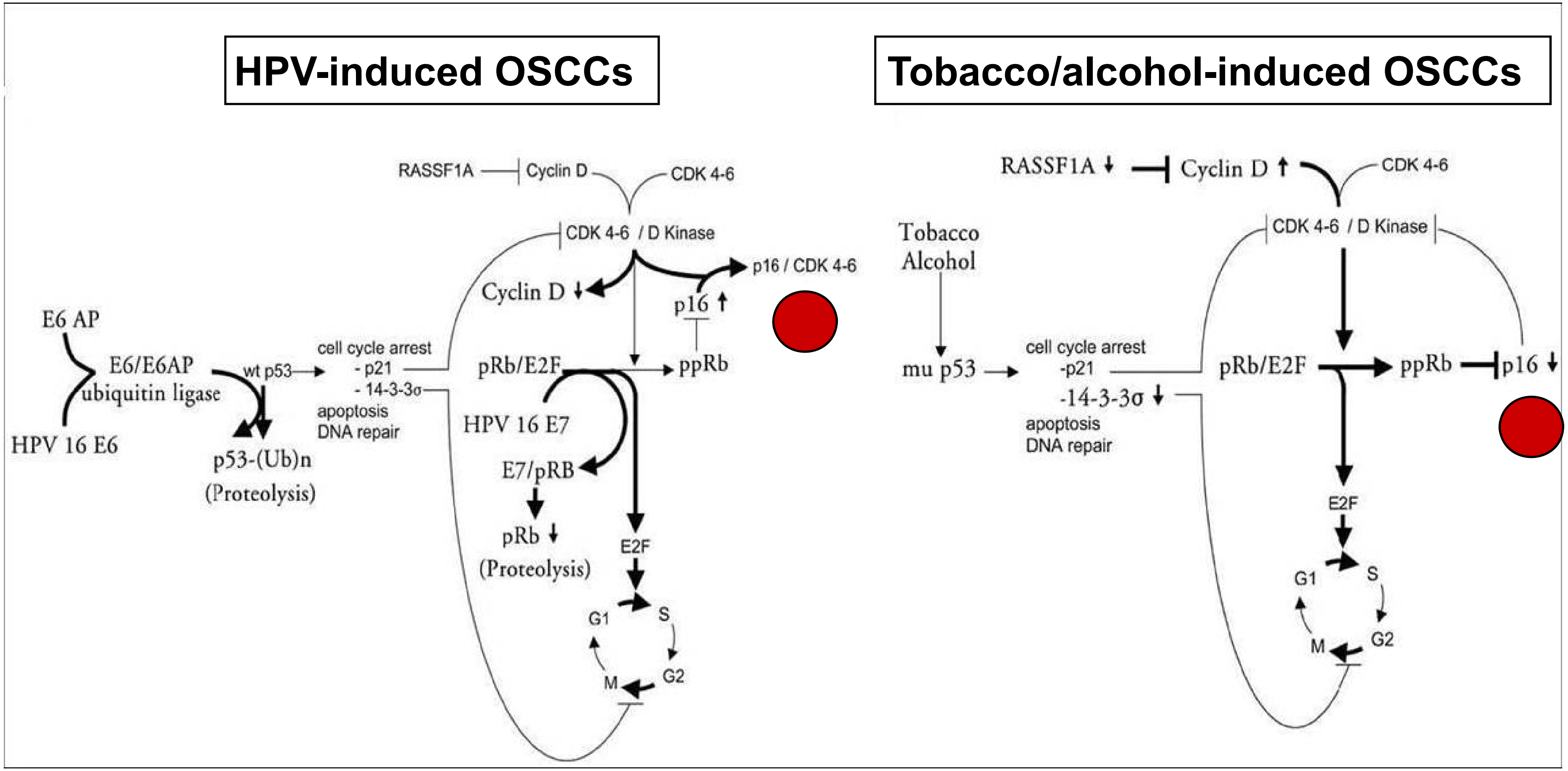


Wilting SM BMC Medical Genomics 2009

HPV: Oral vs Cervix

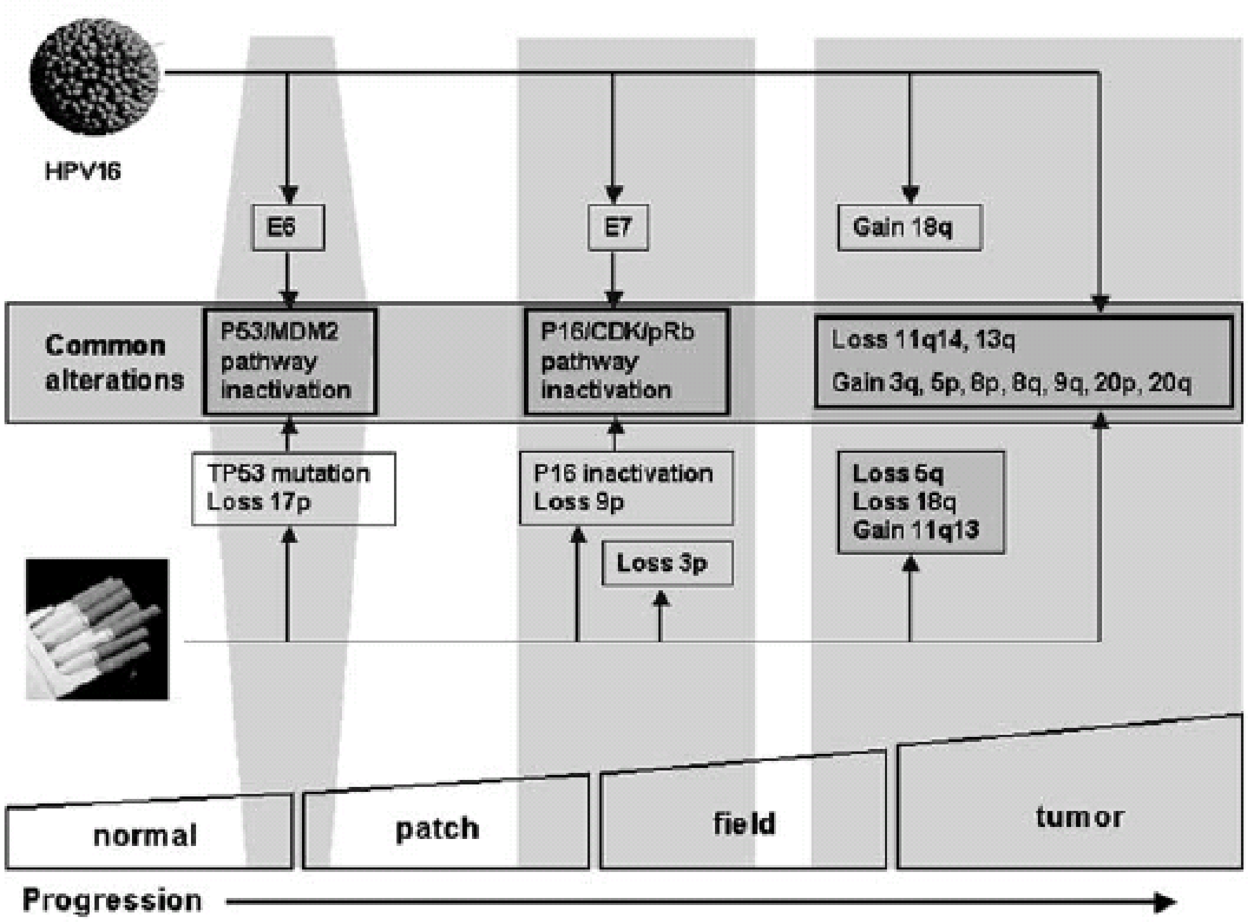
	Oral	Cervix
Prevalence	5/10 less	40%
HPV16	90%	60%
Sex	2/3> M	100%
Age	> with age	Debut sex , menopause
Infection rate		100/1000/year
Viral clearance	Similar?	2 yrs (90%)
Sexual activities	+	+
Salivar transmission	+	?
Incidence US	85.000	530.000
Mortality US	305.000	275.00
HIV	+	++

HPV: Etiologic heterogeneity of OSCCs



Adapted from Gillison ML. Seminars in Oncology, 2004

HPV



Smeets SJ Oncogene 2006

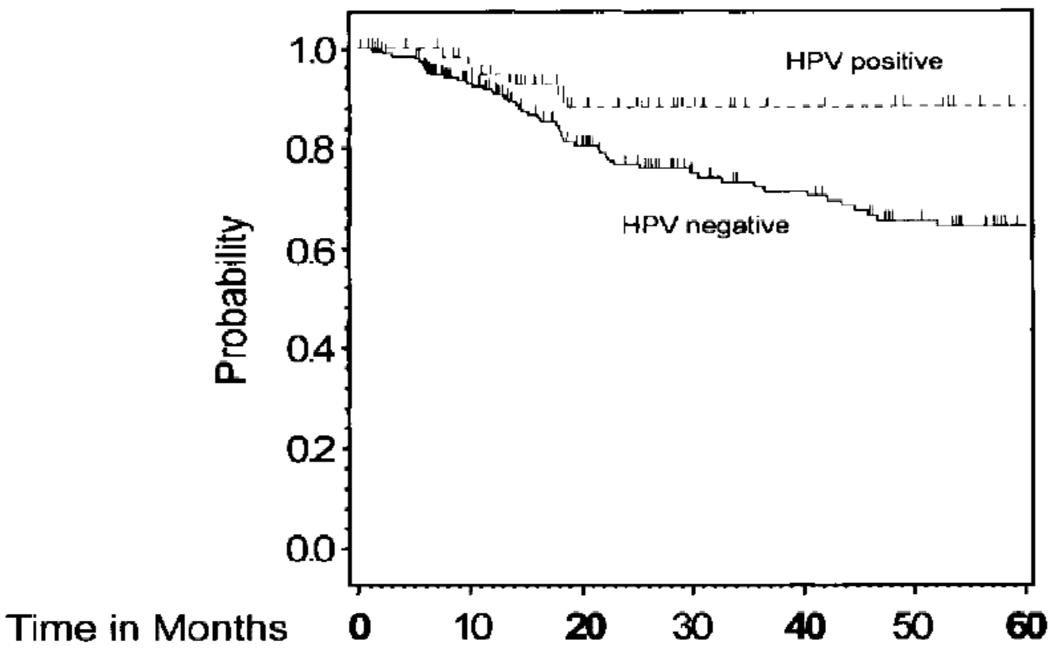
HPV

Evidence for a Causal Association Between Human Papillomavirus and a Subset of Head and Neck Cancers

Maura L. Gillison, Wayne M. Koch, Randolph B. Capone, Michael Spafford, William H. Westra, Li Wu, Marianna L. Zahurak, Richard W. Daniel, Michael Viglione, David E. Symer, Keerti V. Shah, David Sidransky

Gillison JNCI 2000

HPV: Prognostic factor



Number at risk:

HPV positive	61	37	18	10
HPV negative	191	116	75	48

Gillison JNCI 2000

HPV H&N cancer: systematic review

Table 3. Prevalence of HPV in HNSCCs by cancer site and geographic location

	No. studies	No. cases	Overall HPV prevalence (95% CI)	HPV16 prevalence (95% CI)
Oral cavity				
Europe	15	744	16.0 (13.4-18.8)	10.8 (8.6-13.2)
North America	8	577	16.1 (13.2-19.4)	10.1 (7.7-12.8)
Asia	13	1,133	33.0 (30.3-35.8)	22.3 (20.3-25.2)
Other*	2	188	18.1 (12.9-24.3)	14.9 (10.1-20.8)
Oropharynx				
Europe	17	529	28.2 (24.4-32.2)	23.8 (20.2-27.7)
North America	7	285	47.0 (41.1-53.0)	42.1 (36.3-48.1)
Asia	4	54	46.3 (32.6-60.4)	35.2 (22.7-49.4)
Other*	2	101	36.6 (27.3-46.8)	33.7 (24.6-43.8)
Larynx†				
Europe	19	799	21.3 (18.5-24.3)	13.8 (11.5-16.4)
North America	7	297	13.8 (10.1-18.3)	10.1 (7.0-14.1)
Asia	8	306	38.2 (32.8-43.9)	26.5 (21.6-31.8)
Other*	1	33	48.5 (30.8-66.5)	45.5 (28.1-63.6)

*Includes Central and South America, Australia, and Africa.
†Larynx includes cases of the hypopharynx.

Kreimer A, 2005

HPV H&N cancer: systematic review

Group	Overall prevalence (95% CI)	Midyear <2000 (95% CI)	Midyear 2000–2004 (95% CI)	Midyear 2005+ (95% CI)	Midyear NK	*p* value (midyear trend)	*p* value (year group trend)
OPC							
All regions	47.7 (42.9, 52.5) S = 102 *n* = 5396 0.89	40.5 (35.1, 46.1) S = 54 *n* = 2690 0.82	64.3 (56.7, 71.3) S = 22 *n* = 2037 0.9	72.2 (52.9, 85.7) S = 4 *n* = 150 0.8	40.5 (31.1, 50.7) S = 22 *n* = 519	<.0001	<.0001
N. America	59.9 (54.7, 64.9) S = 43 *n* = 2550 0.8	50.7 (42.6, 58.7) S = 19 *n* = 696 0.73	67.6 (61.7, 72.9) S = 17 *n* = 1678 0.79	69.7 (46.8, 85.7) S = 2 *n* = 45 0.76	55.6 (41.4, 69.0) S = 5 *n* = 131	0.0002	0.002
Europe	39.7 (32.8, 47.0) S = 46 *n* = 2278 0.87	35.3 (28.7, 42.5) S = 27 *n* = 1704 0.82	59.0 (30.2, 82.7) S = 4 *n* = 164 0.87	73.1 (39.4, 91.9) S = 2 *n* = 105 0.87	36.2 (24.3, 50.0) S = 13 *n* = 305	0.07	0.004
Other, NK, and mixed regions	32.5 (23.9, 42.4) S = 13 *n* = 568 0.73	32.2 (21.0, 45.9) S = 8 *n* = 290 0.78	— S = 1 *n* = 195	— S = 0 *n* = 0	35.4 (18.5, 56.9) S = 4 *n* = 83	0.46	—
Non-OPC							
All regions	21.8 (18.9, 25.1) S = 236 *n* = 13,972 0.93	22.2 (18.4, 26.4) S = 140 *n* = 2260 0.96	17.2 (11.9, 24.4) S = 37 *n* = 186 0.88	6.1 (0.7, 39.0) S = 5 *n* = 2419 0.91	26.3 (19.3, 34.8) S = 54	0.97	0.07
N. America	12.8 (9.7, 16.6) S = 62 *n* = 3803 0.86	14.1 (10.1, 19.5) S = 38 *n* = 2212 0.87	9.8 (5.2, 17.5) S = 13 *n* = 1204 0.85	— S = 2 *n* = 40	15.1 (7.3, 28.7) S = 9 *n* = 347	0.03	0.08
Europe	23.7 (19.4, 28.7) S = 90 *n* = 4625 0.9	23.6 (18.5, 29.5) S = 53 *n* = 29490 0.9	23.2 (12.7, 38.4) S = 14 *n* = 539 0.87	11.7 (0.9, 67.0) S = 3 *n* = 146 0.93	25.9 (16.3, 38.5) S = 20 *n* = 991	0.27	0.66
Other, NK, and mixed regions	28.8 (22.5, 36.1) S = 84 *n* = 5364 0.95	28.6 (20.4, 38.5) S = 49 *n* = 3766 0.96	23.9 (14.5, 36.7) S = 10 *n* = 517 0.84	— S = 0 *n* = 0	31.7 (19.8, 46.7) S = 25 *n* = 1081	0.53	0.55

Abbreviations: HPV, human papillomavirus; CI, confidence interval; OPC, oropharyngeal cancer; NK, not known; S, number of studies; n = number of patients included; I^2, index statistic measuring heterogeneity.

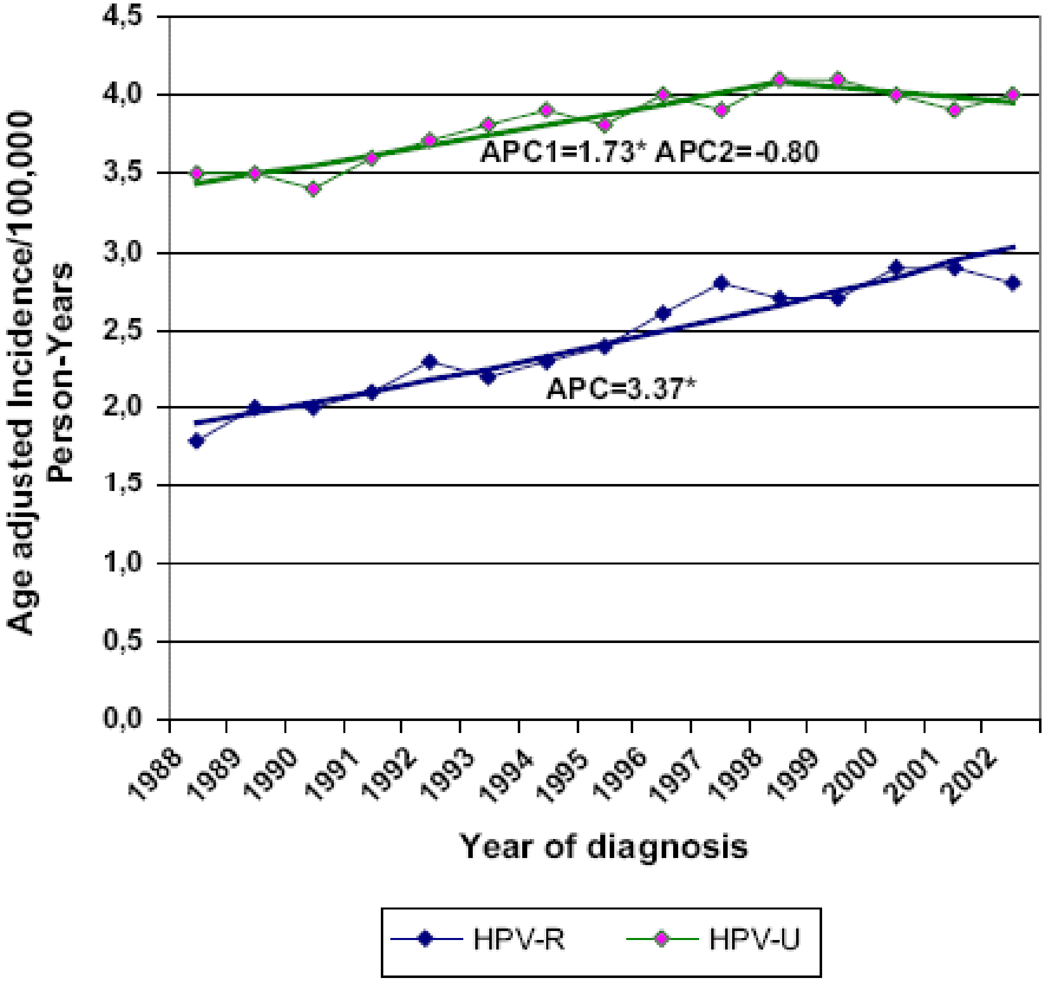
Mehanna Head&Neck 2012

HPV

Human Papillomavirus in HNSCC: A European Epidemiologic Perspective

Lisa Licitra, MD[a,*], Giulia Zigon, PhD[b], Gemma Gatta, MD[b], Maria-José Sánchez, MD, PhD[c], Franco Berrino, MD[b], EUROCARE Working Group[d]

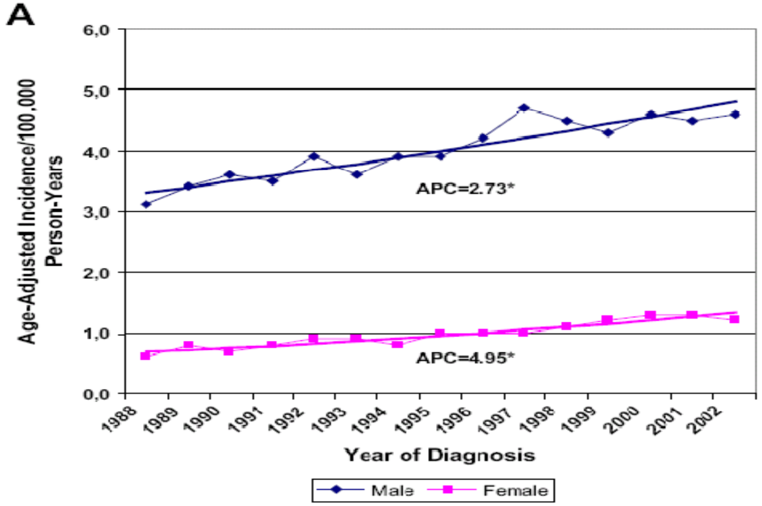
HPV



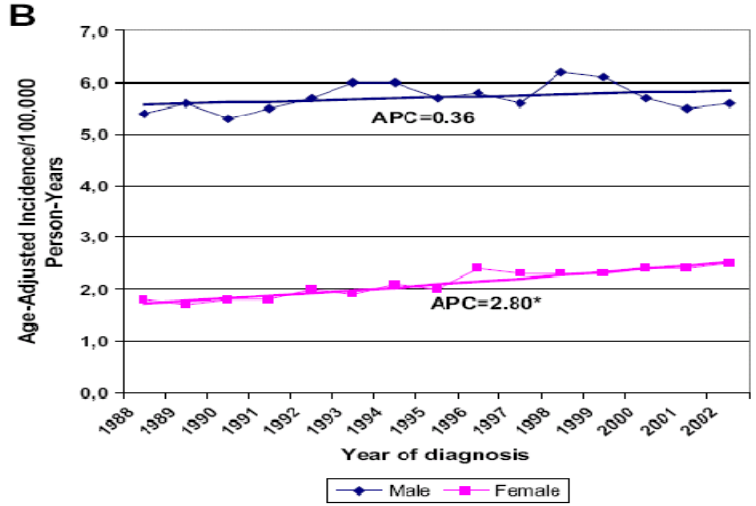
Age adjusted Incidence/100,000 Person-Years
4,5
4,0
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
APC1=1.73* APC2=-0.80
APC=3.37*
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
Year of diagnosis
HPV-R
HPV-U

HPV

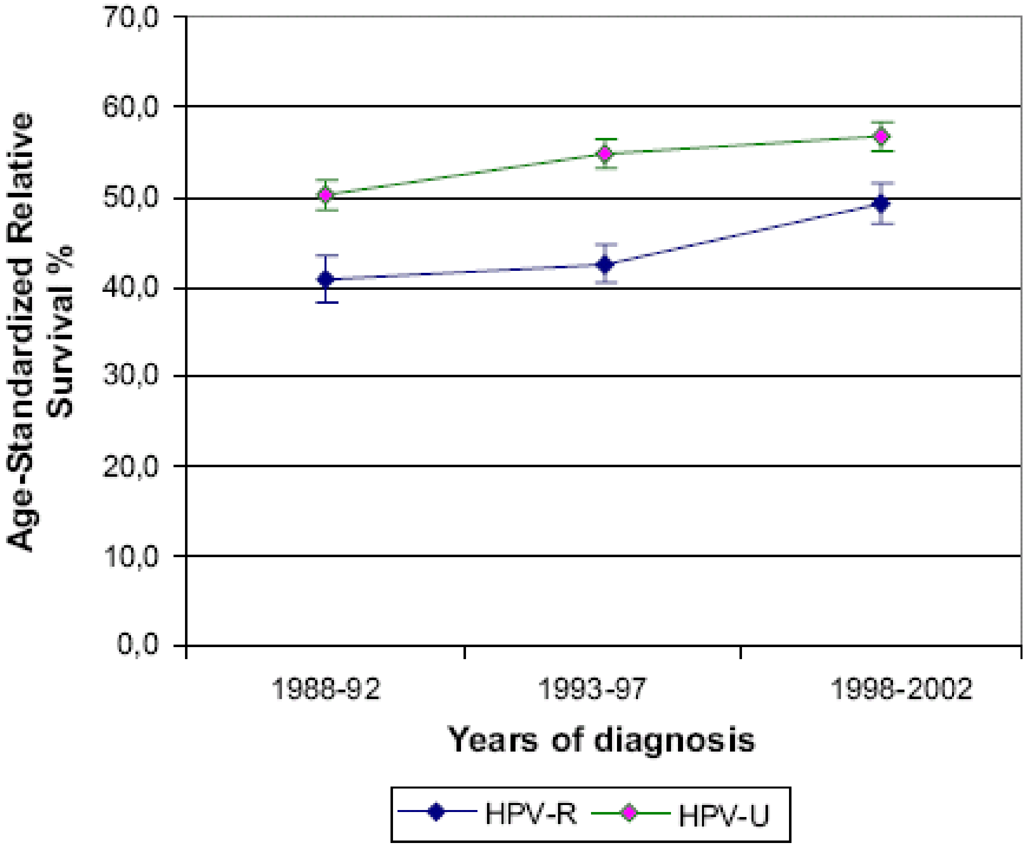
HPV-R



HPV-U



HPV



Hematol Oncol Clin N Am 2008

HPV

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer

Gypsyamber D'Souza, Ph.D., Aimee R. Kreimer, Ph.D., Raphael Viscidi, M.D., Michael Pawlita, M.D., Carole Fakhry, M.D., M.P.H., Wayne M. Koch, M.D., William H. Westra, M.D., and Maura L. Gillison, M.D., Ph.D.

NEJM 2007

HPV

Table 3. Association of Oropharyngeal Cancer with Exposure to HPV and with Biomarkers of Cancer Associated with HPV-16.

Measure of HPV Exposure or Disease	Prevalence		Odds Ratio (95% CI)	
	Case Patients (N=100)	Control Patients (N=200)	Unadjusted	Adjusted*
	number (percent)			
HPV-16 L1 serologic status				
Seronegative	43 (43)	186 (93)	1.00	1.00
Seropositive	57 (57)	14 (7)	17.6 (8.8–34.5)	32.2 (14.6–71.3)
Oral HPV-16 infection†				
Negative	68 (68)	192 (96)	1.00	1.00
Positive	32 (32)	8 (4)	11.3 (5.0–25.7)	14.6 (6.3–36.6)
Any oral HPV infection‡				
Negative	63 (63)	189 (94)	1.00	1.00
Positive	37 (37)	11 (6)	10.0 (4.8–20.7)	12.3 (5.4–26.4)
HPV-16 E6 or E7 serologic status				
Seronegative for E6 and E7	36 (36)	192 (96)	1.00	1.00
Seropositive for E6 or E7	64 (64)	8 (4)	33.3 (16.2–68.6)	58.4 (24.2–138.3)
HPV-16 DNA in tumor				
Absent	28 (28)	—	—	—
Present	72 (72)	—	—	—

NEJM 2007

Risk factors HPV + SCC

- Sexual behaviour
- HPV exposure
- Marijuana consumption

HPV

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Evaluation of Human Papillomavirus Antibodies and Risk of Subsequent Head and Neck Cancer

- 638 HN and Esophageal cancer pts - 1599 controls tested for HPV16 E6/7 antibodies on pre-diagnostic plasma sample collected on average 6 years before

- 34.8% of oropharyngeal cancer pts positive for HPV16 E6 Abs vs 0.6% of controls,

- **OR: 274** (95%CI 110 – 681)

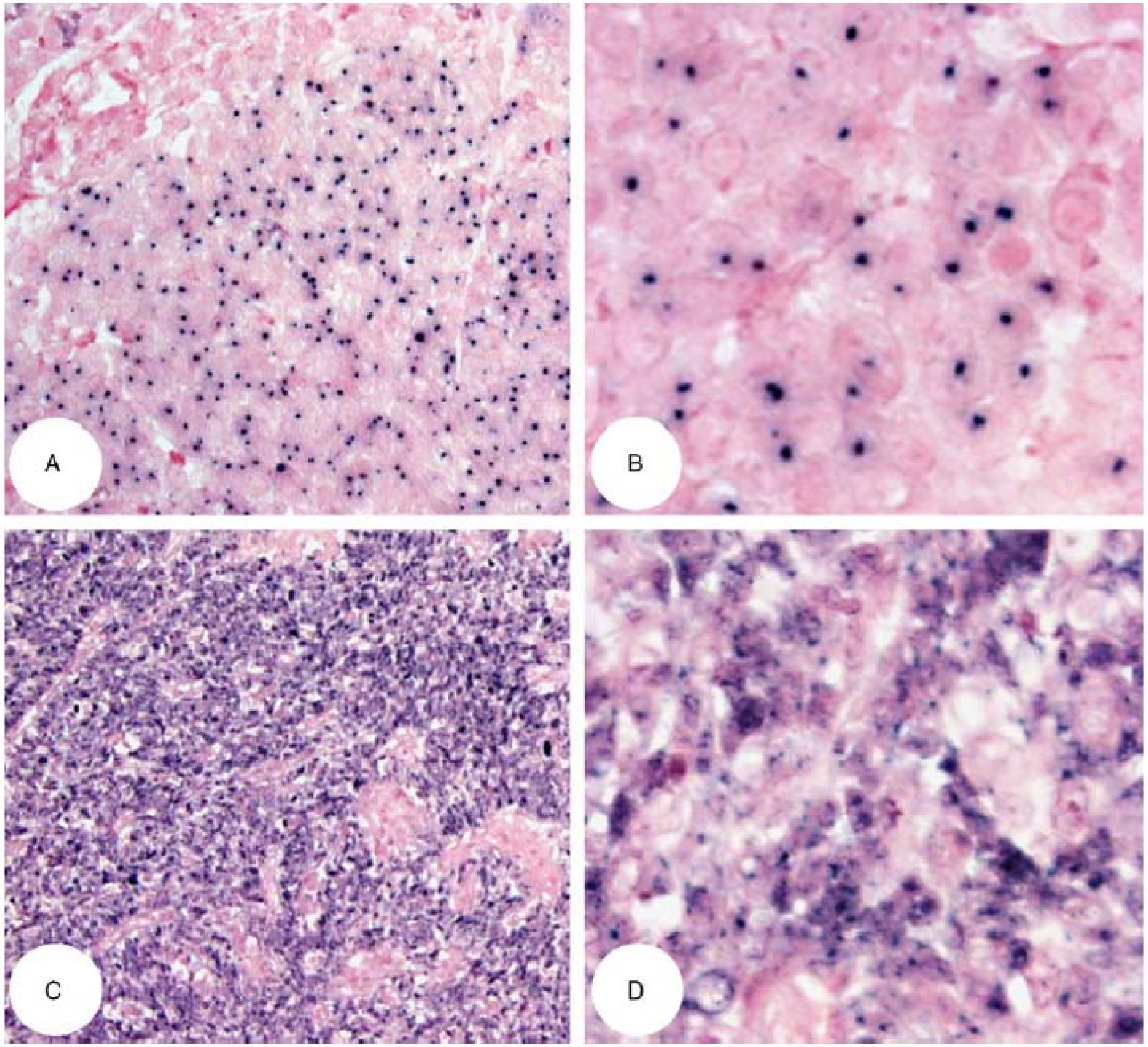
Kreimer AR, JCO June 13

HPV

HPV16 transmission between a couple with HPV-related head and neck cancer

Robert Haddad [a,*], Christopher Crum [b], Zigui Chen [c], Jeffrey Krane [b], Marshall Posner [a], Yi Li [d], Robert Burk [c]

HPV



Gold standard tumor HPV detection

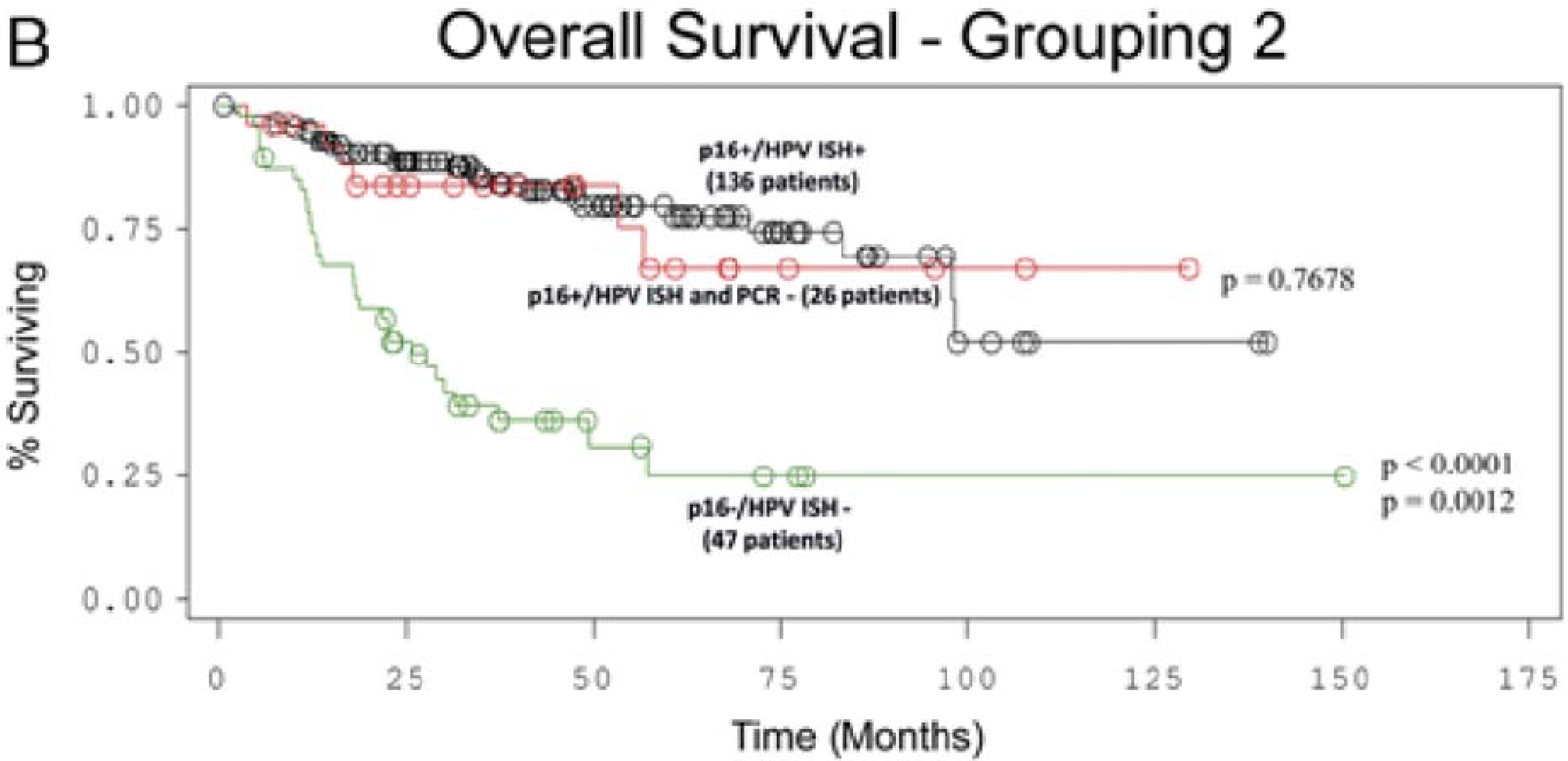
- Traditional PCR too sensitive
- Quantitative viral DNA or mRNA PCR more precise
- ISH not completely sensitive
- p16 is a surrogate marker

HPV: P16 positive tumors

p16 Expression in oropharyngeal primary tumor — no./total no. (%)			HPV +	HPV -
Positive	114/216 (52.8)	101/217 (46.5)	192/206 (93.2)	22/117 (18.8)
Negative	48/216 (22.2)	53/217 (24.4)	7/206 (3.4)	94/117 (80.3)
Unknown	54/216 (25.0)	63/217 (29.0)	7/206 (3.4)	1/117 (0.9)

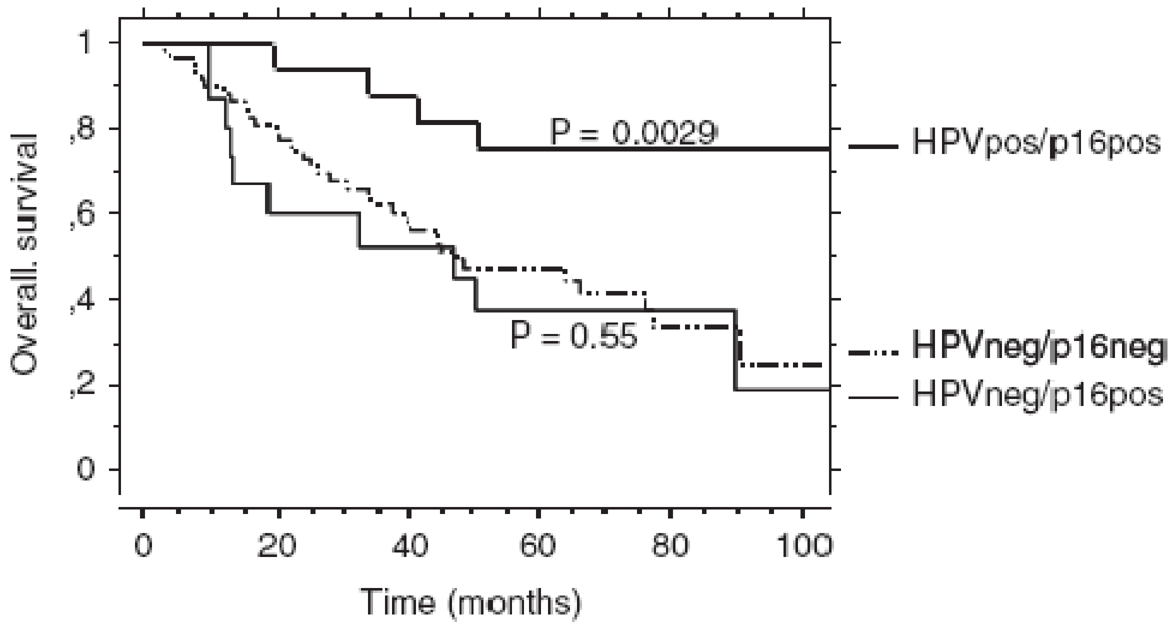
ANG KK 2010

HPV


B
Overall Survival - Grouping 2
1.00
0.75
0.50
0.25
0.00
% Surviving
p16+/HPV ISH+
(136 patients)
p16+/HPV ISH and PCR - (26 patients)
p = 0.7678
p16-/HPV ISH -
(47 patients)
p < 0.0001
p = 0.0012
0
25
50
75
100
125
150
175
Time (Months)

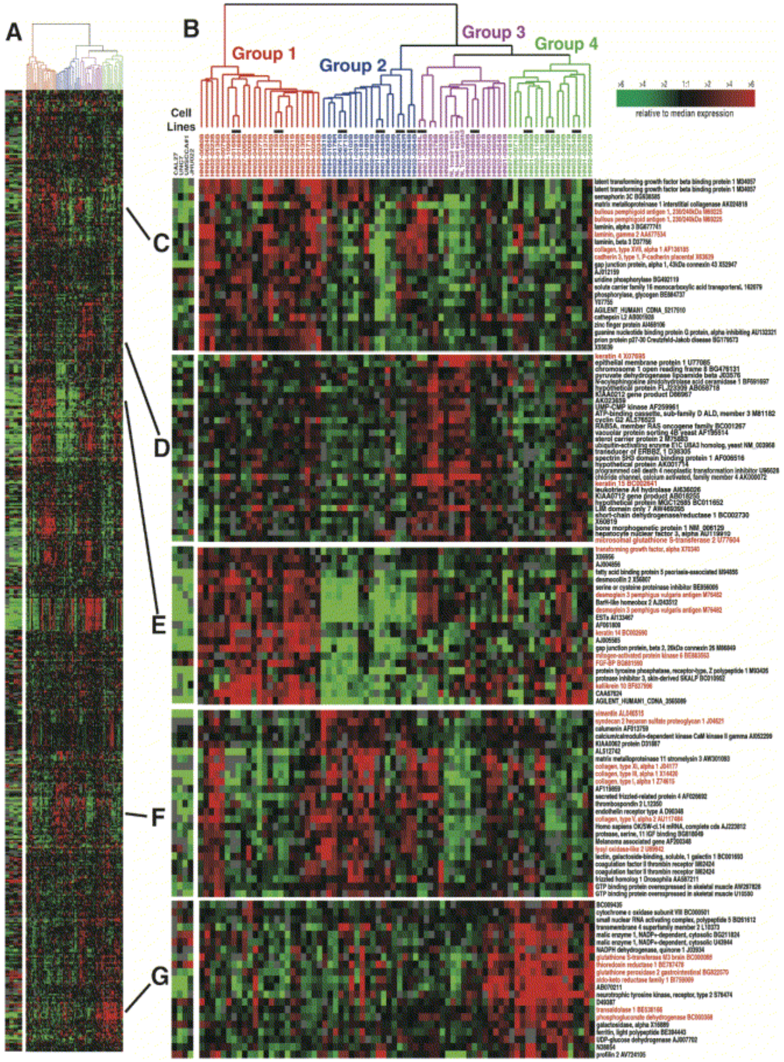
HPV

Am J Surg Pathol • Volume 00, Number 00, ■■ 2011



P16 neg =15 pts
5 non funct mut;
3 overexpr EGFR; overexp cyclin D1;
1 PI3KA mut; 1 gene copy number

SCC Gene Expression

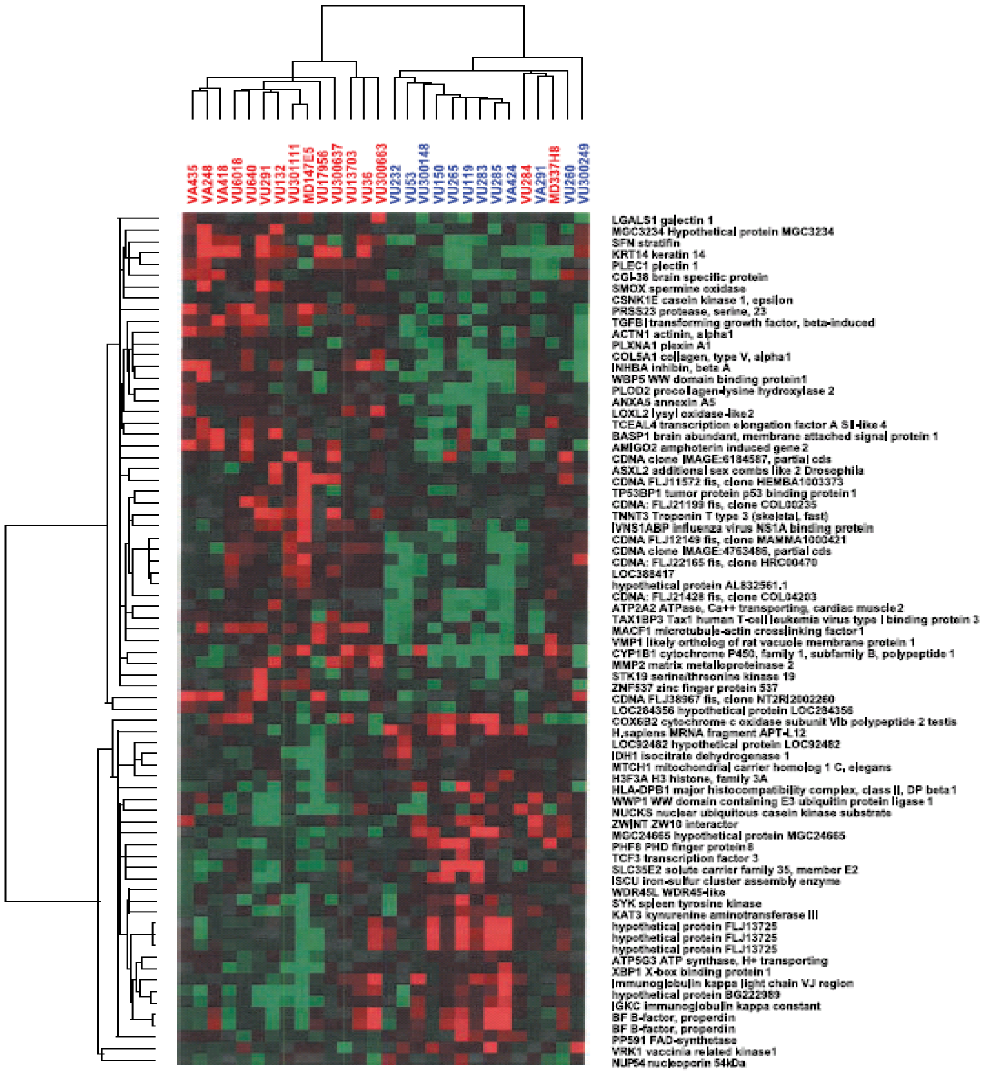


Chung Cancer Cell 2004

4 prognostic groups…

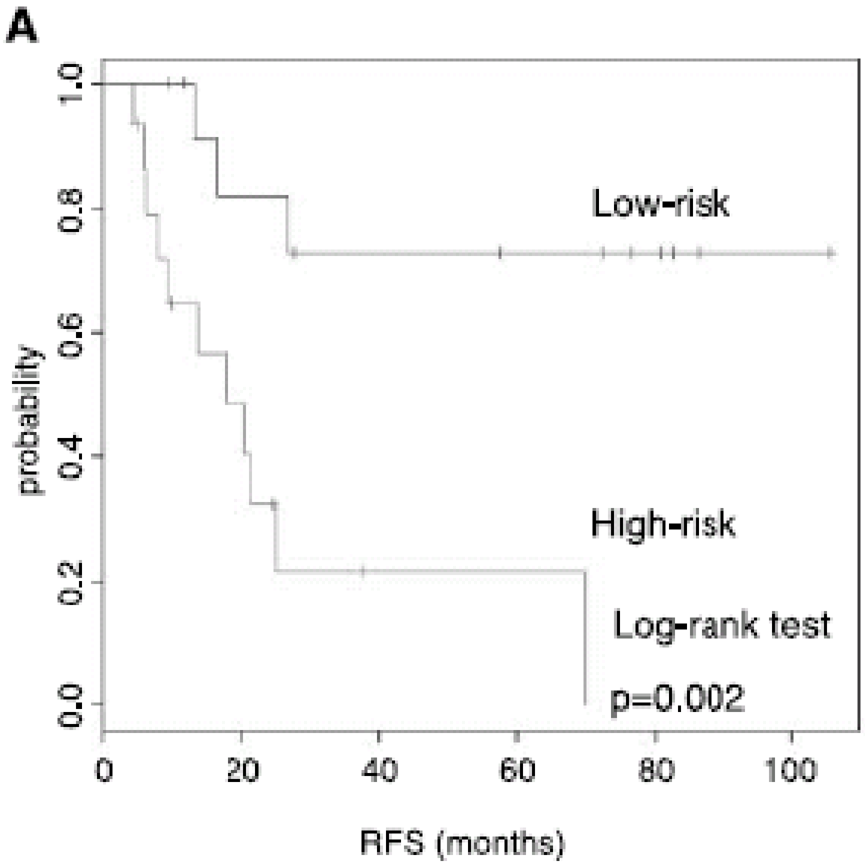
group 1	group 2	group 3	group 4
TGF-alfa	Mesenchimal cell signature	Epithelium like signature	Antioxidant enzymes high levels
EGFR phos			
Angiogenic switch			

SCC Gene Expression



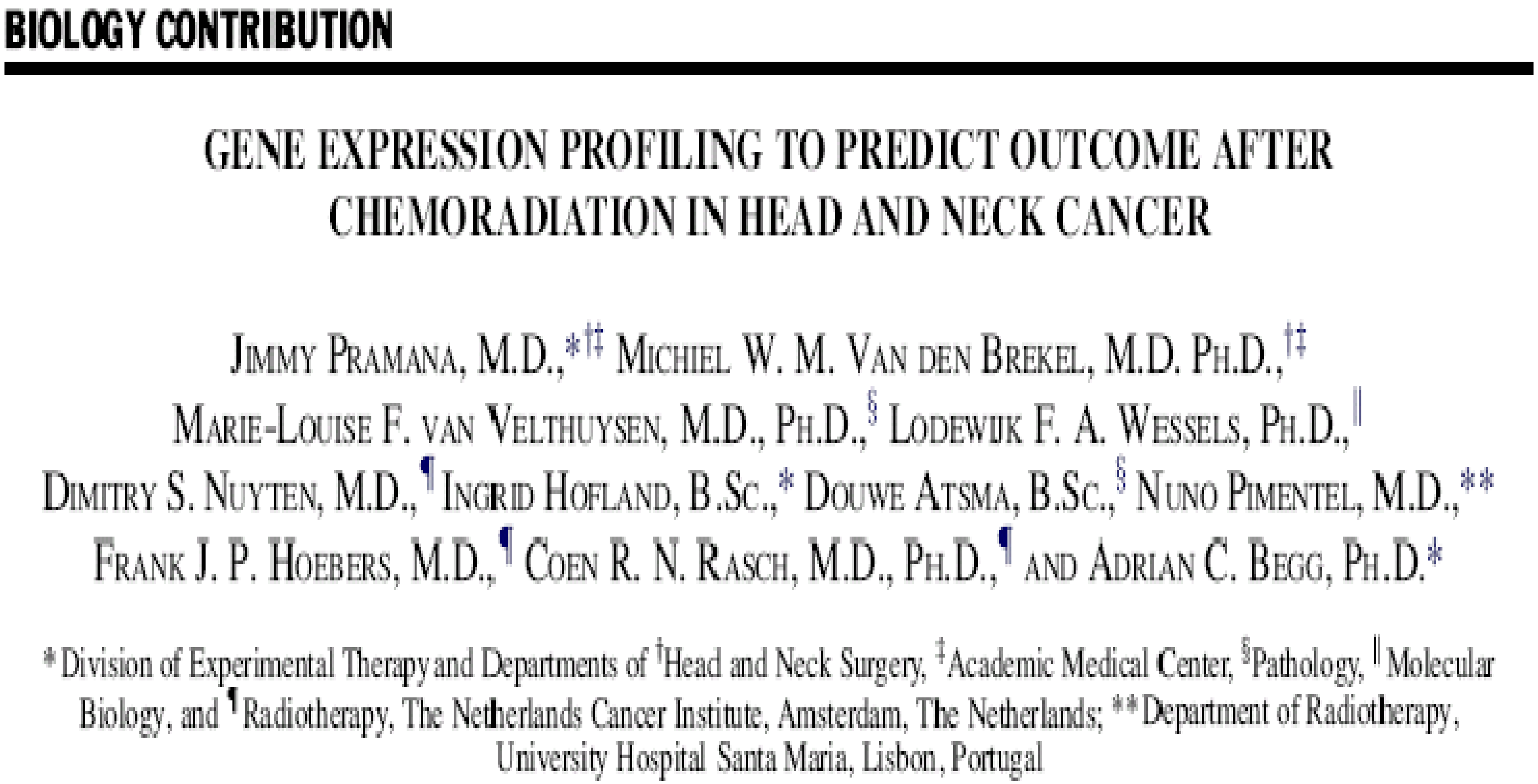
Chung Cancer Cell 2004

SCC Gene Expression



Chung Cancer Cell 2004

SCC Gene Expression


BIOLOGY CONTRIBUTION

GENE EXPRESSION PROFILING TO PREDICT OUTCOME AFTER CHEMORADIATION IN HEAD AND NECK CANCER

Jimmy Pramana, M.D.,[*†‡] Michiel W. M. Van den Brekel, M.D. Ph.D.,[†‡] Marie-Louise F. van Velthuysen, M.D., Ph.D.,[§] Lodewijk F. A. Wessels, Ph.D.,[||] Dimitry S. Nuyten, M.D.,[¶] Ingrid Hofland, B.Sc.,[*] Douwe Atsma, B.Sc.,[§] Nuno Pimentel, M.D.,[**] Frank J. P. Hoebers, M.D.,[¶] Coen R. N. Rasch, M.D., Ph.D.,[¶] and Adrian C. Begg, Ph.D.[*]

[*]Division of Experimental Therapy and Departments of [†]Head and Neck Surgery, [‡]Academic Medical Center, [§]Pathology, [||]Molecular Biology, and [¶]Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [**]Department of Radiotherapy, University Hospital Santa Maria, Lisbon, Portugal

Int J Radiat Oncol Biol Phys 2007

Significant signature by GSEA for HR group…

- Epithelial to mesenchimal transition

  (i.e MM-P2; stratifin)
- Nuclear factor – kB

  (i.e HIF 1-alfa MYC, PTEN, IGFR, HSP90)
- Cellular adhesion

Exome Sequencing of Head and Neck Squamous Cell Carcinoma Reveals Inactivating Mutations in *NOTCH1*

Nishant Agrawal,[1,2]*† Mitchell J. Frederick,[3]* Curtis R. Pickering,[3]* Chetan Bettegowda,[2,4]* Kyle Chang,[5] Ryan J. Li,[1] Carole Fakhry,[1] Tong-Xin Xie,[3] Jiexin Zhang,[6] Jing Wang,[6] Nianxiang Zhang,[6] Adel K. El-Naggar,[7] Samar A. Jasser,[3] John N. Weinstein,[6] Lisa Treviño,[5] Jennifer A. Drummond,[5] Donna M. Muzny,[5] Yuanqing Wu,[5] Laura D. Wood,[8] Ralph H. Hruban,[8] William H. Westra,[8] Wayne M. Koch,[1] Joseph A. Califano,[1,9] Richard A. Gibbs,[5,9] David Sidransky,[1] Bert Vogelstein,[2] Victor E. Velculescu,[2]† Nickolas Papadopoulos,[2] David A. Wheeler,[5] Kenneth W. Kinzler,[2]† Jeffrey N. Myers[3]†

The Mutational Landscape of Head and Neck Squamous Cell Carcinoma

Nicolas Stransky,[1*] Ann Marie Egloff,[2*] Aaron D. Tward,[1,3,4*] Aleksandar D. Kostic,[1,5] Kristian Cibulskis,[1] Andrey Sivachenko,[1] Gregory V. Kryukov,[1,5] Michael S. Lawrence,[1] Carrie Sougnez,[1] Aaron McKenna,[1] Erica Shefler,[1] Alex H. Ramos,[1] Petar Stojanov,[1] Scott L. Carter,[1] Douglas Voet,[1] Maria L. Cortés,[1] Daniel Auclair,[1] Michael F. Berger,[1] Gordon Saksena,[1] Candace Guiducci,[1] Robert C. Onofrio,[1] Melissa Parkin,[1] Marjorie Romkes,[6] Joel L. Weissfeld,[7] Raja R. Seethala,[8] Lin Wang,[8] Claudia Rangel-Escareño,[9] Juan Carlos Fernandez-Lopez,[9] Alfredo Hidalgo-Miranda,[9] Jorge Melendez-Zajgla,[9] Wendy Winckler,[1] Kristin Ardlie,[1] Stacey B. Gabriel,[1] Matthew Meyerson,[1,5,10,11] Eric S. Lander,[1,5,12] Gad Getz,[1] Todd R. Golub,[1,5,11,13,14†] Levi A. Garraway,[1,5,10,11†‡] Jennifer R. Grandis[2,15†‡]

Science 2011

In brief

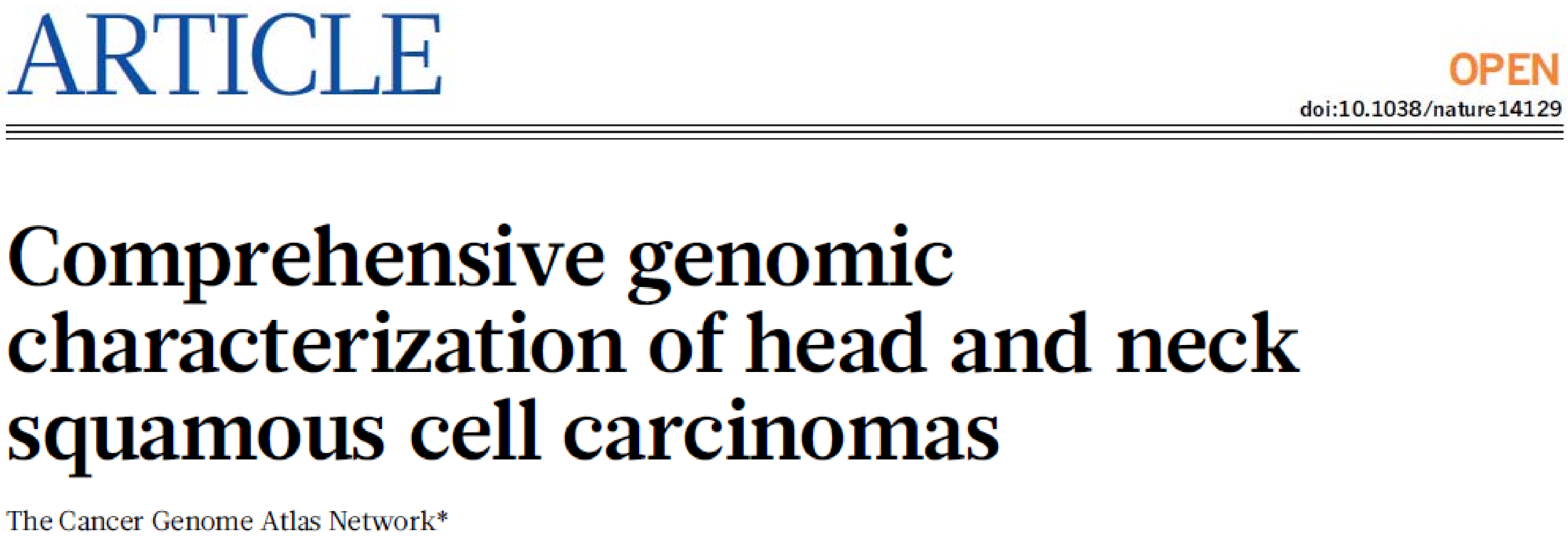
- High Troughput Technique
- P53, CDKN2A (p16), HRAS, PIK3CA, PTEN
- NOTCH (mut) tumor suppressor

SCC Gene Expression

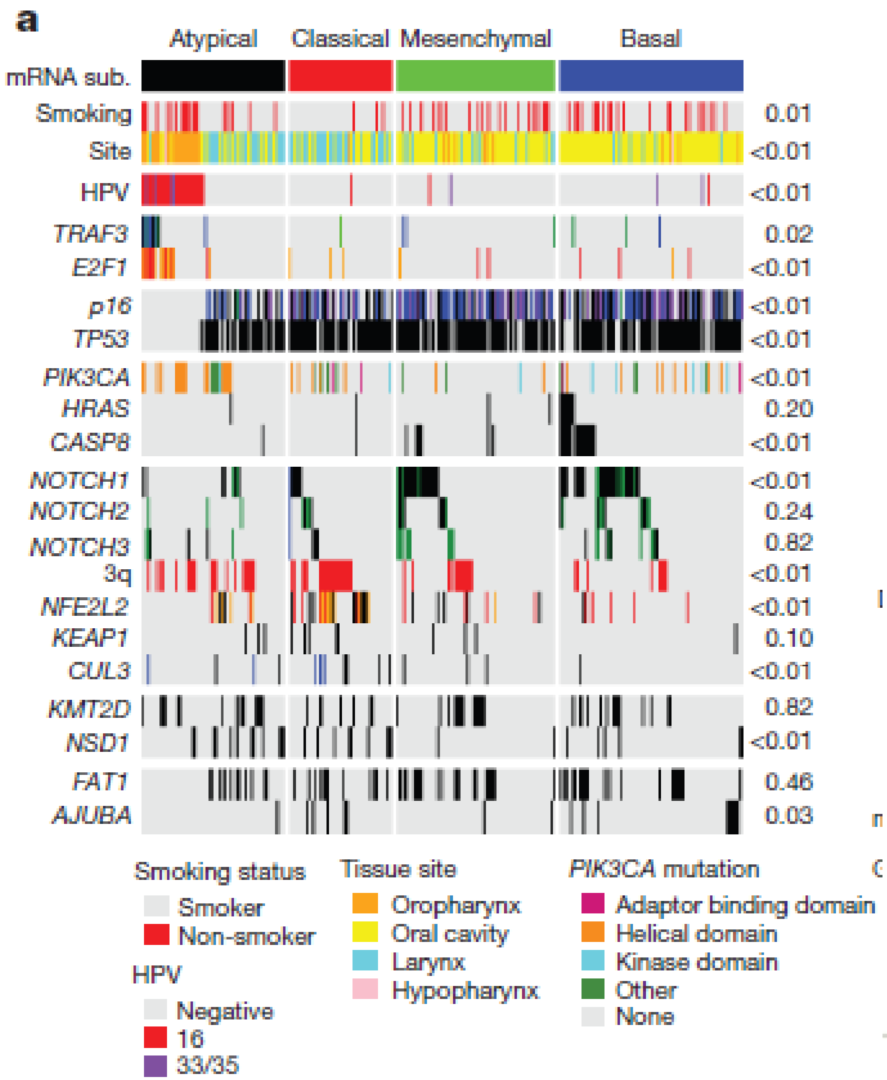
Mutated genes in H&N

Gene symbol	Function	Targets	TX	Mut rate
TP53	Tumor suppressor	p21,BAX, PUMA	Adenovirus based repalcement	40-60%
NOTCH1	Bivalent	Hes/Hey, p21	Secretase i	15%
HRAS	Oncogene	Raf/MEK/ERK PI3K/AKT	Dsi: MEK/AKT i Farnesyltransferase Antisense	4-35%
PIK3CA	Oncogene	Akt, PLCgamma1	PI3Ki Dsi: Akt, mTOR	6-8%
CDKN2A	Tumor suppressor	CDK 4/6	CDKi	9%

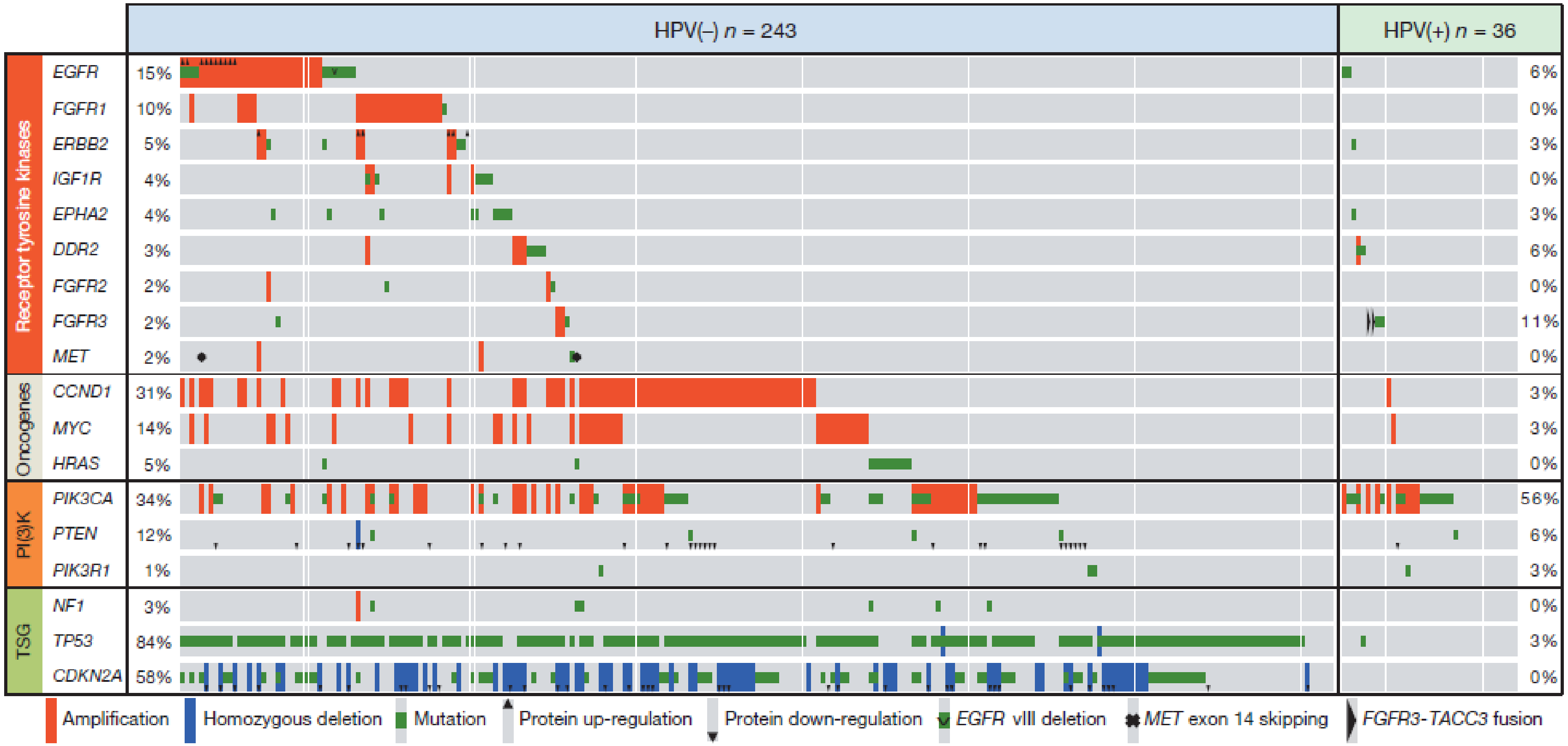
SCC biology


ARTICLE
OPEN
doi:10.1038/nature14129
Comprehensive genomic characterization of head and neck squamous cell carcinomas
The Cancer Genome Atlas Network*

SCC biology

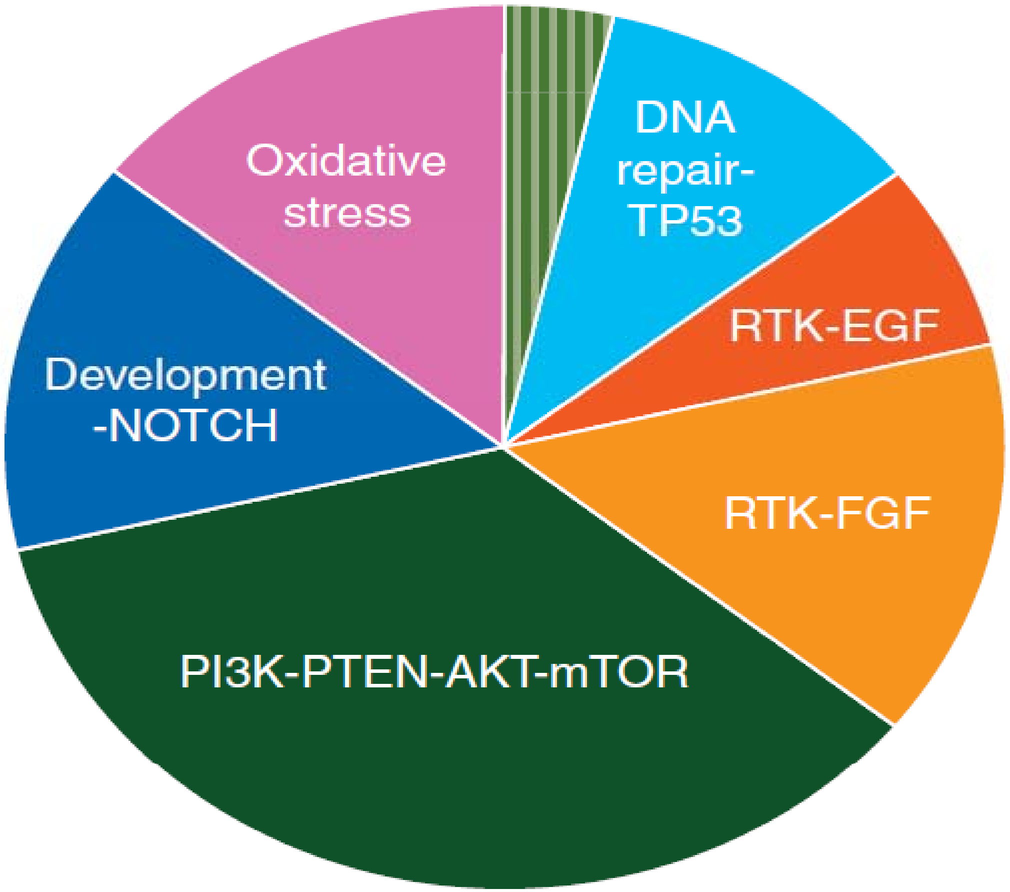

a
Atypical
Classical
Mesenchymal
Basal
mRNA sub.
Smoking
Site
HPV
TRAF3
E2F1
p16
TP53
PIK3CA
HRAS
CASP8
NOTCH1
NOTCH2
NOTCH3
3q
NFE2L2
KEAP1
CUL3
KMT2D
NSD1
FAT1
AJUBA
0.01
<0.01
<0.01
0.02
<0.01
<0.01
<0.01
<0.01
0.20
<0.01
<0.01
0.24
0.82
<0.01
<0.01
0.10
<0.01
0.82
<0.01
0.46
0.03
Smoking status
Smoker
Non-smoker
HPV
Negative
16
33/35
Tissue site
Oropharynx
Oral cavity
Larynx
Hypopharynx
PIK3CA mutation
Adaptor binding domain
Helical domain
Kinase domain
Other
None

SCC biology



HPV(–) n = 243
HPV(+) n = 36
Receptor tyrosine kinases
EGFR 15% 6%
FGFR1 10% 0%
ERBB2 5% 3%
IGF1R 4% 0%
EPHA2 4% 3%
DDR2 3% 6%
FGFR2 2% 0%
FGFR3 2% 11%
MET 2% 0%
Oncogenes
CCND1 31% 3%
MYC 14% 3%
HRAS 5% 0%
PI(3)K
PIK3CA 34% 56%
PTEN 12% 6%
PIK3R1 1% 3%
TSG
NF1 3% 0%
TP53 84% 3%
CDKN2A 58% 0%
Amplification
Homozygous deletion
Mutation
Protein up-regulation
Protein down-regulation
EGFR vIII deletion
MET exon 14 skipping
FGFR3-TACC3 fusion

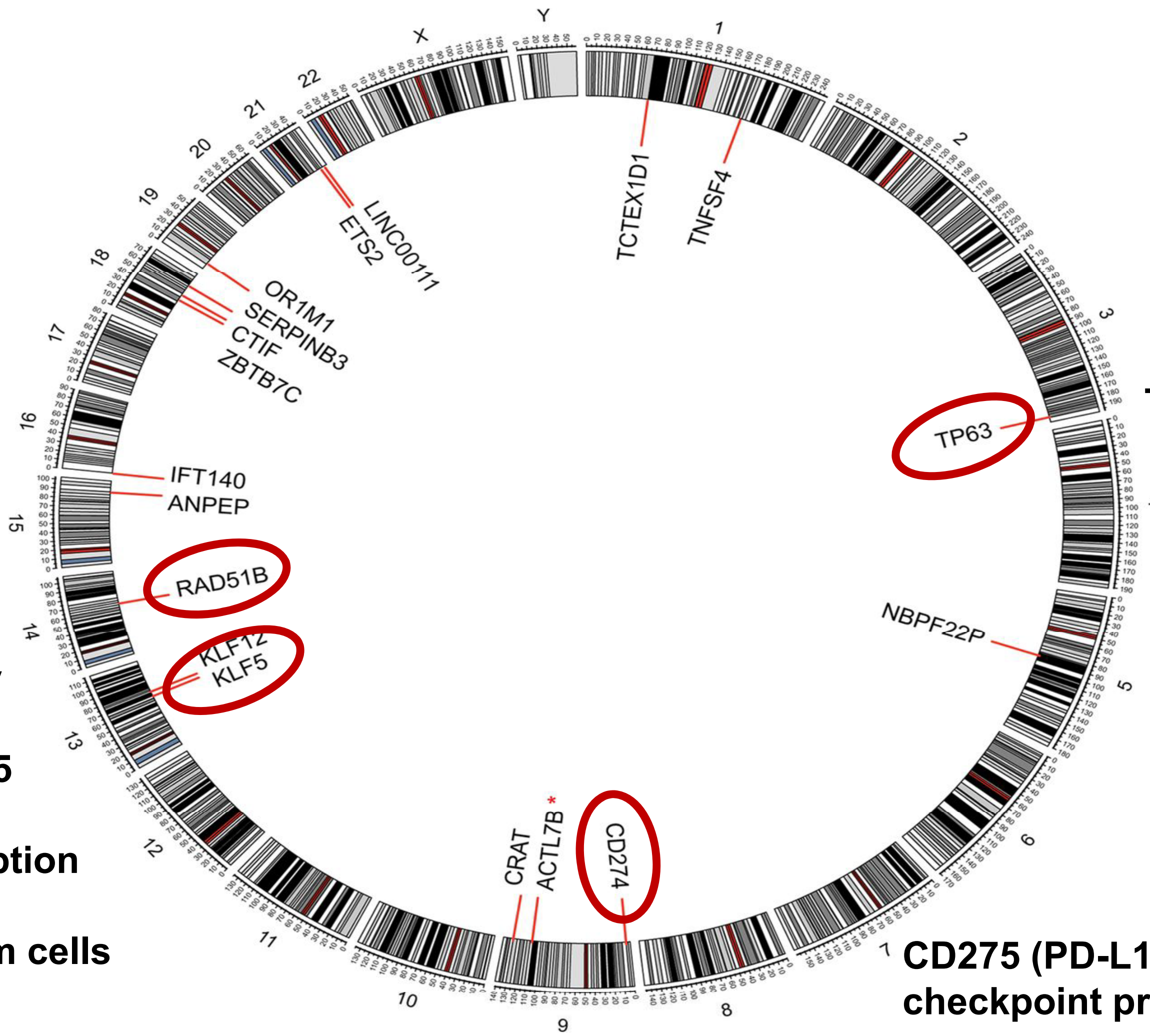
Deregulated pathways in HPV+ HNSCC



Pathway name	% samples altered
PI3K-PTEN-AKT-mTOR	48%
Development-NOTCH	19%
Oxidative stress	19%
RTK-GF-FGF	19%
DNA repair-53	14%
RTK-GF-EGF	10%
Cell cycle-CCND-RB1	5%
Cell cycle-CDKN2A/B-CDK	0%

Chung, et al. Ann Oncol 2015

Integration sites of HPV16 in HNSCC



TP63: a member of the p53 family, tumor suppressor, decrease chemosensitivity

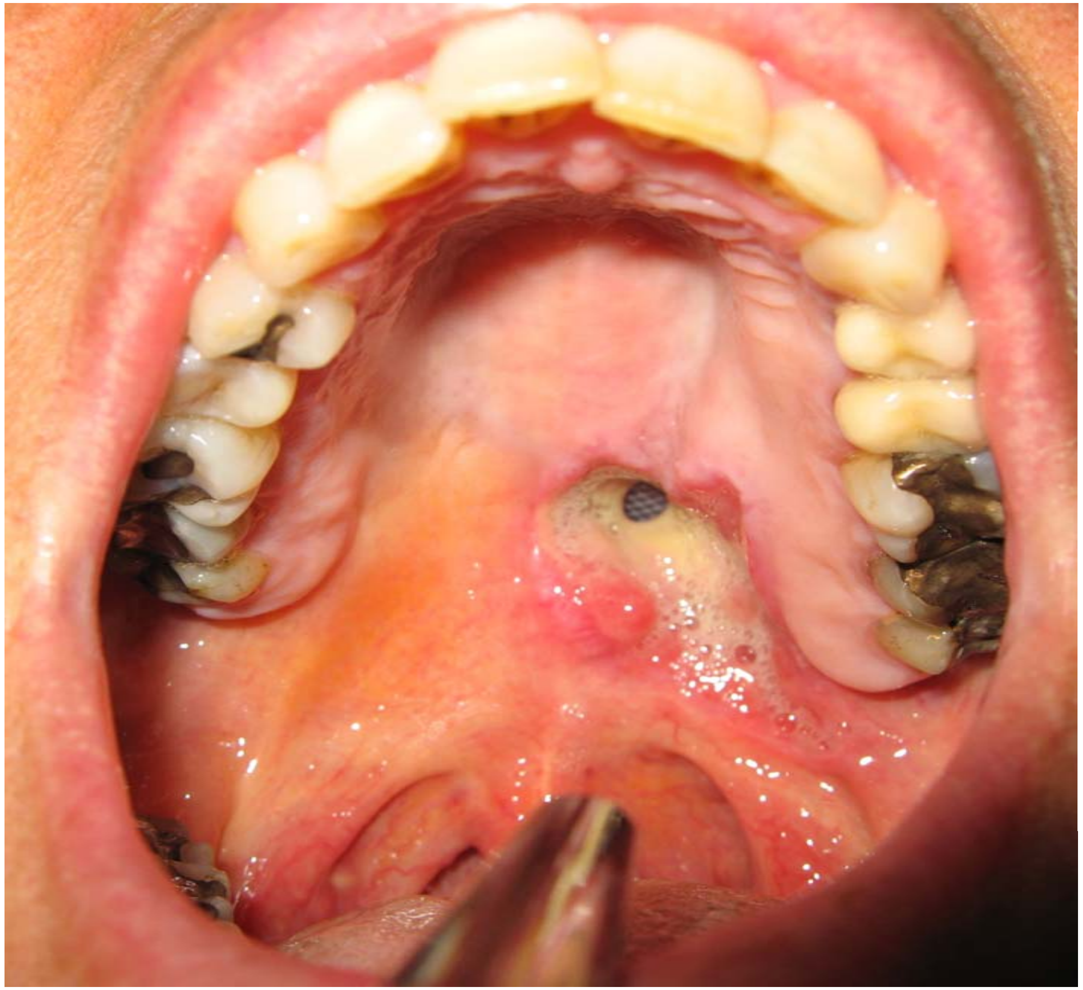
RAD51B: DNA damage repair, radiation sensitivity

Kruppel-like factor 5 (KLF5): zinc-finger-containing transcription factor, maintain pluripotency in stem cells

CD275 (PD-L1, B7-H1): Immune checkpoint protein

Joseph D. Khoury et al. J. Virol. 2013;87:8916-8926

SALIVARY GLAND TUMOR



INCIDENCE SCC

RARECARE

Surveillance of Rare Cancers in Europe

Tumour	Rate	Patients
EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY-GLAND TYPE TUMOURS	**1,31**	**10.514**
Epithelial tumours of major salivary glands	**0,73**	**5.861**
Salivary gland type tumours of head and neck	**0,43**	**3.451**

Rate: Incidence considered as number of cases / 100,000 persons / year

ESTRO School

2005 WHO SGC CLASSIFICATION

Acinic cell carcinoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma
Epithelial-myoepithelial carcinoma
Clear cell carcinoma, NOS
Basal cell adenocarcinoma
Sebaceous carcinoma
Sebaceous lymphadenocarcinoma
Cystadenocarcinoma
Low-grade cribriform cystadenocarcinoma
Mucinous adenocarcinoma

Oncocytic carcinoma
Salivary duct carcinoma
Adenocarcinoma, NOS
Myoepithelial carcinoma
Carcinoma ex pleomorphic adenoma
Carcinosarcoma
Metastatizing pleomorphic adenoma
Squamous cell carcinoma
Small cell carcinoma
Large cell carcinoma
Lymphoepithelial carcinoma
Sialoblastoma

SGC RISK FACTORS

- Radiation exposure
  - Radiation treatment to the head and neck
  - Workplace exposure
- Family history
- Nickel alloy dust silica dust – not certain

HIGH RISK SALIVARY GLAND CANCER

- SDC
- MCC: grading
- ACC: staging (bone), hist. pattern (solid component > 30%), surg margins
- AdC: grading
- MC: grading
- Acinic Cell C: submandibular origin, staging
- EMC recurrence 40%

ESTRO School

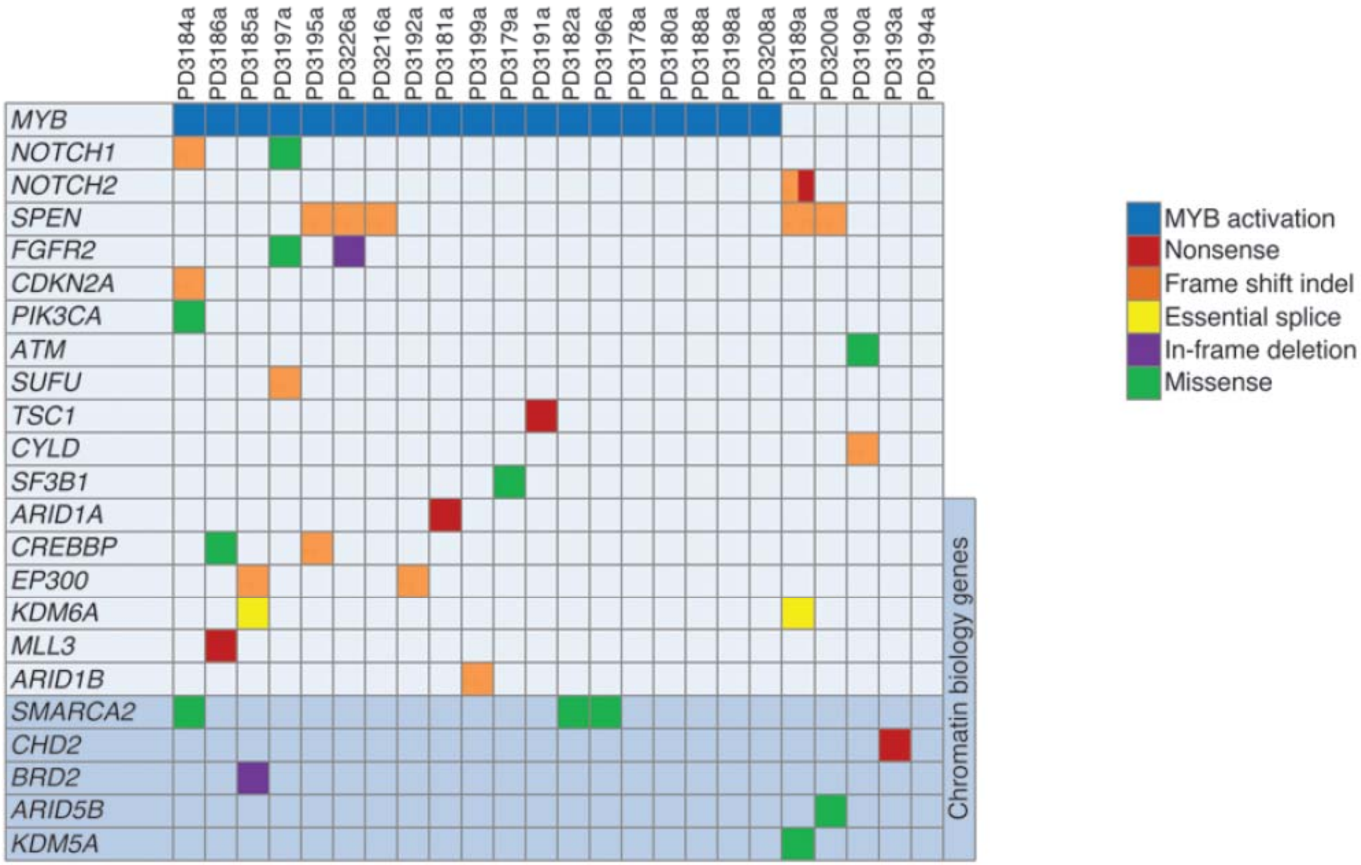
Whole exome sequencing of adenoid cystic carcinoma

Philip J. Stephens,[1] Helen R. Davies,[1] Yoshitsugu Mitani,[2] Peter Van Loo,[1,3] Adam Shlien,[1] Patrick S. Tarpey,[1] Elli Papaemmanuil,[1] Angela Cheverton,[1] Graham R. Bignell,[1] Adam P. Butler,[1] John Gamble,[1] Stephen Gamble,[1] Claire Hardy,[1] Jonathan Hinton,[1] Mingming Jia,[1] Alagu Jayakumar,[1] David Jones,[1] Calli Latimer,[1] Stuart McLaren,[1] David J. McBride,[1] Andrew Menzies,[1] Laura Mudie,[1] Mark Maddison,[1] Keiran Raine,[1] Serena Nik-Zainal,[1] Sarah O'Meara,[1] Jon W. Teague,[1] Ignacio Varela,[1] David C. Wedge,[1] Ian Whitmore,[1] Scott M. Lippman,[4] Ultan McDermott,[1] Michael R. Stratton,[1] Peter J. Campbell,[1] Adel K. El-Naggar,[2] and P. Andrew Futreal[1]

[1]Cancer Genome Project, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, United Kingdom. [2]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA. [3]Human Genome Laboratory, Department of Human Genetics, VIB and KU Leuven, Leuven, Belgium. [4]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

JCI 2013

ACC



PD3184a
PD3186a
PD3185a
PD3197a
PD3195a
PD3226a
PD3216a
PD3192a
PD3181a
PD3199a
PD3179a
PD3191a
PD3182a
PD3196a
PD3178a
PD3180a
PD3188a
PD3198a
PD3208a
PD3189a
PD3200a
PD3190a
PD3193a
PD3194a
MYB
NOTCH1
NOTCH2
SPEN
FGFR2
CDKN2A
PIK3CA
ATM
SUFU
TSC1
CYLD
SF3B1
ARID1A
CREBBP
EP300
KDM6A
MLL3
ARID1B
SMARCA2
CHD2
BRD2
ARID5B
KDM5A
Chromatin biology genes
MYB activation
Nonsense
Frame shift indel
Essential splice
In-frame deletion
Missense

JCI 2013

SALIVARY GLAND CANCER

Human Cancer Biology

Clinical Cancer Research

Comprehensive Analysis of the *MYB-NFIB* Gene Fusion in Salivary Adenoid Cystic Carcinoma: Incidence, Variability, and Clinicopathologic Significance

Yoshitsugu Mitani[1], Jie Li[1], Pulivarthi H. Rao[4], Yi-Jue Zhao[4], Diana Bell[1], Scott M. Lippman[2], Randal S. Weber[3], Carlos Caulin[3], and Adel K. El-Naggar[1]

2010

SALIVARY GLAND CANCER

GENES, CHROMOSOMES & CANCER 49:59–69 (2010)

Unfavorable Prognosis of *CRTC1-MAML2* Positive Mucoepidermoid Tumors with *CDKN2A* Deletions

Sarah L. Anzick,[1] Wei-Dong Chen,[1] Yoonsoo Park,[1] Paul Meltzer,[1] Diana Bell,[2] Adel K. El-Naggar,[2] and Frederic J. Kaye[1]*

[1]Genetics Branch, Center for Cancer Research, NCI, Bethesda, MD
[2]Department of Head and Neck Pathology, University of Texas, Anderson Cancer Center, Houston, TX

ESTRO School

SALIVARY GLAND CANCER

ORIGINAL ARTICLE

A Reappraisal of the MECT1/MAML2 Translocation in Salivary Mucoepidermoid Carcinomas

Raja R. Seethala, MD, Sanja Dacic, MD, PhD, Kathleen Cieply, MS, Lindsey M. Kelly, BS, and Marina N. Nikiforova, MD

A J Surg Pathol 2010

INCIDENCE, PATHOLOGY, RISK FACTORS OF SCC

THANKS!

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

L. Licitra, MD

JOINT EHNS-ESMO-ESTRO MULTIDISCIPLINARY TEACHING COURSE ON HEAD AND NECK ONCOLOGY

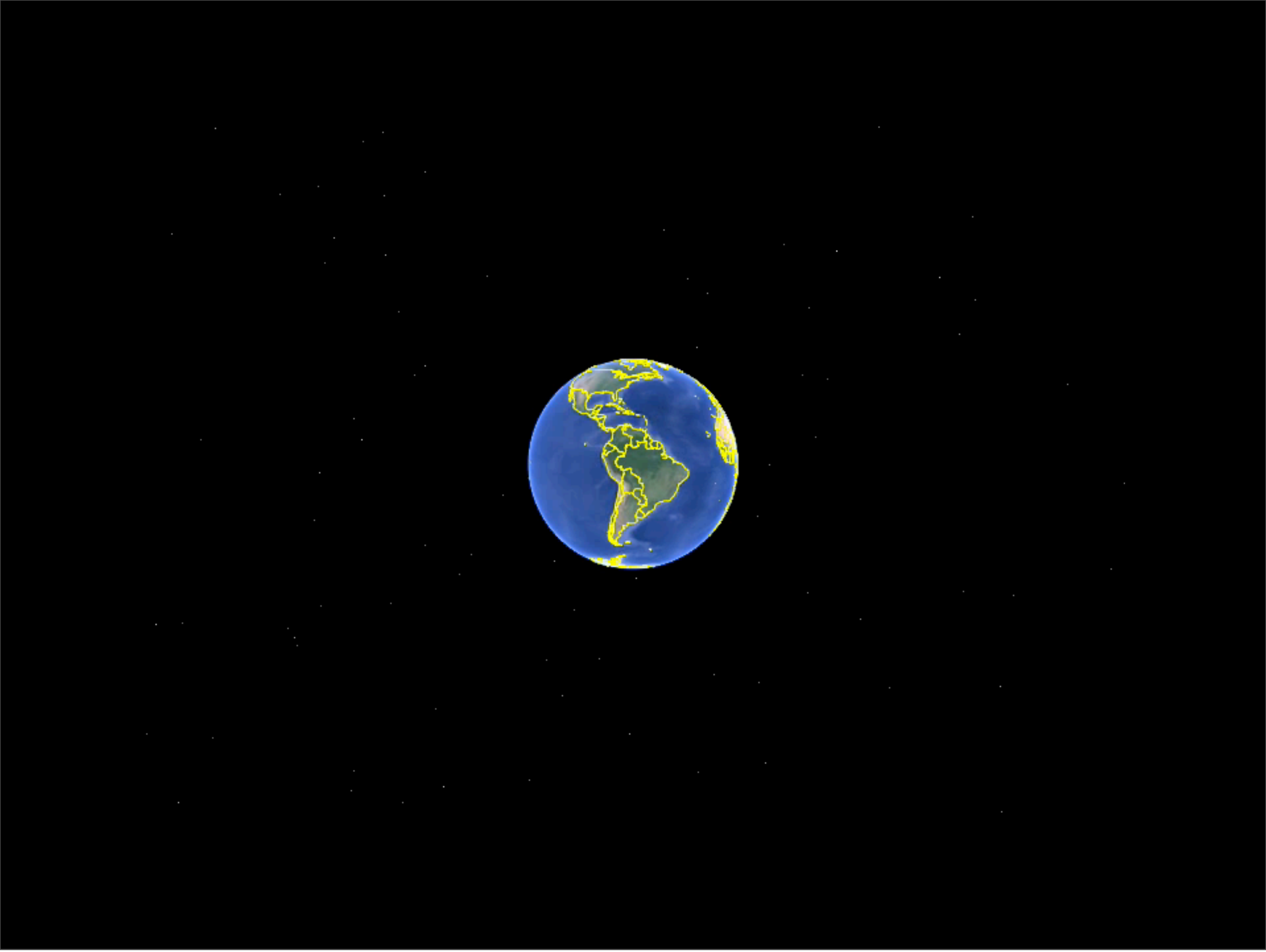
26-29 June
Florence, Italy

Clinical work-up for oral cavity & pharyngo-laryngeal tumors (including nasopharyngeal carcinoma) and staging

Piero Nicolai, MD

Department of Otorhinolaryngology – Head and Neck Surgery

University of Brescia, Italy



mercoledì 29 giugno 16

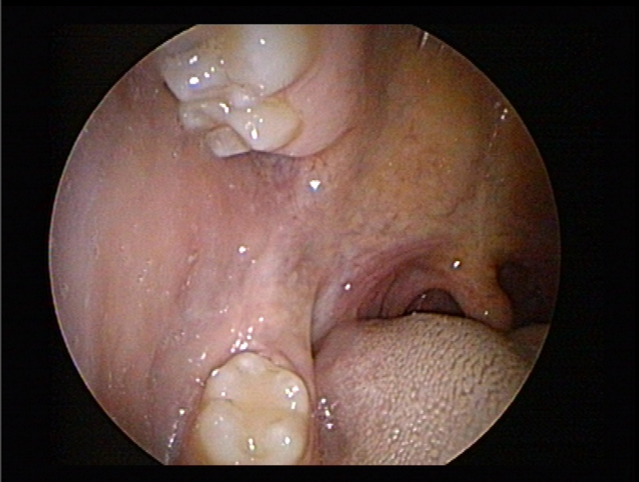


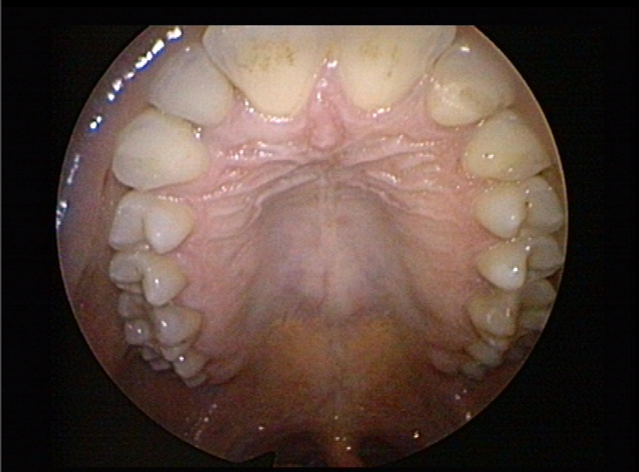



SUBSITES

Oral Cavity

Oropharynx



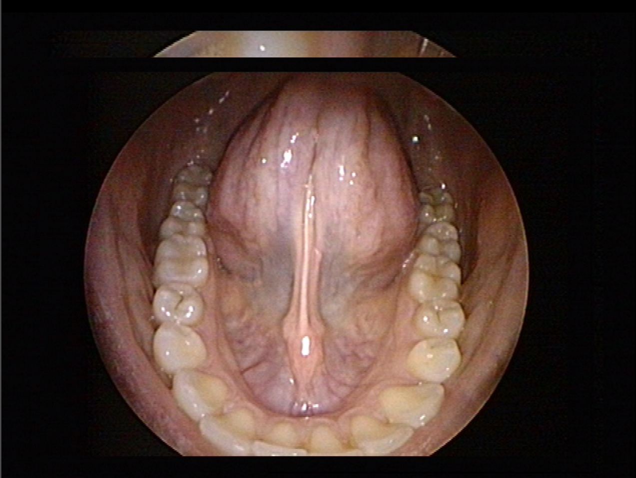


SUBSITES

Oral Cavity

Anterior tongue

Floor of mouth



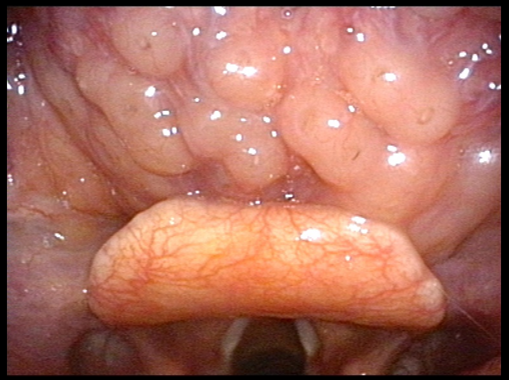
Buccal mucosa

Alveolar ridge or gum

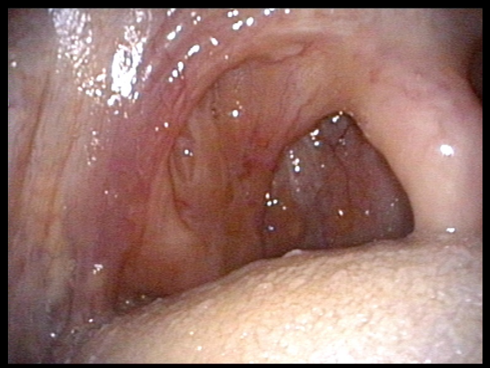
Retromolar trigone

Hard palate

Oropharynx

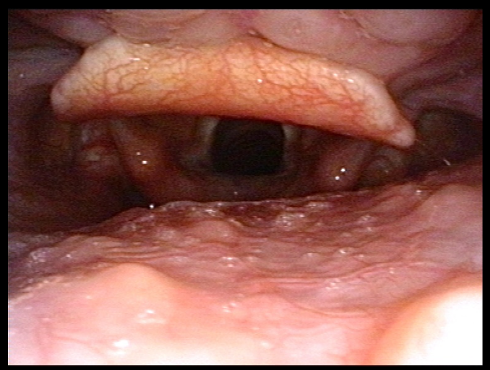


Base of tongue



Tonsil

Soft palate



Pharyngeal wall

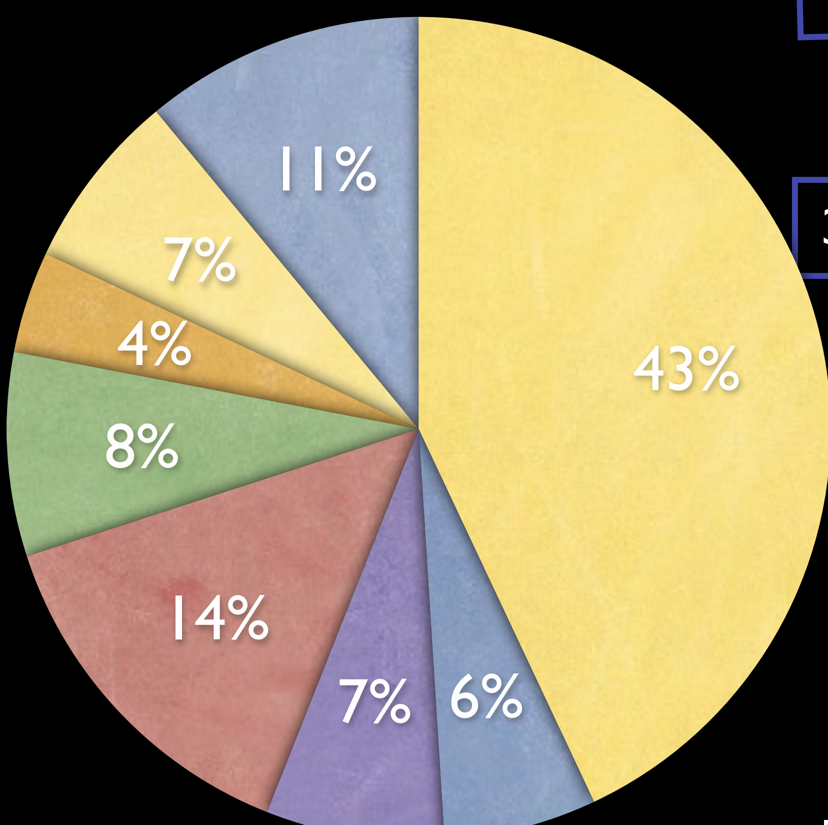
CLINICAL EVALUATION

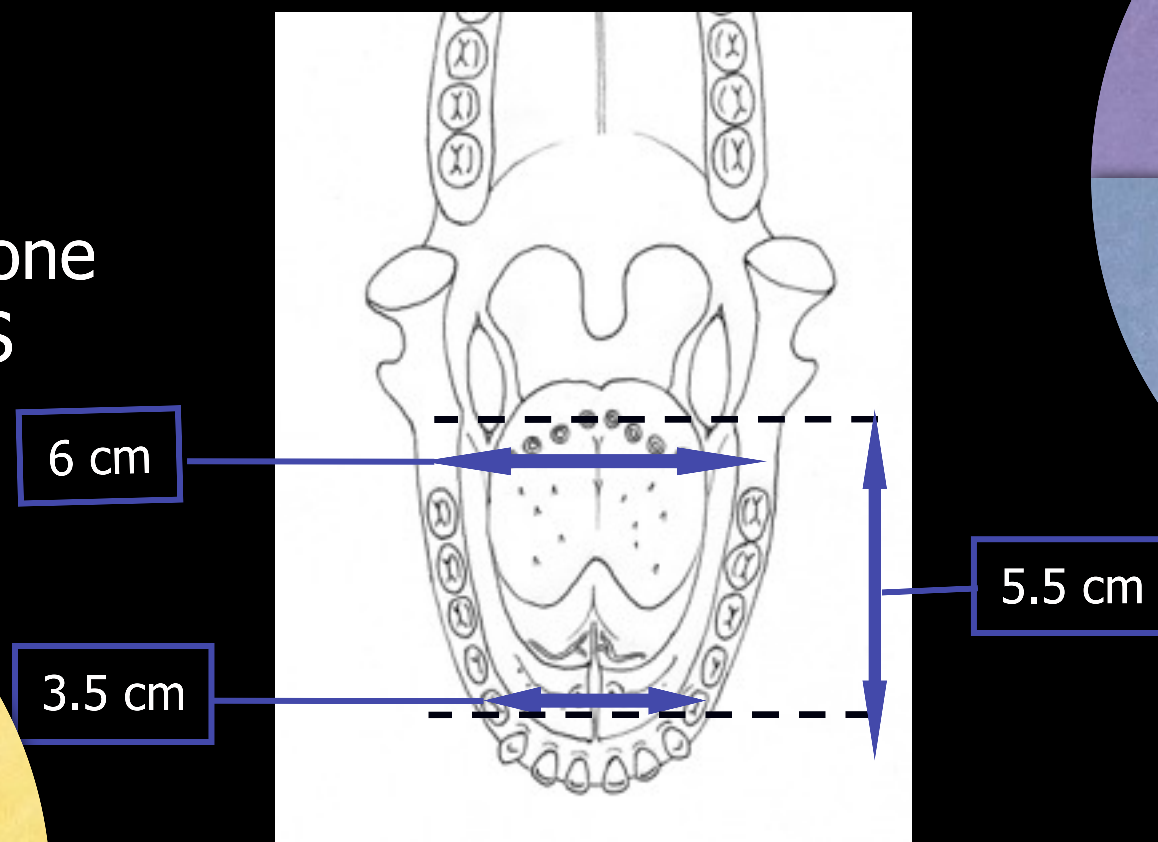
Oral Cavity

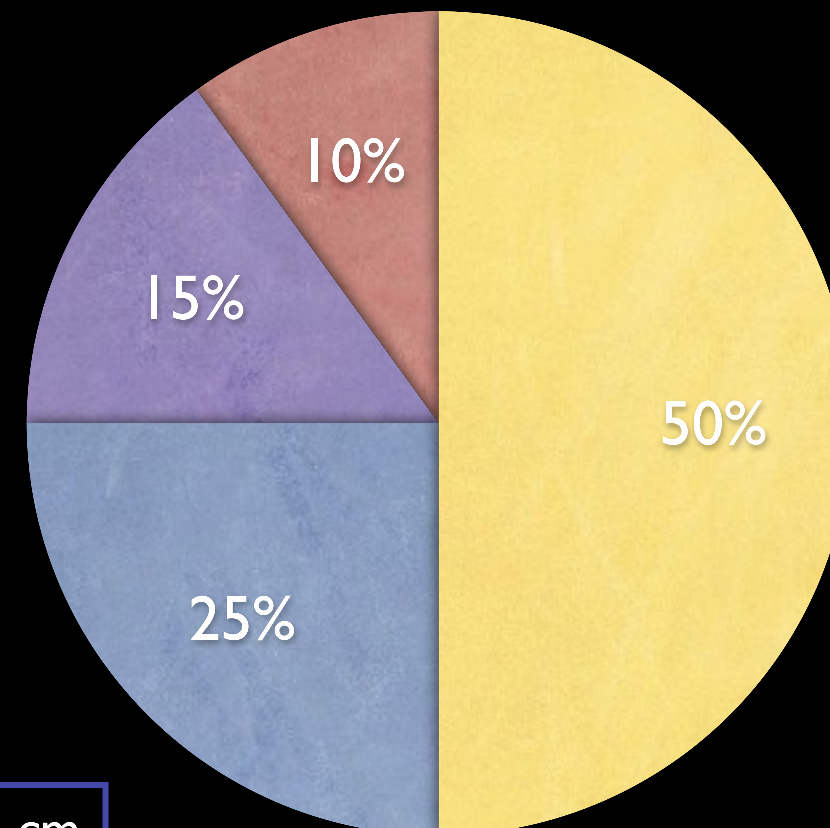
SITE

Oropharynx

- Mobile Tongue
- Maxillary Gum
- Mandibular Gum
- Floor of Mouth
- Buccal Mucosa
- Hard Palate
- Retromolar Trigone
- Oral Cavity, NOS







- Base of Tongue
- Tonsil
- Soft Palate
- Pharyngeal Wall

Data from Memorial Sloan-Kettering Cancer Center, New York

STAGING

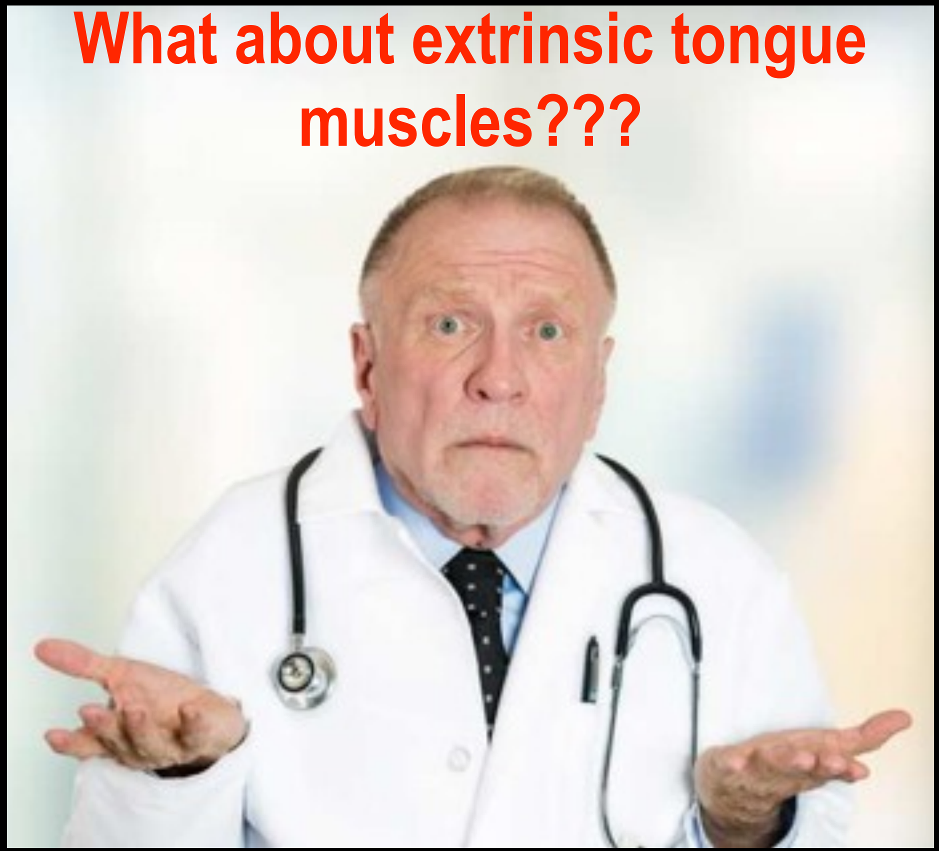
ORAL CAVITY

T1 Tumor 2cm or less in its greatest dimension

T2 Tumor bigger than 2 cm but less than 4 cm in its greatest dimension

T3 Tumor bigger than 4 cm in its greatest dimension

T4 T4a tumor invades adjacent structures (eg. through cortical bone of the mandible, **into deep extrinsic muscle of the tongue**, maxillary sinus, skin of face)
T4b tumor invades masticatory space, pterygoid plates, or skull base and/or encases the internal carotid artery



STAGING

OROPHARYNX

T1	Tumor 2 cm or less in its greatest dimension
T2	Tumor bigger than 2 cm but less than 4 cm in its greatest dimension
T3	Tumor bigger than 4 cm in its greatest dimension
T4	T4a: tumor invades the larynx, deep/extrinsic muscle of the tongue, medial pterygoid muscle, hard palate or mandible T4b: tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx or skull base or encases the carotid artery

HISTOPATHOLOGY

SCC variants

- ✓ spindle cell
- ✓ adenosquamous
- ✓ verrucous
- ✓ papillary

Glandular carcinomas

- ✓ adenocarcinoma
- ✓ mucoepidermoid
- ✓ adenoid cystic
- ✓ acinic cell
- ✓ undifferentiated

HISTOPATHOLOGY

Conventional SCC (G1, G2, G3)

SCC variants

- ✓ spindle cell
- ✓ adenosquamous
- ✓ verrucous
- ✓ papillary

90%

Malignant melanoma

Soft tissues sarcomas

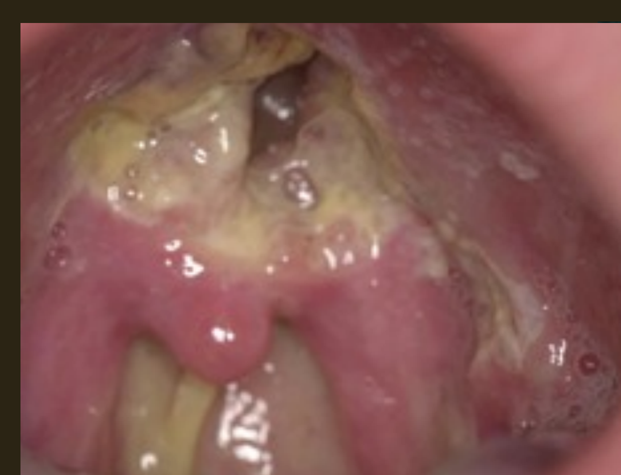
Lymphoproliferative disorders

Secondary tumors (kidney, lung)

Glandular carcinomas

10%

- ✓ adenocarcinoma
- ✓ mucoepidermoid
- ✓ adenoid cystic
- ✓ acinic cell
- ✓ undifferentiated



DIAGNOSTIC WORK-UP

- Clinical evaluation (site, dimension, dentation, trismus)
- Bi-dimensional (superficial) evaluation
  - ✓ HDTV-NBI
  - ✓ Autofluorescence
  - ✓ Toluidine blue
- Three-dimensional (deep) evaluation
  - ✓ Imaging (MRI, CT, neck US)
- “Systemic evaluation”
  - ✓ Imaging (PET, PET-CT, PET-MRI)
- Pathologic examination
  - ✓ Biopsy
  - ✓ HPV
  - ✓ EGFR

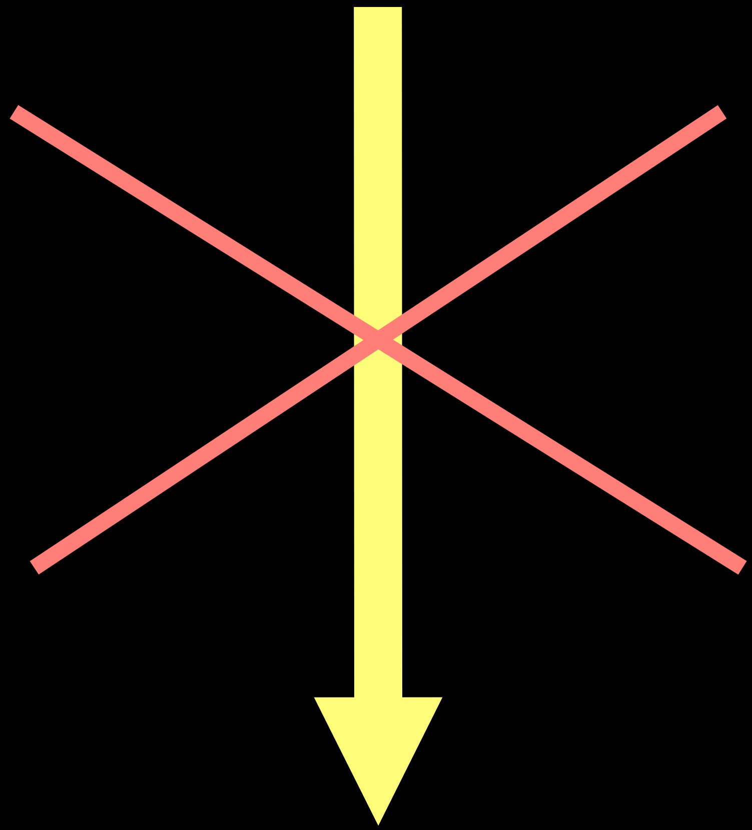
MORPHOLOGY

MACROSCOPIC ASPECT

HISTOPATHOLOGY

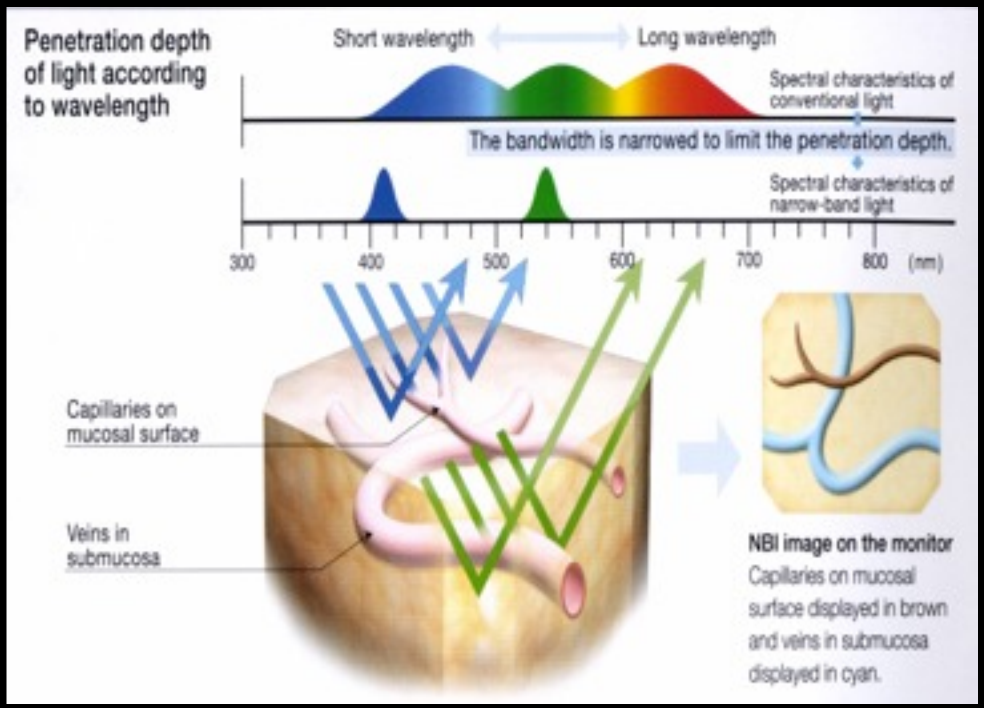
MORPHOLOGY

MACROSCOPIC ASPECT



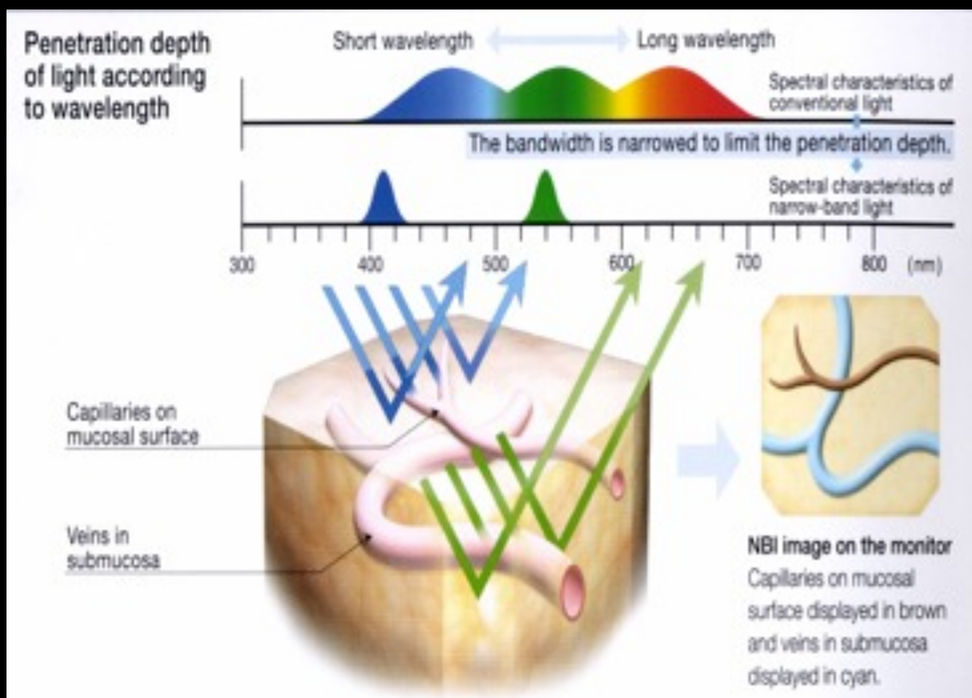
HISTOPATHOLOGY

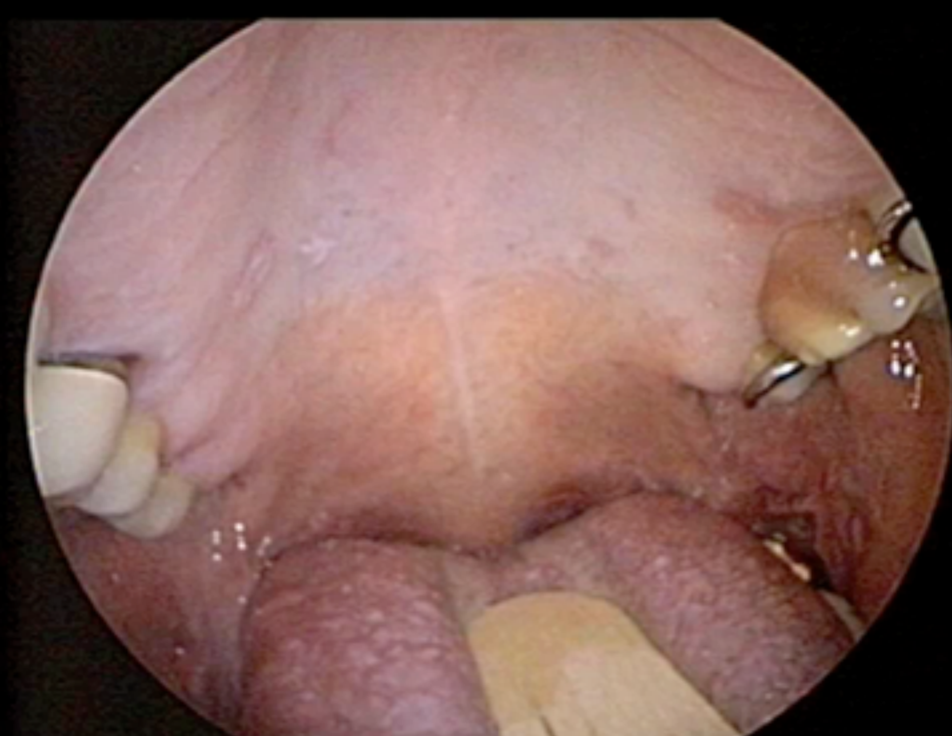
HDTV-WL and NBI (Narrow Band Imaging)



BI-DIMENSIONAL EVALUATION

HDTV-WL and NBI (Narrow Band Imaging)





Optical biopsy

Unknown primaries

Better definition of surgical margins

Identification of synchronous tumors

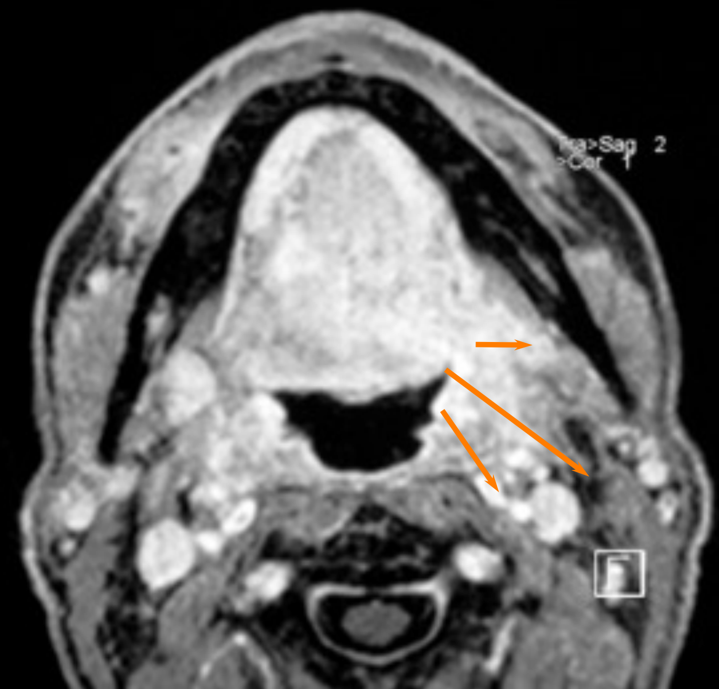
Early detection of persistence/recurrence

Metachronous tumor

IMAGING EVALUATION

PET-CT

IMAGING EVALUATION



CT/MRI

US

PET-CT

Soft tissue extension
(i.e. parapharyngeal space)

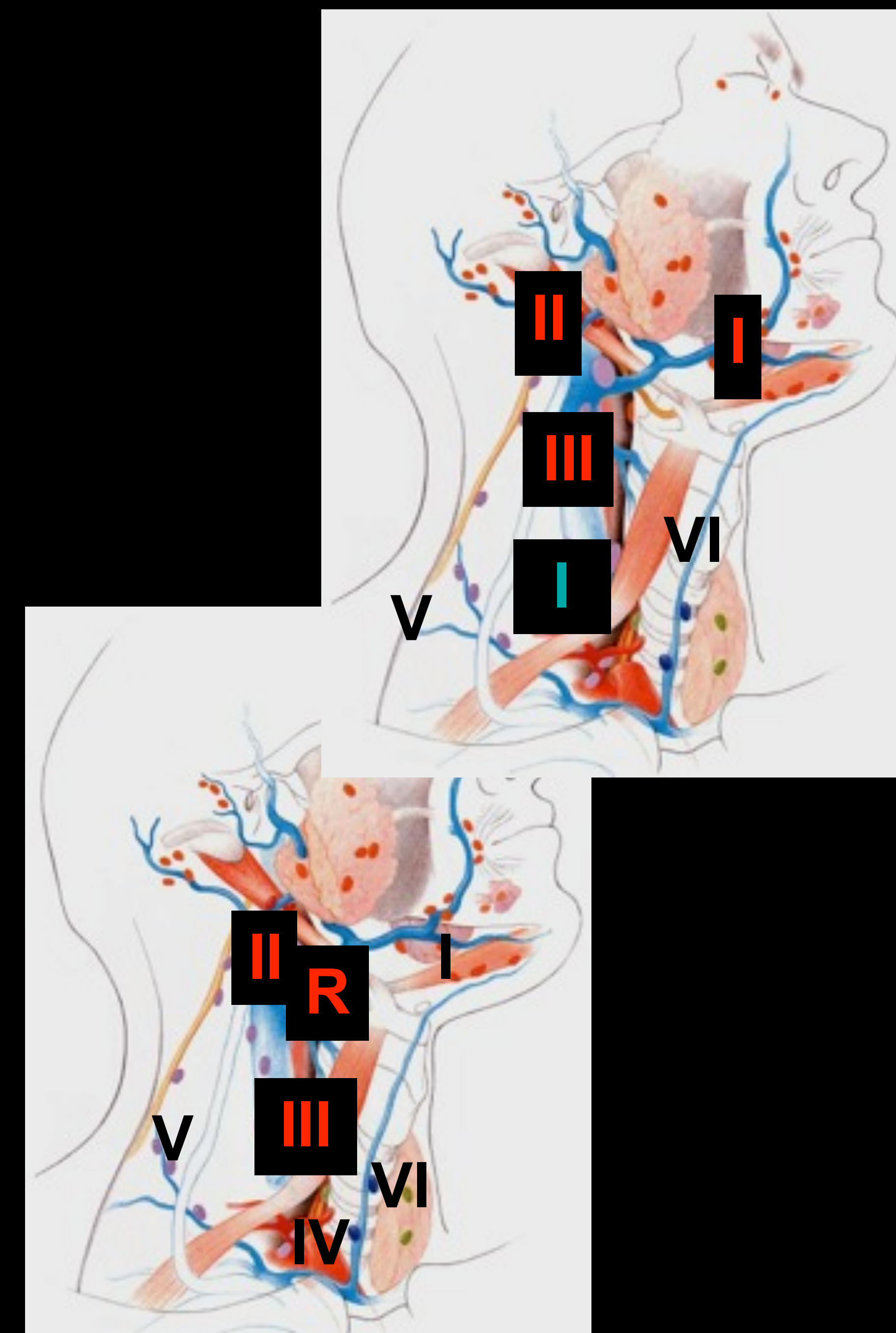
Mandibular involvement

Pterygoid muscles and plates
styloid muscles

Hypoglossal nerve(s)

Lingual artery(ies)

N status

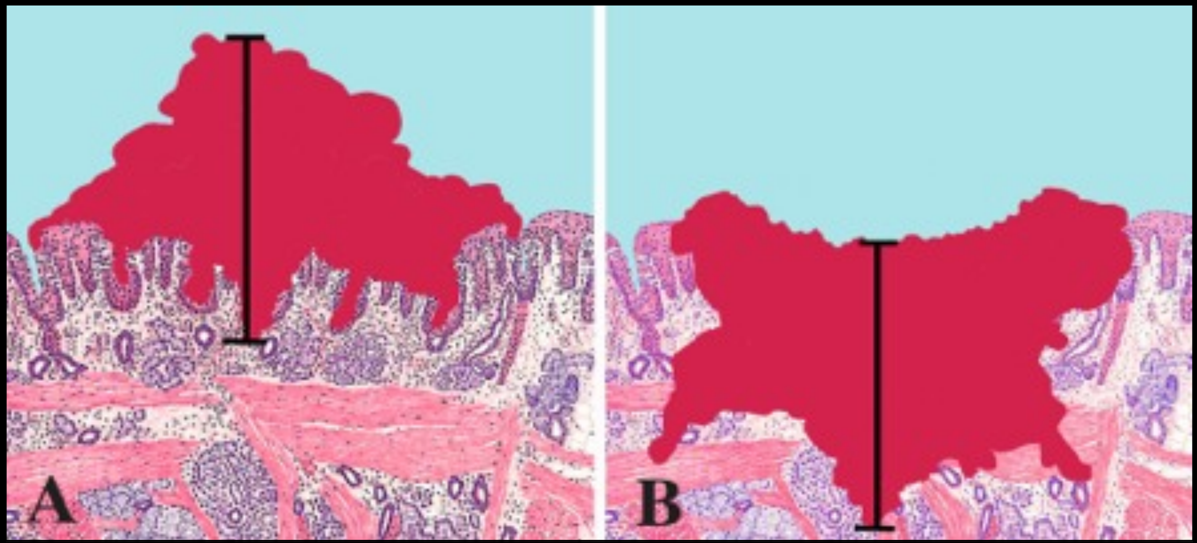


MORPHOLOGY

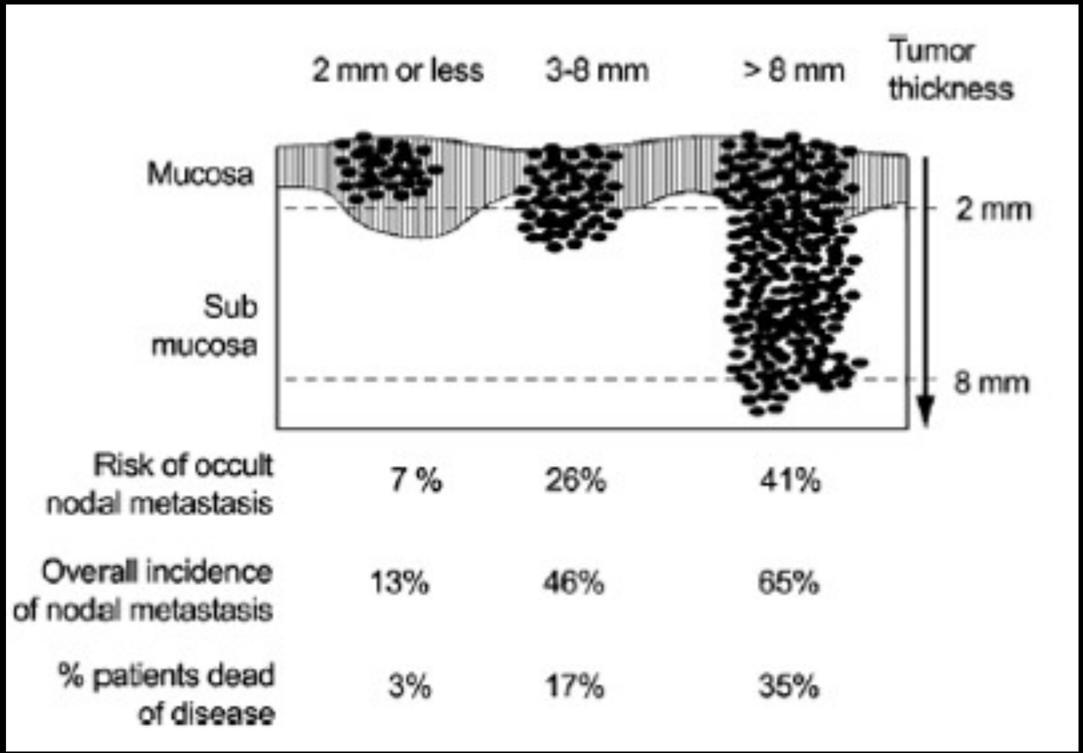
Thickness of the lesion

≠

depth of infiltration



Tumor Thickness	5-year Disease Survival (%)	Treatment Failure (%)
< 2 mm	97	2
2-8 mm	83	45
> 8 mm	65	45



Spiro et al., Am J Surg 1986

Shah et al., Oral Oncol 2009

ORAL CAVITY

INFILTRATION PATTERN

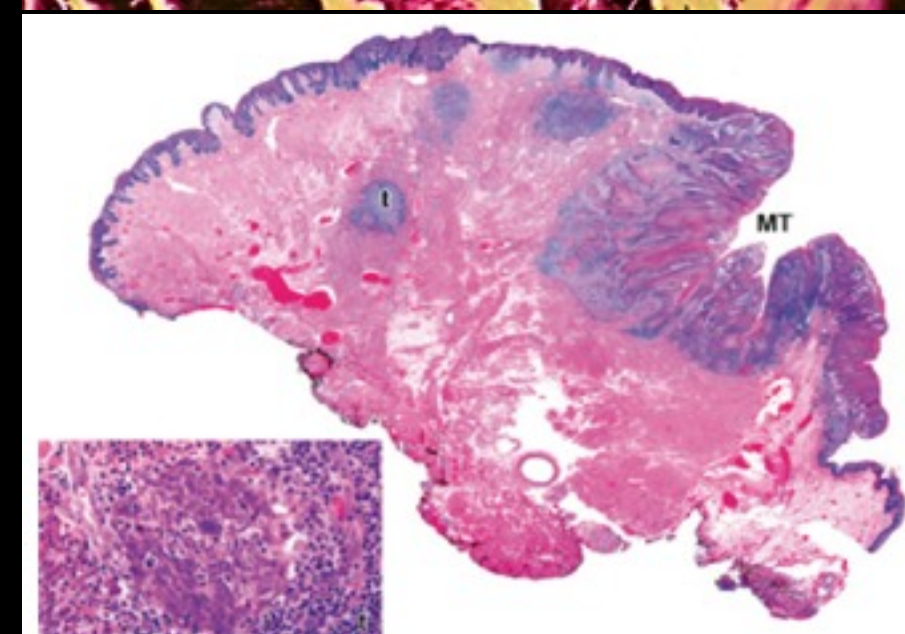
INSIDE LINGUAL MUSCLES - 2 directions:

- perpendicular to the mucosal surface
- longitudinal, in the extrinsic muscles (pT4)

OTHER MINOR RESISTENCE PATHWAYS:

- blood vessels
- lymphatic vessels
- neural fibers

SUBLINGUAL GLAND and MUSCLES OF THE FLOOR OF MOUTH



Calabrese et al., Oral Oncol, 2011
Calabrese et al., Curr Opin Otolaryngol Head Neck Surg, 2013

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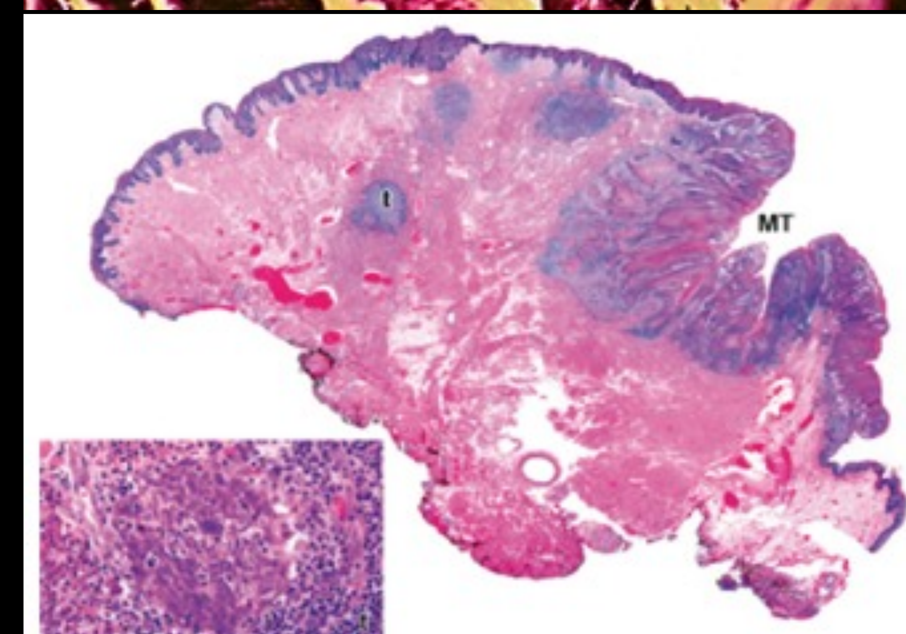


*Satellitosis and **local** micrometastases*

Calabrese et al., Oral Oncol, 2011
Calabrese et al., Curr Opin Otolaryngol Head Neck Surg, 2013

T2 vs T4

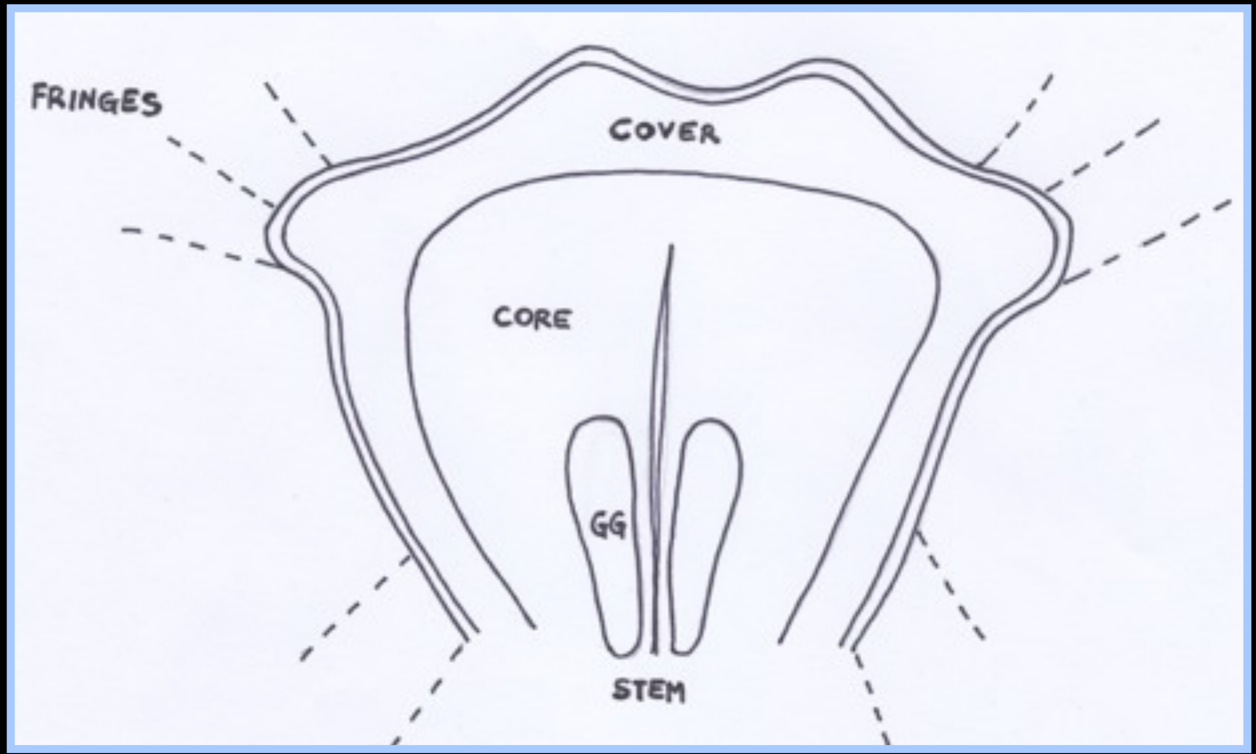
KEY POINTS

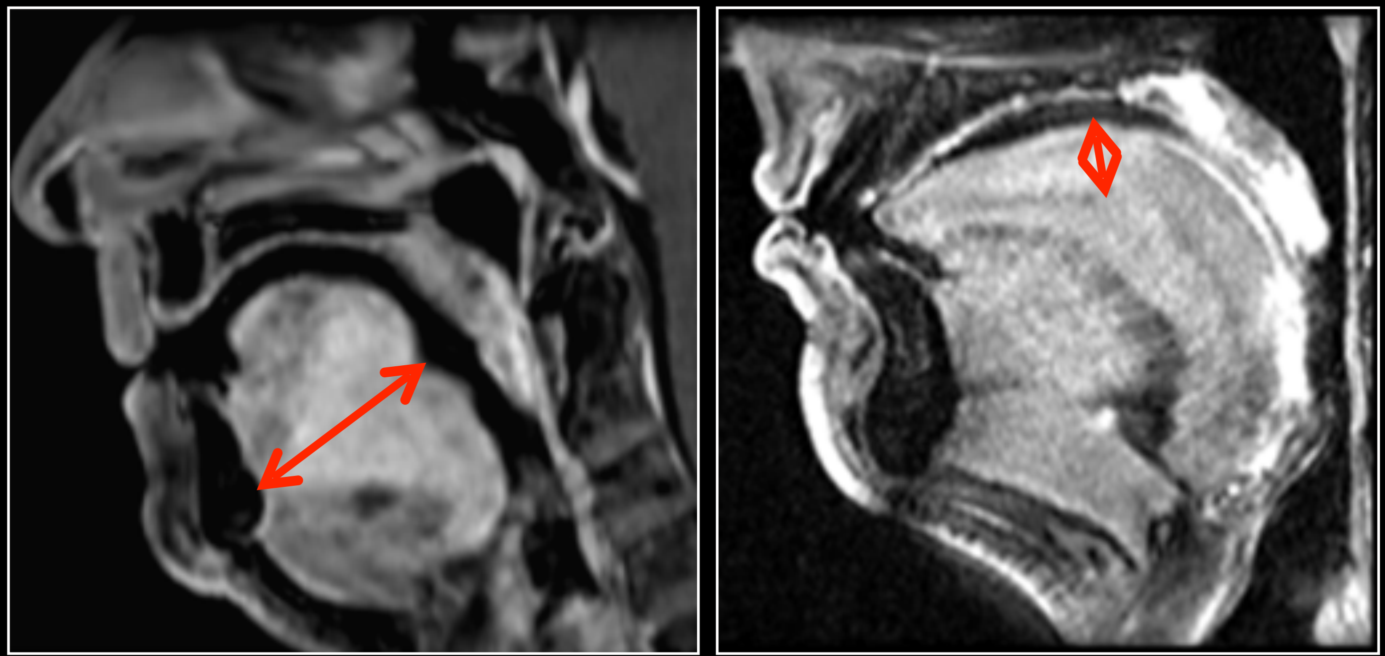
Depth of infiltration

↓

Involvement of extrinsic muscles

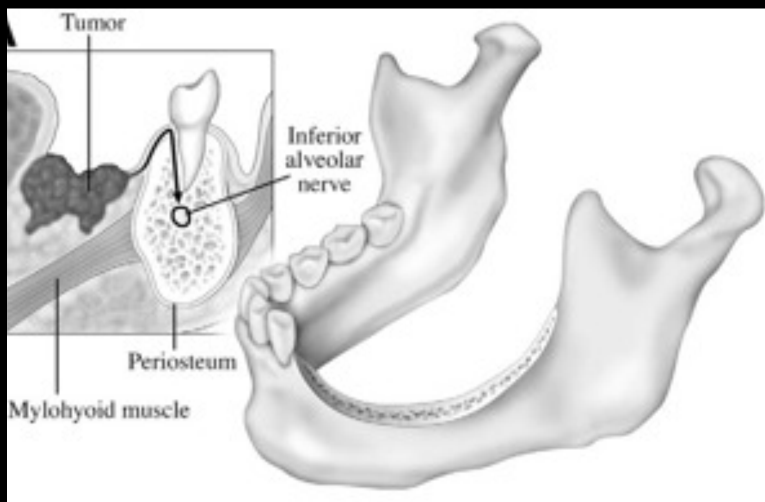
1 cm cut-off



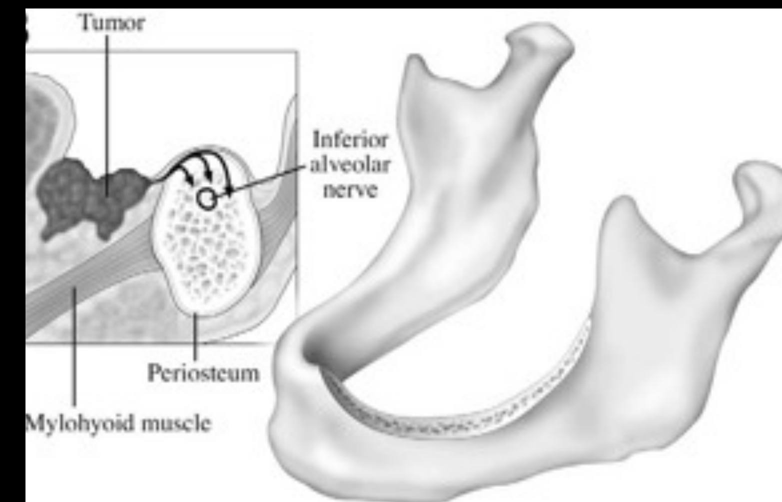


Takemoto, J Speech Lang Hear Res 2001
Napadow et al., J Biomech Eng 2002
Wilhelms-Tricarico R, 2005
Boland et al., Surg Radiol Anat 2013
Sanders et al., Anat Rec 2013

MANDIBULAR INVOLVEMENT



Dentate patients
vs
Edentulous patients



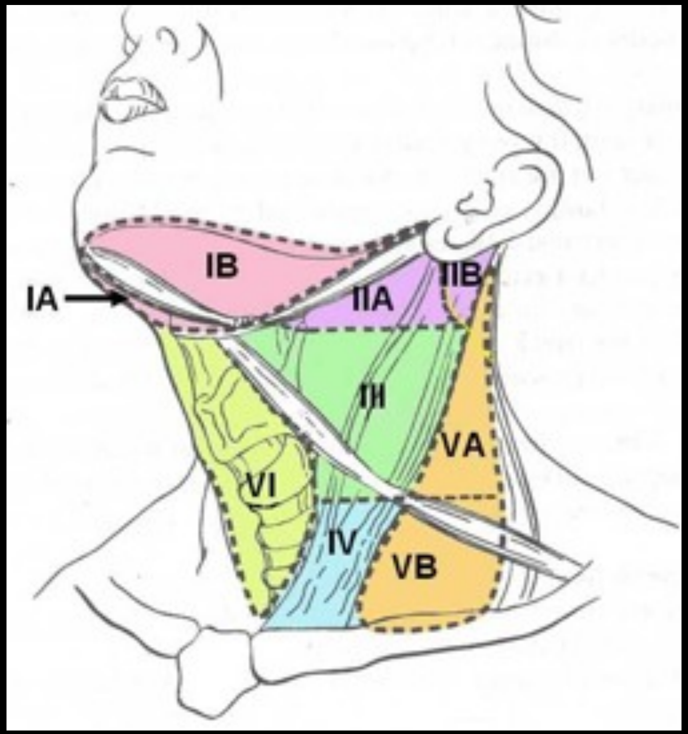
	OPT*	CT#	SPET°	SPECT*	MRI^
SENSITIVITY	50%	96%	95%	95%	93%
SPECIFICITY	94%	87%	48%	72%	93%
PPV	91%	89%	65%	79%	88%
NPV	63%	95%	93%	93%	96%

* : Imola et al., Laryngoscope 2001
# : Mukherji et al., AJR 2001
° : Zieron et al., Head Neck 2001
^ : Bolzoni Villaret et al., Arch Otolaryngol Head Neck Surg, 2004

N STAGING

30-50% of OC/OP tumors are cN+ at the diagnosis
Prevalence of N in relation to subsite

Mobile tongue	50-70%
Floor of the mouth	20-40%
Gengiva (alveolus)	20-40%
Retromolar trigon	20-40%
Base tongue - tonsil	> 70%
Soft palate	45%

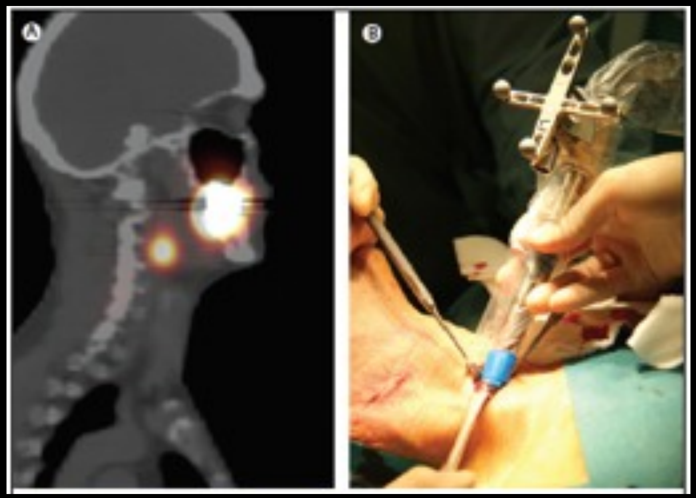


SECOND PRIMARIES

Second primaries in the UADT after a primary in the OC or OP develop in 14% (4-6% every year)

DIAGNOSTIC WORK-UP

SENTINEL NODE BIOPSY



- ✓ In T1-T2 cN0 carcinoma of OC or OP
- ✓ successful staging in 95-100% of cases
- ✓ <5% of regional recurrence in patients staged pN0 (sn)

Stoeckli et al., Eur Arch Otorhinolaryngol, 2009

In comparison, routine elective ND in cN0 SCC carries an approximately 1.6–10% rate of regional recurrence

Schmitz et al., Eur Arch Otorhinolaryngol, 2009
Iype et al. Oral Oncol, 2008
Buck et al., Head Neck, 2008

Additional second stage surgery
Needed in case of pN+(sn)
Admission needed
Injection of radioactive tracers
Intensive labor

DIAGNOSTIC WORK-UP

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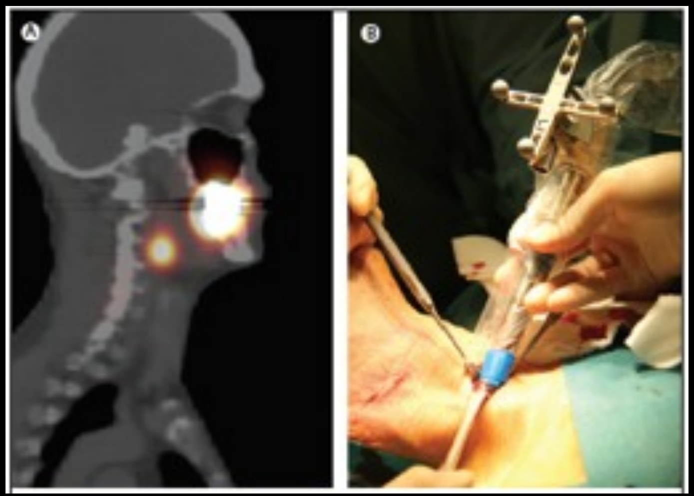

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Minimally invasive Little morbidity Negative predictive value 90-95%	Additional second stage surgery Needed in case of pN+(sn) Admission needed Injection of radioactive tracers Intensive labor

STAGING

LOW RISK

Precancerous lesions

Carcinoma in situ

T1

T2 < 3 cm

T with thickness < 5 mm

N0

HIGH RISK

T with thickness > 4 mm

T2 > 3 cm

T3

T4

N+

STAGING

LOW RISK

Precancerous lesions

Carcinoma in situ

T1

T2 < 3 cm

T with thickness < 5 mm

N0

HIGH RISK

T with thickness > 4 mm

T2 > 3 cm

T3

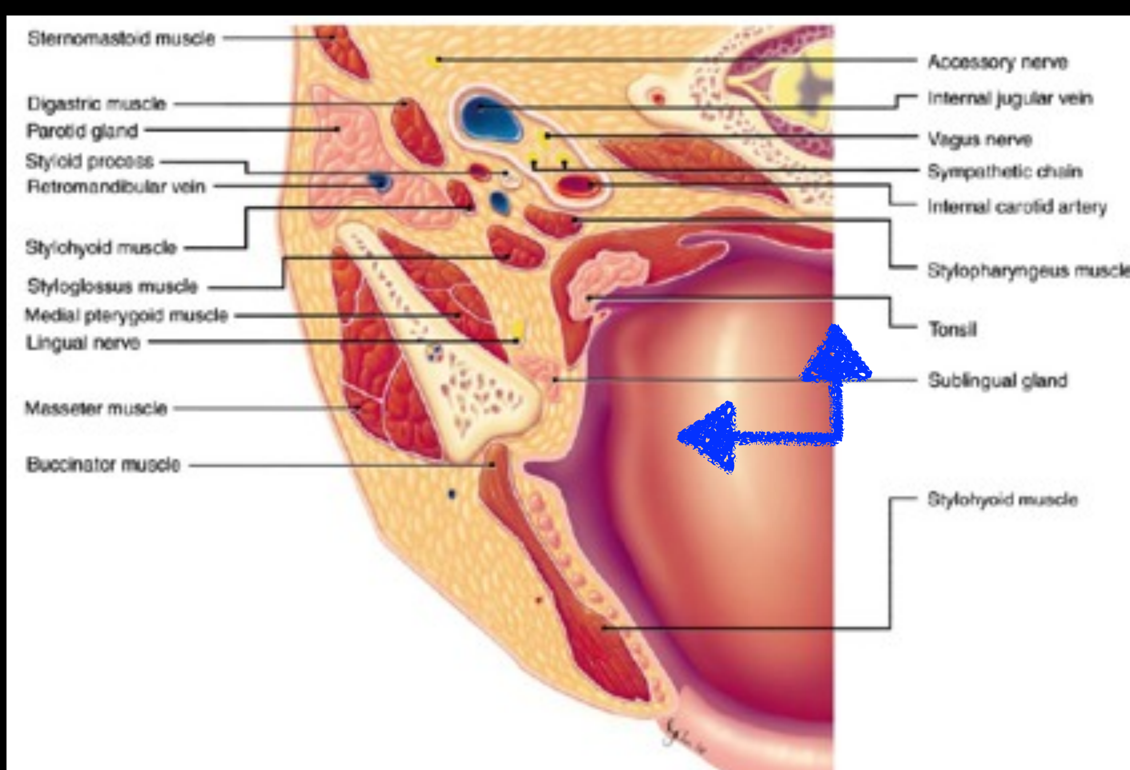
T4

N+

POSTERIOR PHARYNGEAL WALL

Rare

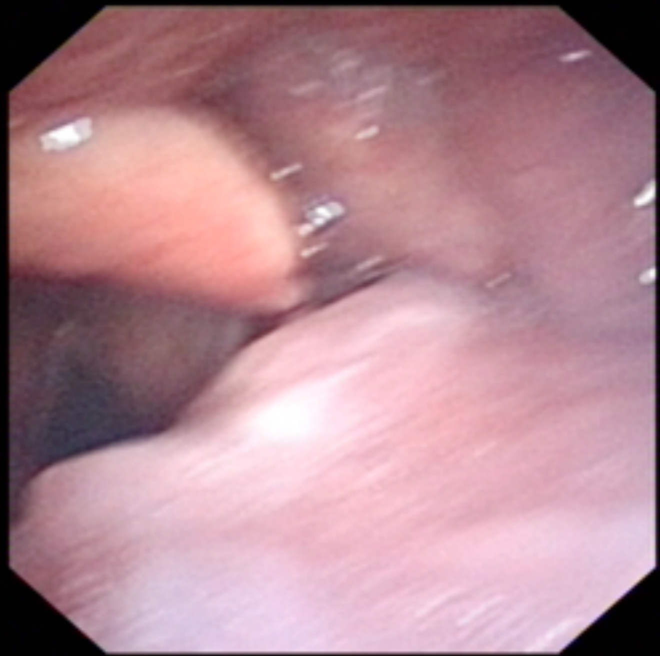
Tend to remain asymptomatic (pain, bleeding and dysphagia) until they gain considerable bulk, often diagnosed at late stages (75%)



Pathways of spreading

- Retropharyngeal and prevertebral spaces
- Lateral extension is uncommon
- Bilateral N involvement (lymphatic spread is found in about 25% of T1 and in 75% or more of T4)

POSTERIOR PHARYNGEAL WALL



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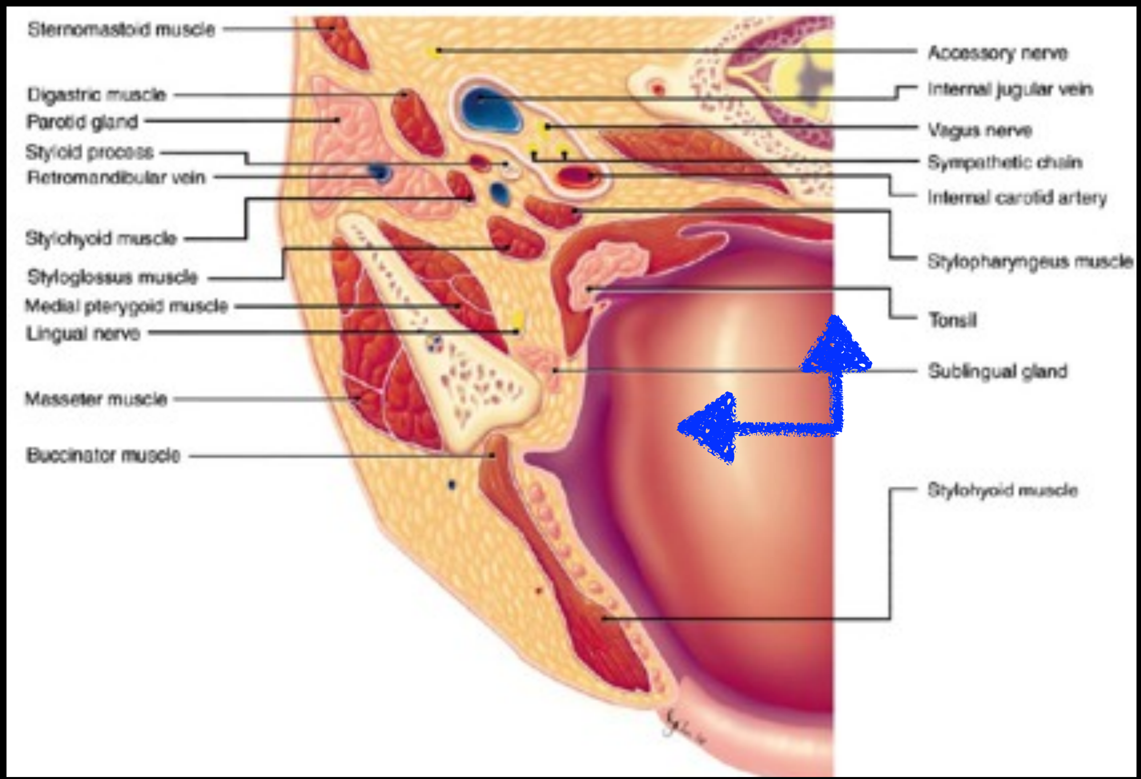

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KEY POINTS:
retropharyngeal involvement
prevertebral space involvement
N status

OROPHARYNX: SUBSITES

BASE OF THE TONGUE

Often poorly differentiated (up to 60%)

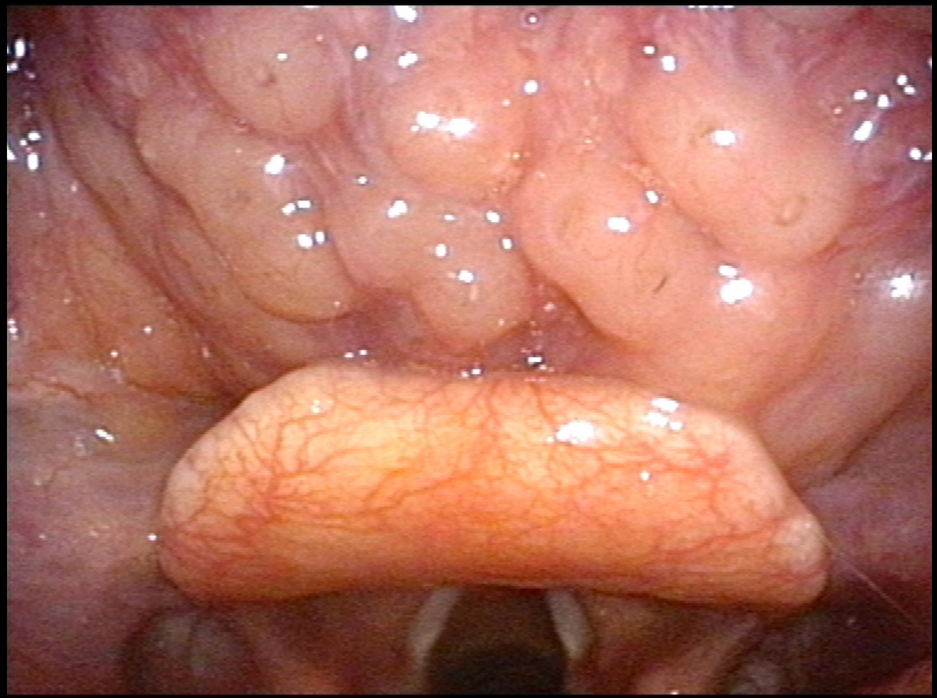
Presentation: 60% of SCC have nodal involvement, bilateral in 30% (levels II-III, IV)

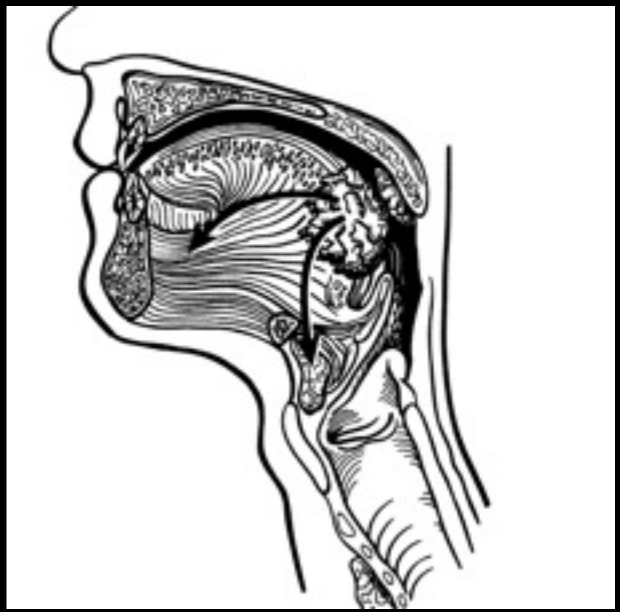
T1-2 present at least with one cervical metastasis, (up to 20% with bilateral N)

30-50% with uncontrolled base of tongue SCC will present M

Symptoms: sore throat and dysphagia

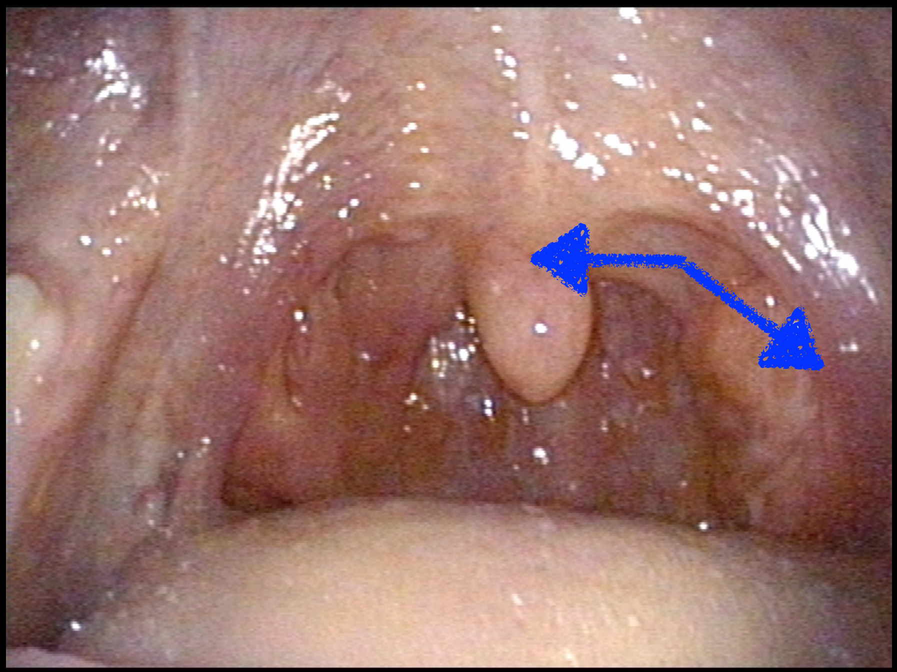
Difficult to detect: often becomes clinically evident in advanced stage (submucosal mass): this due to absence of pain fibers





KEY POINTS:
site, size and relation with the midline
submucosal extension
extension to the mobile tongue and oral cavity
extension to the larynx (preepiglottic space, supraglottis)
N status (levels II, III, IV)
M status

SOFT PALATE



Uncommon, often diagnosed at early stages

Asymptomatic (generally with submucosal growth)

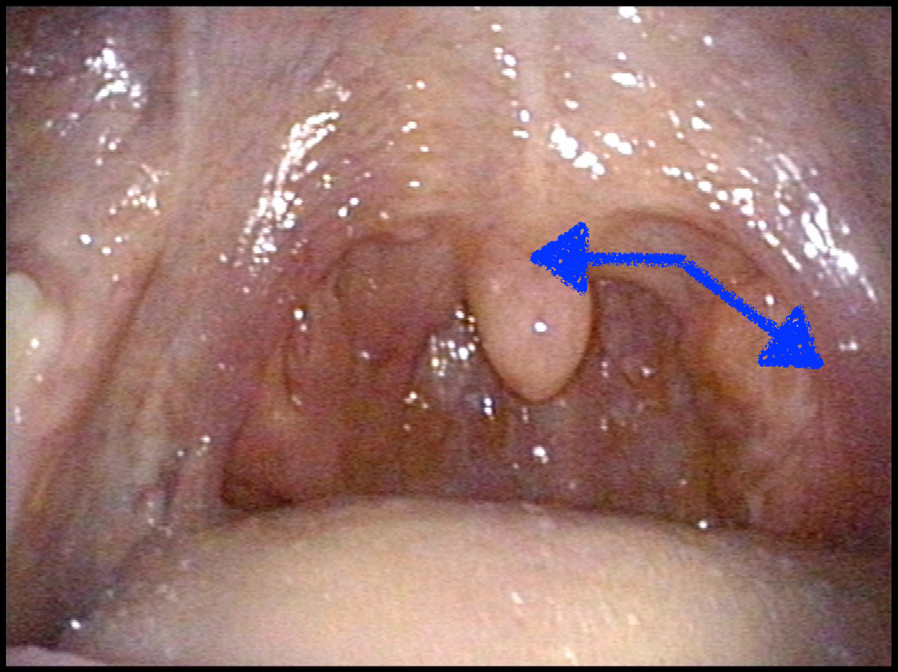
No lateral or medial anatomical barriers (extension to tonsillar complex, cross the midline)

Ipsilateral nodal spread is most often seen, bilateral N are not uncommon, reaching 50% for T3-4 lesions

25% of patients treated for soft palate lesions will present a second primary, commonly on the floor of the mouth

OROPHARYNX: SUBSITES

SOFT PALATE



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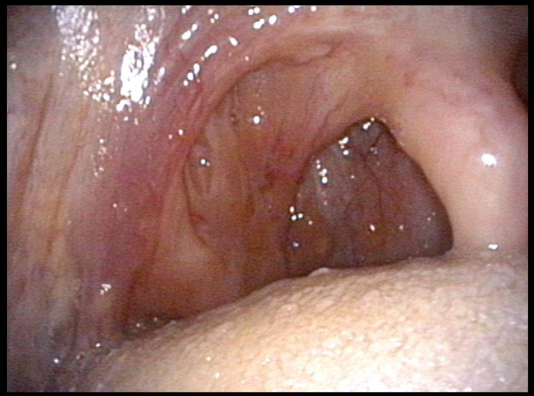
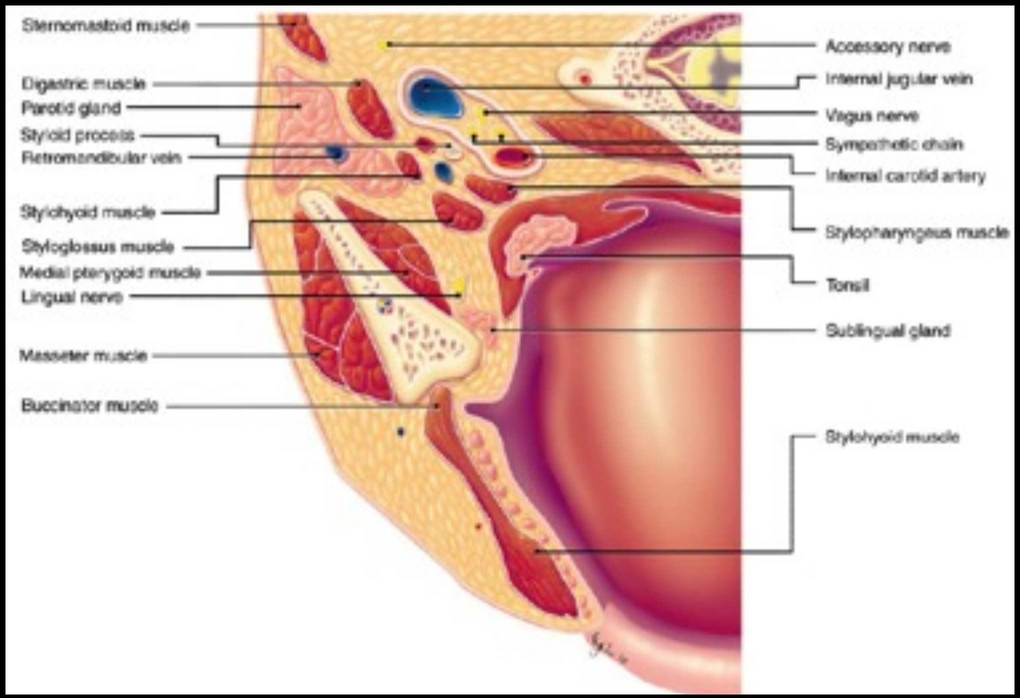
extension to the tonsillar complex
N status

OROPHARYNX: SUBSITES

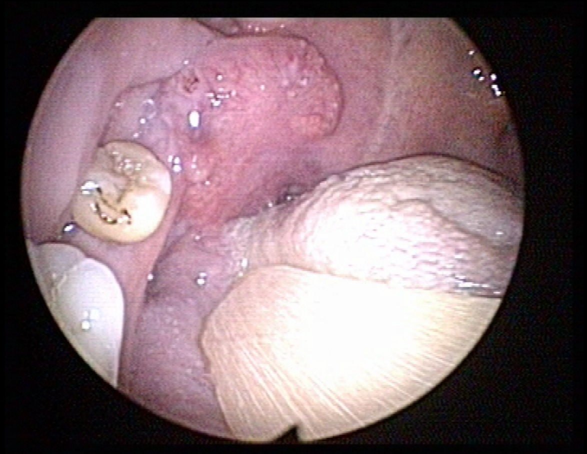


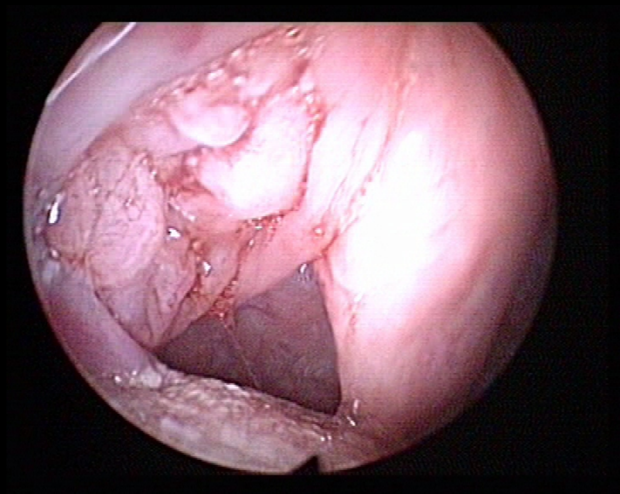
TONSILLAR COMPLEX



Frequent localization of oropharyngeal SCC (HPV-related)

Symptoms: odynophagia, dysphagia, otalgia, bleeding, decreased tongue motility, trismus (invasion of pterygoid muscles)

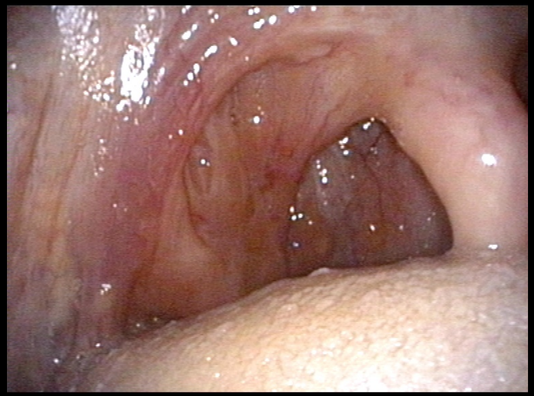




Positive N at the diagnosis: 66-76% (mainly confined to the ipsilateral jugulodigastric nodes) (cystic mets are typical for HPV-related lesions)

Contralateral N+: up to 22% involving the posterior pillar and true tonsil, versus up to 6% with T confined to the anterior pillar

OROPHARYNX: SUBSITES



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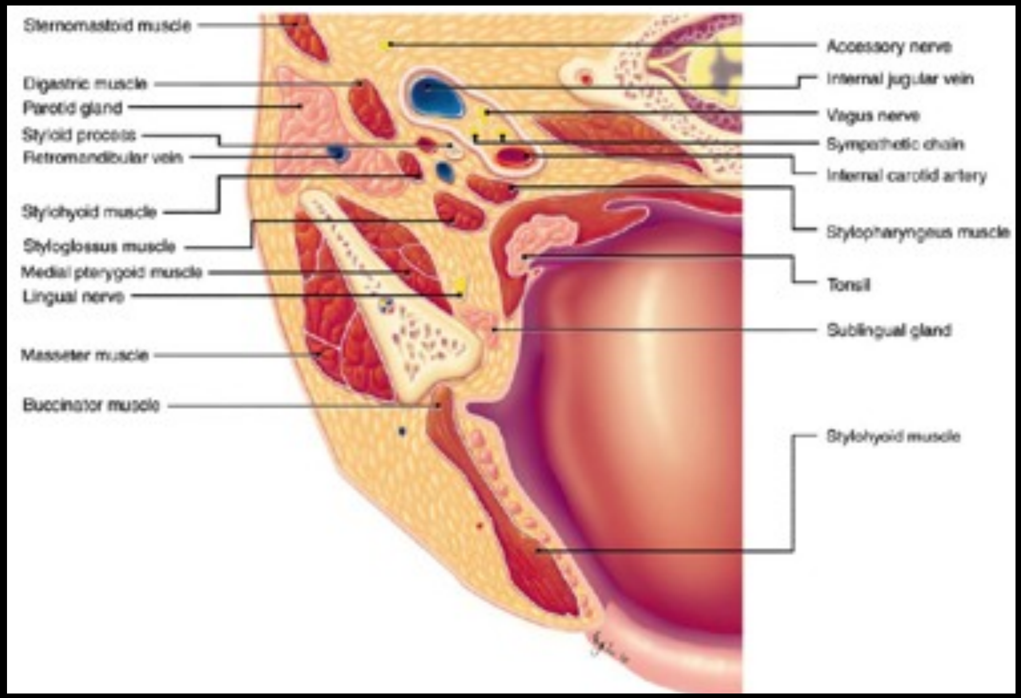

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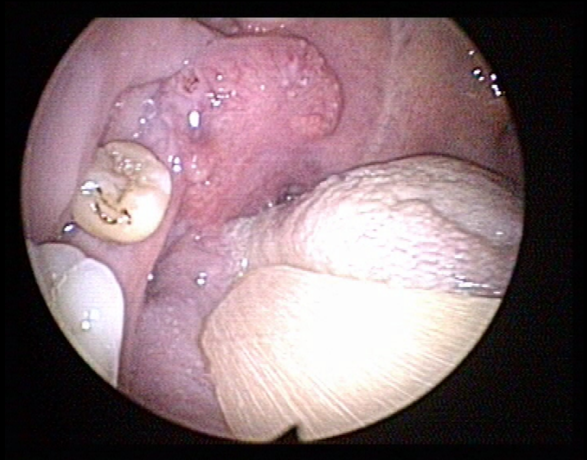

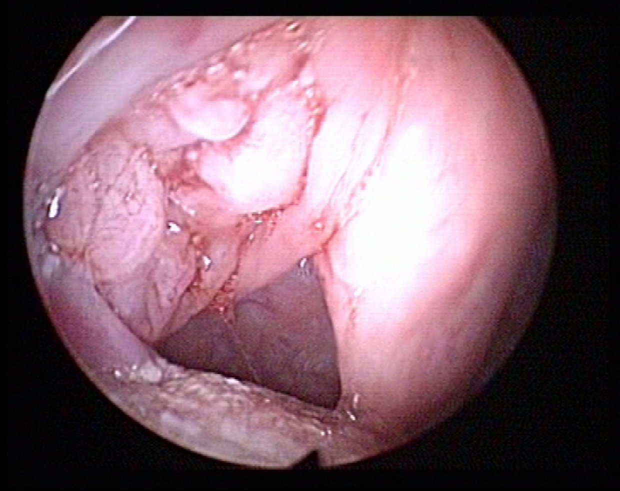

KEY POINTS:

extension to the middle constrictor muscle and parapharyngeal space
extension to the soft palate
extension to nasopharynx
extension to the amigdalo-glosso sulcus and oral tongue
pterygoid muscles and mandible infiltration
site of the internal carotid artery
N status

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Contralateral N+: up to 22% involving the posterior pillar and true tonsil, versus up to 6% with T confined to the anterior pillar

DIAGNOSIS OF HPV-RELATED LESIONS

The mere detection of HPV-DNA is not sufficient to establish causality in HNCs!!!

Castellsagué et al, J Natl Cancer Inst (2016)

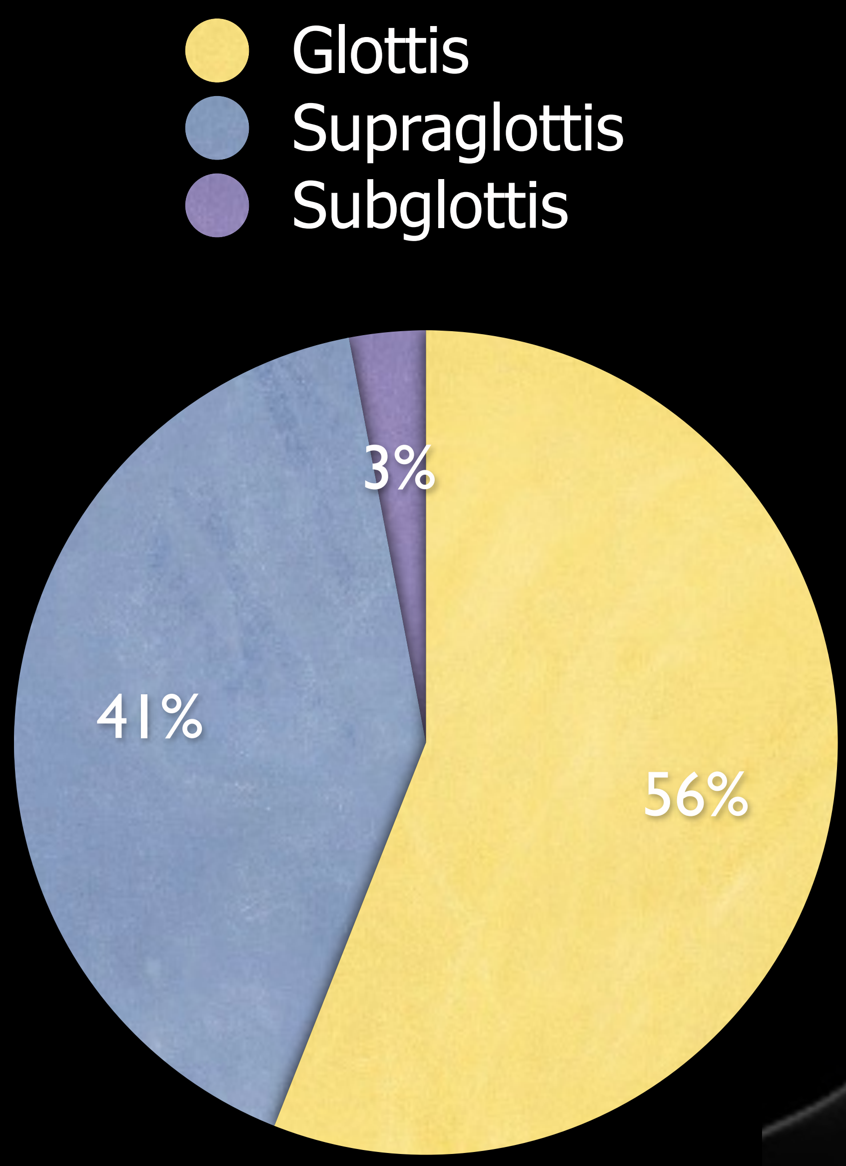
Nowadays no standard test…

IHC/ISH/PCR	PROS	CONS
p16^{INK4a} immunohistochemistry	routinely used as a cost-effective surrogate marker	p16 overexpression may occur independently of HPV
DNA in situ hybridization (ISH)	high specificity for detecting active viruses	less sensitive when there are low viral copy numbers
RNAscope (ISH)	97% sensitivity and relatively inexpensive	
HPV-DNA PCR	experimental settings because of high sensitivity	it does not identify whether the virus is transcriptionally active
E6/E7 HPV-mRNA PCR	*the gold standard*	high costs

Buckley et al, Aust NZ J Surg (2015)

LARYNX

EPIDEMIOLOGY



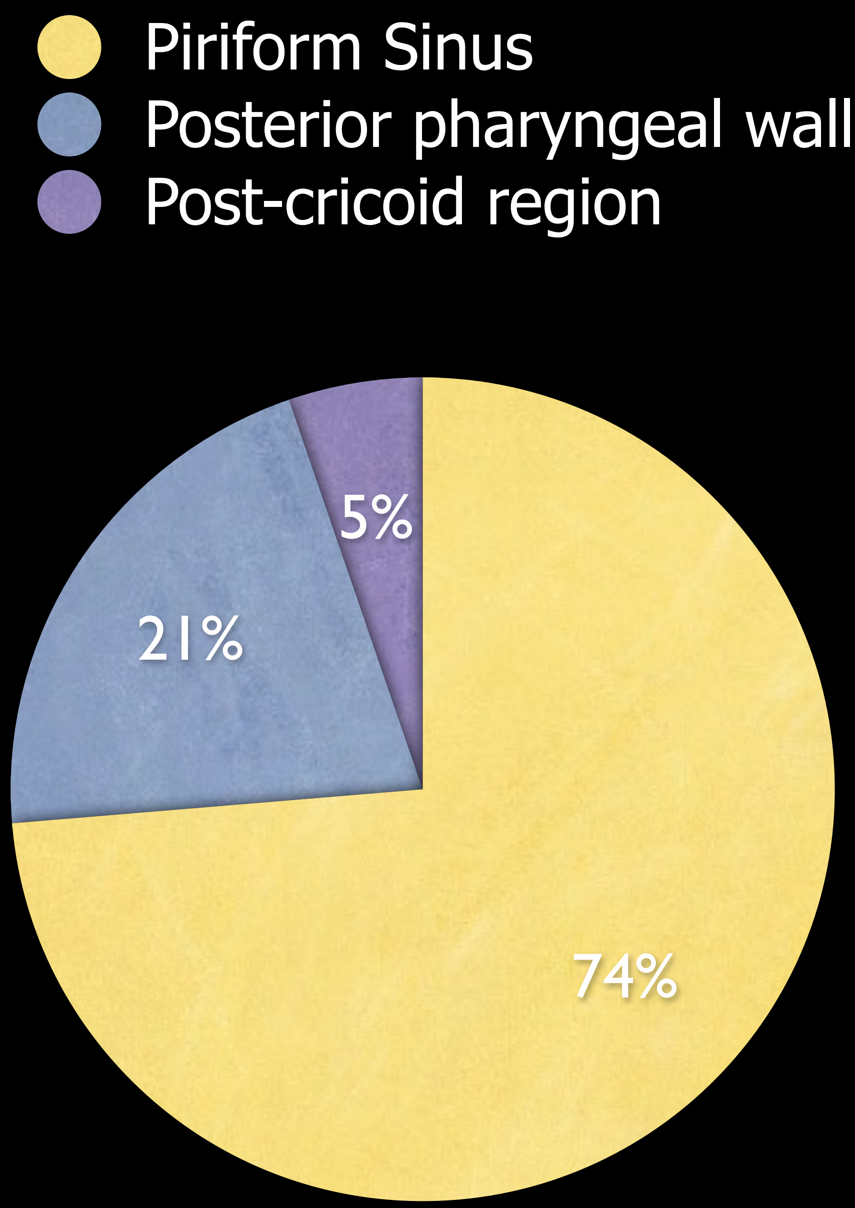
Data from Memorial Sloan-Kettering Cancer Center, New York

- Second most common malignancy of the UADT
- Over 11,000 case/yr in US (2007) with 3,660 deaths
- M:F=3.8:1
- 90% of pts are older than 40 yrs
- 85%-95% squamous cell carcinoma
- Tobacco and alcohol are the two most important risk factors

Data from Cummings, Otolaryngology Head and Neck Surgery, 5th Ed.

HYPOPHARYNX

EPIDEMIOLOGY



Data from Memorial Sloan-Kettering Cancer Center, New York

- Incidence 9.4% 100.000 ab in France, 1% 100.000 ab USA
- M:F=2:1
- 95% squamous cell carcinoma
- Tobacco and alcohol are the 2 most important risk factors
- Plummer-Vinson syndrome
- > 80% stage III-IV

HISTOPATHOLOGY

Conventional SCC (G1, G2, G3)

SCC variants (spindle cell, adenosquamous, basaloid, verrucous, papillary, acantholytic)

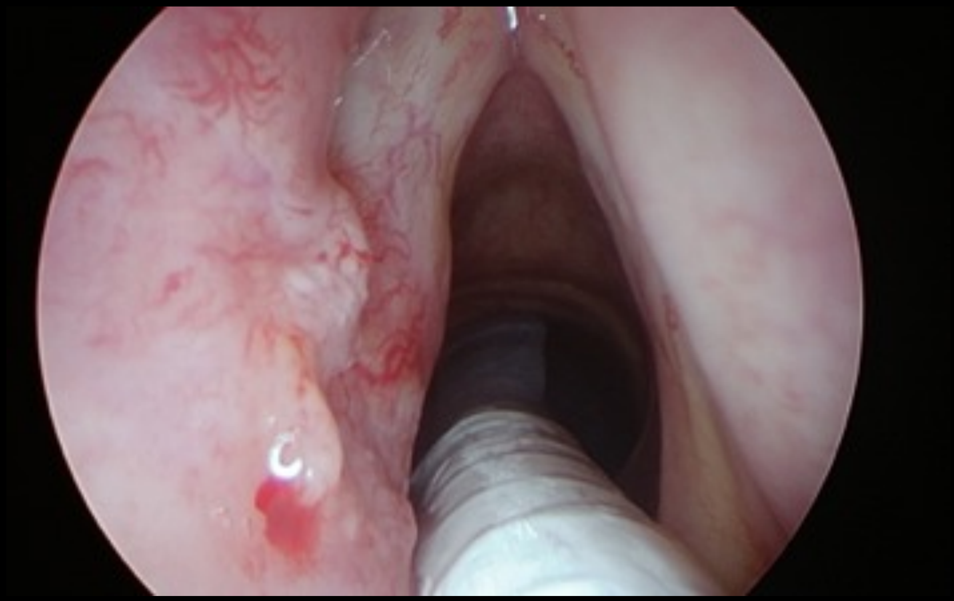
Malignant melanoma

Glandular carcinomas: adenocarcinoma, mucoepidermoid, adenoid cystic, acinic cell

Soft tissues sarcomas (chondrosarcoma!)

Lymphoproliferative disorders

Secondary tumors (kidney, lung)



CLINICAL EVALUATION

SIGNS AND SYMPTOMS

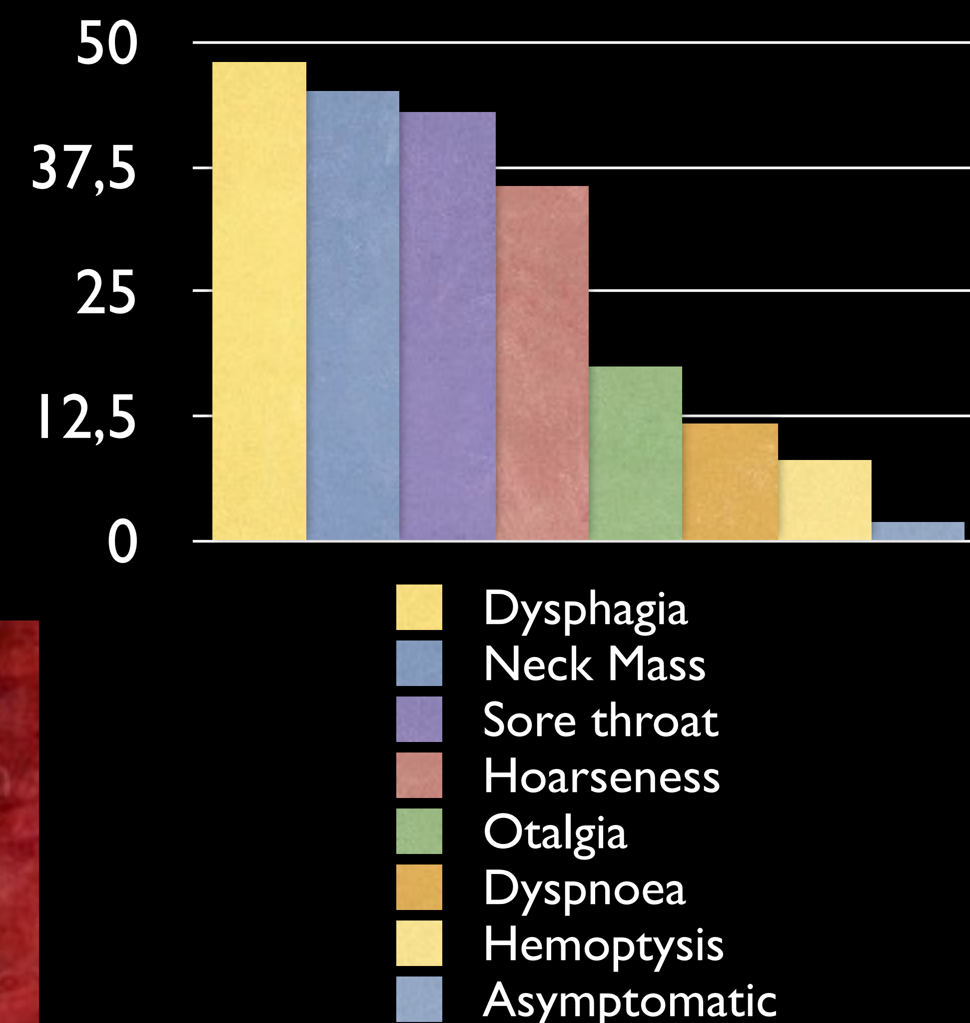
Larynx

Supraglottic cancer → mainly dysphagia and dyspnoea

Glottic cancer → mainly dysphonia

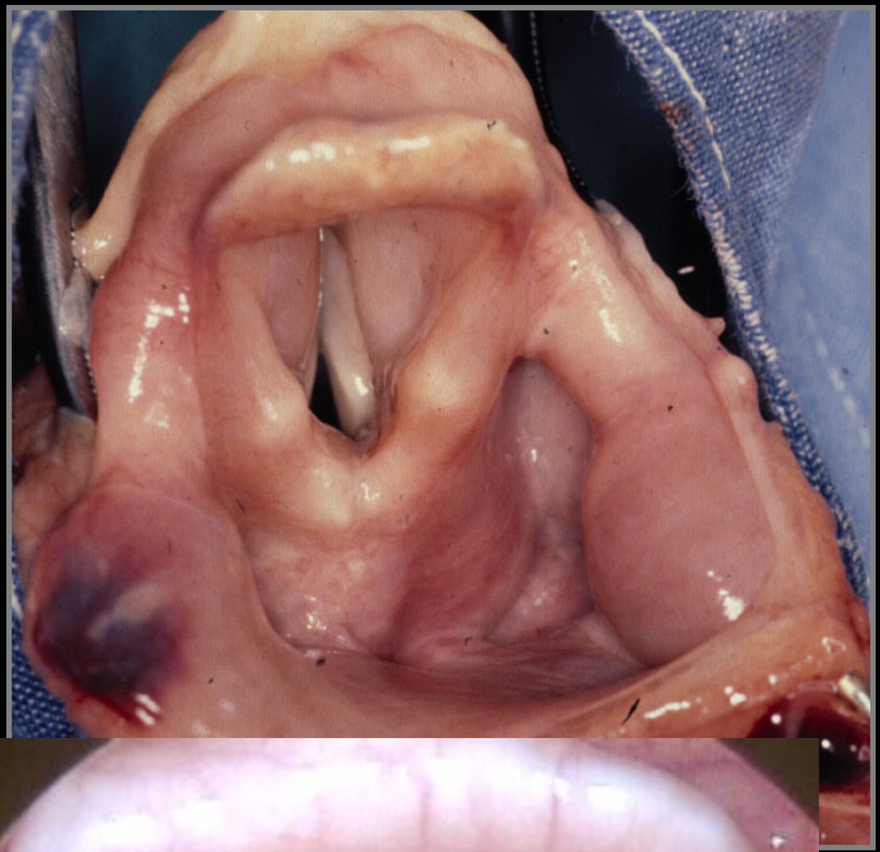
Subglottic cancer → mainly dyspnoea

Hypopharynx



Hoffman HT, et al. Hypopharyngeal cancer patient care evaluation. Laryngoscope 1997;107:1005-17

SPECIAL ISSUES WITH HYPOPHARYNGEAL CANCER



Submucosal spreading

Multifocality

Advanced stage at diagnosis

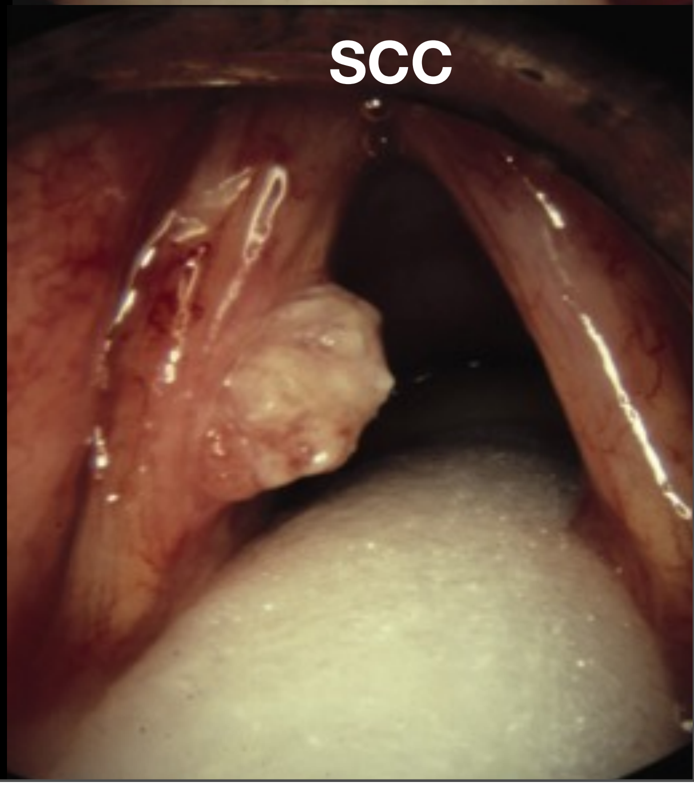
Distant metastasis

Synchronous and metachronous tumors

DIAGNOSTIC WORK UP

TARGETS

- Histology
- Superficial spreading
- Deep/Submucosal invasion
- Multifocality
- Synchronous lesions



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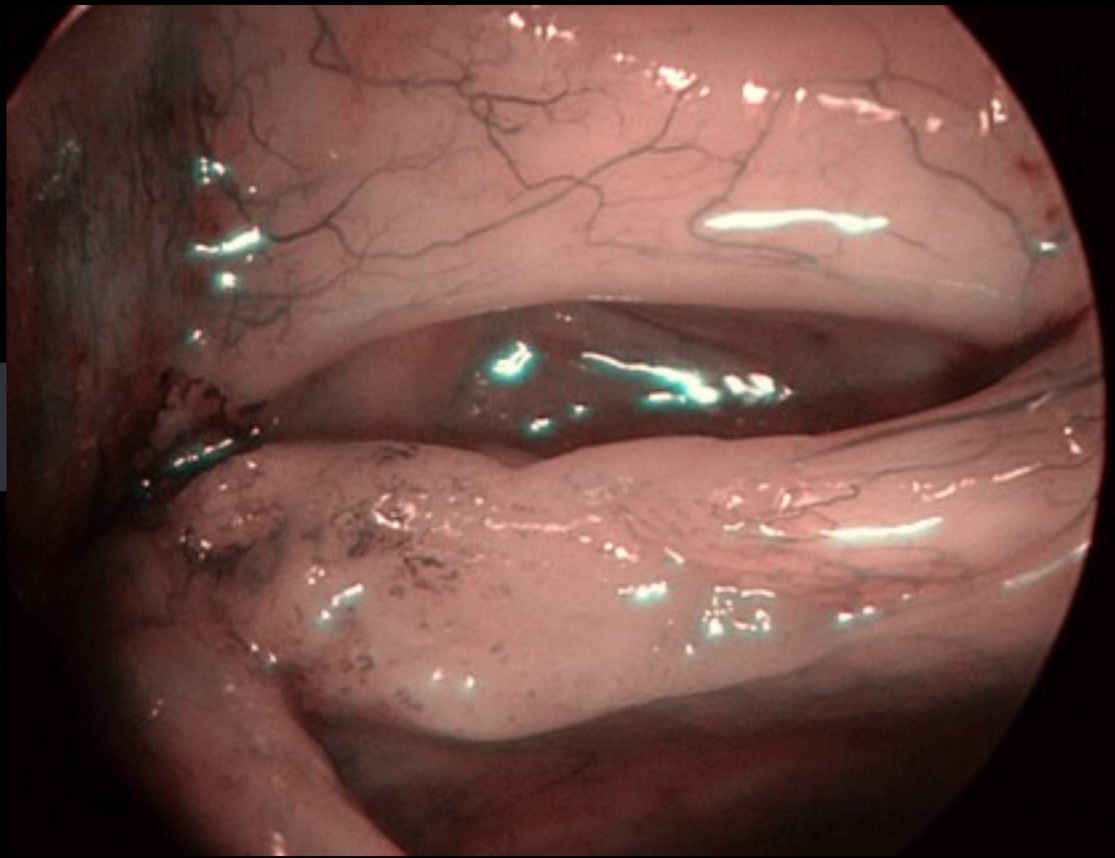

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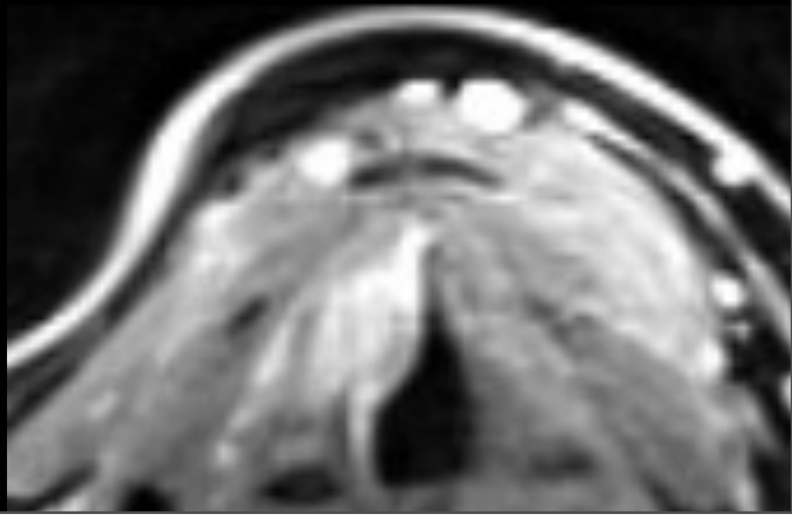

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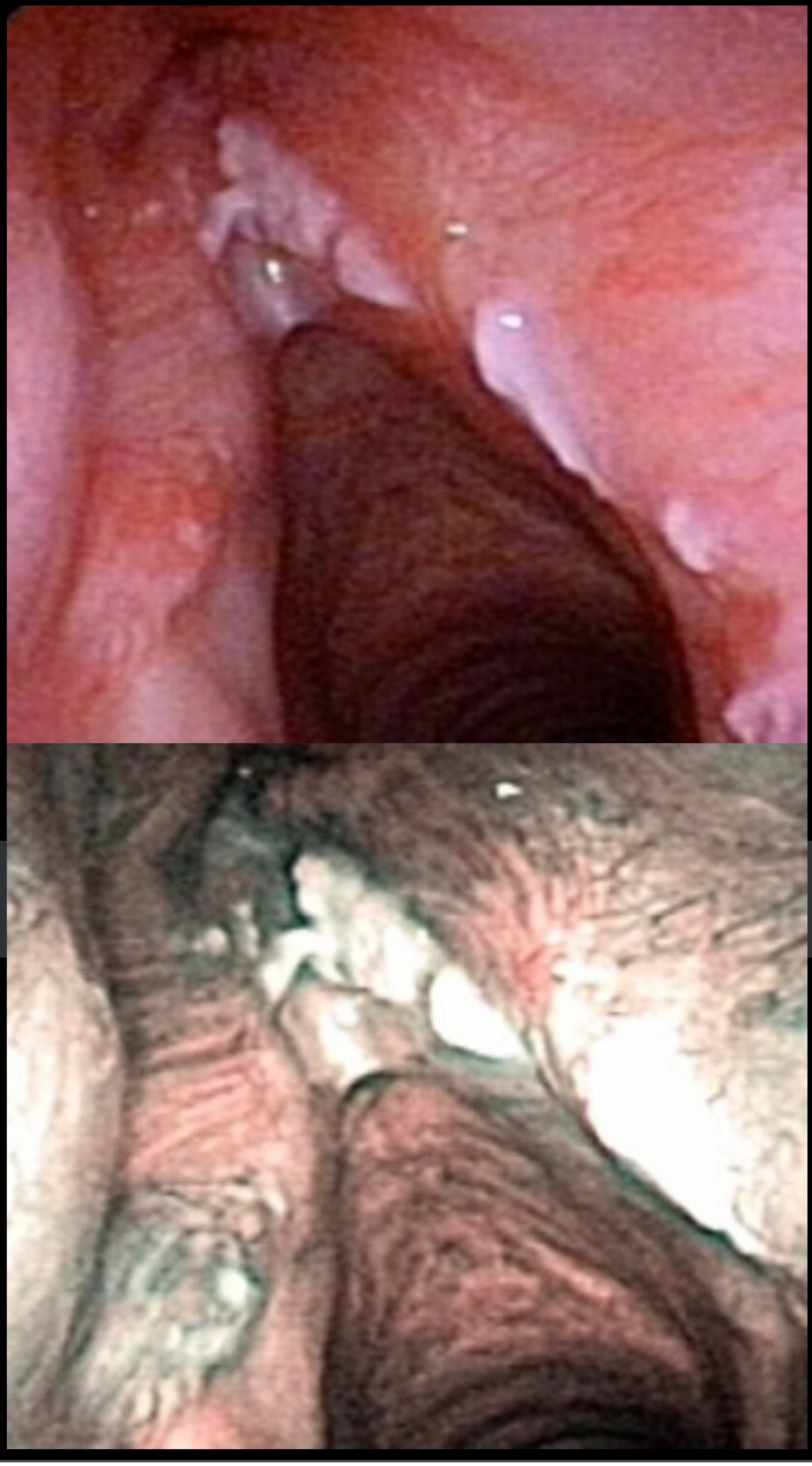

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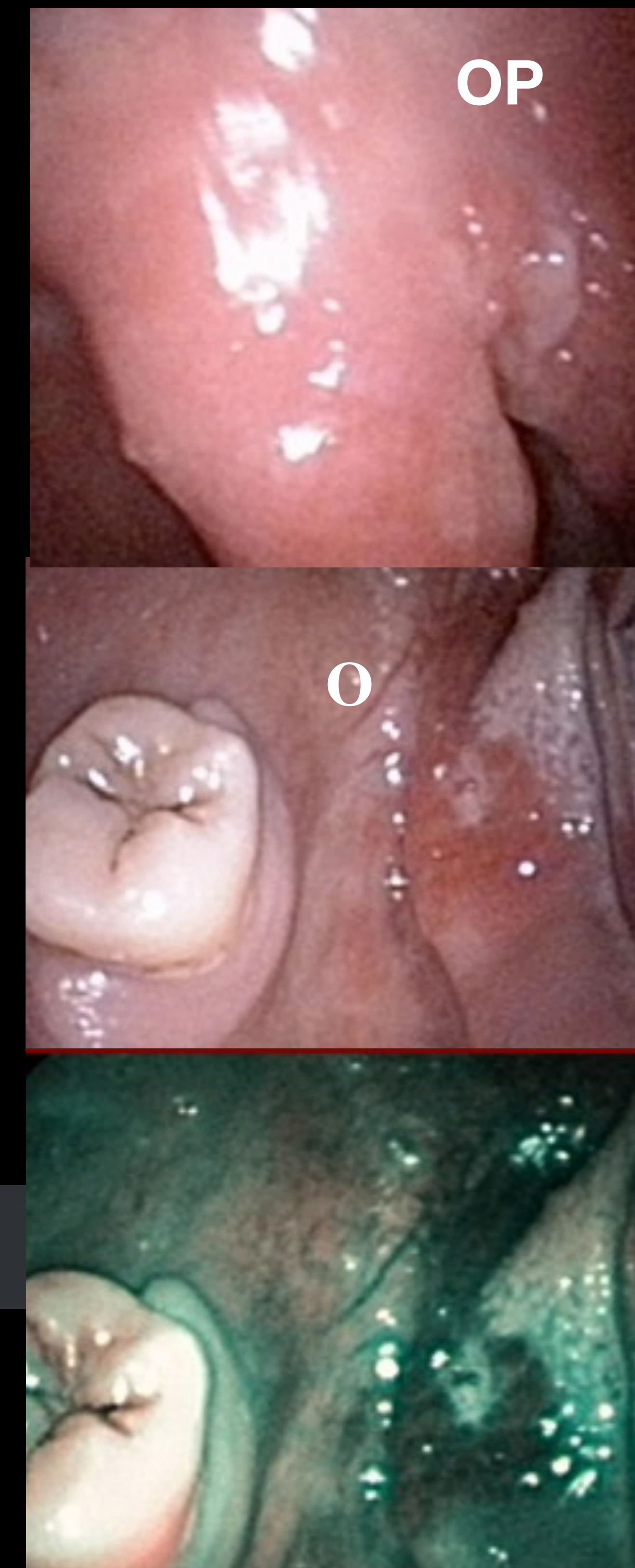

PREOPERATIVE EVALUATION

- Flexible Panendoscopy
- Videolaryngostroboscopy
- Narrow Band Imaging
- Imaging

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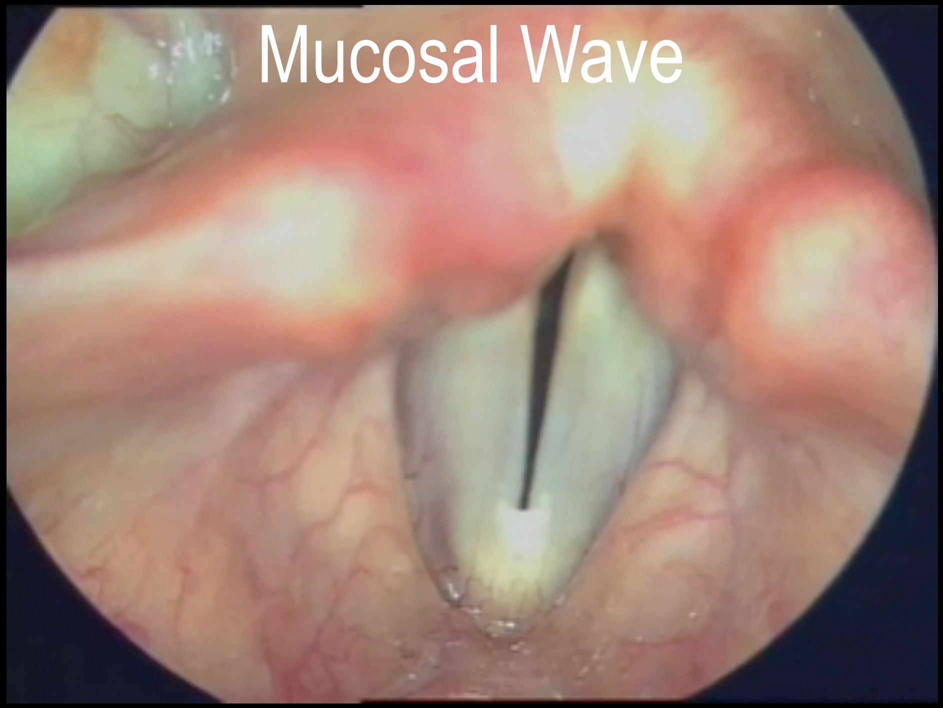
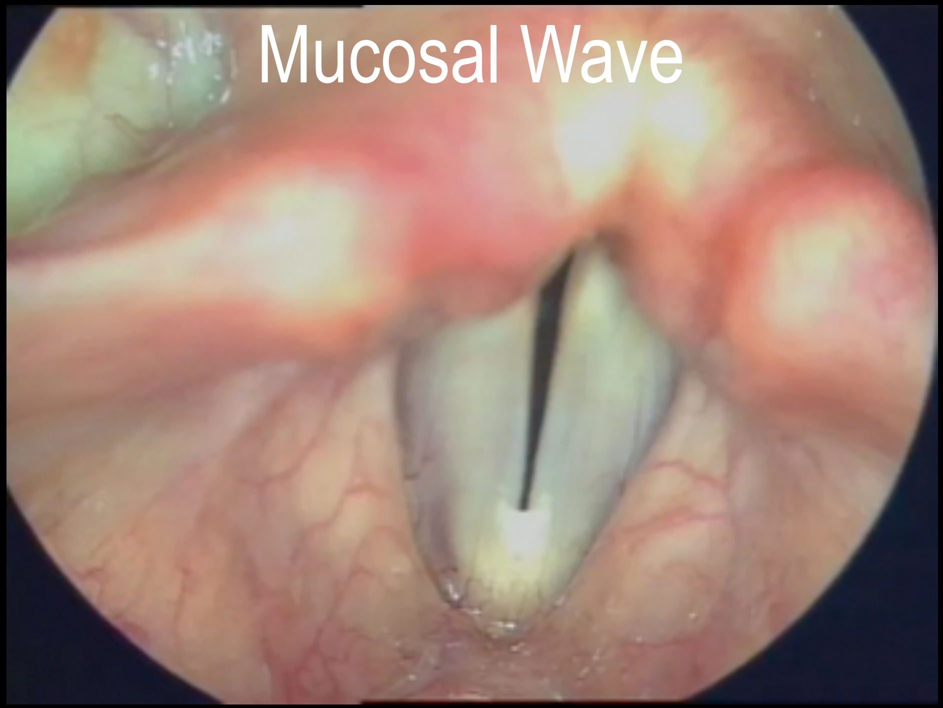
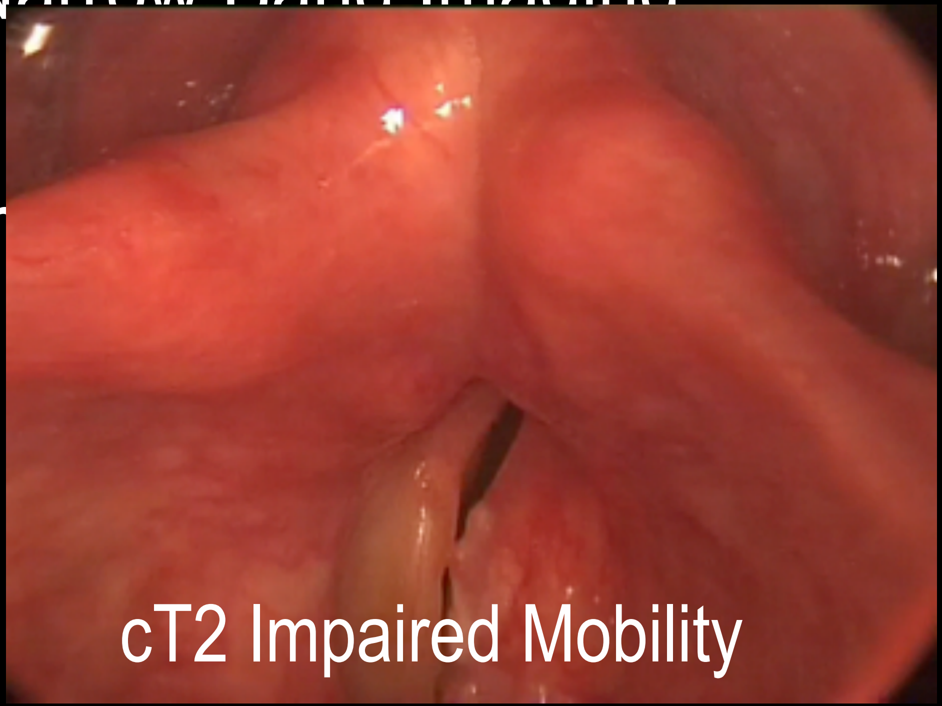


PREOPERATIVE EVALUATION

- Flexible Panendoscopy
- Videolaryngostroboscopy
- Narrow Band Imaging
- Ir





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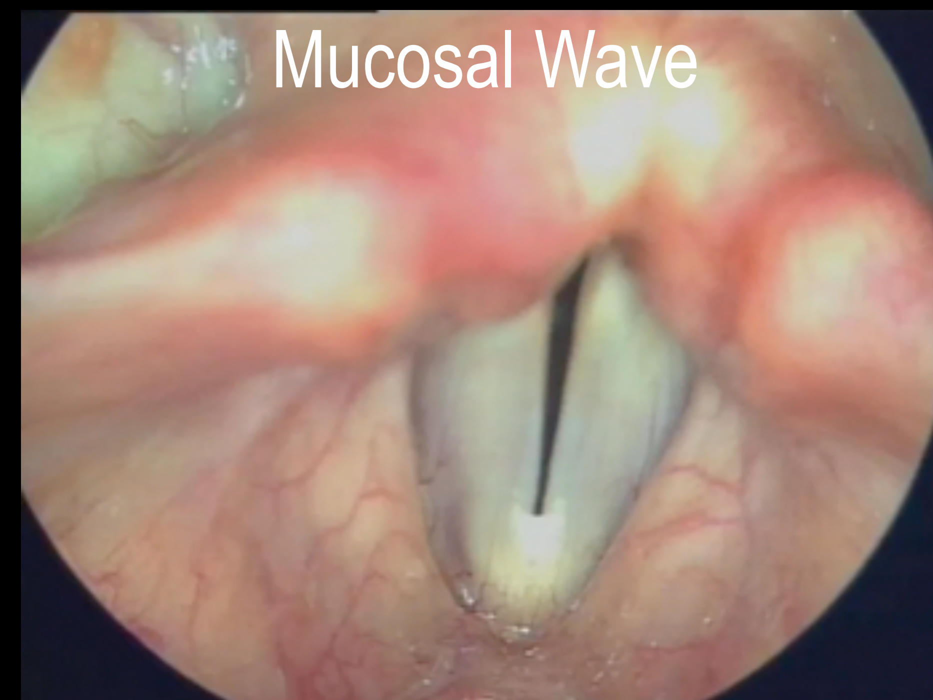
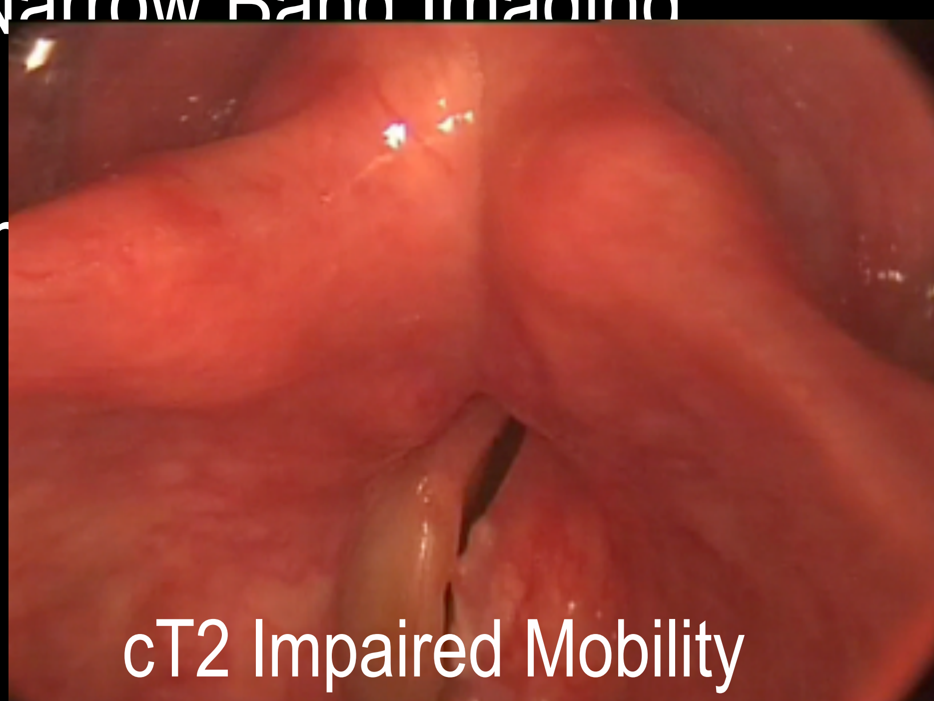
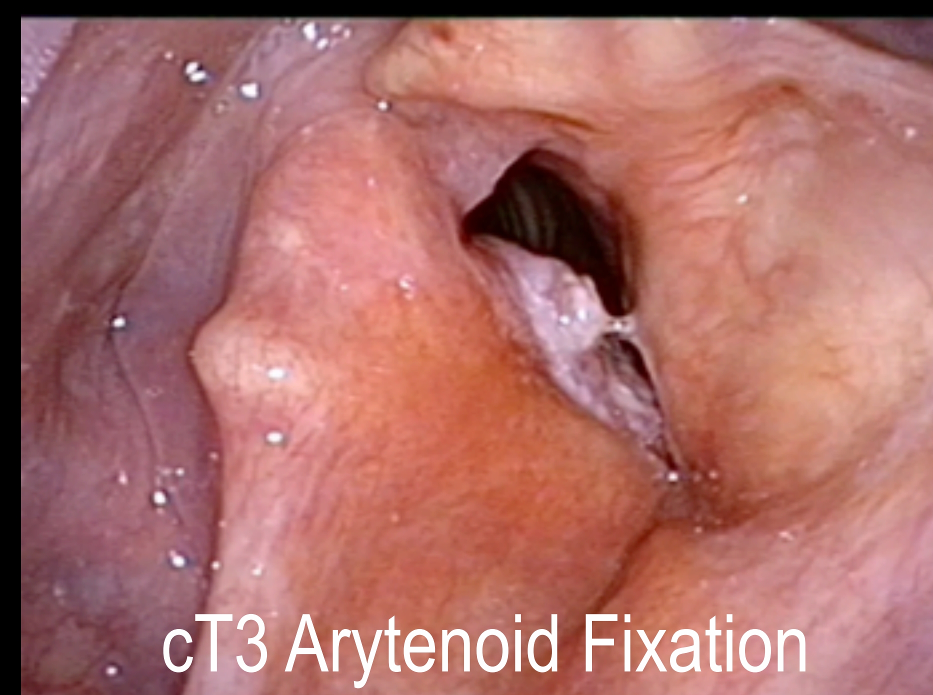
- Narrow Band Imaging
- Ir





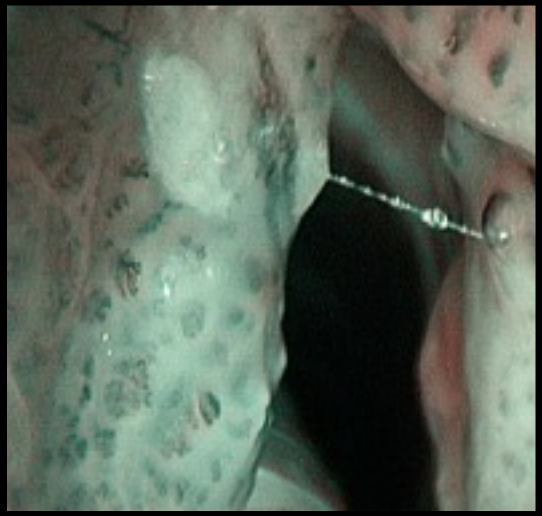


PREOPERATIVE EVALUATION

Narrow Band Imaging

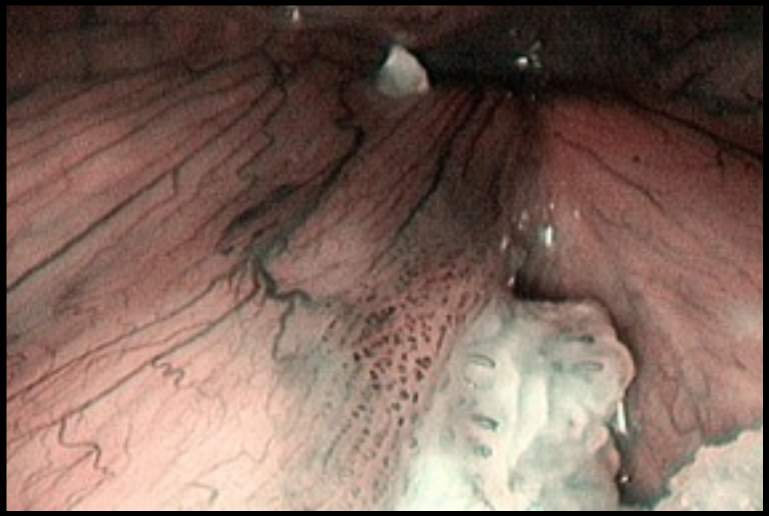
Type I

well-demarcated brownish area with thick dark spots



Type II

undemarcated area with scattered irregular and winding vessels



Type III

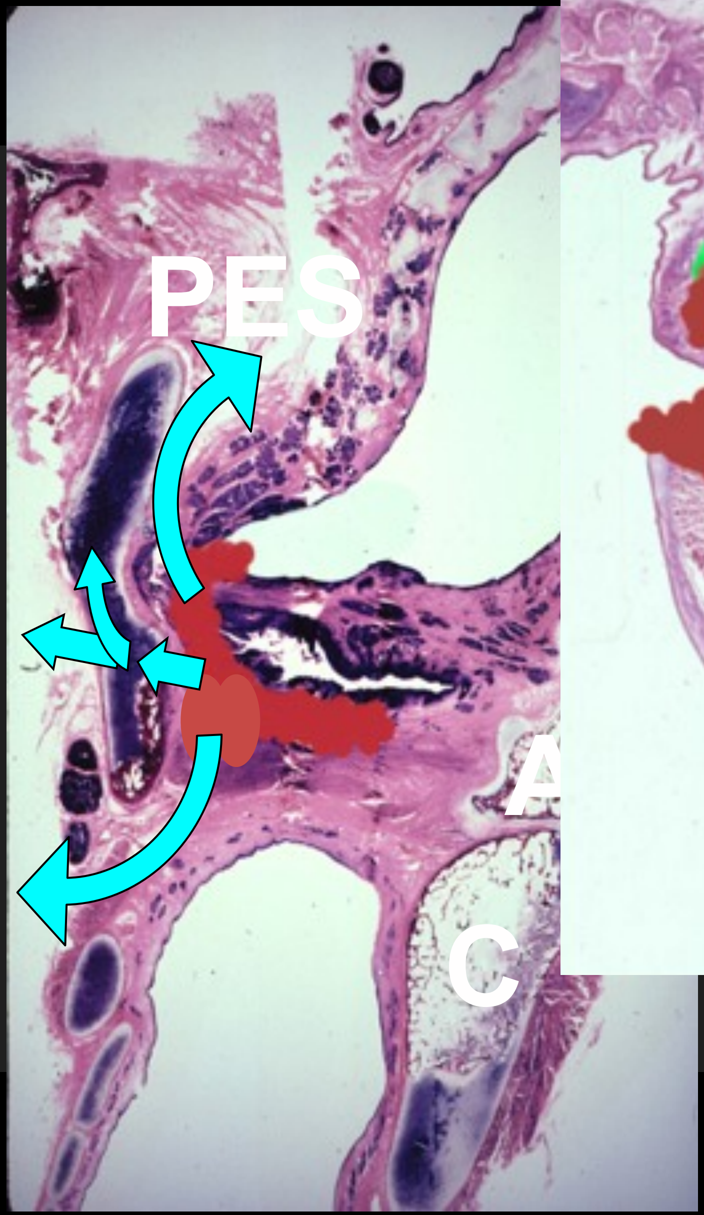
afferent hypertrophic vessel branching out in small vascular loops in the context of the lesion

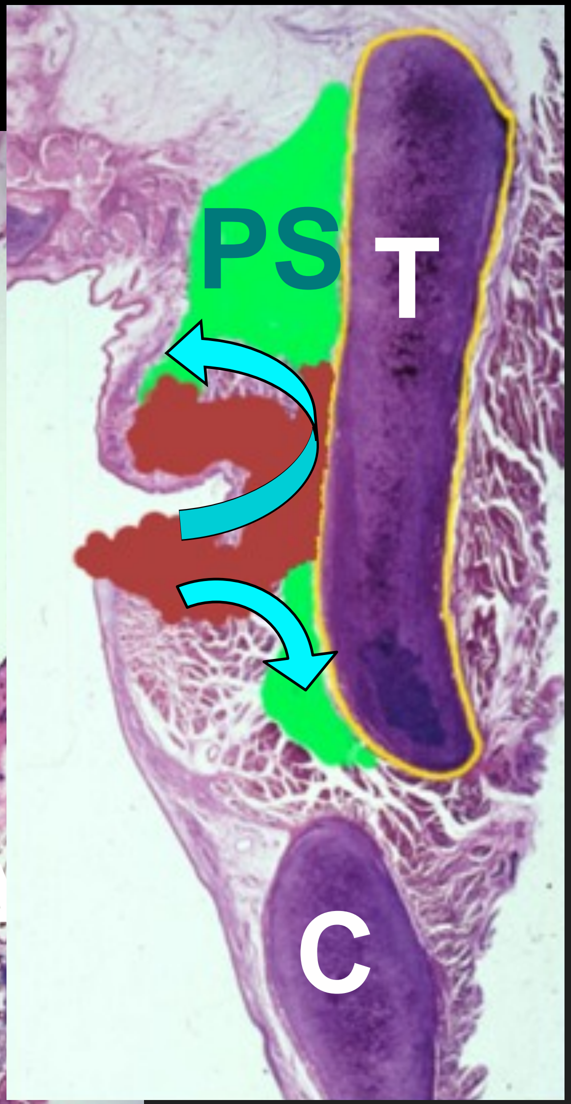
Piazza et al.2009

PREOPERATIVE EVALUATION

- Imaging

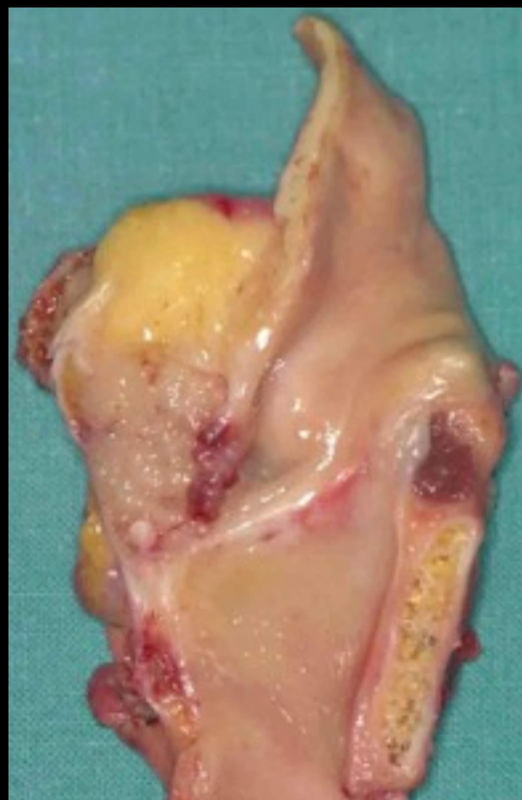
- Laryngeal framework
- Paraglottic and preepiglottic space
- Submucosal spread
- Soft tissues
- N status





PREOPERATIVE EVALUATION

NECK PALPATION AND US



Supraglottis

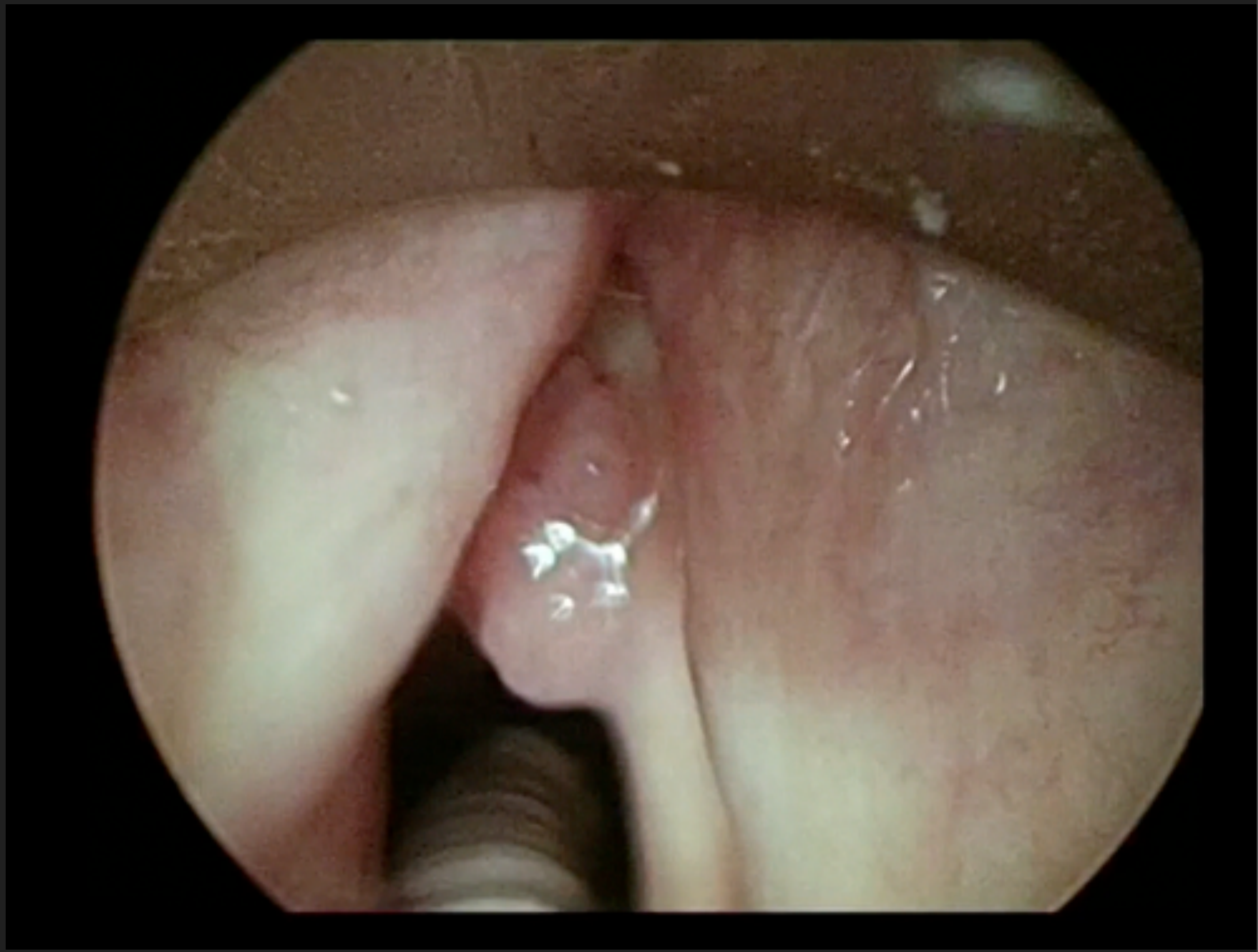
Glottis

Hypopharynx

PRETREATMENT EVALUATION

PRETREATMENT EVALUATION

- Microlaryngoscopy with 0° and angled telescopes
- Narrow Band Imaging with HDTV
- Saline infusion into Reinke's space



STAGING

GLOTTIS

T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility T1a: tumor limited to one vocal cord T1b: tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (eg, inner cortex)
T4	T4a: tumor invades the thyroid cartilage and/or tissues beyond the larynx (eg, trachea, soft tissues of the neck including deep extrinsic muscles of the tongue, strap muscles, thyroid gland, or esophagus) T4b: tumor invades the prevertebral space, encases the carotid artery, or invades mediastinal structures

STAGING

SUPRAGLOTTIS

T1	Tumor limited to one subsite of the supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of the supraglottis or glottis region outside the supraglottis (eg, mucosa of base of the tongue, vallecula, medial wall of the piriform sinus) without fixation of the larynx
T3	Tumor limited to the larynx with vocal cord fixation and/or invading any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or with minor thyroid cartilage erosion
T4	T4a: tumor invades the thyroid cartilage and/or tissues beyond the larynx (eg, trachea, soft tissues of the neck including deep extrinsic muscles of the tongue, strap muscles, thyroid gland, or esophagus) T4b: tumor invades the prevertebral space, encases the carotid artery, or invades mediastinal structures

STAGING

SUBGLOTTIS

T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to the larynx with vocal cord fixation
T4	T4a: tumor invades the cricoid or thyroid cartilage and/or tissues beyond the larynx (eg, trachea, soft tissues of the neck including deep extrinsic muscles of the tongue, strap muscles, thyroid gland, or esophagus) T4b: tumor invades the prevertebral space, encases the carotid artery, or invades mediastinal structures

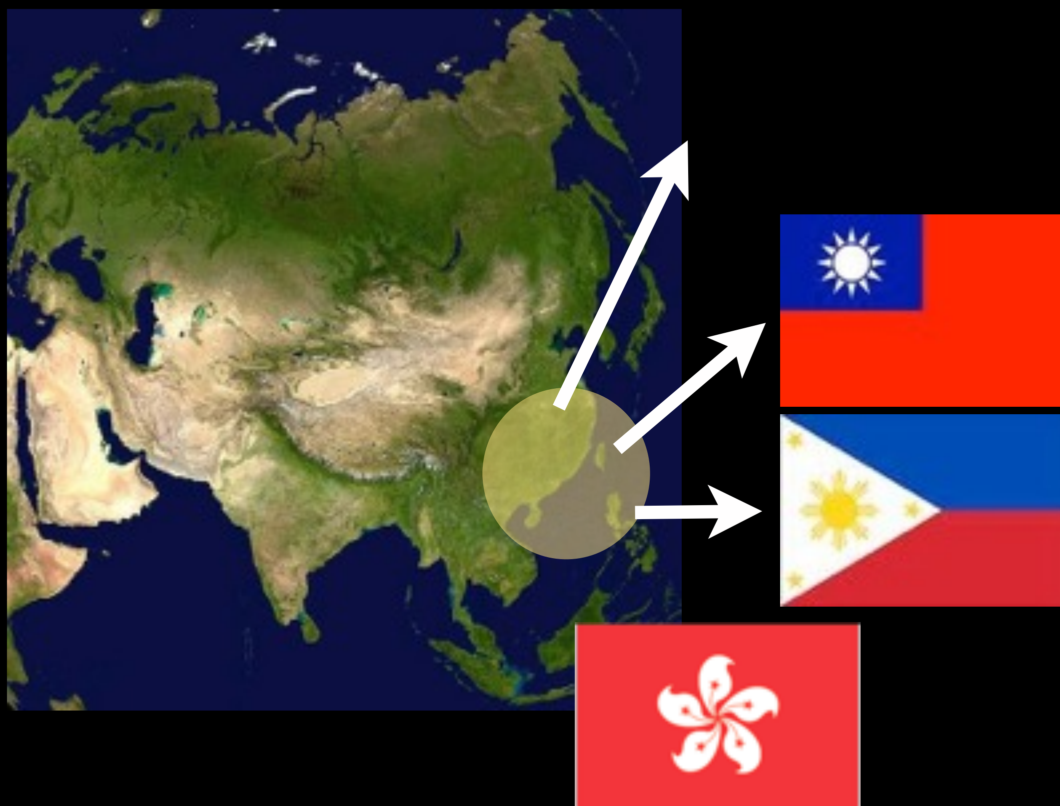
STAGING

HYPOPHARYNX

T1	Tumor limited to one subsite of the hypopharynx and/or less than 2 cm in its greatest dimension
T2	Tumor invades more than one subsite of the hypopharynx or an adjacent site, or measures more than 2 cm but less than 4 cm in its greatest diameter without fixation of the hemilarynx
T3	Tumor more than 4 cm in its greatest dimension with fixation of the hemilarynx
T4	T4a: Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue (prelaryngeal strap muscles and subcutaneous fat) T4b: Tumor invades prevertebral fascia, encases the carotid artery or involves mediastinal structures

NASOPHARYNX

EPIDEMIOLOGY



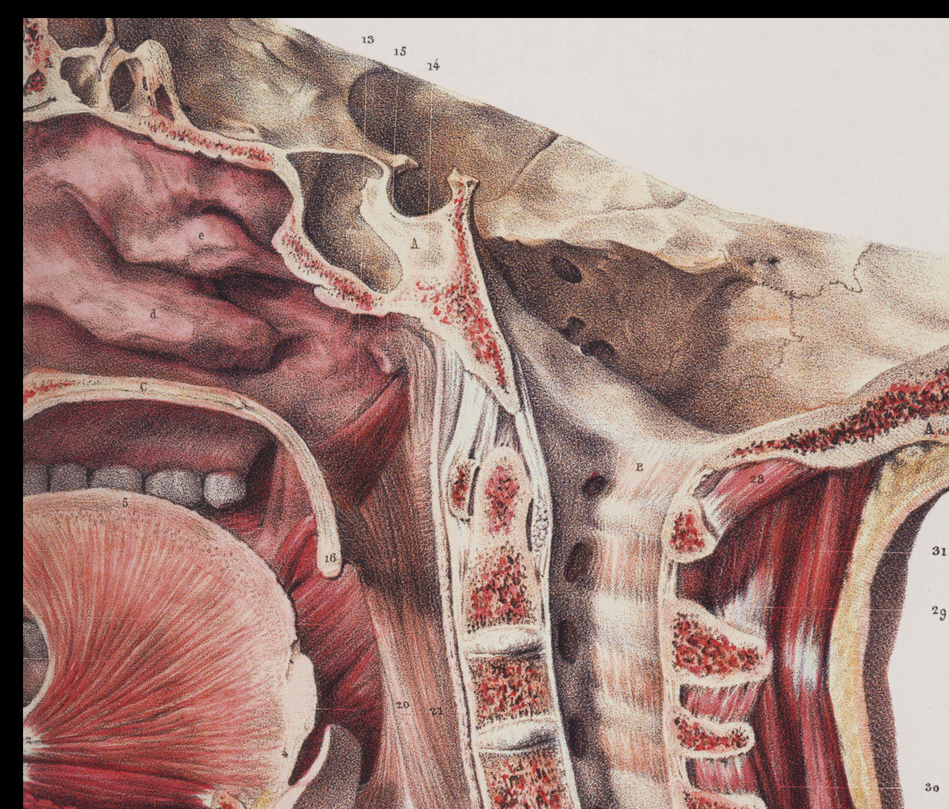
Annual incidence in USA and Europe: <1/100,000 (*Nonkeratinizing differentiated carcinoma)*

Annual incidence in China (Guangzhou): **30/100,000** (*Nonkeratinizing undifferentiated carcinoma)*

M:F=2-3:1

Age:

- China and South-East Asia: 5th-6th decade
- North Africa: 2nd (20%) and 6th decade



WHO CLASSIFICATION 2005

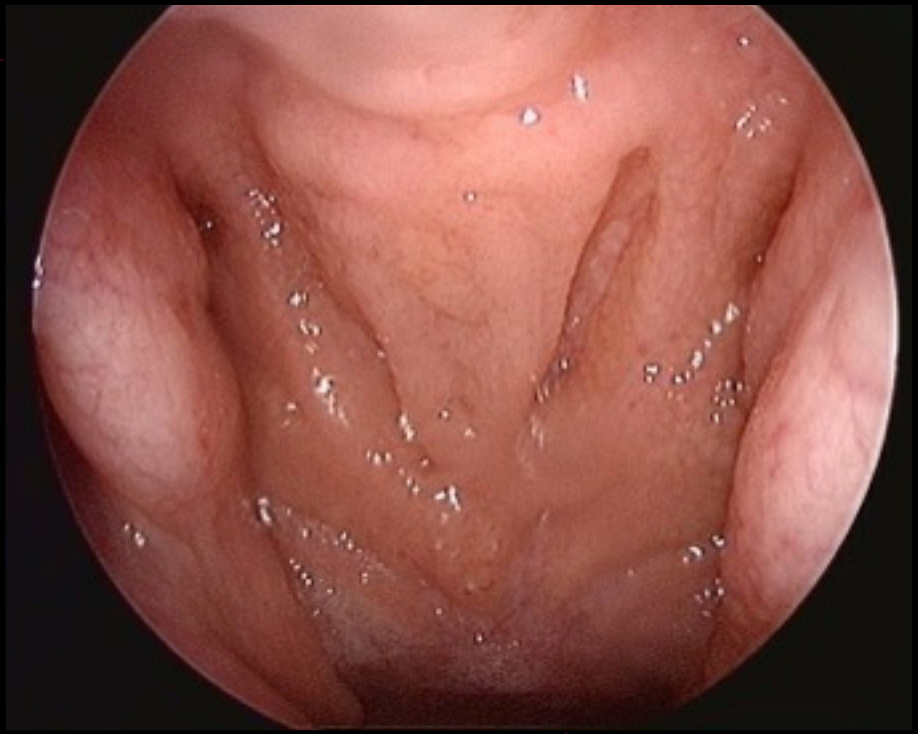
Nasopharyngeal carcinoma

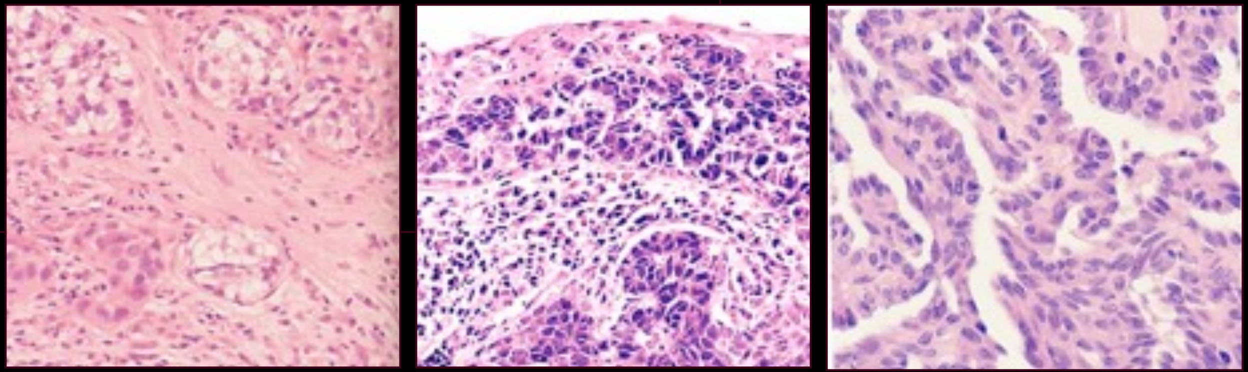
- *Nonkeratinizing carcinoma*
- *Keratinizing squamous cell carcinoma*
- *Basaloid squamous cell carcinoma*

Nasopharyngeal papillary adenocarcinoma

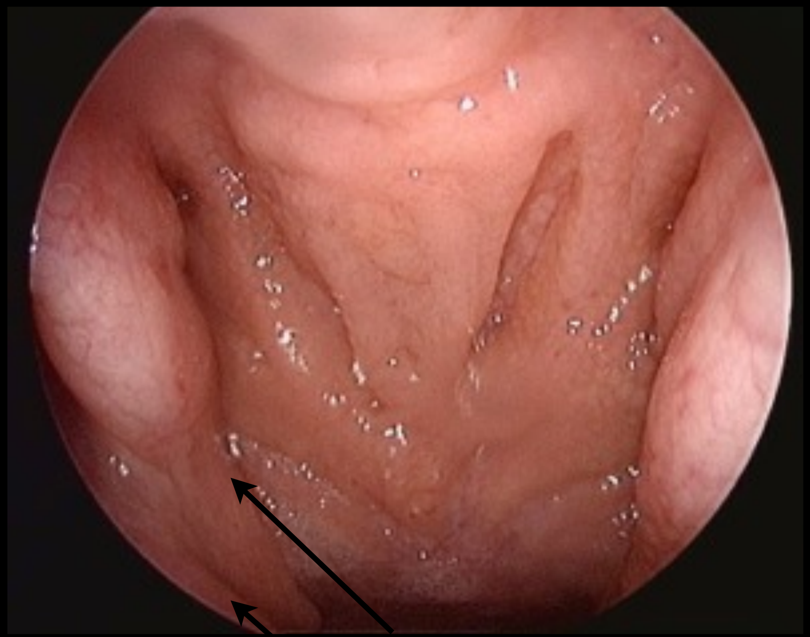
Salivary gland-type carcinomas

- *Adenoid cystic carcinoma*
- *Mucoepidermoid carcinoma*





PATTERN OF SPREADING



Eustachian tube

Nasal cavity

Parapharyngeal space

Paranasal sinuses

Oropharynx

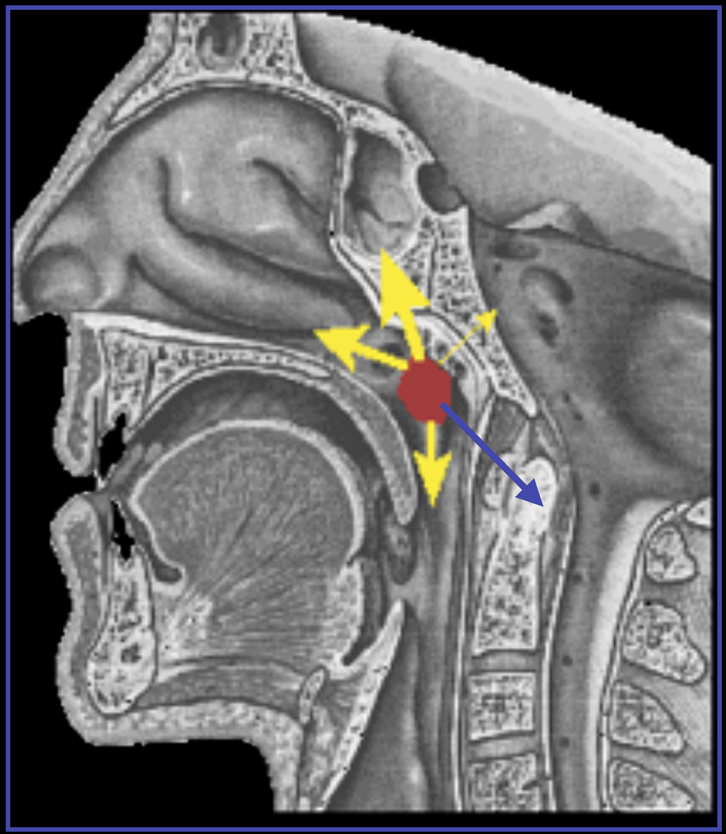
Pterygo-palatine/Infratemporal fossa

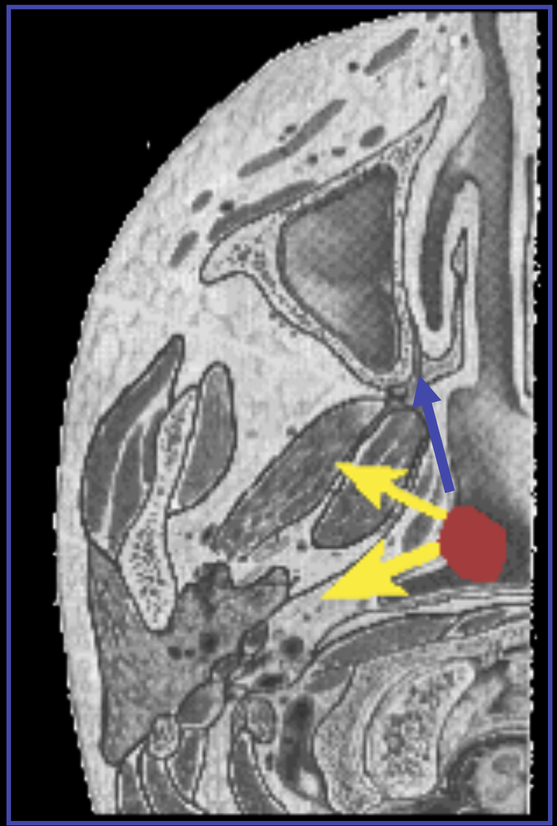
Skull base

Cavernous sinus

Cranial cavity

Cervical spine





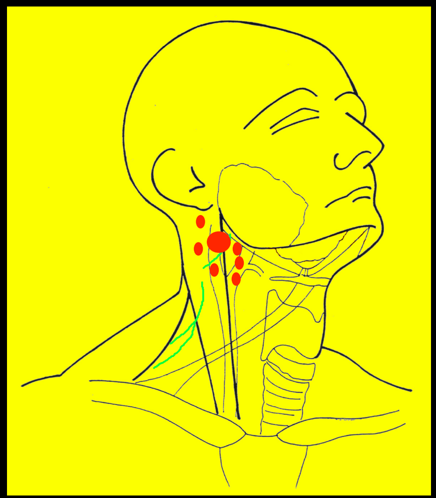
CLINICAL EVALUATION

NECK LUMP

At diagnosis: 60.3 - 75.8%

Retropharyngeal nodes

IIa-IIb
V
III
IV
I



CLINICAL EVALUATION

NASAL SYMPTOMS

At diagnosis: 40.3 - 73.4%

Epistaxis

Nasal obstruction

Mucopurulent discharge

Olfaction impairment

OTOLOGIC SYMPTOMS

At diagnosis: 43.9 - 62.4%

Otitis media

Hearing loss

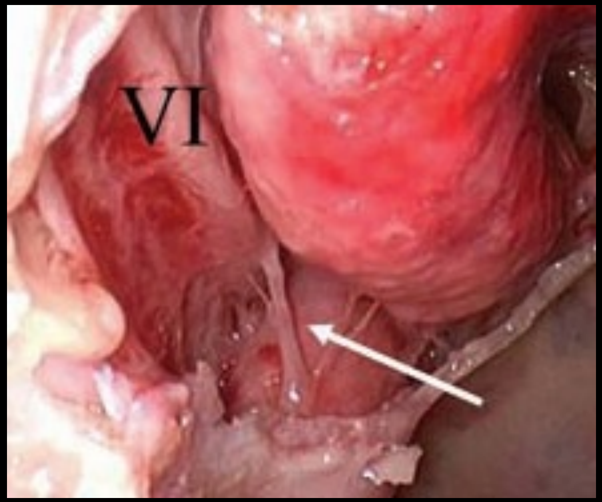
Fullness

Tinnitus

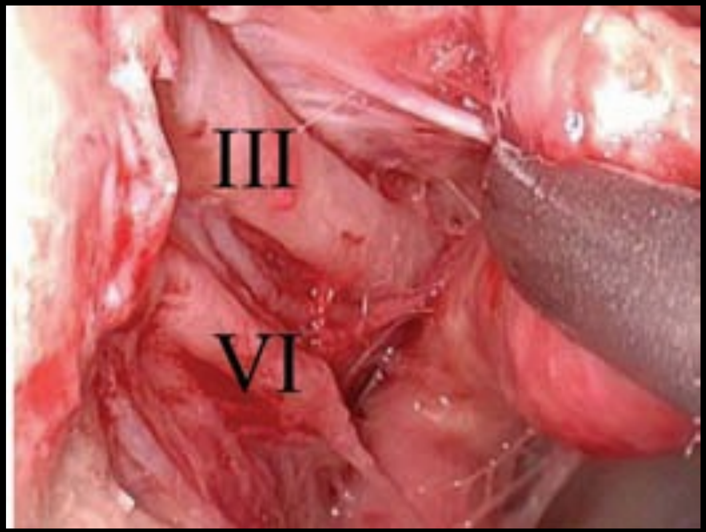
Always look at the nasopharynx
in case of recurrent otitis media

NEUROLOGIC SIGNS AND SYMPTOMS

At diagnosis: 9.4 - 20%



III, IV, and VI CN (cavernous sinus or superior orbital fissure): ophthalmoplegia



V CN: facial pain

Greater petrosal superficial nerve: xerophtalmy

IX, X, and XI CN: different jugular foramen syndromes

XII CN: hemitongue palsy, atrophy, and deviation

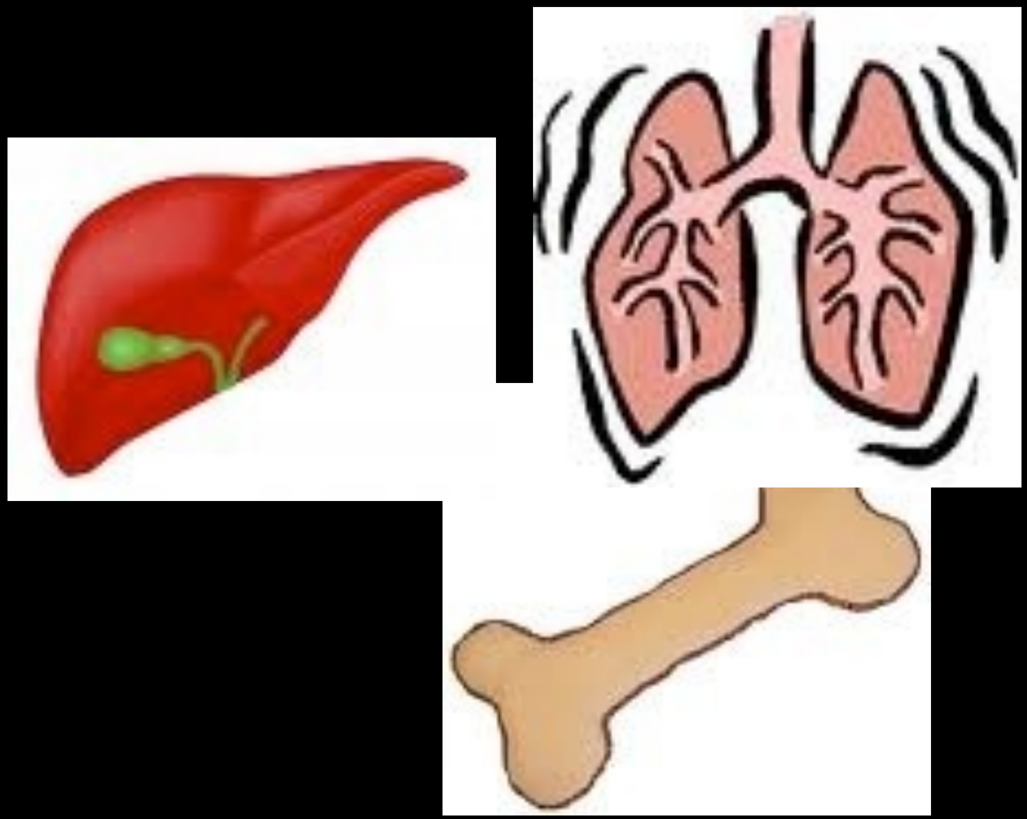
Sympathetic cervical trunk: Claude-Bernard-Horner syndrome

CLINICAL EVALUATION

NEUROLOGIC SIGNS AND SYMPTOMS

Distant metastasis at the diagnosis: <3%

Lung
Liver
Bone



Paraneoplastic syndromes:

- Dermatologic (Dermatomyositis, cutaneous vasculitis)
- Endocrinologic (SIADH, Cushing)
- Hematologic (Fever >38°, leukemic reaction)
- Rheumathologic (Hypertrophic osteoarthopathy)
- Neurologic (Guillain-Barrè syndrome)
- Ocular (Retinopathy)

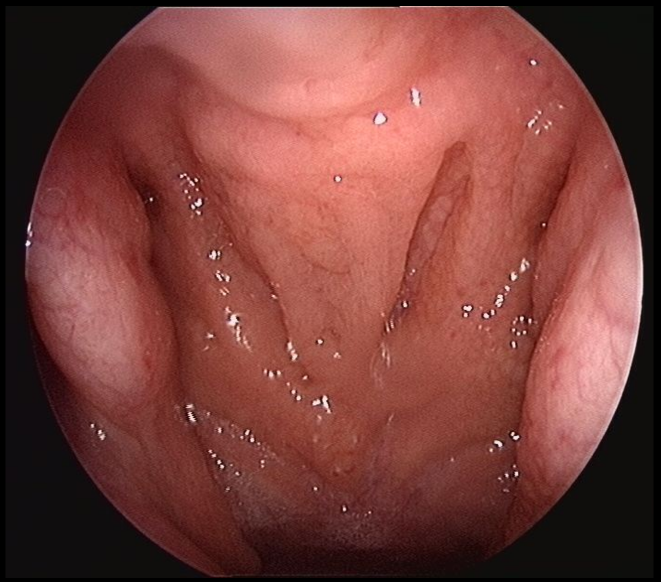
DIAGNOSTIC WORK UP

Rigid or flexible endoscopy (in about 10% of NPC the lesion is submucosal)

Imaging (MRI/CT and neck US)

Biopsy (endoscopy guided)

EBV serology (IgA VCA and IgA EA)



PET-CT

DIAGNOSTIC WORK UP

Endoscopic evaluation

MRI

Normal tissue

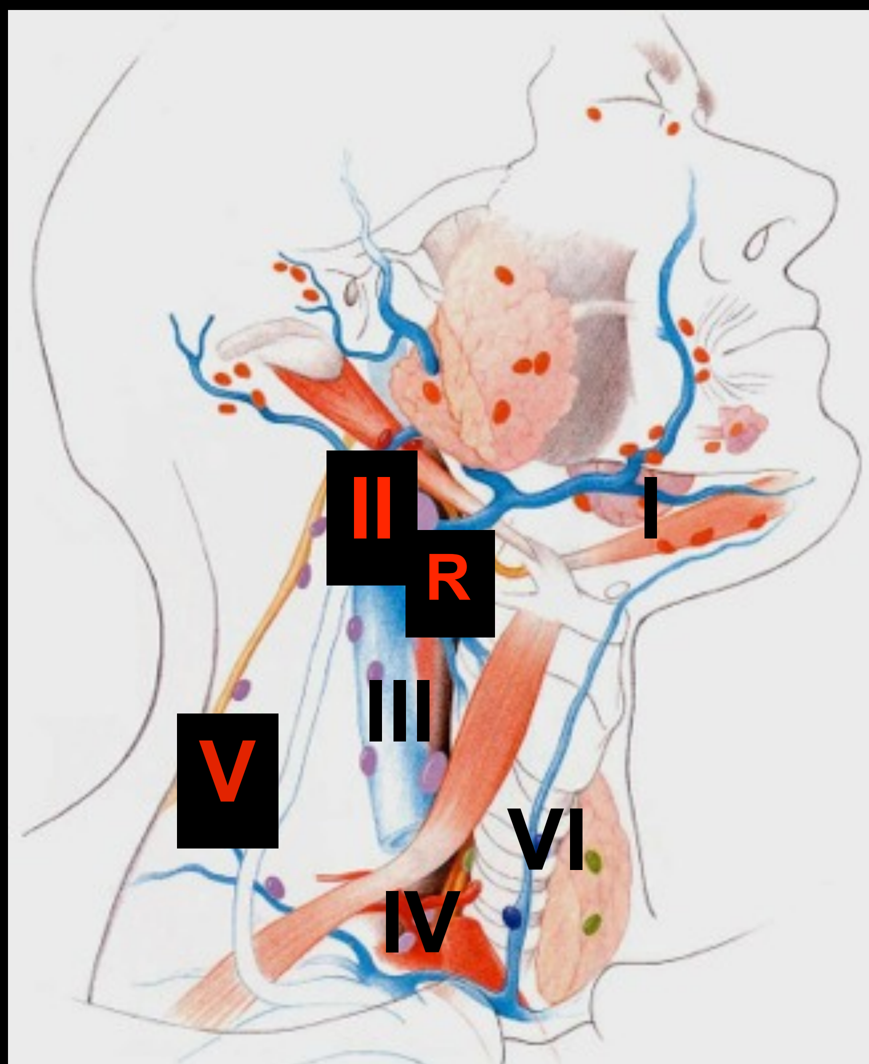
Fibrous tissue

Inflammation

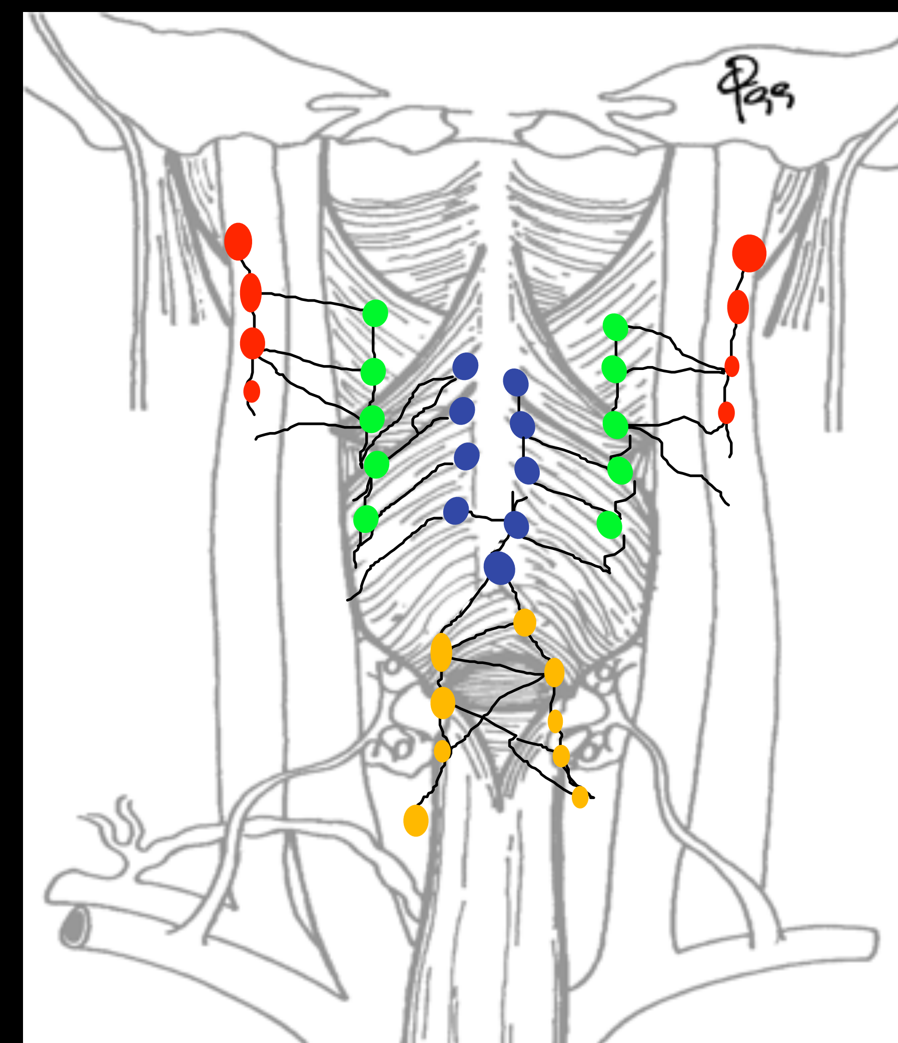
Necrotic tissue

DIAGNOSTIC WORK UP

Palpation and US



CT and/or MRI



DIAGNOSTIC WORK UP

Oral Oncology 47 (2011) 560–565

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

Review

[18]FDG-PET/CT for detecting distant metastases and second primary cancers in patients with head and neck cancer. A meta-analysis

Guo-Zeng Xu[a,b,1], De-Juan Guan[b,1], Zhi-Yi He[c,b,*]

18FDG-PET/CT had higher accuracy than conventional imaging work-up. The pooled sensitivity and specificity with 95% confidence interval for 18FDG-PET/CT were 0.881 (0.792–0.941) and 0.971 (0.953–0.984), respectively, indicating that 18FDG-PETCT had a very high accuracy for distant metastases staging of nasopharyngeal cancer.

In this meta-analysis the obtained values indicate that 18FDG-PET/CT had a very high accuracy also for follow-up after treatment. It may be used as a first-choice imaging technique for detection of distant failure and second primary cancers after treatment in clinical practice

The results of a recent meta-analysis (Zhou et al 2016, J Nucl Med 57:342-7) confirmed the high sensibility and sensitivity of 18FDG-PET/CT in the diagnosis of residual/recurrent nasopharyngeal carcinoma

STAGING

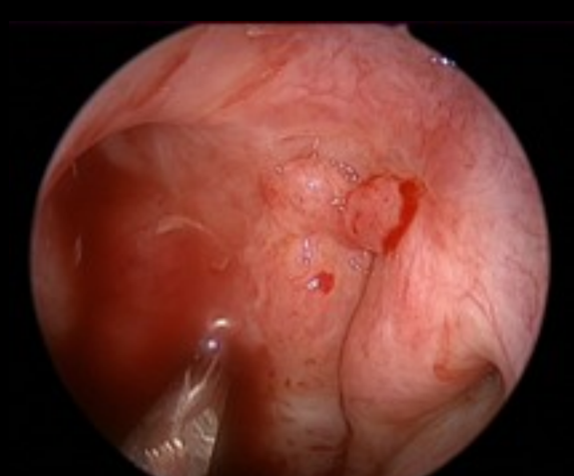
T1	Tumor confined to nasopharynx, or extends to oropharynx and/or nasal cavity
T2	Tumor with parapharyngeal extension
T3	Tumor invades bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or/with extension to the infratemporal fossa/masticator space

N0	No regional lymph node metastasis
N1	Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less in greatest dimension, above the supraclavicular fossa
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
N3	Metastasis in cervical lymph node(s) greater than 6 cm in dimension (a) or in the supraclavicular fossa (b)

NASOPHARYNX

EARLY DIAGNOSIS?

- Initial non-specific symptoms, common in other diseases:
  - ✓ inflammatory diseases
  - ✓ benign neoplastic lesions
- Endoscopy: can be negative (submucosal pattern of growth)



CONCLUSIONS

CORRECT DIAGNOSIS AND STAGING ARE THE KEY FOR A SUCCESSFUL TREATMENT

IN EARLY LESIONS, THE CONCEPT OF BIOLOGIC ENDOSCOPY AND EXCISIONAL BIOPSY IS GAINING WIDESPREAD ACCEPTANCE

IN ADVANCED LESIONS, IMAGING TECHNIQUES PLAY A PIVOTAL ROLE IN GUIDING TREATMENT SELECTION

IN SOME ANATOMIC AREAS, HISTOLOGIC DIAGNOSIS NEEDS TO BE ASSOCIATED WITH ANCILLARY STUDIES

Imaging work-up

CT, MR (PET etc.)

Frank Pameijer, MD, PhD

- Departments of Radiology and Radiation Oncology
- University Medical Center, Utrecht
- The Netherlands

No disclosures

ESTRO School

Head and Neck Cancer Imaging

Frank Pameijer

Depts. of Radiology and Radiation Oncology

Utrecht Medical Center

Head and Neck cancer: Imaging?

- Imaging results in more accurate TNM-staging compared to clinical examination alone!
- Clinical examination and imaging are complementary modalities
  - Findings should be discussed in multidisciplinary setting

Multidisciplinary H&N Oncology meeting

- UMCU: every Wednesday 13.30-16.00
  - All new patients
  - All known patients with new event

Objectives

Imaging techniques for evaluation H&N ca.

- Ultrasound
- Panoramic dental X-ray
- CT
- MRI
- (FDG PET)

Ultrasound

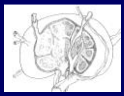
- Indication:
  - Neck swelling / known H&N tumor
- Localisation
  - Relation with surrounding structures
- Characterisation
  - Cystic / solid / vascularity
- Cytologic / histologic material

Neck lymph nodes

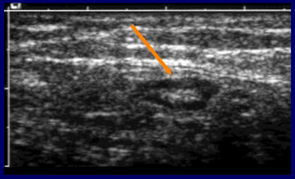
- +/- 300 in H&N
- Differentiation
  - Normal
  - Abnormal
- Modalities
  - **US**, CT, MR

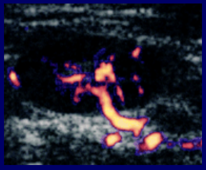
Normal lymph nodes: characteristics?

- Small
- Oval (kidney bean)
- Hilus: present
- Cortex: homogenous
- Vascularity: hilar



Normal

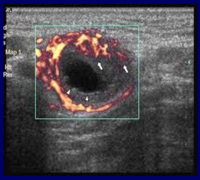




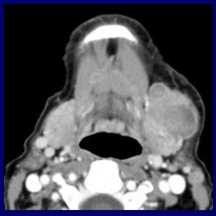
Ahuja AJNR 2001

Abnormal lymph nodes: characteristics?

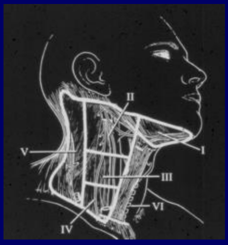
- Enlarged
- Round
- Hilus: absent
- Cortex: heterogenous
- Vascularity: peripheral



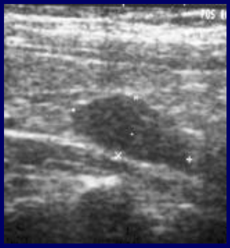
Abnormal



US: Neck lymph nodes

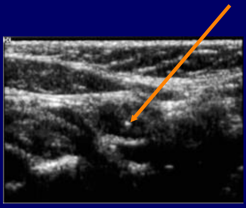


Localisation: level system



Characterisation: ?

Characterisation neck lymph nodes



Fine Needle Aspiration Cytology (FNAC)

Summary Ultrasound

- Superficial technique
  - Primary evaluation of neck swelling
  - H&N ca.: lymph node staging
- Disadvantages:
  - No evaluation of primary tumor
  - Operator dependent
- Advantages:
  - FNAC

Objectives

- Ultrasound
- **Panoramic dental X-ray**
- CT
- MRI

Daily practice: Panoramic X-ray

- Male, 28 years
- Swelling left upper jaw since > 1 year

CT

Soft tissue window

Bone window

Diagnosis??

Radiological diagnosis
Mucocele

- Expanded (part of) paranasal sinus
  - Cystic lesion due to chronic obstruction of the ostium
- Expansion / remodelling of bone
- Slow development of complaints
- Needs surgical therapy

PA diagnose
Odontogenic Myxoma

- WHO: benign mesenchymal tumor
  - Rare; locally invasive
  - From dental papillae / peridontal ligament
- Imaging
  - At 'Tooth bearing areas'
  - Mandible > maxilla
  - Displacement / resorption of dental elements

Odontogenic myxoma

- Male, 28 years
- Therapy: left hemi-maxillectomy

Pre-op **Post-op**

Indications panoramic dental X-ray

- Dental status
  - Infection, retained (parts of) elements
- Planning of extractions pre-radiotherapy
- Planning of reconstruction post-surgery

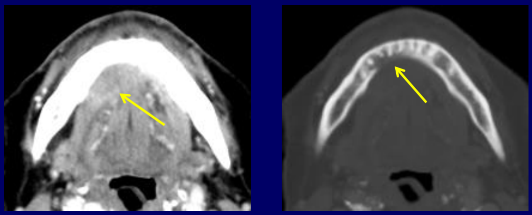
Objectives

- Ultrasound
- Panoramic dental X-ray
- **CT**
- MRI

CT

- Advantages:
  - Quick, widely available, cheap
  - Superior bone detail
  - Preferred method for nodal staging
- Disadvantages:
  - Radiation exposure
  - Administration of iodine-containing agents
  - Inferior soft tissue contrast (vs MRI)
  - Dental filling metallic artifacts

Superior bone detail
Floor of mouth ca.



Soft tissue window Bone window

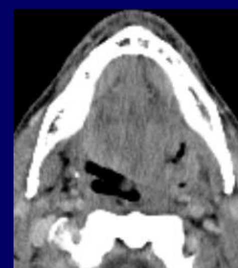
Nodal staging

Hypopharyngeal ca.

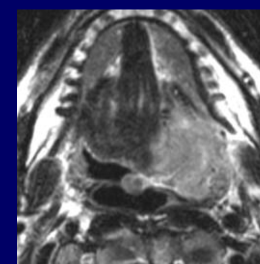
Supraglottic laryngeal ca.

Inferior soft tissue contrast (vs. MRI)

Base of tongue ca.



CT



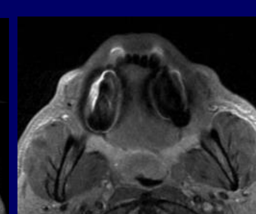
MRI

CT: Dental metallic fillings

'Streak' artifacts

Dental filling artifacts: CT / MRI

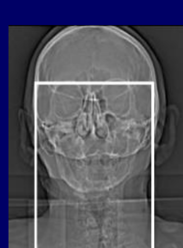
CT



MRI

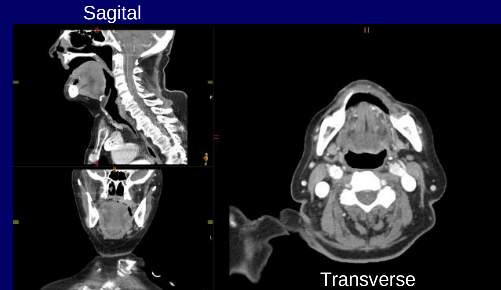
Multi-detector Spiral CT Neck

- 'Box' acquisition
  - Upper orbit / lung apex
- Scanning time: +/- 7 sec.
- +/- 400 sections: 1,5mm
  - Reconstructions: 3mm
  - Standard directions (3)



Standard directions

Sagital



Coronal

Daily practice: CT

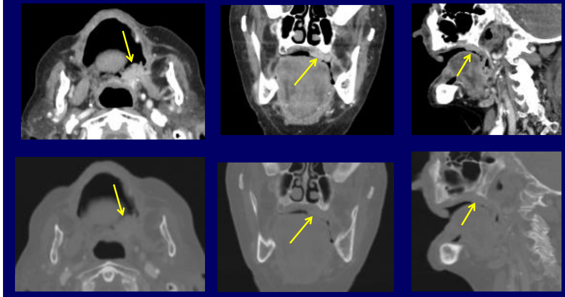
- Female, 89 years
- Since several months painful mouth
- Examination:
  - Lesion soft palate
  - 3,0 cm (T2)

- Biopsy: Squamous cell carcinoma (SCC)

Radiological work-up

- Chest X-ray
  - Normal
- US Neck
  - Normal nodes
  - No FNAC
- CT Neck

Soft tissue window



Bone window

Multidisciplinary H&N meeting

- T2N0 maxillar ca.
- Treatment
  - Partial maxillectomy
  - Palatal obturator

- Path report: verrucous ca. Ø 4,8 cm, near positive surgical ventral margin (<1mm)
- **Conclusion**:
  - pT3N0M0
  - In view of age: clinical follow-up (no post-op RT)

Objectives

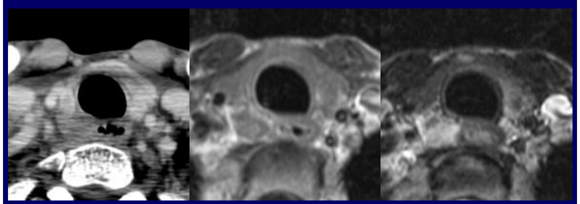
- Ultrasound
- Panoramic dental X-ray
- CT
- **MRI**

Magnetic resonance imaging (MRI)

- Advantages:
  - No radiation
  - Allergies to iv contrast (Gadolinium) extremely rare
  - Superior soft tissue contrast (vs. CT)
  - Less dental filling metallic artifacts
- Disadvantages:
  - Limited availability; expensive
  - Long acquisition time => ↑motion degradation
  - More contraindications (claustrophobia, ICD, CI, etc.)

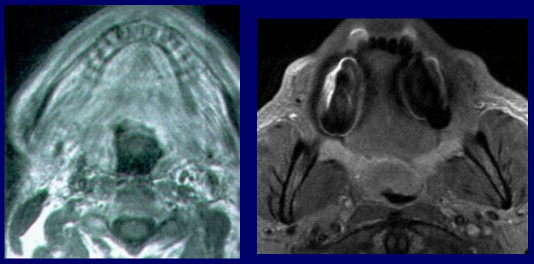
Superior soft tissue contrast (vs. CT)

Patient with hoarseness



CT | MR T1 + C | MR T2

Artifacts



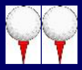
Movement | Dental fillings

Technique

Classic sequences:

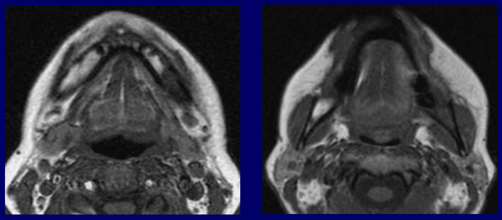
- T1
  - Without / with i.v. contrast
  - Fatsuppressed

- T2



T1 without i.v. contrast

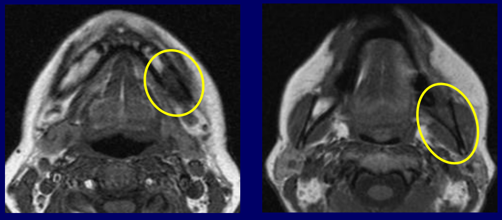
- “Fat is your friend” (anatomical orientation)



T1 | T1

T1 without i.v. contrast

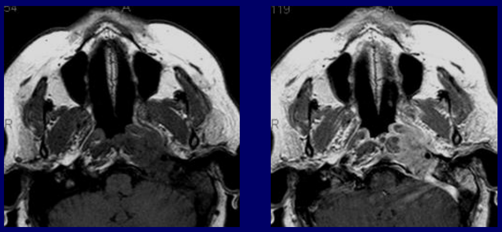
- “Fat is your friend” (anatomical orientation)



T1 | T1

T1 with i.v. contrast

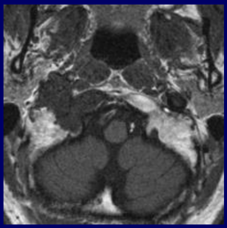
- Improved delineation of enhancing lesions from surrounding normal anatomy



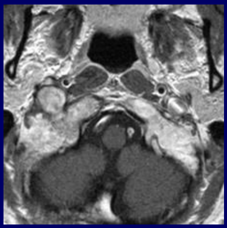
T1 | T1 + C

T1 with i.v. contrast

- May obscure enhancing lesions surrounded by fat !!



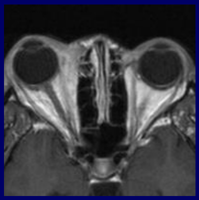
T1



T1 + C

T1 + C + Fat Suppression (FS)

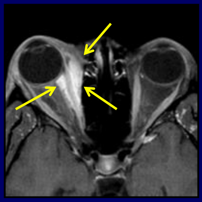
- Improved delineation of enhancing lesions surrounded by fat



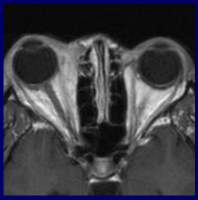
T1 + C

T1 + C + Fat Suppression (FS)

- Improved delineation of enhancing lesions surrounded by fat



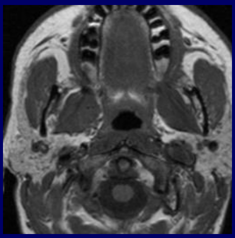
T1 + C + **FS**



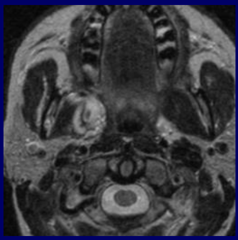
T1 + C

T2

- Lesion detection



T1



T2

Technique

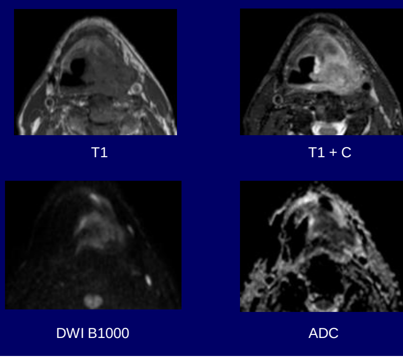
Classic sequences:

- T1 
  - Without / with i.v. contrast
  - Fatsuppressed
- T2 
- **New sequences**

Diffusion weighted imaging

- DWI: May be helpful in narrowing of differential diagnosis
- Restricted diffusion seen in
  - Benign lesions e.g.
    - Cholesteatoma, epidermoid
  - Malignant lesions e.g.
    - (Head & Neck) Cancer
    - Lymphoma, leukemia, metastasis

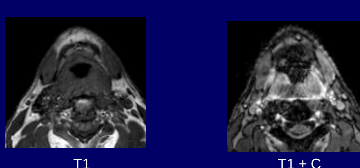
Supraglottic laryngeal ca.



DWI Future

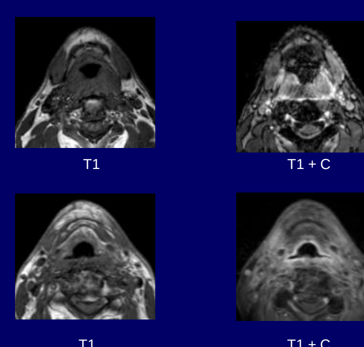
- Detection of recurrence
  - vs PET
- Early response monitoring

Posterior pharyngeal wall ca.



Pre-Tx

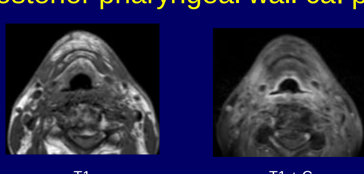
Posterior pharyngeal wall ca.



Pre Tx

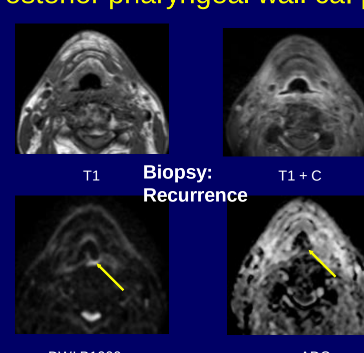
Post
Chemo-RT

Posterior pharyngeal wall ca. post Tx



Post
Chemo-RT

Posterior pharyngeal wall ca. post Tx



**Biopsy:
Recurrence**

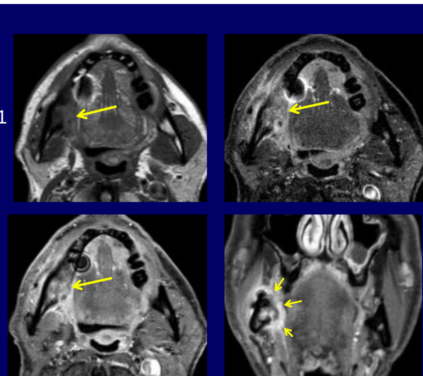
Daily practice: MRI

- Male, 65 years
- 42 pack years
- Recently extraction 48
  - No healing
- Examination:
  - Tumor right gingival ridge
  - 2,5 x 3,5cm (T2)
  - Invasion of mandible? (T4a)
- Biopsy: Squamous cell carcinoma (SCC)

Radiological work-up

- Chest X-ray: normal
- US Neck:
  - FNAC right neck Level I / II
  - Cytology report: no malignant cells
- Panoramic dental X-ray
- MRI

T1

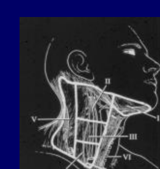


T2

T1 + C + FS

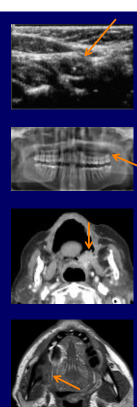
Multidisciplinary H&N meeting

- T4aN0 right gingival carcinoma
- Treatment
  - Segmental mandibular resection
  - Neck dissection level I-III
- Path report
  - Tumor excision: radical
  - Neck dissection level I-III: no lymph node mets
- **Conclusion**:
  - pT4aN0M0
  - Clinical follow-up (no post-operative RT needed)



Objectives

- Ultrasound
- Panoramic dental X-ray
- CT
- MRI



Imaging work-up

CT, MR (PET etc.)

Frank Pameijer, MD, PhD

- Departments of Radiology and Radiation Oncology
- University Medical Center, Utrecht
- The Netherlands

No disclosures

ESTRO School

Radiobiological principles in head and neck radiotherapy

Cai Grau

Professor, MD, DMSc

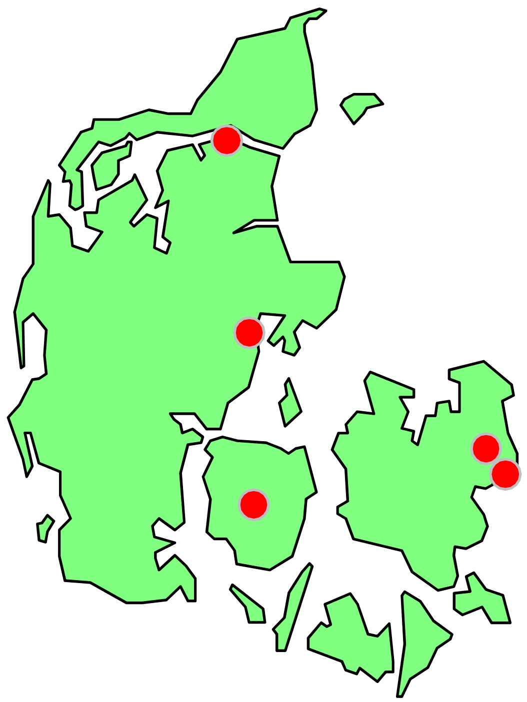
Department of Oncology, Aarhus University Hospital
Aarhus, Denmark, caigrau@dadlnet.dk; www.cirro.dk

Firenze June 2016

ESTRO School

DAHANCA

The Danish Head and Neck Cancer Group



- Established 1976
- National database
- Registration and follow up of all patients with head and neck cancer
- National treatment strategy
- Clinical trials
- Quality assurance

Role of RT in head and neck cancer

- Primary radiotherapy
- Adjuvant radiotherapy
- Palliative radiotherapy

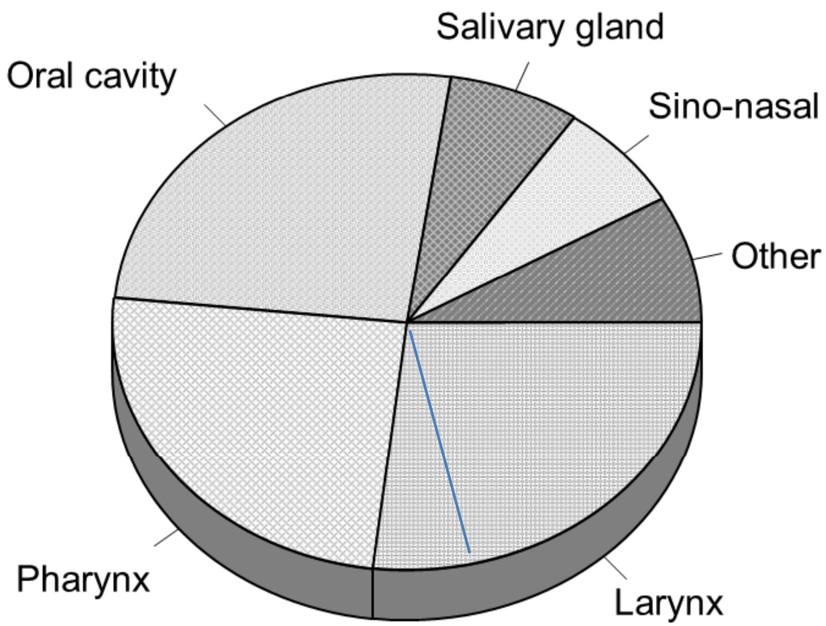
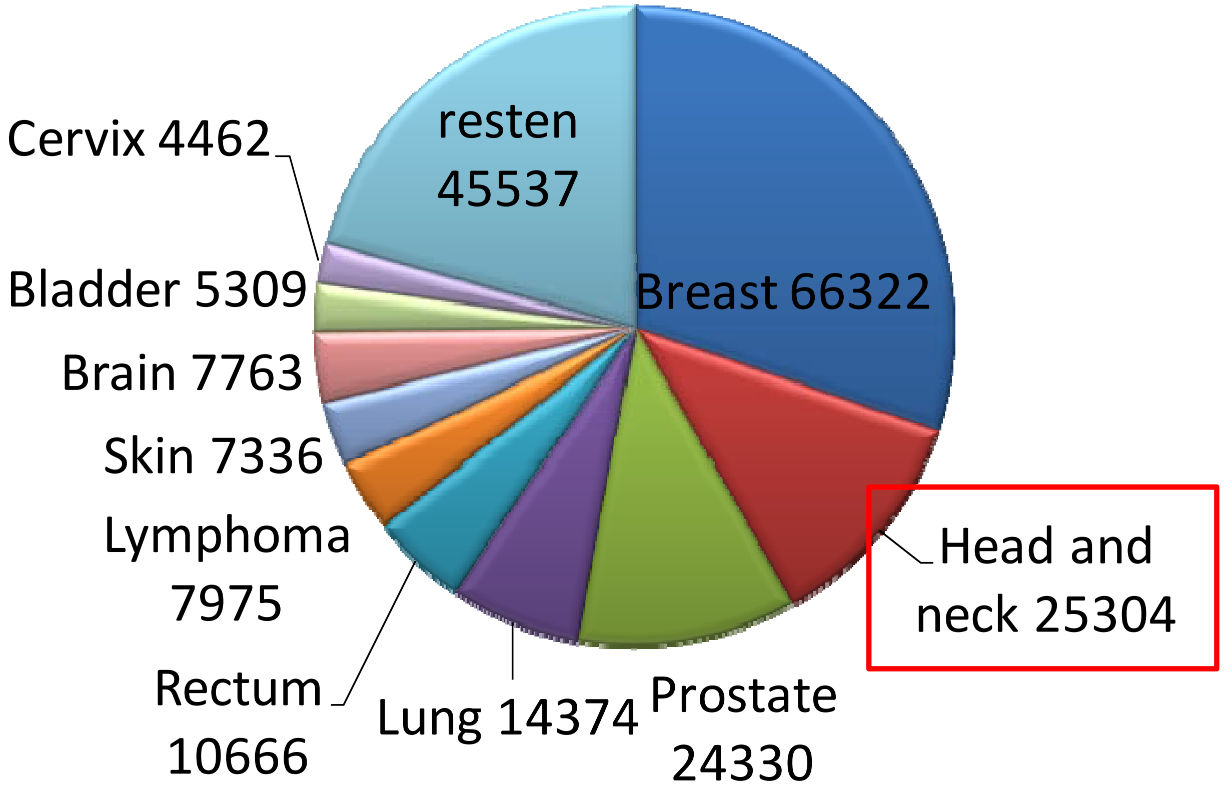


TABLE 3
Optimal Radiotherapy Utilization Rate by Cancer Type

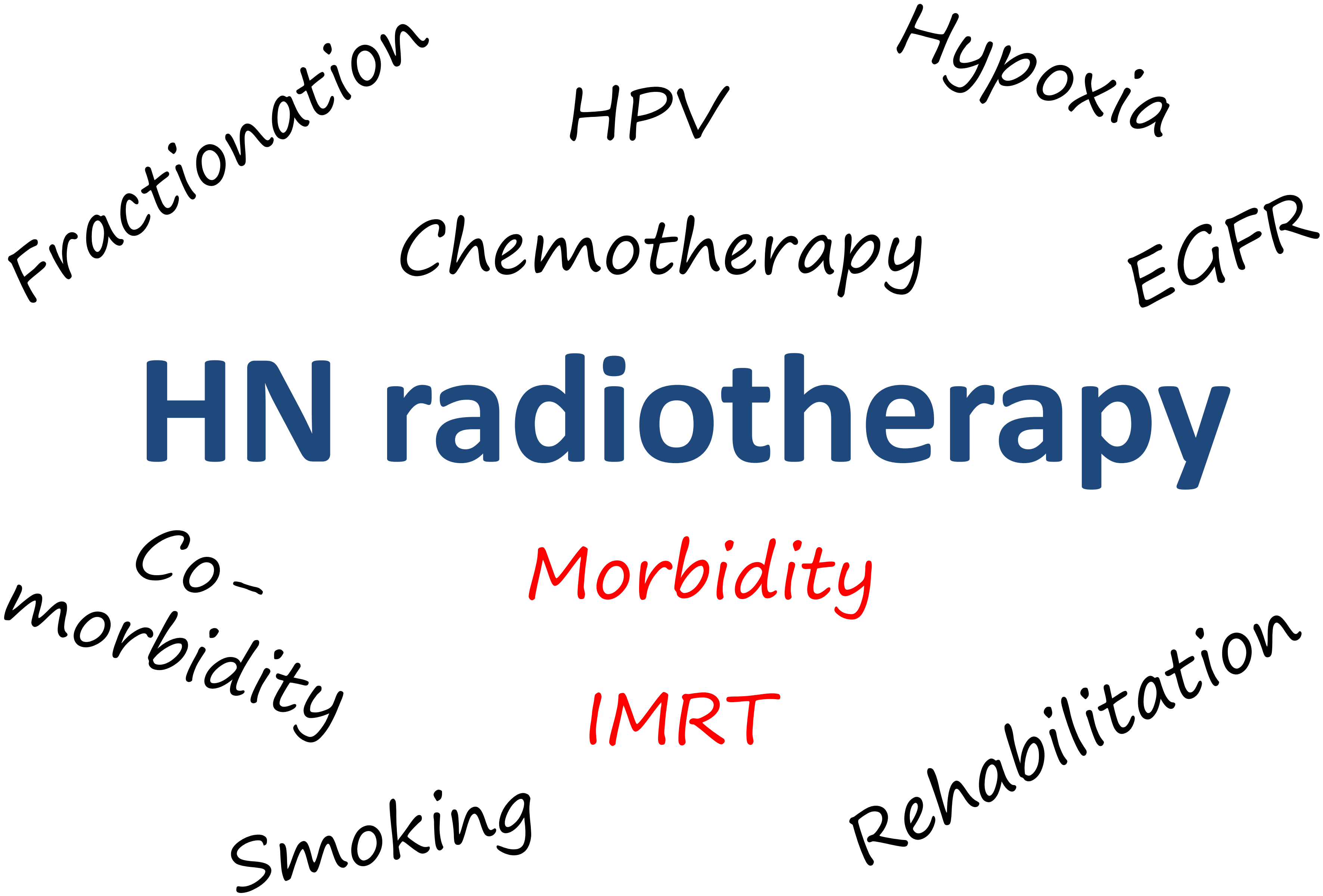
Tumor type	Proportion of all cancers	Proportion of patients receiving radiotherapy	Patients receiving radiotherapy (% of all cancers)	Reference
Breast	0.13	83	10.8	Delaney et al.[12]
Lung	0.10	76	7.6	Delaney et al.[13]
Melanoma	0.11	23	2.5	Delaney et al.[14]
Prostate	0.12	60	7.2	Delaney et al.[16]
Gynecologic	0.05	35	1.8	Delaney et al.[18,19]
Colon	0.09	14	1.3	Delaney et al.[15]
Rectum	0.05	61	3.1	Delaney et al.[15]
Head and neck	0.04	78	3.1	Delaney et al.[17]
Gall bladder	0.01	13	0.1	Delaney et al.[15]
Liver	0.01	0	0.0	Delaney et al.[15]
Esophageal	0.01	80	0.8	Delaney et al.[15]
Stomach	0.02	68	1.4	Delaney et al.[15]
Pancreas	0.02	57	1.1	Delaney et al.[15]
Lymphoma	0.04	65	2.6	Featherstone et al.[20]
Leukemia	0.03	4	0.1	Featherstone et al.[21]
Myeloma	0.01	38	0.4	Featherstone et al.[21]
Central nervous system	0.02	92	1.8	Delaney et al.[22]
Renal	0.03	27	0.8	Delaney et al.[16]
Bladder	0.03	58	1.7	Delaney et al.[16]
Testis	0.01	49	0.5	Delaney et al.[16]
Thyroid	0.01	10	0.1	Delaney et al.[22]
Unknown primary	0.04	61	2.4	Delaney et al.[22]
Other	0.02	50	1.0	See citations in text
Total	1.00	-	52.3	

Radiotherapy fractions Denmark

- 2007
- Total 217.579 fractions
- 12.891 patients

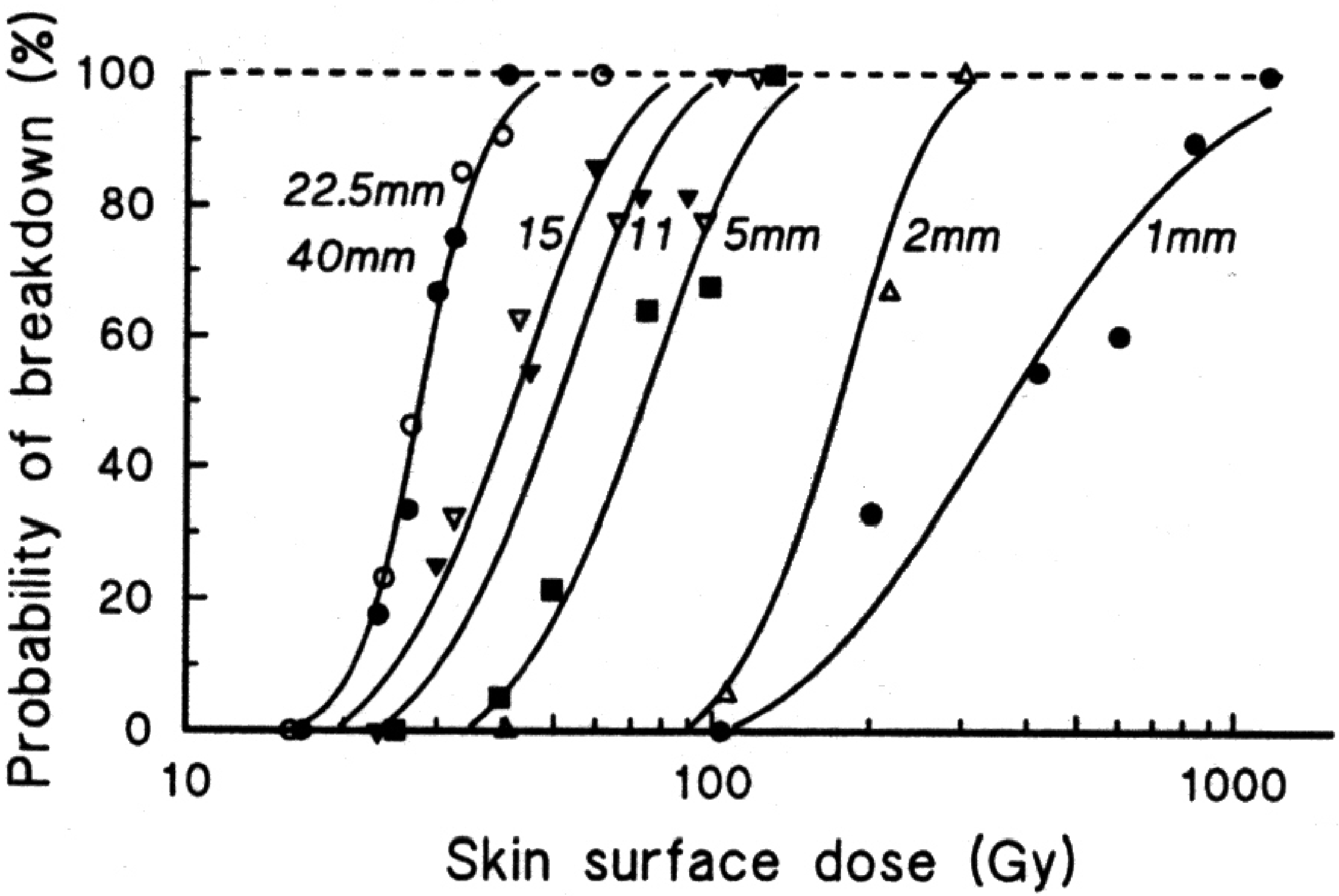



Fractionation
HPV
Hypoxia
Chemotherapy
EGFR
HN radiotherapy
Co-morbidity
Morbidity
IMRT
Smoking
Rehabilitation

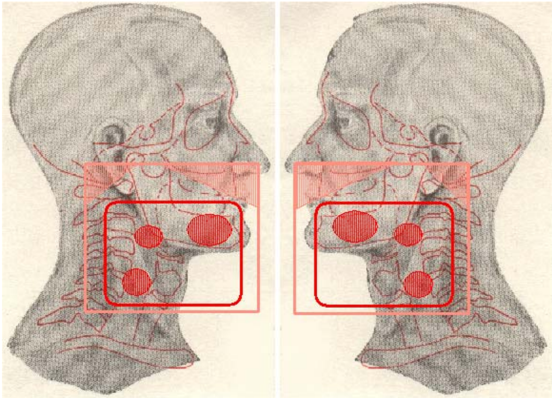

Fractionation
HPV
Hypoxia
Chemotherapy
EGFR
HN radiotherapy
Co-morbidity
Morbidity
IMRT
Smoking
Rehabilitation

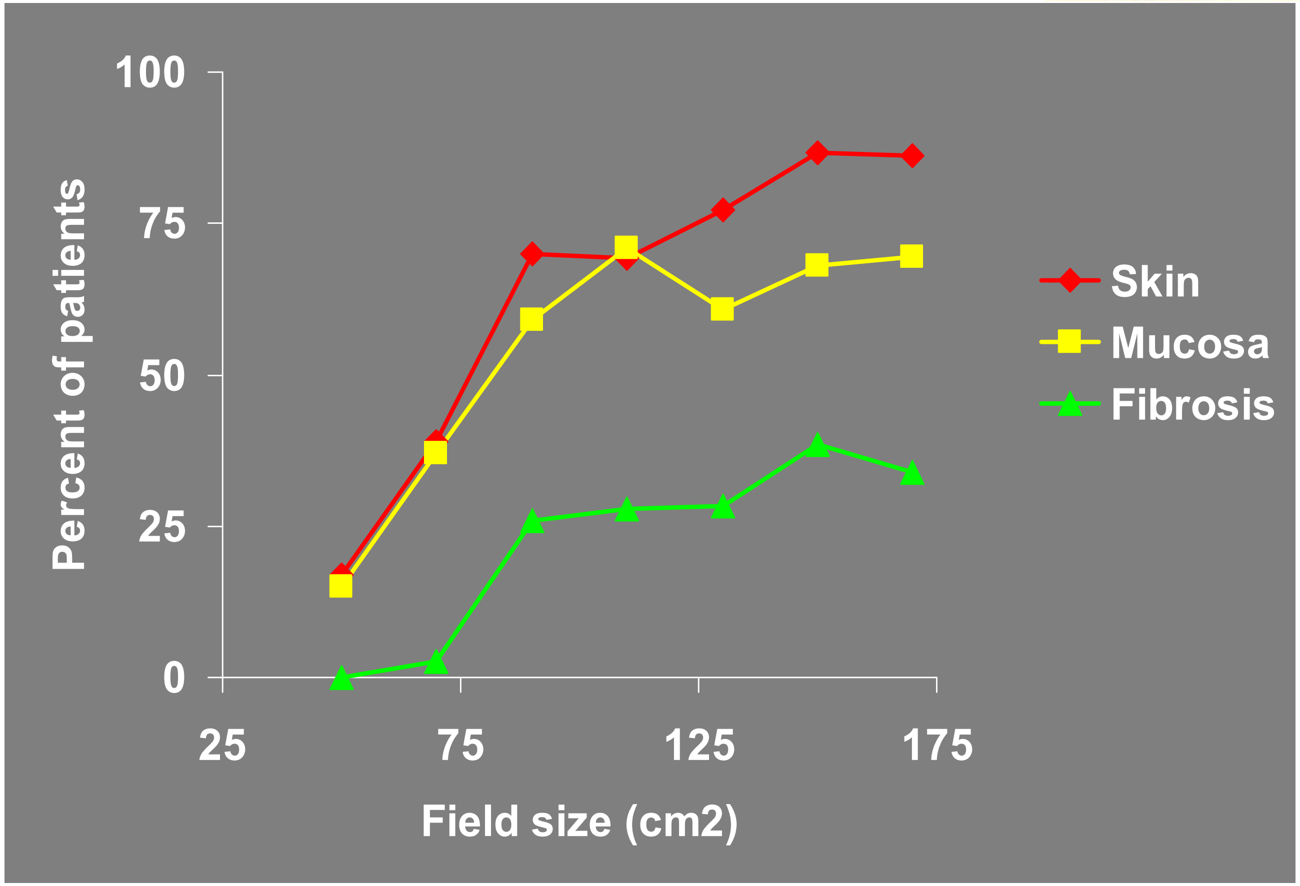
Volume effect

Dose-volume-effect



Volume and morbidity in HN radiotherapy



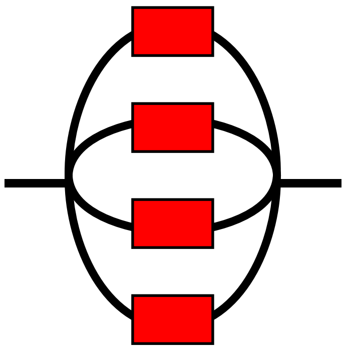


Data from IAEA MMC trial

Parallel vs. serial organization af tissues

Serial

Spinal cord
Brain stem
Optic nerves
Chiasm
Inner ear



Parallel

Salivary glands
T-M joints
Oral cavity
Swallowing structures?

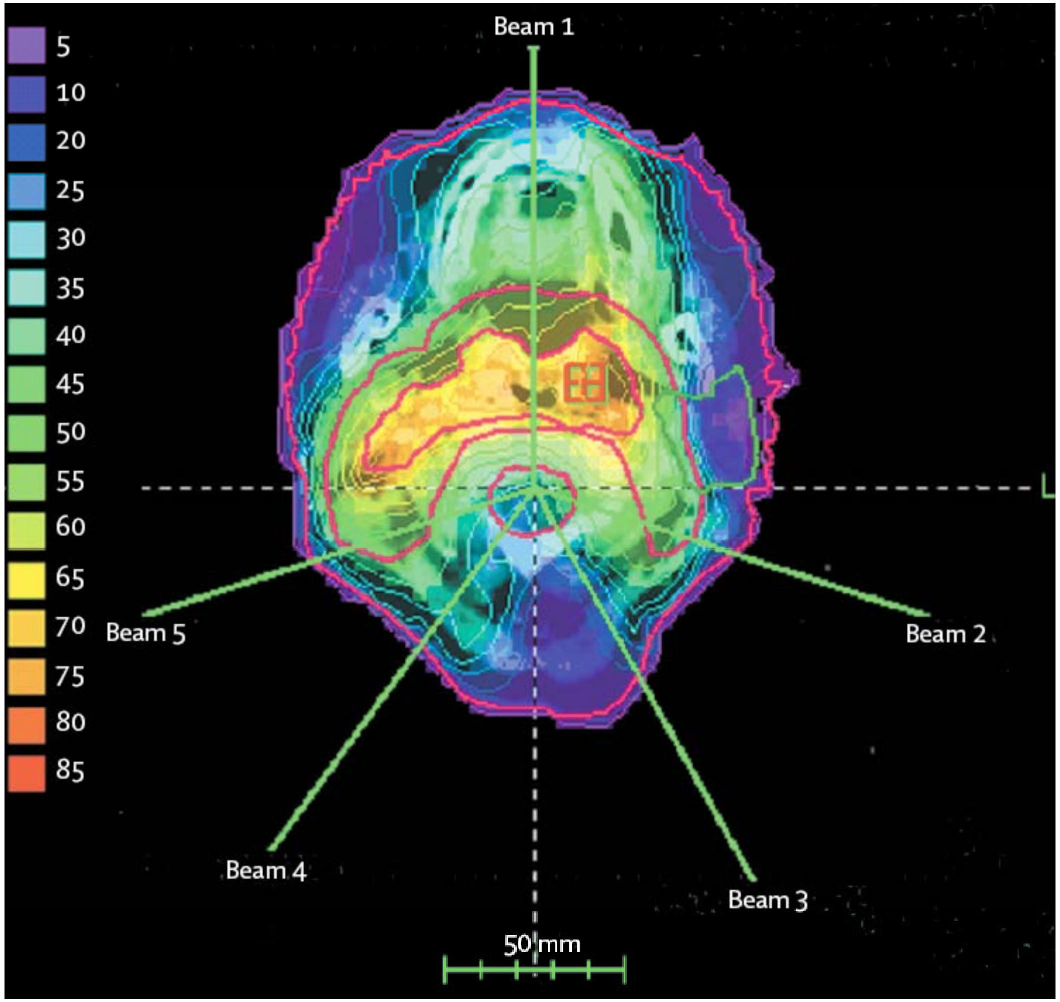
Volume effect

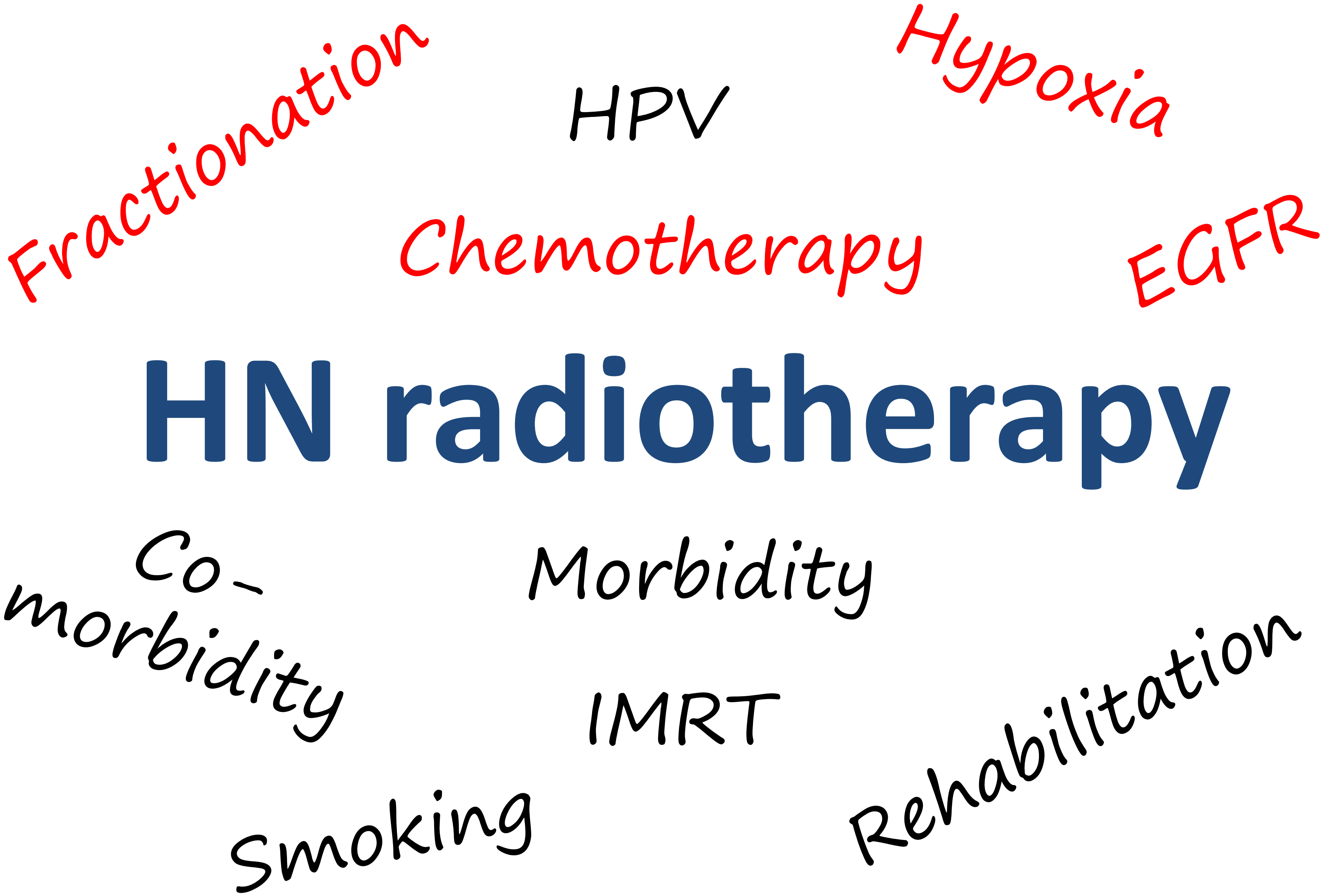
Normal tissue tolerance

- **<u>Serial tissue: Dose constraints</u>**
  - Tolerance is not related to the irradiated volume
  - Max dose
  - E.g. ’max 50 Gy to spinal cord’ ’max 54 Gy to optic chiasm’

- **<u>Parallel tissue: Dose volume constraints</u>**
  - Tolerance is dependent on the irradiated volume
  - DVH constraints
  - E.g. ’mean dose below 30 Gy to oral cavity’, ’mean dose below 26 Gy to parotids’, ’2/3 of larynx below 50 Gy’

Intensity Modulated RT (IMRT)




Fractionation
HPV
Hypoxia
Chemotherapy
EGFR
HN radiotherapy
Co-morbidity
Morbidity
IMRT
Smoking
Rehabilitation

Radiotherapy intensifiers

- 20.000+ pre-clinical studies
- 2.000+ phase I-II trials
- 200+ randomized trials
- 20+ metaanalyses

- In less than 45 minutes…

Therapeutic ratio

Effect

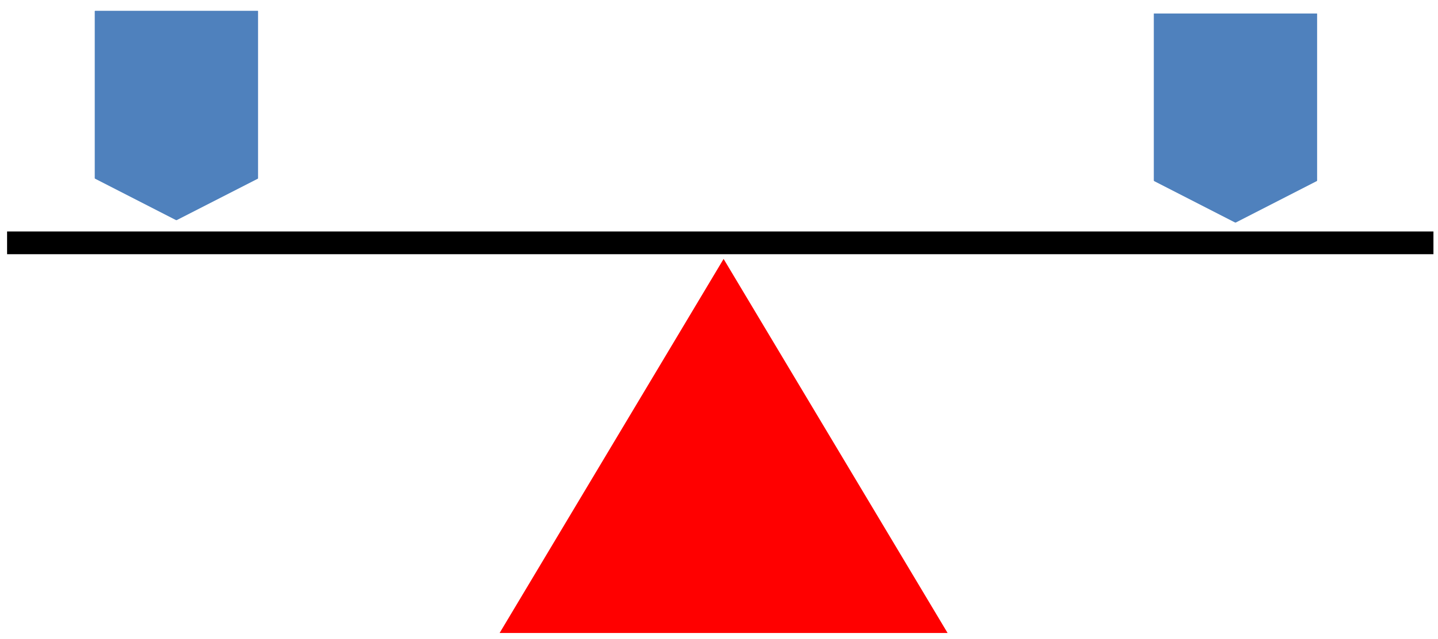
Tumor control

Survival

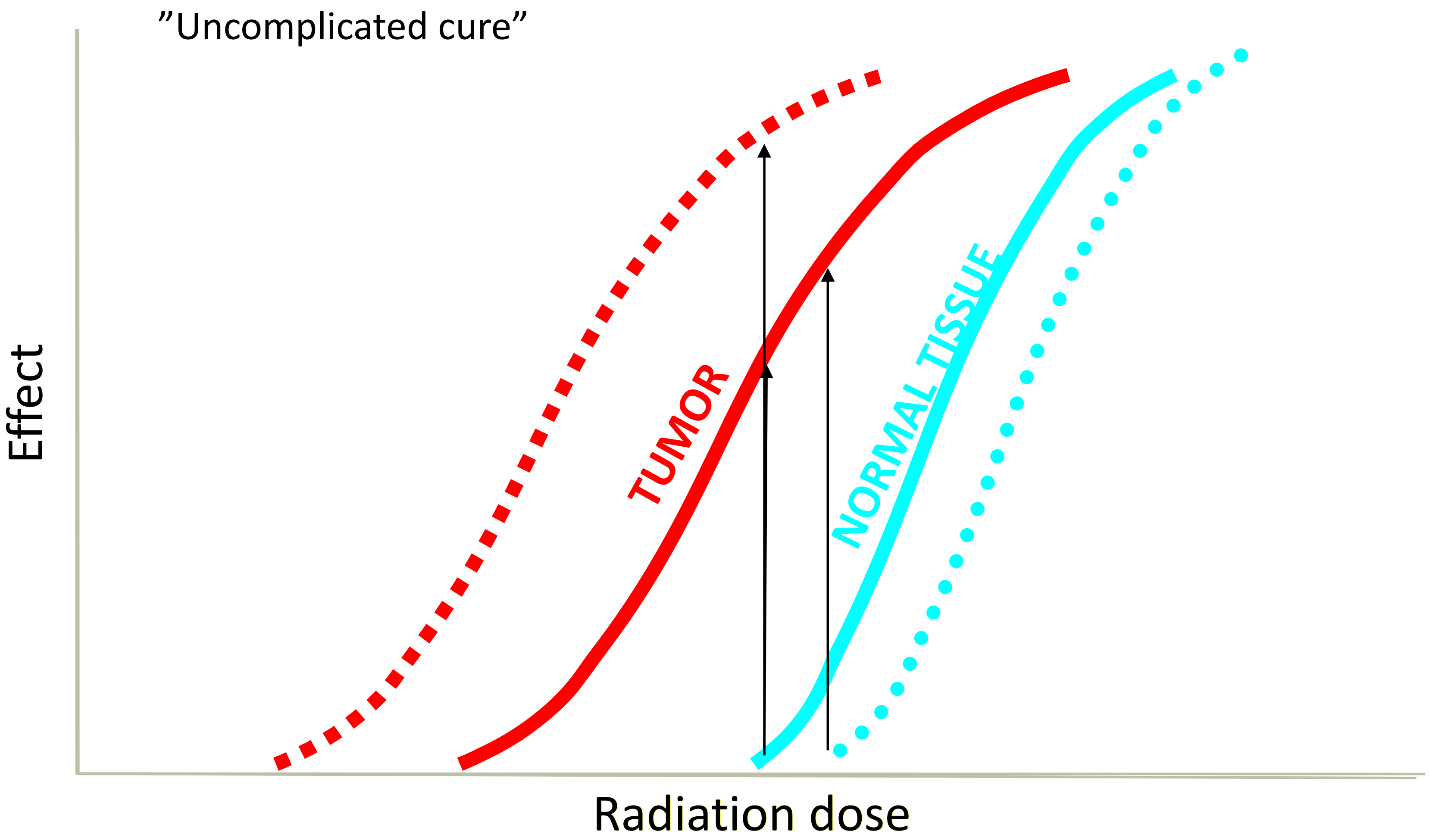
Side effect

Acute

Late



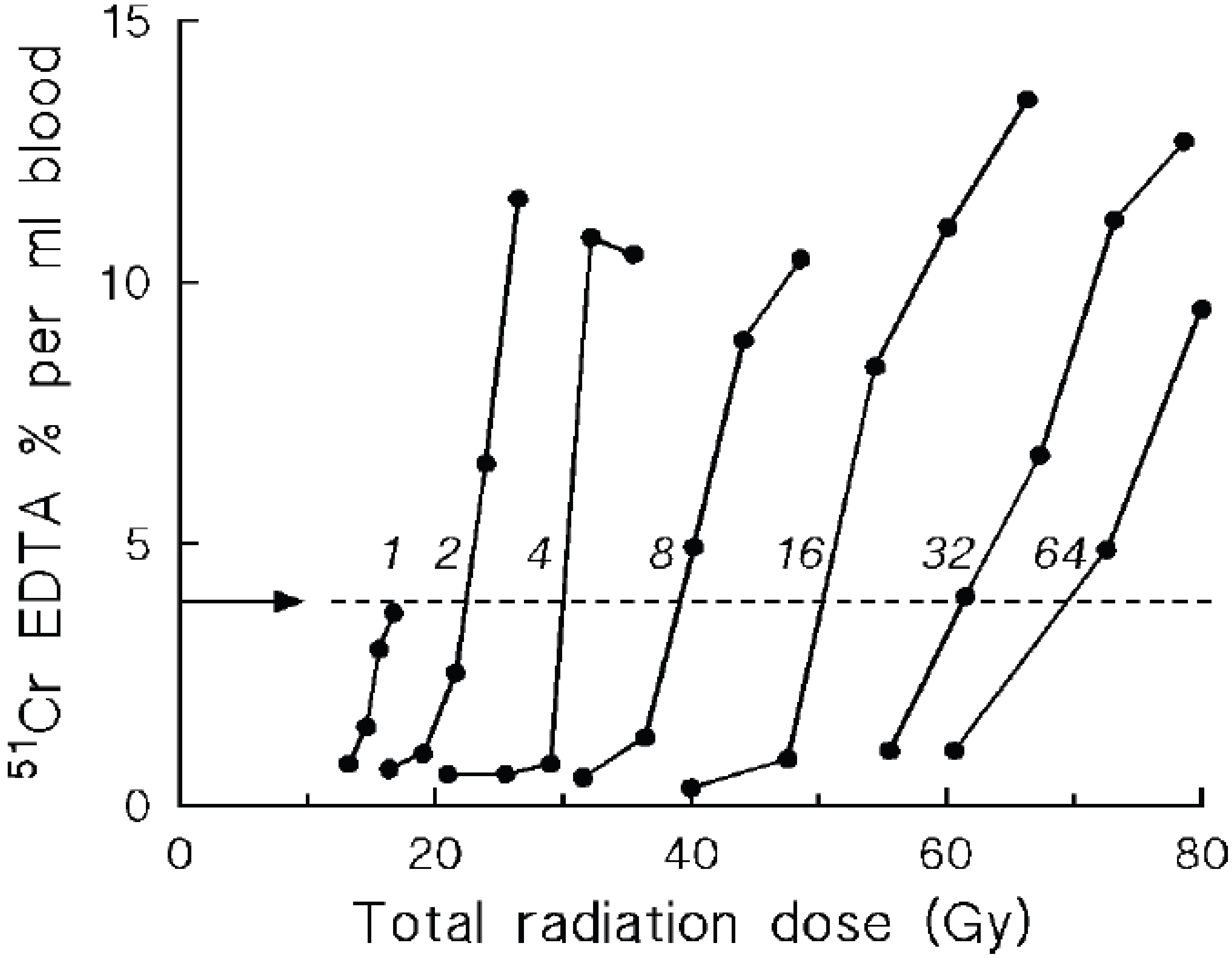
Therapeutic ratio



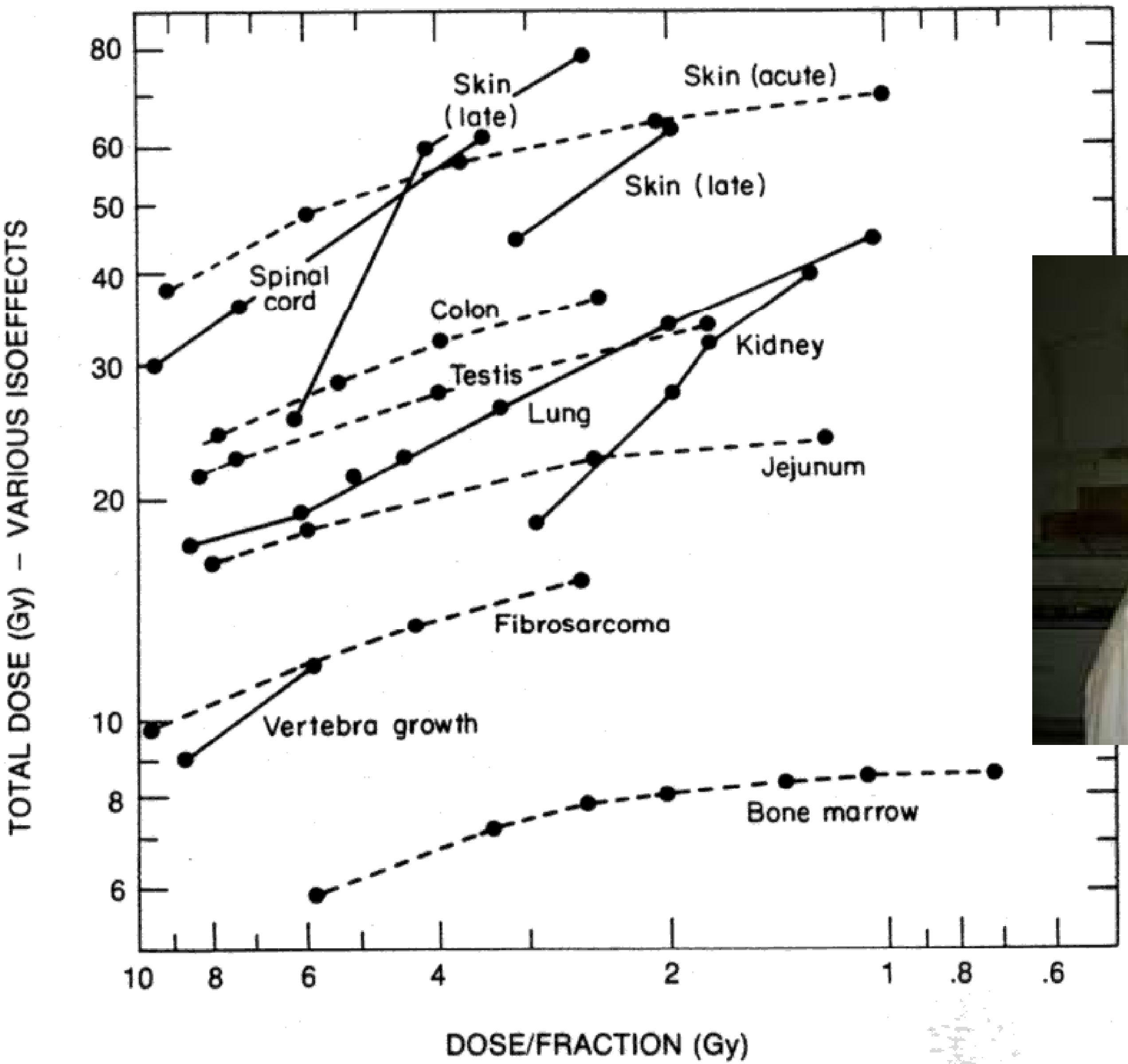
cg/02

Fractionation

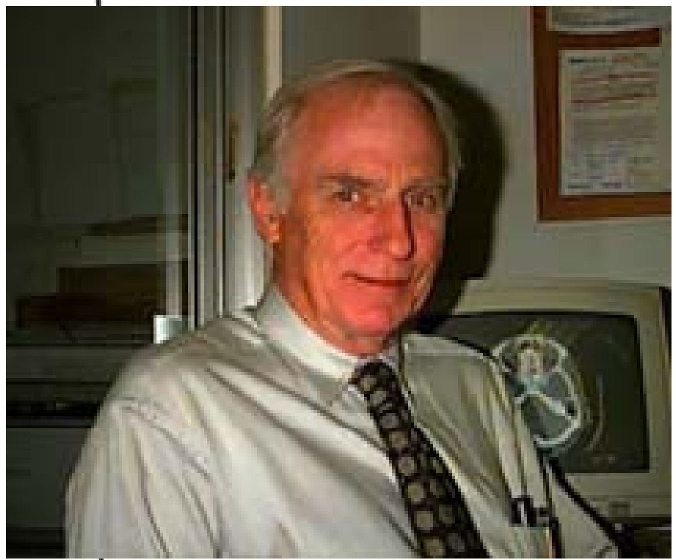
Fractionation and iso-effect



Fractionation sensitivity - The spaghetti plot



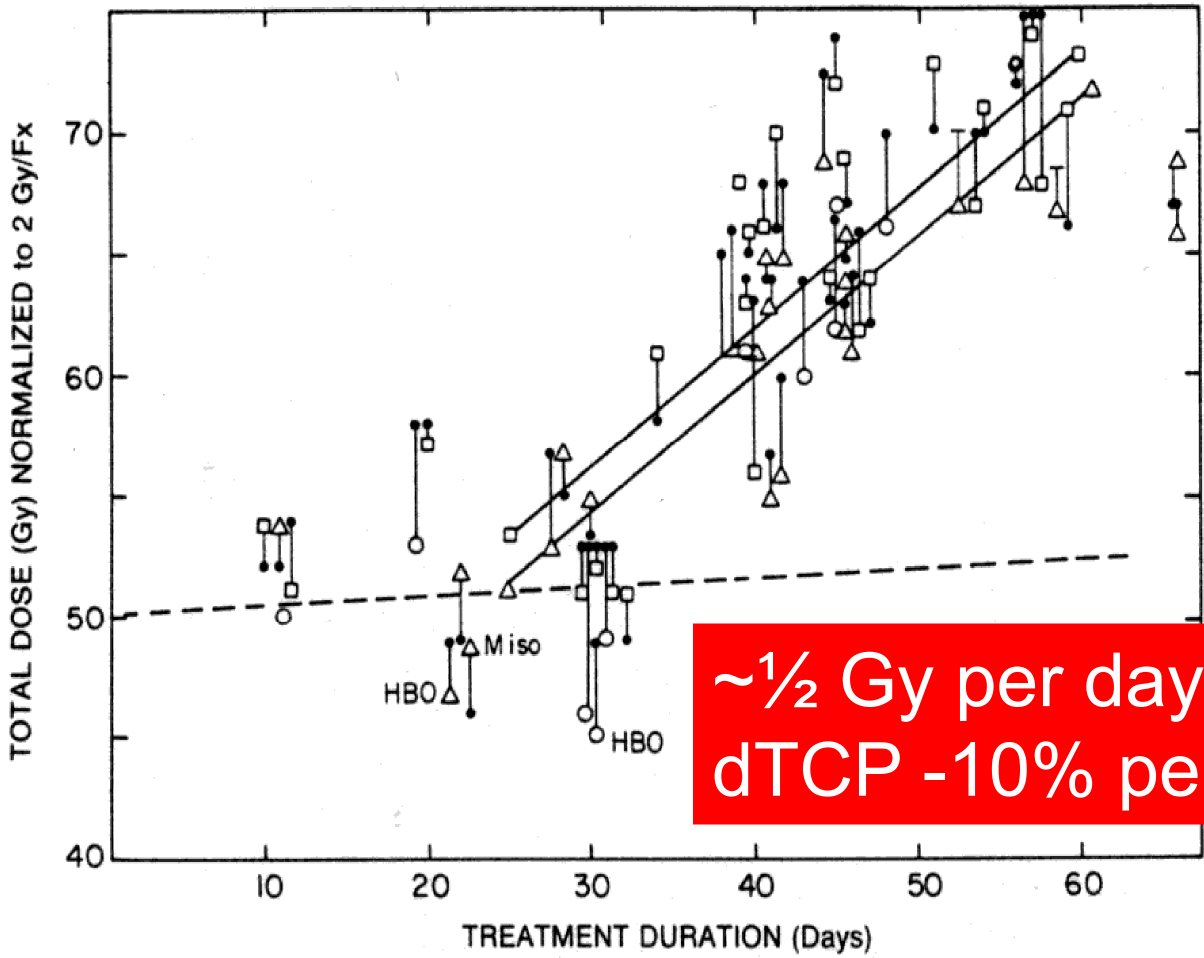
H.R. Withers Cancer 55: 2086, 1985



Fractionation sensitivity

Early reacting normal tissues	Late reacting normal tissues
• Low fractionation sensitivity	• High fractionation sensitivity
• Small increase in tolerance with decreasing dose per fraction	• Large increase in tolerance with decreasing dose per fraction
• High alpha-beta (8-30 Gy)	• Low alpha-beta (2-4 Gy)
• Time factor (repopulation)	• No time factor

ACCELERATED REPOPULATION



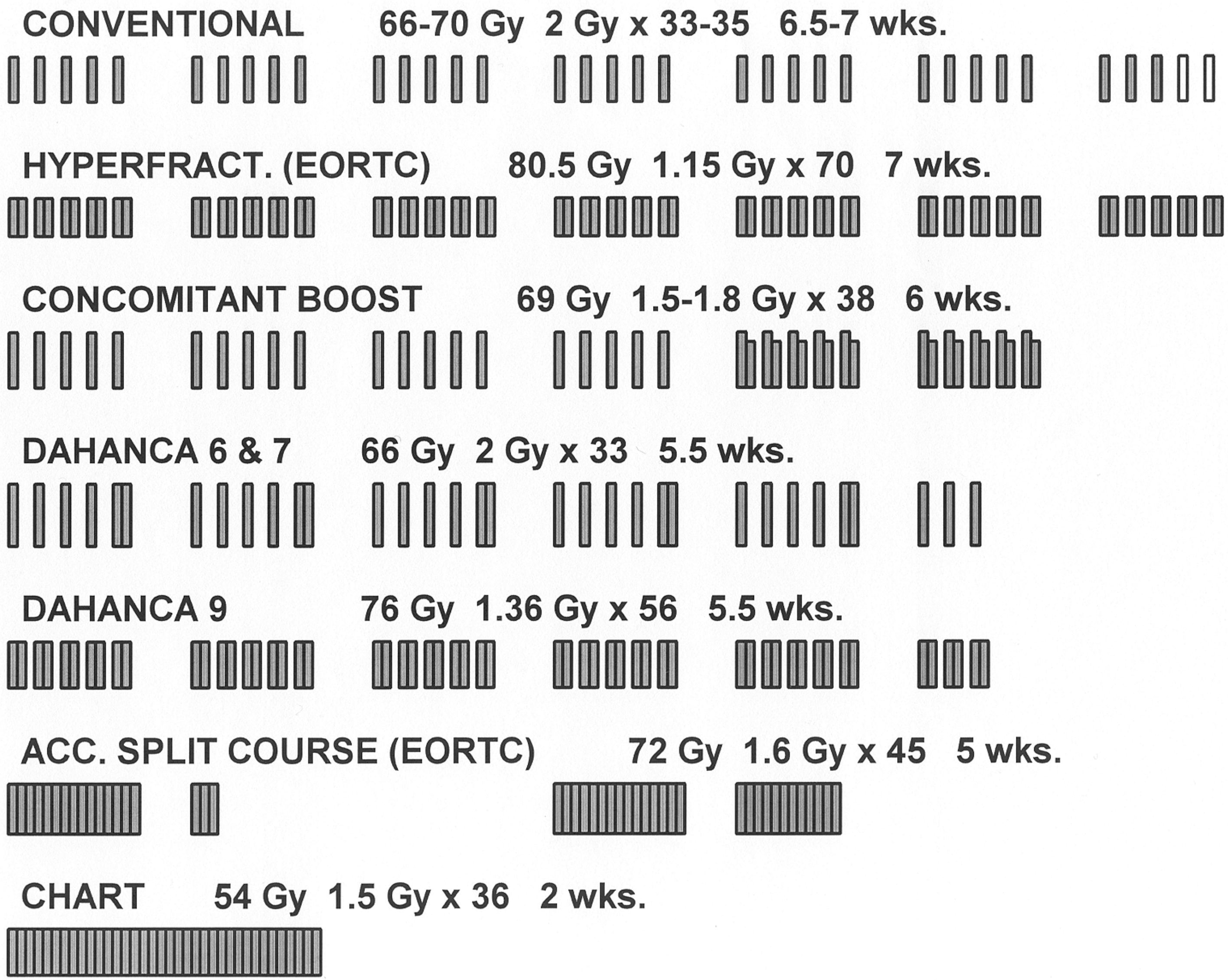
~½ Gy per day
dTCP -10% per week

Withers et al. Acta Oncologica 1988

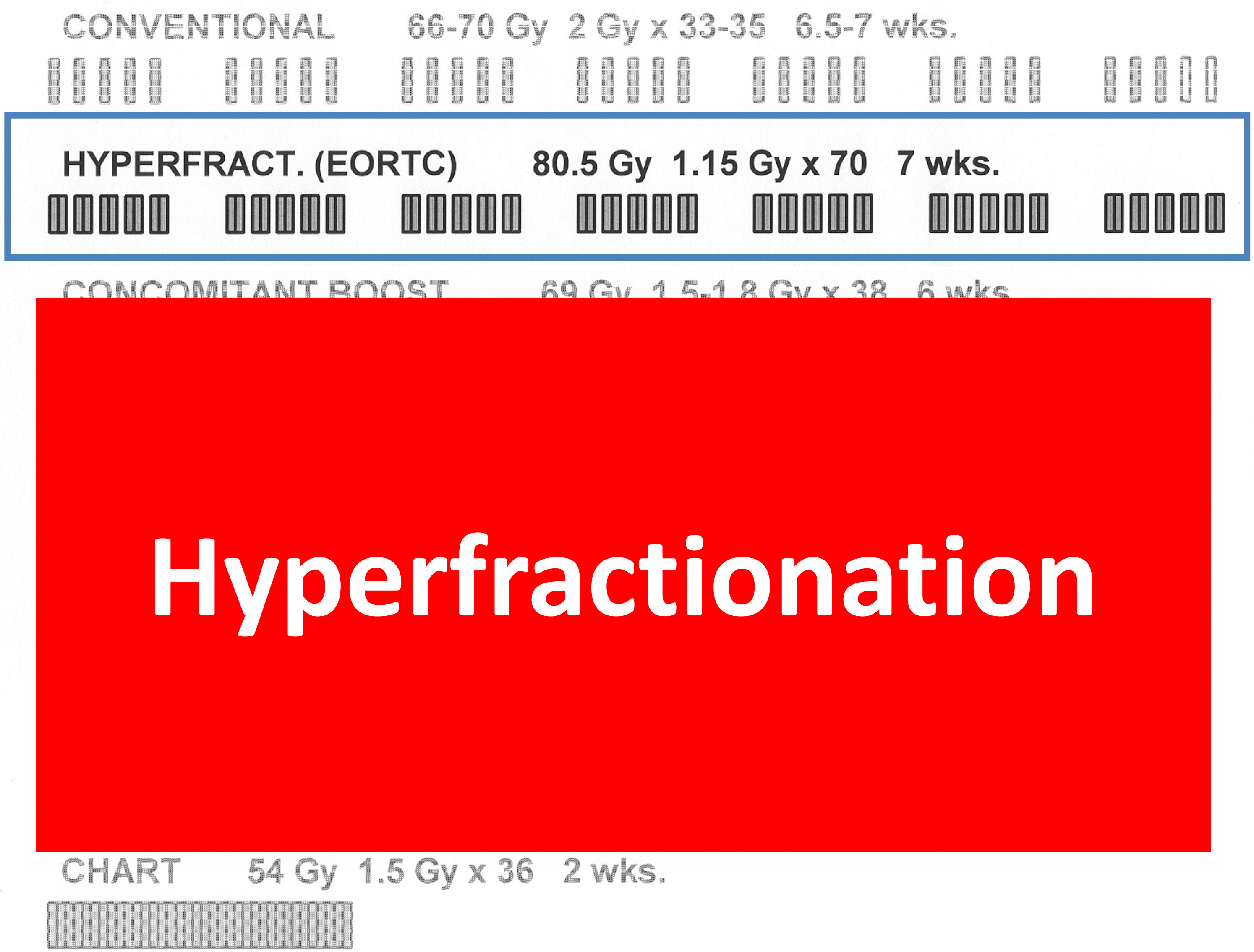
Fractionation principles

- **Conventional fractionation**: Dose per fraction 1.8-2.0 Gy, 5 fx/wk
- **Hyperfrationation**: Dose per fraction <1.8 Gy
- **Hypofractionation**: Dose per fraction >2.0 Gy
- **Split-course**: A treatment break (weeks), resulting in prolonged overall treatment time
- **Accelerated fractionation**: Reduced overall treatment time

Fractionation studies in head and neck cancer



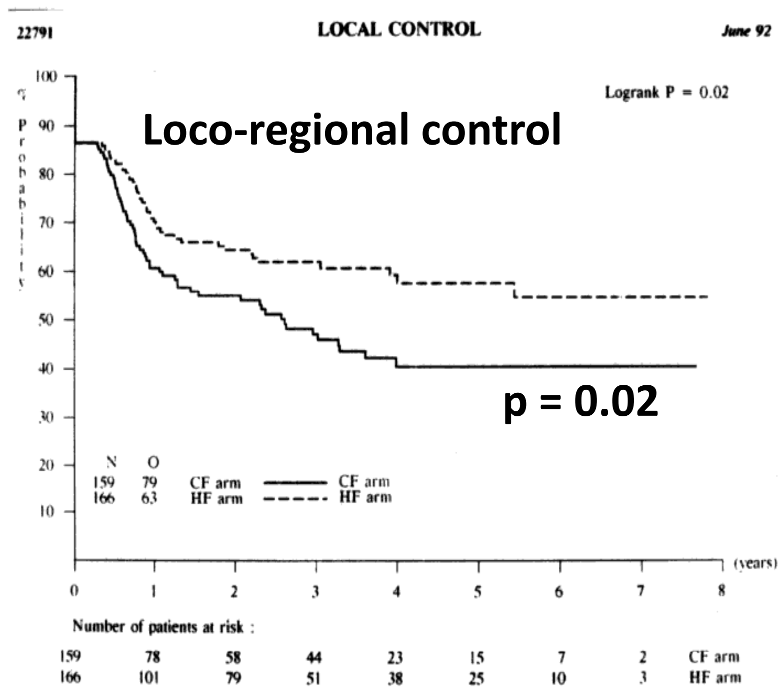
Fractionation studies in head and neck cancer

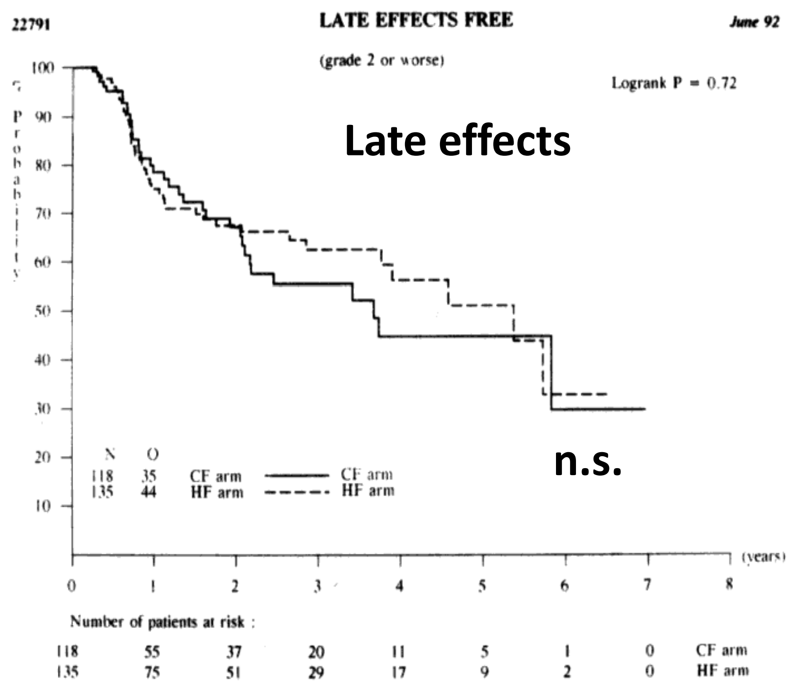


EORTC 22791

Hyperfractionation

356 pts. T2-T3 N0-N1 oropharynx



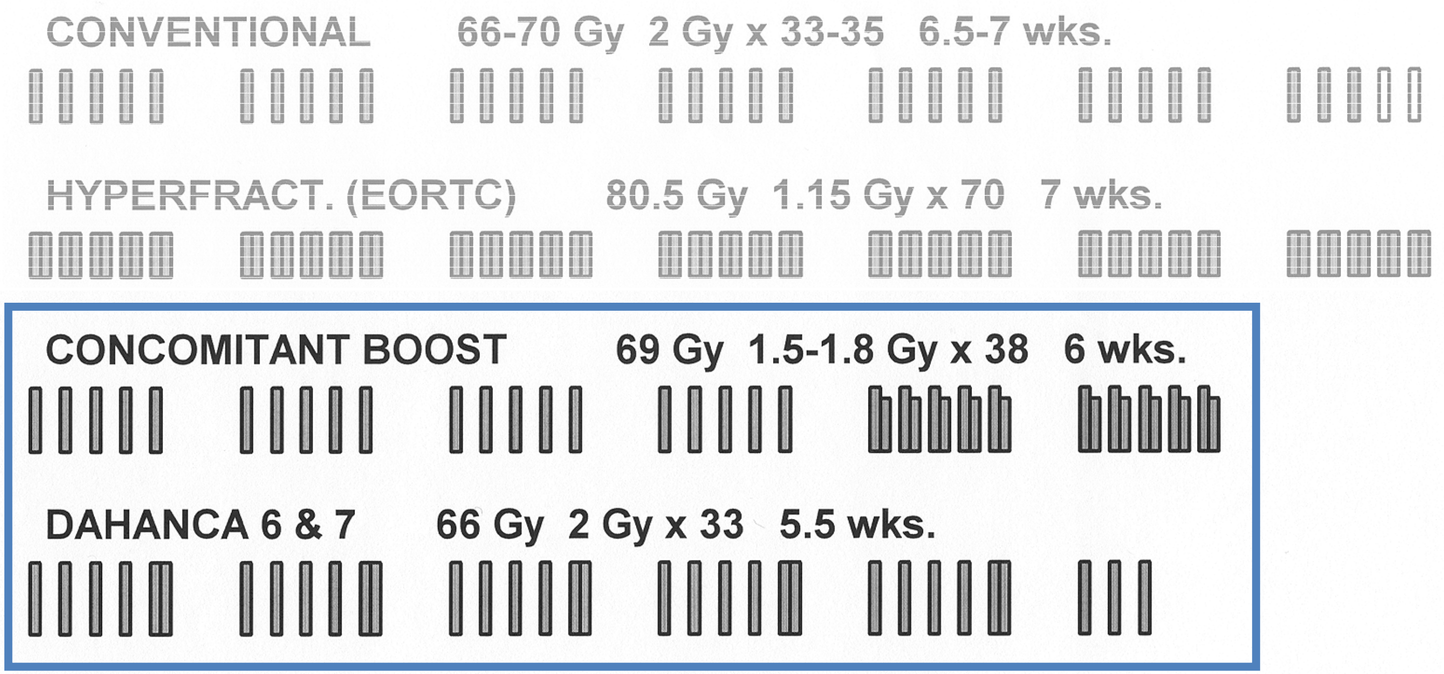


Improved Terapeutic Ratio:

Increase in tumor control with same late morbidity

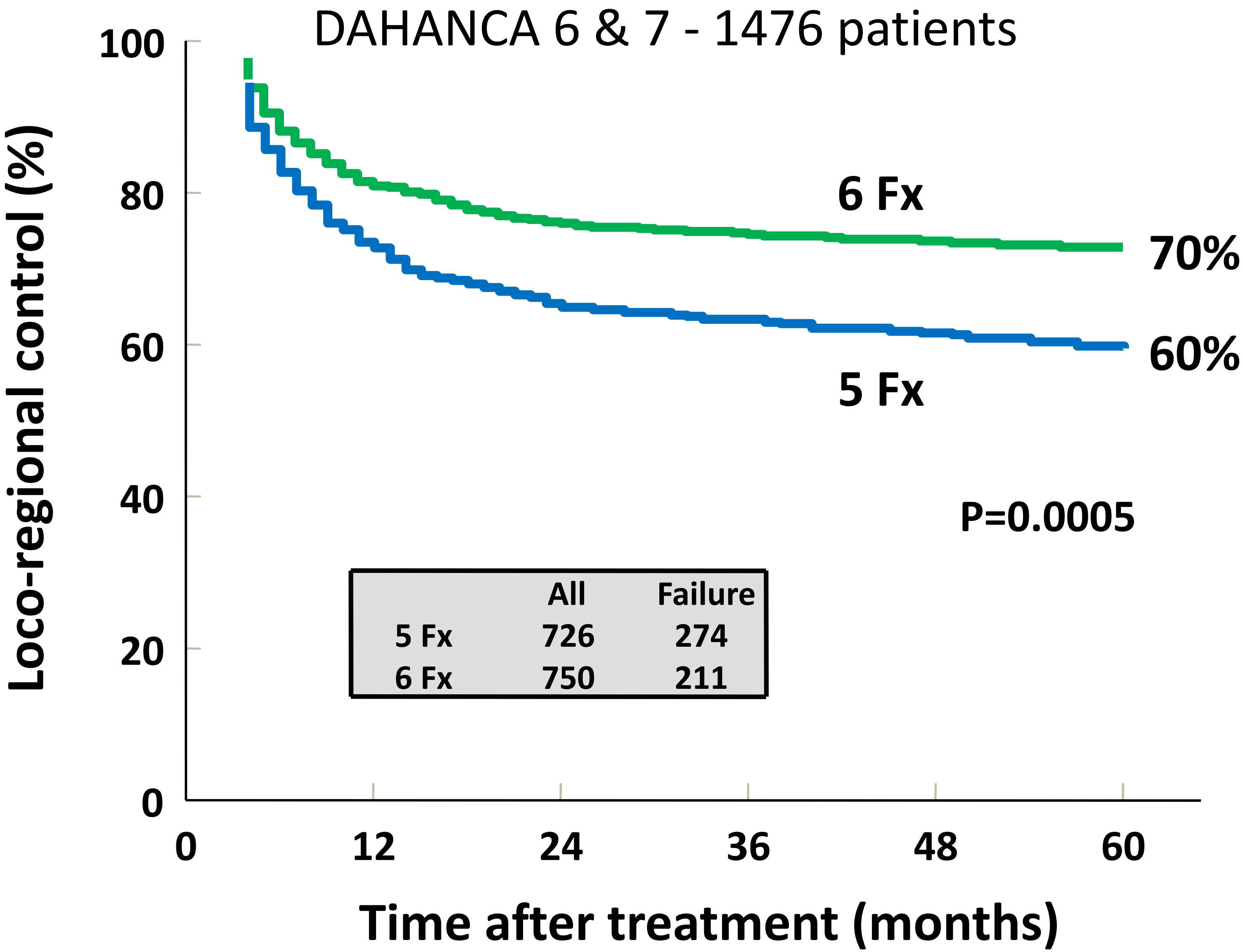
Horiot et al. Radiother. Oncol. 1992

Fractionation studies in head and neck cancer



Accelerated fractionation

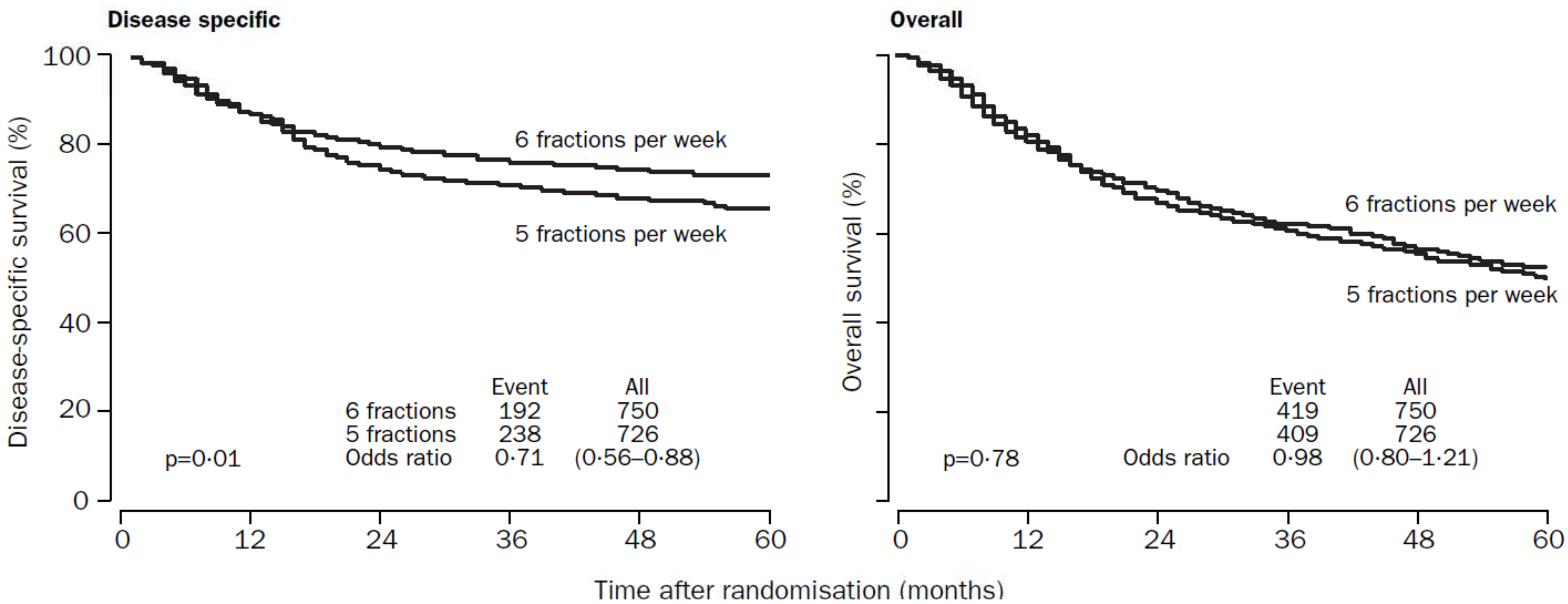
Loco-regional control – acc. RT



Overgaard *et al.* Lancet 2003

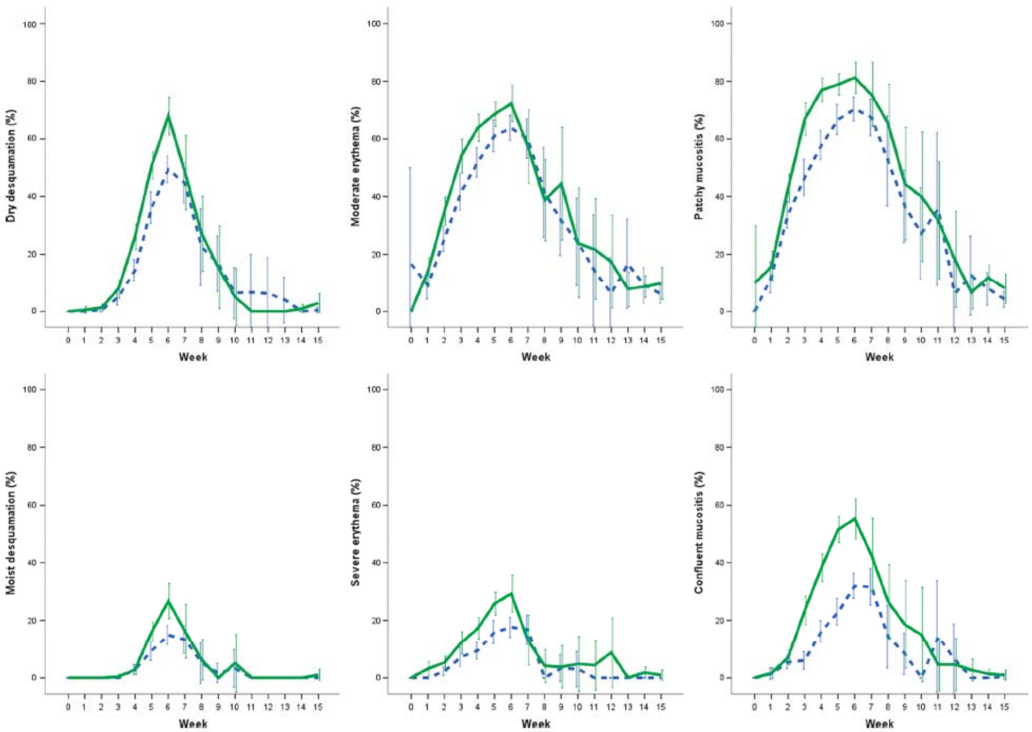
DAHANCA 6&7

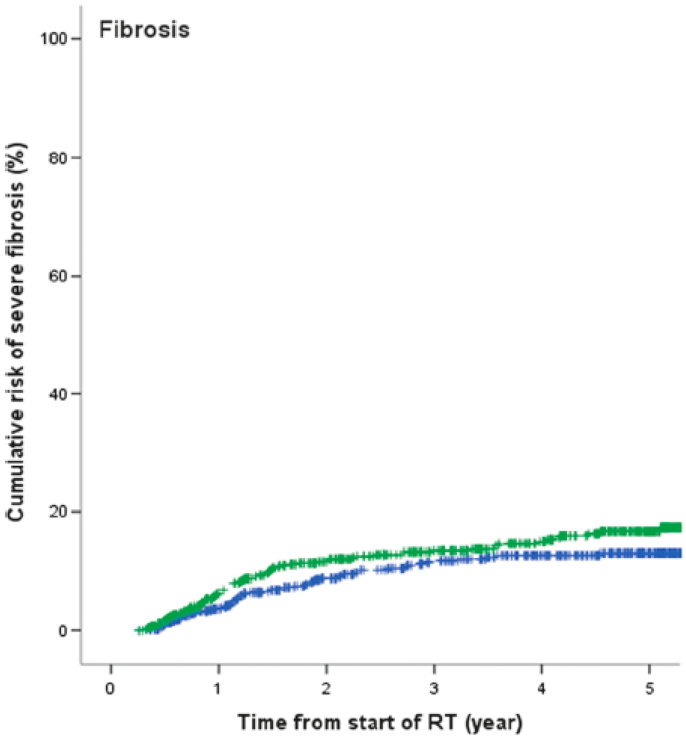
Survival



Overgaard *et al.* Lancet 2003

Morbidity – acc. radiotherapy DAHANCA 6 & 7

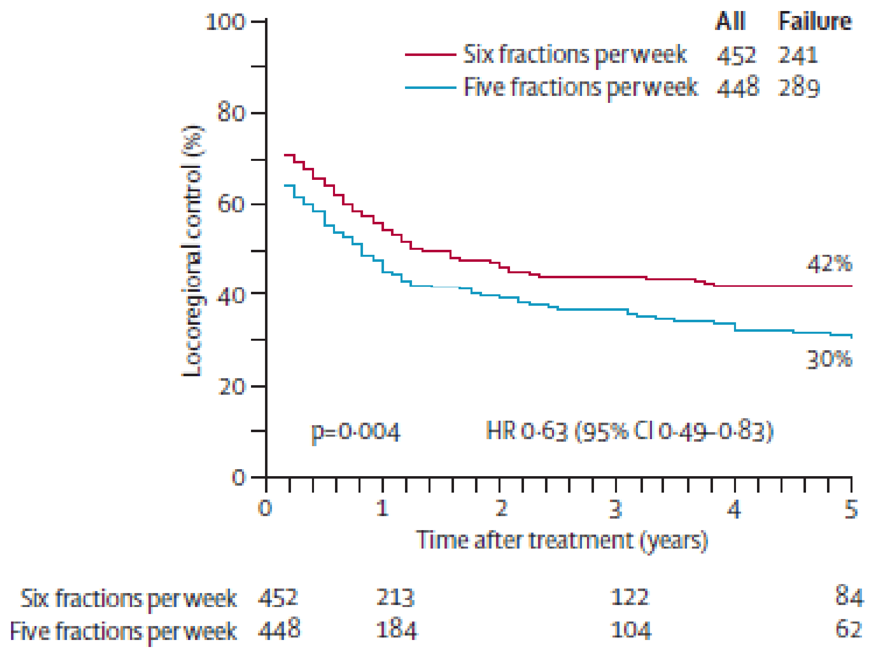




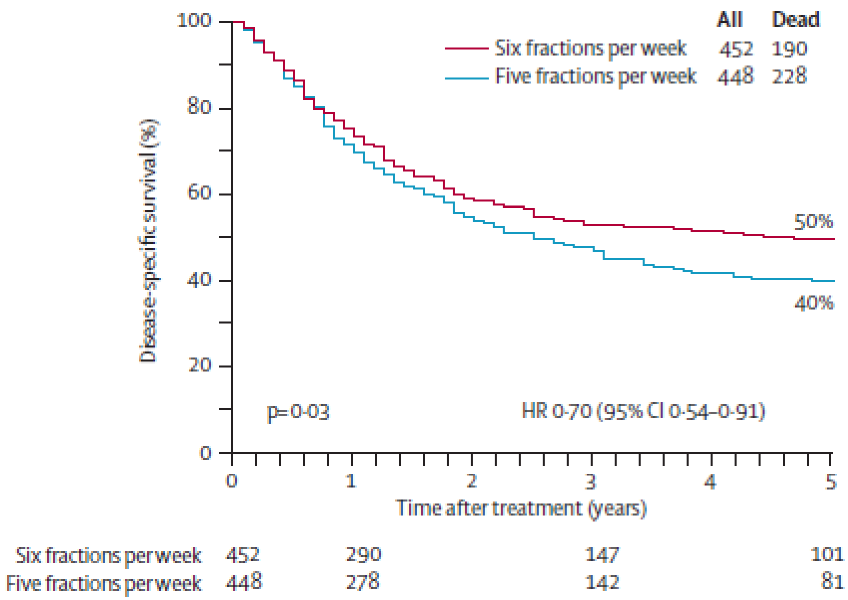
Mortensen et al, Radiother Oncol, 2012

IAEA-ACC study

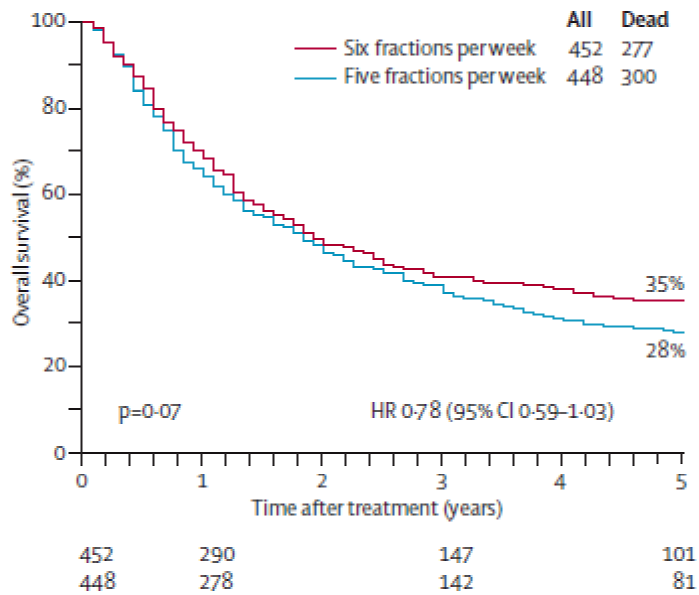
	Five fractions per week (N=448)	Six fractions per week (N=452)
Recruiting centre		
New Delhi	126 (28%)	128 (28%)
Peshawar	104 (23%)	105 (23%)
Islamabad	70 (16%)	69 (15%)
Mumbai	64 (14%)	63 (14%)
Tallinn	53 (12%)	53 (12%)
Santiago	14 (3%)	12 (3%)
Riyadh	9 (2%)	10 (2%)
Cape Town	6 (1%)	10 (2%)
Beirut	2 (1%)	2 (1%)



A



B



Lancet Oncol 2010; 11: 553–60

Lancet 2006; 368: 843–54

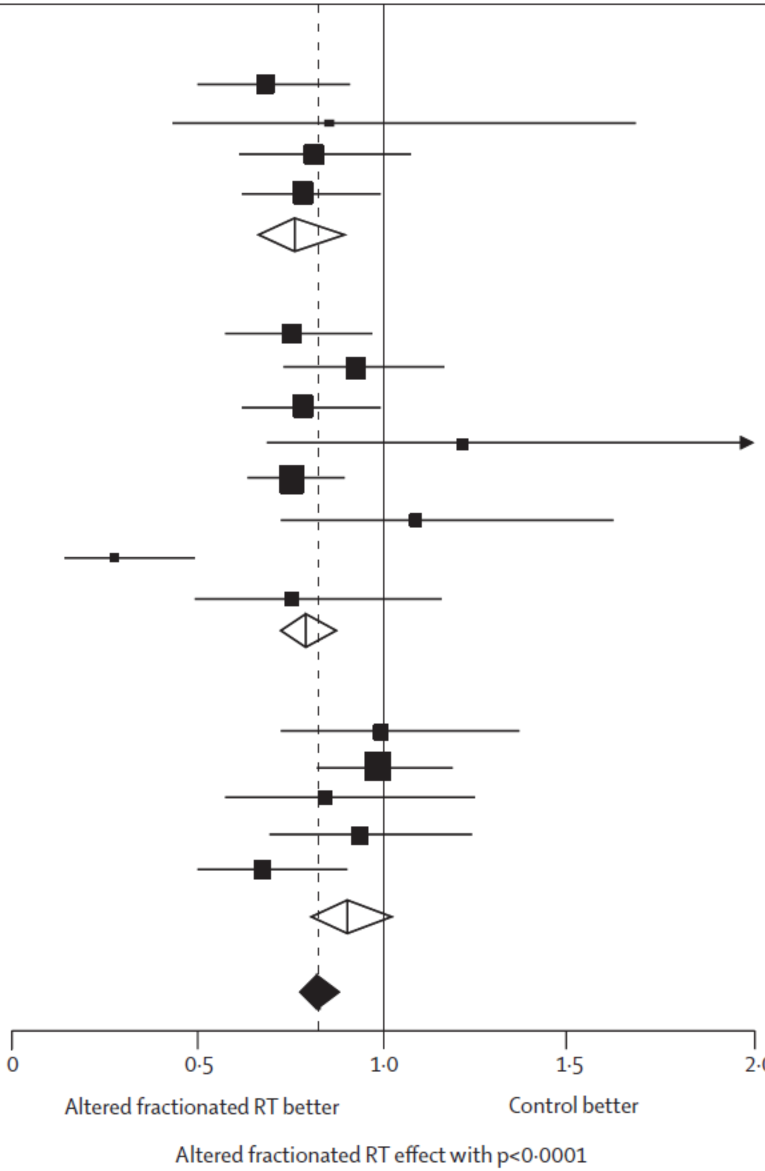
Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis

Jean Bourhis, Jens Overgaard, Hélène Audry, Kian K Ang, Michele Saunders, Jacques Bernier, Jean-Claude Horiot, Aurélie Le Maître, Thomas F Pajak, Michael G Poulsen, Brian O'Sullivan, Werner Dobrowsky, Andrzej Hliniak, Krzysztof Skladowski, John H Hay, Luiz H J Pinto, Carlo Fallai, Karen K Fu, Richard Sylvester, Jean-Pierre Pignon, on behalf of the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group*

Loco-regional control

	Number events/number entered: Altered fractionated RT	Control	O–E	Variance	HR (95% CI)
A Hyperfractionation					
EORT C22791[3]	78/180	99/176	−17·0	43·8	
RIO[4]	18/52	16/51	−1·4	8·2	
PMH Toronto[5]	91/172	101/164	−10·3	47·8	
RTOG 9003 HF[6]	123/276	147/279	−16·6	67·3	
Subtotal	310/680	363/670	−45·3	167·1	0·76 (0·66–0·89)
B Accelerated fractionation without total dose reduction					
EORTC 22851[7]	97/257	122/255	−16·0	54·6	
RTOG 9003 S[6]	143/281	147/279	−6·1	72·4	
RTOG 9003 B[6]	121/277	147/279	−16·4	66·9	
BCCA 9113[8]	25/41	21/41	−2·2	11·5	
DA HANCA[9]	230/755	292/730	−37·6	130·4	
Oro 9301[10]	47/65	47/63	−1·9	23·3	
CAIR[11]	13/51	31/49	−13·3	10·0	
KBN PO 79[12]	36/196	49/199	−6·1	21·2	
Subtotal	712/1923	856/1895	−91·5	390·3	0·79 (0·72–0·87)
C Accelerated fractionation with total dose reduction					
RTOG 7913[13]	77/106	74/104	−0·6	37·6	
CHART[14]	295/552	196/366	−1·8	117·4	
Vienna[15]	49/78	57/81	−4·6	26·4	
TROG 9101[16]	87/174	94/176	−3·3	45·2	
GORTEC 9402[17]	80/137	101/131	−17·9	44·6	
Subtotal	588/1047	522/858	−28·2	271·3	0·90 (0·80–1·02)
Total	1610/3650	1741/3423	−165·0	828·7	0·82 (0·77–0·88)

HR of locoregional control (altered fractionated RT/control)



χ^2 test for heterogeneity p=0·03

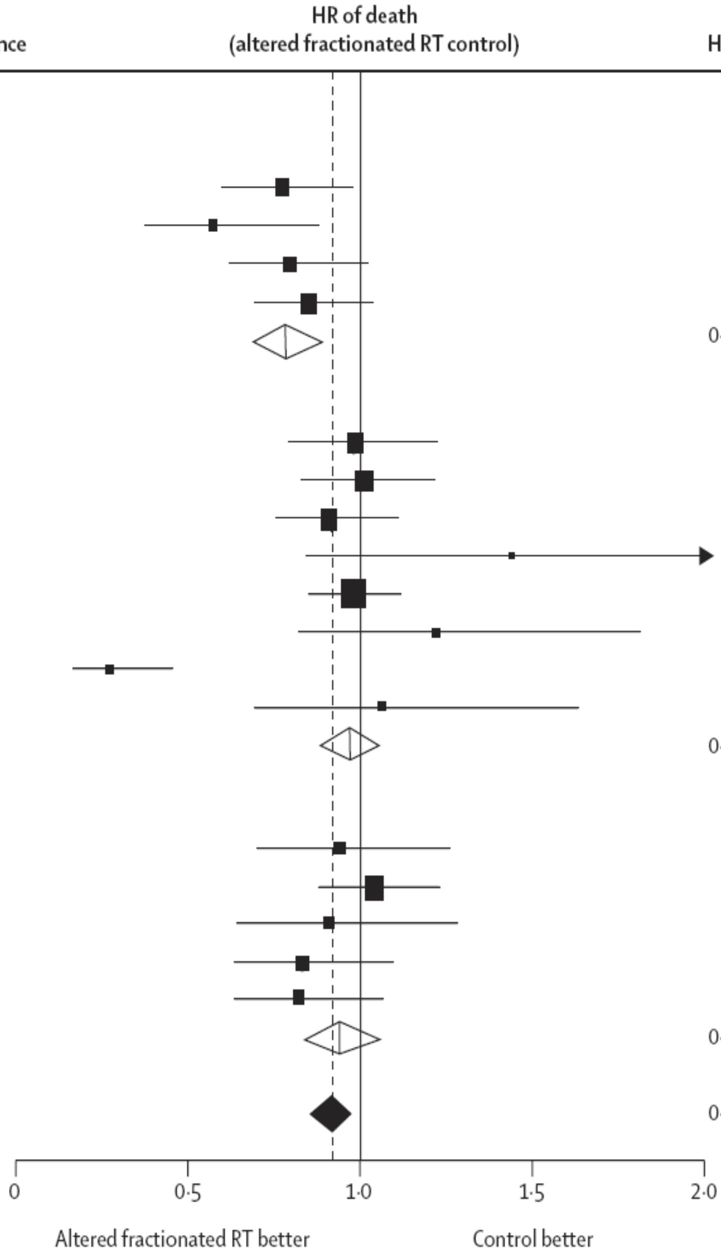
χ^2 test for interaction p=0·15

I^2=44%

Lancet 2006; 368: 843–54

Survival

	Number events/number entered				
	Altered fractionated RT	Control	O–E	Variance	HR (95% CI)
A Hyperfractionation					
EORT C22791[3]	126/180	135/176	−17·2	64·2	
RIO[4]	41/52	47/51	−11·5	20·6	
PMH Toronto[5]	119/172	124/164	−13·8	59·6	
RTOG 9003 HF[6]	184/276	201/279	−15·9	95·9	
Subtotal	470/680	507/670	−58·4	240·4	0·78 (0·69–0·89)
B Accelerated fractionation without total dose reduction					
EORTC 22851[7]	171/257	164/255	−1·3	83·3	
RTOG 9003 S[6]	205/281	201/279	1·2	101·5	
RTOG 9003 B[6]	190/277	201/279	−9·0	97·6	
BCCA 9113[8]	30/41	23/41	4·8	13·1	
DA HANCA[9]	422/755	413/730	−5·0	208·6	
Oro 9301[10]	51/65	48/63	4·8	24·4	
CAIR[11]	19/51	37/49	−16·5	12·6	
KBN PO 79[12]	42/196	41/199	1·3	20·7	
Subtotal	1130/1923	1128/1895	−19·9	561·8	0·97 (0·89–1·05)
C Accelerated fractionation with total dose reduction					
RTOG 7913[13]	91/106	87/104	−2·9	44·1	
CHART[14]	359/552	227/366	5·7	140·2	
Vienna[15]	62/78	66/81	−3·1	31·9	
TROG 9101[16]	96/174	109/176	−9·4	51·1	
GORTEC 9402[17]	105/137	111/131	−10·5	53·4	
Subtotal	713/1047	600/858	−20·2	320·6	0·94 (0·84–1·05)
Total	2313/3650	2235/3423	−98·5	1122·9	0·92 (0·86–0·97)



χ^2 test for heterogeneity p=0·001

χ^2 test for interaction p=0·02

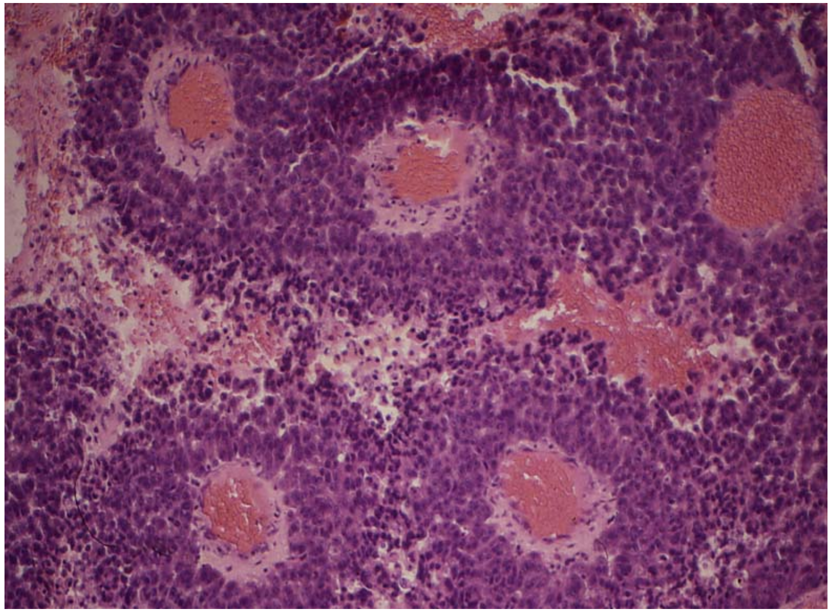
Altered fractionated RT effect with p=0·003

Lancet 2006; 368: 843–54

Conclusion - fractionation

- Awareness of the fractionation sensitivity of tumors and normal tissues is critical
- Clinical studies and meta-analysis have shown that moderately accelerated radiotherapy improves loco-regional control
- Hyperfractionated RT improves loco-regional control and survival
- Altered fractionation is thus recommended for primary radiotherapy of head and neck cancer

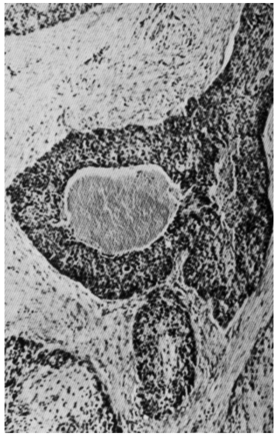
Hypoxia

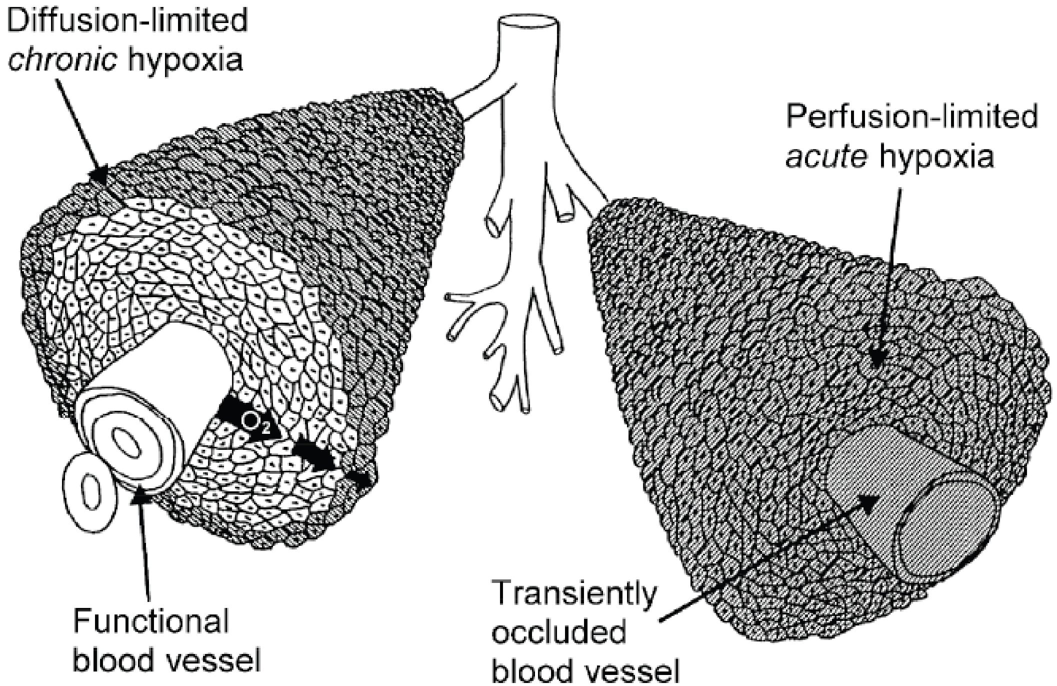


Hypoxia in human tumors

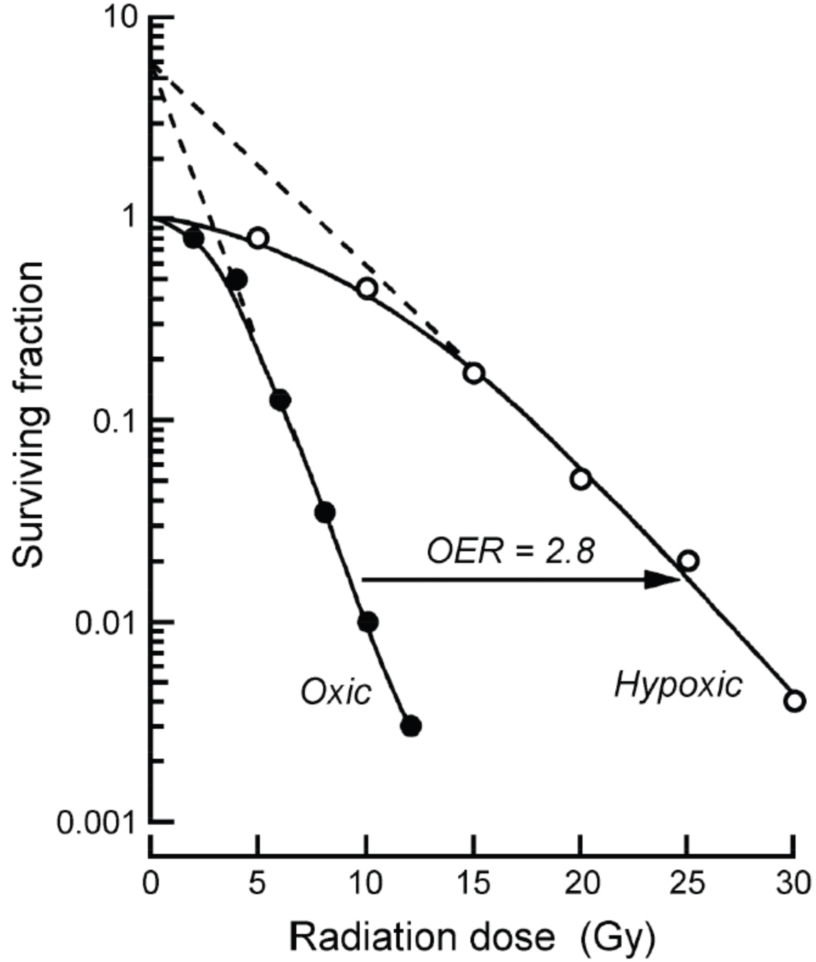
Thomlinson & Gray 1955

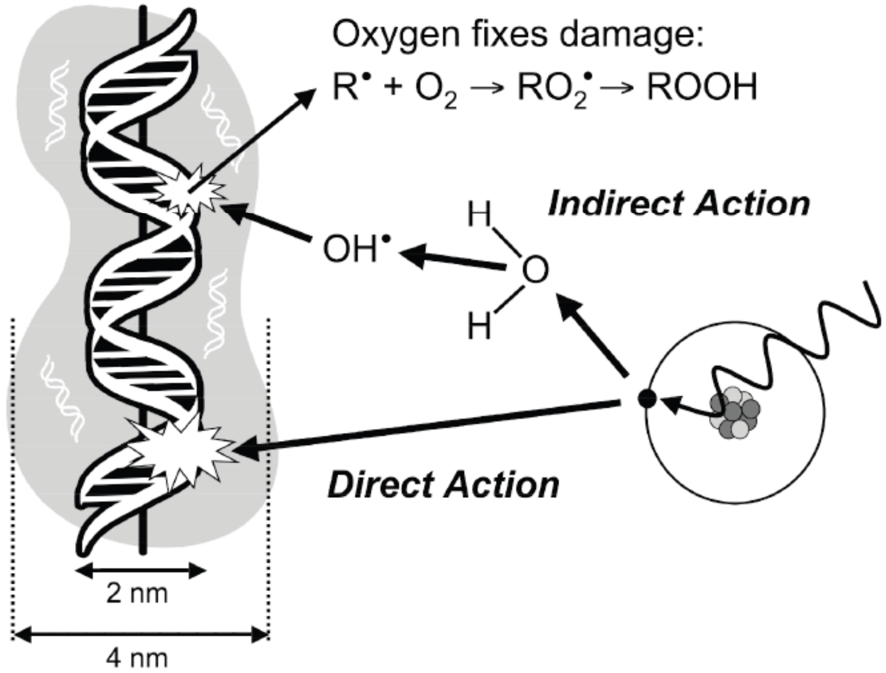
Cord structure in lung cancer (150 μm)



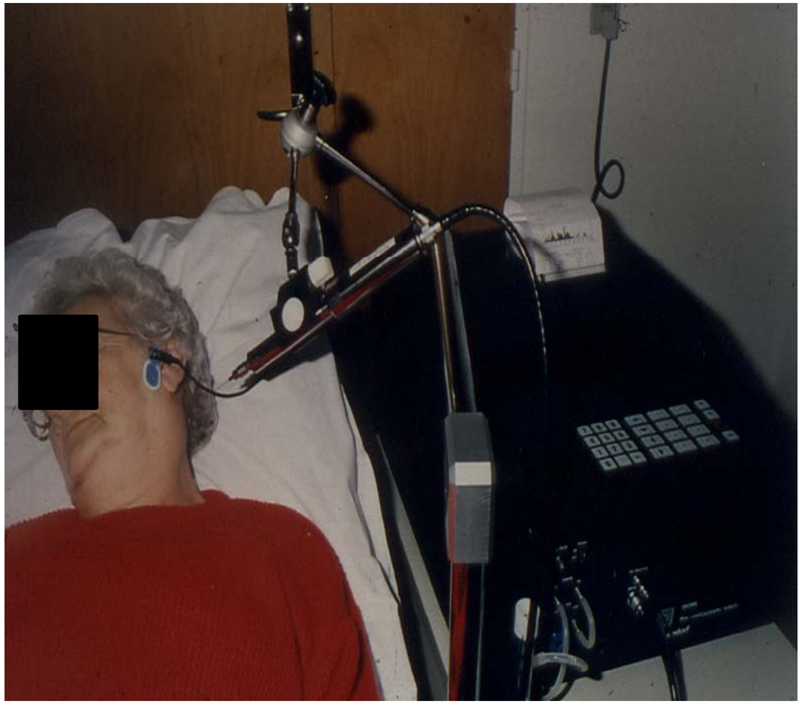


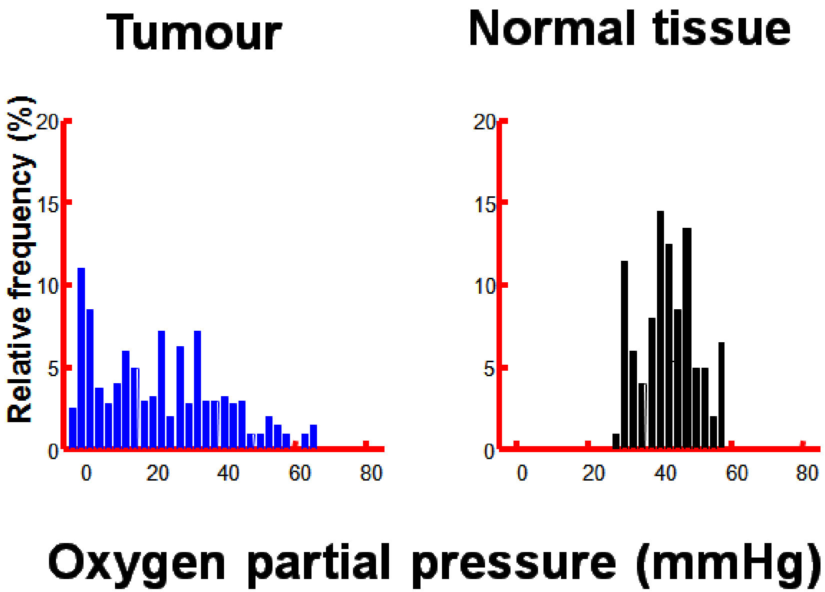
Oxygen effect





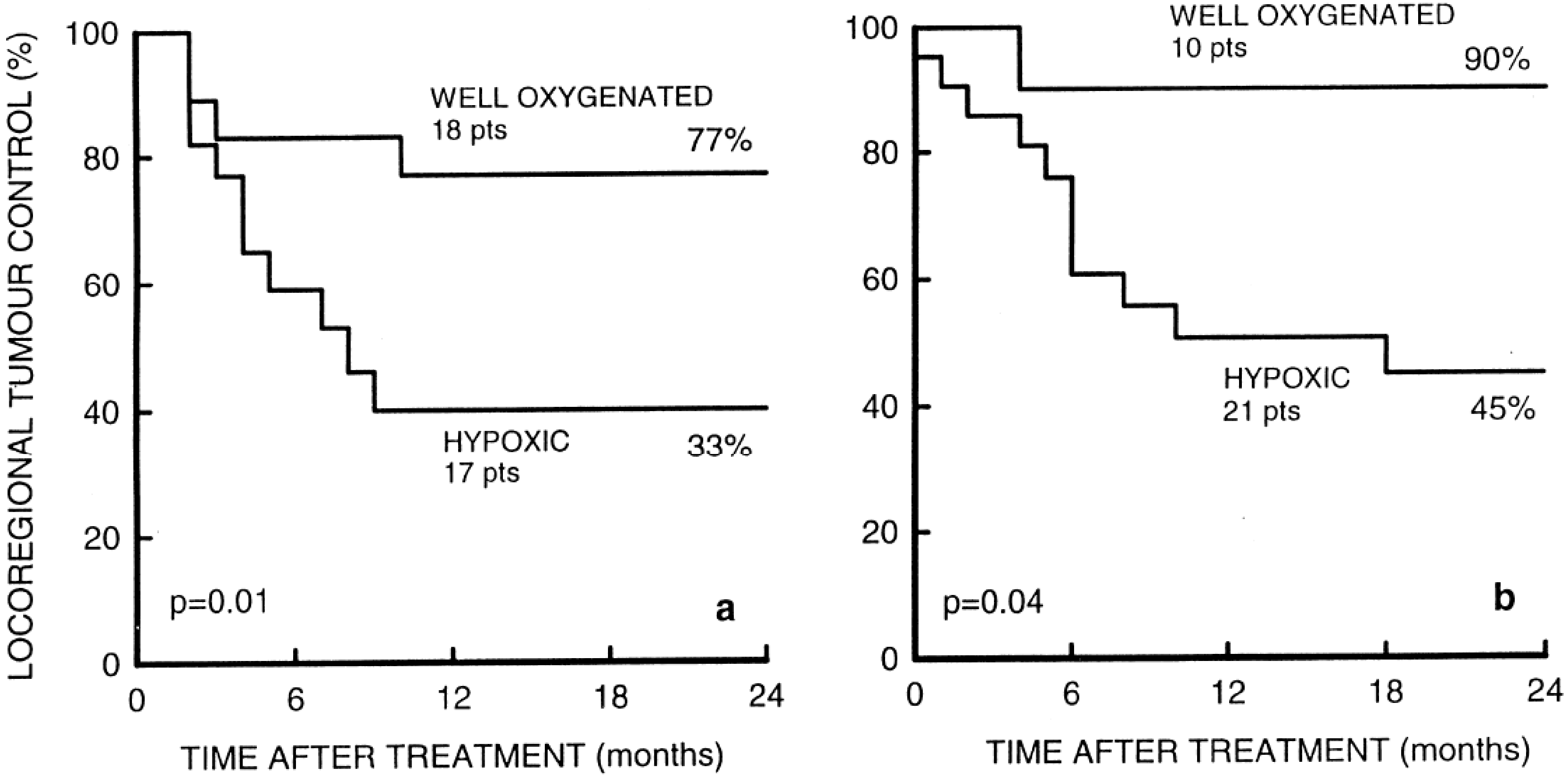
pO2 measurement with Eppendorph electrode





Nordsmark et al. Acta Oncol 1994

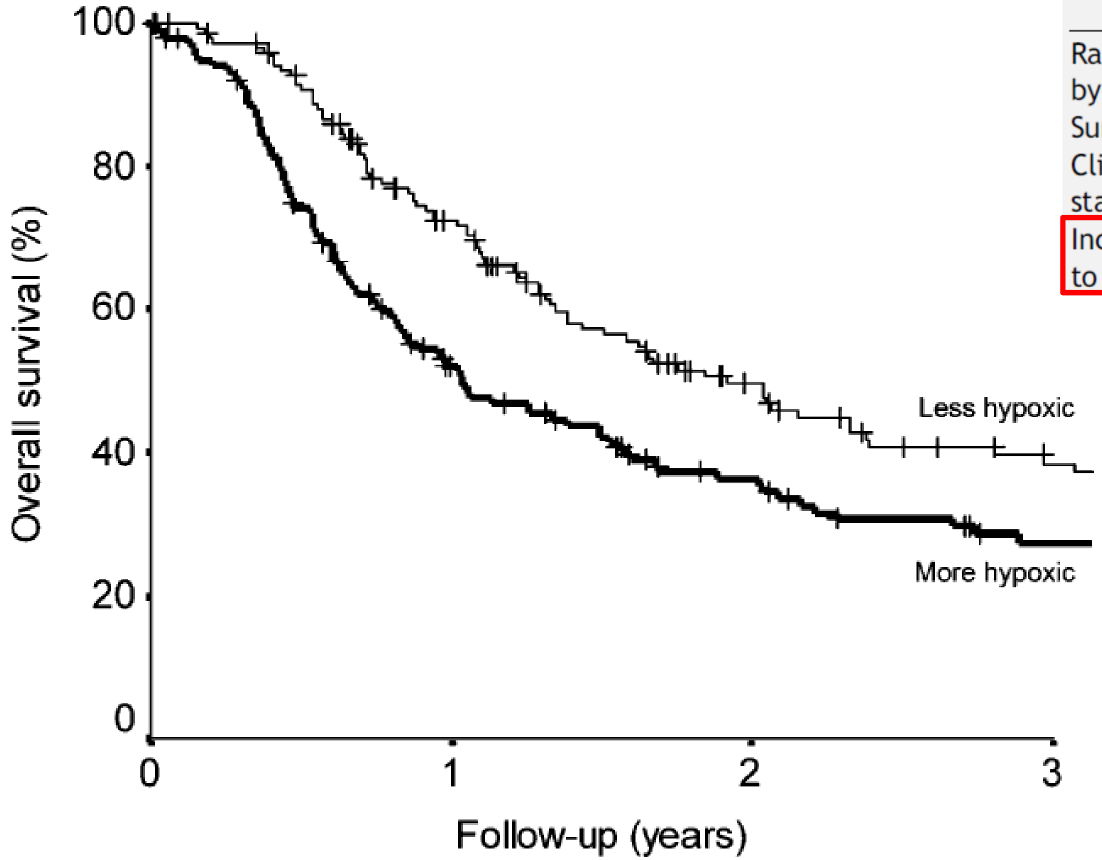
pO2 and loco-regional control



Nordsmark & Overgaard Radiother Oncol 2000

pO2 and survival – pooled data

HN cancer, pooled data from 7 studies (n=397)

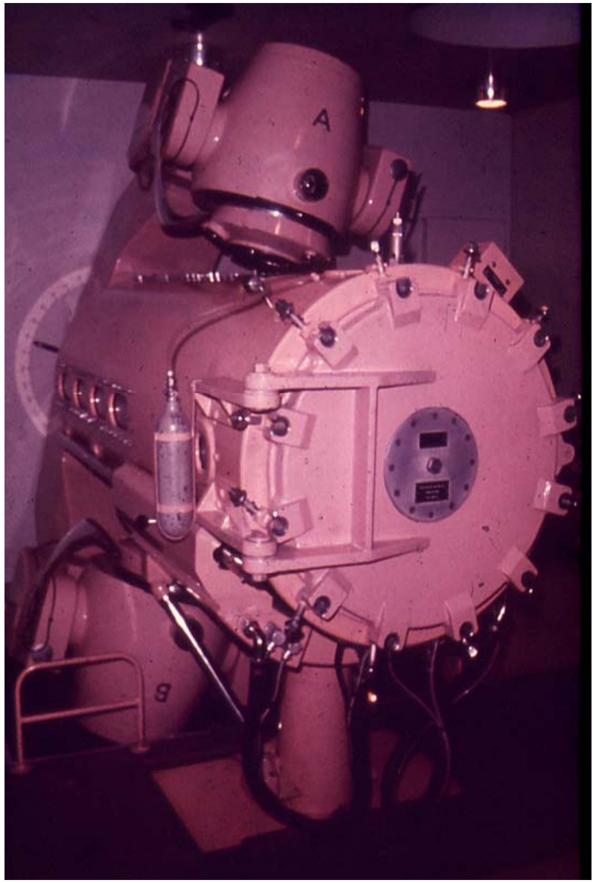


Relative risk estimates		
Change in characteristic	Relative risk	95% Confidence limits
Radiation dose increased by 2 Gy	0.88	0.86, 0.90
Surgery	0.46	0.22, 0.94
Clinical stage increased stage I-III vs. stage IV)	1.66	1.00, 2.80
Increase in $HP_{2.5}$ from 30 to 40%	1.13	1.07, 1.19

Tumor hypoxia is associated with a poor prognosis in patients with advanced head and neck cancer.

Nordsmark et al. Radiotherapy and Oncology 77 (2005) 18–24

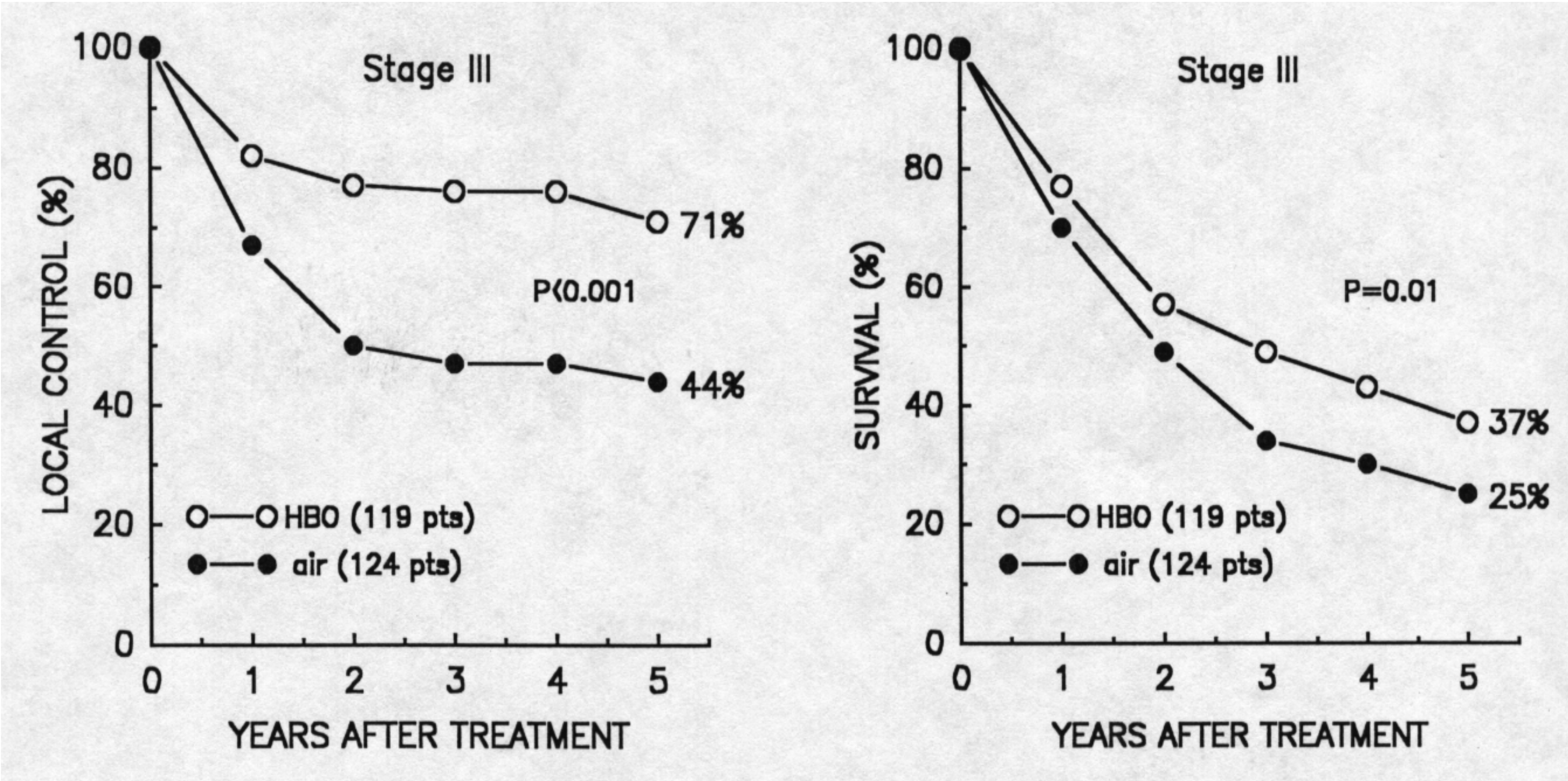
Hyperbaric oxygen



First hyperbaric oxygen treatment. 1955, St. Thomas’ Hospital, London

Hyperbaric oxygen and radiotherapy

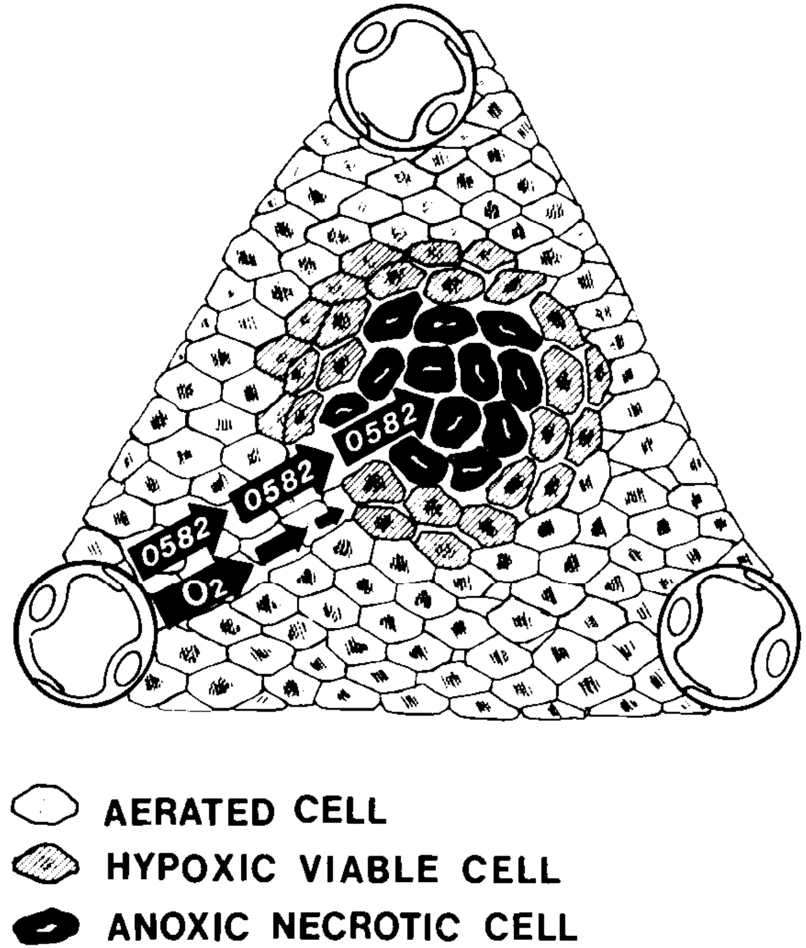
MRC trial (cervix)



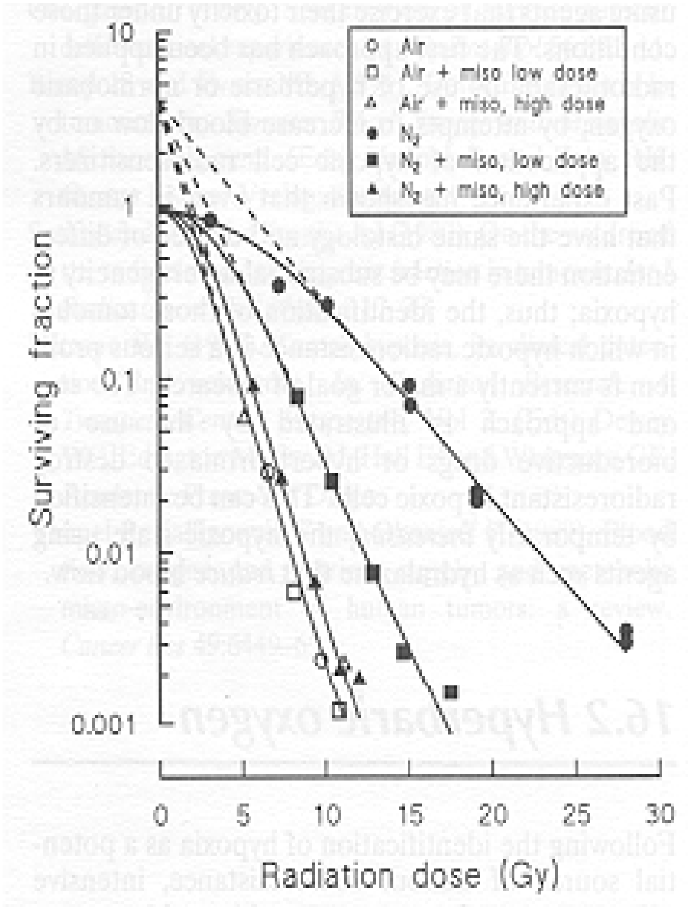
Watson *et al. (1978).*

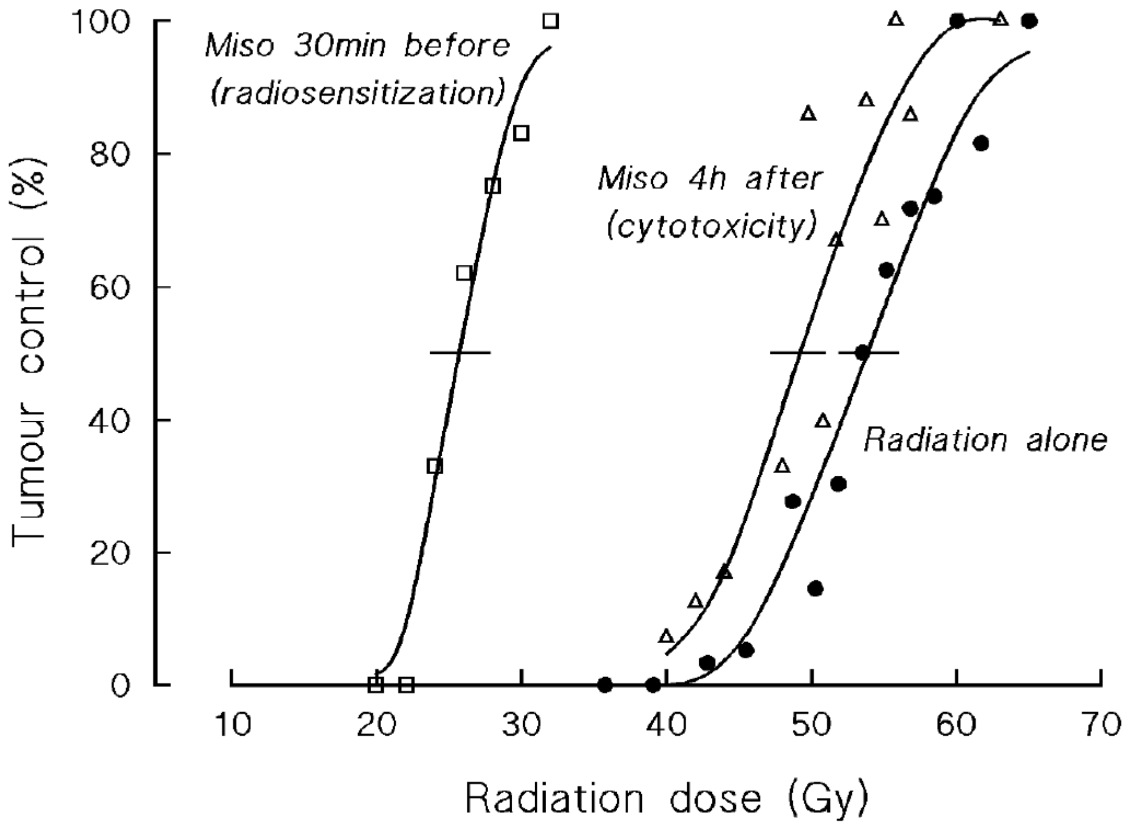
Hypoxic cell radiosensitizers

A drug which selectively sensitizes hypoxic cells to the effect of ionizing irradiation by mimicking the role of oxygen in radiation damage fixation



Hypoxic cell radiosensitizers: misonidazole

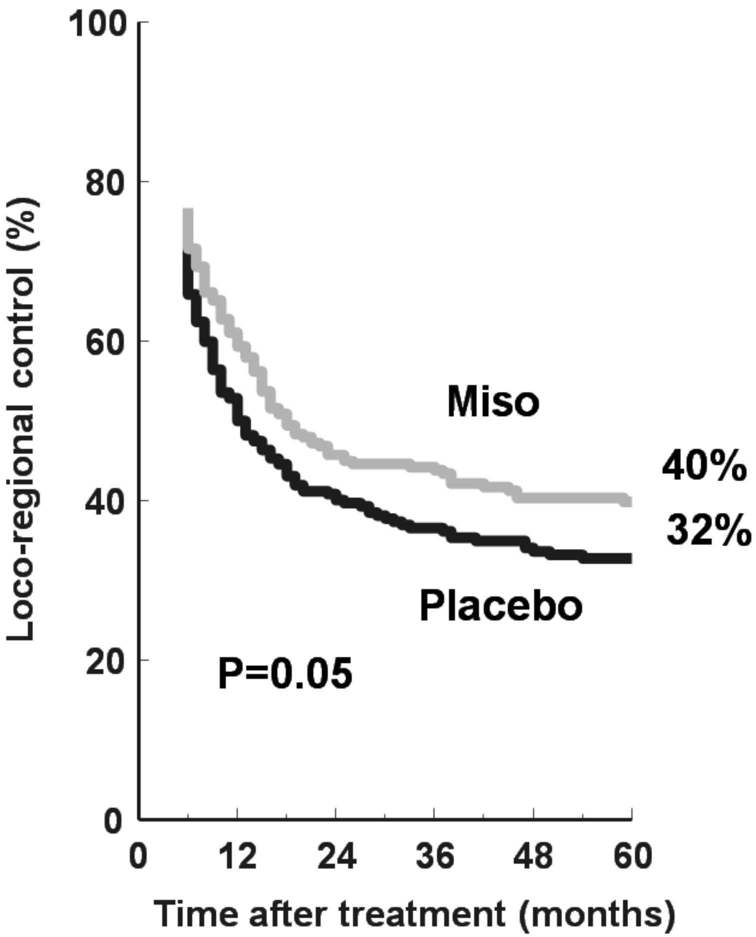


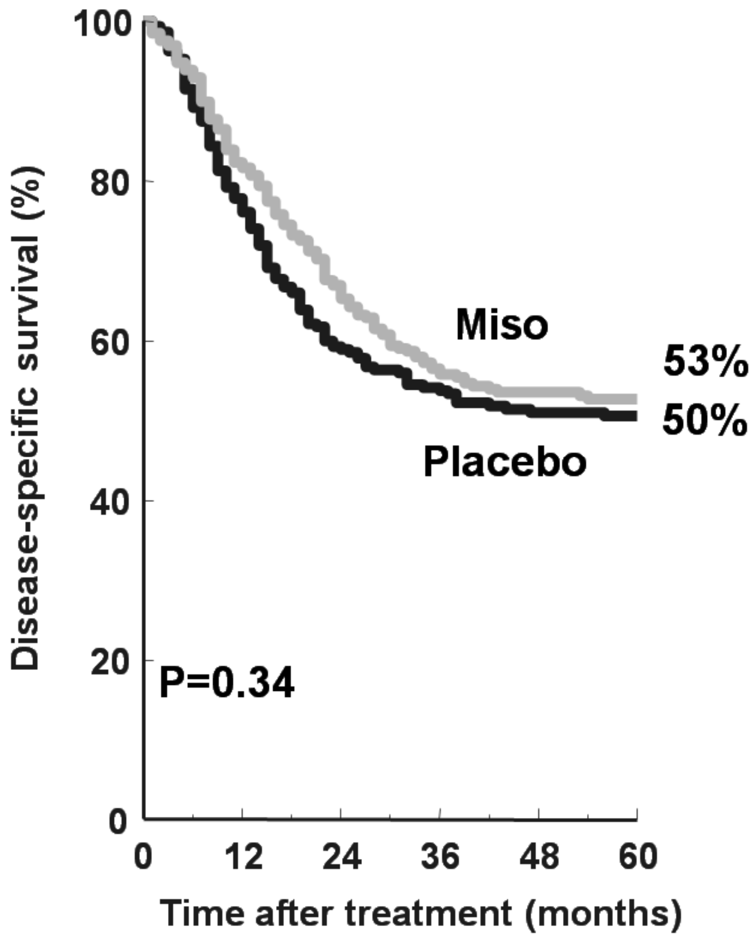


DAHANCA 2

LARYNX AND PHARYNX - 622 pts.

MISONIDAZOLE vs PLACEBO (66 Gy/ 33 fx - 9.5 wk, split-course)



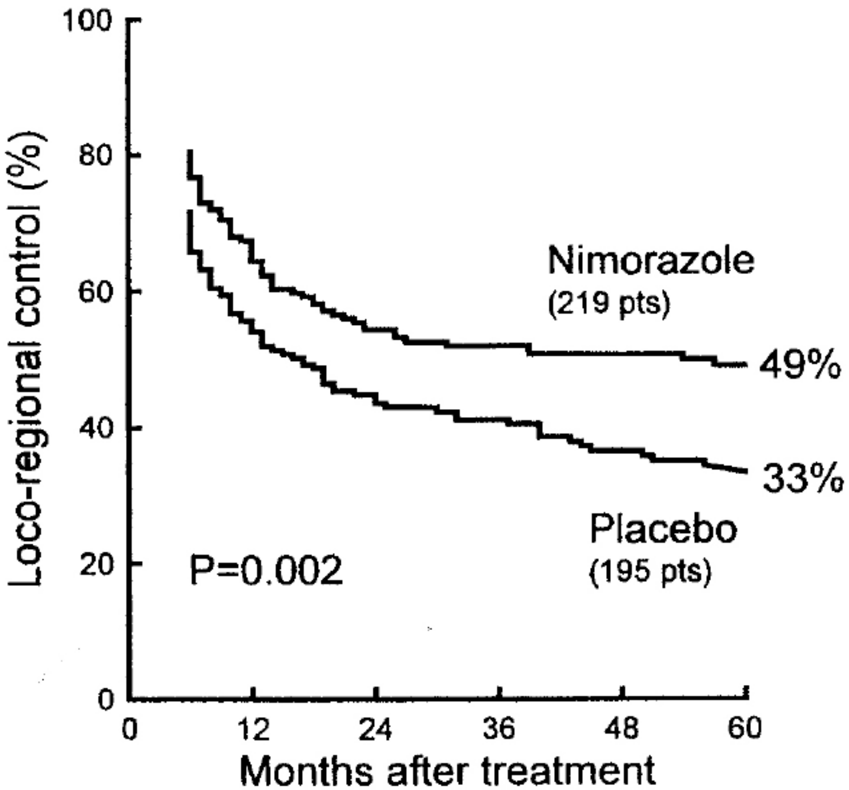


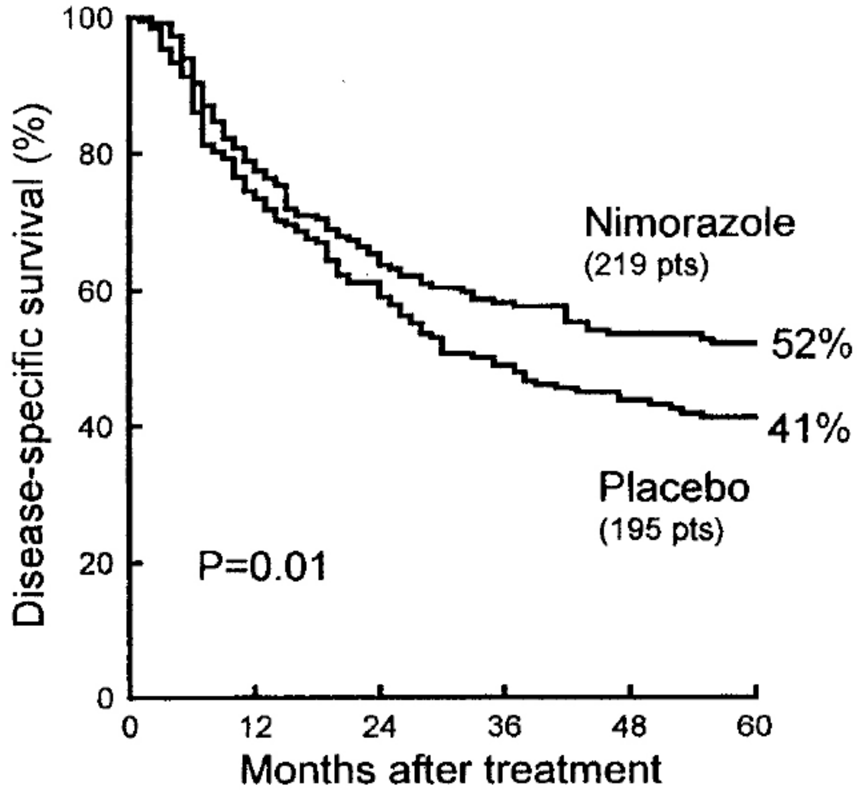
DAHANCA

DAHANCA 5

SUPRAGLOTTIC AND PHARYNX - 414 pts.

NIMORAZOLE vs PLACEBO (66 Gy/ 33 fx - 6.5 wk)

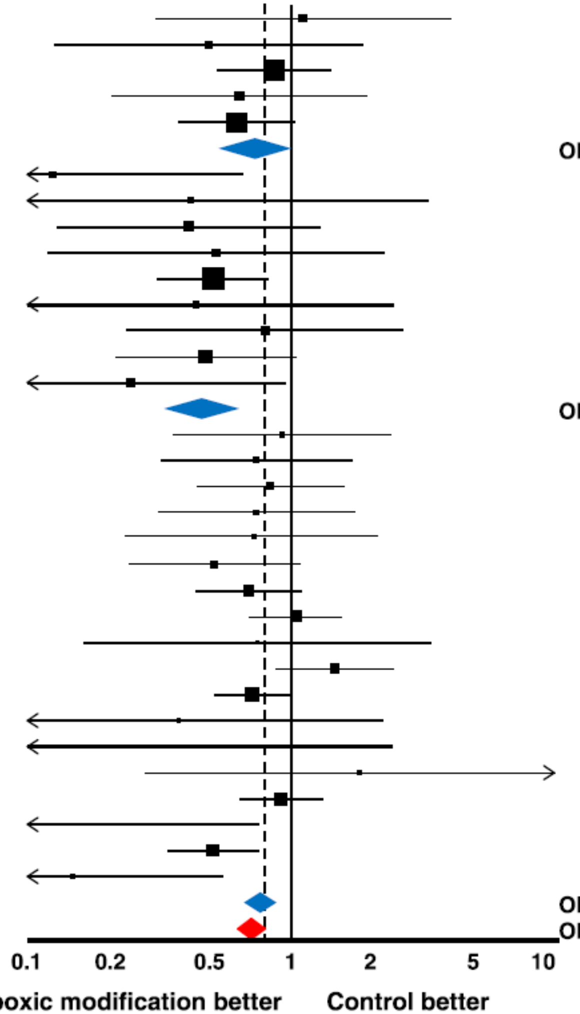




Since 1991 nimorazole has been standard for all HN SCC patients undergoing primary radiotherapy in Denmark.

Endpoint: Loco-regional failure

	Trial	Modification	Events / Total: Hypoxic modification	Events / Total: Control	Odds ratio and 95% CI	
Normobaric oxygen	1970 Evans 1	O2	7 / 15	11 / 25		
	1975 Evans 2	O2	13 / 20	19 / 24		
	1979 RTOG 70-02	Carbogen	53 / 121	63 / 133		
	2005 Mendelhall	Carbogen	6 / 50	9 / 51		
	2010 ARCON	Carb+Nic	32 / 171	47 / 174		
	Subtotal (Normobaric oxygen)		**111 / 377**	**149 / 407**	**OR: 0.73 (0.53-1.00)**	**p=0.05**
Hyperbaric oxygen	1968 van den Brenk	HBO	5 / 17	10 / 13		
	1971 Tobin 1971	HBO	5 / 9	6 / 8		
	1973 Chang 1973	HBO	8 / 26	13 / 25		
	1973 Shigamatsu	HBO	8 / 15	11 / 16		
	1977 MRC 1.trial	HBO	51 / 125	87 / 151		
	1979 MRC 3.trial	HBO	3 / 9	8 / 15		
	1979 Sause	HBO	8 / 21	10 / 23		
	1986 MRC 2.trial	HBO	21 / 53	29 / 50		
	1999 Haffty	HBO	13 / 23	21 / 25		
	Subtotal (Hyperbaric oxygen)		**122 / 298**	**195 / 326**	**OR: 0.46 (0.33-0.64)**	**p<0.001**
Hypoxic sensitizer	1982 Sealy 1	MISO	11 / 50	11 / 47		
	1983 Brunin	MISO	15 / 51	18 / 50		
	1984 MRC 10 fx	MISO	51 / 82	53 / 80		
	1984 MRC 20 fx	MISO	25 / 43	30 / 46		
	1984 Panis	MISO	14 / 26	16 / 26		
	1986 Sealy 2	HBO/MISO	34 / 60	46 / 64		
	1986 EORTC 228111	MISO	103 / 167	114 / 163		
	1987 European trial	ETA	94 / 187	92 / 187		
	1987 IAEA study	Ornidazole	13 / 18	14 / 18		
	1987 RTOG 79-15	MISO	113 / 147	104 / 150		
	1989 Dahanca 2	MISO	182 / 328	187 / 294		
	1989 RTOG 79-04	MISO	16 / 21	17 / 19		
	1989 Galecki	Metro	3 / 18	5 / 17		
	1992 Giaux	MISO	28 / 30	23 / 26		
	1995 RTOG 85-27	ETA	154 / 252	159 / 252		
	1996 Huilgol	AK-2123	2 / 9	7 / 9		
	1998 Dahanca 5	NIM	104 / 219	125 / 195		
	2006 Ullal	AK-2123	8 / 23	18 / 23		
	Subtotal (Hypoxic sensitizer)		**970 / 1731**	**1039 / 1666**	**OR: 0.76 (0.66-0.88)**	**p<0.001**
All trials with hypoxic modification			**1203 / 2406**	**1383/ 2399**	**OR: 0.71 (0.63-0.80)**	**p<0.001**



Test for heterogeneity: p = 0.12

Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

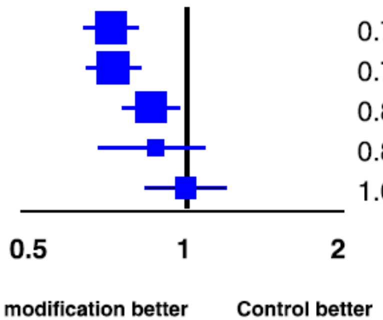
Hypoxic modification – meta-analysis

4805 patients; 32 randomized clinical trials – Overgaard 2011

Head and neck cancer - meta analysis - summary

Endpoint	Events / Total: Hypoxic modification	Events / Total: Control	Odds ratio	Risk Reduction	NNT**
Loco-regional control	1203 / 2406	1383 / 2399	0.71 (0.63-0.80)*	8% (5-10%)*	13
Disease specific survival	1175 / 2335	1347 / 2329	0.73 (0.64-0.82)	7% (5-10%)	14
Overall survival	1450 / 2312	1519 / 2305	0.87 (0.77-0.98)	3% (0-6%)	31
Distant metastasis	159 / 1427	179 / 1391	0.87 (0.69-1.09)	2% (-1-4%)	57
Radiotherapy complications	307 / 1864	297 / 1822	1.00 (0.82-1.23)	0% (-3-2%)	>>

Odds ratio and 95% CI



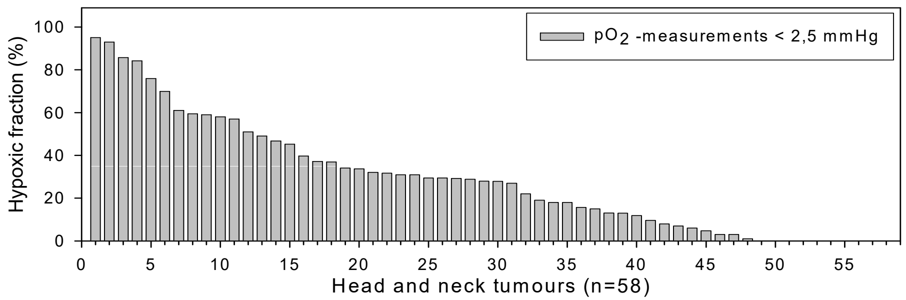
Hypoxic modification works
- but is it relevant for all patients?

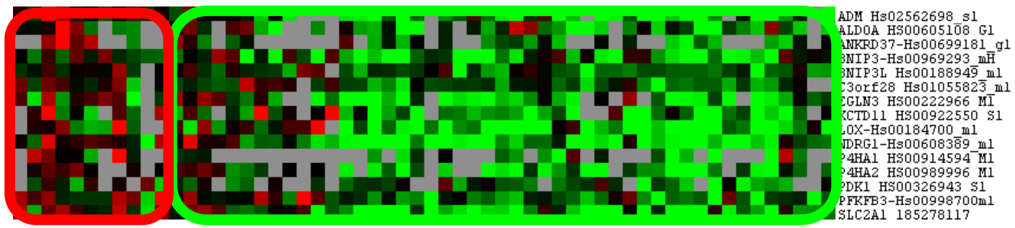
Overgaard J. Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck – A systematic review and meta-analysis.
Radiother Oncol (2011)

Hypoxia-classification

15-gene hypoxia classifier

- Based on hypoxia induced genes (in vitro/in vivo validated)
- Classification based on gene expression similarity to either ”more” or ”less” hypoxic tumours as estimated with pO_2-electrode in an independent trainingset of 58 H&N cancer patients





Toustrup K et al, Cancer Res; 71(17); 5923-31, 2011

Validating the hypoxia classifier

Independent clinical dataset

414 patients enrolled in the DAHANCA 5 trial

219 randomly assigned to radiotherapy and nimorazole

195 randomly assigned to radiotherapy and placebo

52 excluded from classification (2 failed in PCR, 50 did not have tumour tissue for PCR)

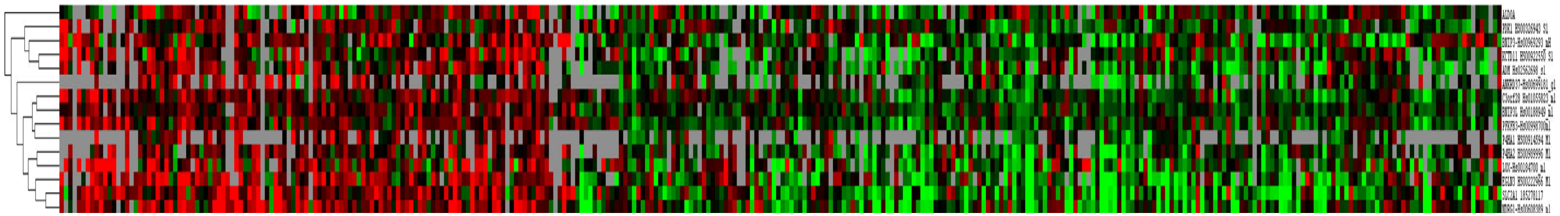
39 excluded from classification (1 failed in PCR, 38 did not have tumour tissue for PCR)

323 tumour samples for classification

Classification

”More” hypoxic (114)

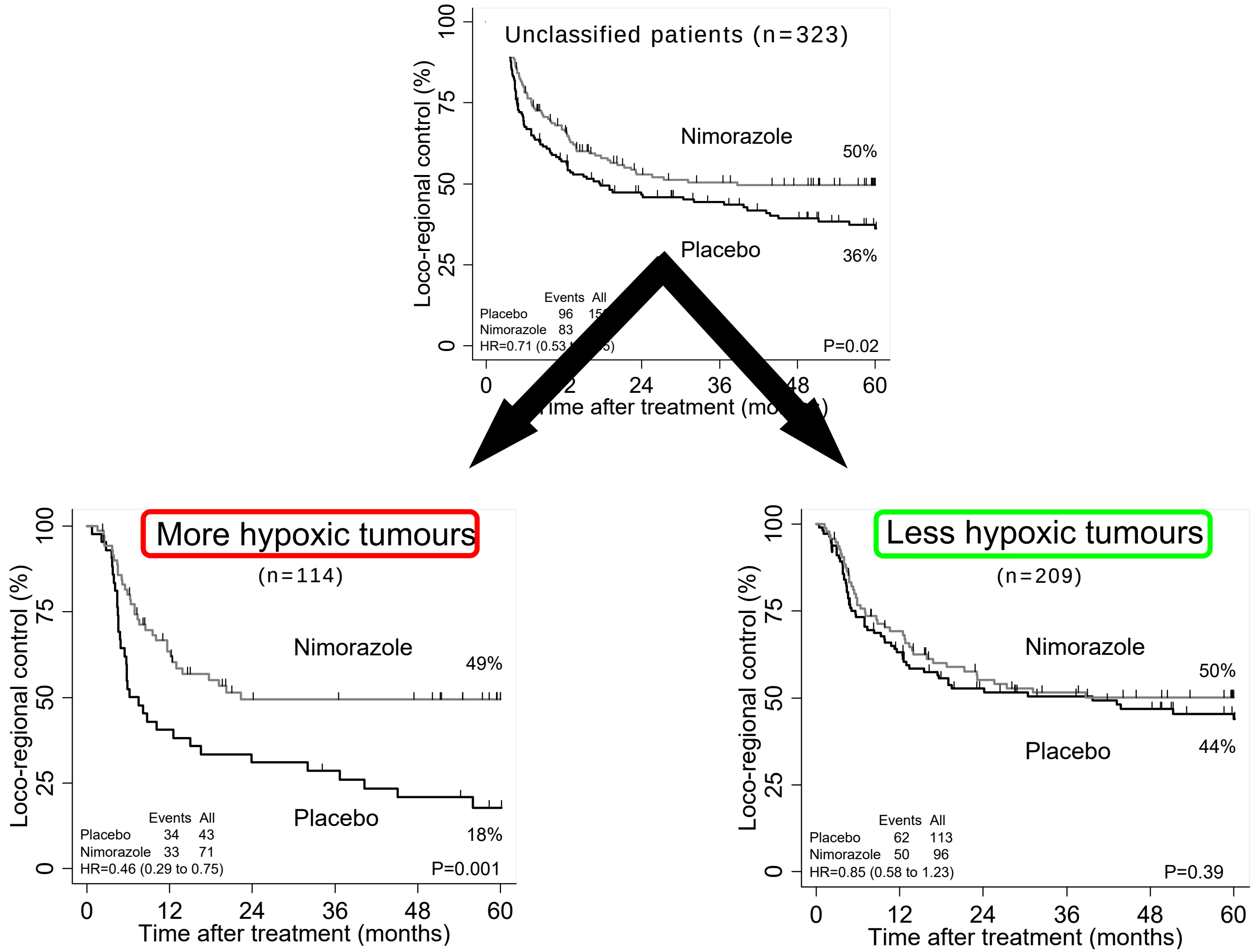
”Less” hypoxic (209)



Toustrup K et al, Radiother Oncol; 102; 122-129, 2012

Hypoxia-classification

15-gene hypoxia classifier



-Toustrup K et al, Radiother Oncol; 102; 122-129, 2012

EORTC/DAHANCA 29 randomized phase III

Role of Nimorazole in chemo-radiation of HPV neg HNSCC

LARYNX, PHARYNX* * Except NPC

HPVneg (p16); Stage 3-4 (T2-4,N0-3)

Stratify:

Stage
Site
Inst.
Hypox.
Gene profile
(retro-spective)

RANDOMIZE

Accl RT(6 fx/wk) +cisPl

640 patients – (>200 with positive hypoxic gene profile).

Pivotal trial to establish the true indication of Nimorazole in Chemoradiotherapy of advanced HNSCC and the value of the hypoxic gene profile

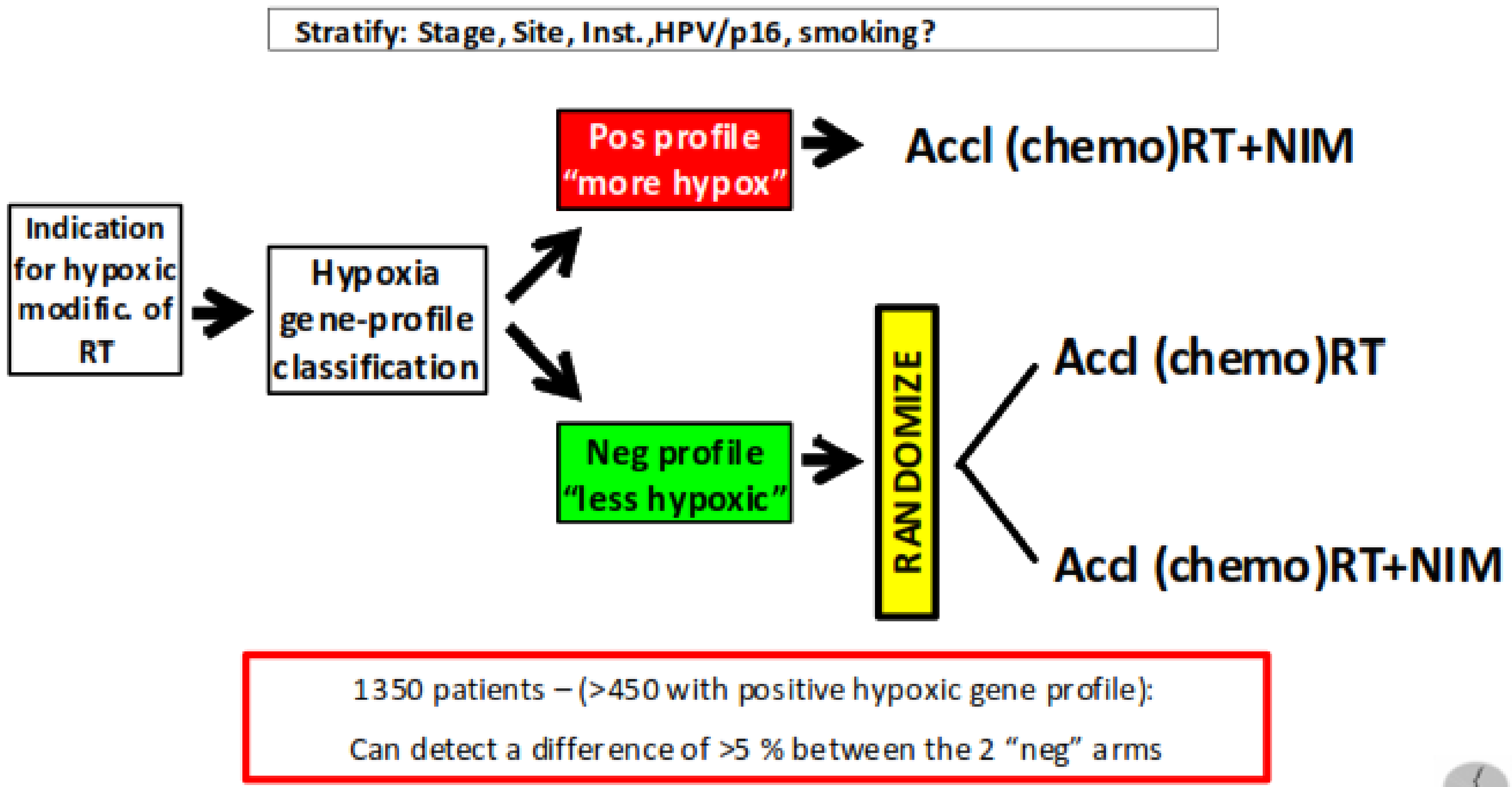
Accl RT(6 fx/wk) +cisPl

+ Nimorazole (1.2 g/m2)

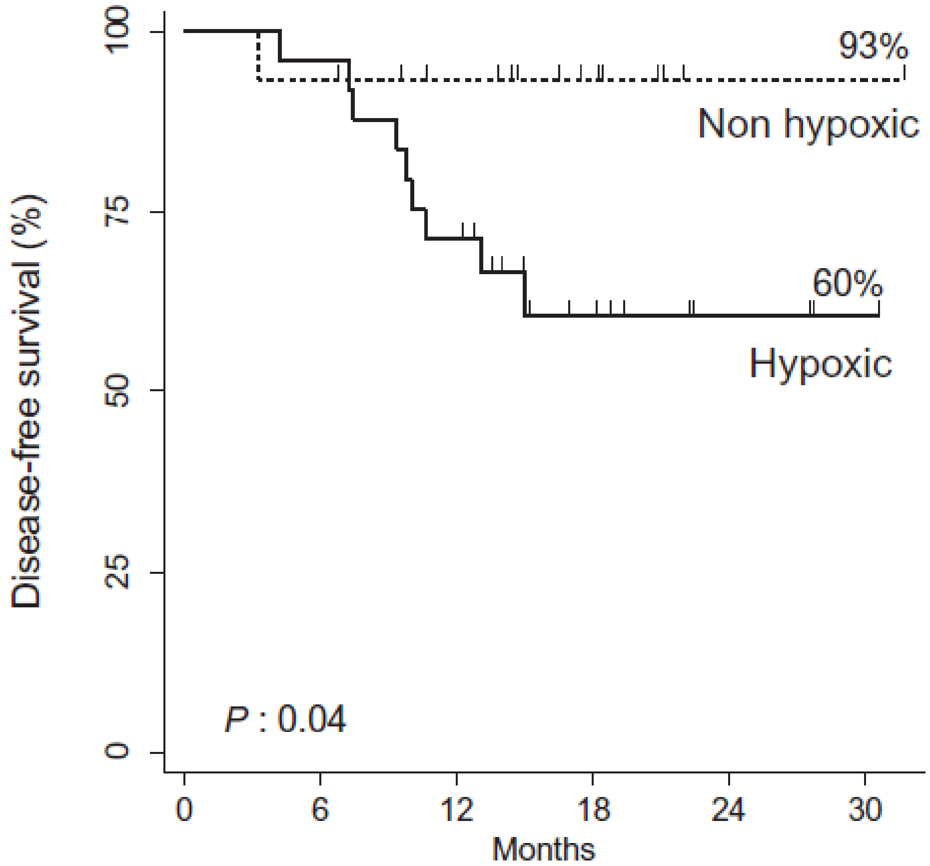
DAHANCA randomized phase III-trial

DAHANCA 30 randomized phase III

Evaluation of the hypoxic-gene profile
to predict benefit of hypoxic modification of radiotherapy in HNSCC



FAZA-PET



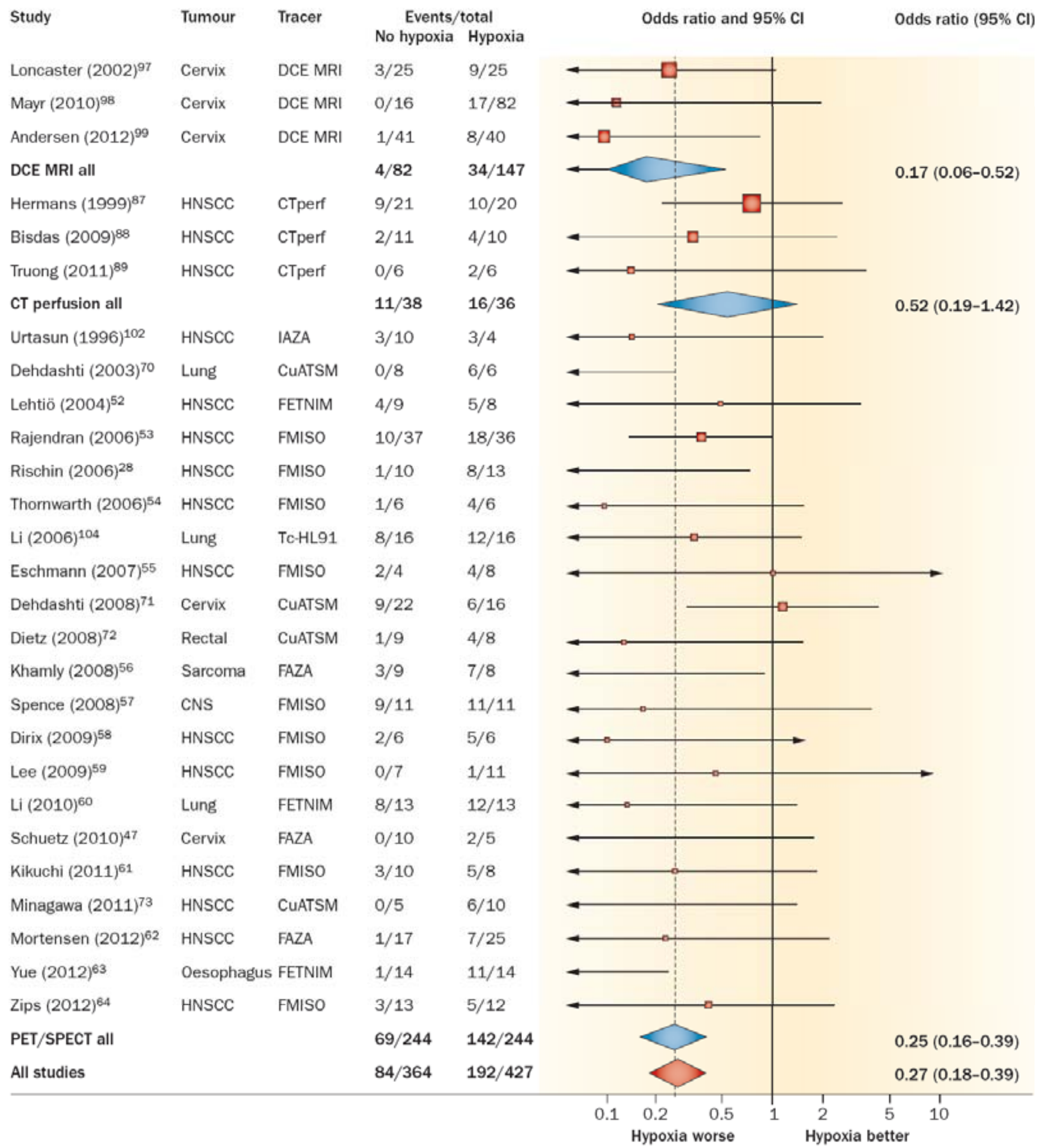
Pts at risk:						
Non hypoxic:	15	14	11	6	1	1
Hypoxic:	25	24	17	8	3	1

L.S. Mortensen et al. / Radiotherapy and Oncology 105 (2012) 14–20

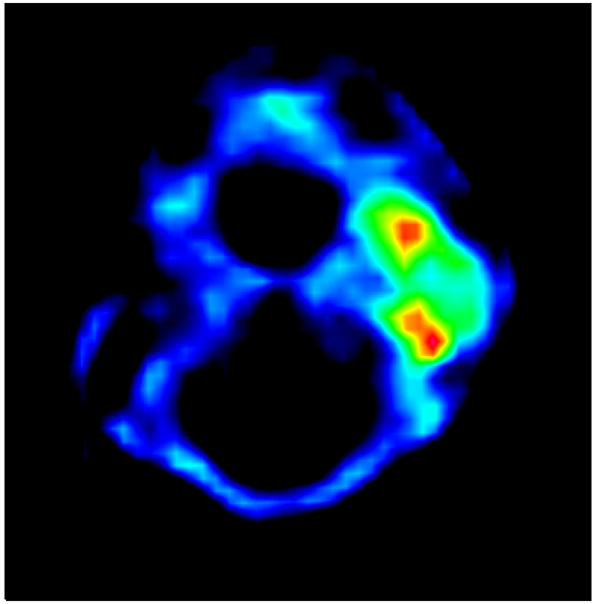
Pre-treatment hypoxia imaging with CT-perfusion, DCE-MRI and PET is prognostic for outcome of HN RT

Prognostic….

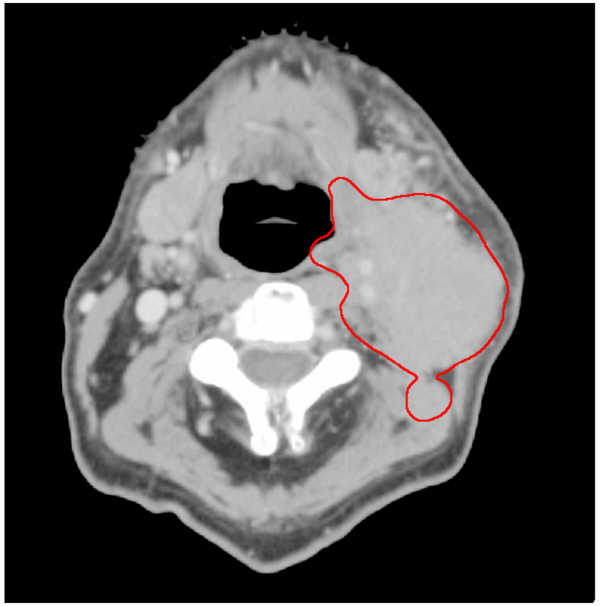
Not Predictive



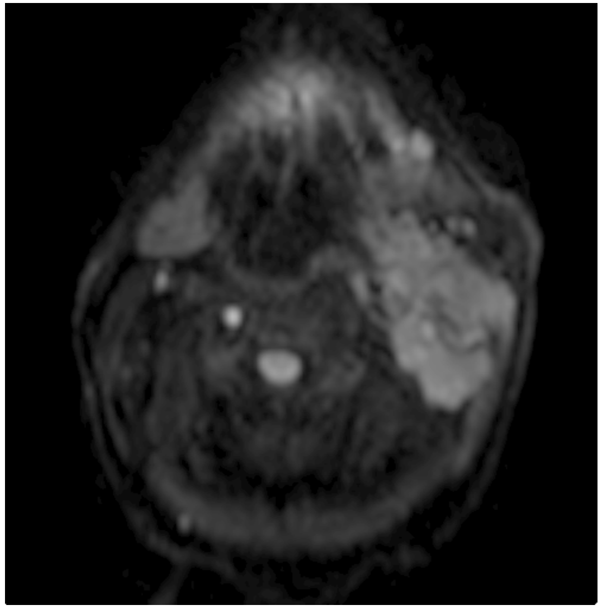
Horsman, M. R. *et al. Nat. Rev. Clin. Oncol.* 9, 674–687 (2012)



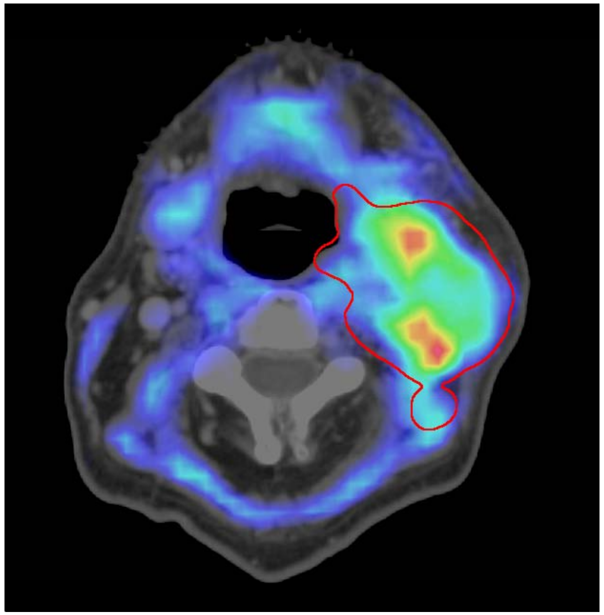
F-AZA PET



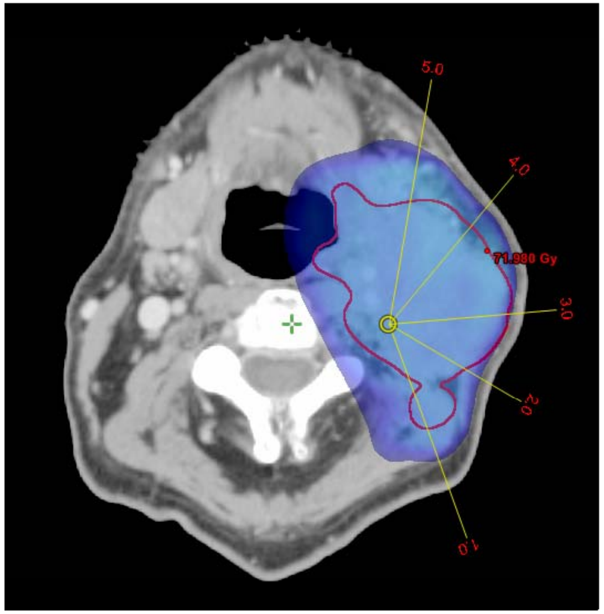
CT with GTV outlined



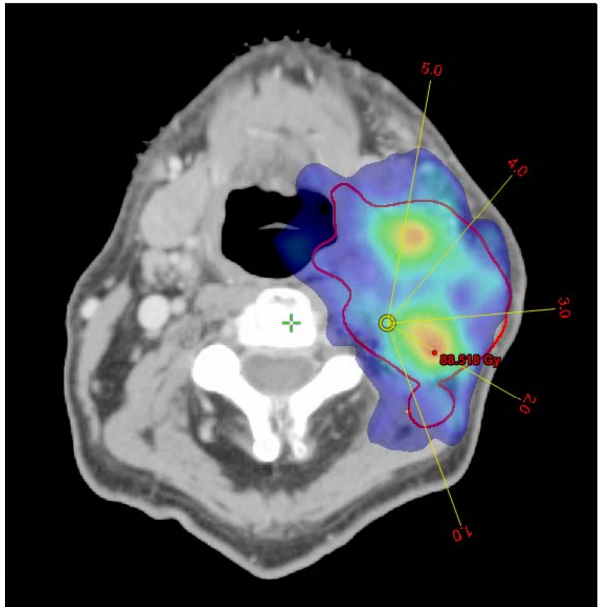
Diffusion weighted MRI



FAZA PET-CT



IMRT



Hypoxic dosepaint IMRT

Petersen, Mortensen et al. Aarhus University Hospital

Conclusions – hypoxia

- A significant proportion of HN squamous cell carcinomas contains hypoxic regions
- Patients with hypoxic tumours have poorer loco-regional control and survival
- Hypoxic modification (sensitizers, HBO, hypoxic cytotoxins) during RT results in improved loco-regional control and survival
- Predictive assays, hypoxic imaging and dosepainting is emerging but still investigational

Systemic therapy

Rationale for combining radiotherapy and systemic therapy

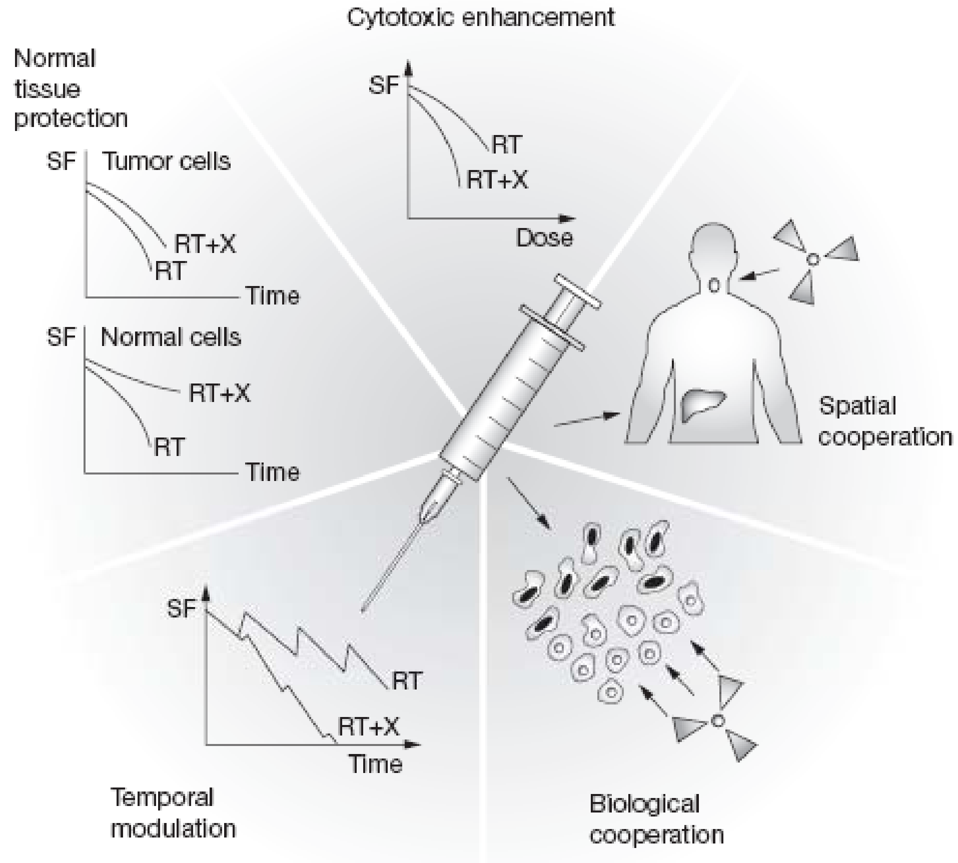
Spatial cooperation

Cytotoxic enhancement

Biological cooperation

Temporal modulation

Normal tissue protection



Bentzen SM Nature Clin Pract Oncol 2007

Meta-analysis II 2009

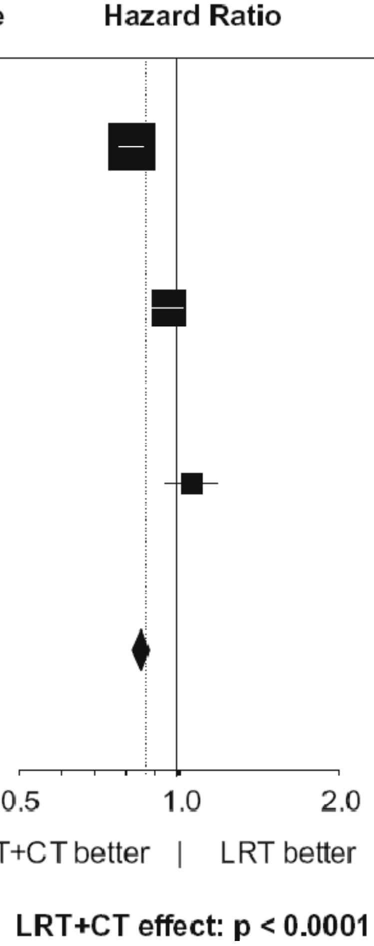
HR of death

Timing	No. Deaths / No. Entered LRT+CT	No. Deaths / No. Entered LRT	O-E	Variance	HR [95% CI]
Concomitant	3171/4824	3389/4791	-326.4	1587.7	0.81 [0.78;0.86]
Induction	1877/2740	1813/2571	-40.0	900.7	0.96 [0.90;1.02]
Adjuvant	631/1244	661/1323	17.9	317.4	1.06 [0.95;1.18]
Total	**5679/8808**	**5863/8685**	**-348.5**	**2805.8**	**0.88 [0.85;0.92]**

Test for heterogeneity: $\chi^2_{107} = 179.8$ p < 0.0001

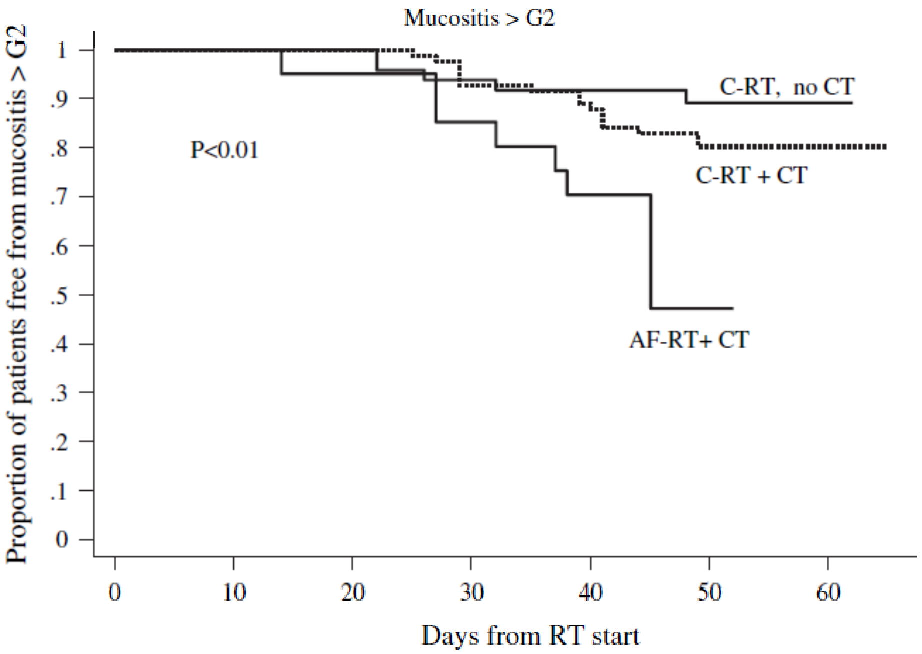
Test for interaction: $\chi^2_{2} = 26.60$ p < 0.0001

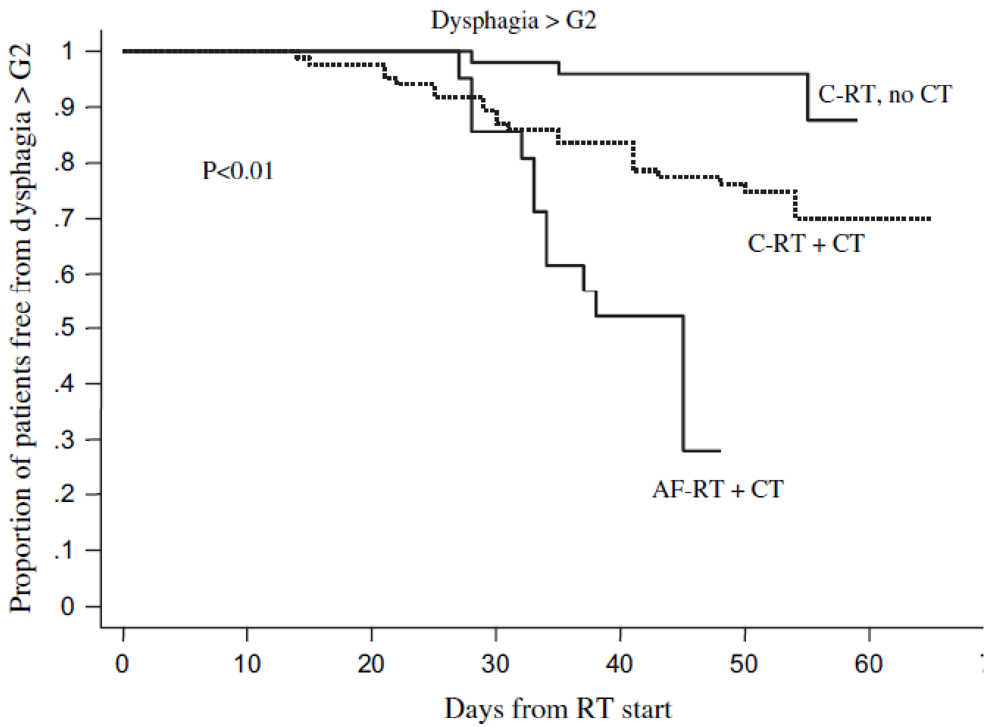
$I^2 = 41\%$



Pignon JP Radiother Oncol 2009

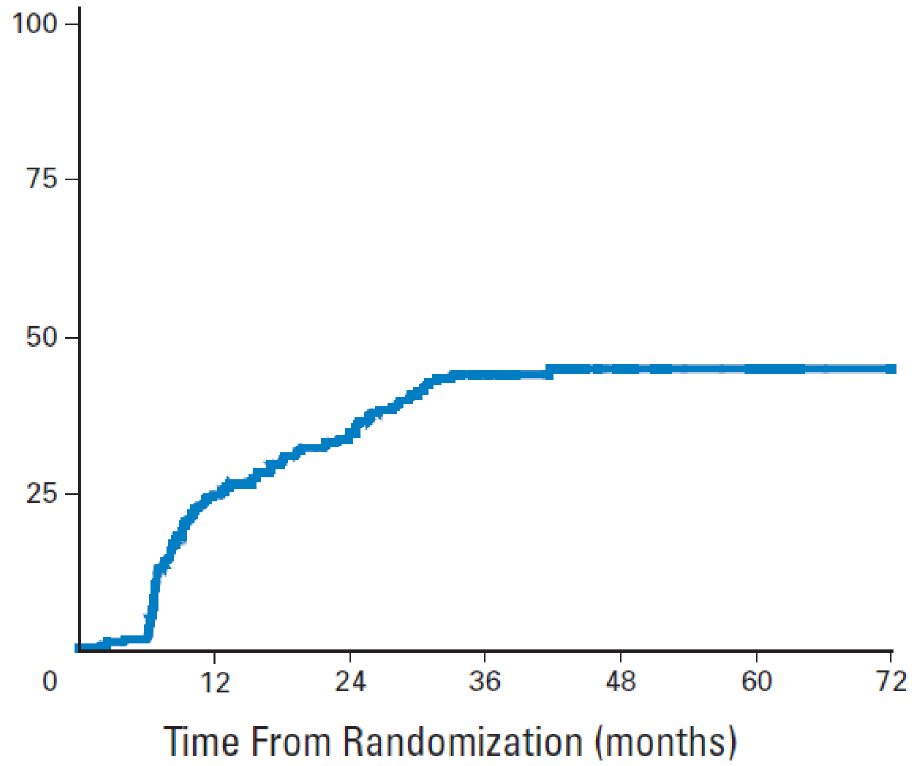
Acute toxicity





Palazzi et al, Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 2, pp. 330–337, 2008

Late morbidity



Analysis of 3 RTOG trial with C-RT

(RTOG 91-11, 97-03, and 99-14)

230 patients

43% severe late morbidity

40% laryngeal/pharyngeal dysfunction

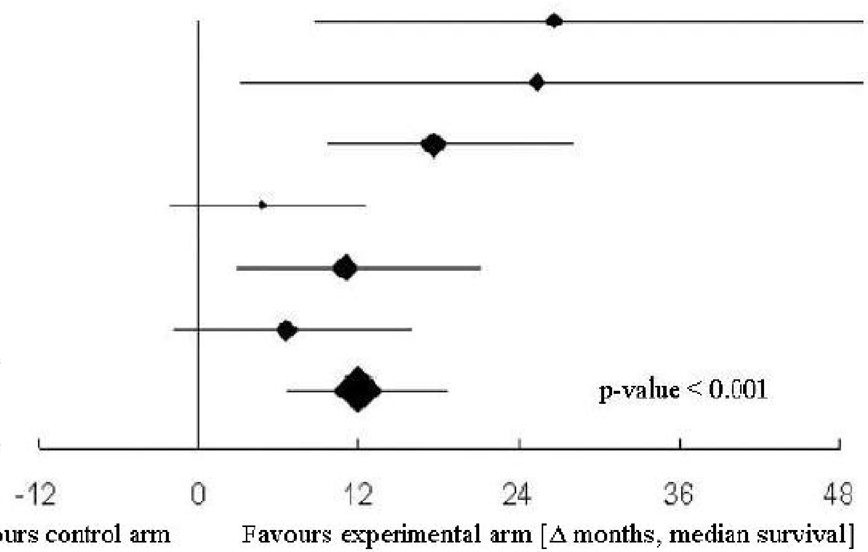
13% tube feeding >2 years after RT

Machtay M JCO 2008;

Unconventional fractionation ±concurrent chemo

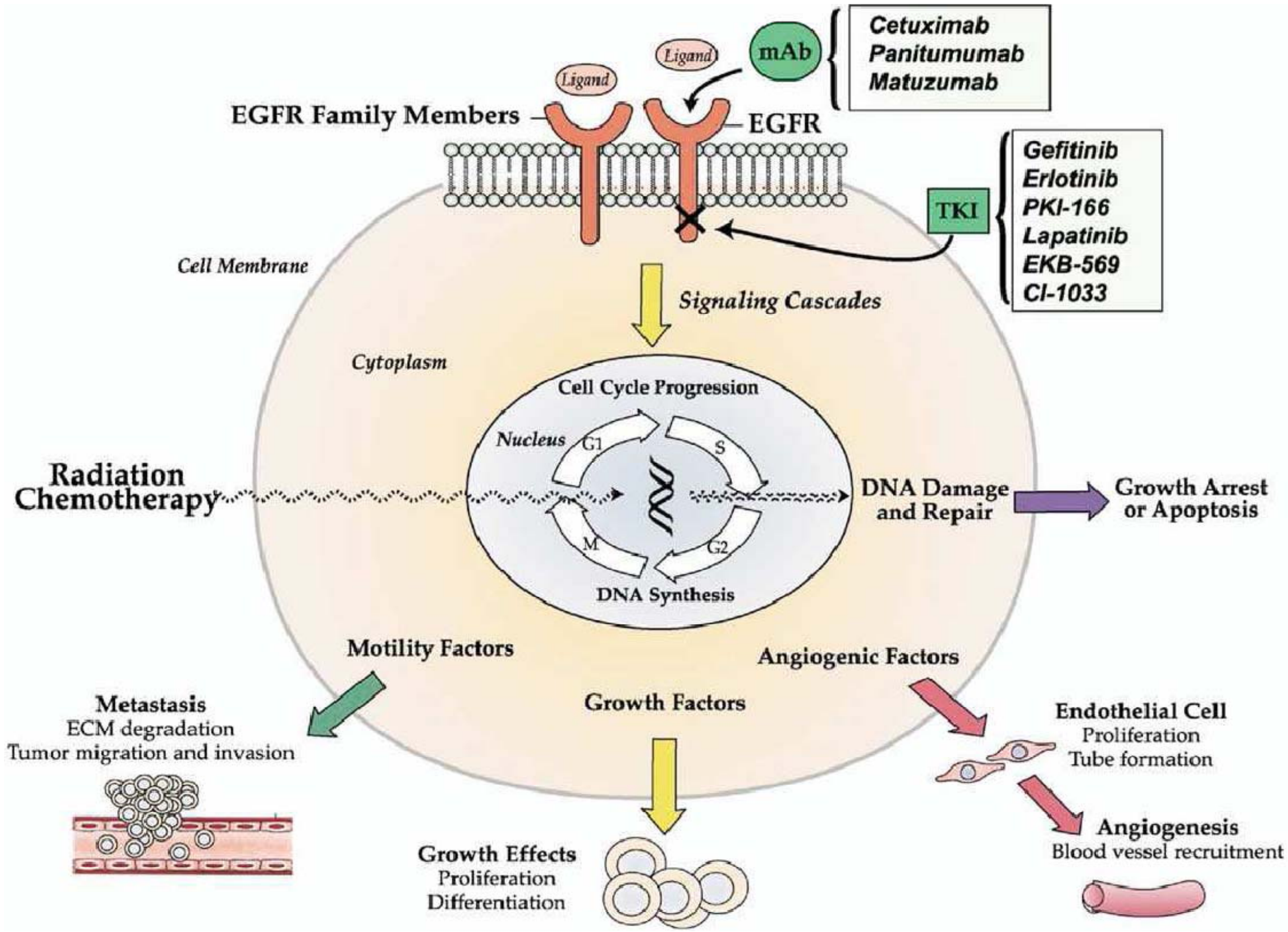
publication	delta 2 year OS [%]	delta months	LCL	UCL	N weight
Jeremic [33]	+21.6	26.6	8.6	52.9	130
Brizel [34]	+18.1	25.3	3.1	62.0	116
Wendt [35]	+25.1	17.7	9.8	28.0	270
Staar [36]	+7.8	4.9	-2.1	12.7	240
Dobrowsky [37]	+17.6	11.0	2.8	21.3	161
Budach [12]	+6.8	6.6	-2.0	16.1	384
total	14.7 (8.9-20.3)*	12.0	6.7	18.8	1301

Test for heterogeneity:	variance	mean(sq)	chi-square	p
	0.60	0.58	1.05	0.959



Budach W BMC Cancer 2006

EGFR



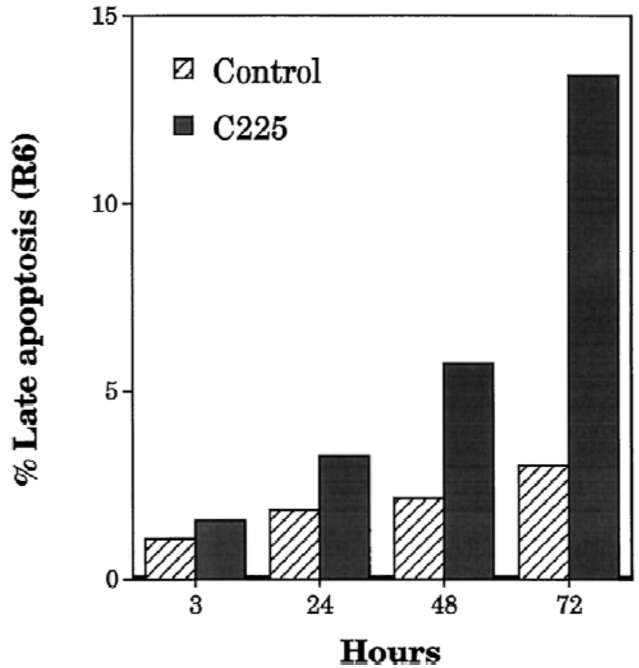
Harari PM Semin Radiat Oncol 2006

RT + EGFR inhibition synergies

Ionizing radiation → G2/M-block

EGFr-I → G1- block

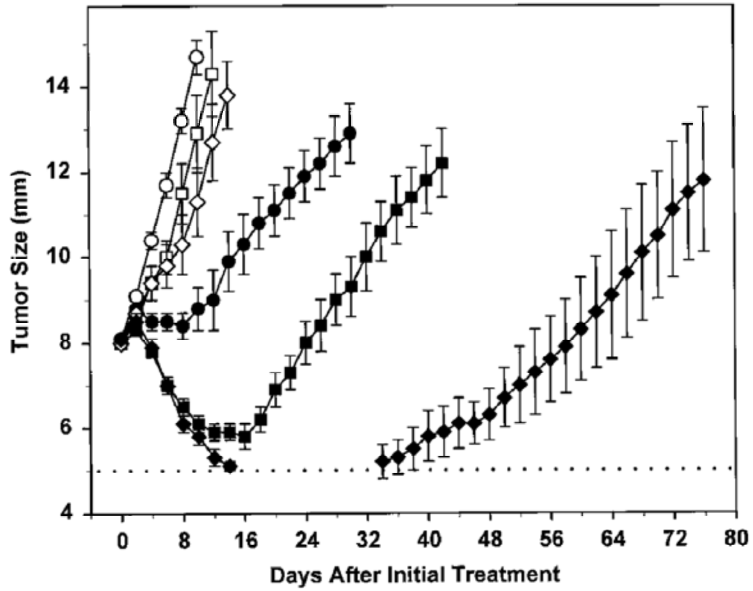
- EGFr-I induces apoptosis (~ 2 fold)
- RT induces apoptosis (6 Gy – 2 fold)
- RT and EGFr-I synergistic effect (5-6 fold)

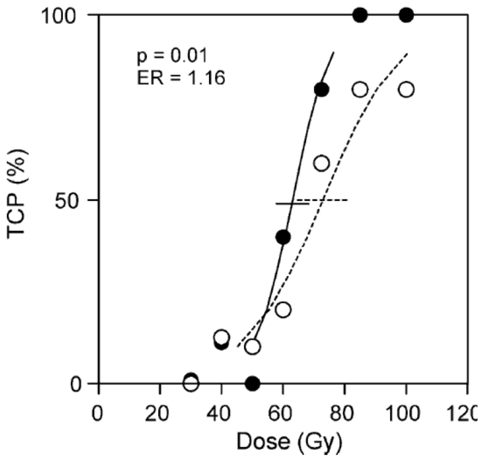


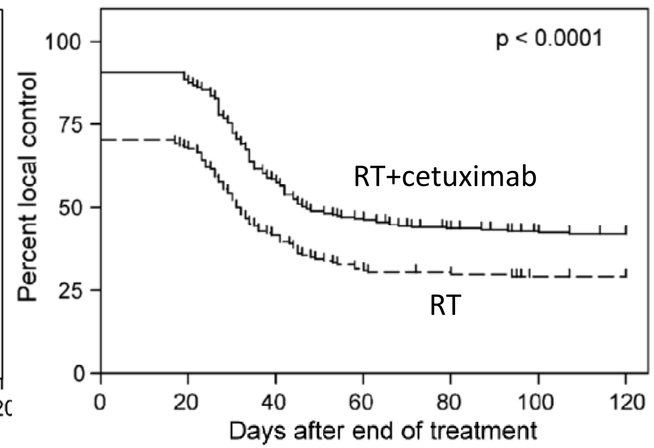
Huang SM Cancer Res 1999; Harari PM IJROBP 2001;

Nyati MK Clin Cancer Res 2004

EGFR inhibition - pre-clinical data



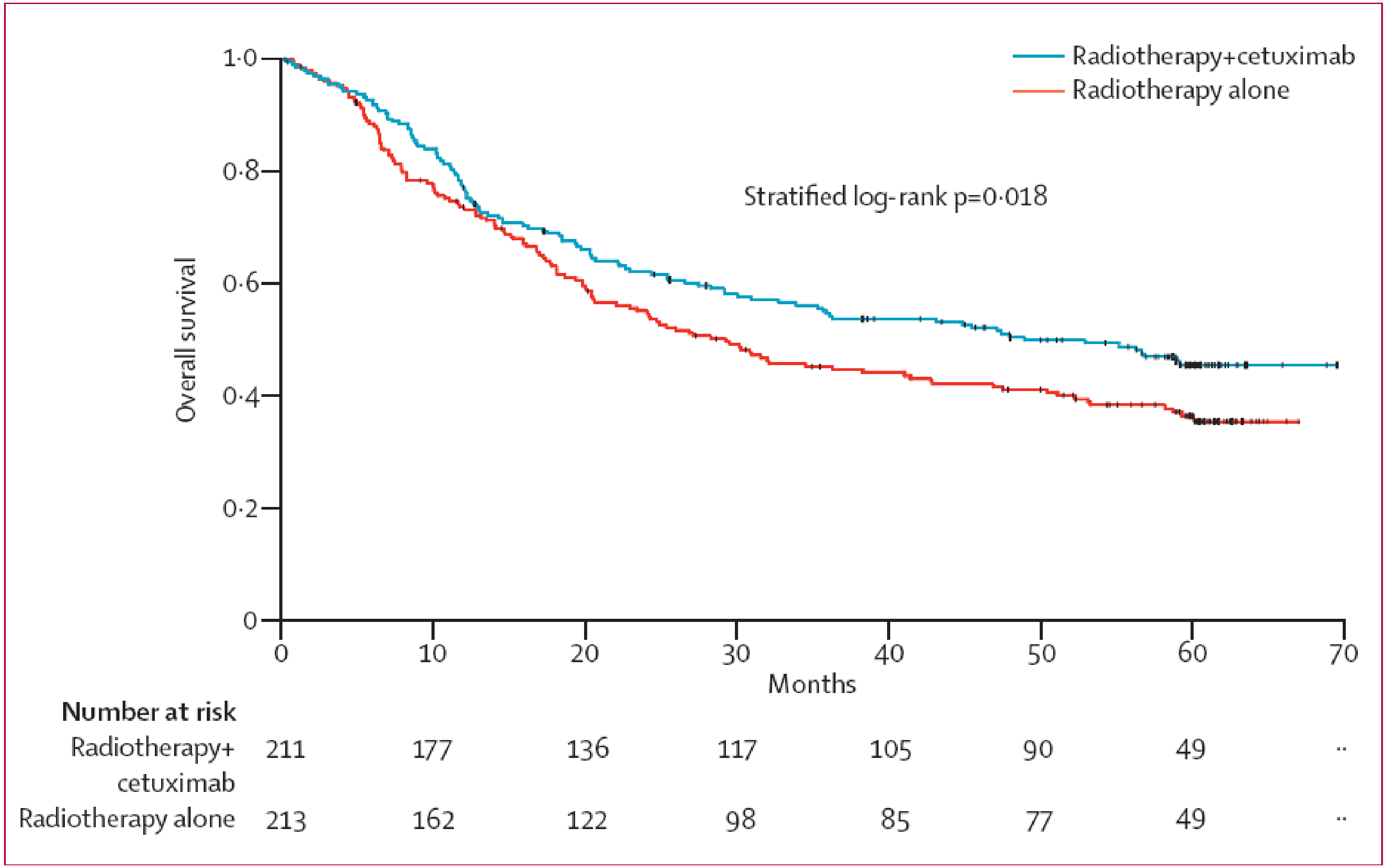




Akimoto T Clin Cancer Res 1999; Schmidt-Ullrich Oncogene 1997

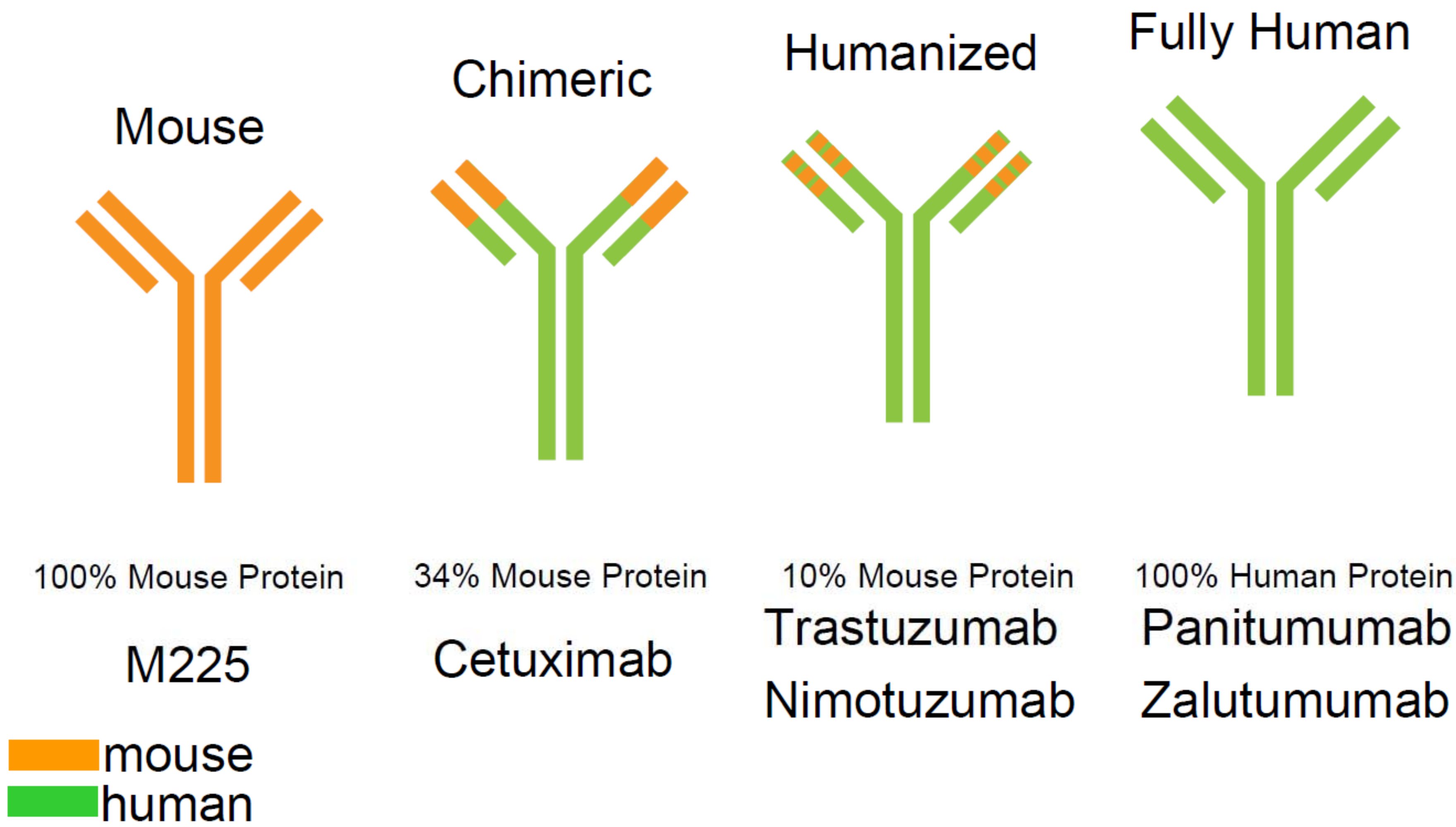
Milas L Clin Cancer Res 2000; Krause M Radiother Oncol 2005

RT ±Cetuximab



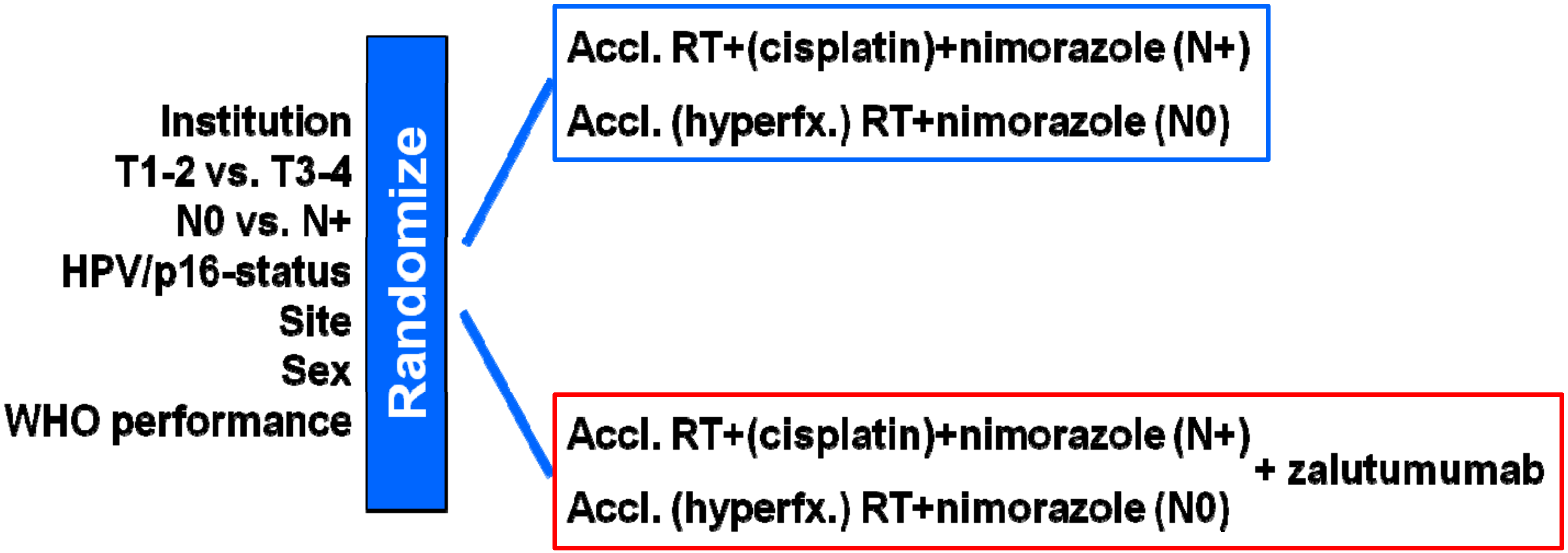
Bonner JA Lancet Oncol 2010

Monoclonal antibodies



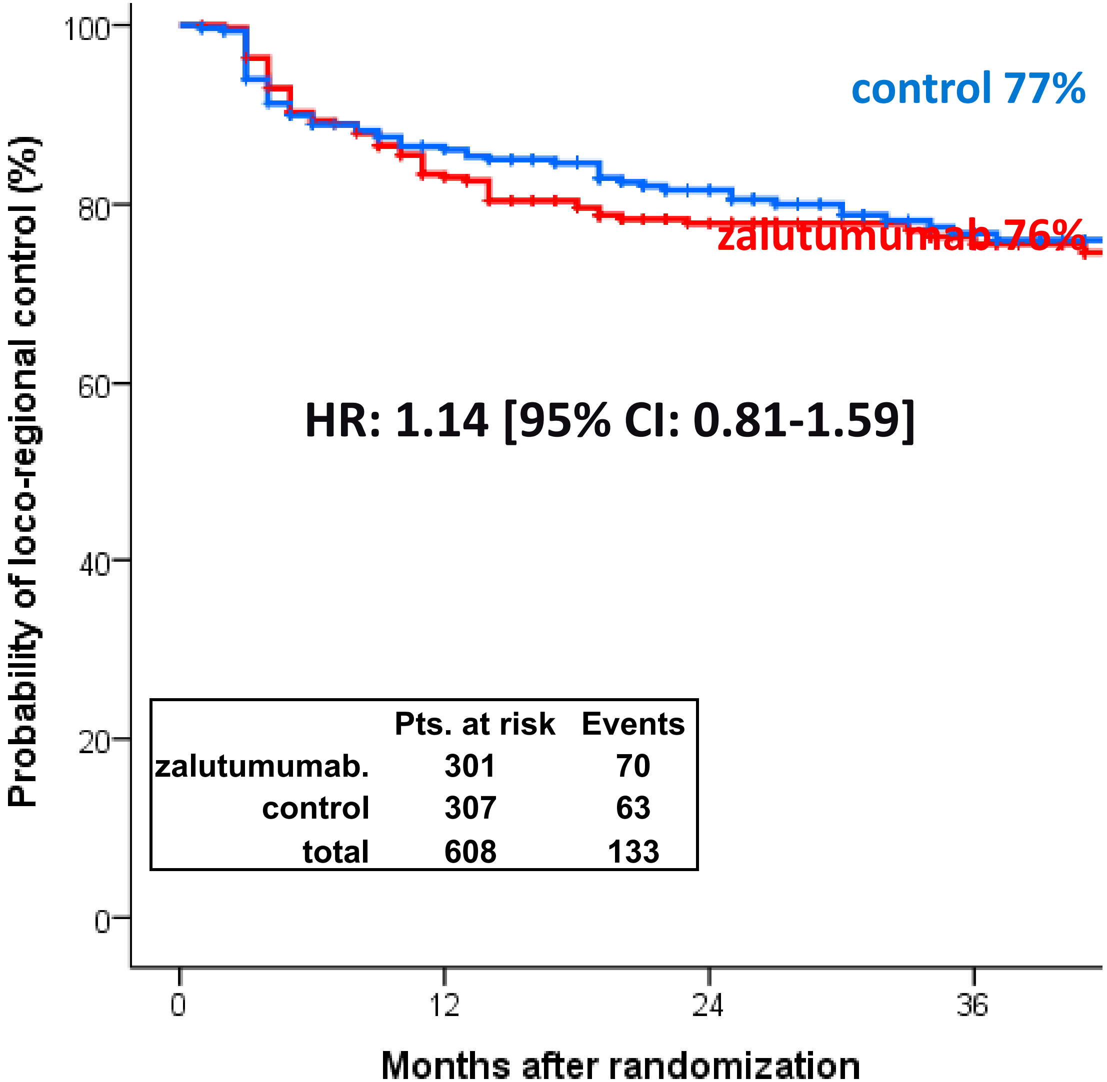
Courtesy Jesper G. Eriksen

DAHANCA19: RT/CRT ± Zalutumumab



Eriksen, H&N Arizona 2014

DAHANCA19: Loco-regional control

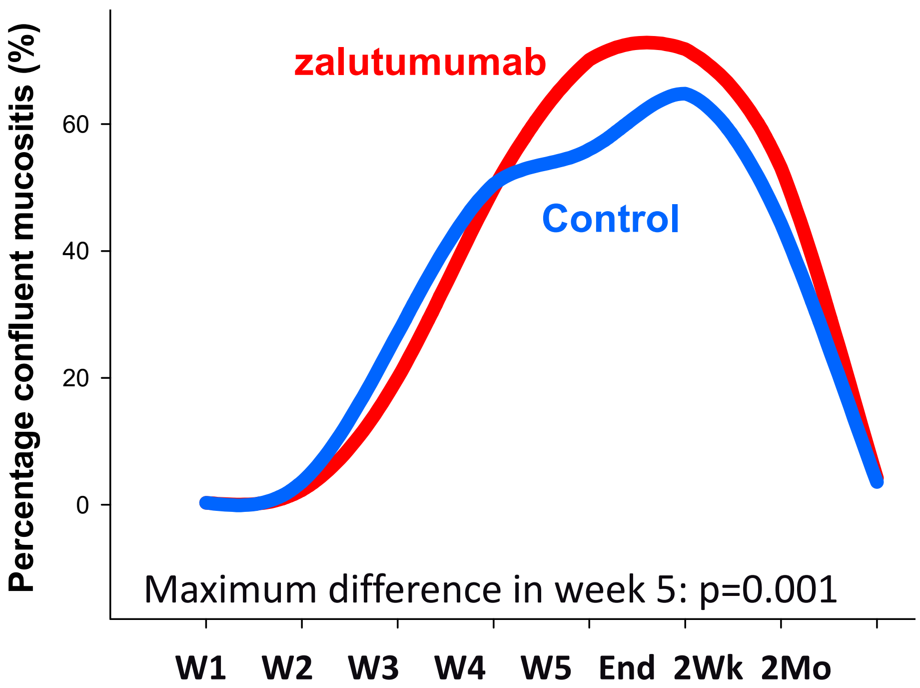


	Pts. at risk	Events
zalutumumab.	301	70
control	307	63
total	608	133

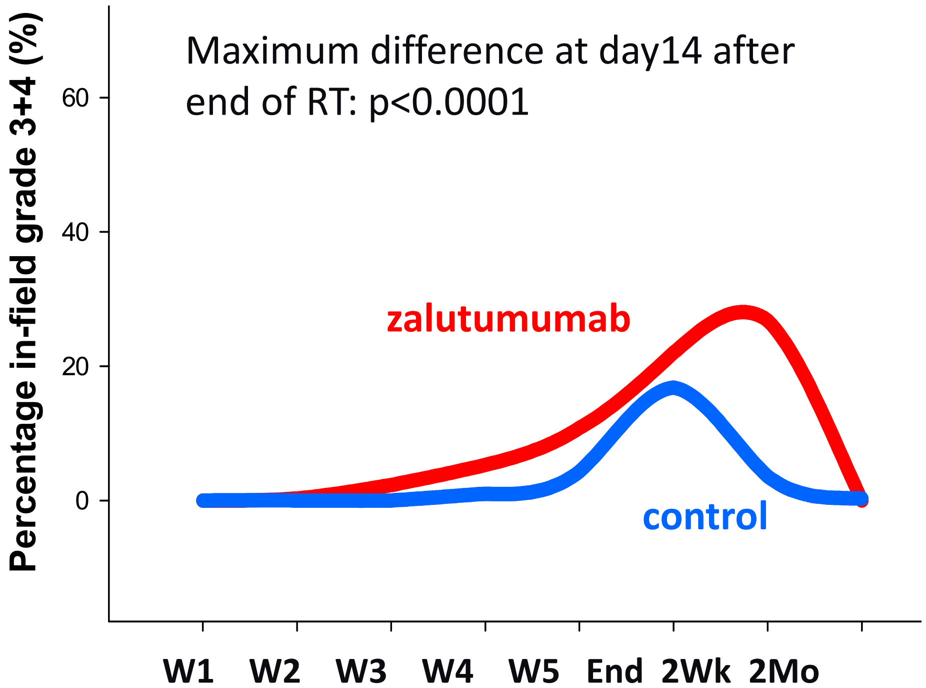
Eriksen, H&N Arizona 2014

DAHANCA19 - Acute morbidity

Confluent mucositis



Grade 3-4 in-field reaction



Need for tube-feeding at end of treatment:
No difference (50% vs. 50%)

Eriksen, H&N Arizona 2014

Conclusions
RT and systemic therapy

- Sound biological rationale for combining local and systemic treatment
- The main clinical effect is by improving RT-induced loco-regional control
- Largest effect and tolerability in younger patients in good performance status
- Acute and late toxicity is increased

May look straightforward, but…….

Combination of RT and systemic therapy

The devil is in the details:

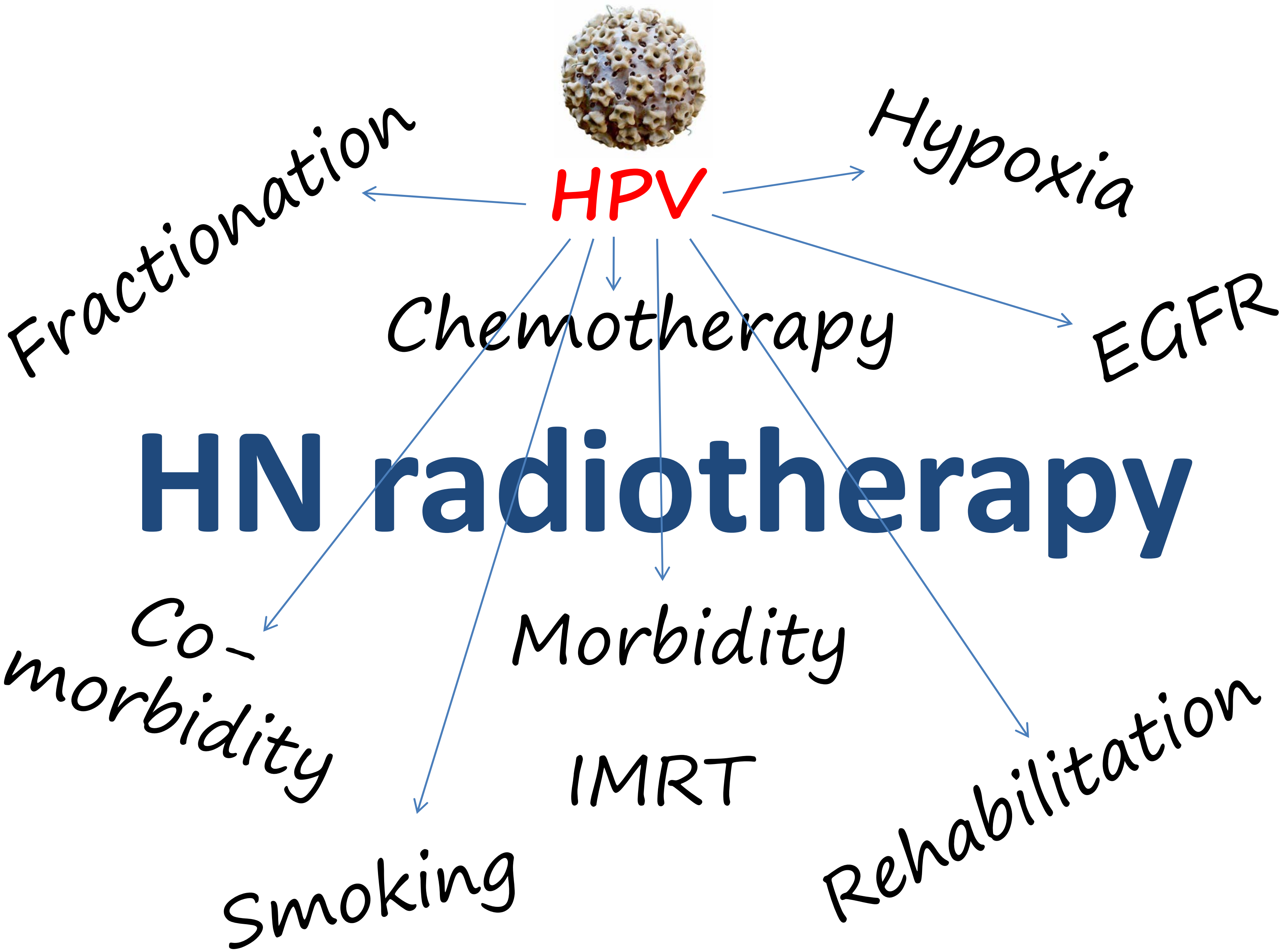
- Induction chemotherapy? Evidence versus clinical practise…
- Concomitant chemoRT:
  - Which drugs?
  - Frequency: weekly or every three weeks?
- Does it (really) work with altered fractionation?
- Combination of two and more systemic agents..
  - Doublet versus triplet
- What about toxicity – is there a true therapeutic gain?

….will be addresssed in this course…

Fractionation
HPV
Hypoxia
Chemotherapy
EGFR
HN radiotherapy
Co-morbidity
Morbidity
IMRT
Smoking
Rehabilitation

Summary – key points

- Modified fractionation (hyperfractionation and/or acceleration) is superior to conventional fractionation
- Hypoxic sensitizers (e.g. nimorazole) improves tumor control and survival without enhancing radiation morbidity
- Concomitant platinum-based chemotherapy is more effective than RT alone for younger patients in good performance status with and advanced stage tumours. Acute and late toxicity is increased
- EGFR inhibition combined with radiotherapy (but not chemoRT) results in enhancement of tumor response
- The optimal combination of these ’radiotherapy intensifiers’ is still unsettled



HPV
Fractionation
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EGFR
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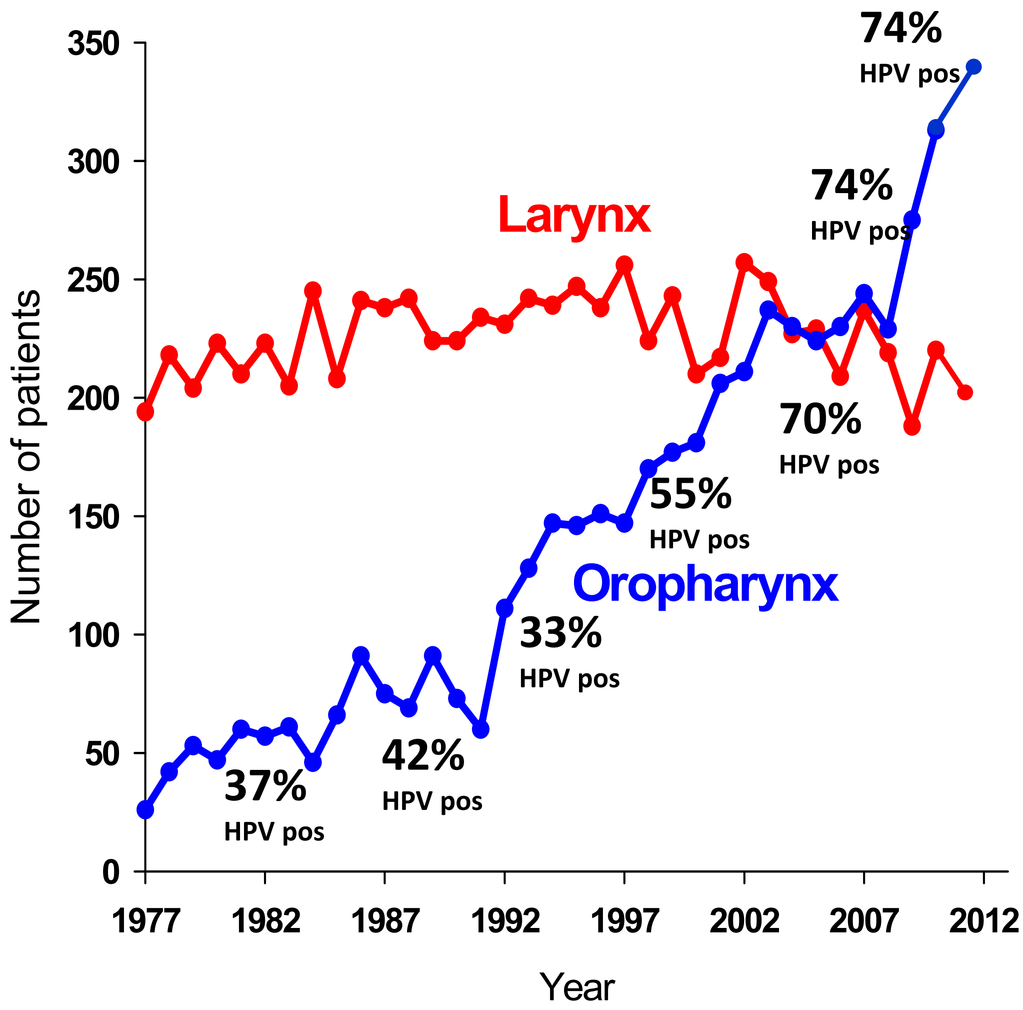
Morbidity
IMRT
Smoking
Rehabilitation

Incidence of oropharyngeal cancer i DK

Denmark

1977-2012

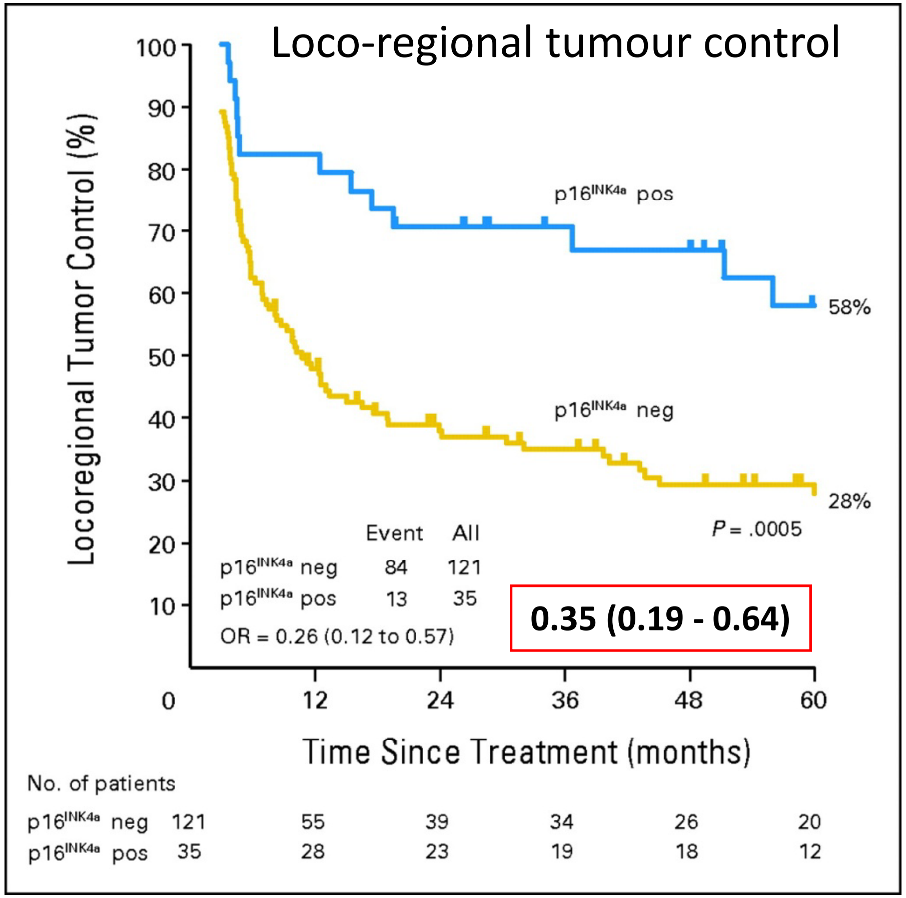
DAHANCA

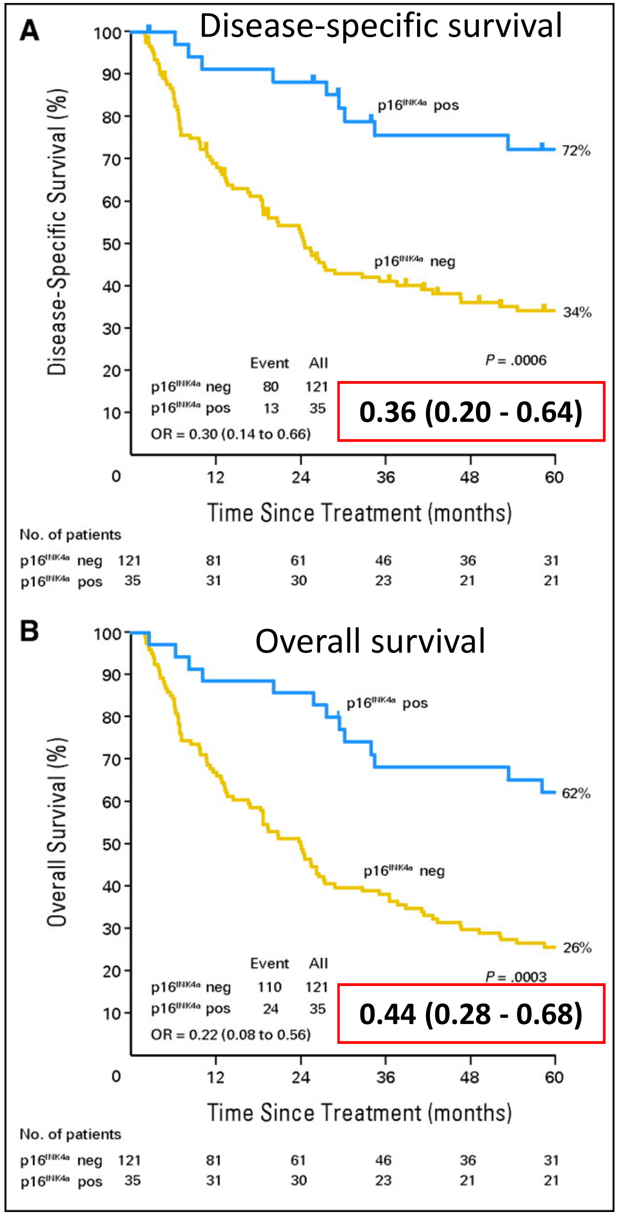


Updated from Lassen Radiother Oncol 2010

Influence of p16/HPV on radiotherapy outcome in HNSCC (5fx/week)

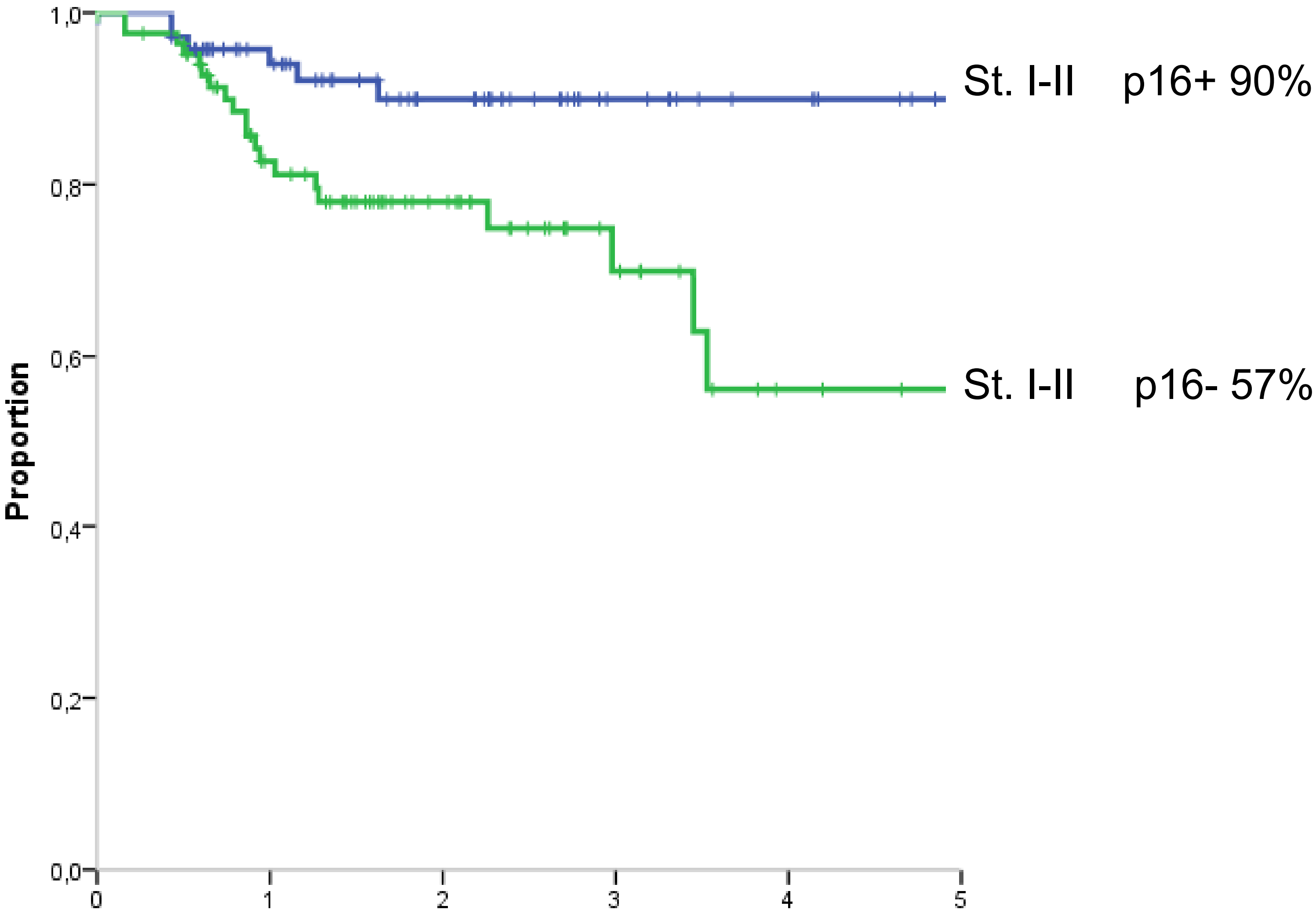
DAHANCA 5 (N=156)





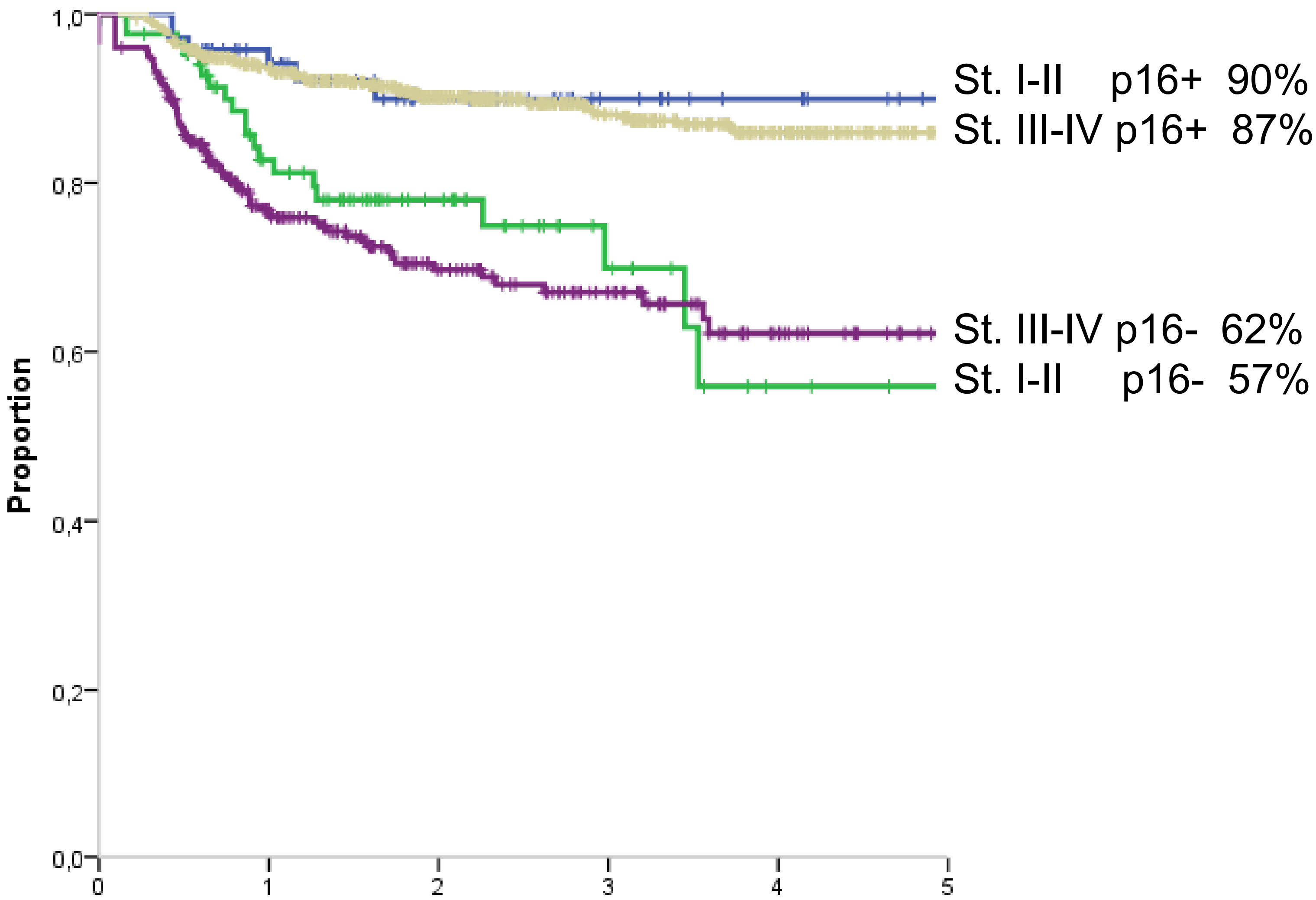
Lassen et al. JCO 27:1992-98,2009

Loco-regional control and p16



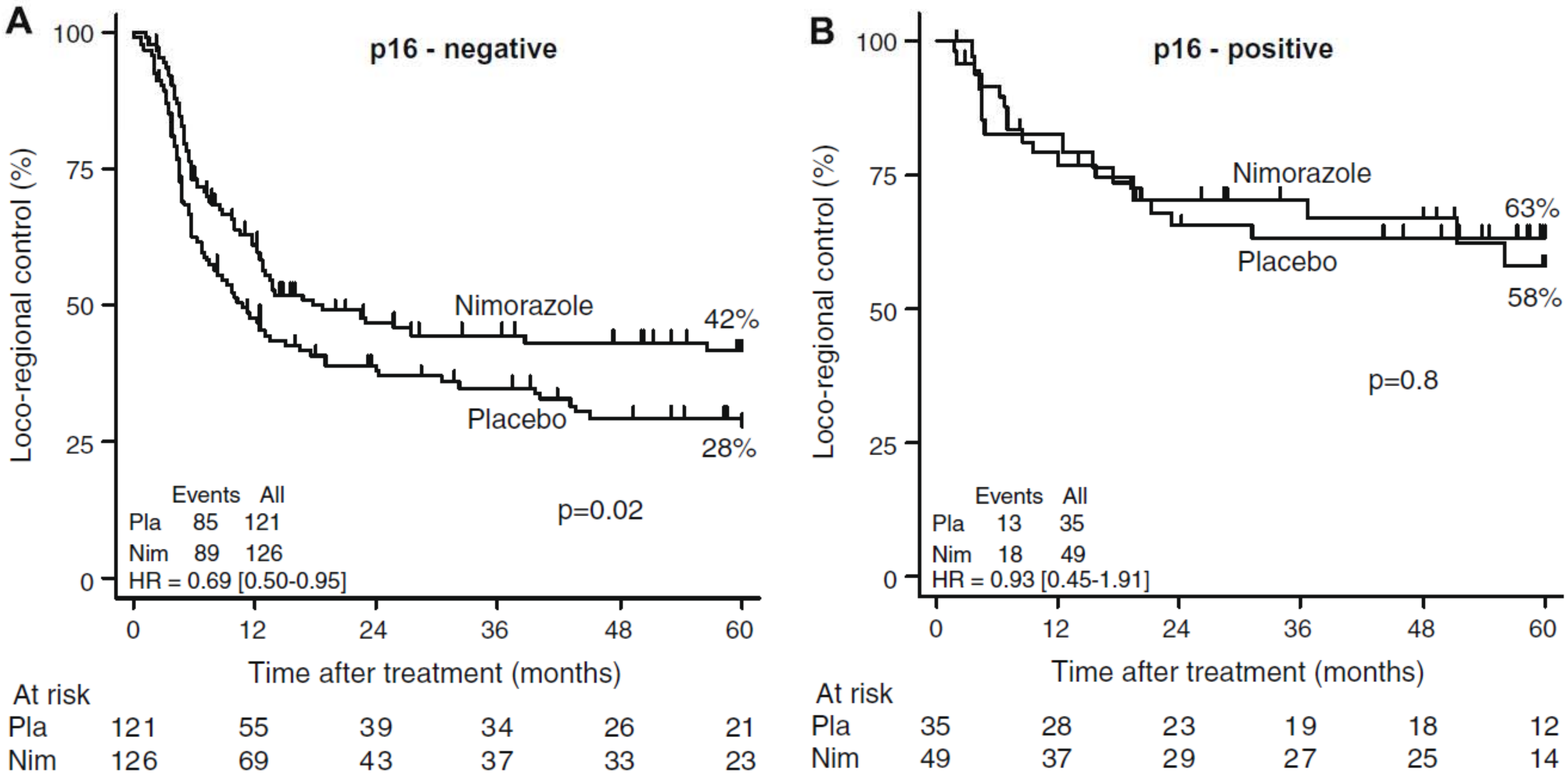
DAHANCA 2000-2013, curative intent RT, oropharynx patients with known p16 status (n=1163)

Loco-regional control and p16



DAHANCA 2000-2013, curative intent RT, oropharynx patients with known p16 status (n=1163)

Influence of HPV status on outcome of hypoxic modification (nimorazole)

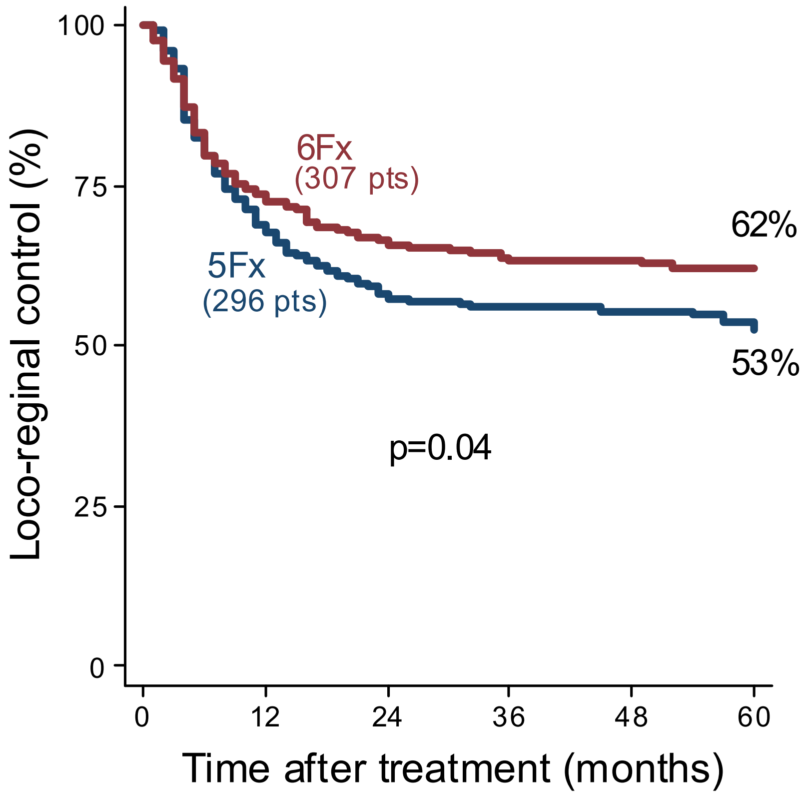


Lassen P et al. Radiother Oncol 94, 2010

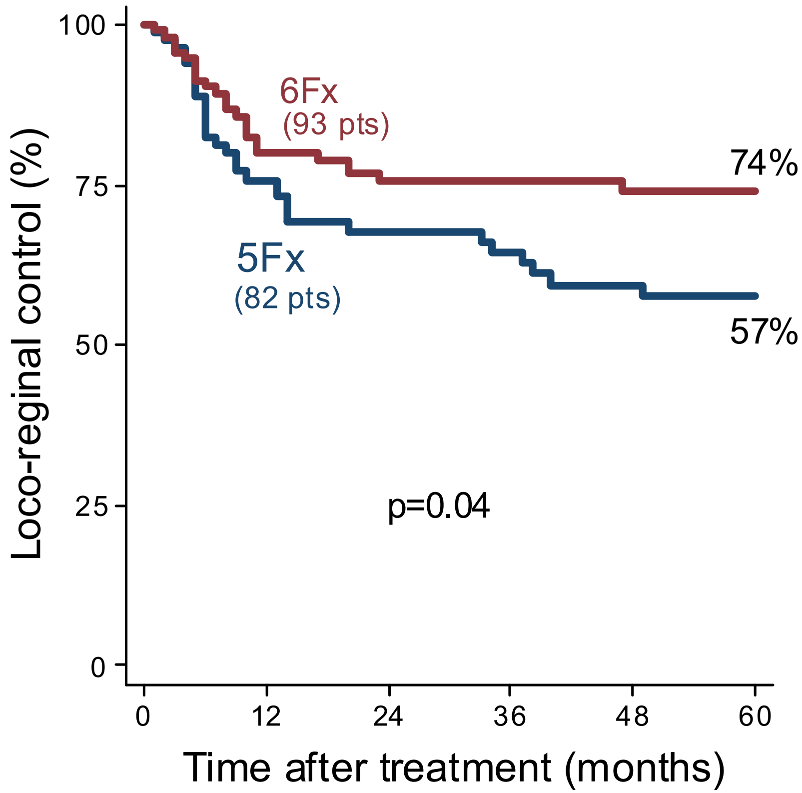
Influence of HPV status on outcome of accelerated fractionation

DAHANCA 6&7

p16 negative
N=603



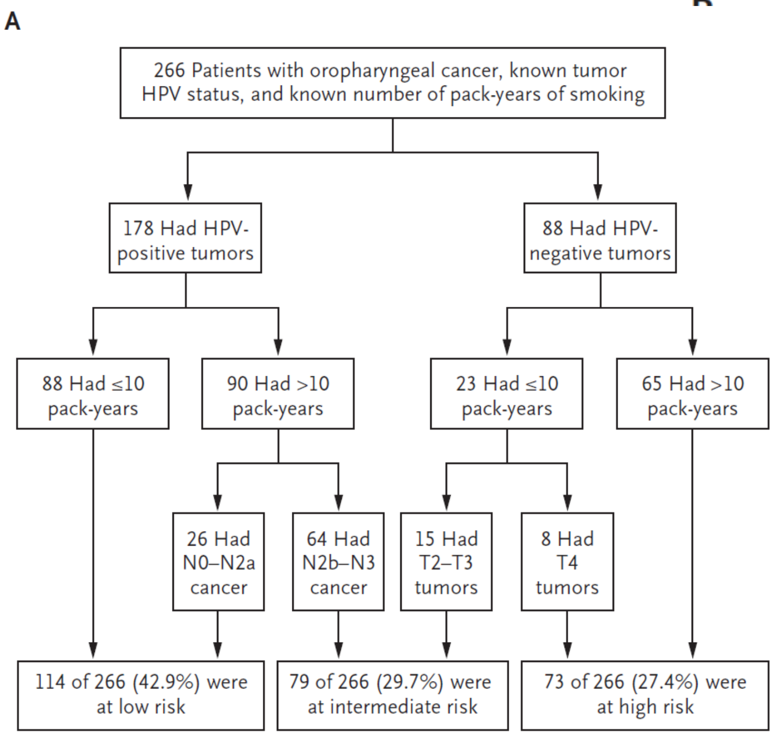
p16 positive
N=175

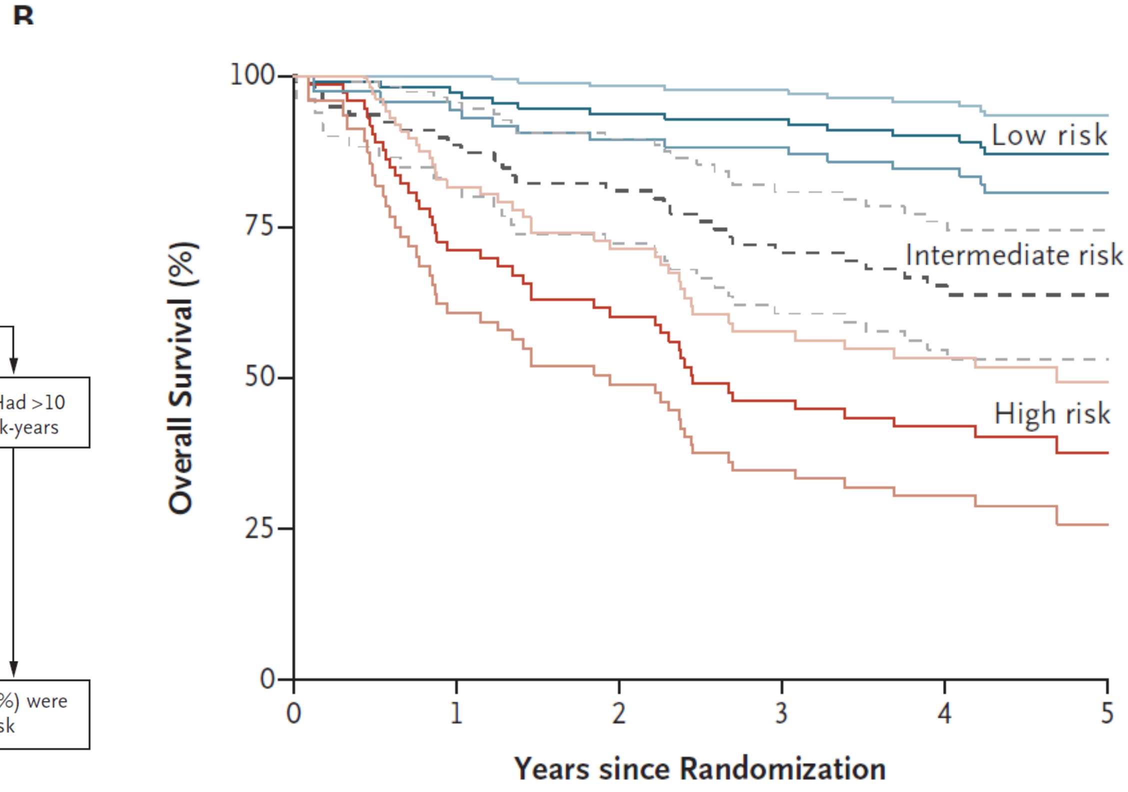


Lassen P et al. ECCO Berlin, 2009 - Euro J Cancer Suppl 2009;7:11

HPV, smoking and risk groups

RTOG 0129: concurrent chemoRT +acc



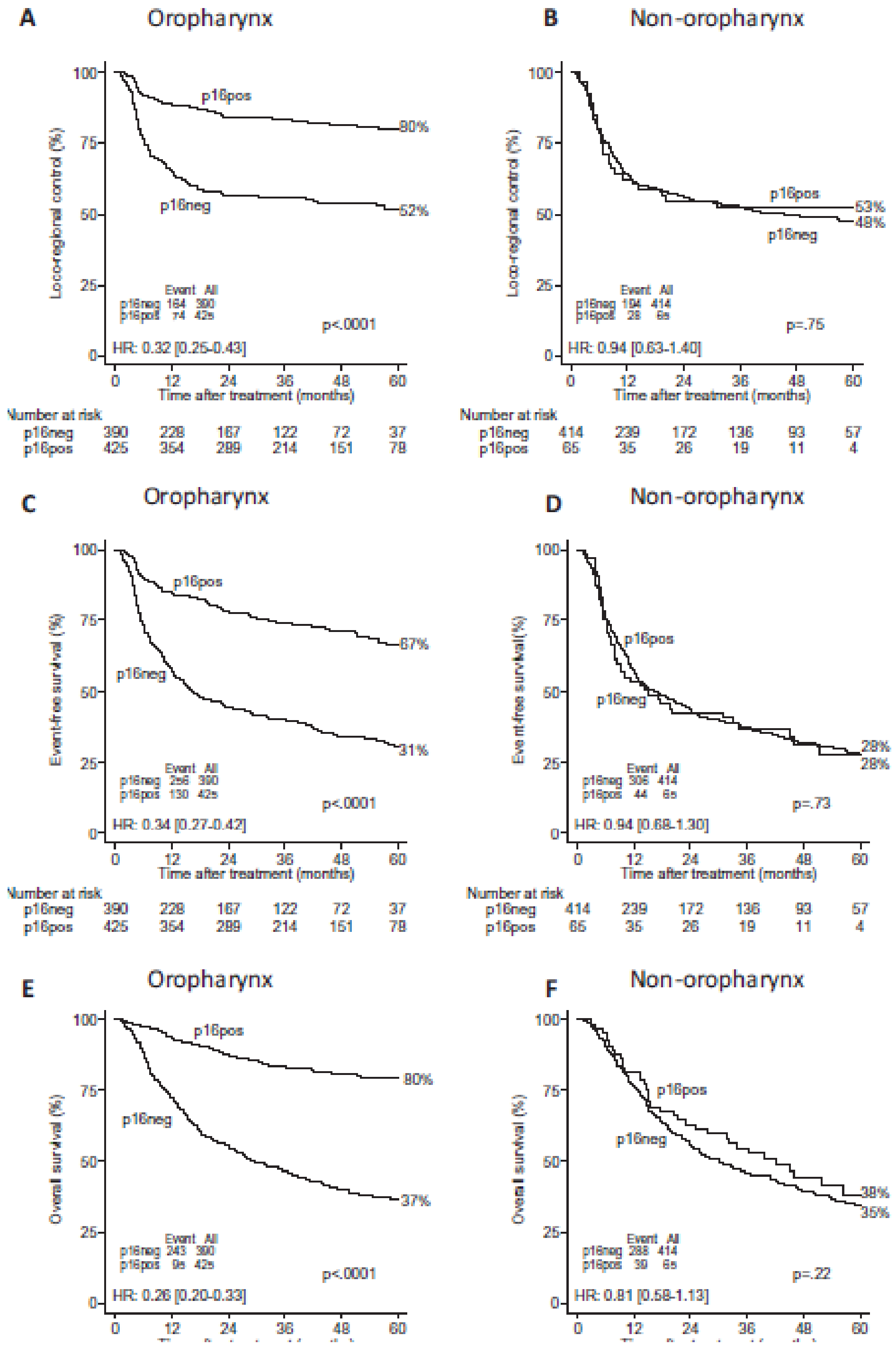


No. at Risk

	0	1	2	3	4	5
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8

Ang N Engl J Med 2010 363;1

P16 effect on RT outcome - oropharynx only?



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journal homepage: www.thegreenjournal.com

Donal Hollywood Award 2014

Impact of HPV-associated p16-expression on radiotherapy outcome in advanced oropharynx and non-oropharynx cancer ☆

Pernille Lassen[a,*], Hanne Primdahl[b], Jørgen Johansen[c], Claus A. Kristensen[d], Elo Andersen[e], Lisbeth J. Andersen[f], Jan F. Evensen[g], Jesper G. Eriksen[a], Jens Overgaard[a], On behalf of the Danish Head and Neck Cancer Group (DAHANCA)

[a] Department of Experimental Clinical Oncology, Aarhus University Hospital; [b] Department of Oncology, Aarhus University Hospital; [c] Department of Oncology, Odense University Hospital; [d] Department of Oncology, Rigshospitalet; [e] Department of Oncology, Herlev Hospital, Copenhagen; [f] Department of Oncology, Aalborg Hospital, Denmark; and [g] Department of Oncology, Oslo University Hospital, Norway

HPV (p16) oro vs. non-oro

Endpoint/variable	Oropharynx HR [95% CI][b]	Non-oropharynx HR [95% CI][b]
Overall death		
Age <60 years vs. >60 years	0.72 [0.58–0.90]	0.85 [0.68–1.06]
Female vs. male	0.84 [0.64–1.09]	0.65 [0.49–0.88]
T1–2 vs. T3–4	0.43 [0.34–0.54]	0.62 [0.48–0.81]
N0 vs. N+	0.48 [0.35–0.67]	0.44 [0.33–0.58]
p16pos vs. p16neg	0.38 [0.29–0.49]	0.82 [0.59–1.16]
Nim vs. no nim	0.78 [0.56–1.09]	1.25 [0.90–1.73]
6Fx/week vs. 5Fx/week	0.60 [0.46–0.78]	0.69 [0.53–0.90]
Chemo vs. no chemo	0.36 [0.24–0.53]	0.52 [0.34–0.79]

…. our data suggests that patients with p16-positive tumors of the larynx and hypopharynx should be considered candidates for enhanced, multimodality treatment schedules in line with p16-negative HNSCC.

Lassen et al. RO 2015

RTOG 1016 de-escalation study

p16+ oropharyngeal carcinomas

T1-2,N2a-3 or T3-4 any N

Stratify:
T 1-2
T3-4
N0-2a
N2b-c
>10 PY>
Zubrod 1-2

RANDOMIZE

RT 70Gy/35f/6 wks + cisplatin 100mg/m^2 x 2

Closed 2013 after 987 patients accrued

RT 70Gy/35f/6 wks + cetuximab for 8 weeks

Summary – key points

- Modified fractionation (hyperfractionation and/or acceleration) is superior to conventional fractionation
- Hypoxic sensitizers (e.g. nimorazole) improves tumor control and survival without enhancing radiation morbidity
- Concomitant platinum-based chemotherapy is more effective than RT alone for younger patients in good performance status with and advanced stage tumours. Acute and late toxicity is increased
- EGFR inhibition combined with radiotherapy (but not chemoRT) results in enhancement of tumor response
- The optimal combination of these ’radiotherapy intensifiers’ is still unsettled
- **All of the above in turn needs to be re-evaluated in the light of the major impact of HPV on radiation response and prognosis**
- **HPV status needs to be taken into account whenever a clinical trial is conducted or interpreted (identification, stratification..)**
- **Until such evidence is collected, HPV-status should not influence intensity of treatment**
- **De-escalation trials for HPV+ patients are ongoing**
- **Although there is currently much focus on the HPV-positive patients, it is important not to forget the HPV-negative patients, who have poor prognosis and need better strategies!**

[redacted]

Suggested literature

- Overgaard, J. et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial. The Lancet 362: 933-940, 2003.
- Bourhis J et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006; 368: 843–54.
- Overgaard J. Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck – A systematic review and meta-analysis. Radiother Oncol (2011)
- Nordsmark et al. Prognostic value of tumor oxygenation in 397 head and neck tumors after primary radiation therapy. An international multi-center study. Radiotherapy and Oncology 77 (2005) 18–24
- Bernier J, Licitra L. Chemoradiation in head-and-neck cancer—are we any closer? Nature reviews | clinical oncology volume 7, May 2010
- Pignon JP et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 2000;355:949-55.
- Pignon JP et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiotherapy and Oncology 92 (2009) 4–14
- Budach W. et al. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer 2006, 6:28
- Bernier J et. al. Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer. N Engl J Med 350;19, 2004
- Cooper JS et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-44.
- Bonner JA et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010; 11: 21–28

Beijing, 14-17. June 2015

Radiobiological principles in head and neck radiotherapy

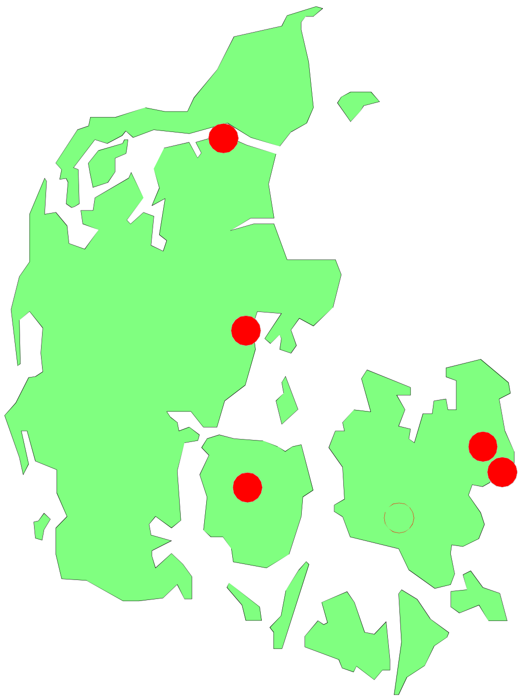
-volume, fractionation, hypoxia, combination with systemic therapy

Jesper Grau Eriksen and Cai Grau

ESTRO School

DAHANCA

The Danish Head and Neck Cancer Group



- Established 1976
- National database
- Registration and follow up of all patients with head and neck cancer
- National treatment strategy
- Clinical trials
- Quality assurance

Role of RT in head and neck cancer

- Primary radiotherapy
- Adjuvant radiotherapy
- Palliative radiotherapy

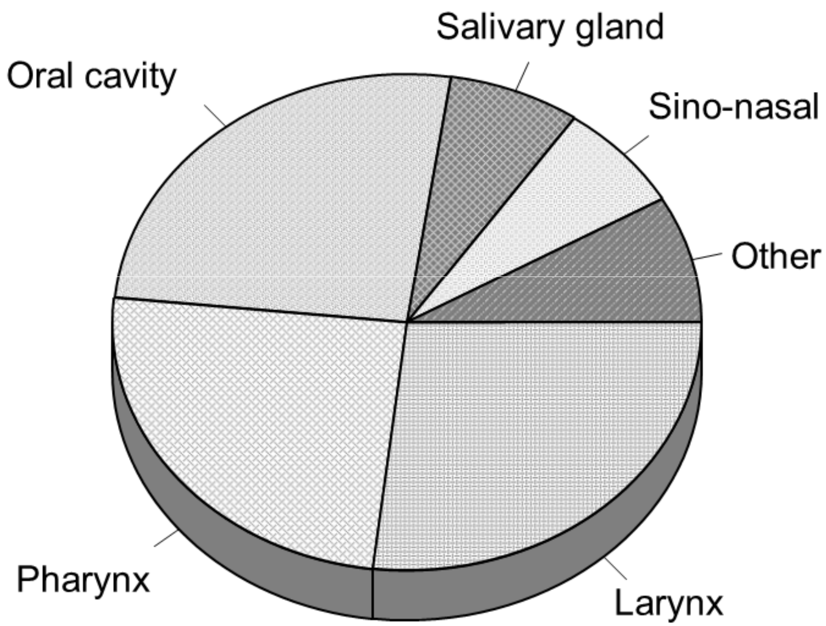
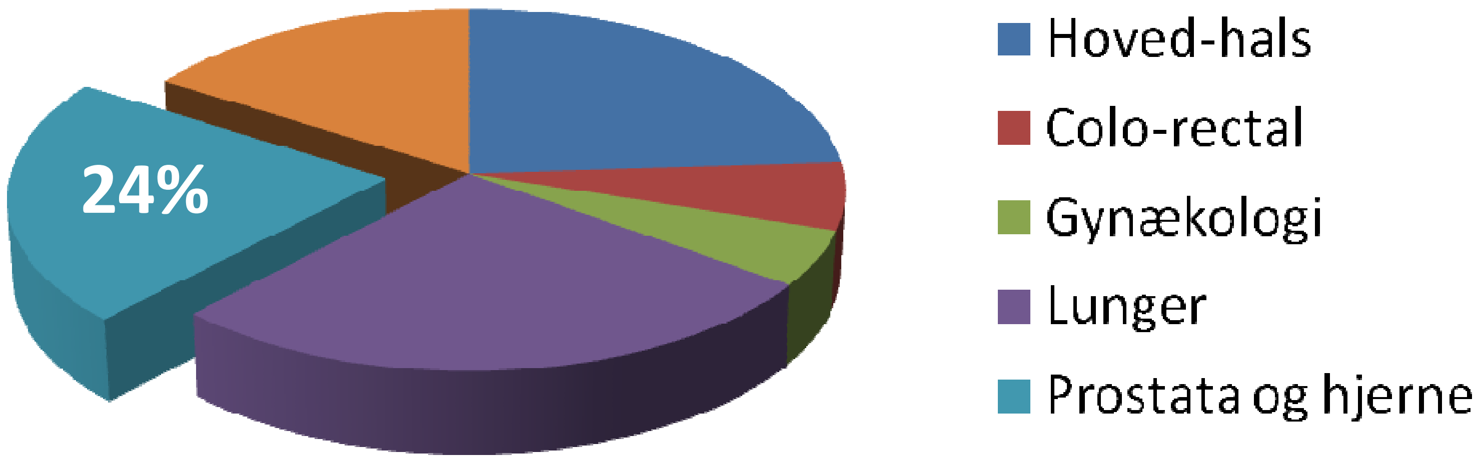


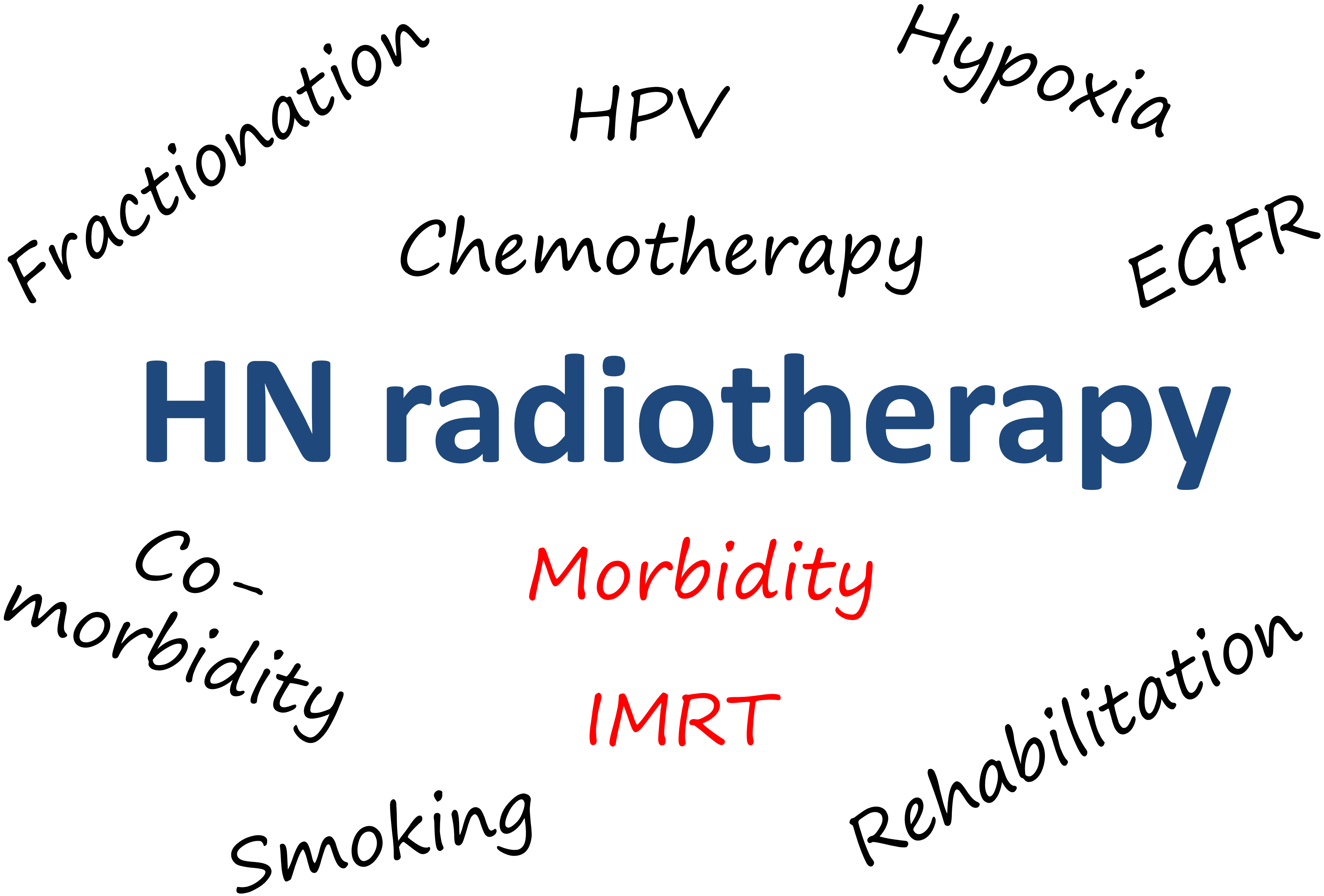
TABLE 3
Optimal Radiotherapy Utilization Rate by Cancer Type

Tumor type	Proportion of all cancers	Proportion of patients receiving radiotherapy	Patients receiving radiotherapy (% of all cancers)	Reference
Breast	0.13	83	10.8	Delaney et al.[12]
Lung	0.10	76	7.6	Delaney et al.[13]
Melanoma	0.11	23	2.5	Delaney et al.[14]
Prostate	0.12	60	7.2	Delaney et al.[16]
Gynecologic	0.05	35	1.8	Delaney et al.[18,19]
Colon	0.09	14	1.3	Delaney et al.[15]
Rectum	0.05	61	3.1	Delaney et al.[15]
Head and neck	0.04	78	3.1	Delaney et al.[17]
Gall bladder	0.01	13	0.1	Delaney et al.[15]
Liver	0.01	0	0.0	Delaney et al.[15]
Esophageal	0.01	80	0.8	Delaney et al.[15]
Stomach	0.02	68	1.4	Delaney et al.[15]
Pancreas	0.02	57	1.1	Delaney et al.[15]
Lymphoma	0.04	65	2.6	Featherstone et al.[20]
Leukemia	0.03	4	0.1	Featherstone et al.[21]
Myeloma	0.01	38	0.4	Featherstone et al.[21]
Central nervous system	0.02	92	1.8	Delaney et al.[22]
Renal	0.03	27	0.8	Delaney et al.[16]
Bladder	0.03	58	1.7	Delaney et al.[16]
Testis	0.01	49	0.5	Delaney et al.[16]
Thyroid	0.01	10	0.1	Delaney et al.[22]
Unknown primary	0.04	61	2.4	Delaney et al.[22]
Other	0.02	50	1.0	See citations in text
Total	1.00	-	52.3	

Odense 2014 - i alt 36.951 fraktioner

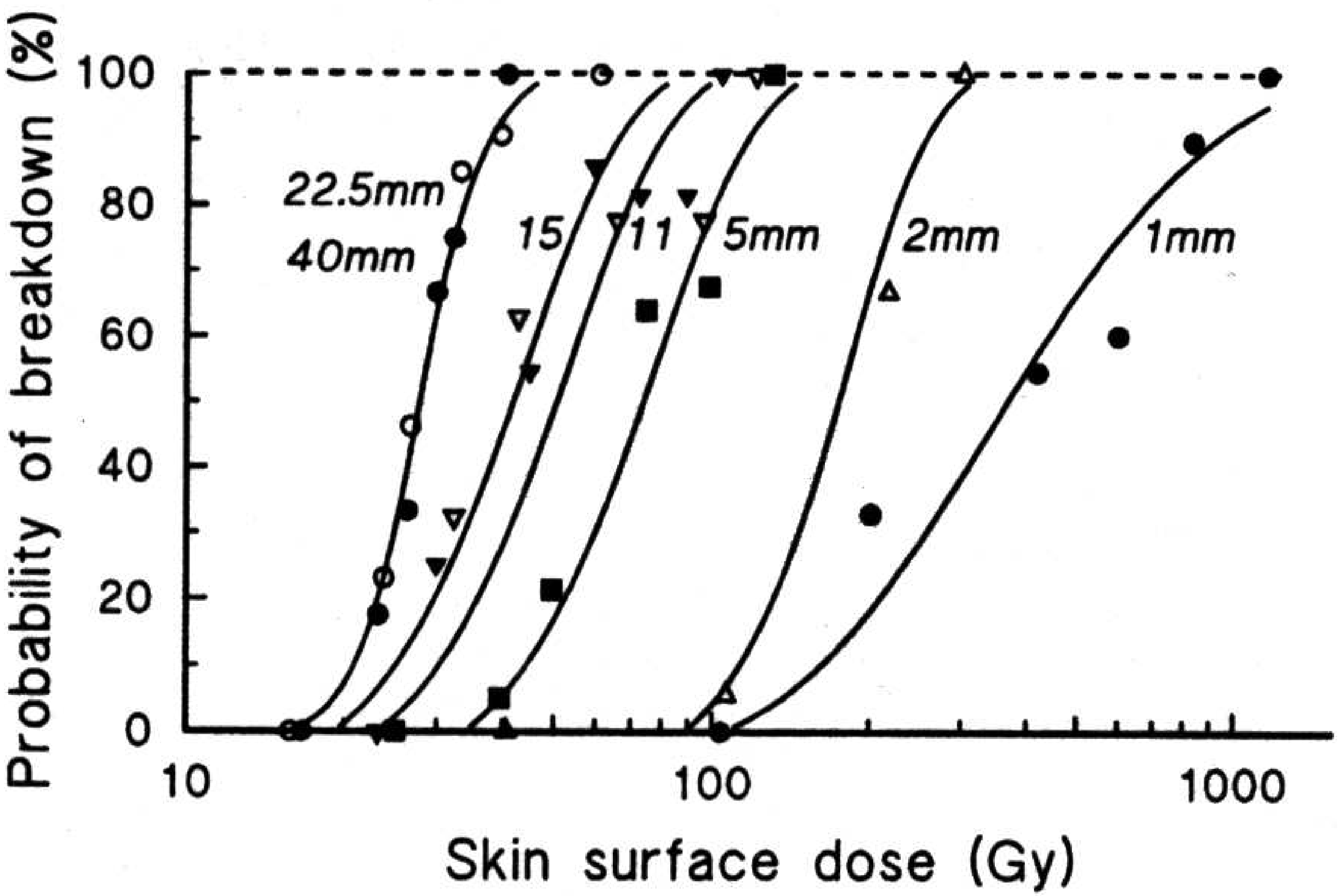



Fractionation
HPV
Hypoxia
Chemotherapy
EGFR
HN radiotherapy
Co-morbidity
Morbidity
IMRT
Smoking
Rehabilitation

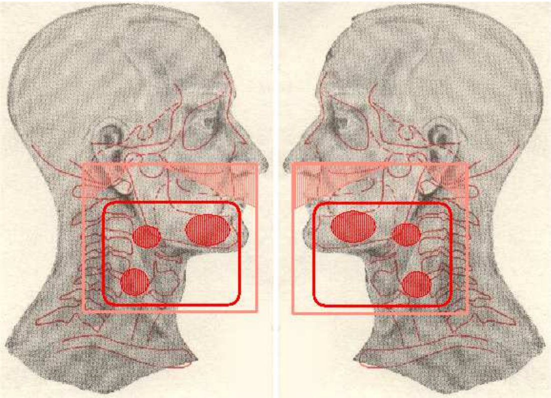

Fractionation
HPV
Hypoxia
Chemotherapy
EGFR
HN radiotherapy
Co-morbidity
Morbidity
IMRT
Smoking
Rehabilitation

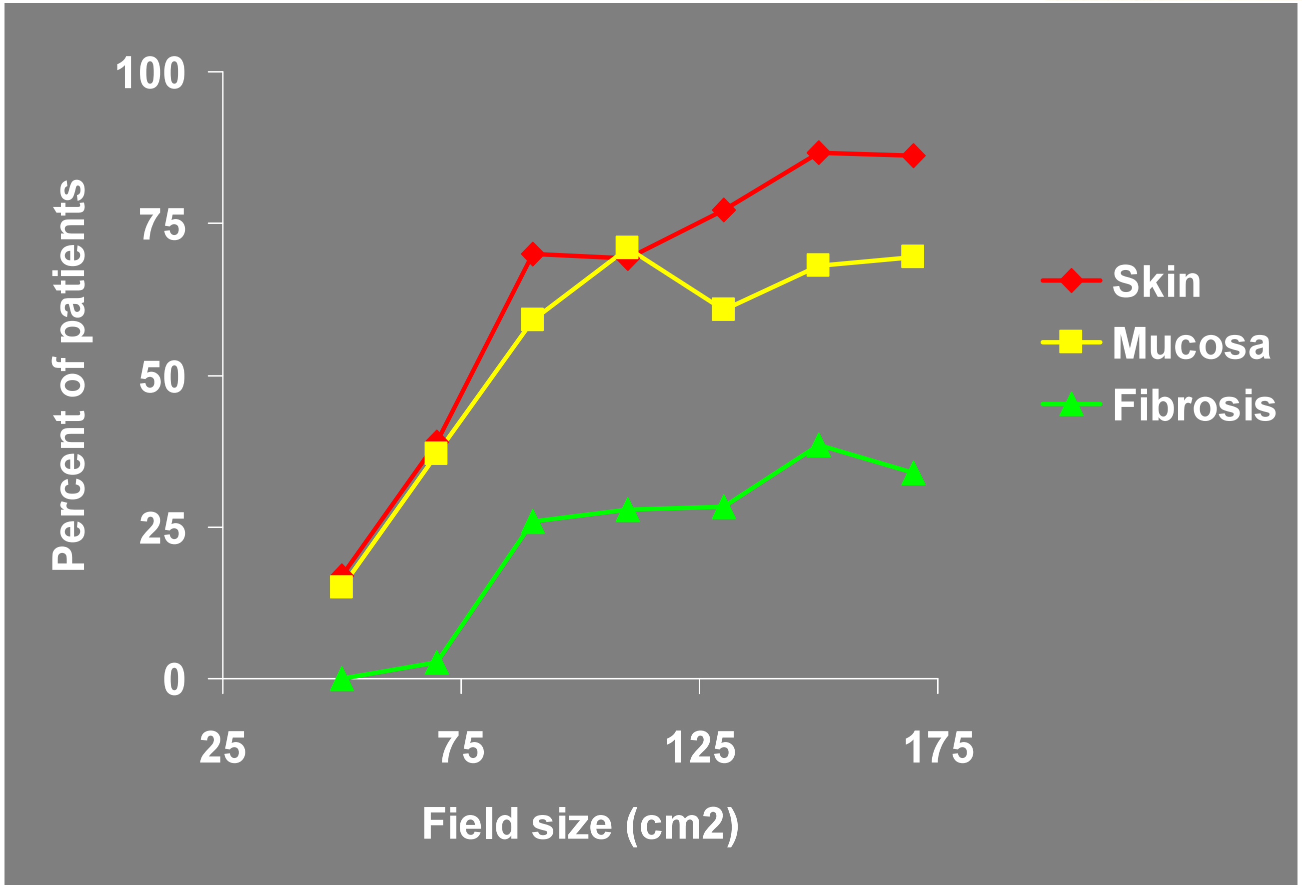
Volume effect

Dose-volume-effect



Volume and morbidity in HN radiotherapy



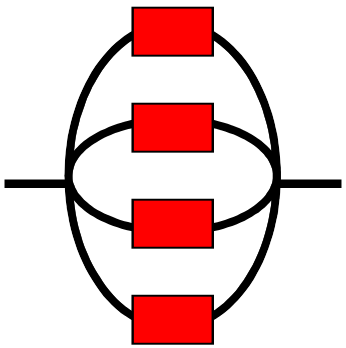


Data from IAEA MMC trial

Parallel vs. serial organization af tissues

Serial

Spinal cord
Brain stem
Optic nerves
Chiasm
Inner ear



Parallel

Salivary glands
T-M joints
Oral cavity
Swallowing structures?

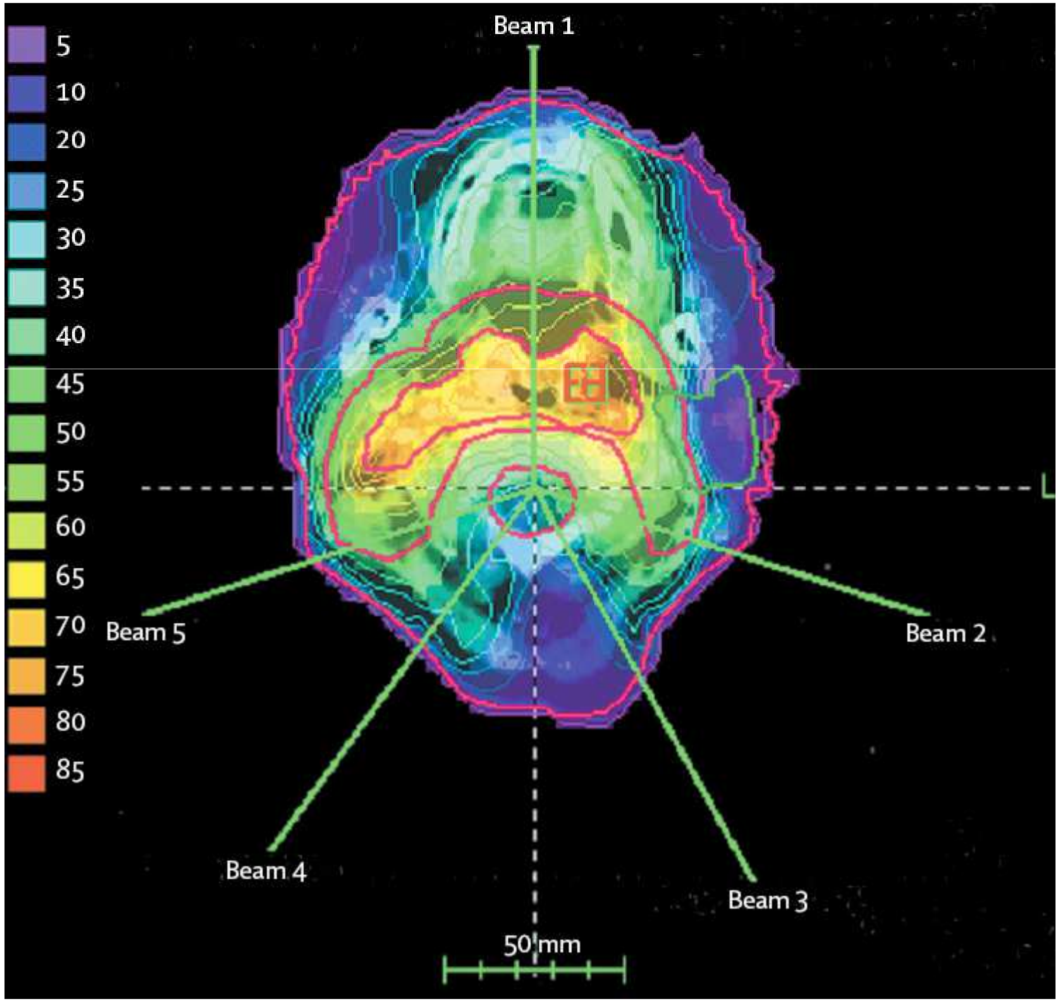
Volume effect

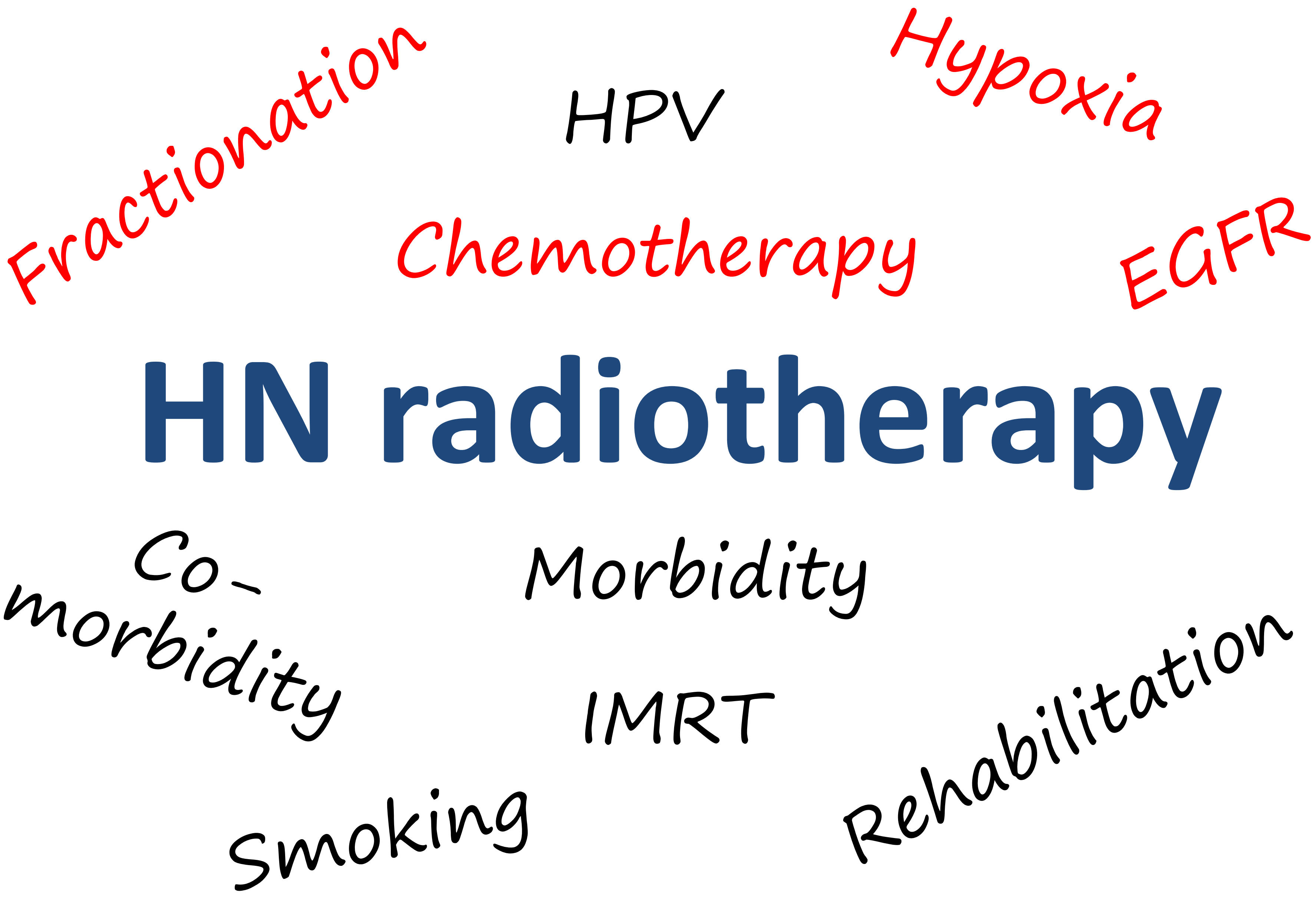
Normal tissue tolerance

- **<u>Serial tissue: Dose constraints</u>**
  - Tolerance is not related to the irradiated volume
  - Max dose
  - E.g. ’max 50 Gy to spinal cord’ ’max 54 Gy to optic chiasm’

- **<u>Parallel tissue: Dose volume constraints</u>**
  - Tolerance is dependent on the irradiated volume
  - DVH constraints
  - E.g. ’mean dose below 30 Gy to oral cavity’, ’mean dose below 26 Gy to parotids’, ’2/3 of larynx below 50 Gy’

Intensity Modulated RT (IMRT)




Fractionation
HPV
Hypoxia
Chemotherapy
EGFR
HN radiotherapy
Co-morbidity
Morbidity
IMRT
Smoking
Rehabilitation

Radiotherapy intensifiers

- 20.000+ pre-clinical studies
- 2.000+ phase I-II trials
- 200+ randomized trials
- 20+ metaanalyses

- In less than 45 minutes…

Therapeutic ratio

Effect

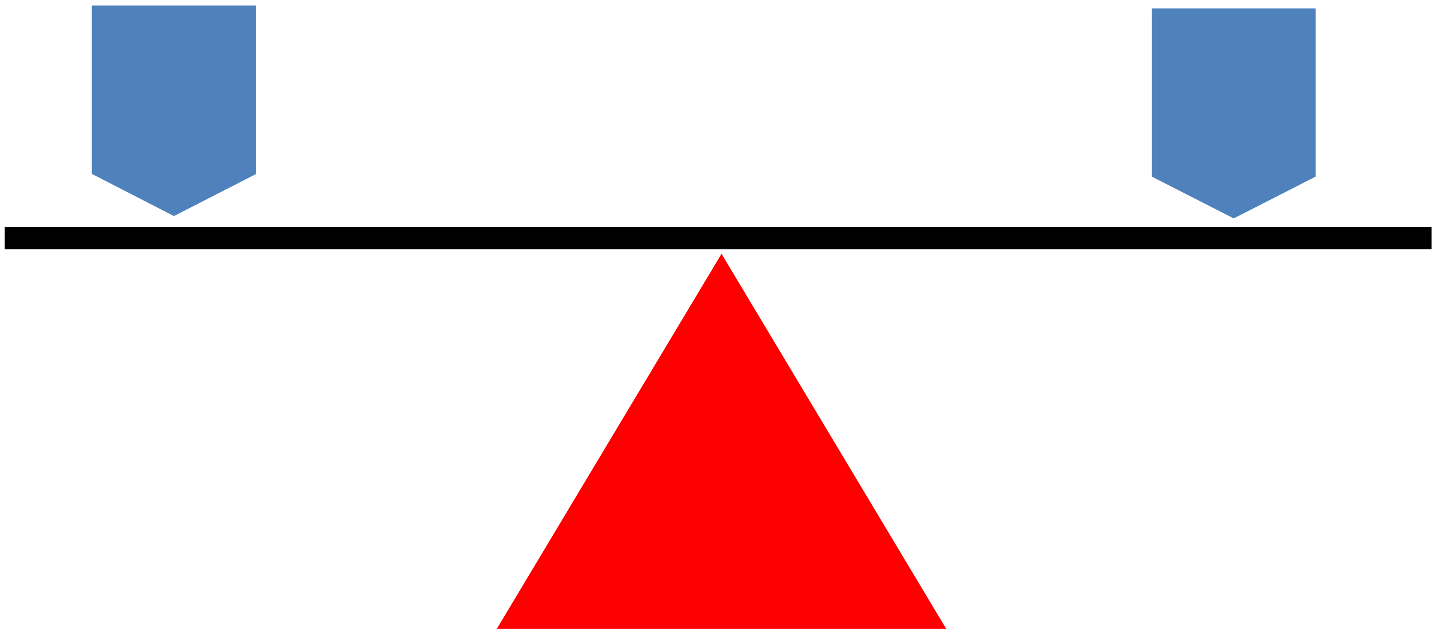
Tumor control

Survival

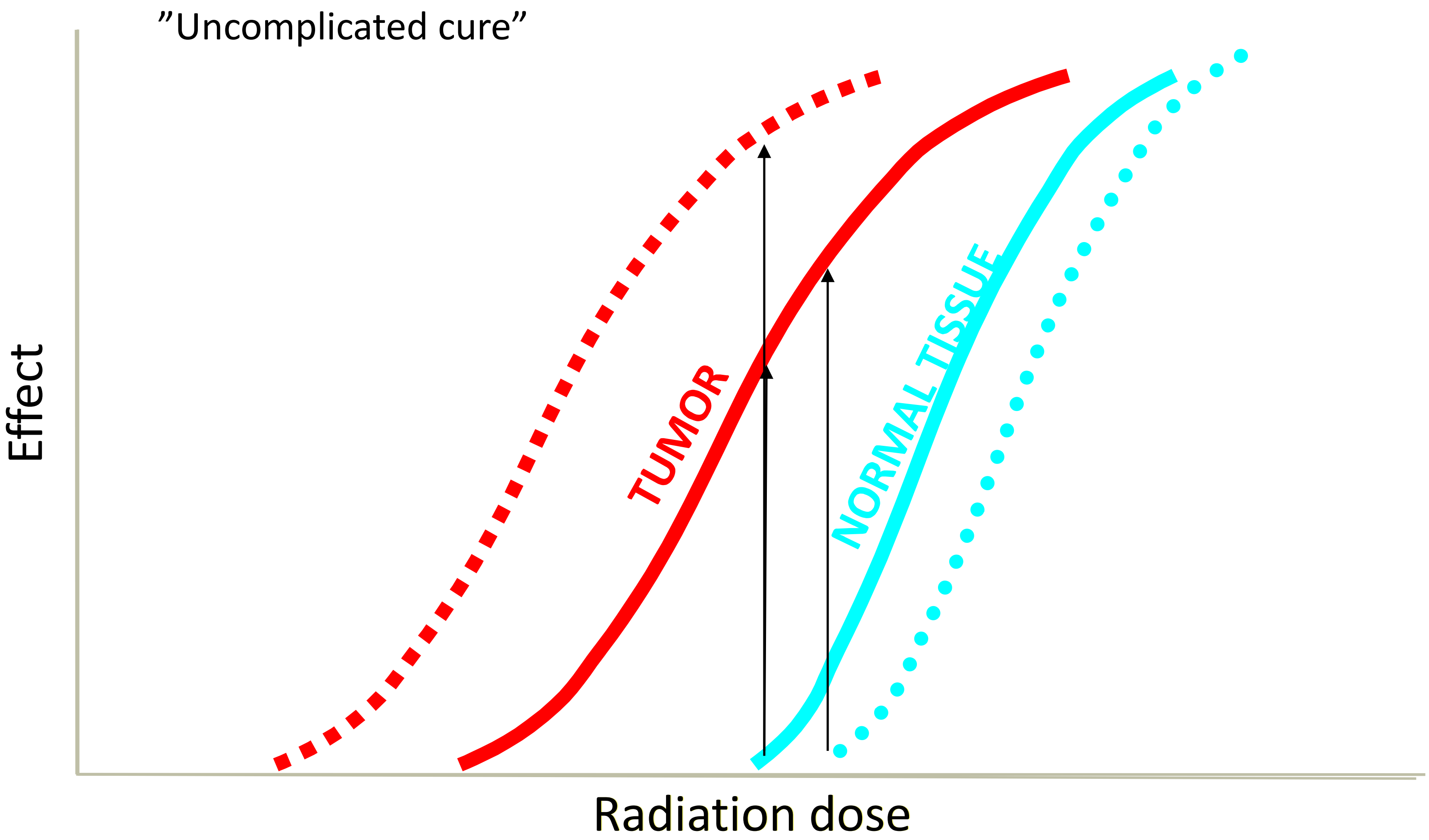
Side effect

Acute

Late



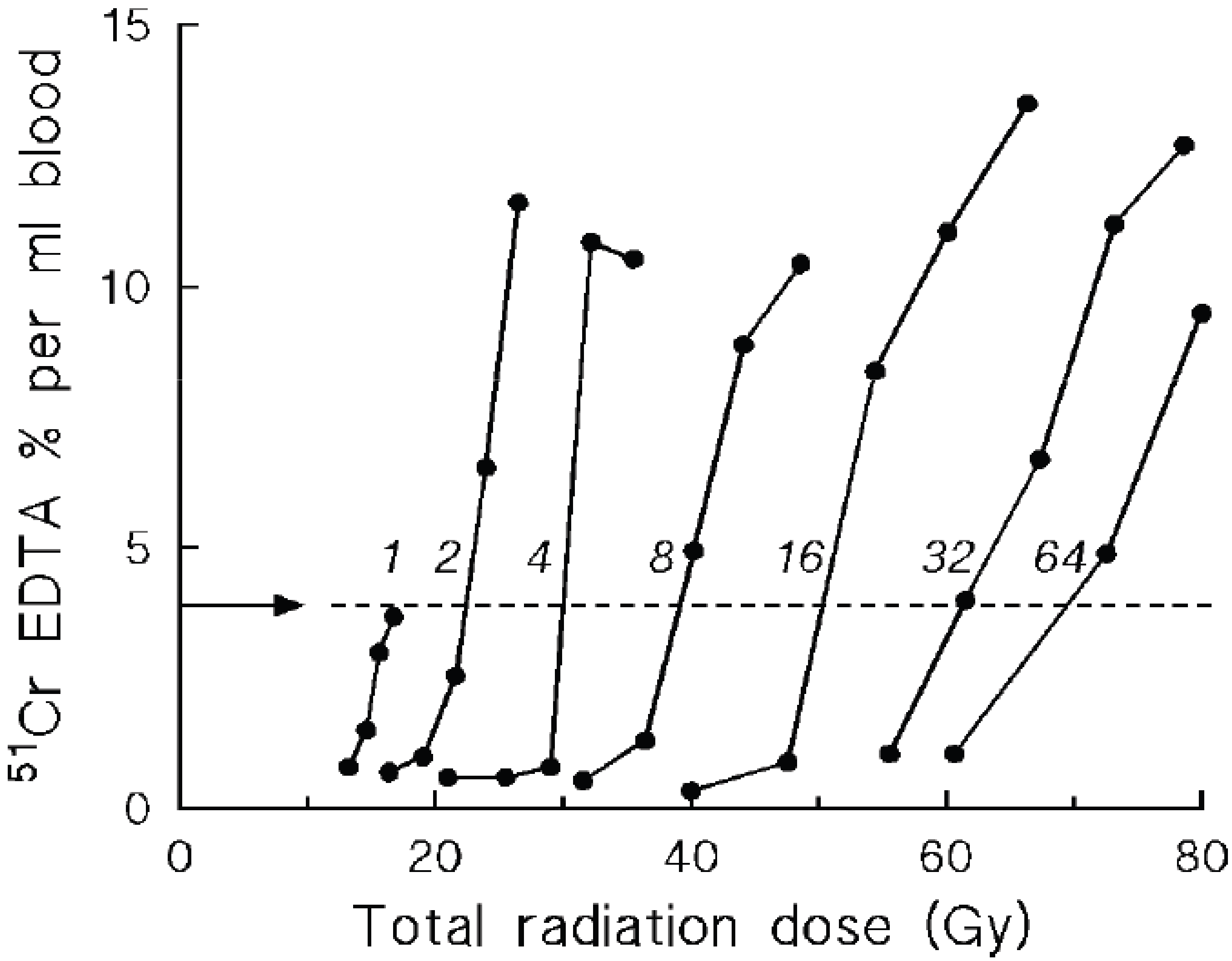
Therapeutic ratio



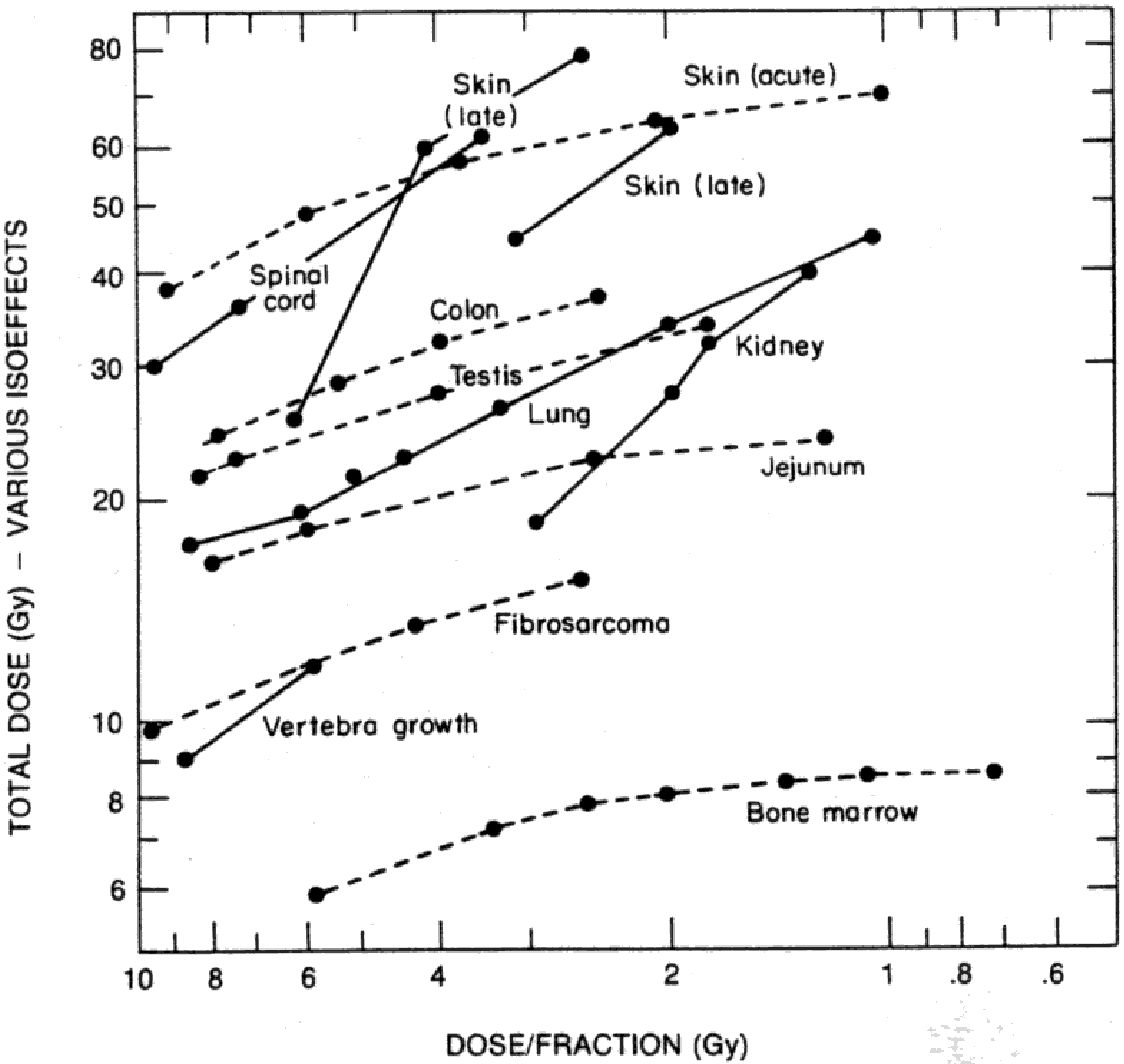
cg/02

Fractionation

Fractionation and iso-effect



Fractionation sensitivity - The spaghetti plot



H.R. Withers Cancer 55: 2086, 1985

Fractionation sensitivity

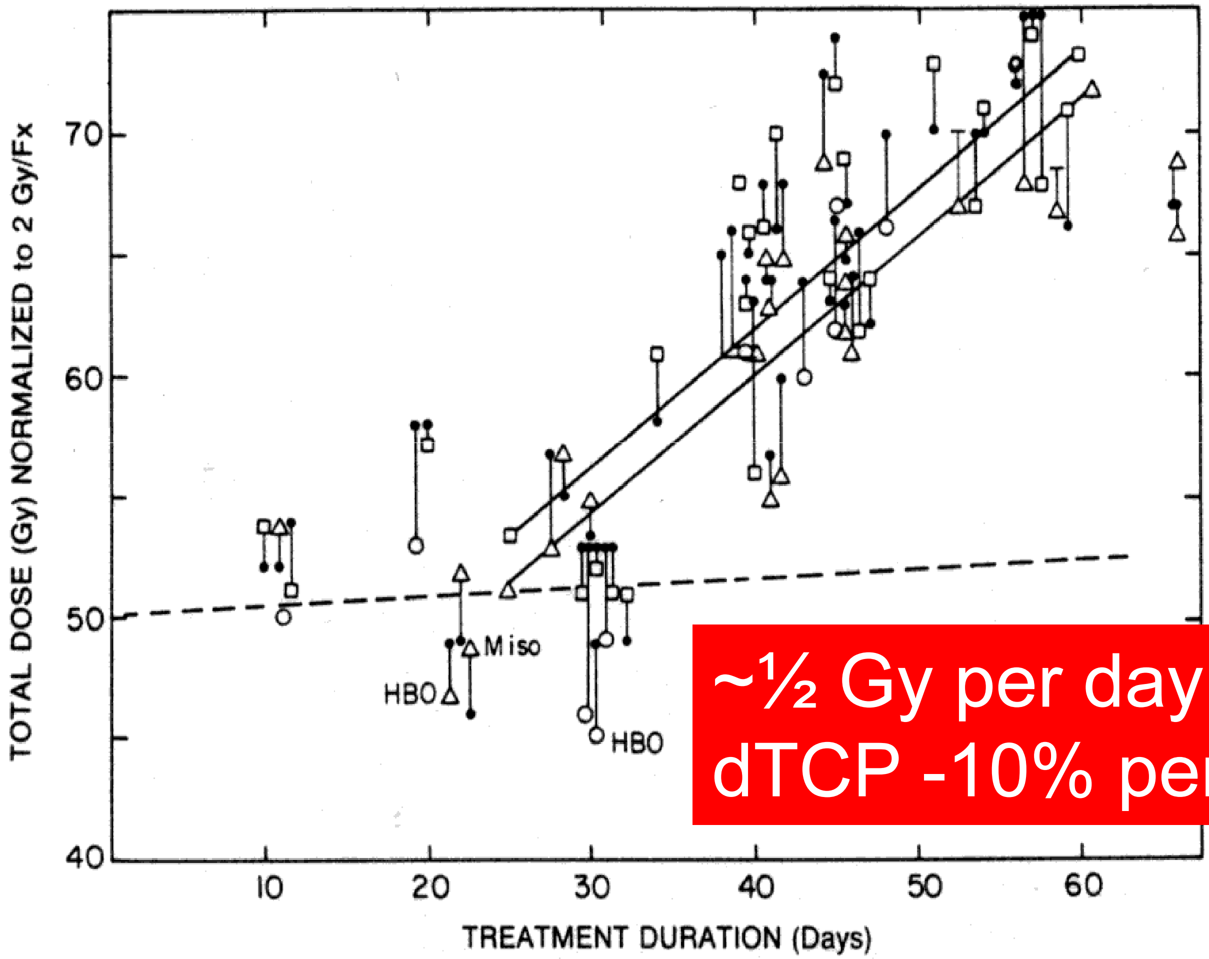
Early reacting normal tissues

- Low fractionation sensitivity
- Small increase in tolerance with decreasing dose per fraction
- High alpha-beta (8-30 Gy)
- Time factor (repopulation)

Late reacting normal tissues

- High fractionation sensitivity
- Large increase in tolerance with decreasing dose per fraction
- Low alpha-beta (2-4 Gy)
- No time factor

ACCELERATED REPOPULATION



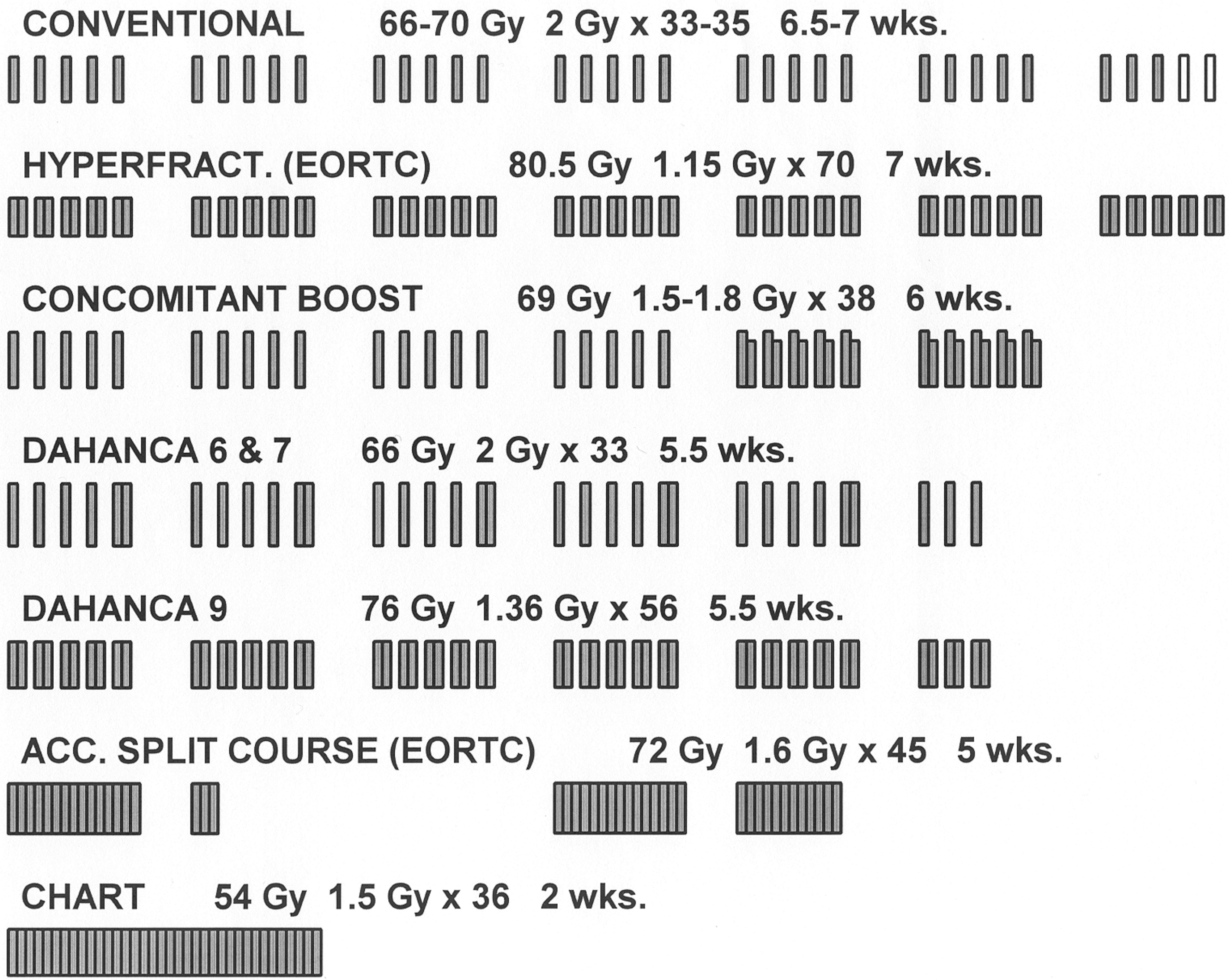
~½ Gy per day
dTCP -10% per week

Withers et al. Acta Oncologica 1988

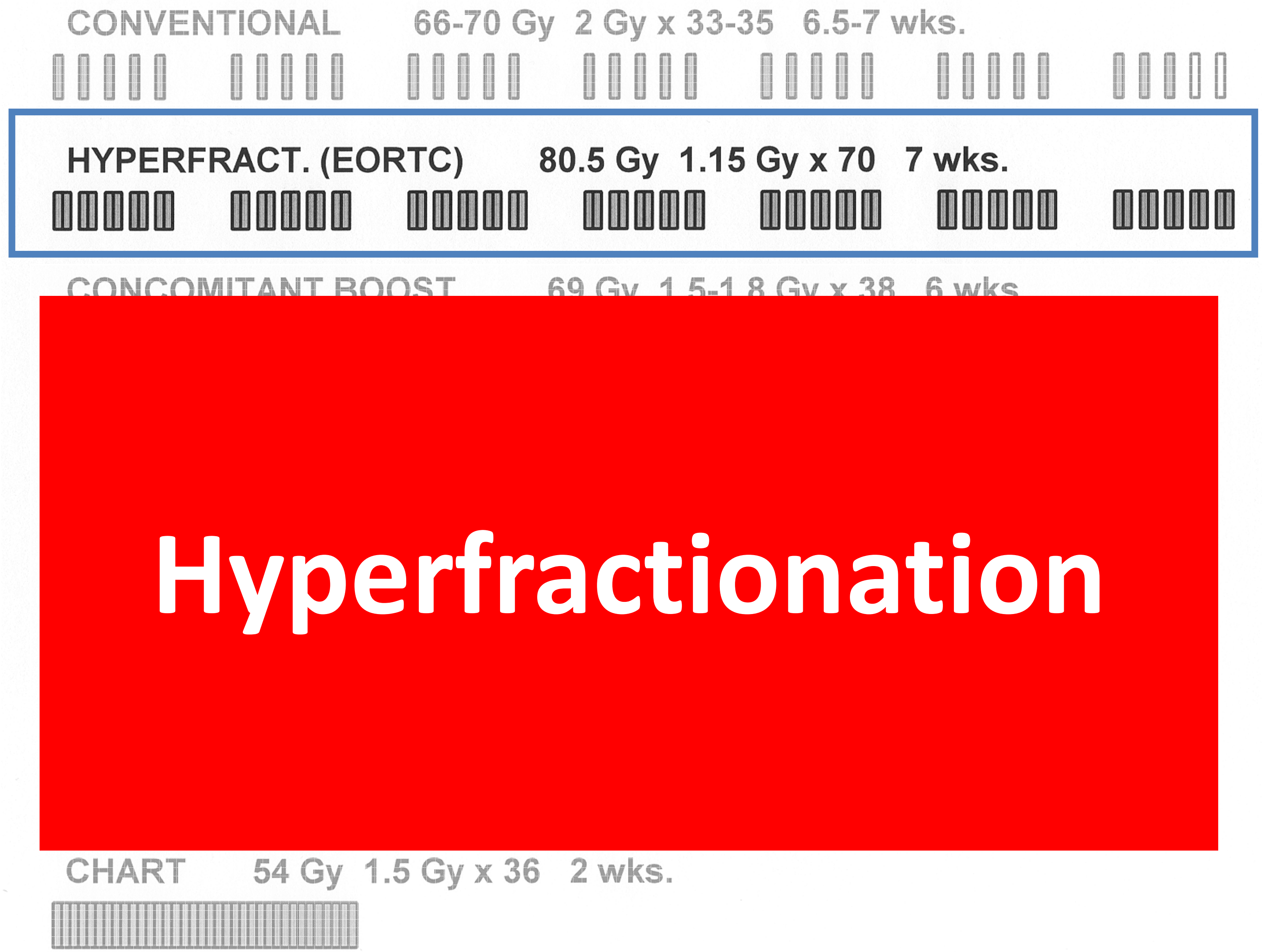
Fractionation principles

- **Conventional fractionation**: Dose per fraction 1.8-2.0 Gy, 5 fx/wk
- **Hyperfrationation**: Dose per fraction <1.8 Gy
- **Hypofractionation**: Dose per fraction >2.0 Gy
- **Split-course**: A treatment break (weeks), resulting in prolonged overall treatment time
- **Accelerated fractionation**: Reduced overall treatment time

Fractionation studies in head and neck cancer



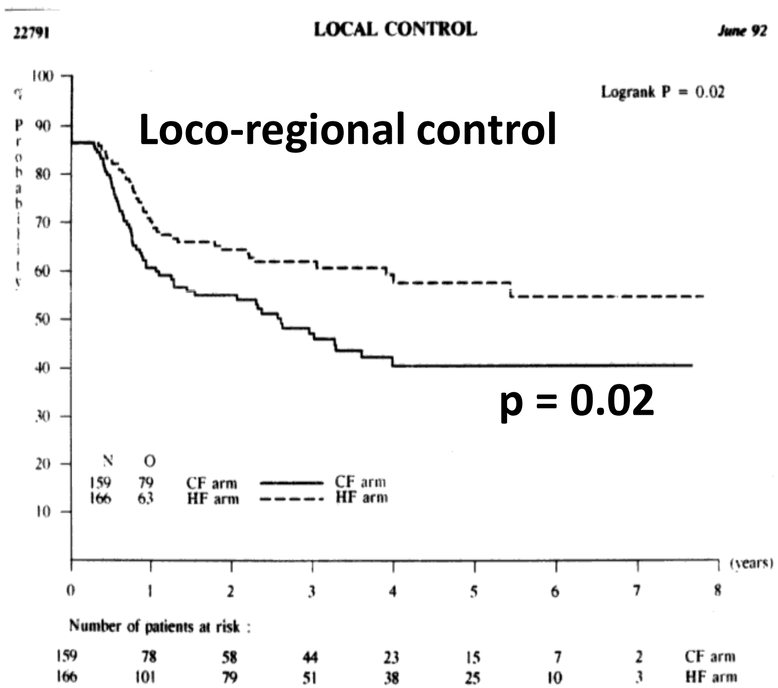
Fractionation studies in head and neck cancer

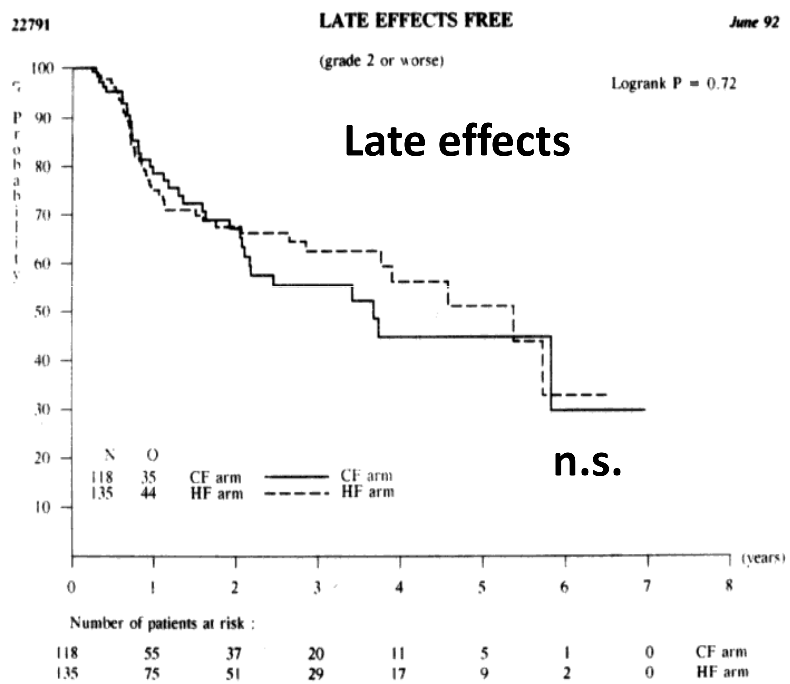


EORTC 22791

Hyperfractionation

356 pts. T2-T3 N0-N1 oropharynx



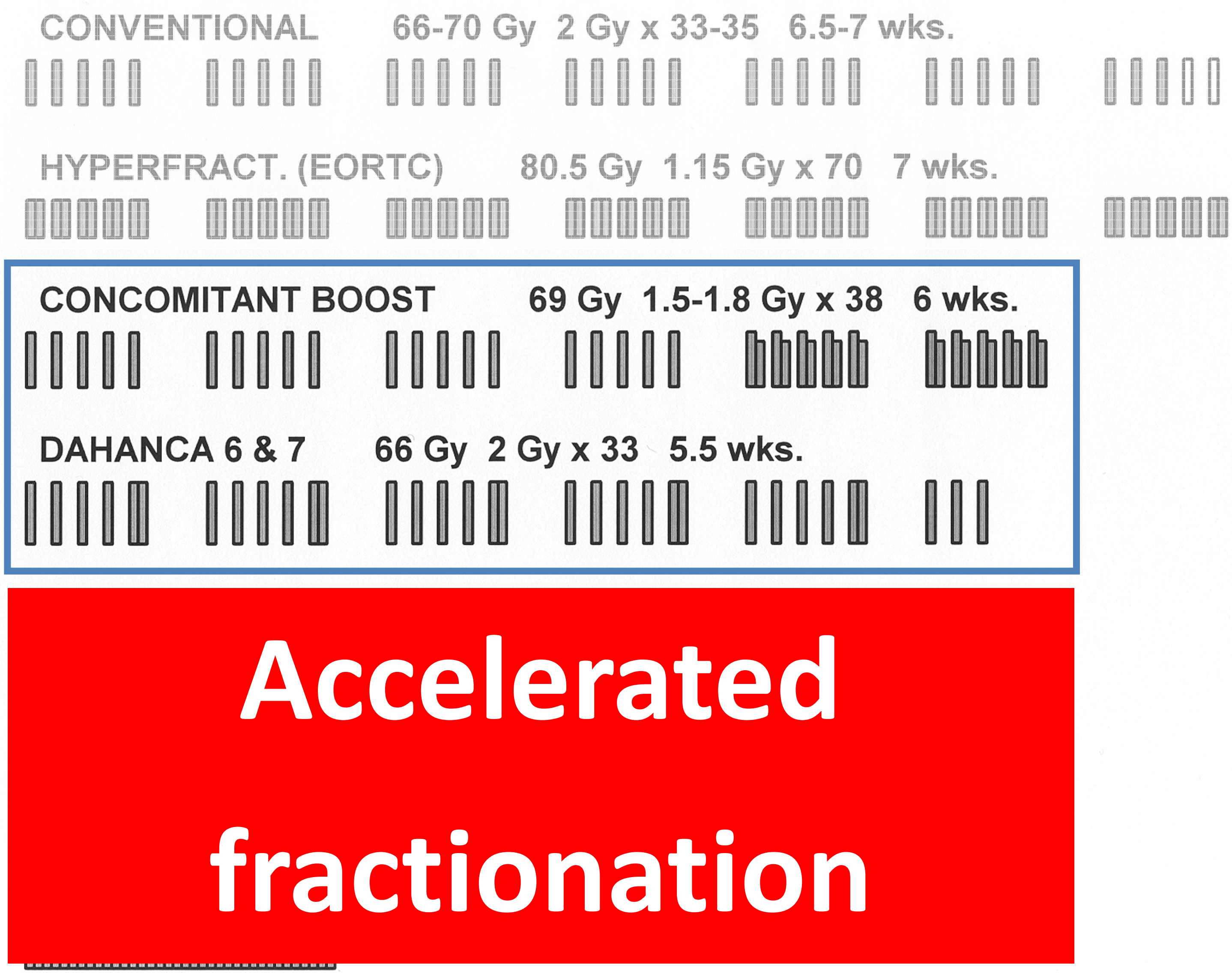


Improved Terapeutic Ratio:

Increase in tumor control with same late morbidity

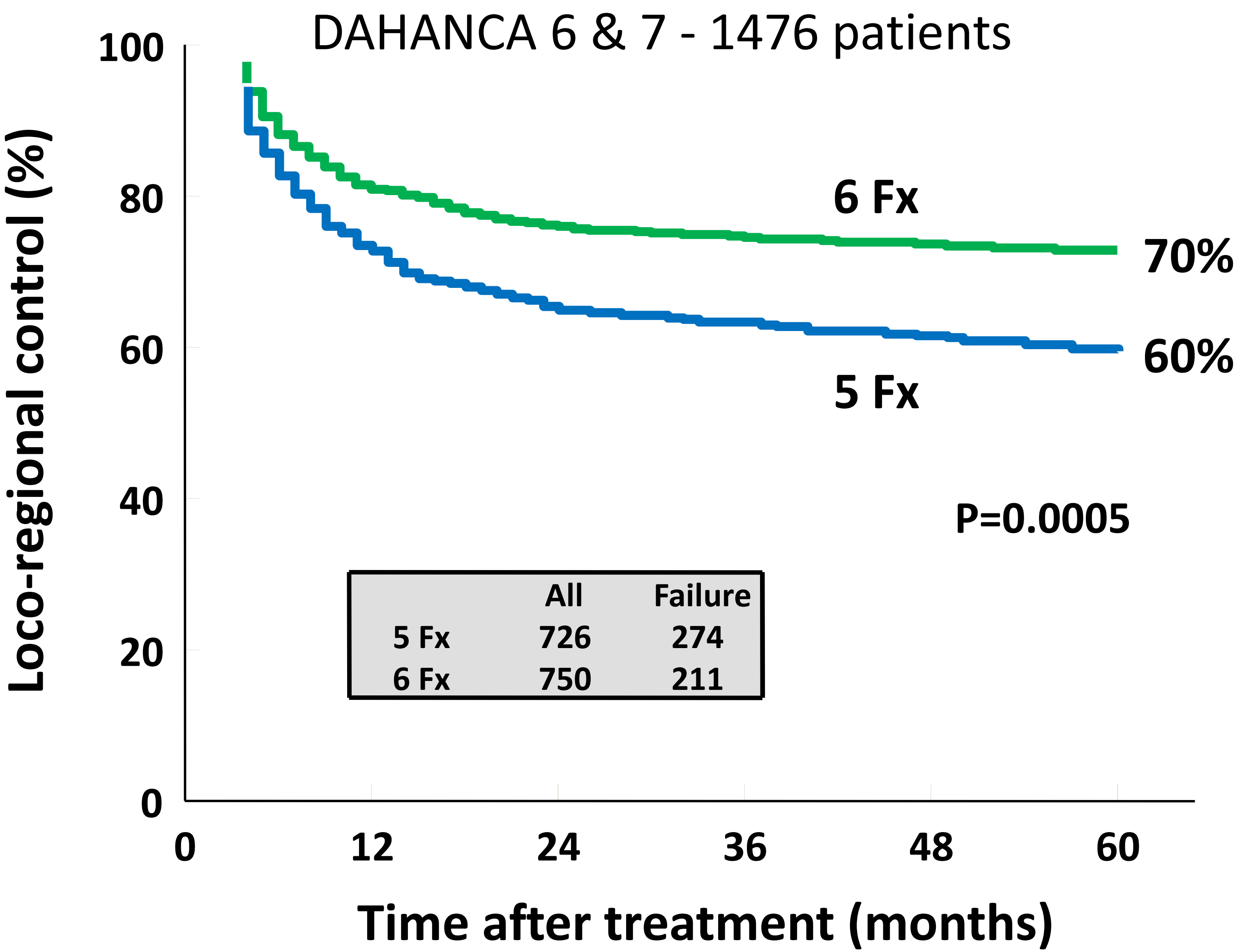
Horiot et al. Radiother. Oncol. 1992

Fractionation studies in head and neck cancer



Accelerated fractionation

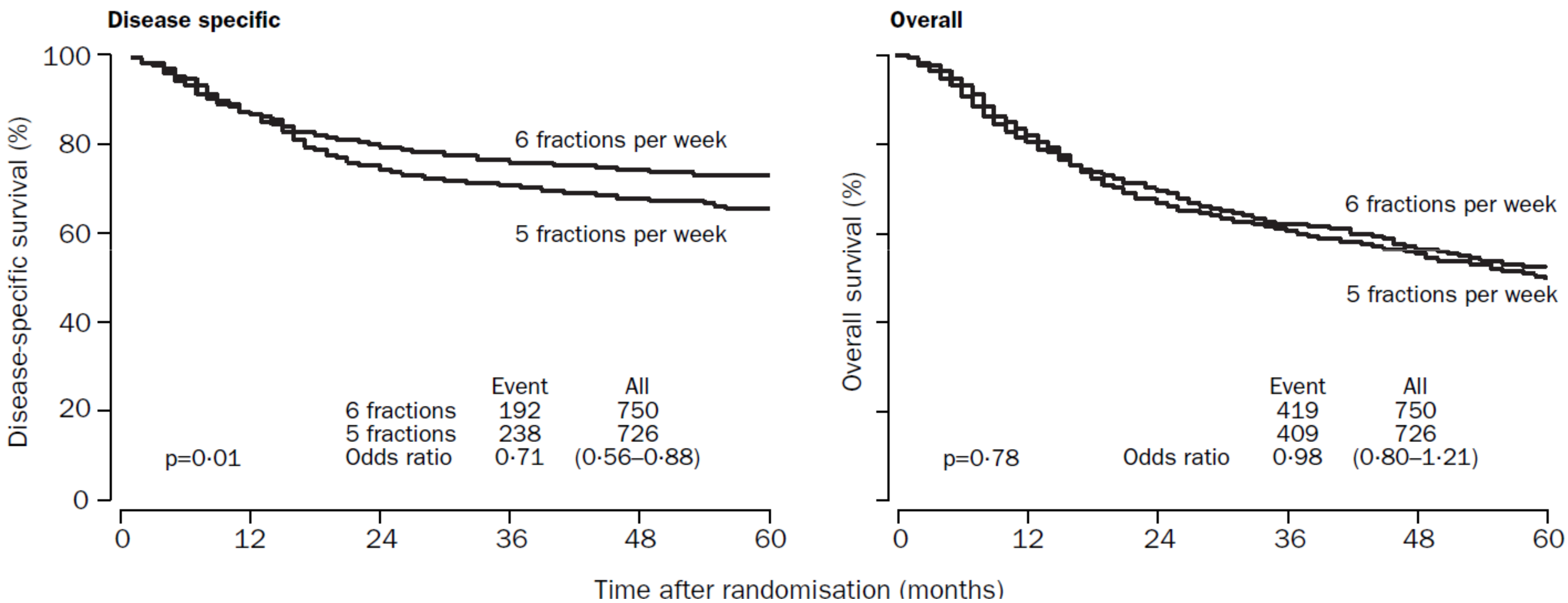
Loco-regional control – acc. RT



Overgaard *et al.* Lancet 2003

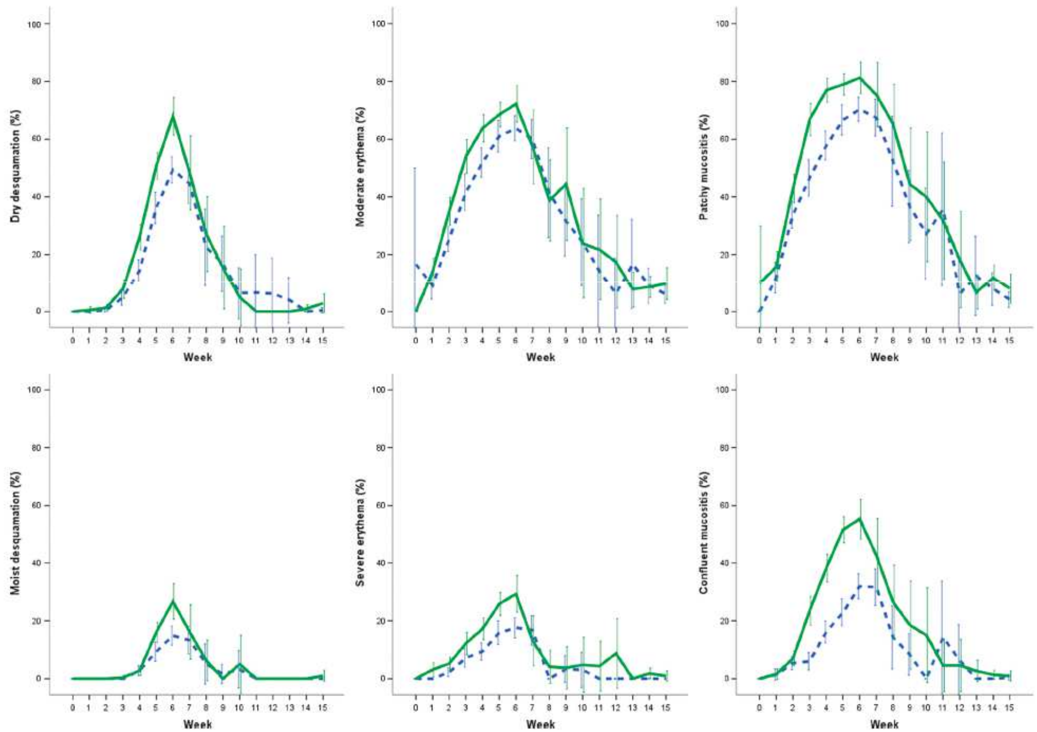
DAHANCA 6&7

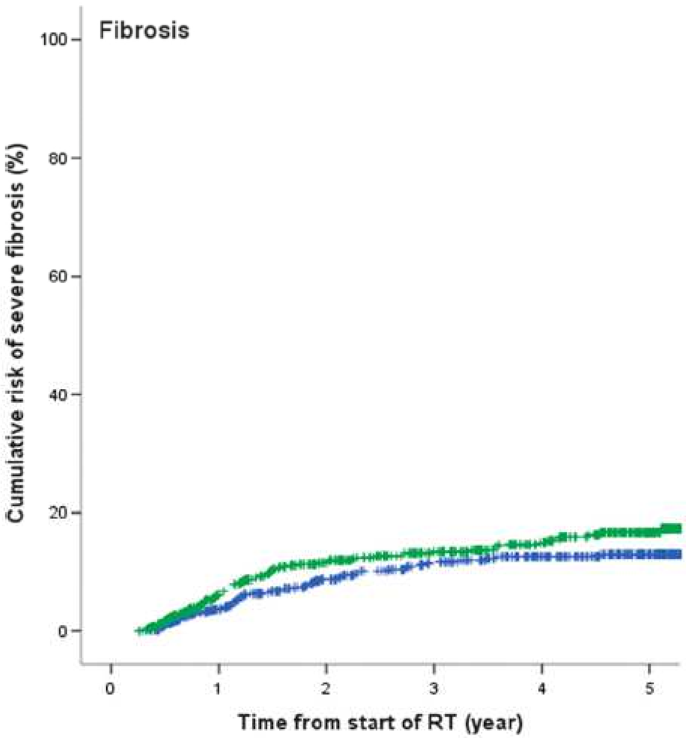
Survival



Overgaard *et al.* Lancet 2003

Morbidity – acc. radiotherapy DAHANCA 6 & 7

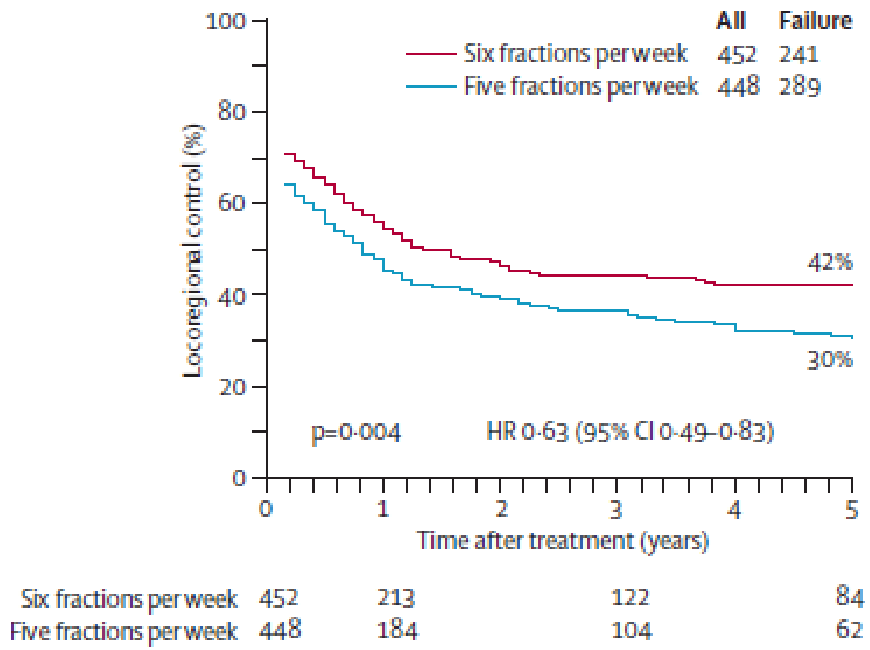


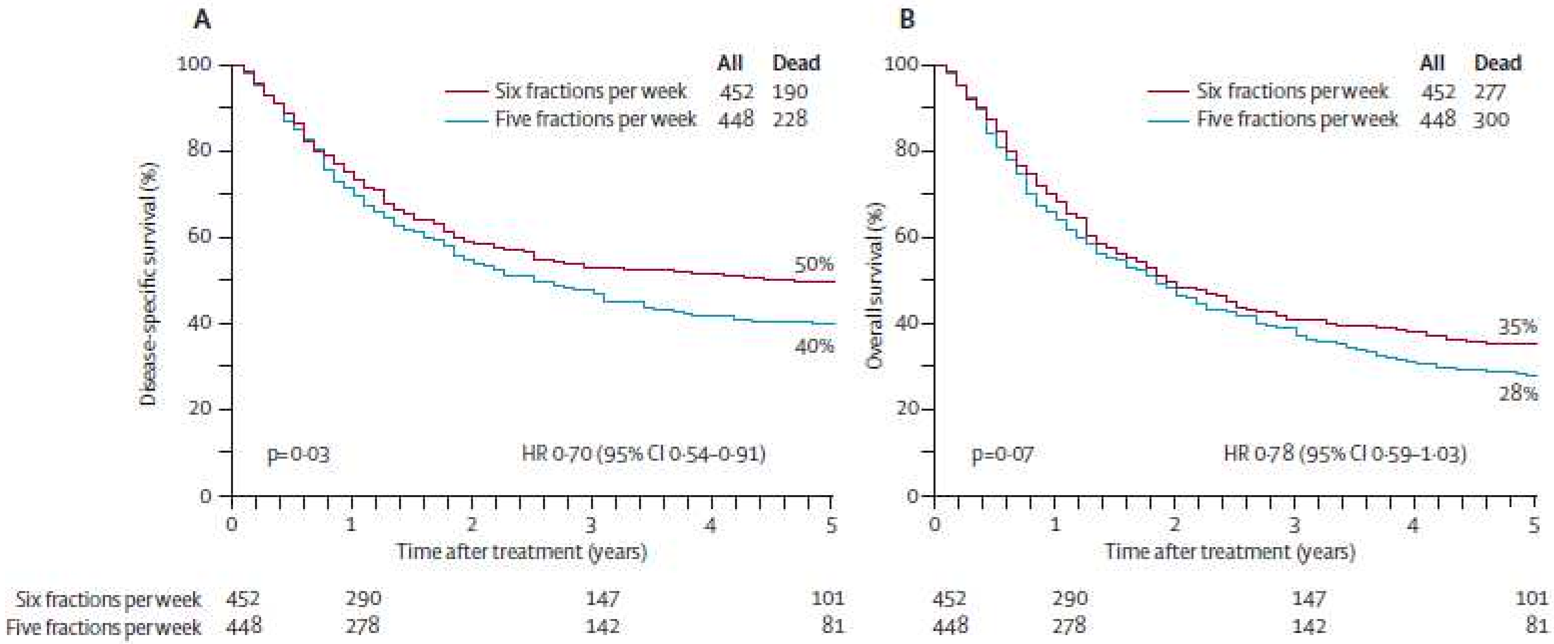


Mortensen et al, Radiother Oncol, 2012

IAEA-ACC study

	Five fractions per week (N=448)	Six fractions per week (N=452)
Recruiting centre		
New Delhi	126 (28%)	128 (28%)
Peshawar	104 (23%)	105 (23%)
Islamabad	70 (16%)	69 (15%)
Mumbai	64 (14%)	63 (14%)
Tallinn	53 (12%)	53 (12%)
Santiago	14 (3%)	12 (3%)
Riyadh	9 (2%)	10 (2%)
Cape Town	6 (1%)	10 (2%)
Beirut	2 (1%)	2 (1%)





Lancet Oncol 2010; 11: 553–60

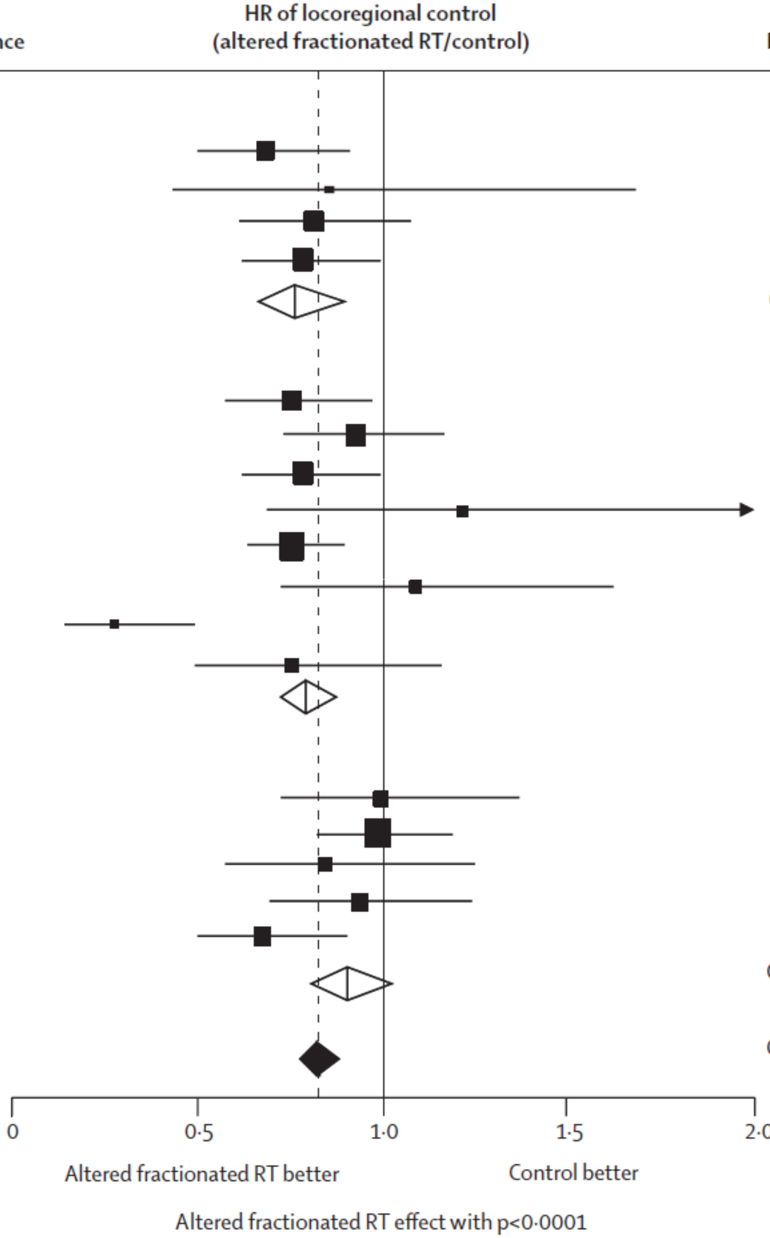
Lancet 2006; 368: 843–54

Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis

Jean Bourhis, Jens Overgaard, Hélène Audry, Kian K Ang, Michele Saunders, Jacques Bernier, Jean-Claude Horiot, Aurélie Le Maître, Thomas F Pajak, Michael G Poulsen, Brian O'Sullivan, Werner Dobrowsky, Andrzej Hliniak, Krzysztof Skladowski, John H Hay, Luiz H J Pinto, Carlo Fallai, Karen K Fu, Richard Sylvester, Jean-Pierre Pignon, on behalf of the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group*

Loco-regional control

	Number events/number entered				
	Altered fractionated RT	Control	O–E	Variance	HR (95% CI)
A Hyperfractionation					
EORT C22791[3]	78/180	99/176	−17·0	43·8	
RIO[4]	18/52	16/51	−1·4	8·2	
PMH Toronto[5]	91/172	101/164	−10·3	47·8	
RTOG 9003 HF[6]	123/276	147/279	−16·6	67·3	
Subtotal	310/680	363/670	−45·3	167·1	0·76 (0·66–0·89)
B Accelerated fractionation without total dose reduction					
EORTC 22851[7]	97/257	122/255	−16·0	54·6	
RTOG 9003 S[6]	143/281	147/279	−6·1	72·4	
RTOG 9003 B[6]	121/277	147/279	−16·4	66·9	
BCCA 9113[8]	25/41	21/41	−2·2	11·5	
DA HANCA[9]	230/755	292/730	−37·6	130·4	
Oro 9301[10]	47/65	47/63	−1·9	23·3	
CAIR[11]	13/51	31/49	−13·3	10·0	
KBN PO 79[12]	36/196	49/199	−6·1	21·2	
Subtotal	712/1923	856/1895	−91·5	390·3	0·79 (0·72–0·87)
C Accelerated fractionation with total dose reduction					
RTOG 7913[13]	77/106	74/104	−0·6	37·6	
CHART[14]	295/552	196/366	−1·8	117·4	
Vienna[15]	49/78	57/81	−4·6	26·4	
TROG 9101[16]	87/174	94/176	−3·3	45·2	
GORTEC 9402[17]	80/137	101/131	−17·9	44·6	
Subtotal	588/1047	522/858	−28·2	271·3	0·90 (0·80–1·02)
Total	1610/3650	1741/3423	−165·0	828·7	0·82 (0·77–0·88)

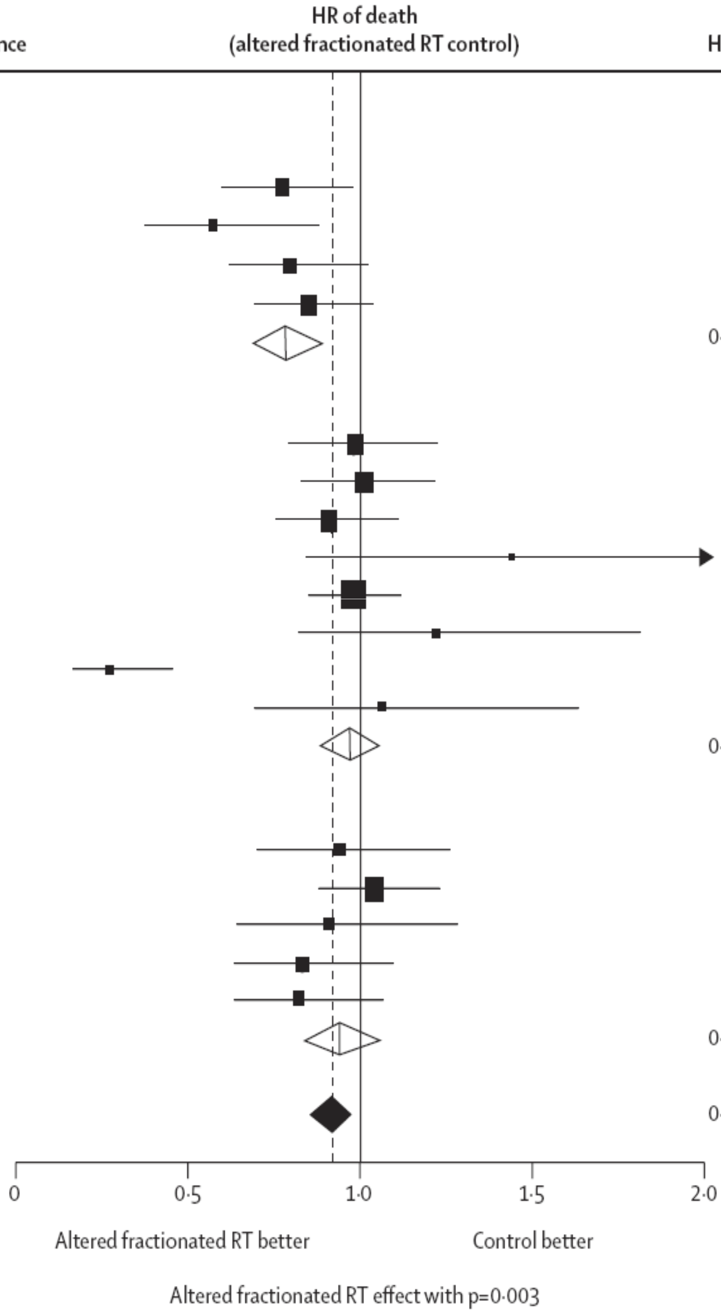


χ^2 test for heterogeneity p=0·03
χ^2 test for interaction p=0·15
I^2=44%

Lancet 2006; 368: 843–54

Survival

	Number events/number entered: Altered fractionated RT	Control	O–E	Variance	HR (95% CI)
A Hyperfractionation					
EORT C22791[3]	126/180	135/176	–17·2	64·2	
RIO[4]	41/52	47/51	–11·5	20·6	
PMH Toronto[5]	119/172	124/164	–13·8	59·6	
RTOG 9003 HF[6]	184/276	201/279	–15·9	95·9	
Subtotal	470/680	507/670	–58·4	240·4	0·78 (0·69–0·89)
B Accelerated fractionation without total dose reduction					
EORTC 22851[7]	171/257	164/255	–1·3	83·3	
RTOG 9003 S[6]	205/281	201/279	1·2	101·5	
RTOG 9003 B[6]	190/277	201/279	–9·0	97·6	
BCCA 9113[8]	30/41	23/41	4·8	13·1	
DA HANCA[9]	422/755	413/730	–5·0	208·6	
Oro 9301[10]	51/65	48/63	4·8	24·4	
CAIR[11]	19/51	37/49	–16·5	12·6	
KBN PO 79[12]	42/196	41/199	1·3	20·7	
Subtotal	1130/1923	1128/1895	–19·9	561·8	0·97 (0·89–1·05)
C Accelerated fractionation with total dose reduction					
RTOG 7913[13]	91/106	87/104	–2·9	44·1	
CHART[14]	359/552	227/366	5·7	140·2	
Vienna[15]	62/78	66/81	–3·1	31·9	
TROG 9101[16]	96/174	109/176	–9·4	51·1	
GORTEC 9402[17]	105/137	111/131	–10·5	53·4	
Subtotal	713/1047	600/858	–20·2	320·6	0·94 (0·84–1·05)
Total	2313/3650	2235/3423	–98·5	1122·9	0·92 (0·86–0·97)



χ^2 test for heterogeneity p=0·001

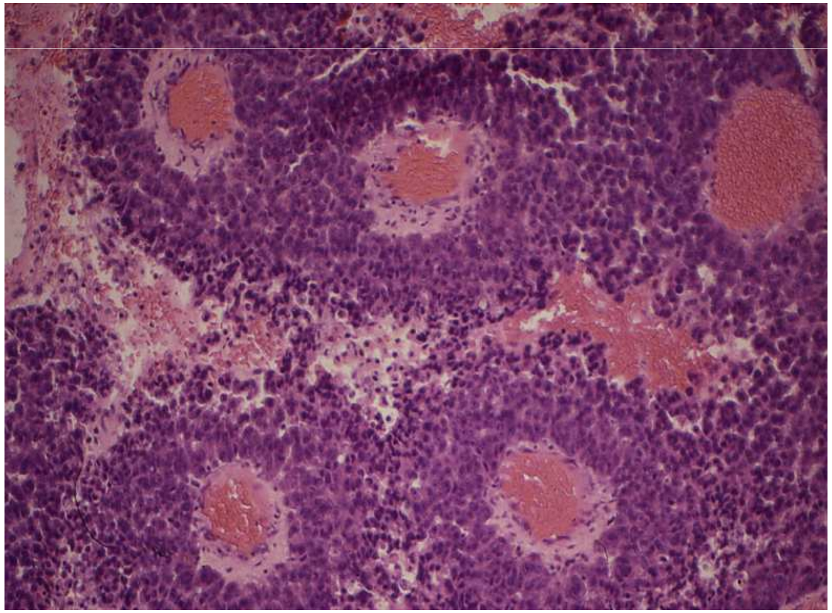
χ^2 test for interaction p=0·02

Lancet 2006; 368: 843–54

Conclusion - fractionation

- Awareness of the fractionation sensitivity of tumors and normal tissues is critical
- Clinical studies and meta-analysis have shown that moderately accelerated radiotherapy improves loco-regional control
- Hyperfractionated RT improves loco-regional control and survival
- Altered fractionation is thus recommended for primary radiotherapy of head and neck cancer

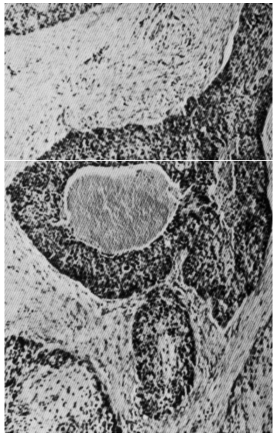
Hypoxia

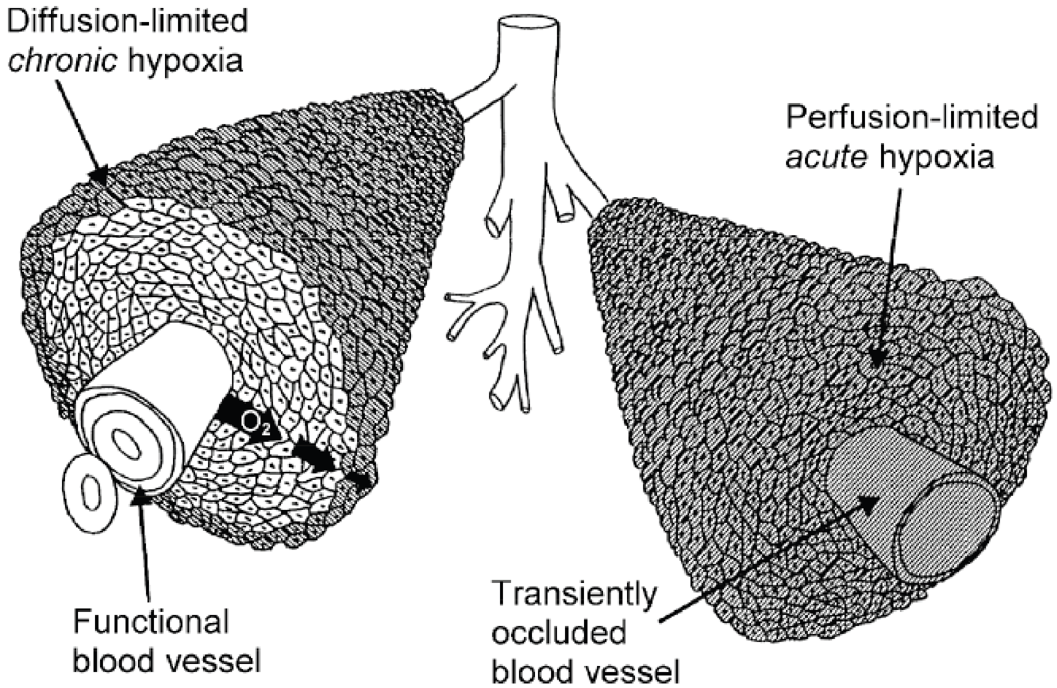


Hypoxia in human tumors

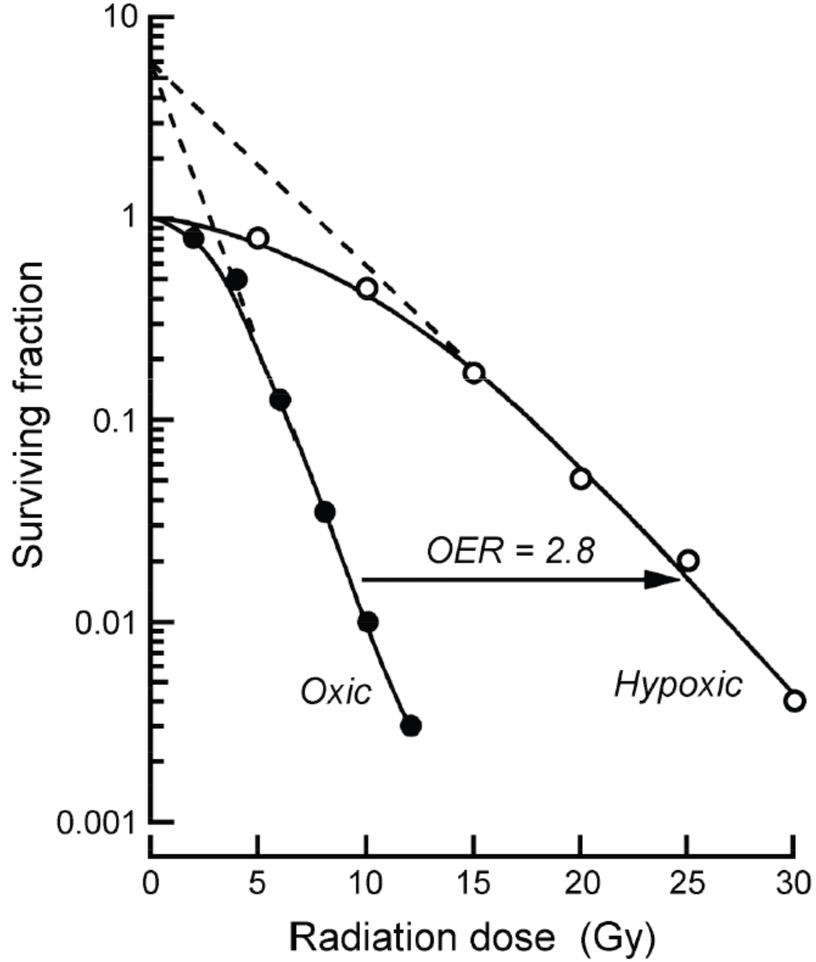
Thomlinson & Gray 1955

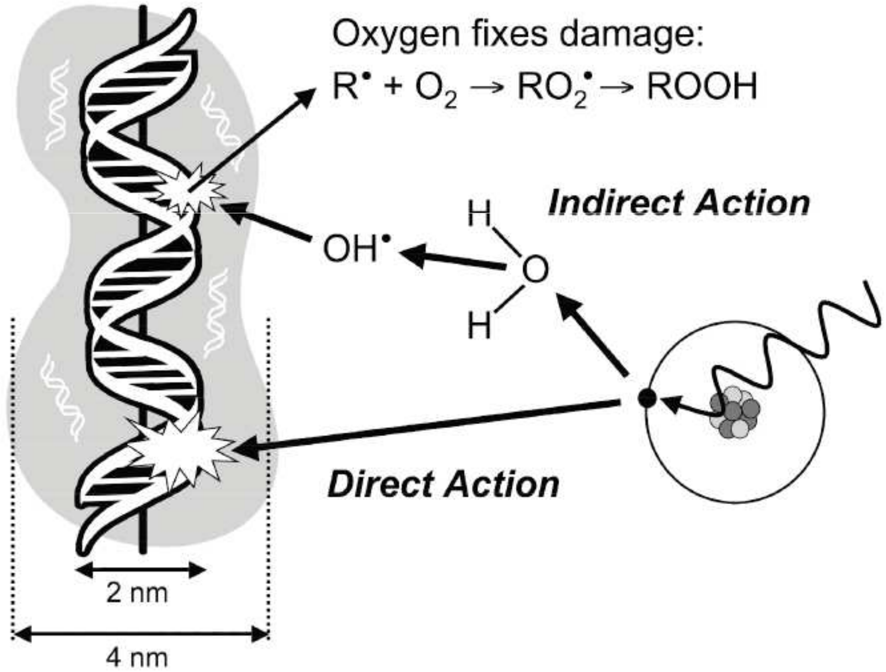
Cord structure in lung cancer (150 µm)



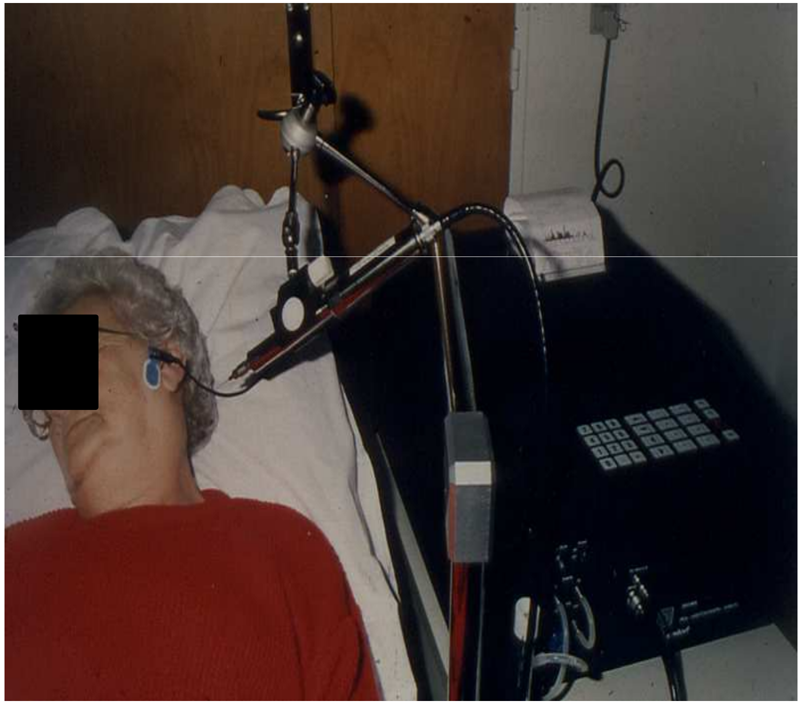


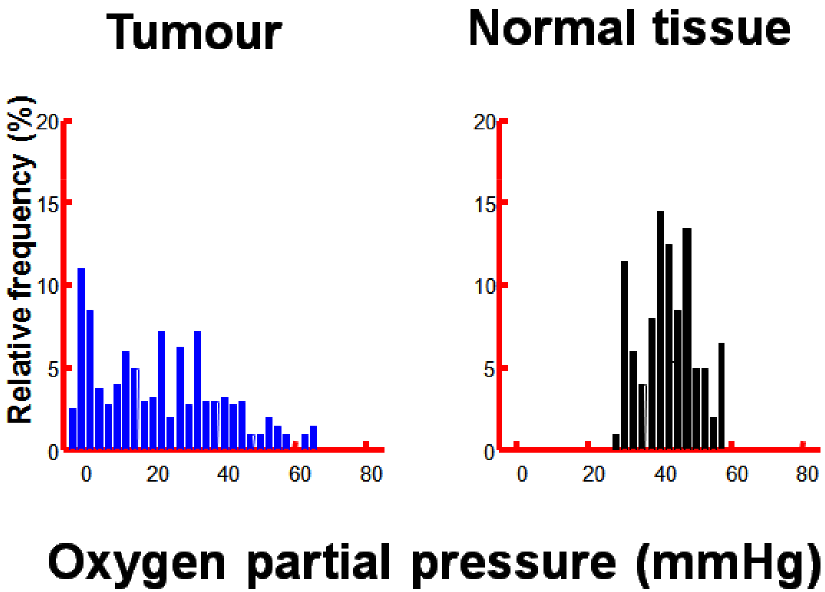
Oxygen effect





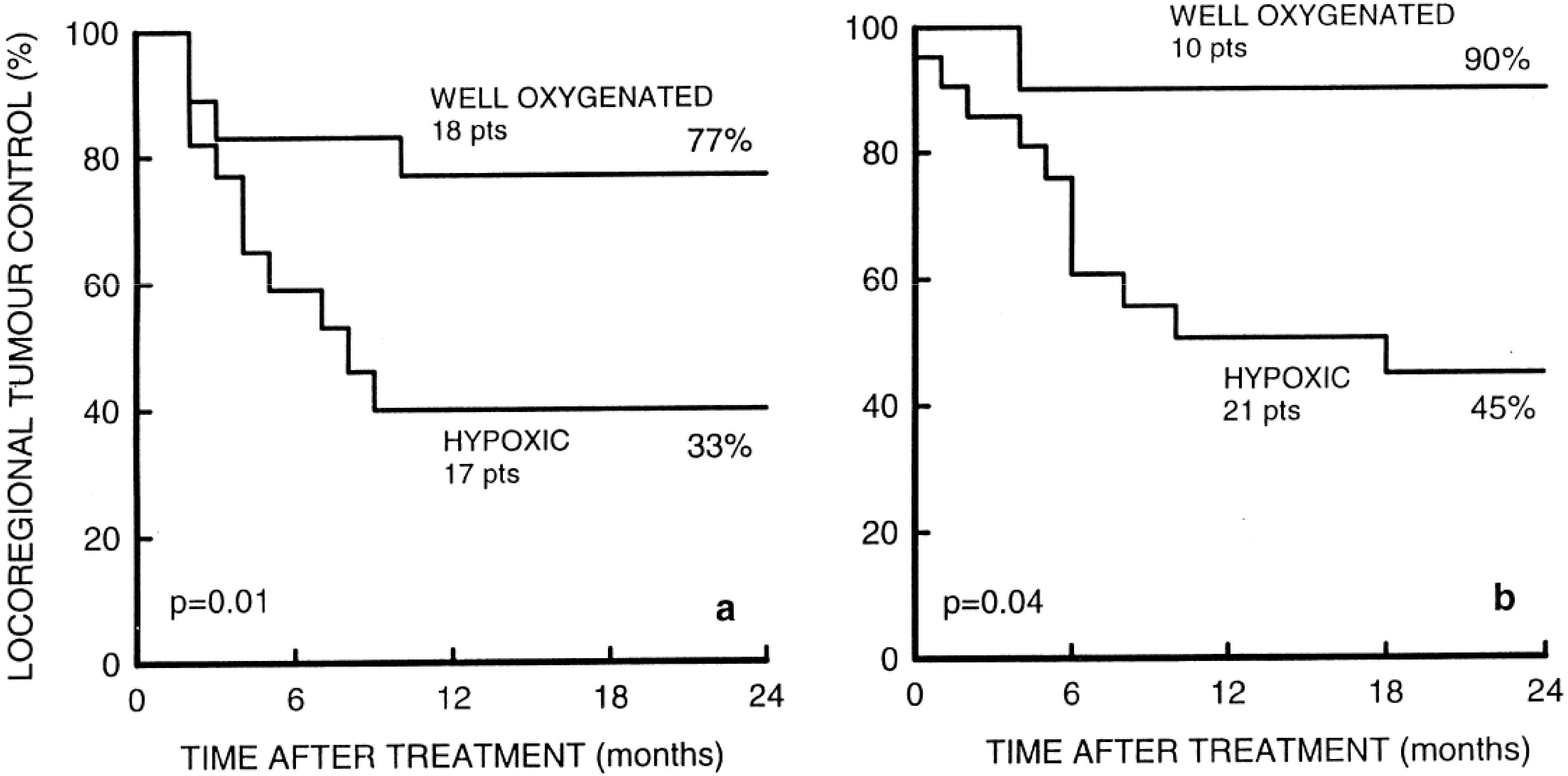
pO2 measurement with Eppendorph electrode





Nordsmark et al. Acta Oncol 1994

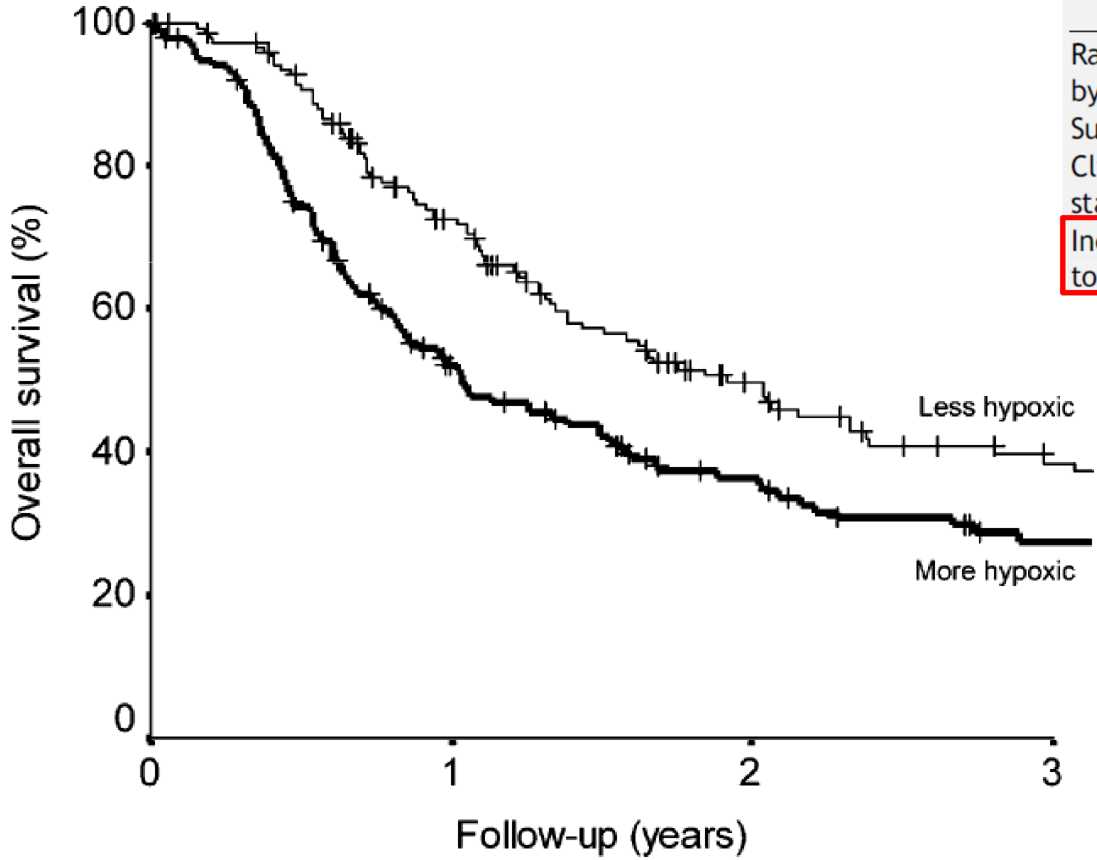
pO2 and loco-regional control



Nordsmark & Overgaard Radiother Oncol 2000

pO2 and survival – pooled data

HN cancer, pooled data from 7 studies (n=397)



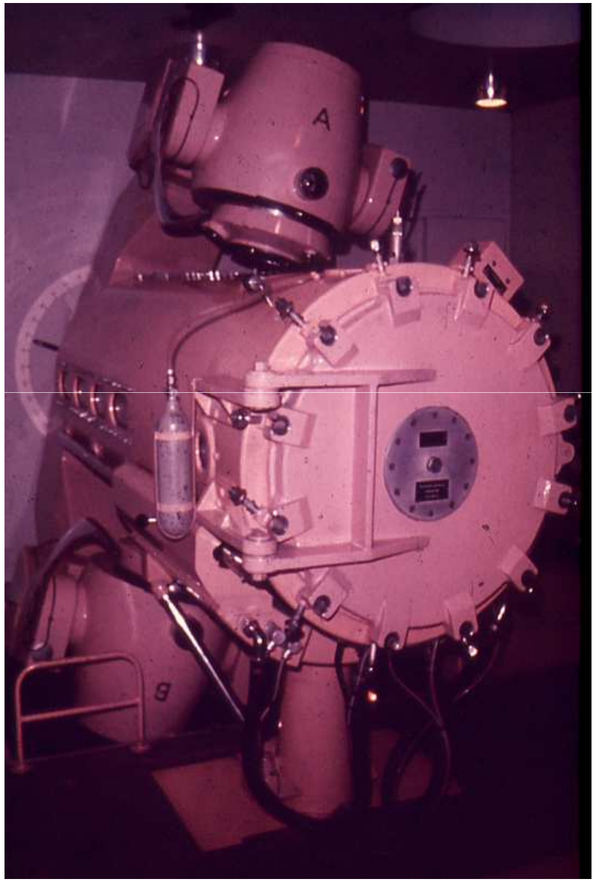
Relative risk estimates

Change in characteristic	Relative risk	95% Confidence limits
Radiation dose increased by 2 Gy	0.88	0.86, 0.90
Surgery	0.46	0.22, 0.94
Clinical stage increased stage I-III vs. stage IV)	1.66	1.00, 2.80
Increase in $HP_{2.5}$ from 30 to 40%	1.13	1.07, 1.19

Tumor hypoxia is associated with a poor prognosis in patients with advanced head and neck cancer.

Nordsmark et al. Radiotherapy and Oncology 77 (2005) 18–24

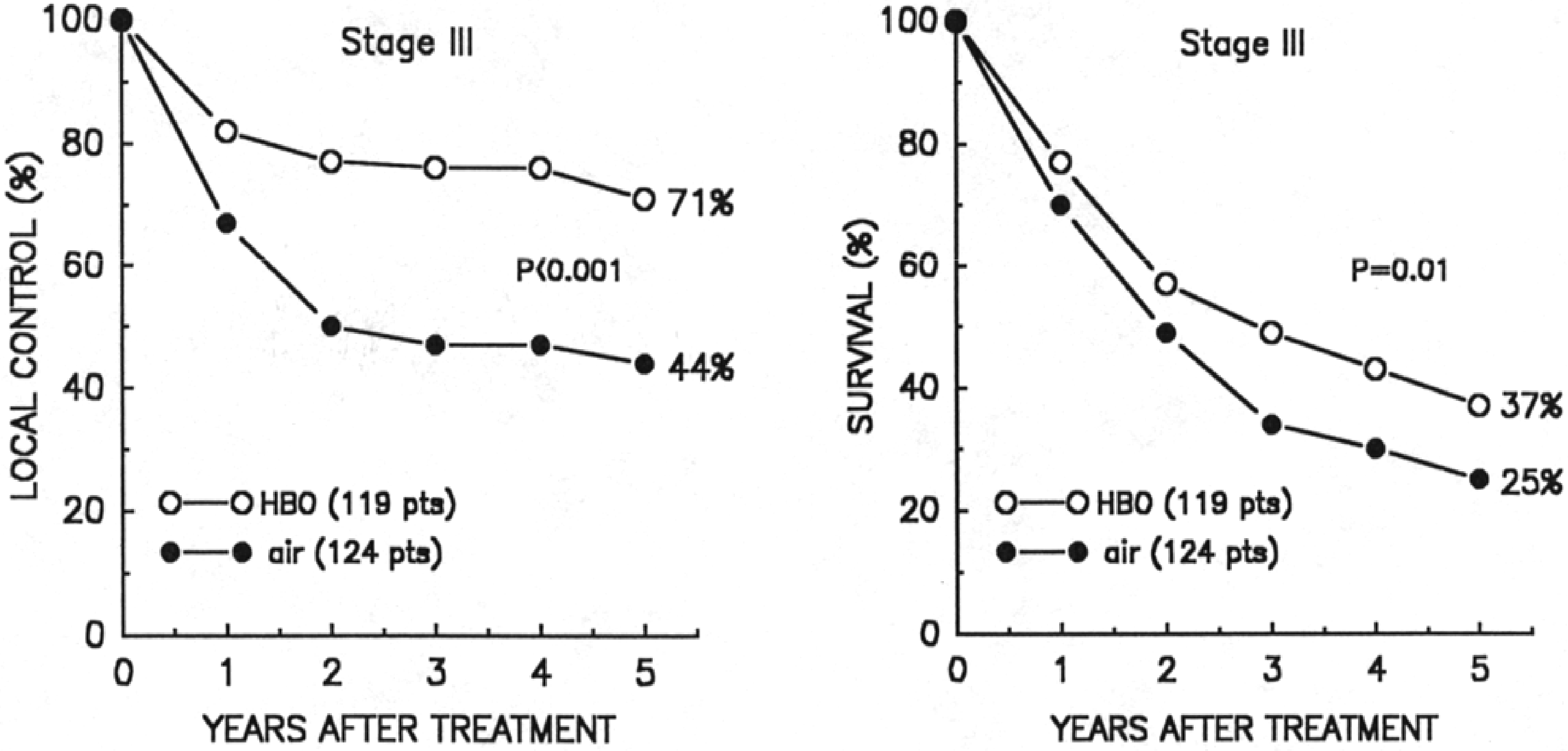
Hyperbaric oxygen



First hyperbaric oxygen treatment. 1955, St. Thomas' Hospital, London

Hyperbaric oxygen and radiotherapy

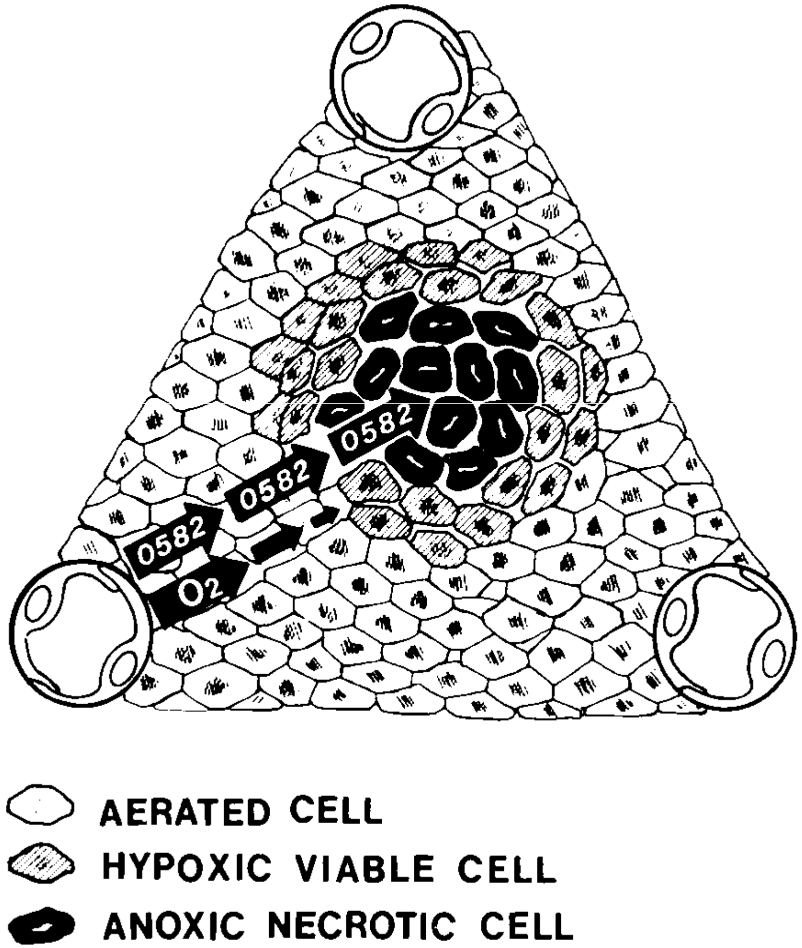
MRC trial (cervix)



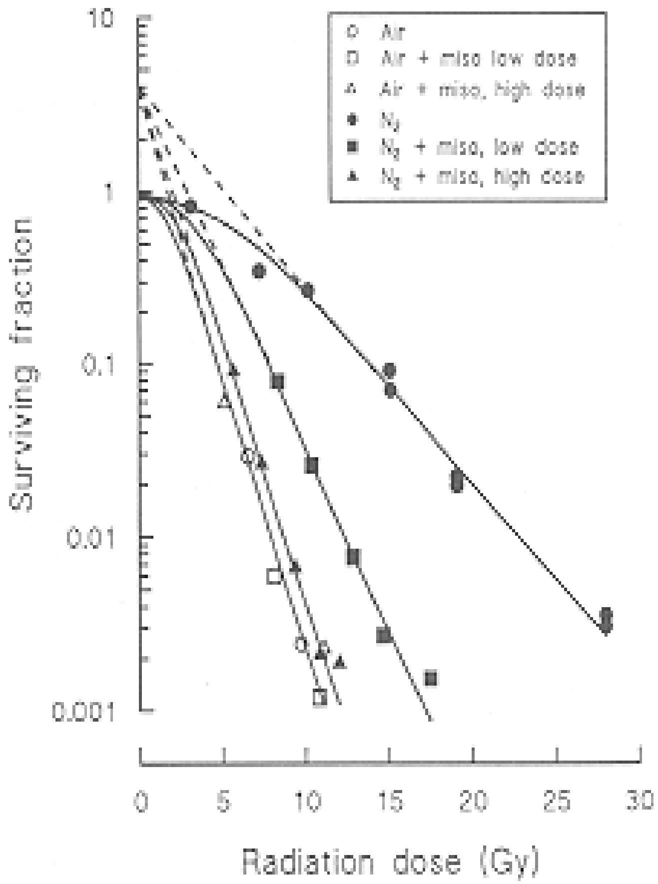
Watson *et al. (1978).*

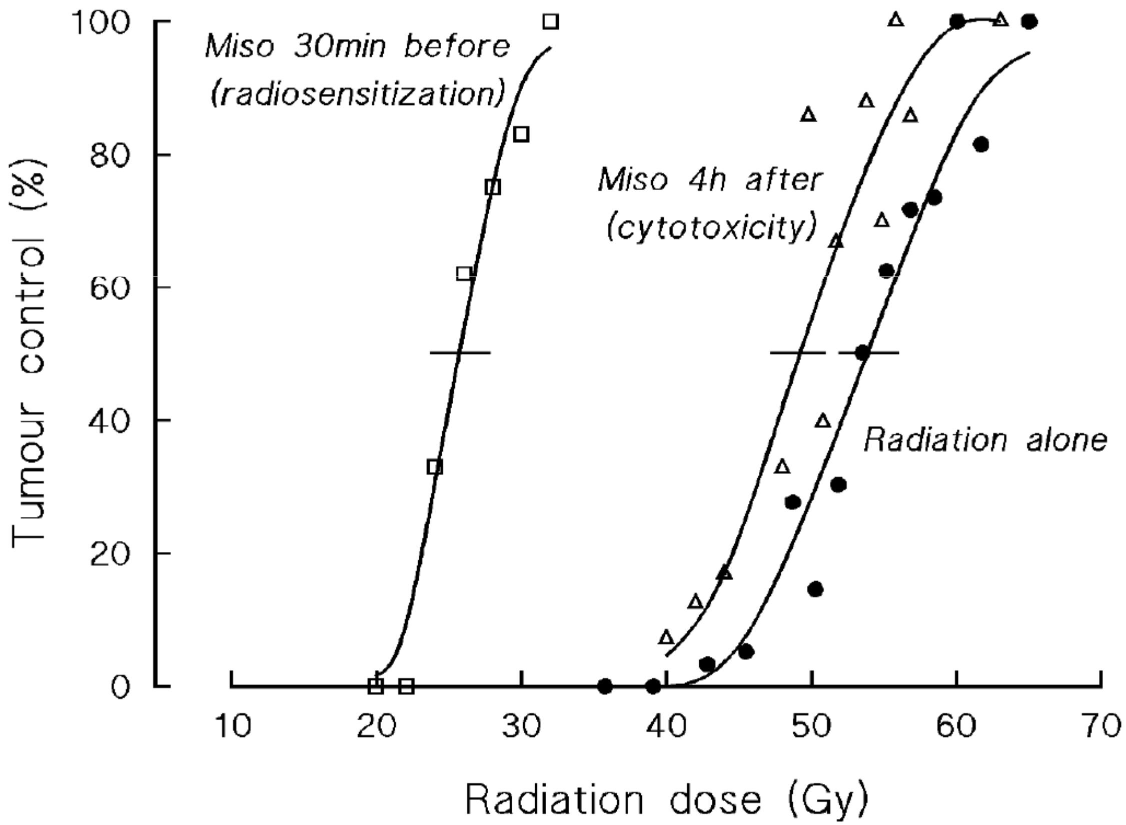
Hypoxic cell radiosensitizers

A drug which selectively sensitizes hypoxic cells to the effect of ionizing irradiation by mimicking the role of oxygen in radiation damage fixation



Hypoxic cell radiosensitizers: misonidazole

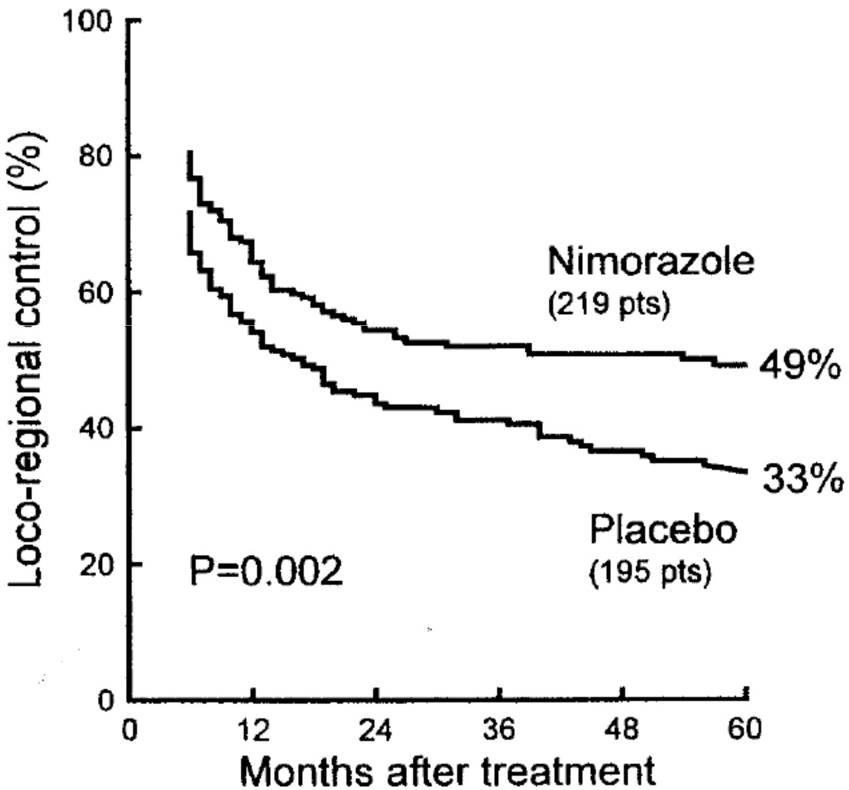


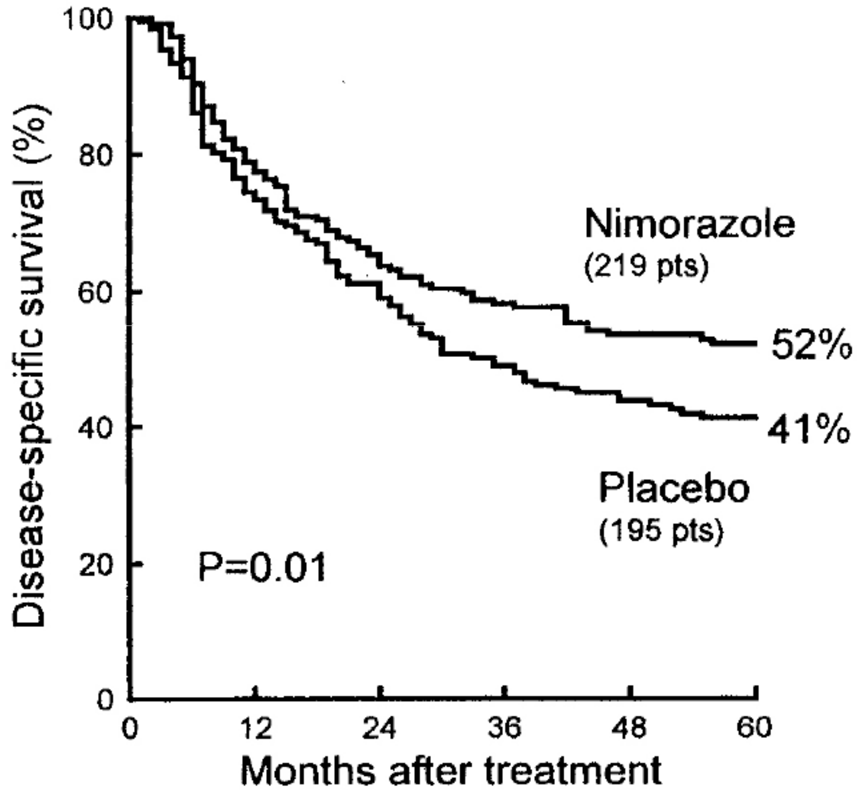


DAHANCA 5

SUPRAGLOTTIC AND PHARYNX - 414 pts.

NIMORAZOLE vs PLACEBO (66 Gy/ 33 fx - 6.5 wk)

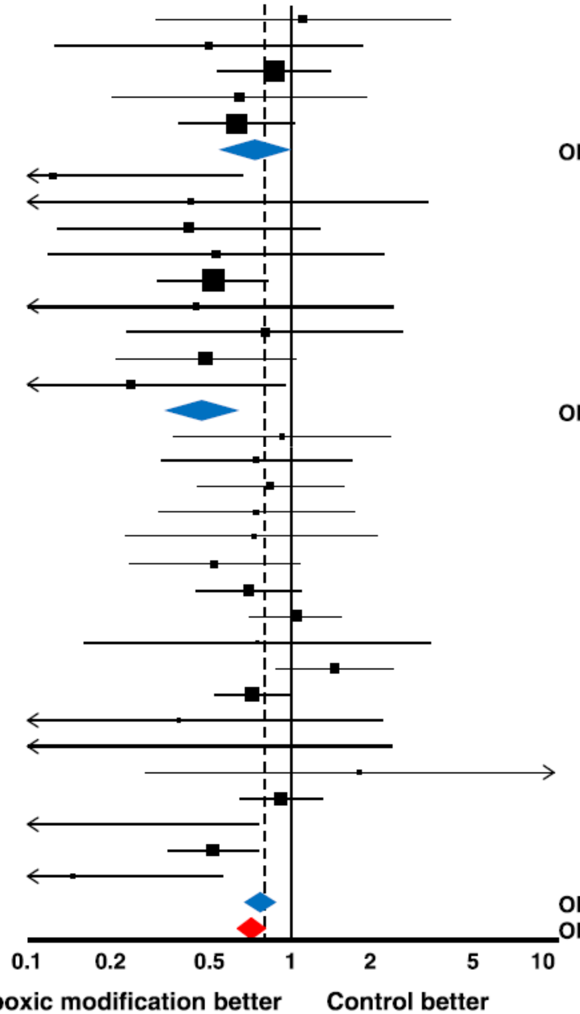




Since 1991 nimorazole has been standard for all HN SCC patients undergoing primary radiotherapy in Denmark.

Endpoint: Loco-regional failure

	Trial	Modification	Events / Total: Hypoxic modification	Events / Total: Control	Odds ratio and 95% CI	
Normobaric oxygen	1970 Evans 1	O2	7 / 15	11 / 25		
	1975 Evans 2	O2	13 / 20	19 / 24		
	1979 RTOG 70-02	Carbogen	53 / 121	63 / 133		
	2005 Mendelhall	Carbogen	6 / 50	9 / 51		
	2010 ARCON	Carb+Nic	32 / 171	47 / 174		
	Subtotal (Normobaric oxygen)		**111 / 377**	**149 / 407**	**OR: 0.73 (0.53-1.00)**	**p=0.05**
Hyperbaric oxygen	1968 van den Brenk	HBO	5 / 17	10 / 13		
	1971 Tobin 1971	HBO	5 / 9	6 / 8		
	1973 Chang 1973	HBO	8 / 26	13 / 25		
	1973 Shigamatsu	HBO	8 / 15	11 / 16		
	1977 MRC 1.trial	HBO	51 / 125	87 / 151		
	1979 MRC 3.trial	HBO	3 / 9	8 / 15		
	1979 Sause	HBO	8 / 21	10 / 23		
	1986 MRC 2.trial	HBO	21 / 53	29 / 50		
	1999 Haffty	HBO	13 / 23	21 / 25		
	Subtotal (Hyperbaric oxygen)		**122 / 298**	**195 / 326**	**OR: 0.46 (0.33-0.64)**	**p<0.001**
Hypoxic sensitizer	1982 Sealy 1	MISO	11 / 50	11 / 47		
	1983 Brunin	MISO	15 / 51	18 / 50		
	1984 MRC 10 fx	MISO	51 / 82	53 / 80		
	1984 MRC 20 fx	MISO	25 / 43	30 / 46		
	1984 Panis	MISO	14 / 26	16 / 26		
	1986 Sealy 2	HBO/MISO	34 / 60	46 / 64		
	1986 EORTC 228111	MISO	103 / 167	114 / 163		
	1987 European trial	ETA	94 / 187	92 / 187		
	1987 IAEA study	Ornidazole	13 / 18	14 / 18		
	1987 RTOG 79-15	MISO	113 / 147	104 / 150		
	1989 Dahanca 2	MISO	182 / 328	187 / 294		
	1989 RTOG 79-04	MISO	16 / 21	17 / 19		
	1989 Galecki	Metro	3 / 18	5 / 17		
	1992 Giaux	MISO	28 / 30	23 / 26		
	1995 RTOG 85-27	ETA	154 / 252	159 / 252		
	1996 Huilgol	AK-2123	2 / 9	7 / 9		
	1998 Dahanca 5	NIM	104 / 219	125 / 195		
	2006 Ullal	AK-2123	8 / 23	18 / 23		
	Subtotal (Hypoxic sensitizer)		**970 / 1731**	**1039 / 1666**	**OR: 0.76 (0.66-0.88)**	**p<0.001**
All trials with hypoxic modification			**1203 / 2406**	**1383/ 2399**	**OR: 0.71 (0.63-0.80)**	**p<0.001**



Test for heterogeneity: p = 0.12

Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

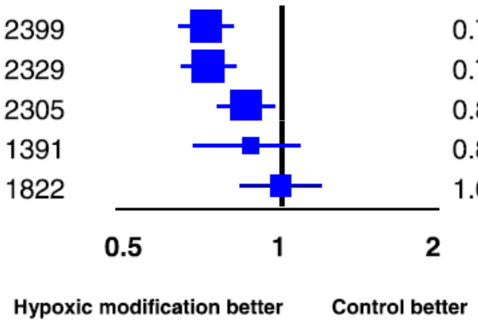
Hypoxic modification – meta-analysis

4805 patients; 32 randomized clinical trials – Overgaard 2011

Head and neck cancer - meta analysis - summary

Endpoint	Events / Total: Hypoxic modification	Events / Total: Control	Odds ratio	Risk Reduction	NNT**
Loco-regional control	1203 / 2406	1383 / 2399	0.71 (0.63-0.80)*	8% (5-10%)*	13
Disease specific survival	1175 / 2335	1347 / 2329	0.73 (0.64-0.82)	7% (5-10%)	14
Overall survival	1450 / 2312	1519 / 2305	0.87 (0.77-0.98)	3% (0-6%)	31
Distant metastasis	159 / 1427	179 / 1391	0.87 (0.69-1.09)	2% (-1-4%)	57
Radiotherapy complications	307 / 1864	297 / 1822	1.00 (0.82-1.23)	0% (-3-2%)	>>

Odds ratio and 95% CI



Hypoxic modification works
- but is it relevant for all patients?

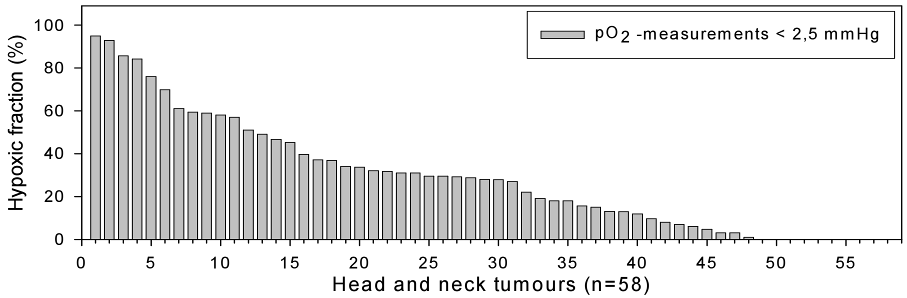
Overgaard J. Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck – A systematic review and meta-analysis.
Radiother Oncol (2011)

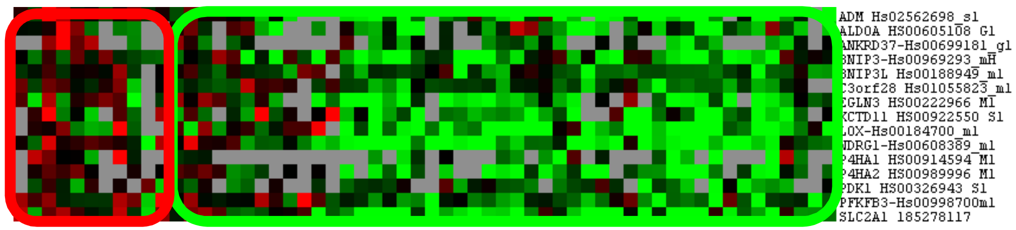
Hypoxia-classification

15-gene hypoxia classifier

- Based on hypoxia induced genes (in vitro/in vivo validated)
- Classification based on gene expression similarity to either ”more” or ”less” hypoxic tumours as estimated with pO_2-electrode in an independent trainingset of 58 H&N cancer patients

Toustrup K et al, Cancer Res; 71(17); 5923-31, 2011





More Hypoxic

Less Hypoxic

Validating the hypoxia classifier

Independent clinical dataset

414 patients enrolled in the DAHANCA 5 trial

219 randomly assigned to radiotherapy and nimorazole

195 randomly assigned to radiotherapy and placebo

52 excluded from classification (2 failed in PCR, 50 did not have tumour tissue for PCR)

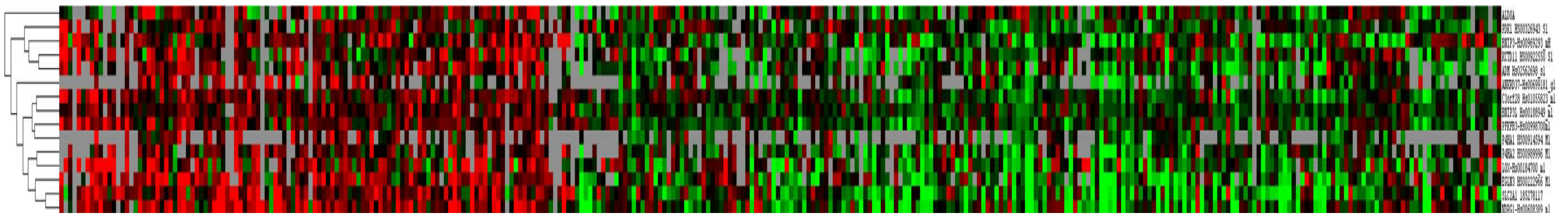
39 excluded from classification (1 failed in PCR, 38 did not have tumour tissue for PCR)

323 tumour samples for classification

Classification

”More” hypoxic **(114)**

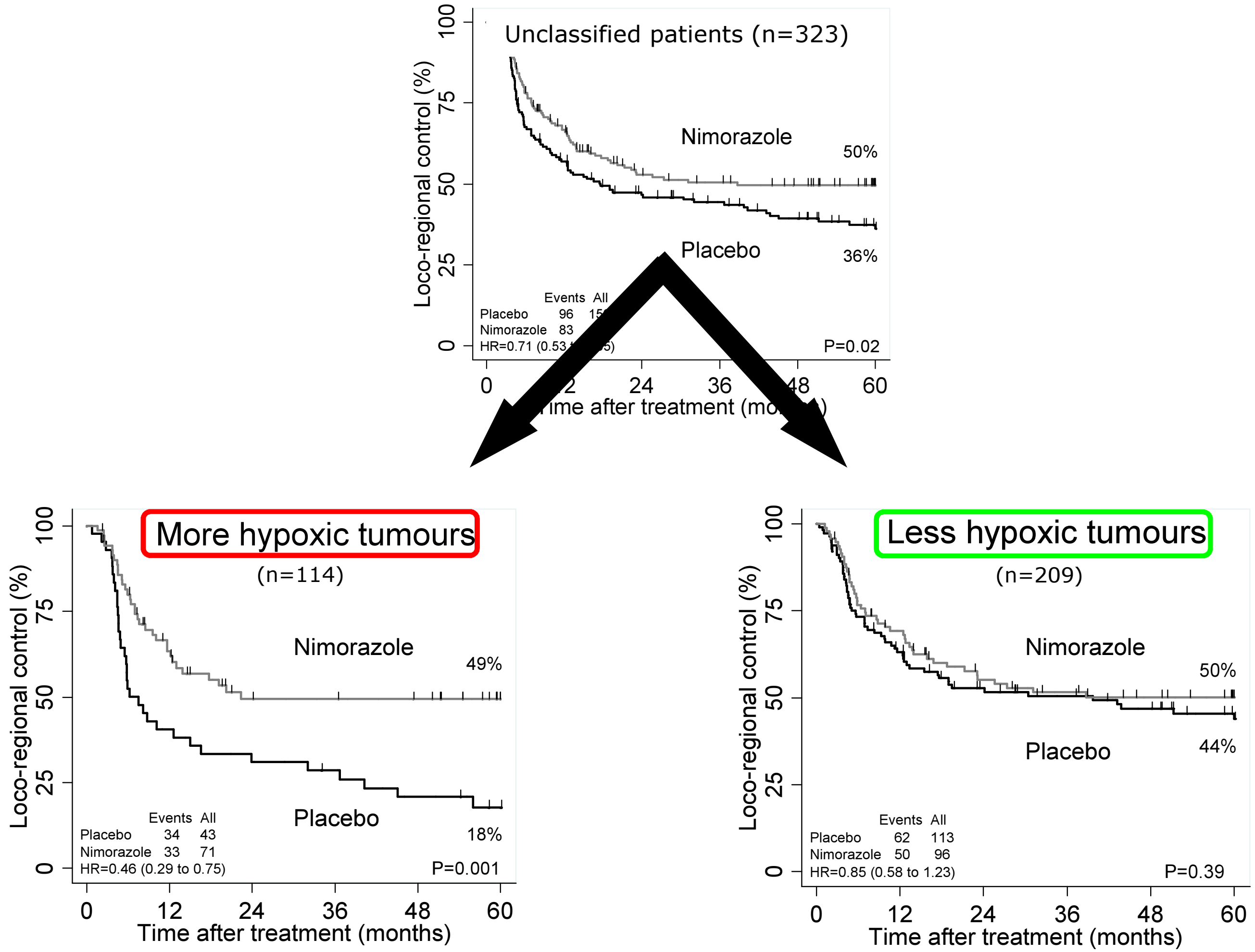
”Less” hypoxic (209)



Toustrup K et al, Radiother Oncol; 102; 122-129, 2012

Hypoxia-classification

15-gene hypoxia classifier

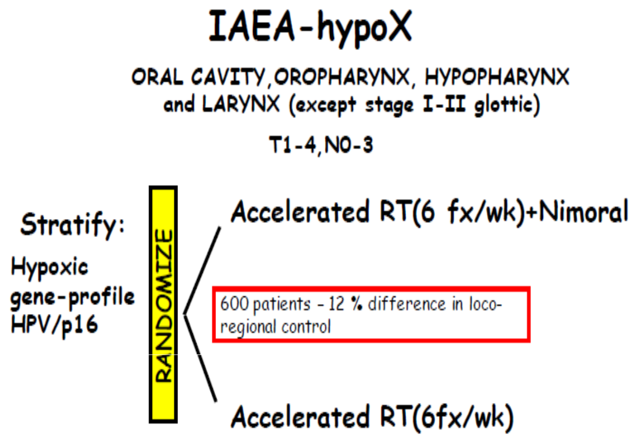


-Toustrup K et al, Radiother Oncol; 102; 122-129, 2012

On-going validation studies

IAEA-HypoX

- Randomized phase III; accelerated radiotherapy ± Nimorazole
  - hypoxia gene expression and HPV/p16
  - Eastern Europe, Asia
  - Recruitment opened 2012

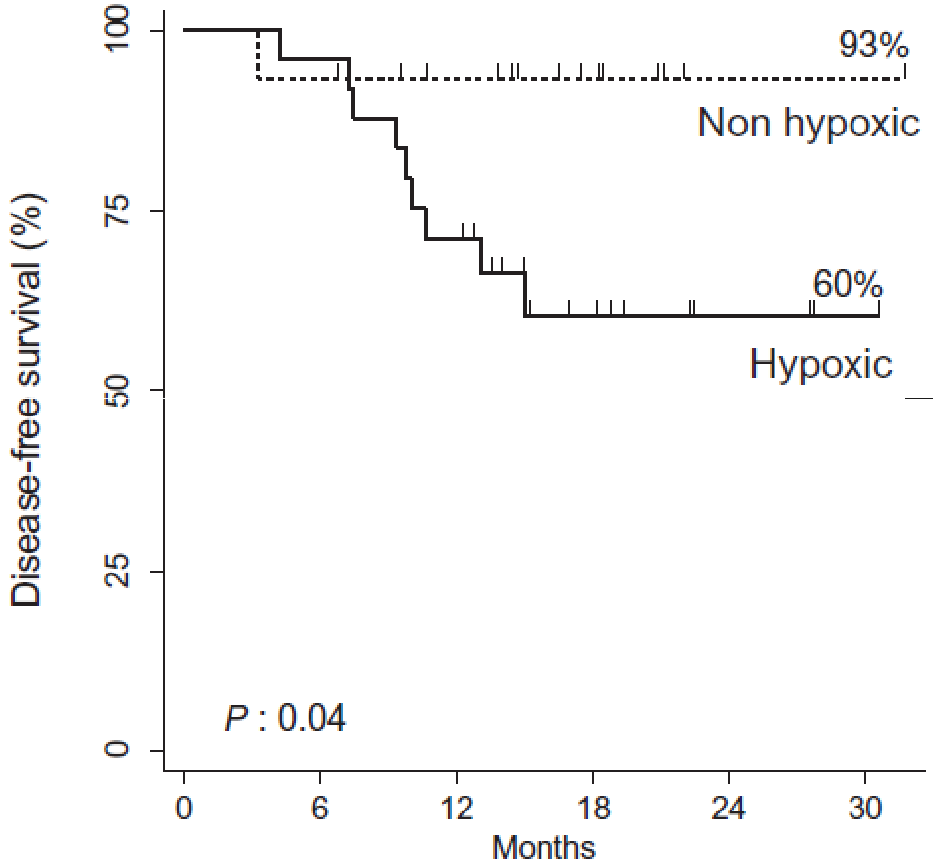


Intergroup EORTC - ROG HNCG 1219 DAHANCA

- Randomized phase III; accelerated chemoradiotherapy ± Nimorazole
  - hypoxia gene expression and HPV/p16
  - Europe, Canada
  - Recruitment starting 2013

www.azanta.com

FAZA-PET



Pts at risk:						
Non hypoxic:	15	14	11	6	1	1
Hypoxic:	25	24	17	8	3	1

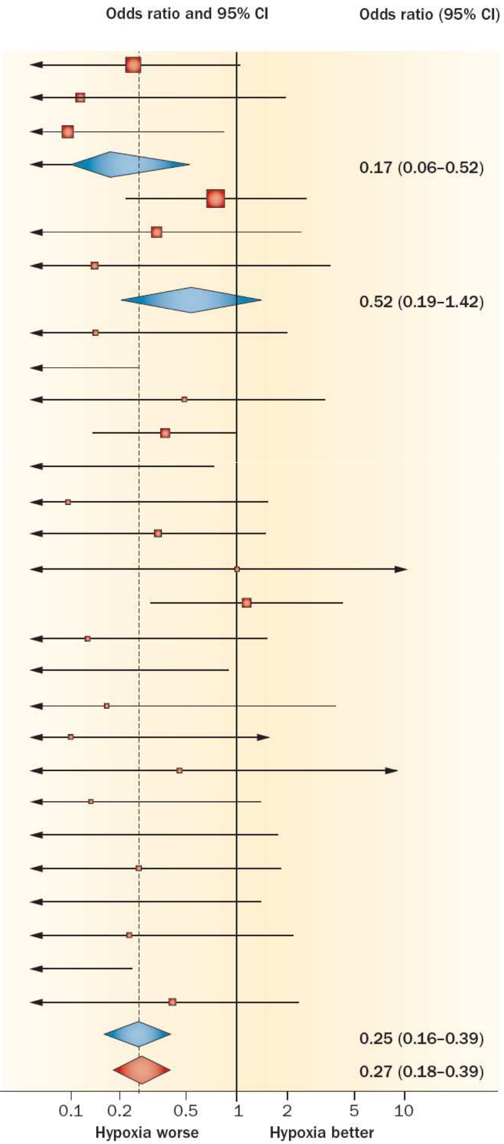
L.S. Mortensen et al. / Radiotherapy and Oncology 105 (2012) 14–20

Pre-treatment hypoxia imaging with CT-perfusion, DCE-MRI and PET is prognostic for outcome of HN RT

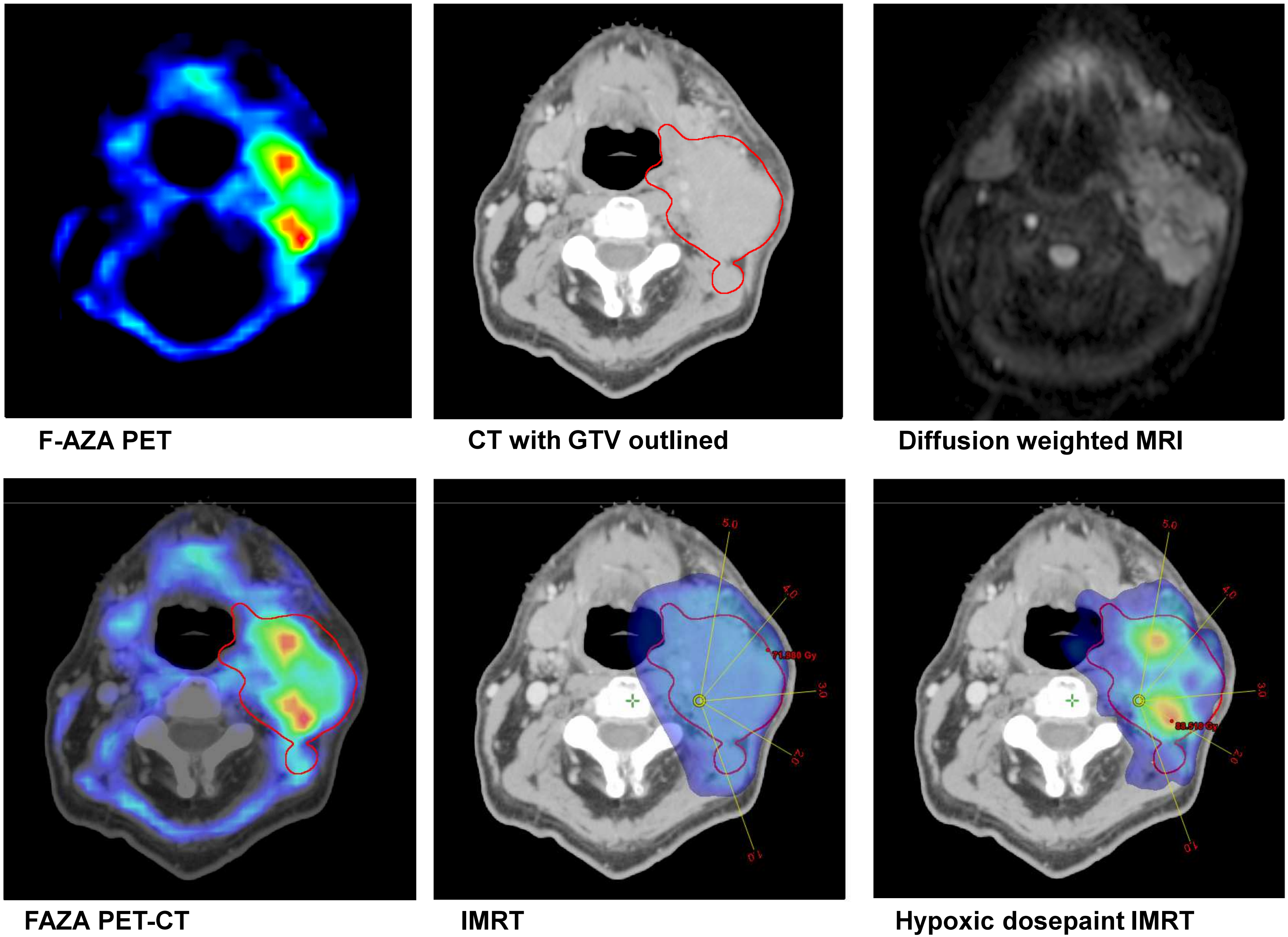
Prognostic….

Not Predictive

Study	Tumour	Tracer	Events/total No hypoxia	Events/total Hypoxia	Odds ratio (95% CI)
Loncaster (2002)[97]	Cervix	DCE MRI	3/25	9/25	
Mayr (2010)[98]	Cervix	DCE MRI	0/16	17/82	
Andersen (2012)[99]	Cervix	DCE MRI	1/41	8/40	
DCE MRI all			**4/82**	**34/147**	0.17 (0.06–0.52)
Hermans (1999)[87]	HNSCC	CTperf	9/21	10/20	
Bisdas (2009)[88]	HNSCC	CTperf	2/11	4/10	
Truong (2011)[89]	HNSCC	CTperf	0/6	2/6	
CT perfusion all			**11/38**	**16/36**	0.52 (0.19–1.42)
Urtasun (1996)[102]	HNSCC	IAZA	3/10	3/4	
Dehdashti (2003)[70]	Lung	CuATSM	0/8	6/6	
Lehtiö (2004)[52]	HNSCC	FETNIM	4/9	5/8	
Rajendran (2006)[53]	HNSCC	FMISO	10/37	18/36	
Rischin (2006)[28]	HNSCC	FMISO	1/10	8/13	
Thornwarth (2006)[54]	HNSCC	FMISO	1/6	4/6	
Li (2006)[104]	Lung	Tc-HL91	8/16	12/16	
Eschmann (2007)[55]	HNSCC	FMISO	2/4	4/8	
Dehdashti (2008)[71]	Cervix	CuATSM	9/22	6/16	
Dietz (2008)[72]	Rectal	CuATSM	1/9	4/8	
Khamly (2008)[56]	Sarcoma	FAZA	3/9	7/8	
Spence (2008)[57]	CNS	FMISO	9/11	11/11	
Dirix (2009)[58]	HNSCC	FMISO	2/6	5/6	
Lee (2009)[59]	HNSCC	FMISO	0/7	1/11	
Li (2010)[60]	Lung	FETNIM	8/13	12/13	
Schuetz (2010)[47]	Cervix	FAZA	0/10	2/5	
Kikuchi (2011)[61]	HNSCC	FMISO	3/10	5/8	
Minagawa (2011)[73]	HNSCC	CuATSM	0/5	6/10	
Mortensen (2012)[62]	HNSCC	FAZA	1/17	7/25	
Yue (2012)[63]	Oesophagus	FETNIM	1/14	11/14	
Zips (2012)[64]	HNSCC	FMISO	3/13	5/12	
PET/SPECT all			**69/244**	**142/244**	0.25 (0.16–0.39)
All studies			**84/364**	**192/427**	0.27 (0.18–0.39)



Horsman, M. R. *et al. Nat. Rev. Clin. Oncol.* 9, 674–687 (2012)



Petersen, Mortensen et al. Aarhus University Hospital

Conclusions – hypoxia

- A significant proportion of HN squamous cell carcinomas contains hypoxic regions
- Patients with hypoxic tumours have poorer loco-regional control and survival
- Hypoxic modification (sensitizers, HBO, hypoxic cytotoxins) during RT results in improved loco-regional control and survival
- Predictive assays, hypoxic imaging and dosepainting is emerging but still investigational

Systemic therapy

Rationale for combining radiotherapy and systemic therapy

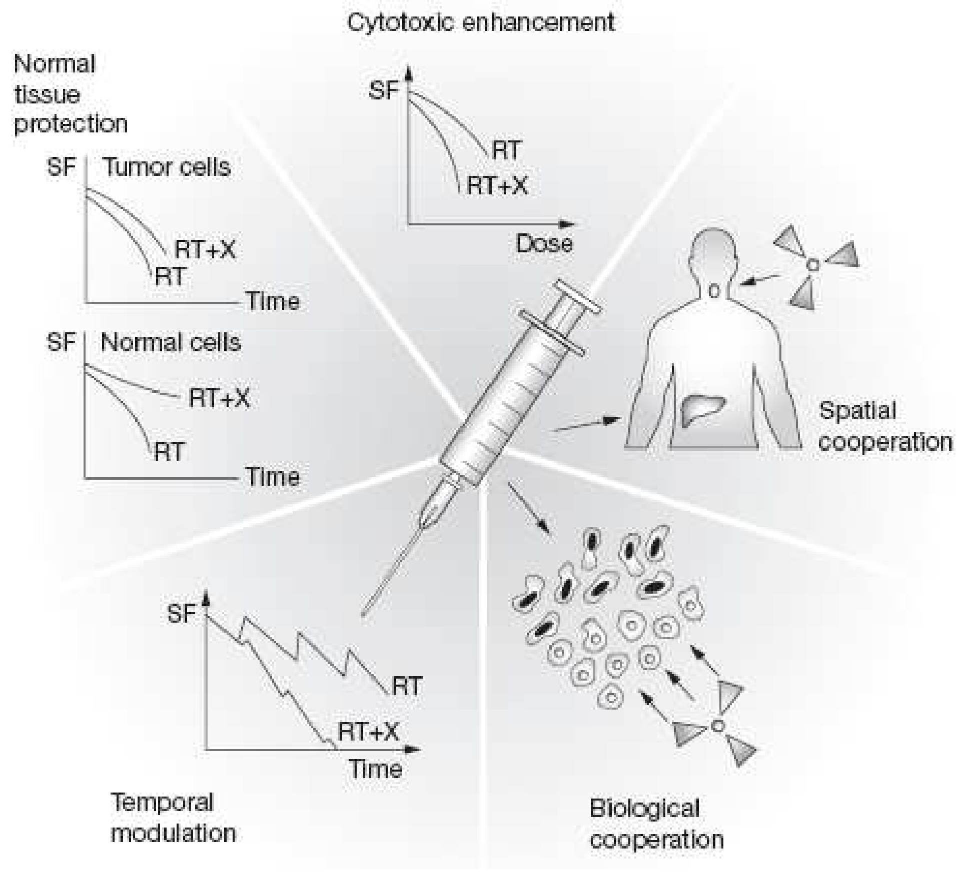
Spatial cooperation

Cytotoxic enhancement

Biological cooperation

Temporal modulation

Normal tissue protection

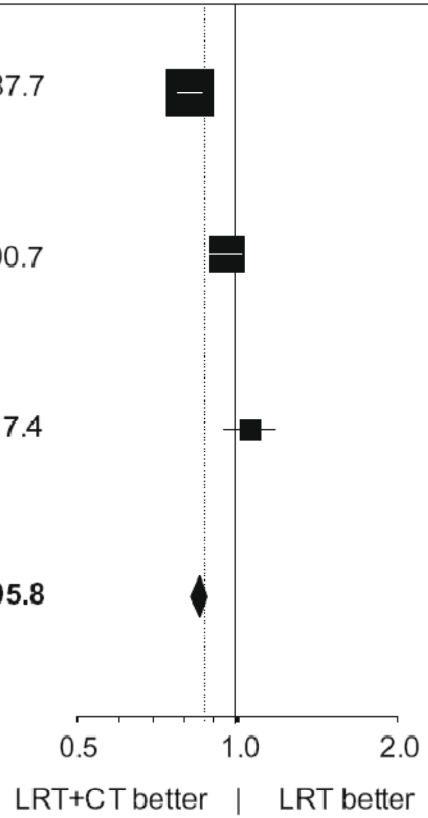


Bentzen SM Nature Clin Pract Oncol 2007

Meta-analysis II 2009

HR of death

Timing	No. Deaths / No. Entered LRT+CT	No. Deaths / No. Entered LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Concomitant	3171/4824	3389/4791	-326.4	1587.7		0.81 [0.78;0.86]
Induction	1877/2740	1813/2571	-40.0	900.7		0.96 [0.90;1.02]
Adjuvant	631/1244	661/1323	17.9	317.4		1.06 [0.95;1.18]
Total	**5679/8808**	**5863/8685**	**-348.5**	**2805.8**		**0.88 [0.85;0.92]**



Test for heterogeneity: $\chi^2_{107} = 179.8$ p < 0.0001

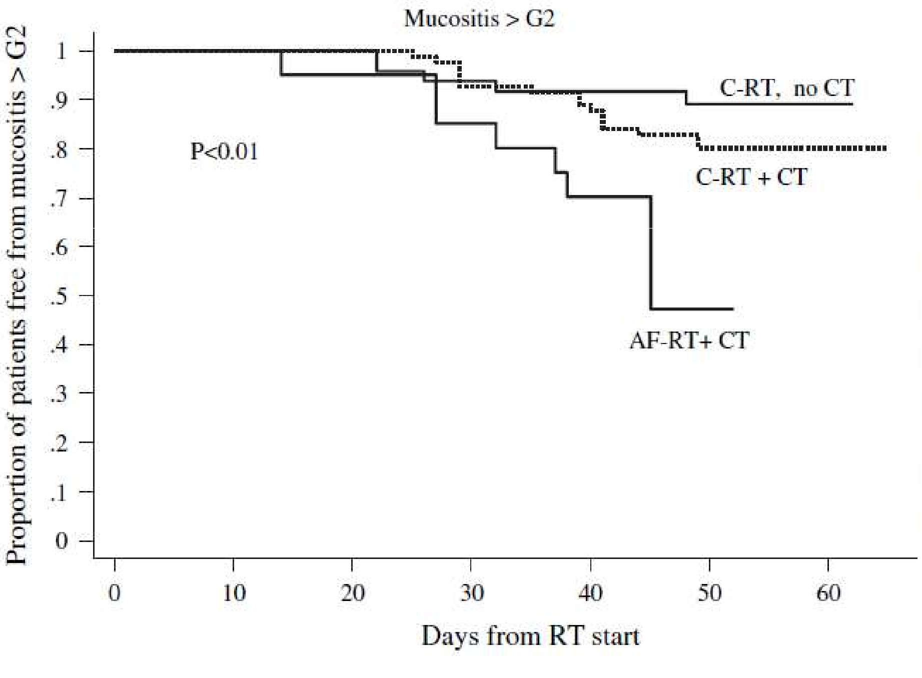
$I^2 = 41\%$

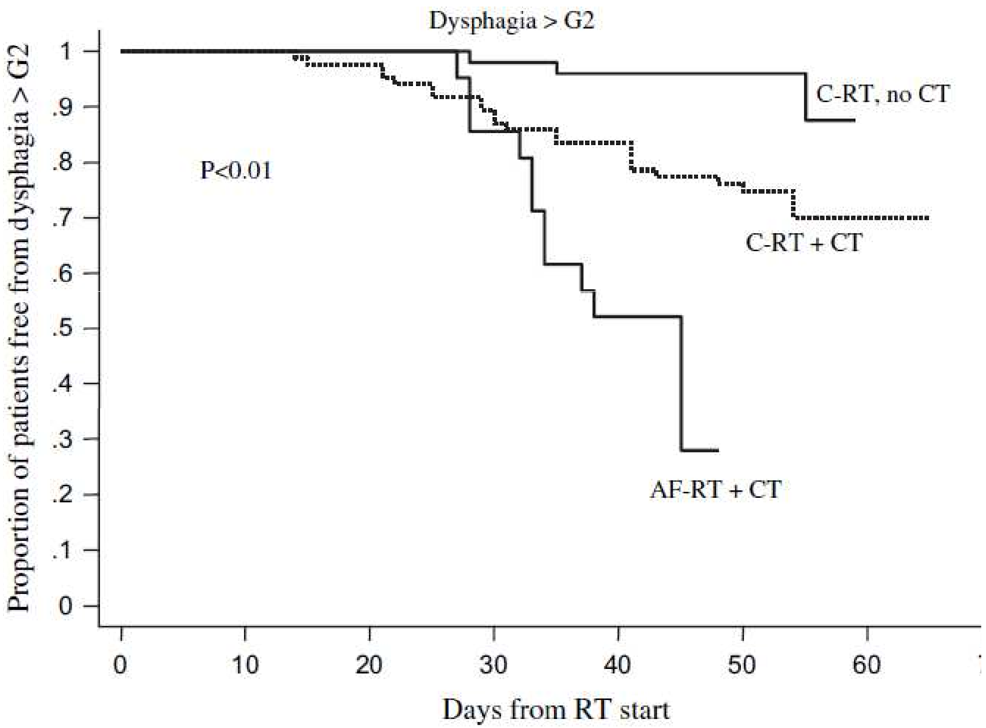
Test for interaction: $\chi^2_{2} = 26.60$ p < 0.0001

LRT+CT effect: p < 0.0001

Pignon JP Radiother Oncol 2009

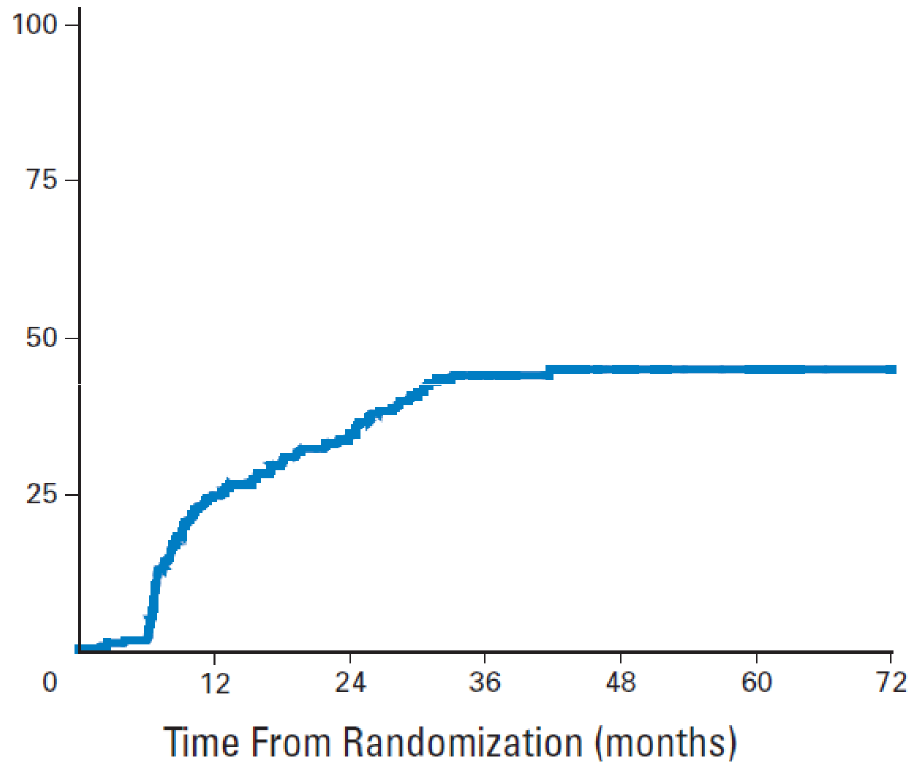
Acute toxicity





Palazzi et al, Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 2, pp. 330–337, 2008

Late morbidity



Analysis of 3 RTOG trial with C-RT

(RTOG 91-11, 97-03, and 99-14)

230 patients

43% severe late morbidity

40% laryngeal/pharyngeal dysfunction

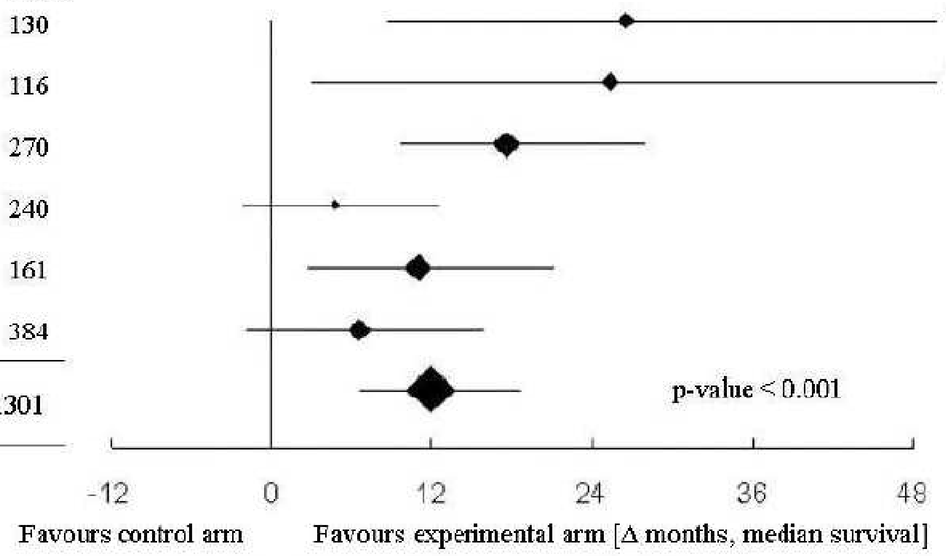
13% tube feeding >2 years after RT

Machtay M JCO 2008;

Unconventional fractionation ±concurrent chemo

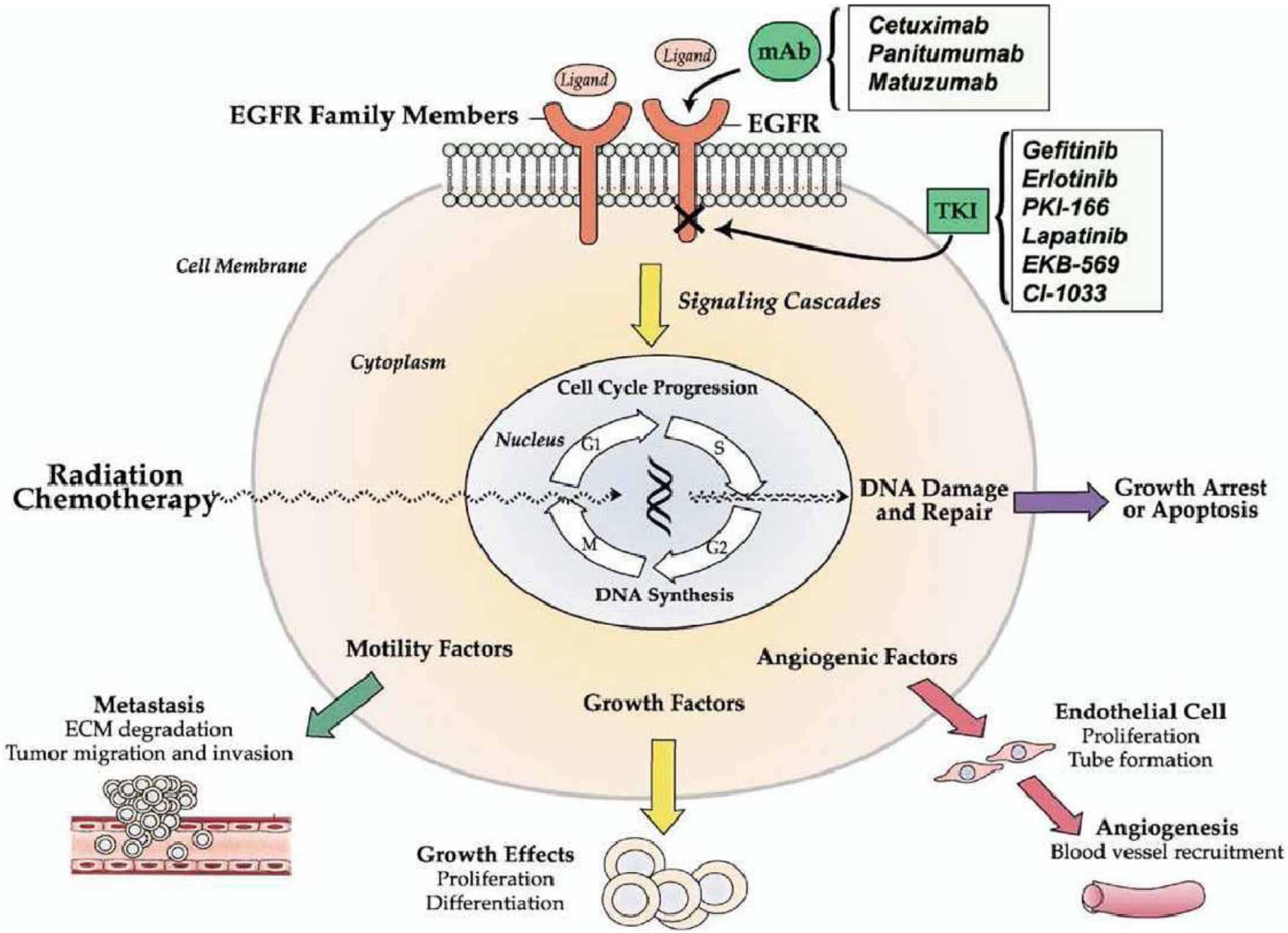
publication	delta 2 year OS [%]	delta months	LCL	UCL	N weight
Jeremic [33]	+21.6	26.6	8.6	52.9	130
Brizel [34]	+18.1	25.3	3.1	62.0	116
Wendt [35]	+25.1	17.7	9.8	28.0	270
Staar [36]	+7.8	4.9	-2.1	12.7	240
Dobrowsky [37]	+17.6	11.0	2.8	21.3	161
Budach [12]	+6.8	6.6	-2.0	16.1	384
total	14.7 (8.9-20.3)*	12.0	6.7	18.8	1301

Test for heterogeneity:	variance	mean(sq)	chi-square	p
	0.60	0.58	1.05	0.959



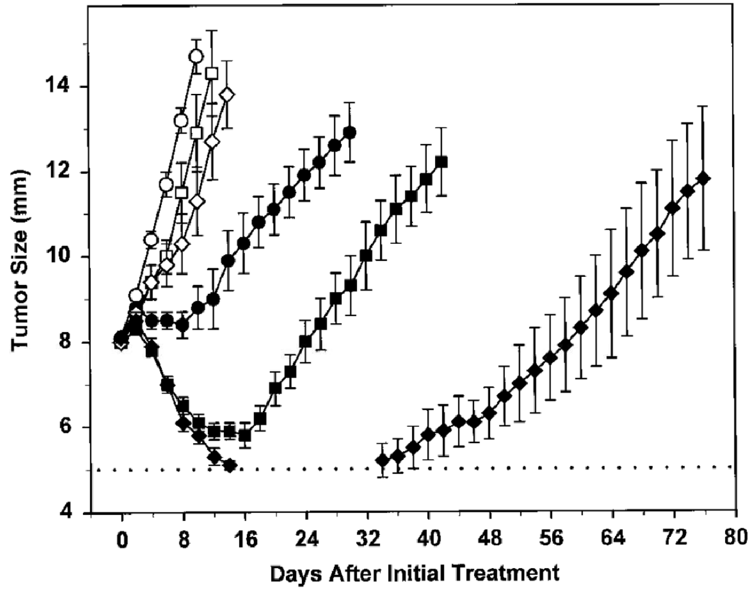
Budach W BMC Cancer 2006

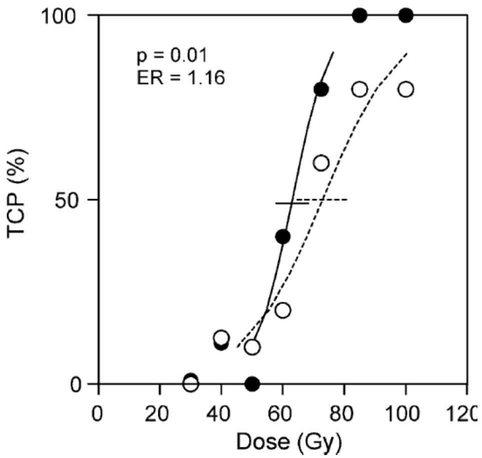
EGFR

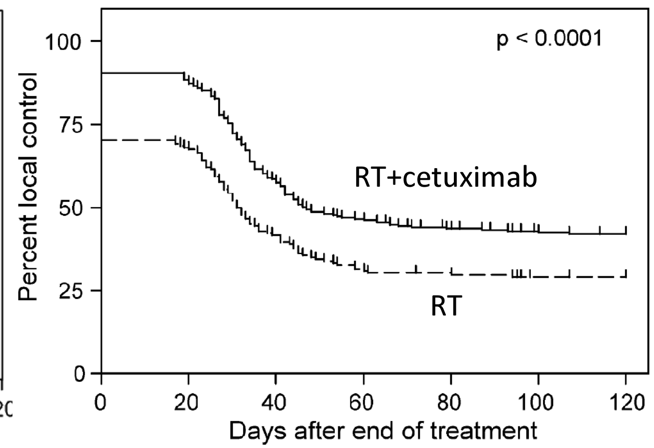


Harari PM Semin Radiat Oncol 2006

EGFR inhibition - pre-clinical data



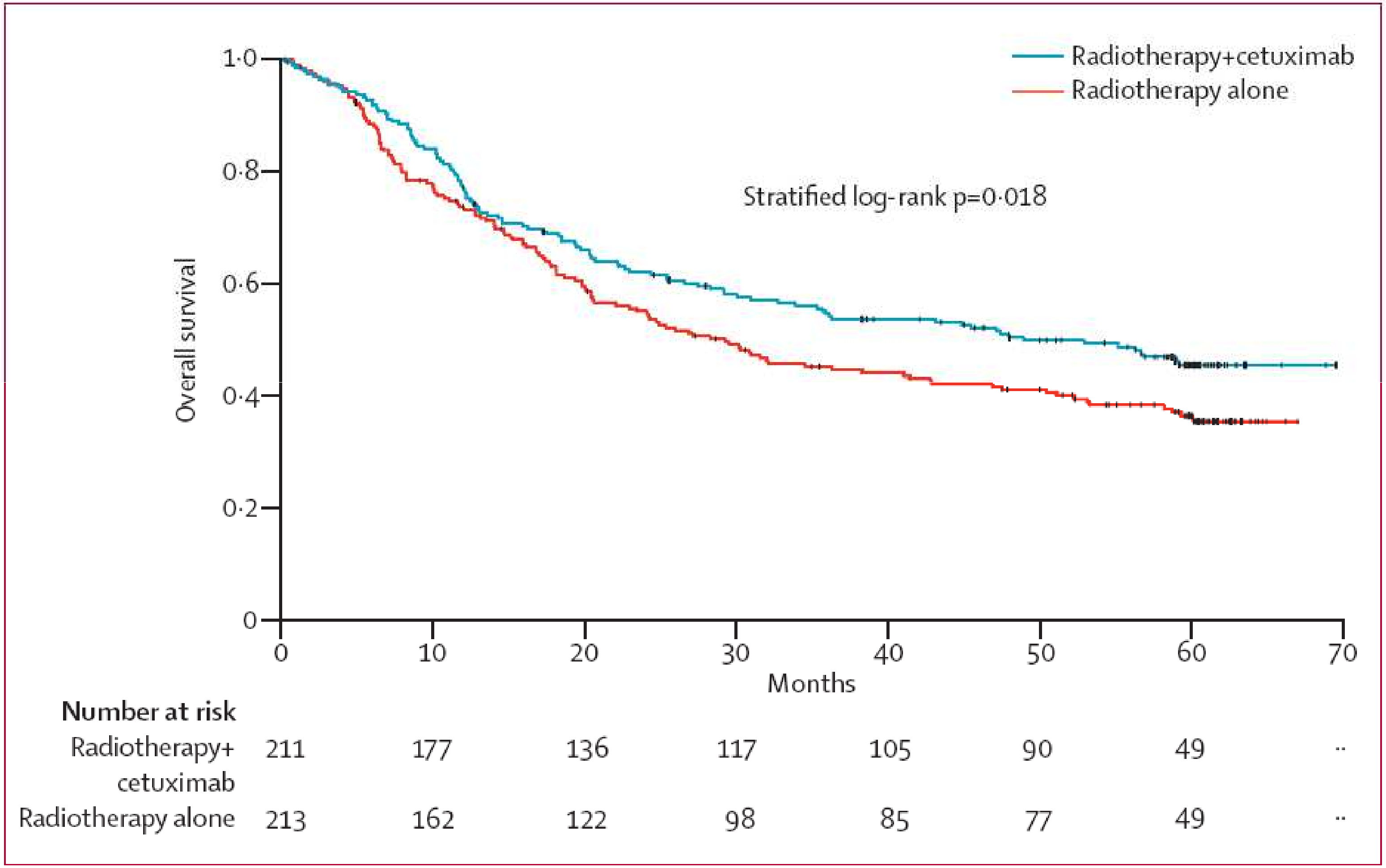




Akimoto T Clin Cancer Res 1999; *Schmidt-Ullrich Oncogene 1997*

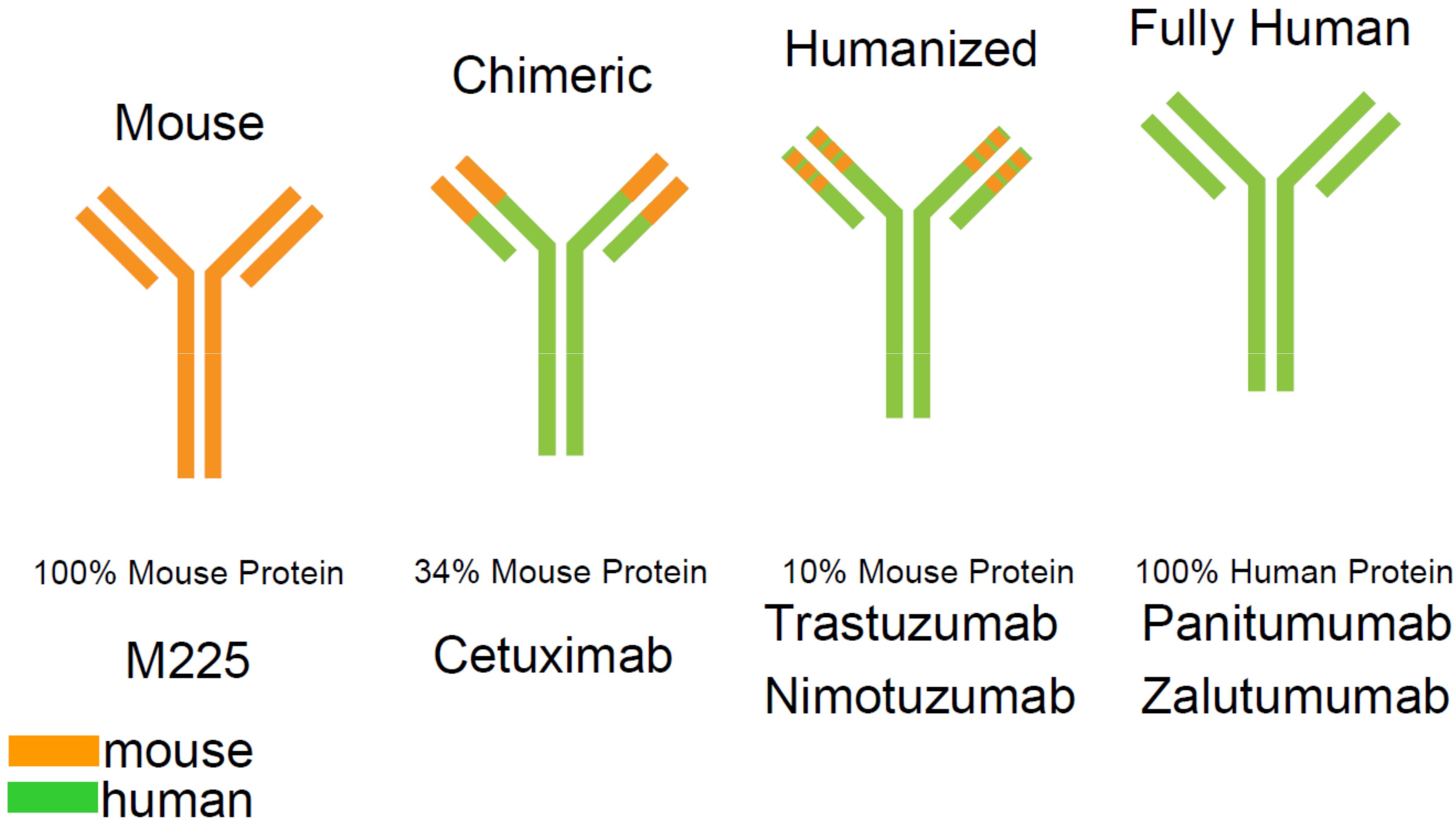
Milas L Clin Cancer Res 2000; *Krause M Radiother Oncol 2005*

RT ±Cetuximab



Bonner JA Lancet Oncol 2010

Monoclonal antibodies



Courtesy Jesper G. Eriksen

Conclusions
RT and systemic therapy

- Sound biological rationale for combining local and systemic treatment
- The main clinical effect is by improving RT-induced loco-regional control
- Largest effect and tolerability in younger patients in good performance status
- Acute and late toxicity is increased

May look straightforward, but…….

Combination of RT and systemic therapy

The devil is in the details:

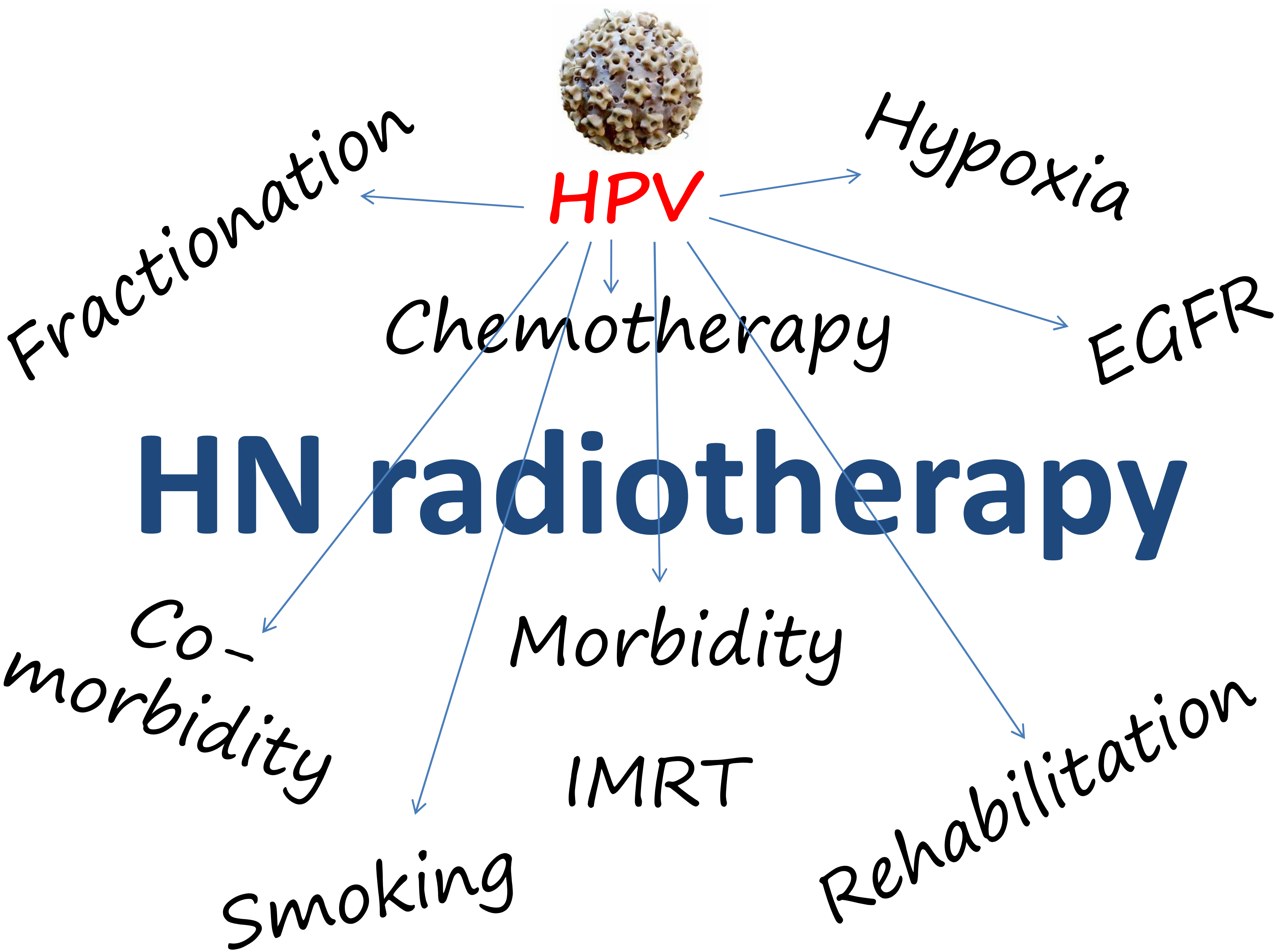
- Induction chemotherapy? Evidence versus clinical practise…
- Concomitant chemoRT:
  - Which drugs?
  - Frequency: weekly or every three weeks?
- Does it (really) work with altered fractionation?
- Combination of two and more systemic agents..
  - Doublet versus triplet
- What about toxicity – is there a true therapeutic gain?

….will be addresssed in this course…


HN radiotherapy
Fractionation
HPV
Hypoxia
Chemotherapy
EGFR
Co-morbidity
Morbidity
IMRT
Smoking
Rehabilitation

Summary – key points

- Modified fractionation (hyperfractionation and/or acceleration) is superior to conventional fractionation
- Hypoxic sensitizers (e.g. nimorazole) improves tumor control and survival without enhancing radiation morbidity
- Concomitant platinum-based chemotherapy is more effective than RT alone for younger patients in good performance status with and advanced stage tumours. Acute and late toxicity is increased
- EGFR inhibition combined with radiotherapy (but not chemoRT) results in enhancement of tumor response
- The optimal combination of these ’radiotherapy intensifiers’ is still unsettled


HPV
Fractionation
Hypoxia
Chemotherapy
EGFR
HN radiotherapy
Co-morbidity
Morbidity
IMRT
Smoking
Rehabilitation

Induction chemotherapy for organ preservation

Lisa Licitra
Head & Neck Medical Oncology Dep
Istituto Nazionale Tumori
Milano

European Journal of Cancer (2015) 51, 2130–2143

ELSEVIER

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

EJC

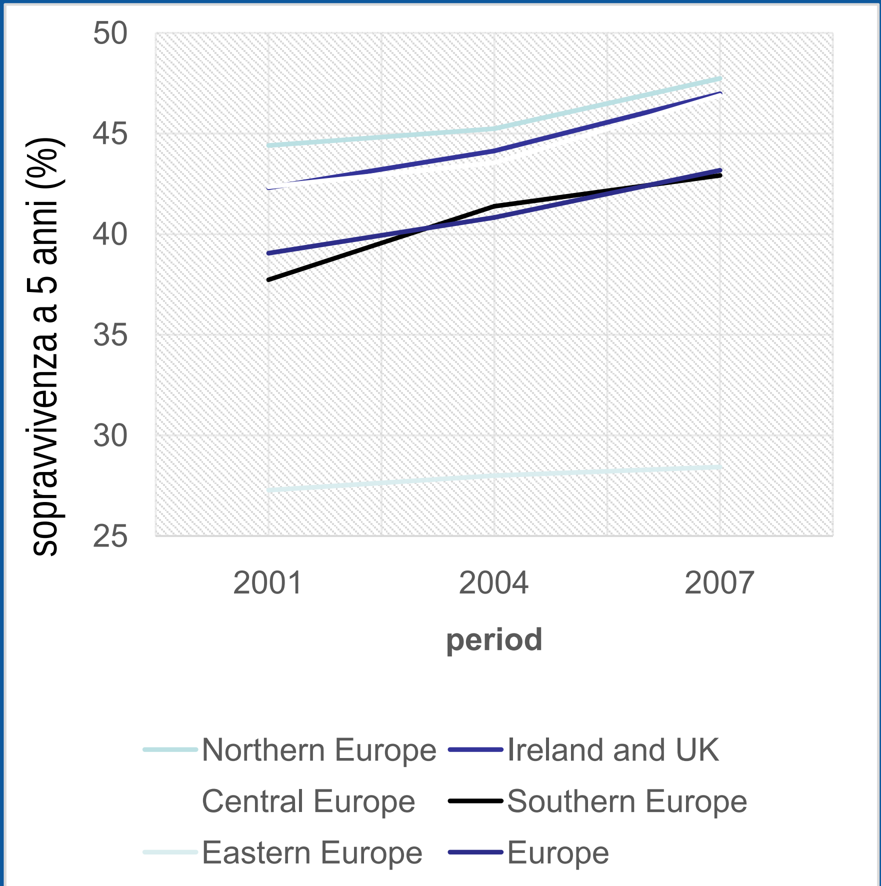
Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study

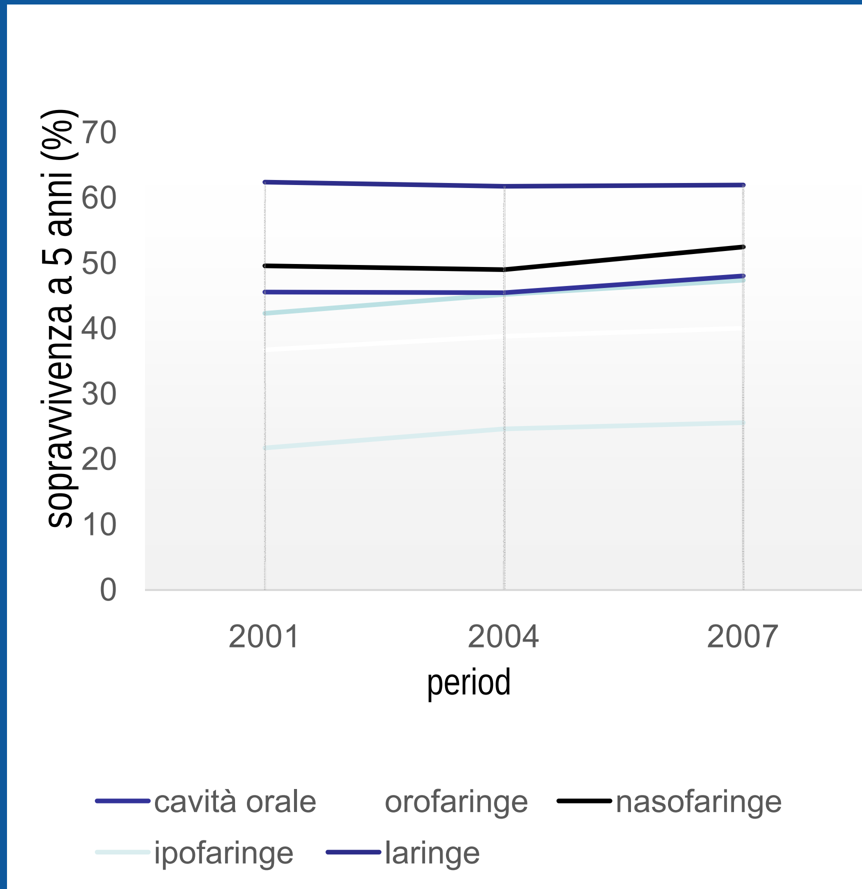
CrossMark

Gemma Gatta [a,*], Laura Botta [a], María José Sánchez [b,c], Lesley Ann Anderson [d], Daniela Pierannunzio [e], Lisa Licitra [f], and the EUROCARE Working Group [1]

Survival Trends in Europe epidemiological data

Survival trends in EU by subsite



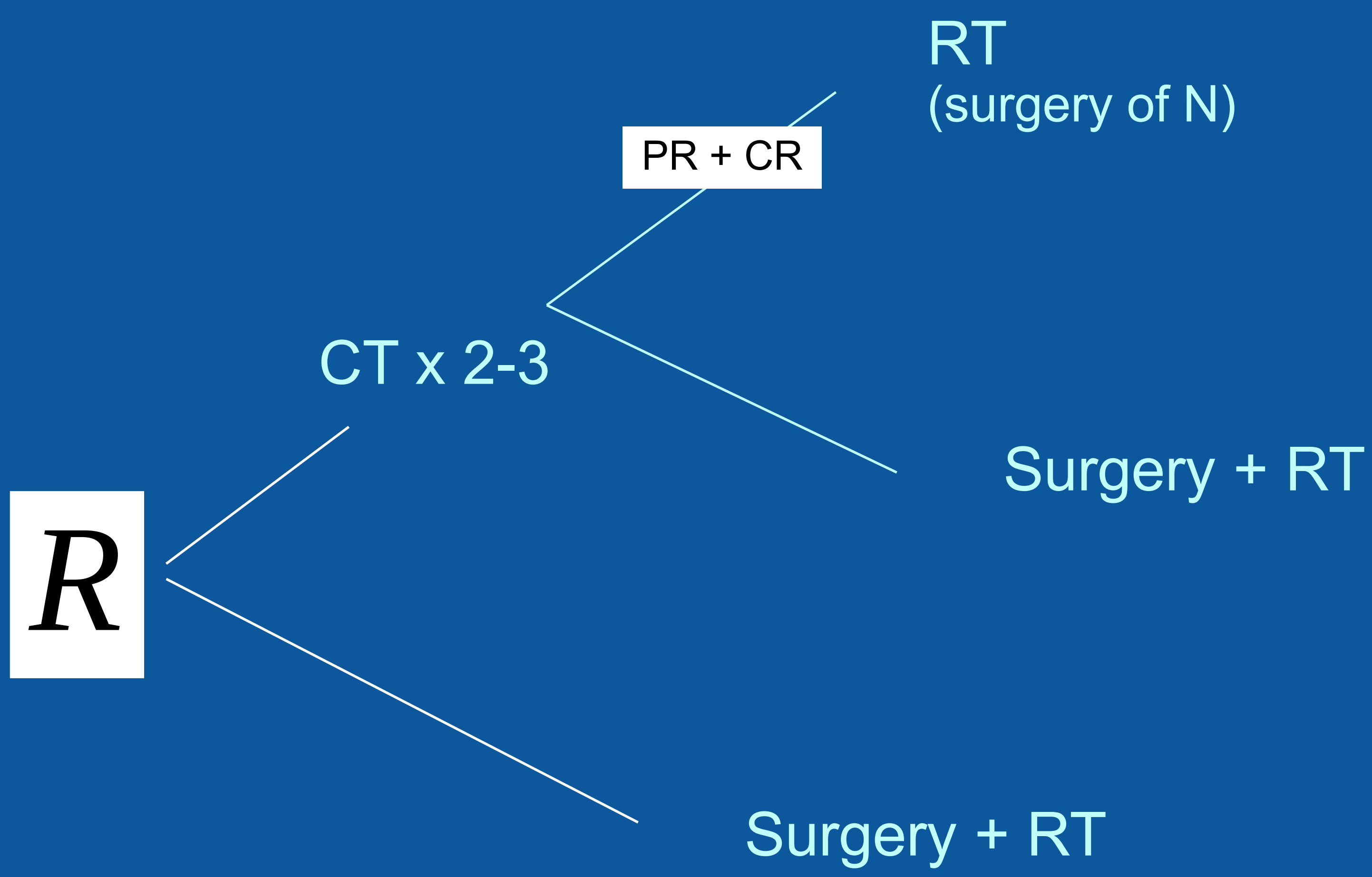


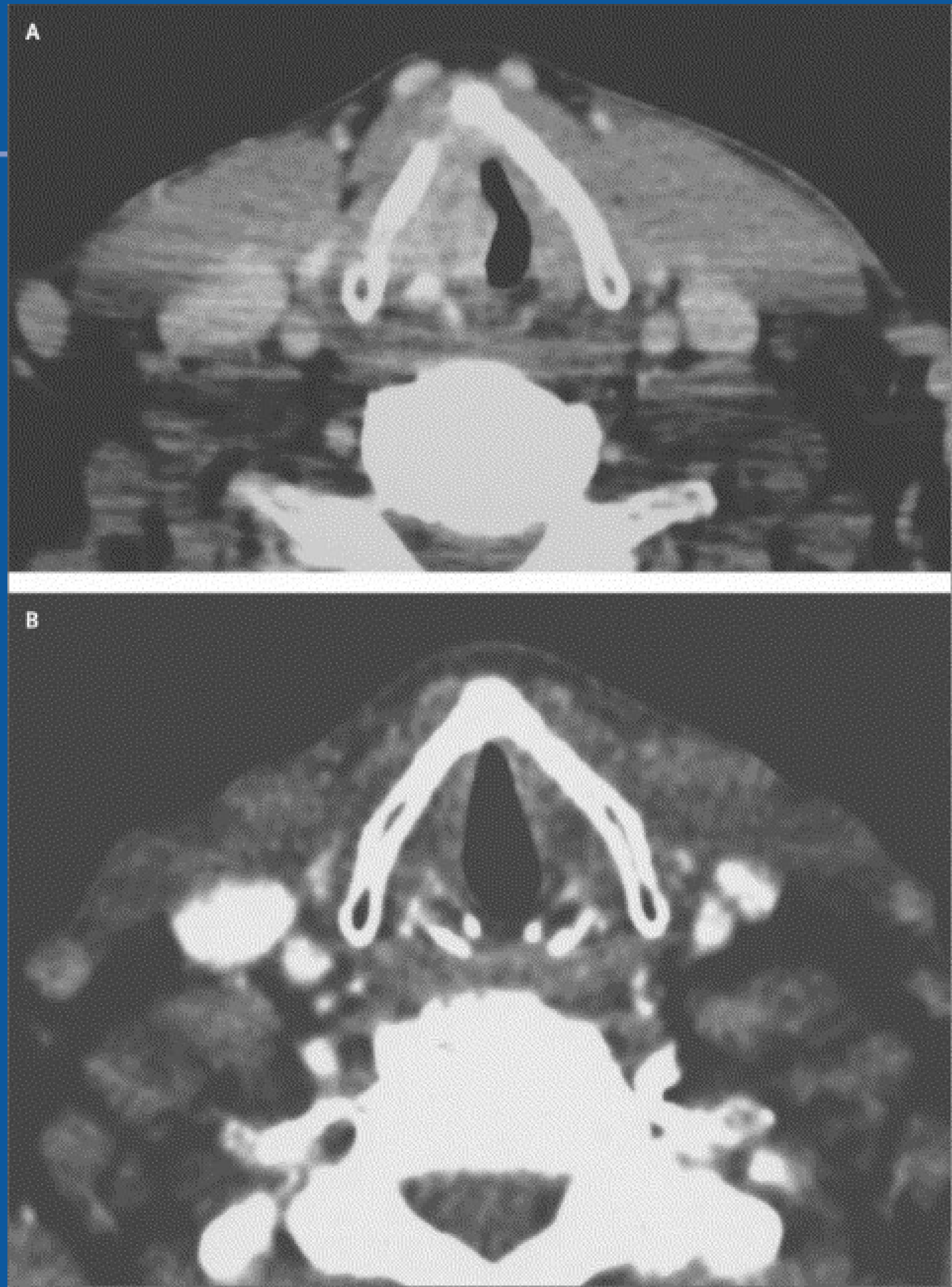
Gatta G EJC i2015

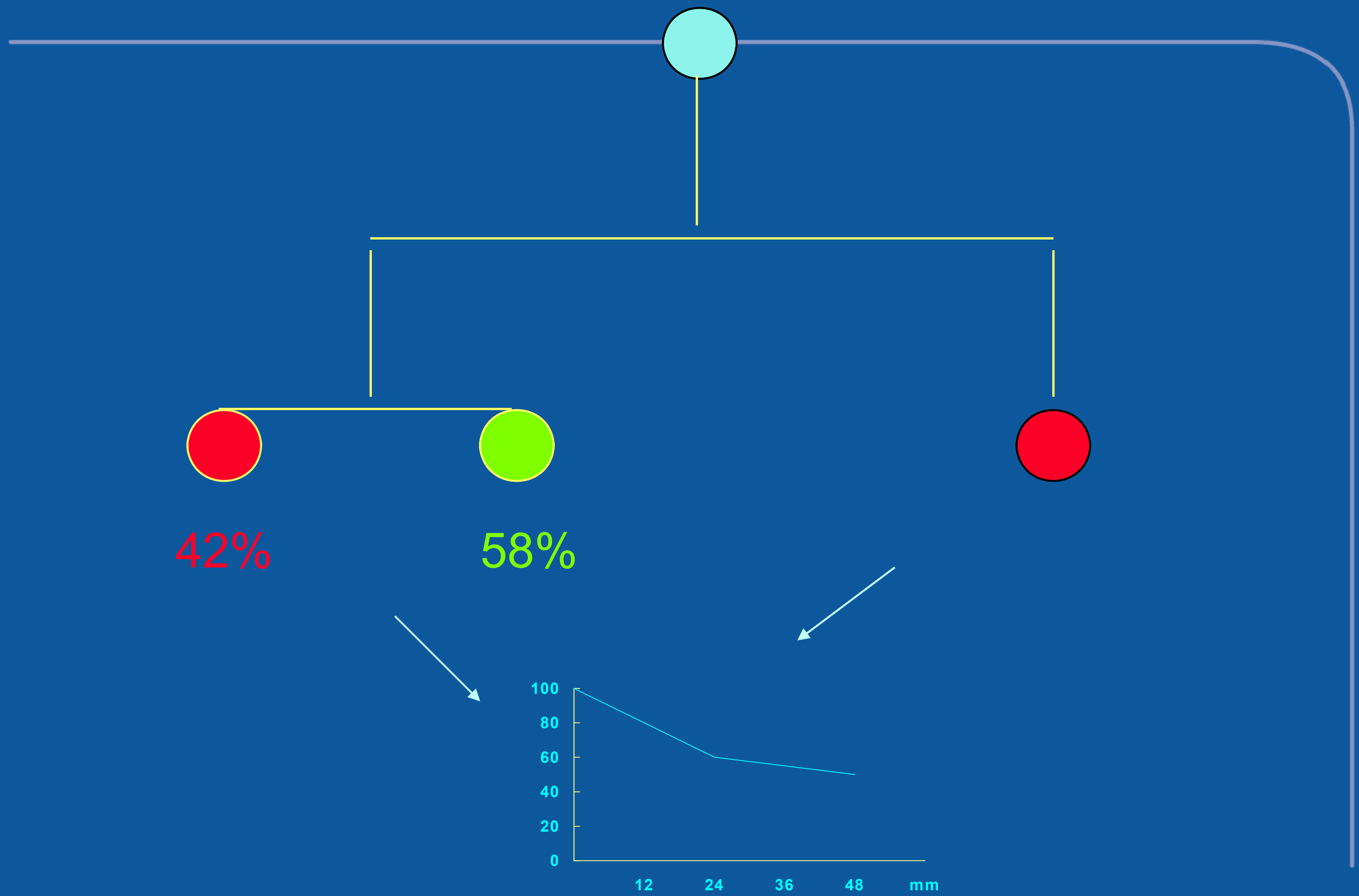
INDUCTION CHEMOTHERAPY PLUS RADIATION COMPARED WITH SURGERY PLUS RADIATION IN PATIENTS WITH ADVANCED LARYNGEAL CANCER

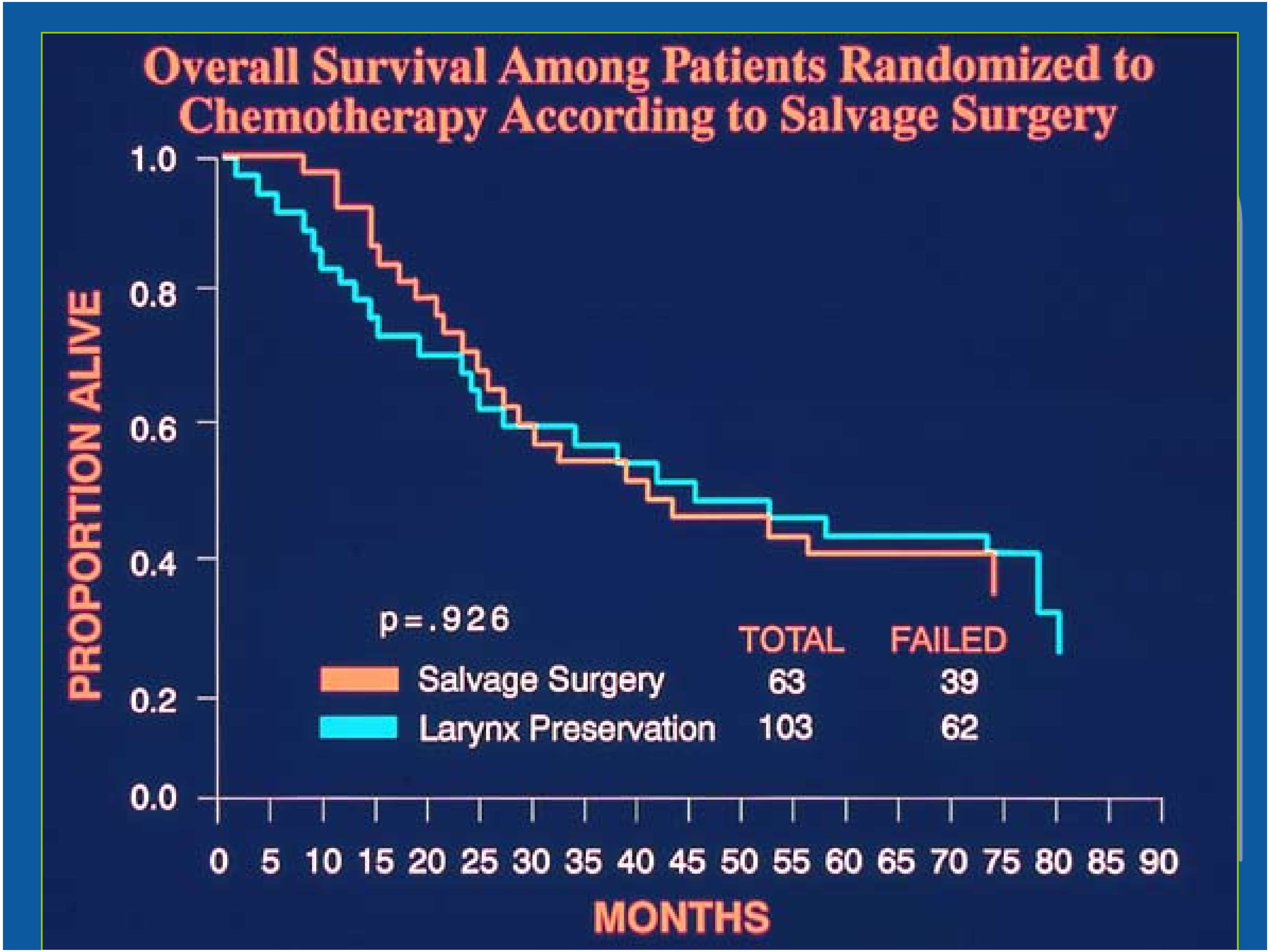
THE DEPARTMENT OF VETERANS AFFAIRS LARYNGEAL CANCER STUDY GROUP*

N Engl J Med 1991; 324: 1685-1690


R
CT x 2-3
PR + CR
RT
(surgery of N)
Surgery + RT
Surgery + RT


A
B


42%
58%
100
80
60
40
20
0
12
24
36
48
mm


Overall Survival Among Patients Randomized to Chemotherapy According to Salvage Surgery
PROPORTION ALIVE
1.0
0.8
0.6
0.4
0.2
0.0
p=.926
TOTAL
FAILED
Salvage Surgery
63
39
Larynx Preservation
103
62
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
MONTHS

VA Trial: Larynx Preservation

• RANDOMIZED PATIENTS	**166**
– Larynx preserved	**103 (62%)**
– Laryngectomy	**63**
• PATIENTS ALIVE	**79**
– With larynx	**52 (66%)**
– Without larynx	**27**

Pattern of relapse

	Surg+RT	CT > RT (Surg)
local	2%	12%
regional	5%	8%
distant	17%	11%

CLINICAL FACTORS FOR LP

- Supraglottic cancers
- Mobile vocal cords
- No involvement of cartilage
- Stage III
- < T4
- T size (> 4, 4-9, 10-14, >15 cm)
- Growth pattern

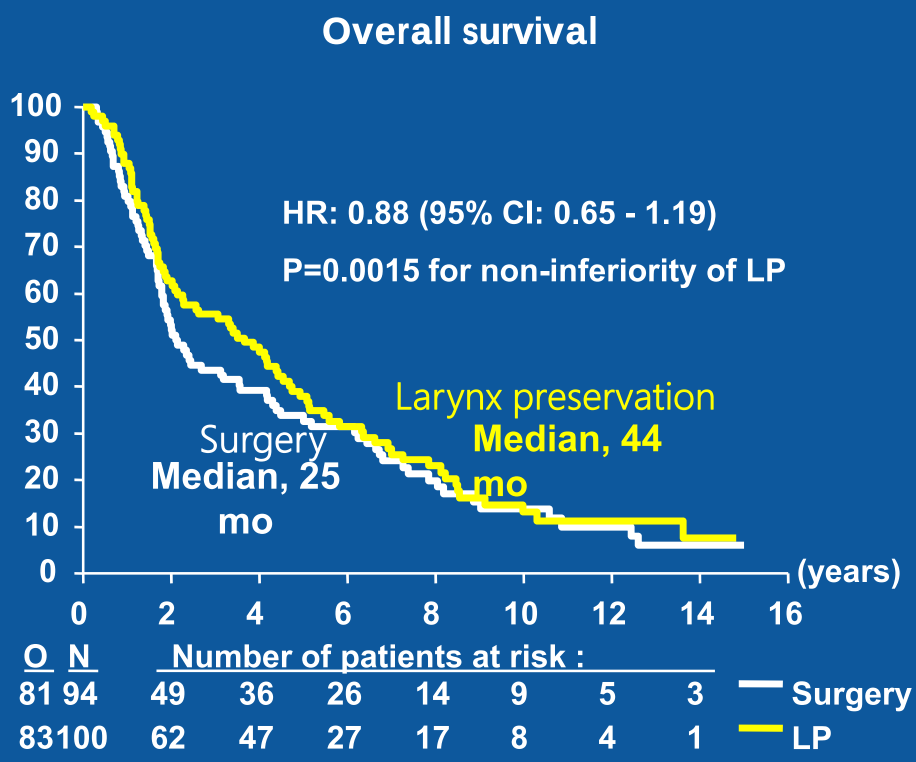
Is Laryngeal Preservation (LP) With Induction Chemotherapy (ICT) Safe in the Treatment of Hypopharyngeal SCC? Final Results of the Phase III EORTC 24891 Trial.

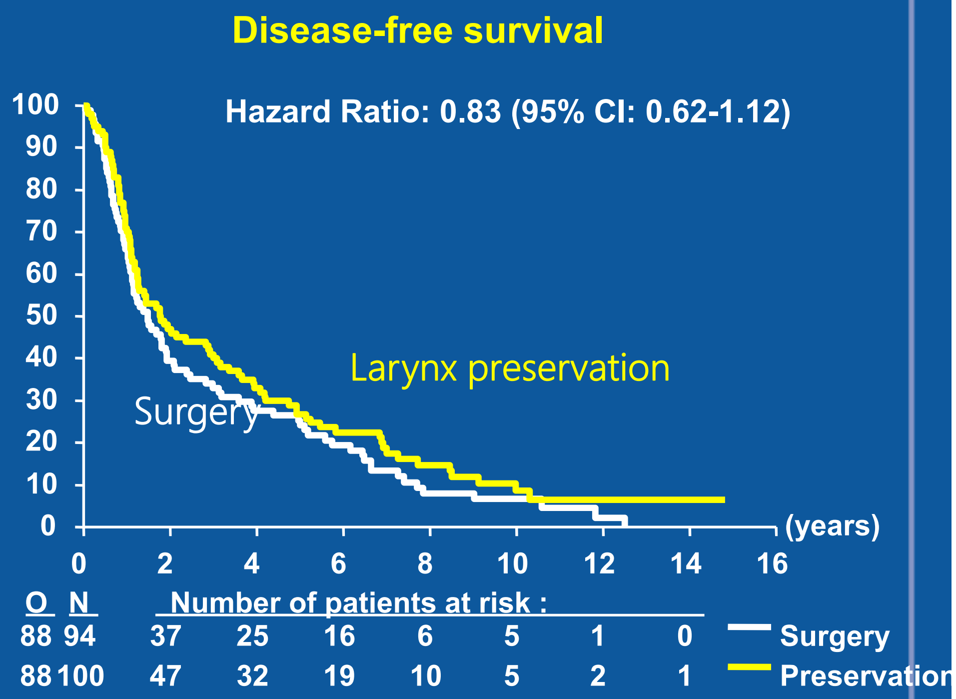
J. L. Lefebvre, D. Chevalier, B. Luboinski, L. Traissac, G. Andry, D. De Raucourt, L. Collette, J. Bernier, EORTC Head and Neck Cancer Cooperative Group.

F R A N C E

Last Update: ASCO 2004

Overall Survival and DFS

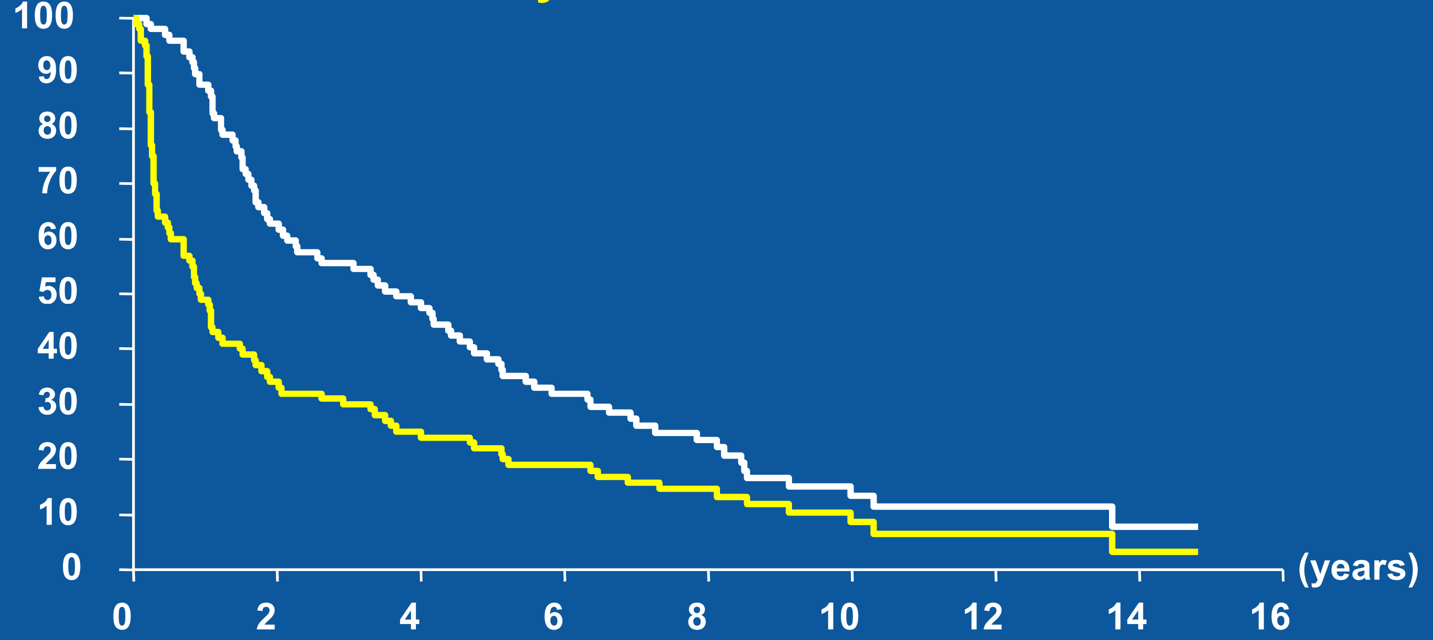




Lefebvre JL, et al. ASCO 2004: Abstract 5531.

Larynx Preservation Arm

Survival and Larynx Preservation in the Larynx Preservation Arm



O	N	Number of patients at risk :						
83	100	62	48	28	17	8	4	1
90	100	34	25	18	11	5	3	1

Overall survival
Survival with Larynx

13% of patients stopped chemotherapy due to toxicity

Lefebvre JL, et al. ASCO 2004: Abstract 5531.

Avoiding total laryngectomy with induction CT : meta-analysis of 3 randomized trials

and additional data ICT vs CT-RT

Jean Bourhis, MD for the MACH-NC team

MACH-NC

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Larynx preservation with induction CT : 3 randomized trials

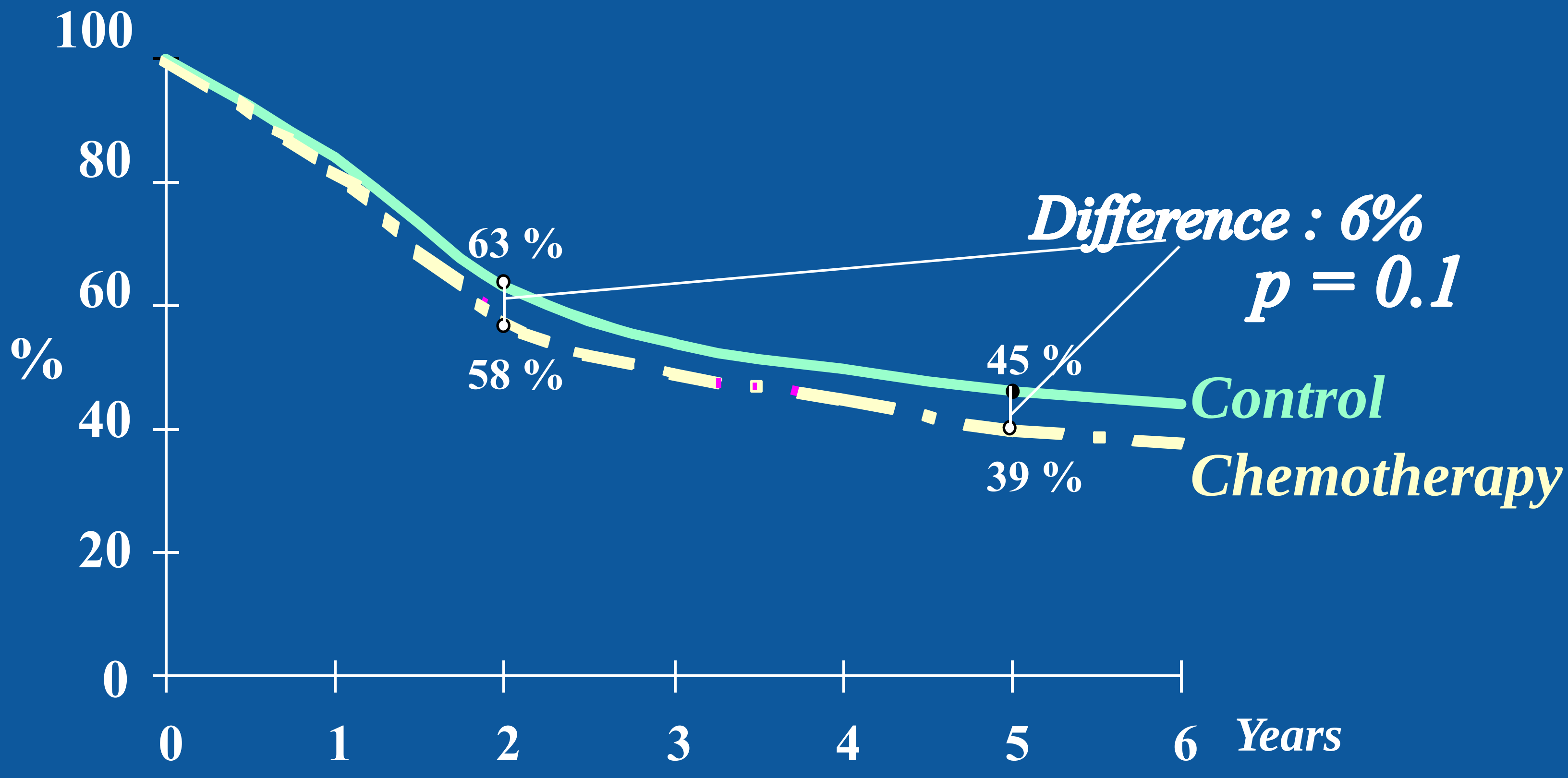
Trial		Subsite	
VALCSG	Larynx (n=332)	Glottic/subglottic Supraglottic	37 % 63 %
GETTEC	Larynx (n=68)	Glottic/subglottic Supra glottic 2/3 sites	41 % 31 % 28 %
EORTC	Hypopharynx (n=202)	Hypopharynx Lateral epilarynx	78 % 22 %

Lancet 2000;355:949-55

MACH-NC

Overall survival

Meta-Analysis of Chemotherapy in Head & Neck Cancer

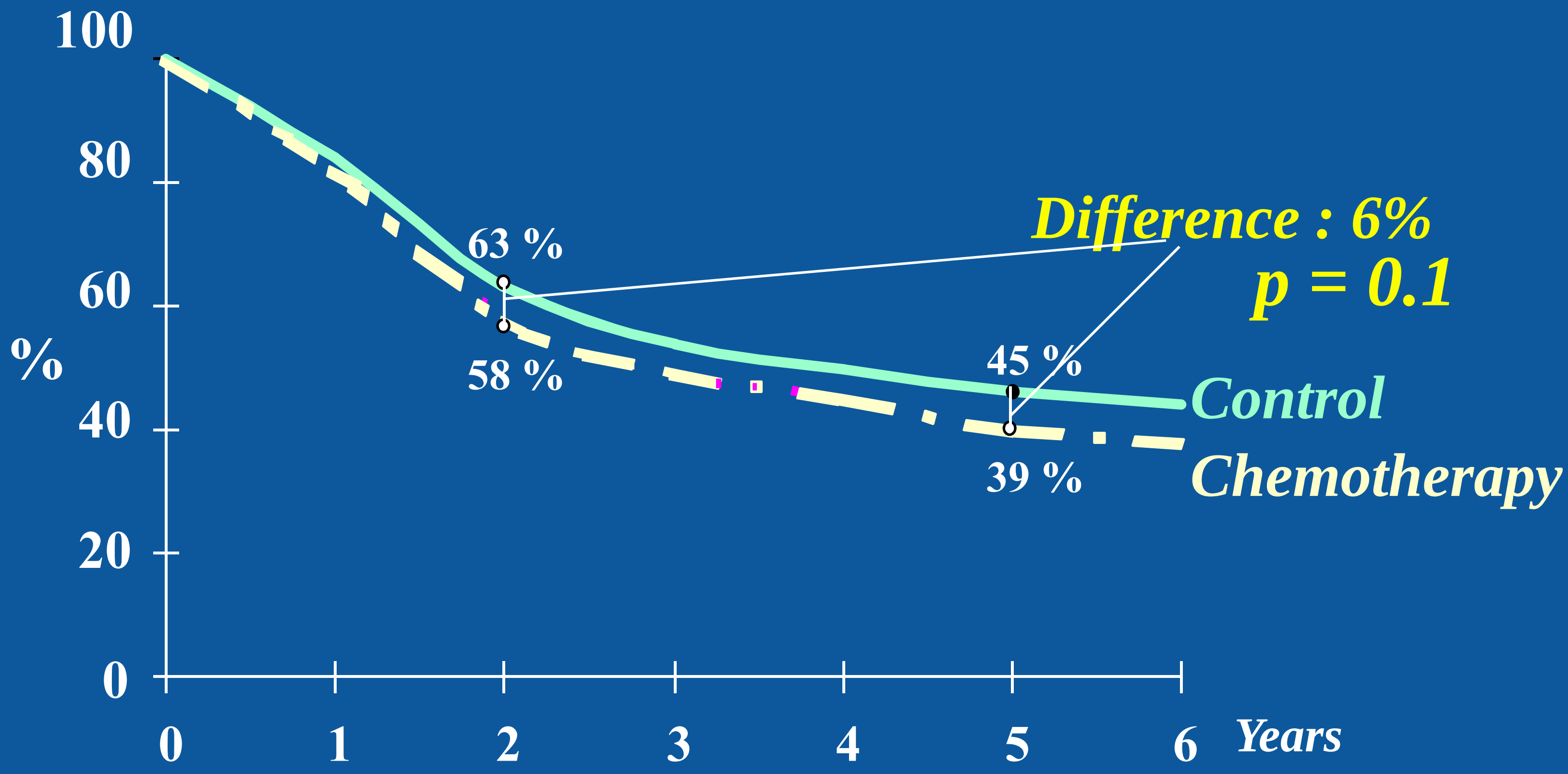


Control :	297	251	188	161	119	86	56
Chemotherapy	305	258	199	165	117	77	54

DFS by treatment

MACH-NC

Meta-Analysis of Chemotherapy in Head & Neck Cancer



Control :	297	251	188	161	119	86	56
Chemotherapy	305	258	199	165	117	77	54

VOLUME 31 · NUMBER 7 · MARCH 1 2013

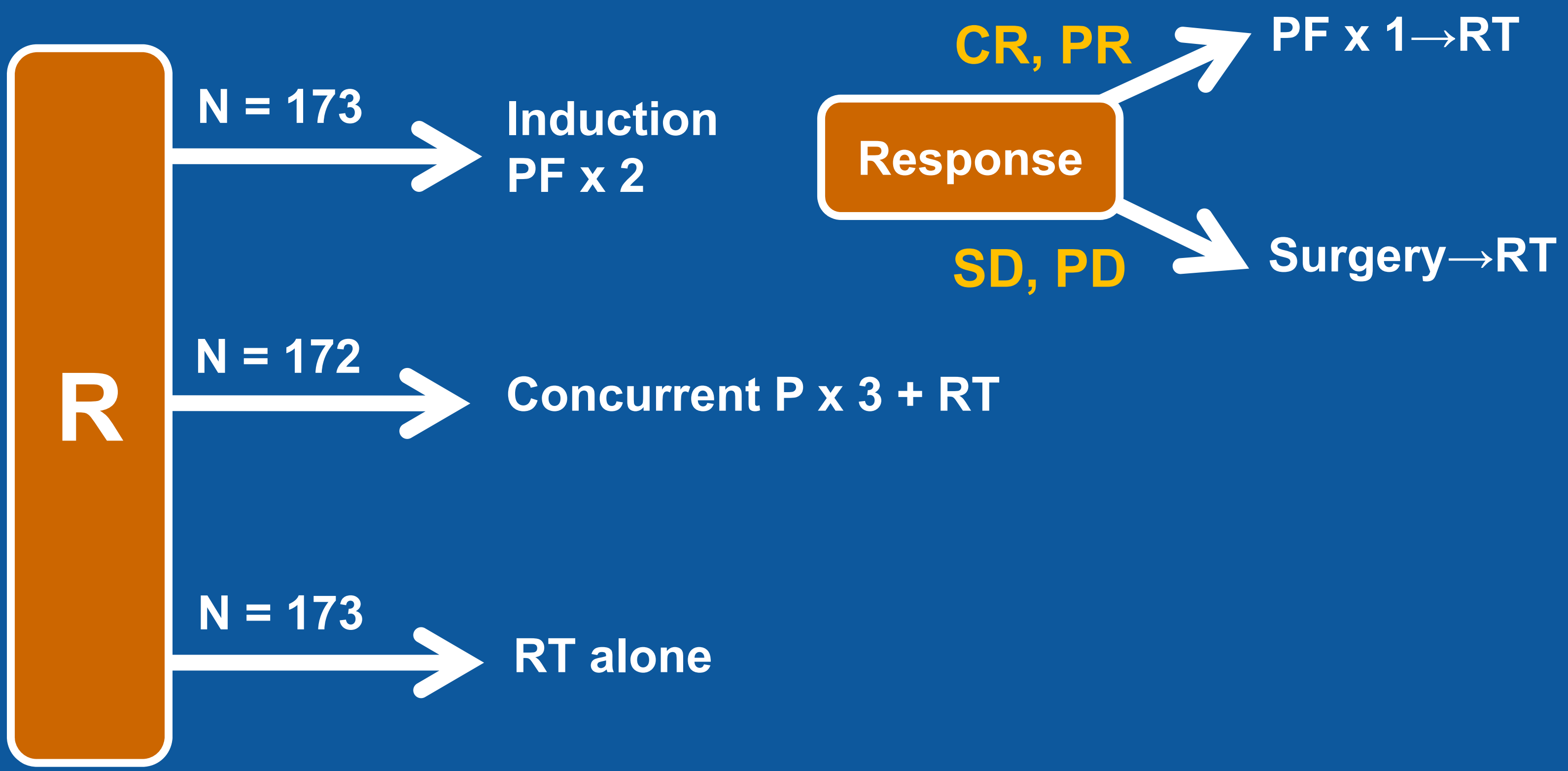
JOURNAL OF CLINICAL ONCOLOGY

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

Study Design



Primary endpoint: Larynx preservation

Secondary endpoints: OS, DFS, laryngectomy-free survival

Primary organ preservation with surgical salvage accepted for all 3 study arms.
Neck dissection included N_2 N_3 disease.

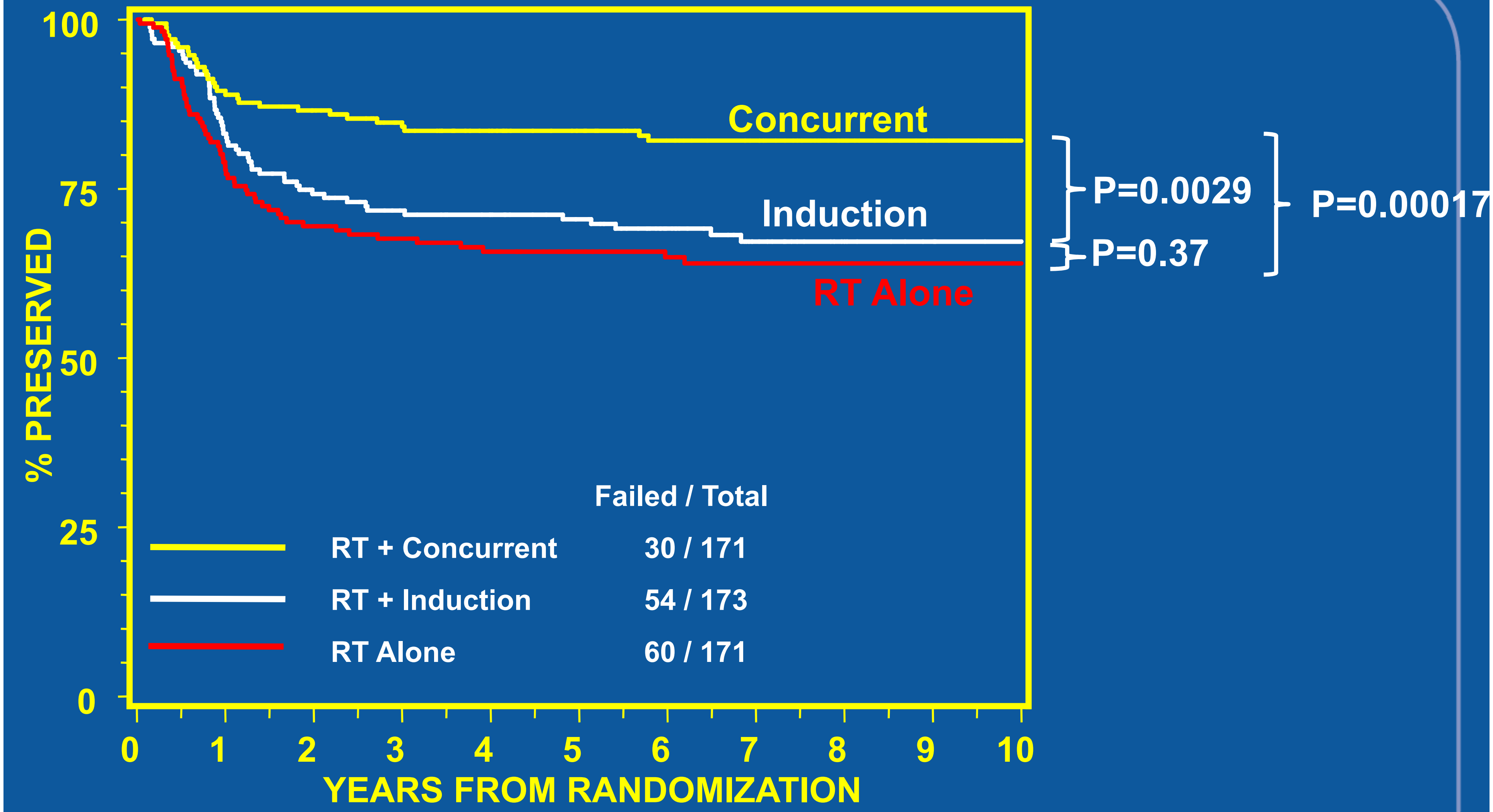
Forastiere AA, et al. N Engl J Med 2003;349:2091-8; Forastiere AA et al. ASCO 2006. Abstract 5517.

Patient Characteristics

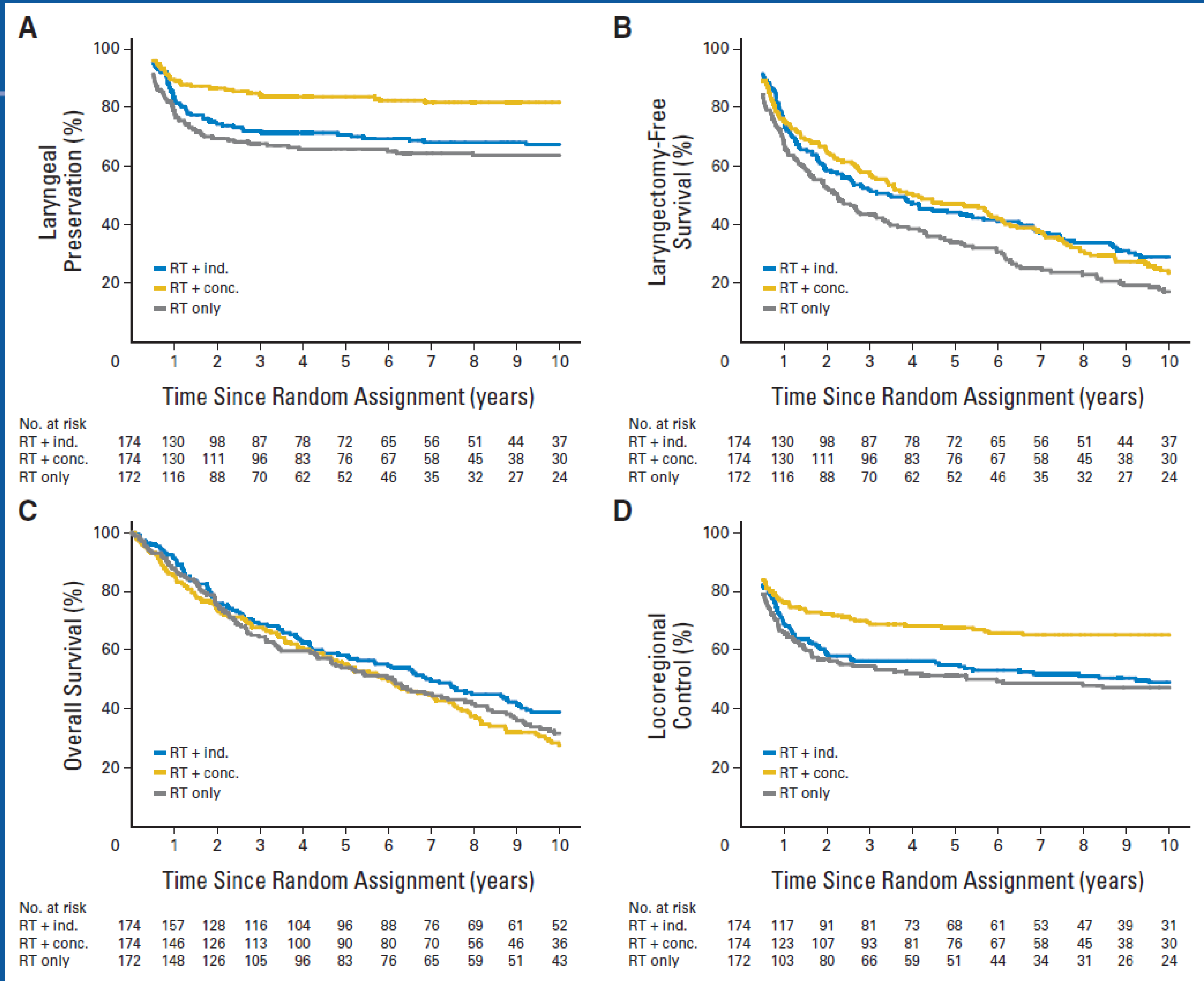
Characteristic	Induction n = 173 (%)	Concurrent n = 172 (%)	RT (N=173) (%)
Supraglottis	68	66	72
Glottis	32	34	28
Karnofsky PS 90-100	71	81	69
80	22	16	24
60-70	7	4	2
Stage III	64	67	64
T T2	11	12	12
T3 fixed cord	47	48	44
T3 no fixation	31	30	35
T4	10	10	9
N N0	50	50	50
N1	22	23	18
N2a	1	4	2
N2b	10	8	8
N2c	15	13	21
N3	2	2	1

Forastiere AA, et al. N Engl J Med 2003;349:2091-8.

Larynx Preservation

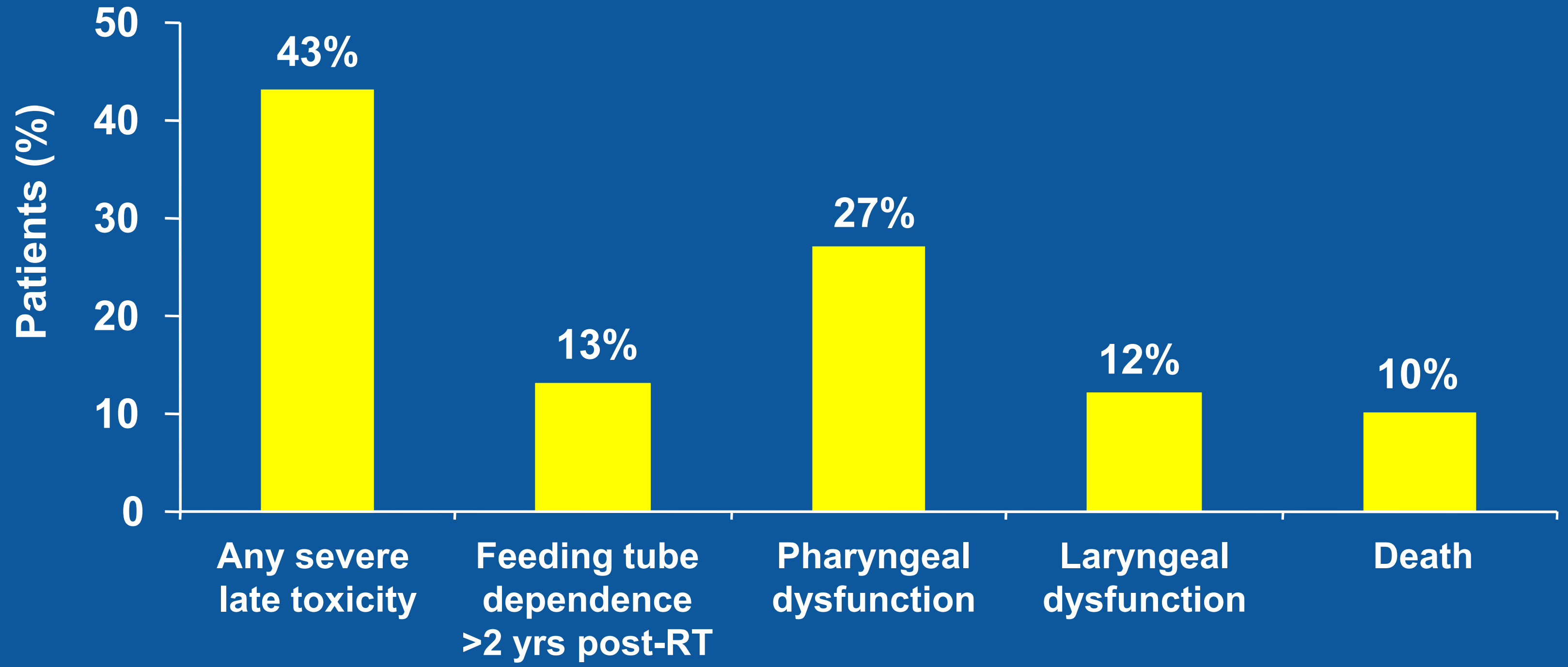


Forastiere AA et al. ASCO 2006. Abstract 5517.


A
Laryngeal Preservation (%)
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10
RT + ind.
RT + conc.
RT only
Time Since Random Assignment (years)
No. at risk
RT + ind. 174 130 98 87 78 72 65 56 51 44 37
RT + conc. 174 130 111 96 83 76 67 58 45 38 30
RT only 172 116 88 70 62 52 46 35 32 27 24
B
Laryngectomy-Free Survival (%)
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10
RT + ind.
RT + conc.
RT only
Time Since Random Assignment (years)
No. at risk
RT + ind. 174 130 98 87 78 72 65 56 51 44 37
RT + conc. 174 130 111 96 83 76 67 58 45 38 30
RT only 172 116 88 70 62 52 46 35 32 27 24
C
Overall Survival (%)
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10
RT + ind.
RT + conc.
RT only
Time Since Random Assignment (years)
No. at risk
RT + ind. 174 157 128 116 104 96 88 76 69 61 52
RT + conc. 174 146 126 113 100 90 80 70 56 46 36
RT only 172 148 126 105 96 83 76 65 59 51 43
D
Locoregional Control (%)
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10
RT + ind.
RT + conc.
RT only
Time Since Random Assignment (years)
No. at risk
RT + ind. 174 117 91 81 73 68 61 53 47 39 31
RT + conc. 174 123 107 93 81 76 67 58 45 38 30
RT only 172 103 80 66 59 51 44 34 31 26 24

CRT: Late toxicity

- Analysis of 230 patients receiving CRT in 3 studies (RTOG 91-11, 97-03, 99-14)
- Factors associated with development of severe late toxicity[a]
  – Older age (p=0.001), advanced T-stage (p=0.0036), larynx/hypopharynx primary (p=0.004), neck dissection after RT (p=0.018)



[a] Chronic grade 3-4 pharyngeal/laryngeal toxicity and/or requirement for feeding tube >2 years after registration and/or potential treatment-related death within 3 years

Machtay M, et al. J Clin Oncol 2008;26: e-pub June 16

Pts at risk

- Primary site (larynx, hypopahrynx)
- Age
- CT
- Previous planned dissection

ARTICLE

Randomized Trial of Induction Chemotherapy With Cisplatin and 5-Fluorouracil With or Without Docetaxel for Larynx Preservation

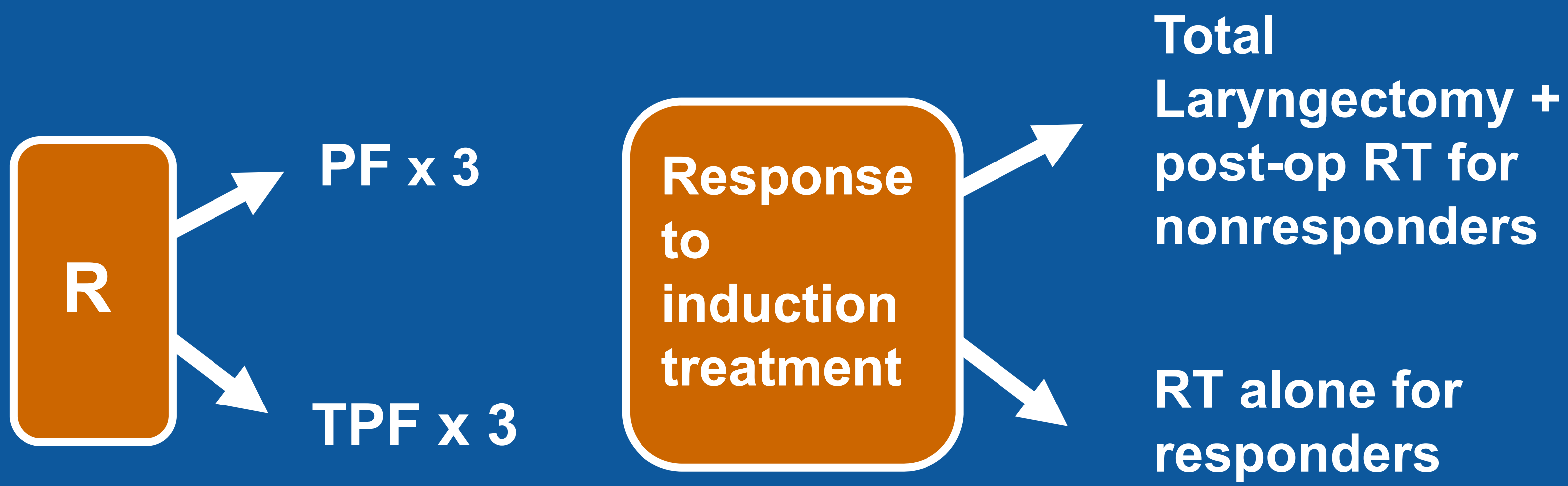
Yoann Pointreau, Pascal Garaud, Sophie Chapet, Christian Sire, Claude Tuchais, Jacques Tortochaux, Sandrine Faivre, Stephane Guerrif, Marc Alfonsi, Gilles Calais

JNCI 2009

Study Design

N = 220 patients (7 ineligible)

110 in TPF arm and 103 in the PF arm



Primary endpoint:

- Larynx preservation

Secondary endpoints

- Overall survival, DFS, toxicity

Calais G, et al.

Patient Characteristics

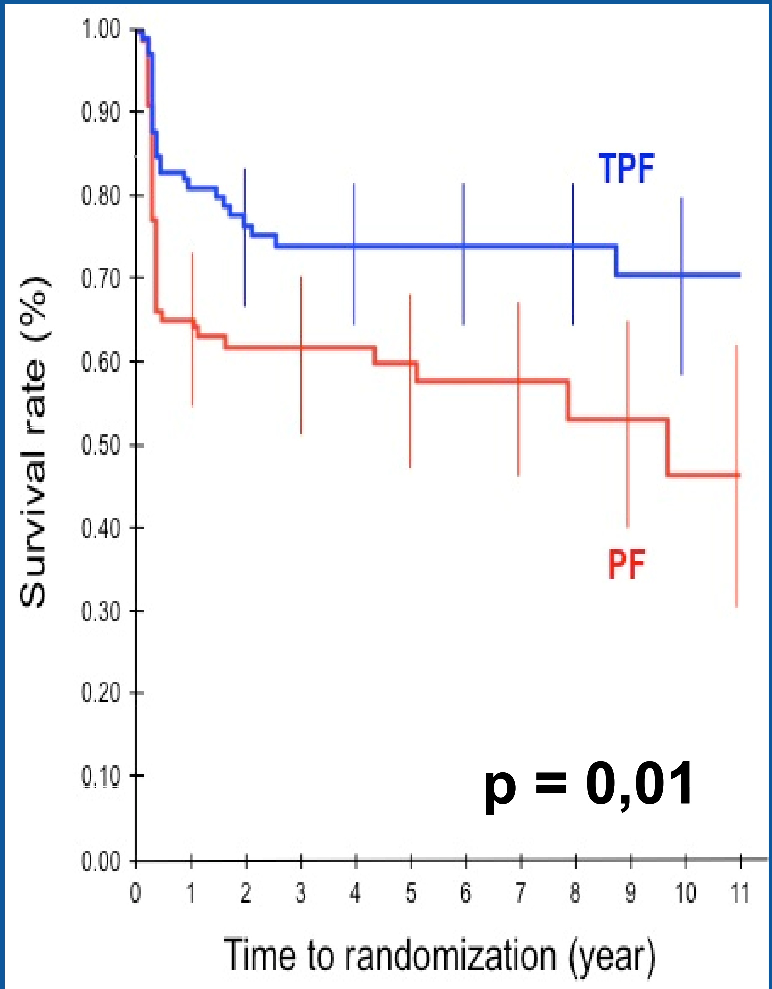
Characteristic	TPF n = 110	PF n = 103
Hypopharynx	61	54
Larynx	49	49
PS = 0 / 1	51/59	51/52
TN Classification		
T2	15	22
T3	77	61
T4	14	16
N0	32	47
N1	28	21
N2a	12	10
N2b	13	13
N2c	14	6
N3	7	2

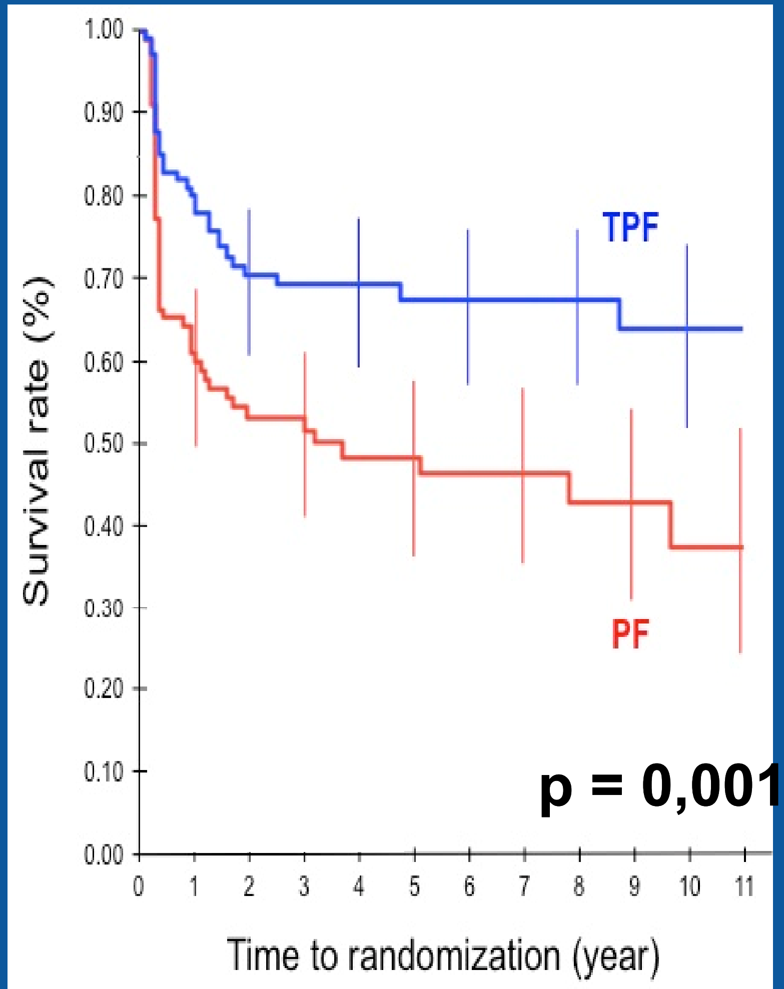
Calais G, et al.

Results

Larynx DysFunction Free Survival

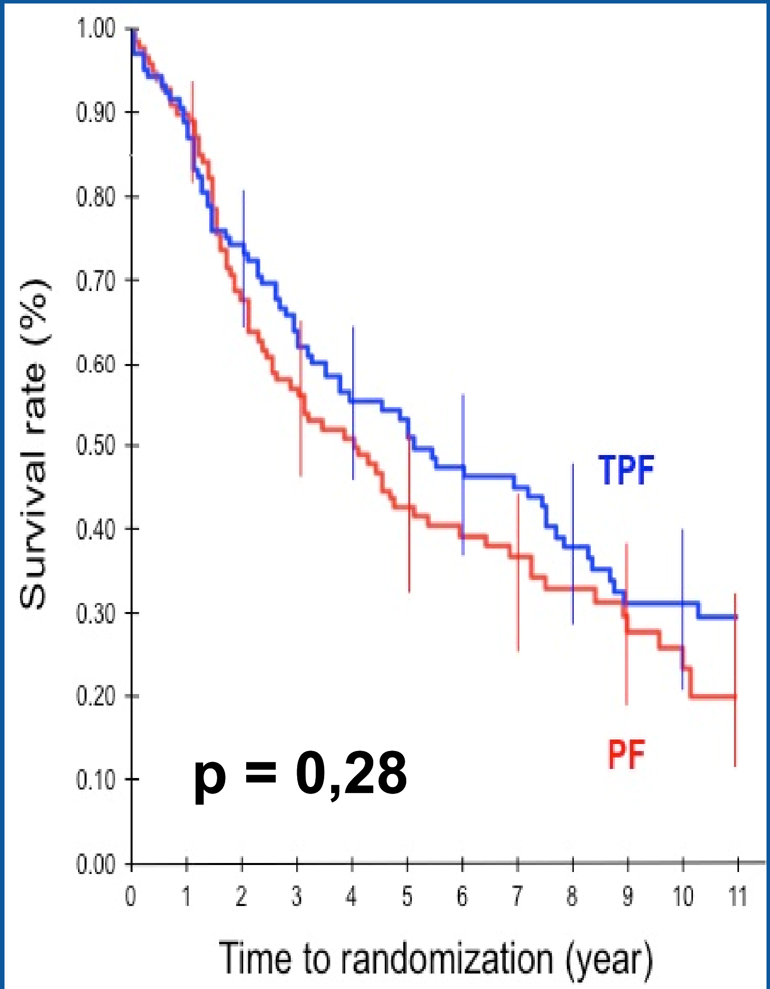
Larynx Preservation



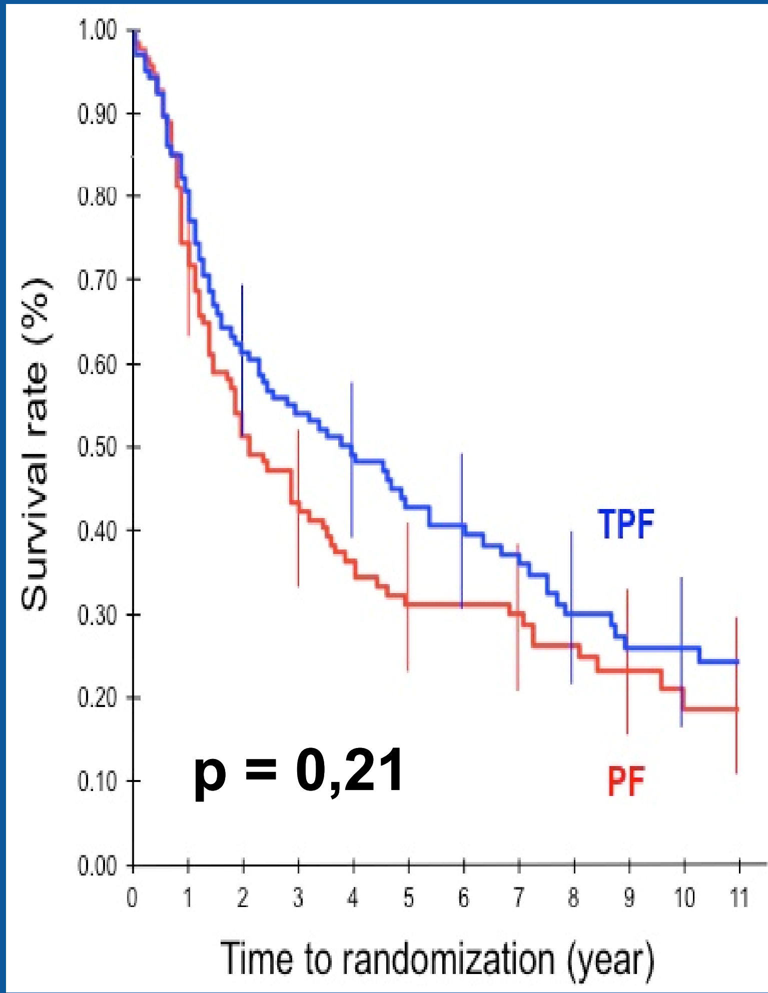


Results

Overall Survival



Disease Free Survival



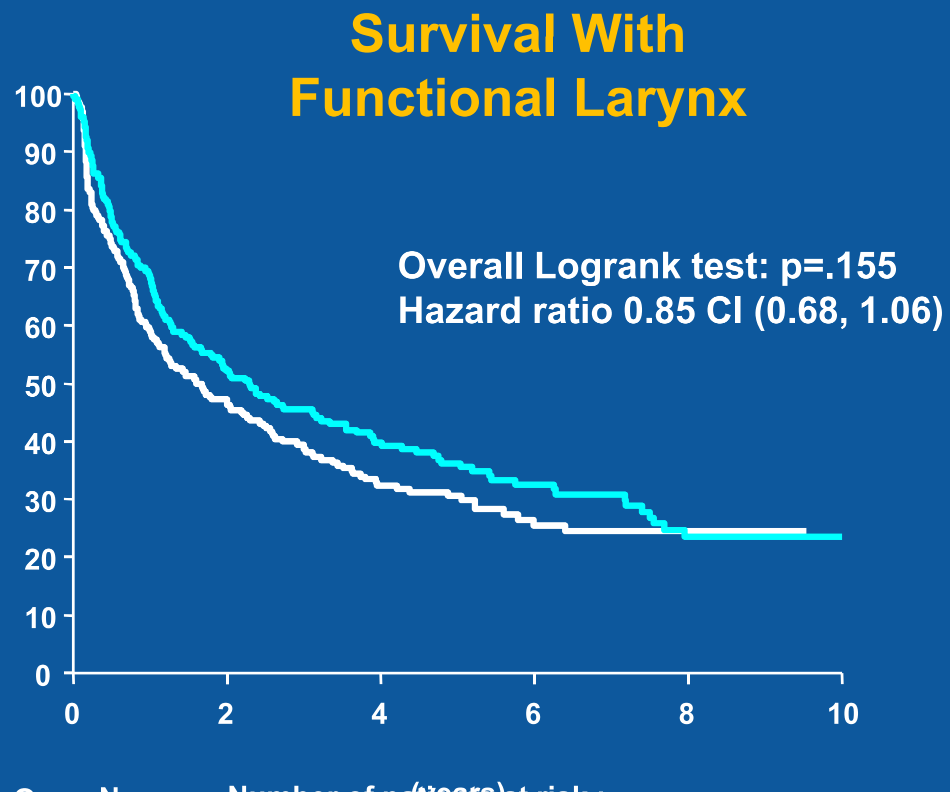
Phase 3 Randomized Trial on Larynx Preservation Comparing Sequential vs Alternating Chemotherapy and Radiotherapy

J. L. Lefebvre, F. Rolland, M. Tesselaar, E. Bardet, C. R. Leemans, L. Geoffrois, P. Hupperets, L. Barzan, D. de Raucourt, D. Chevalier, L. Licitra, F. Lunghi, R. Stupp, D. Lacombe, J. Bogaerts, J. C. Horiot, J. Bernier, J. B. Vermorken; for the EORTC Head and Neck Cancer Cooperative Group and the EORTC Radiation Oncology Group

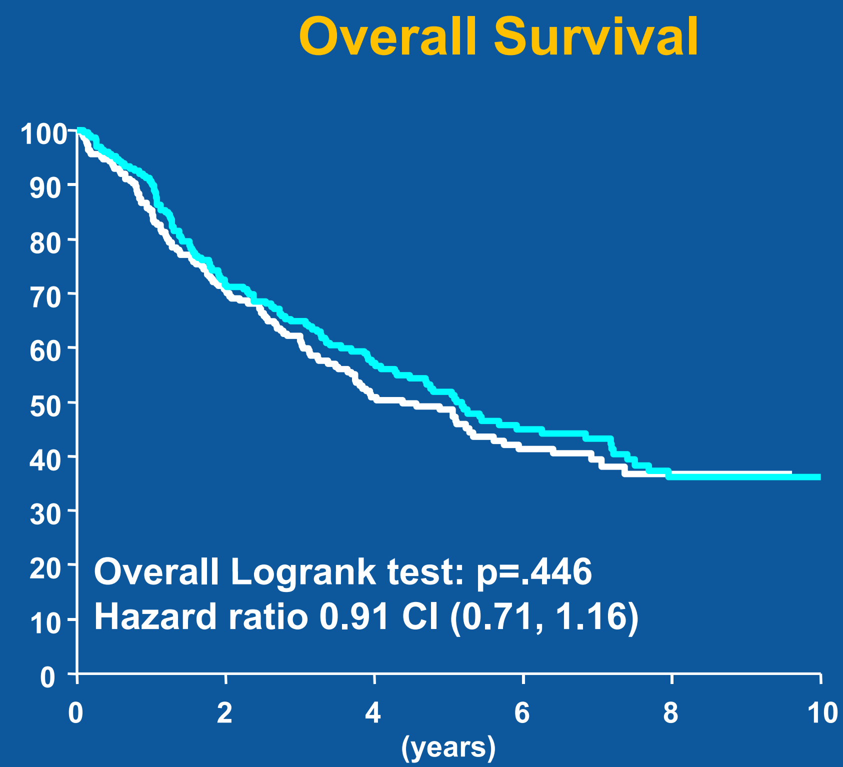
JNCI 2009

Survival

Median follow-up: 6.5 years



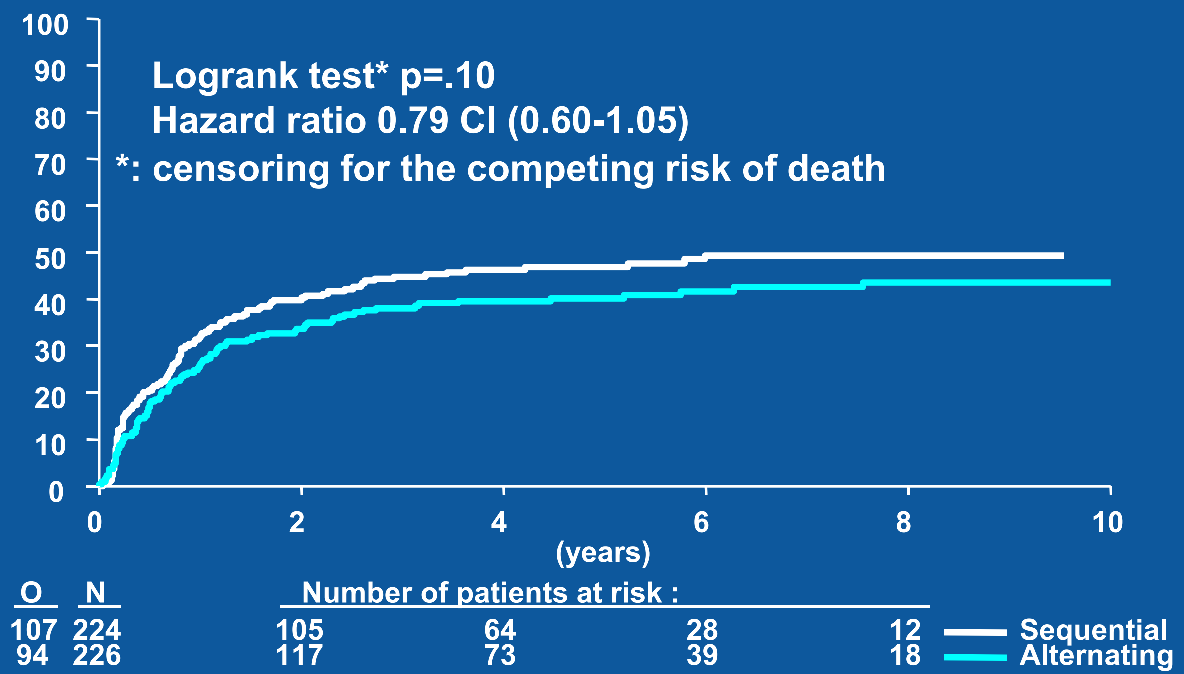
O	N	Number of patients at risk :				
160	224	105	64	28	12	Sequential
154	226	117	73	39	18	Alternating



O	N	Number of patients at risk :				
125	224	157	97	52	20	Sequential
122	226	160	105	57	29	Alternating

Lefebvre et al. *ASCO* 2007. Abstract LBA6016.

Larynx Preservation



	SEQ (N)	ALT (N)
Speaking: Intelligible /sociable	125	145
Swallowing: Normal diet, intake	111	135
Breathing: No dyspnea	111	131

Of patients without laryngectomy at their last report of functioning.

Lefebvre et al. *ASCO* 2007. Abstract LBA6016.

VOLUME 31 · NUMBER 7 · MARCH 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Induction Chemotherapy Followed by Either Chemoradiotherapy or Bioradiotherapy for Larynx Preservation: The TREMPLIN Randomized Phase II Study

Jean Louis Lefebvre, Yoann Pointreau, Frederic Rolland, Marc Alfonsi, Alain Baudoux, Christian Sire, Dominique de Raucourt, Olivier Malard, Marian Degardin, Claude Tuchais, Emmanuel Blot, Michel Rives, Emile Reyt, Jean Marc Tourani, Lionel Geoffrois, Frederic Peyrade, Francois Guichard, Dominique Chevalier, Emmanuel Babin, Philippe Lang, Francois Janot, Gilles Calais, Pascal Garaud, and Etienne Bardet

See accompanying editorial on page 833 and article on page 845

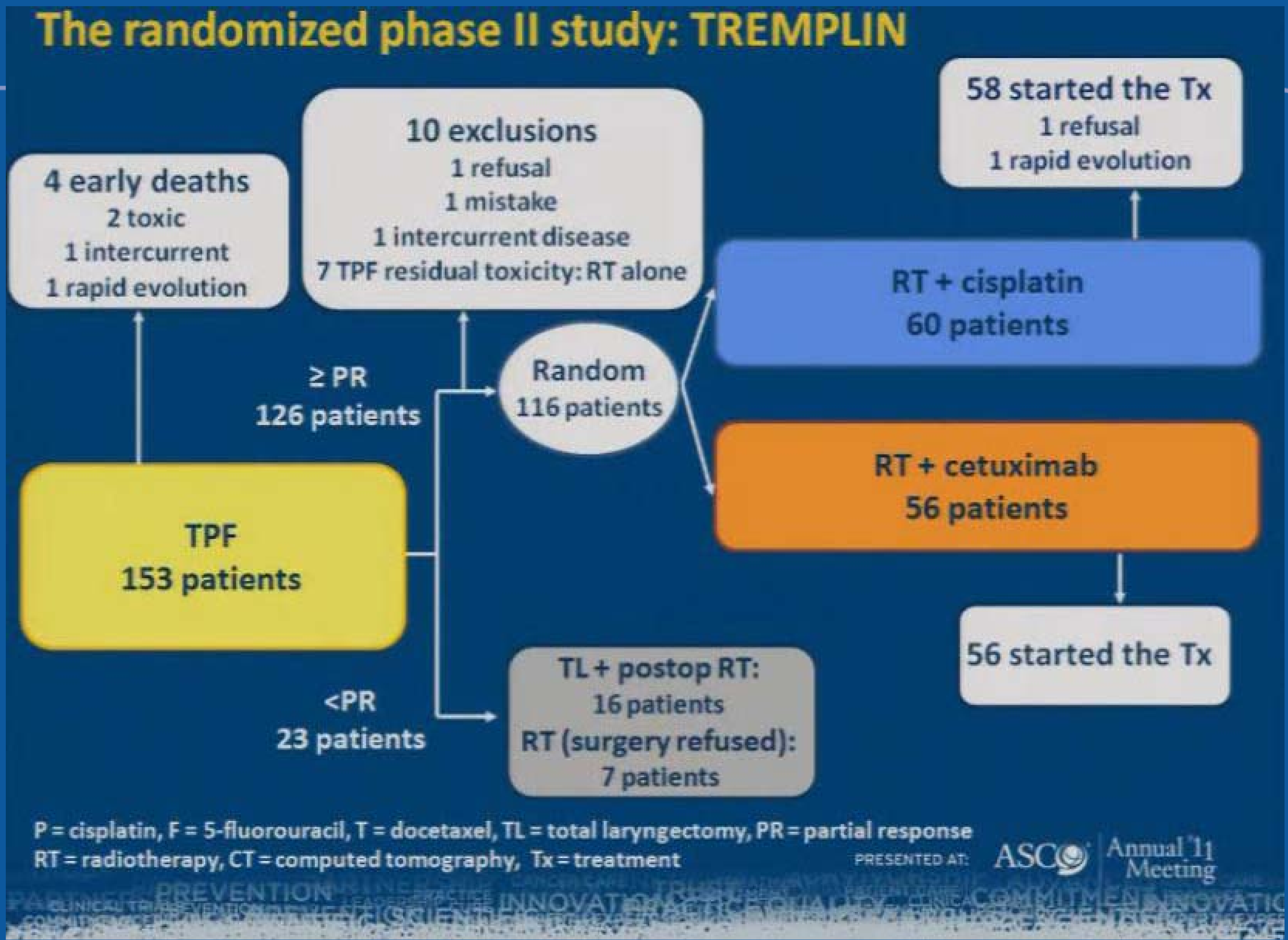

The randomized phase II study: TREMPLIN
4 early deaths
2 toxic
1 intercurrent
1 rapid evolution
10 exclusions
1 refusal
1 mistake
1 intercurrent disease
7 TPF residual toxicity: RT alone
58 started the Tx
1 refusal
1 rapid evolution
RT + cisplatin
60 patients
≥ PR
126 patients
Random
116 patients
RT + cetuximab
56 patients
TPF
153 patients
56 started the Tx
<PR
23 patients
TL + postop RT:
16 patients
RT (surgery refused):
7 patients
P = cisplatin, F = 5-fluorouracil, T = docetaxel, TL = total laryngectomy, PR = partial response
RT = radiotherapy, CT = computed tomography, Tx = treatment
PRESENTED AT: ASCO Annual '11 Meeting

Table 3. Acute Toxicity

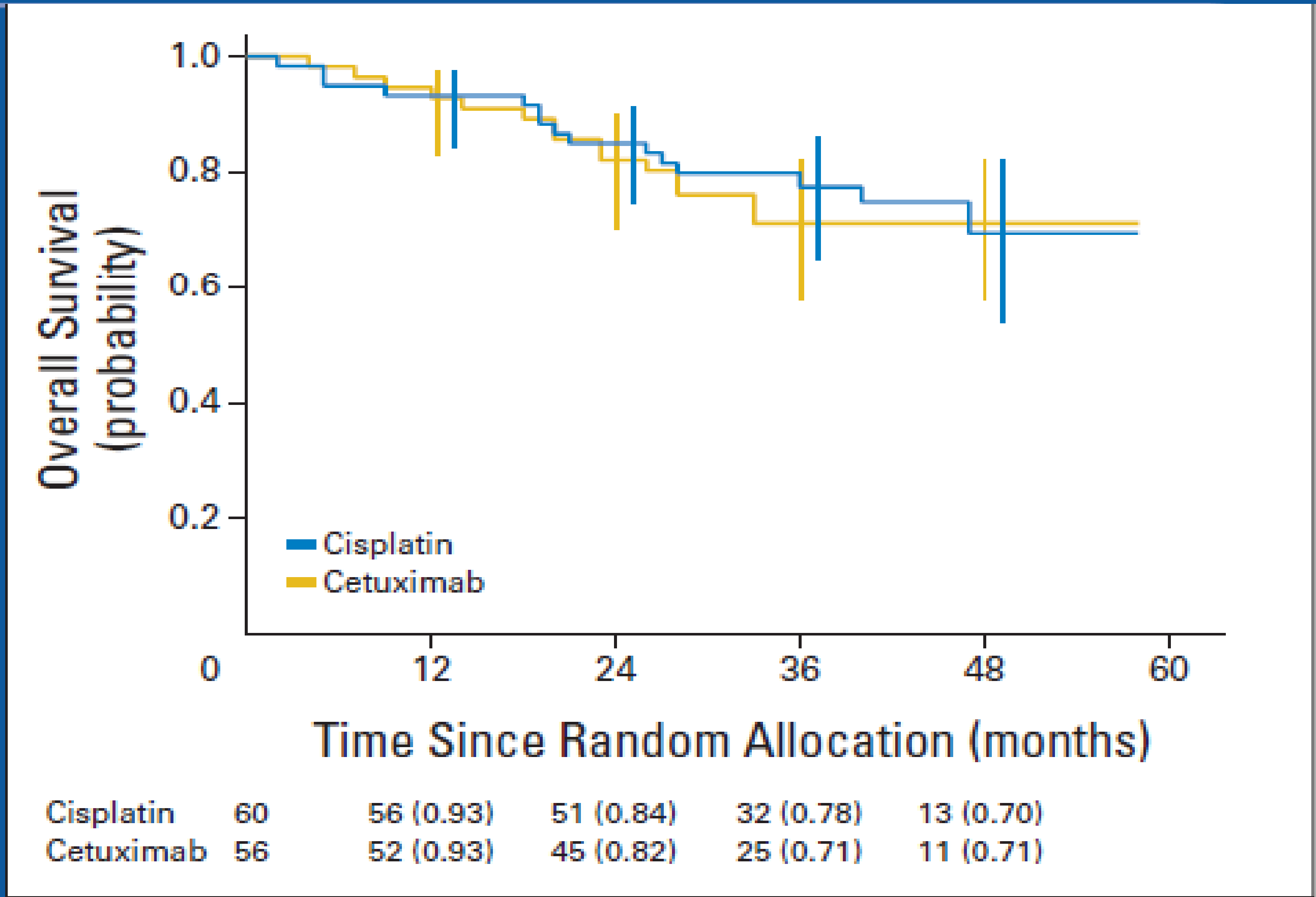
Variable	Cisplatin		Cetuximab	
	No.	%	No.	%
No. of patients	58*		56	
Mucositis grade				
3	25	43	24	43
4	2	3	1	2
In-field skin toxicity grade				
3	14	24	29	52
4	1	2	3	5
Other toxicity, any grade, justifying protocol modification				
Renal	9	15.5	0	
Hematologic	8	14	0	
Poor performance	7	12	1	1.7
Infusion-related reaction	0		3	5
Protocol modification due to acute toxicity	33	57	19	34

*Two patients did not start treatment.

Table 5. Treatment Failures and Salvage Surgery

	Patients 18 Months Post-Treatment				Patients at Last Evaluation*			
	Cisplatin		Cetuximab		Cisplatin		Cetuximab	
Variable	No.	%	No.	%	No.	%	No.	%
Local (with or without regional) failure	5†	8.3	8	14.3	8	13.3	12	21.4
Surgery feasible	**0**		**7**		**1**		**9‡**	
Surgery successful					**0**		**6**	
Ultimate local failure					8	13.3	6	10.7
Regional failure only	5	8.3	5	8.9	4	6.7	5	8.9
Surgery feasible					**1**		**4**	
Surgery successful					**0**		**1**	
Ultimate regional failure					4		4	
Distant metastases					5	8.3	3	5.4
Second primary cancer					7	11.7	8	14.3

*Median follow-up, 36 months; maximum follow-up, 58 months in each arm.
†One patient with uncontrolled disease lost to follow-up.
‡One patient refused all further treatment, including salvage surgery.



Overall Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
12
24
36
48
60
Time Since Random Allocation (months)
Cisplatin
Cetuximab
Cisplatin 60 56 (0.93) 51 (0.84) 32 (0.78) 13 (0.70)
Cetuximab 56 52 (0.93) 45 (0.82) 25 (0.71) 11 (0.71)

Conclusions

- Organ preservation in selected stage III and IV laryngeal/hypopharyngeal cancer pts is a SOC option
- MDT is essential
- Tumor biology will help in pt selection

Management of nasopharyngeal cancer

Cai Grau

Professor, MD, DMSc, Department of Oncology
Aarhus University Hospital, Aarhus, Denmark
caigrau@dadlnet.dk
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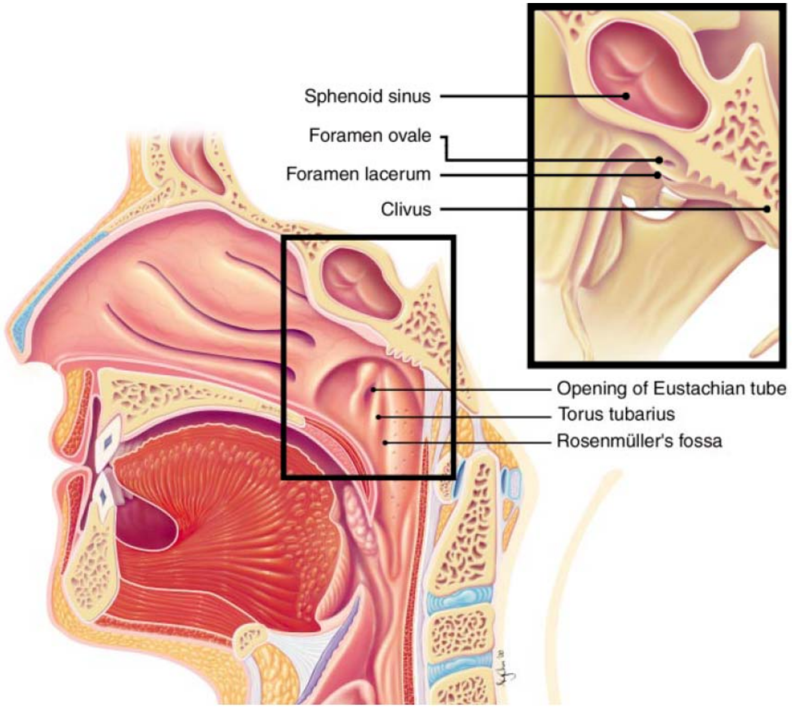
Firenze 2016

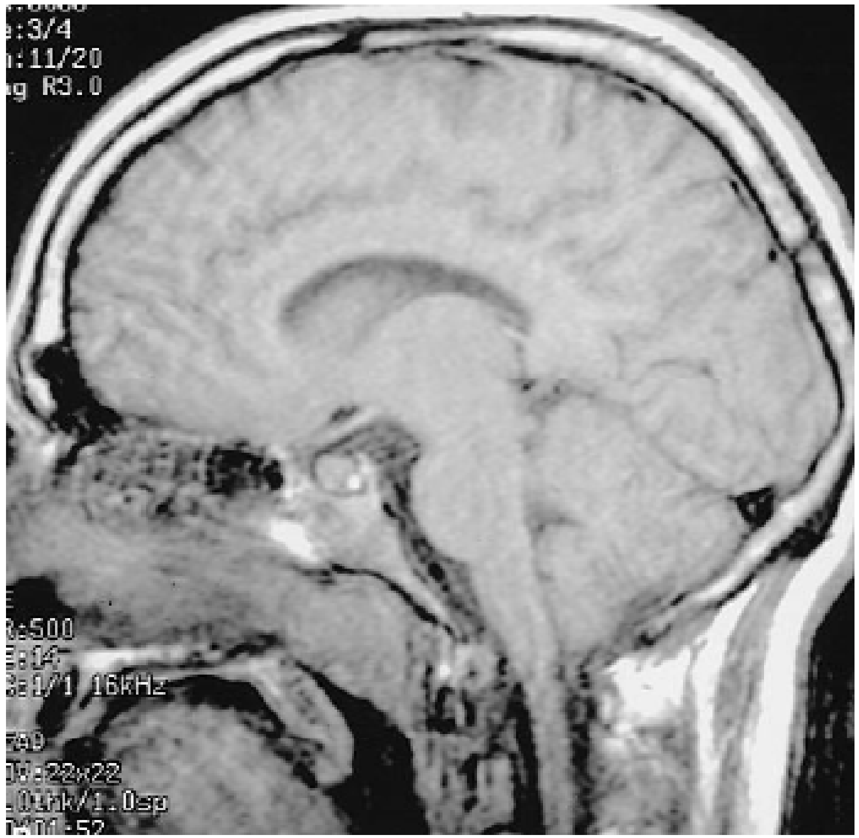
ESTRO School

Topics

- Anatomy, aetiology, pathology, staging
- Radiotherapy (IMRT, volumes, techniques)
- Chemotherapy
- Radiotherapy morbidity
- Novel approaches
- Salvage treatment of loco-regional recurrences (re-irradiation, surgery, brachy)



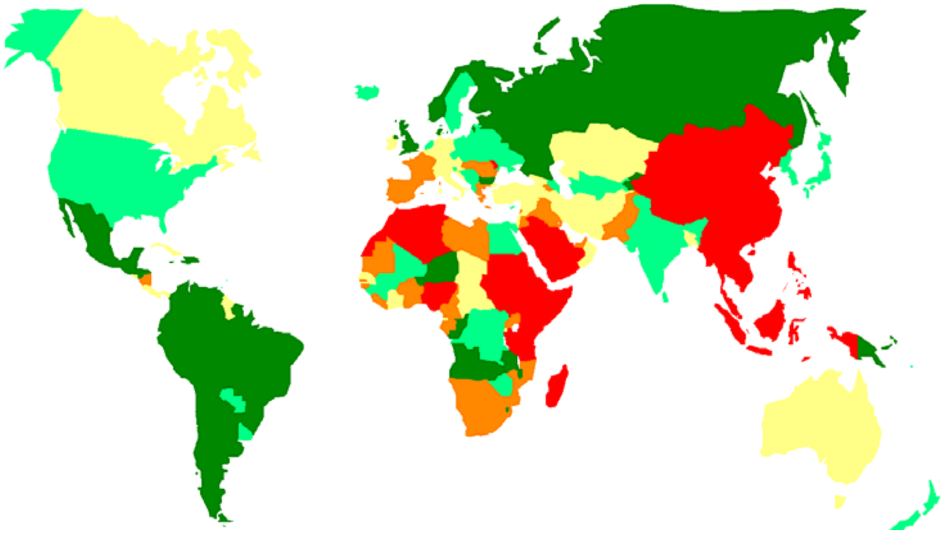
Anatomy



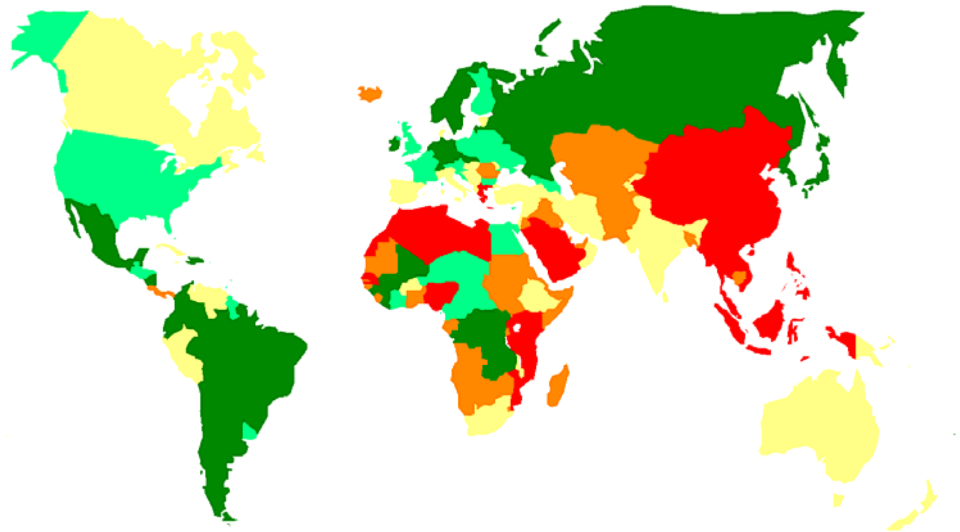
- Nasal cavity
- Oropharynx
- Base of skull
- C1 (odontoid proces)

- Spinal cord, brain stem
- Parotid gland
- Inner ear
- Pituitary gland
- Optic chiasm
- Temporal lobes

Global Incidence



Males



Females

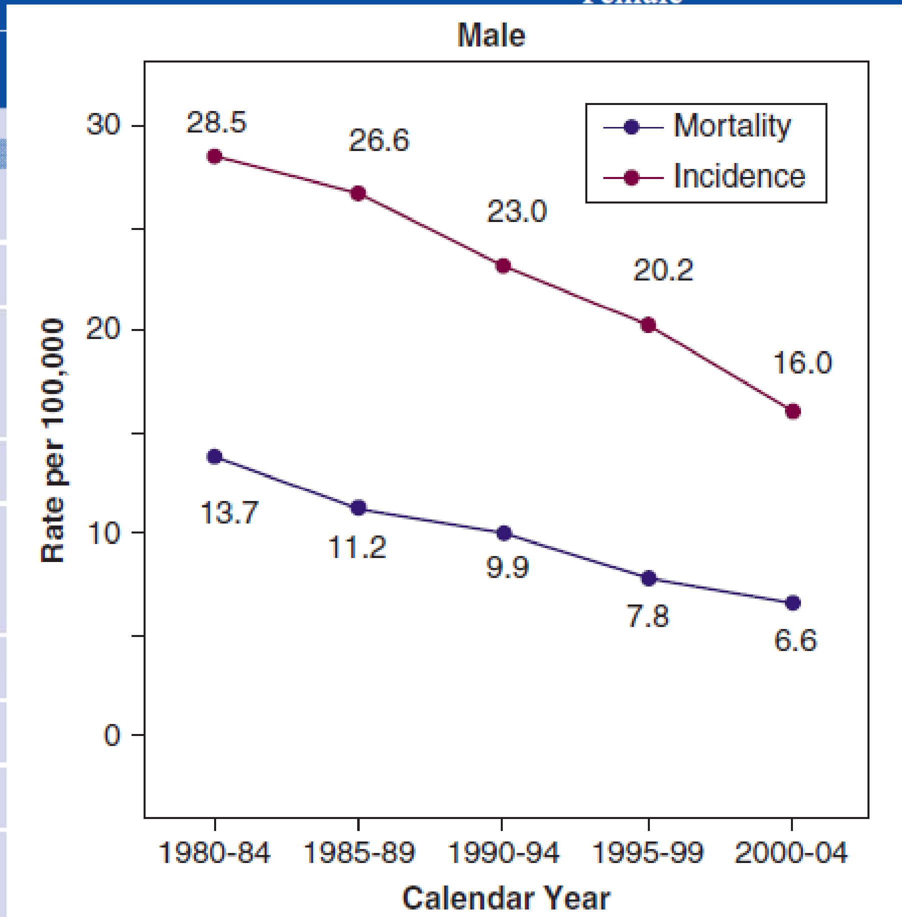
- ASR (cases/100.000/year) is <1 among Caucasians compared to >20 among Southern Chinese males
- Chinese immigrant populations to western countries have progressively lower NPC risk, but their incidence remains higher than the 'native' populations
- NPC incidence rate in Chinese born in the Orient 20.5, compared with 1.3 for Chinese born in Canada, and 0.2 for white people born in Canada
- First-degree relatives of NPC patients have 4–10 fold excess risk

Pathology

WHO	I Keratinizing squamous cell ca	II Non-keratinizing carcinoma	III Undifferentiated carcinoma
USA	25%	12%	63%
Southern China	2%	3%	95%

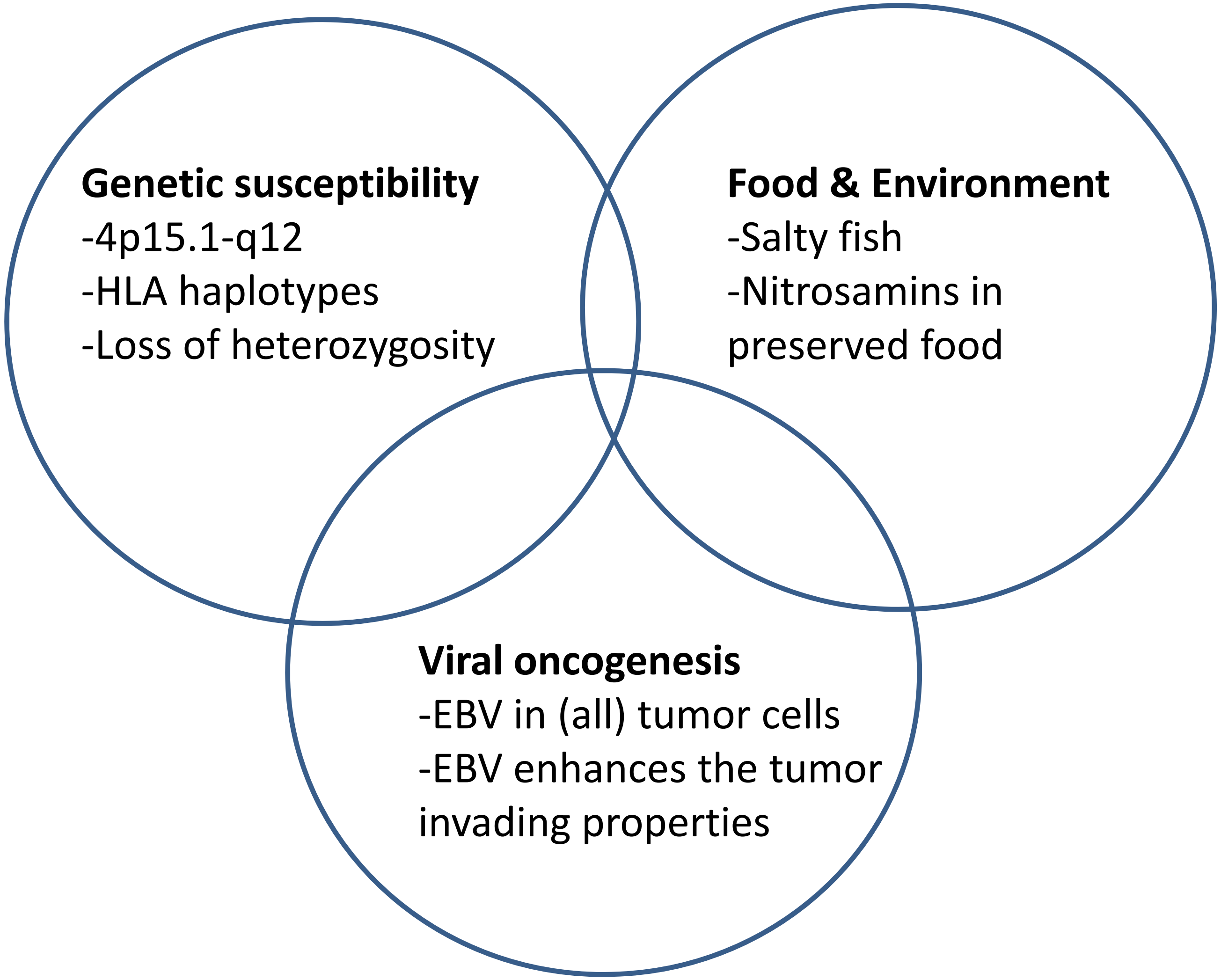
Incidence in different communities during different periods

Year	Male				Female			
	1978–1982						1988–1992	1993–1997
China								
Hong Kong	30.0						9.5	8.3
Shanghai	4.4						1.8	1.5
Singapore								
Chinese	18.1						7.3	5.4
Indian	0.3						0.5	0.1
United States								
SEER: White	NA						0.2	0.2
SEER: Black	NA						0.2	0.3
LA: Chinese	9.9						2.8	2.4
England	0.4						0.2	0.2
Australia								
NSW	0.8	0.8	0.9	0.9	0.3	0.2	0.3	0.4



From Lee A.W. M. et al. (2009): Nasopharynx. In "Function Preservation and Quality of Life in Head and Neck Radiotherapy".

Ethiological factors



Diagnostic work-up

- Clinical examination, inspection, palpation
- Flexible endoscopy
- MRI / CT
- PET/CT

- Lab tests
- Chest X-ray / CT
- (Bone scan)

Nasopharynx – 7th edition

T1 Nasopharynx, oropharynx or nasal cavity (was T2a) without parapharyngeal extension

T2 Parapharyngeal extension (was T2b)

T3 Bony structures of skull base and/or paranasal sinuses

T4 Intracranial, cranial nerves, hypopharynx, orbit, infratemporal fossa/ masticator space

N1 Unilateral cervical, unilateral or bilateral retropharyngeal lymph nodes, above supraclavicular fossa; $\leq$ 6 cm

N2 Bilateral cervical above supraclavicular fossa; $\leq$ 6 cm

N3a >6 cm; N3b Supraclavicular fossa

Anatomical Stage Groups

Stage I	T1	N0
Stage II	T1	N1
	T2	N0, N1
Stage III	T1, T2	N2
	T3	N0, 1, 2
Stage IVA	T4	N0, 1, 2
Stage IVB	Any T	N3
Stage IVC	Any T	Any N
M1		

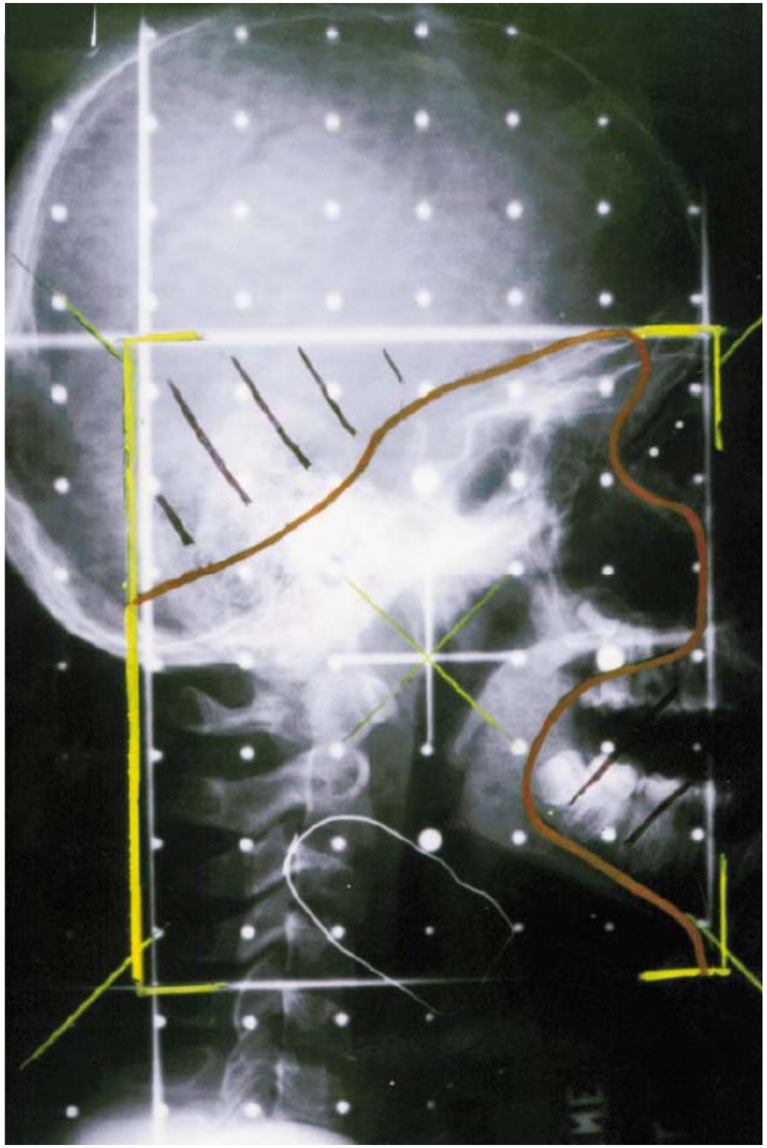
Stage II compressed

←Changes from TNM 6

Treatment options

- External beam radiotherapy

- Chemotherapy
- Brachytherapy boost
- Surgery



Nodal involvement

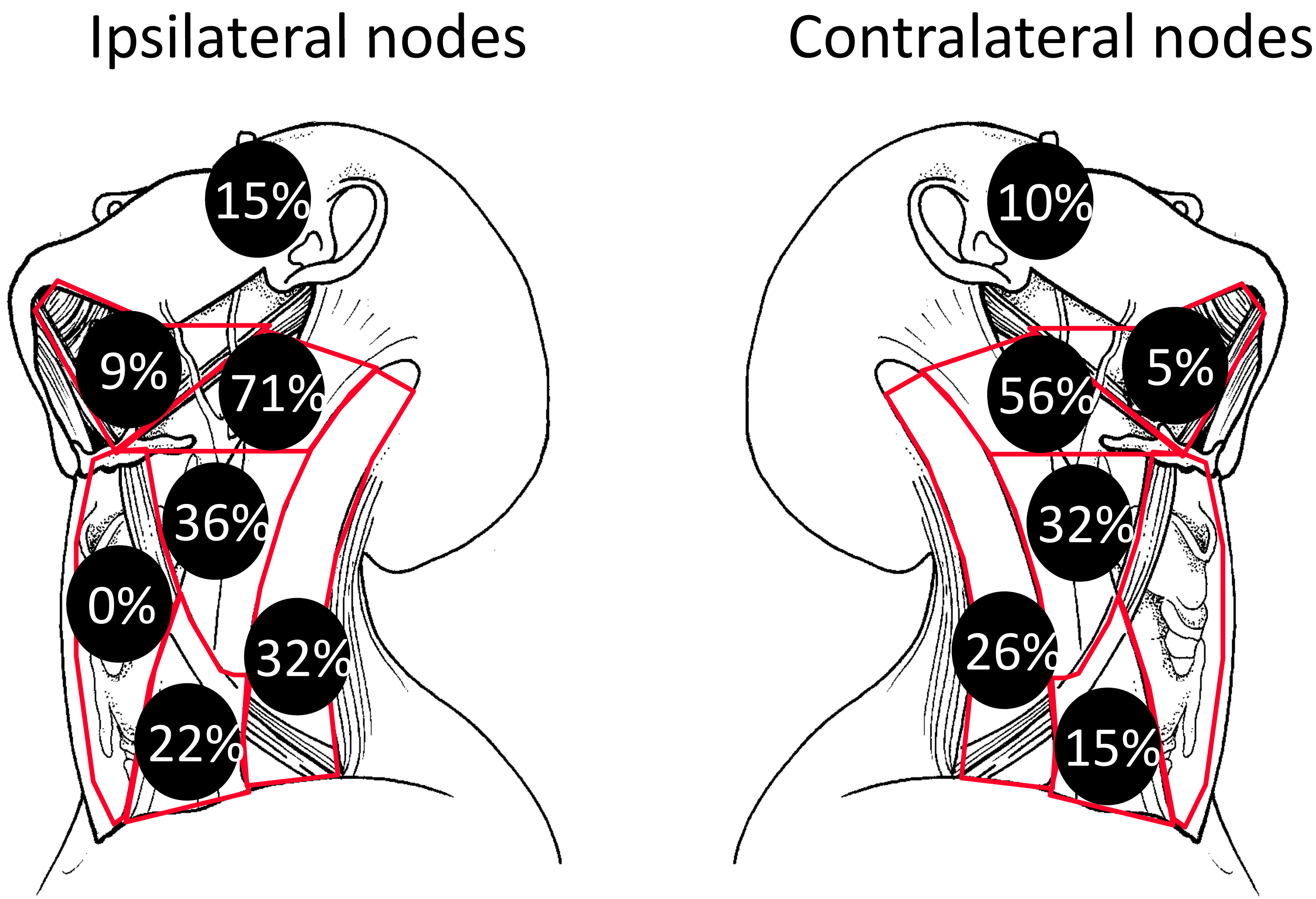
Distribution of clinical metastatic neck nodes from head and neck squamous cell carcinomas[a]

Tumor site	Patients with N+ (%)	Distribution of metastatic lymph nodes per level (percentage of the node- positive patients)					
		I	II	III	IV	V	Other[b]
Oral cavity (n = 787)	36	42/3.5[c]	79/8	18/3	5/1	1/0	1.4/0.3
Oropharynx (n = 1479)	64	13/2	81/24	23/5	9/2.5	13/3	2/1
Hypopharynx (n = 847)	70	2/0	80/13	51/4	20/3	24/2	3/1
Supraglottic larynx (n = 428)	55	2/0	71/21	48/10	18/7	15/4	2/0
Nasopharynx (n = 440)	80	9/5	71/56	36/32	22/15	32/26	15/10

[a] Redrawn from Refs. [3,28,49].
[b] Parotid, buccal nodes.
[c] Ipsilateral/contralateral nodes.

V. Gregoire et al. Radiotherapy and Oncology 56 (2000)

Distribution of lymph node metastasis in nasopharyngeal tumors (clinical examination)

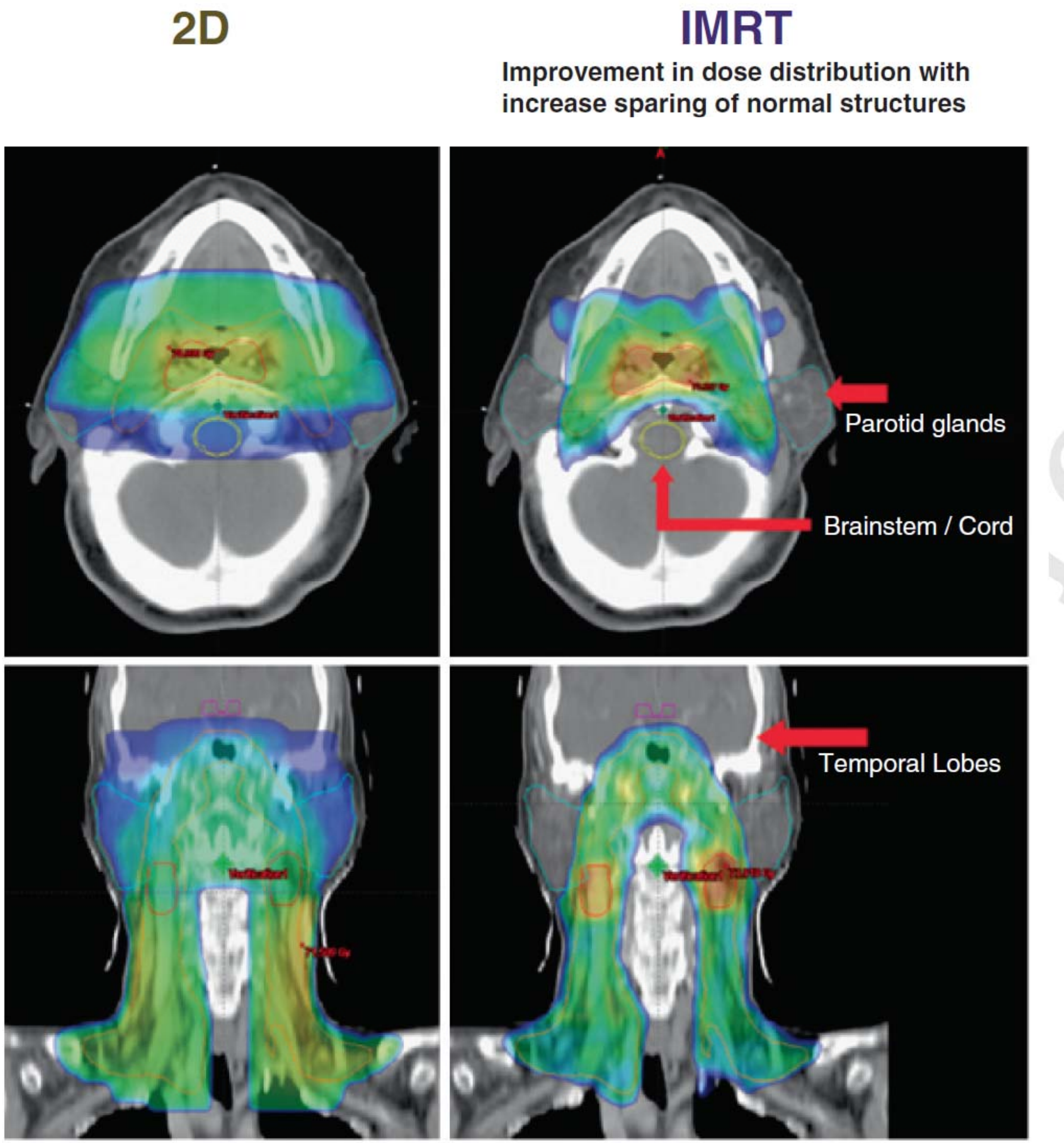


From Gregoire (2000) based on Lindberg and Sham

CTV Elective lymph nodes NPC

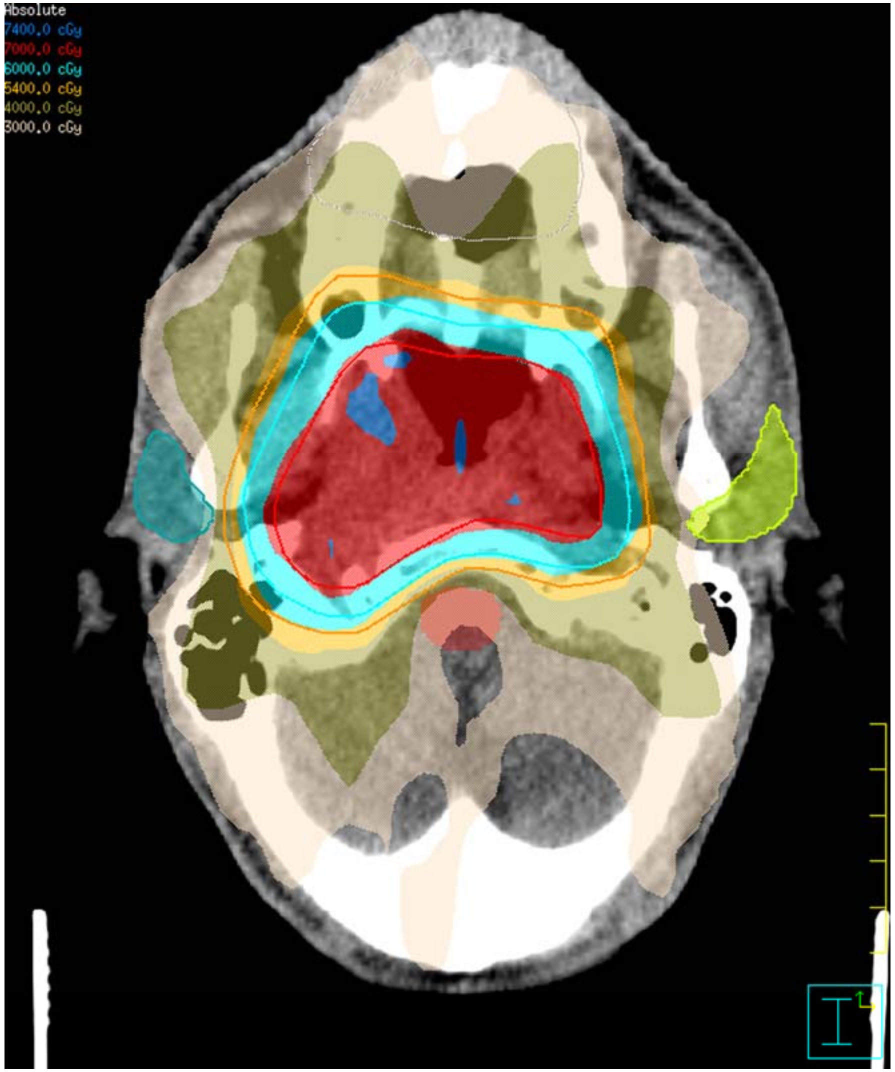
Stage	Ipsilateral neck	Contralateral neck
N0-N1	II-III-IV-V + RP	II-III-IV-V + RP
N2a-N2b	II-III-IV-V + RP	II-III-IV-V + RP
N2c	According to N stage on each side of the neck	According to N stage on each side of the neck
N3	II-III-IV-V +RP ± adjacent structures according to clinical judgment	II-III-IV-V +RP

V. Gregoire et al. Radiotherapy and Oncology 56 (2000)



From Lee A.W. M. et al. (2009): Nasopharynx. In “Function Preservation and Quality of Life in Head and Neck Radiotherapy”.

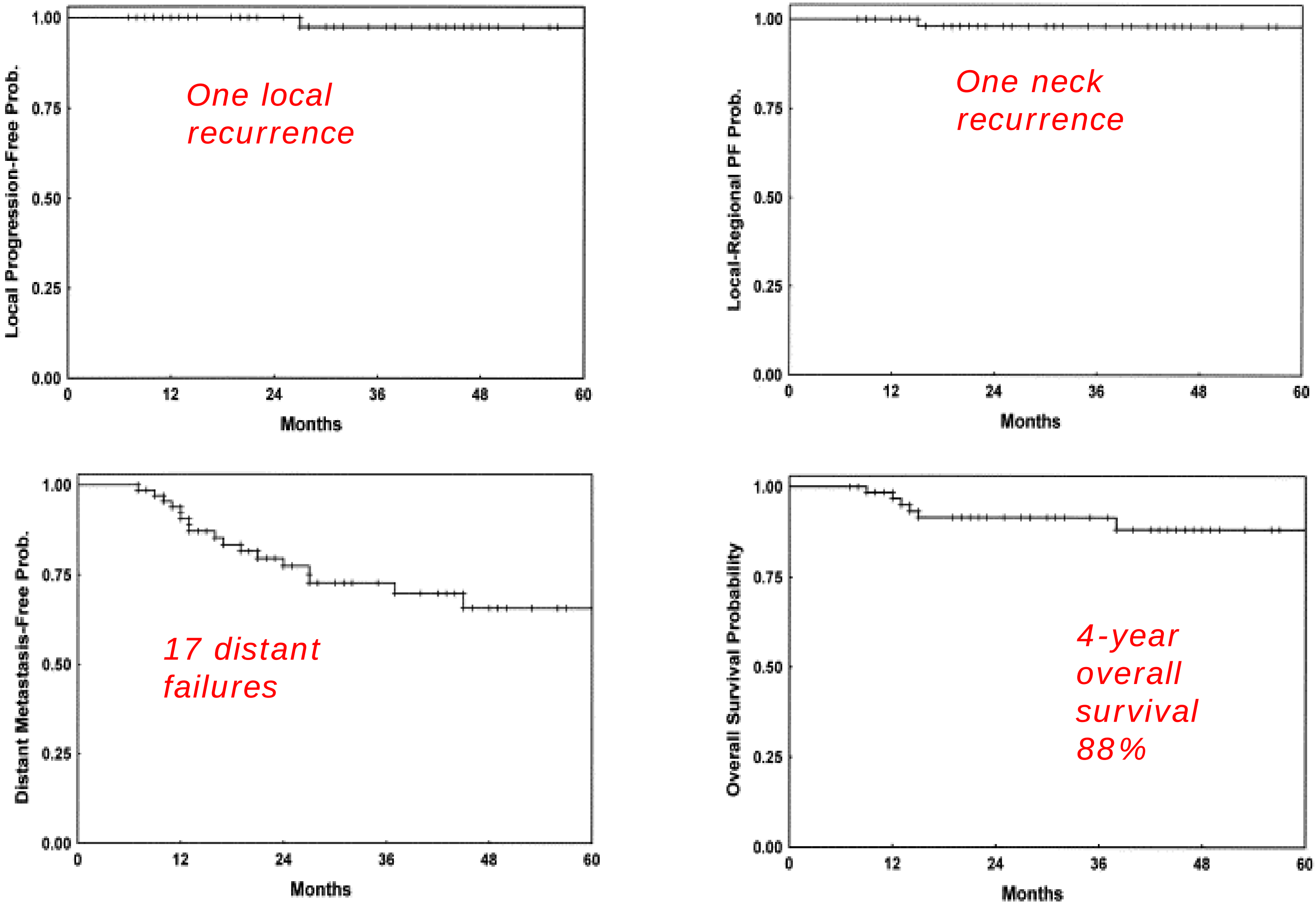
SIB – simultaneous integrated boost



Wong, Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 1, pp. 138–145, 2010

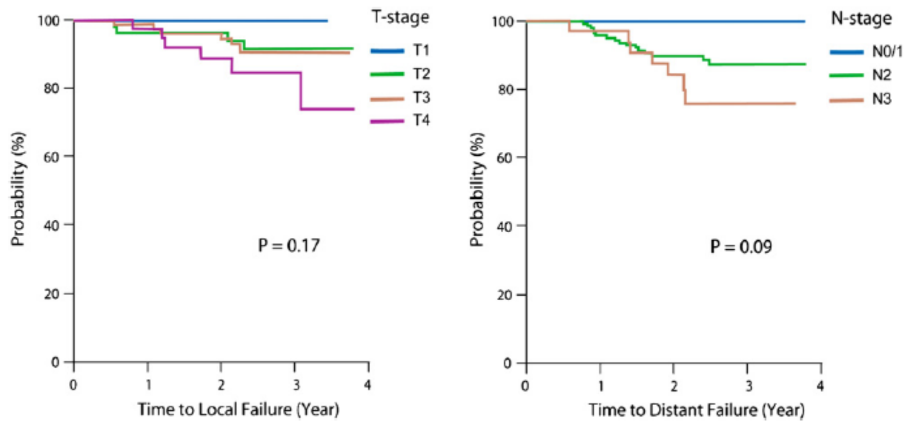
IMRT for NPC

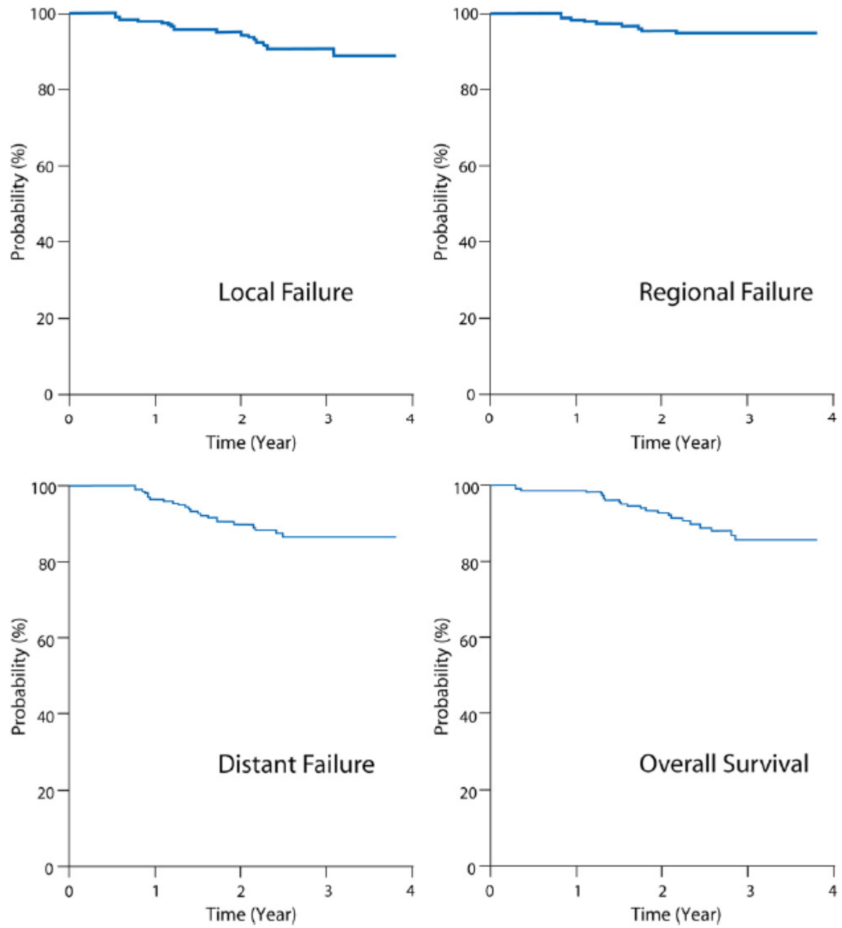
67 pts - 70% stage 3-4 – UCSF 1995-2000 - Lee *et al.* IJROBP 53:12-22,2002



IMRT for NPC

193 NPC patients; 93% had Stage III/IV disease





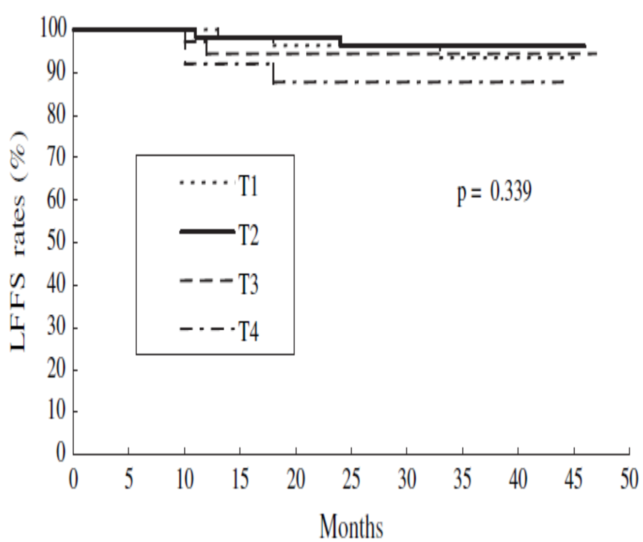
Ng, Hong Kong, Int. J. Radiation Oncology Biol. Phys. 2010

SIB – IMRT

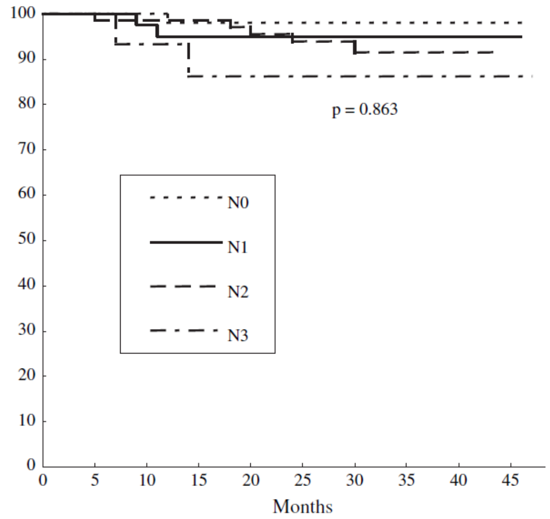
(Hong Kong, n=179)

70 Gy, 60 Gy, and 54 Gy in 33 fx in 6.5 weeks (2.17 Gy/fx), 70% received chemo

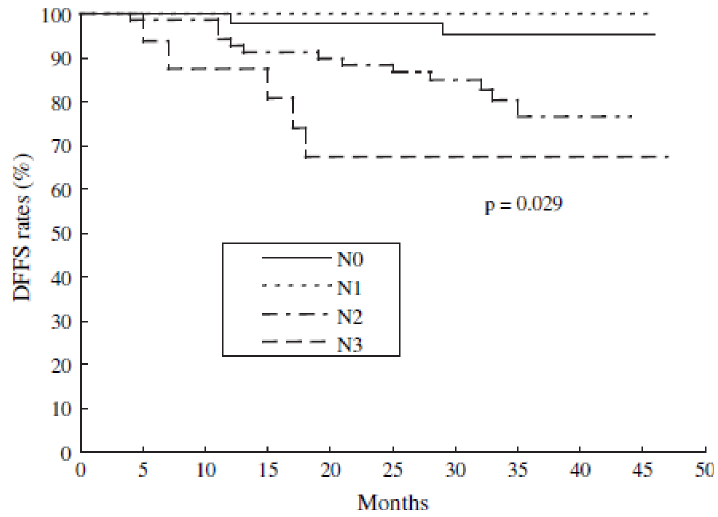
Local



Regional



Distant

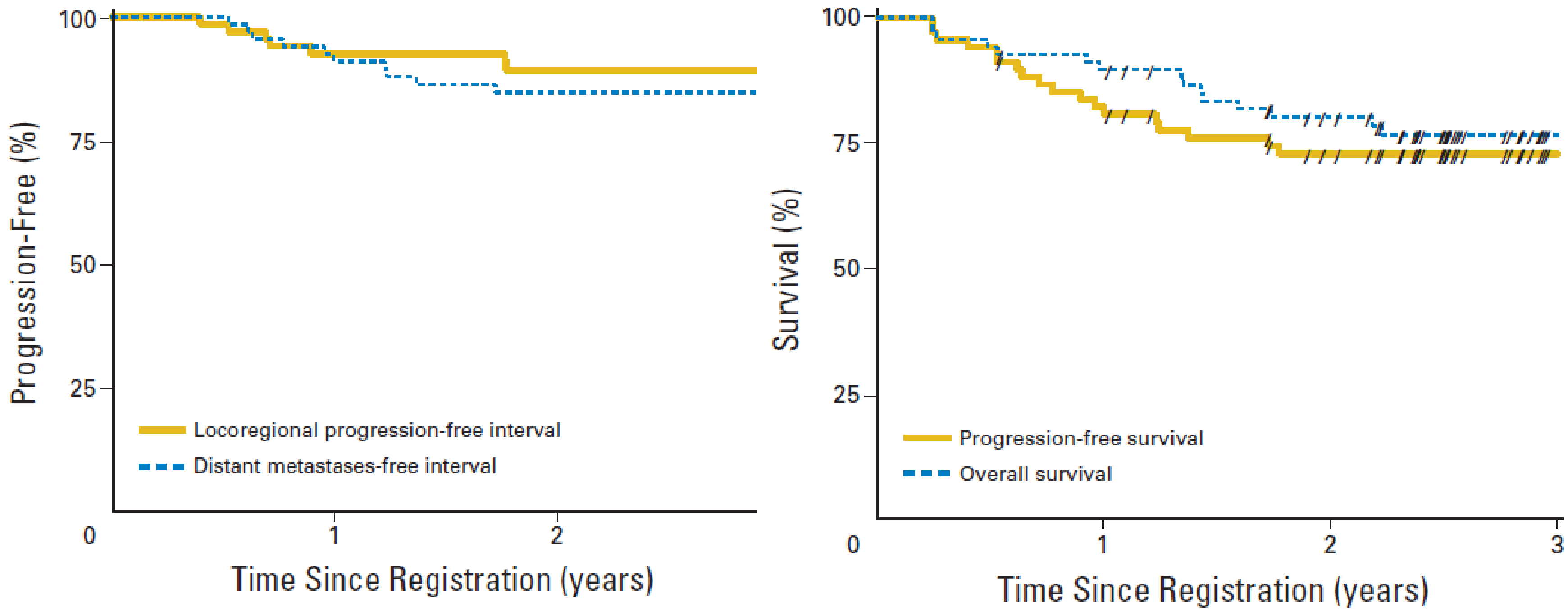


No late Grade 3 or 4 **toxicities**, but short median follow-up

Wong, Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 1, pp. 138–145, 2010

NPC IMRT

Phase II multi-institutional RTOG 0225 (n=68)



..feasible to transport IMRT with or without chemotherapy in the treatment of NPC to a multi-institutional setting with 90% LRPF rate reproducing excellent reports from single institutions. Minimal grade 3 and lack of grade 4 xerostomia

Lee N, J Clin Oncol 27:3684-3690, 2009

Topics

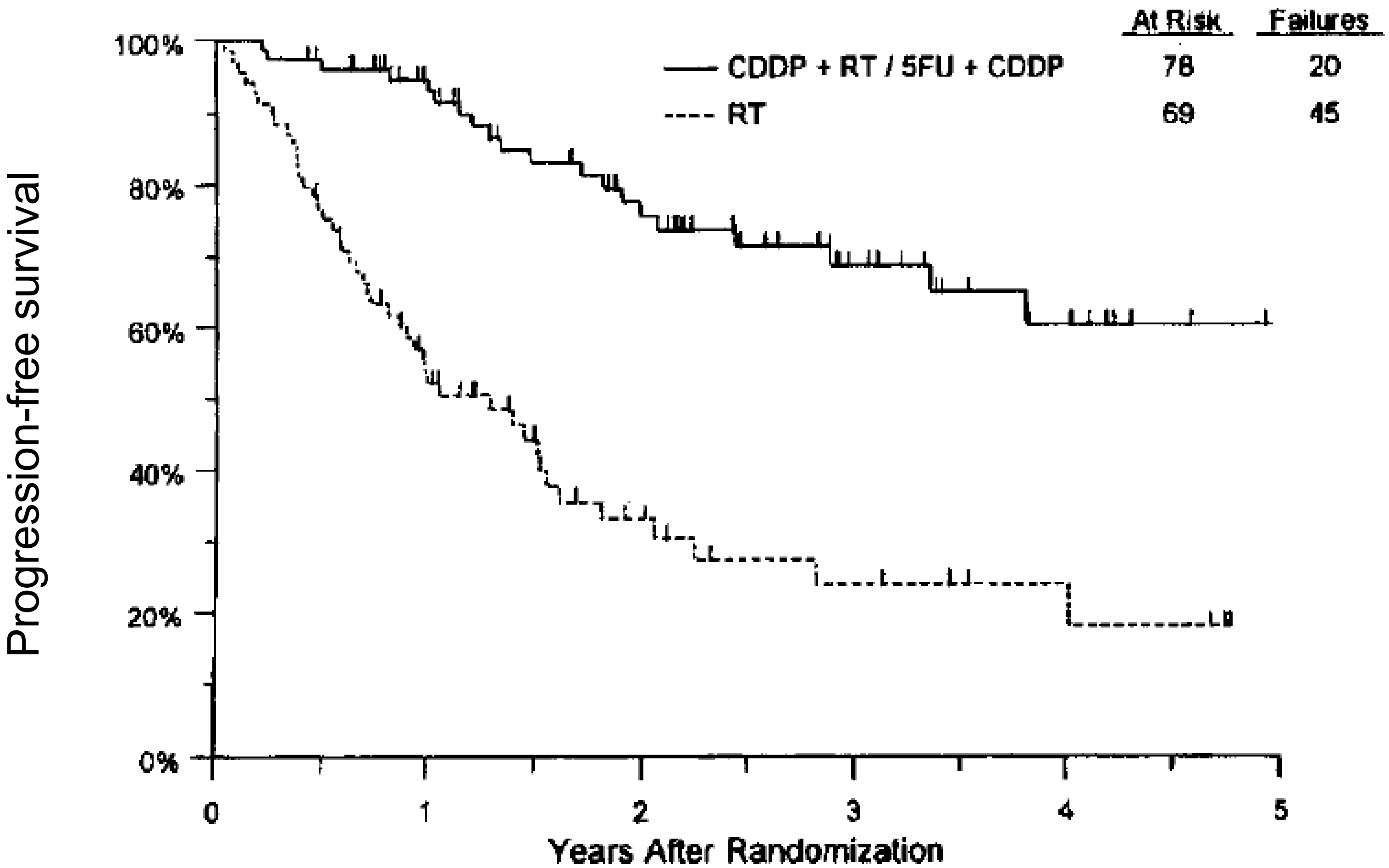
- Anatomy, aetiology, pathology, staging
- Radiotherapy (IMRT, volumes, techniques)
- Chemotherapy
- Radiotherapy morbidity
- Novel approaches
- Salvage treatment of loco-regional recurrences (re-irradiation, surgery, brachy)

NPC - chemotherapy

- Induction chemotherapy ?
- Concomitant chemo-radiation ?
- Adjuvant chemotherapy ?

NPC RT ±chemo (cis + adj cis-FU)

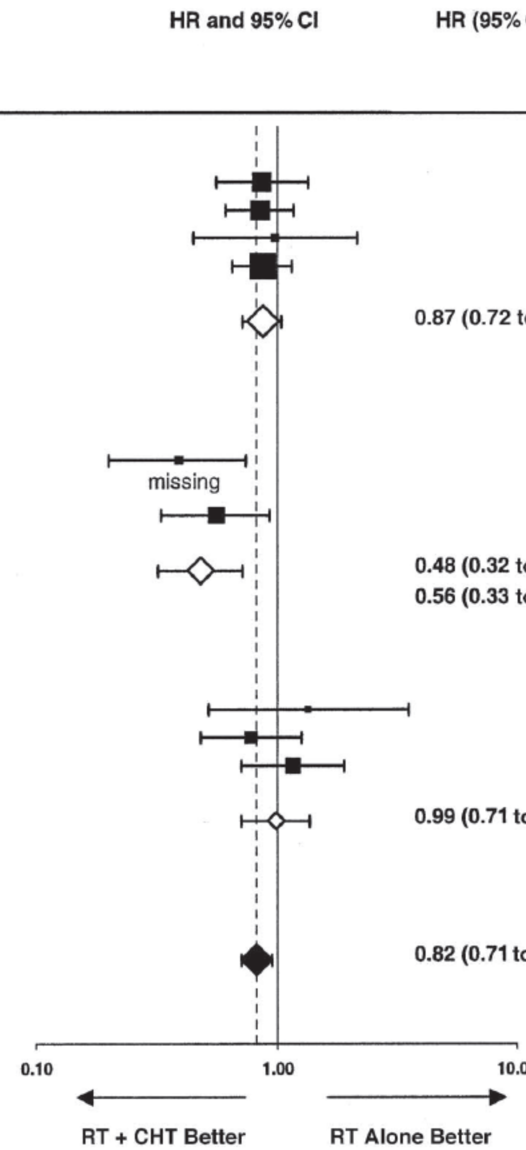
Intergroup 0099 (n=147)



Al-Sarraf et al, JCO 1998

Meta-analysis NPC RT ± chemo

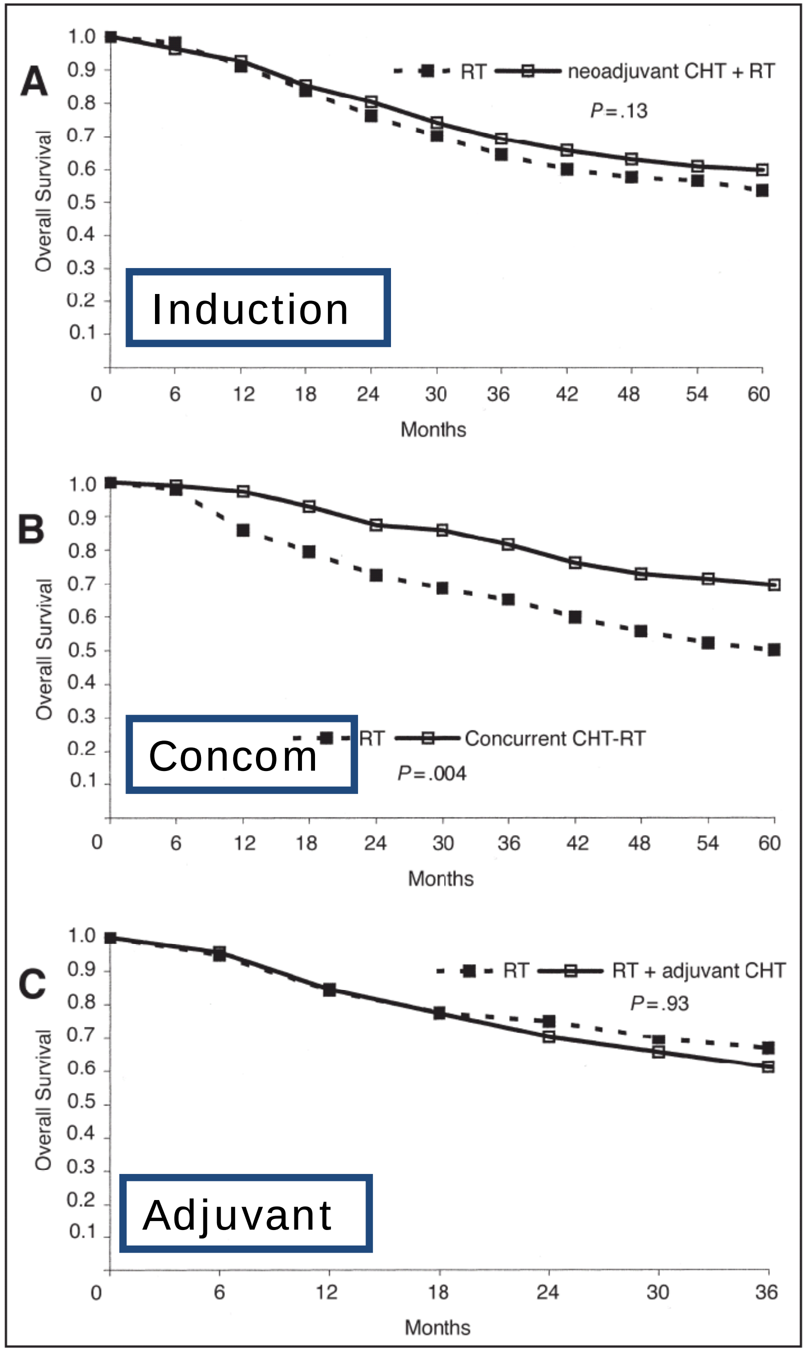
Study		Events/Patients: RT Alone	Events/Patients: RT + CHT	Statistics: $(O-E)$	Statistics: Var	HR (95% CI)
Neoadjuvant chemotherapy						
1	Chua 1998	41/167	36/167	−3.0	20.0	
2	Cvitcovics 1996	74/168	72/171	−6.0	35.0	
3	Hareyama 2002	16/40	15/40	−0.15	6.2	
4	Ma 2001	76/228	62/228	−7.0	48.7	
	Subtotal	**207/603 (34.3%)**	**185/606 (30.5%)**	**−16.0**	**110.6**	**0.87 (0.72 to 1.04)**
Concurrent chemotherapy						
1	Al-Sarraf 1998	29/69	16/78	−8.8	9.2	
2	Chan 2002	missing	missing			
3	Lin 2003	45/143	25/141	−8.5	14.5	
	Subtotal	**74/212 (34.9%)**	**41/219 (18.7%)**	**−17.3**	**23.8**	**0.48 (0.32 to 0.72)[1]** **0.56 (0.33 to 0.93)[2]**
Adjuvant chemotherapy						
1	Chan 1995	10/40	13/37	1.3	4.4	
2	Chi 2002	34/77	29/77	−4.1	16.8	
3	Rossi 1988	33/116	44/116	2.4	15.9	
	Subtotal	**77/233 (33.1%)**	**86/230 (37.4%)**	**−0.5**	**37.1**	**0.99 (0.71 to 1.36)**
	Total	**358/1224**	**312/1226**	**−33.8**	**171.4**	**0.82 (0.71 to 0.95)**



Treatment effect: $\chi^2_1 = 10.8$; $P = .01$

Test for interaction: $\chi^2_2 = 7.64$; $P = .02$

Langendijk JCO 2004



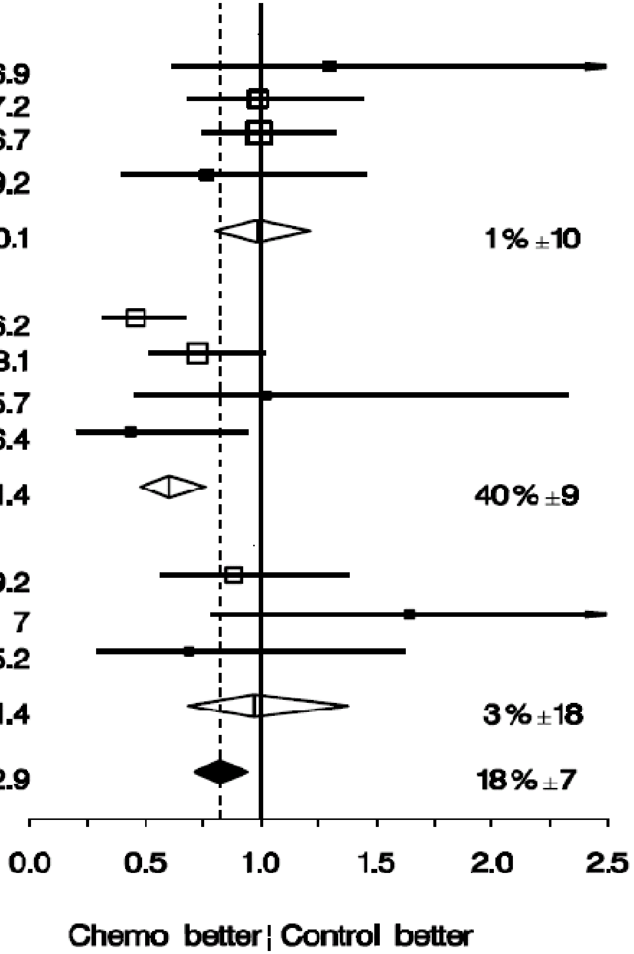
NPC
Meta-analysis
n = 2,455

survival benefit of 20% after 5 years

Langendijk JCO 2004

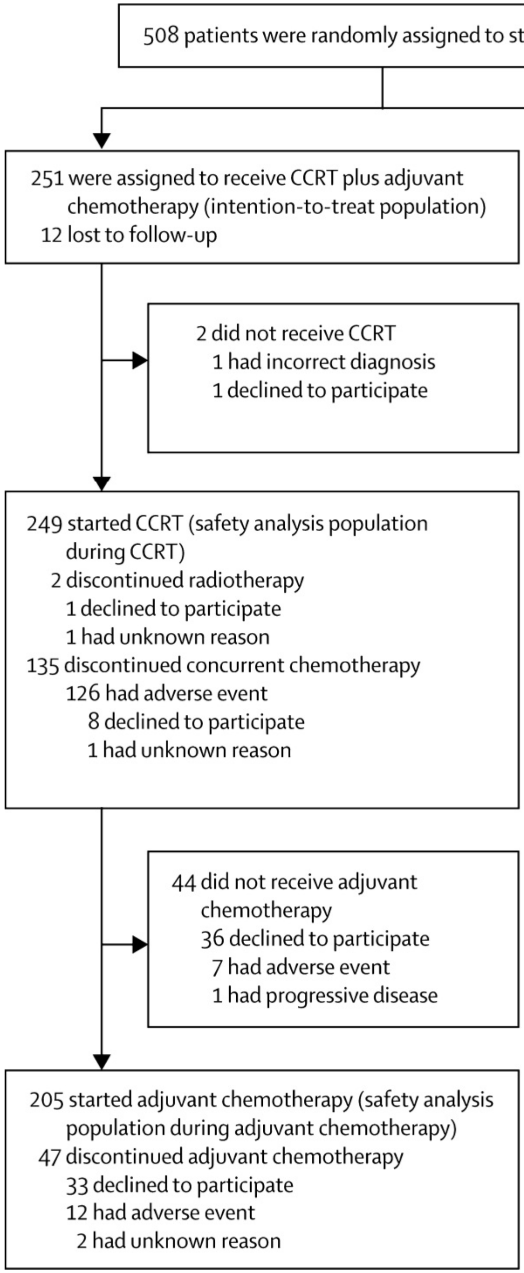
CHEMOTHERAPY IN LOCALLY ADVANCED NPC: AN INDIVIDUAL PATIENT DATA META-ANALYSIS OF 8 RANDOMIZED TRIALS AND 1753 PATIENTS

(a) Induction					
PWH−88	15/37	13/40	1.8	6.9	
AOCOA	54/167	55/167	−0.3	27.2	
VUMCA−89	94/171	93/168	−0.2	46.7	
Japan−91	17/40	20/40	−2.5	9.2	
Subtotal (a)	180/415	181/415	−1.2	90.1	1% ± 10
(b) Concomitant					
INT 0099	42/97	66/96	−20.3	26.2	
PWHQEH−94	60/174	73/176	−10.6	33.1	
QMH−95Conc	12/56	11/55	0.2	5.7	
QMH−95Conc+	9/57	17/54	−5.3	6.4	
Subtotal (b)	123/384	167/381	−36.1	71.4	40% ± 9
(c) Adjuvant					
TCOG−94	35/80	42/78	−2.4	19.2	
QMH−95Adj	17/54	11/55	3.5	7	
QMH−95Adj+	9/57	12/56	−2	5.2	
Subtotal (c)	61/191	65/189	−0.9	31.4	3% ± 18
Total (a ... c)	364/990	413/985	−38.1	192.9	18% ± 7



Test for heterogeneity : $\chi^2_{10} = 19.9$ 2P = 0.03

Baujat et al, Head&Neck 2006



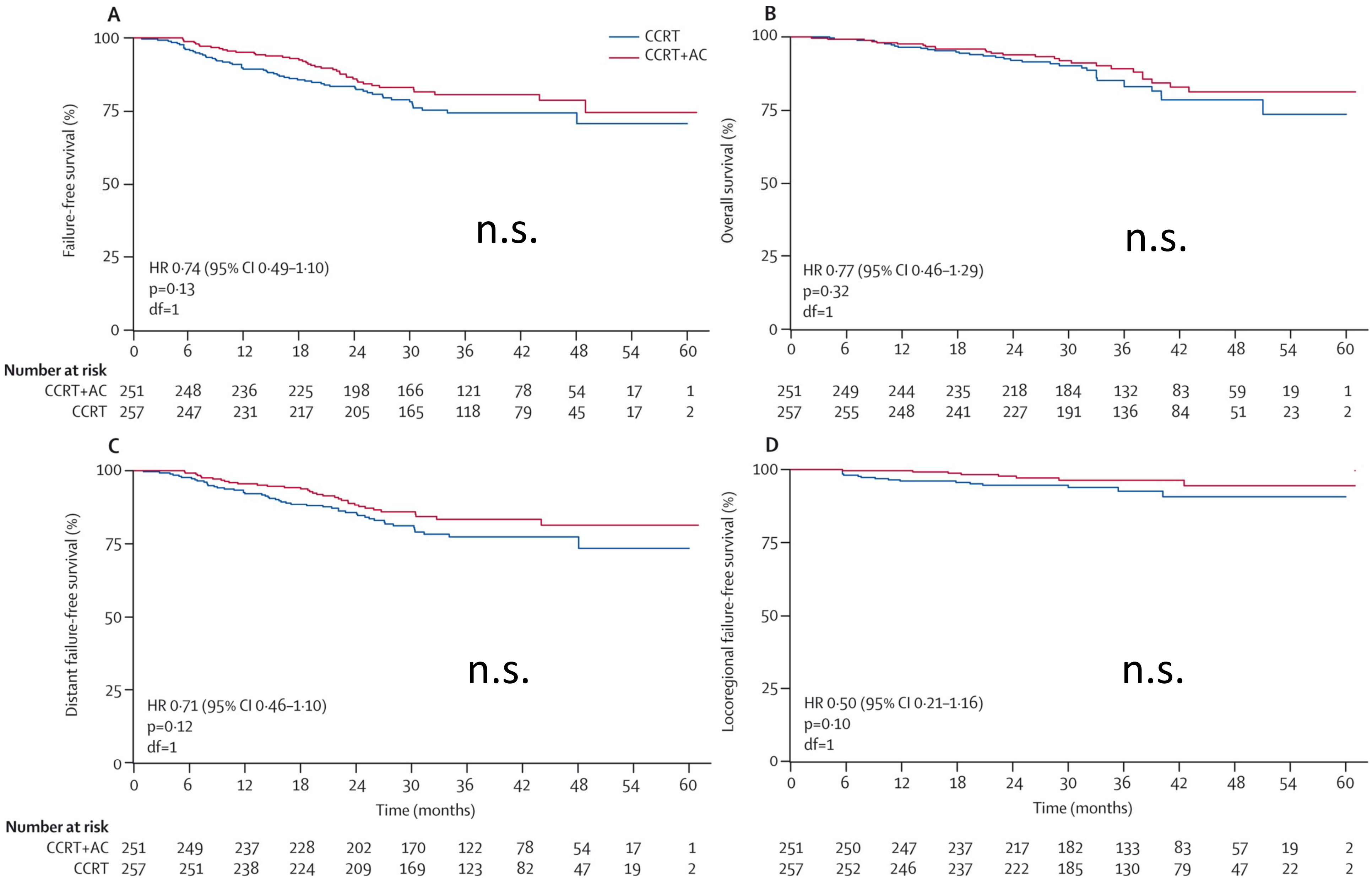
Role of adjuvant Cis-FU

Hong Kong trial (n=508)

Weekly cisplatin 40 mg/m2

$\underline{+}$postirr. adjuvant chemotherapy 3 cycles
- cisplatin (80 mg/m2) and 5-FU (800 mg/m2/day for 120h)

Chen et al. Lancet Oncology 2012; 13:163-171.



Chen et al. Lancet Oncology 2012; 13:163-171.

Conclusions - chemotherapy

- The addition of chemotherapy to standard RT provides a significant survival benefit in patients with NPC.
- This benefit is essentially observed when chemotherapy is administered concomitantly with RT.
- The role of induction chemotherapy is questionable – trials w/ new drugs are ongoing
- Adjuvant chemotherapy after chemoradiotherapy has been questioned

Topics

- Anatomy, aetiology, pathology, staging
- Radiotherapy (IMRT, volumes, techniques)
- Chemotherapy
- Radiotherapy morbidity
- Novel approaches
- Salvage treatment of loco-regional recurrences (re-irradiation, surgery, brachy)

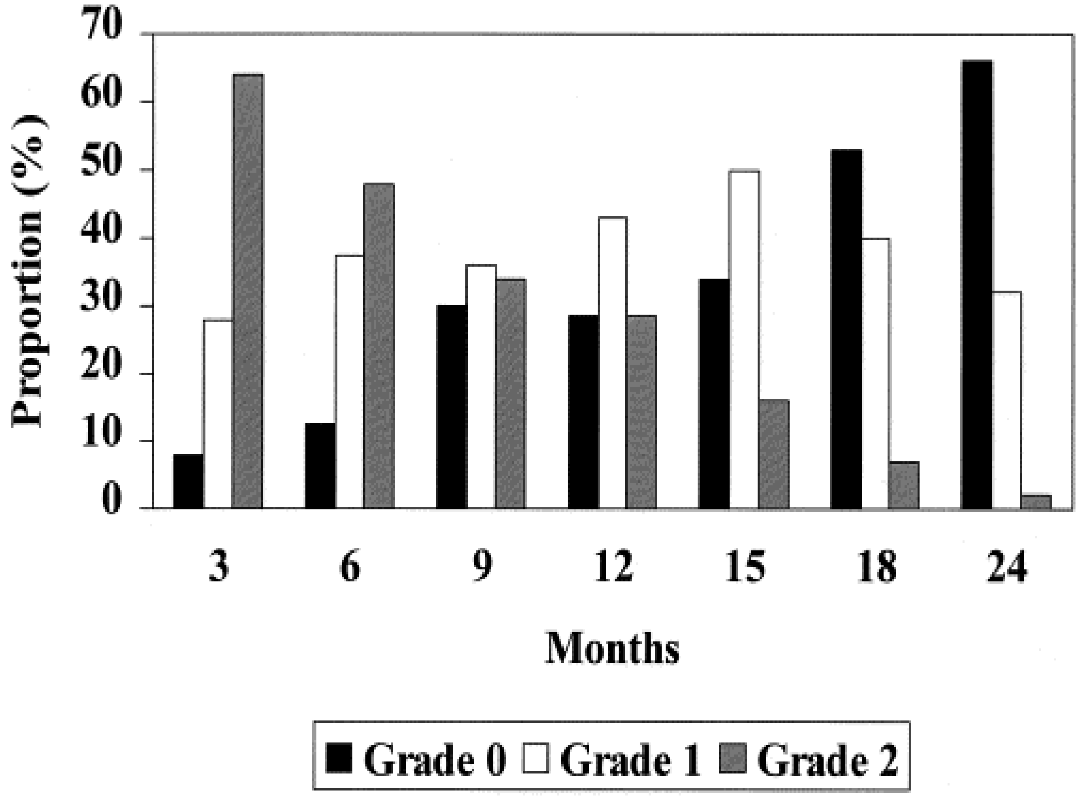
Morbidity

- Xerostomia
- Dysphagia
- Dental problems
- Soft-tissue fibrosis
- Hearing loss
- Temporal lobe necrosis
- Brain stem myelopathy
- Carotid artery stenosis / rupture
- Pituitary gland insufficiency
- …

QUANTEC
Int J Radiat Oncol Biol Phys 76, Supplement 1, March 2010

Xerostomia after IMRT

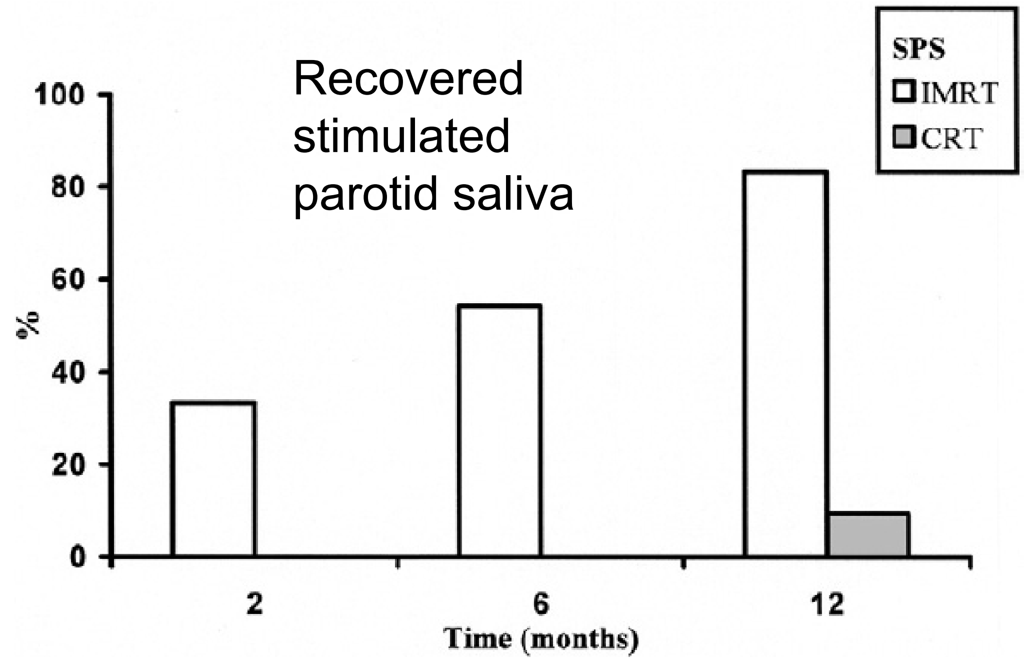
IMRT for NPC. Lee *et al.* IJROBP 53:12-22,2002



Randomized trial
3D-CRT vs. IMRT

Pow et al.

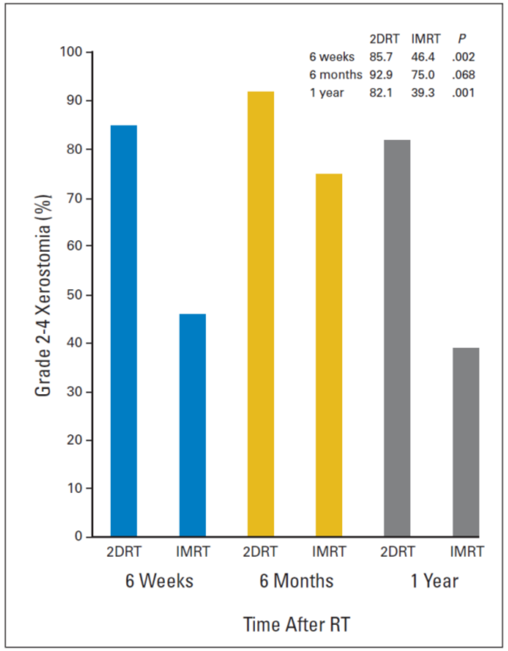
- **Hong Kong**
- **51 NPC patients**
- **T2, N0/N1, M0**
- **randomized trial**
- **IMRT vs. CRT**

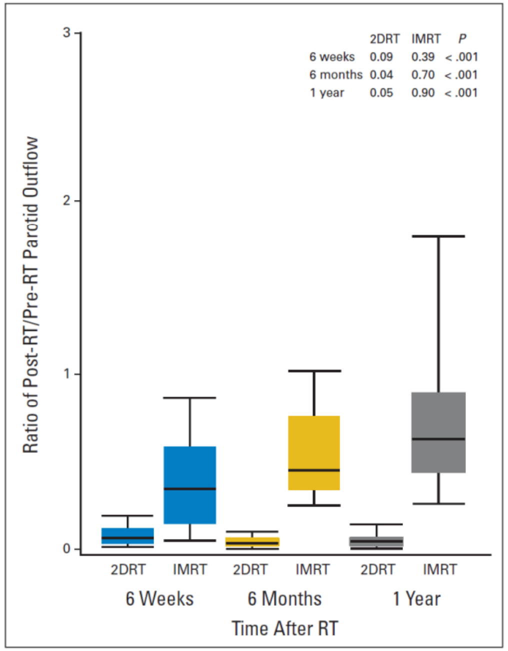


Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 4, pp. 981–991, 2006

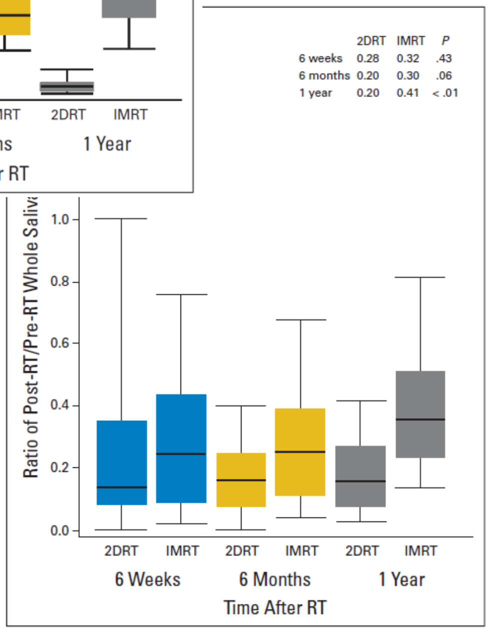
2D-RT vs. IMRT

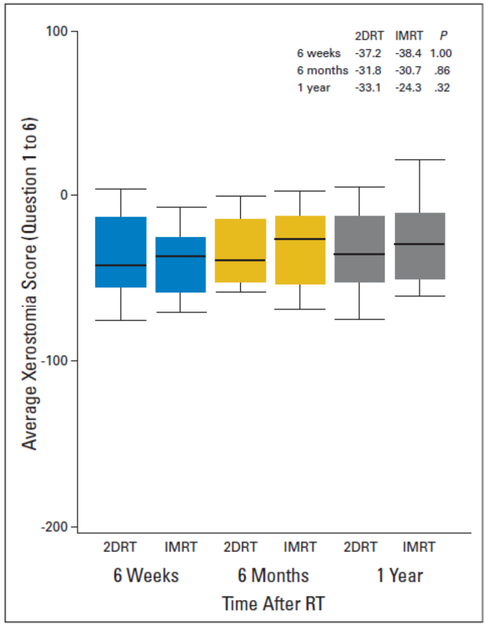
(n=60, T1-2bN0-1M0 NPC)





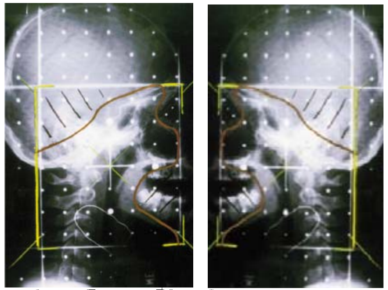
IMRT improved ***parotid flow*** but there was no significant difference in whole-saliva or patient-reported outcome between the two arms





Kam et al, J Clin Oncol 25:4873-4879, 2007

Brain stem



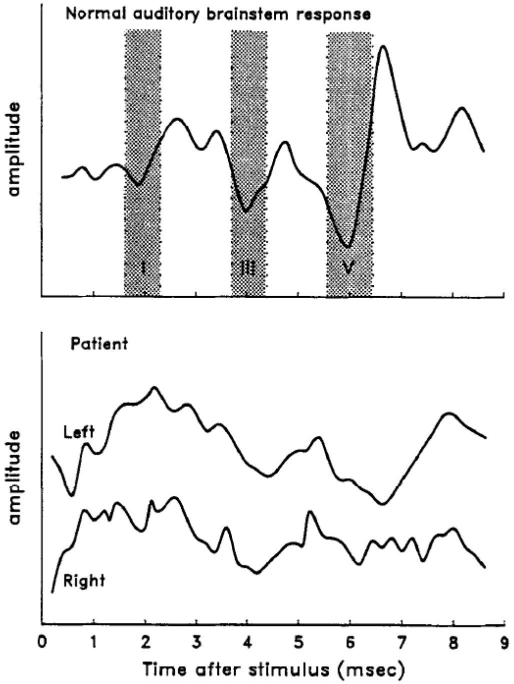


Table 1. Auditory Brain Stem Responses in Patients Who Received Radiation Therapy for Nasopharyngeal Carcinomas

Patient no.	Age (yr)	Sex	Tumor stage T	Tumor stage N	Radiation therapy: *Tumor (dose [Gy]/no. of fractions/d)*	Radiation therapy: *Brainstem (dose [Gy]/no. of fractions/d)*	Time to ABR (mo)	Type of ABR
1	71	M	1	2	66/33/73 split*	0	54	Normal
2	52	M	2	1	68/34/58	0	30	Normal
3	50	M	1	0	61/22/67 split†	0	42	Normal
4	27	M	4	0	66/33/71 split*	0	72	Normal
5	51	M	1	0	60/30/42	0	39	Normal
6	49	M	1	0	62/31/44	0	33	Normal
7	41	M	1	0	50/25/35	0	84	Normal
8	63	M	1	1	61/22/76 split†	39/11/52	61	Normal
9	31	M	1	1	66/33/71 split*	40/20/28	36	Normal
10	65	M	X‡	3	66/33/49	46/23/34	16	Normal
11	26	M	4	2	68/34/46	46/23/31	16	Normal
12	67	M	1	1	64/32/58	48/24/43	49	Normal
13	76	M	3	1	68/34/57	50/25/38	15	Normal
14	71	M	1	2	66/33/76 split*	50/25/61	39	Normal
15	79	F	1	3	59/21/64 split†	59/21/64	54	Normal
16	54	F	3	0	68/34/48	68/34/48	12	Normal
17	59	M	2	1	68/34/50	68/34/50	7	Normal
18	22	M	4	3	68/34/53	68/34/53	8	Abnormal
19	57	M	4	2	68/34/71 split*	68/34/71	60	Abnormal
20	62	M	4	3	68/34/51	68/34/51	12	Abnormal
21	67	F	4	0	68/34/64	68/34/64	25	Abnormal

Table 2. Distribution of Auditory Brain Stem Respons as a Function of Dose of Radiation

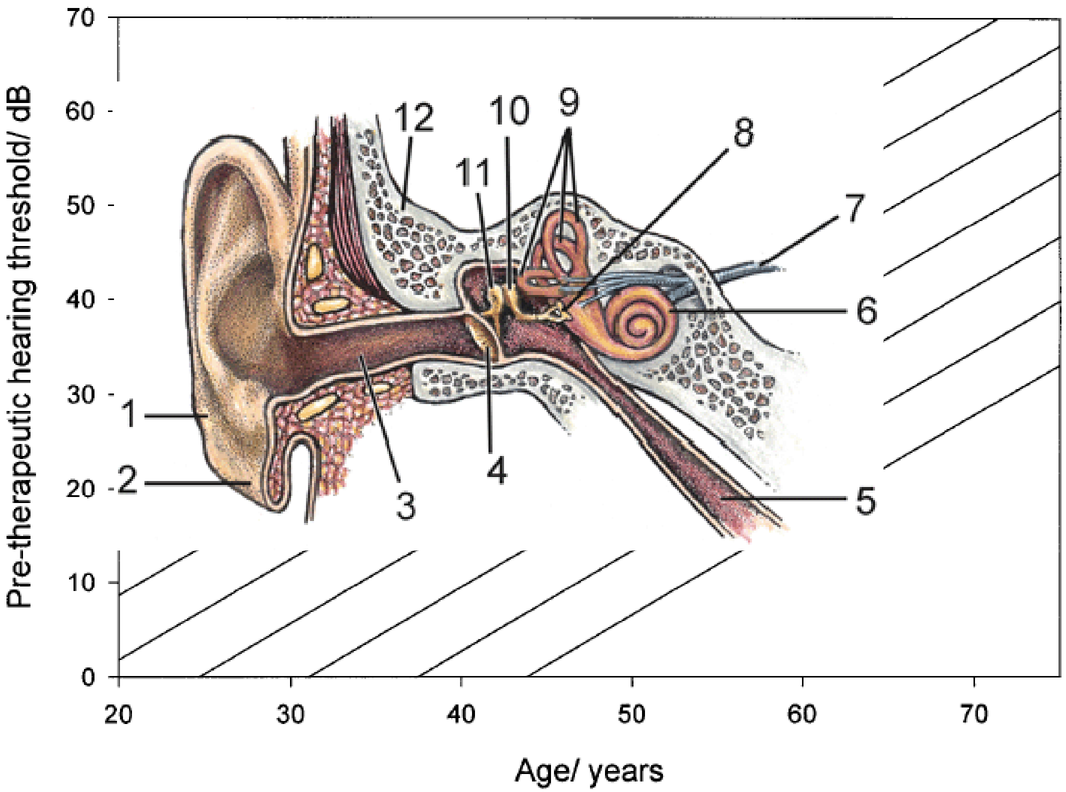
ABR	Control subjects	Patients: Brain stem dose (Gy) *0*	Patients: Brain stem dose (Gy) *39–59*
Normal	30	7	8
Abnormal	0	0	0

ABR: auditory brain stem response.
* Fisher's exact test: $P = 0.03$ (68 Gy compared with 39–59 Gy).

Grau C et al Cancer 70:2396-2401, 1992

Sensori-neural hearing loss (SNHL)

Fig. 2. Axial computed tomography image through the skull base. EAC = external acoustic canal; C = cochlea; V = vestibule; IAC = internal auditory canal.



Honoré, H.B., Bentzen, S.M., Møller, K., Grau, C
Radiotherapy and Oncology 65 (2002) 9–16

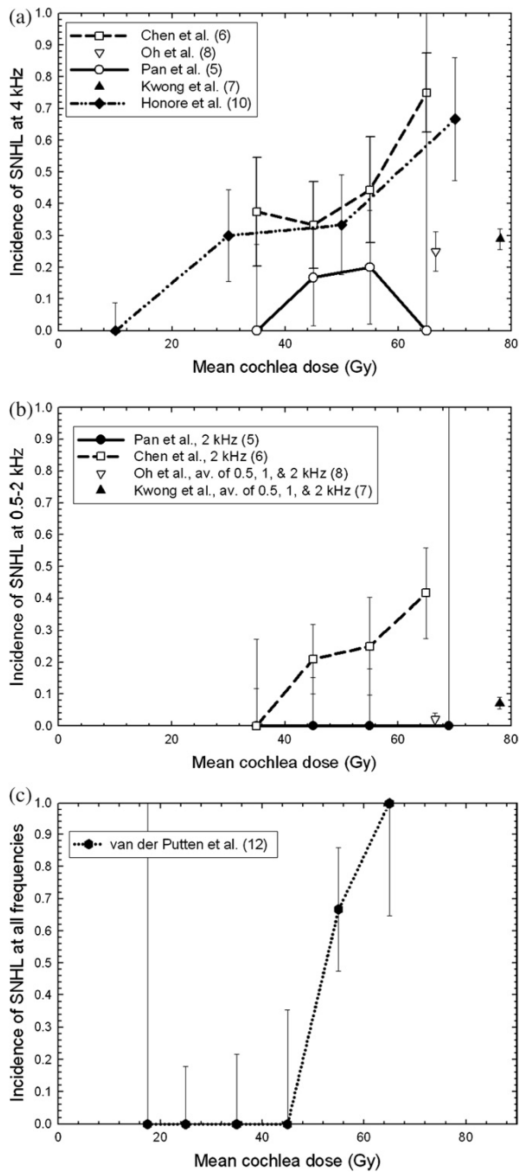
Mean inner ear doses producing a 15% risk of SNHL as a function of pre-therapeutic hearing threshold and age

Inner ear - SNHL

4 kHz

0.5-2 kHz

All frequencies



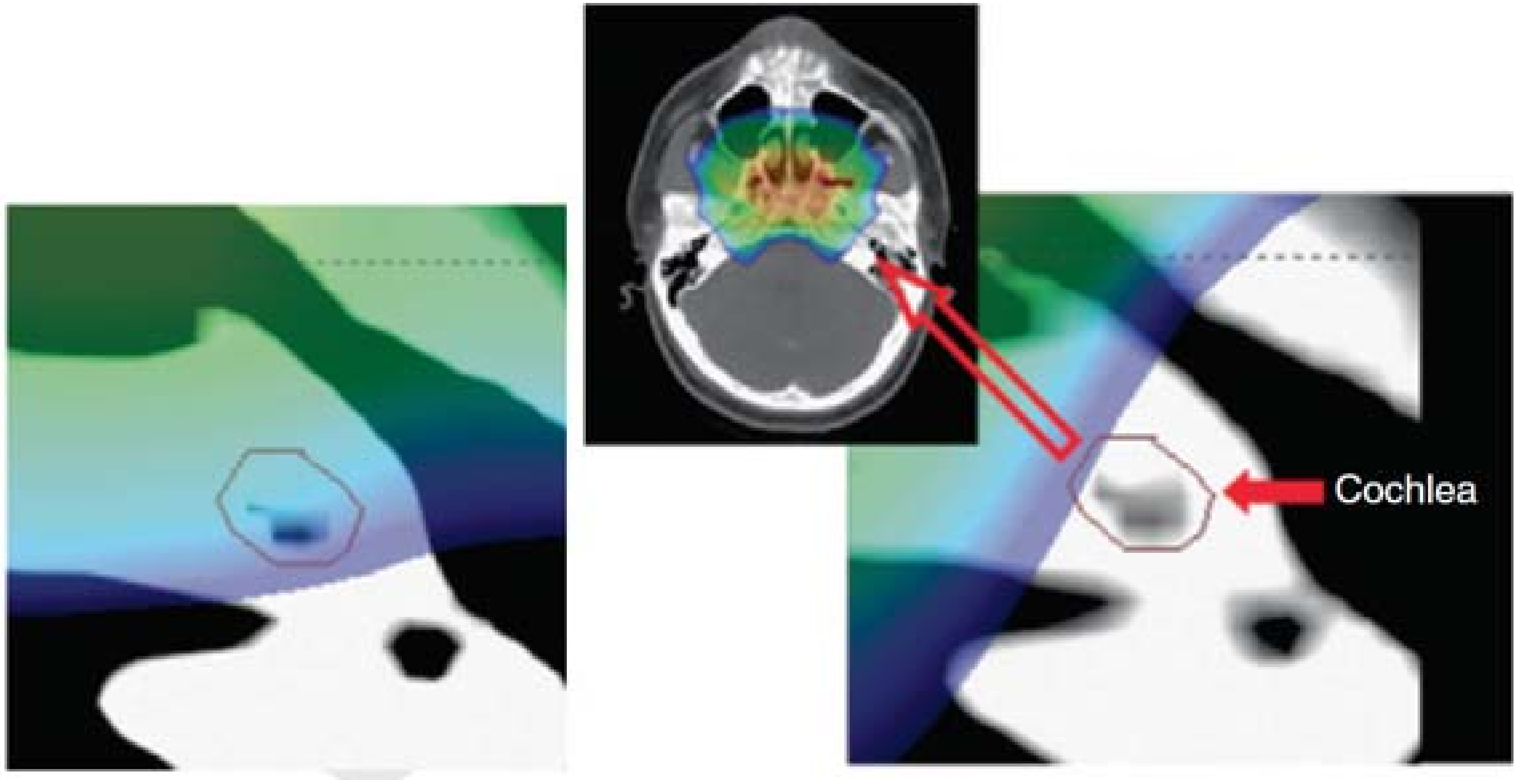
Deasy (QUANTEC 2010) Int. J. Radiation Oncology Biol. Phys

RECOMMENDED DOSE–VOLUME LIMITS FROM QUANTEC:

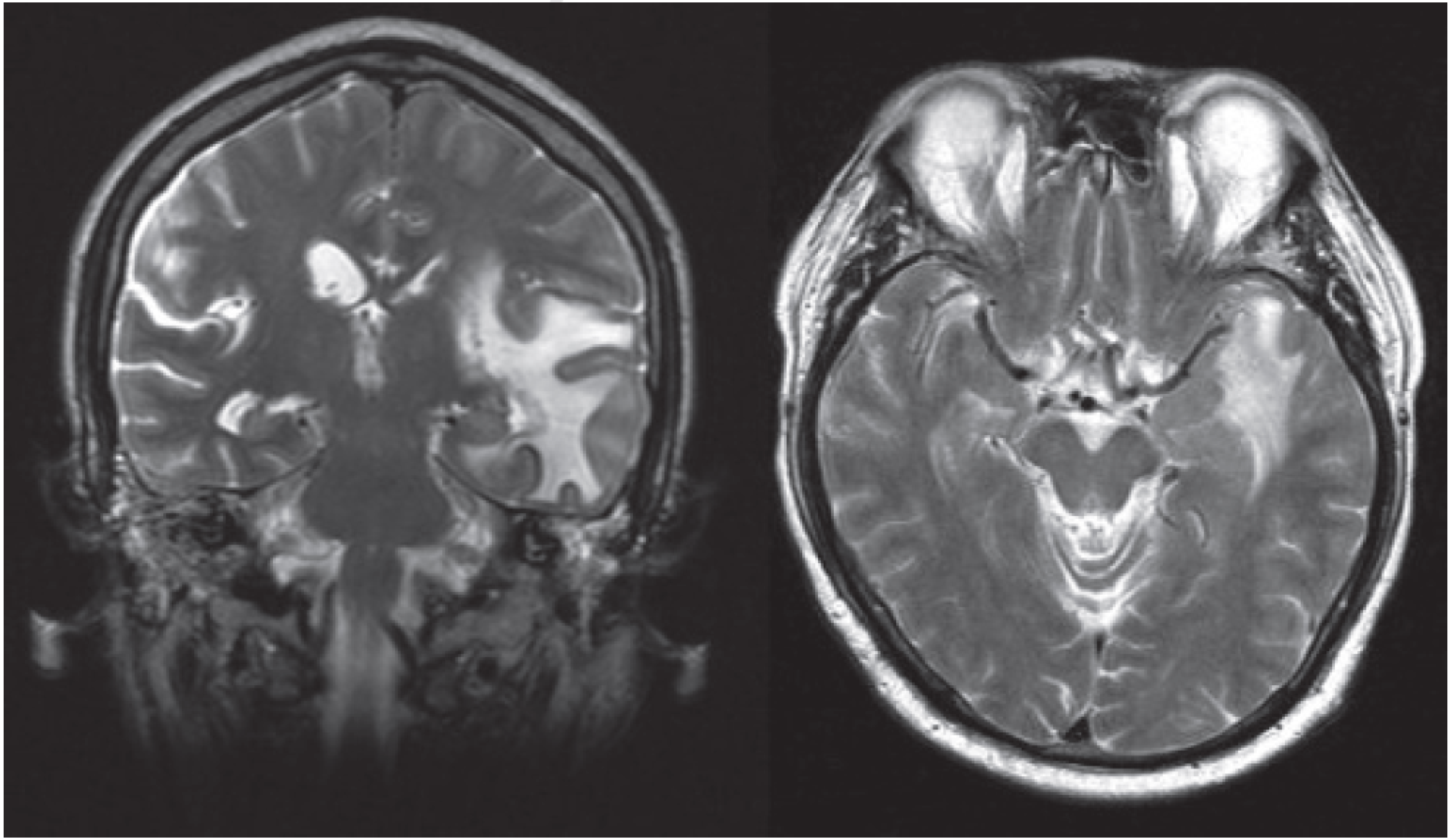
Because a threshold for SNHL cannot be determined from the present data, to prevent SNHL, the dose to the cochlea should *be kept as low as possible.*

For conventionally fractionated RT, the mean dose to the cochlea should be limited to **<45 Gy**

IMRT – cochlear sparing

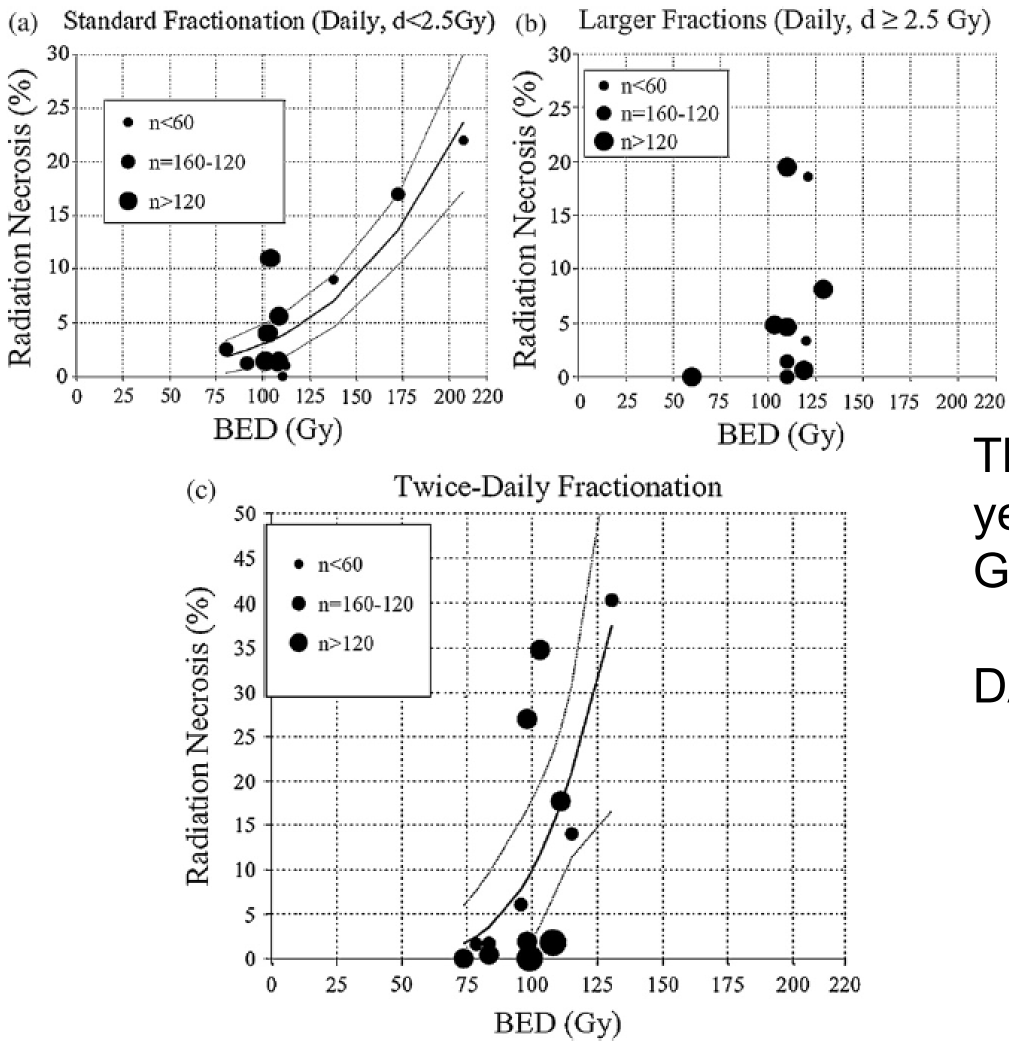


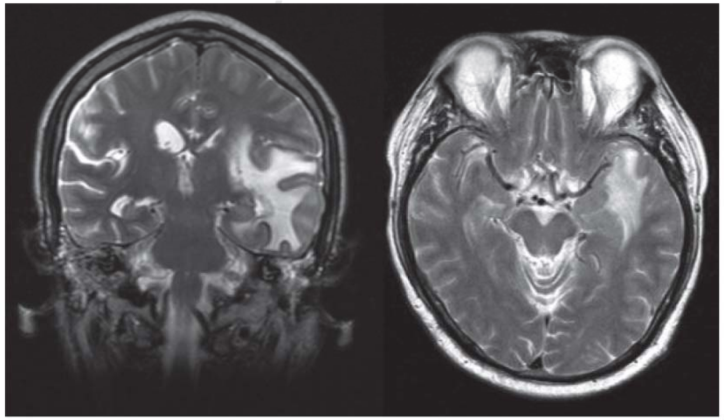
Temporal lobe necrosis



Temporal lobe (brain) necrosis

I. J. Radiation Oncology ● Biology ● Physics Volume 76, Number 3, Supplement, 2010





The dose constraint for <5% risk at 5 years for normally fractionated RT is 72 Gy (range 60–84).

DAHANCA constraint: Dmax <60 Gy

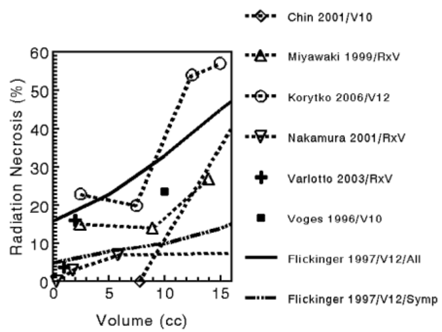


Fig. 1. Relationship between volume receiving high-dose irradiation and incidence of radiation necrosis in single-fraction stereotactic radiosurgery. Studies differed in their completeness of follow-up,

Topics

- Anatomy, aetiology, pathology, staging
- Radiotherapy (IMRT, volumes, techniques)
- Chemotherapy
- Radiotherapy morbidity
- Novel approaches
- Salvage treatment of loco-regional recurrences (re-irradiation, surgery, brachy)

Novel RT approaches

- Altered fractionation
- Stereotactic boost
- Protons

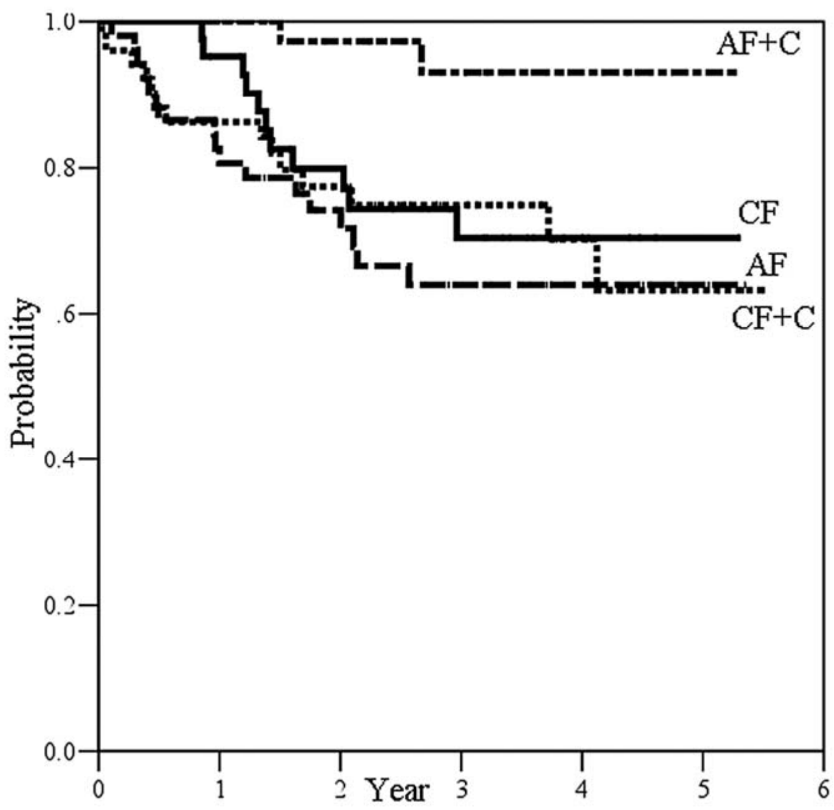
NPC-9902 TRIAL – Hong Kong

- 4 arm trial
- T3-4 N0-1
- N=189 (planned 464)
- >66 Gy at 2 Gy per fraction
  - **Five vs. six fractions/week**
- Chemotherapy
  - ±concurrent cisplatin plus adjuvant cisplatin and 5-fluorouracil (Intergroup 0099 regimen)

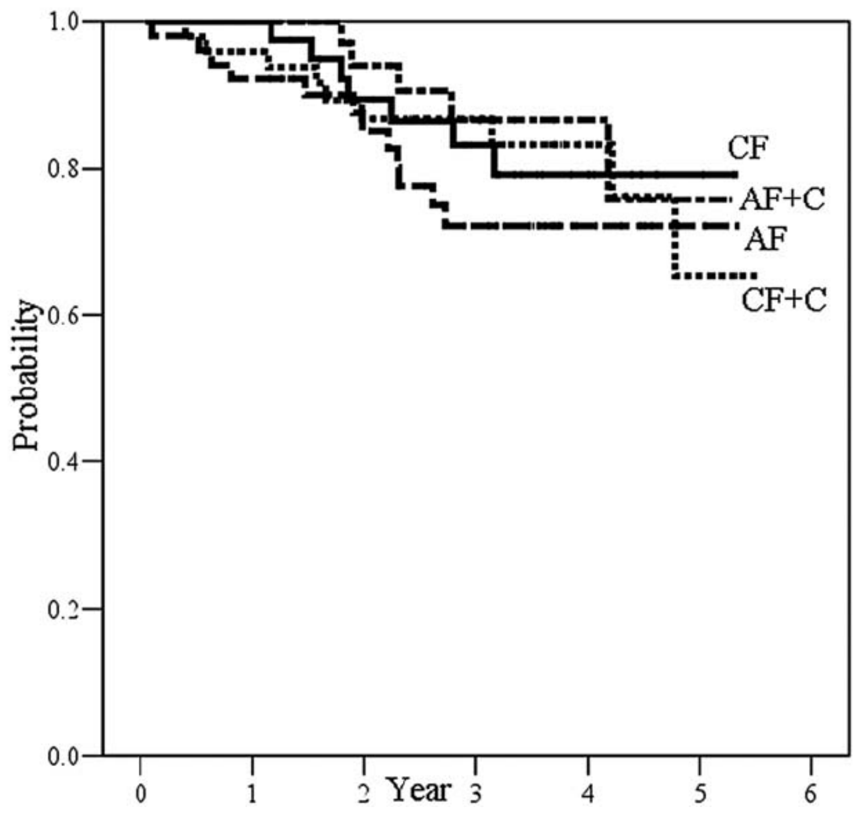
Lee A, Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 1, pp. 142–151, 2006

NPC – altered fractionation NPC-9902

Loco-regional control

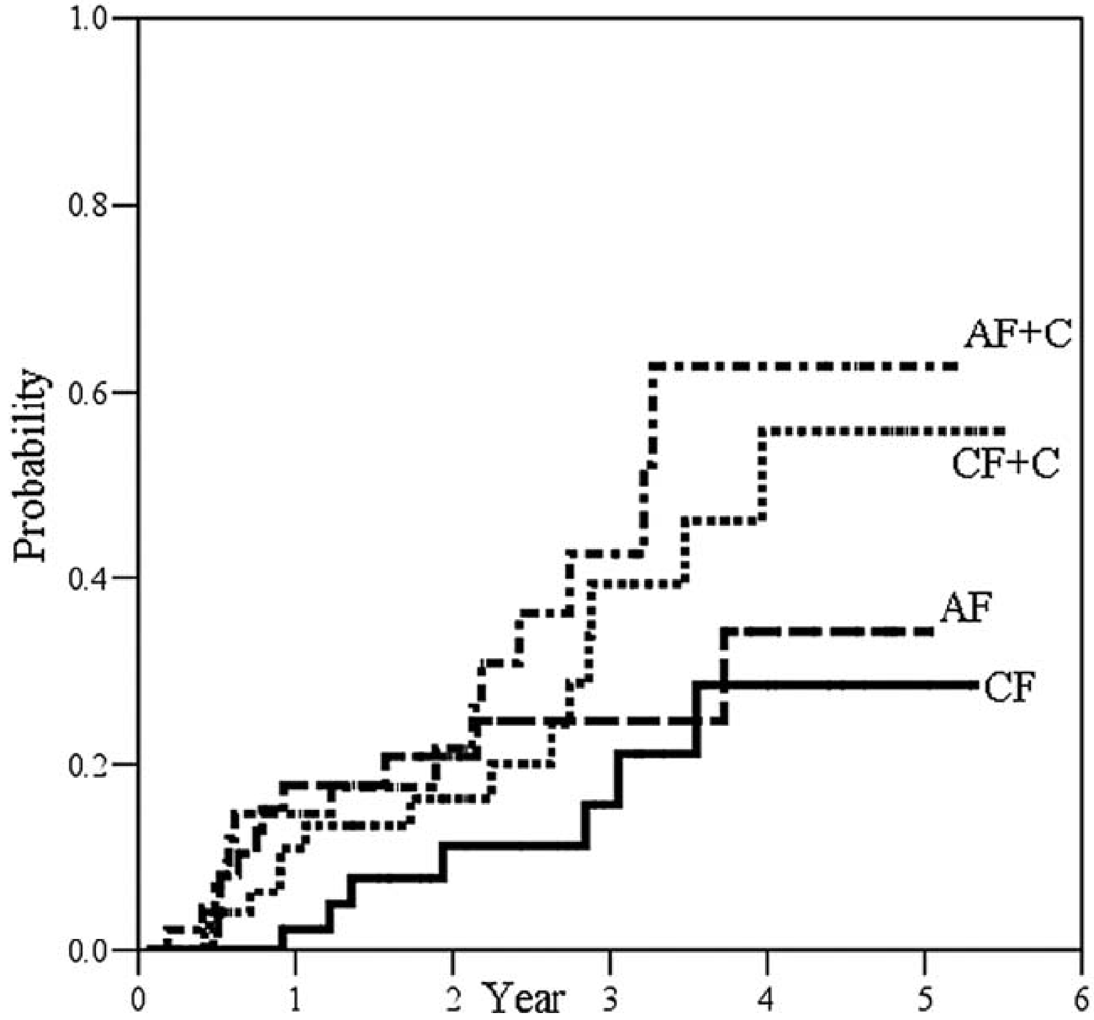


Overall survival



Lee A, Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 1, pp. 142–151, 2006

Late toxicity – NPC 9902



Lee A, Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 1, pp. 142–151, 2006

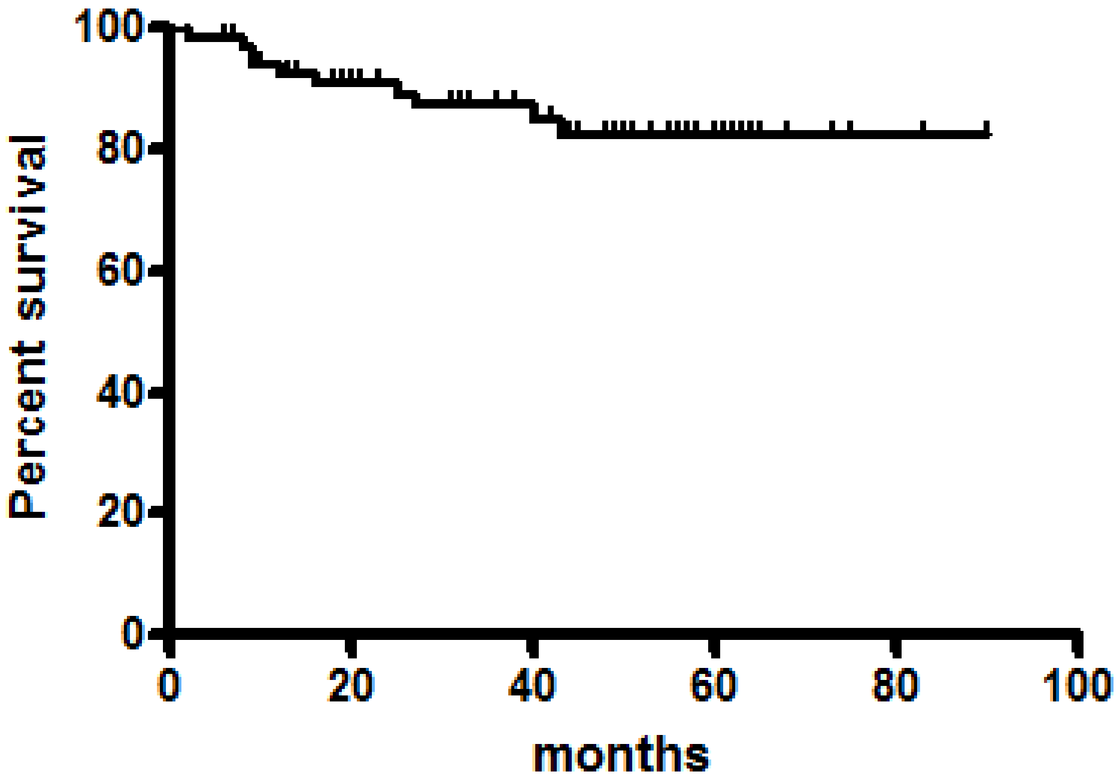
Acc. fractionation concomitant cisplatin + nimorazole

TNM stage (UICC 2002)
Stage 1 :7
Stage 2a : 3
Stage 2b : 11
Stage 3 :26
Stage 4a : 17
Stage 4b : 7

Patient Demography:
- 71 patients were included from jan 1. 2003 to dec 31. 2008
- 46 males and 25 females
- Median age 49 years (r 17-79)

Histopathology
- Keratinizing high differentiated : 1
- Keratinizing moderate differentiated: 2
- Keratinizing low differentiated : 11
- Non keratinizing undifferentiated : 46
- Non keratinizing differentiated : 10
- Other : 1

Locoregional control. Dahanca 14



5 Year loregional control 82%

DAHANCA14, Bentzen et al, ESTRO 2011

Author	No.	Stage IV (%)	Radiotherapy		Chemotherapy			Tumor control (%)			
			Dose (Gy)	Time (weeks)	Induction	Concurrent	Adjuvant	Time-point (year)	LR-FFR	D-FFR	OS
Concurrent-adjuvant chemo-radiotherapy with accelerated fractionation											
Wolden et al. (2001)	50	44	70	6	–	P	PF	3	L:89	79	84
Jian et al. (2002)	48	>77	74	7	–	P	PF	3	L:91	NR	72
Lin et al. (1996)	63	NR	72–74	6	–	PF	±PF	3	L:89	74	74
Induction-concurrent chemo-radiotherapy with conventional fractionation											
R et											
O (2											
J et											
A et											
C (2004)											
Hui et al. (2007)	30	NR	66	6.5	DP	P	–	2	NR	NR	93
Induction-concurrent chemo-radiotherapy with accelerated fractionation											
Lee et al. (2005c)	49	100	70	6	PF	P	–	3	77	75	71
Yau et al. (2006)	37	100	70	6	PG	P	–	3	78	76	76

Role of accelerated fractionation +/- altered chemotherapy sequencing remains open

Stereotactic boost

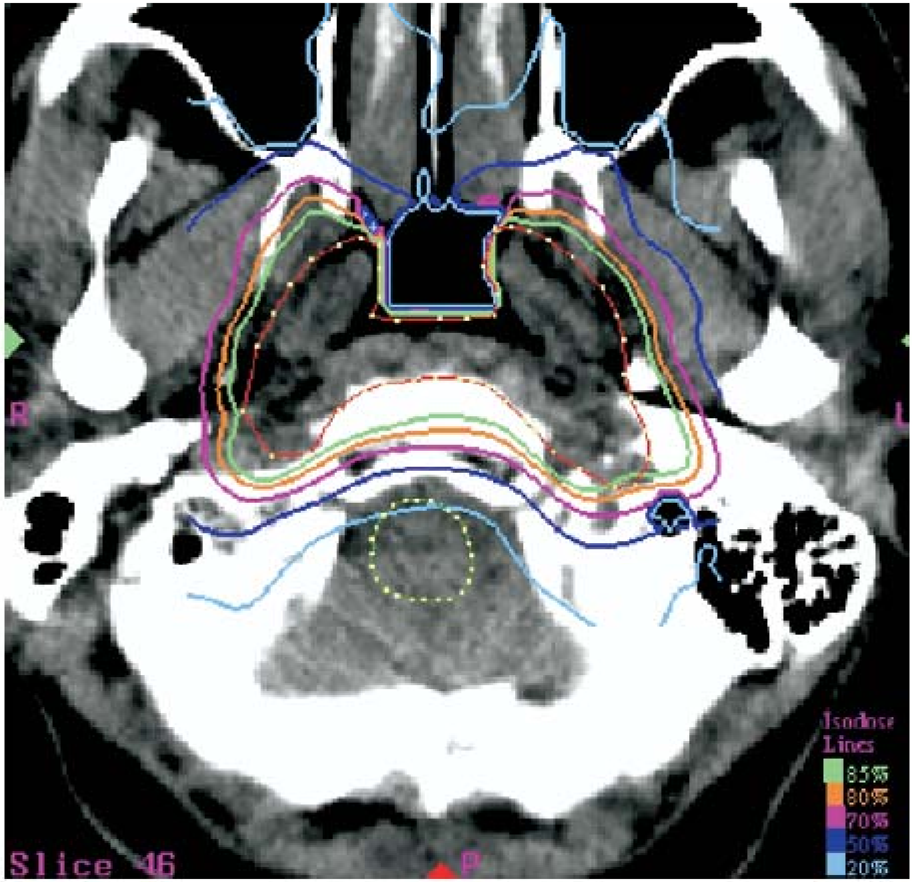


Fig. 1. The isodose distribution of the stereotactic body radiation therapy boost in an original T2 tumor. Green line indicates the 85% isodose line.

EXPERIENCE IN FRACTIONATED STEREOTACTIC BODY RADIATION THERAPY BOOST FOR NEWLY DIAGNOSED NASOPHARYNGEAL CARCINOMA

Helen H. W. Chen, M.D.,*† Sen-Tien Tsai, M.D.,*‡ Mei-Shu Wang, B.S.,* Yuan-Hua Wu, M.D.,* Wei-Ting Hsueh, M.D.,* Ming-Wei Yang, M.D.,* I-Chun Yeh, M.D.,* and Jin-Ching Lin, M.D., Ph.D.*§‖

*Department of Radiation Oncology, †Institute of Clinical Medicine, College of Medicine, and ‡Department of Otorhinolaryngology, National Cheng Kung University Hospital, Tainan, Taiwan; §Department of Radiation Oncology, Taichung Veterans General Hospital, Taichung, Taiwan; ‖Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan

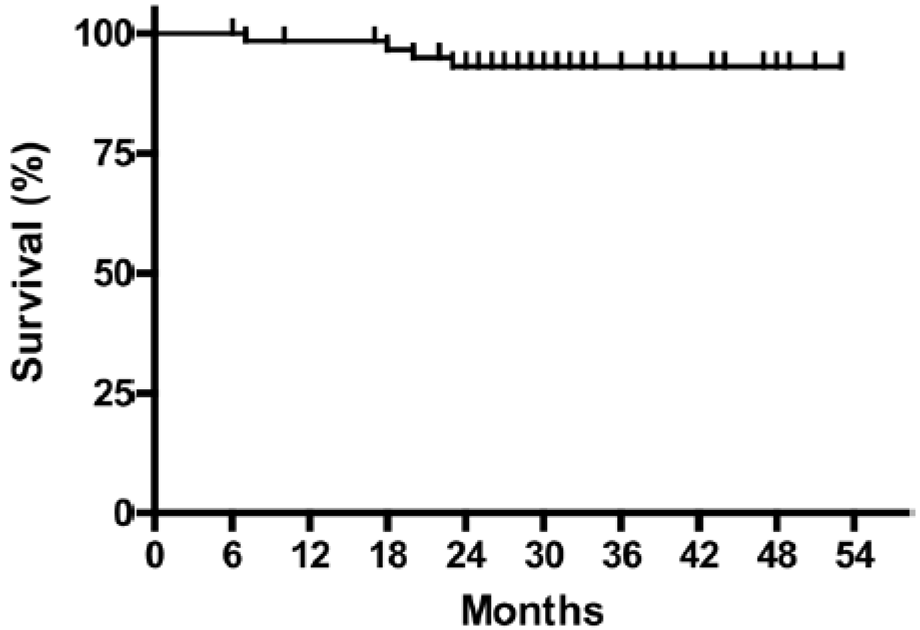


Fig. 3. Nasopharynx disease-free survival of 64 patients treated using conventional radiotherapy + stereotactic body radiation therapy boost.

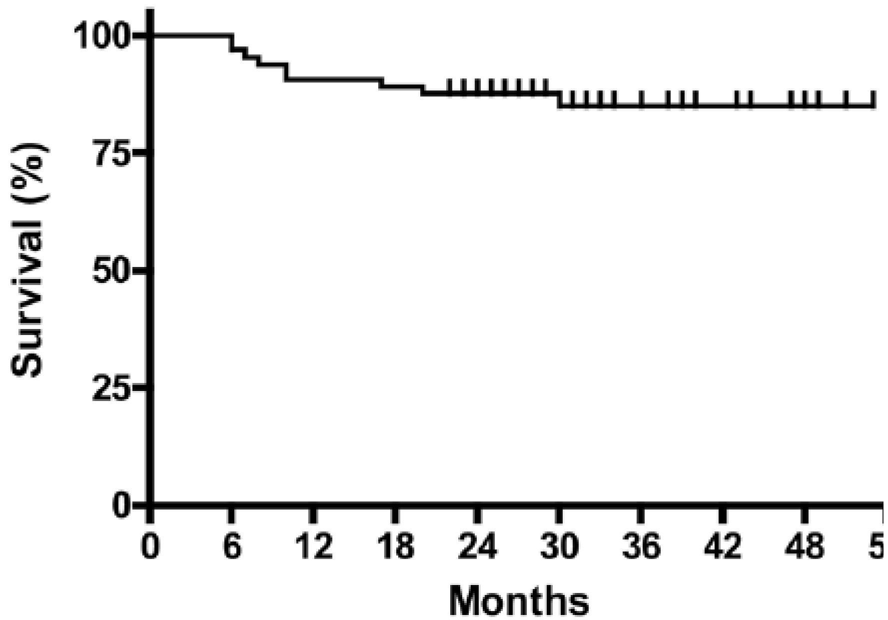
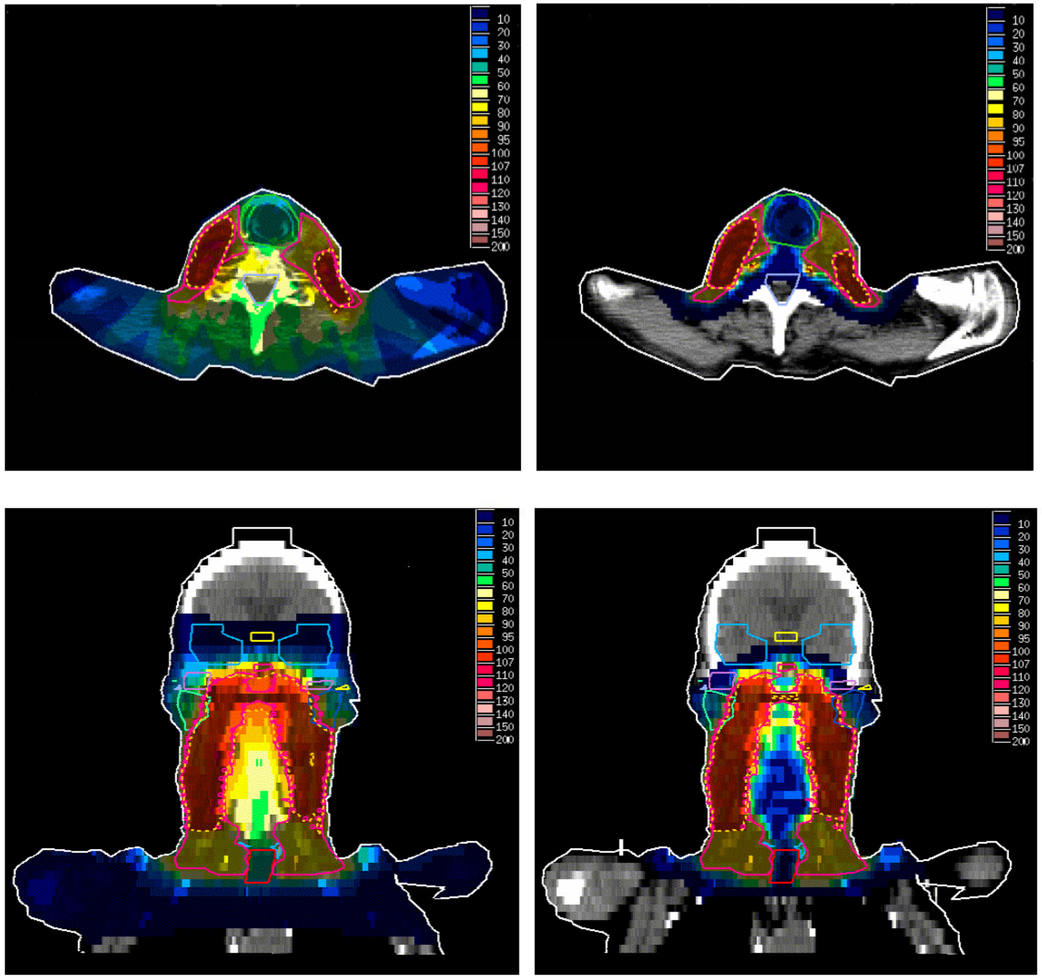
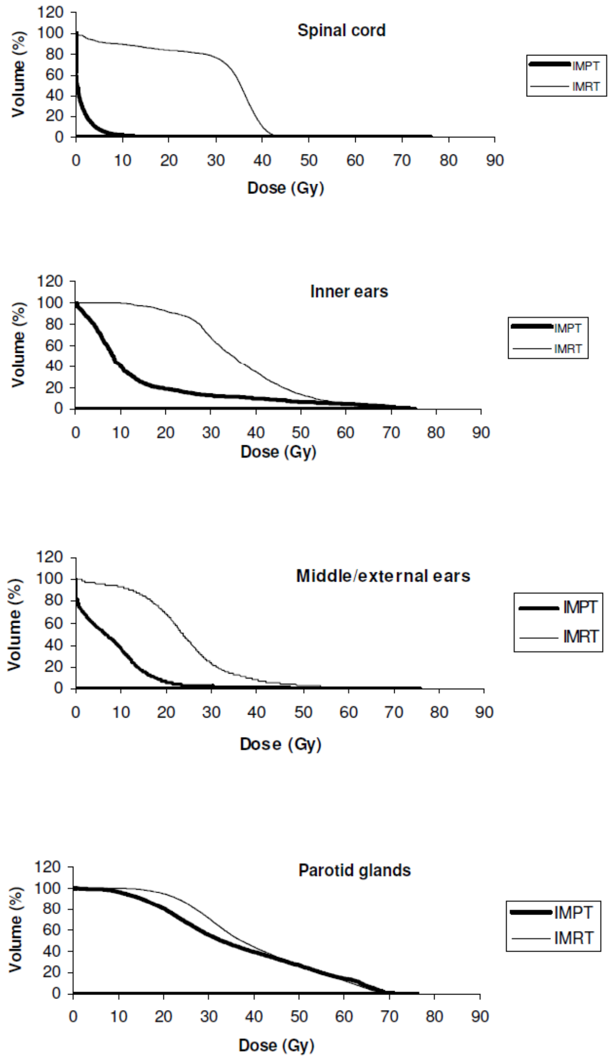


Fig. 4. Overall survival of 64 patients treated using conventioı radiotherapy + stereotactic body radiation therapy boost.

Protons (IMPT)

IMRT IMPT





Taheri-Kadkhoda et al, Radiat Oncol 2008

Topics

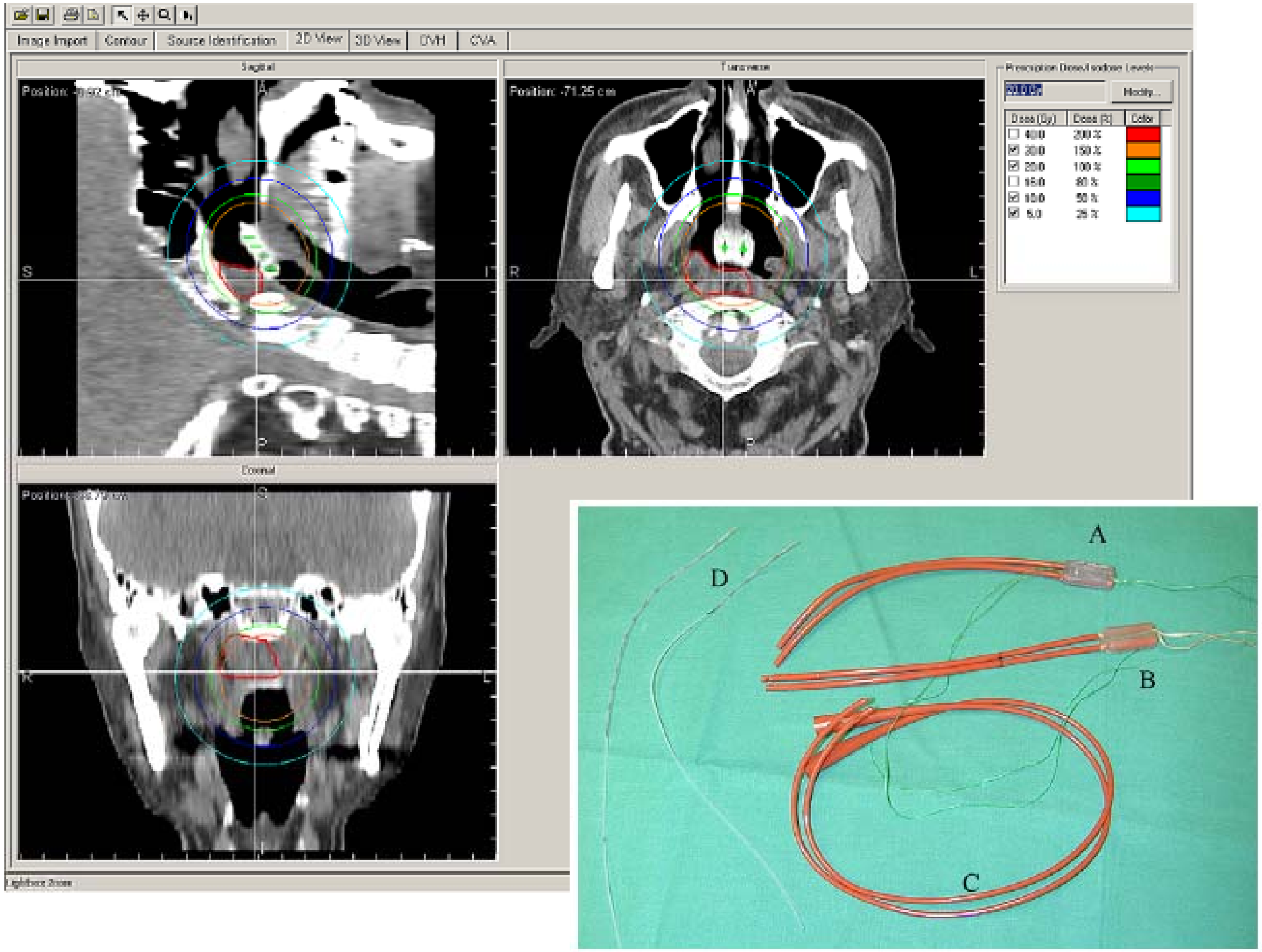
- Anatomy, aetiology, pathology, staging
- Radiotherapy (IMRT, volumes, techniques)
- Chemotherapy
- Radiotherapy morbidity
- Novel approaches
- Salvage treatment of loco-regional recurrences (re-irradiation, surgery, brachy)

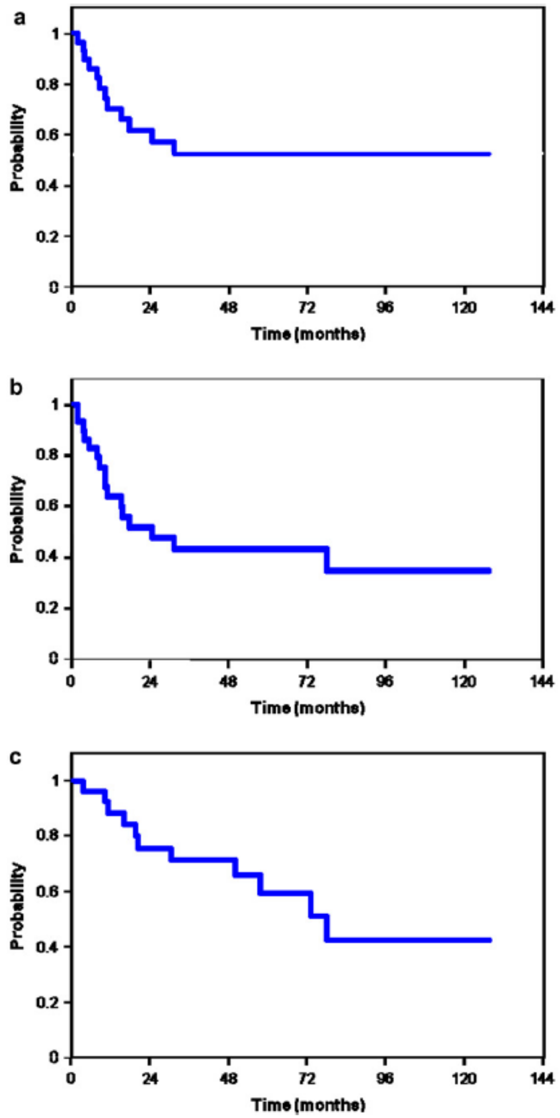
Loco-regional recurrence

- Re-irradiation
  - IMRT
  - Brachytherapy
  - Proton therapy
  - Stereotactic RT
- Surgery
  - nasopharyncectomy or
  - endoscopic resections
- Chemotherapy

NPC re-irradiation brachy

29 patients: 13 patients EBRT+ intracavitary brachy; 16 EBRT alone (MSKKC)





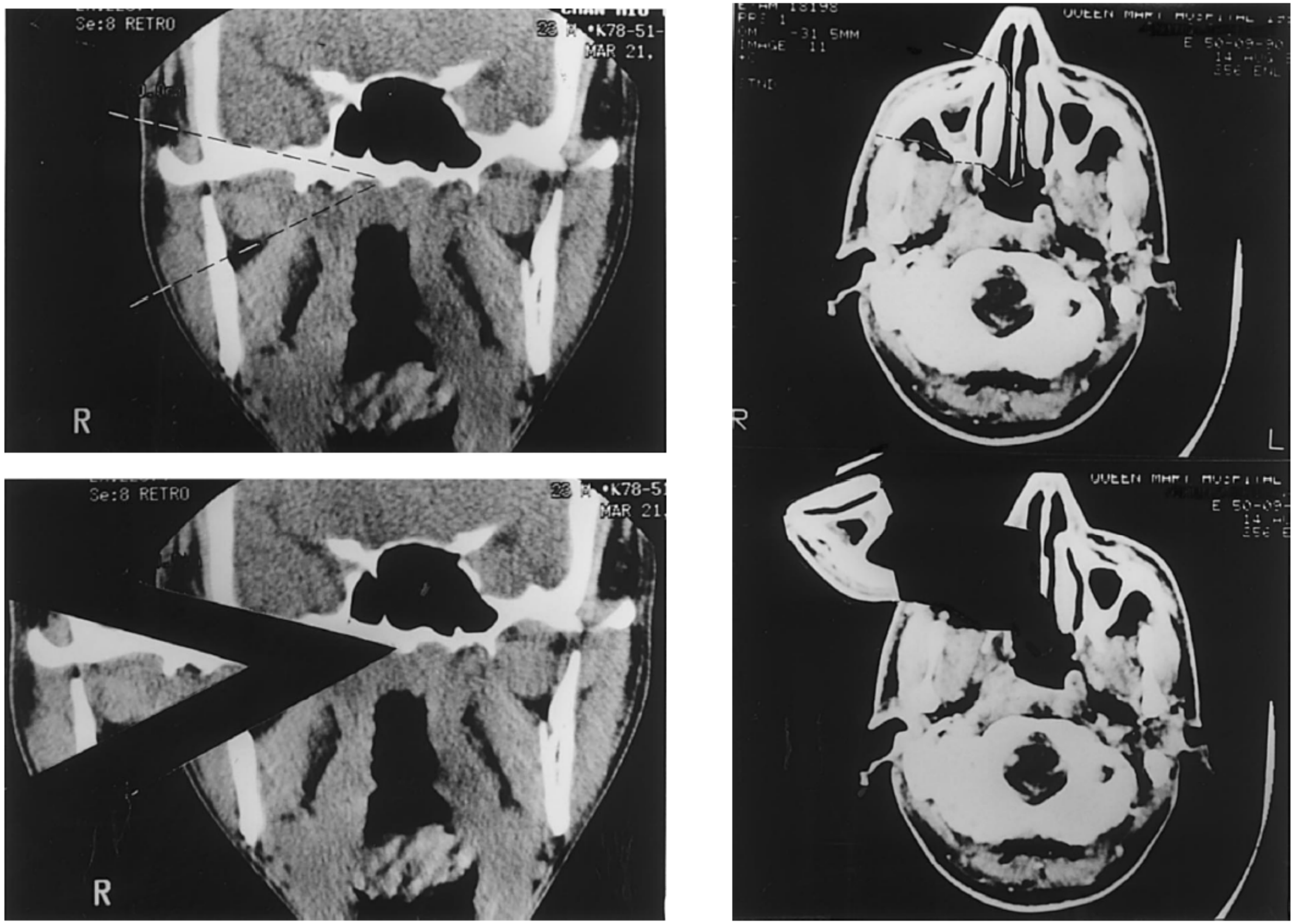
Koutcher, Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 1, pp. 130–137, 2010

NPC re-irradiation results

Reirradiation series (reference)	Years in which patients were treated	No. of patients	Median follow-up (y)	3-y actuarial survival (%)	5-y actuarial survival (%)
Lee, 1997 (12)	1976–1992	654	1.4	—	16
Chua, 1998 (13)	1984–1995	97	1.5	46	36
Hwang, 1998* (14)	1957–1995	74	1.7	49	37
Teo, 1998 (8)	1984–1989 (primary radiation)	123†	1.7	—	9
Chang, 2000 (15)	1982–1995	186	3.5	22	12
Leung, 2000 (16)	1990–1999	91	2.25/2.9/4.6	—	30
Syed, 2000 (17)	1978–1997	41‡	7	48 (2-y)	30
Law, 2002 (18)	1989–1996	118‖	6.5¶	—	61
Pai, 2002 (6)	1994–1999	36	1.8	54	31
Lu, 2004 (19)	2001–2002	49	0.75	100 LRC (0.75 y)	—
Oksuz, 2004 (20)	1979–2000	41	1.9	48 (2-y)	28
Poon, 2004 (21)	1994–2002	35	1.5	45 (2-y)	26
Shin, 2004 (22)	1995–2000	21	4.1	—	32
Chua, 2005 (23)	2001–2004	31	.92	30-40 (2-y)	—
Yu, 2005 (24)	1996–2000 (primary radiation)	159	Unclear	74#	—
Low, 2006 (25)	1995–2003	31	4.2§	—	53
Wu, 2007 (26)	1999–2005	56	13.3	46 DSS	—
Chua, 2007 (27)	1994–2005	74	3.5§	78 (SRS); 66 (BT)	—
Present series	1996–2008	29	3.75	71	60
				~45%	**~30%**

From Koutcher, IJROBP, 2010

Nasopharyngectomy



Wei WI, Critical Reviews in Oncology:Hematology 33 (2000) 91–98

Salvage therapy

	Number of patients	Stage of recurrence	Local control/survival rate	Complications	Treatment-related mortality
Reirradiation (conventional)[142]	706	T1 to T3	5-year survival rate 14%; 10-year survival rate 9%	Late sequelae 24%	1·8%
Stereotactic radiosurgery[75]	18	T1 and T2	2-year local control rate 72%	5·6%	0
Re-irradiation (IMRT)[77]	49	T1 to T4	9-month local control 100%	0	0
Brachytherapy (Gold grain)[143]	106	T1	5-year local control, residual 87%, recurrent 62%; 5-year disease-free survival, residual 68%, recurrent 60%	19%	0
Nasopharyngectomy (Maxillary swing)[144]	109	T1	5-year local control rate 68%, 5-year disease-free survival 54%	25%	0
Nasopharyngectomy (transpalatal)[145]	37	T1 to T3	5-year local control rate 67%, 5-year disease-free survival 52%	54%	3%

Wei W et al. Lancet 2005

Topics

- Anatomy, aetiology, pathology, staging
- Radiotherapy (IMRT, volumes, techniques)
- Radiotherapy morbidity
- Novel approaches
- Salvage treatment of loco-regional recurrences (re-irradiation, surgery, brachy)

Management of metastatic disease?

In the case discussion later today

Key points - NPC

- Very specific racial and geographic distribution
- Etiology includes both
  - genetic predisposition
  - environmental factors
  - virus
- Oncogenetic association of Epstein-Barr virus with nonkeratinizing NPC
- Nodal involvement at presentation in 80% of cases

Key points - NPC

- The current treatment recommendation is
  - radiotherapy alone for early stage
  - concurrent chemoradiotherapy (cisplatin-based) for locally advanced stages (III–IVB, bulky IIb)
- IMRT is recommended for target coverage and normal tissue sparing (xerostomia, etc)
- Beware of the many critical normal tissues at risk!
- Loco-regional control in excess of 90% at 2–4 years with IMRT and concurrent chemotherapy
- 5-year overall survival of ~70%

Key points - NPC

- Distant failures remain a problem
- Role of accelerated fractionation and/or altered chemotherapy sequencing remains open
- Local recurrences may be salvaged by re-irradiation, brachytherapy, or nasopharyngectomy, but morbidity is significant

[redacted]

Suggested literature

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Al-Sarraf M, LeBlanc M, Giri PG et al. (1998a) Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 16(4):1310–1317

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Lee AW, Tung SY, Chan AT et al. (2006) Preliminary results of a randomized study (NPC-9902 Trial) on therapeutic gain by concurrent chemotherapy and/or accelerated fractionation for locally-advanced nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 66:142–151

Lee N, Xia P, Quivey JM et al. (2002b) Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys 53:12-22

Pow HN, Kwong LW, McMillan S et al. (2006) Xerostomia and quality of life after intensity-modulated radiotherapy vs conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 66(4):981–991

Wei WI, Sham JST (2005) Nasopharyngeal carcinoma. Lancet; 365: 2041–54

Chen L, Hu CS, Chen XZ et al (2012) Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. Lancet Oncol 13:163–171

Oral Cancer: Surgical Aspects

C. René Leemans, MD, PhD
Professor and Chair

Otolaryngology-Head and Neck Surgery
VU University Medical Center
Amsterdam, The Netherlands

MULTIDISCIPLINARY MANAGEMENT
OF HEAD AND NECK ONCOLOGY
Florence, Italy. June 26-29, 2016

- 6th most common cancer worldwide
- Incidence is increasing
- Tobacco and excessive alcohol
- Betel Quid etc.
- Role of Human Papilloma Virus

Changing Management Philosophy

The last decade has witnessed increasing emphasis on quality of life after treatment

Consequently surgeons have found procedures that preserve function and form

Treatment Aims for Oral Cancer

- Cure of cancer
- Preservation of function and form
- Maintain or improvement of quality of life
- Prevention or early detection of second primary cancers

Treatments for Oral Cancer

- Surgery
- Radiotherapy
- Chemotherapy
- Biological therapies
- Photodynamic therapy
- Combined therapies

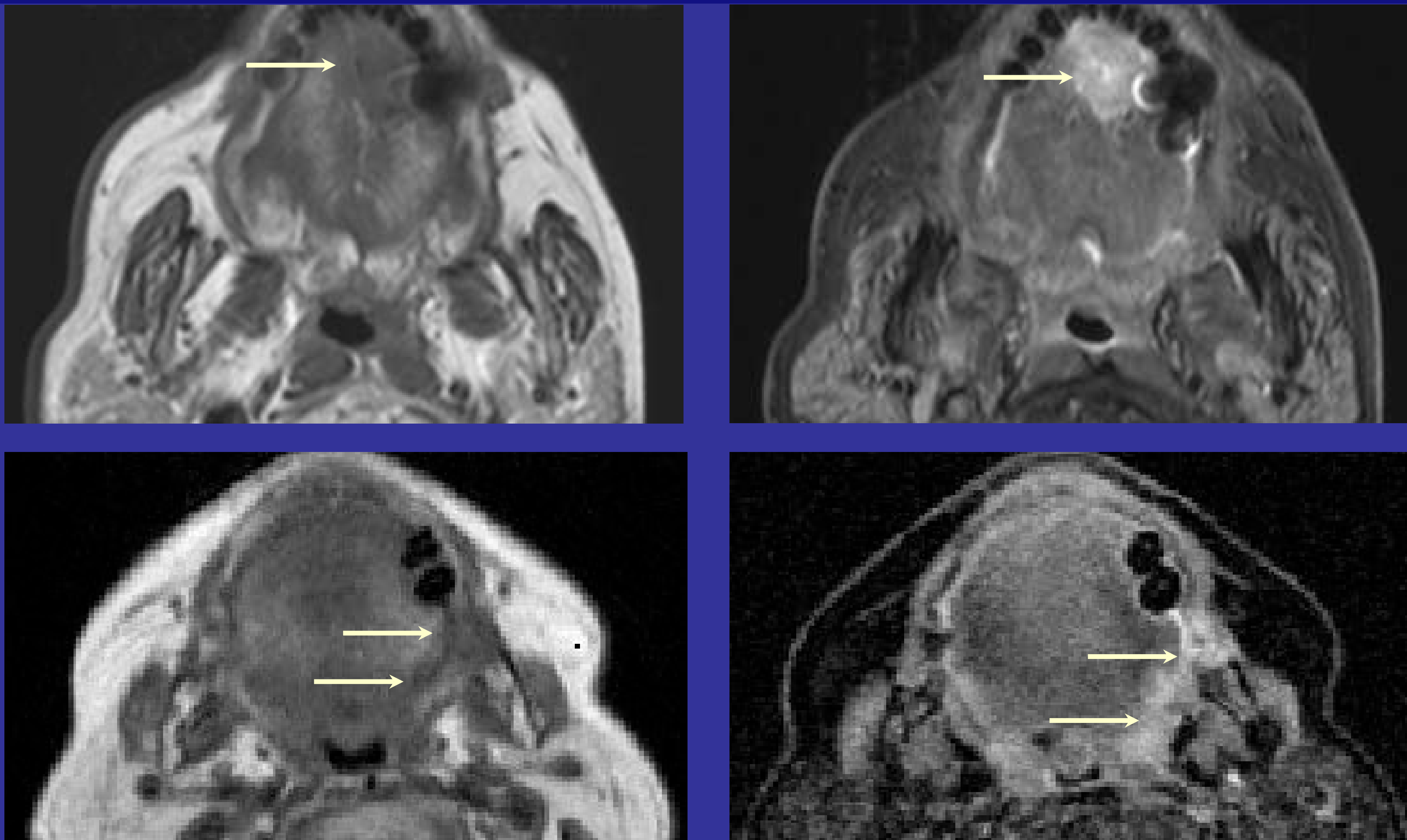
Choice of Treatment

Stage I and II:	Single modality treatment preferable
Stage III and IV:	Multimodal therapy is essential

Treatment dictated by:

- Tumor factors (imaging, examination, histology)
- Patient factors (biological age, comorbidity, patient’s wishes/expectations)
- Physician/Institutional/Provider factors

Management of Oral Cancer



T1 SE STIR

STIR: superior tumor delineation

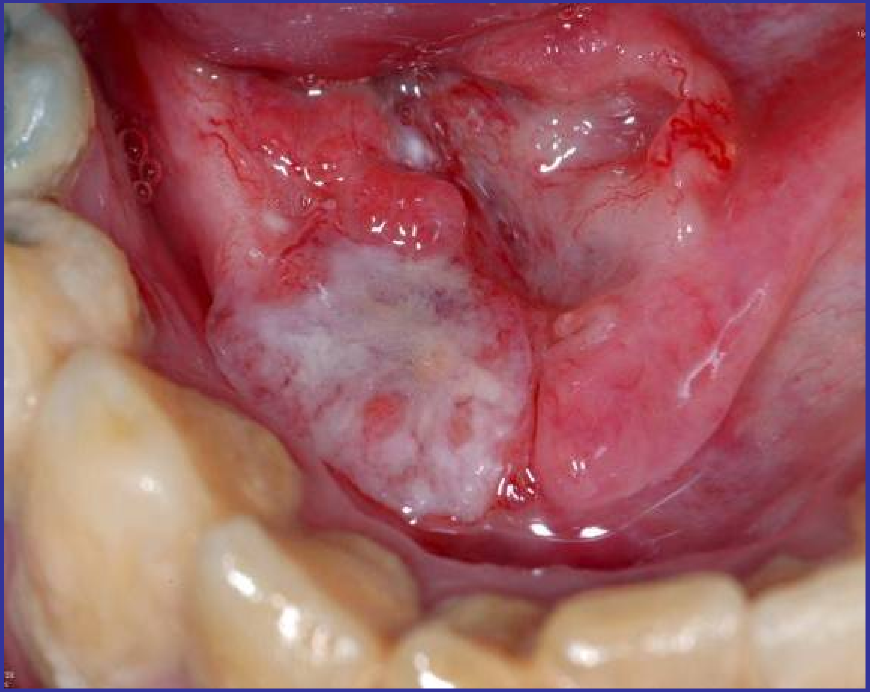
VU university medical center

Tumor Factors

- Sub-site/Location (invasion of structures)
- Size (T stage)
- Status of neck nodes (N stage)
- M-stage
- Proximity/Involvement of bone
- Multiplicity
- Previous treatment
- Pathological characteristics (tumor type, depth of invasion)

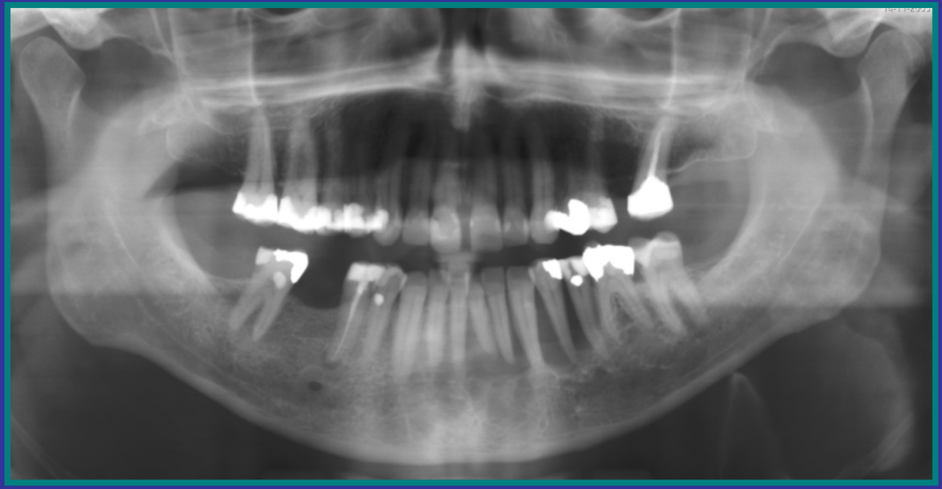
Early Lesion Inferior Alveolar Process

T2 Floor-of-Mouth Cancer



Large Lesion on Posterior Mobile Tongue

Bone Invasion



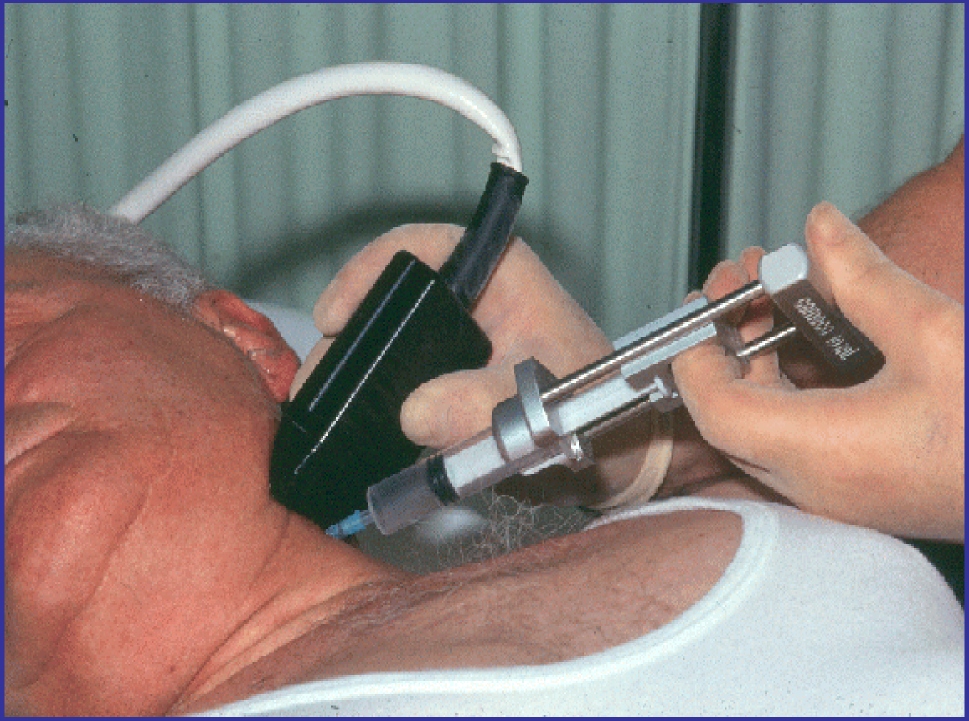
Surgical Approaches

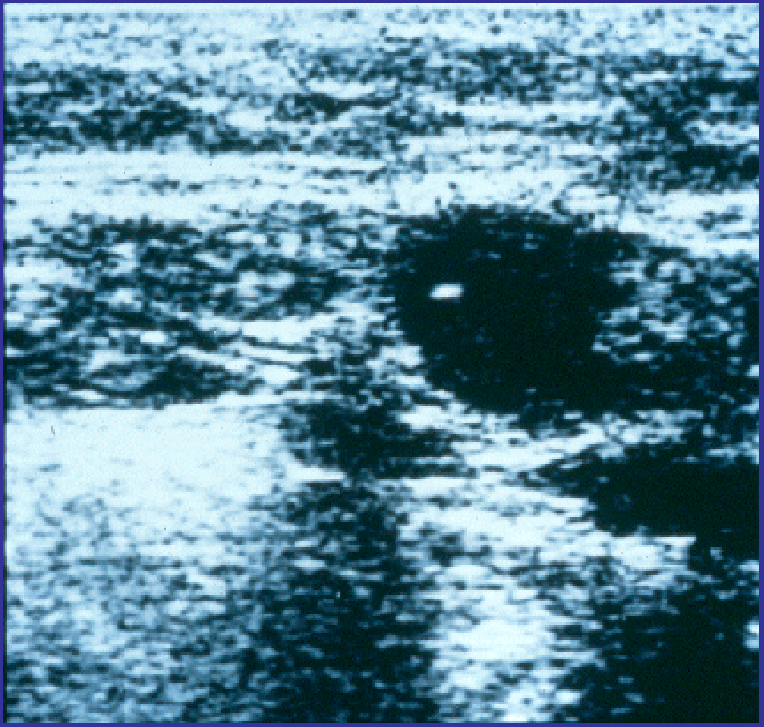
- Per oral
- Pull through
- Lower cheek flap
- Upper cheek flap
- Visor flap
- Mandibulotomy

Approach towards the N0-neck

- Elective treatment
  - If the risk of occult metastases exceeds 20% (?)
  - In case the neck is entered for technical reasons
- Wait-and-see
  - If the risk of occult metastases is below 20% (?)
  - If strict follow-up can be ensured

US-FNAC

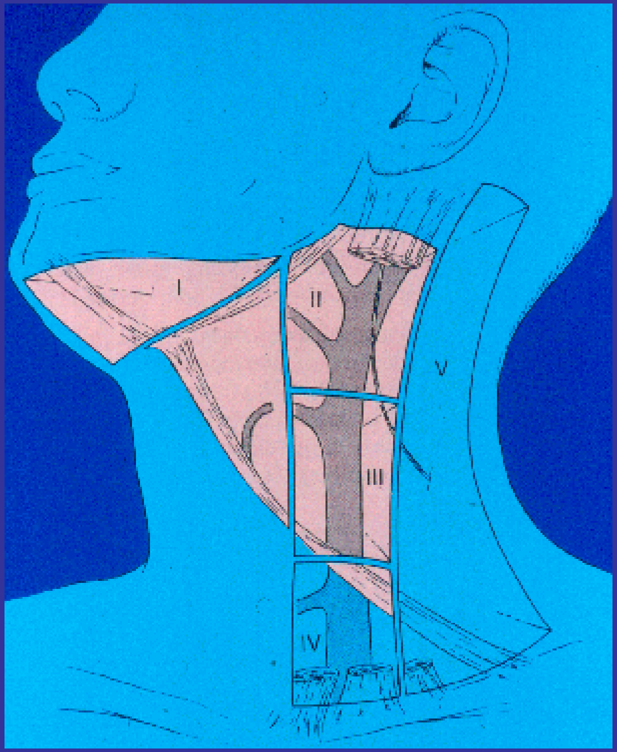


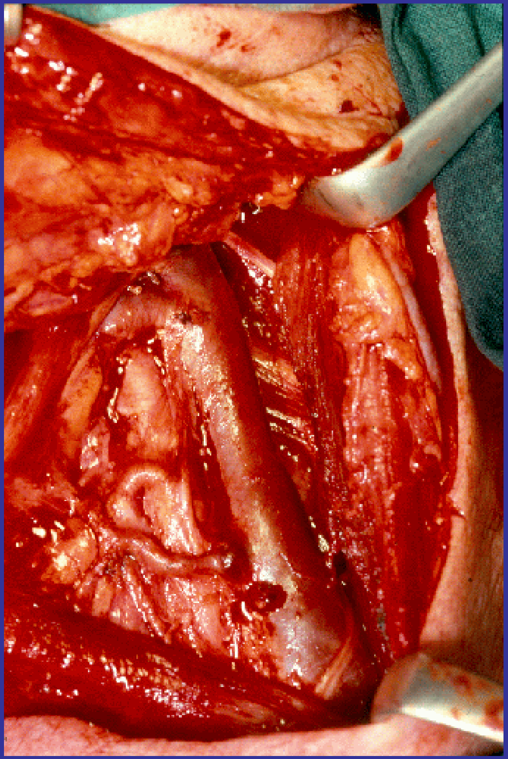


Options Towards the cN0 neck

- Elective neck irradiation
- Elective neck surgery
- Observation based on better risk assessment; i.e., a personalised approach based on predictive markers

Selective Neck Dissection (I-III)





Patient-tailored Approach

(i.e., Investigation and Observation if Negative)

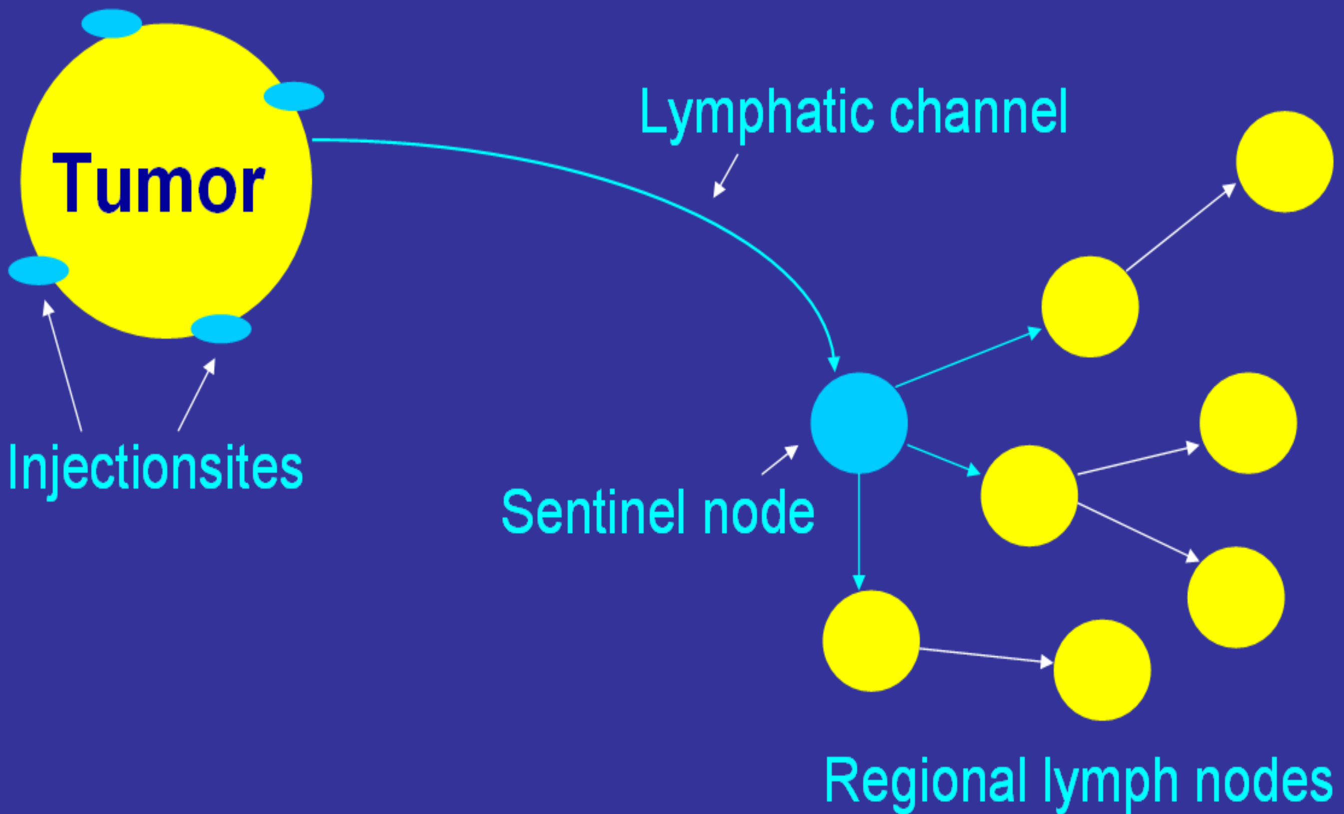
- Sentinel node investigation
- Ultrasound-guided fine needle aspiration cytology (US-FNAC)

- Clinico-pathologic tumor characteristics
- Molecular tumor characteristics

Sentinel Lymph Node Concept

- Tumor spreads via lymphatics to a primary node
- Examination of primary echelon nodes for tumor directs the need for surgical management of the nodal basins

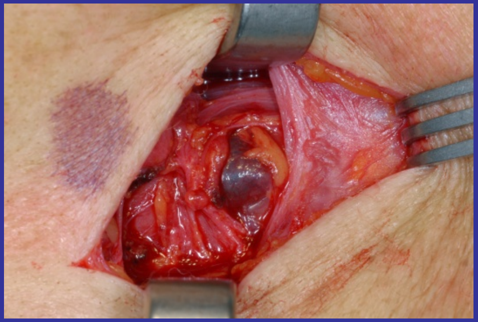
Management of Oral Cancer

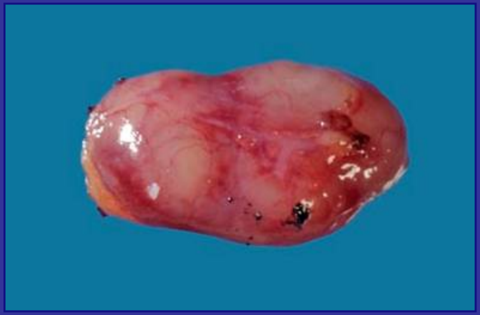


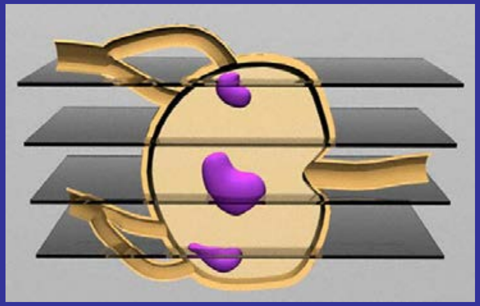
Peritumoral 99mTc-labelled Colloidal Albumin

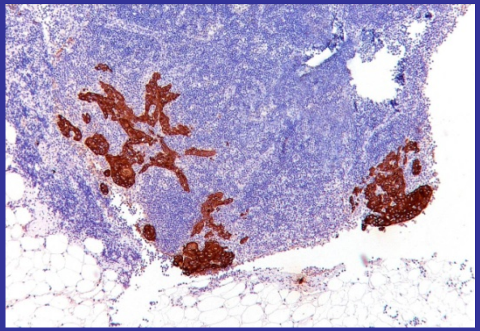
Lymphoscintigraphy

Management of Oral Cancer









Finished and Ongoing Trials

- Sentinel node European trial (SENT)
  - Ross and McGurk *et al*.
  - Alkureishi *et al.*
- American College of Surgeons Oncology Group (ACOSOG) study
  - Civantos *et al*.

Management of Oral Cancer

	All SNB					
	Success	Total	(%)	SN +	All +	Sensitivity/NPV
FoM tumors	37	42	88%	12	15	80%/88%
Other tumors	88	92	96%	30	31	97%/98%
All tumors	125	134	93%	42	46	91%/95%
Statistical significance	$P = 0.138$			$P = 0.034$		

Conclusion:

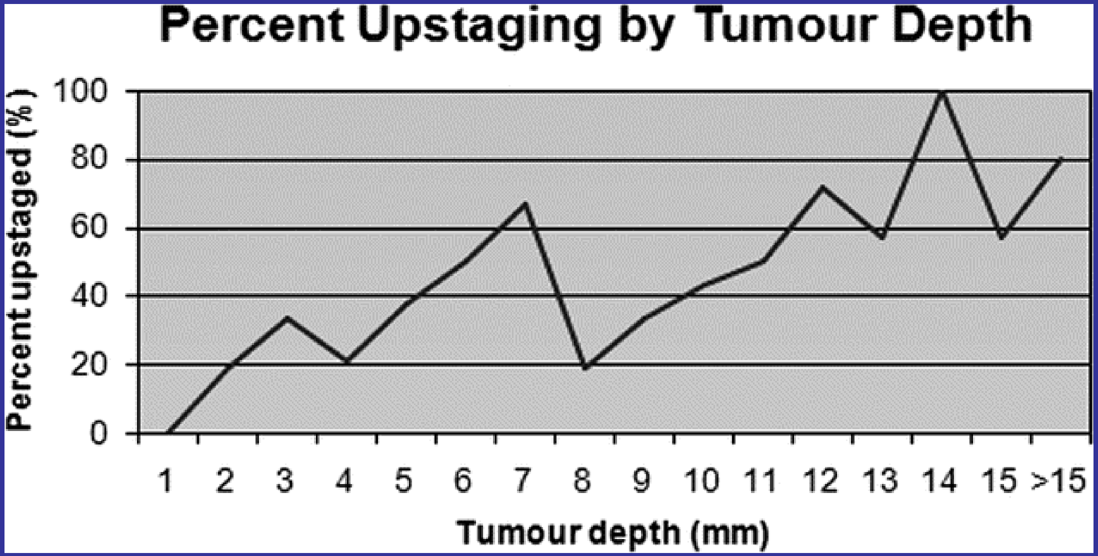
- SNB is reliable and reproducible means of staging cN0 neck
- Sole staging tool for majority of cT1/T2 HNSCC
    - For FOM SNB not recommended as sole staging, but combined with level I node clearance

Alkureishi *et al*. Ann Surg Oncol 2010

Clinico-pathologic Tumor Characteristics

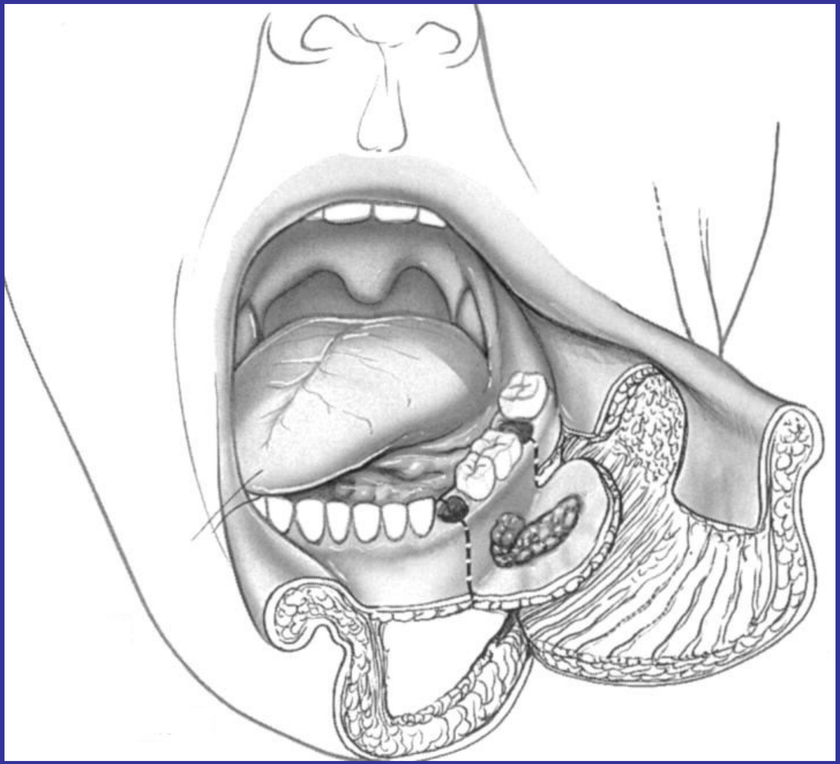
- Tumor thickness or depth (4 mm)

Does Tumor Depth Affect Nodal Upstaging?

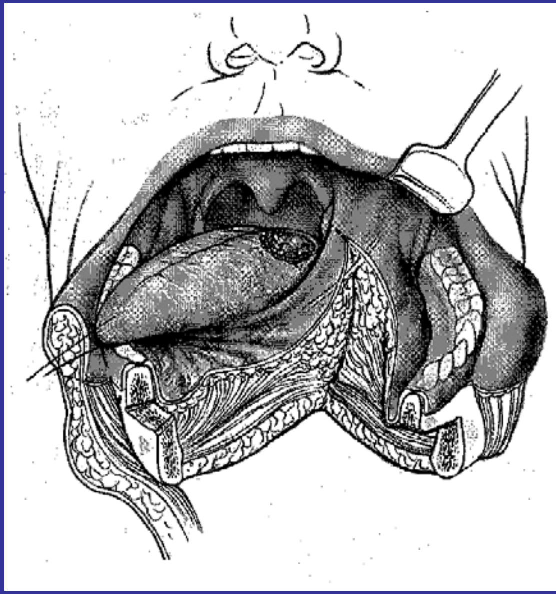


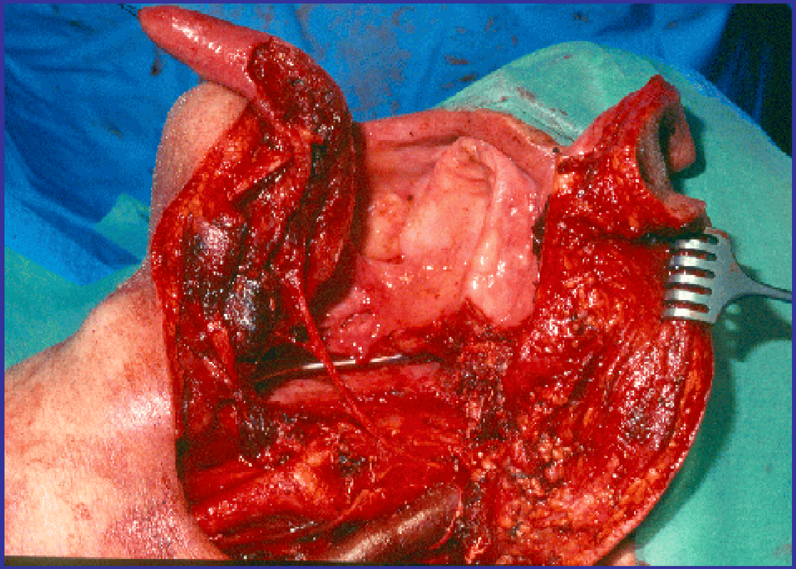
Alkureishi *et al*. Laryngoscpe 2008;118:629-34

Lower Cheek Flap

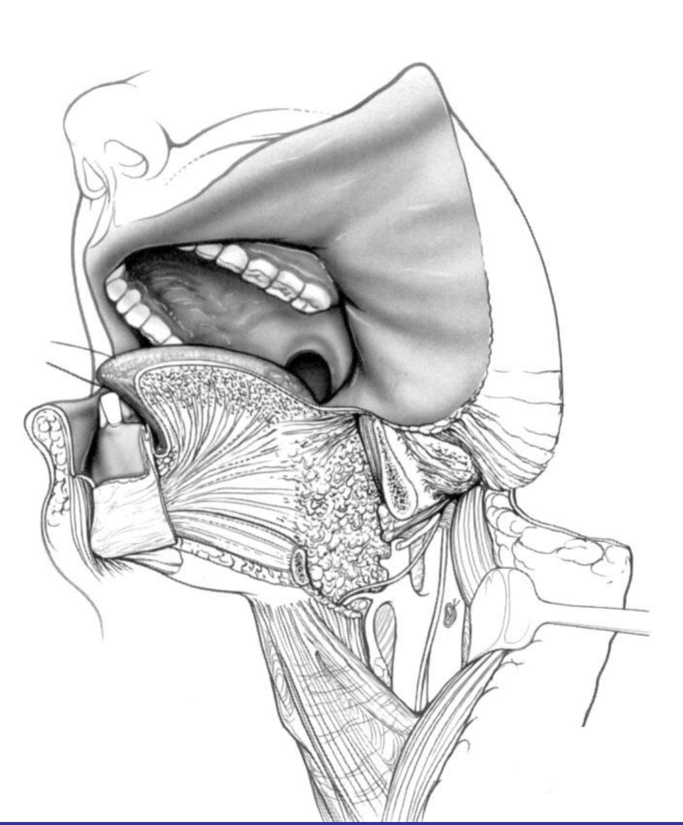


Mandibulotomy Approach





Composite Resection with Segmental Mandibular Resection

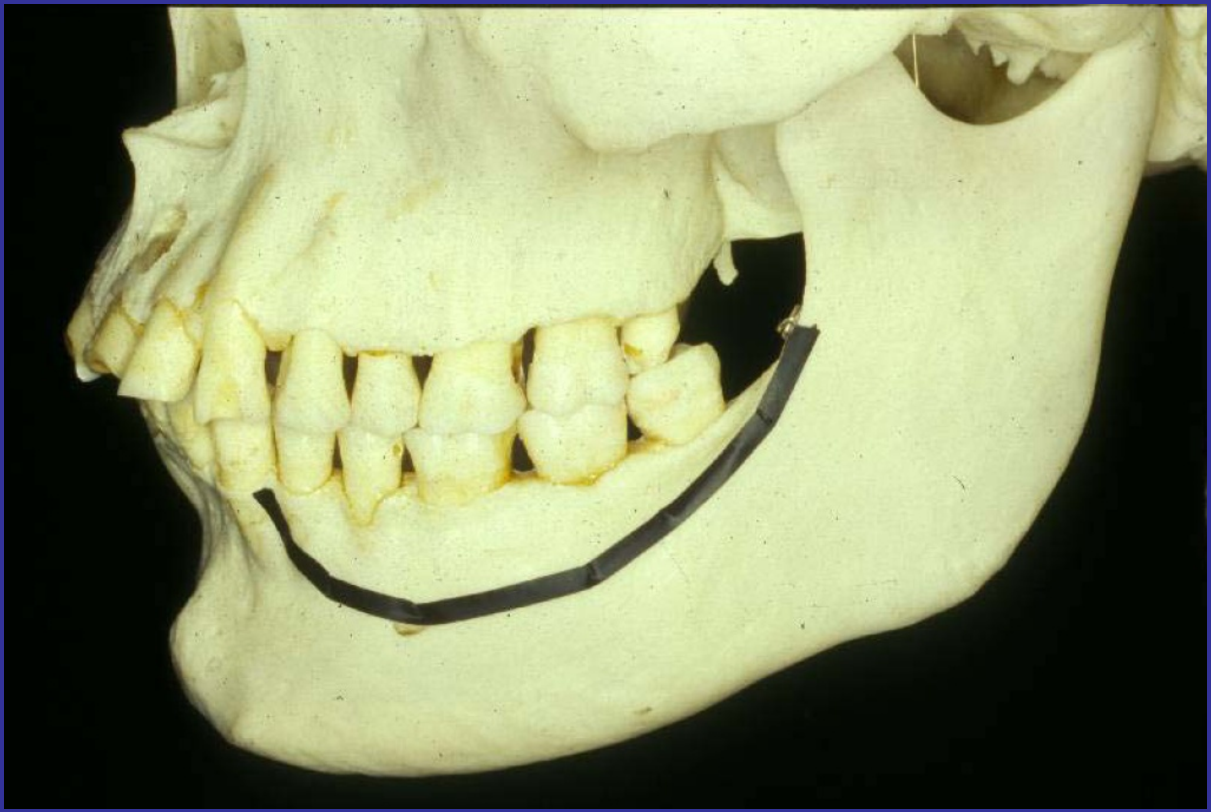


Management of Mandible

Marginal mandibulectomy feasible if:

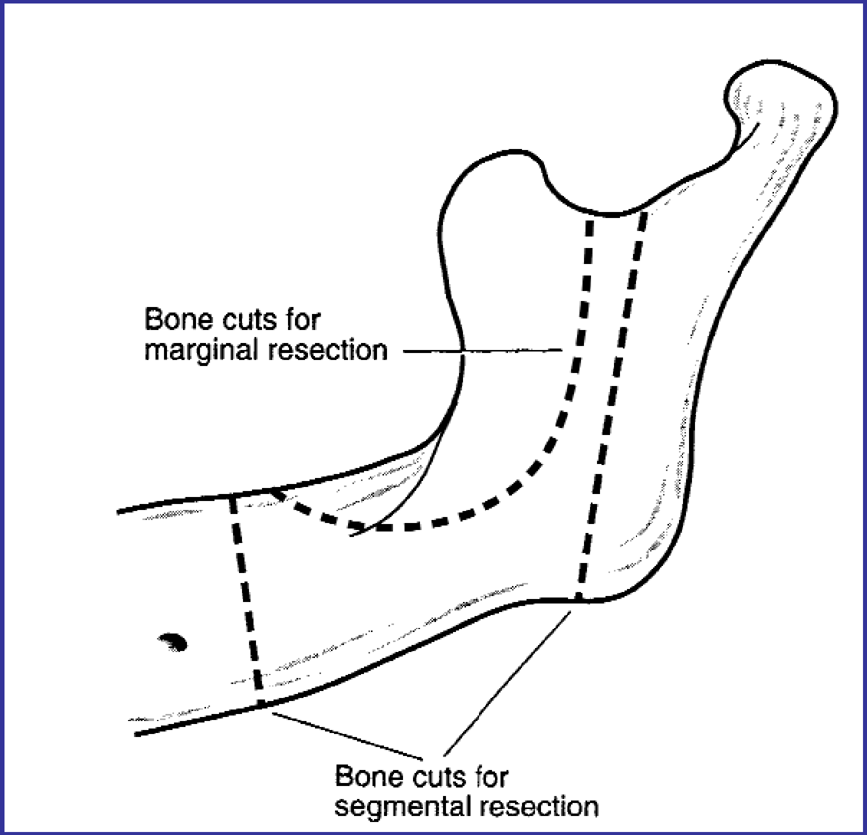
- Tumor superior to mylohyoid muscle
- Needed for margin
- Minimal erosion of cortex/alveolar process
- In dentate patient also when limited invasion of alveolar process

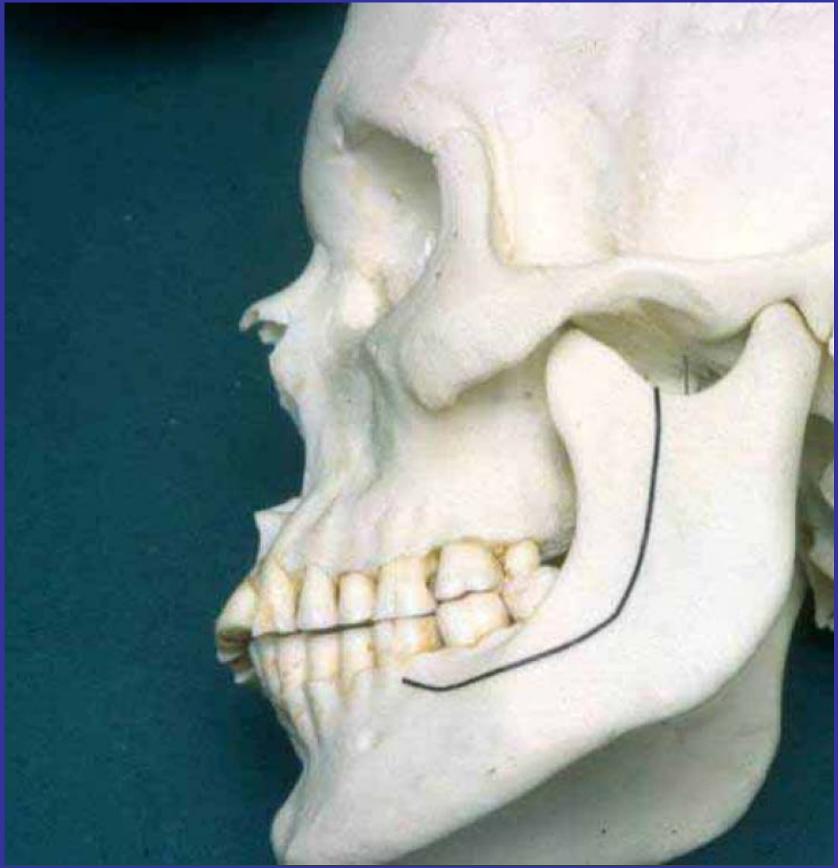
Boat-shaped Resection of Mandible



For Posteriorly Located Lesions:

Remove Coronoid Process

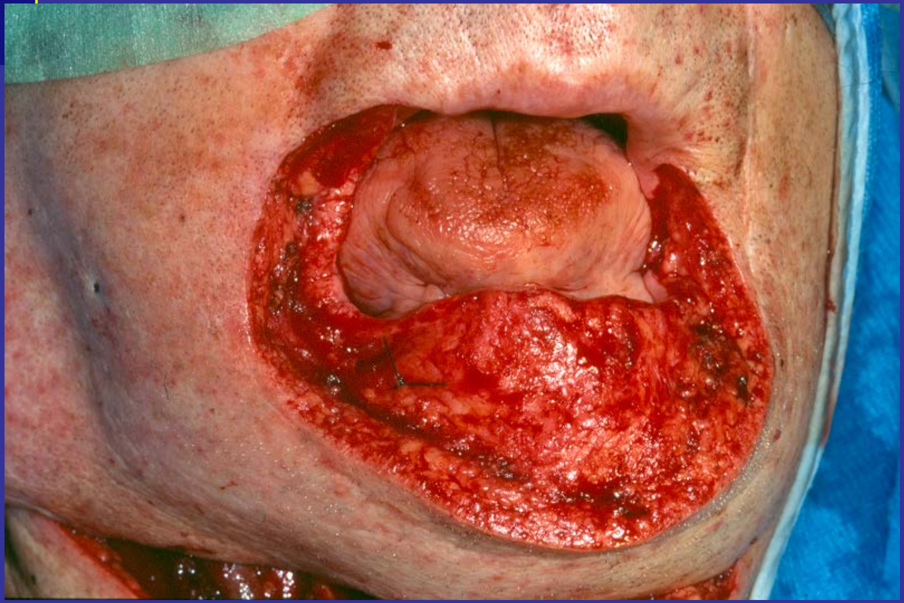


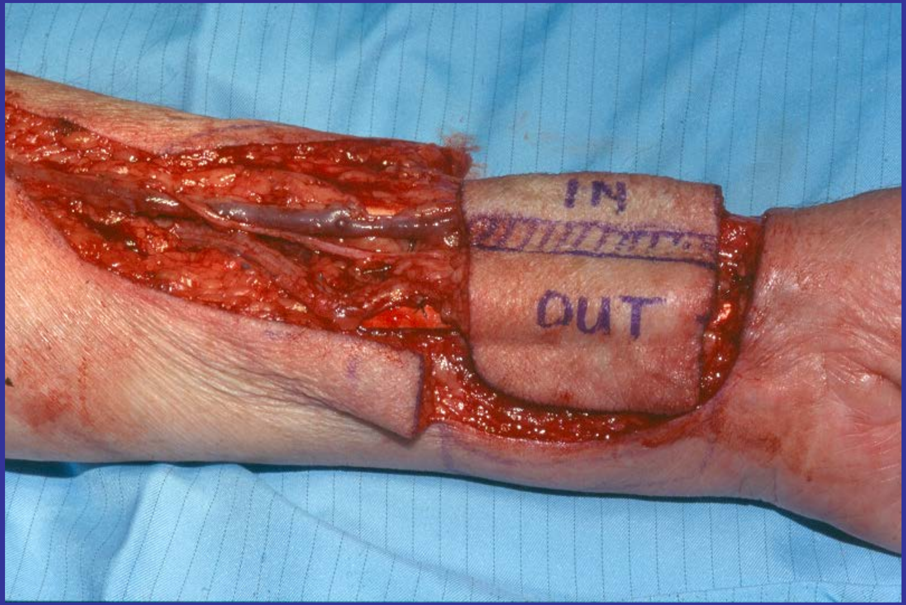


Excision and Reconstruction

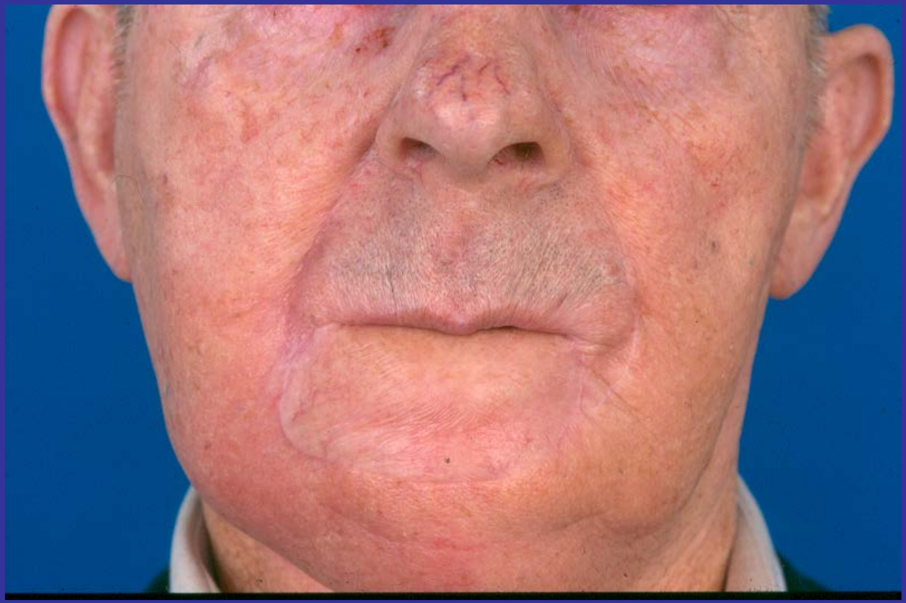
- Primary closure
- Secondary intention healing
- Skin graft
- Local flap
- Regional flap
- Free flap

Total Lower Lip Reconstruction (RFFF)





Total Lower Lip Reconstruction (RFFF)

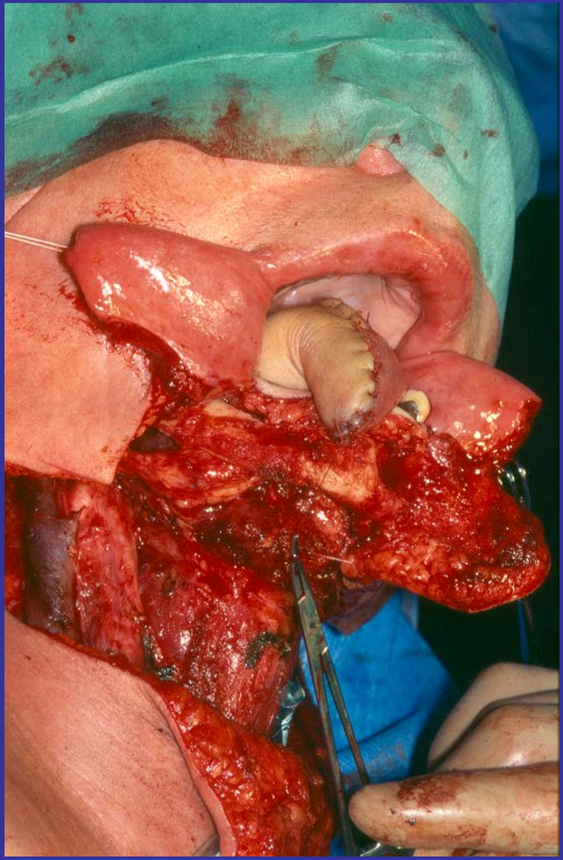


Lip Function 3 Years after Reconstruction of Lower Lip-Chin in a Male of 72 Years

	measurement	normal value*
Intercommissural distance (mm)	60	66
Soft tissue gape (mm)	30	44
Sphincteric power (g)	240	290
Two-point discrimination (mm)	10	3.2

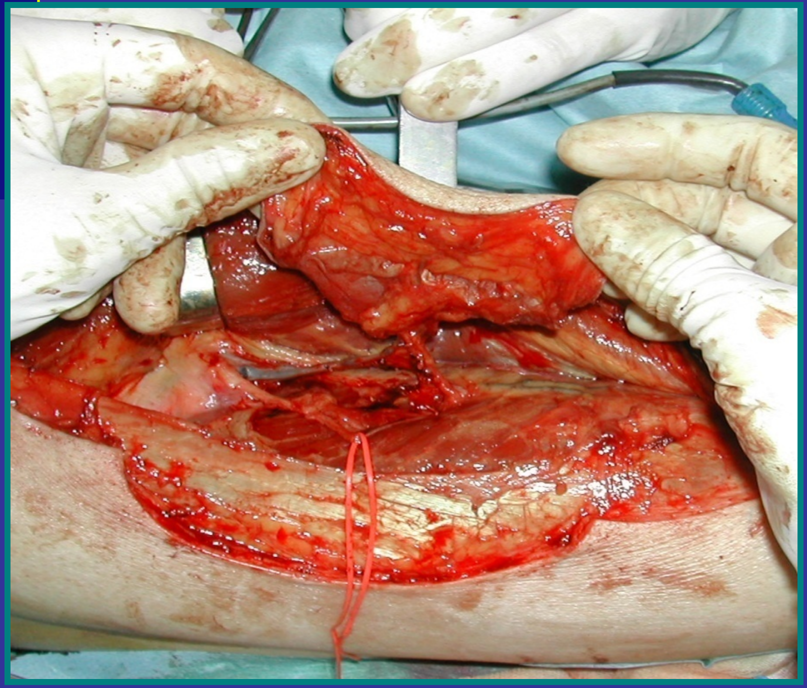
*Stranc MF, Fogel M. BJPS 1984;37:550-557

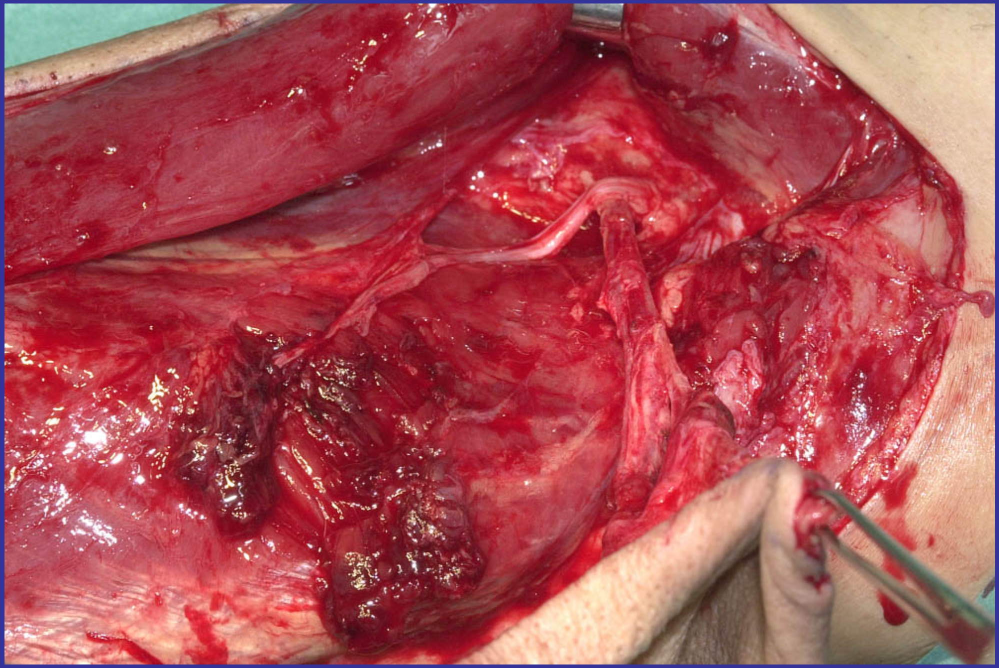
Partial Glossectomy (Bilobed RFFF)



Through-and-through Cheek Defect (RFFF)

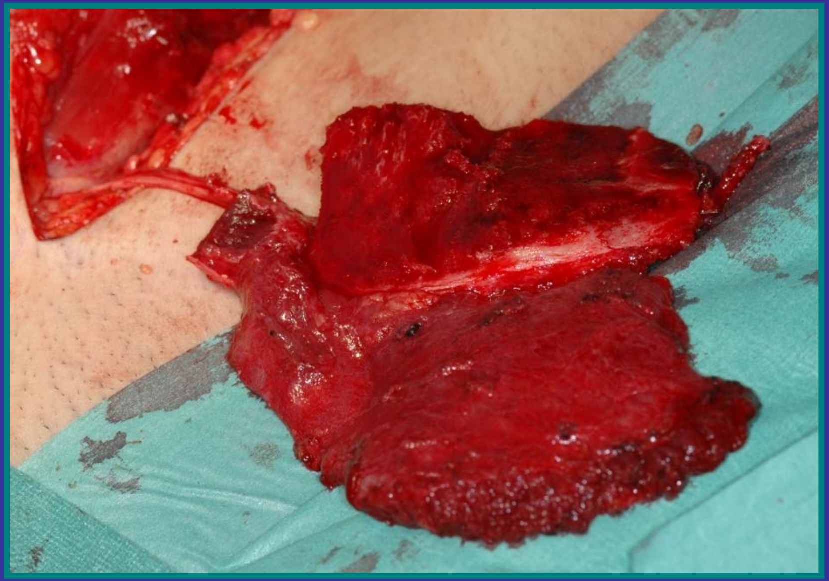
Anterolateral Thigh Flap





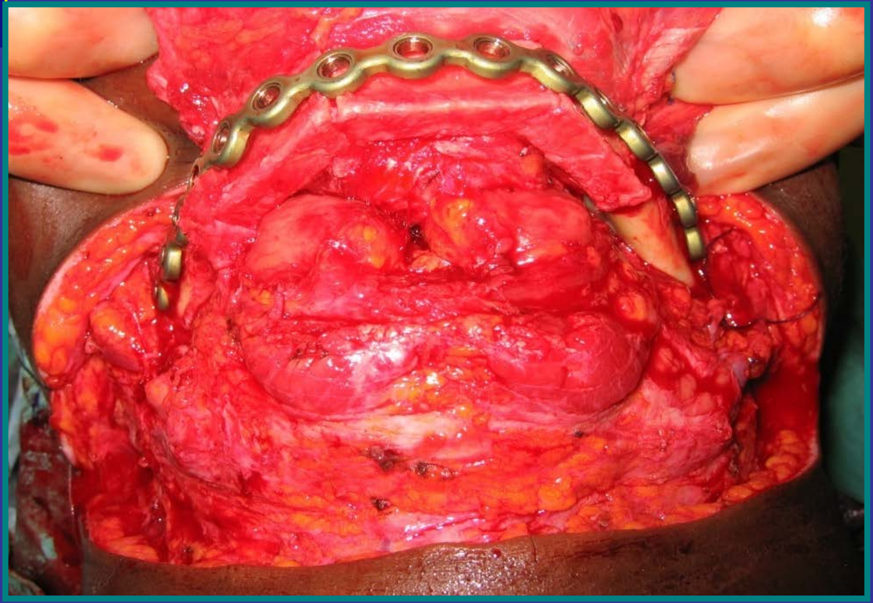
Bony Reconstruction

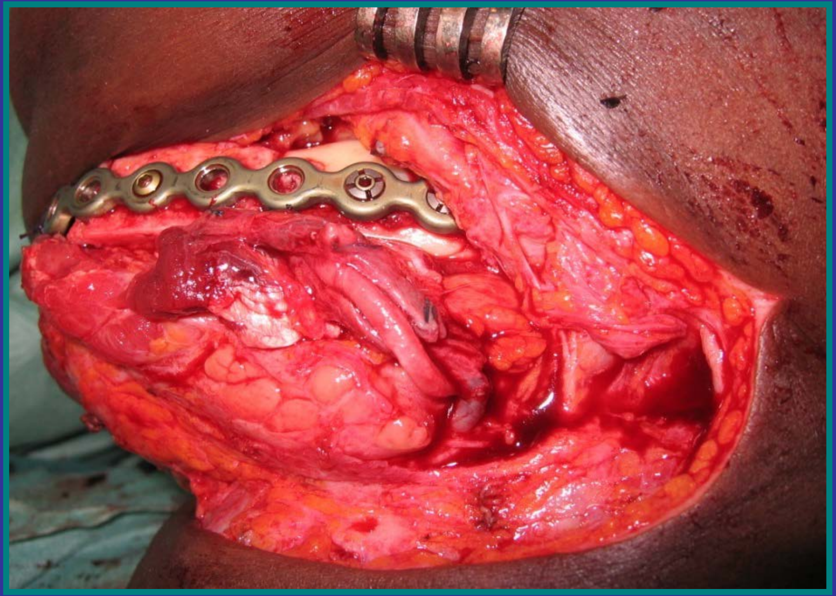
Fibula



DCIA

Mandibular Reconstruction

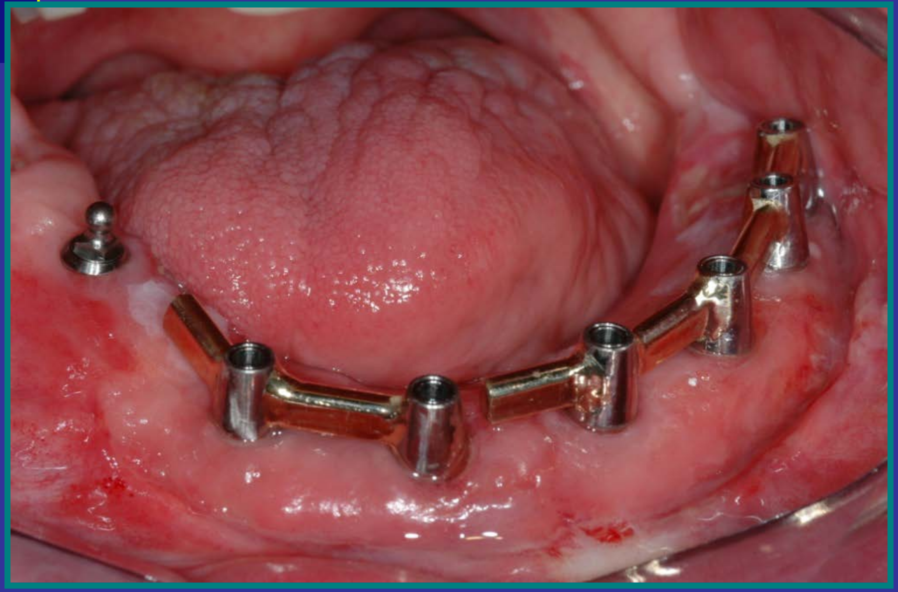




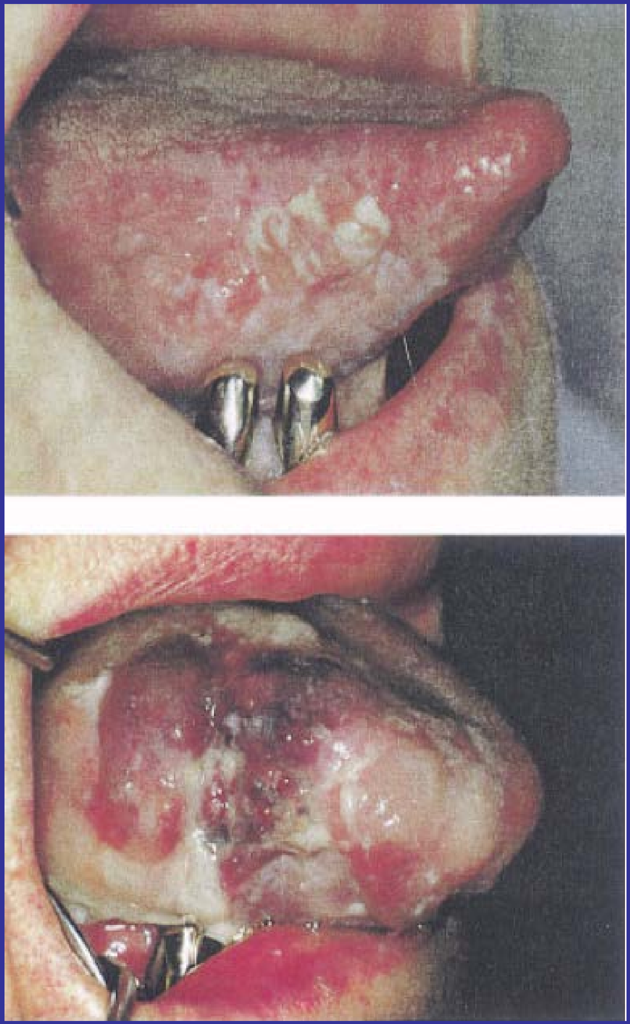
Result after Fibula Flap Reconstruction

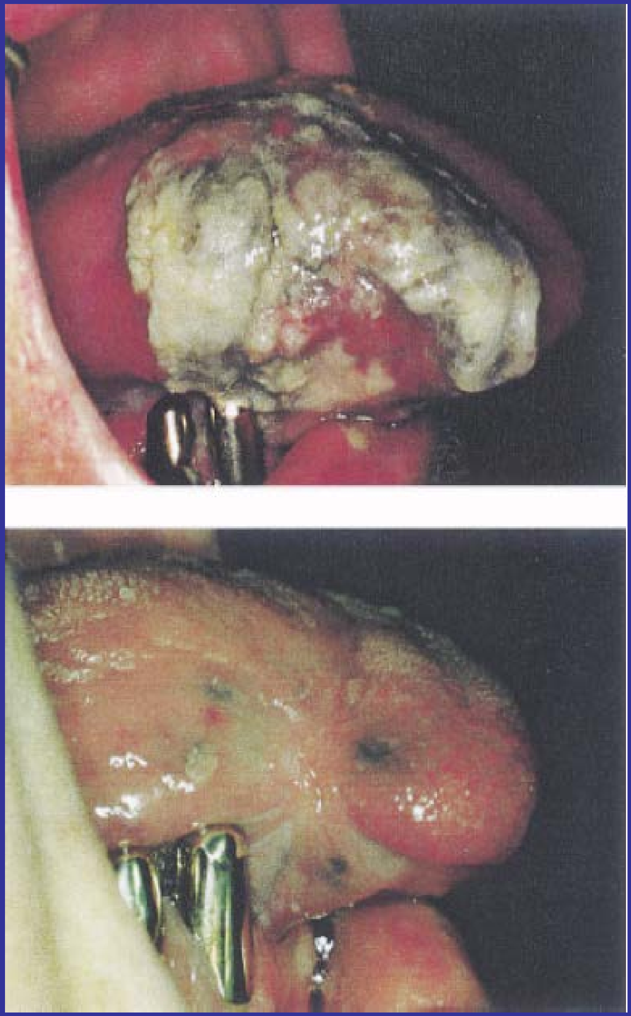
Osseointegrated Implants and Teeth

Osseointegrated Implants and Denture



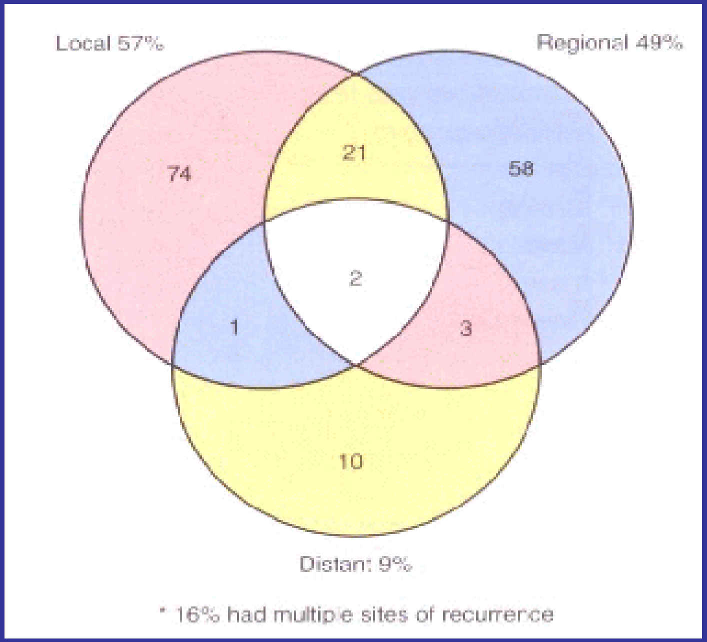
Management of Oral Cancer





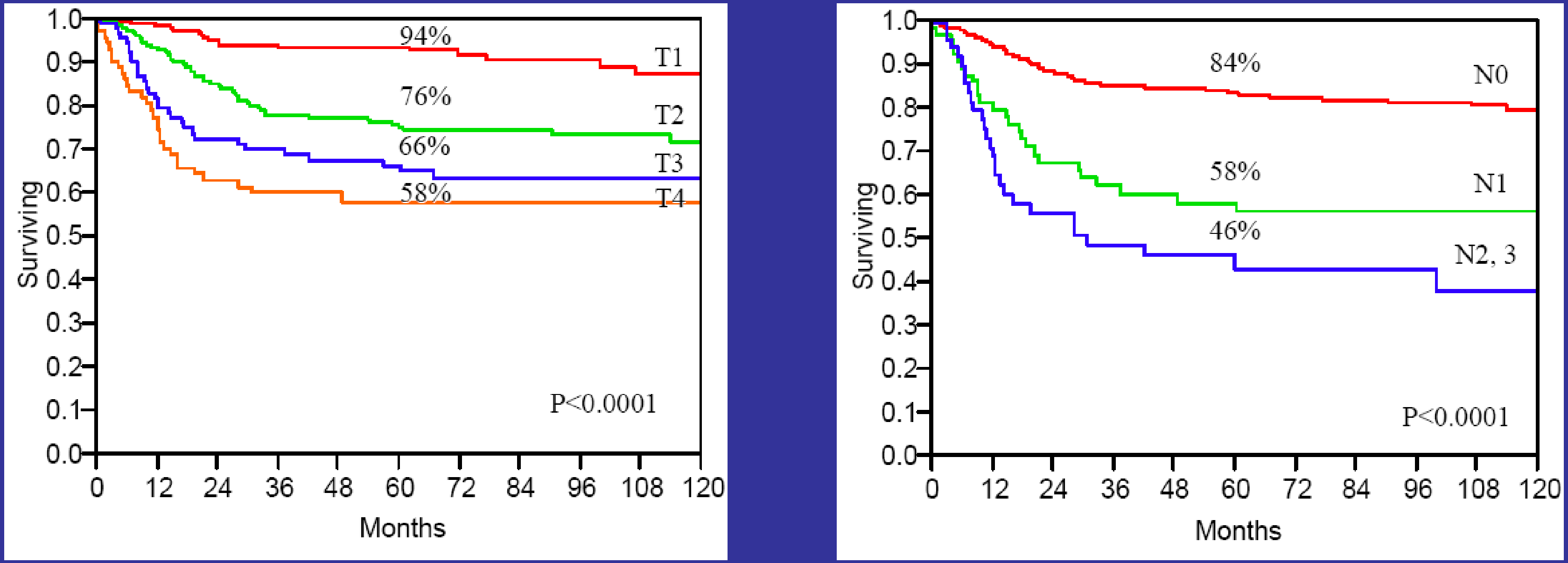
Hopper C, Foscan 01 Study Group. Int. J. Cancer 2004;111:138–146

Patterns of Failure



Patel SG, Shah JP. In: Oral Cancer 2003:387-394

Disease-specific Survival



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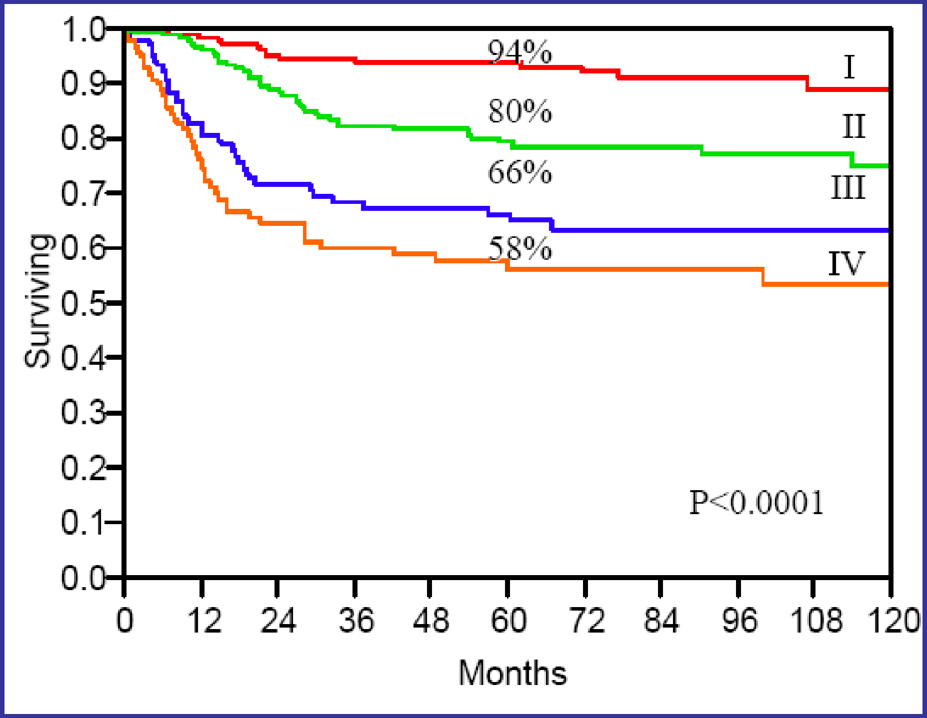
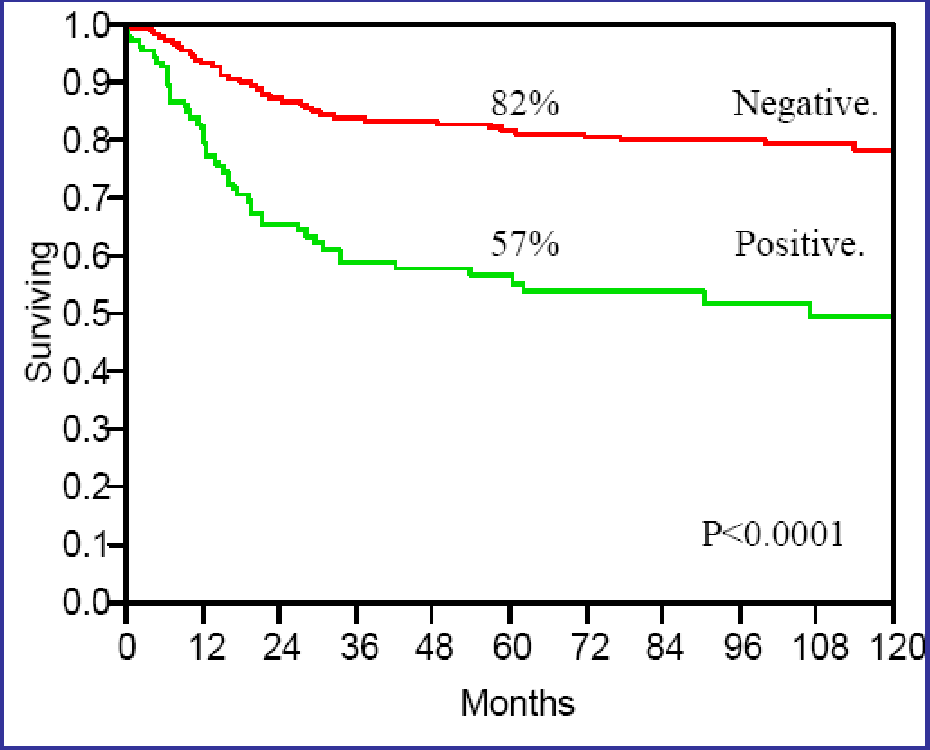
Disease-specific Survival



Patel SG, Shah JP. In: Oral Cancer 2003:387-394

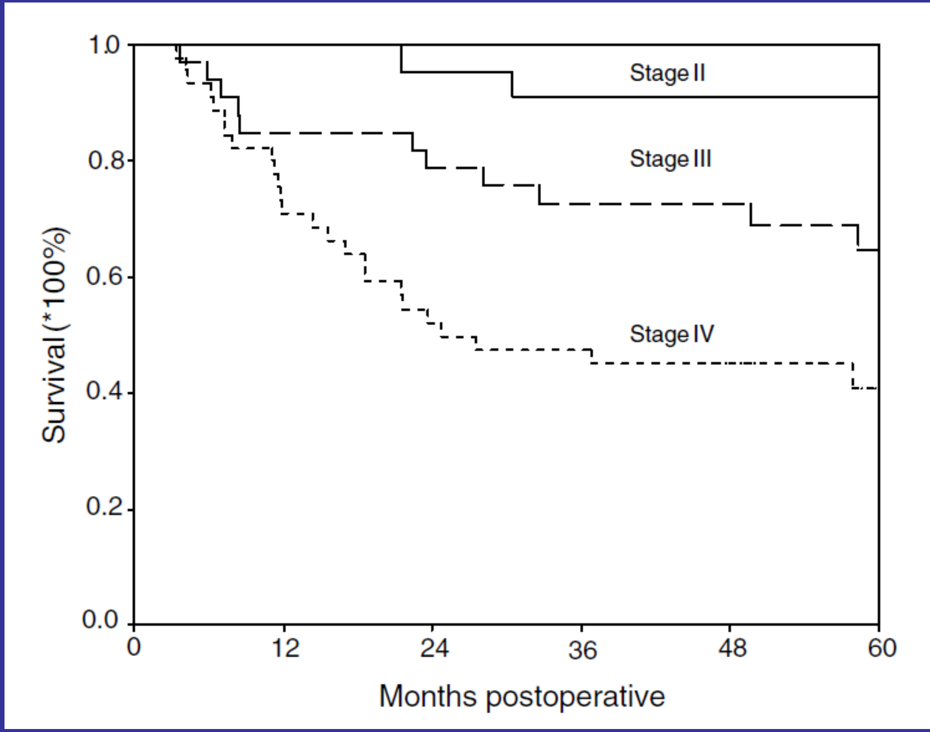
Disease-specific Survival



Margins

Patel SG, Shah JP. In: Oral Cancer 2003:387-394

Overall Survival



Borggreven et al. Oral Oncology 2005;41:358–364

Summary

- Early detection
- Adequate surgical removal using modern techniques
- Appropriate neck management
- Contemporary soft tissue and bone reconstruction
- Adjuvant (chemo)radiotherapy
- Osseointegrated implants

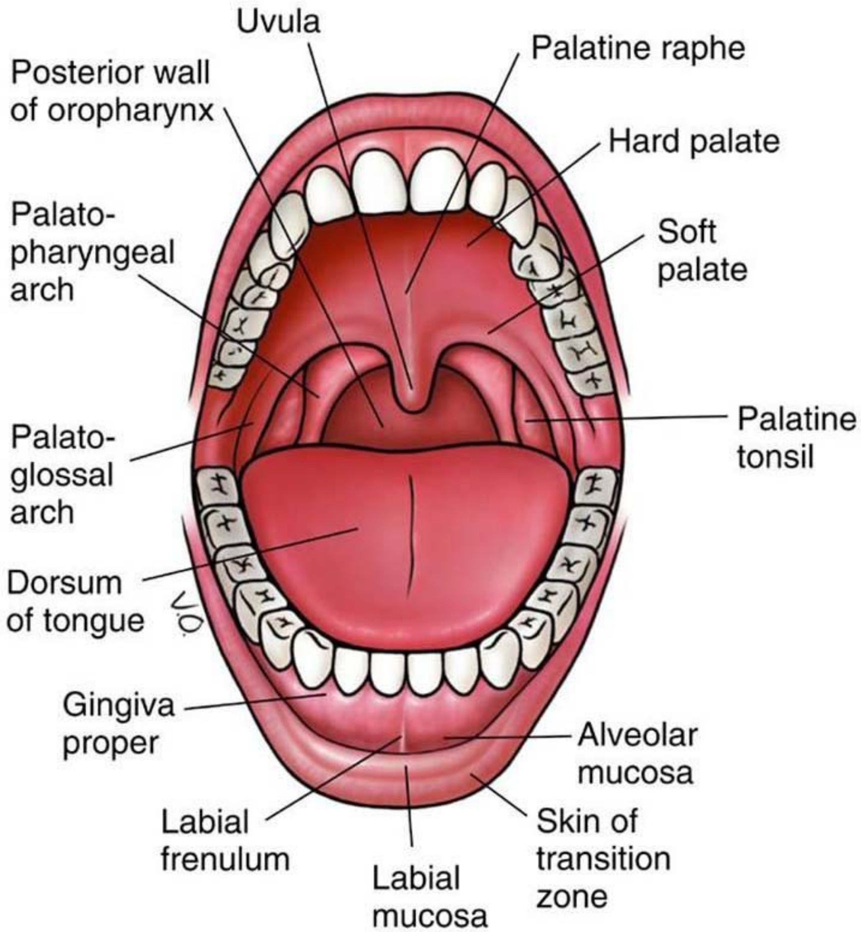
Management of oral cavity SCC: radiotherapy

Jesper Grau Eriksen

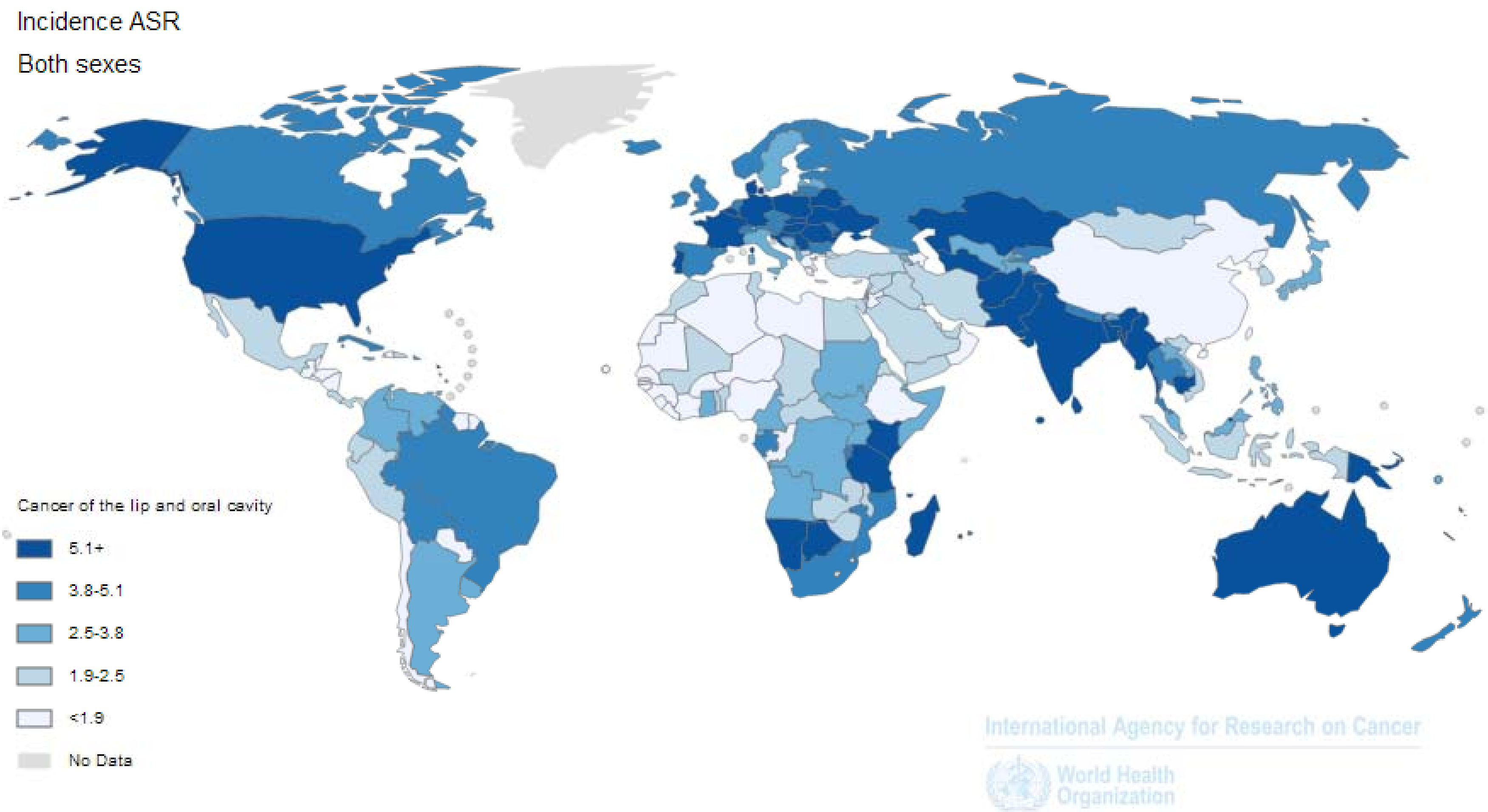
Oral cavity

AJCC/UICC of OSCC:

- From the mucosal lip
- Anterior 2/3 of oral tongue
- Buccal mucosa
- Floor of mouth
- Hard palate
- Alveolus/ gingiva
- Retromolar trigone



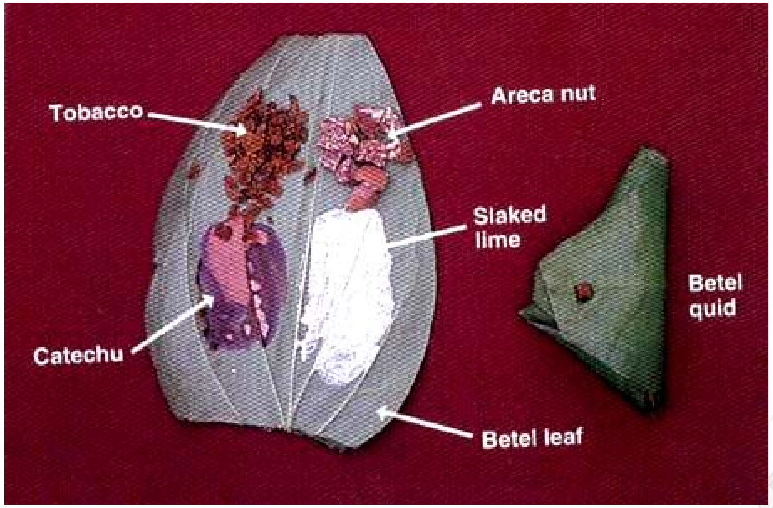
The world-standardized incidence of oral cancer



IARC, Globocan 2012

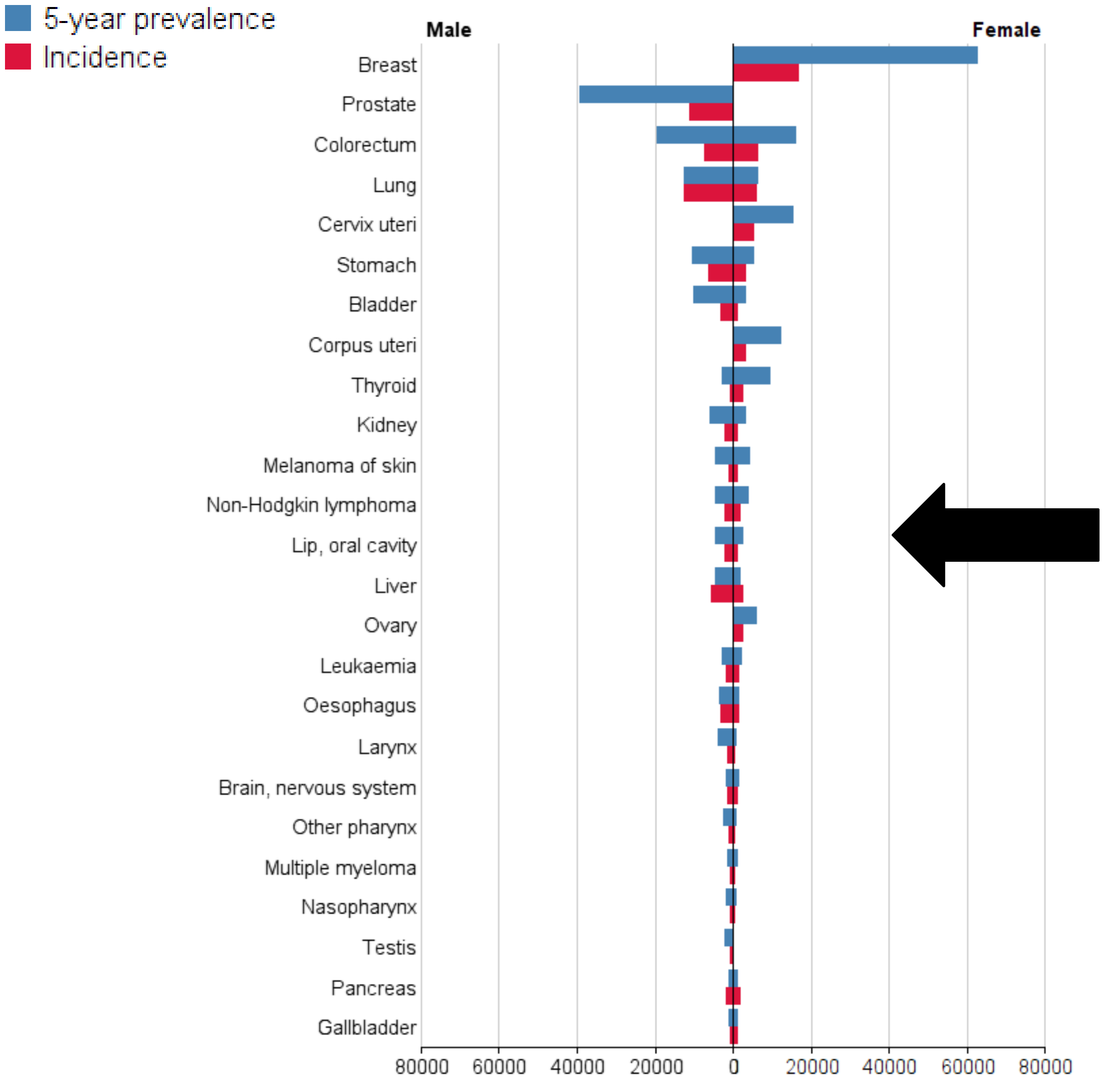
ESTRO School

Etiology



Leukoplakia

Male/female ratio

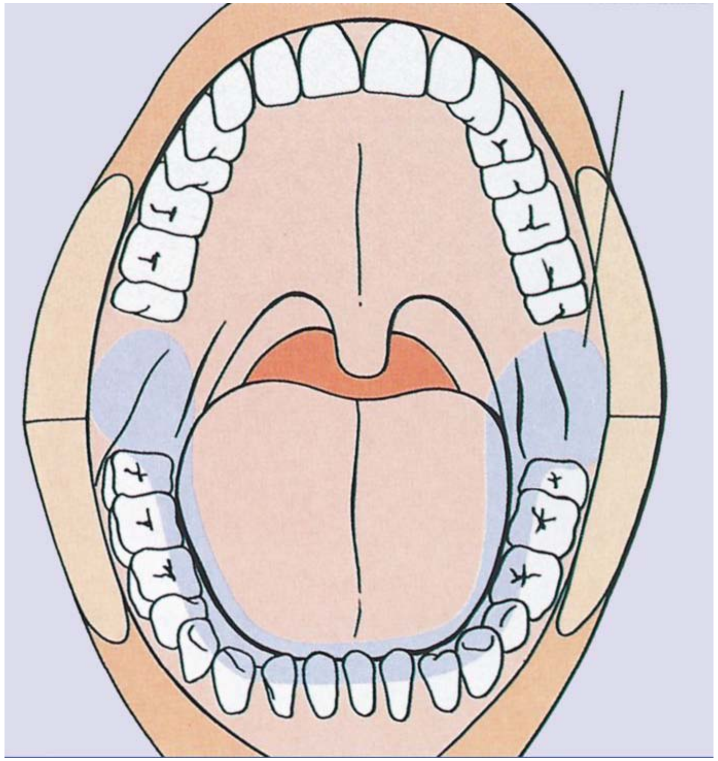


IARC, Globocan 2012

Location

N=3327

Site	N	%
Buccal mucosa	462	14%
Gingival mucosa	524	16%
Hard palate	107	3%
Tongue	1088	35%
Floor of mouth	1054	32%



Blue areas: where the saliva pools

What to do???

Primary surgery?

Primary radiotherapy?

PORT?

C-PORT?

B-PORT?

RT-only?

C-RT?

B-RT?

Brachytherapy?

Surgery is the primary modality

Caravaggio 1607

RT and C-RT in oral cavity cancer

	External Beam Radiotherapy (EBRT)	Chemotherapy	Interstitial Brachytherapy
Primary setting	• Early disease when patient intolerant of surgery • Early disease when anticipated cosmetic consequence of surgery is a concern, especially for lip cancer involving commissure • Unresectable disease, usually combined with chemotherapy • Advanced disease for patients intolerant of surgery due to poor performance status or comobidities	• Advanced disease or unresectable disease, in combination with radiotherapy	• Early and superficial well-defined tumor located more than 5 mm from the mandible
Adjuvant setting	• Unfavor[illegible] fe[illegible] [illegible]nd [illegible] nodal [illegible]ion	[illegible] with [illegible]otherapy for positive resection margins or extracapsular nodal extension	• Brachytherapy alone for positive resection margins • In combination with external beam radiotherapy to augment radiotherapy dose to the high risk area
[illegible]	[illegible]Adjuvant treatment after salvage surgery • Primary treatment modality, usually combined with chemotherapy if further surgery is not feasible	• Combined with radiotherapy	• Especially useful for re-irradiation: – for persistent or recurrent disease after previous radiation, – 2^{nd} primary cancer occurrence within previous radiation field

Many treatments…only a few are randomized
Low level of EBM…..local or national politics

Huang Med Oral Patol Oral Cir Bucal 2013

ESTRO School

Radiotherapy in the primary setting

Radiotherapy only

Chemo-radiotherapy

Brachytherapy

Radiotherapy in the primary setting

Radiotherapy only

Chemo-radiotherapy

Brachytherapy

Advantages of brachytherapy

- High localized dose
- Rapid fall-off at periphery
- Continuous low dose rate
- Short overall treatment duration

Limits:

- Size of tumour (3 cm)
- Diffuse growth
- Distant or node-positive disease
- Proximity to mandible
- Expertise.....

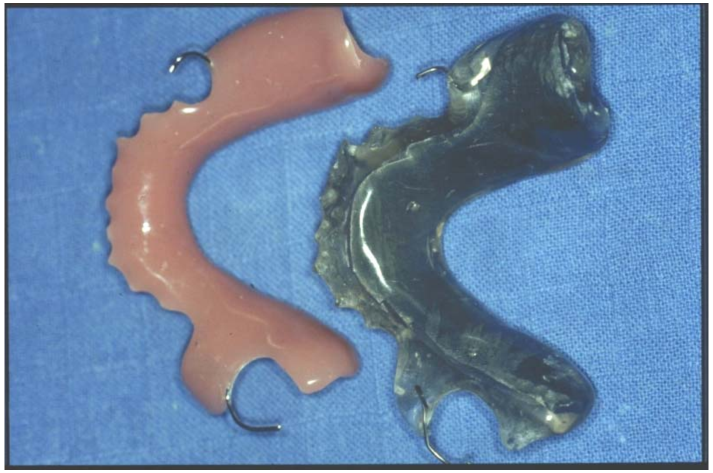
Sites for oral brachytherapy

- Anterior 2/3 tongue
- Lips
- Buccal mucosa
- Floor of mouth
- Soft palate

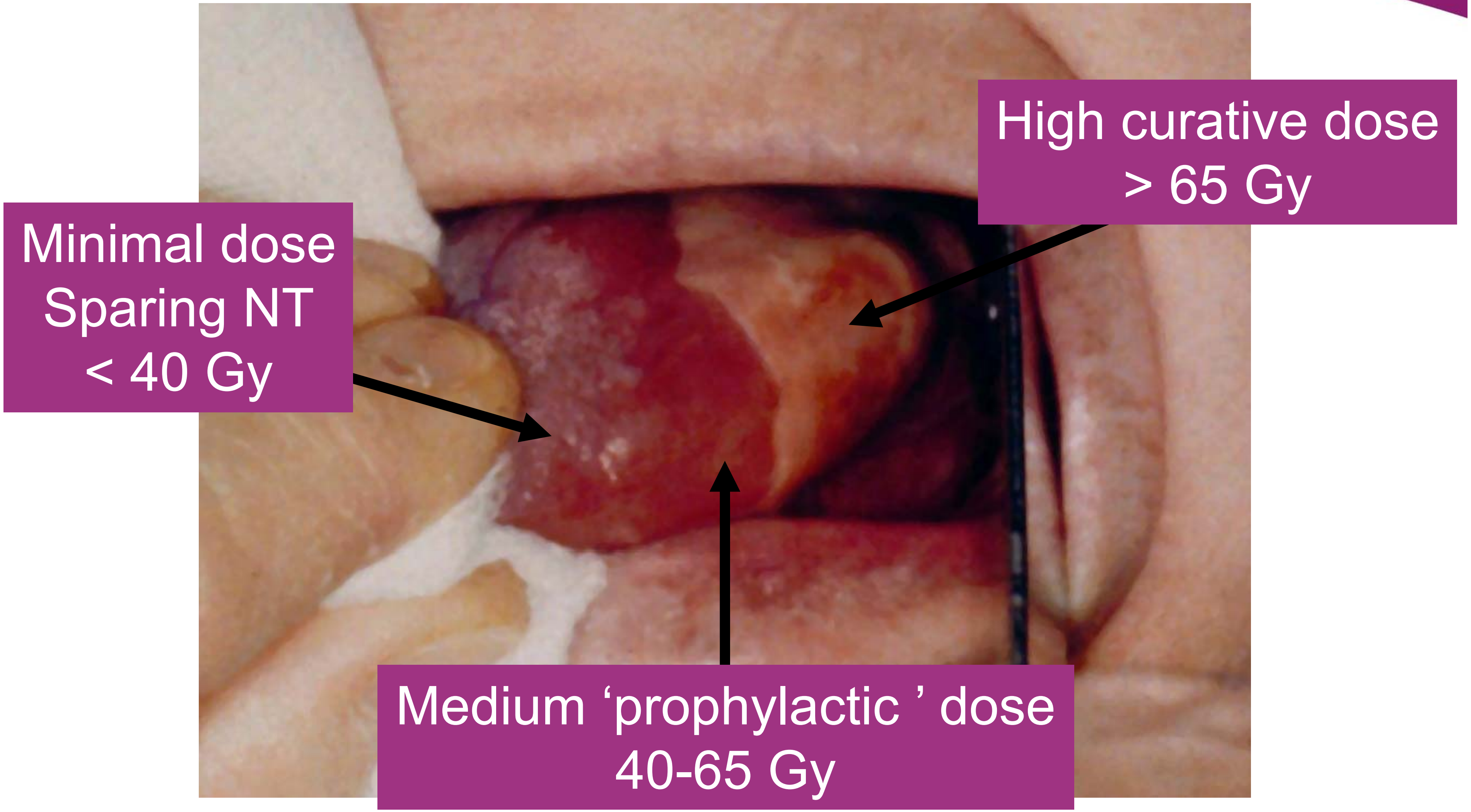
- Base of tongue as boost
- Tonsil

Patient selection

- Early disease, < 3 cm and node-negative
- No distant metastasis
- Site accessible, superficial and away from bone
- Pt accept
- Radical treatment intent
- Suitable for anesthesia



Mucositis (3-6 weeks)



Modified from Lartigeau 2012

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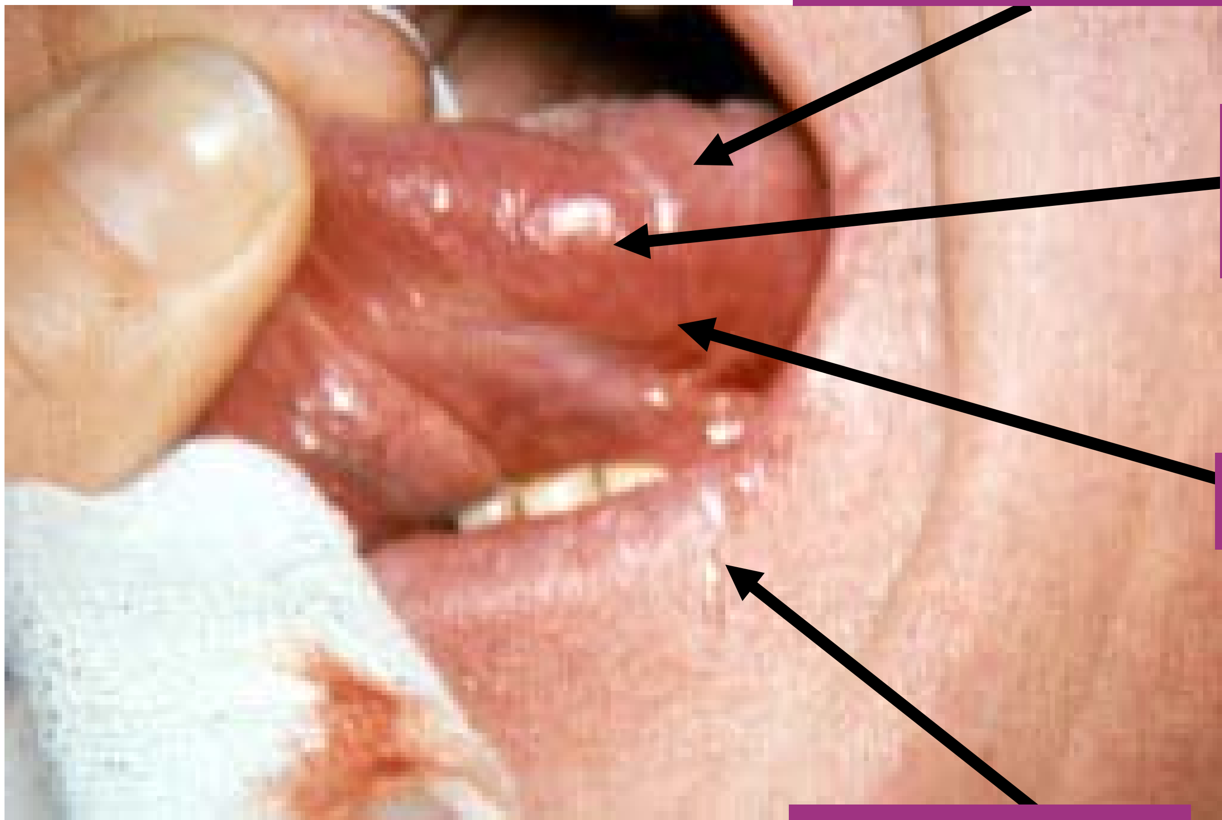
Healing after 2 months



Modified from Lartigeau 2012

Mobile tongue: Iridium Series >100pts (LDR)

	# pts	Technique	Local control	Late morbidity	5 y.survival
Decroix	602	BT +/-EBI+/-Surg	**76%**	13%	36%
Haie	269	**BT** EBI + BT	**87%** **49%**	 8%	62% 30%
Mazeron	121	**BT** 55-60 Gy **BT** 65-75 Gy	**73%** **92%**	T2 N0 7%	
Wendt	103	**BT** BT+ EBI <40 Gy BT+ EBI >40 Gy EBI	**65%** **92%** **69%** **28%**	0 4% 17% 0	89% 78% 71% 57%
Hareyama	130	BT EBI + BT	**86%**		
Shibuya	370	**BT** BT + EBI	**75%** **48%**	4%	
Lefebvre	283	**BT**	**83%**	6%	NP
Pernot	448	BT EBI + BT	 **68%**	9% (3 % grade 3)	 44%
Matsura	173	**BT** EBI + BT	**84 - 95%** **74 - 80%**		69 - 84%

2500 Patients 65-95%

Modified from Lartigeau 2012

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Comparative institutional studies

T2 N0 series: 5-Y local control

	# patients	Brachy alone	EBRT+Brachy
Pernot (Nancy)	147	90%	51%
Benk (Paris)	110	88%	36%
Haie (Villejuif)	77	93%	80%

Pernot et al : Radiother Oncol; 1992;23: 223- 228
Benck et al : Radiother Oncol; 1990;18: 339- 347
Haie et al : Actual Carcinol Cervicofac;1983;9: 52- 57

Modified from Lartigeau 2013

T1/T2 lip cancer

 

Iridium^{192}; 60-70 Gy; 0.4 to 0.7 Gy/h

Local Control : 90-95 % at 5 years

Cosmetic results: "good to excellent": 80-95 %

(telangiectasias, fibrosis)

Modified from Lartigeau 2013

Radiotherapy only

Chemo-radiotherapy

Brachytherapy

Primary RT of oral cavity carcinomas

Primary RT is overall not first choice but may be relevant for:

- Early stage disease to avoid functional/cosmetic defects (soft palate)
- Unresectable disease
- High risk pts. due to comorbidity or poor PS
- Recurrent disease where previous multiple surgeries have been undertaken and further surgery would be irrelevant
- Patient's preference

Equal efficient modalities in early stage oral cancers

Retrospective analysis of 244 patients
with T1-2 tumours of the mobile tongue

Five-year survival rates.

	Implant	Electron	Cryosurgery	Surgery	Total
Stage I	0.67 ± 0.07[a]	0.79 ± 0.08	0.92 ± 0.08	–[b]	0.73 ± 0.05
Stage II	0.74 ± 0.04	0.57 ± 0.13	–[b]	0.77 ± 0.12	0.71 ± 0.04
Total	0.72 ± 0.04	0.71 ± 0.07	0.70 ± 0.10	0.71 ± 0.10	0.72 ± 0.03

[a] Standard error.
[b] Survival rates for subsets of patients less than ten are not shown.

....but a difference in toxicity!

Akine Radiat Oncol 1991

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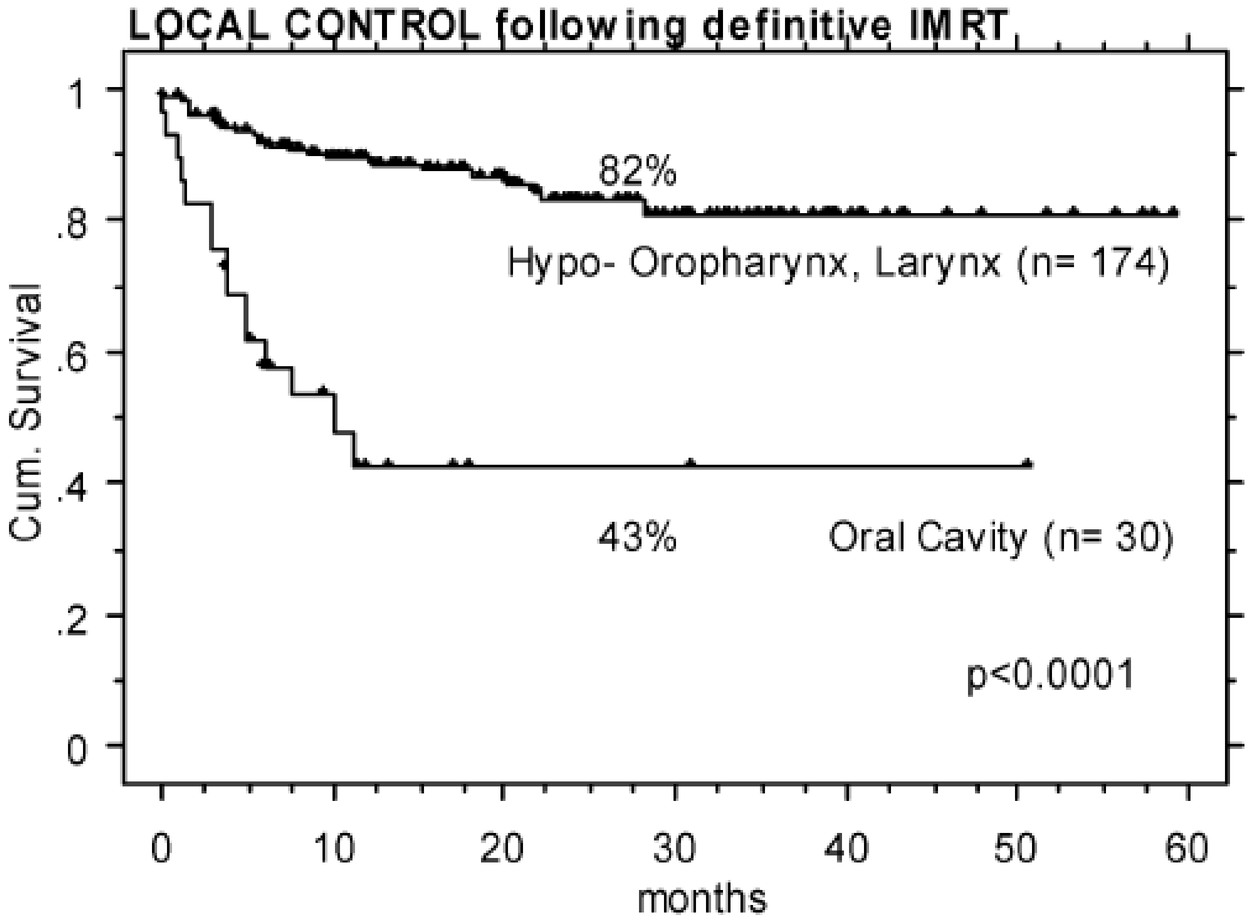
Primary RT of advanced oral cavity carcinomas

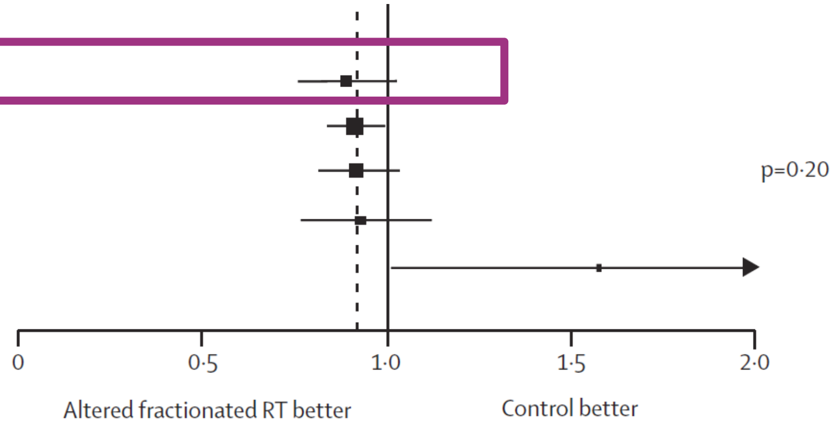


- Institutional series
- 2002-7: 346 pts.
- 69% T3/T4
- 60-70 Gy

Studer Radiat Oncol 2007

Conventional vs. altered fractionation

Site				
Oral cavity	346/458	345/428	−20·5	167·5
Oropharynx	1086/1585	1060/1494	−49·1	528·5
Larynx	589/1234	557/1143	−23·9	278·0
Hypopharynx	232/294	223/281	−8·3	109·5
Others	52/69	45/72	8·9	19·6



Bourhis Lancet 2006

Radiotherapy only

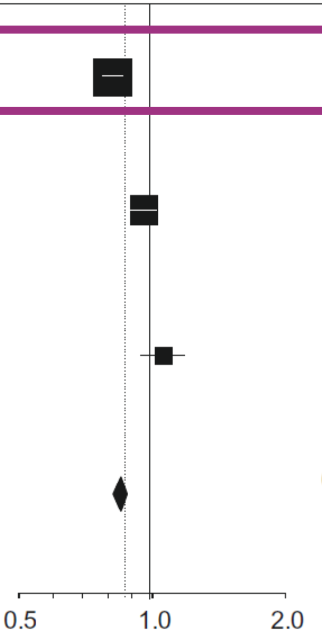
Chemo-radiotherapy

Brachytherapy

C-RT to locally advanced HNSCC

(a) Hazard ratio of death.

Timing	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Concomitant	3171/4824	3389/4791	-326.4	1587.7		0.81 [0.78;0.86]
Induction	1877/2740	1813/2571	-40.0	900.7		0.96 [0.90;1.02]
Adjuvant	631/1244	661/1323	17.9	317.4		1.06 [0.95;1.18]
Total	**5679/8808**	**5863/8685**	**-348.5**	**2805.8**		**0.88 [0.85;0.92]**



Test for heterogeneity: $\chi^2_{107} = 179.8$ $p < 0.0001$ $I^2 = 41\%$

Test for interaction: $\chi^2_{2} = 26.60$ $p < 0.0001$

LRT+CT effect: p < 0.0001

Pignon Radiother Oncol 2009

Primary C-RT of oral cavity carcinomas

Available comparisons: n=105 (17 493 patients)

→ Exclusion of a comparison with no description of tumour location (36 patients)

Available comparisons: n=104 (17 457 patients)

→ Exclusion of the 999 patients with the following tumour locations:
- nasopharynx (728 patients)
- pharynx, precise location not available (54 patients)
- cervical node (4 patients)
- other/unknown (213 patients)

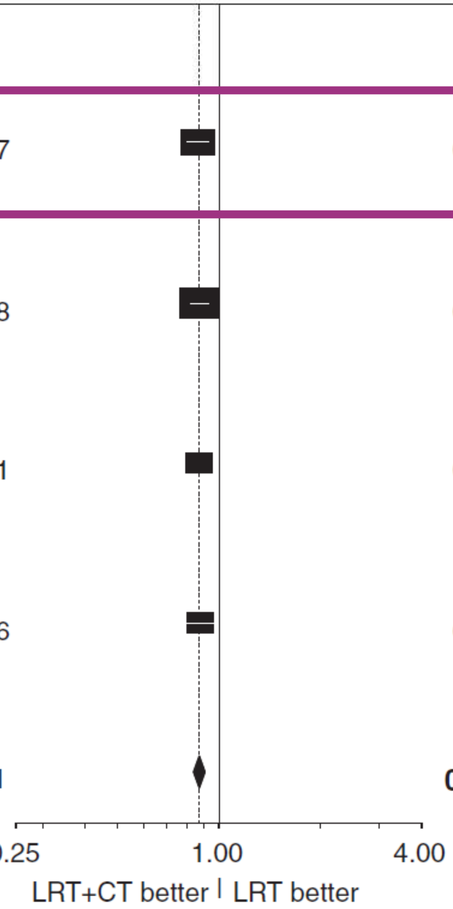
Available comparisons: n=104 (16 458 patients)

Number of comparisons (patients – percent) excluded due to a small number of patients (<10 patients per comparison)	**Comparisons (patients) in the final analysis**
Oral cavity: 10 comparisons out of 91 (48 patients - 1,1%)	81 (4 331 patients)
Oropharynx: 8 comparisons out of 90 (41 patients - 0,7%)	82 (5 878 patients)
Larynx: 15 comparisons out of 76 (66 patients - 2%)	61 (3 216 patients)
Hypopharynx: 18 comparisons out of 84 (111 patients - 3,9%)	66 (2 767 patients)

Blanchard Radiother Oncol 2011

Primary C-RT of oral cavity carcinomas

Category	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Oral cavity	1400/2182	1449/2149	-96.2	664.7		0.87 [0.80;0.93]
Oropharynx	1981/2954	2097/2924	-127.4	980.8		0.88 [0.82;0.93]
Larynx	925/1623	949/1593	-60.2	447.1		0.87 [0.80;0.96]
Hypopharynx	958/1380	1001/1387	-58.9	460.6		0.88 [0.80;0.96]
Total	**5264/8139**	**5496/8053**	**-342.7**	**2553.1**		**0.87 [0.84;0.91]**



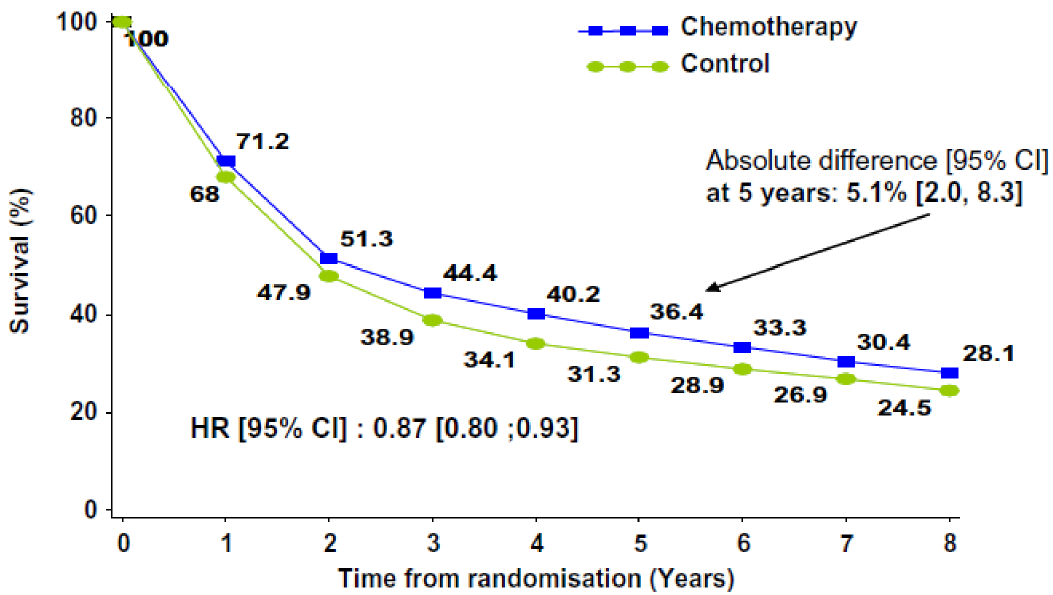
LRT+CT effect: p < 0.0001

Test for interaction: p = 0.99   I² = 19 %

Blanchard Radiother Oncol 2011

Primary C-RT of oral cavity carcinomas

		Timing of chemotherapy			Test of interaction*
		Adjuvant	Neoadjuvant	Concomitant	
Oral cavity	HR [95% CI] 5-year abs benefit [CI]	0.94 [0.76; 1.17] +0.4% [−7.6; 8.4]	0.93 [0.82; 1.05] +2.2% [−2.9; 7.3]	0.80 [0.72; 0.89] +8.9% [4.4; 13.4]	$p = 0.15$



Number of deaths/person-years:

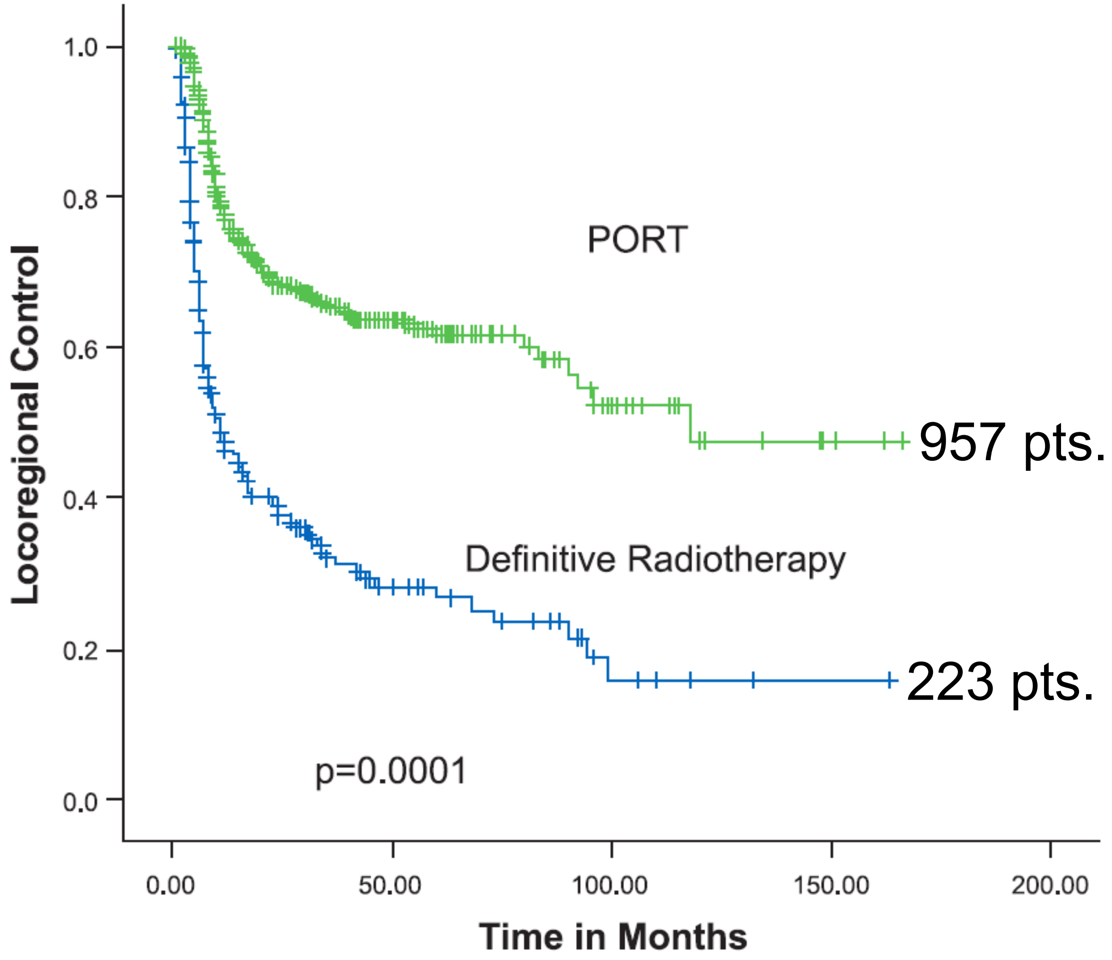
	Years 0-2	Years 2-5	Years >=6
LRT+CT	1008/3031	253/2165	139/1620
LRT	1070/2846	280/1771	99/1204

Blanchard Radiother Oncol 2011

Radiotherapy only?

Chemo-radiotherapy?

Primary RT of oral cavity carcinomas

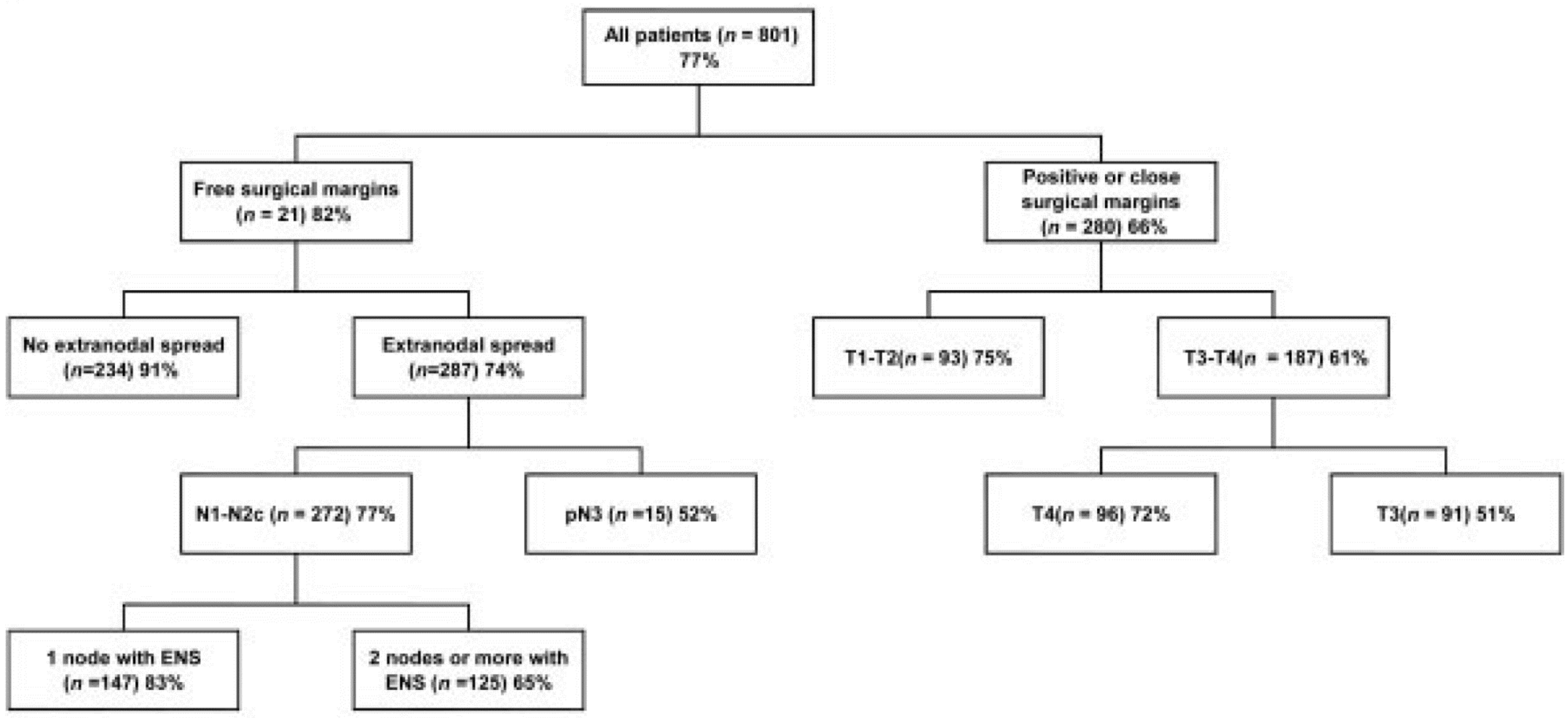


- Institutional series
- 1990-2004: 1180 pts.
- 66-70Gy/33-35fx

Murthy J Cancer Res Ther 2010

Postoperative RT of oral cavity cancer

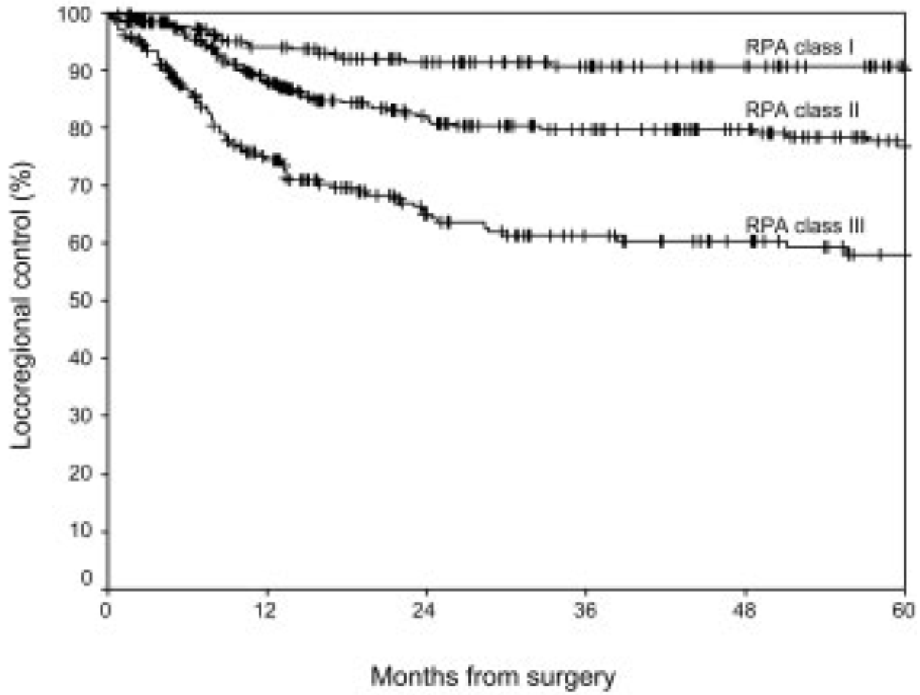
Surgery: 20% local excision, 644 extensive resections; 91% neck dissection
2D RT: 63.5Gy (bed+1 cm), range 38-70.5Gy; elective 46-50Gy



Langendijk Cancer 2005

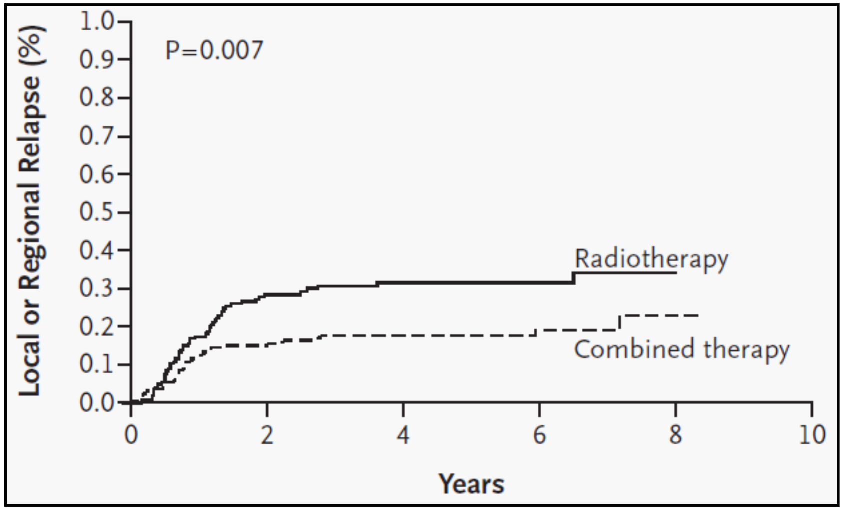
Postoperative RT of oral cavity cancer

RPA class	Definition(s)
Class I (intermediate risk)	Free surgical margins and no extranodal spread
Class II (high risk)	T1, T2, and T4 tumors with close or positive surgical margins
	One lymph node metastasis with extranodal spread
Class III (very high risk)	T3 tumors with close or positive surgical margins
	Multiple lymph node metastases with extranodal spread
	N3 neck

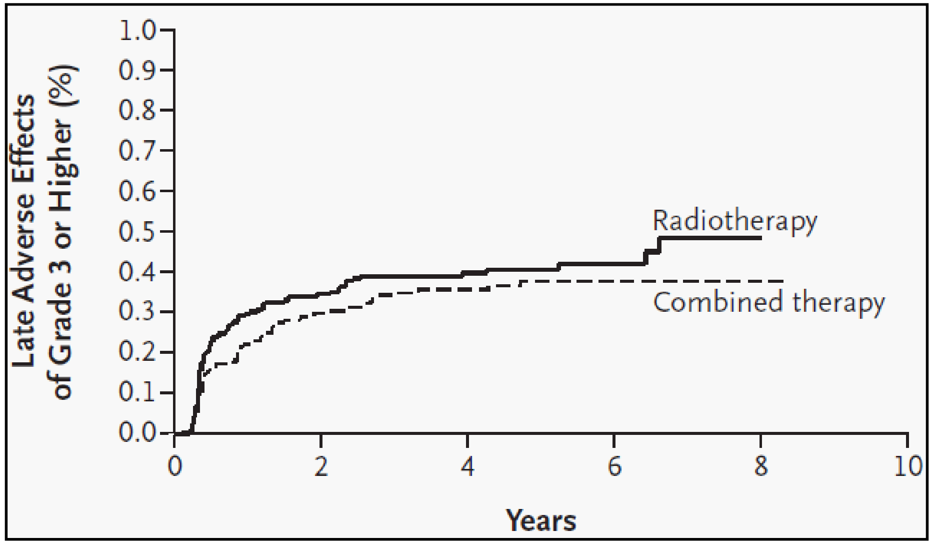


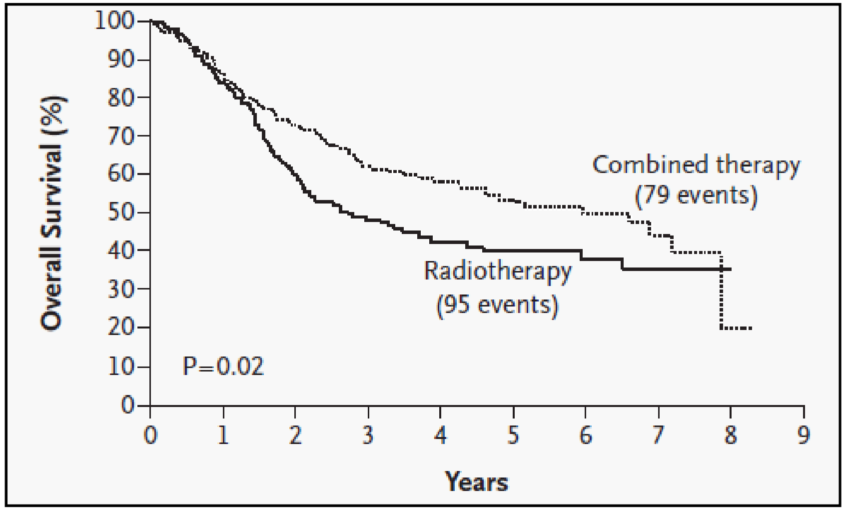
Langendijk Cancer 2005

Adjuvant C-RT after surgery



EORTC 22931





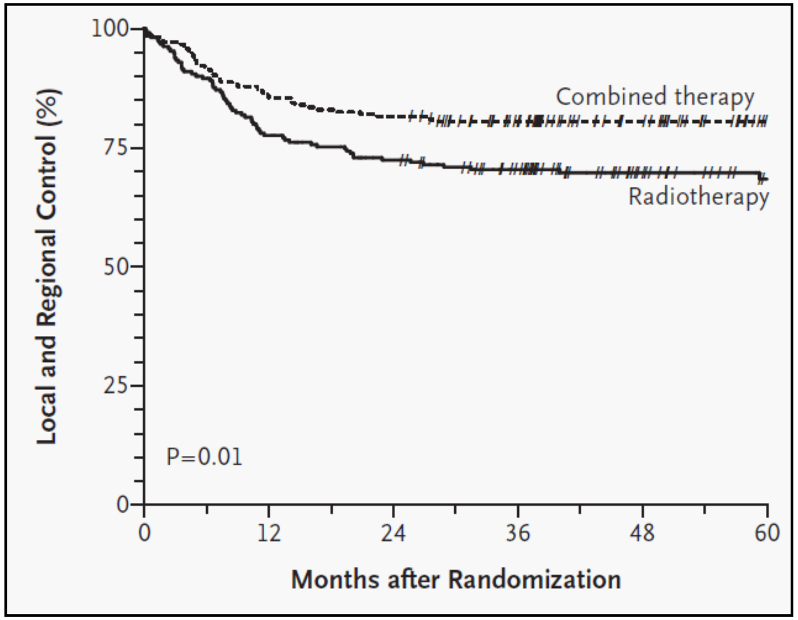
334 ptt, st. III-IV, 66Gy conventional fx + cisplatin 100mg/m² , 3-weekly

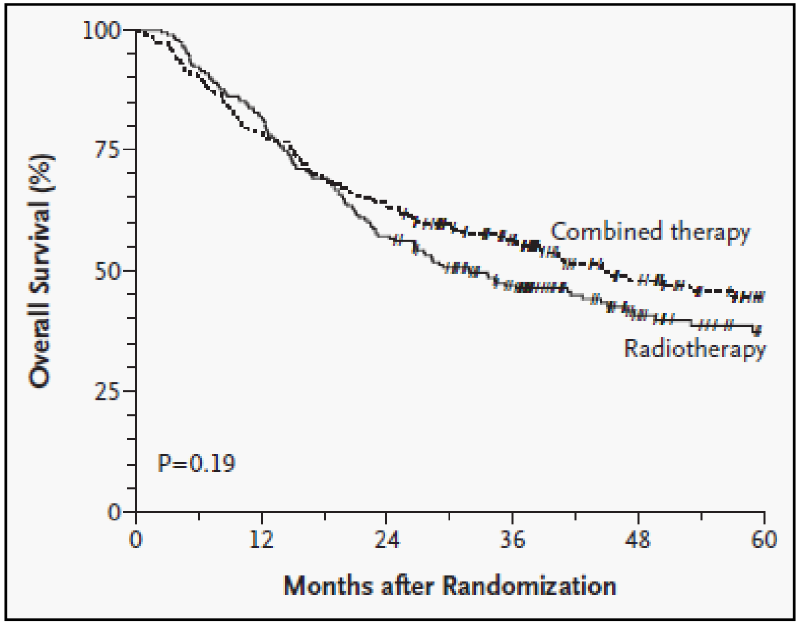
Bernier et al. 2004

Adjuvant C-RT after surgery

RTOG 9501 ECOG R9501 SWOG 9515

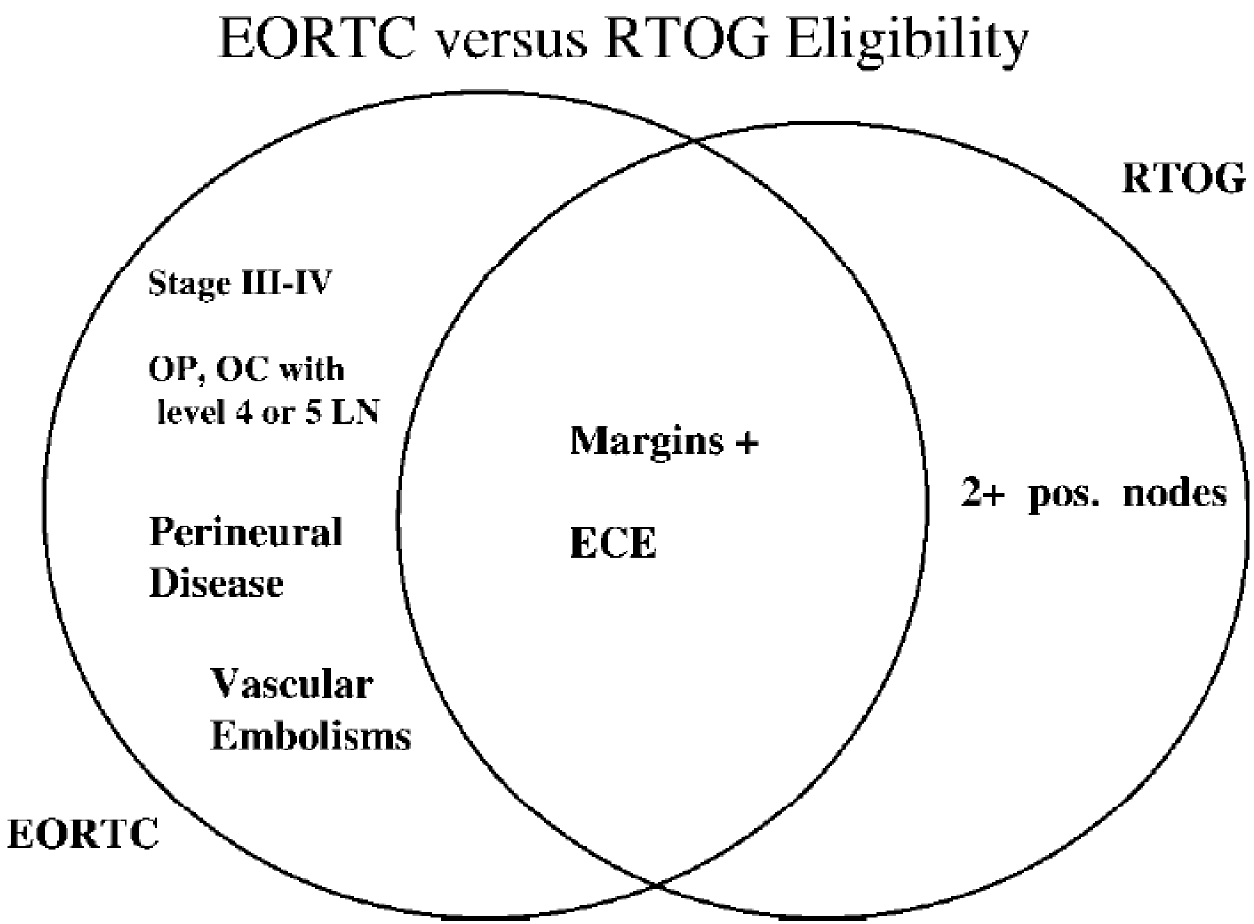
N=459, st. III-IV, 66Gy conventional fx + cisplatin 100mg/m², 3-weekly





Cooper et al.2004

Postoperative C-RT - results of two phase III trials

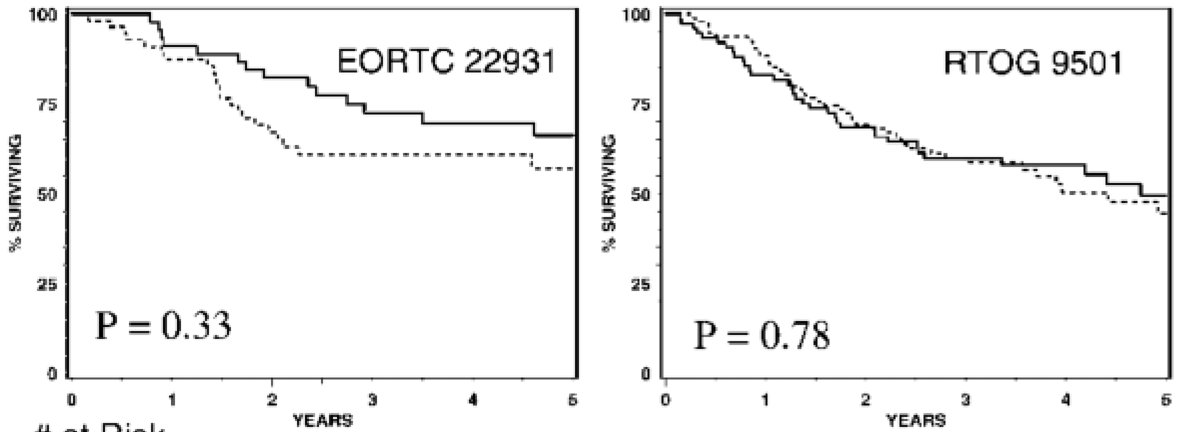


Bernier Head&Neck 2005

Postoperative C-RT - results of two phase III trials

Overall survival

Patients <u>without</u> positive margins and/or ECE



\# at Risk

Year	0	2	5	0	2	5
RCT ——	45	36	16	76	52	11
RT - - -	56	34	15	94	65	14

Bernier Head&Neck 2005

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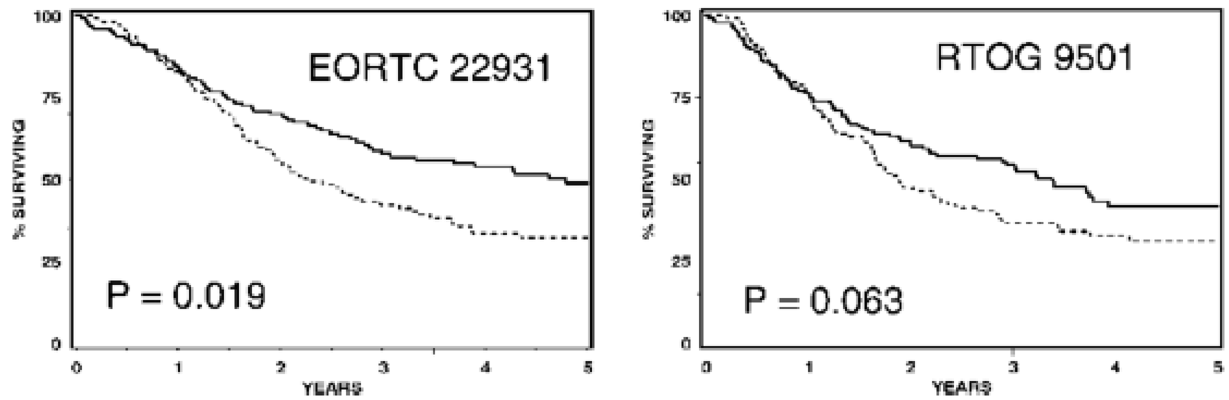
Postoperative C-RT - results of two phase III trials

Overall survival

Patients <u>with</u> positive margins and/or ECE

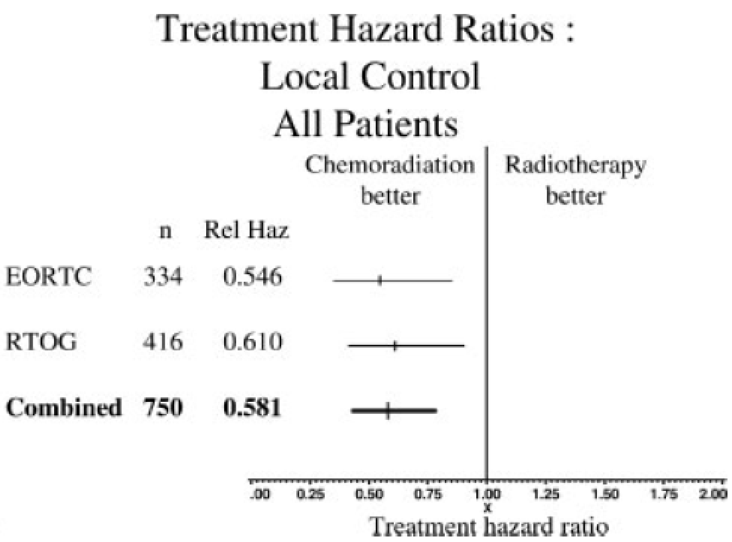


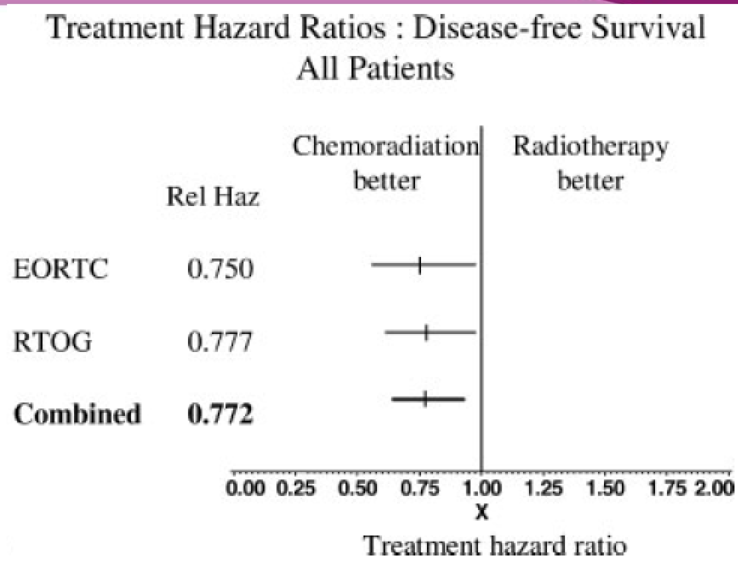
at Risk

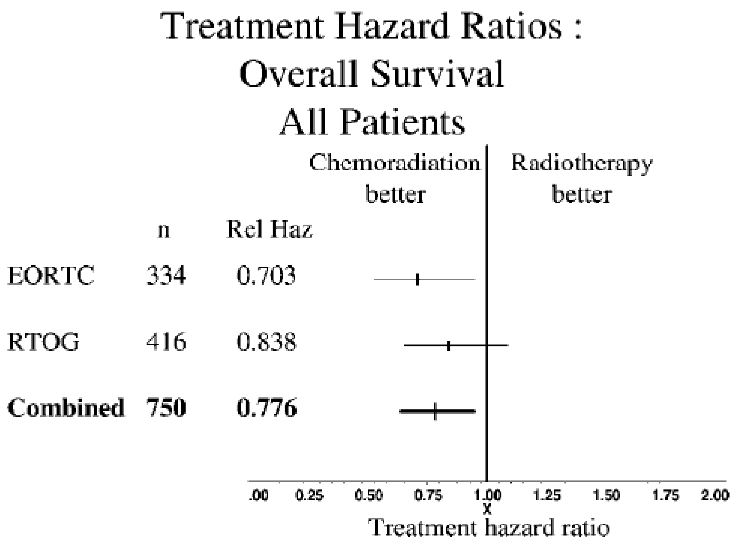
Year	0	2	5	0	2	5
RCT ——	122	82	31	130	80	16
RT - - -	111	59	16	116	55	11

Bernier Head&Neck 2005

Postoperative C-RT - results of two phase III trials

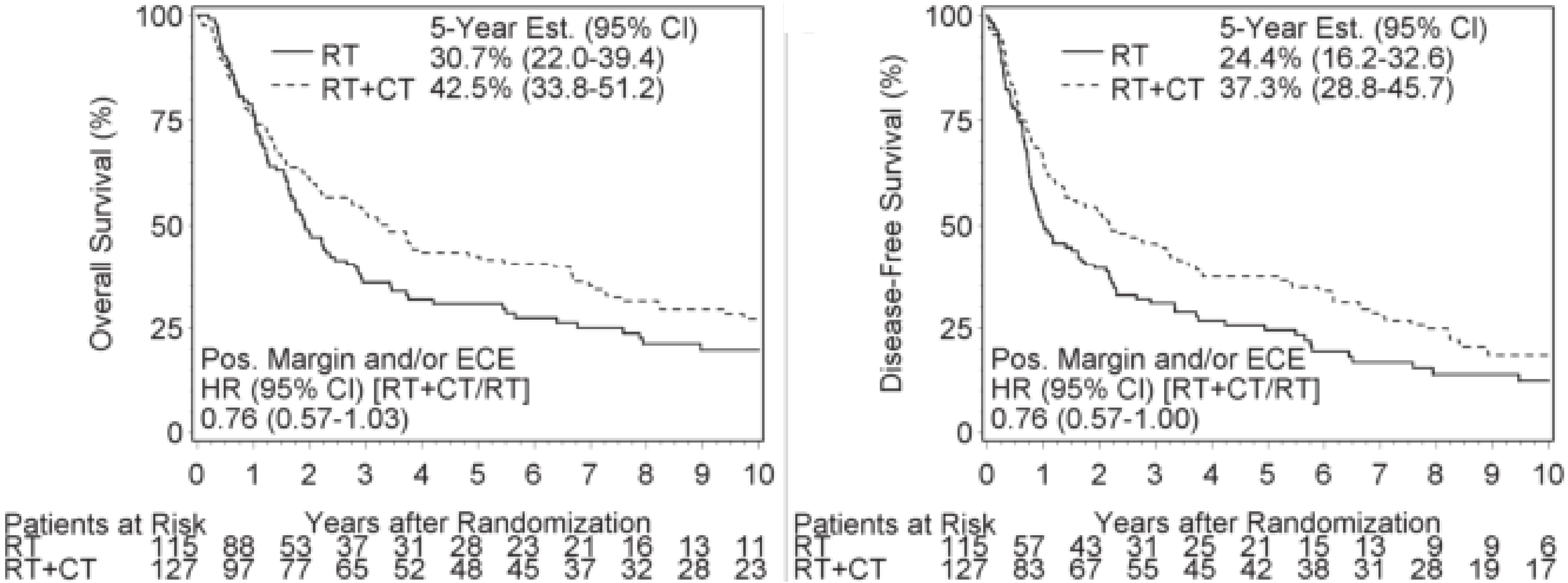






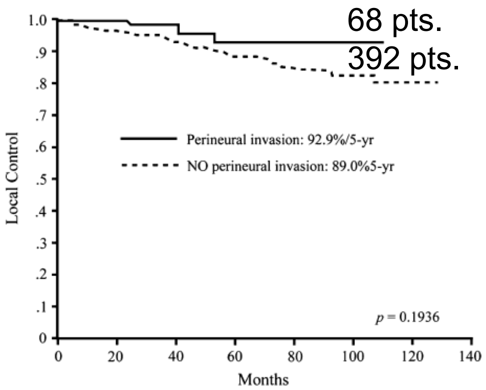
Bernier Head&Neck 2005

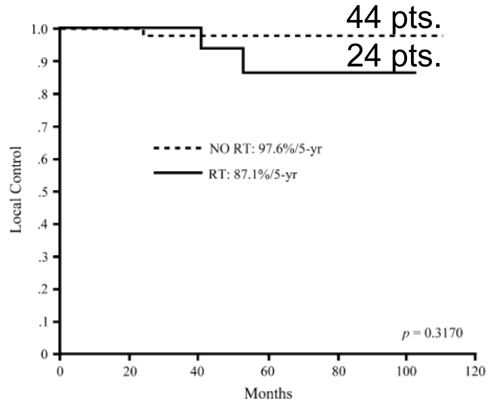
Long time follow-up on the combined trials



Cooper et al. 2012

Perineural or lympho-vascular invasion

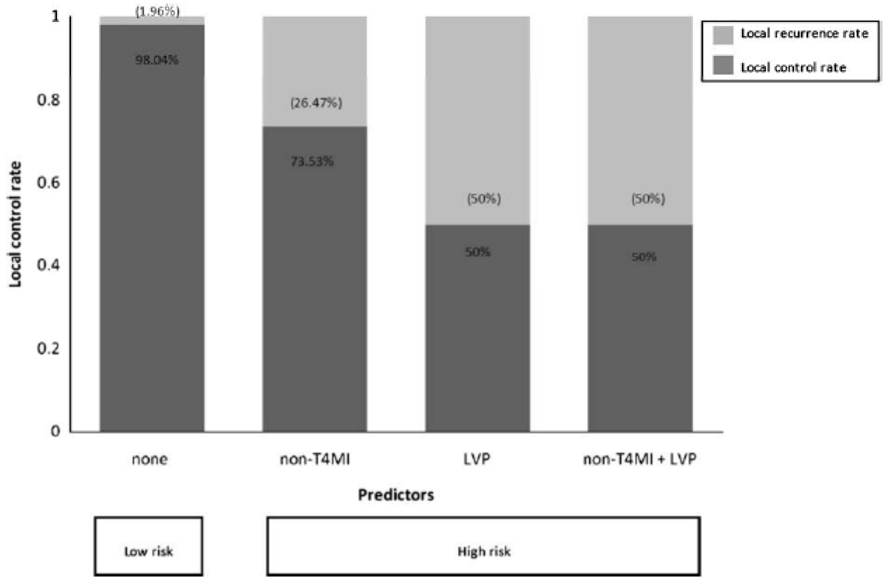




460 pts. T1-3N0 +/- perineural invasion

148 pts. with neg. surg. margins +/- lymphovascular invasion

(T4MI = muscular invasion)

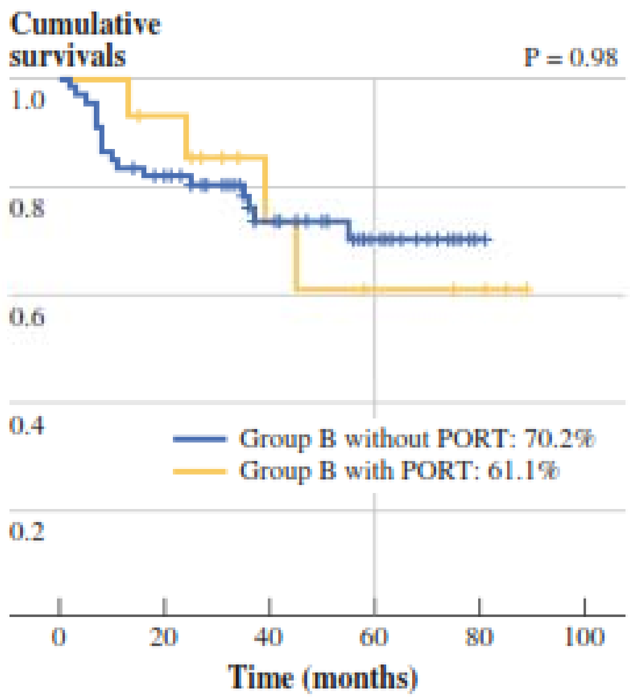


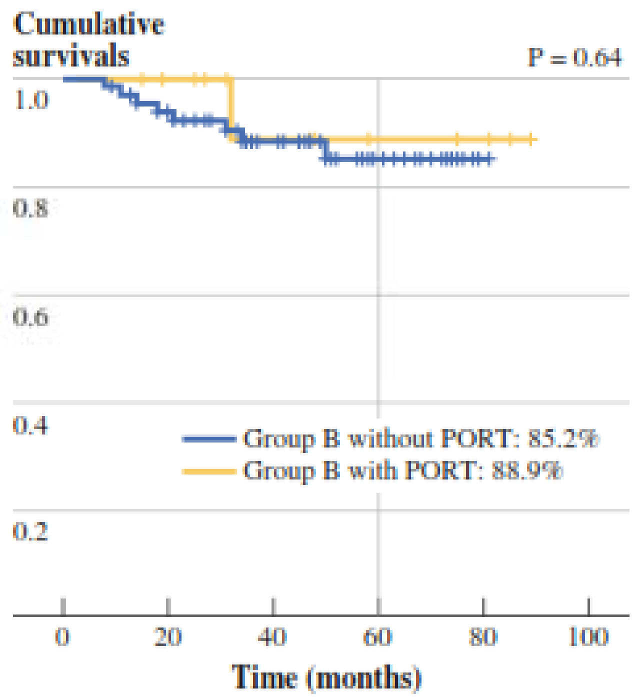
Liao IJROBP 2008 and Huang Oral Oncol 2010

Perineural or lympho-vascular invasion

442 pts; 360 without PNI/LVI and 82 pts. with PNI and/or LVI
TI-II oral cancer

DFS



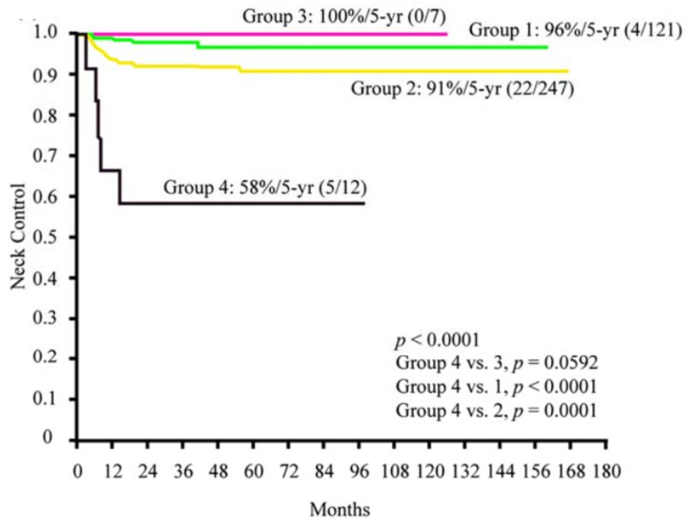


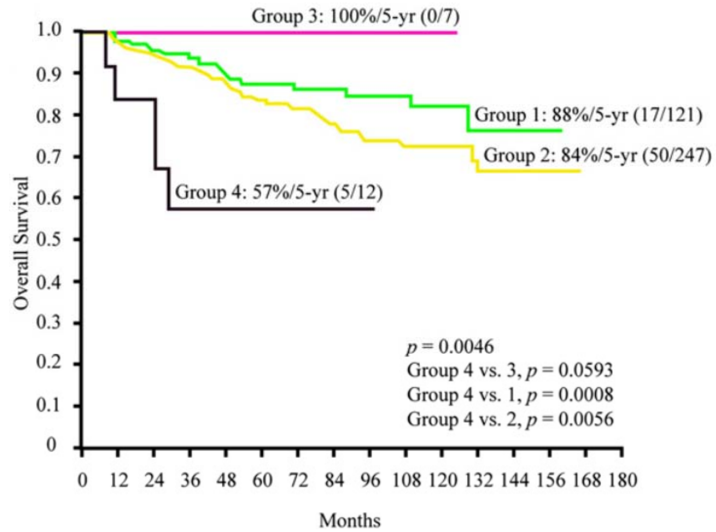
OS

Chen Ann surg Oncol 2013

Depth of invasion

- 457 consecutive pts with OCC
- One institution 1996-2008
- pT1-2N0M0
- stratified pts accoring to
  - histopathology
  - depth ≥ 4mm
  - lympho-vascular invasion





Fan IJROBP 2010; Liao IJROBP 2012

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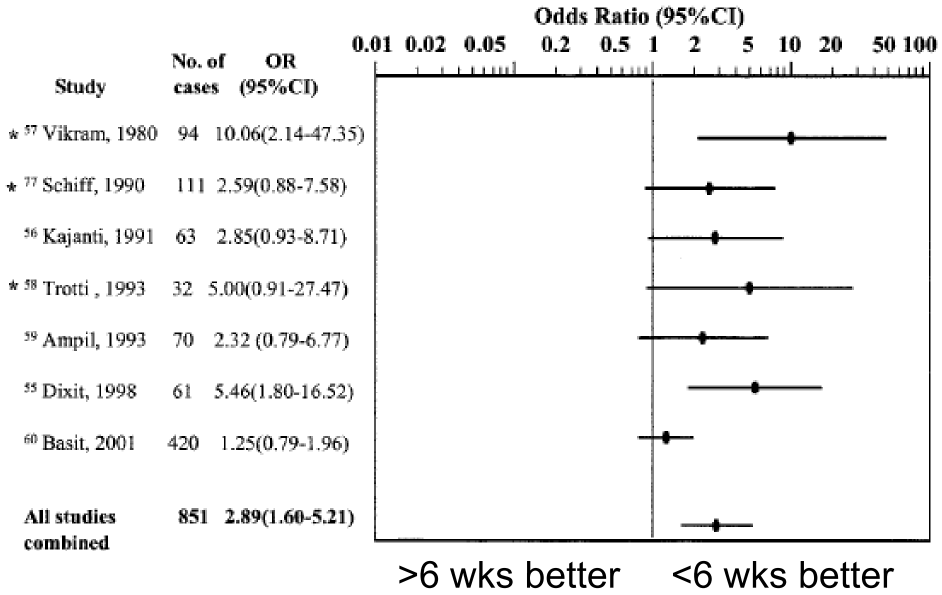
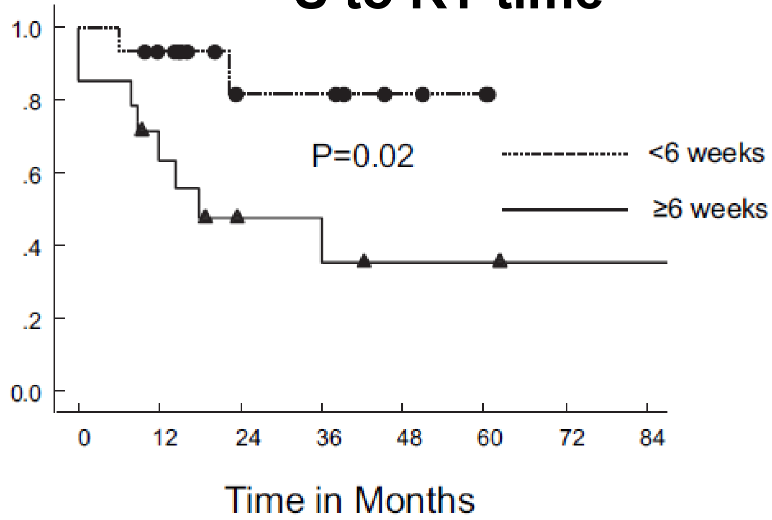
Time from surgery to PORT

“6 weeks limit”



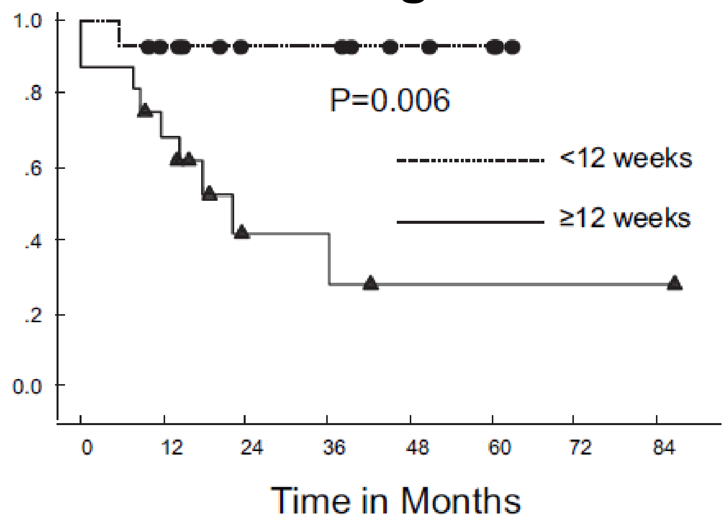
Overall OR: 2.9

S to RT time



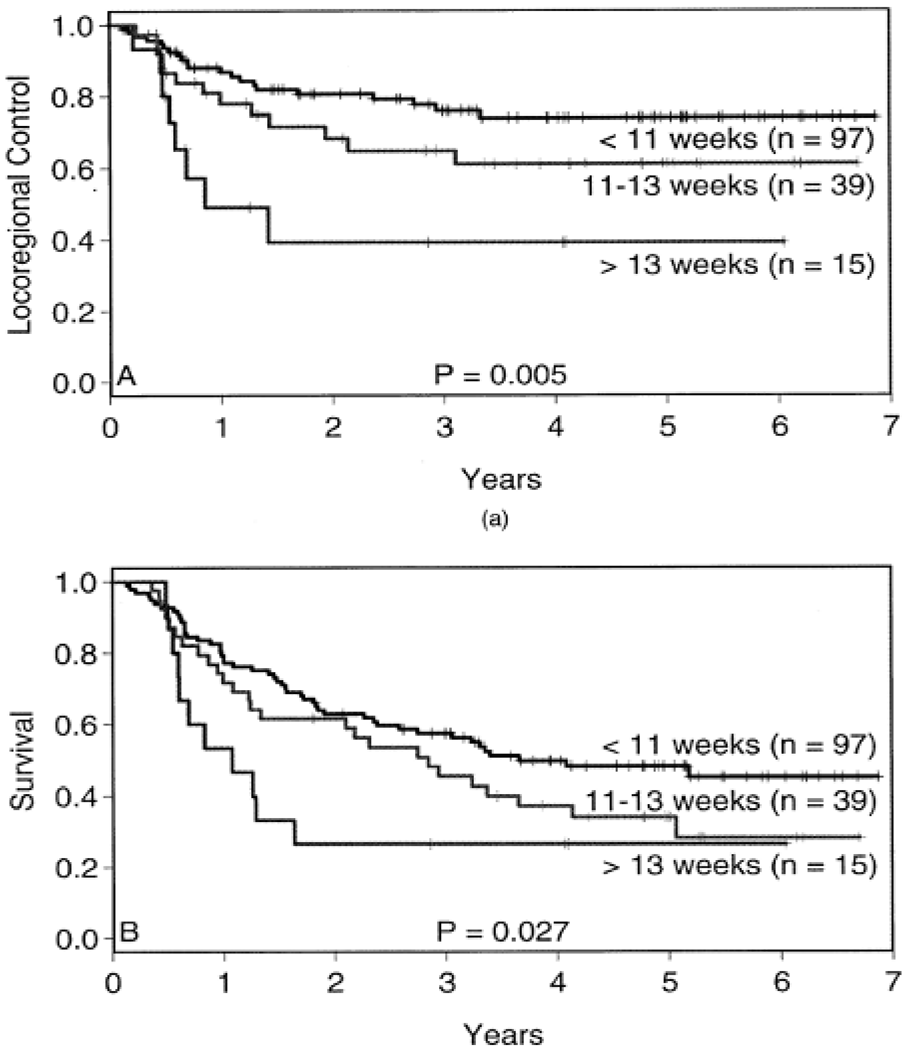
N=30

Package time



Huang JCO 2003 and Daly IJROBP 2011

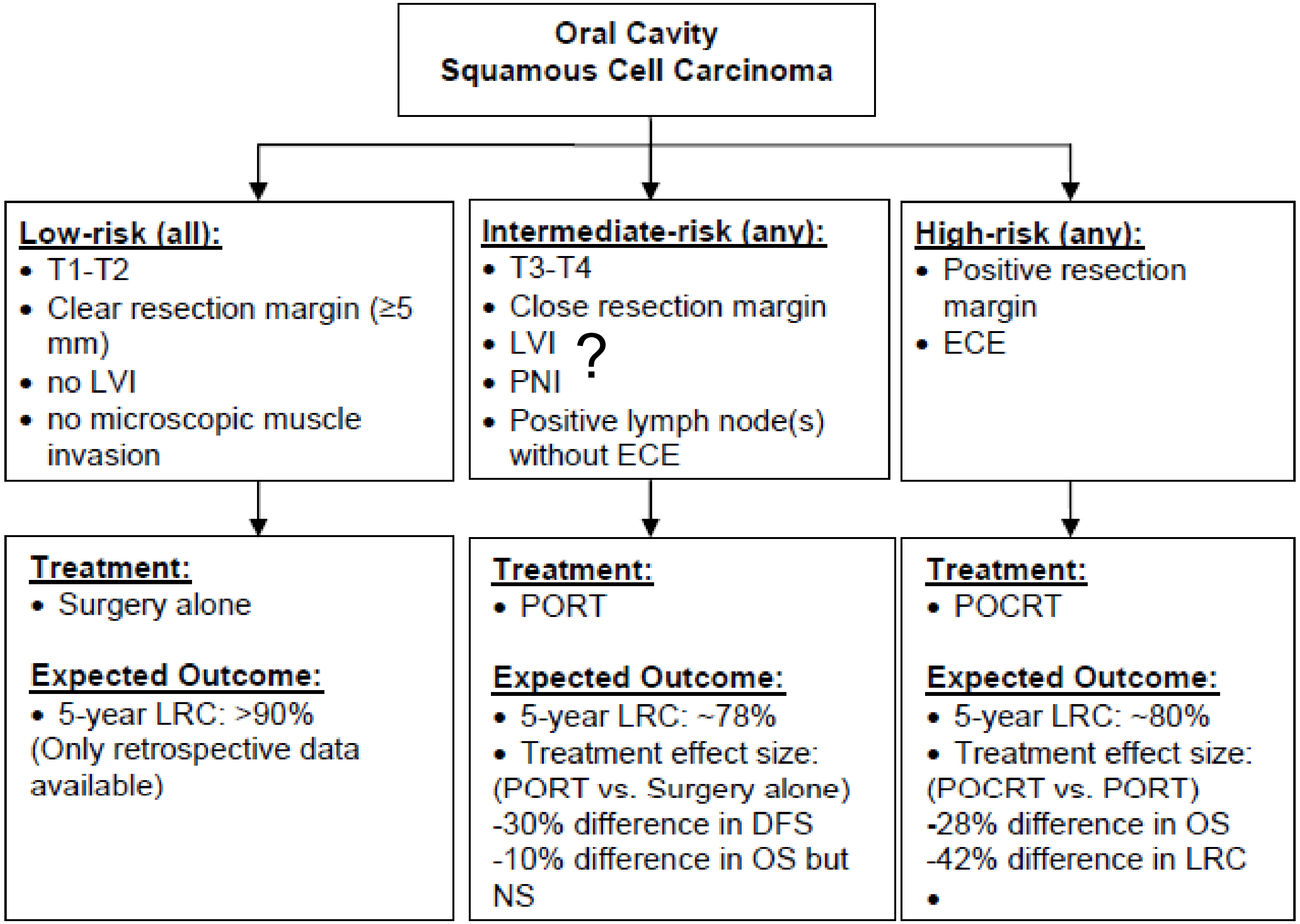
Total time from surgery to end of PORT



Post-hoc analysis
randomized trial
N=213

Ang IJROBP 2001

Postoperative RT of oral cavity cancer

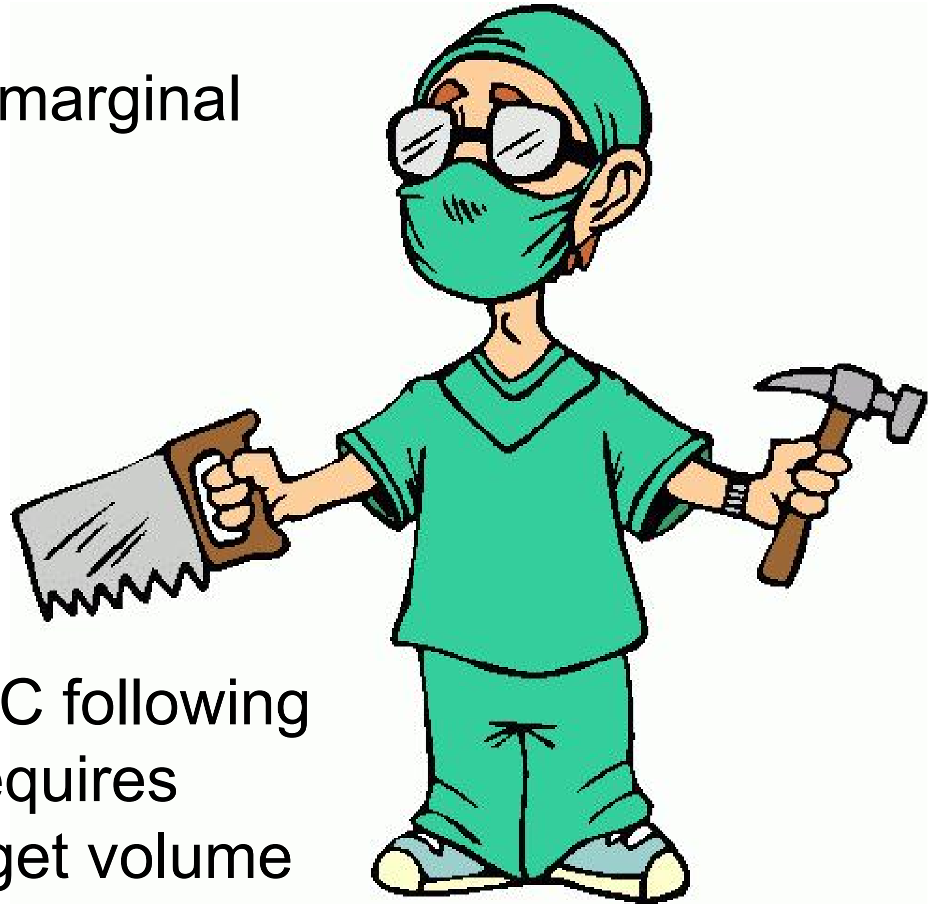


Huang Med Oral Patol Oral Cir Bucal 2013

ESTRO School

Have you talked to your surgeon today?

12 of 38 LR recurrences were marginal or out-of-field following PORT



"Postoperative IMRT for OCSCC following gross total surgical resection requires careful and comprehensive target volume delineation"

Chan oral oncol 2012

DAHANCA RT guidelines in English: Go to dahanca.oncology.com; go to “Til fagfolk”, click on guidelines and find the document: “DAHANCA Radiotherapy Guidelines 2013 (version 2.0)”

Oropharyngeal Cancer: Surgical Aspects

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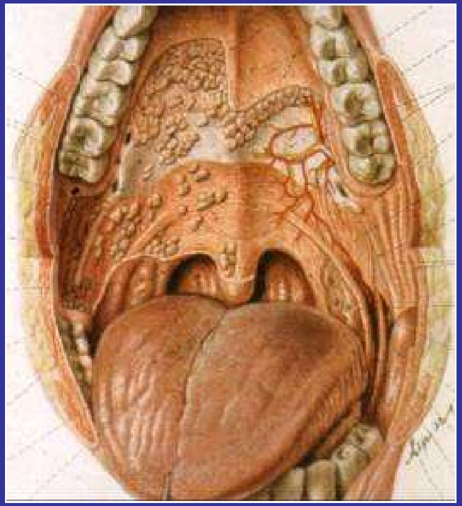
Professor and Chair

Otolaryngology-Head and Neck Surgery
VU University Medical Center
Amsterdam, The Netherlands

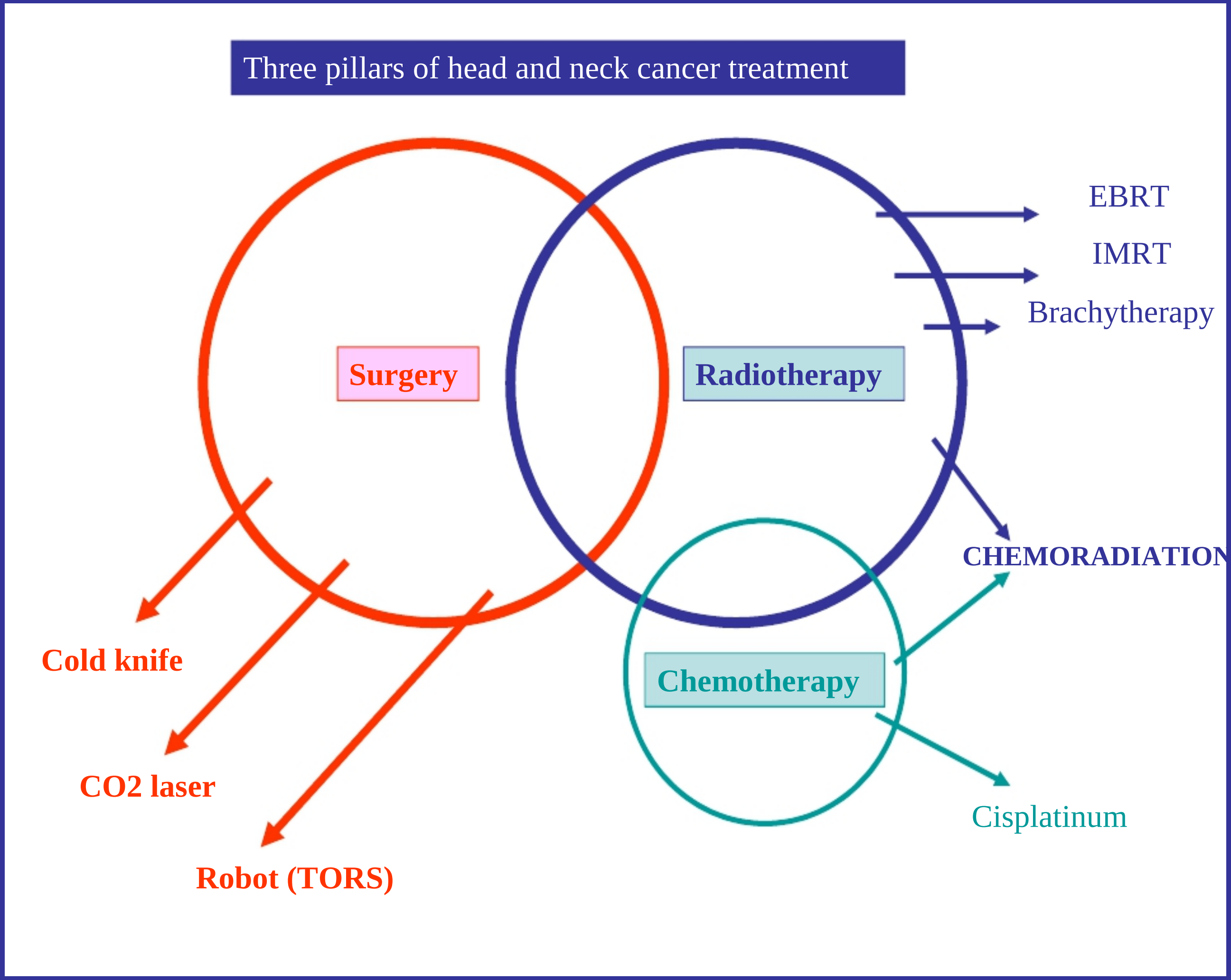
MULTIDISCIPLINARY MANAGEMENT
OF HEAD AND NECK ONCOLOGY
Florence, Italy. June 26-29, 2016

Subdivision of the Oropharynx

- Soft palate
- Tonsillar Fossae
- Base-of-Tongue
- Posterior Wall



Oropharynx Cancer



Early T-staged SCC: Surgery is Preferred Modality ?

- High cure rates
- Morbidity of small resections, combined with W&S for the neck or SND, is limited
- Possibility to avoid RT in many cases
- Leaves other options open

Surgical vs Non-surgical management of T1-2 Oropharynx carcinoma

- 5 yrs DSS after surgery **81-100%** (+/- RT)
  after primary RT **77- 89%**

- Surgical treatment allows accurate staging and avoidance of RT for patients with clear margins

O' Hara et al. Eur Arch Otorhinolaryngol 2011;268:437

Oropharynx Cancer

	Surgery + PORT Mean (95% CI)	Chemoradiotherapy Mean (95% CI)	*P*-value
Pain	9.0 (3.2–14.7)	10.7 (4.8–16.7)	0.810
Swallowing	36.2 (24.1–48.3)	19.3 (11.3–27.4)	0.042
Senses	25.6 (14.7–36.6)	22.0 (13.5–30.6)	0.715
Speech	30.3 (18.6–42.0)	16.8 (10.8–22.7)	0.056
Social eating	26.6 (16.1–37.1)	14.0 (7.2–20.7)	0.038
Social contact	14.9 (5.4–24.3)	4.7 (0.89–10.3)	0.002
Sexuality	23.7 (9.7–37.7)	15.6 (5.5–25.7)	0.462
Teeth	20.5 (8.4–32.6)	39.8 (27.4–52.2)	0.049
Open mouth	14.1 (5.4–22.8)	32.2 (19.8–44.7)	0.036
Dry mouth	38.5 (24.9–52.0)	58.1 (47.6–68.5)	0.022
Sticky saliva	35.9 (21.7–50.1)	52.7 (41.4–64.0)	0.044
Coughing	15.4 (3.8–26.9)	24.7 (13.8–35.6)	0.123
Felt ill	6.4 (2.9–15.7)	0.0 (0.0–0.0)	0.119
Painkillers	38.5 (18.4–58.5)	19.3 (4.6–34.1)	0.113
Nutritional supplements	23.1 (5.7–40.4)	22.6 (7.0–38.2)	0.965
Feeding tube	3.8 (0.1–11.8)	6.4 (2.7–15.6)	0.664
Weight loss	23.1 (5.7–40.4)	16.1 (2.4–29.8)	0.512
Weight gain	11.5 (1.6–24.7)	25.8 (9.5–42.1)	0.178

	Surgery + PORT Mean (95% CI)	Chemoradiotherapy Mean (95% CI)	*P*-value
Physical functioning	79.2 (70.9–87.5)	87.7 (80.7–94.8)	0.043
Role functioning	85.2 (74.9–95.6)	91.0 (83.8–98.1)	0.357
Social functioning	84.6 (74.2–95.0)	93.5 (86.4–100.0)	0.036
Emotional functioning	76.2 (66.0–86.3)	84.7 (78.0–91.4)	0.210
Cognitive functioning	85.9 (77.2–94.6)	90.3 (84.2–96.4)	0.392
Global QoL	68.6 (60.11–77.0)	79.8 (72.8.9–86.9)	0.027
Fatigue	22.9 (13.9–31.9)	12.9 (5.9–19.8)	0.047
Nausea and vomiting	6.4 (0.7–13.5)	2.1 (1.3–5.6)	0.152
Pain	21.8 (12.3–31.3)	8.6 (3.6–13.6)	0.027
Dyspnea	10.3 (1.9–18.6)	14.0 (6.4–21.6)	0.368
Sleep disturbance	9.0 (2.9–15.1)	10.7 (1.6–19.9)	0.661
Appetite loss	12.8 (3.4–22.2)	11.8 (5.1–18.6)	0.842
Diarrhea	5.1 (1.1–11.4)	2.1 (0.9–5.2)	0.482
Constipation	16.7 (5.7–27.6)	14.0 (4.6–23.3)	0.660
Financial impact	15.4 (5.1–25.6)	14.0 (4.1–23.8)	0.598

- Surgical patients more problems with swallowing, social eating and social contacts.
- CCRT greater problems with teeth, dry mouth and sticky saliva

Boscolo-Rizzo P et al. Oral Oncol 2009;45:953-7

Surgery versus RT for T1-2N0-1

Con Surgery
- Morbidity of composite resection
- SND / RT for neck

Pro Surgery
- Morbidity is limited if surgery is transorally (TORS/CO_2)
- SND gives pathology of neck
- Possible to withhold RT in about 50% or decrease dosage
- Keep RT for unfavorable cases and second primaries/recurrences

Pro -RT
- Mostly single modality
- Easy elective neck treatment

Con RT/CRT
- Once a lifetime
- Costs / duration
- Salvage surgery has poor results
- Long term toxicity
  - CVA (5-7x)
  - Fibrosis/xerostomia/ nerve dysfunctioning

Resection?

- Cold knife
- CO_2 laser
- TORS

Functional and Oncologic Results following Transoral Laser Microsurgical Excision of Base of Tongue Carcinoma

- Retrospective evaluation of long-term results after transoral laser surgical resection
- Histologically identified carcinomas of the base of tongue, considered as resectable by laser surgery
- Resectability was defined depending on the tumor size and especially on the exposition
- No metastases

Camp AA et al. Otolaryngol Head Neck Surg 2009;141:66-69

Functional and Oncologic Results following Transoral Laser Microsurgical Excision of Base of Tongue Carcinoma

- Evaluation time of 10 years
- 71 patients were treated transorally by laser microsurgery
- Intraoperative examination until resection margins were tumor-free
- Neck dissection at the time of laser surgery

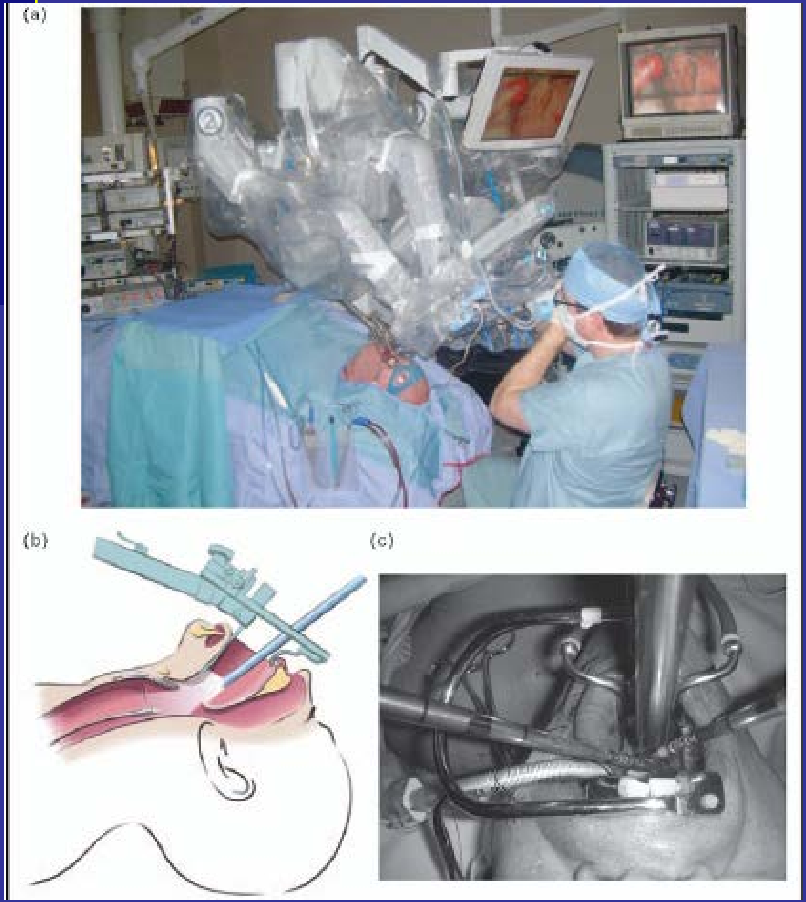
Camp AA et al. Otolaryngol Head Neck Surg 2009;141:66-69

Functional and Oncologic Results following Transoral Laser Microsurgical Excision of Base of Tongue Carcinoma

- Adjuvant (C)RT in majority of cases
- Follow-up of 24 months
- Survival rate of 94%
- Locoregional recurrences were observed in 10% of the cases
- Excellent results in the context of other studies

Camp AA et al. Otolaryngol Head Neck Surg 2009;141:66-69

Trans Oral Robotic Surgery



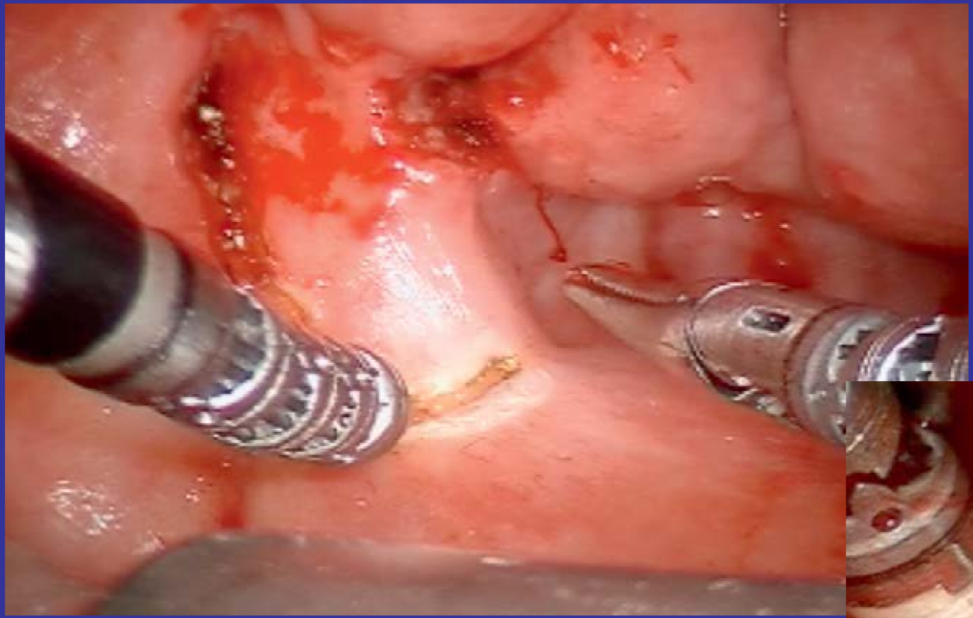
Weinstein
ORL

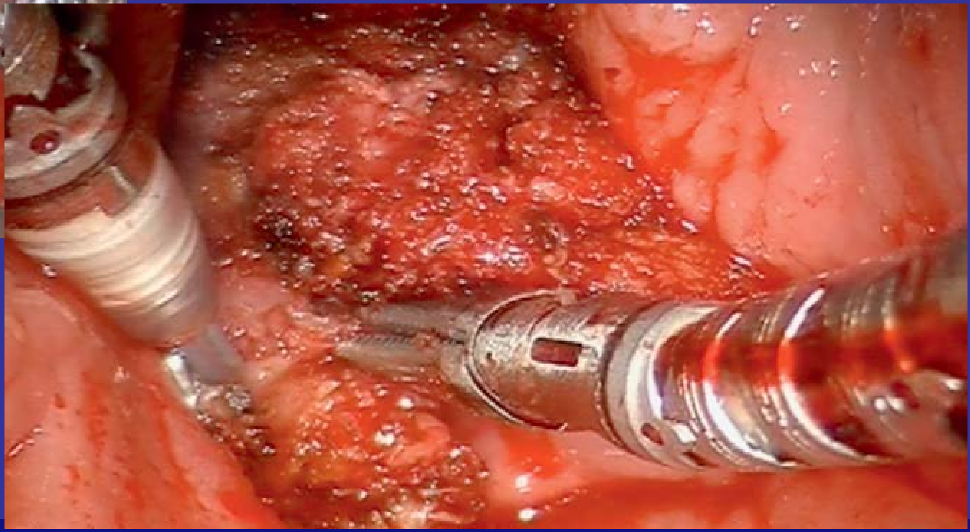
O' Malley
ORL

Quon
Rad Onc

Oropharynx Cancer

TORS BOT Resection (G. Peretti)





Functional Outcome after TORS

- 9% temporary tracheostomy
- 83% oral intake within 14 days
- Good functional postoperative results regarding the function of respiration and swallowing indicate that TORS is developing into an alternative to current therapeutic options

Iseli TA et al. Otolaryngol Head Neck Surg 2009;141:166-171

Issues with TORS

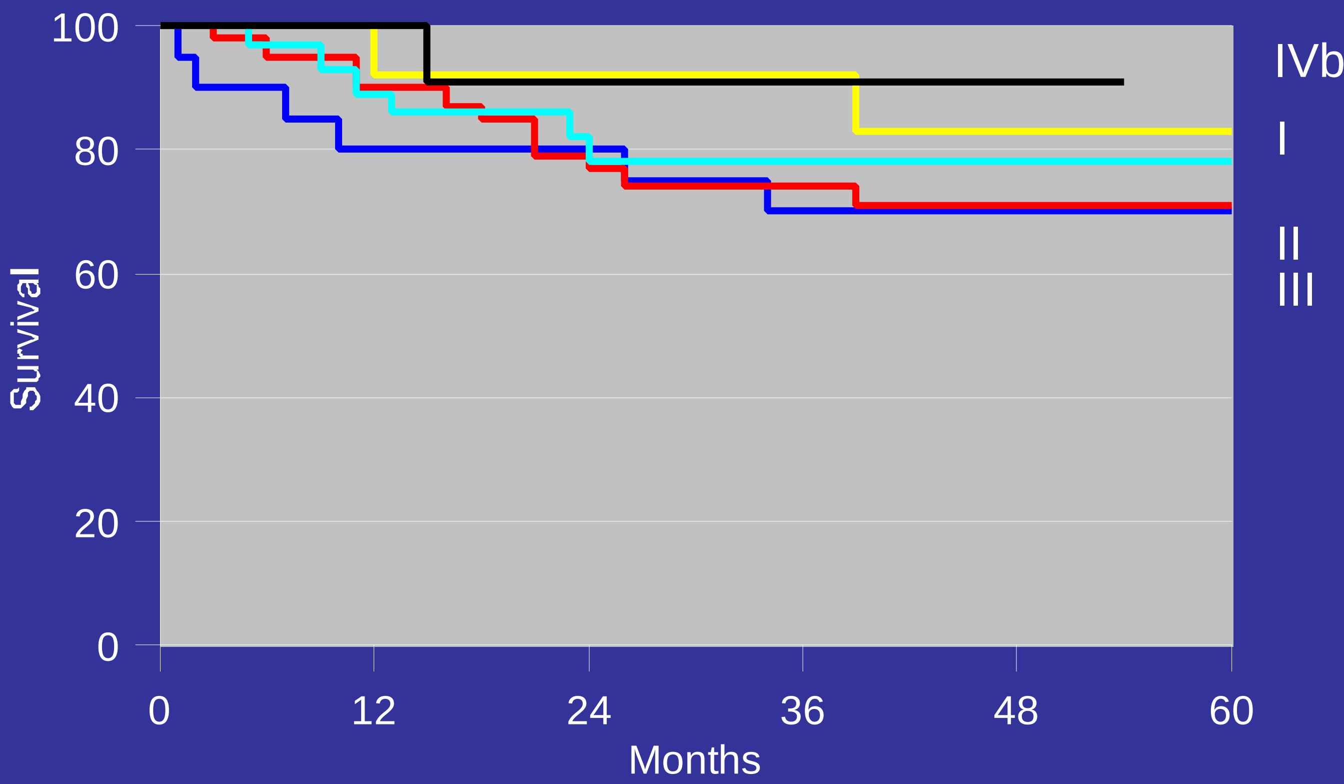
- Is it possible to reduce the rate of R1-resections with TORS
- Value of volume reduction before CRT
- Cannot influence N-status
- Cost

Evolution of Management of Advanced Cancers

- Movement towards surgery in early 20th century
- Primary radiotherapy in 1960-70s
- Renewed interest in surgery in 1980-90s
- Recent interest in non-surgical modalities in 2000-10s

Oropharynx Cancer

Loco-regional Control Tonsillar Carcinoma 1975-1993 n=221



Loco-regional Control Tonsillar Carcinoma

	S +/- RT (VUmc 2001; n=118)	***RT +/- S (UFCM 2000; n=400)***
Stage I	83%	63%
Stage II	70%	73%
Stage III	71%	85%
Stage IVa	78%	65%
Stage IVb	90%	52%
Overall	74%	70%

Quality-of-life

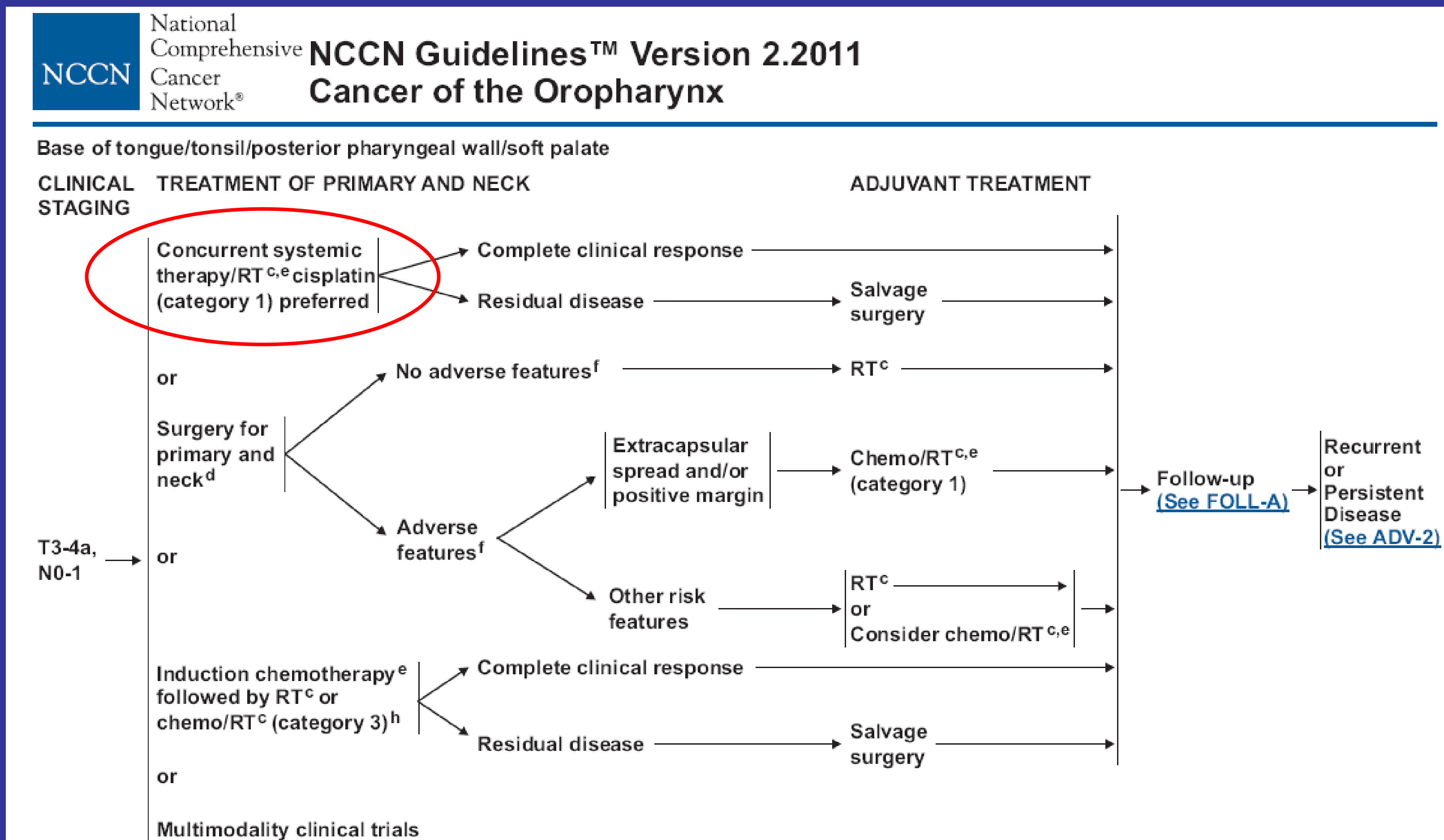
	Pretreatment	6 months	12 months	Significance	
	Mean	Mean	Mean	p_{P-6}	p_{6-12}
EORTC QLQ-C30					
Functioning scales[a]					
Physical functioning	87.7	80.5	85.9	**0.005**	**0.044**
Role functioning	79.5	75.4	84.8	.237	**0.005**
Cognitive functioning	85.6	84.1	87.9	.685	0.262
Emotional functioning	70.3	86.0	84.7	**0.000**	0.602
Social functioning	89.0	86.7	90.2	0.486	0.297
Global quality of life	75.9	76.3	80.7	0.903	0.064
Symptom scales or single items[b]					
Fatigue	24.7	23.0	18.9	0.616	0.136
Emesis	1.9	5.3	2.7	0.071	0.197
Pain	29.2	10.6	12.1	**0.000**	0.652
Dyspnea	10.6	12.1	7.6	0.710	0.160
Insomnia	36.4	23.5	17.4	0.055	0.221
Appetite loss	12.1	13.6	10.6	0.772	0.210
Constipation	13.6	3.0	3.0	**0.046**	1.00
Diarrhea	6.8	5.3	5.3	0.599	1.00
Financial impact	7.6	17.8	15.2	**0.036**	0.583

Borggreven PA *et al*. Head Neck 2005;27:785-93,
Oral Oncol 2007;43:1034-42, Head Neck 2007;29:638-47

Transition

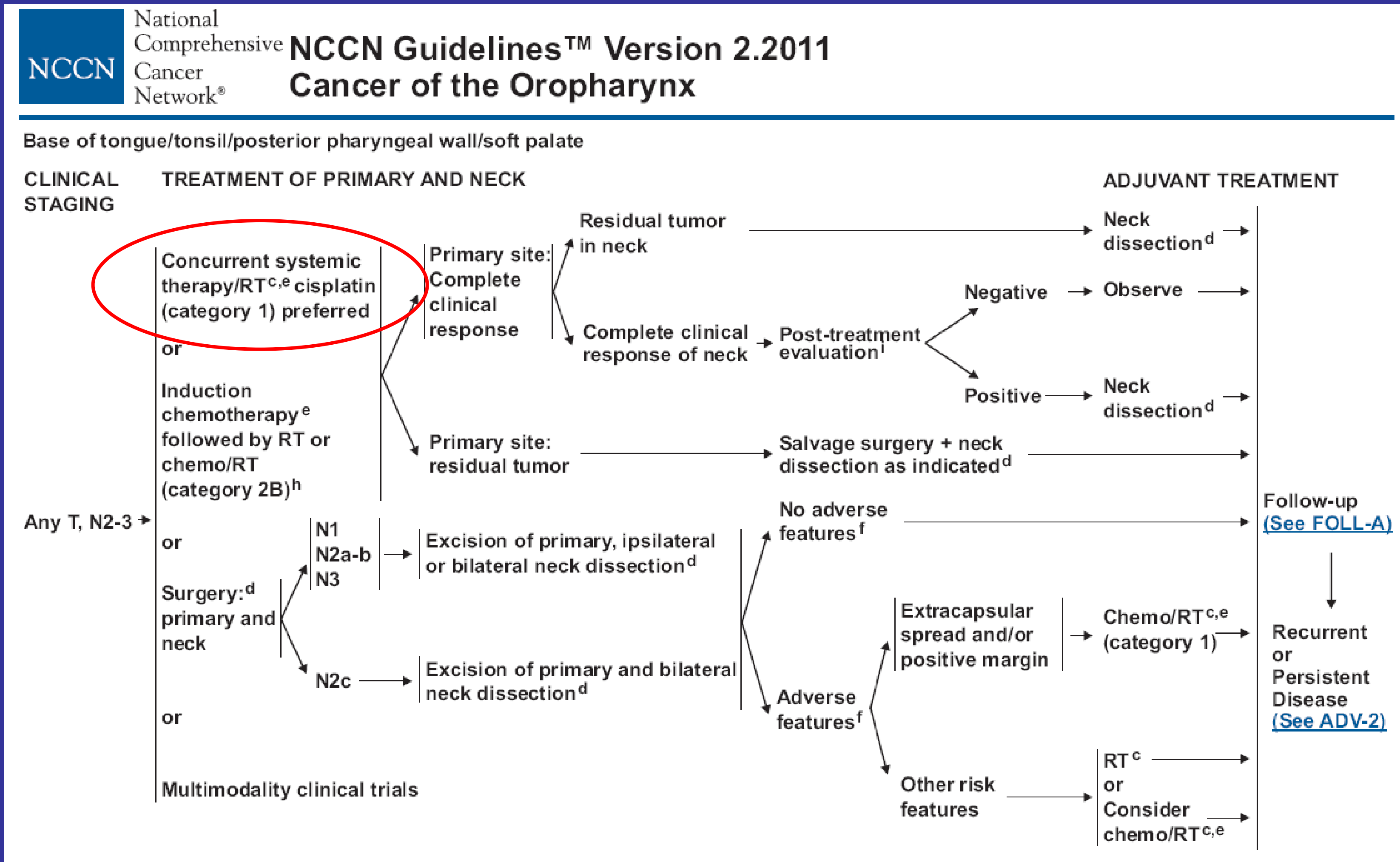
- Around turn of the century
- The switch to from surgery to chemoradiation was non RCT-based
- Never compared to surgery
- Improved protocols
- Parallel to changing epidemiology

Oropharynx Cancer



VU university medical center

Oropharynx Cancer



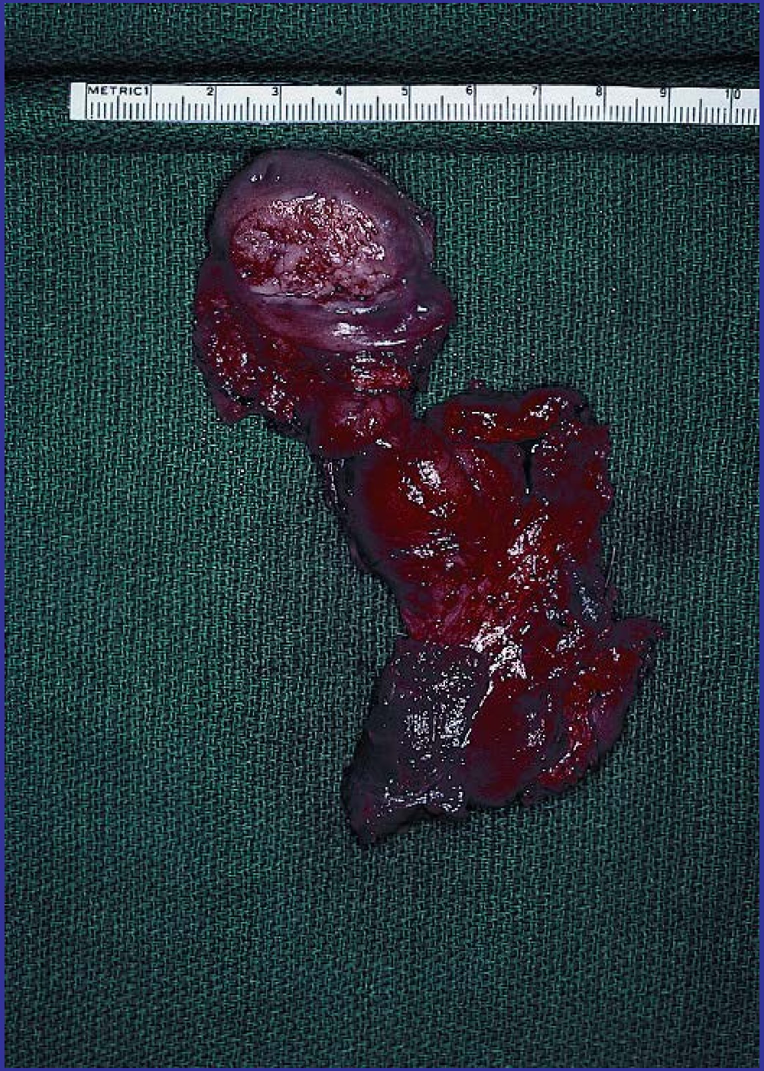
VU university medical center

Open Surgery

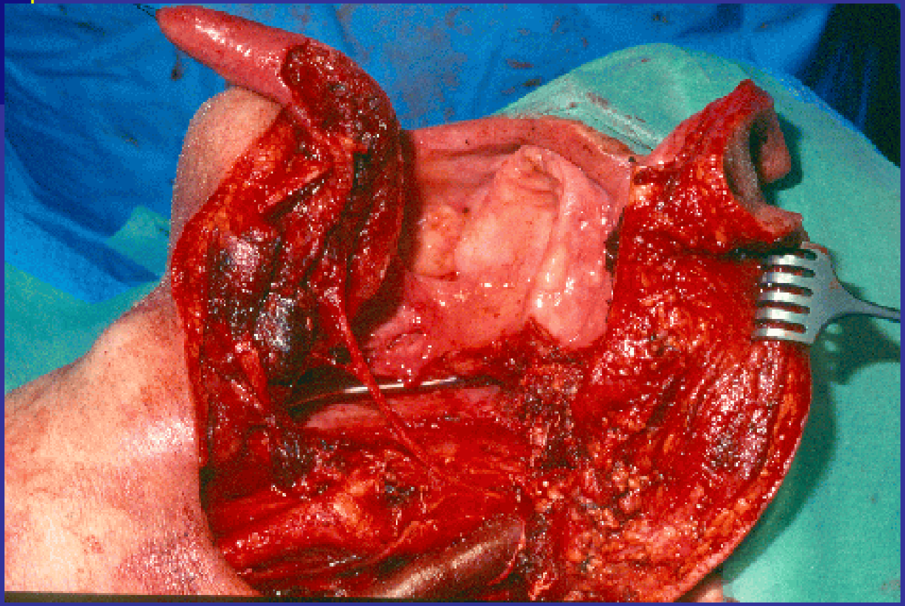
- Surgical Approach:
    - Suprahyoid pharyngotomy
    - Lateral pharyngotomy
    - Mandibular lingual release
    - mandibulotomy
- Neck dissection
- Reconstruction
    - Local/regional/free flap

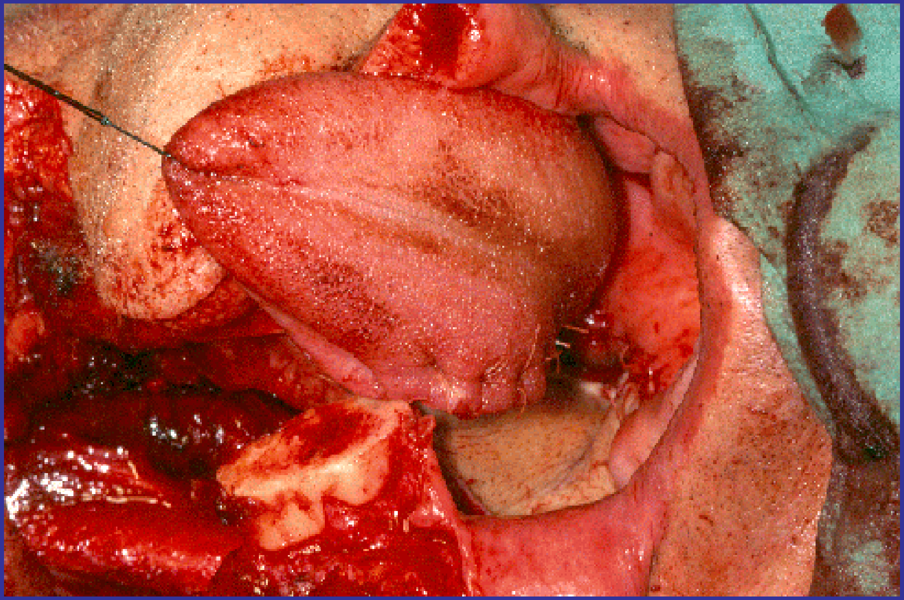
Oropharynx Cancer

Oropharynx Cancer

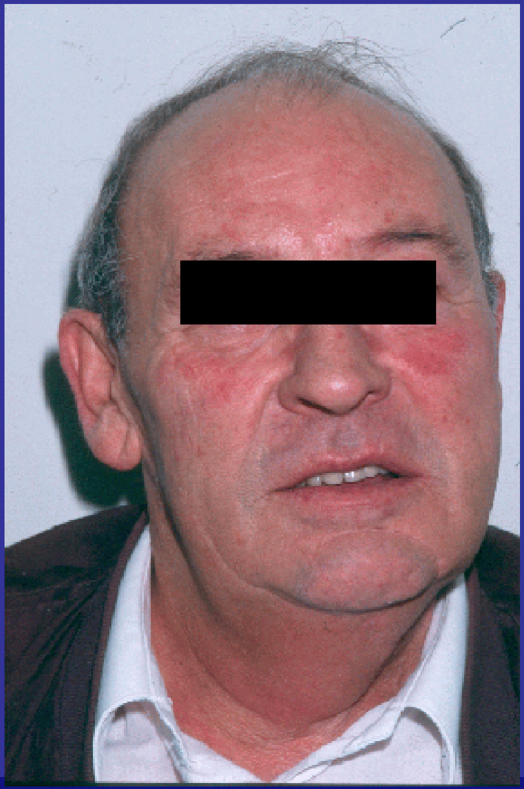


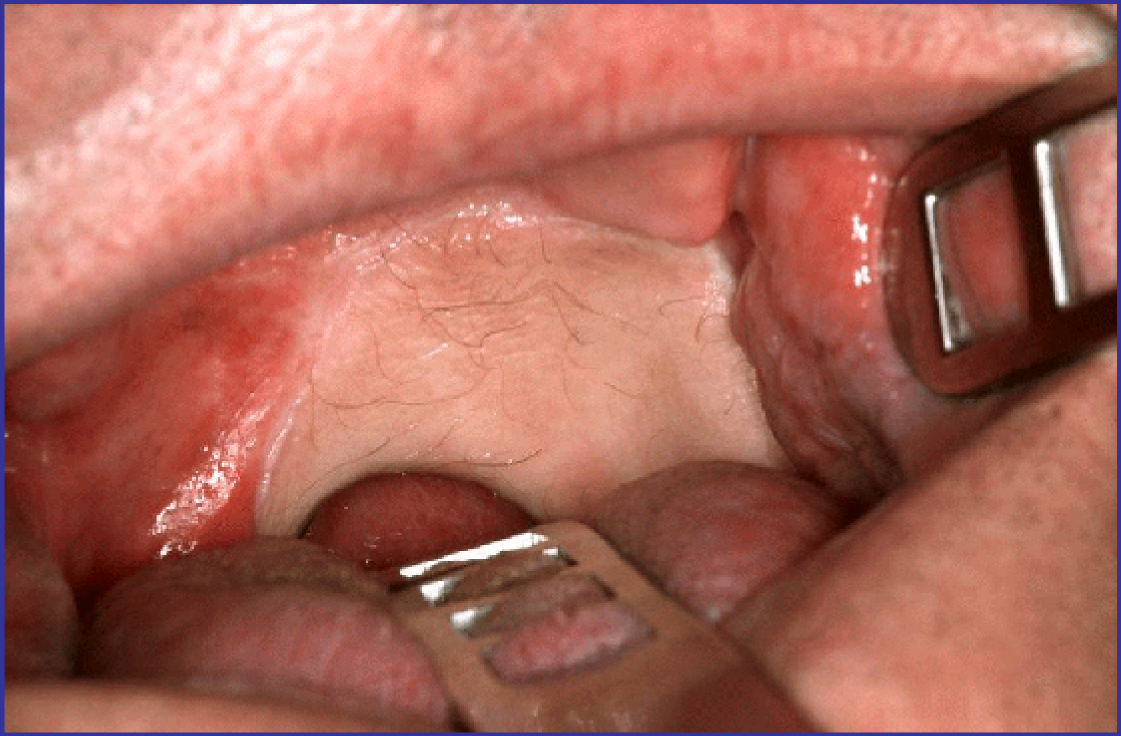
Excision and Reconstruction Tonsillar Carcinoma





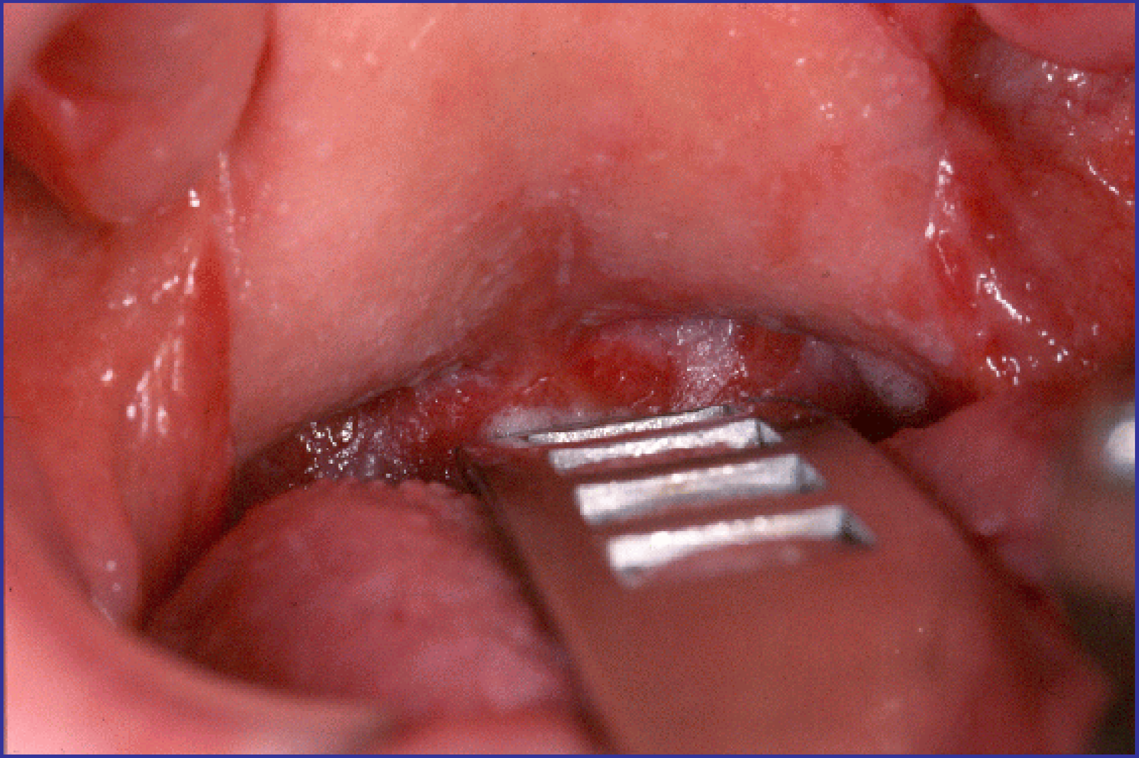
Reconstruction of Soft Palate + Lateral Oropharynx (RFFF)



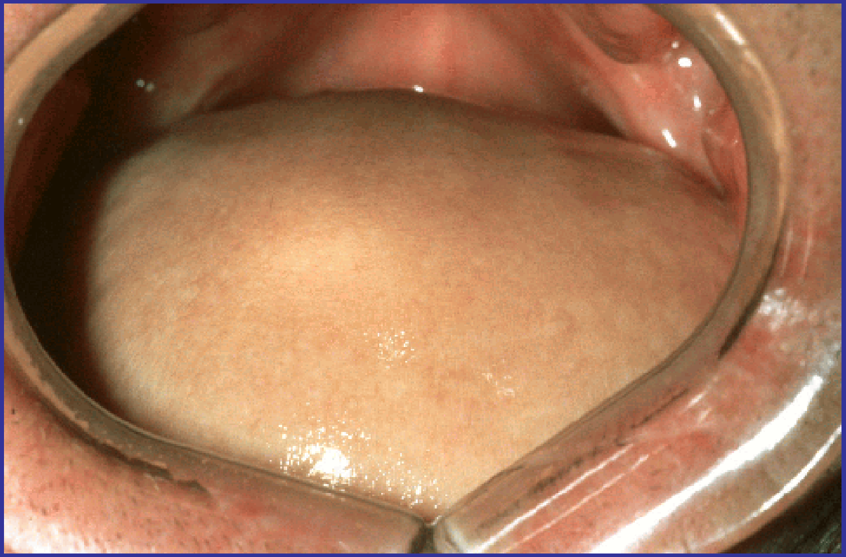


Reconstruction of Soft Palate + Lateral Oropharynx (RFFF)

Reconstruction of Total Soft Palate (RFFF)



Total Glossectomy (Rectus/DIEP)



Salvage Surgery OPSCC

Recurrence after chemoradiation for OPSCC (n=394)

- LR Recurrence n=102
  - Salvage surgery n=17
  - No salvage surgery n=85
    - Distant Metastases n=47
    - Physical condition n=11
    - Refusal by patient n=6
    - Inoperability tumor n=21

Postoperative Complications

Author	Year	N	Stage III/IV (%)	Complications (%)
Agra et al.	2003	70	76	42
Zafereo et al.	2009	41	63	46
Kostrzewa et al.	2010	36	78	36
Nicols et al.	2011	29	90	41

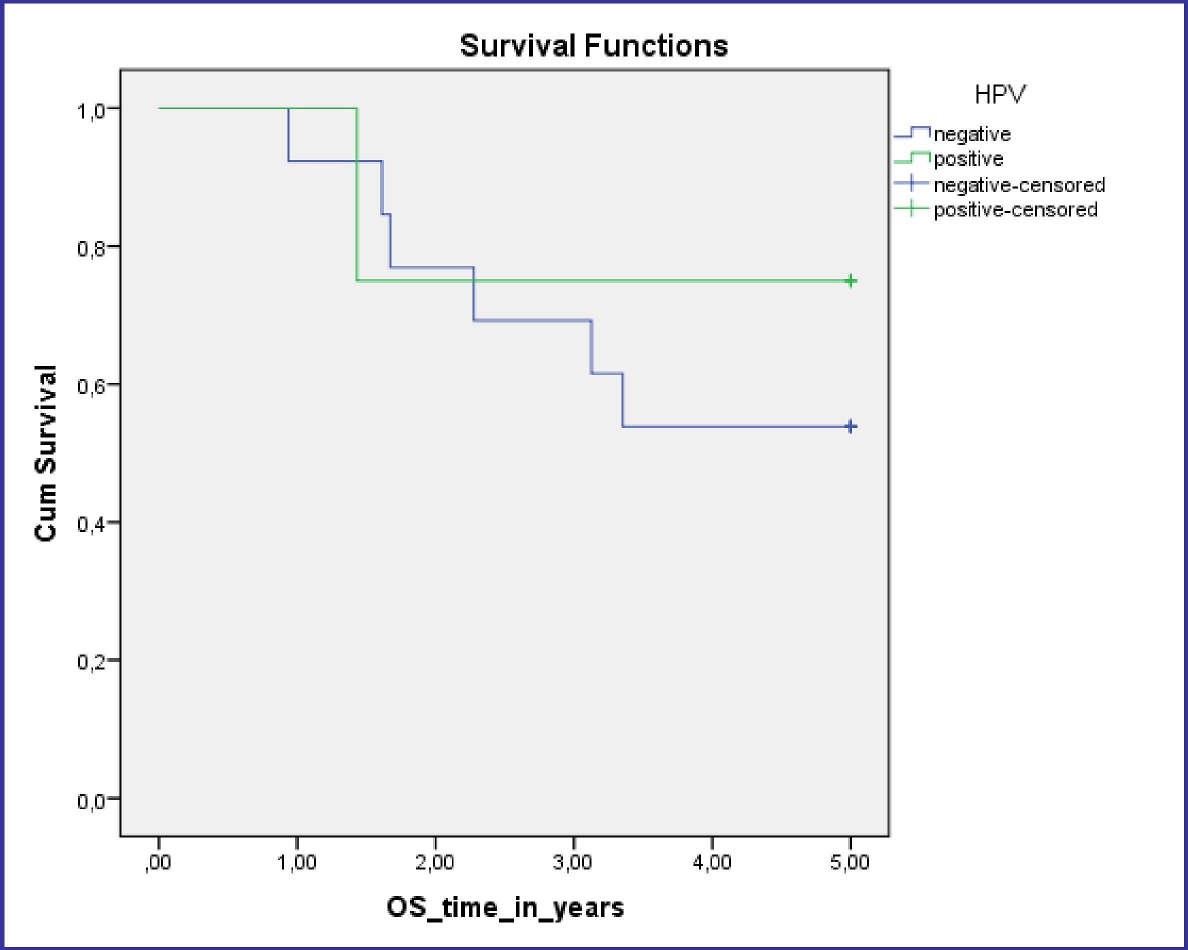
Reconstruction after Salvage Surgery

Author	Year	N	PM (%)	FRFF (%)	Rectus (%)	Other (%)
Goodwin	2000	31	30			
Agra et al.	2006	70	47			
Zafereo et al.	2009	41	12	18		32
Kostrzewa et al.	2010	36		75	8	17
Nicols et al.	2011	29		50		

Long-term Complications

Author	Year	N	PEG/NGT (%)	Tracheostomy (%)
Zafereo et al.	2009	41	32	13
Kostrzewa et al.	2010	36	53	-
Nicols et al.	2011	29	83	-
White et al.	2013	64	31	-

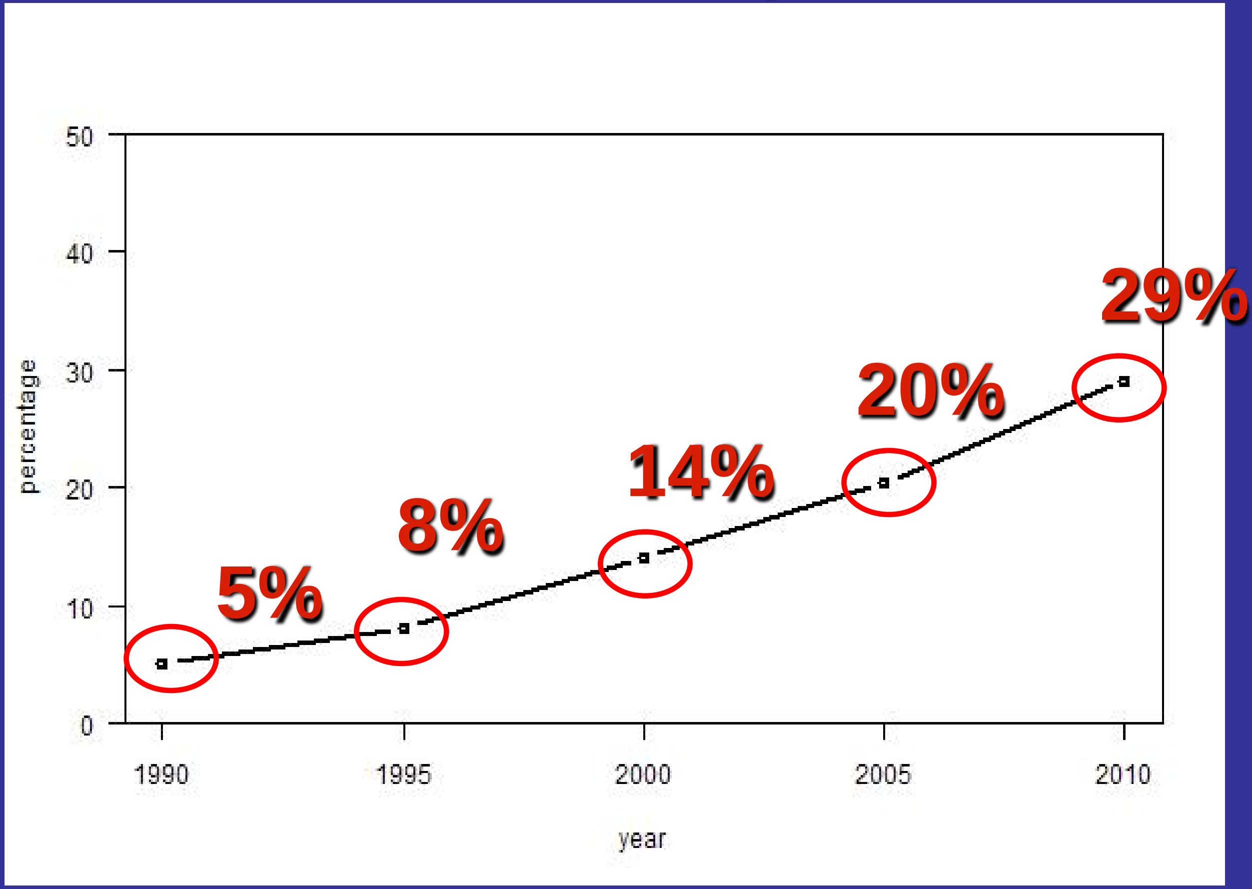
5y OS Salvage Surgery OPSCC



Survival after Salvage Surgery OPSCC

Author	Year	N	Stage III/IV (%)	% Salvage	DFS (%)	OS (%) (5 yrs)
Goodwin	2000	31	64	-	26 (2 yr)	26
Agra et al.	2006	70	76	-	-	26
Zafereo et al.	2009	41	63	24	26 (3 yr)	28
Röösli et al.	2009	18	95	12	20 (4 yr)	25
Kostrzewa et al.	2010	36	78	-	-	44
Nicols et al.	2011	29	90	38	-	43
White et al.	2013	64	59	-	43 (2 yr)	-
Sedee et al.	2014	17	83	17		58

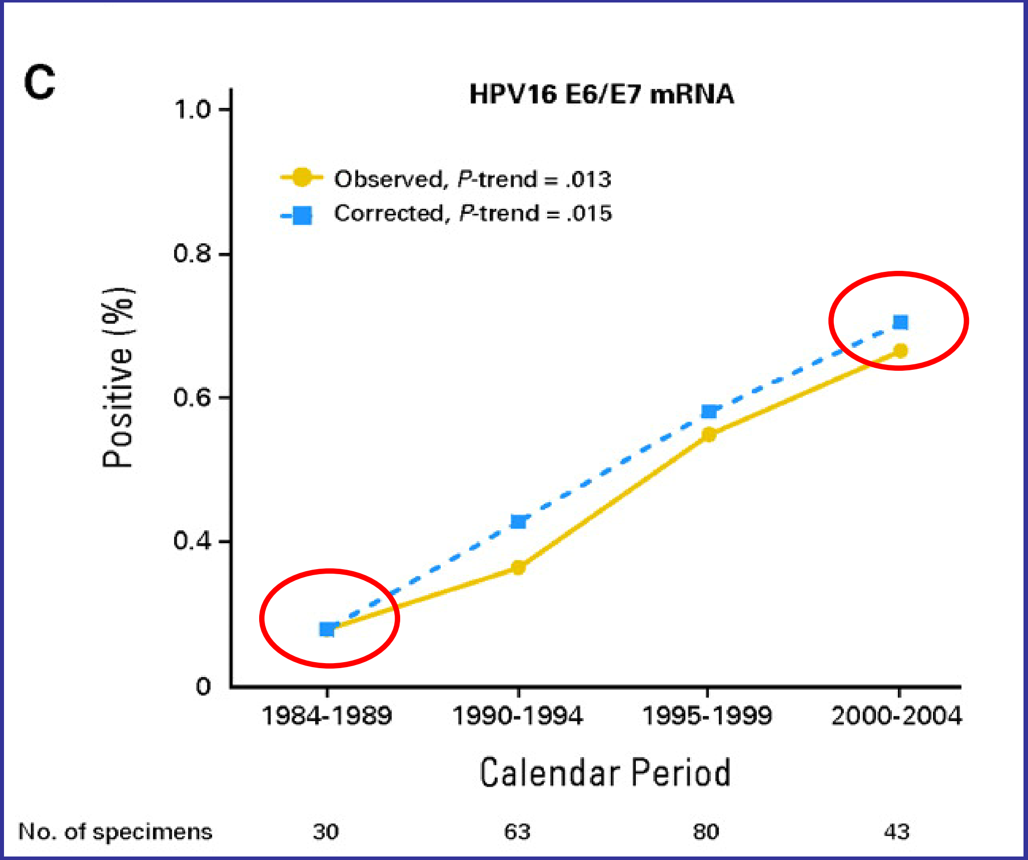
Results Time Trend Analysis VUmc



Cochrane-Armitage test for trend (p< 0.001)

Rietbergen MM *et al*. Int J Cancer 2013;132:1565-1571

Rising Oropharyngeal HPV-Prevalence in US



16.3% in 1984-1989→ 70.0% in 2000-2004 in the USA

Chaturvedi A K *et al*. J Clin Oncol 2011;29:4294-4301

How to Explain better Response of HPV+?

- Intrinsic higher radiosensitivity
- Lack of TP53 mutation
- No field cancerization
- Immunology related

Transoral Robotic-assisted Surgery

- **Multi-institutional study (4 centres)**
- **64 TORS cases matched to 64 open approaches by TNM**

White H *et al*. JAMA Otolaryngol Head Neck Surg 2013;139:773-778

Transoral Robotic-assisted Surgery

- Lower incidence of tracheostomy
- Lower incidence of feeding tube use
- Shorter overall hospital stays
- Decreased operative time
- Less blood loss (49 mL vs 331 mL; P < .001),
- Decreased incidence of positive
- Higher 2-year recurrence-free survival

White H *et al*. JAMA Otolaryngol Head Neck Surg 2013;139:773-778

Transoral Robotic-assisted Surgery

- **Same criteria as for primary TORS**
- **Some re-resection to achieve free margins**
- **Selection bias:**
  - **Exposure/trismus**
  - **Bone involvement**

White H *et al*. JAMA Otolaryngol Head Neck Surg 2013;139:773-778

Surgery vs. Organ-Preservation

- Different treatment philosophies
- Salvage surgery is integral part of organ-preservation protocols, but NOT always possible

Role of Surgeon

- Central Part of Multidisciplinary Team

Surgery Must Treat Complications and Sequelae of Chemotherapy/Radiotherapy

- Oro-nasopharyngeal stenosis
- Laryngeal edema and obstruction
- Radionecrosis of the larynx
- Strictures of pharyngo-esophagus
- ORN of mandible other bones

Conclusions

- Early staged cancers are well treated by surgery
- Limited role in advanced staged cancers, except for salvage
- Modified role surgeon

1666 – Girl with a pearl earring
by Johannes Vermeer

Thank you for your attention

VU university medical center

Management of oropharyngeal SCC: radiotherapy

Vincent GREGOIRE, MD, PhD, Hon. FRCR

Head and Neck Oncology Program, Radiation Oncology Dept. & Center for Molecular Imaging, Radiotherapy and Oncology, Université Catholique de Louvain, St-Luc University Hospital, Brussels, Belgium

Staging of oropharyngeal tumors (TNM-UICC 2010)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*
T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4a Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate or mandible
T4b Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Regional lymph node and metastasis staging

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node, >6 cm in greatest dimension

Distant Metastasis (M)

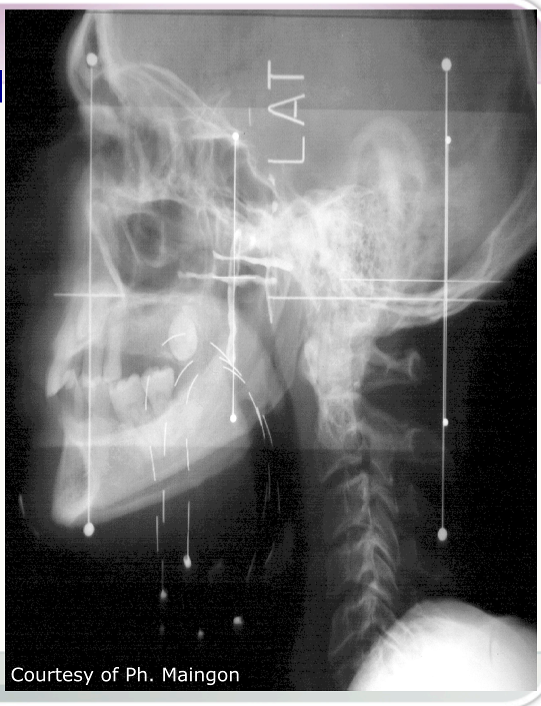
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Transoral surgery

- Cold / cautery knife
- CO2 laser
- TORS

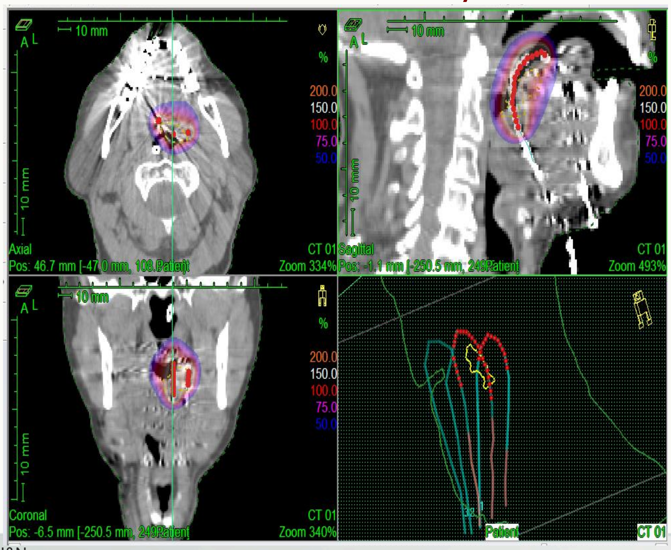
Courtesy of M. Hamoir

Brachytherapy for oropharyngeal SCC



Brachytherapy for oropharyngeal SCC

Boost after 50 Gy



Courtesy of Ph. Maingon

Brachytherapy for oropharyngeal SCC

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journal homepage: www.thegreenjournal.com

ELSEVIER

GEC-ESTRO recommendations

GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas

Jean-Jacques Mazeron [a,*], Jean-Michel Ardiet [b], Christine Haie-Méder [c], György Kovács [d], Peter Levendag [e], Didier Peiffert [f], Alfredo Polo [g], Angels Rovirosa [h], Vratislav Strnad [i]

Anatomical site	Patient selection	Implant technique	Safety margin	Dose	Result
Lip	T1-3	RN	5–10 mm	60–75 Gy LDR-PDR	LC: 90–95% N: 2–10%
Buccal mucosa	<4 cm	PT	5–10 mm	65–70 Gy LDR-PDR (25–30 Gy boost if 45–50 Gy ERT)	LC: 80–90% N: <10%
Mobile tongue	T1-3	PT	5 mm	65–75 Gy LDR-PDR (25–30 Gy boost if 40–45 Gy ERT)	LR: >90% N: 10–20%
Floor of mouth	T1-2N0	RN or PT	>5 mm	65 Gy LDR-PDR (10–25 Gy boost if 46-50 Gy ERT)	LR: >90% N: 10–30%
Oropharynx	< 5 cm	PT	>10 mm	LDR-PDR: 25–35 Gy boost following 45–50 Gy ERT HDR 21–30 Gy/3 Gy fractions or 21–24 Gy/ 4 Gy fractions boost following 45–50 Gy ERT	Base of tongue: LR: T1-2 80–90% T3-4 65–80%. N 25% Faucial arch: LR: T1-2: up to 90%. T3: 67% N: 20%

Mazeron et al, 2009

Treatment strategies

Key parameters influencing treatment choice

- Tumor: extension and location
- Neck: lymph node status
- Patients: general status, co-morbidities and personal choice
- Outcome: efficacy, functionality and morbidity

Treatment strategies

Conservation Surgery - Indications

Early tumors (T1-T2, N0-N1)

Resection of the tumor <u>and</u> neck dissection when organ-function sparing surgery is suitable.

➡ Avoid multiple treatment when only one modality is enough!

Hyper- and accelerated fractionation

CF — 70Gy/ 2.0 Gy/ 7w

HF — 80.5Gy/ 2x1.15 Gy/ ti=6h/ 7w

Expectations

- Increased tumor control
- More severe early reactions
- Unchanged or less late reactions

CF — 70Gy/ 2.0 Gy/ 7w

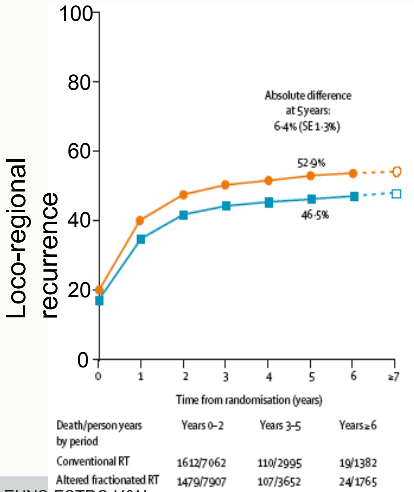
CB — 70Gy/ 2.0 Gy/ 5w

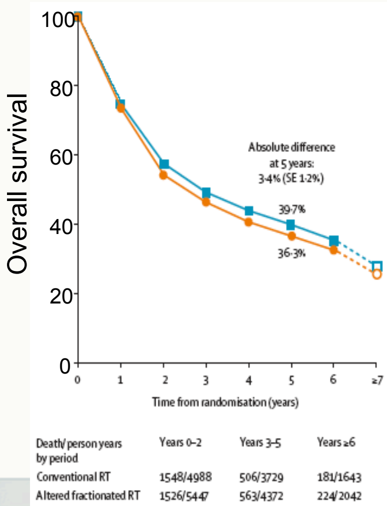
Expectations:

- Increased tumor control
- Increased early reactions
- Unchanged or decreased late damage

Meta-analysis on altered fractionation HNSCC

Randomized trials 1970-1998 (no postop RT)
15 trials included (6515 patients, individual data)





Bourhis, Pignon 2006

Acute toxicity of HF or AF in HNSCC

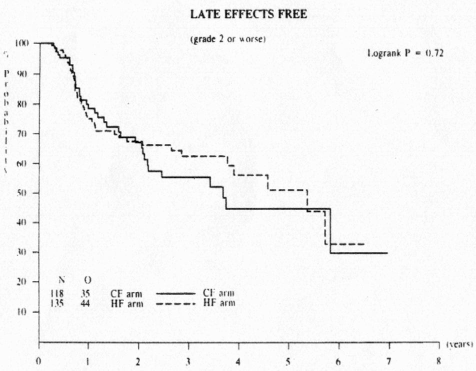
Author	Regimen	Grade 3-4 mucositis Control	Experimental
Horiot (n=356)	HF	49%	67%
Horiot (n=512)	Acc. fract. + split	50%	67%
Dische (n=918)	CHART	43%	73%
Fu (n=536)	Acc. frac (CB)	25%	46%
Fu (n=542)	Acc. fract. + split	25%	41%
Fu (n=507)	HF	25%	42%
Skladowski (n=99)	Acc. Fract.	26%	56%

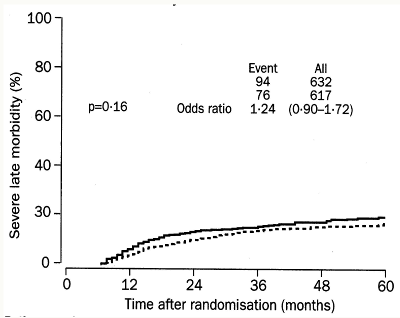
Dishes, 1997 Fu, 2000
Horiot, 1992 Skladowski, 2000

Late toxicity of HF or AF in HNSCC

HF ||||| ||||| ||||| ||||| ||||| ||||| |||||
||||| ||||| ||||| ||||| ||||| ||||| |||||
80.5Gy/ 2x1.15 Gy/ ti=6h/ 7w

AF |||||| |||||| |||||| |||||| |||||| ||||||
64-68 Gy/ 2.0 Gy/ 5.5w





Horiot et al. R&O, 1992
Overgaard et al. Lancet, 2003

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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

Hazard ratio of death.

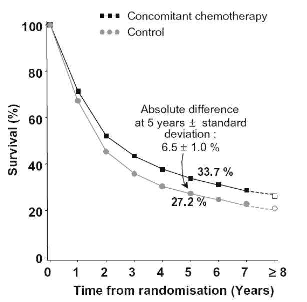
Timing	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	HR [95% CI]
Concomitant	3171/4824	3389/4791	-326.4	1587.7	0.81 [0.78;0.86]
Induction	1877/2740	1813/2571	-40.0	900.7	0.96 [0.90;1.02]
Adjuvant	631/1244	661/1323	17.9	317.4	1.06 [0.95;1.18]
Total	5679/8808	5863/8685	-348.5	2805.8	0.88 [0.85;0.92]

Test for heterogeneity: $\chi^2_{107} = 179.8$ $p < 0.0001$ $I^2 = 41\%$
Test for interaction: $\chi^2_{2} = 26.60$ $p < 0.0001$

Hazard Ratio: 0.5 1.0 2.0 — LRT+CT better | LRT better

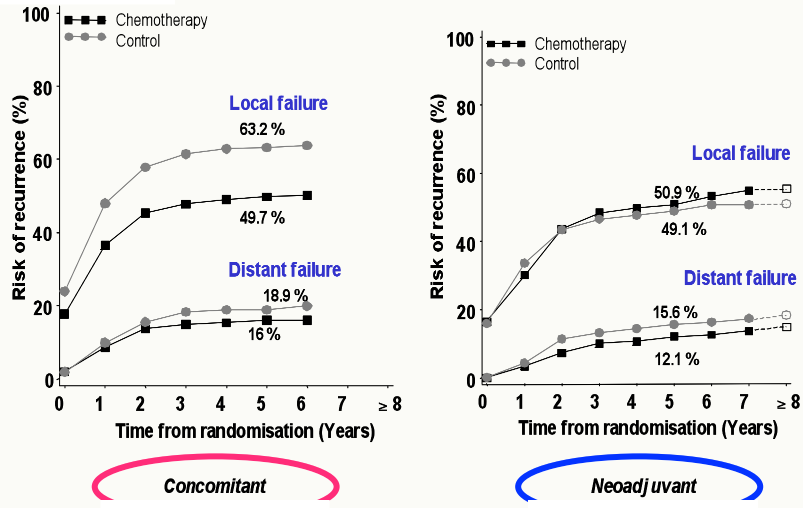
LRT+CT effect: p < 0.0001

(a) Concomitant chemotherapy.



Pignon et al, Radioth Oncol 2009

Platin-5FU: concomitant *vs* induction ?



Platin-5FU Platin-5FU

Bourhis, Pignon 2009

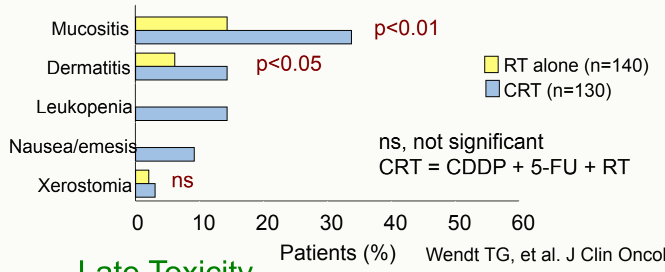
Up-date MACH-NC : summary

- Small benefit of CT on survival : confirmed
- Higher benefit with concomitant CH: confirmed (8%)
- Benefit with concomitant CDDP: 11% at 5 years
- Benefit of CT observed in post-op, and with definitive RT (conventional / hyperfractionated)

Bourhis, Pignon 2009

Toxicity of concomitant CH-RxTh for HNSCC

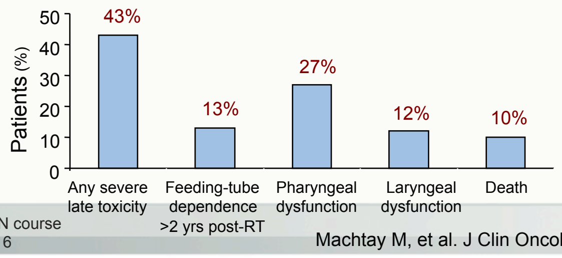
Acute adverse effects: Grade ≥3



Wendt TG, et al. J Clin Oncol 1998;16:1318–1324

Late Toxicity

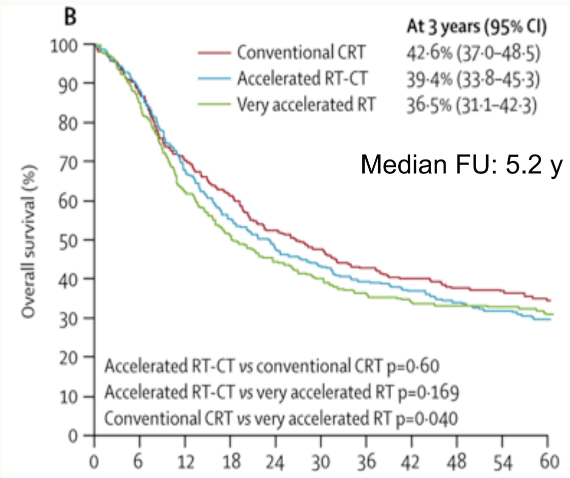
Analysis of 230 patients receiving CRT in 3 studies (RTOG 91-11, 97-03, 9-14)



Machtay M, et al. J Clin Oncol 2008; 26: 3582–3589

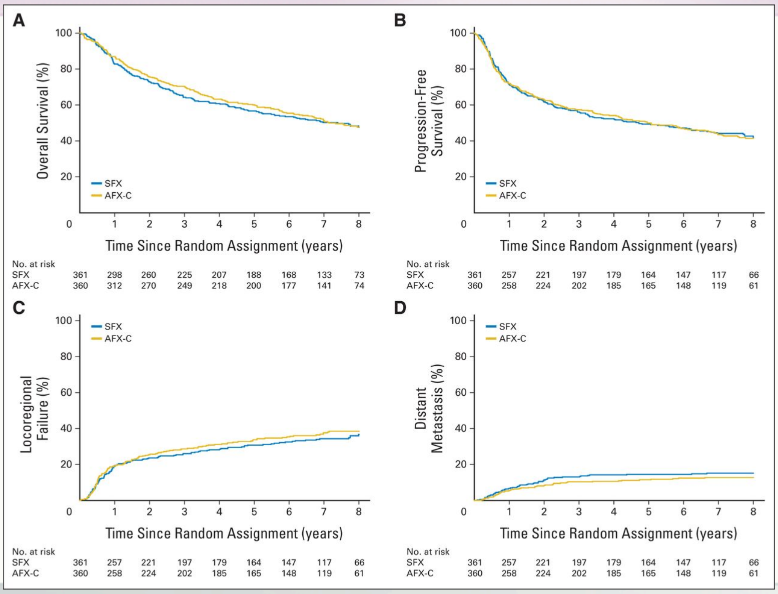
CH-RxTh or altered fractionation or a mix in HNSCC ?

GORTEC 9902: overall survival



Bourhis et al. Lancet Oncol, 2012

CH-RxTh or altered fractionation or a mix in HNSCC ?

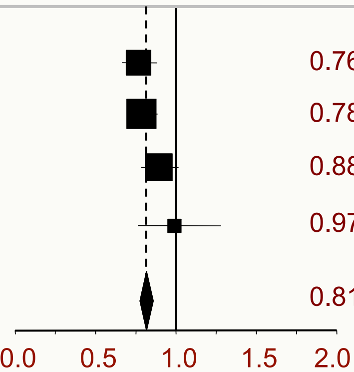


Nguyen-Tan, JCO 2010

Treatment of H&N SCC in the elderly in 2007

MACH-NC: Overall survival by age

Category	No. Events / No. Entered	Hazard ratio (Chemotherapy / Control)	HR [95% CI]
=<50	1 663 / 2 584		0.76 [0.66 - 0.86]
51-60	2 267 / 3 306		0.78 [0.70 - 0.87]
61-70	1 960 / 2 698		0.88 [0.78 - 1.00]
>70	533 / 692		0.97 [0.76 - 1.23]
Total	6 423 / 9 280		0.81 [0.77 - 0.86]



Test of interaction: p = 0.02

Test for trend: p = 0.003

Chemo better | Control better

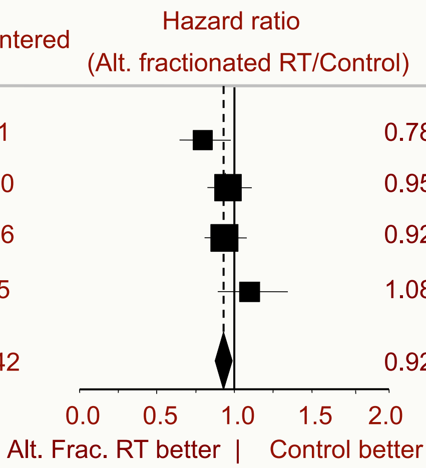
Chemo effect p < 0.0001

Bourhis et al., 2006

Treatment of H&N SCC in the elderly in 2007

MACH-NC: Overall survival by age

Category	No. Events / No. Entered	HR [95% CI]
=<50	768 / 1 311	0.78 [0.65 - 0.94]
51-60	1 455 / 2 300	0.95 [0.83 - 1.09]
61-70	1521 / 2 346	0.92 [0.81 - 1.06]
>70	784 / 1 085	1.08 [0.89 - 1.30]
Total	4 528 / 7 042	0.92 [0.86 - 0.97]



Test of interaction: p = 0.02

Test for trend: p = 0.007 Alt. fractionated RT effect p=0.02

Bourhis et al., 2006

Treatment of H&N SCC in the elderly in 2007

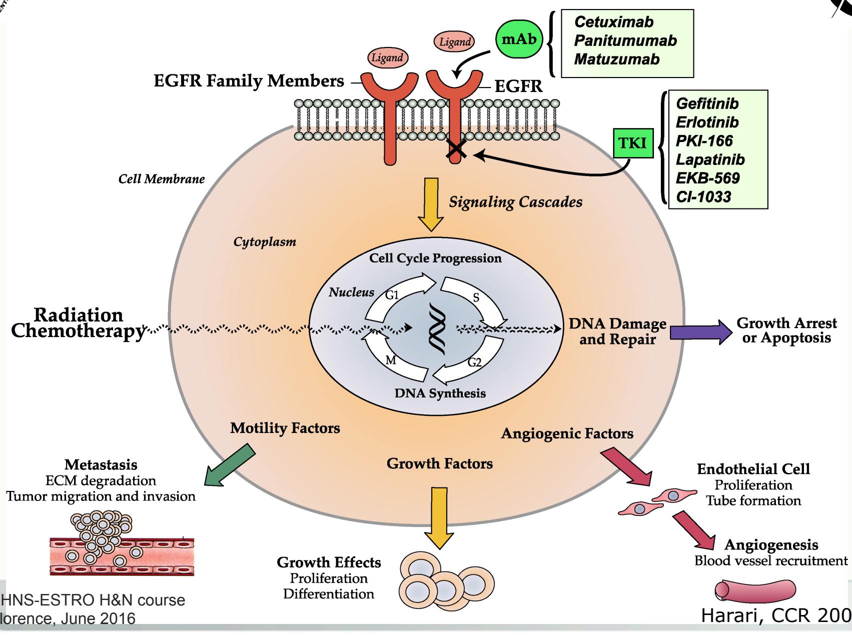
Cause of death

MARCH	=<50	51 - 60	61 - 70	>70	p
Cancer death	74.7 %	68.1 %	60.8 %	47.2 %	
Non cancer death	18.2 %	23.8 %	29.3 %	41.2 %	<0.0001
Unknown cause of death	7.0 %	8.1 %	9.9 %	11.6 %	

MACH-NC	=<50	51 - 60	61 - 70	>70	p
Cancer death	80.4 %	73.1 %	68.8 %	54.6 %	
Non cancer death	14.6 %	21.3 %	26.5 %	38.7 %	<0.0001
Unknown cause of death	5.0 %	5.6 %	4.7 %	6.7 %	

Bourhis et al., 2006

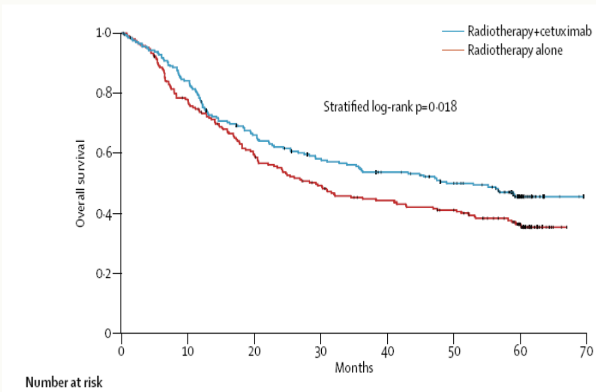
The EGFR pathway



Harari, CCR 2004

EGF-R inhibitor and RxTh in HNSCC efficacy

Randomized phase III: n=424



Number at risk								
Radiotherapy+ cetuximab	211	177	136	117	105	90	49	..
Radiotherapy alone	213	162	122	98	85	77	49	..

Bonner, Lancet Oncol 2010

EGF-R inhibitor and RxTh in HNSCC: toxicity

% Toxicity	RT (N=212)		RT+E (N=208)	
	All Gr.	Gr. 3/4	All Gr.	Gr. 3/4
Skin reaction	91	18	97*	34**
Mucositis/Stomatitis	93	52	91	54
Dysphagia	63	30	64	25
Xerostomia	70	3	64	4
Fatigue/Malaise	50	5	52	4
Infusion reaction#	2	–	14**	3*

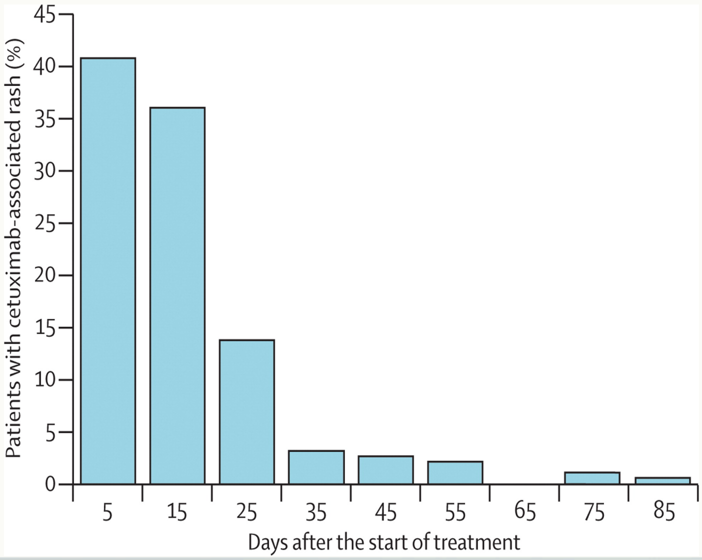
Listed for its relationship to cetuximab
* $p < 0.05$, ** $p < 0.001$, Fisher's exact test

Bonner, NEJM, 2006

Skin rash with EGFR-inhibiteur

Segaert S, Van Cutsem E. Ann Oncol, 2005

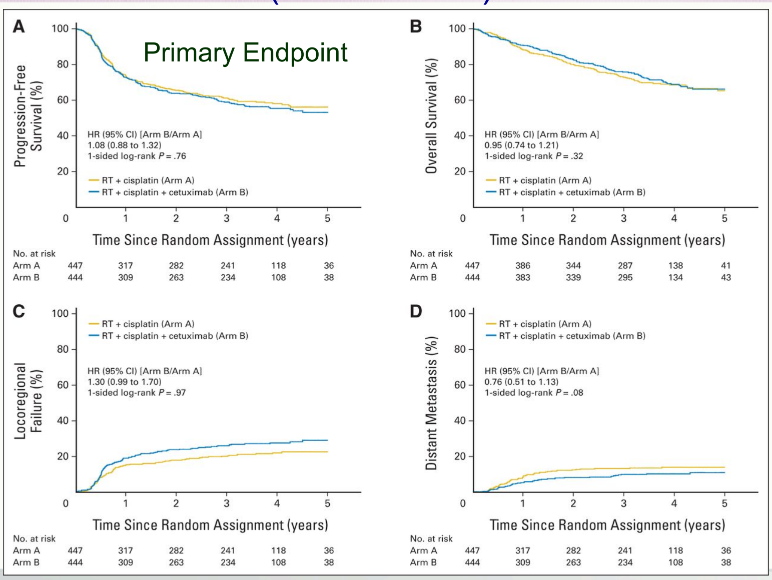
Most Common Adverse Events: skin rash



EHNS-ESTRO H&N course
Florence, June 2016

Bonner, Lancet Oncology, 2010

Concomitant cddp-radiotherapy ± cetuximab (RTOG 0522)

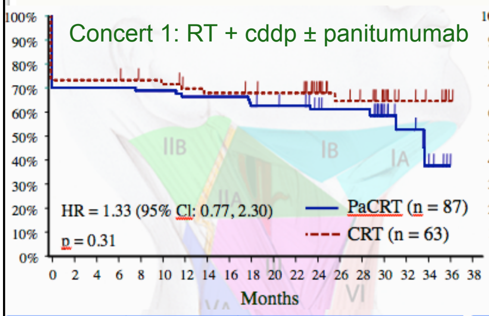


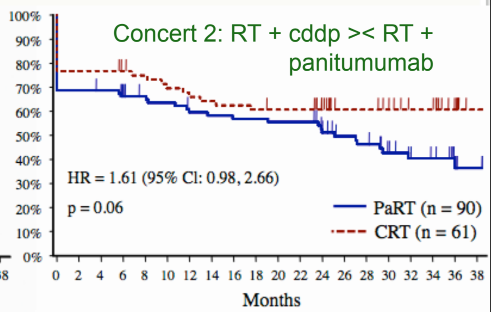
EHNS-ESTRO H&N course
Florence, June 2016

Ang et al., 2014

Radiotherapy ± cddp ± Panitumumab

Local-Regional Control





KM estimate (95% CI)	CRT	PaCRT	Difference
LRC at 24 months	68% (54%, 78%)	61% (50%, 71%)	-7% (-23%, 9%)

KM estimate (95% CI)	CRT	PaRT	Difference
LRC at 24 months	61% (47% , 72%)	51% (40% , 62%)	-9% (-23% , 9%)

- Oral cavity, oropharynx, hypopharynx and larynx
- Stade III and IV SCC
- IMRT and 3D-CRT

Giralt et al., 2013

Radiotherapy ± cddp ± Panitumumab

Acute toxicity

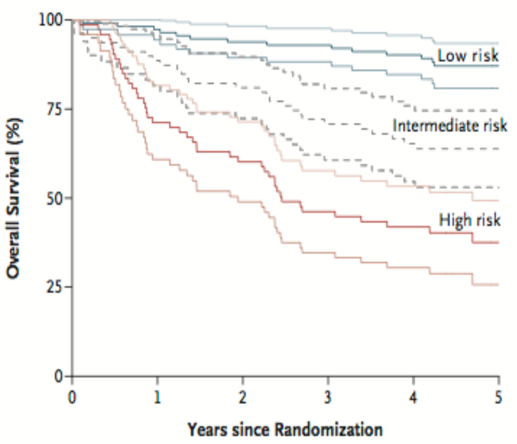
Grade ≥ 3 Adverse Event	CONCERT 1 CRT (N = 63)	CONCERT 1 PaCRT (N = 87)	CONCERT 2 CRT (N = 62)	CONCERT 2 PaRT (N = 89)
Oral toxicity				
Mucosal inflammation	24%	54%	40%	38%
Odynophagia	8%	6%	16%	7%
Dysphagia	25%	36%	27%	35%
Skin toxicity				
Radiation skin injury	13%	28%	11%	24%
Rash	0%	11%	0%	9%
Dermatitis	0%	7%	0%	16%
Other				
Neutropenia	11%	2%	13%	0%
Febrile neutropenia	5%	1%	8%	0%
Dehydration	3%	7%	6%	2%

Giralt et al., 2013

And in HPV⁺ patients?

- Better outcome for HPV+ patients
- Not the proper time yet for treatment de-intensification or change in treatment strategy!
- Different trials for HPV+ and HPV- patients
- Routine p16 staining for oropharyngeal SCC

HPV in H&N cancer



≈88% at 5y

≈65% at 5y

≈38% at 5y

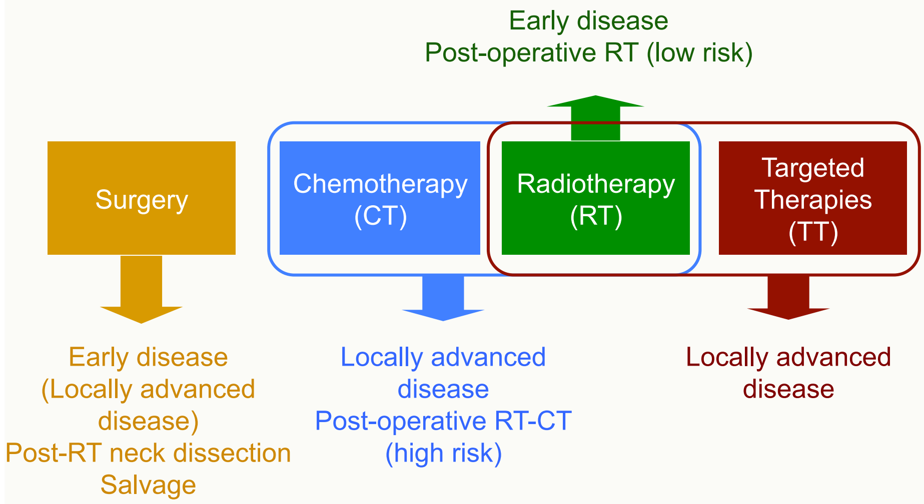
No. at Risk

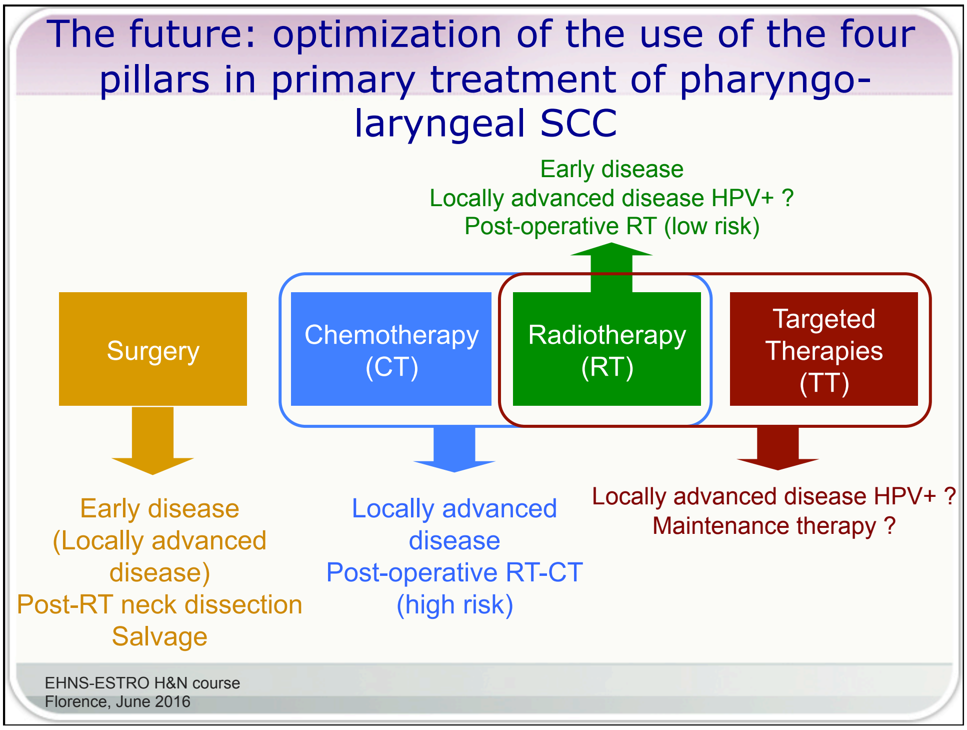
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8

Ang et al, 2010

The past: the two pillars in primary treatment of pharyngo-laryngeal SCC

The present: the four pillars in primary treatment of pharyngo-laryngeal SCC




The future: optimization of the use of the four pillars in primary treatment of pharyngo-laryngeal SCC
Early disease
Locally advanced disease HPV+ ?
Post-operative RT (low risk)
Surgery
Chemotherapy (CT)
Radiotherapy (RT)
Targeted Therapies (TT)
Early disease
(Locally advanced disease)
Post-RT neck dissection
Salvage
Locally advanced disease
Post-operative RT-CT (high risk)
Locally advanced disease HPV+ ?
Maintenance therapy ?
EHNS-ESTRO H&N course
Florence, June 2016

JOINT EHNS-ESMO-ESTRO MULTIDISCIPLINARY TEACHING COURSE ON HEAD AND NECK ONCOLOGY

26-29 June
Florence, Italy

Management of Laryngeal and Hypopharyngeal tumors: **Surgery**

Piero Nicolai, MD
Professor and Chairman

Department of Otorhinolaryngology - Head and Neck Surgery

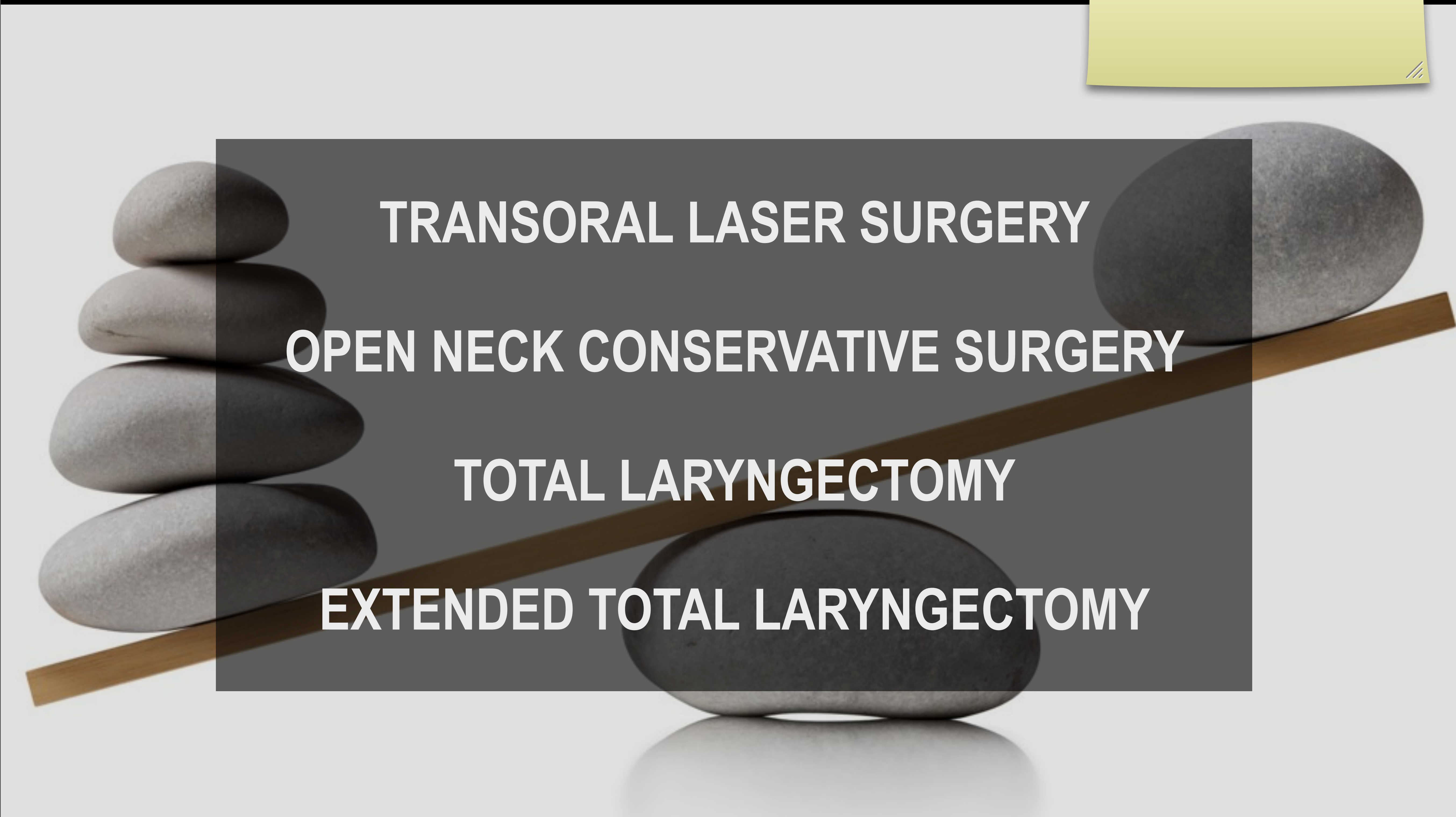
University of Brescia, Italy

LARYNX

SURGICAL OPTIONS

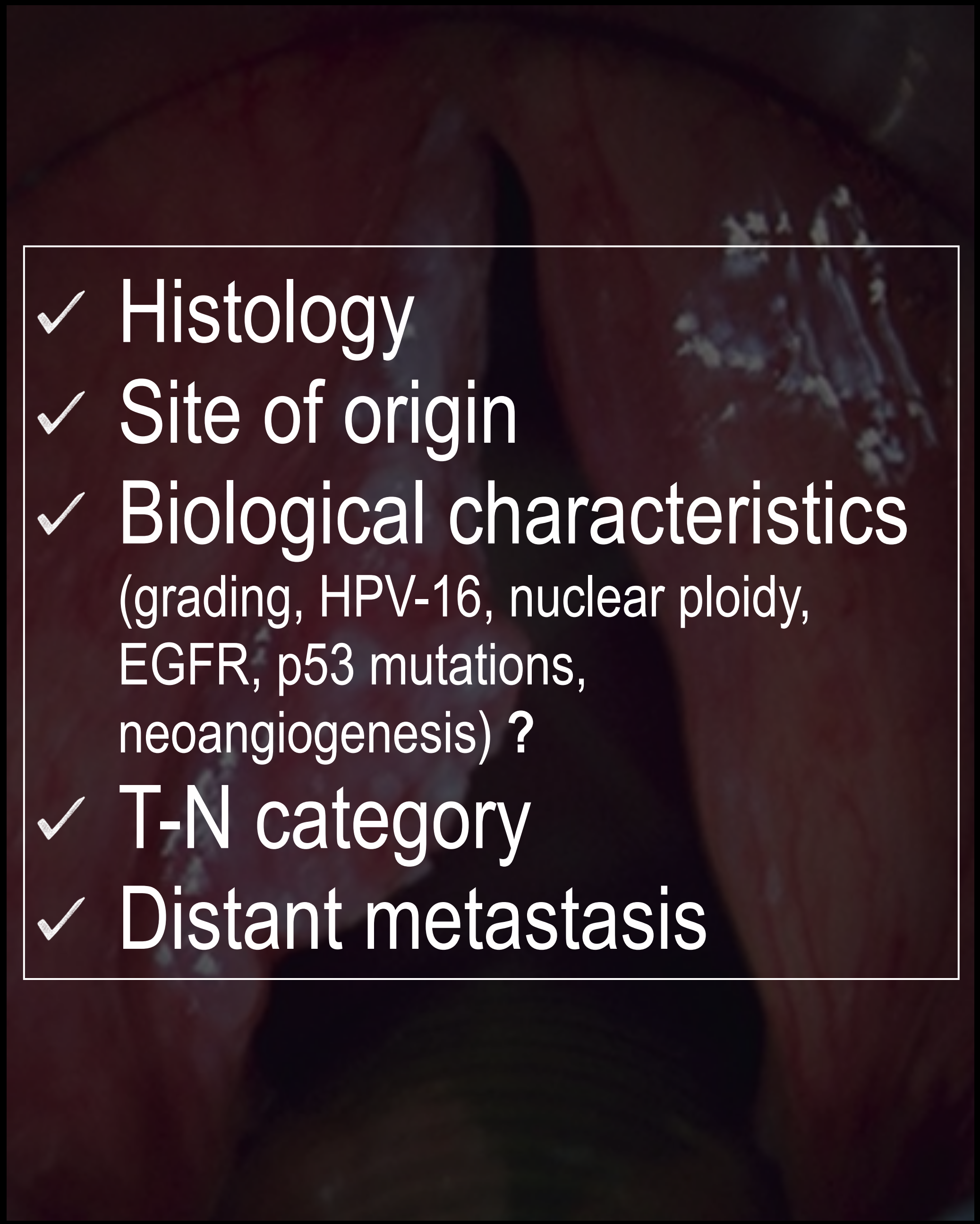
A matter of balance…

Nausica Montalto 19 giu 2016, 11:46
non surgical options



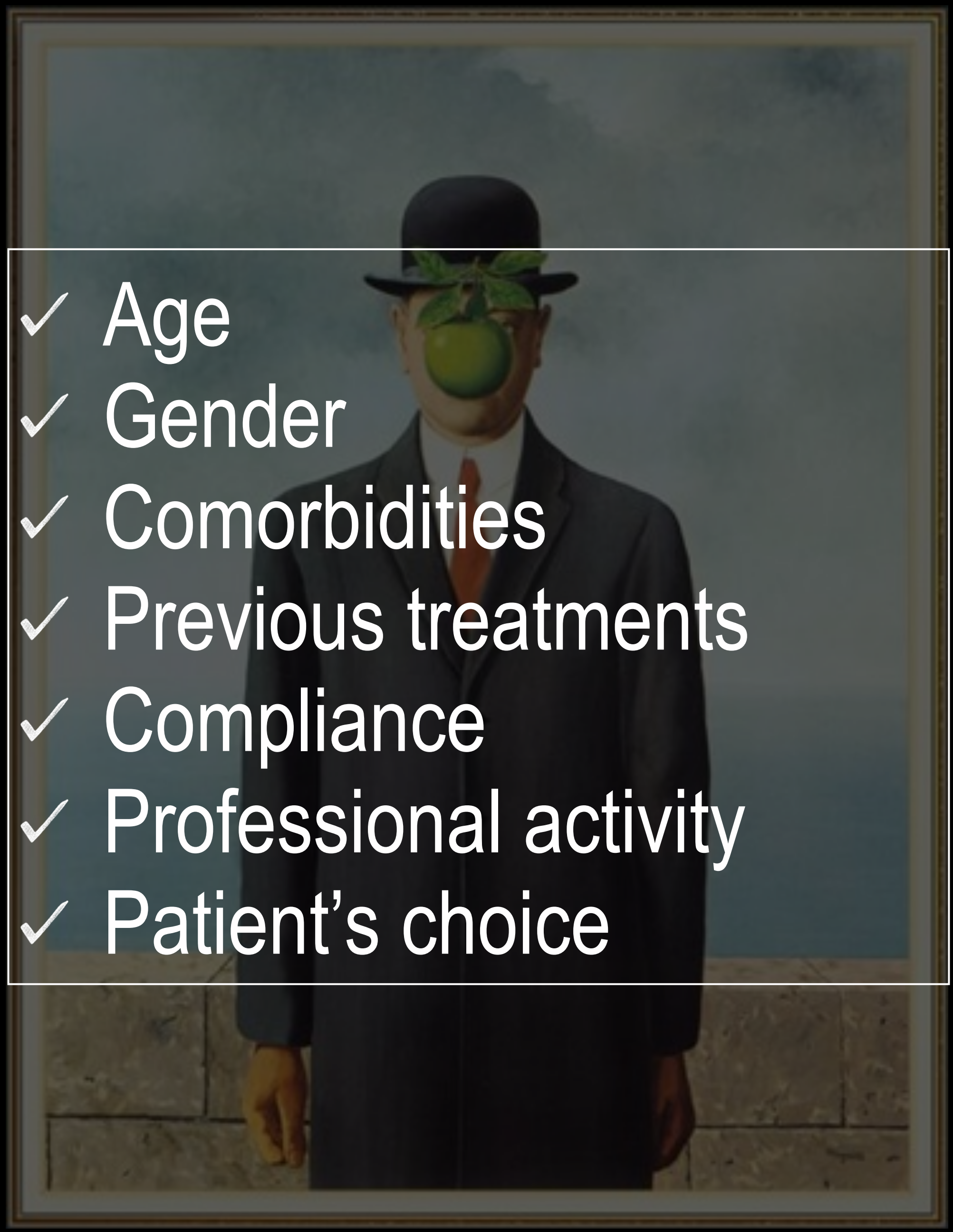
FACTORS INFLUENCING TREATMENT CHOICE

Tumor related



- ✓ Histology
- ✓ Site of origin
- ✓ Biological characteristics
  (grading, HPV-16, nuclear ploidy, EGFR, p53 mutations, neoangiogenesis) **?**
- ✓ T-N category
- ✓ Distant metastasis

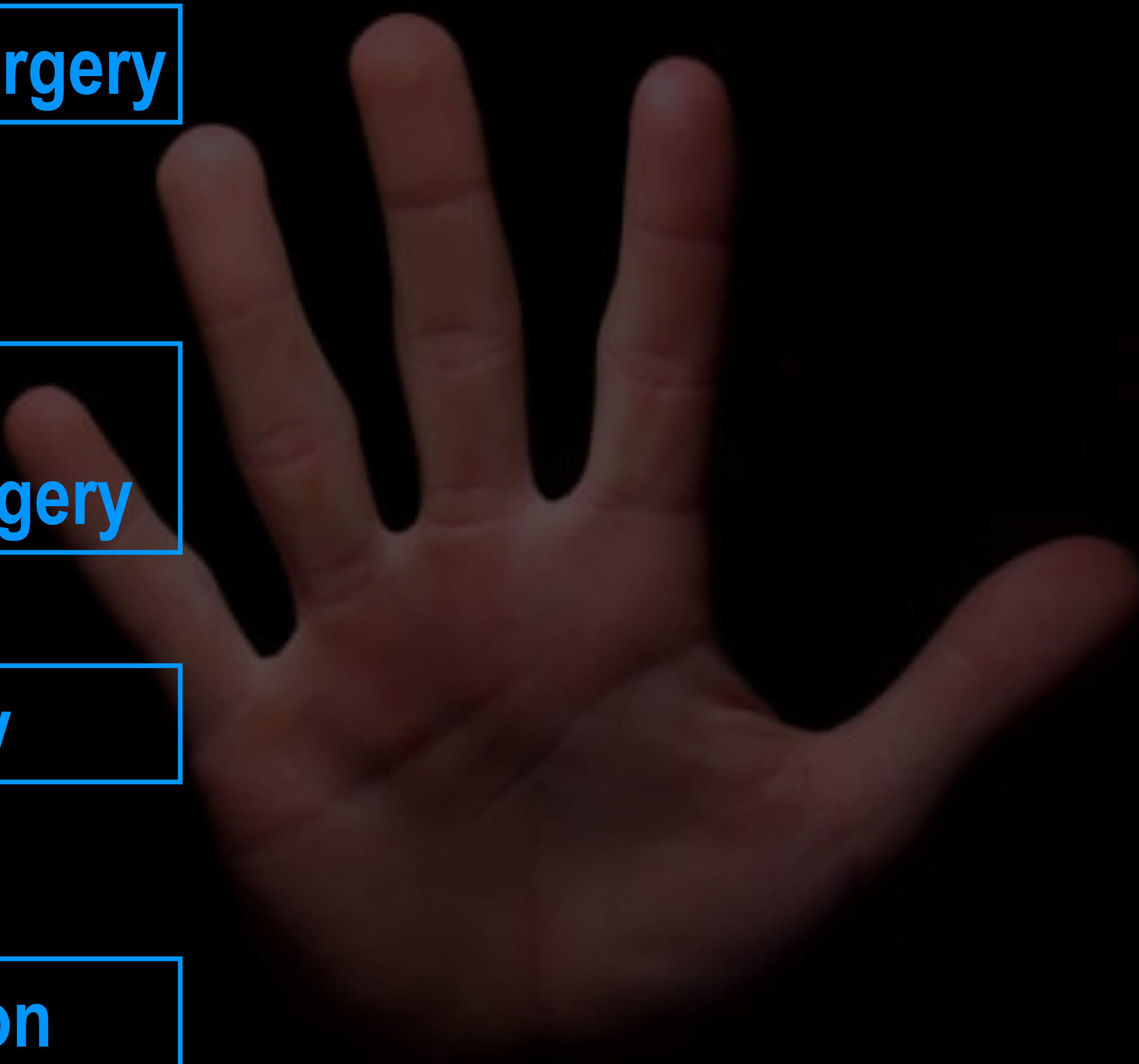
Patient related



- ✓ Age
- ✓ Gender
- ✓ Comorbidities
- ✓ Previous treatments
- ✓ Compliance
- ✓ Professional activity
- ✓ Patient's choice

FACTORS RELATED TO THE PATIENT

CONTRAINDICATIONS



Transoral laser surgery

Open neck conservative surgery

Radiotherapy

Chemoradiation

FACTORS RELATED TO THE PATIENT

CONTRAINDICATIONS

Treatment	Contraindications
Transoral laser surgery	✓ inadequate exposure of the larynx ✓ involvement of posterior commissure ✓ thyroid/cricoid cartilage involvement ✓ extensive subglottic involvement ✓ massive extralaryngeal extension ✓ poor compliance for a strict follow-up
Open neck conservative surgery	✓ poor respiratory performance status ✓ poor neurologic performance status
Radiotherapy	✓ previous RT (?) ✓ young age (?)
Chemoradiation	✓ previous RT (?) ✓ young age (?) ✓ cardiological/hepatic/renal diseases

TRANSORAL LASER MICROSURGERY

TRANSORAL CO2 LASER MICROSURGERY

Diagnosis and treatment
Tis/T1

Favourable oncologic outcomes

Minimal morbidity
no tracheotomy nor nasogastric feeding tube

Short hospitalization time

Preservation
of the laryngeal framework, extrinsic musculature, superior laryngeal nerves, tongue base, pharyngeal constrictors, hyoid bone

Custom-tailored resection

Does not preclude subsequent surgical/non-surgical, adjuvant or salvage treatments

Good vocal outcome for Tis/T1 not involving AC

TLM FOR GLOTTIC TUMORS

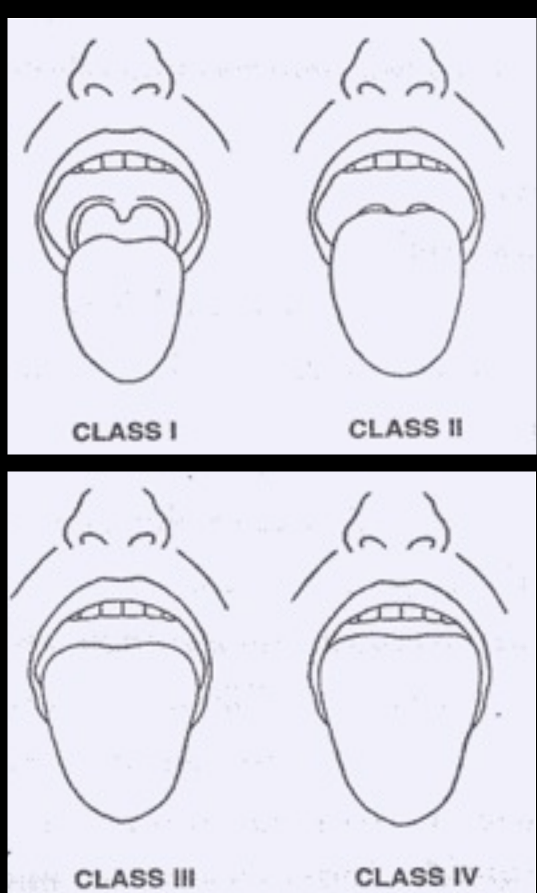
The Laryngoscore

Predictors of difficult laryngeal exposure

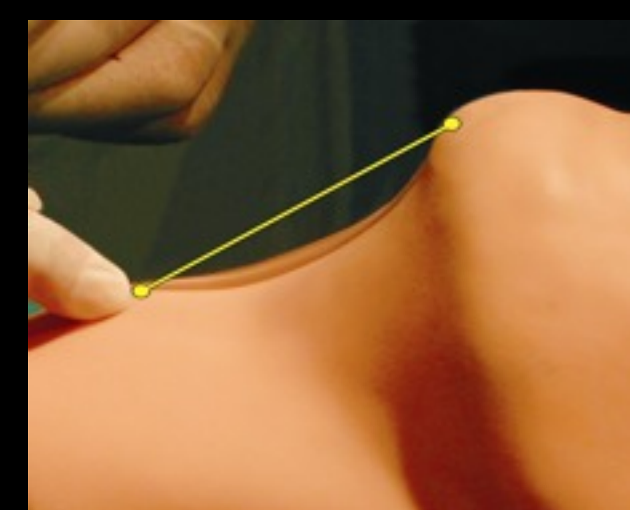
The Laryngoscope
© 2014 The American Laryngological, Rhinological and Otological Society, Inc.

Preoperative Clinical Predictors of Difficult Laryngeal Exposure for Microlaryngoscopy: The Laryngoscore

Cesare Piazza, MD; Stefano Mangili, MD; Francesca Del Bon, MD; Alberto Paderno, MD; Paola Grazioli, MD; Diego Barbieri, MD; Pietro Perotti, MD; Sabrina Garofolo, MD; Piero Nicolai, MD; Giorgio Peretti, MD



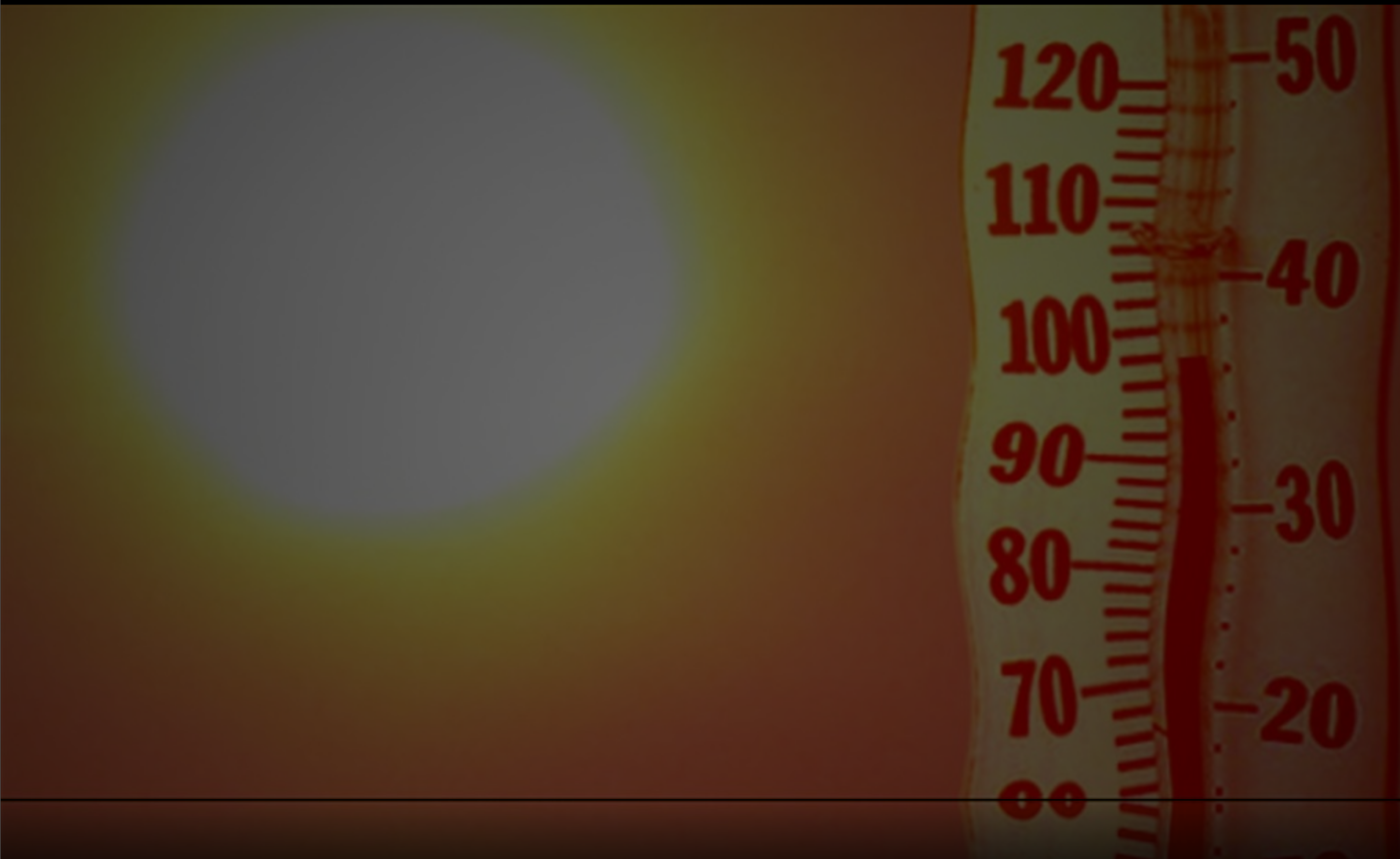
Interincisors gap (>/= 4 cm, <4 cm)
Thyromental distance (>6.5 cm, 6-6.5 cm, < 6cm)
Teeth
Trismus
Tongue
Previous treatments
Ability to prognath
Neck extension (>90°, 80-90°, <80°)
Mallampati's class
BMI (</=25, > 25)



Piazza et al, Laryngoscope (2014)

TRANSORAL CO2 LASER MICROSURGERY

HOT TOPICS



TRANSORAL CO2 LASER MICROSURGERY

HOT TOPICS

Margin status

Anterior/posterior commissure

AC involvement in the cranio-caudal plane (T2-3)

Extralaryngeal extension

Arytenoid fixation

Subglottic involvement

Functional outcomes in T2-T3 and QoL

Massive infiltration of PES and PGS

Thyroid cartilage/thyrohyoid membrane infiltration

TRANSORAL CO2 LASER MICROSURGERY

HOT TOPICS

Margin status

Anterior/posterior commissure

AC involvement in the cranio-caudal plane (T2-3)

Extrala

Subg

n

CURRENT OPINION

Reasonable limits for transoral laser microsurgery in laryngeal cancer

Giorgio Peretti[a], Cesare Piazza[b], Francesco Mora[a], Sabrina Garofolo[a], and Luca Guastini[a]

Peretti et al, Curr Opin Otorhinolaryngol Head Neck Surg (2016)

T2-T3 and QoL

Massive infiltration of PES and PGS

Thyroid cartilage/thyrohyoid membrane infiltration

GLOTTIS

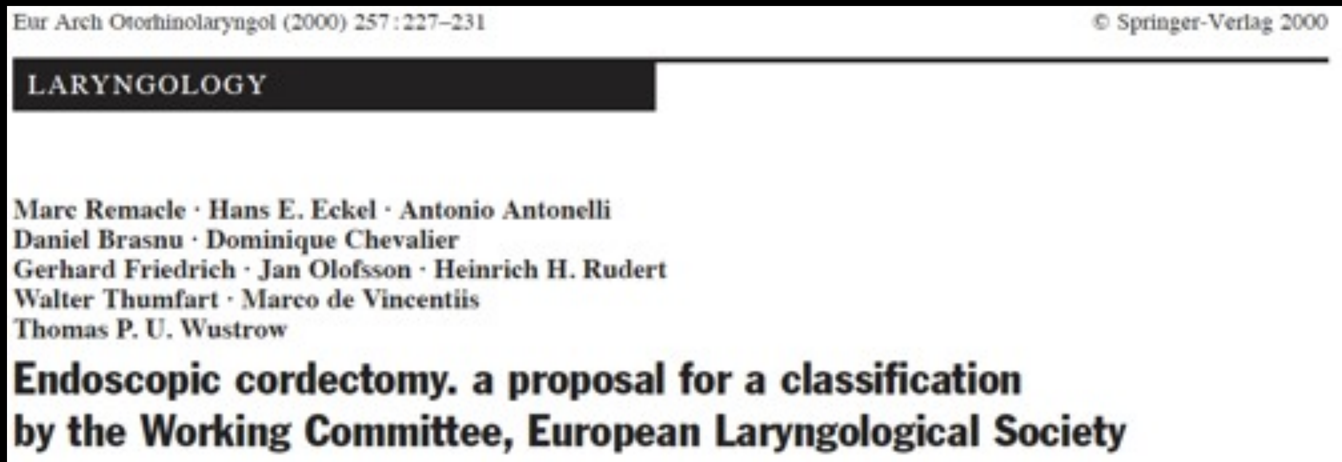
TLM FOR GLOTTIC TUMORS

INDICATIONS

- ✓ Tis-T1-T2 and selected T3
  (with limited involvement of the PGS)
- ✓ Salvage surgery after RT for rT1-rT2
- ✓ Poorly radiosensitive histologies

- ✓ Inadequate exposure
- ✓ Posterior commissure involvement
- ✓ Extensive subglottic extension
- ✓ Crico-arytenoid joint involvement
- ✓ Laryngeal framework infiltration

CONTRAINDICATIONS

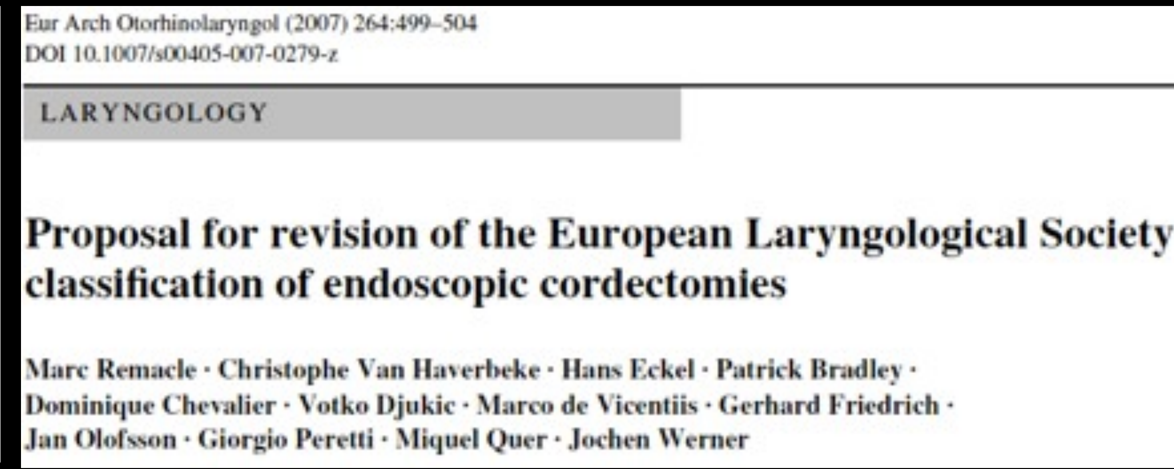


Eur Arch Otorhinolaryngol (2000) 257 : 227–231

LARYNGOLOGY

Marc Remacle · Hans E. Eckel · Antonio Antonelli
Daniel Brasnu · Dominique Chevalier
Gerhard Friedrich · Jan Olofsson · Heinrich H. Rudert
Walter Thumfart · Marco de Vincentiis
Thomas P. U. Wustrow

Endoscopic cordectomy. a proposal for a classification by the Working Committee, European Laryngological Society

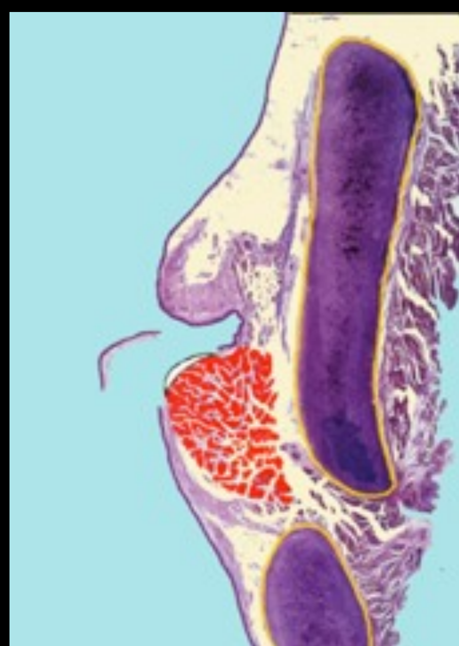


Eur Arch Otorhinolaryngol (2007) 264:499–504
DOI 10.1007/s00405-007-0279-z

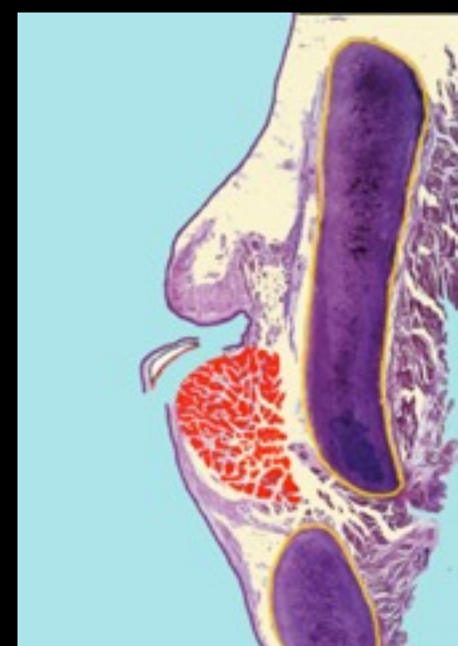
LARYNGOLOGY

Proposal for revision of the European Laryngological Society classification of endoscopic cordectomies

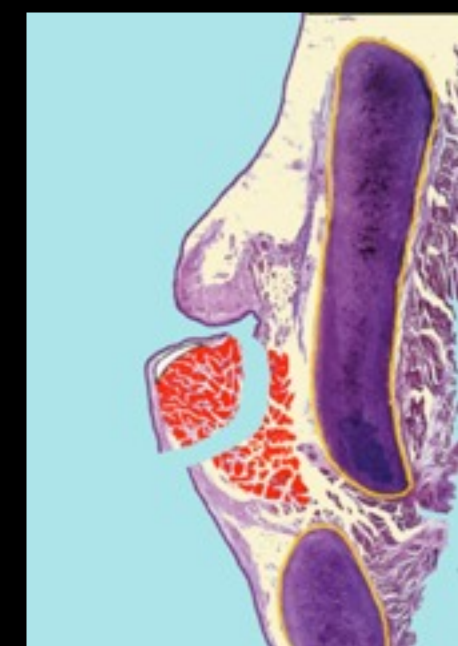
Marc Remacle · Christophe Van Haverbeke · Hans Eckel · Patrick Bradley · Dominique Chevalier · Votko Djukic · Marco de Vicentiis · Gerhard Friedrich · Jan Olofsson · Giorgio Peretti · Miquel Quer · Jochen Werner



Type I



Type II



Type III

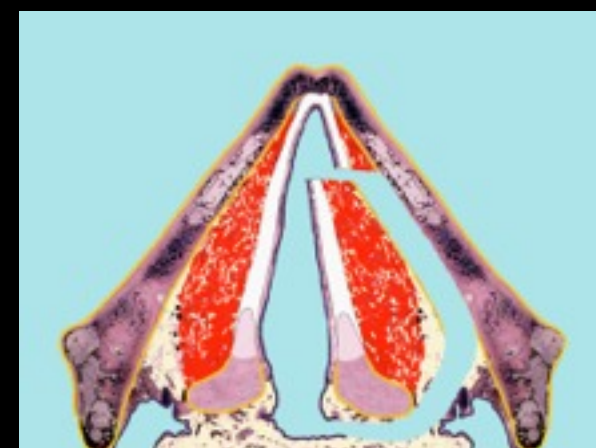
Remacle et al. 2000, 2007

TRANSORAL CO_2 LASER MICROSURGERY

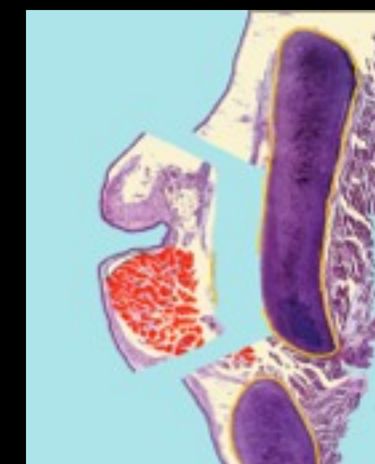
ENDOSCOPIC CORDECTOMIES

Type IV

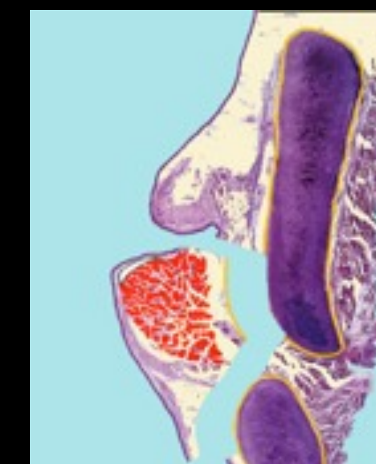
Type Va



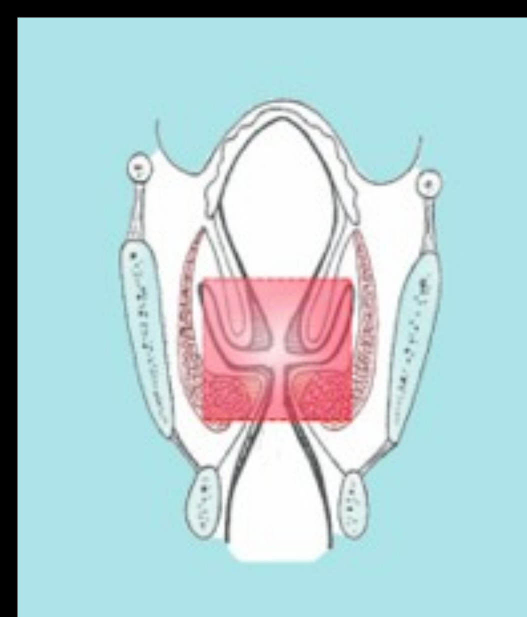
Type Vb



Type Vc



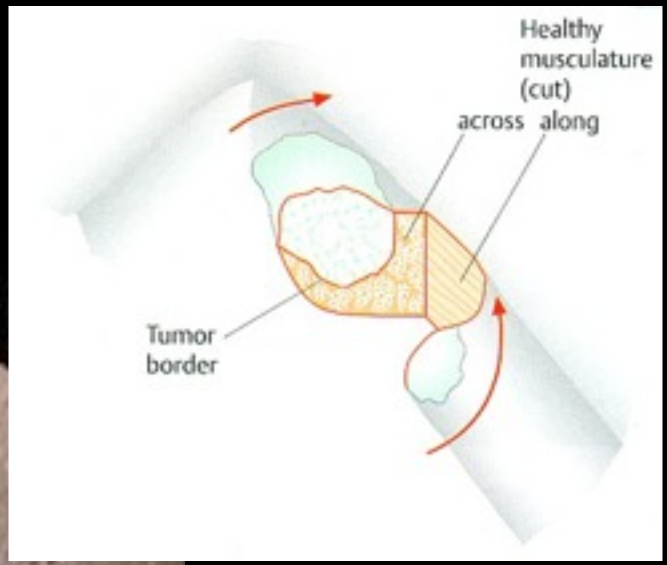
Type Vd

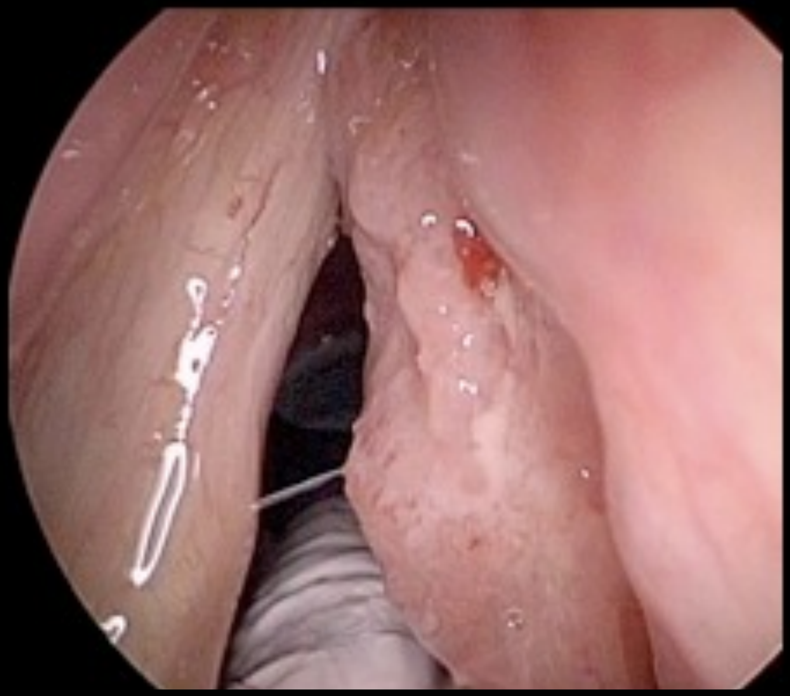


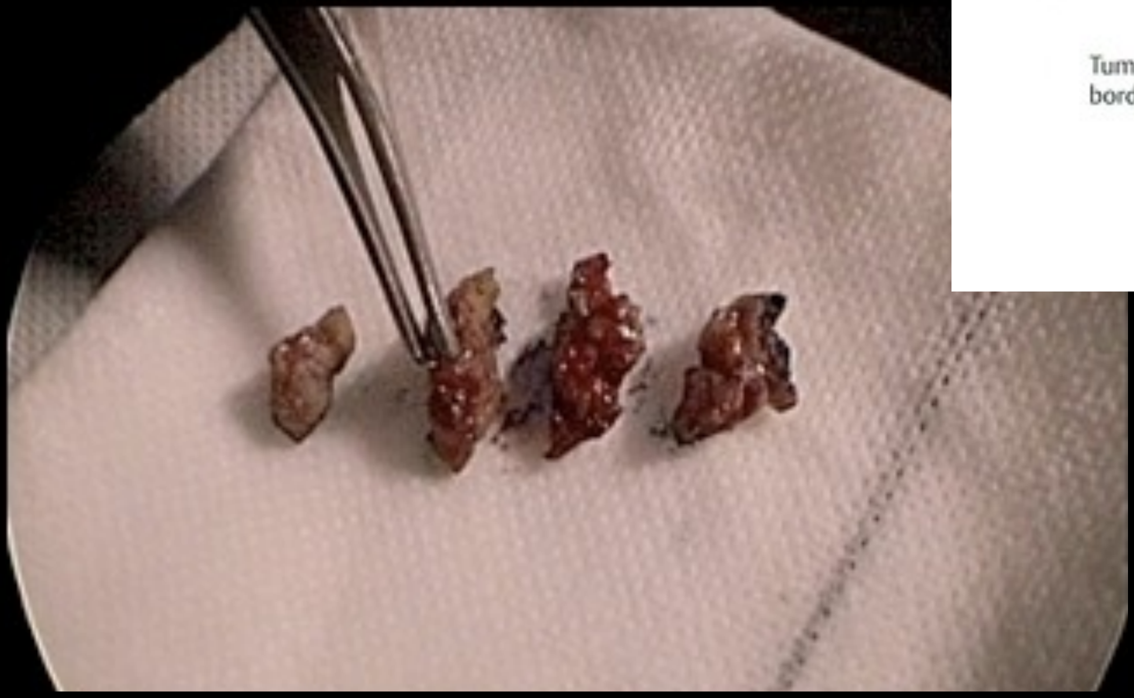
Type VI

Remacle et al. 2000, 2007

“MULTIBLOC” TECHNIQUE







ONCOLOGIC RESULTS OF GLOTTIC CANCER

5-year local control

T1

95%

T2

I 85.3%

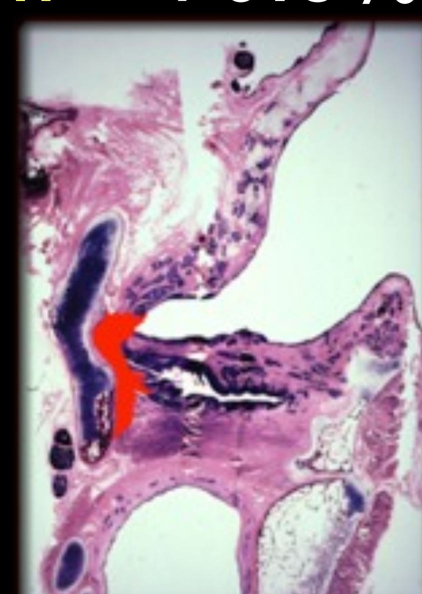
II 100%

IV 88.5%

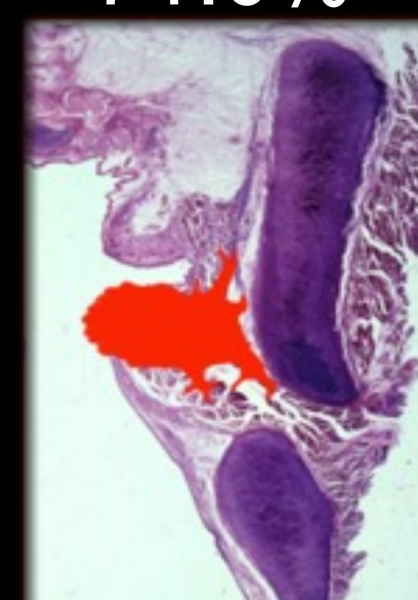
CUT OFF:
85%

T2

III 70.8%



71.6%

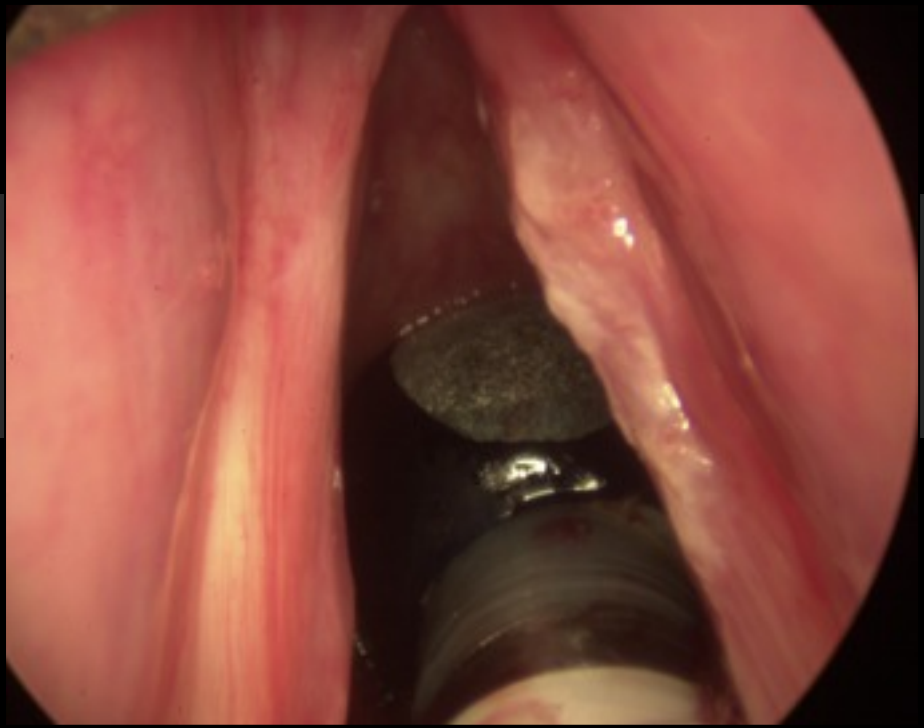


cT2/pT3

Peretti et al. Head Neck, 2010

SURGICAL MARGINS AFTER TLM

Voice preservation



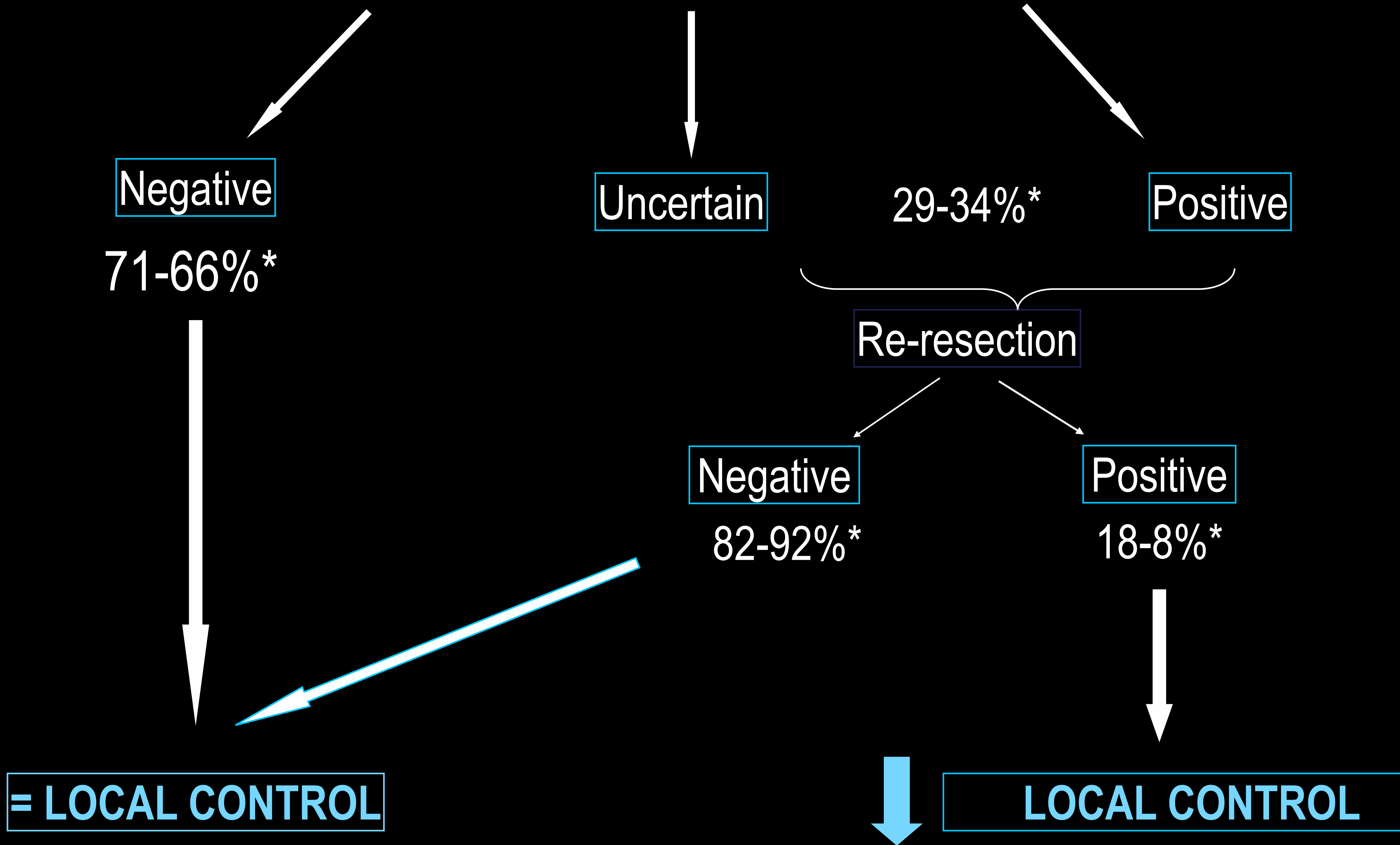
Local disease control

Glottic resection margins may be limited as 1 to 2 mm

Ossoff et al. Ann Otol Rhinol Laryngol 1985
Nakayama et al. ORL J Otorhinolaryngol Relat Spec 2009

TRANSORAL CO2 LASER MICROSURGERY

SURGICAL MARGINS AFTER TLM

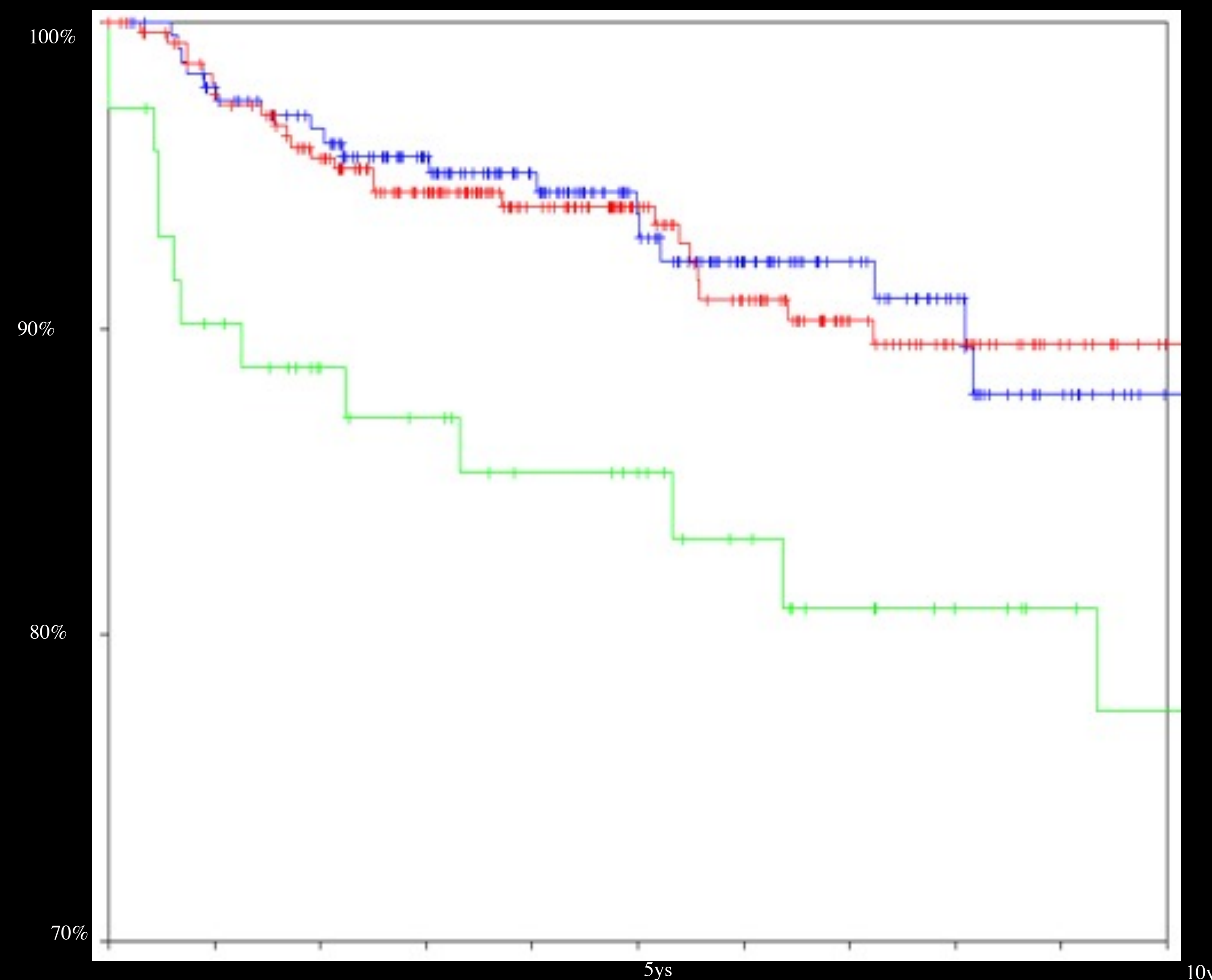


Jackel et al. Laryngoscope 2007
*Ansarin et al. Arch Otolaryngol Head Neck Surg 2009

TRANSORAL CO2 LASER MICROSURGERY

SURGICAL MARGINS AFTER TLM

ESTIMATED
5-YEAR **LOCAL CONTROL**



NEGATIVE 94.2%

POSITIVE SUP 93.2%

POSITIVE DEEP 84.9%

P=NS

P=0.003

Peretti et al. Head Neck 2010

TRANSORAL CO2 LASER MICROSURGERY

FUNCTIONAL RESULTS

Eur Arch Otorhinolaryngol
DOI 10.1007/s00405-013-2461-9

LARYNGOLOGY

Function preservation using transoral laser surgery for T2–T3 glottic cancer: oncologic, vocal, and swallowing outcomes

Giorgio Peretti · Cesare Piazza · Francesca Del Bon ·
Renzo Mora · Paola Grazioli · Diego Barbieri ·
Stefano Mangili · Piero Nicolai

VHI and GRBAS showed mild to moderate dysphonia

Mean values of Jitter, Shimmer, and noise-to-harmonic ratio by MDVP resulted 7.87%, 24.8%, and 0.37, respectively

Mean value of MDADI was 95.75

Only 2% of patients at VEES and 4% at VFS showed tracheal aspiration

In elderly patients (over 75 y-o) functional results are comparable with younger patients

TRANSORAL CO2 LASER MICROSURGERY

ONCOLOGIC RESULTS FOR GLOTTIC CANCER

Author	Site	N° of pts.	Local control (5 yrs)
Steiner, 2005	Glottic	212 (T2a-b)	84 (T2a) 74 (T2b)
Motta, 2005	Glottic	236 T2	61
Mortuaire, 2006	Glottic	104 T1a-b	84
Puxeddu, 2006	Glottic	96 T1a-b	98.3
Peretti, 2010	Glottic	404 (312 T1a; 92 T1b)	99
Peretti, 2010	Glottic	109 T2	98
Vilaseca, 2010	Glottic	51 (T3)	**47**
Lee, 2013	Glottic	118 (T1-T2)	88
Canis, 2013	Glottic	391 (T2-T3)	76

TRANSORAL CO2 LASER MICROSURGERY

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SUPRAGLOTTIS

TLM FOR SUPRAGLOTTIC TUMORS

INDICATIONS

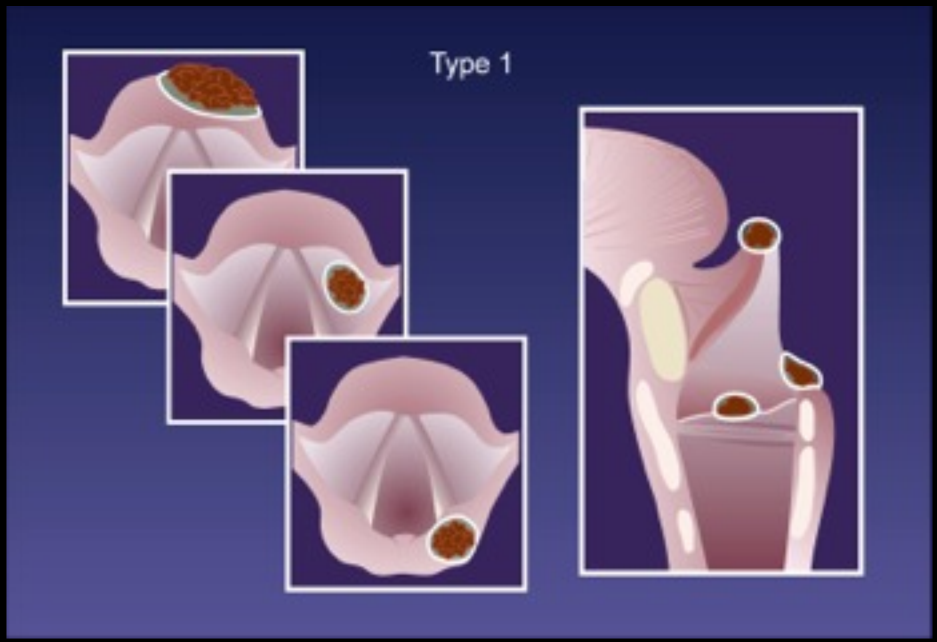
- T1-T2 and selected T3
  (with limited involvement of the PES)
- Salvage surgery after RT for rT1-rT2
- Poorly radiosensitive histologies

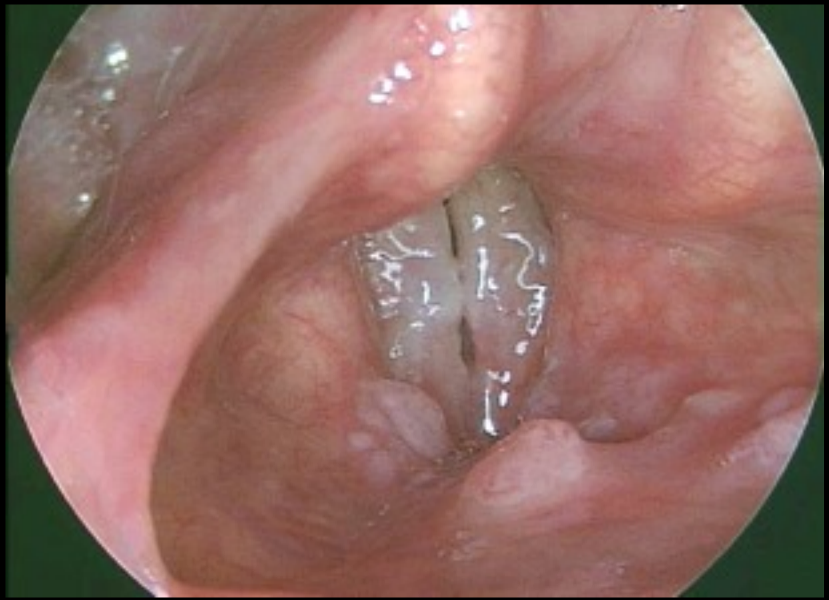
- Inadequate exposure
- Crico-arytenoid joint and/or PGS involvement
- Massive PES involvement
- Laryngeal framework infiltration
- “Extension to the glottis”

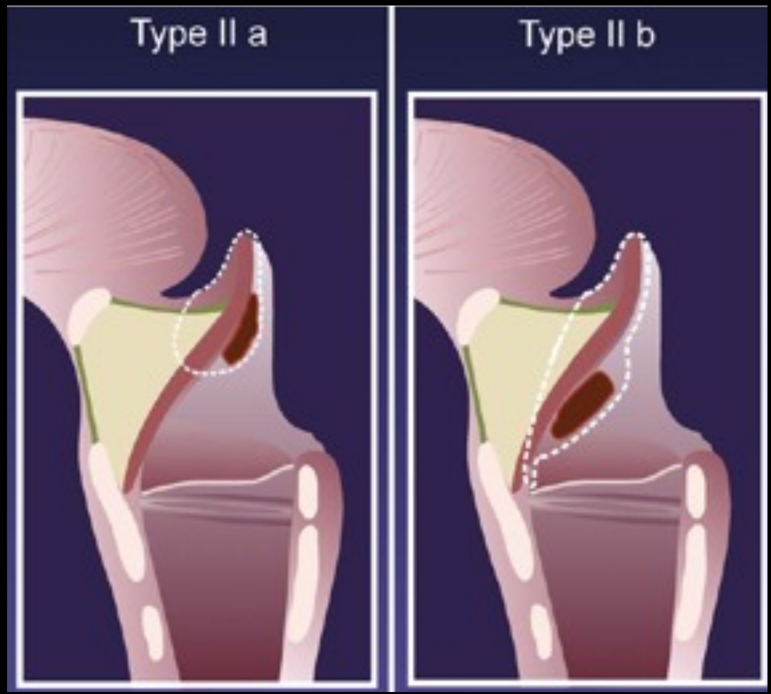
CONTRAINDICATIONS

TLM FOR SUPRAGLOTTIC TUMORS

ENDOSCOPIC SUPRAGLOTTIC LARYNGECTOMIES



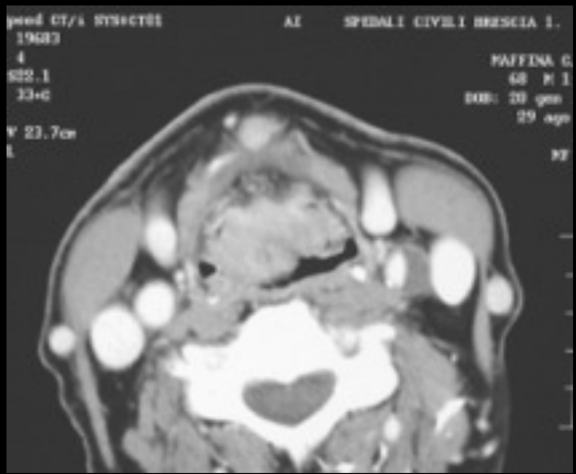


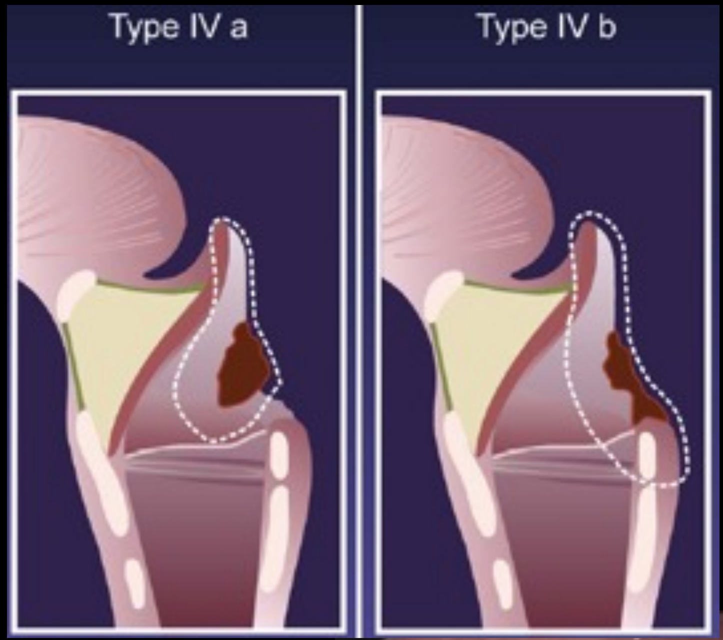


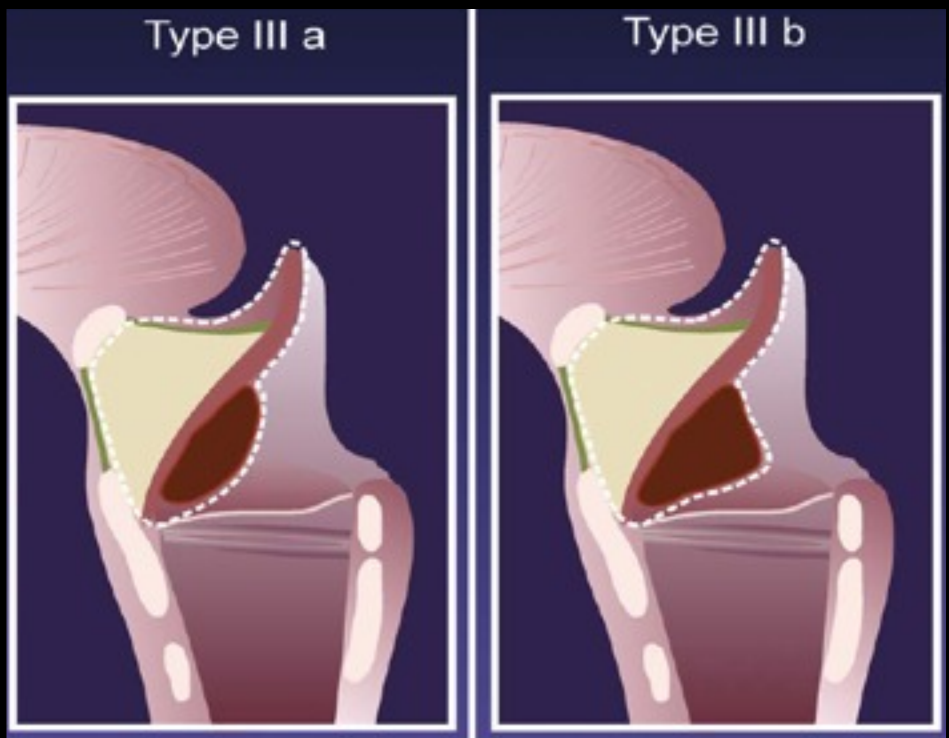
Remacle et al. 2009

TLM FOR SUPRAGLOTTIC TUMORS

ENDOSCOPIC SUPRAGLOTTIC LARYNGECTOMIES







Remacle et al. 2009

TLM FOR SUPRAGLOTTIC TUMORS

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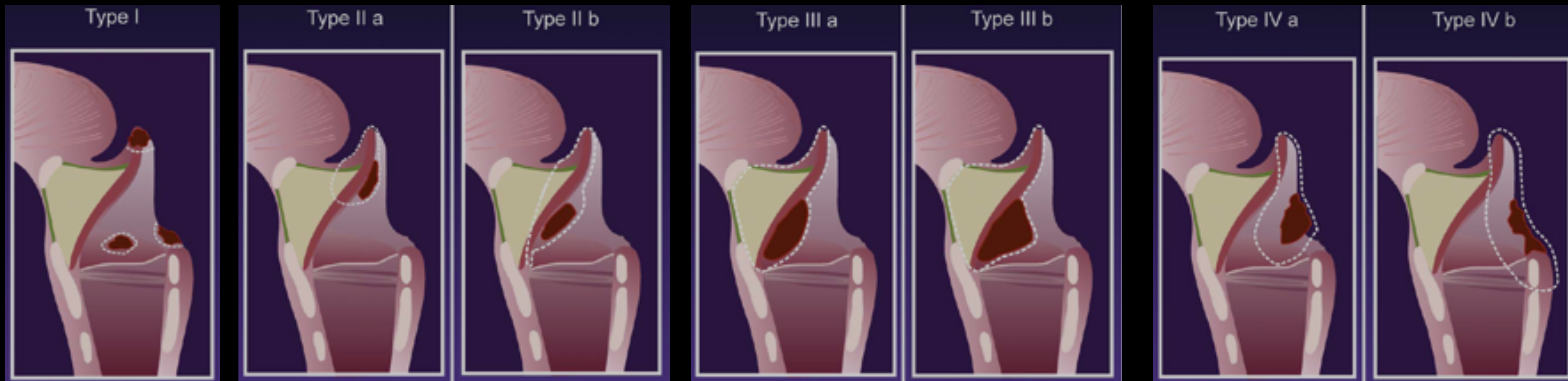
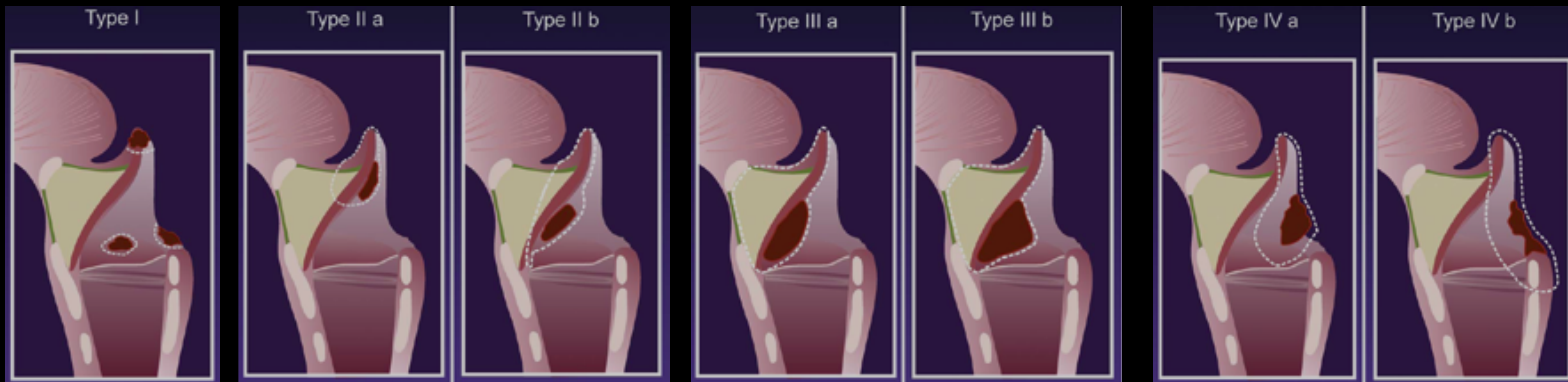


Donzelli's scale	type I-II	type III-IV
1 normal	86%	64,00%
2 penetration	14,00%	29,00%
3 aspiration	0,00%	**7,00%**

Piazza et al, The Laryngoscope (2015)

TLM FOR SUPRAGLOTTIC TUMORS

ENDOSCOPIC SUPRAGLOTTIC LARYNGECTOMIES



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ENDOSCOPIC SUPRAGLOTTIC LARYNGECTOMIES

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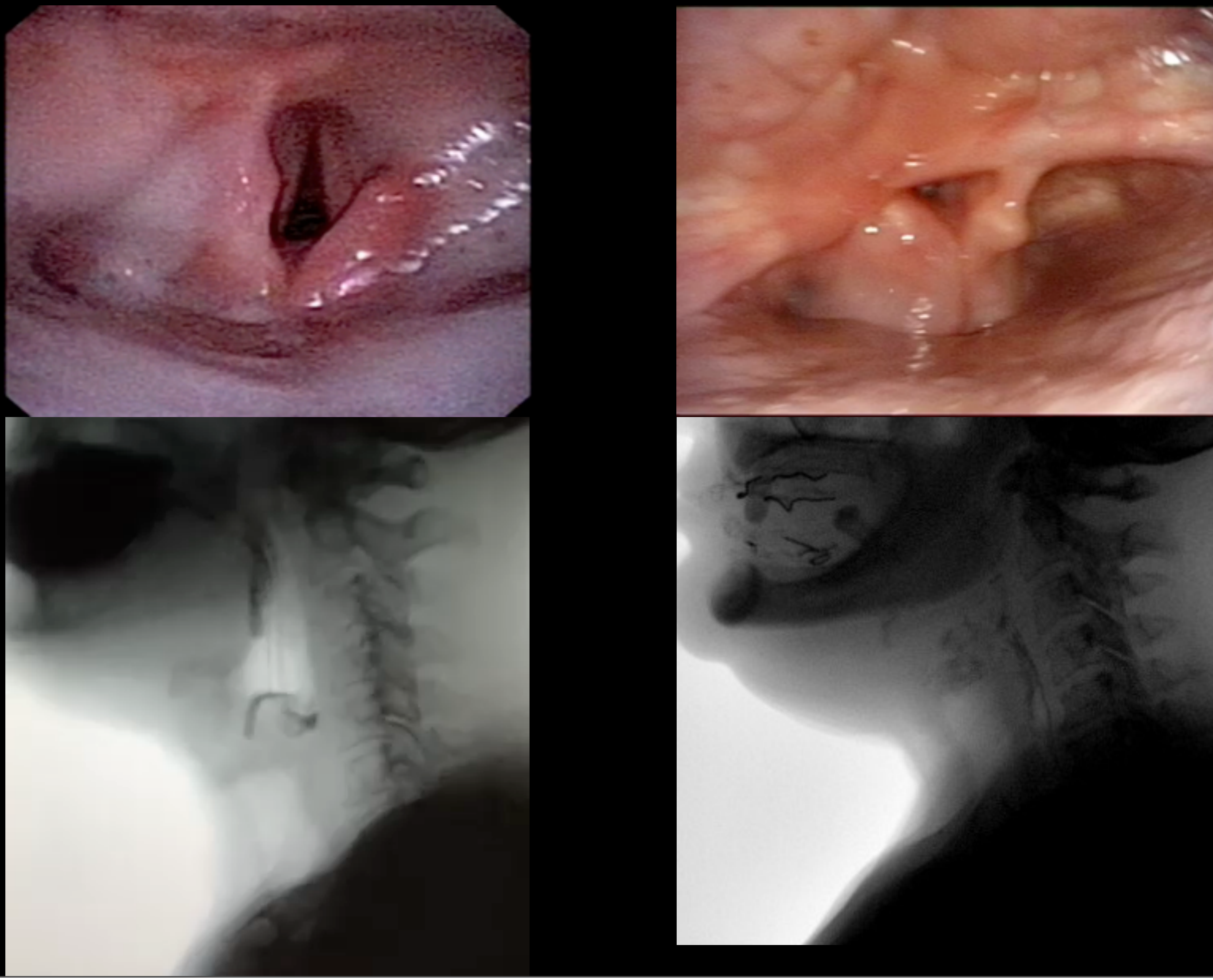

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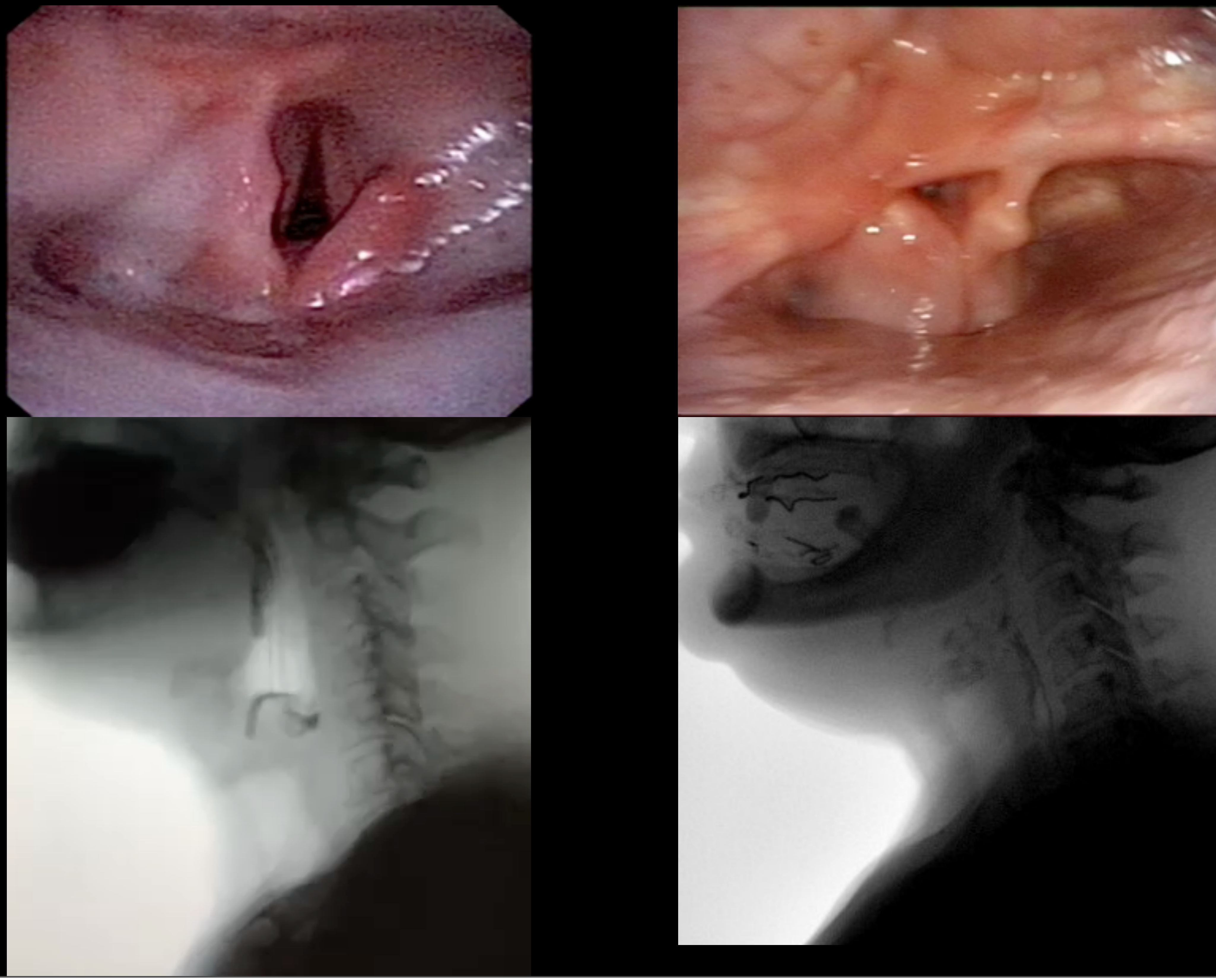

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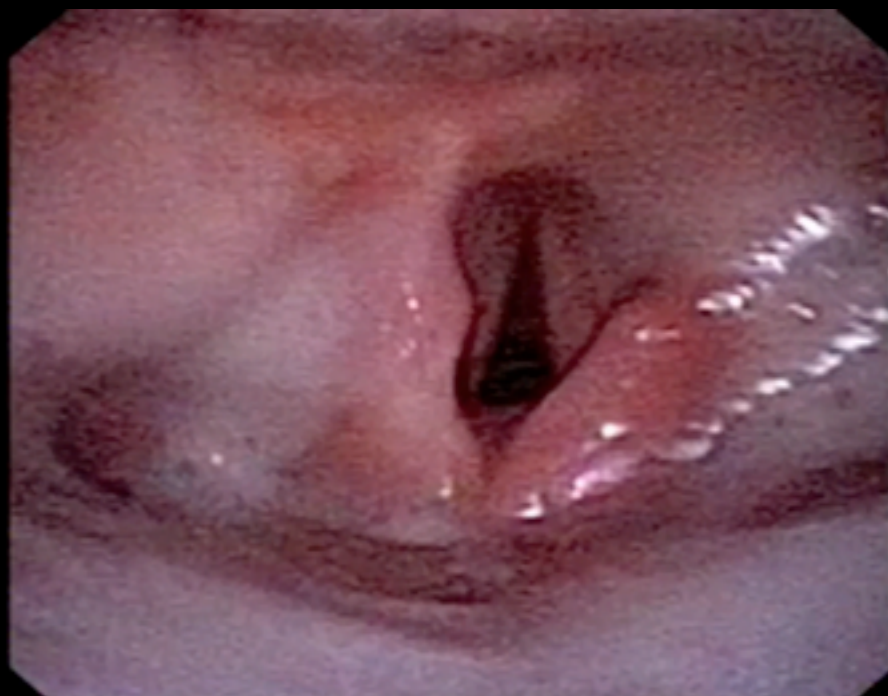

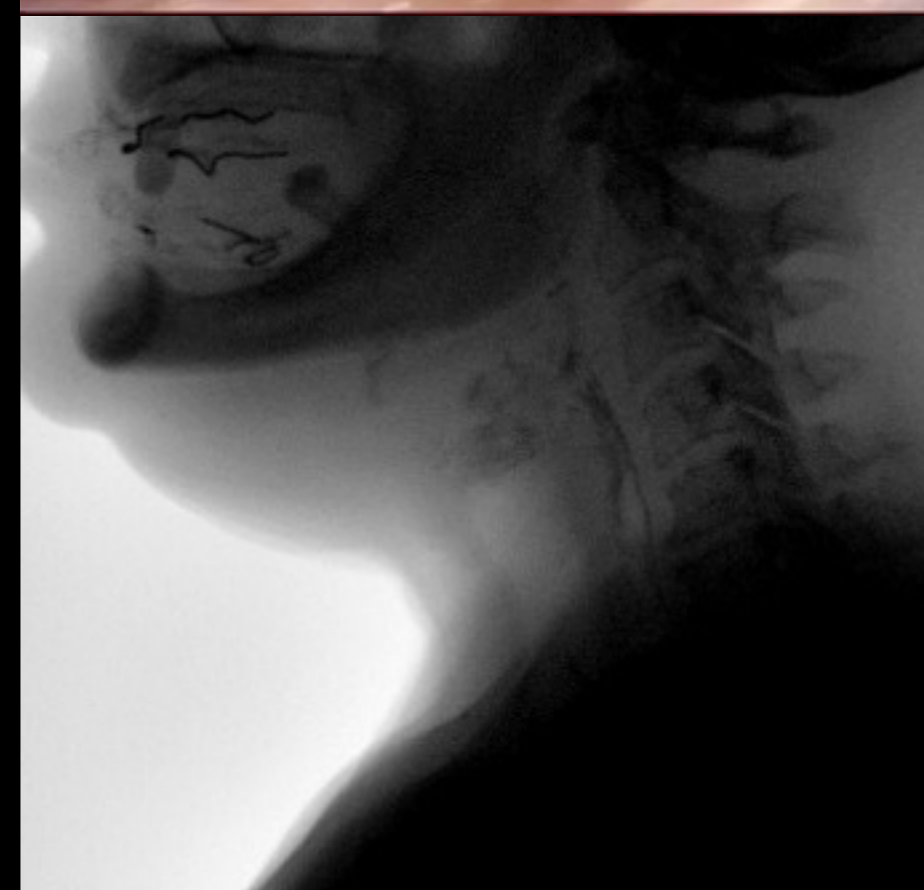

TRANSORAL CO2 LASER MICROSURGERY

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Ambrosch,1998	Supraglottic	12 (T1) 36 (T2)	100 89
Rudert, 2000	Supraglottic	56 (T1-T4)	77
Davis, 2004	Supraglottic	46 (T2)	97
Cabanillas, 2008	Supraglottic	15 (T3)	70
Peretti, 2010	Supraglottic	80 (Tis-T3)	97
Vilaseca, 2010	Supraglottic	96 (T3)	70
Csanàdy, 2011	Supraglottic	55 (T1-T2)	72
Gonzales-Marquez, 2012	Supraglottic	49 (T1-T3)	86
Canis, 2013	Supraglottic	277 (T1-T4)	86

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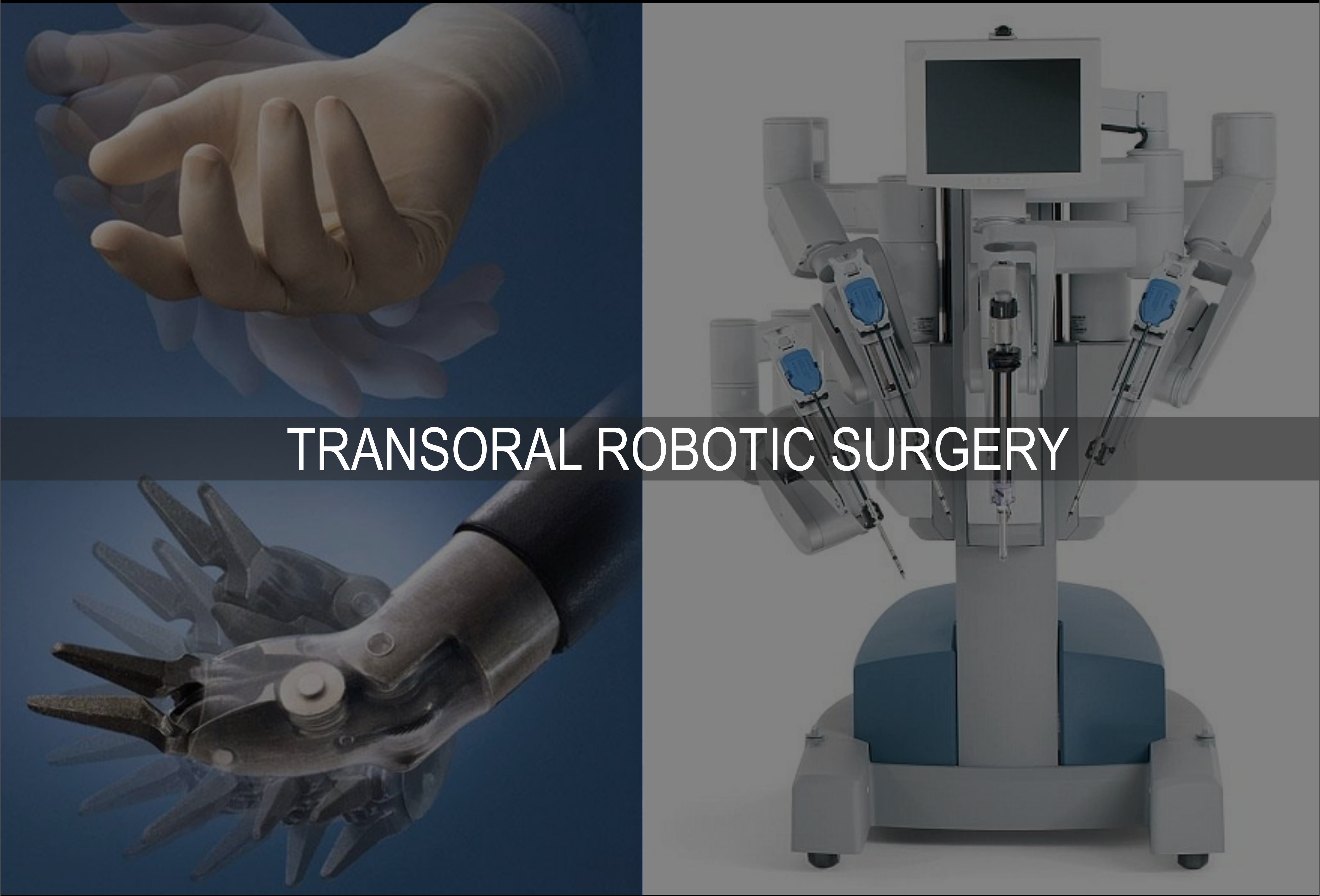
TRANSORAL ROBOTIC SURGERY



TLM vs TORS for supraglottic laryngectomy

10 patients each technique

20% TORS candidates have a difficult laryngeal exposure with consequent switch to TLM

If there is a good exposure en bloc resection is easier with TORS

Post-op dysphagia and pain were more frequent in TORS

More positive margins in TORS

More thermal damage TORS than with CO2 laser?

Ansarin et al, Int J Med Robotics Comput Assist Surg 2013

OPEN NECK vs TORS for supraglottic laryngectomy

34 pts with Supraglottic Carcinoma (T1-T3)

Neck Dissection and PORT/CRT
No difference of STAGE

Functional evaluation
MDADI: **TORS better** than ONPL
Acoustic waveform analysis: no differences

Average Operation time
ONPL 401 min ***vs*** **TORS 265 min**

2 yrs OS: ONPL 94% ***vs*** TORS 92%
2 yrs DFS: ONPL 92 % ***vs*** TORS 98%

Significant differences for TORS: swallowing function, time to decannulation, and hospitalization

Park et al, Clinical Otolaryngology, 2013

OPEN NECK vs TORS for supraglottic laryngectomy

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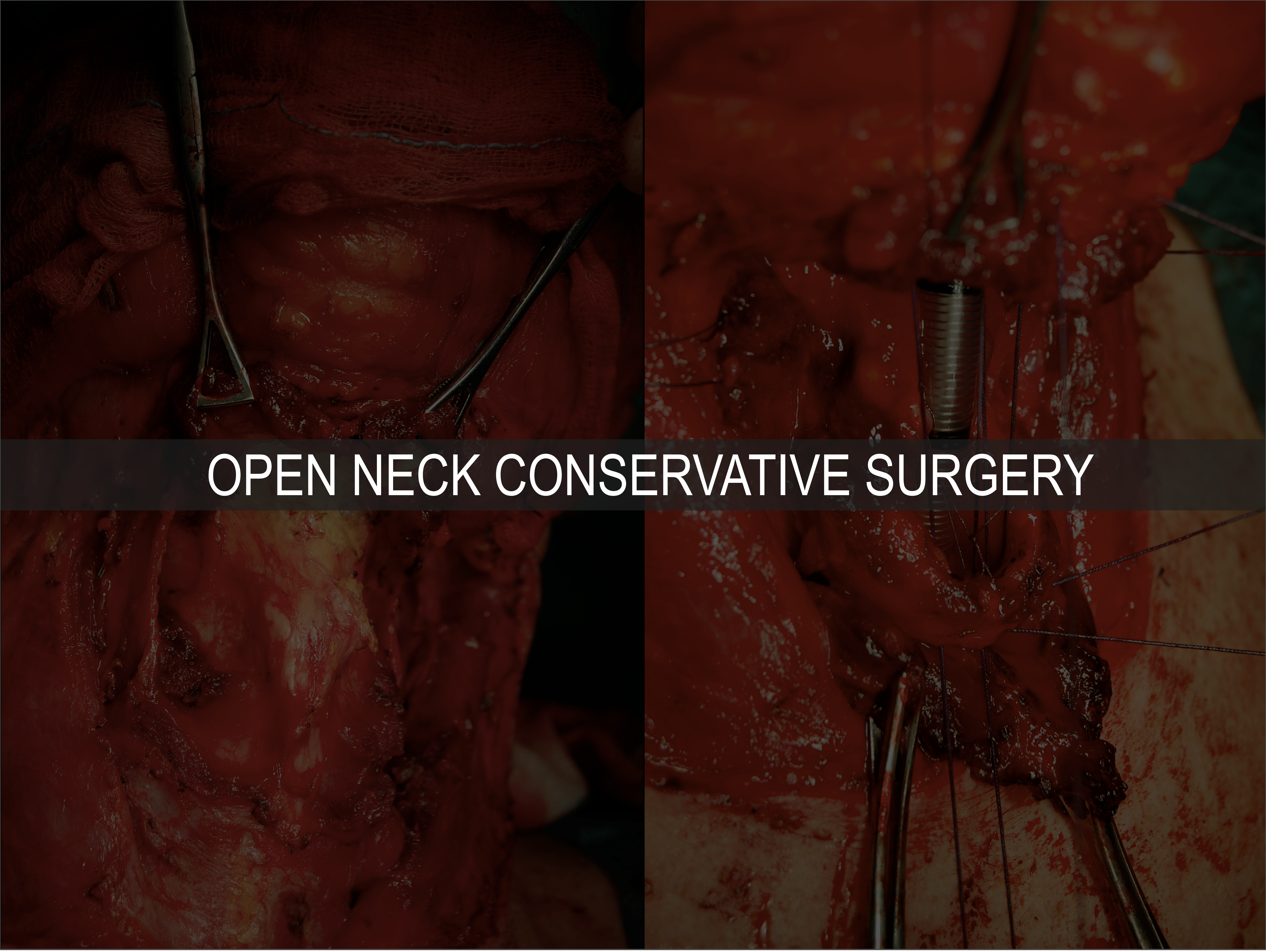
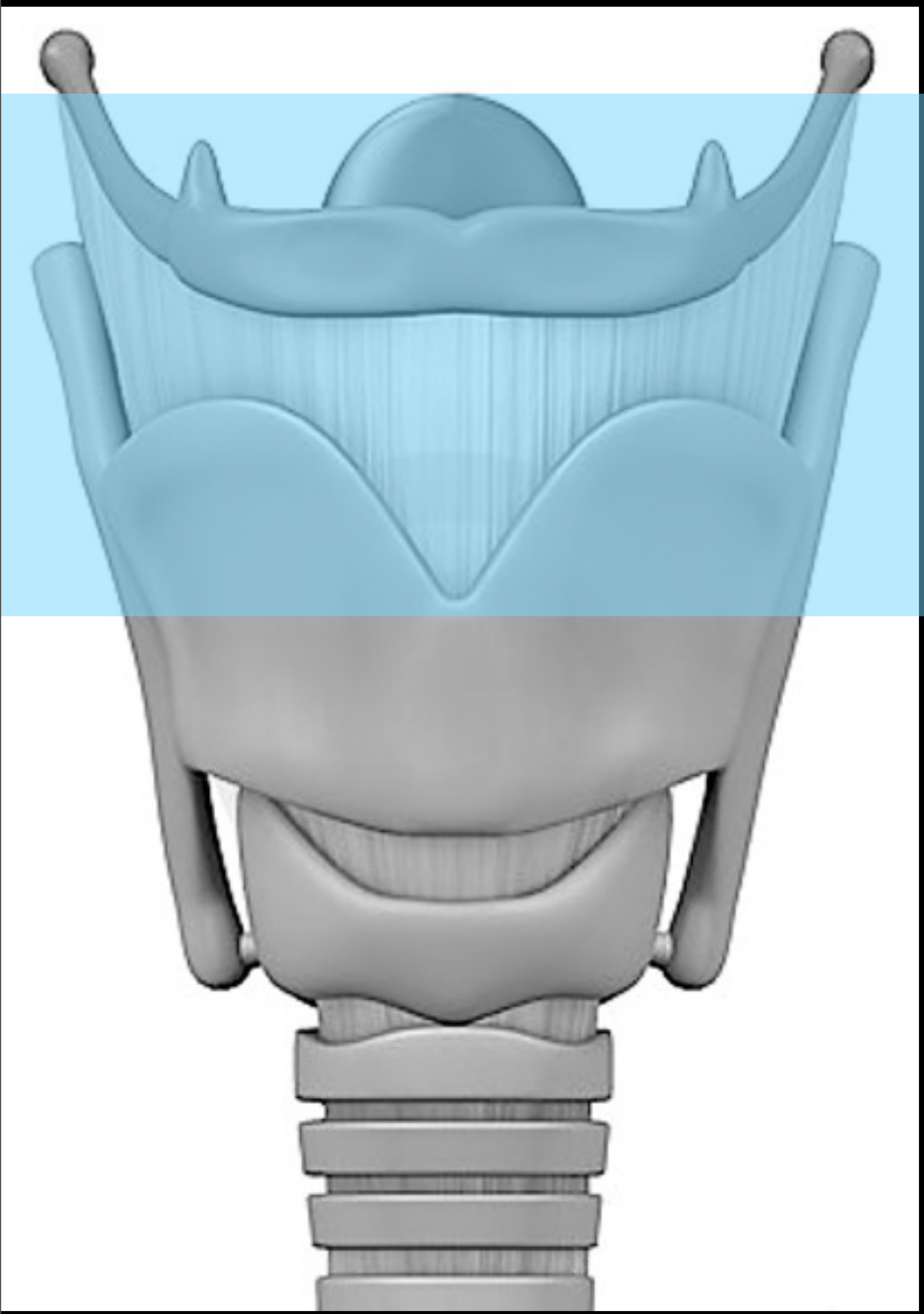

OPEN NECK CONSERVATIVE SURGERY

OPEN-NECK CONSERVATIVE SURGERY

A proposal for classification:
Horizontal Laryngectomies

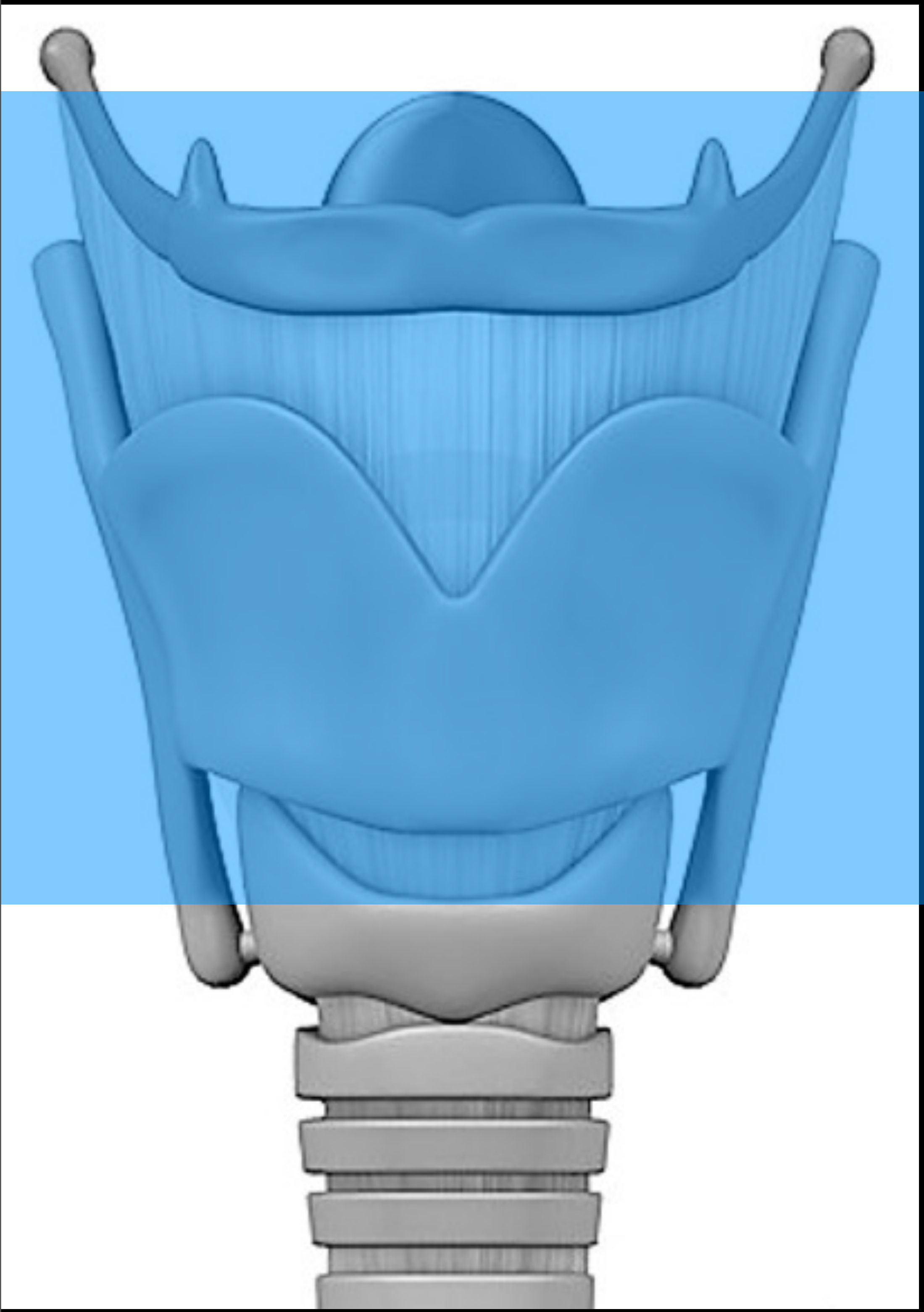


Type 1:
Supraglottic Laryngectomy

Succo et al., Eur Arch Otorhinolaryngol, 2014

OPEN-NECK CONSERVATIVE SURGERY

A proposal for classification:
Horizontal Laryngectomies

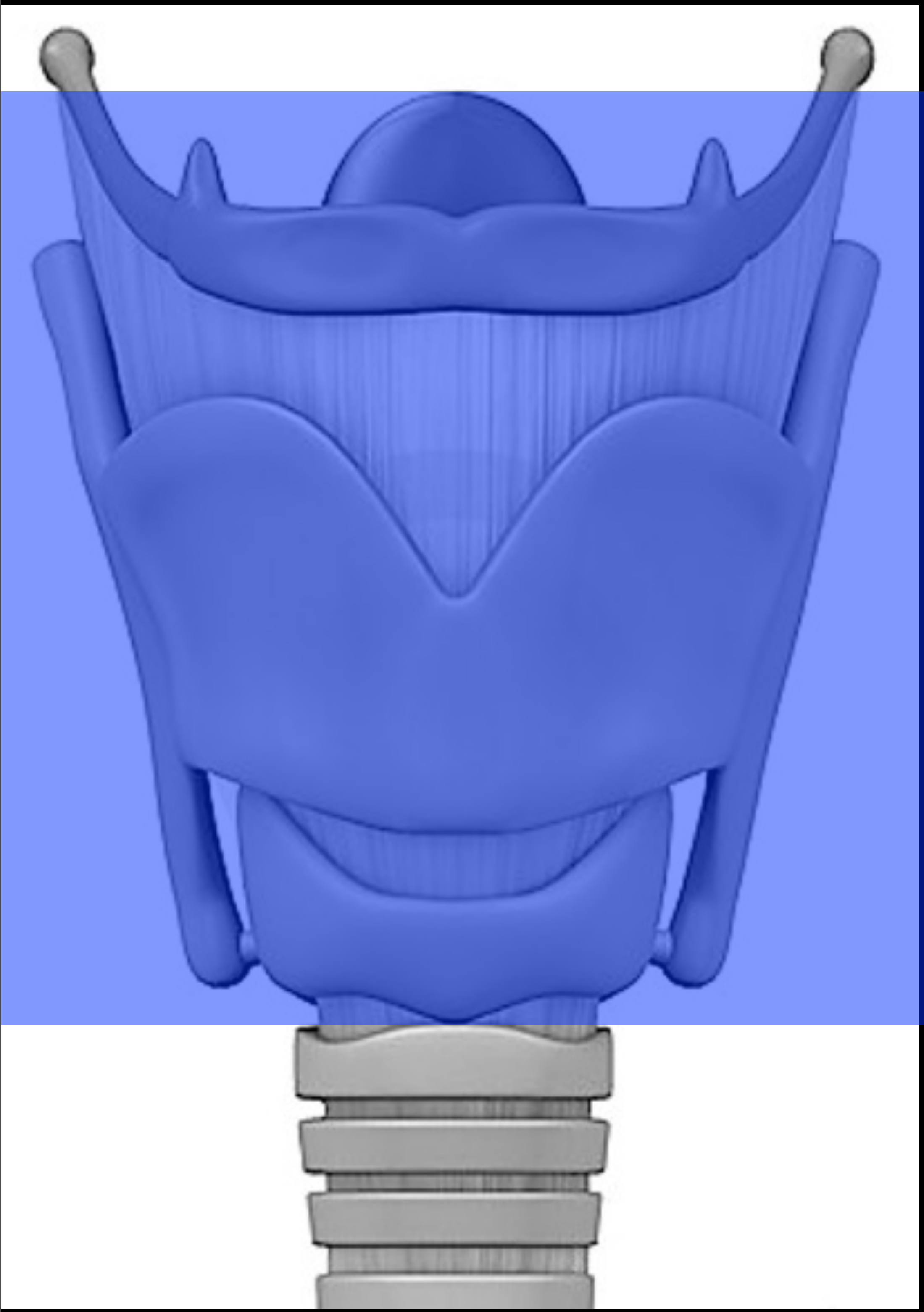


Type 2:
Supracricoid Laryngectomy

Succo et al., Eur Arch Otorhinolaryngol, 2014

OPEN-NECK CONSERVATIVE SURGERY

A proposal for classification:
Horizontal Laryngectomies



Type 3:
Supratracheal Laryngectomy

Succo et al., Eur Arch Otorhinolaryngol, 2014

OPEN-NECK CONSERVATIVE SURGERY

Supraglottic Laryngectomy

INDICATIONS

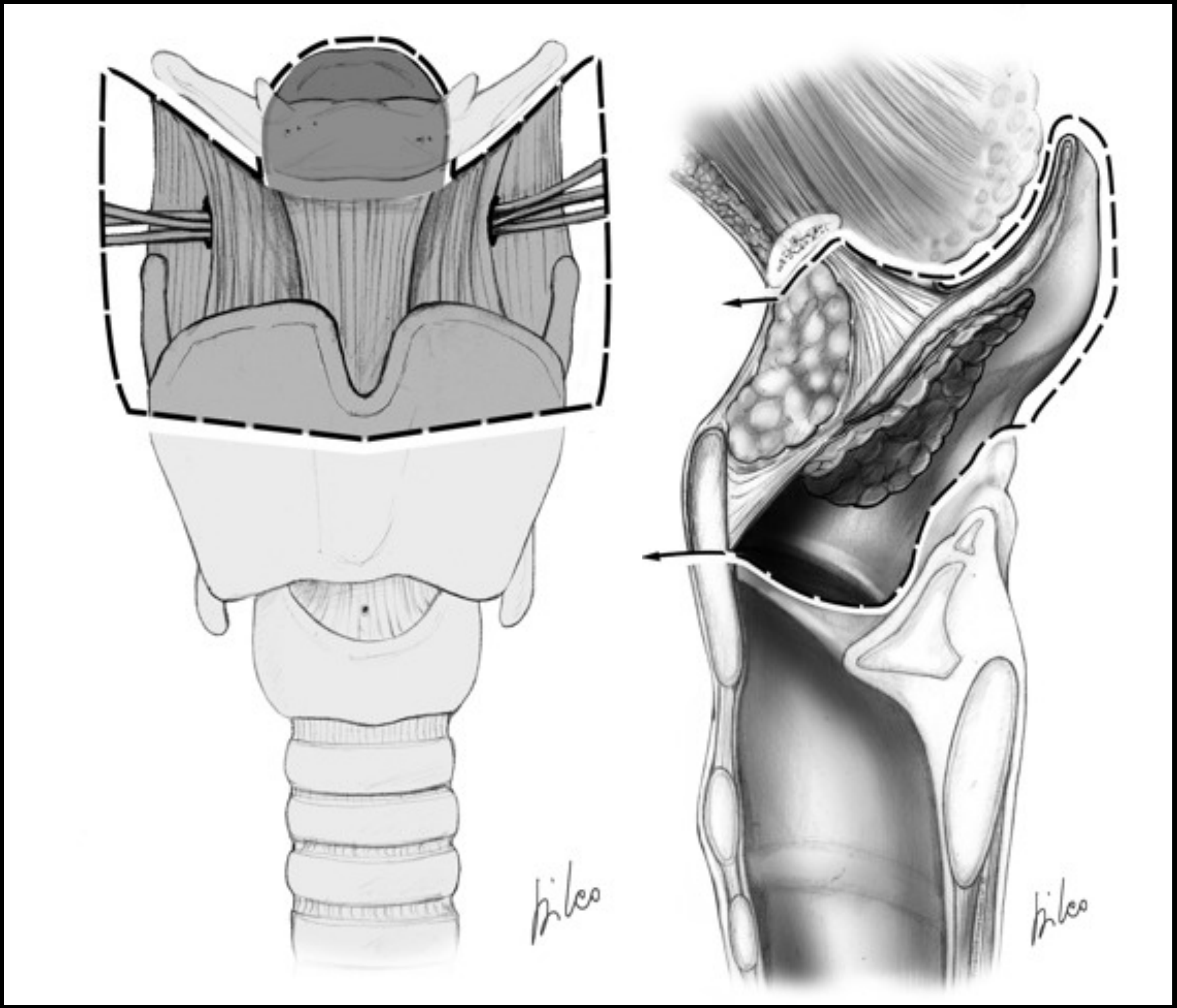
- ✓ Supraglottic T2-3 with extension limited to the upper medial wall of the pyriform sinus or mucosa of the base of the tongue
- ✓ Supraglottic T3 with PES involvement

- ✓ Invasion of cricoid/thyroid cartilage
- ✓ Bilateral involvement of the ARYs
- ✓ Invasion of the PC/AC
- ✓ Fixation of the ARY/VF
- ✓ Involvement of the base of tongue closer than 1 cm to the circumvallate papillae or with impaired mobility of base of tongue

CONTRAINDICATIONS

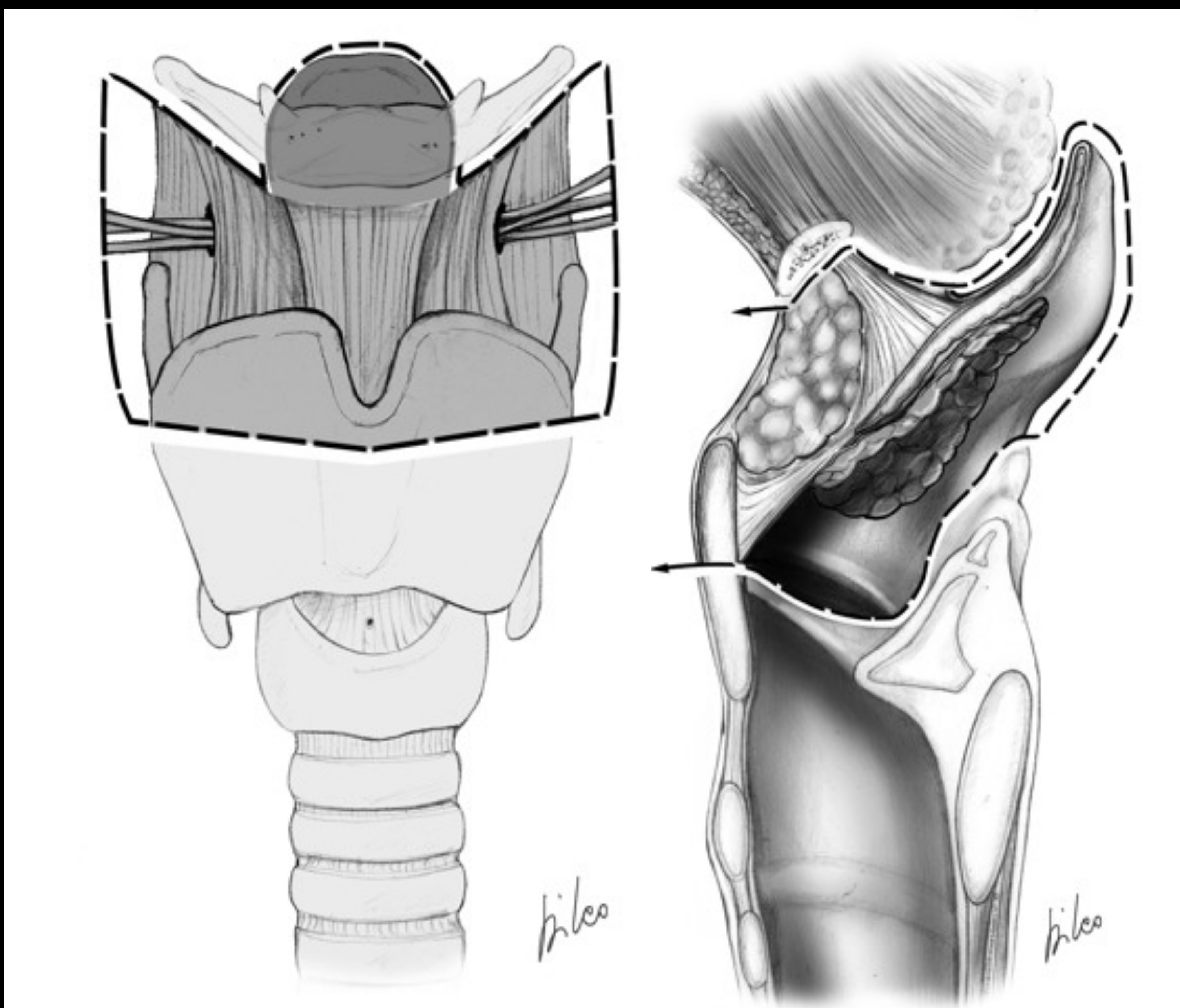
OPEN-NECK CONSERVATIVE SURGERY

Supraglottic Laryngectomy



OPEN-NECK CONSERVATIVE SURGERY

Supraglottic Laryngectomy



Supracricoid Laryngectomy

INDICATIONS

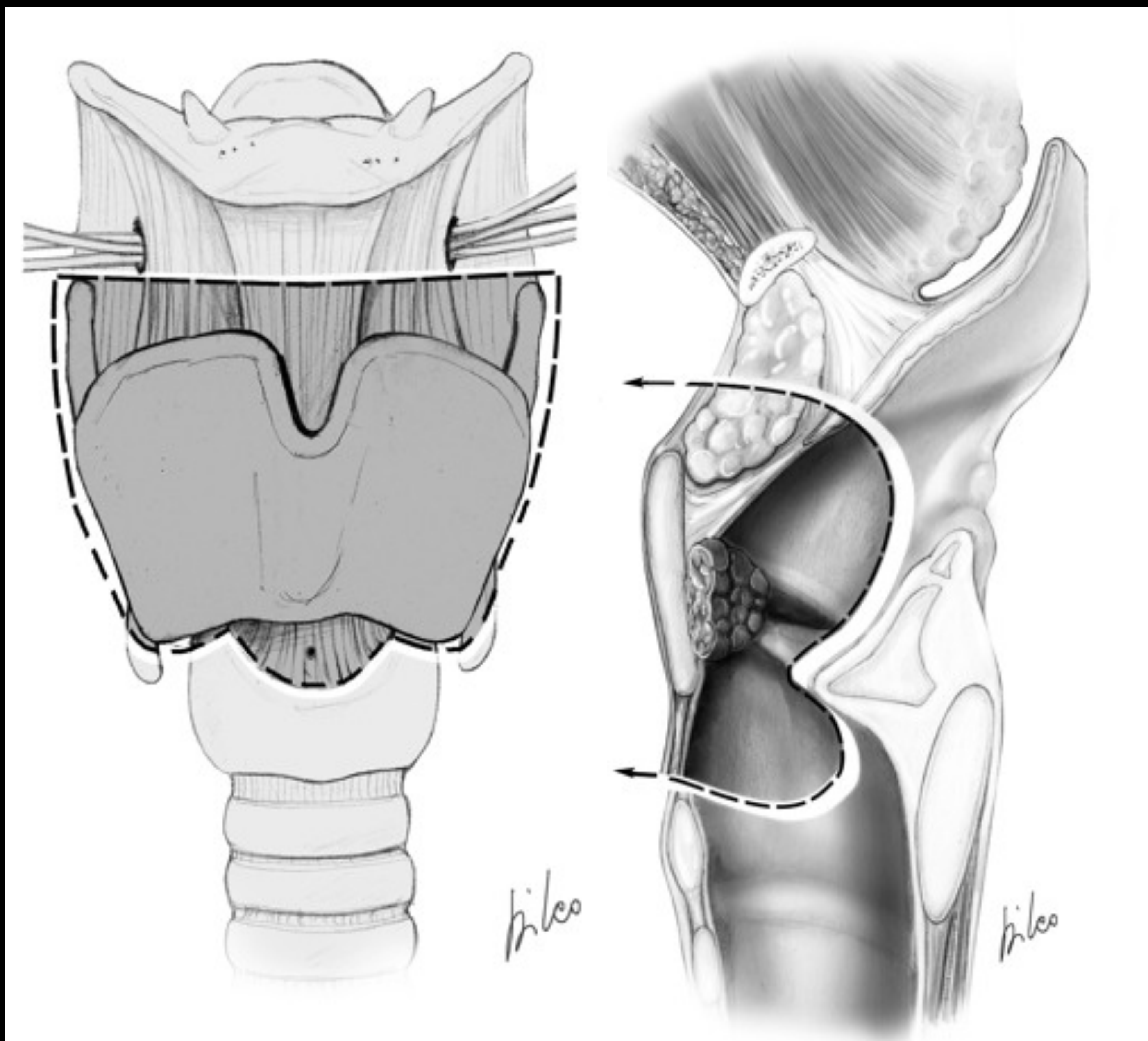
- ✓ T1-2 supraglottic lesions extending to the ventricle, the posterior third of the false vocal cord, the glottis, or the AC
- ✓ T3 transglottic carcinomas
- ✓ T3 of the supraglottis with VF fixation or **massive** invasion of the PES
- ✓ Erosion of the thyroid cartilage not going beyond the outer perichondrium
- ✓ Selected glottic tumors originating at the AC with PES or supraglottic invasion

- ✓ Fixation of both ARYs
- ✓ Subglottic extension >10 mm anteriorly and >5 mm postero-laterally or reaching the upper border or invading the cricoid cartilage
- ✓ T4a with pre-laryngeal muscle infiltration

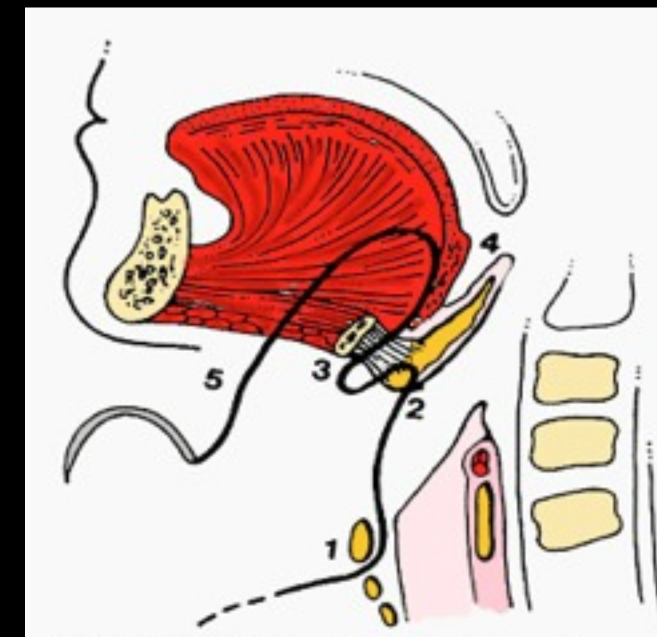
CONTRAINDICATIONS

OPEN-NECK CONSERVATIVE SURGERY

Supracricoid Laryngectomy



CHEP



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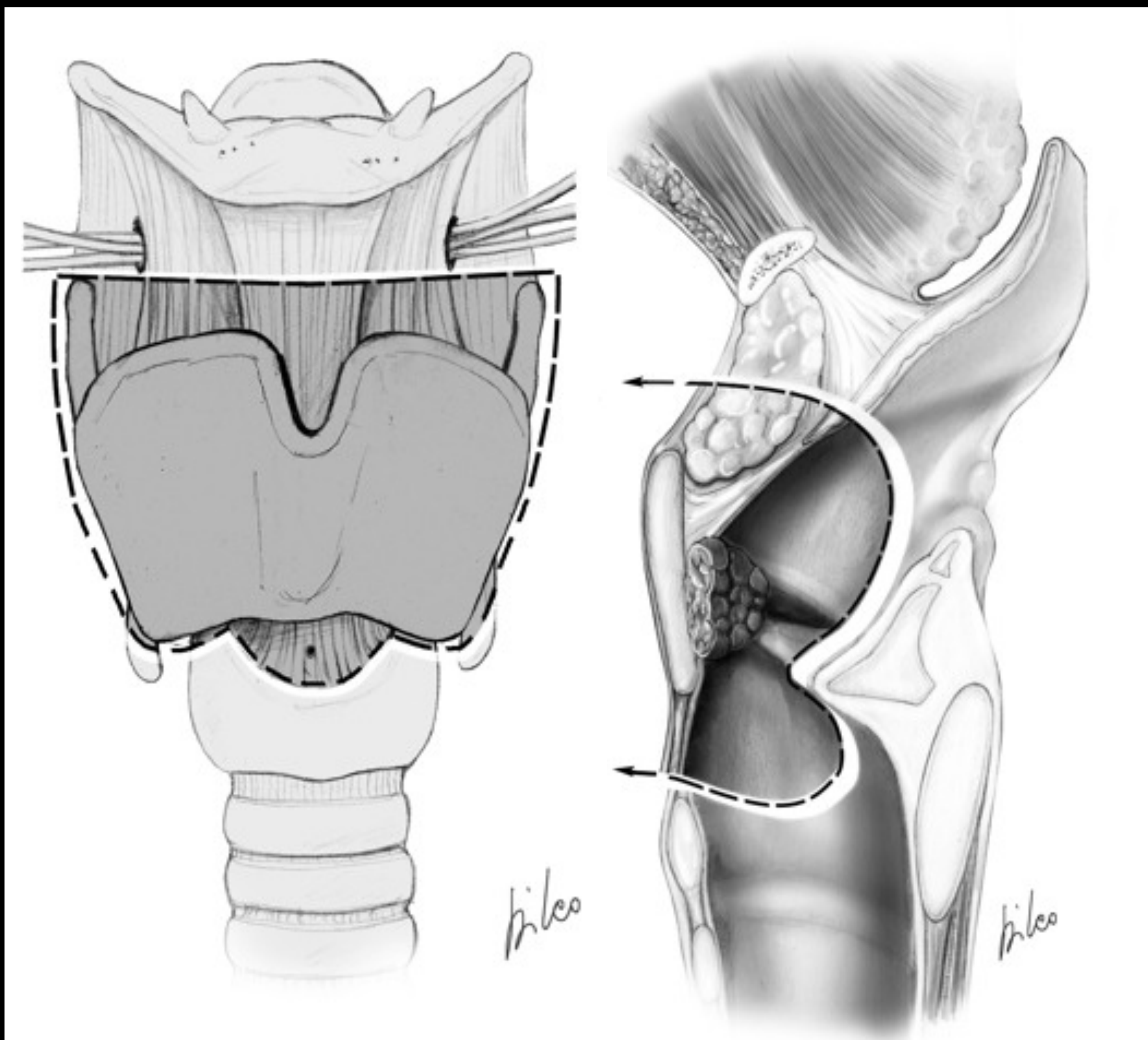

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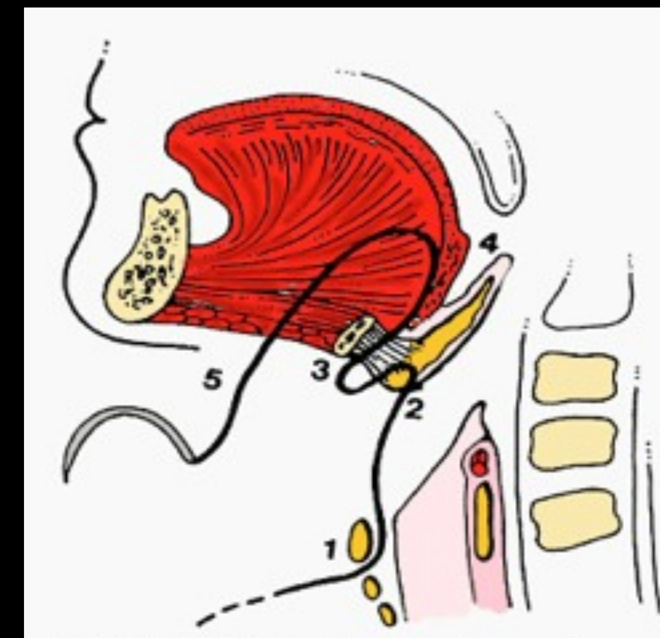

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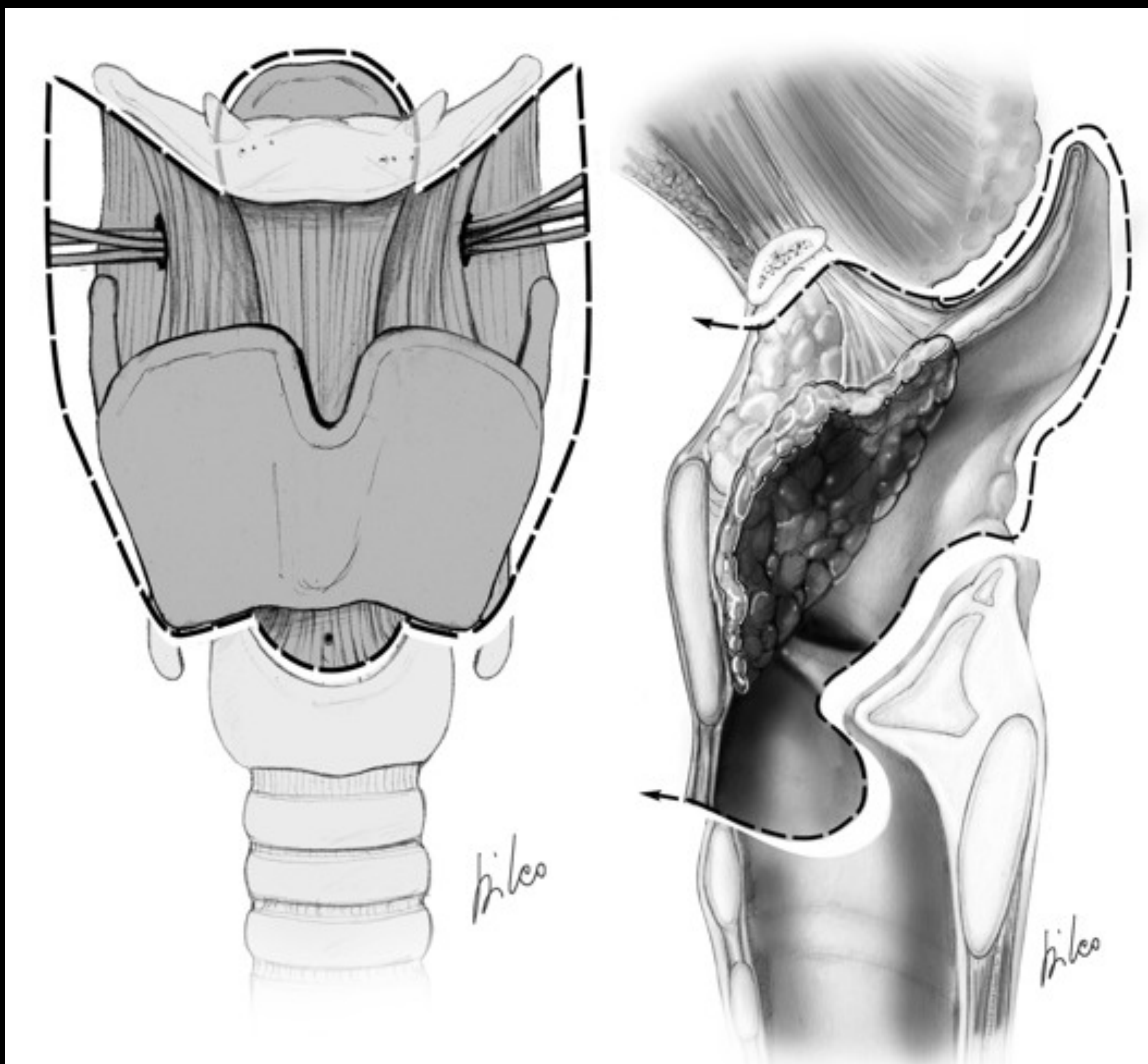
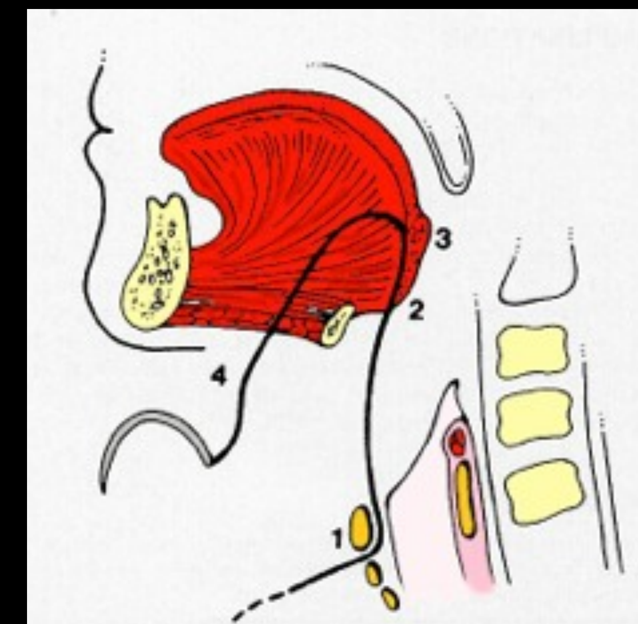
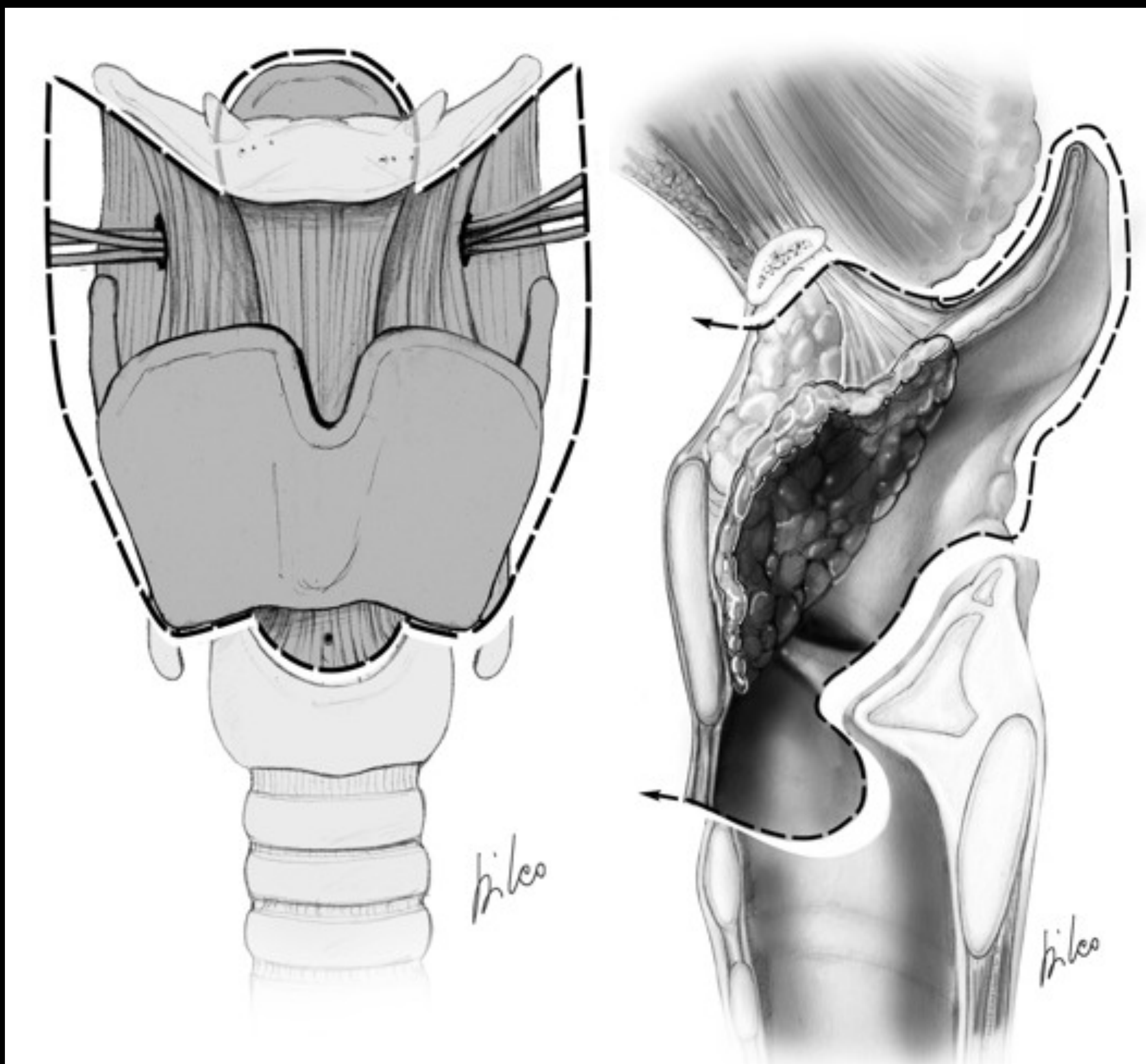


CHP



OPEN-NECK CONSERVATIVE SURGERY

Supracricoid Laryngectomy



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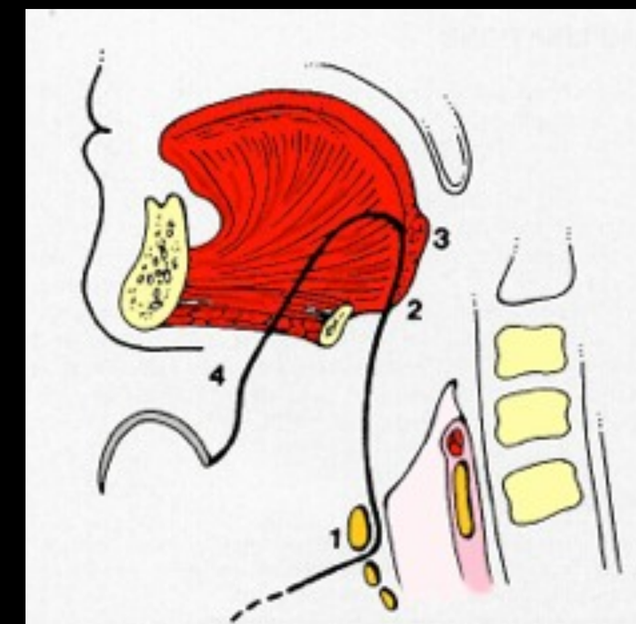
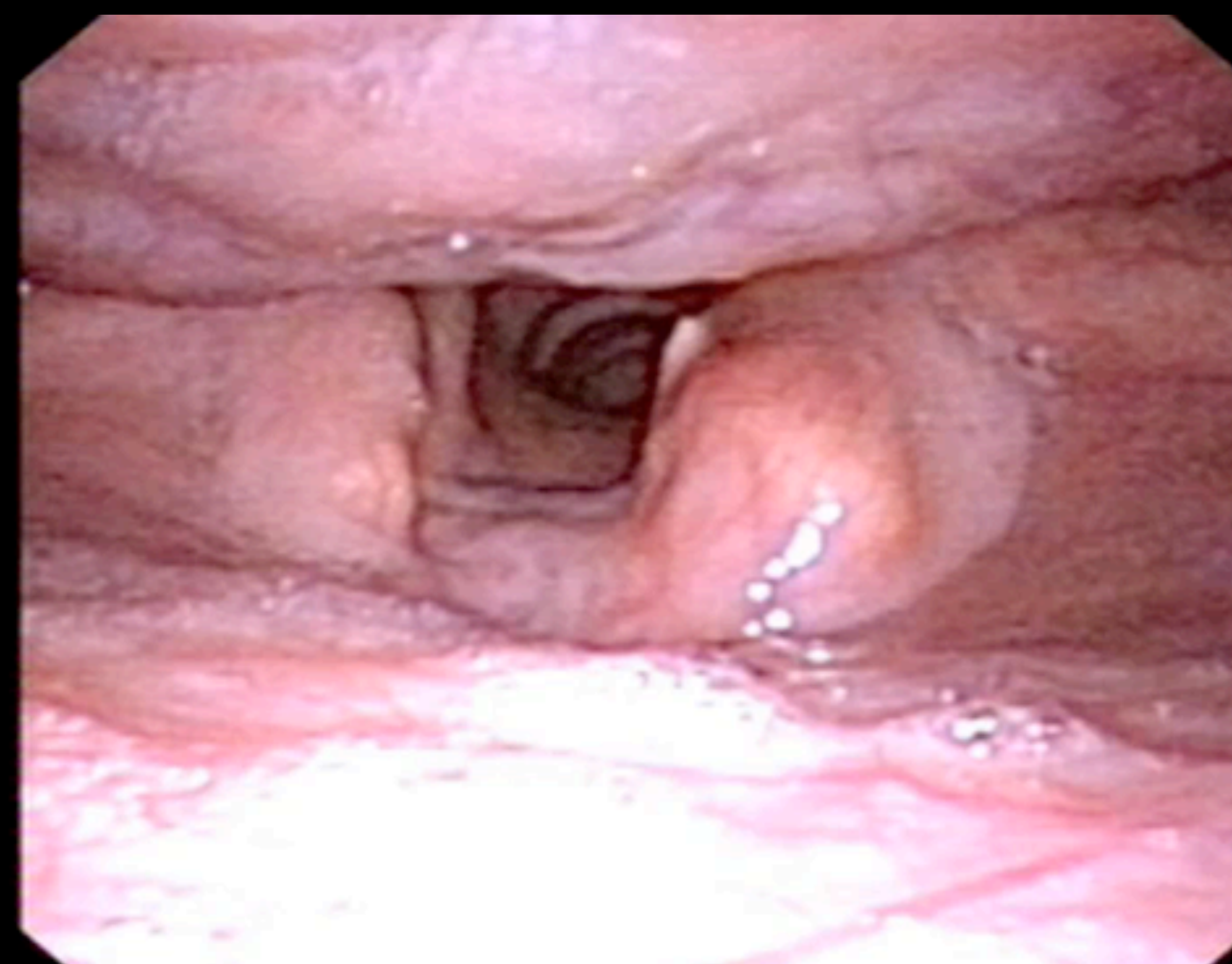




OPEN-NECK CONSERVATIVE SURGERY

Supratracheal Laryngectomy

INDICATIONS

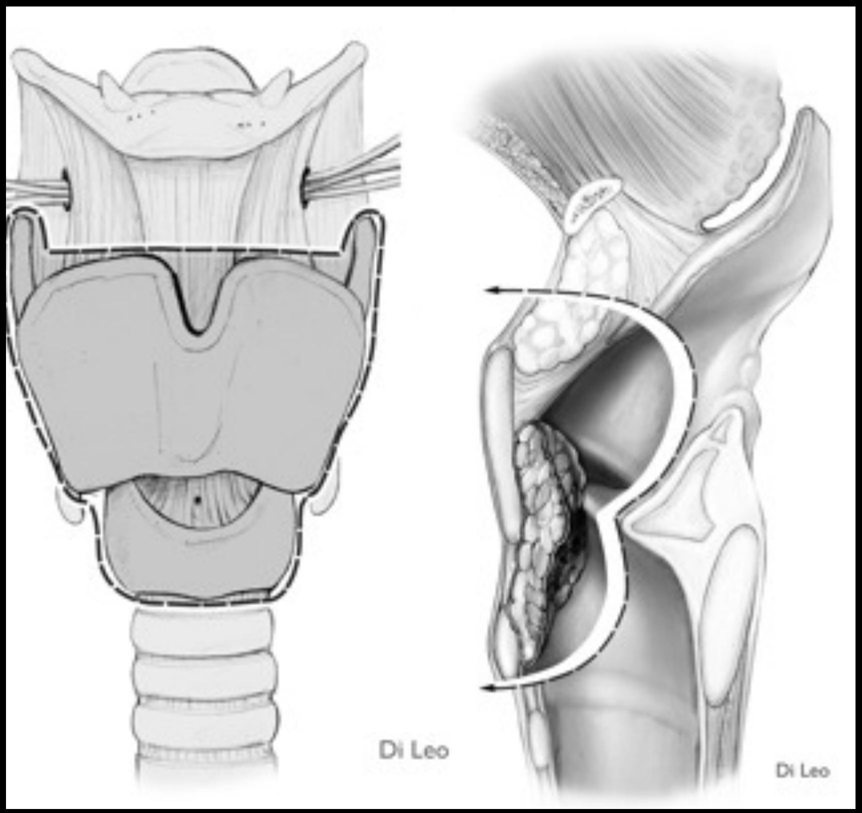
- ✓ Lateral/anterior transglottic cancer with fixation of one VF and/or of one ARY, with normal mobility of the opposite one
- ✓ Subglottic extension reaching the superior border of cricoid cartilage
- ✓ Posterior PGS invasion
- ✓ Cricoid cartilage erosion

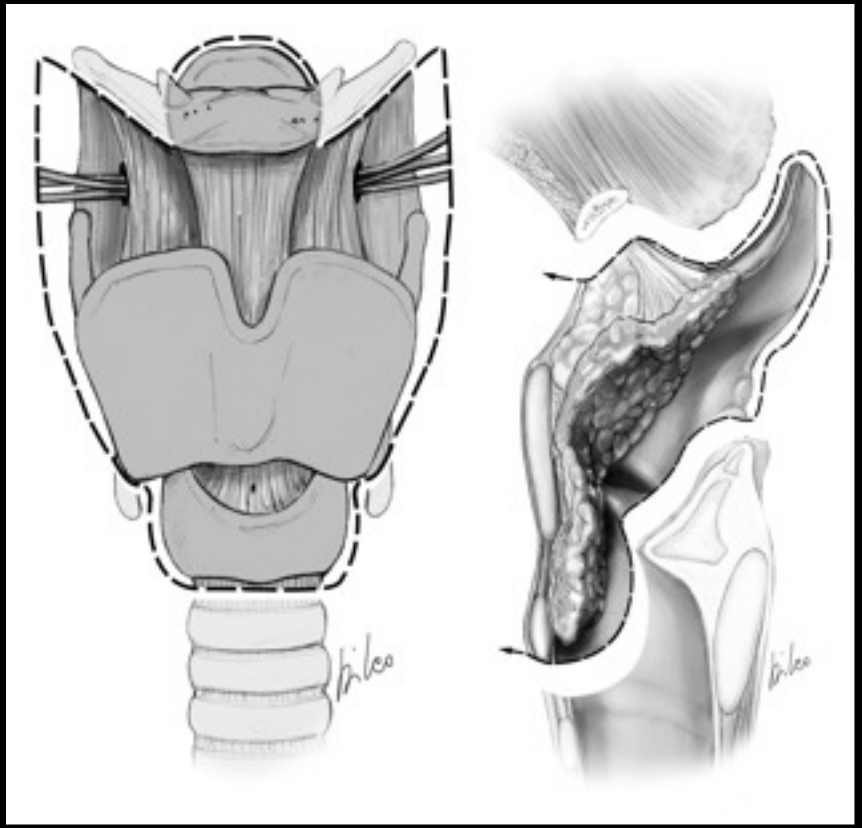
- ✓ T4a with pre-laryngeal muscle infiltration
- ✓ Fixation of both ARYs
- ✓ Tracheal infiltration

CONTRAINDICATIONS

OPEN-NECK CONSERVATIVE SURGERY

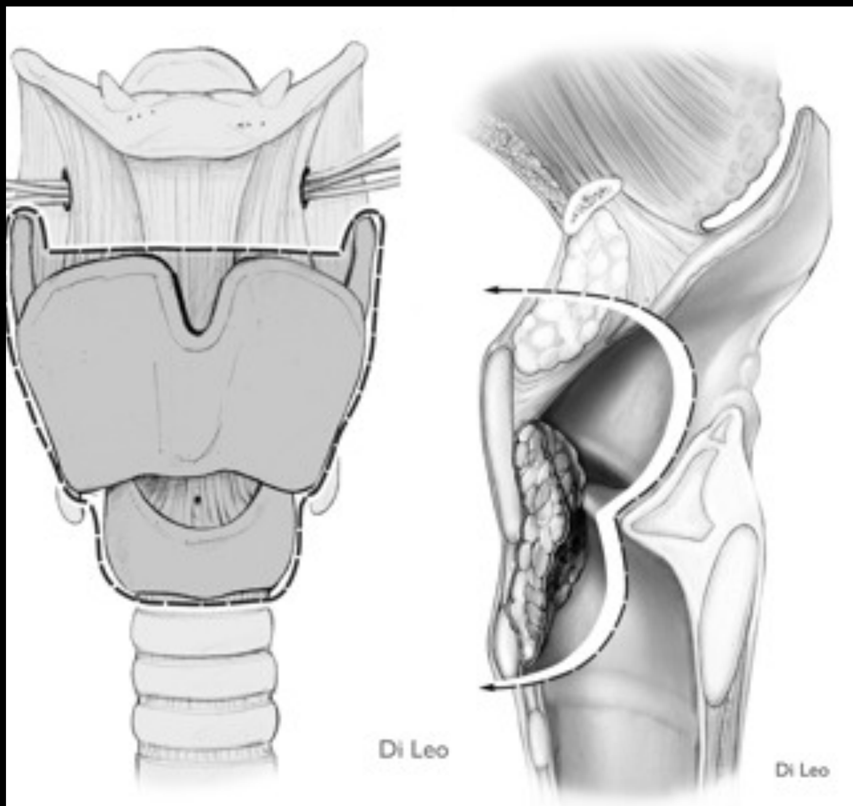
Supratracheal Laryngectomy

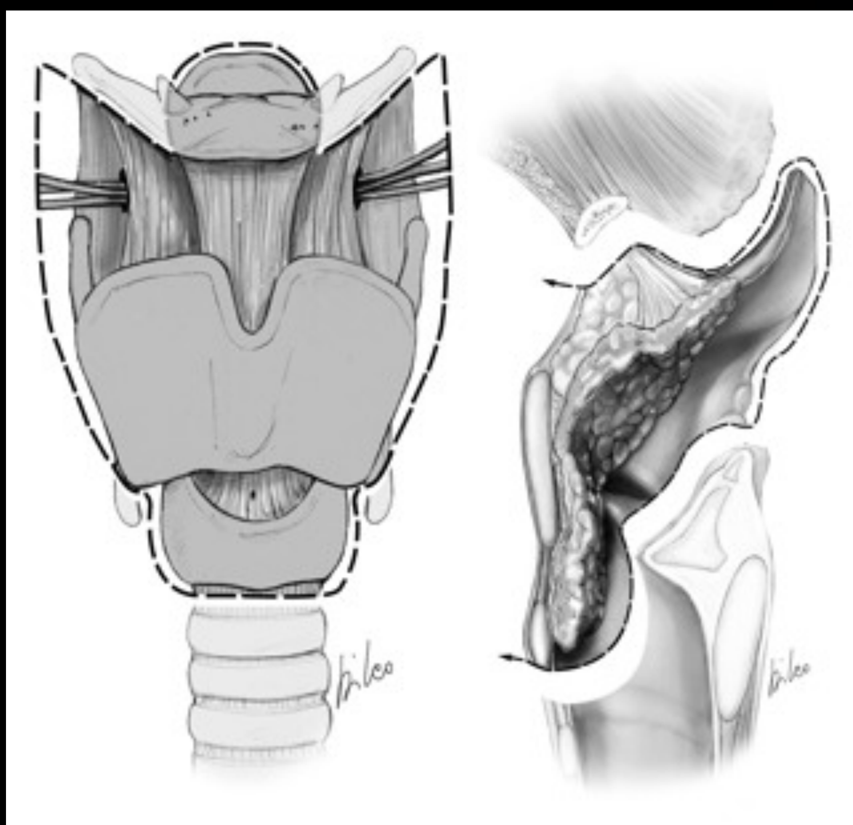


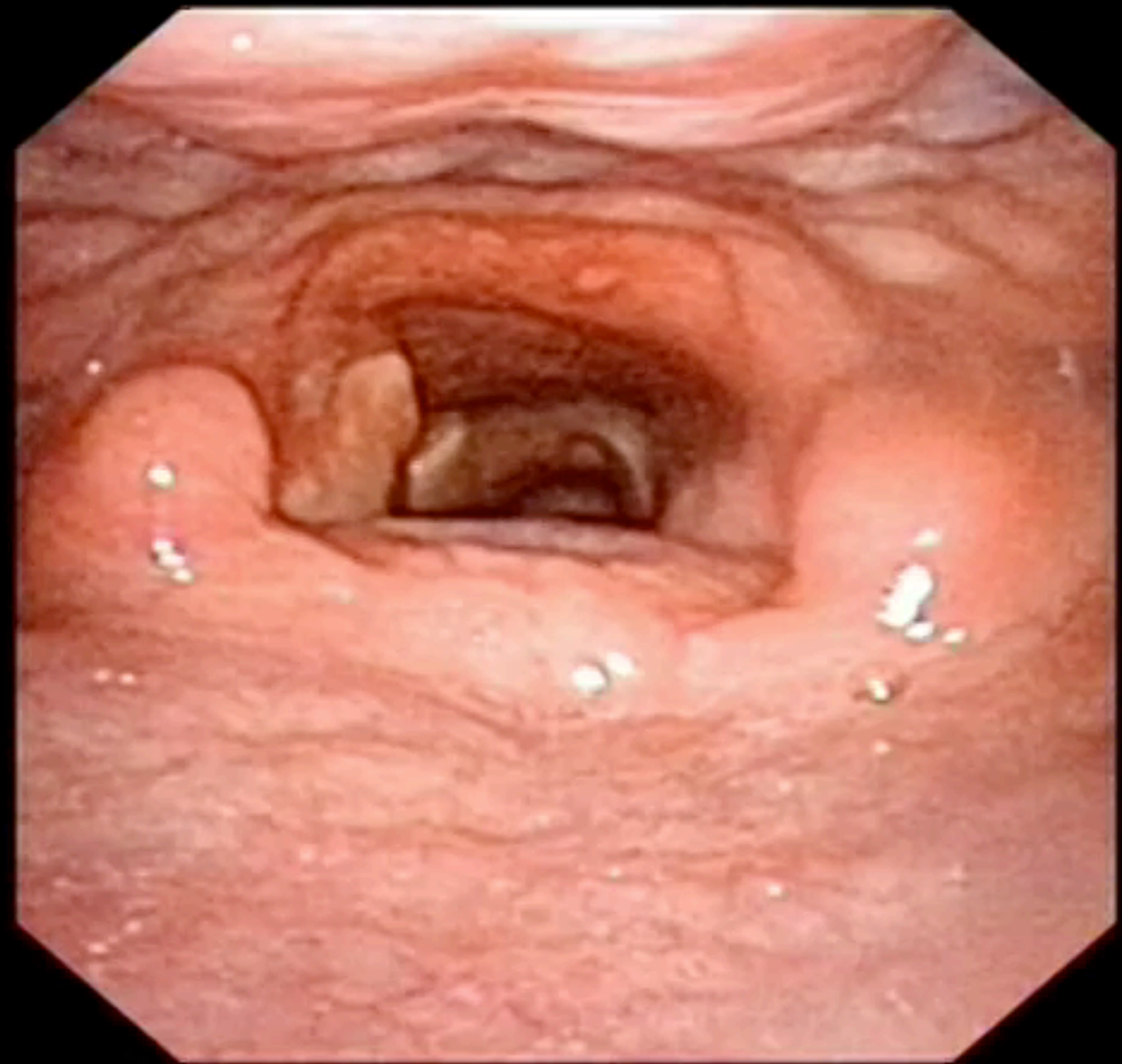


OPEN-NECK CONSERVATIVE SURGERY

Supratracheal Laryngectomy

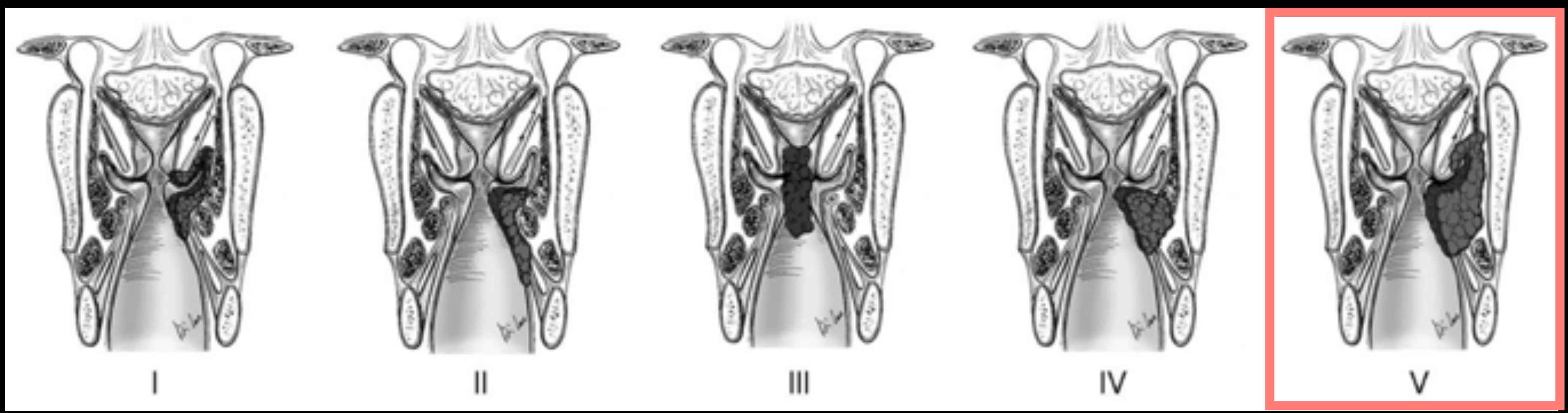






OPEN-NECK CONSERVATIVE SURGERY

Benefits and drawbacks of open partial horizontal laryngectomies,
Part A: **Early-intermediate** stage glottic carcinoma
Succo et al. Head Neck 2015



cT2 tumors

216 patients

Overall Survival 93.1%

Local Control 97.5%

Upstaging (cT2/pT3) in **16.7%**

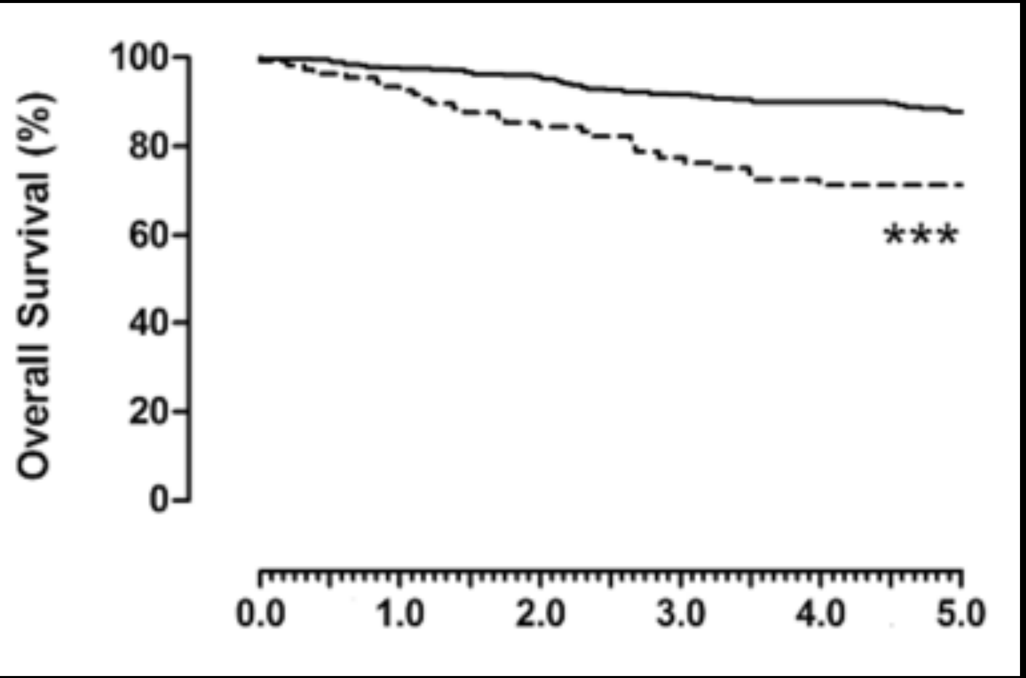
Optimal survival

Even in more aggressive disease

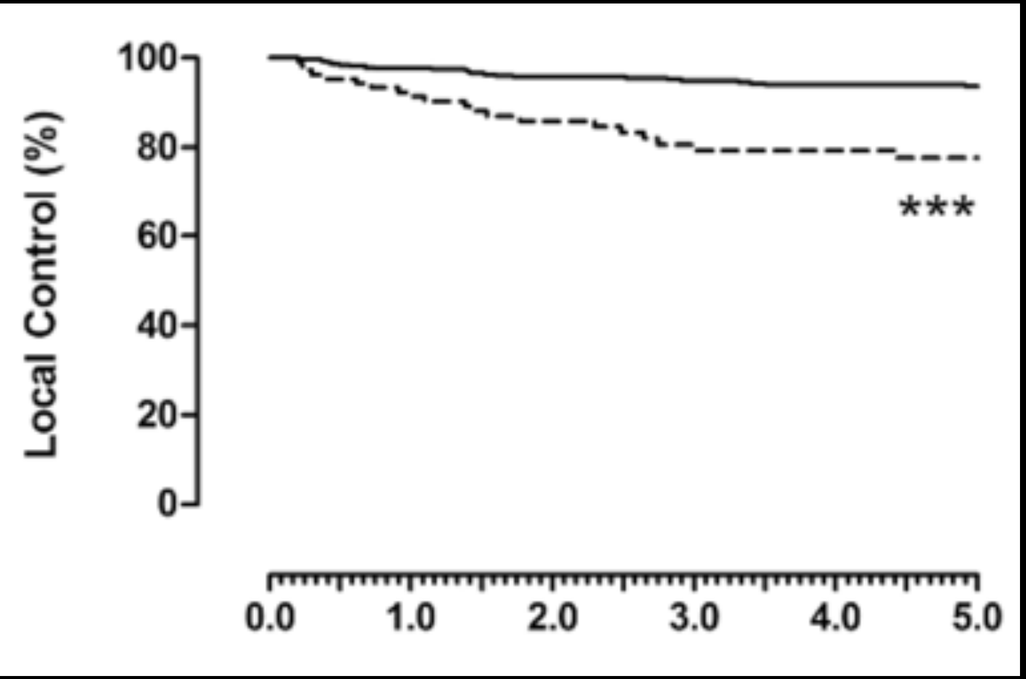
- pT2 with vocal cord fixation
- cT2/pT3 for PGS involvement

OPEN-NECK CONSERVATIVE SURGERY

Benefits and drawbacks of open partial horizontal laryngectomies,
Part B: **Intermediate and selected advanced** stage laryngeal carcinoma
Succo et al. Head Neck 2015



pT3
pT4a



pT3
pT4a

cT3/cT4a tumors

555 patients → **442 pT3** / **113 pT4a**

12.9% adjuvant RT

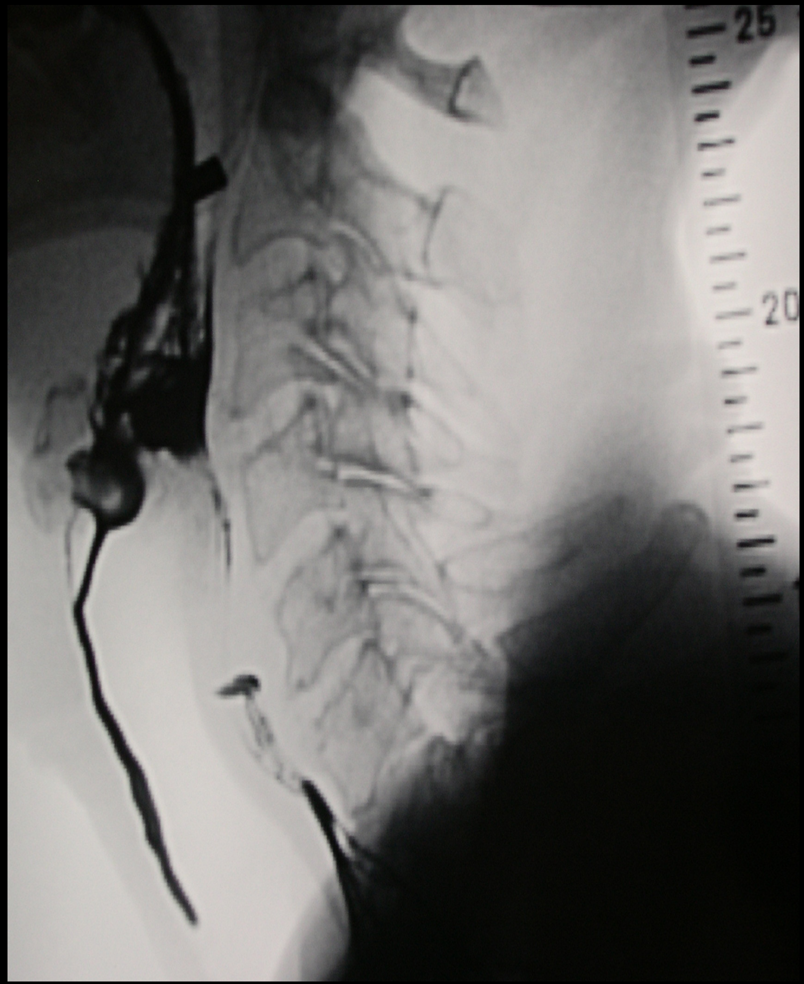
Overall Survival 84.6%

Local Control 90.6%

Late sequelae	
Laryngeal soft tissue stenosis	54/555 (9.7%)
Aspiration pneumonia	25/555 (4.5%)
Dyspnea	6/555 (1.1%)

FUNCTIONAL RESULTS

Supracricoid partial laryngectomies



Benito et al, Head Neck, 2011
Succo et al, Head Neck, 2015

OPEN-NECK CONSERVATIVE SURGERY

FUNCTIONAL RESULTS

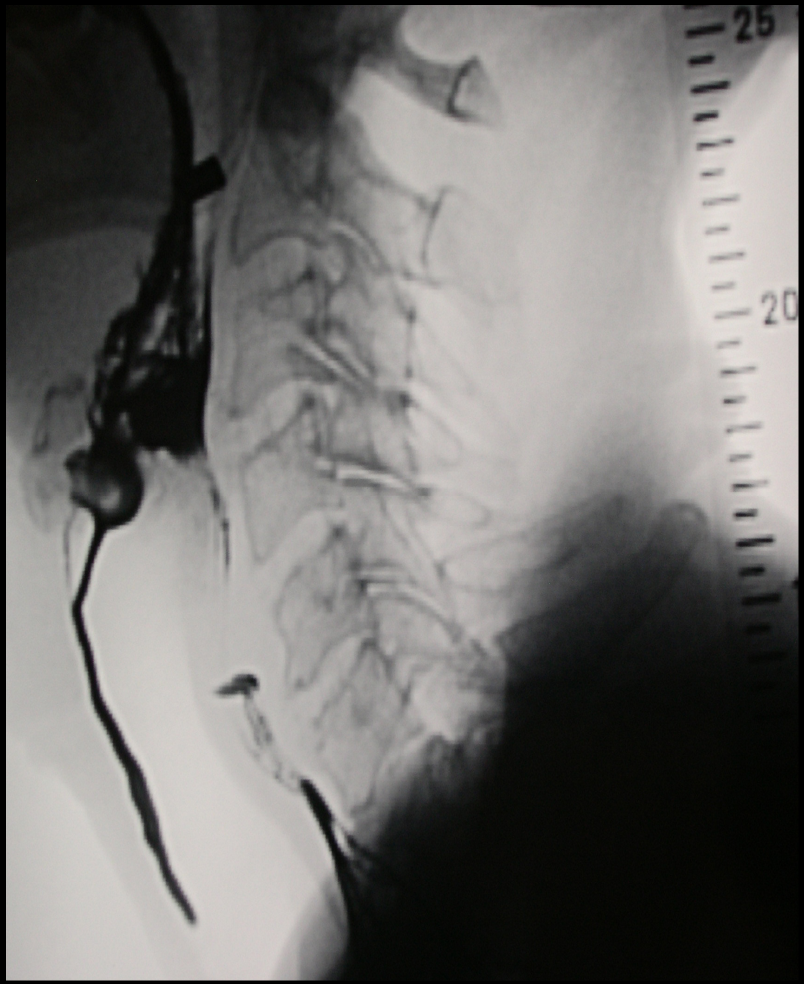
Supracricoid partial laryngectomies

Normal swallowing: **52.1-58.9%**

Laryngeal function preservation: **91.2%**

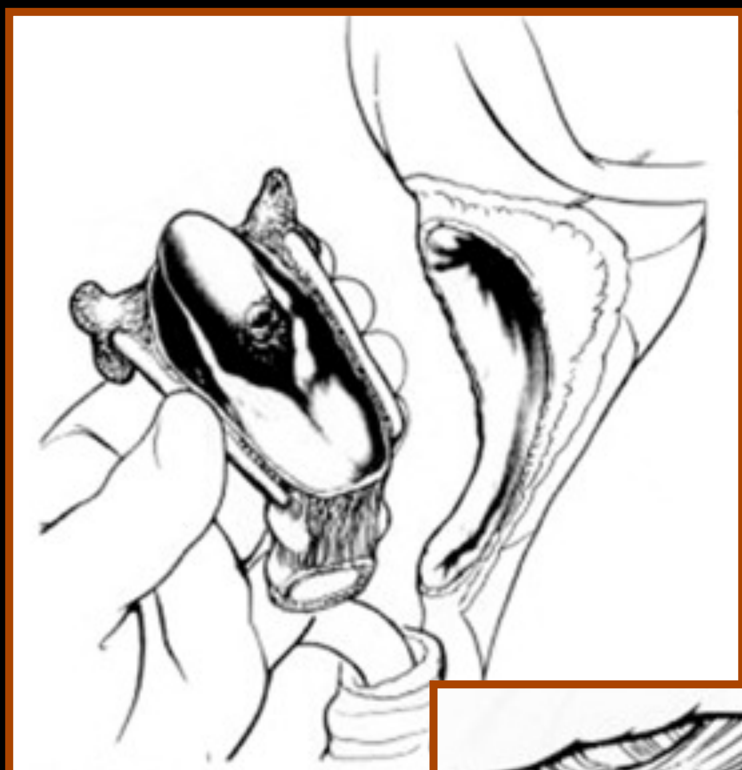
Laryngectomy free survival: **93.3%**

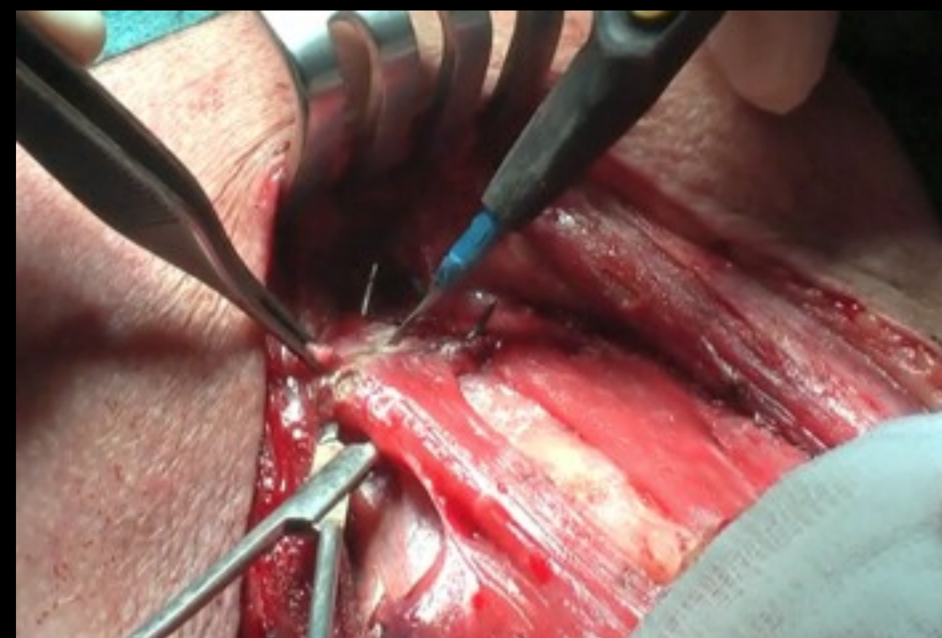
Permanent gastrostomy: **1.4%**

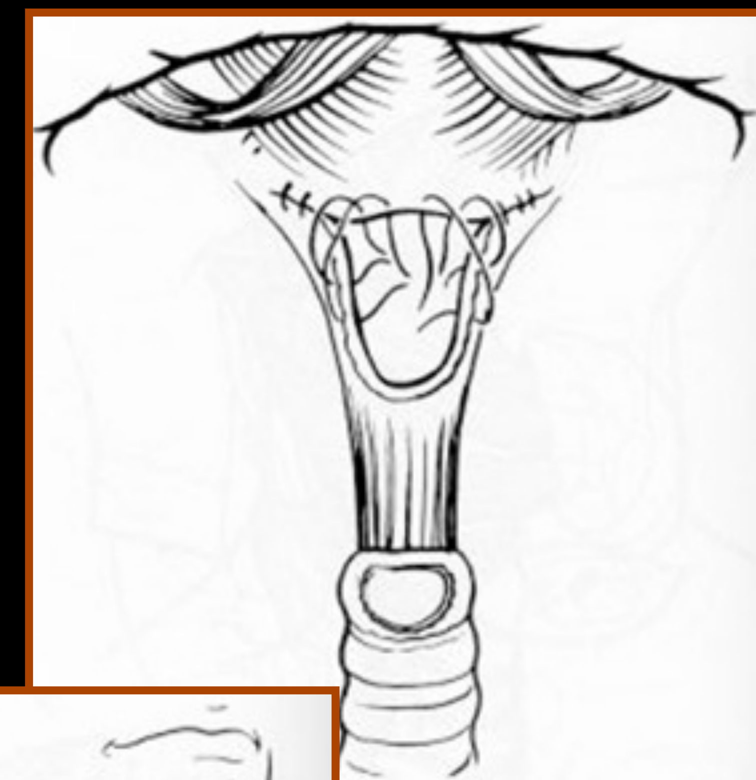


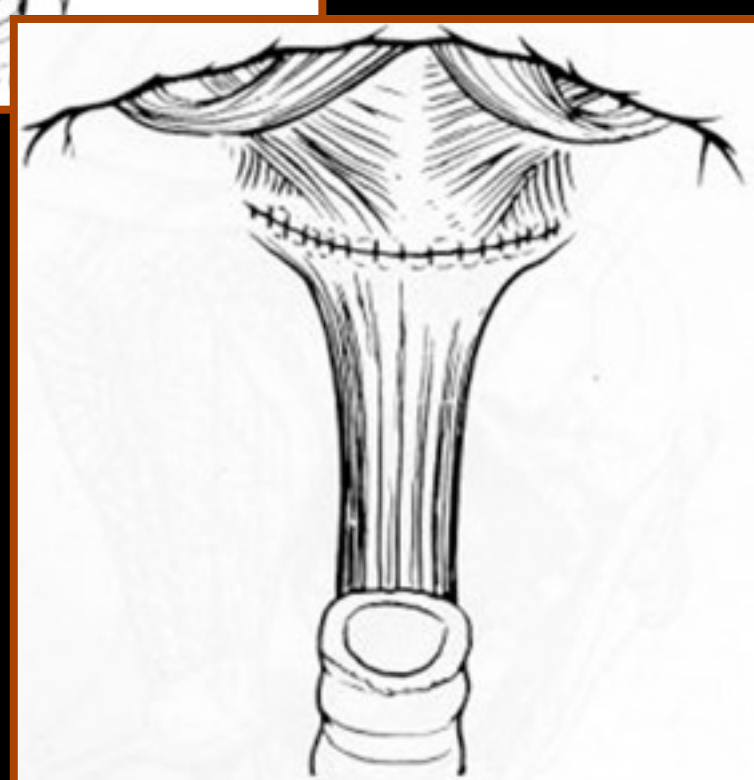
Benito et al, Head Neck, 2011
Succo et al, Head Neck, 2015

TOTAL LARYNGECTOMY

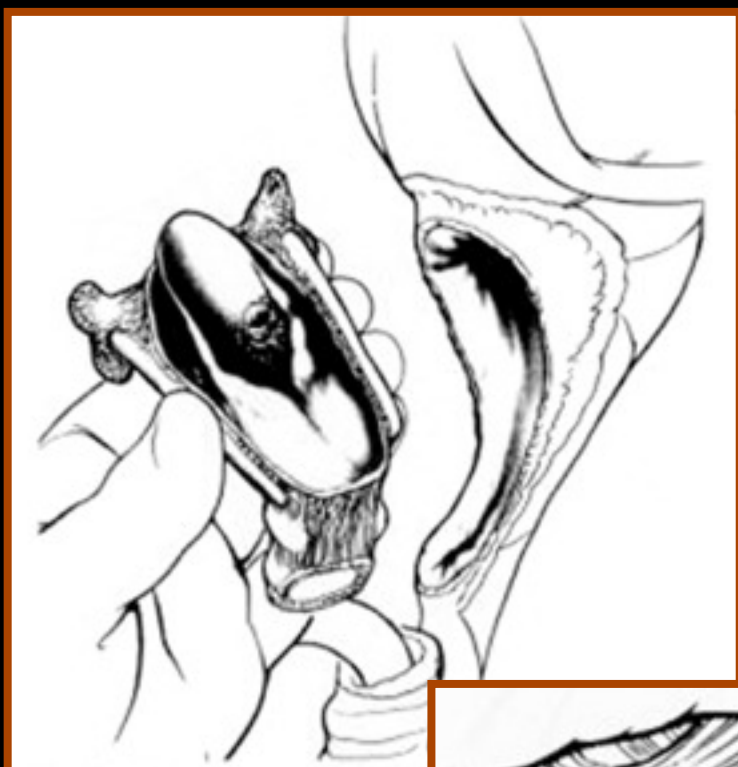


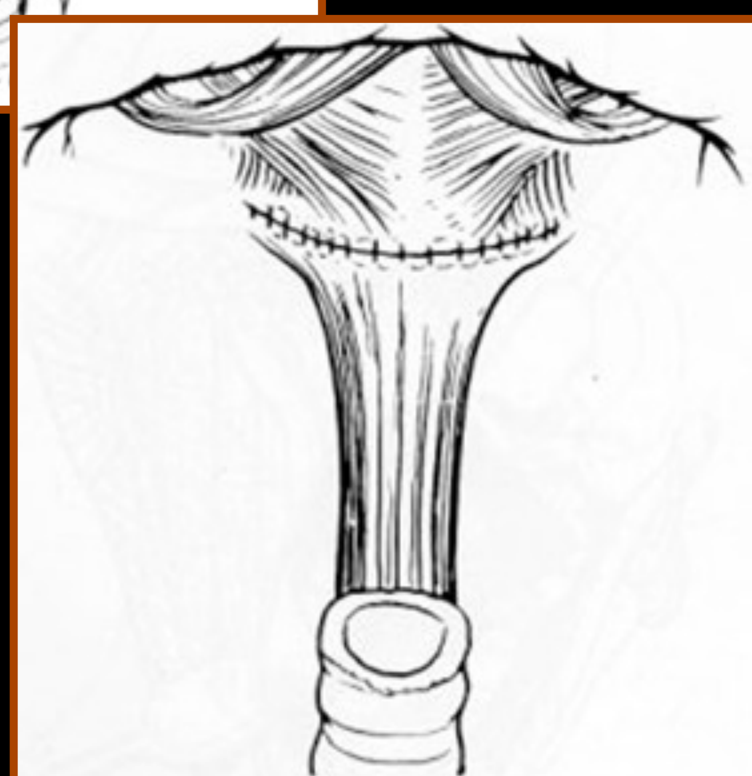


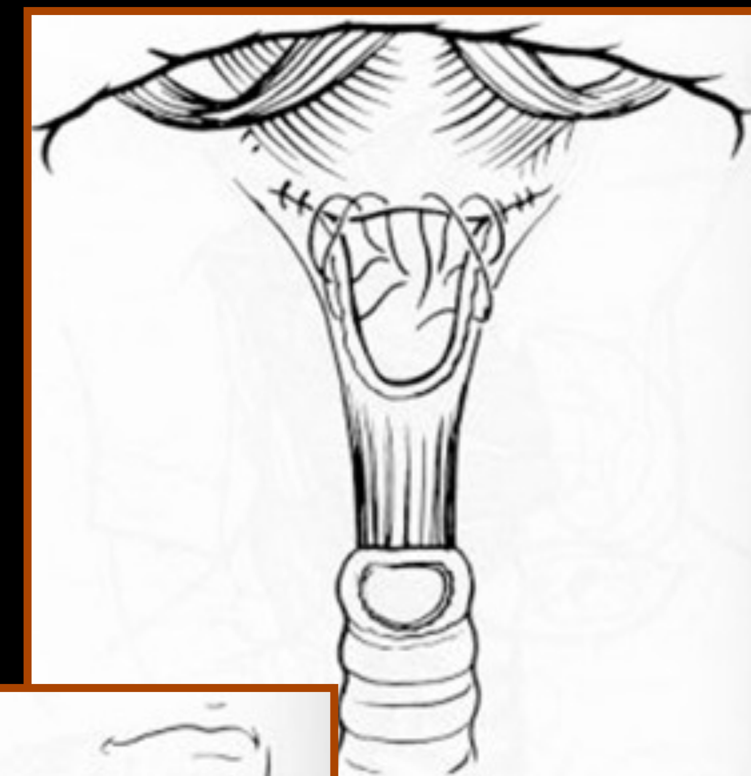


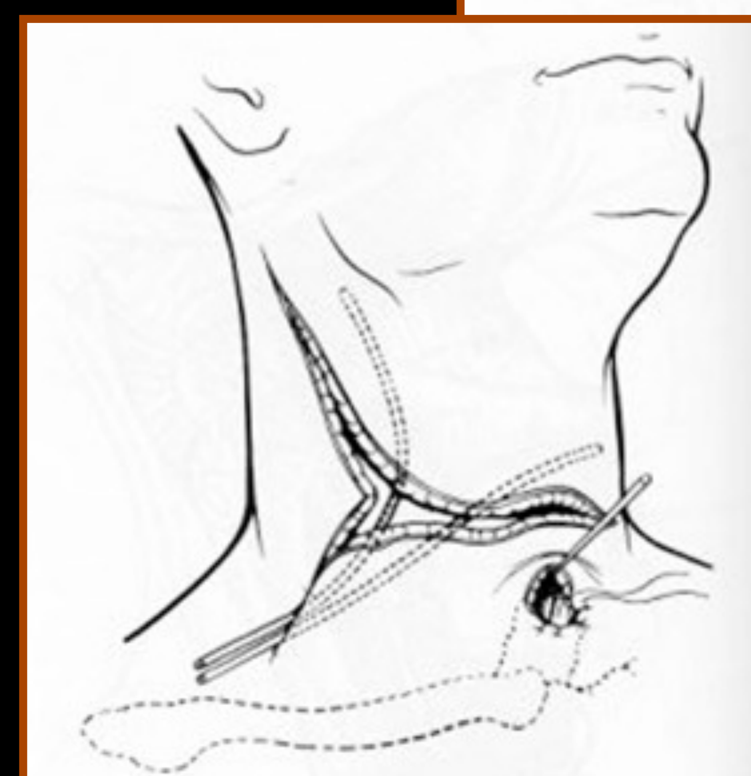


TOTAL LARYNGECTOMY









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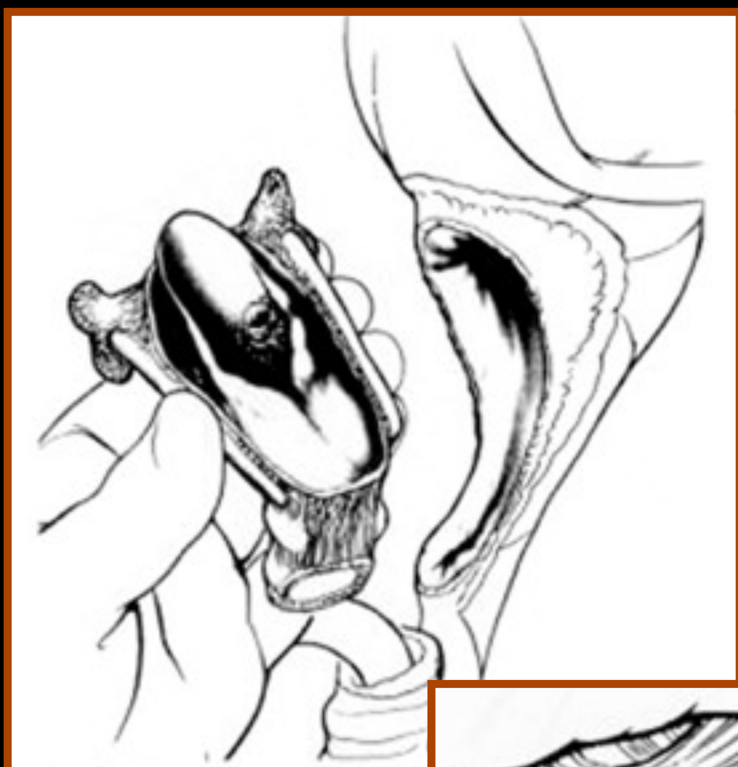
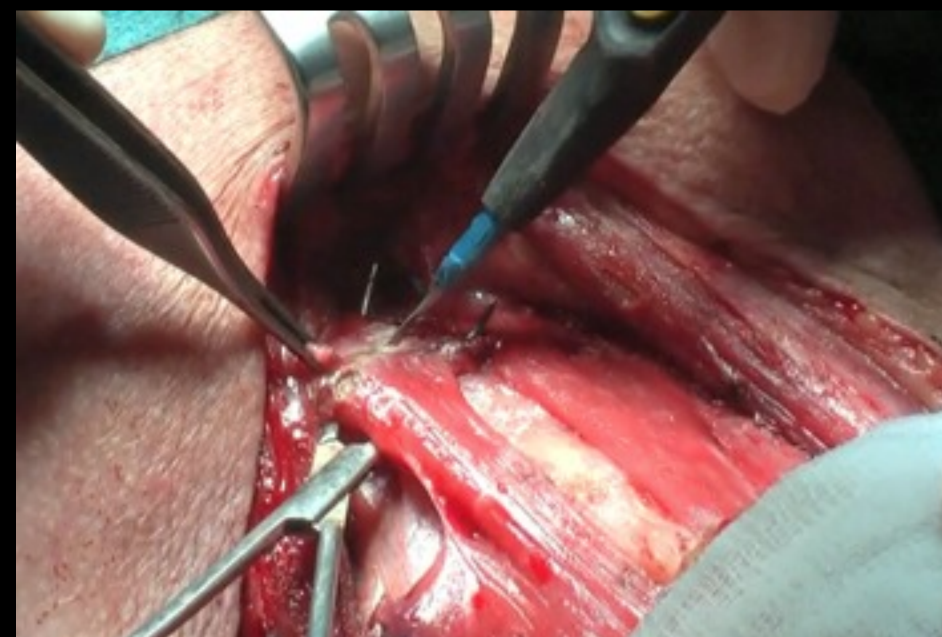
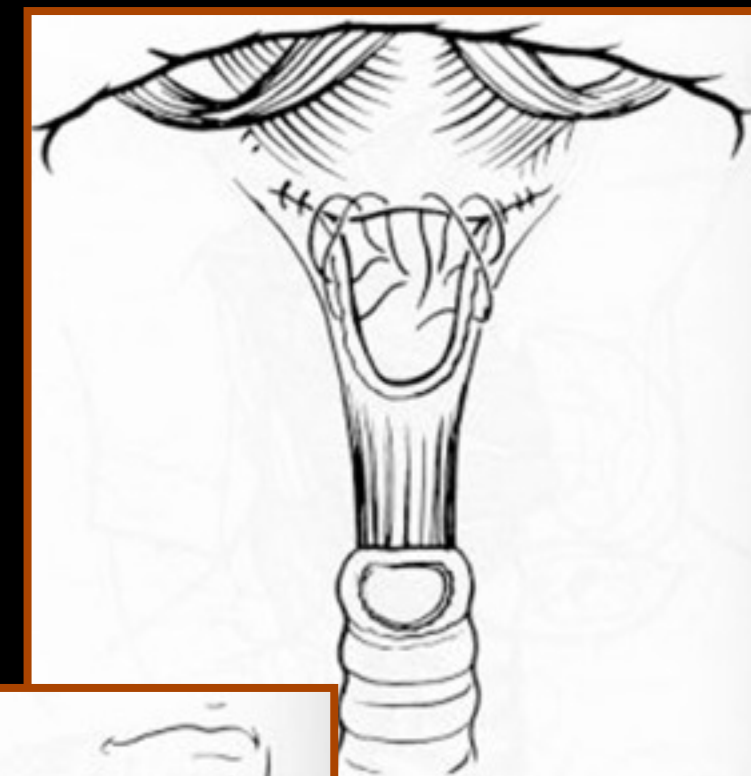
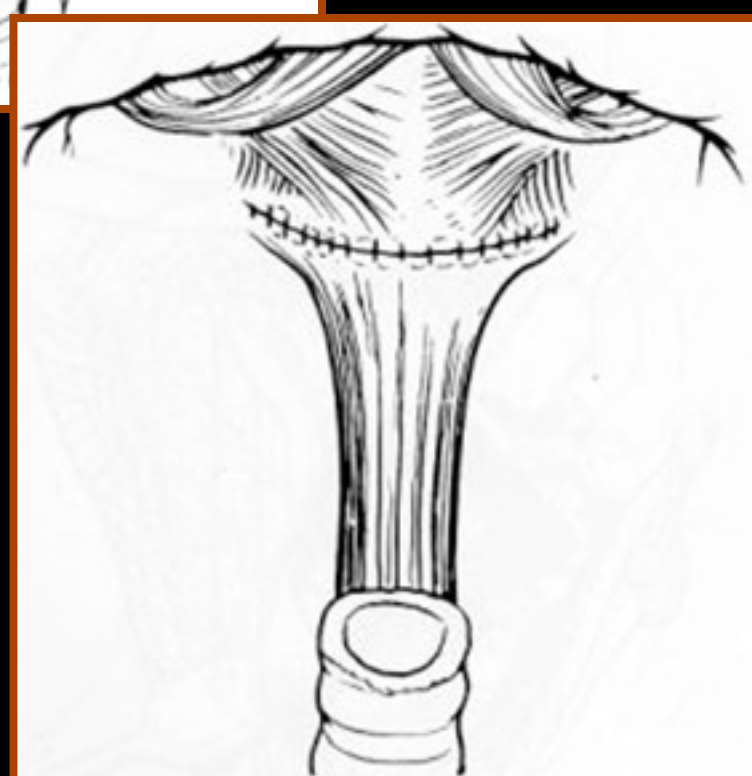








HYPOPHARYNX

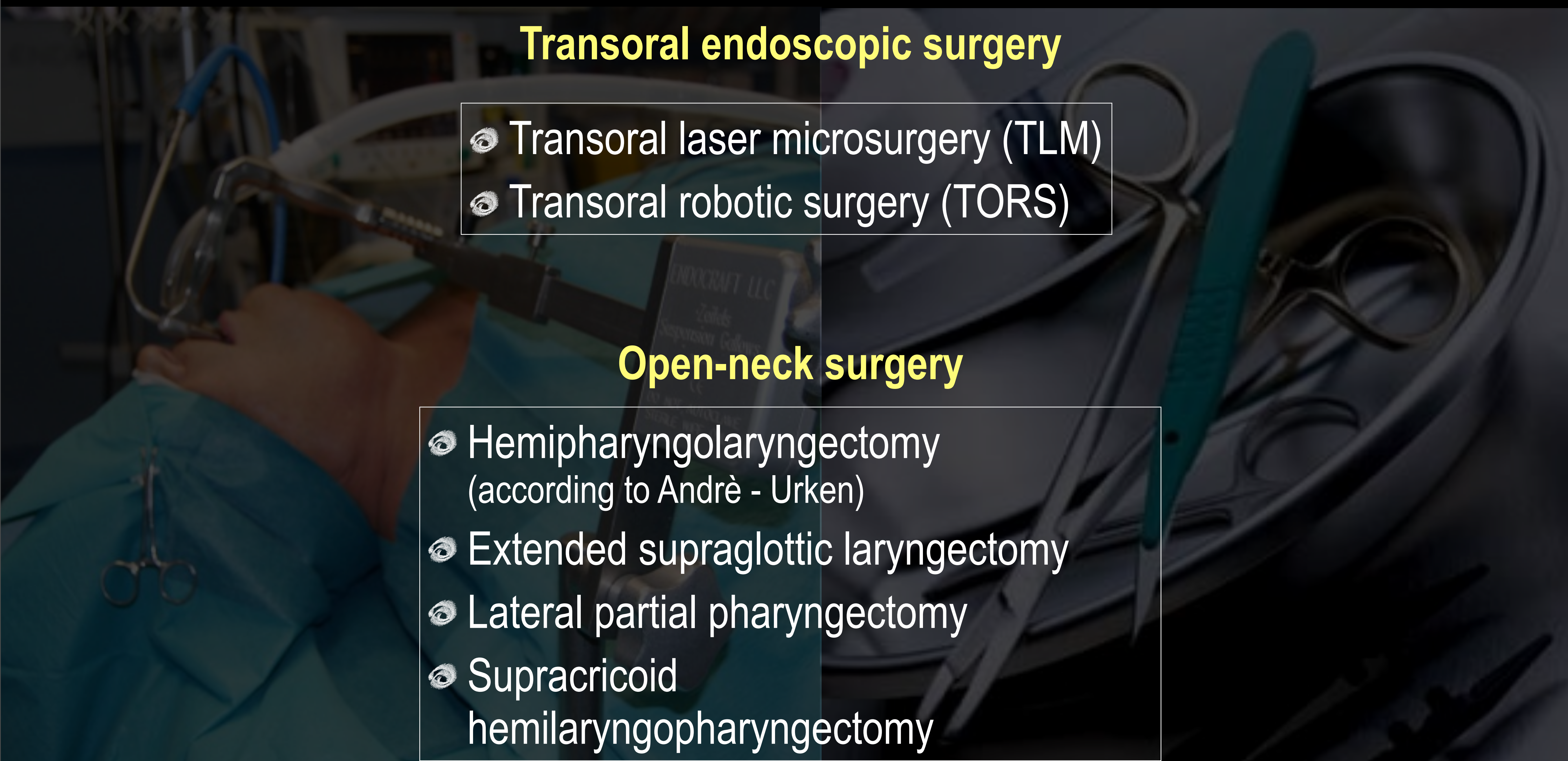
TREATMENT OPTIONS

Hypopharyngeal SCC

- **Non surgical** larynx-preservation protocols
  - RT
  - CHT-RT
  - Induction CHT
- Surgical approaches
  - **Surgical** larynx-preservation approaches
    - Endoscopic approaches
    - Open-neck partial surgery
  - **Total laryngectomy + partial/ circumferential pharyngectomy**

CONSERVATIVE SURGERY

Larynx preservation



Transoral endoscopic surgery

- Transoral laser microsurgery (TLM)
- Transoral robotic surgery (TORS)

Open-neck surgery

- Hemipharyngolaryngectomy
  (according to Andrè - Urken)
- Extended supraglottic laryngectomy
- Lateral partial pharyngectomy
- Supracricoid hemilaryngopharyngectomy

ENDOSCOPIC APPROACHES

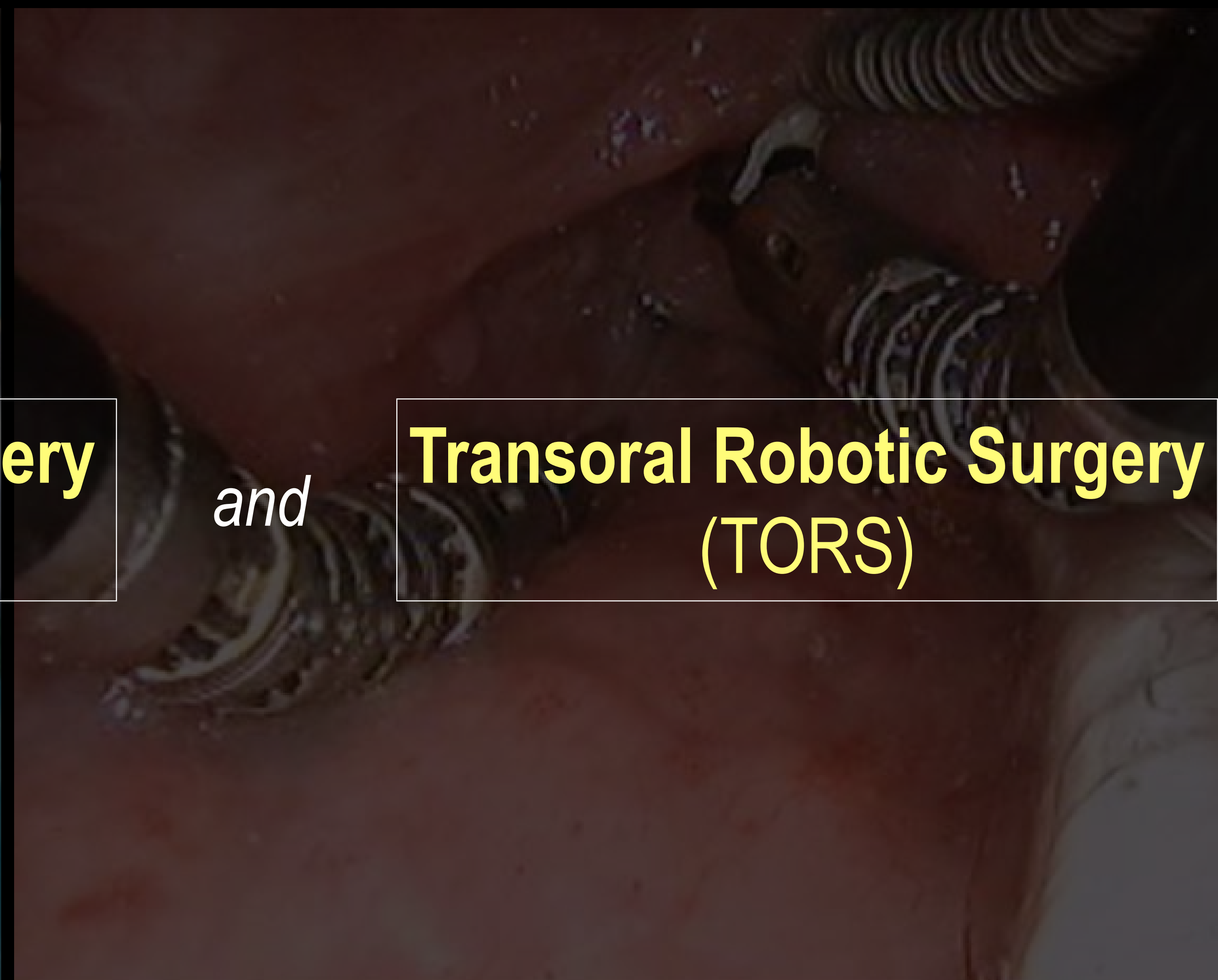
Minimally invasive organ- and function-preserving surgery
has been introduced in the surgical armamentarium to increase post-operative QoL

Both oncological and functional effective alternatives to organ preservation protocols

IN EARLY STAGES

ENDOSCOPIC APPROACHES

Minimally invasive organ- and function-preserving surgery
has been introduced in the surgical armamentarium to increase post-operative QoL



Transoral Laser Microsurgery
(TLM)

and

Transoral Robotic Surgery
(TORS)

Both oncological and functional effective alternatives to organ preservation protocols

IN EARLY STAGES

TRANSORAL LASER MICROSURGERY

Indications

- ✓ T1-T2, mainly involving the upper part of the piriform sinus
- ✓ Adequate exposure is mandatory
- ✓ Retrocricoid neoplasms: only without cartilage/ cricoarytenoid joint involvement
- ✓ Preservation of at least one mobile arytenoid

Contraindications

- ✳ invasion of the thyroid/cricoid cartilage
- ✳ invasion of the paraglottic space lateral to the true vocal cord
- ✳ deep involvement of the neck
- ✳ involvement of the upper esophagus
- ✳ required bilateral arytenoid resection

Lindholm's laryngoscope

Vilaseca et al, Curr Opin Otolaryngol Head Neck Surg 2012
Steiner et al, Otolaryngol Head Neck Surg 2001
Martin et al, Laryngoscope 2008

TRANSORAL LASER MICROSURGERY

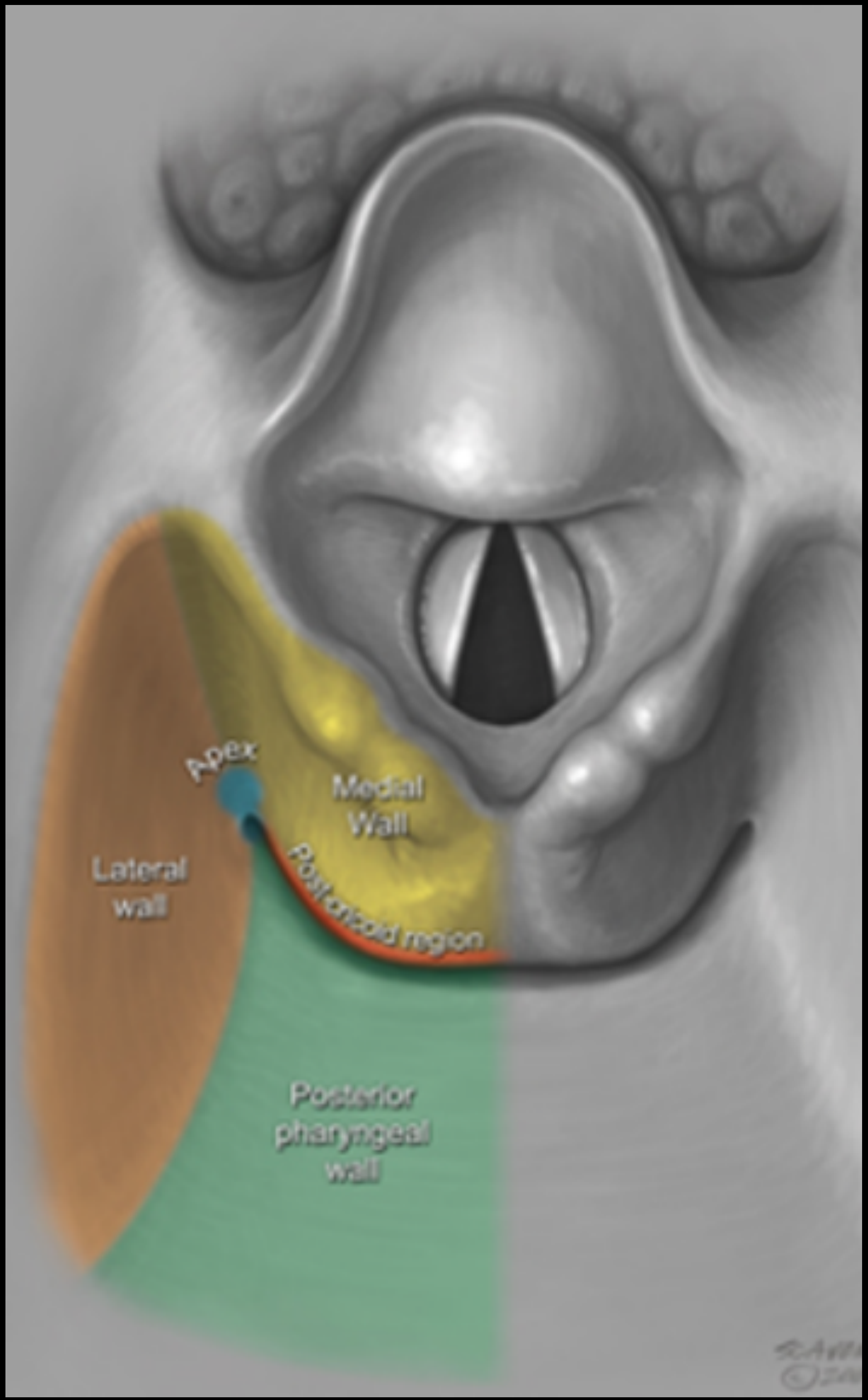
SURGICAL APPROACH

MEDIAL AND ANTERIOR WALL

Safe resection is possible in superficial tumors

Tumor exposure may be favoured by partial resection of:

- Epiglottis
- Aryepiglottic fold
- Arytenoid region
- Pharyngoepiglottic fold



TRANSORAL LASER MICROSURGERY

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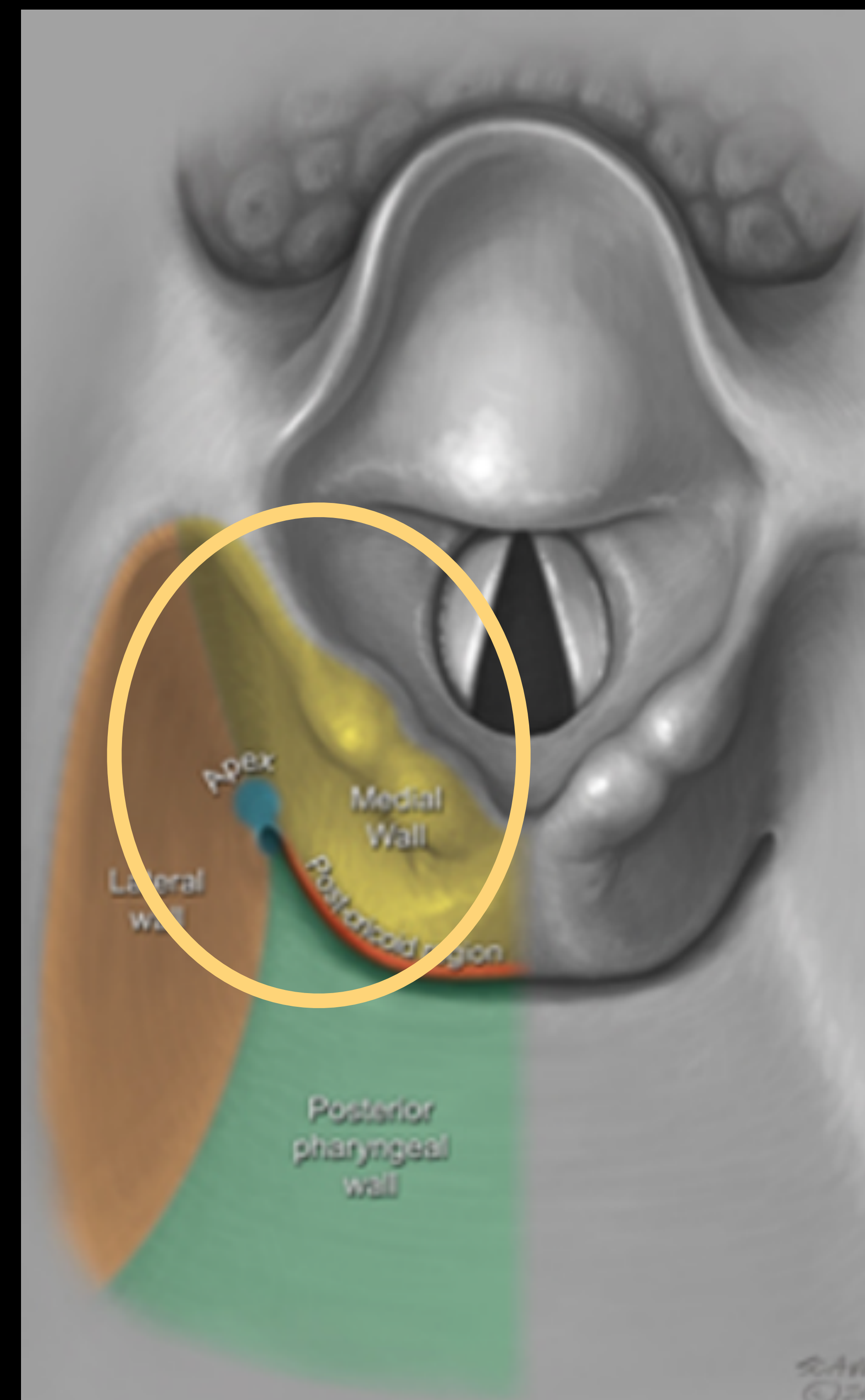
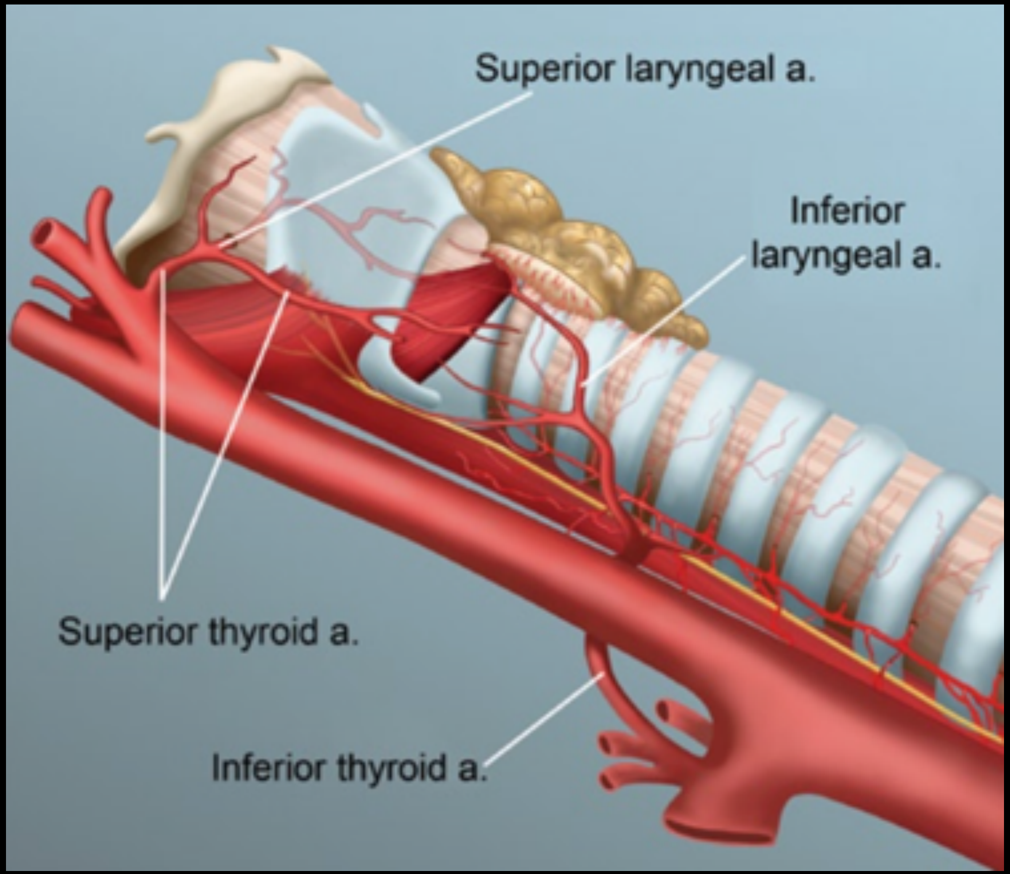
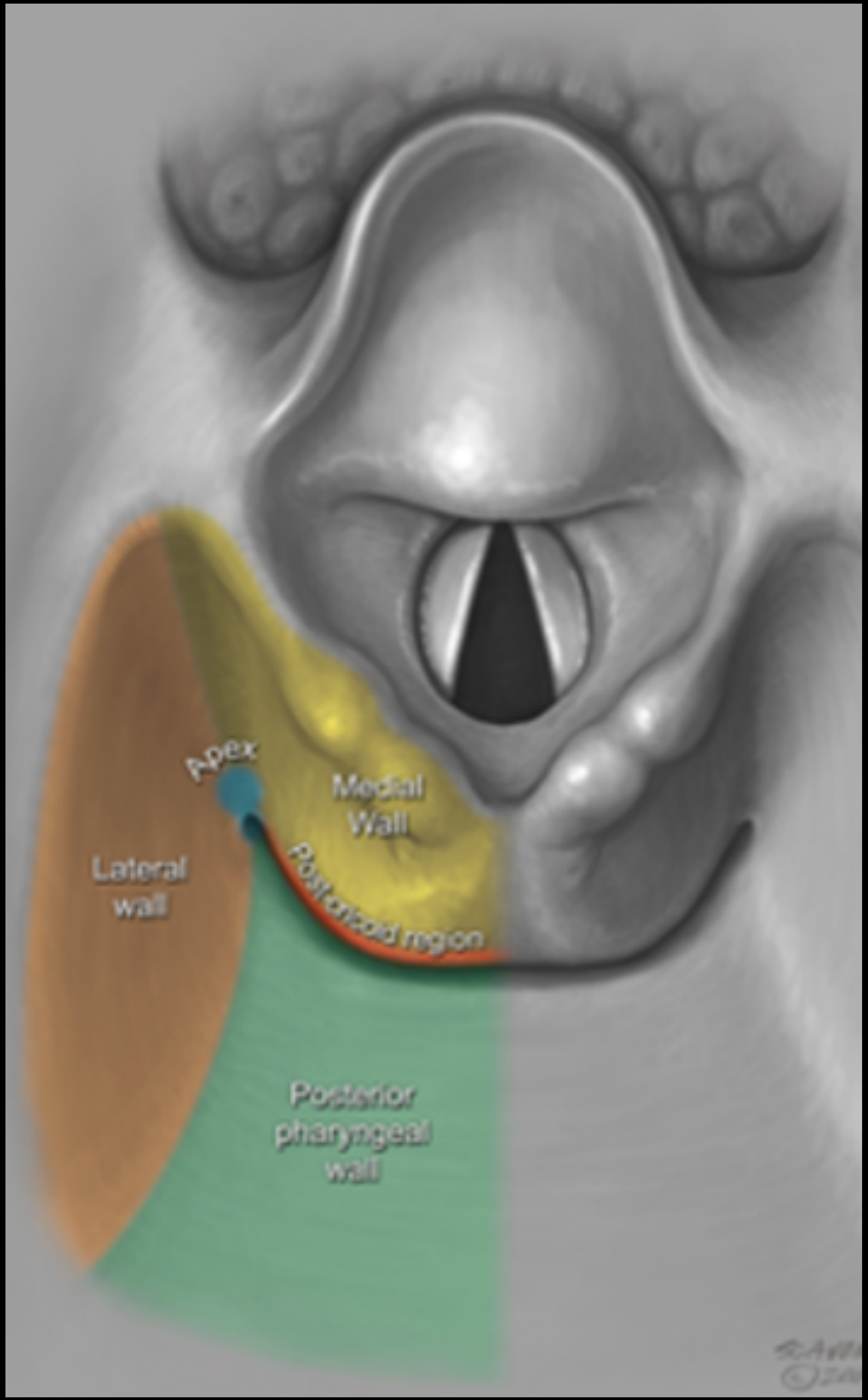


SURGICAL APPROACH

LATERAL AND POSTERIOR WALL

Safe resection is possible in superficial tumors with limited infiltration of the muscle and no extension to the parapharyngeal space





TRANSORAL LASER MICROSURGERY

SURGICAL APPROACH

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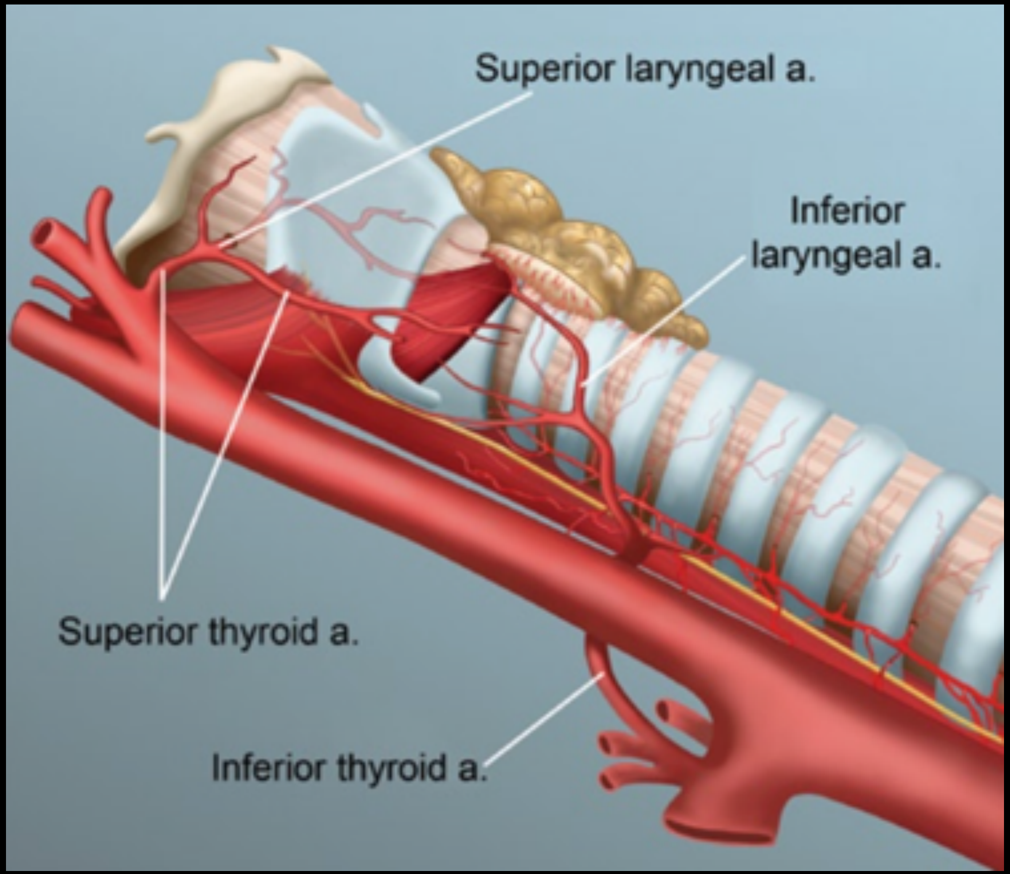
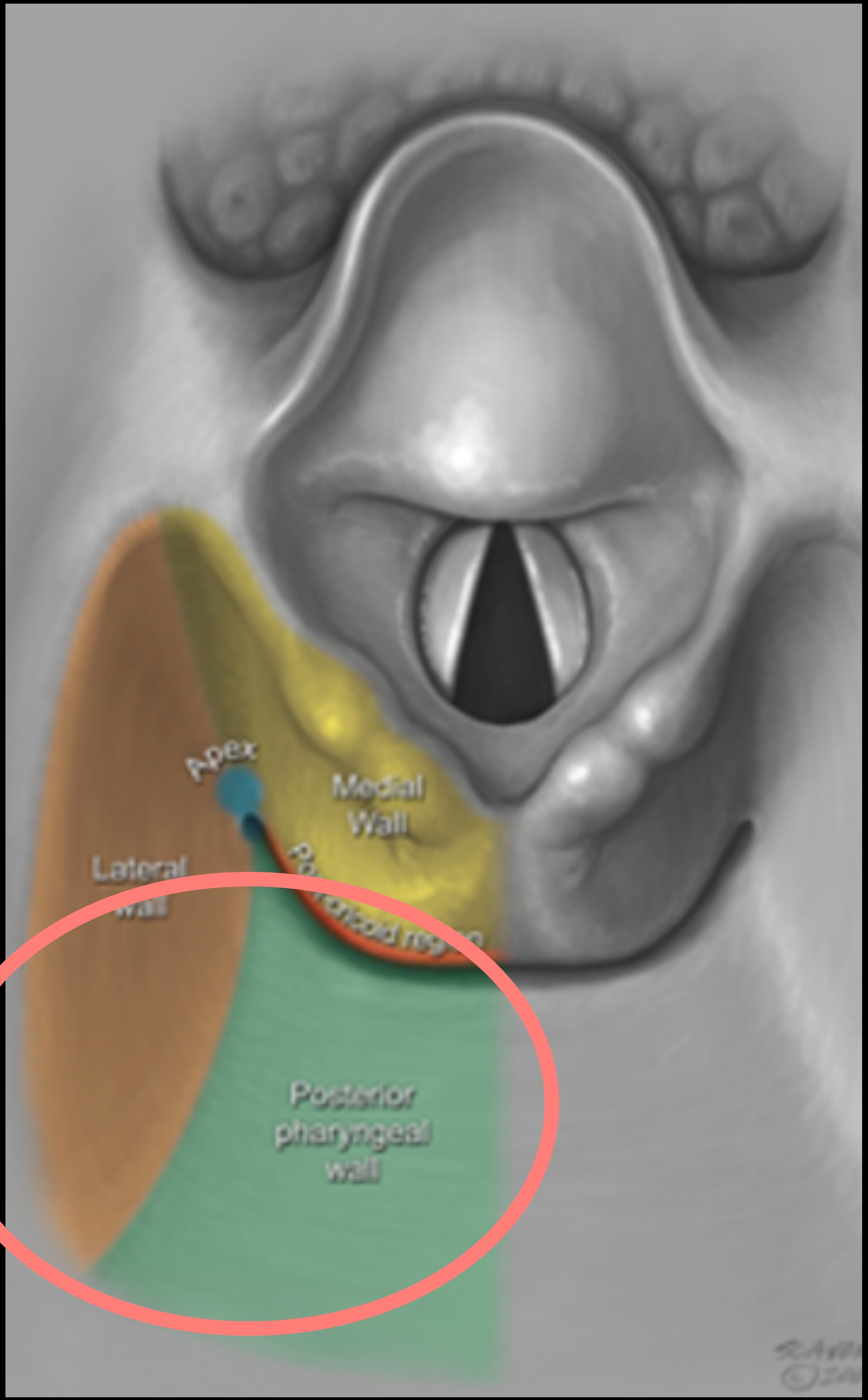




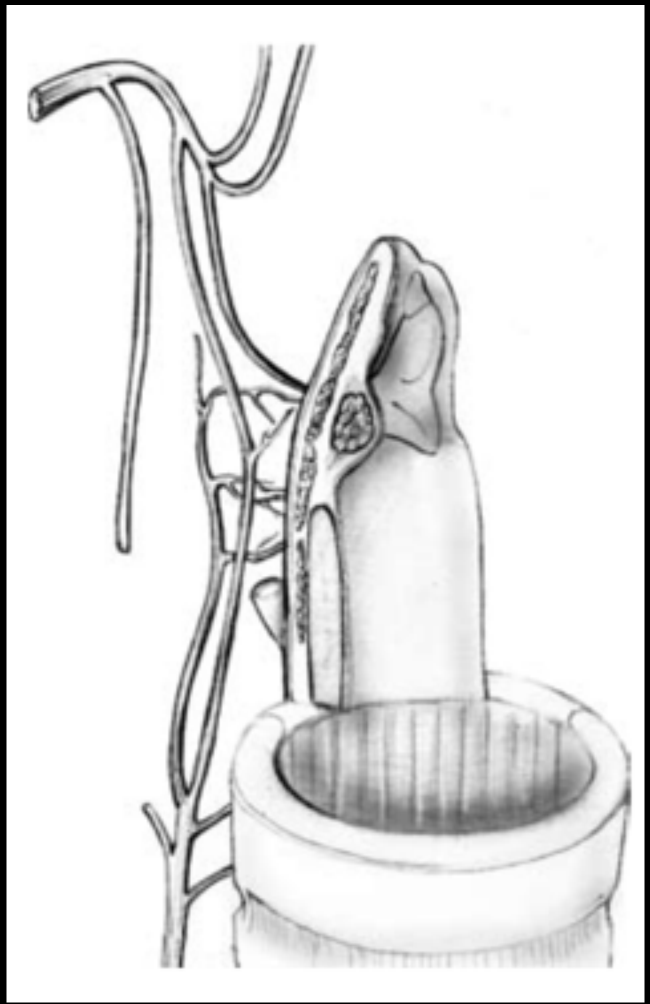
TRANSORAL LASER MICROSURGERY

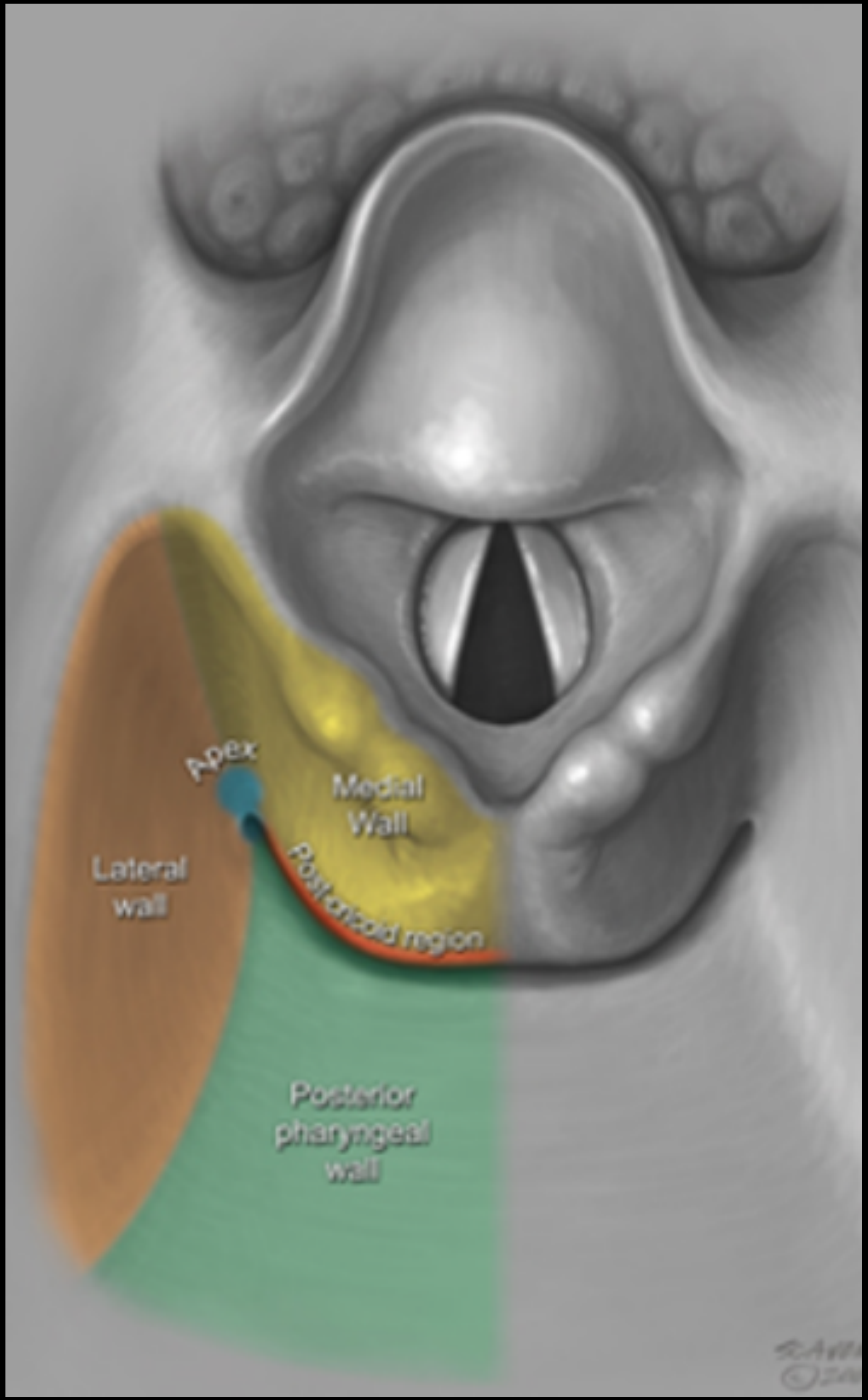
SURGICAL APPROACH

RETROCRICOID AND PERI-ARYTENOID REGION

Such tumors should be managed according to principles applied in conventional laryngeal surgery

CRICO-ARYTENOID JOINT INVOLVEMENT





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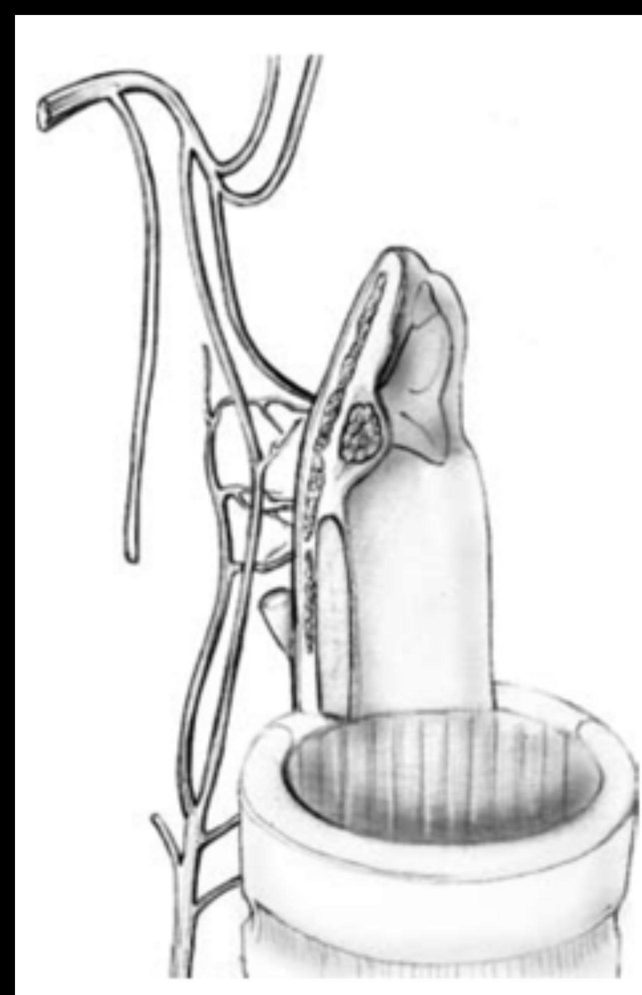
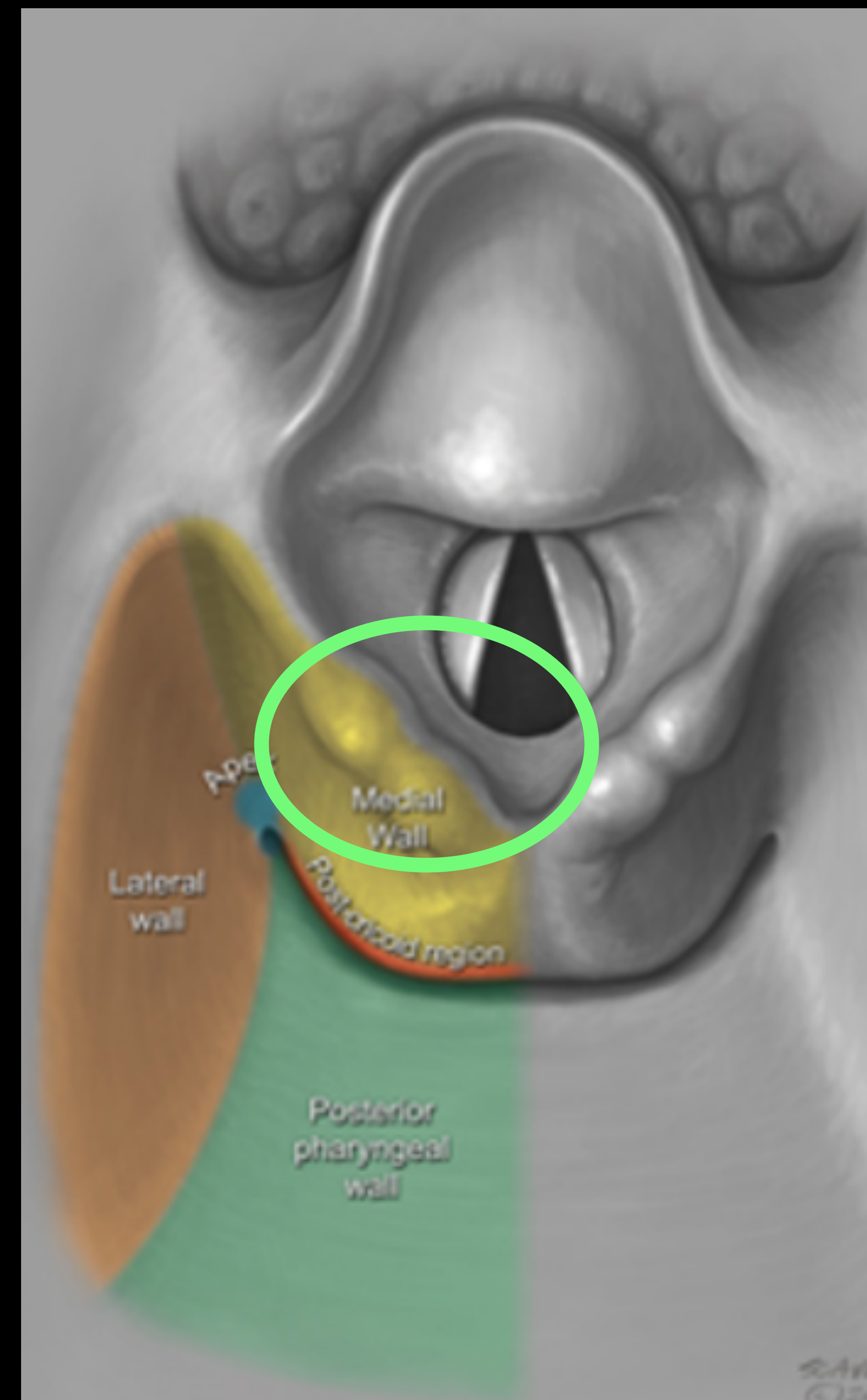
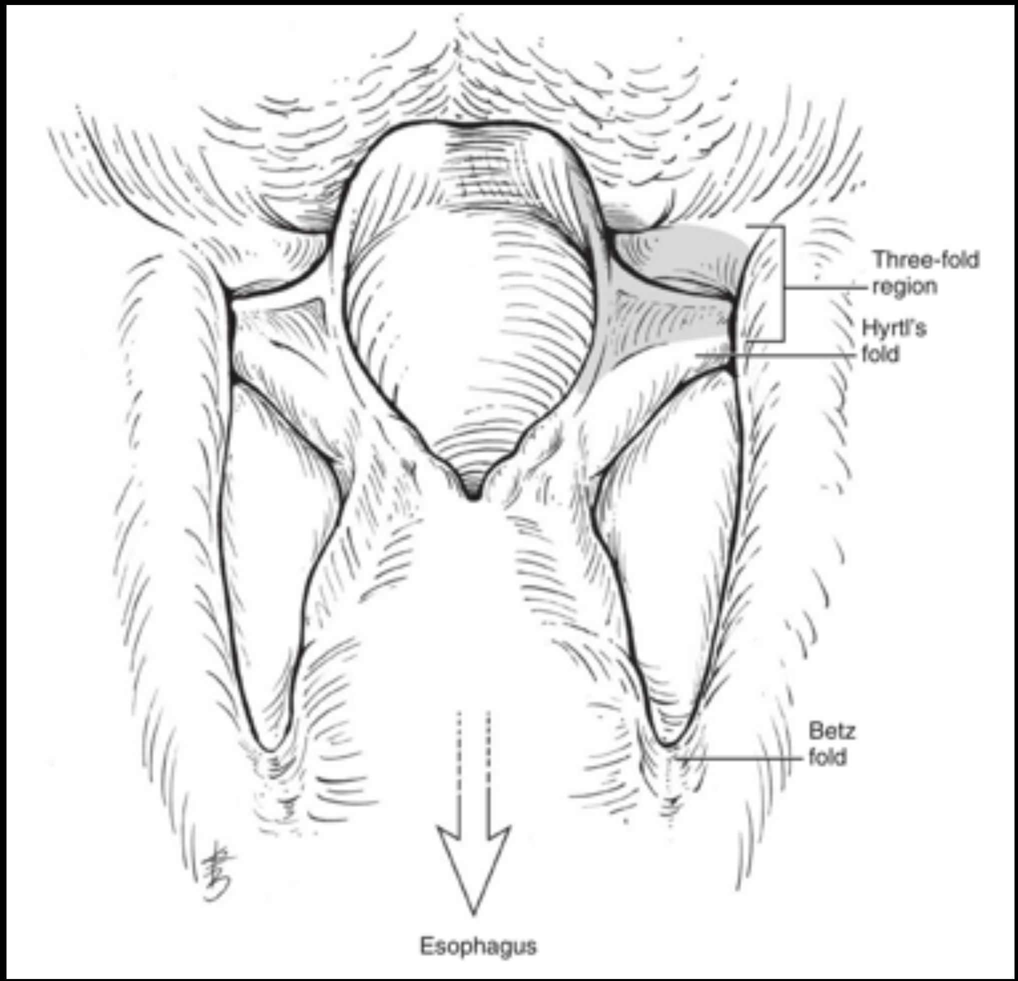


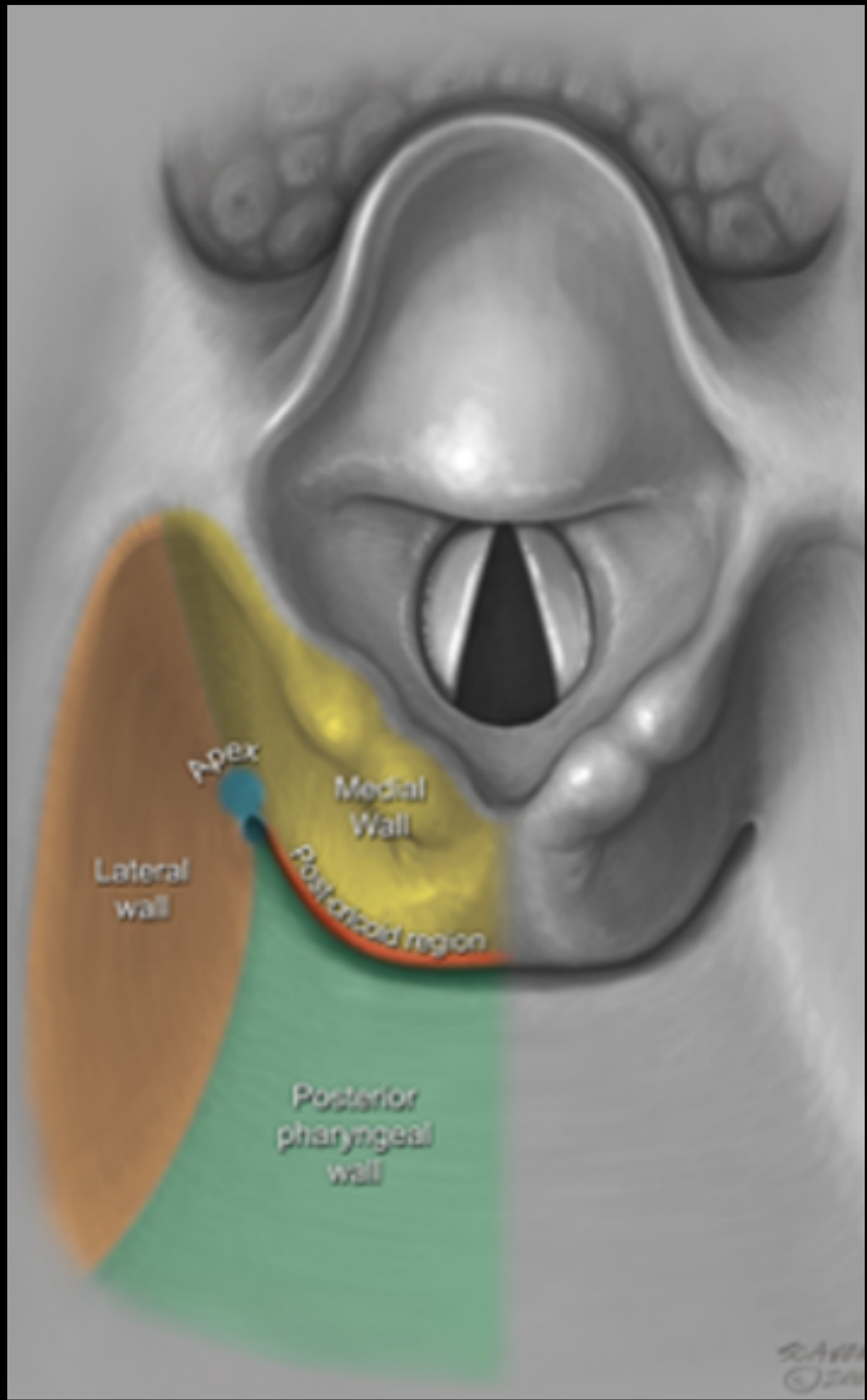


TRANSORAL LASER MICROSURGERY

SURGICAL APPROACH

EXTENSION TO UPPER ESOPHAGUS BELOW BETZ' FOLD



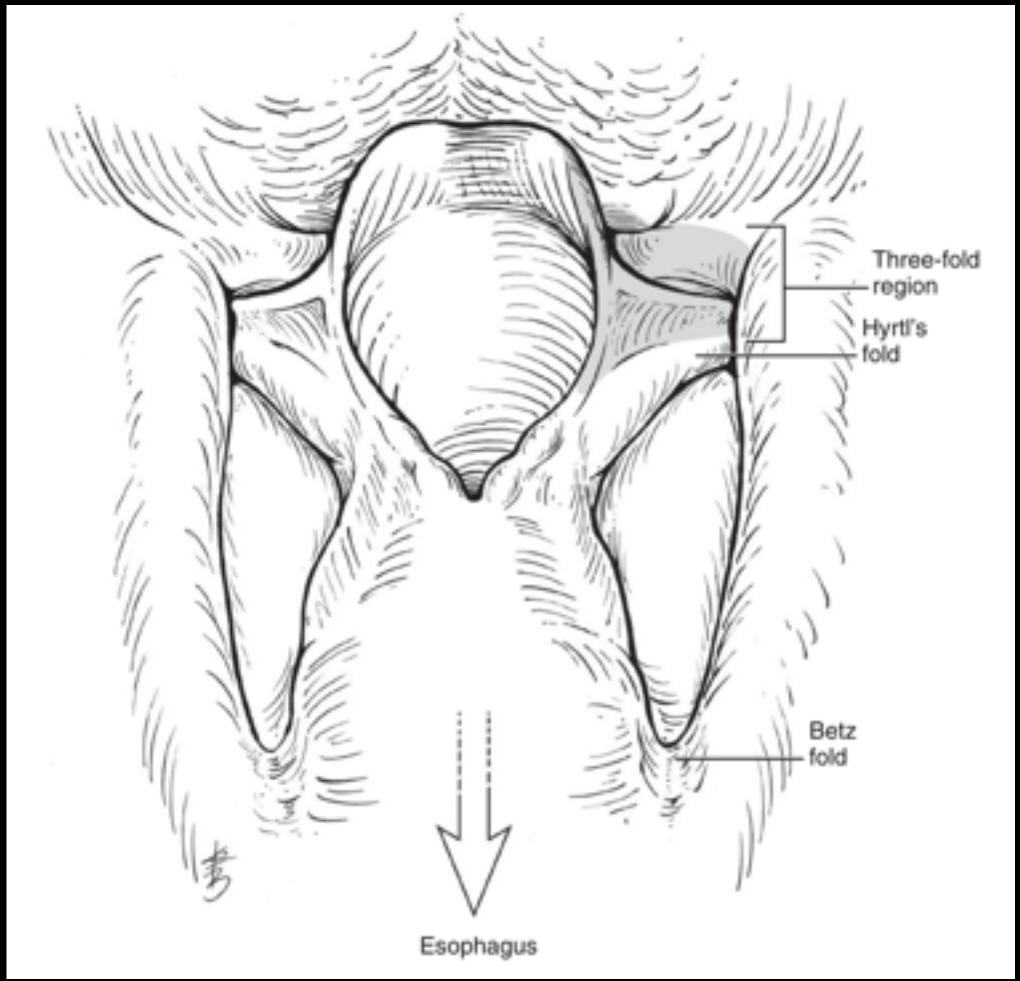


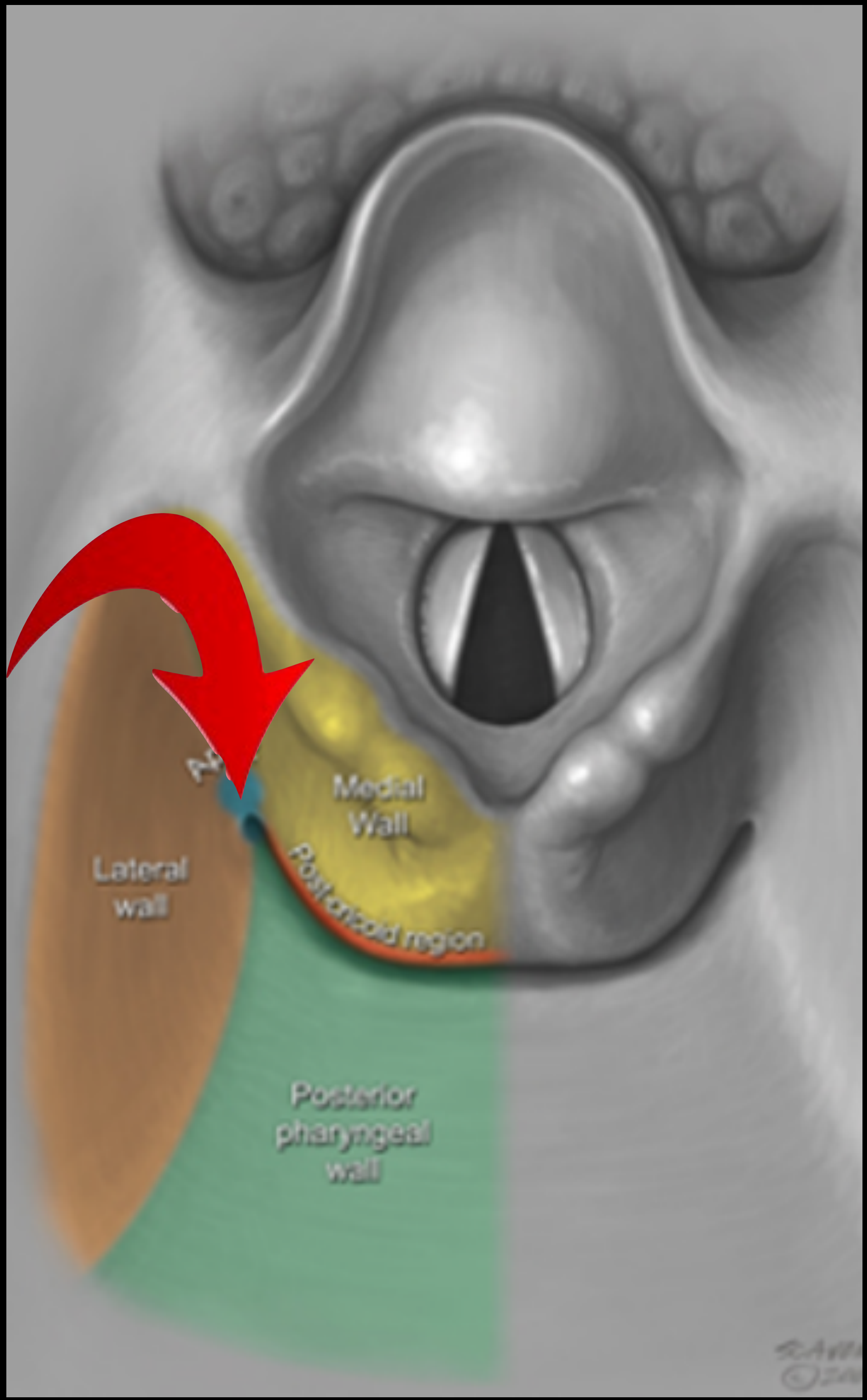
RISK OF BLEEDING AND POSTOPERATIVE STRICTURE

TRANSORAL LASER MICROSURGERY

SURGICAL APPROACH

EXTENSION TO UPPER ESOPHAGUS BELOW BETZ' FOLD





RISK OF BLEEDING AND POSTOPERATIVE STRICTURE

TRANSORAL LASER MICROSURGERY

Oncological results in early T-stages (T1-2)

	T1	T2
OS (5-yy)	44-78.8%	48-60.1%
DSS	77,8%	70,0%
Larynx-preservation	87-100%	78,5%
PEG	2.5-5.2%	**21,4%**
Tracheotomies	0-2.5%	1,7%

Vilaseca et al, Curr Opin Otolaryngol Head Neck Surg 2012

TRANSORAL LASER MICROSURGERY

Oncological results in advanced T-stages (T3-4)

Experience with TLM is still very limited and only few institutions have a consistent cohort

Author	N° pt	Stage	Survivals	Local control
Steiner 2001	129	Stage III+IV	**Stage III+IV (5 yy)** OS: 47% RFS: 69%	-
Vilaseca 2004	28	Stage II+IV	**Stage II+IV (4 yy)** OS: 43%	LC T3 56.2% (n=49) LC T4 100% (n=1) organ preserv 79%
Martin 2008	172	Stage III+IV	**Stage III (5 yy)** OS: 64% DSS: 86% **Stage IV (5 yy)** OS: 41% DSS: 57%	LC T3 75% (n=75) (82% plus adjuvant RT vs 66% without) LC T4 57% (n=28)

After TLM for III-IV stage, patients received adjuvant (C)RT → Local control rates are better than those obtained with (C)RT alone

Can the intensity of adjuvant treatment be really reduced after TLM or will it only increase side-effects???

Vilaseca et al, Curr Opin Otolaryngol Head Neck Surg 2012

TRANSORAL ROBOTIC SURGERY

Only preliminary results…

- ✓ Early lesions (T1/2)
- ✓ The pharyngeal constrictors as deep margin
- ✓ Healing via secondary intention
- ✓ Temporary G-tube in few cases (depending on the extension of resection)
- ✓ Full recovery of swallowing function by 6 months post-operatively in 80% of patients

Dziegielewski et al, J Surg Oncol 2015

- ✳ More complicated peri-operative hemorrhage management
- ✳ More thermal damage for the use of unipolar cautery than for a laser
- ✳ Costs and scarce data on oncological results
- ✳ Intraoperative exposure
- ✳ Coverage with local flap/fibrin sealant to prevent hemorrhage

The future combination of CO_2 laser with robotic arms will solve the lack of precision

Park et al, Oral Oncol (2010)
Verges et al, Otolaryngol Head Neck Surg 2012
Kucur et al, Head Neck 2015
Durmus et al, J Craniofac Surg 2015

Open-neck approaches

Partial pharyngectomies:
back to the future???

Leroux-Robert, 1957

Ogura, 1960

Andre, 1965

Ferguson, 1976

Laccourreye H, 1986

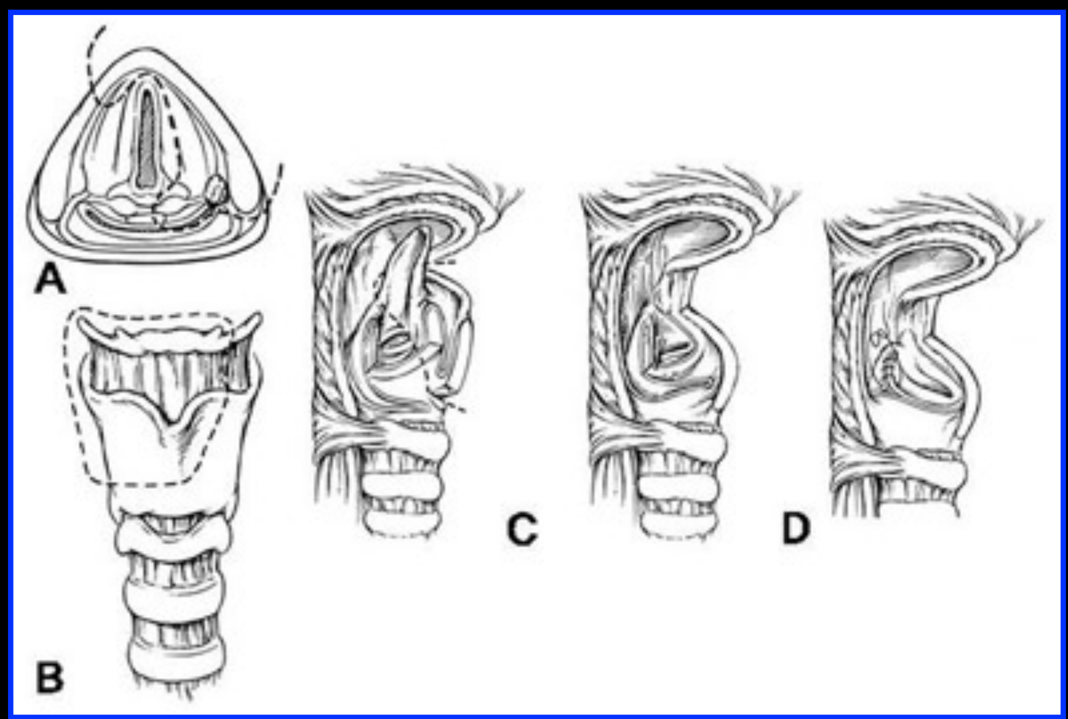
Laccourreye H, 1987

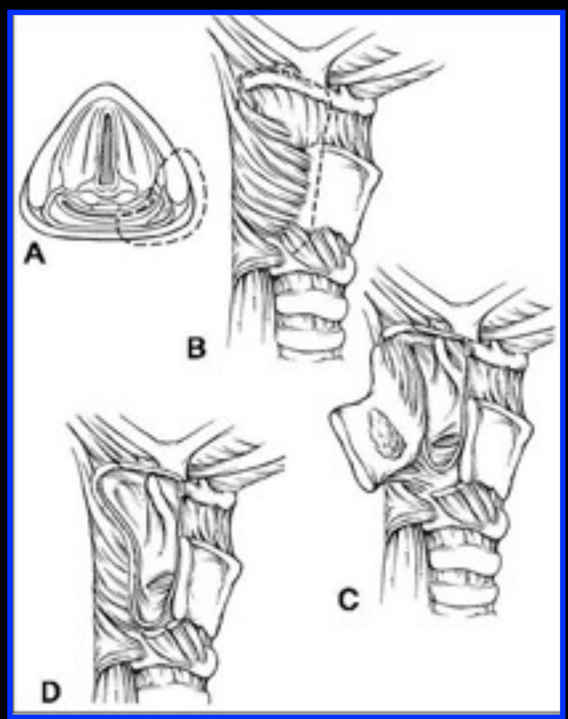
Laccourreye et al, Ann Otol Rhinol Laryngol. 2005
Kania et al, Ann Otol Rhinol Laryngol. 2005
Holsinger et al, Head Neck 2006
Papacharalampous et al, World J Surg Oncol 2009

- Few published reports
- Most examine early-stage disease
- Selection criteria vary widely
- The exact location and extent of the tumor are not always specified

Partial pharyngectomies

- Hemipharyngolaryngectomy (according to Andrè - Urken)
- Extended supraglottic laryngectomy
- Lateral partial pharyngectomy
- Supracricoid hemilaryngopharyngectomy





Often integrated in a complex oncological strategy: neoadjuvant CHT, partial surgery and adjuvant (CHT)RT if necessary

Kania et al, Ann Otol Rhinol Laryngol. 2005
Holsinger et al, Head Neck 2006

Open-neck approaches

Pharyngolaryngectomy

- High-stage lesions involving **more than two thirds of the hypopharyngeal circumference**
- **Residual and recurrent disease after failure of CHT-RT**

Total laryngectomy + partial/circumferential pharyngectomy + bilateral neck dissection

In most cases, adjuvant CHT-RT, if not already performed, is necessary

5-yr DSS
40-50%

Takes et al, Head Neck 2005

The pharyngoesophageal defects

	Disa et al, Plast Reconstr Surg 2003	Urken, Atlas of Regional and Free Flaps for Head and Neck Reconstruction 2011
Type 0	minimal defects - amenable to primary closure	minimal defects - amenable to primary closure
Type I	< 50% - **NOT amenable to primary closure**	**non-circumferential** defect, minimum of 2 cm in width, with a viable strip of mucosa
Type II	> 50%	**circumferential** defect extended no further cephalad than the level of the vallecula
Type III	other anatomical regions (nasopharynx, oropharynx, or of the mouth or jaw)	circumferential/non-circumferential defect **extended cephalad to the level of the vallecula**
Type IV	extension to cervical oesophagus	any resection that extends caudal to the level of the clavicles

Open-neck approaches

The pharyngoesophageal defects

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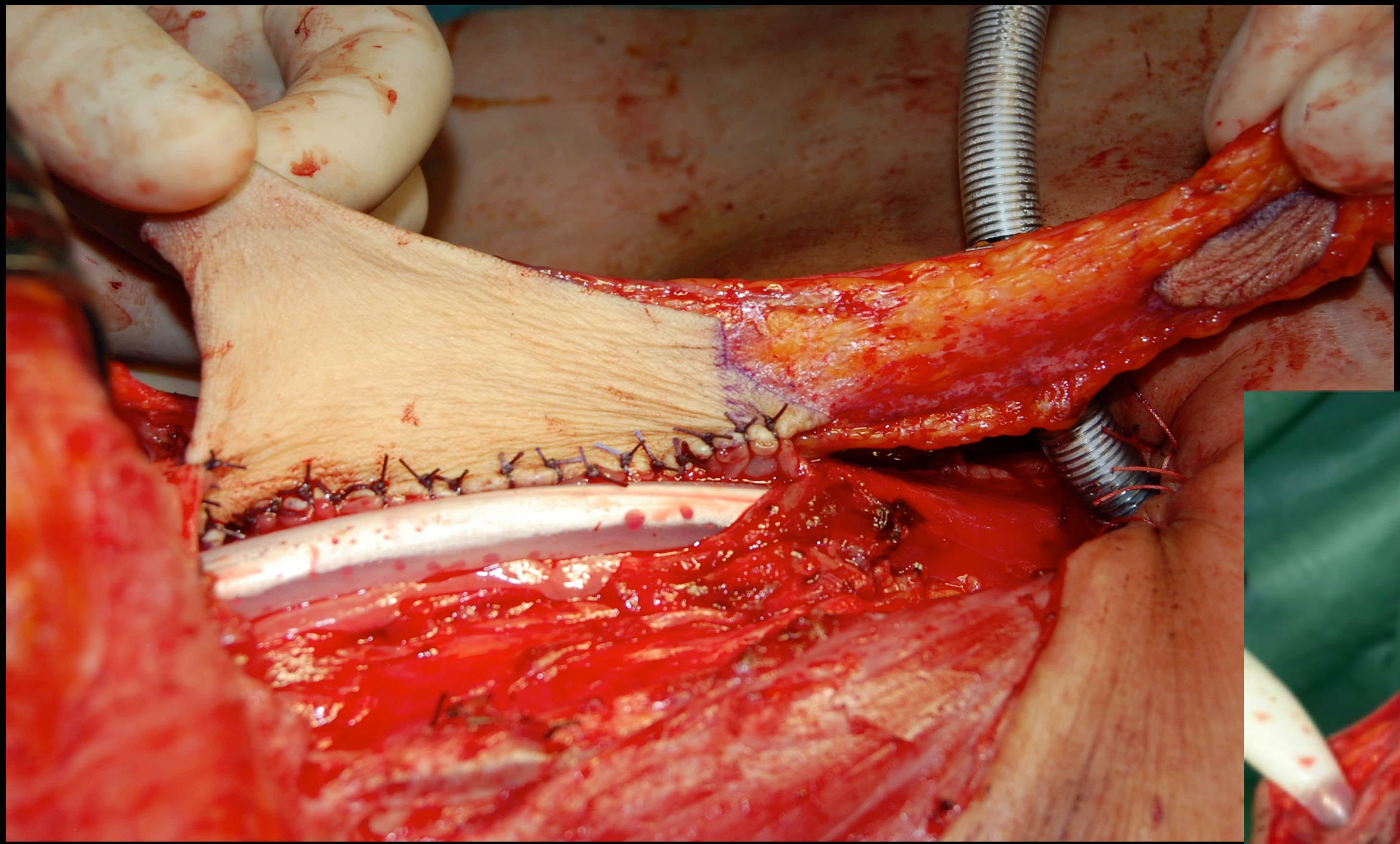
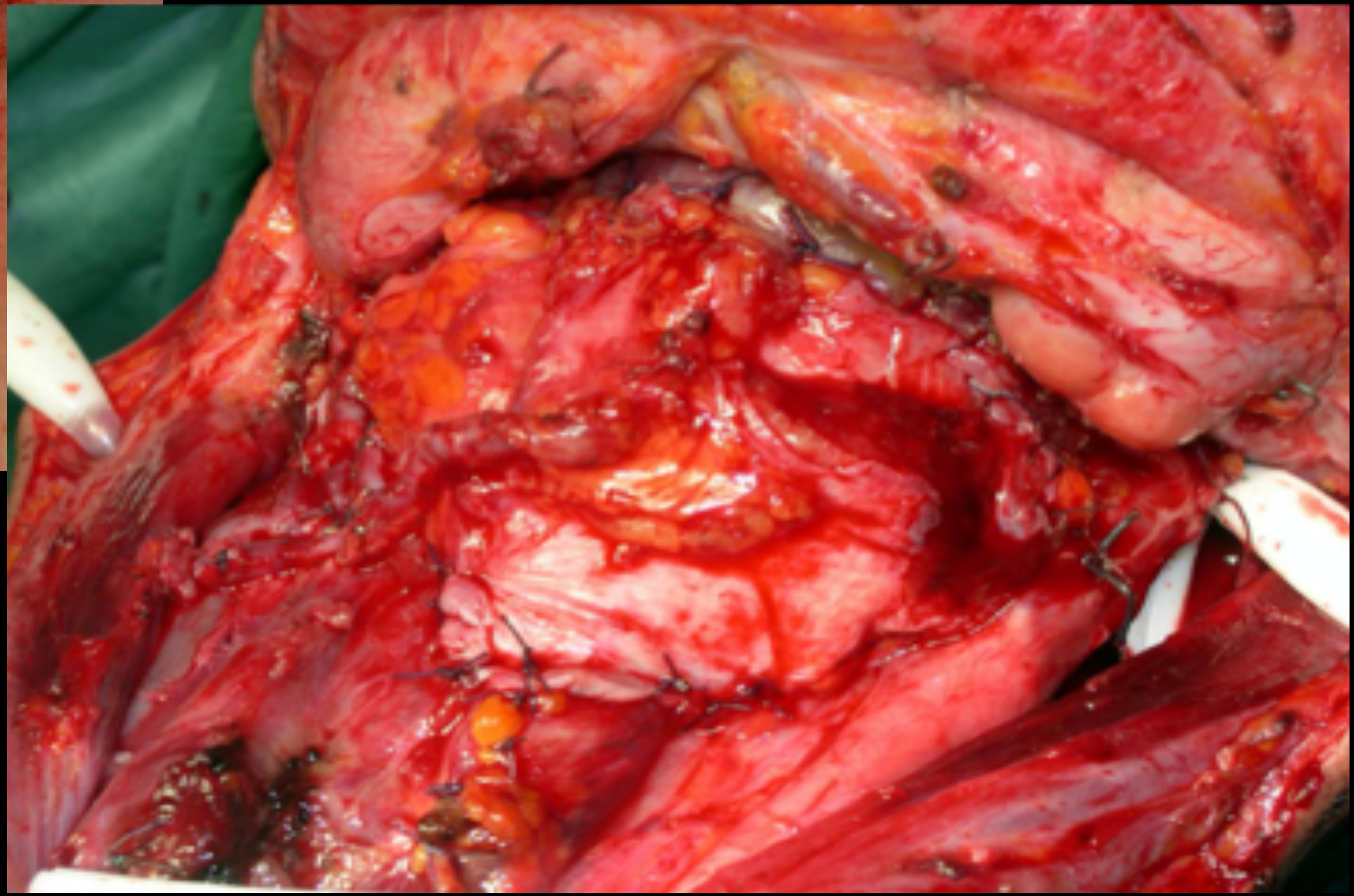
The pharyngoesophageal defects





MENU OF RECONTRUCTIVE MODALITIES

Myo-cutaneous (or myo-fascial) pedicled flaps
Pectoralis major

Fascio-cutaneous free flaps
Radial forearm
Antero-lateral thigh

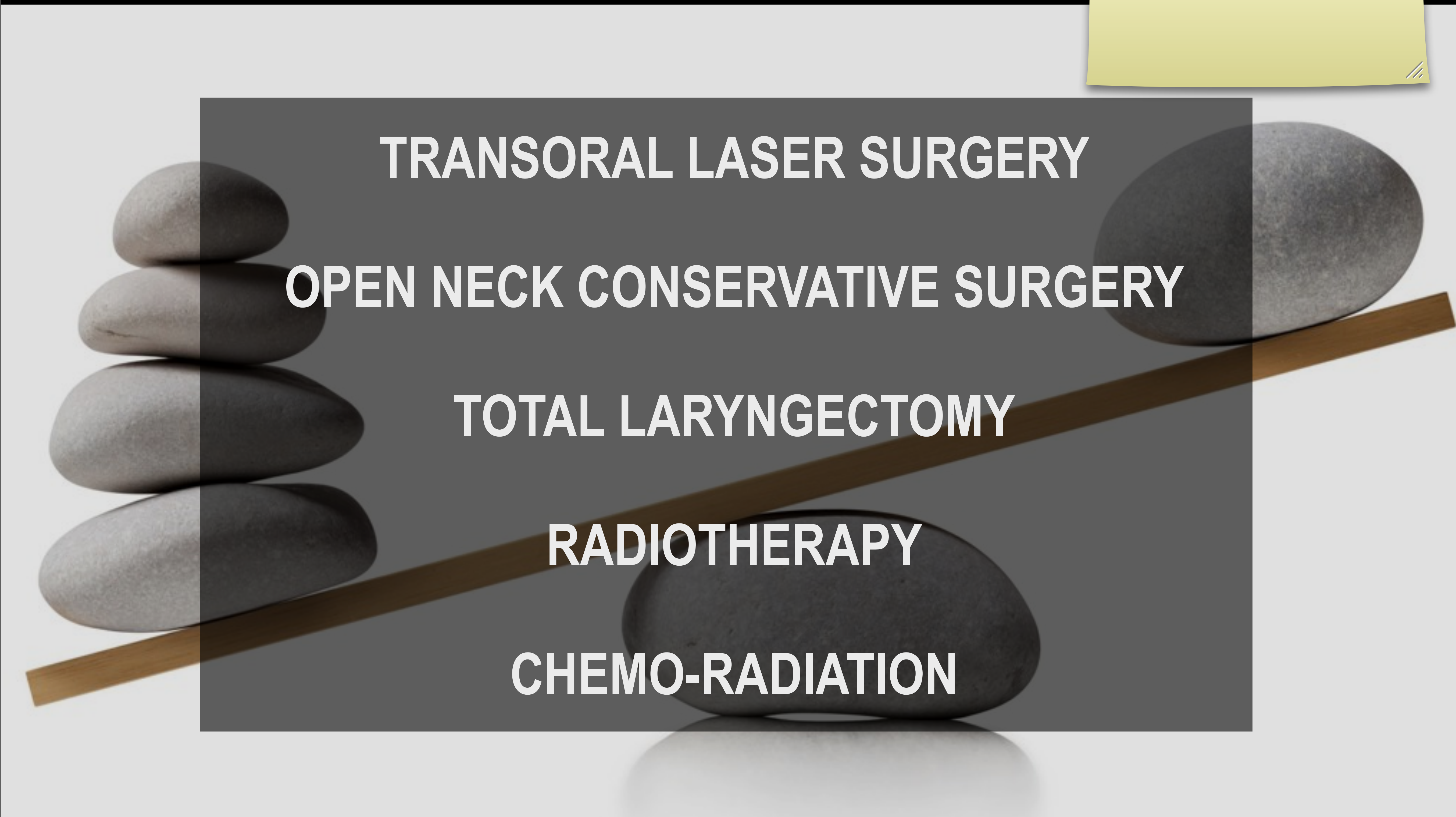
Visceral pedicled flaps
Ileo-colic transposition
Gastric pull-up

Visceral free flaps
Jejunum

SURGICAL OPTIONS

Nausica Montalto 19 giu 2016, 11:46
non surgical options

A matter of balance… and personalized tre



TRANSORAL LASER SURGERY

OPEN NECK CONSERVATIVE SURGERY

TOTAL LARYNGECTOMY

RADIOTHERAPY

CHEMO-RADIATION

Management of hypopharyngeal and laryngeal SCC: radiotherapy

Vincent GREGOIRE, MD, PhD, Hon. FRCR

Head and Neck Oncology Program, Radiation Oncology Dept. & Center for Molecular Imaging, Radiotherapy and Oncology, Université Catholique de Louvain, St-Luc University Hospital, Brussels, Belgium

Staging of laryngeal tumors (TNM-UICC 2010)

Primary Tumor (T)

Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ

Supraglottis

T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3 Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx, (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Staging of laryngeal tumors (TNM-UICC 2010)

Subglottis

T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation
T4a Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Staging of hypoparyngeal tumors (TNM-UICC 2010)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor limited to one subsite of hypopharynx and ≤ 2 cm in greatest dimension
T2 Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures > 2 cm but not > 4 cm in greatest dimension without fixation of hemilarynx
T3 Tumor > 4 cm in greatest dimension or with fixation of hemilarynx
T4a Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue (including prelaryngeal strap muscles and subcutaneous fat)
T4b Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

Regional lymph node and metastasis staging

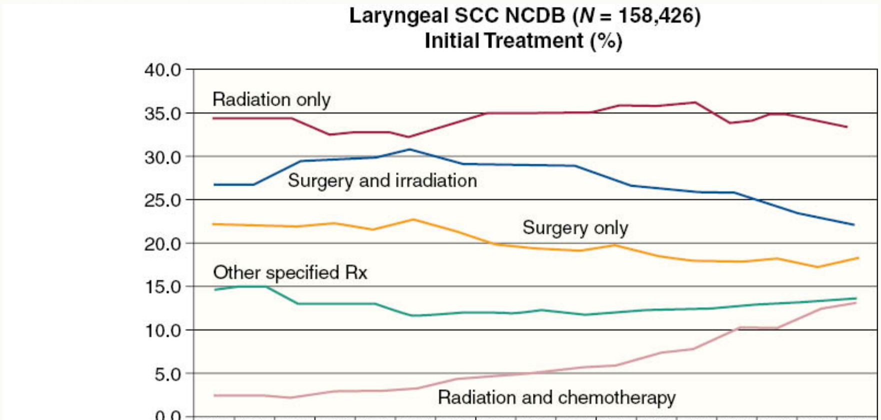
Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N2a Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3 Metastasis in a lymph node, >6 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Evolution in the management of laryngeal SCC

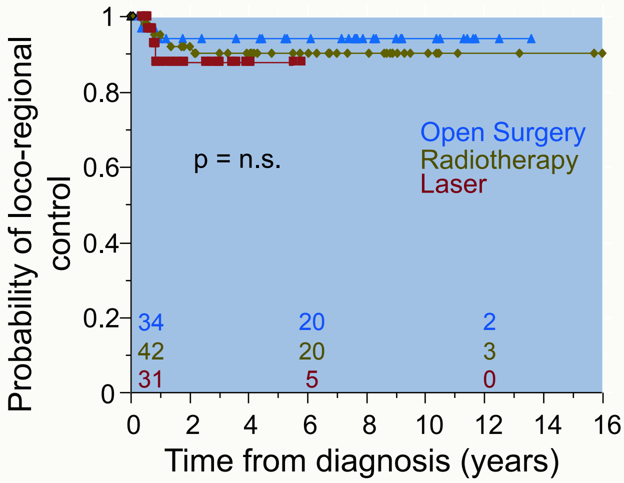


	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Radiation only	34.1	34.1	33.9	32.3	32.5	32.2	33.4	35.1	34.7	34.8	35.6	35.6	36.0	33.7	35.1	33.9	33.1
Surgery & radiation	26.7	26.5	29.2	29.6	29.6	30.7	29.1	29.0	28.6	28.7	27.0	26.4	26.0	25.7	24.1	23.0	22.0
Surgery only	22.3	22.0	22.0	22.3	21.7	22.6	21.4	19.7	19.4	19.2	19.6	18.6	17.9	18.0	18.2	17.5	19.2
Other specified Rx	14.6	15.0	12.9	13.0	13.2	11.5	11.9	11.5	12.3	11.7	12.0	12.3	12.2	12.7	12.5	13.4	13.6
Radiation & chemotherapy	2.3	2.4	2.0	2.7	2.9	3.1	4.2	4.6	4.0	5.5	5.8	7.2	7.8	10.0	10.0	12.3	13.2

(From Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. Laryngoscope. 2006;116[Suppl 111]:1-13.)

Hoffman, Laryngoscope, 2006

Evidence-based management of T1N0 glottic carcinomas: level 3



Rosier, *R&O*, 1998

Radiotherapy in early stage glottic cancers: level 3

T_2 Carcinoma of the Glottis : Local Control with Radiotherapy and Surgical Salvage

Reference	Patients (*n*)	Initial Local Control	Ultimate Local Control
Elman et al (1979)[64]	T_{2a}, 146 T_{2b}, 82	T_{2a}, 80% T_{2b}, 72%	T_{2a}, 96% T_{2b}, 96%
Fletcher and Hamberger (1974)[65]	175	74%	94%
Mittal at al (1983)[66]	327	69%	___
Howell-Burke at al (1985)[67]	114	68%	76%
Amornmarn et al (1985)[67]	34	88%	94%
Karim et al (1987)[76]	156	81%	95%
Wang (1990)[71]	173	69%	86%
Le (1997)[71]	83	67%	___
Mendenhall et al (2001)[72]	120	75%	95%
Frata et al (2005)[77]	256	70%	85%

Radiotherapy in early stage supraglottic cancers: level 3

Local Control after Radiotherapy for Early-Stage Supraglottic Carcinoma			
Series	Stage	Patients (*n*)	Local Control
Fletcher et al (1980)[79]	T_1	24	88%
	T_2	56	79%
Ghossein et al (1974)[80]	T_1	17	94%
	T_2	64	73%
Wall et al (1985)[81]	T_1	38	89%
	T_2	132	74%
Wang and Montgomery (1991)[82]	T_1	23	89%
	T_2	79	89%
Nakfoor et al (1998)[83]	T_1	24	96%
	T_2	73	86%
Skyes et al (2000)[84]	T_1	65	92%
	T_2	136	81%
Hinerman et al (2002)[85]	T_1	22	100%
	T_2	125	86%
Johansen et al (2002)[86]	T_1	154	64%
	T_2	86	62%

Radiotherapy in early stage hypopharyngeal cancers: level 3

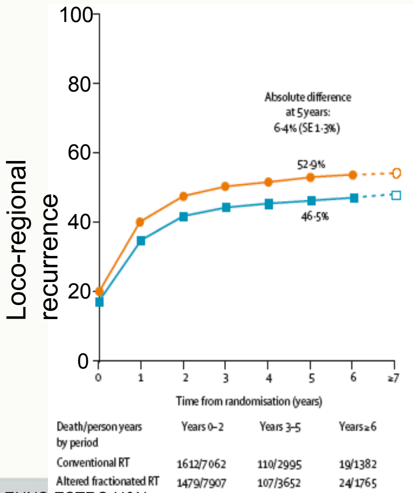
Local Control after Radiotherapy for Early-Stage Hypopharynx Cancer					
Reference	Stage	Patients, *n*	Site	Initial Local Control	Ultimate Local Control
Mendenhall et al (1993)[51]	T_1	17	PS	88%	94%
	T_2	56	PS	79%	91%
Garden et al (1996)[50]	T_1	19	All	89% (2-yr)	NR
	T_2	63	All	77%	NR
Amdur et al (2001)[95]	T_1	19	PS	89%	95%
	T_2	67		82%	91%
Nakamura (2006)[96]	T_1	39	All	74%	87%
	T_2	76	All	58%	74%

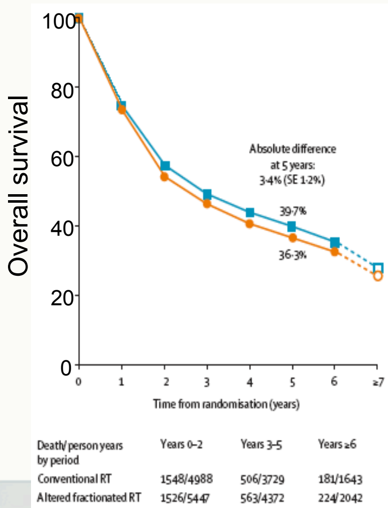
Radiotherapy or surgery in laryngeal/ hypopharyngeal cancers?

- T/N stage
- A single procedure?
- Partial >< total laryngectomy or pharyngo-laryngectomy?
- Patient's co-morbidity, medical history and age
- Patient's preference

Meta-analysis on altered fractionation HNSCC

Randomized trials 1970-1998 (no postop RT)
15 trials included (6515 patients, individual data)





Bourhis, Pignon 2006

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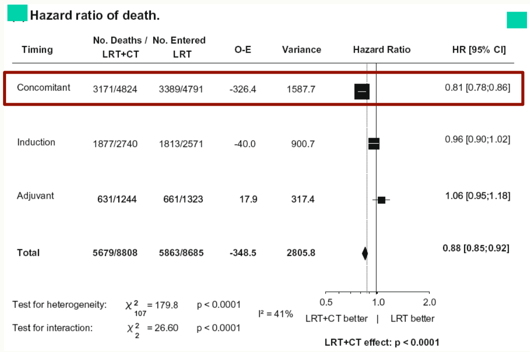
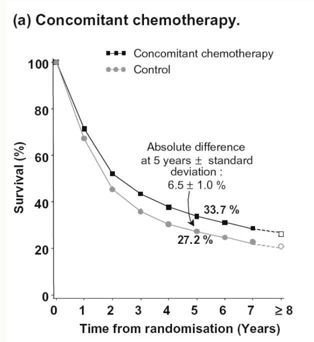
Meta analysis

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

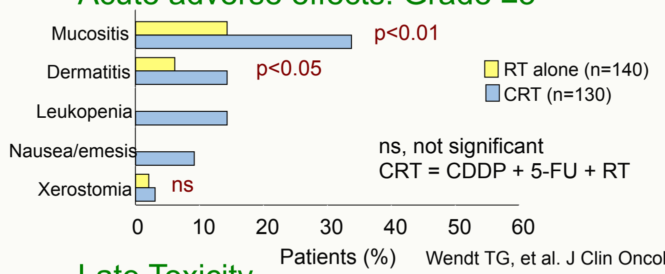




Pignon et al, Radioth Oncol 2009

Toxicity of concomitant CH-RxTh for HNSCC

Acute adverse effects: Grade ≥3

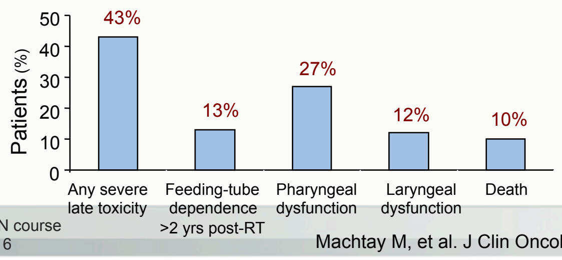


ns, not significant
CRT = CDDP + 5-FU + RT

Wendt TG, et al. J Clin Oncol 1998;16:1318–1324

Late Toxicity

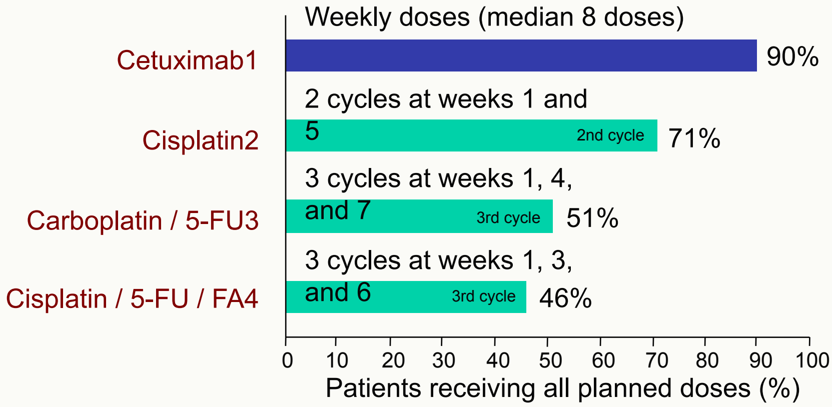
Analysis of 230 patients receiving CRT in 3 studies (RTOG 91-11, 97-03, 9-14)



Machtay M, et al. J Clin Oncol 2008; 26: 3582–3589

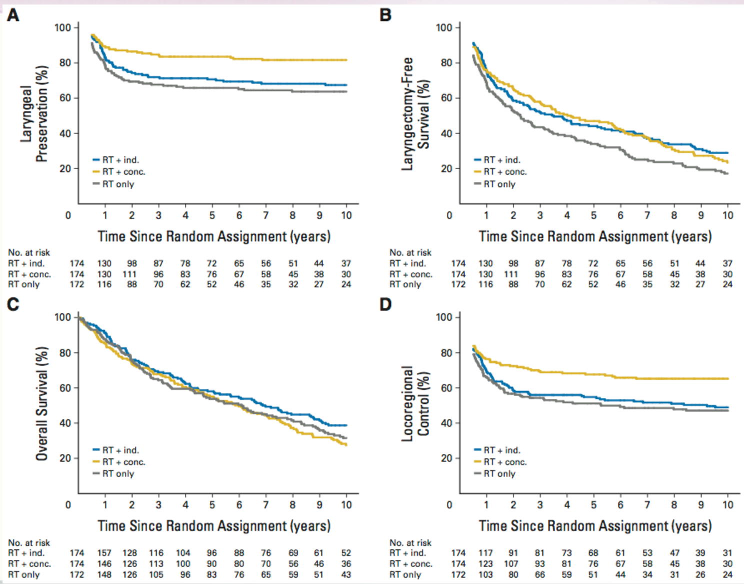
Treatment compliance to CRT or RT-EGFR-inh.

CRT arms of studies comparing CRT vs RT alone



1Bonner JA, et al. N Engl J Med 2006; 354: 567–578
2Huguenin P, et al. J Clin Oncol 2004; 22: 4665–4673
3Calais G, et al. J Natl Cancer Inst 1999; 91: 2081–2086
4Wendt TG, et al. J Clin Oncol 1998; 16: 1318–1324

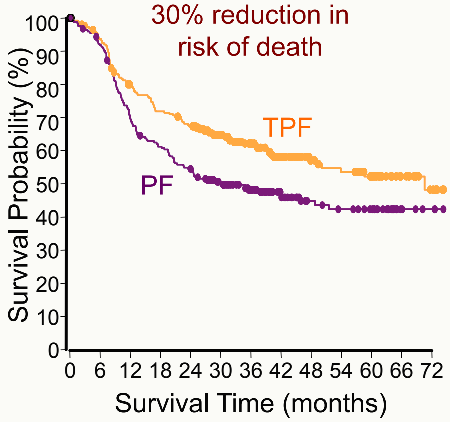
Chemotherapy: Induction or Concomitant?



Forastiere, 2013

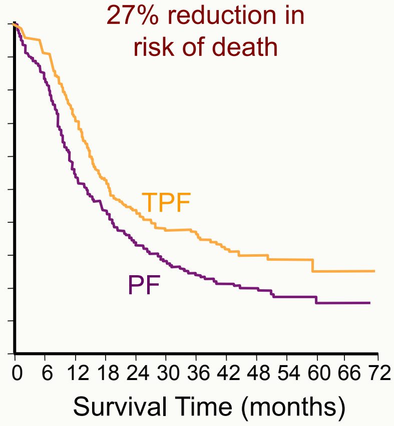
Induction chemotherapy revisited with TPF

TAX 324
30% reduction in risk of death



Posner et al, NEJM 2007
Resectable/unresectable disease

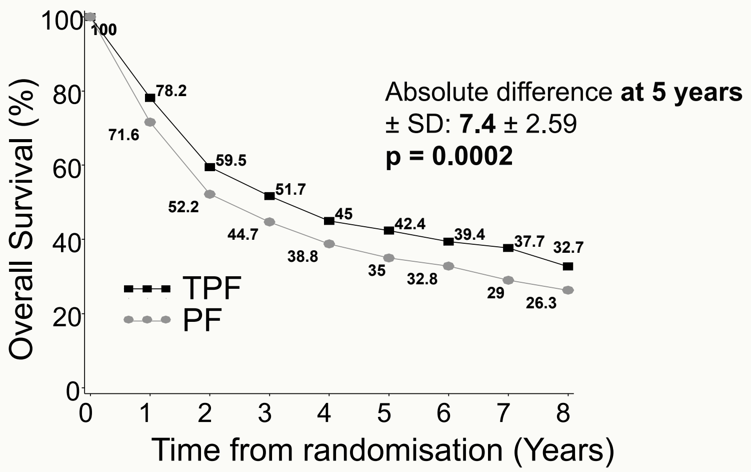
TAX 323
27% reduction in risk of death



Vermorken et al, NEJM 2007
Unresectable disease

MACH-NC
Meta-Analysis of Chemotherapy in Head & Neck Cancer

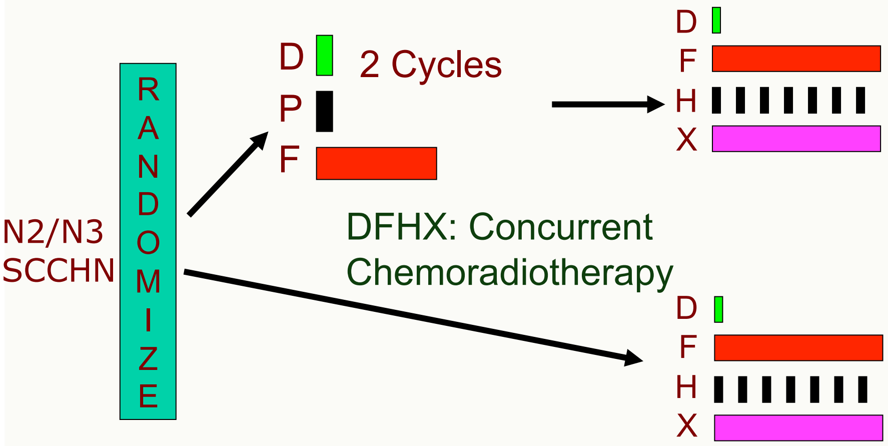
Meta-analysis on induction chemotherapy with TPF



Bourhis, personal communication 2011

CH-RT >< induction chemo + CH-RT

DeCIDE

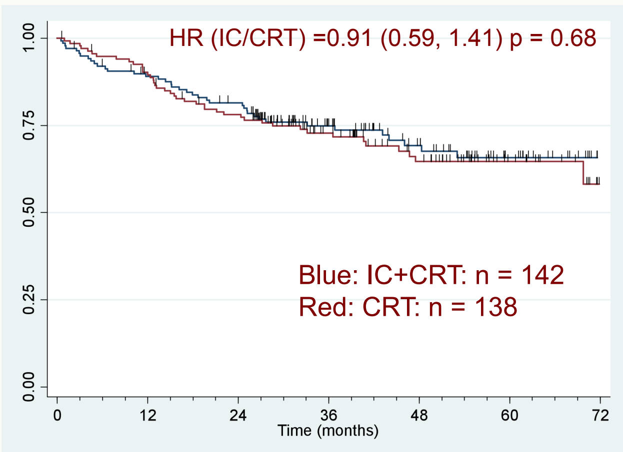


TPF: Docetaxel (75 mg/m^2) + Cisplatin (75 mg/m^2) + 5-FU (750 mg/m^2, 120 hours) Q3 weeks
DFHX: Docetaxel + Hydroxyurea + 5FU + Hyperfractionated RT

Courtesy of Cohen et al., ASCO 2012

CH-RT >< induction chemo + CH-RT

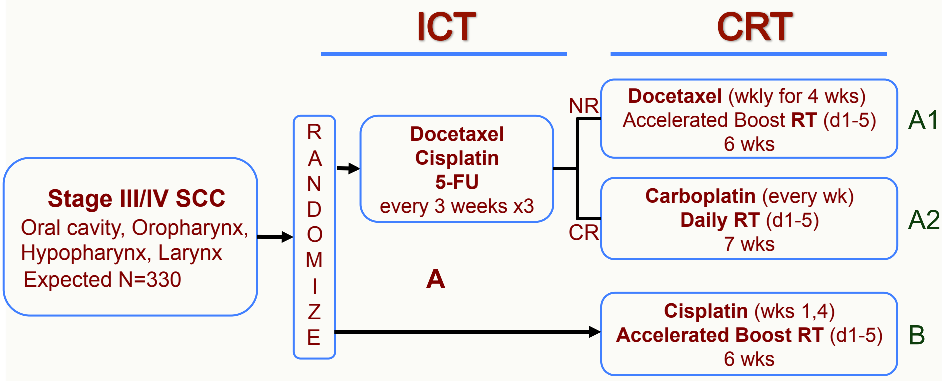
DeCIDE
Primary Endpoint: Overall Survival



Courtesy of Cohen et al., ASCO 2012

CH-RT >< induction chemo + CH-RT

PARADIGM Study Design

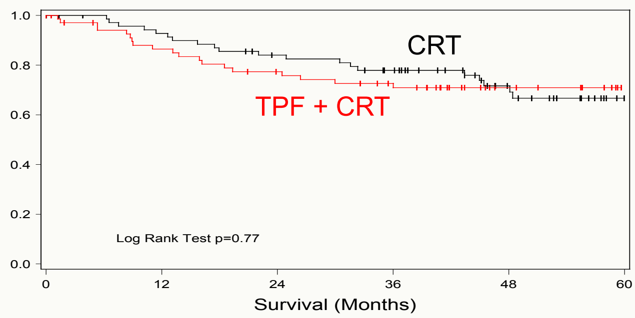


EHNS-ESTRO H&N course
Florence, June 2016

Courtesy of Haddad et al., ASCO 2012

CH-RT >< induction chemo + CH-RT

PARADIGM
Primary Endpoint: Overall Survival



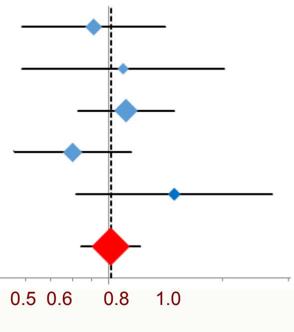
EHNS-ESTRO H&N course
Florence, June 2016

Courtesy of Haddad et al., ASCO 2012

Meta-analysis on induction chemotherapy with TPF

Overall survival

Reference	n	HR	95% CL-	95% CL+	p
Cohen et al. J Clin Oncol 2014	273	0.910	0.590	1.410	0.671
Haddad et al. Lancet Oncol 2013	145	1.090	0.590	2.030	0.785
Hitt et al. Ann Oncol 2013	283	1.109	0.825	1.489	0.492
Paccagnella et al. Ann Oncol 2010 / Ghi et al. ASCO 2014	258	0.800	0.560	1.150	0.224
Takácsi-Nagy et al. Strahlenther Onkol 2015	63	1.490	0.817	2.717	0.203
Total	**1022**	**1.010**	**0.841**	**1.213**	**0.915**



Budach, R&O, 2016

Non-surgical treatments for locally-advanced laryngeal cancers

- Efficacy RT-CH > RT alone (meta-analysis)
- Efficacy HF or AF > RT alone (meta-analysis)
- Efficacy C225-RT > RT alone (1 study!)
- Efficacy EGFR inh-RT-CH ≤ RT-CH (≥ 2 studies)
- Efficacy Acc RT-CH ≈ RT-CH (2 studies)
- Efficacy Ind CH + RT (responders) ≈ TL + RT (2 studies)
- Efficacy Ind-CH (TPF) > Ind-CH (PF) (2 studies)
- Efficacy Ind CH + RT-CH ≈ RT-CH (3 studies)
- Early & late toxicity RT + … > RT (many studies)

Post-operative Radiotherapy: risk factors

- Extracapsular extension / soft tissue extension (ECE/STE)
- Oral cavity tumors
- R1 surgical margins
- Nerve invasion
- >1 neck nodes
- >1 positive node levels
- Node size > 3 cm
- > 6 week interval between surgery and RxTh

Low risk (LR): no adverse feature

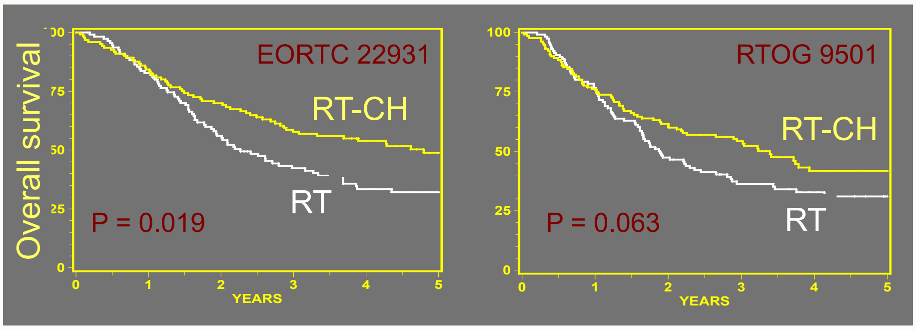
Intermediate risk (IR): risk factors other than R1 or ECE/STE

High risk (HR): R1 or ECE/STE

Peters, IJROBP, 1993

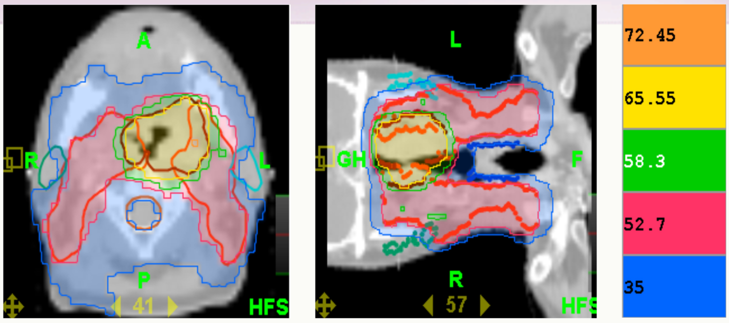
Post-operative Radiotherapy: overall survival

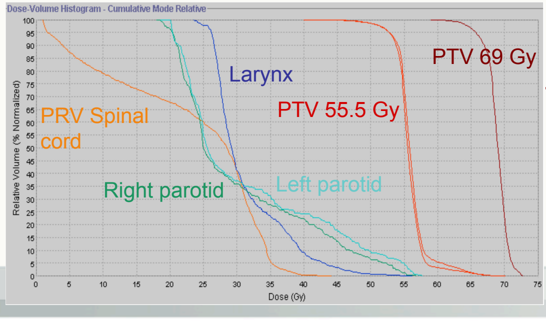
Patients with positive margin and/or ECE



Bernier, NEJM, 2004
Cooper, NEJM, 2004

IMRT for Head and Neck Tumors





Oropharyngeal SCC
T2-N0-M0
SIB-IMRT: 30x2.3 Gy
30x1.85 Gy

Clinical example

Clinical Target Volumes (CTV)

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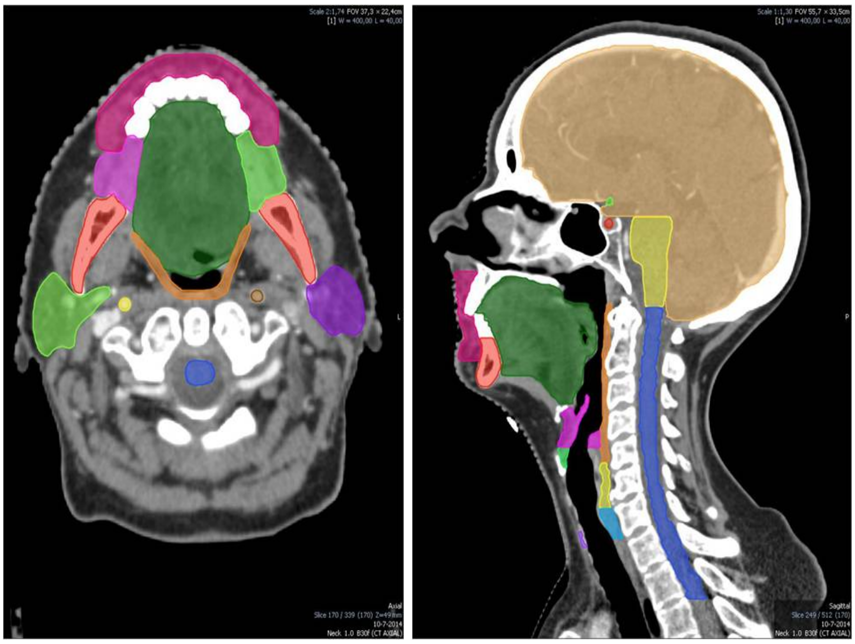
Original article

Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines ☆

Vincent Grégoire [a,*], Kian Ang [b], Wilfried Budach [c], Cai Grau [d], Marc Hamoir [e], Johannes A. Langendijk [f], Anne Lee [g], Quynh-Thu Le [h,i], Philippe Maingon [j], Chris Nutting [k], Brian O'Sullivan [l], Sandro V. Porceddu [m], Benoit Lengele [n]

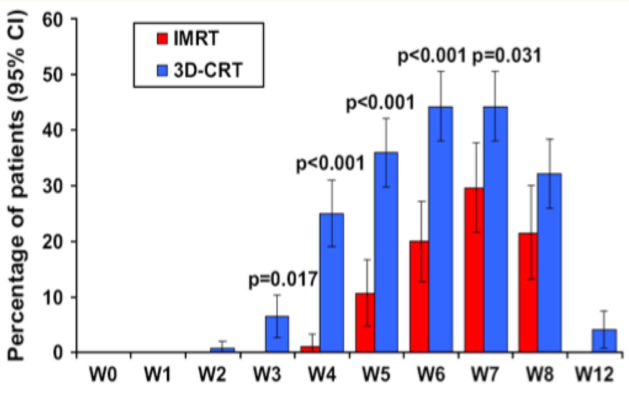
Radiother Oncol. 2014 Jan;110(1):172-81.



Brouwer et al., 2015

Acute toxicity with IMRT

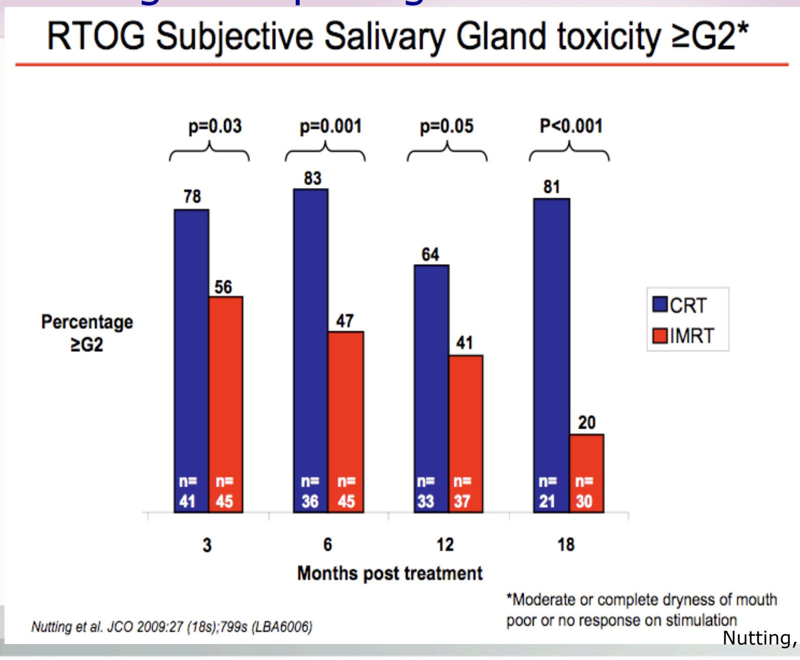
≥ grade 3 mucositis: IMRT vs 3D-CRT



Note:The prevalence of grade 3 or higher mucositis was significantly lower among IMRT-treated patients. This is most likely due to the SIB-technique used with a lower dose per fraction and a longer overall treatment time of radiation for the elective part of the target volume.

Vergeer, 2009

Parotid gland sparing in IMRT for HNSCC



Nutting, 2009

This house believes that …

- RO will be (even more) multidisciplinary…
- RO will be conformal (e.g. IMRT, proton, hadrons)…
- RO will be tailored (based on imaging and molecular profiling) and adaptive …
- RO will be associated with targeted agents …

Management of the Neck Following Chemo-radiotherapy

C. René Leemans, MD, PhD
Professor and Chair

Otolaryngology-Head and Neck Surgery
VU University Medical Center
Amsterdam, The Netherlands

MULTIDISCIPLINARY MANAGEMENT
OF HEAD AND NECK ONCOLOGY
Florence, Italy. June 26-29, 2016

Current Treatment Philosophy for Cancers of the Oro- Hypopharynx and Larynx

- Definitive treatment with chemo-radiation and surgical salvage
- Post-treatment management of the N+ neck is evolving and has become a source of controversy

Contents - Issues

- Own series
- The need to perform a “planned” neck dissection routinely
- The timing of the neck dissection
- The extent of the neck dissection

Study Objectives

To determine:

- **Regional failure after chemoradiation**
- **Diagnostic accuracy**
- **Efficacy of salvage (non-planned) neck dissections, based on: clinical, imaging (anatomic and metabolic), cytological abnormality**

Van der Putten L *et al*. Submitted

Population

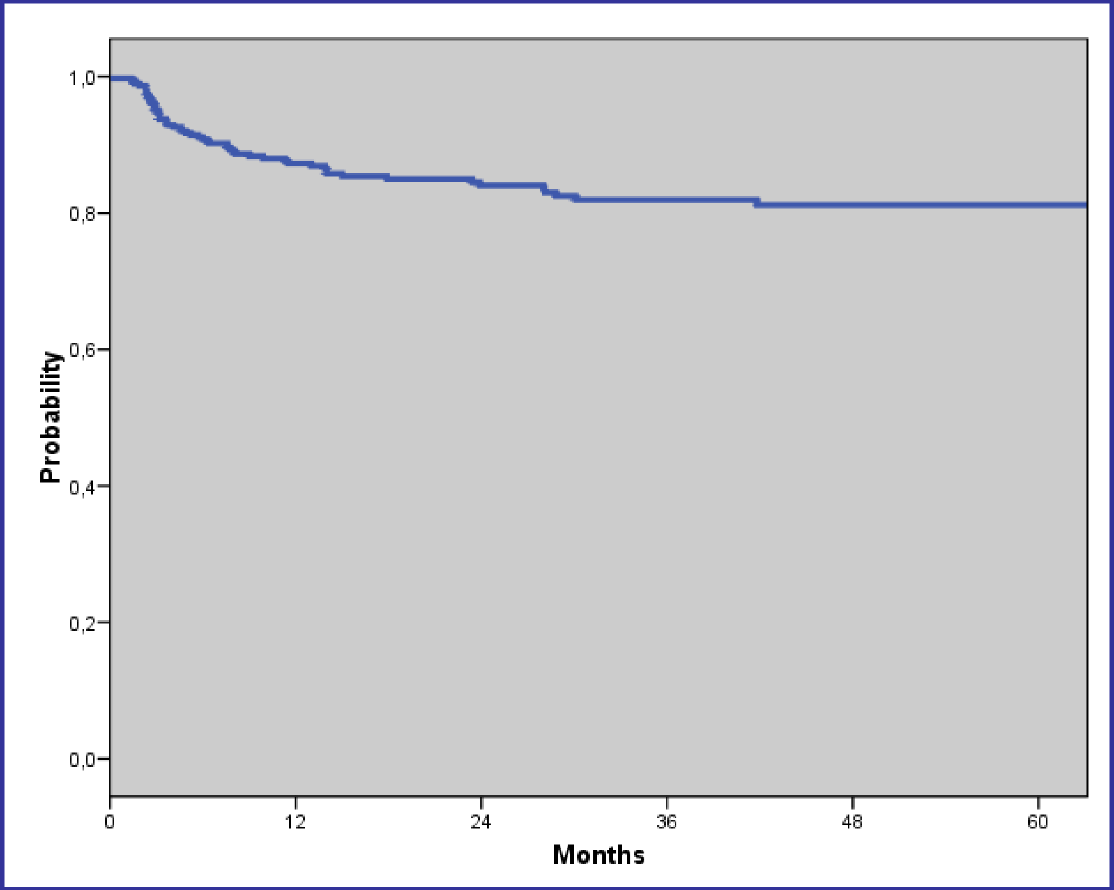
- N=401 Chemoradiation Patients

Stage	N0	N1	N2a	N2b	N2c	N3	Total
T1	0	0	1	7	0	1	9
T2	5	8	8	17	7	3	48
T3	51	22	10	41	41	3	168
T4	56	27	4	35	40	14	176
Total	112	57	23	100	88	21	401

Regional Failure

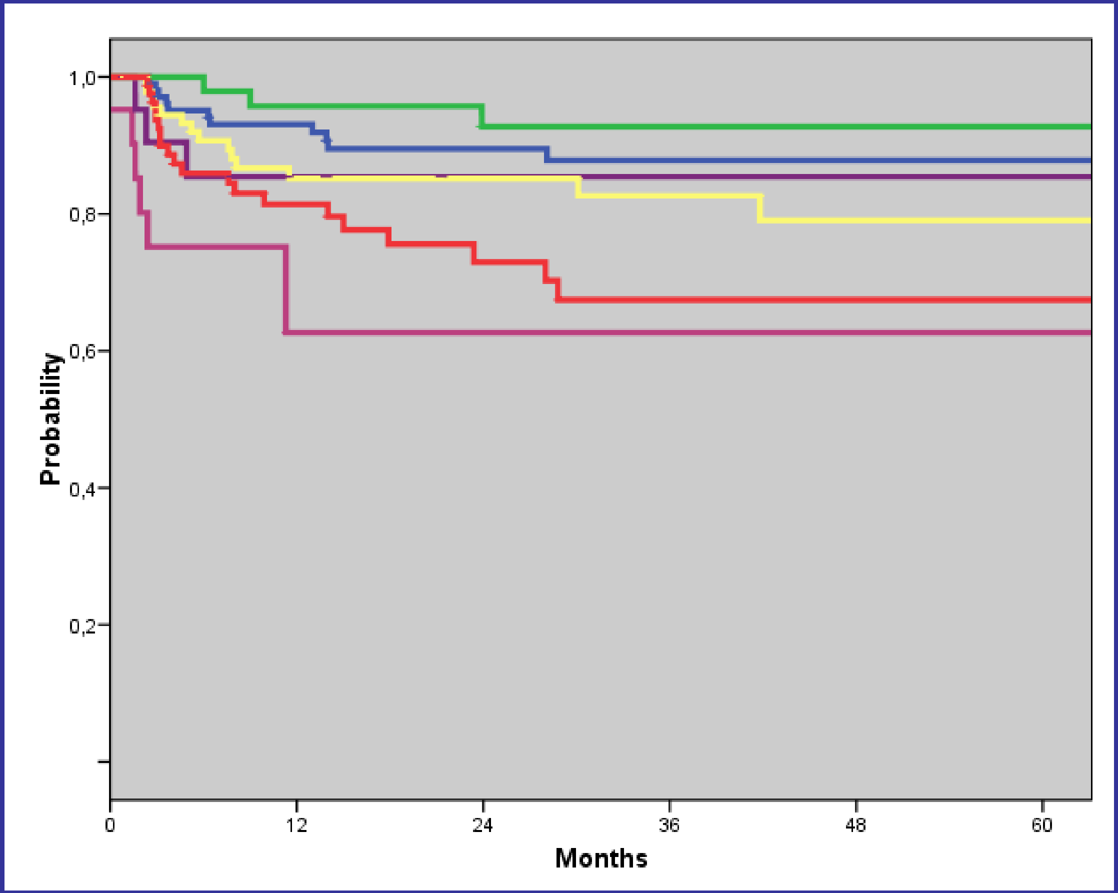
N-stage	No regional recurrence	Regional recurrence
N0	101	11 (10%)
N1	54	3 (5%)
N2a	20	3 (13%)
N2b	84	15 (15%)
N2c	68	20 (23%)
N3	15	6 (29%)
Total	342	58 (15%)

Regional Control after CRT



82%

Regional Control after CRT



N0
N1
N2a
N2b
N2c
N3

Imaging: MRI (n=164)

	MRI Neck Sensitive test (equivocal = +ve)	MRI Neck Conservative test (equivocal = -ve)
Sensitivity	**42%**	**23%**
Specificity	**85%**	**98%**
PPV	**34%**	**67%**
NPV	**89%**	**87%**

Imaging: FDG-PET-CT (n=115)

	PET Neck Sensitive test (equivocal = +ve)	PET Neck Conservative test (equivocal = -ve)
Sensitivity	**35%**	**22%**
Specificity	**86%**	**95%**
PPV	**38%**	**50%**
NPV	**84%**	**83%**

Patients Not Salvaged (n=22)

Reason	#	%
DM	12	55
Unresectable	7	32
Poor condition	2	9
Died	1	4

Details of Surgery

Characteristics	All patients (N=36)	(Pharyngo) laryngectomy (N=6)	Composite resection (N=2)	Lymph node dissection (N=28)
Flap reconstruction				
No	10 (28%)	1 (17%)	0 (0%)	11 (39%)
Yes	26 (72%)	5 (83%)	2 (100%)	17 (61%)
Type of reconstruction				
No	12 (33%)	1 (17%)	0 (0%)	11 (39%)
PM	21 (58%)	4 (66%)	0 (0%)	17 (61%)
RFFF	1 (3%)	0 (0%)	1 (50%)	0 (0%)
Rectus Abdominis	1 (3%)	0 (0%)	1 (50%)	0 (0%)
Fibula + Gracilis	1 (3%)	1 (17%)	0 (0%)	0 (0%)
Re-operation with flap				
No	27 (75%)	5 (83%)	1 (50%)	21 (75%)
Yes	9 (25%)	1 (17%)	1 (50%)	7 (25%)

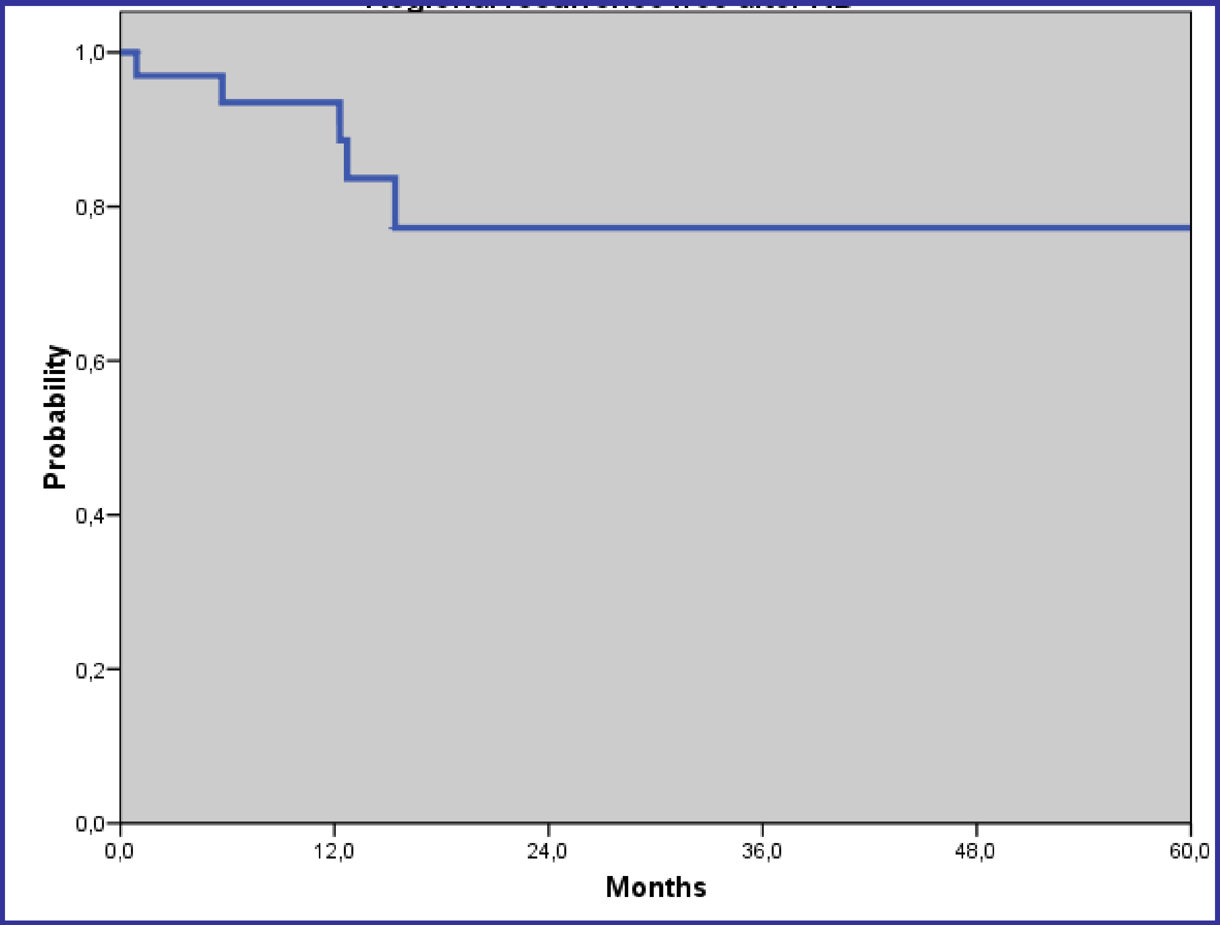
Complications (n=36)

Complications	#	%
No	18	62
Fistula	3	8
Infection/ Delayed wound healing	14	39
Free flap failure	1	3
Patients with ≥ 1 complications	19	53

Histopathology Salvage Neck Dissection

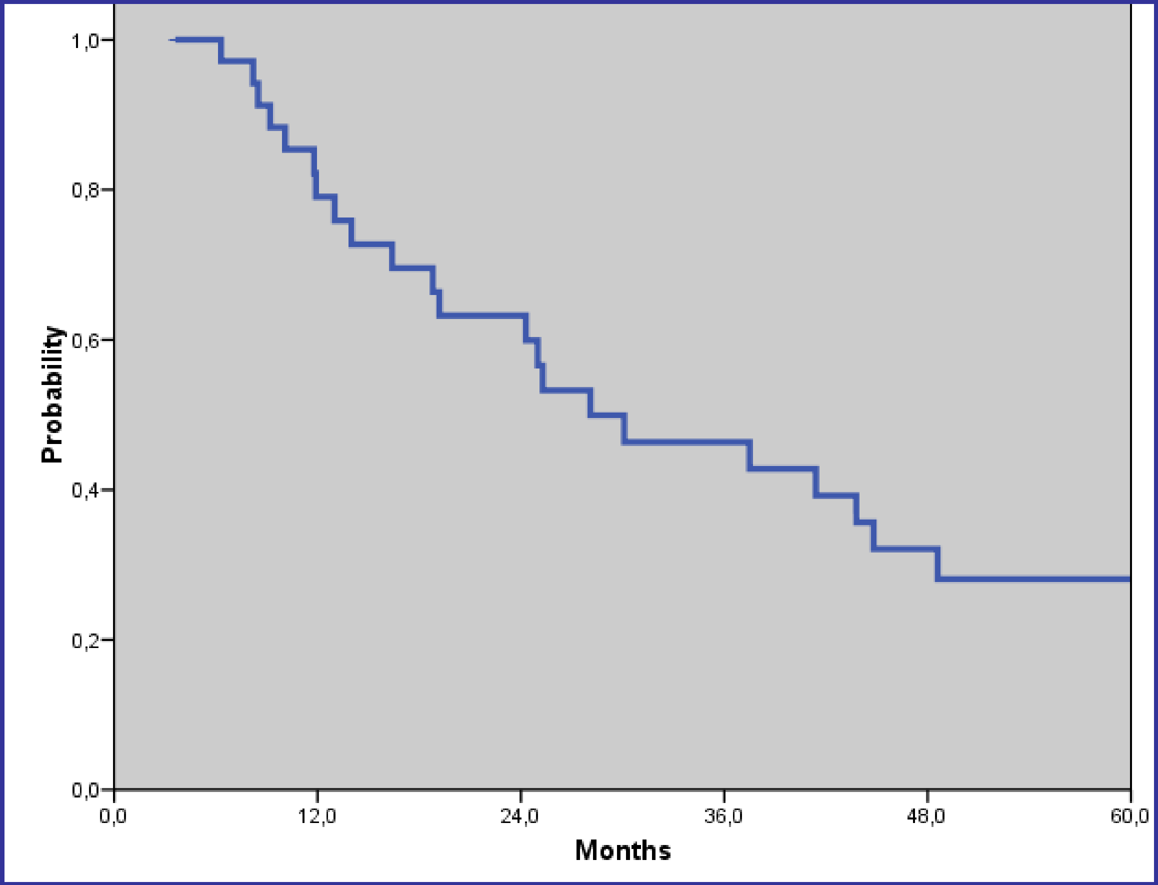
Pathology	#	%
R0	30	84
Close	3	8
Positive	3	8

Neck Control after Salvage Neck Dissection



77%

Survival after Salvage Neck Dissection

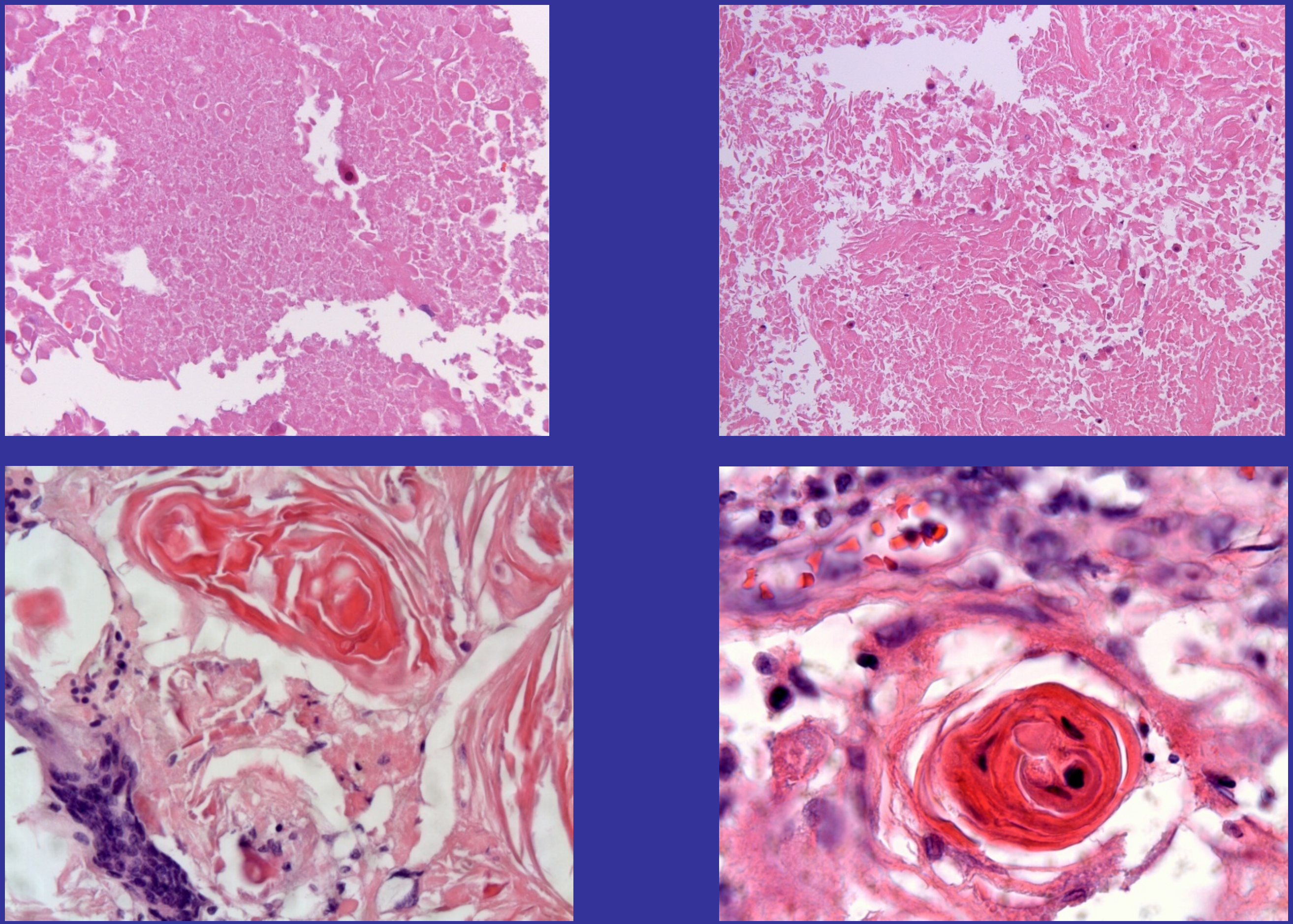


28%

Issue 1

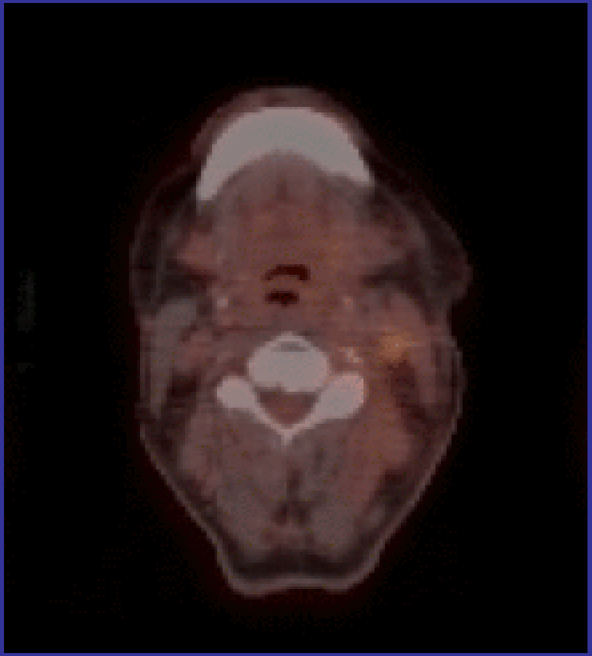
- Is it necessary to routinely dissect the N+ neck after treatment with radiation with or without chemotherapy?

Non-vital Tumor

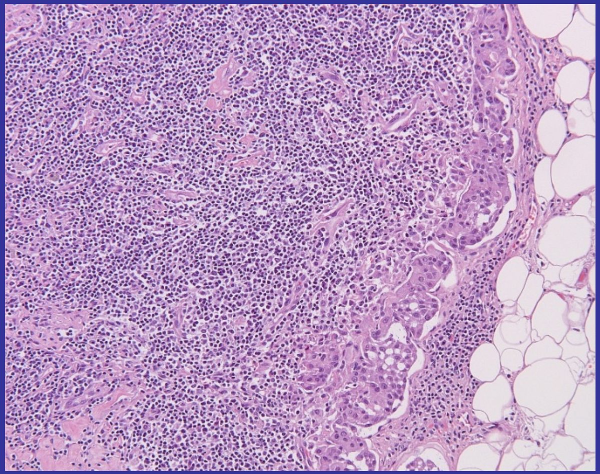


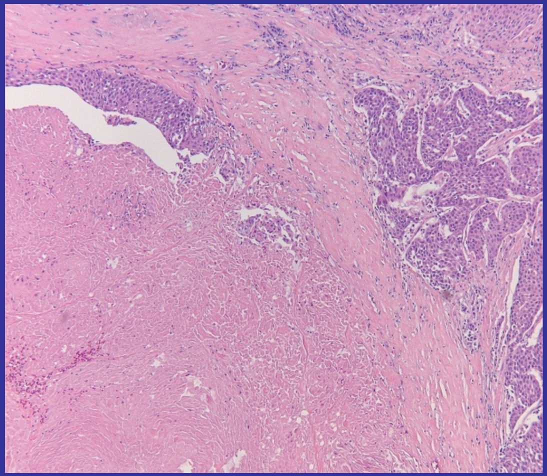
Case: Male, 69

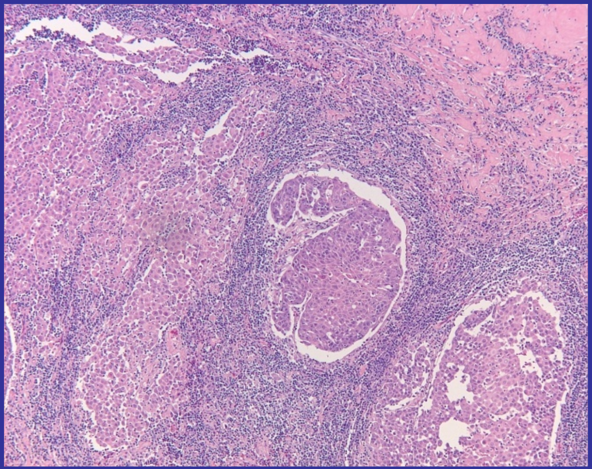
- T2N2b oropharyngeal cancer
- Recurrent swelling neck 9 months after chemoradiation
- PET positive
- Primary controlled
- Modified radical neck dissection



Neck Dissection and Chemoradiation







Histopathology MRND-specimen:

- Level II: 2 metastases with extranodal spread, maximal diameter 2.5 cm
- Level III: 4 metastases with extranodal spread and (lymph) angio-invasion
- Level IV: 1 metastasis with (lymph) angio-invasion.
- 10 nodes without tumor

Pros

- “MND still appears to confer a disease-free survival and overall survival advantage with acceptably low morbidity” …….in patients with N2-3 disease undergoing CRT
- BUT, do all patients with N2-3 disease need it?

Brizel D *et al.* Int J Rad Oncol Biol Phys 2004;58:1418

Study

- Retrospective Study: 108 patients, advanced HNSCC
- Hyperfractionated radiotherapy and concurrent cisplatin and 5-FU

Neck Dissection	#
"Modified"	65
None*	29

* Physician and or patient preference

Brizel D *et al*. Int J Rad Oncol Biol Phys 2004;58:1418

4-years Survival

N-Stage	Neck Dissection	DFS	Overall
N1	**Yes**	**70%**	
	No	**70%**	
N2-3	**Yes**	**75%**	**77%**
	No	**53%**	**50%**

p = .04

Brizel D *et al.* Int J Rad Oncol Biol Phys 2004;58:1418

Cons

- Less than one third have histological evidence of nodal metastases
- In cases with a CR: probability of an isolated recurrence in the neck is low (0% - 11%)

Corry J *et al*. Cancer J 2001, 7:472
Robbins KT *et al*. Arch otolaryngolg Head Neck Surg 1999, 125:670
Chan AW *et al*. Int J Radiat Oncol Biol Phys 2001, 50:367

Amsterdam Head and Neck Group Study

- 68 neck dissections in 61 patients
- Suspicion of residual or recurrent regional disease after CRT
- 42 SND and 26 MRND

Van der Putten L *et al*. Head Neck 2009;31:593–603

Efficacy of Salvage ND following CRT

cN-Stage	Recurrence	Salvage
0-1	11%	3.5%
2+	32%	16%

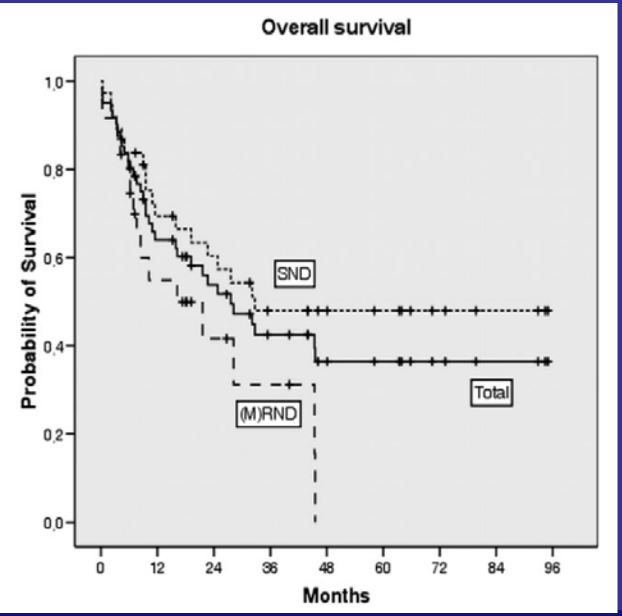


Table 5. Univariate analysis and multivariate analysis for overall survival.

Variable	Univariate (p value)	Multivariate (p value)
T classification	.75	.81
N classification	.33	.47
Chemoradiation scheme	.17	.43
Tumor site	.96	.29
Tumor stage	.70	.70
Residual/recurrent disease	.08	.03
Viable tumor	.03	.61
Type of neck dissection	.04	.06
Surgical margins	<.001	<.001

Van der Putten L *et al*. Head Neck 2009;31:593–603

Planned Neck Dissection for All N>1?

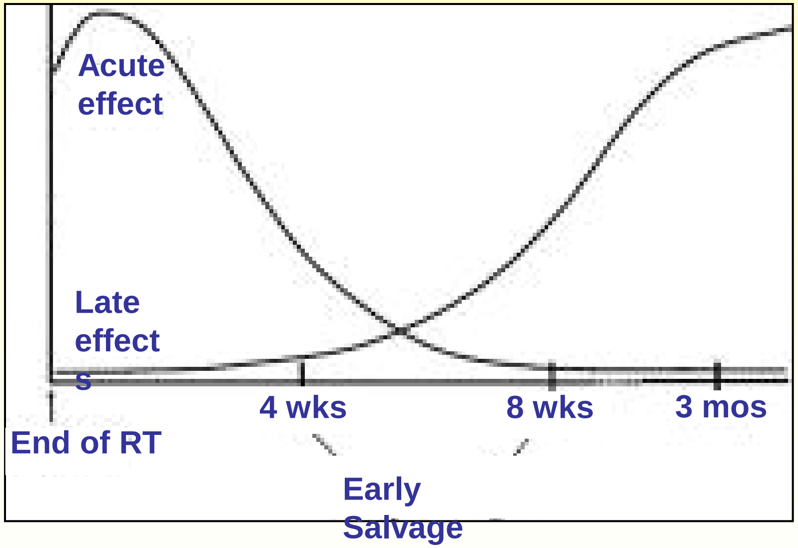
- **The paradigm to perform routine neck dissection based on N-staging is obsolete**

Corry J *et al*. Cancer J 2001, 7:472
Robbins KT *et al*. Arch otolaryngol Head Neck Surg 1999, 125:670

Issue 2

- The timing of the neck dissection
- Related to regression after treatment and accuracy (esp. NPV) of imaging modalities

Time Window Response Evaluation



Window for response evaluation,

when acute inflammatory reactions subside and before long-term soft tissue damage is maximal

Dilemma: early diagnostics less reliable

Yom SS *et al*. Am J Clin Oncol 2005;28:385-92

FDG-PET-CT: Regional Control

Accuracy PET for detection of lymph node metastases is interval dependent:

Author	Interval after chemoradiation	Negative Predictive Value	
Rogers	4 weeks	14%	(95%CI: 3%-45%)
McCollum	4-12 weeks	73%	(95%CI: 46%-99%)
Yao; Porceddu	> 8 weeks	97% - 100%	(95%CI: 87%-99% en 96%-100%)

Rogers JW *et al*. Int J Radiat.Oncol Biol Phys 2004;58:694-7
McCollum AD *et al*. Head Neck 2004;26:890-6
Yao M *et al* Int J Radiat Oncol Biol Phys 2005;63:991-9
Porceddu SV *et al.* Head Neck 2005;27:175-81

Clinical or Imaging Abnormality

PET-CT / MRI at 12 weeks

positive → Neck Dissection

negative → Observation

Issue 3

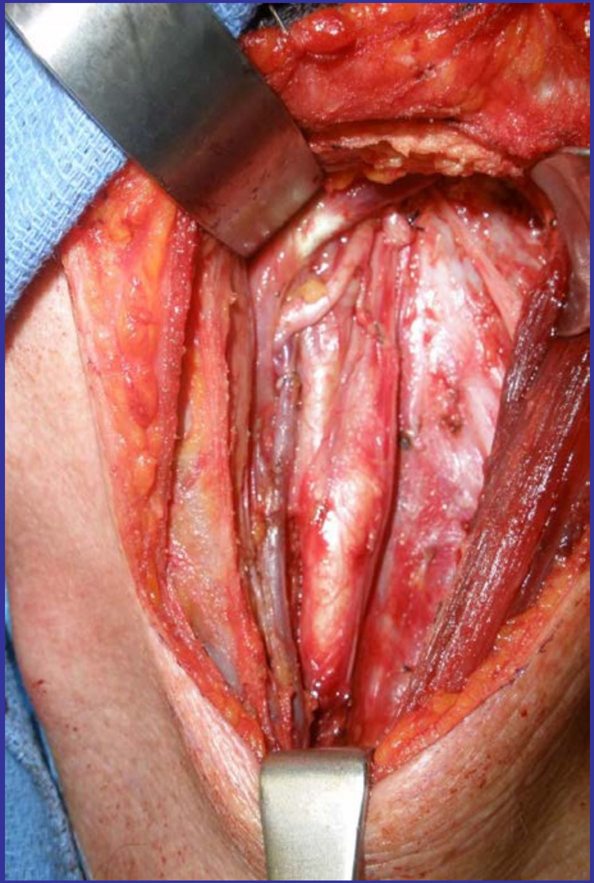
- The extent of the neck dissection

Trend Towards more Selective Neck Dissection

Author	Selective Neck Dissection	Recurrence in the Neck
Stenson *et al*.	**56**	**1 (2%)**
Robbins *et al.*	**33**	**1 (3%)**

Stenson K *et al*. Arch Otolaryngol 2000;126:950
Robbins KT *et al*. 2004 J Am Coll Surg 199:913

(Super) Selective Neck Dissection



Courtesy of Dr. Jesus E. Medina

Location of Positive Nodes

- Is single level dissection Feasible and safe?

Robbins KT *et al.* Arch Otolaryngol 2007;133:486

Clinical Residual Adenopathy Confined to One Level (RADPLAT)

- Number of Neck Dissections 57
- Number of Patients 54

- Positive node beyond 2*/54 (3.7%)

*one in a contiguous level

Robbins KT *et al.* Arch Otolaryngol 2007;133:486

Summary

- Evolving role of neck dissection in 21st century
- Planned dissections based on cN-stage are not recommended
- Evaluations at 3 months (NOT earlier)
- Trend towards more selective procedures

1632 - Anatomy lesson of dr. Nicolaes Tulp
Rembrandt van Rijn

Thank you for your attention

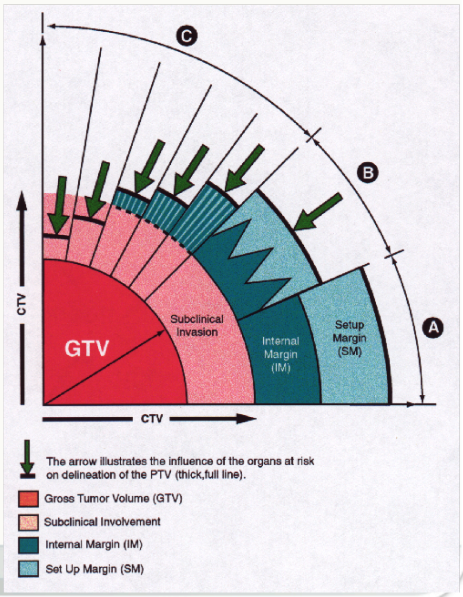
Concepts behind selection and delineation of target volumes in radiotherapy

Vincent GREGOIRE, MD, PhD, Hon. FRCR

Head and Neck Oncology Program, Radiation Oncology Dept. & Center for Molecular Imaging, Radiotherapy and Oncology, Université Catholique de Louvain, St-Luc University Hospital, Brussels, Belgium

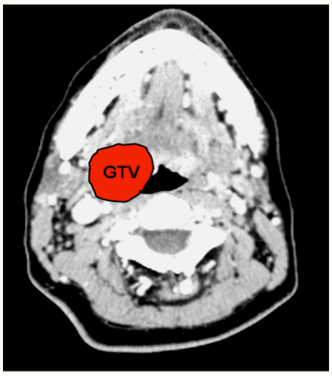
Target volumes in Radiation Oncology: ICRU definition

- Gross Tumor Volume: GTV
- Clinical Target Volume: CTV
- Planning Target Volume: PTV
- Organ at Risk (OAR)
- Planning Organ at Risk Volume (PRV)

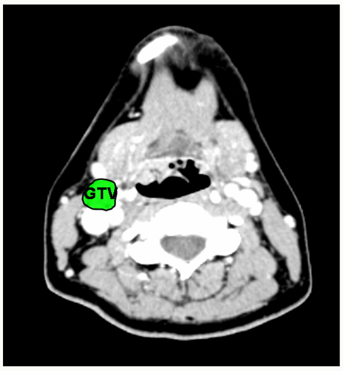


T2 N1 M0 Tonsil Cancer

Primary Tumor

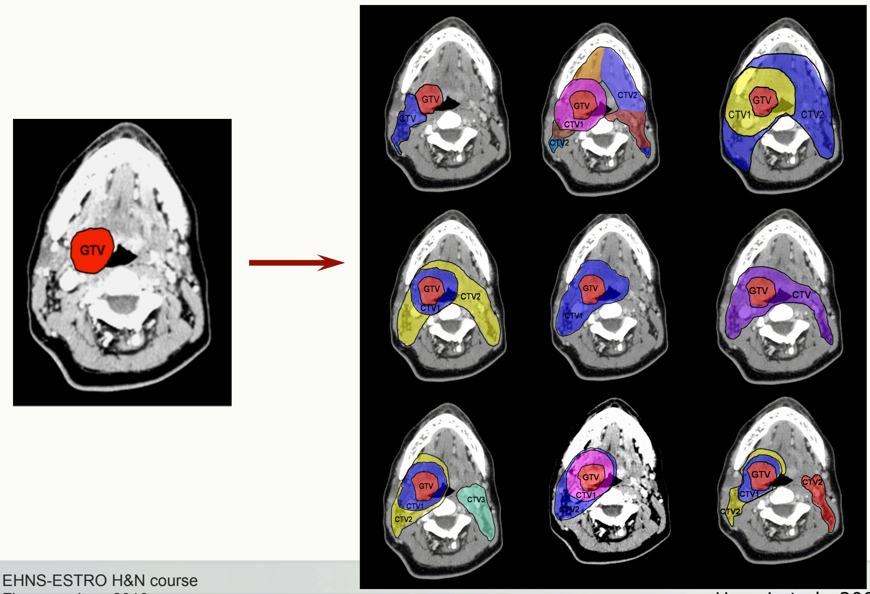


Neck Node



Harari et al., 2004

H&N IMRT practice heterogeneity



Harari et al., 2004

Conformal radiotherapy and IMRT in Head and Neck Tumors

Sources of information

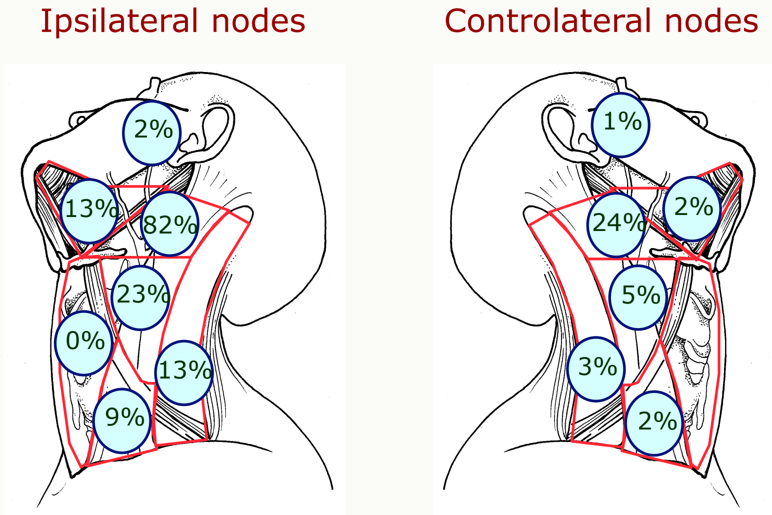
- Anatomy if the lymphatic system
- Lymph node distribution:
  clinical
  radiological
  pathological
- Pattern of failure after selective treatment

Definition of the extend of the CTV in the neck

State of the art

- Predictive pattern of lymph node involvement in HNSCC
- Selective neck treatment (irradiation or dissection) for selected N stage

Distribution of lymph node metastasis in oropharyngeal tumors (clinical examination)



From Bataini and Lindberg

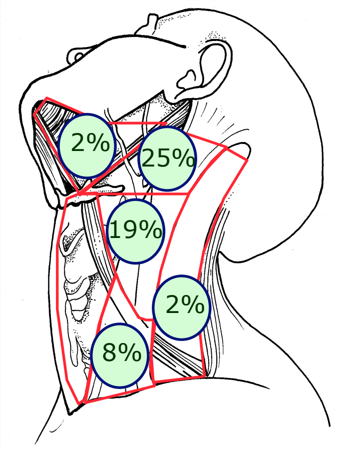
Incidence of retropharyngeal lymph nodes in head and neck squamous cell carcinomas

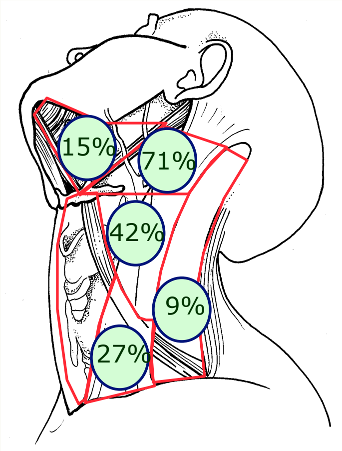
	N0 neck	N+ neck
Oropharynx		
pharyngeal wall (n=93)	16%	21%
soft palate (n=53)	5%	19%
tonsillar fossa (n=176)	4%	12%
base of tongue (n=121)	0%	6%
Hypopharynx (n=136)	0%	9%
Supraglottic larynx (n=196)	0%	4%
Nasopharynx (n=474)	17%	47%

From McLaughlin, Chua, Chong

Incidence of pathologic lymph node metastasis in oropharyngeal tumors

Clinically N0 neck (n=48) Clinically N^+ neck (n=165)

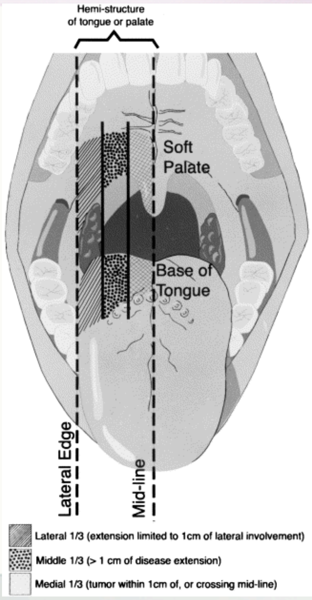




From Candela, 1990

Unilateral or bilateral neck treatment?

- 228 tonsil SCC: T1-T3, N0 or unilteral N+
- Unilateral wedge-pair fields
- Contralateral neck failure: 8/228 (3.5%)
- Unilateral treatment if < 1 cm soft palate and/or base of tongue infiltration

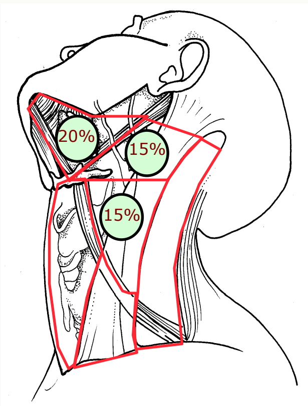


O'Sullivan B, *IJROBP* 2001

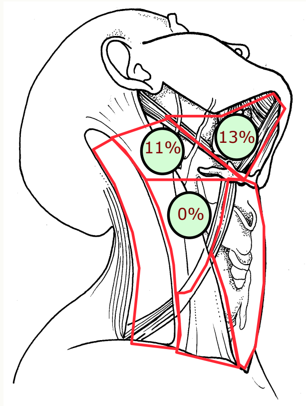
Incidence of ipsilateral and controlateral pathologic lymph nodes

Supraomohyoid neck dissection for lip (44%), oral cavity (82%), or other SCC.

Ipsilateral nodes



Controlateral nodes



From Kowalski et al., 1993

Pattern of neck failure after selective neck treatment by IMRT for HNSCC

Authors	Site	Neck treatment	Neck failure (%)	
			treated level	untreated level
Bayman (2014)	HNSCC (n=136)	IMRT ± CH	2%	0%
Chen (2010)	HNSCC (n=90)	ND + IMRT	14%	8%
Chao (2002)	HNSCC (n=126)	IMRT	8%	4%
		ND + IMRT	7%	4%
Dandekar (2014)	HNSCC (n=114)	IMRT + CH	9%	2%
Dawson (2000)	HNSCC (n=57)	IMRT ± ND	9%	5%
O 'Sullivan (2001)	Tonsillar fossa (n=228)	Ipsilateral 2D-RxTh	17%[1]	3.5%[2]

[1]ipsilateral recurrences
[2]controlateral recurrences

Pattern of neck failure after selective neck treatment by IMRT for HNSCC

Reference	No. patients	Tumour site	Median follow-up/months	No. patients with locoregional failure	Marginal failures	Out-of-field locoregional failures
[24]	126	HNSCC	26	17 (including persistent disease)	3 (also 5 in anterior neck field)	0
[22]	133	Non-nasopharyngeal HNSCC	32	21	4	0
[19]	150	HNSCC	18	11	1	0
[25]	280	HNSCC	23	77 (including persistent disease)	1	3
[26]	100	HNSCC	37	10	2	0
[27]	107	Oropharynx	29	8	0	0
[17]	776	Oropharynx	54	77	7 (inside lower dose planning target volume)	5
[21]	131	Oropharynx	40	35	0	4

Bayman et al., Clin. Oncol., 2014

Which CTV for the neck?

Oral cavity Carcinoma

Nodal stage (AJCC 1997)	Levels to be included in the CTV: Ipsilateral neck	Levels to be included in the CTV: Contralateral neck
N0 - N1 (in level I, II or III)	I, II[1], III + IV for anterior tongue tumor	I, II[1], III + IV for anterior tongue tumor
N2a - N2b	I, II, III, IV, V[2]	I, II[1], III + IV for anterior tongue tumor
N2c	According to N stage on each side of the neck	According to N stage on each side of the neck
N3	I, II, III, IV, V ± adjacent structures according to clinical and radiological data	I, II[1], III + IV for anterior tongue tumor

[1]level IIb could be omitted for N0 patients
[2]level V could be omitted if only level I-III are involved

Grégoire et al., 2000

Which CTV for the neck?

Oropharyngeal Carcinoma

Nodal stage (AJCC 1997)	Levels to be included in the CTV	
	Ipsilateral neck	Contralateral neck
N0 - N1 (in level II, III or IV)	II-III-IV + RP[1] for post. pharyngeal wall tumor	II-III-IV + RP[1] for post. pharyngeal wall tumor
N2a - N2b	Ib, II, III, IV, V + RP	II-III-IV + RP[1] for post. pharyngeal wall tumor
N2c	According to N stage on each side of the neck	According to N stage on each side of the neck
N3	I, II, III, IV, V + RP ± adjacent structures according to clinical and radiological data	II-III-IV + RP[1] for post. pharyngeal wall tumor

[1]retropharyngeal nodes

Grégoire et al., 2000

Which CTV for the neck?

Hypopharyngeal Carcinoma

Nodal stage (AJCC 1997)	Levels to be included in the CTV	
	Ipsilateral neck	Contralateral neck
N0	II[1]-III-IV + RP[2] for post. phar. wall tumor + VI for apex of pirif. sinus or esophageal extension	II[1]-III-IV + RP[2] for post. phar. wall tumor + VI for esophageal extension
N1 - N2a - N2b	Ib, II, III, IV, V + RP + VI for pirif. sinus or esophageal extension	II[1]-III-IV + RP[2] for post. phar. wall tumor + VI for esophageal extension
N2c	According to N stage on each side of the neck	According to N stage on each side of the neck
N3	I, II, III, IV, V + RP + VI pirif. sinus or for esophageal extension ± adjacent structures according to clinical and radiological data	II[1]-III-IV + RP[2] for post. pharyngeal wall tumor + VI for esophageal extension

Level IIb could be omitted for N0 patients
[2]retropharyngeal nodes

Grégoire et al., 2000

Which CTV for the neck?

Laryngeal Carcinoma

Nodal stage (AJCC 1997)	Levels to be included in the CTV	
	Ipsilateral neck	Contralateral neck
N0 - N1 (in level II, III or IV)	II[1]-III-IV + VI for trans- or sub-glottis extension	II[1]-III-IV + VI for trans- or sub-glottis extension
N2a - N2b	II, III, IV, V + VI for trans- or sub-glottis extension	II[1]-III-IV + VI for trans- or sub-glottis extension
N2c	According to N stage on each side of the neck	According to N stage on each side of the neck
N3	Ib, II, III, IV, V + VI for trans- or sub-glottis extension ± adjacent structures according to clinical and radiological data	II[1]-III-IV + VI for trans- or sub-glottis extension

[1]Level IIb could be omitted for N0 patients

Grégoire et al., 2000

Which CTV for the neck?

Nasopharyngeal Carcinoma

Nodal stage (AJCC 1997)	Levels to be included in the CTV	
	Ipsilateral neck	Contralateral neck
N0 - N2	II-III-IV-V + RP[1]	II-III-IV-V + RP[1]
N3	II-III-IV-V + RP[1] ± adjacent structures according to clinical and radiological data	II-III-IV-V + RP[1]

[1]retropharyngeal nodes

Grégoire et al., 2000

Guidelines for the treatment of the neck of patients with HNSCC: unilateral - bilateral?

Unilateral treatment

- lower gum
- lateral border of mobile tongue
- lateral floor of mouth
- retromolar trigone
- Cheek
- tonsillar fossa / tonsillar pillars
- lateral wall of piriform sinus

Conformal radiotherapy and IMRT in Head and Neck Tumors

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Radiotherapy and Oncology 56 (2000) 135–150

RADIOTHERAPY & ONCOLOGY

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Review article

Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience

Vincent Grégoire[a,*], Emmanuel Coche[b], Guy Cosnard[b], Marc Hamoir[c], Hervé Reychler[d]

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Received 20 September 1999; received in revised form 28 March 2000; accepted 13 April 2000

Conformal radiotherapy and IMRT in Head and Neck Tumors

ELSEVIER

Radiotherapy and Oncology 69 (2003) 227–236

Radiotherapy & Oncology

www.elsevier.com/locate/radonline

CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines

Vincent Grégoire[a,*,1], Peter Levendag[b,1], Kian K. Ang[c], Jacques Bernier[d], Marijel Braaksma[b], Volker Budach[e], Cliff Chao[c], Emmanuel Coche[f], Jay S. Cooper[c], Guy Cosnard[f], Avraham Eisbruch[c], Samy El-Sayed[g], Bahman Emami[c], Cai Grau[h], Marc Hamoir[i], Nancy Lee[c], Philippe Maingon[j], Karin Muller[b], Hervé Reychler[k]

DAHANCA: http://www.dshho.suite.dk/dahanca/guidelines.html
EORTC: http://www.eortc.be/home/ Radio/EDUCATION.htm
RTOG: http://www.rtog.org/hnatlas/main.htm

CT-based delineation of lymph node levels in the neck

"Difficulties in the surgical-based definition of neck node levels"

- Cranial limit of level II
- Cranial, caudal and posterior limits of level V
- Caudal limit of level IV

Clinical Target Volumes (CTV)

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

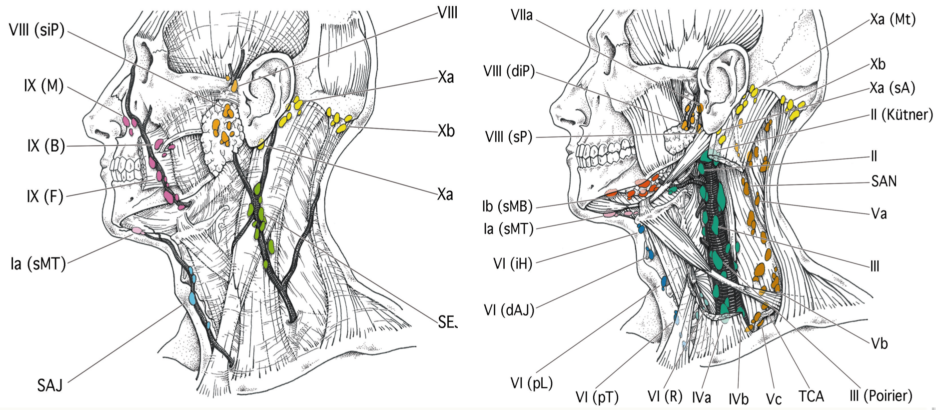
Original article

Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines ☆

Vincent Grégoire[a,*], Kian Ang[b], Wilfried Budach[c], Cai Grau[d], Marc Hamoir[e], Johannes A. Langendijk[f], Anne Lee[g], Quynh-Thu Le[h,i], Philippe Maingon[j], Chris Nutting[k], Brian O'Sullivan[l], Sandro V. Porceddu[m], Benoit Lengele[n]

Radiother Oncol. 2014 Jan;110(1):172-81.

CT-based delineation of lymph node levels in the neck (revised version 2013)

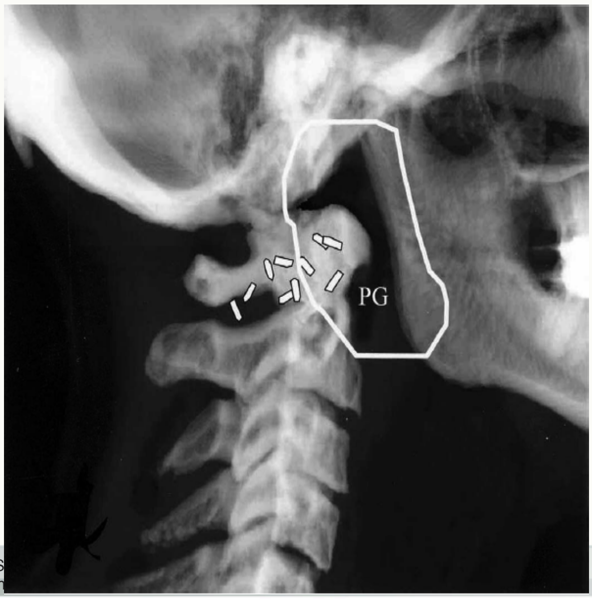


CT-based delineation of lymph node levels in the neck (revised version 2013)

TNM atlas for lymph nodes of the neck		Node levels modified from Robbins	
Group number	Terminology	Level	Terminology
1	submental nodes	Ia	submental group
2	submandibular nodes	Ib	submandibular group
3	cranial jugular nodes	II	upper jugular group
4	middle jugular nodes	III	middle jugular group
5	caudal jugular nodes	IVa	lower jugular group
		IVb	medial supraclavicular group
6	dorsal cervical nodes along the spinal accessory nerve	V Va Vb	posterior triangle group - upper posterior triangle nodes - lower posterior triangle nodes
7	supraclavicular nodes	Vc	lateral supraclavicular group
8	prelaryngeal and paratracheal nodes	VI VIa VIb	anterior compartment group: - prelaryngeal & pretracheal nodes - paratracheal & recurrent nerve nodes
9	retropharyngeal nodes	VII VIIa VIIb	prevertebral compartment group: - retropharyngeal nodes - retro-styloid nodes
10	parotid nodes	VIII	parotid group
11	buccal nodes	IX	bucco-facial group
12	retroauricular and occipital nodes	X Xa Xb	Posterior skull group: - retroauricular nodes - occipital nodes

Grégoire, 2014

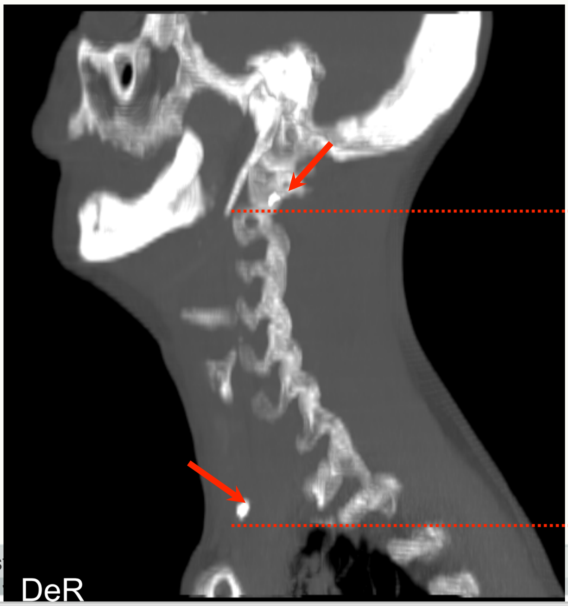
CT-based delineation of lymph node levels in the neck



Cranial limit of level II after SND (II-V) for N0 pts (n=10)

Levendag et al., 2005

CT-based delineation of lymph node levels in the neck

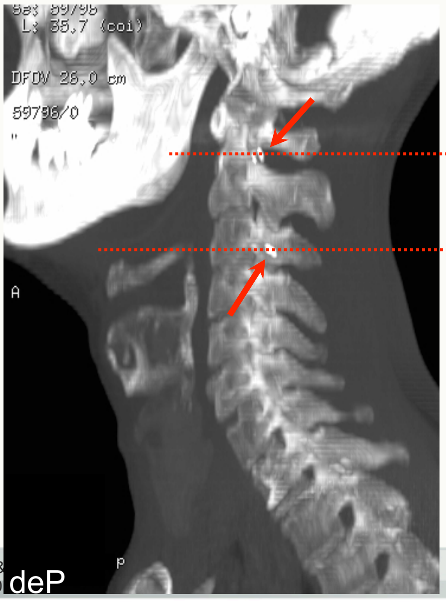


Upper limit of level II

Lower limit of level IV

EHNS-ES
Florence,

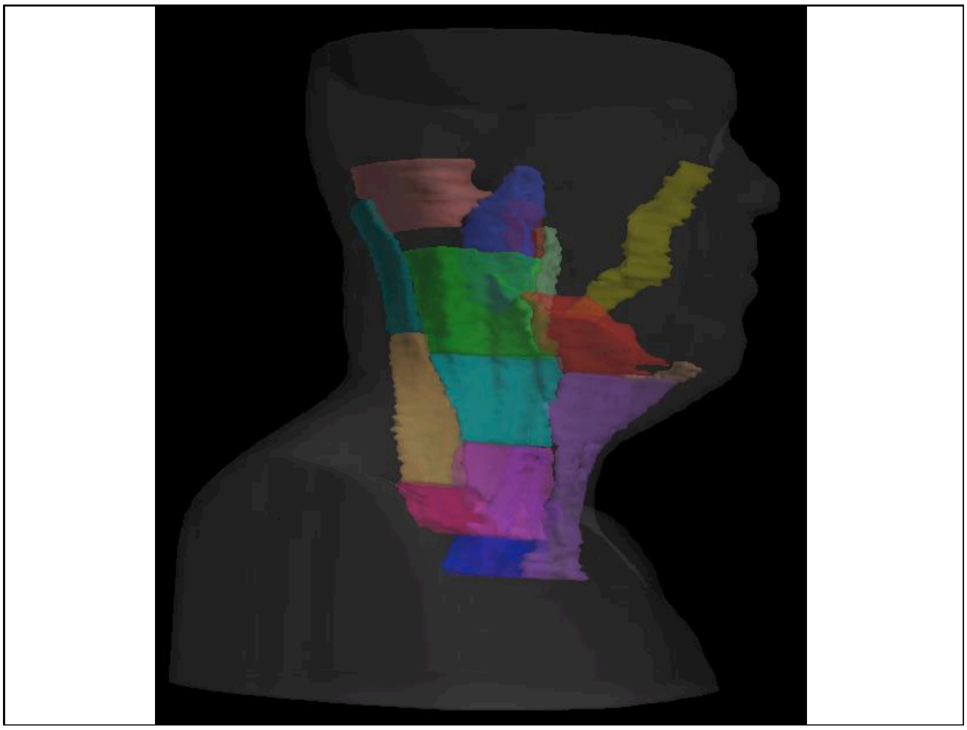
CT-based delineation of lymph node levels in the neck

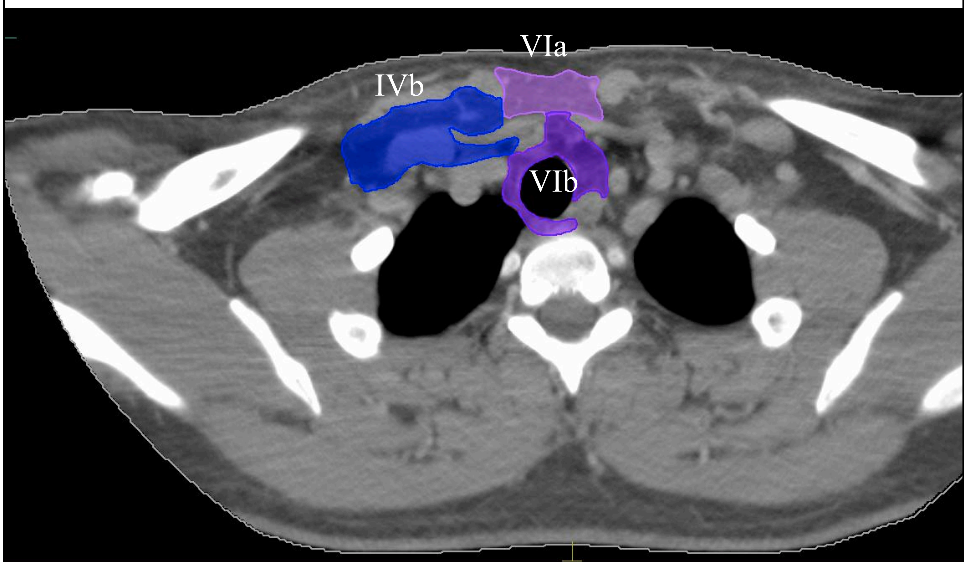


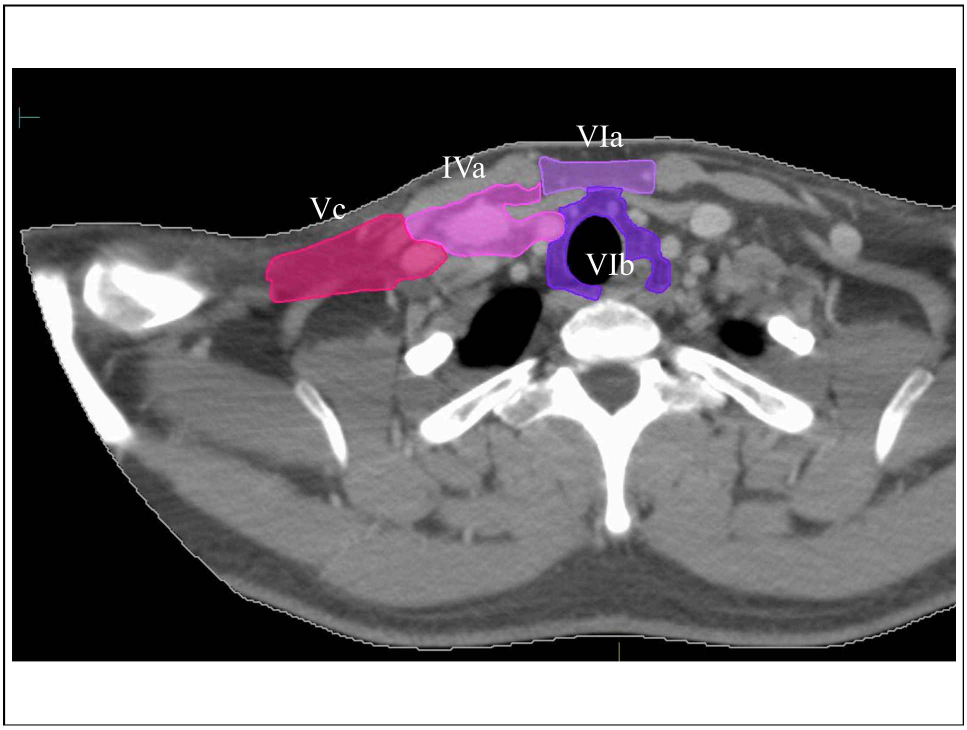
Upper limit of level II

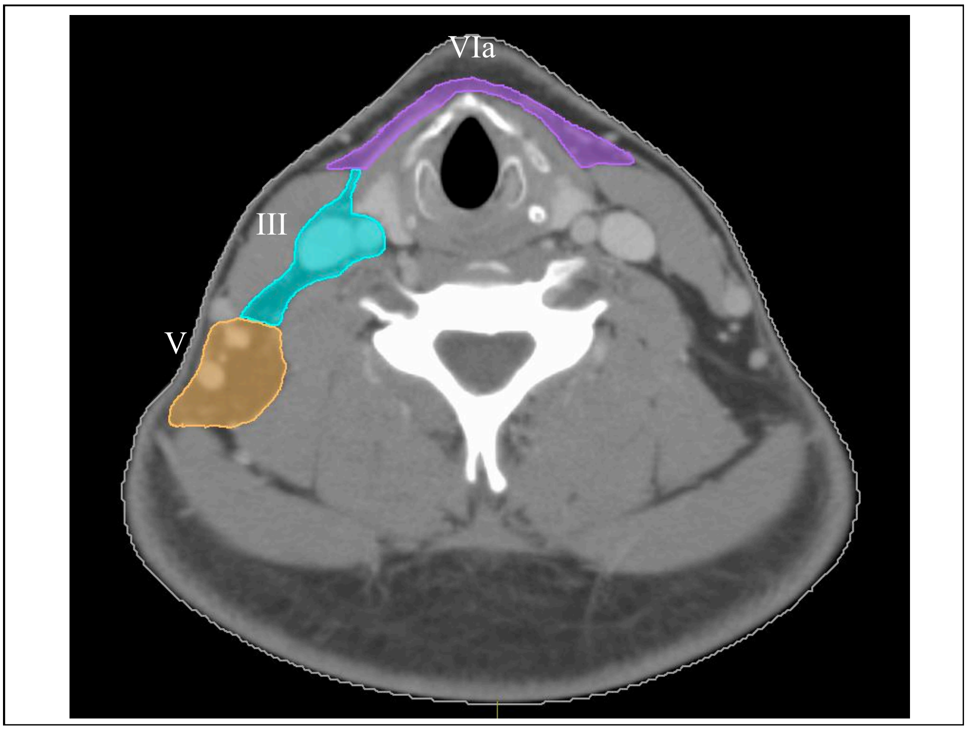
Upper limit of level V

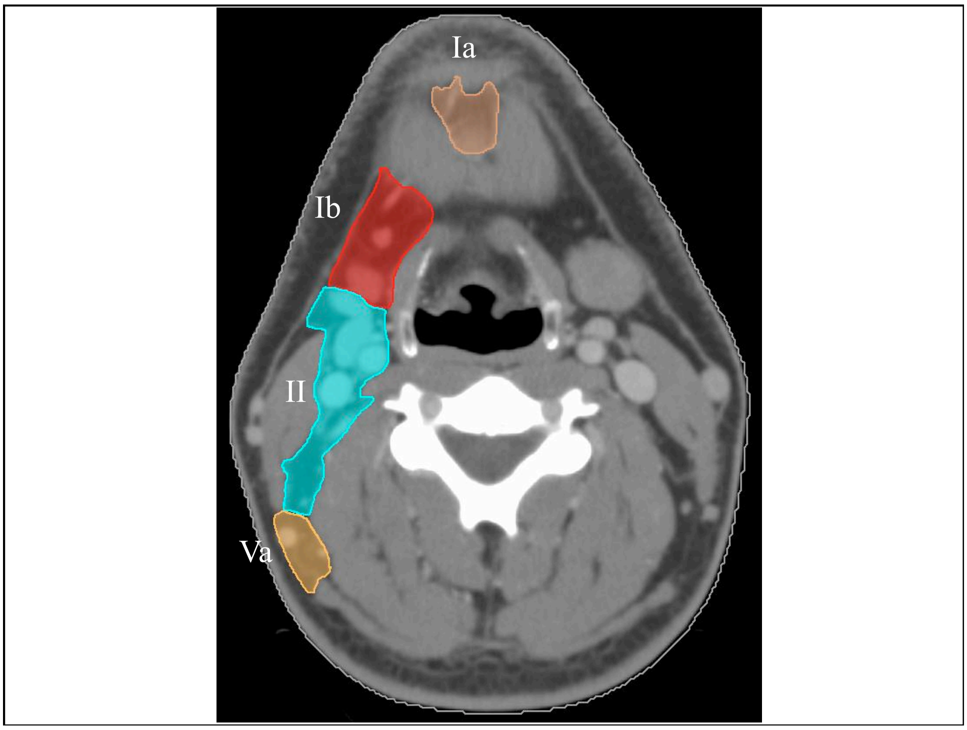
EHNS-ESTRO H&
Florence, June 20

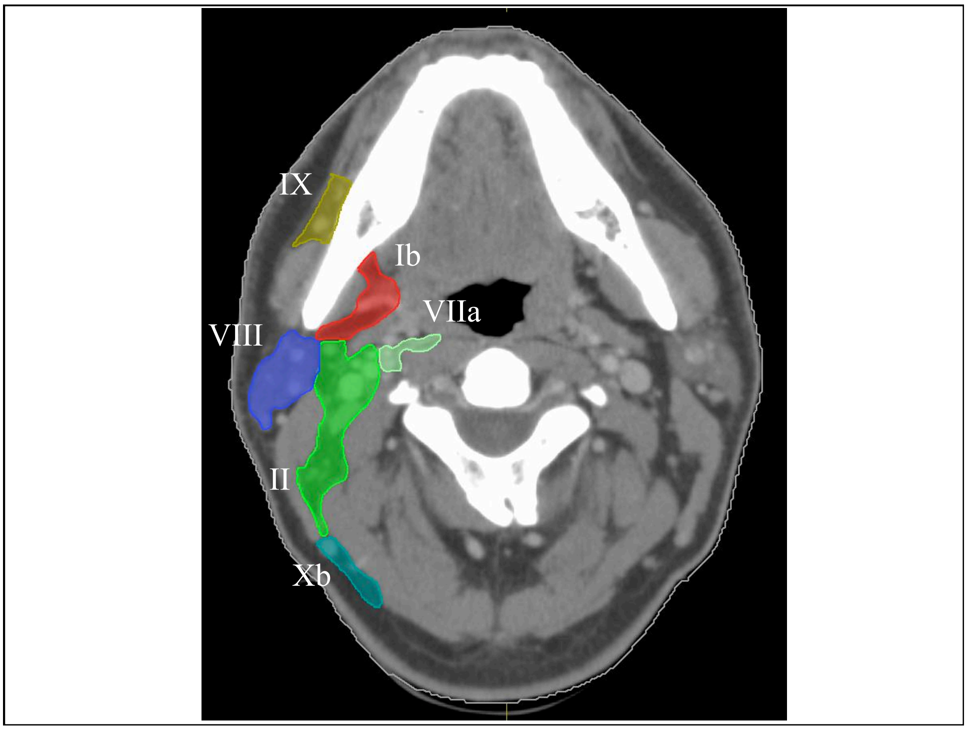


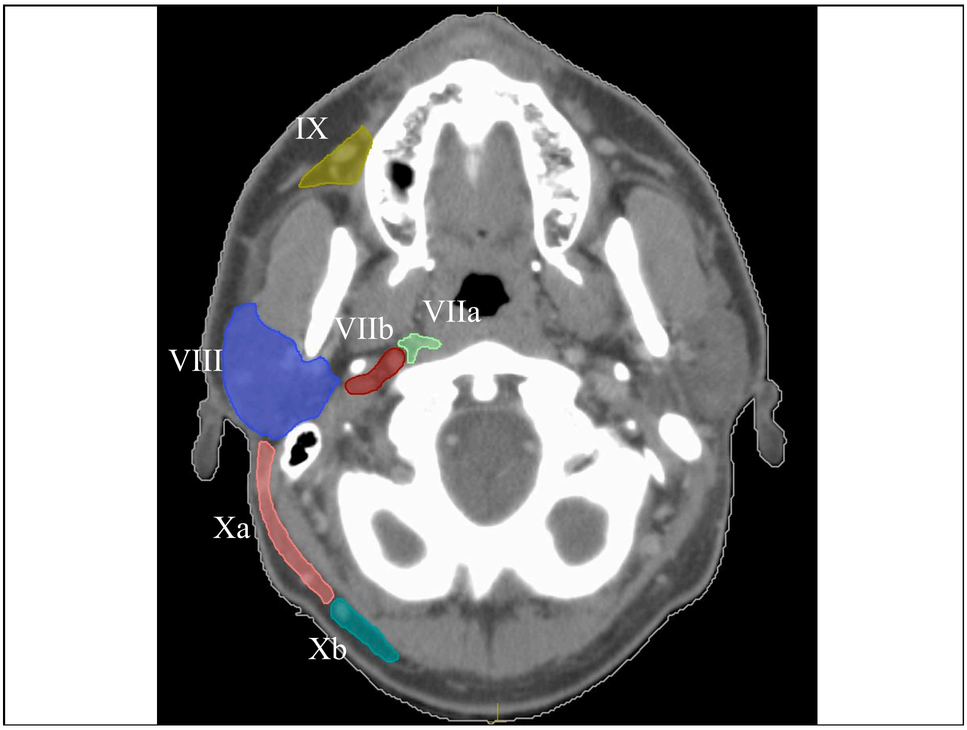

VIa
IVb
VIb


VIa
IVa
Vc
VIb


VIa
III
V


Ia
Ib
II
Va


IX
Ib
VIIa
VIII
II
Xb


IX
VIIb
VIIa
VIII
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The consensus guidelines for the deline...
Discussion: From nodal levels to the cre...
Conclusion
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Radiotherapy and Oncology
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Original article
Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines
Vincent Grégoire, Kian Ang, Wilfried Budach, Cai Grau, Marc Hamoir, Johannes A. Langendijk, Anne Lee, Quynh-Thu Le, Philippe Maingon, Chris Nutting, Brian O'Sullivan, Sandro V. Porceddu, Benoit Lengele
Show more
http://dx.doi.org/10.1016/j.radonc.2013.10.010
Abstract
In 2003, a panel of experts published a set of consensus guidelines for the delineation of the neck node levels in node negative patients (Radiother Oncol, 69: 227–36, 2003). In 2006, these guidelines were extended to include the characteristics of the node positive and the post-operative neck (Radiother Oncol, 79: 15–20, 2006). These guidelines did not fully address all nodal regions and some of the anatomic descriptions were ambiguous, thereby limiting consistent use of the recommendations.
In this framework, a task force comprising opinion leaders in the field of head and neck radiation oncology from European, Asian, Australia/New Zealand and North American clinical research organizations was formed to review and update the previously published guidelines on nodal level delineation.
Based on the nomenclature proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery, and in alignment with the TNM atlas for lymph nodes in the neck, 10 node groups (some being divided into several levels) were defined with a concise description of their main anatomic boundaries, the normal structures juxtaposed to these nodes, and the main tumor sites at risk for
EHNS-
Florence,

From primary nodal GTV to "high dose" CTV

Table 4. Incidence of ECE in tumor-positive neck nodes by size

Study or source	Distribution of LN size (mm) % <10	% 10-30	% >30
Johnson *et al.*, 1981 (8)	n.a.	65	75
Snow *et al.*, 1982 (9)	22	52	74
Snyderman *et al.*, 1985 (10)	n.a.	38	67
Carter *et al.*, 1987 (11)	17	83	95
Hirabayashi *et al.*, 1991 (12)	43	n.a.	81
Current study	48	60	n.a.

Ghadjar et al. IJROBP, 2010

From primary nodal GTV to "high dose" CTV

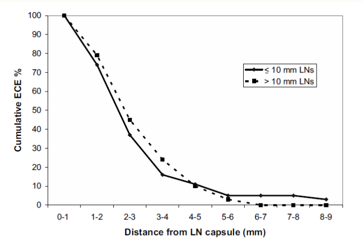
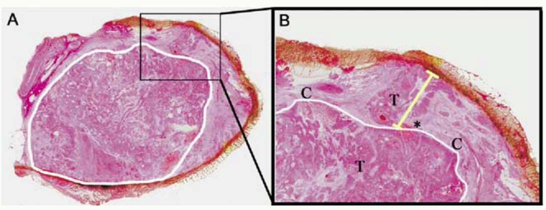


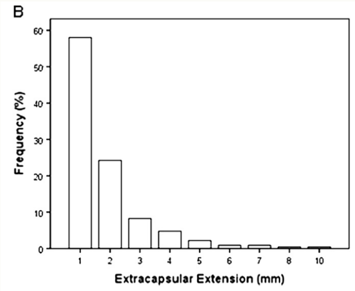
Fig. 4. Cumulative extracapsular extension percentage as a function of distance from the lymph node capsule according to lymph node size.



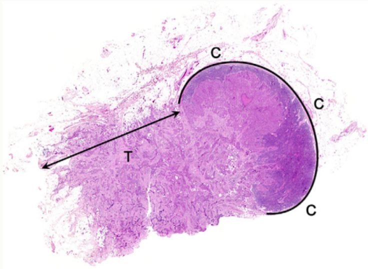
"For N1 nodes that are at high risk for ECE but not grossly infiltrating musculature, 1 cm clinical target volume margins around the nodal gross tumor volume are recommended to cover microscopic nodal extension in head-and-neck cancer."

Apisarnthanarax et al. IJROBP, 2006

From primary nodal GTV to "high dose" CTV



- 231 lymph nodes in 98 patients
- 97% within 5 mm



Ghadjar et al. IJROBP, 2010

Recommendations for volume selection and delineation in HNSCC

Limit of validity

•Post-operative irradiation ?

•N1-N3 neck ?

" Similar principles adapted according to sound clinical, radiological and pathological information"

Which CTV for the node positive and the post-operative neck?

Radiotherapy and Oncology 79 (2006) 15-20
www.thegreenjournal.com

Target volume delineation

Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck

Vincent Grégoire[a,*], Avraham Eisbruch[b], Marc Hamoir[c], Peter Levendag[d]

[a]*Department of Radiation Oncology, Head and Neck Oncology Program and Center for Molecular Imaging and Experimental Radiation Oncology, Université Catholique de Louvain, Brussels, Belgium,* [b]*Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA,* [c]*Department of Head and Neck Surgery and Head and Neck Oncology Program, Université Catholique de Louvain, Brussels, Belgium,* [d]*Department of Radiation Oncology, Rotterdam, The Netherlands*

Recommendations for the node-positive neck

- In case of involvement of level II, delineation of the **retrostyloid space** (level VIIb)
- In case of involvement of level IV and/or Vb, delineation of the **subclavicular fossae** (level IVb and/or Vc)
- When a node is located at the boundary between two levels (e.g. level Ib and II), delineation of the two levels
- When node(s) abut a muscle (e.g. SCM or para-spinal), delineation of the muscle by 10-20 mm in all directions

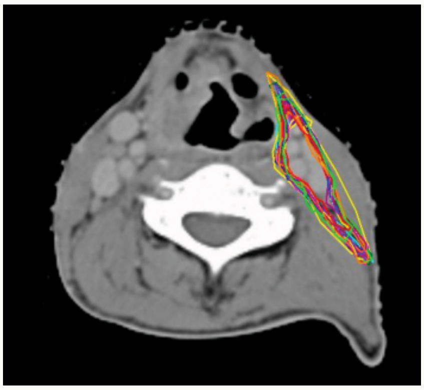
Grégoire et al., 2006

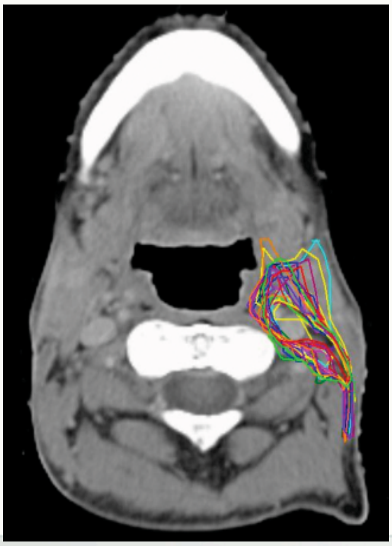
Recommendations for the post-operative neck

- The entire operative bed (identified by inflammation, edema, fibrosis, …) should be included in the CTV
- In case of pathological involvement of level II, delineation of the **retrostyloid space** (level VIIb)
- In case of pathological involvement of level IV and/or Vb, delineation of the **subclavicular fossae** (level IVb and/or Vc)
- For pharyngeal primaries with node positive neck, inclusion of the retropharyngeal nodes (level VIIa)
- When a pathological node is located at the boundary between two levels (e.g. level Ib and II), delineation of the two levels
- When pathological node(s) abut a muscle (e.g. SCM or para-spinal), delineation of the muscle by 10-20 mm in all directions

Grégoire et al., 2006

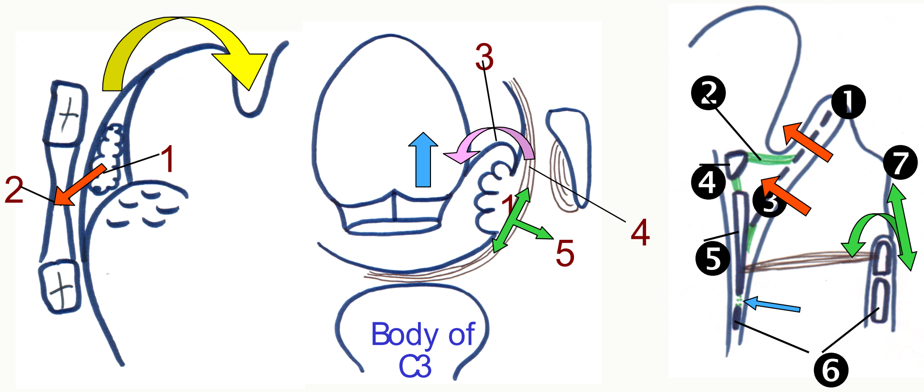
H&N IMRT practice heterogeneity among Dutch Radiation Oncologists





Rasch et al., 2007

Clinical Target Volume (CTV) for pharyngo-laryngeal SCC



From primary tumor GTV to CTV

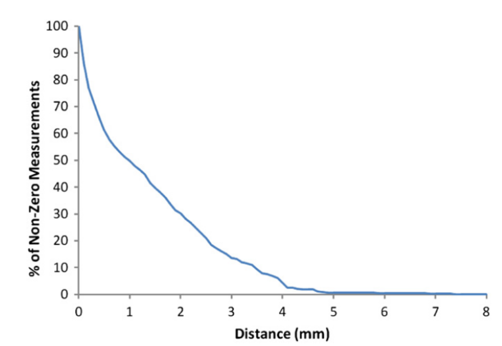


Fig. 8. Graph showing the percentage of nonzero measurements against distance from the gross tumor volume.

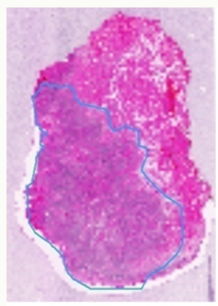
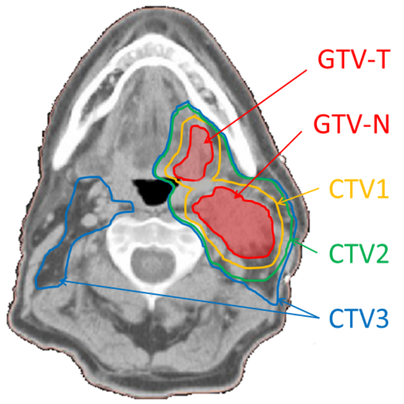


Fig. 4. Image at ×4 magnification and naked eye resolution with gross tumor volume contoured in blue.

88 oral cancers, 44 (50%) had signs of microscopic extension. The maximum distance from the border was 7.8 mm. Ninety-nine percent of all MD was within 4.75 mm and 95% was within 3.95 mm of the GTV.

Campbell et al. IJROBP, 2012

DAHANCA 2013 CTV selection



GTV: Macroscopic tumor in T and N position, based on all available information.

CTV1: Includes GTV-T and GTV-N with a concentric margin of **5 mm in all directions**, modified for air and bone. Larger margin if ill-defined tumor.

CTV2: Includes CTV1 and the volume surrounding CTV1 with the highest risk of subclinical spread; CTV1 with a **concentric margin of 5 mm** in all directions, modified for air and bone.

CTV3: CTV2 and the elective nodal regions In N+ also include nodal areas at least **2 cm cranial and caudal to GTV-N**, and if invading muscle, include muscle at least **2 cm cranial and caudal to GTV-N.**

Morbidity after Surgery

C. René Leemans, MD, PhD
Professor and Chair

Complications / Side-effects / Morbidity

General
- Anesthetic
- Metabolic
- DVT

Surgical
- Acute
- Late

Related to Surgery

- Bleeding
  - Intra-operative
  - Post-operative
- Chyle leakage
- Infection
- Wound healing
- Flap failure

Related to Surgery

- Nerve injury
  - Cranial N. XI
  - Cranial N. V, VII, IX, X and XII
  - Brachial plexus
  - Phrenic
  - RLN
  - Sympathatic chain

Most Frequent Side-effect after Neck Dissection

- Pain
- Impaired range of motion
    - Abduction
    - Anteflexion
- Drooping of scapula
- Important in health-related quality of life

Shoulder Syndrome depends on:

- Preservation of spinal accessory nerve
- Modified radical neck dissection
- Dissection level V
- Selective neck dissection

Shoulder Dysfunction after Different Types of Neck Dissection

Type of neck dissection	SDQ-score 0–100 mean (STD)	Abductie 0°–180° mean (STD)	Anteflexie 0°–180° mean (STD)
Radical: 12 sides in 12 patients	45 (±24)	90 (±34)	119 (±28)
Modified radical:[a] 26 sides in 22 patients	32 (±29)	134 (±31)	152 (±16)
Selective: 13 sides in 9 patients	20 (±31)	143 (±26)	159 (±14)
p	0.1[b]	0.001[b]	0.0002[b]

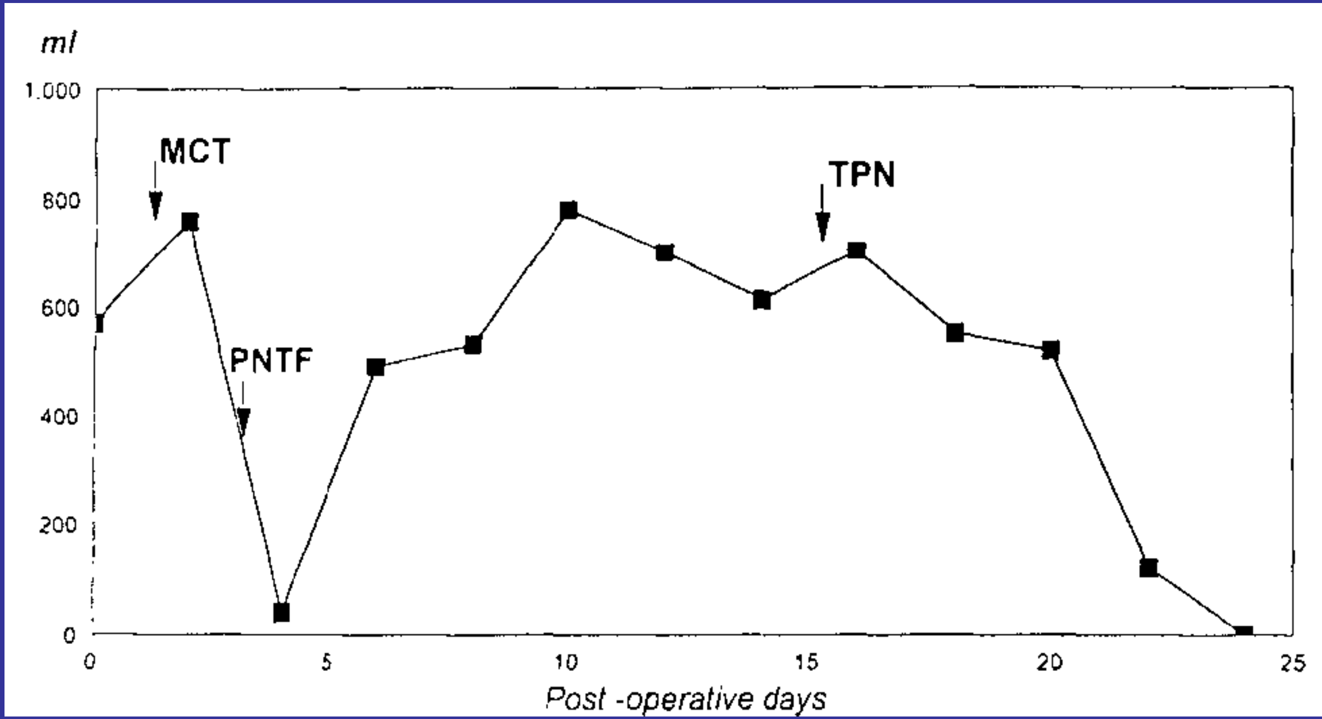
van Wouwe M. et al. Radiother Oncol 2009;90:196–201

Chylous Leak

- Lymphatic leak through wound drain
- Injury to ductus thoracicus
- Several cc to a liter or more per 24 hrs
- Loss of fluids
- Loss of electrolytes
- Loss of WBC

Clinical Picture

Morbidity after Surgery



Management

- MCT diet
- Parentral nutrition
- Re-operation
- Thoracosopic ligation
- Interventional radiology

Reconstructive Objectives

- Adequate wound healing
- Maximize residual function
- Restoration of sensation
- Bulk replacement

Current Reconstructive Philosophy

- Replacement of resected tissue with tissue that mimics its complex movements and changes in shape is currently not feasible

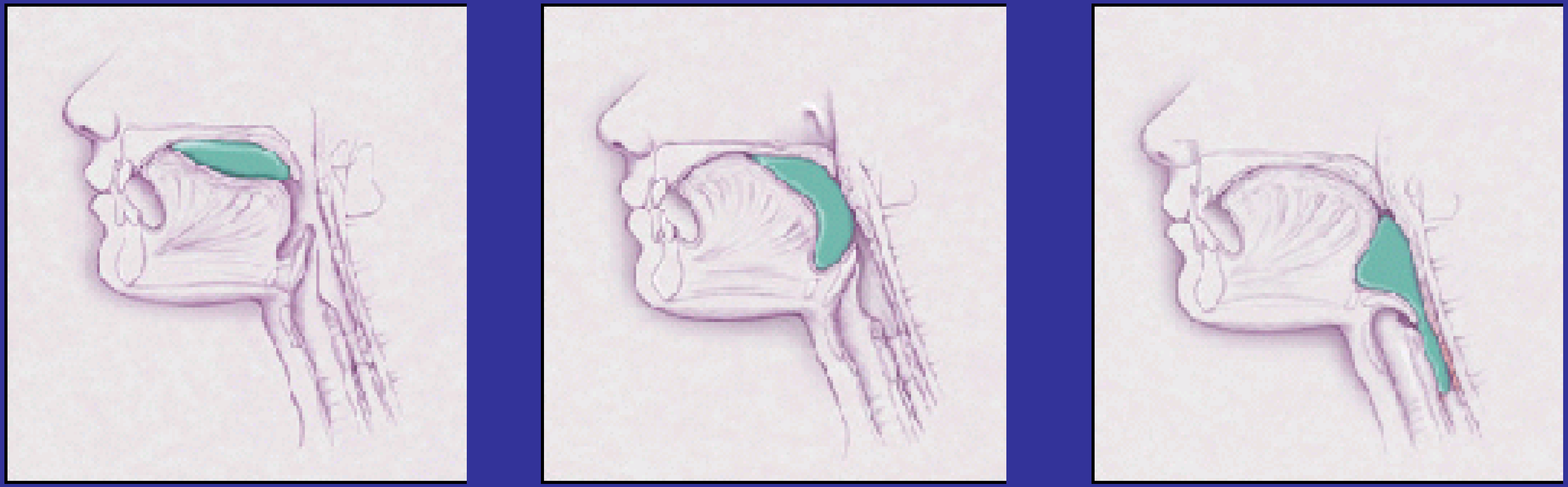
Current Reconstructive Philosophy

- Attempts that maximize the patient's possibility for compensatory mechanisms

Normal Physiology of Swallowing

- Oral phase (completely voluntary)
- Pharyngeal phase (reflective action)
- Esophageal phase (completely involuntary)

Normal Physiology of Swallowing



Oral Phase

- Entry of food into the oral cavity and preparation for swallowing
- During this phase:

  -mixing with saliva

  -mastication

  -formation of a cohesive bolus

Oral Phase

- It requires coordination of:

-Lips

-Tongue

-Teeth

-Mandible

-Soft palate

Pharyngeal Phase

- Initiated as tongue propels bolus posteriorly and the base of tongue contacts the posterior pharyngeal wall
- Eliciting a reflective action that begins a complex series of events

Pharyngeal Phase

- Soft palate elevates to prevent nasal reflux
- Constrictor pharyngeal muscle contracts
- Epiglottis inverts
- Vocal cords adduct
- Hyolaryngeal complex moves antero-superiorly
- Cricopharyngeus muscle relaxes

Esophageal Phase

- peristaltic waves

Total swallow time from lips to stomach is less than 20 seconds

Normal Physiology of Swallowing

Lingual Driving Force

Pharyngeal Clearing Force

Oropharyngeal Propulsion Pump

+

Effective Pharyngeal Swallowing

-

Hypopharyngeal Suction Pump

Oral Cavity

- Predicable but complex swallowing problems

  -Location

  -Size

  -Tumor extent

  -Reconstruction procedure

Oral Cavity

- Chewing
- Controlling food in the mouth
- Initiating the swallow

Oral Cavity

- Resections of up to one third of tongue result in only transient swallowing problems
- Maximal function after composite resections with neural control and some tongue movement
- These patients can regain oral nutrition 1 month postoperatively (if no other structures are involved)

Oral Cavity

- More severe problems when tongue tethering to floor-of-mouth or hypoglossal nerve sacrifice
- Resections of hard palate or tongue result in loss of pressure needed to propel the bolus into pharynx

Oropharynx

- Excision usually causes more severe dysphagia since tongue base plays a critical role in

  -initiating swallow

  -propelling bolus through pharynx

  -efficient pharyngeal peristalsis

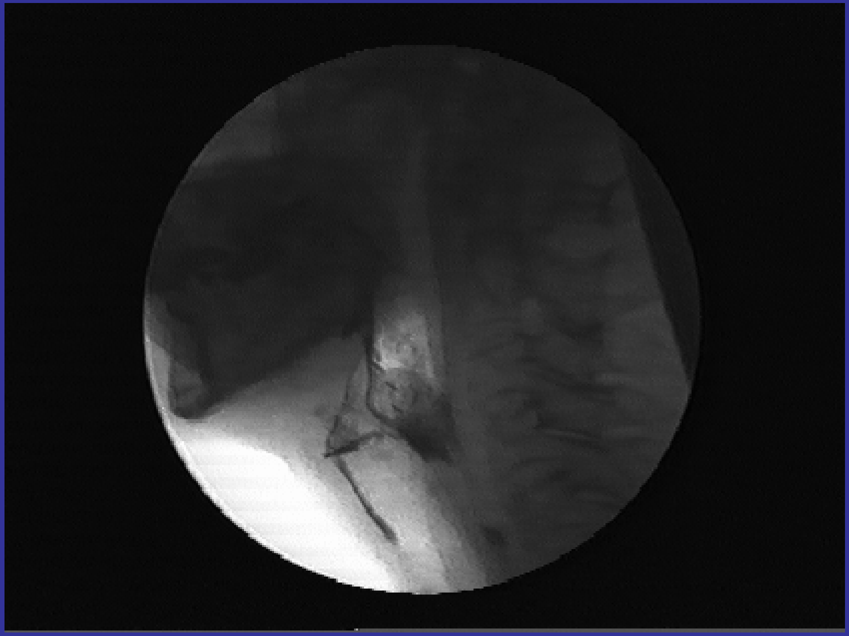
Oropharynx

- Any procedure that minimizes the tongue base to posterior pharyngeal wall contact can result in:
  - Delayed initiation of the swallow resulting in aspiration before swallow
  - Reduced pressure generation causing pharyngeal stasis post-swallow
  - Reduced hyolaryngeal elevation causing pharyngeal stasis and post-swallow aspiration

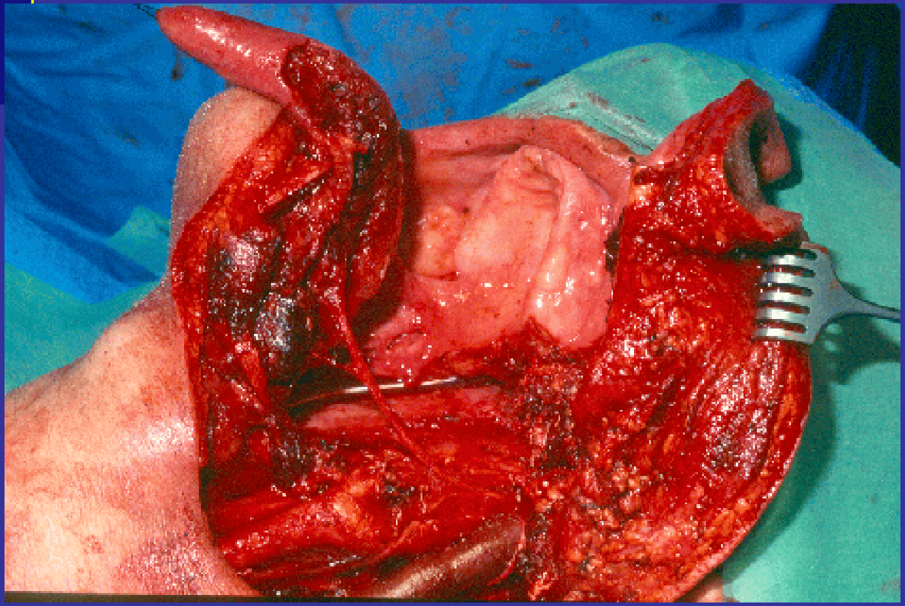
Oropharynx

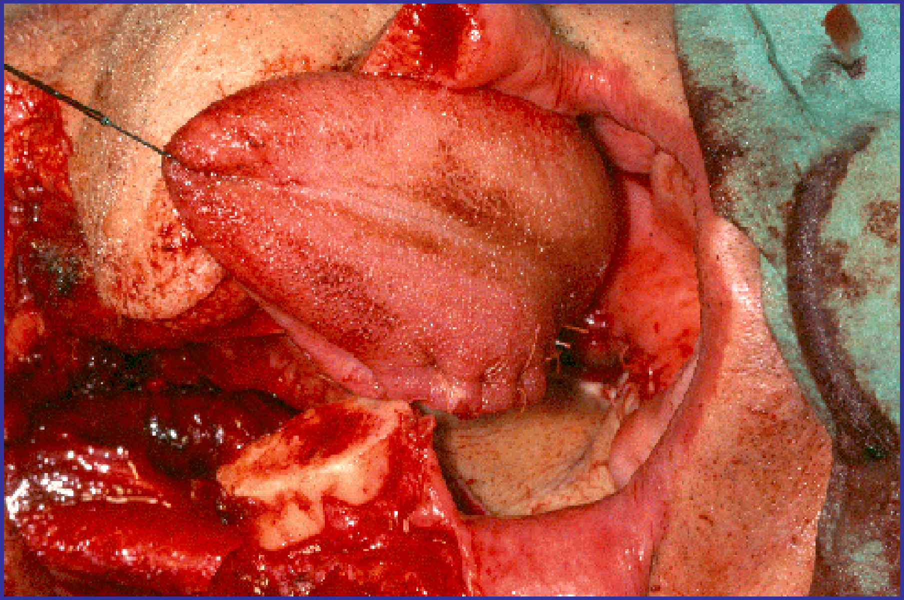
- Combined resections of soft palate and tonsillar pillars may impact bolus transport causing nasopharyngeal reflux and pharyngeal stasis

Videofluoroscopy



Excision and Reconstruction Tonsillar Carcinoma





Quality-of-life

	Pretreatment	6 months	12 months	Significance	
	Mean	Mean	Mean	p_{P-6}	p_{6-12}
EORTC QLQ-C30					
Functioning scales[a]					
Physical functioning	87.7	80.5	85.9	**0.005**	**0.044**
Role functioning	79.5	75.4	84.8	.237	**0.005**
Cognitive functioning	85.6	84.1	87.9	.685	0.262
Emotional functioning	70.3	86.0	84.7	**0.000**	0.602
Social functioning	89.0	86.7	90.2	0.486	0.297
Global quality of life	75.9	76.3	80.7	0.903	0.064
Symptom scales or single items[b]					
Fatigue	24.7	23.0	18.9	0.616	0.136
Emesis	1.9	5.3	2.7	0.071	0.197
Pain	29.2	10.6	12.1	**0.000**	0.652
Dyspnea	10.6	12.1	7.6	0.710	0.160
Insomnia	36.4	23.5	17.4	0.055	0.221
Appetite loss	12.1	13.6	10.6	0.772	0.210
Constipation	13.6	3.0	3.0	**0.046**	1.00
Diarrhea	6.8	5.3	5.3	0.599	1.00
Financial impact	7.6	17.8	15.2	**0.036**	0.583

Borggreven PA *et al*. Head Neck 2005;27:785-93,
Oral Oncol 2007;43:1034-42, Head Neck 2007;29:638-47

Morbidity after Surgery

Quality-of-Life

	Pretreatment	6 months	12 months	Significance	
	Mean	Mean	Mean	p_{P-6}	p_{6-12}
EORTC QLQ-H&N35					
Pain	33.0	21.8	19.5	**0.010**	0.443
Swallowing	18.9	35.4	25.8	**0.001**	**0.003**
Senses	4.2	17.8	19.7	**0.000**	0.452
Speech	9.1	11.4	9.7	0.420	0.518
Social eating	20.3	30.8	23.6	0.050	**0.023**
Social contact	3.9	6.9	5.9	**0.029**	0.542
Sexuality	19.3	22.1	24.0	0.931	0.673
Teeth	18.2	27.8	22.5	**0.020**	0.413
Opening mouth	19.7	37.9	33.3	**0.018**	0.360
Dry mouth	22.0	68.9	56.1	**0.000**	**0.005**
Sticky saliva	17.4	47.6	47.6	**0.000**	0.781
Coughing	11.4	23.5	24.2	**0.001**	0.855
Feeling ill	4.5	3.8	6.8	0.660	0.290

Borggreven *et al*. Oral Oncol 2007;10:1034-1042

Comparison Advanced Oropharyngeal Carcinomas

	Surgery +/- RT	Chemoradiation*
Number	42	75
Period	1998-2000	2000-
Mean age (yrs)	55	58
HPV positive (%)	27	26

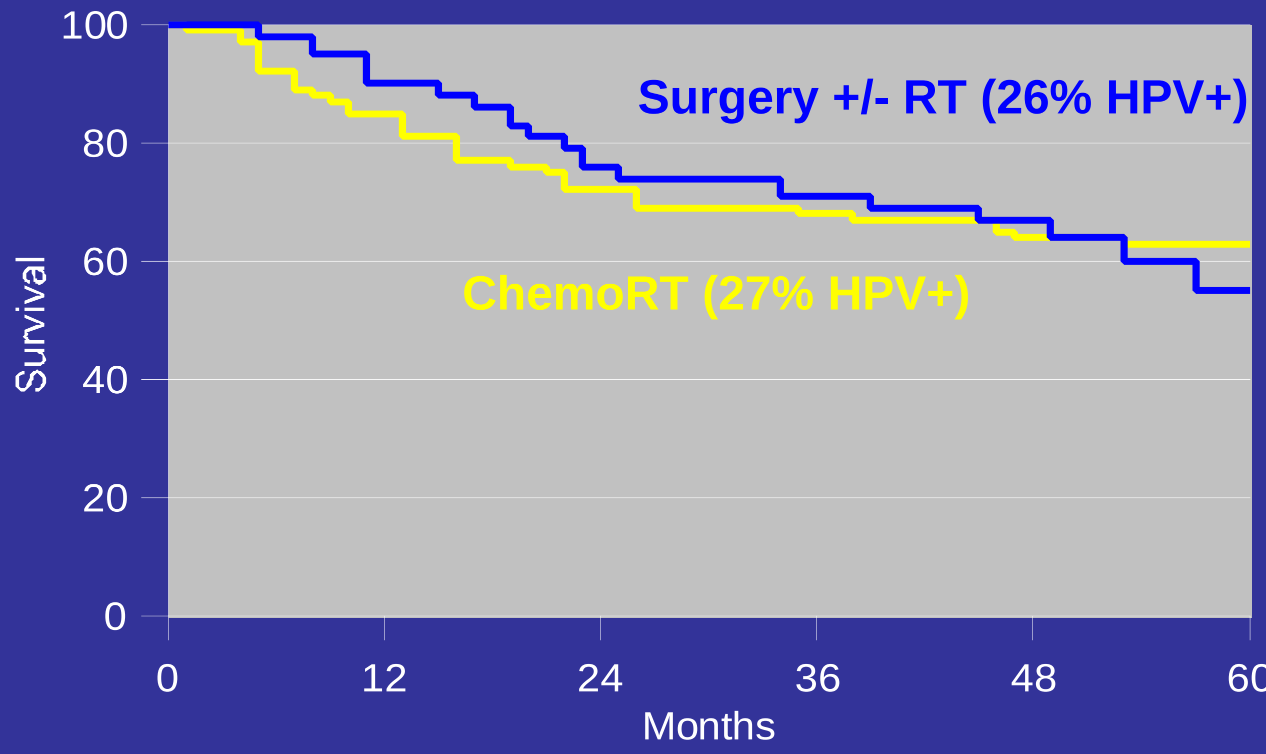
*With salvage surgery if needed

Non-significant difference in gender distribution and comorbidity

Leemans CR *et al*. in preparation

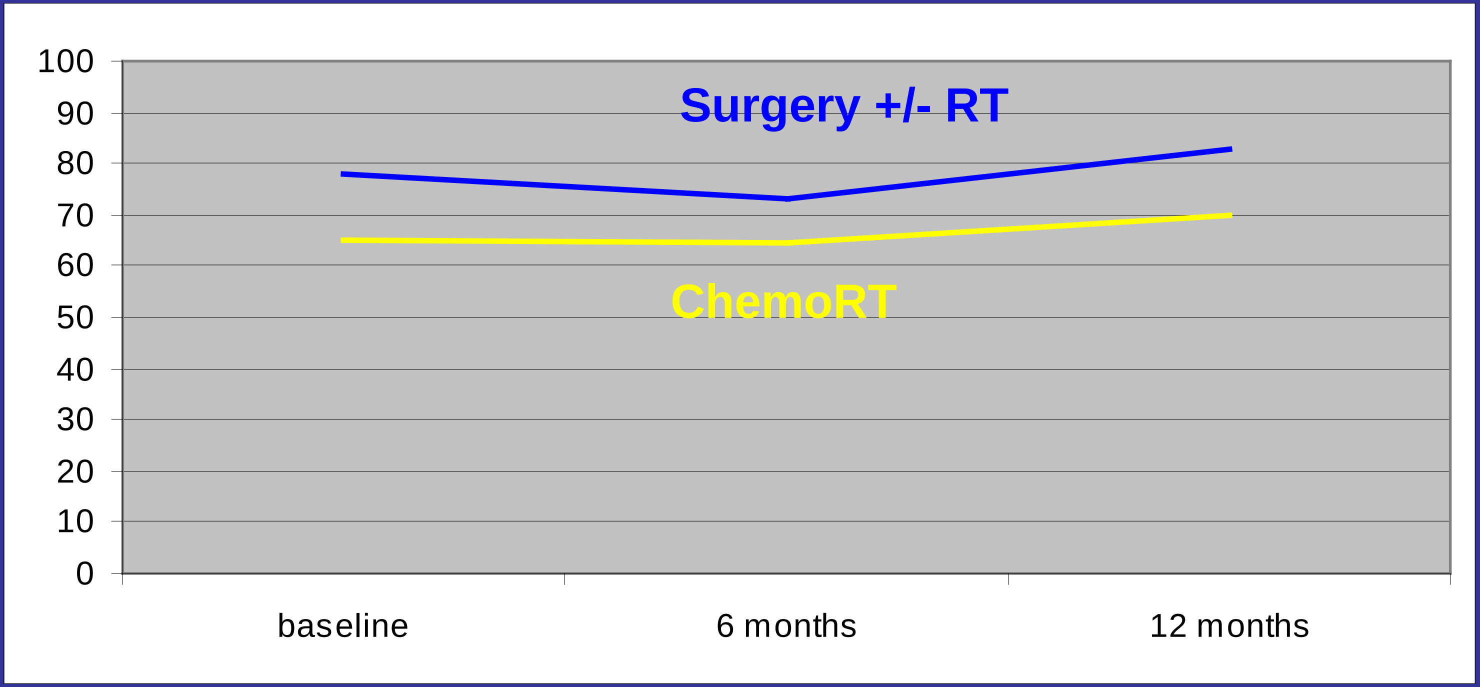
Morbidity after Surgery

Overall Survival (n=117)



Leemans CR *et al*. in preparation

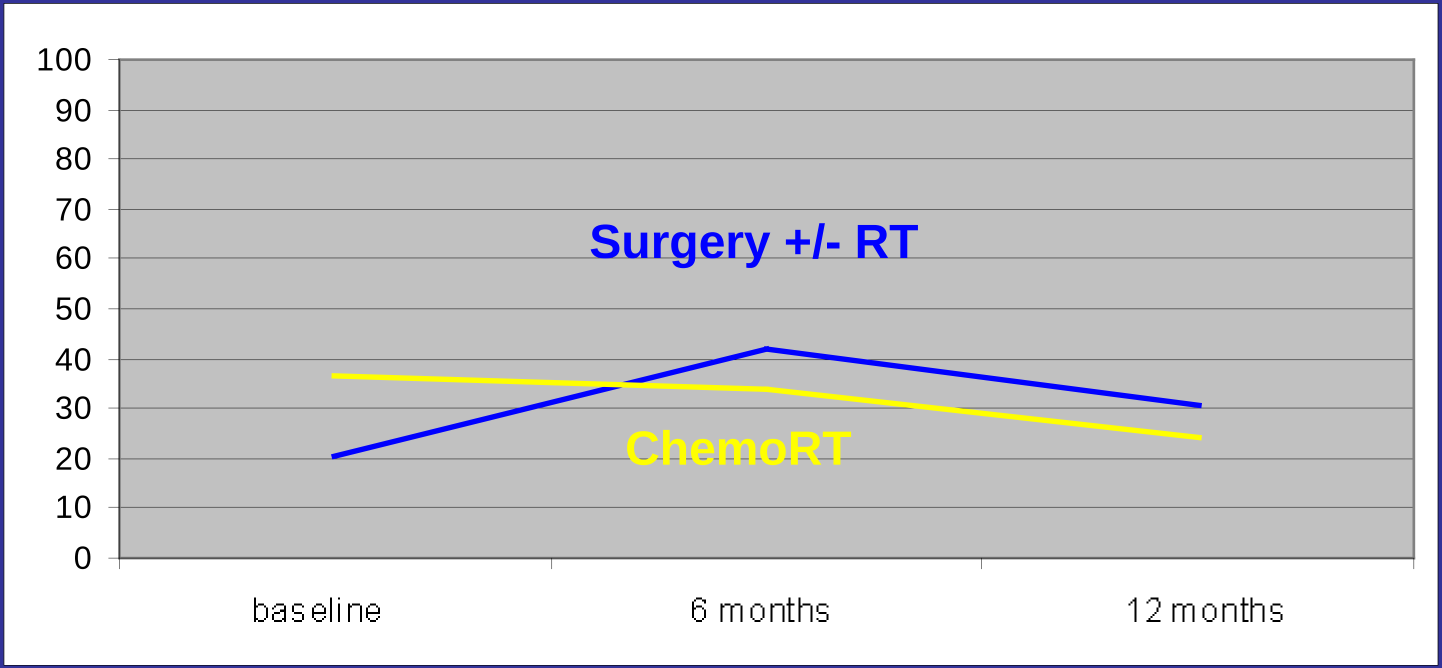
Global Quality of Life (n=117)



Leemans CR *et al*. in preparation

Morbidity after Surgery

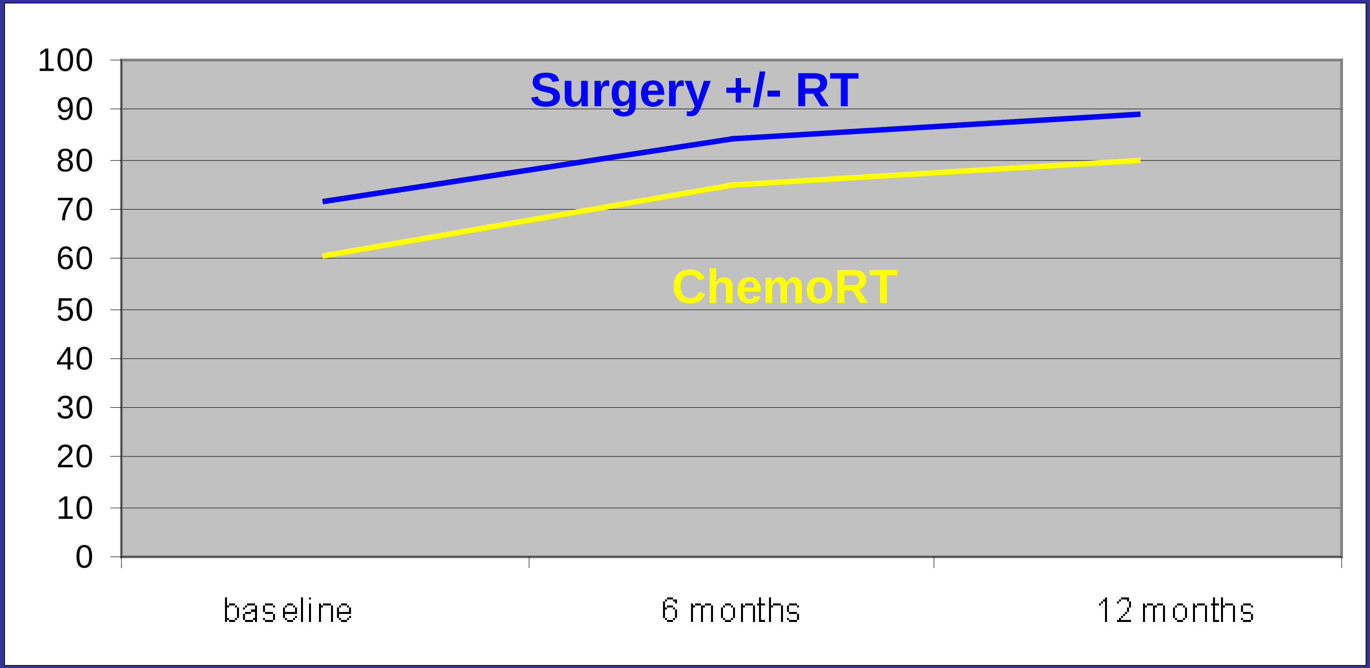
Swallowing (n=117)



Verdonck IM *et al*. in preparation

VU university medical center

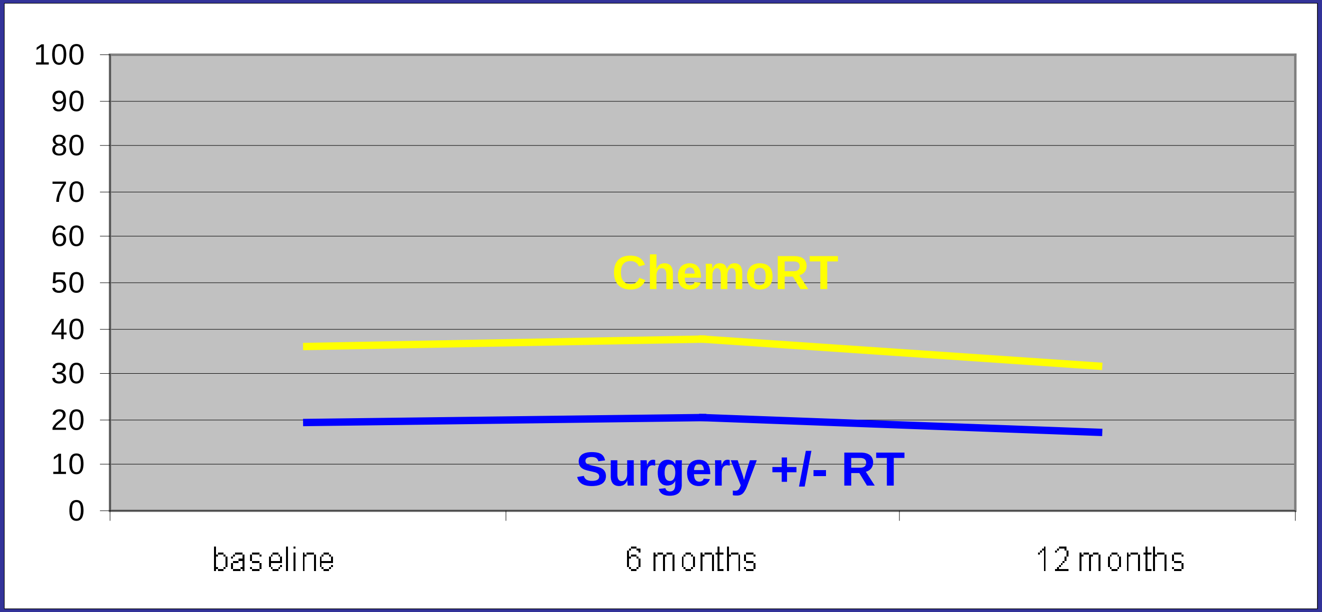
Emotional Functioning (n=117)



Verdonck IM *et al*. in preparation

Morbidity after Surgery

Fatigue (n=117)



Verdonck IM *et al*. in preparation

Conclusions

- Adequate patient counselling
- Prevention starts during surgery
- Close monitoring as to complications
- Early intervention if indicated

Morbidity (acute and late) after RT, RT-CH, RT-EGFR inhibitors

Jesper Grau Eriksen

Therapeutic ratio

Effect

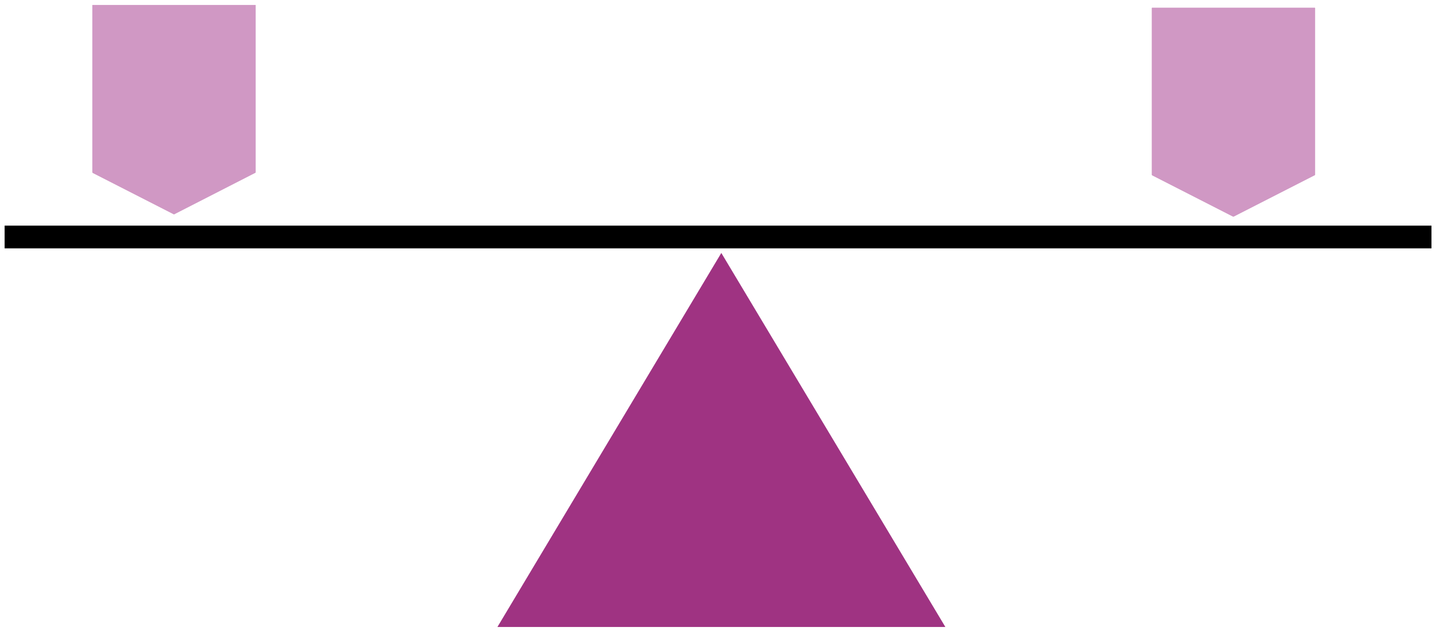
Tumor control

Survival

Side effect

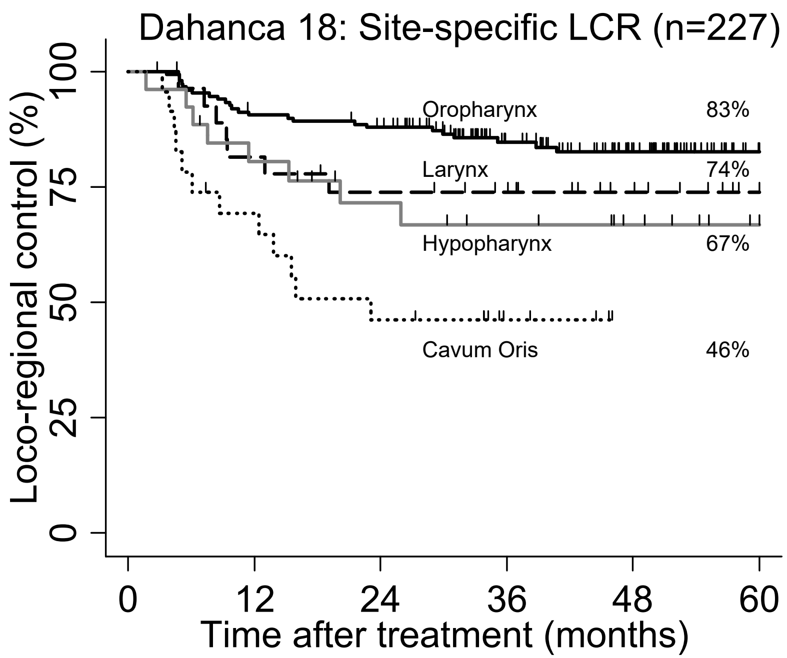
Acute

Late

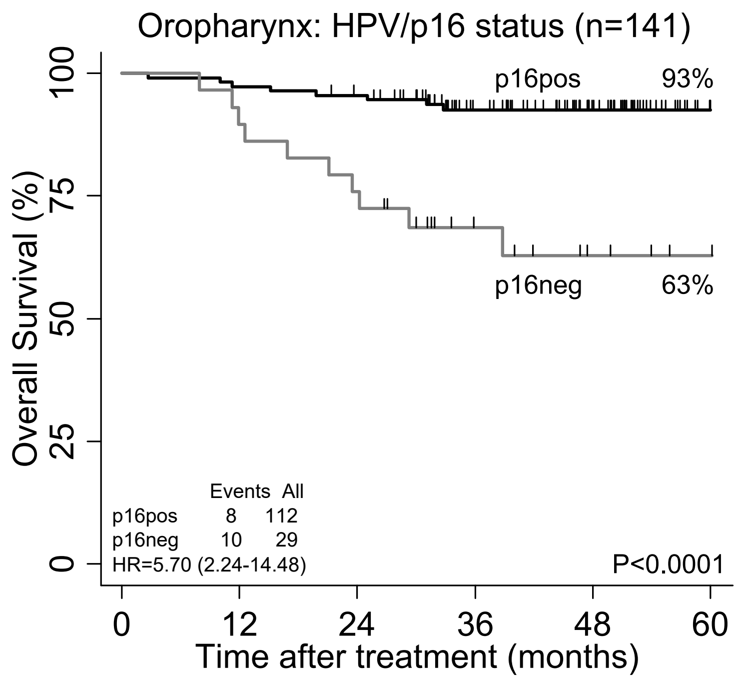


Why should we care?

DAHANCA 18: concomitant chemoradiotherapy



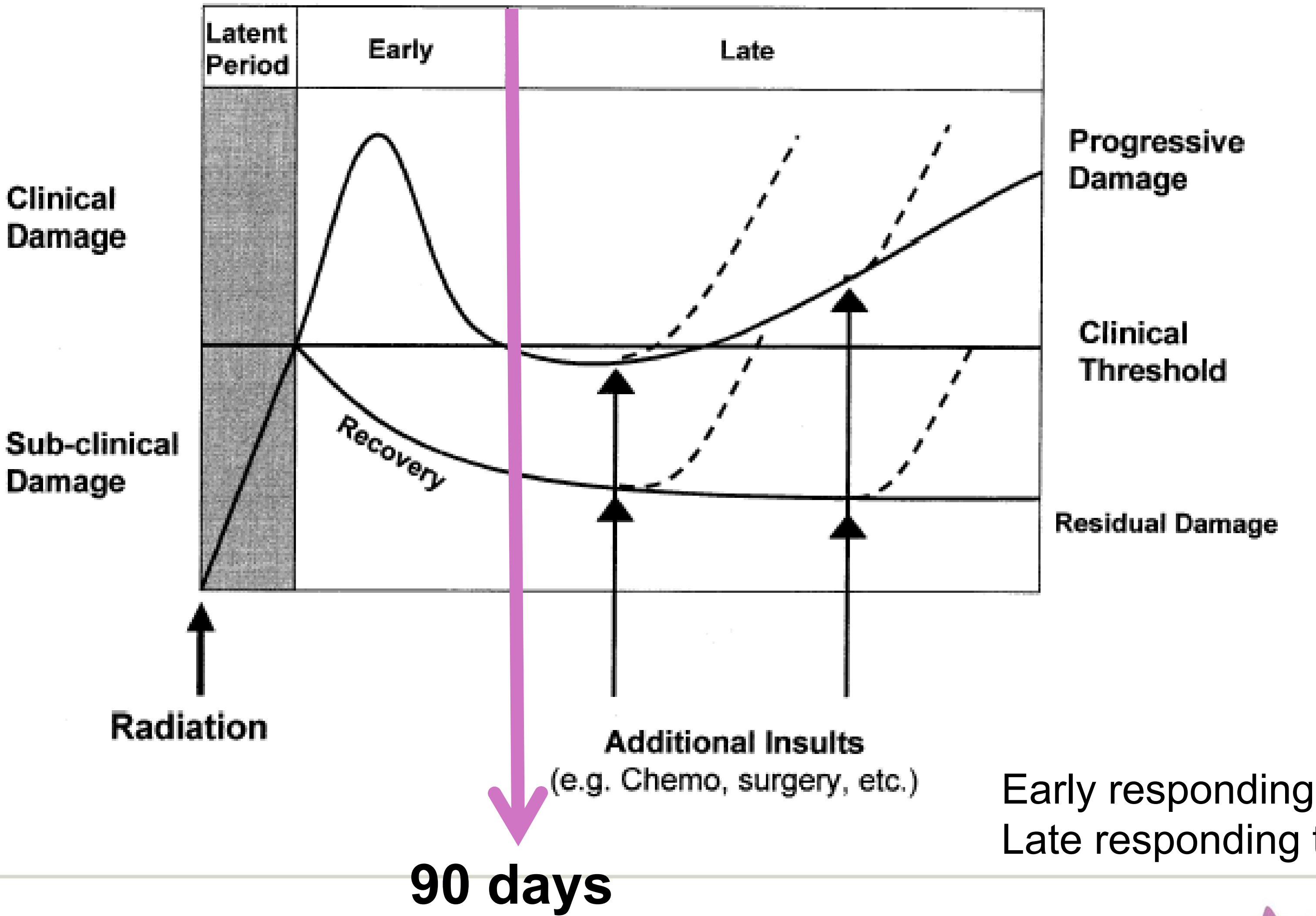
At risk						
Larynx	28	22	19	16	9	2
Oropharynx	150	134	128	86	53	17
Hypopharynx	26	20	15	12	8	3
Cavum Oris	23	15	10	4	0	0



At risk						
p16pos	112	109	105	75	46	14
p16neg	29	26	22	12	6	3

Benzten et al Acta Oncol 2015

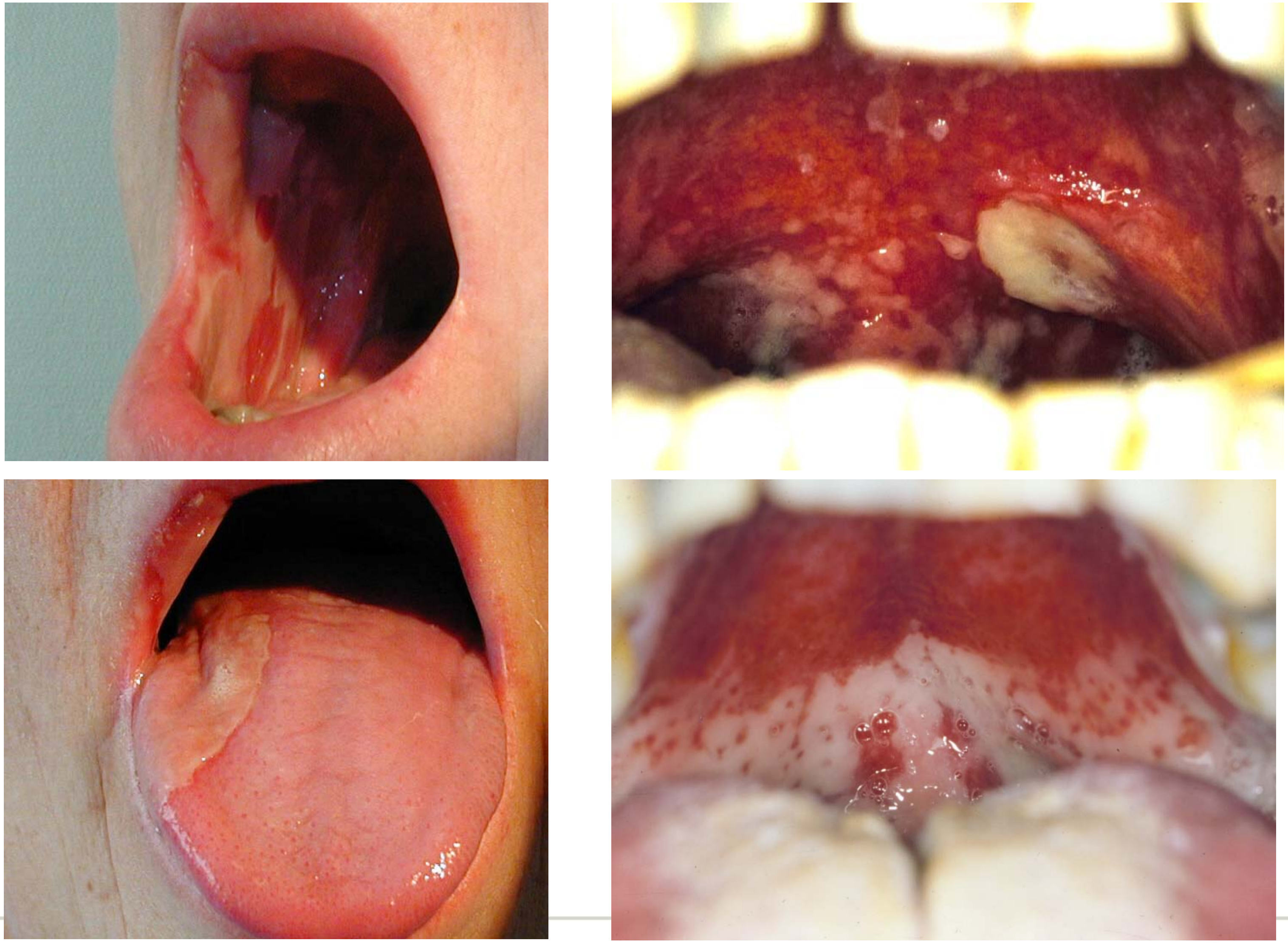
Definitions



Early responding tissues
Late responding tissues

Rubin IJROBP 1995

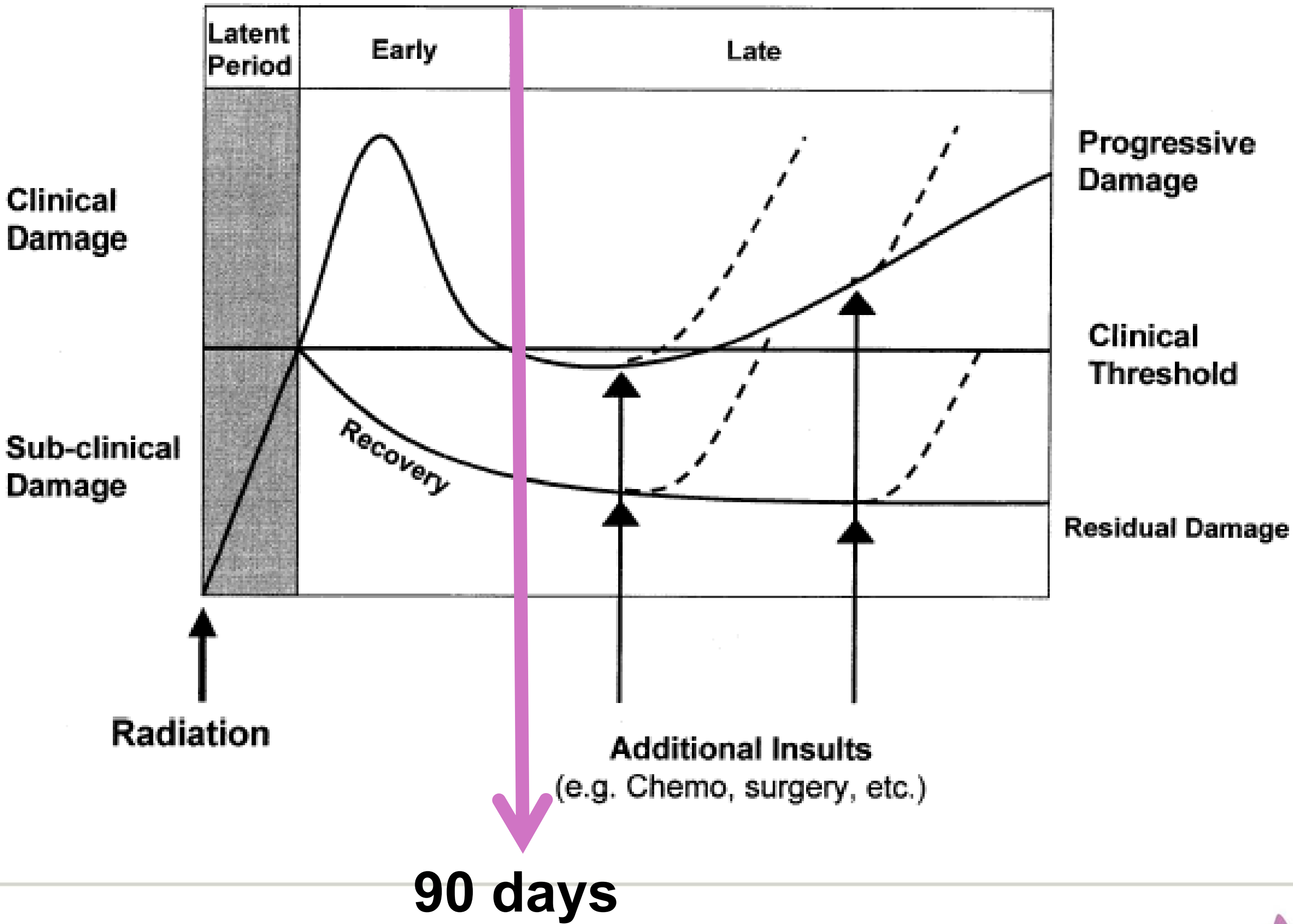
Mucositis



Oral candidiasis

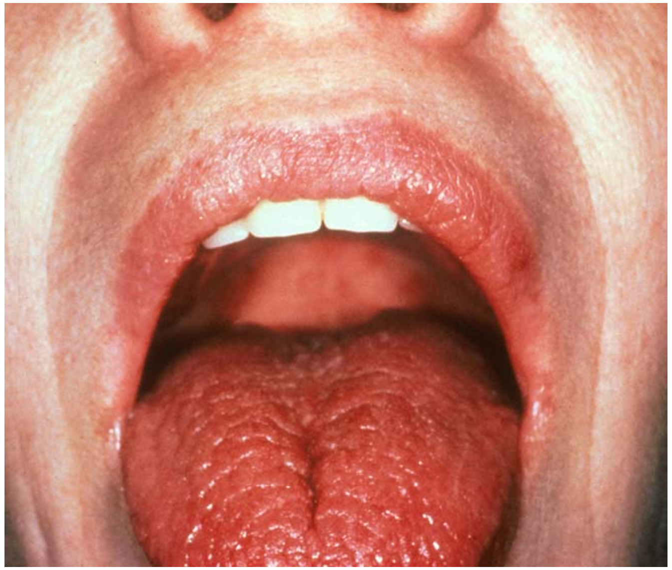
Skin reactions

Definitions



Rubin IJROBP 1995

Late effects

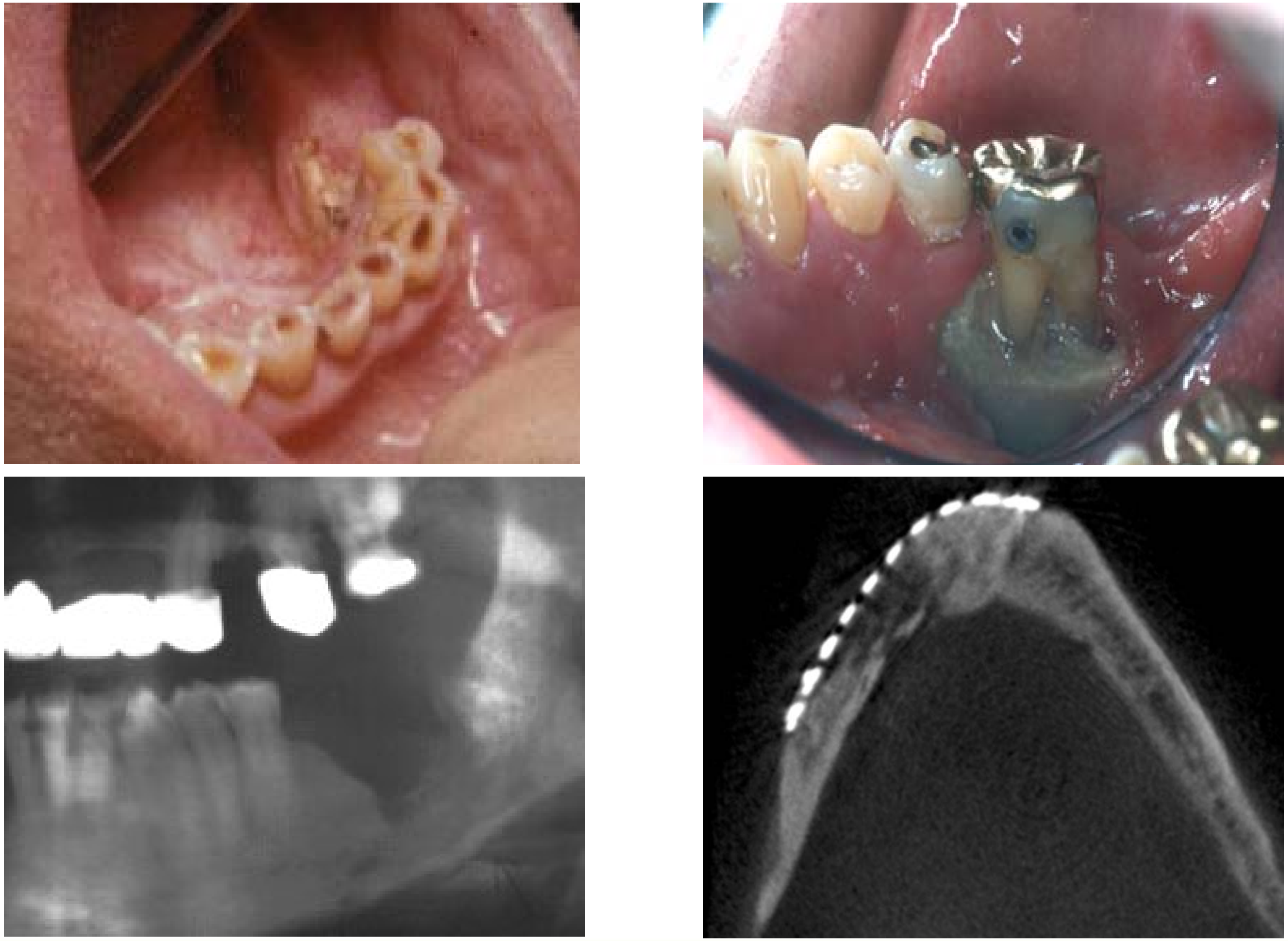


Trismus

800.638.6771
Western Division:
800.262.8828
Canada:
800.668.9139

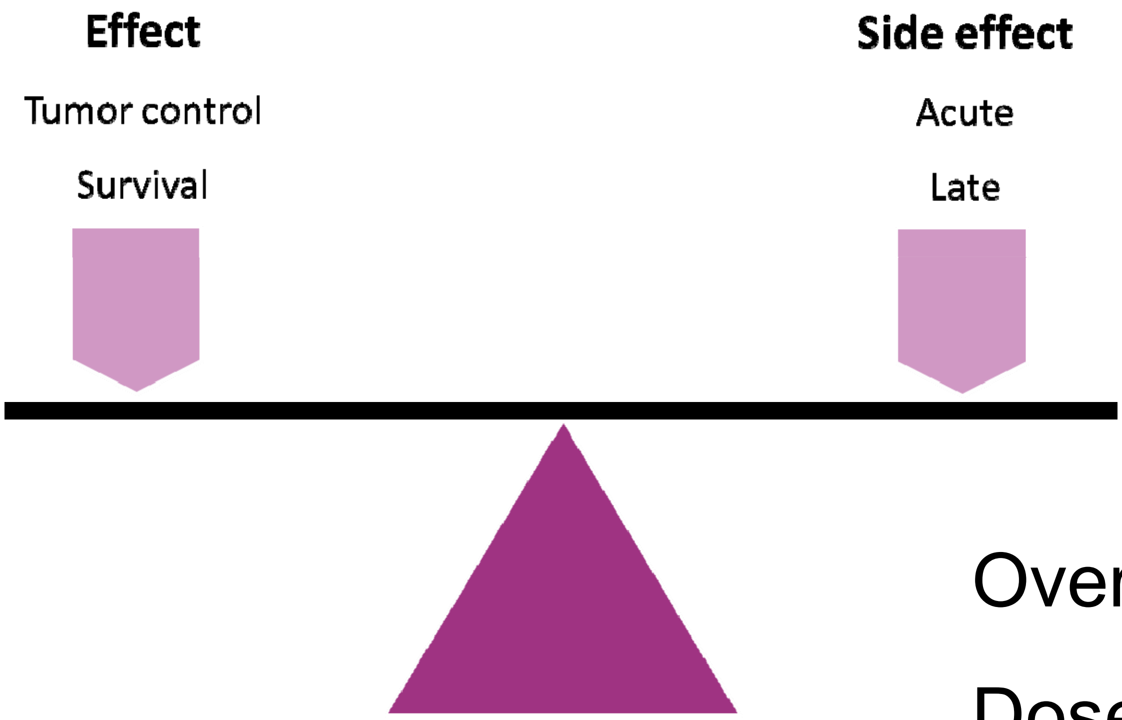
Dysphagia

Osteoradionecrosis



Modified from Lartigeau 2012

Late effects

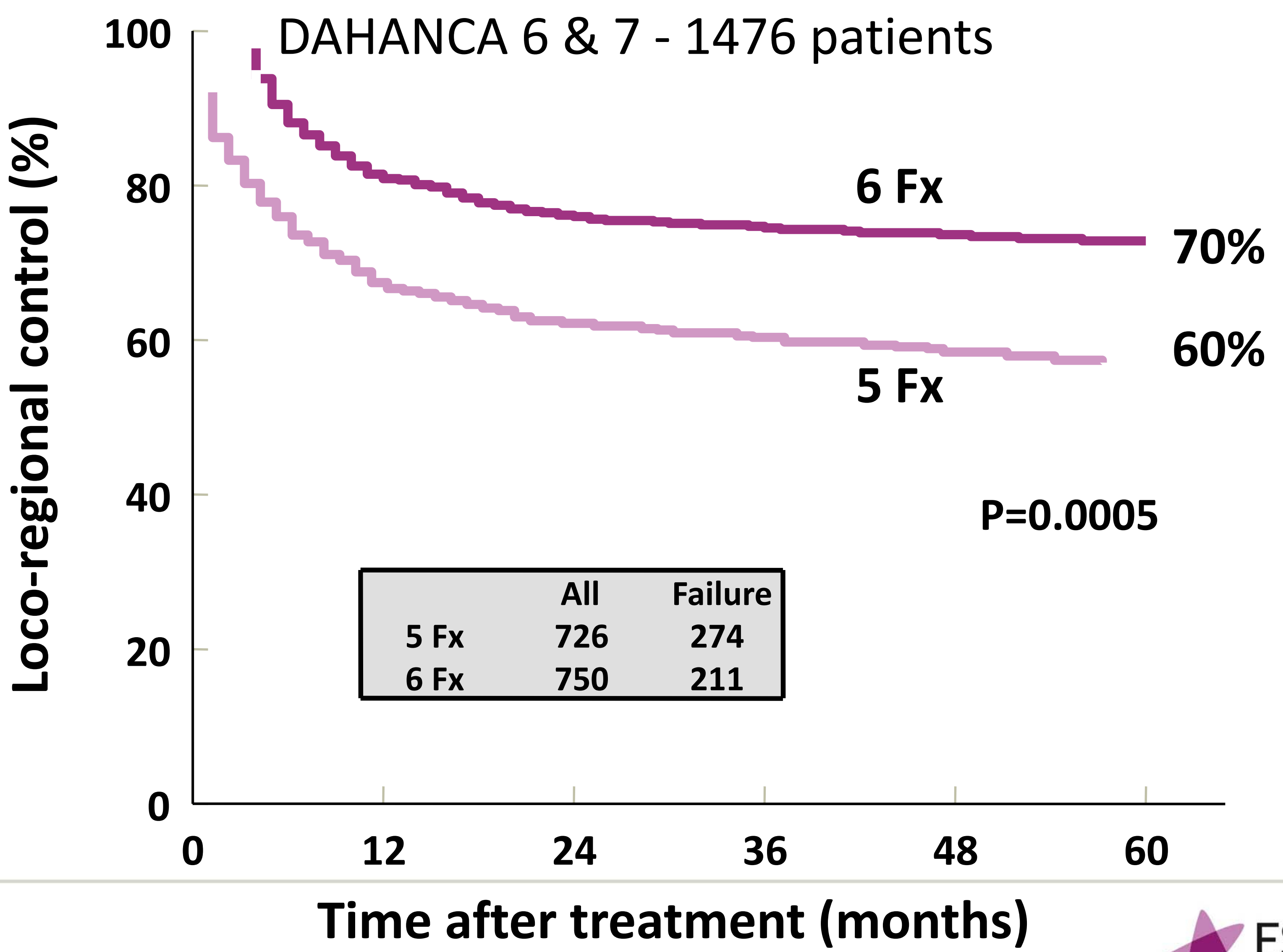


Overall treatment time

Dose per fraction

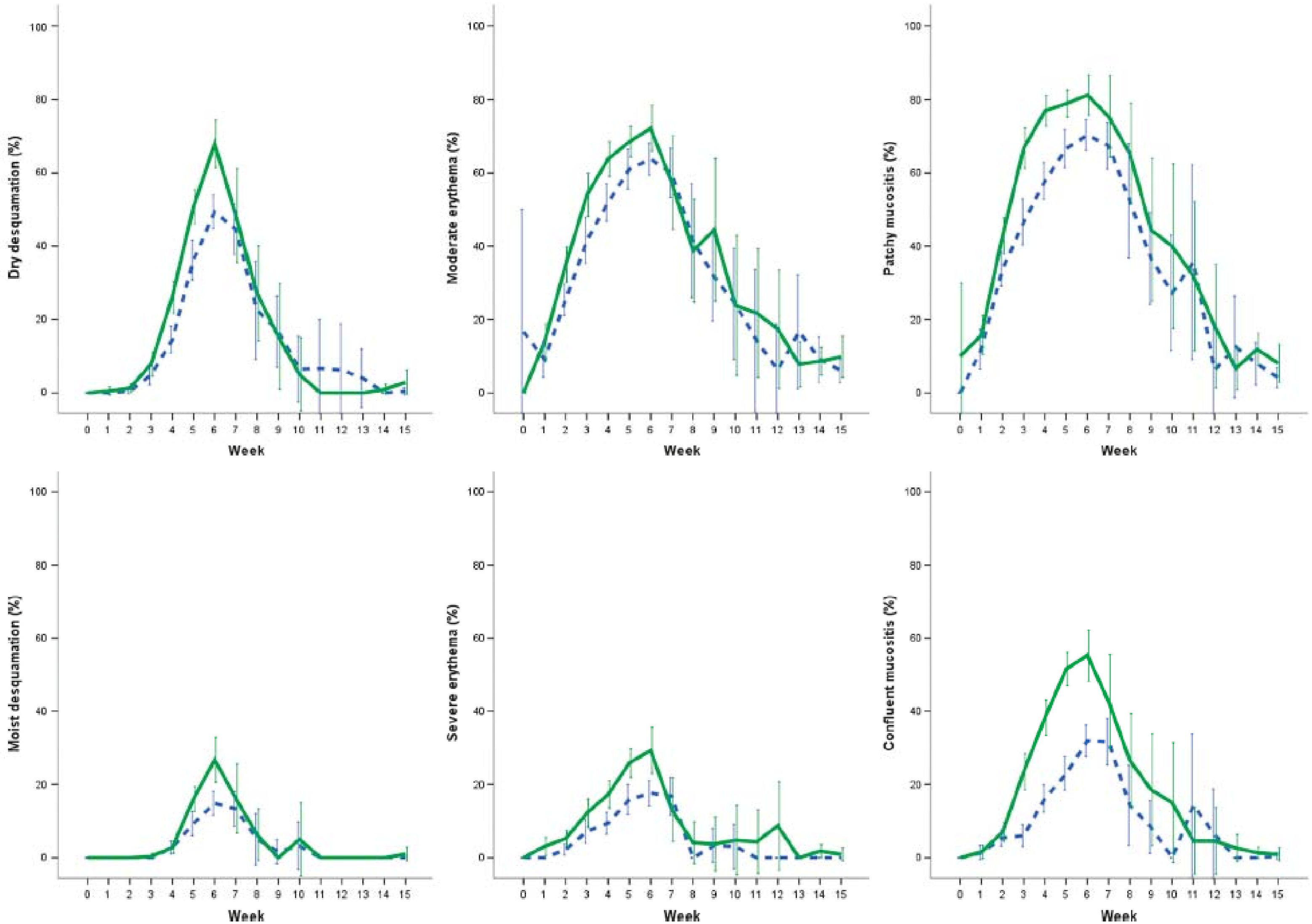
volume

Accelerated Radiotherapy



Overgaard 2003

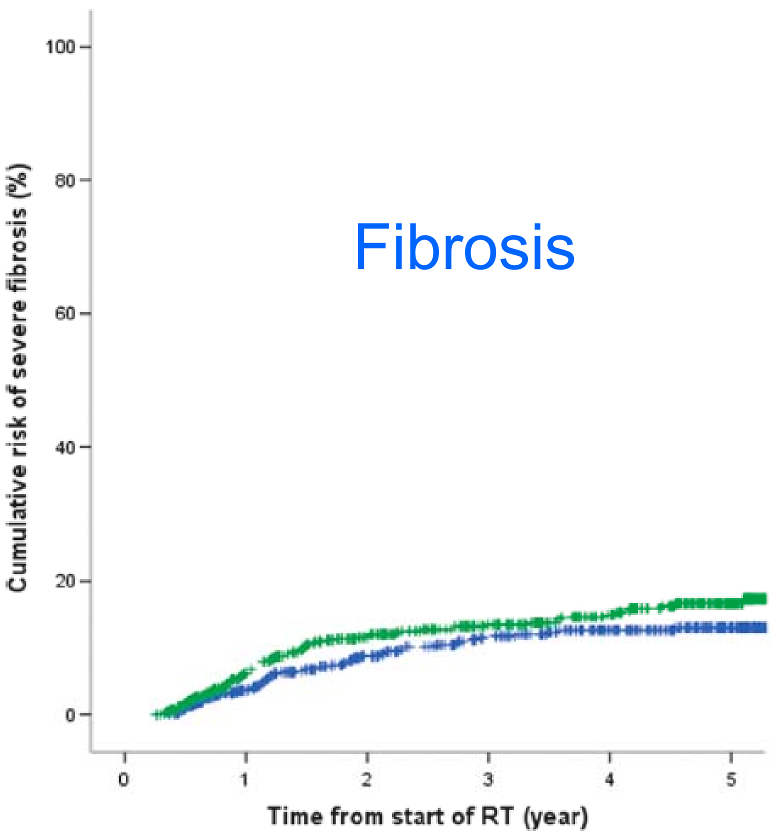
Acute morbidity - DAHANCA 6 & 7

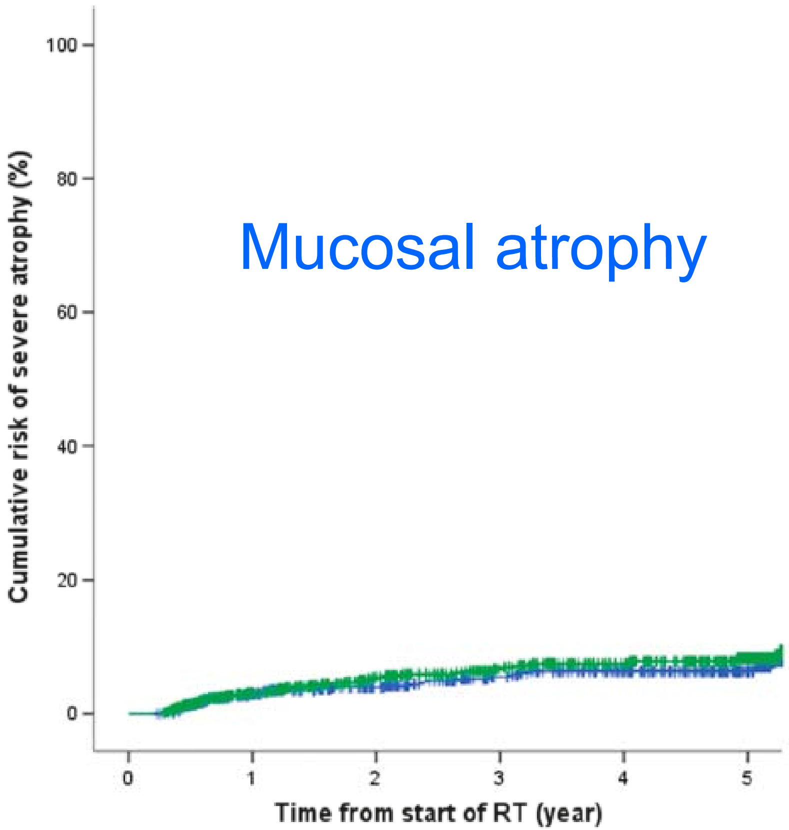


Mortensen et al 2012

ESTRO School

Late morbidity - DAHANCA 6 & 7





Mortensen et al 2012

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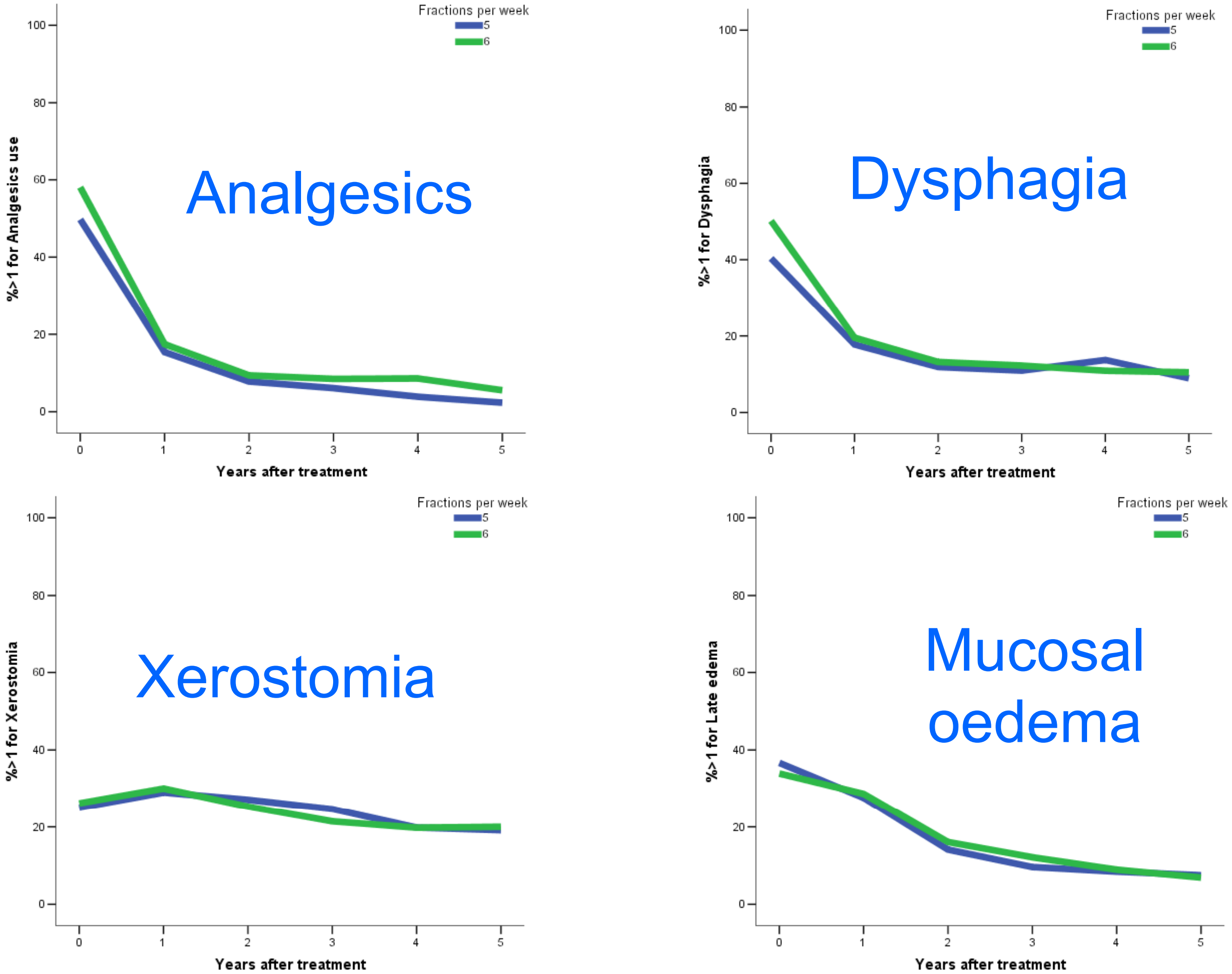
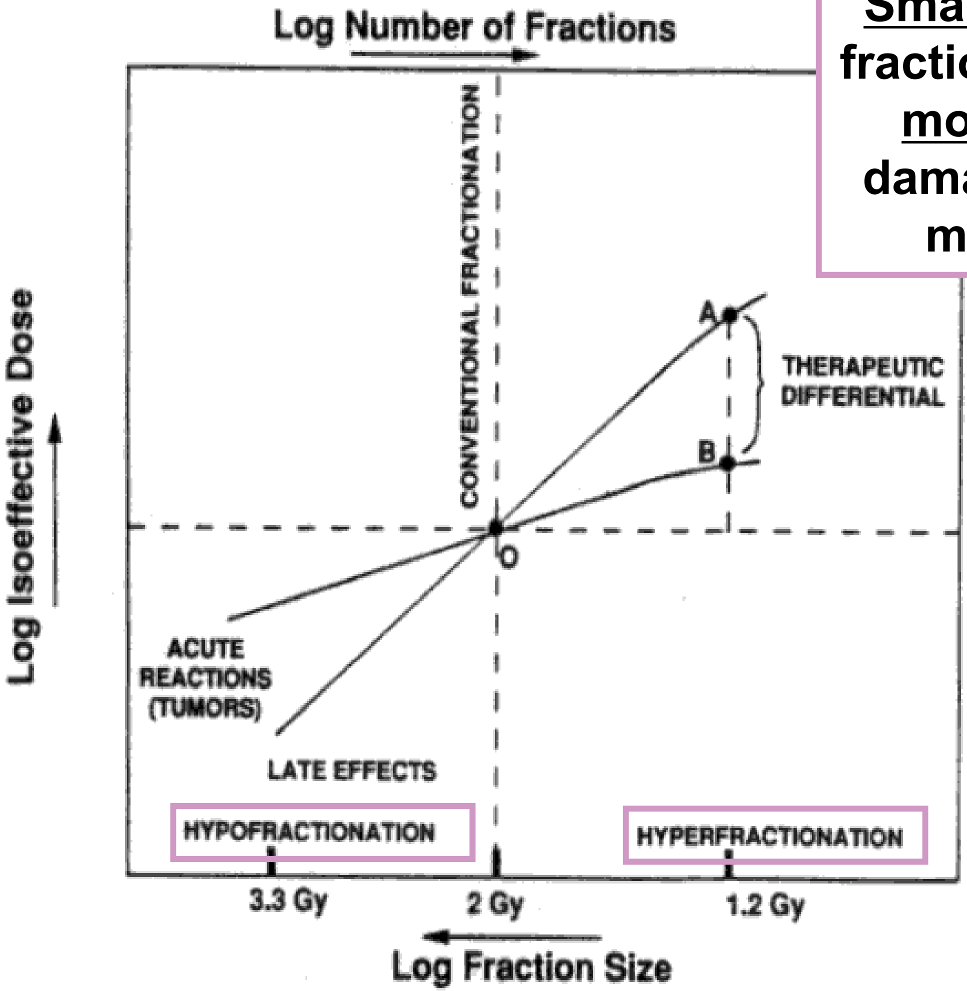


Mortensen et al 2012

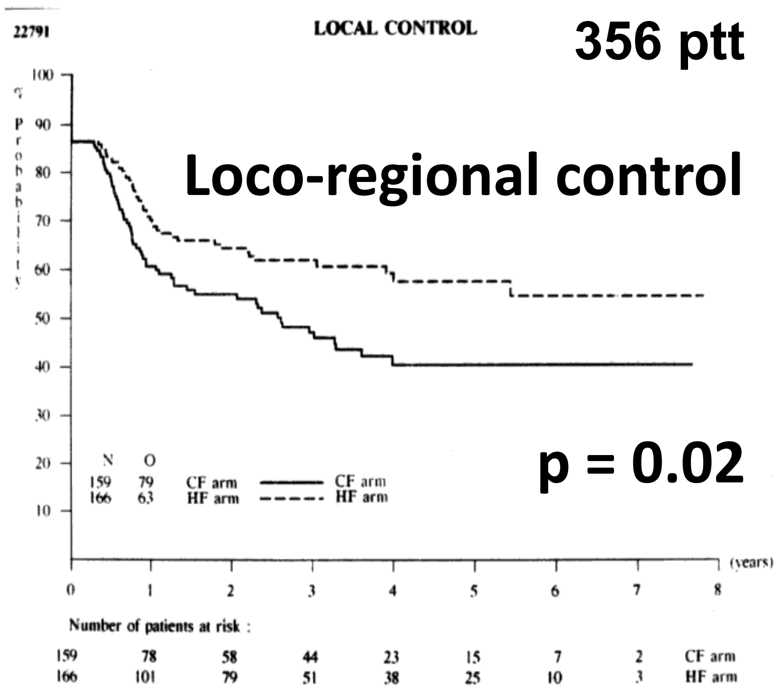
Rationale for hyperfractionation

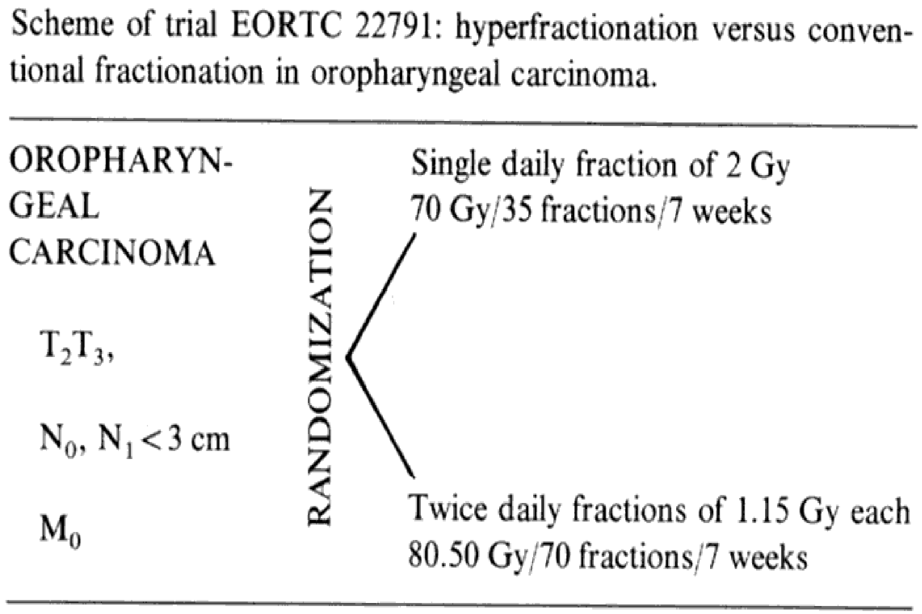
Therapeutic ratio
vs
dose per fraction



<u>Small dose</u> per fraction: Relative <u>more</u> tumor damage vs late morbidity

Hyperfractionation: EORTC 22791





Improved Terapeutic Ratio:

Increase in tumour control

Increased acute toxicity (Confl. mucositis - conv: 49%; HFX: 67%)

But same late morbidity

Horiot 1992

Accelerated fractionation: EORTC 22791

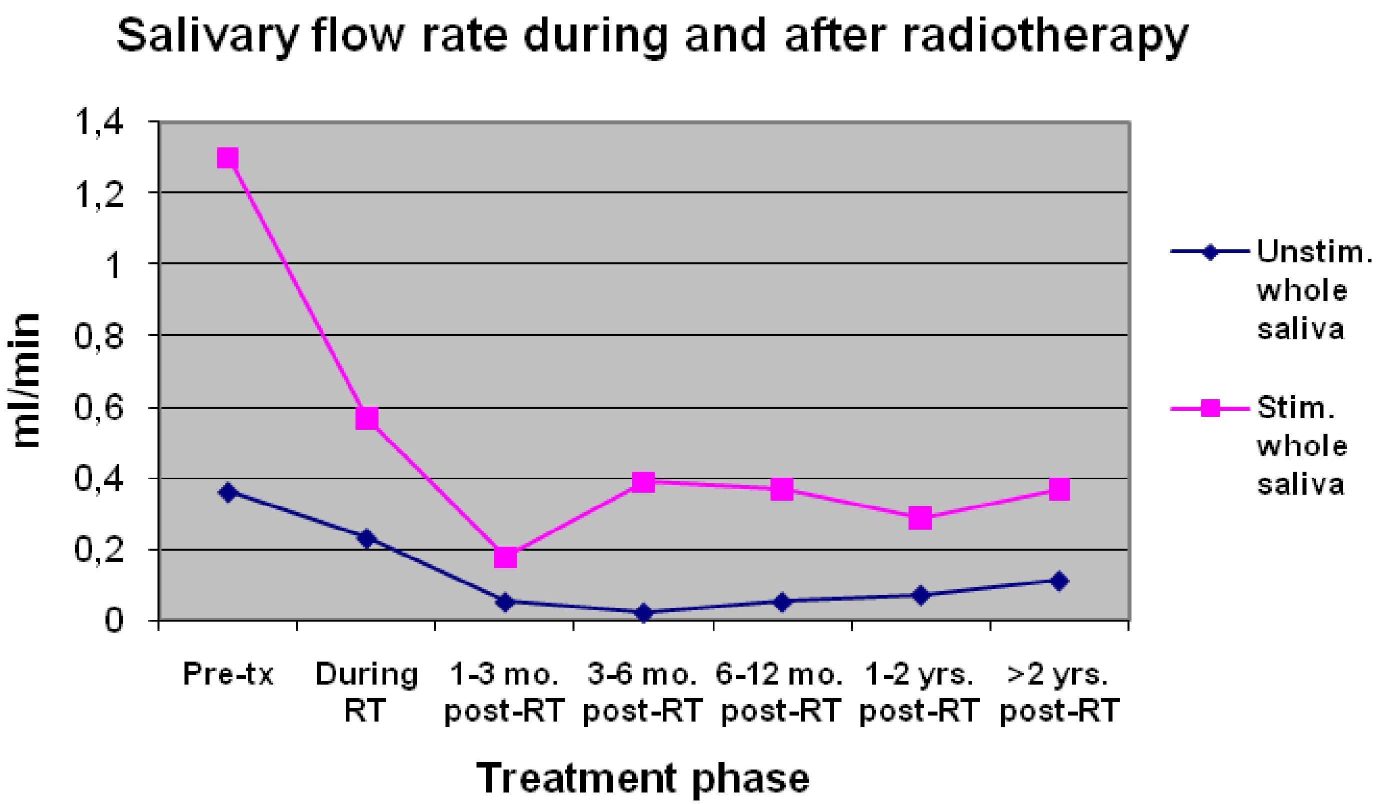
Acute side effects

Acute toxicity

Grades 3–4	No. of patients (%)	
	CF arm (n = 245)	AF arm (n = 240)
FMR during treatment	111 (45)	162 (68)
OMR during treatment	123 (50)	160 (67)
FMR 6 weeks after treatment	72 (29)	154 (64)
OMR 6 weeks after treatment	84 (34)	168 (70)
Life threatening (14 weeks after treatment)	5 (2)	13 (5)

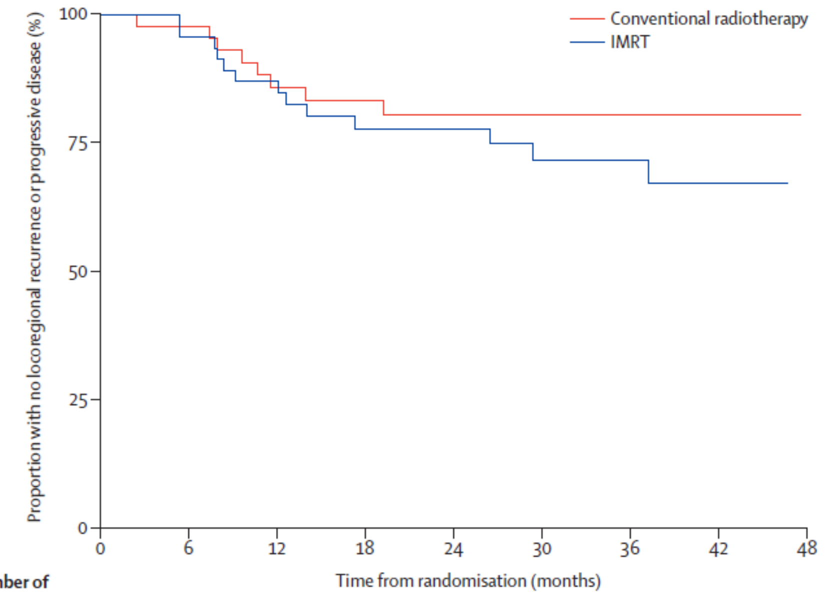
FMR, functional mucosal reactions reported by the patients.
OMR, objective mucosal reactions scored by the physician.
Analysis November 1995.

Horiot Radiother Oncol 1997

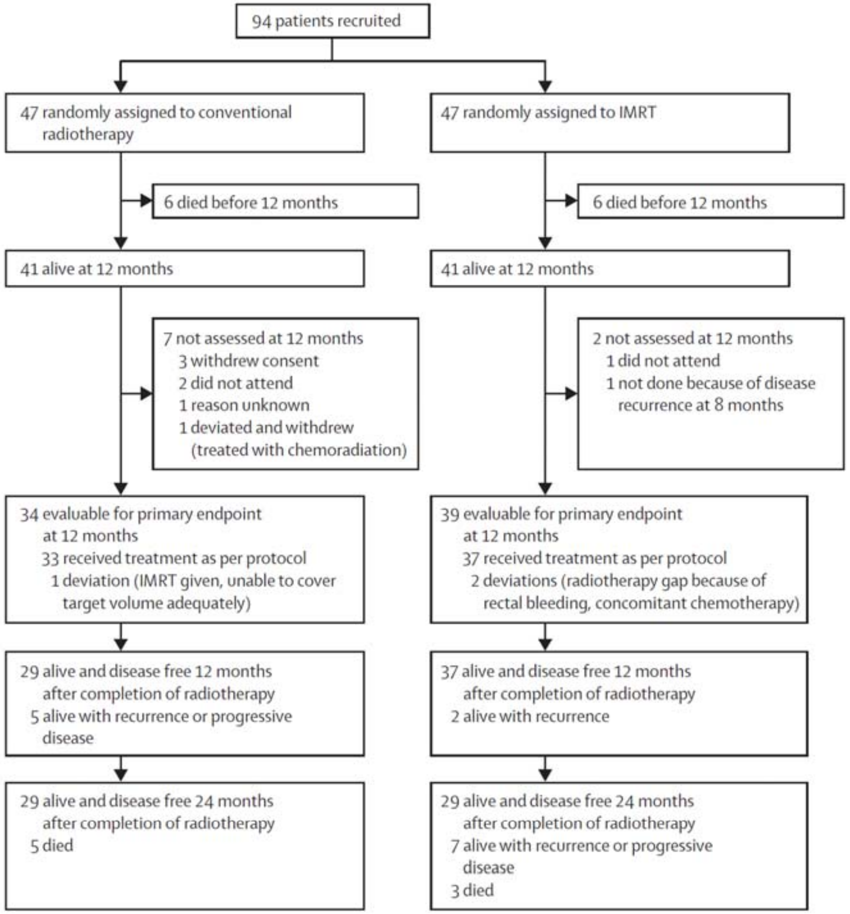


Jensen J Support Care Cancer 2010

IMRT versus conformal treatment

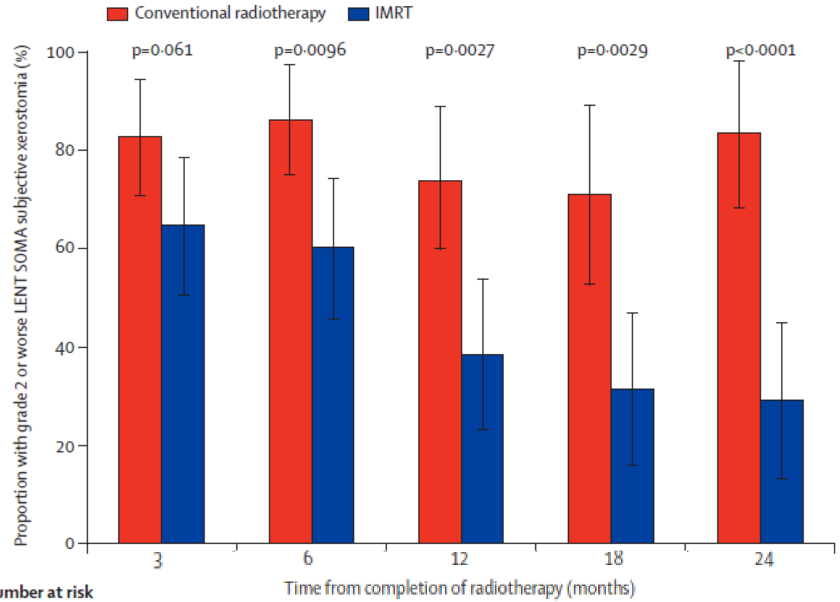


Number of events/at risk	0	6	12	18	24	30	36	42	48
Conventional radiotherapy	0/47	1/42	5/34	1/30	1/29	0/23	0/19	0/15	0/8
IMRT	0/47	2/44	4/39	4/31	0/28	2/22	0/18	1/15	0/11

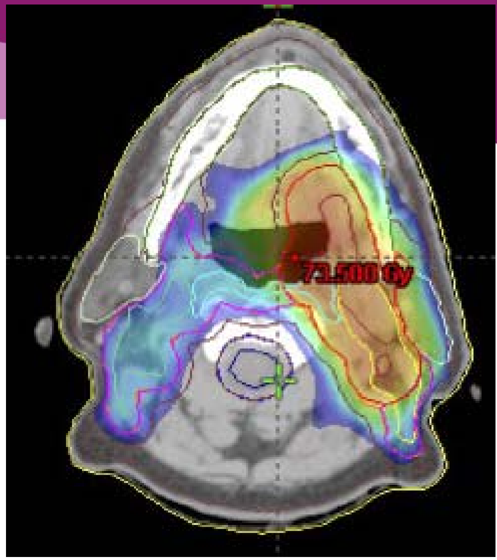


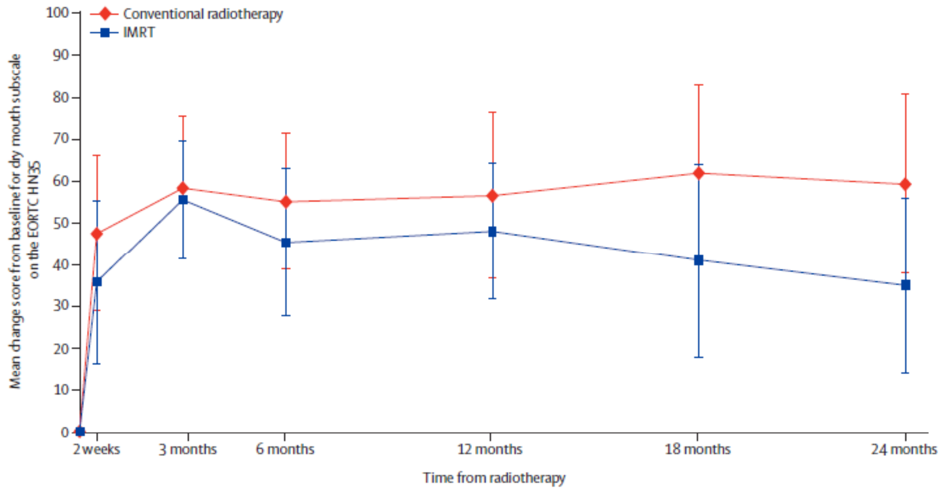
Nutting Lancet Oncol 2011

IMRT versus conformal treatment



Number at risk					
Conventional radiotherapy	40	36	34	24	24
IMRT	45	45	39	35	31





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 Lancet Oncol 2011

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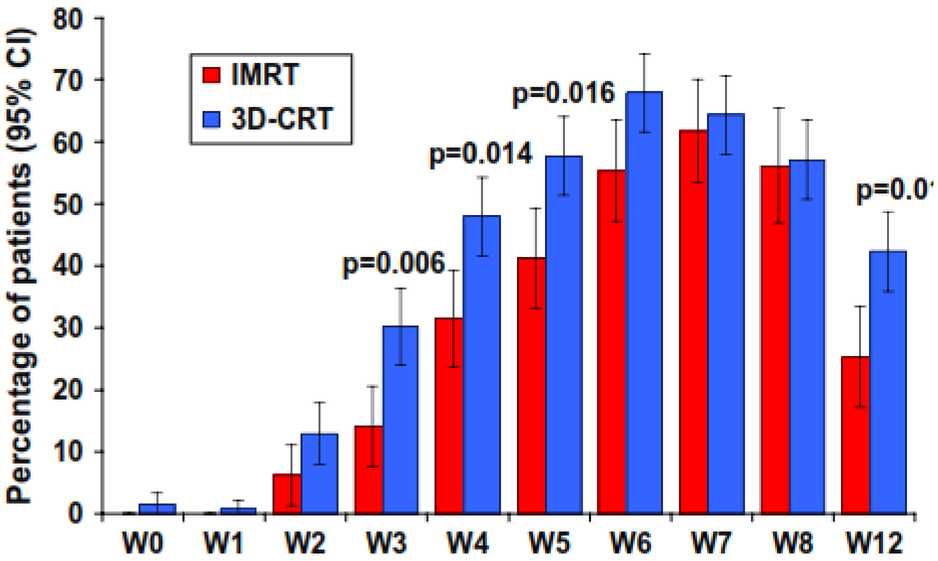
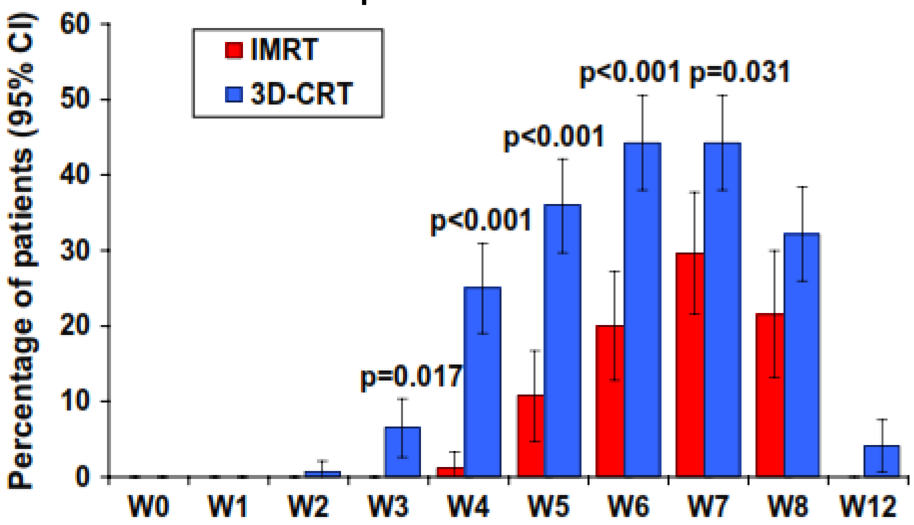
IMRT versus conformal treatment

Retrospective analysis; 241 patients.
150 before Oct. 2004 with 3-D RT; 91 after Oct. 2004 with IMRT



Acute xerostomia grade ≥ 2

p=0.002

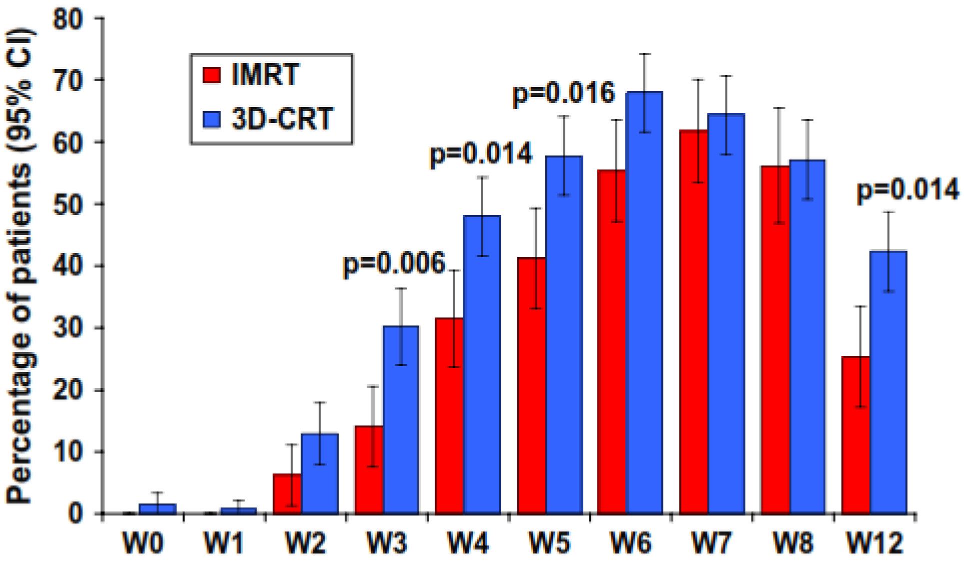


Acute mucositis grade ≥3

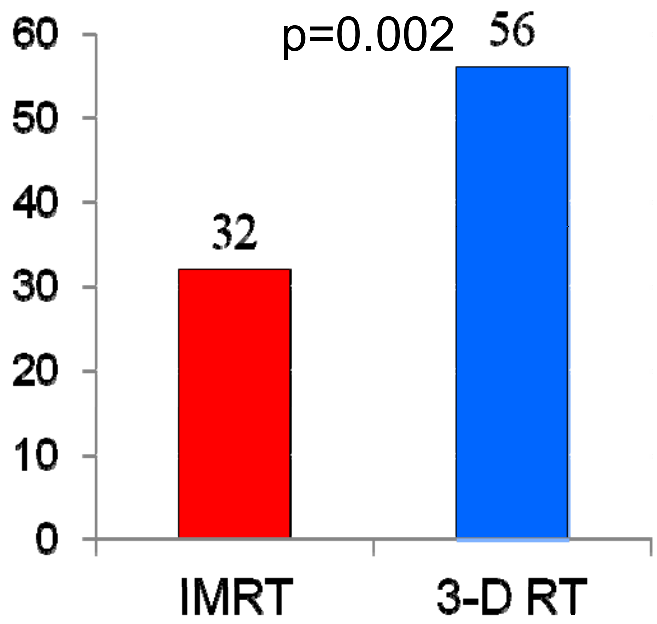
Vergeer IJROBP 2009

IMRT versus conformal treatment

Retrospective analysis; 241 patients.
150 before Oct. 2004 with 3-D RT; 91 after Oct. 2004 with IMRT



Acute xerostomia grade ≥ 2



Late xerostomia grade ≥ 2

Vergeer IJROBP 2009

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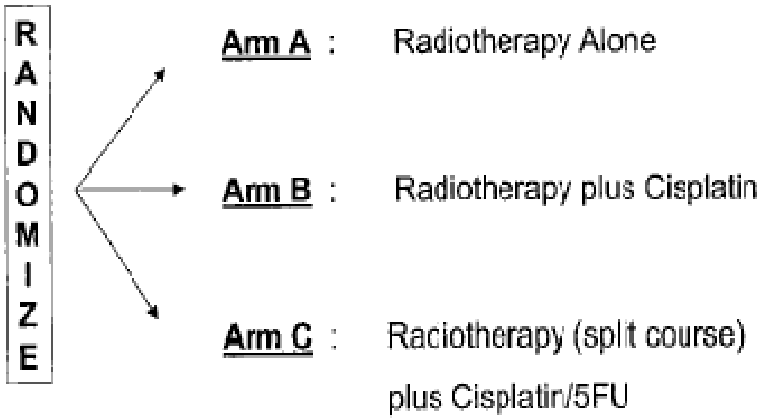
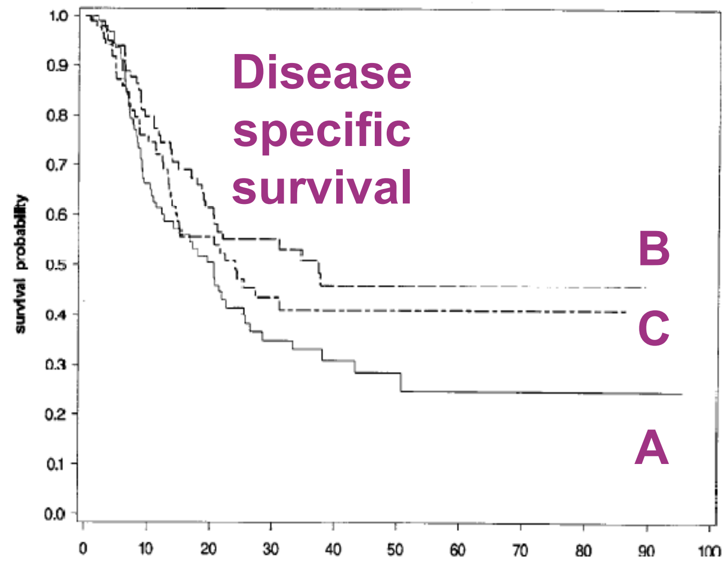
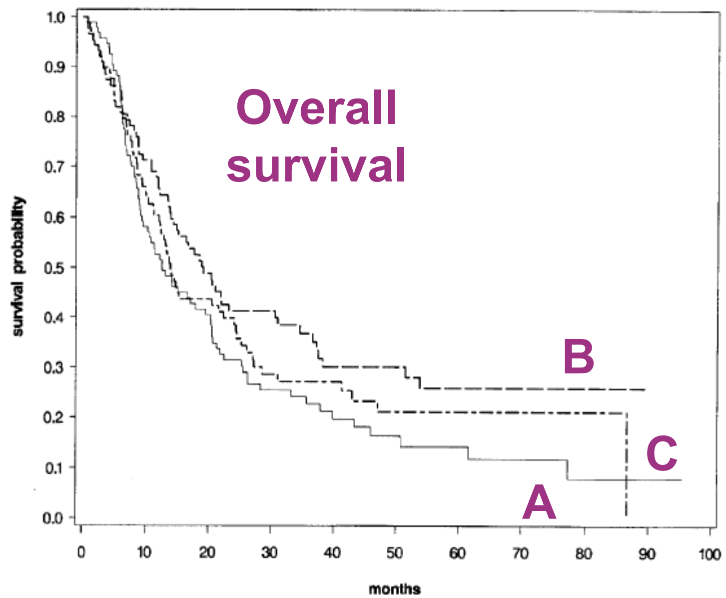
Chemo-radiotherapy

ECOG/SWOG: Head and neck intergroup (295 pts.)







Morbidity

Table 4. Toxicity (grade 3-5)

	Arm			P		
	A (N = 98)	B (N = 95)	C (N = 94)	A versus B	A versus C	B versus C
Nausea/vomiting	6	15	8	.03		
Mucositis/dysphagia	32	43	44	.08	.06	
Leukopenia	1	40	29	< .001	< .001	< .001
Thrombocytopenia	0	3	3			
Anemia	0	17	18	< .001	< .001	
Renal	1	8	0	.01		.01
Skin	13	7	2		.005	
All grade 3-5	51	85	72	< .0001	< .001	.02

Adelstein et al. 2003

Acute side effects: C-SRT versus C-ART

Stage III & IV larynx and pharynx carcinomas (-T1N+ and T2N1)

Statified by nodal stage and KPS

Randomize

AFX-CB 72Gy/42fx, 6fx/w + CDDP 100mg/m² x 2

SFX 70Gy/35fx, 5fx/w + CDDP 100mg/m² x 3

N=721 for analysis

RTOG 0129

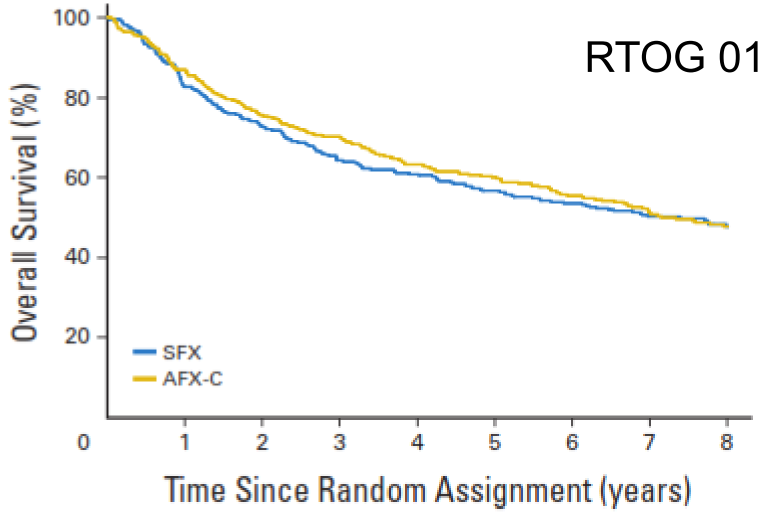


Table 3. Grade 3 to 5 Toxicity Summary

		SFX + Cisplatin			AFX-C + Cisplatin			
Toxicity	No. of Days From Start of RT	No. of Patients With Toxicity/Total	Toxicity (%)	95% CI (%)	No. of Patients With Toxicity/Total	Toxicity (%)	95% CI (%)	P*
Nonhematologic	≤ 90	266/361	73.7	69.1 to 78.2	261/360	72.5	67.9 to 77.1	.74
Mucositis/stomatitis	≤ 90	141/361	39.1	34.0 to 44.1	119/360	33.1	28.2 to 37.9	.10
Mucositis/stomatitis	> 90	13/351	3.7	1.7 to 5.7	16/343	4.7	2.4 to 6.9	.57
Any	≤ 90	297/361	82.3	78.3 to 86.2	278/360	77.2	72.9 to 81.6	.10
Any	> 90	128/351	36.5	31.4 to 41.5	130/343	37.9	32.8 to 43.0	.75

Abbreviations: AFX-C, accelerated fractionation with concomitant boost radiotherapy; RT, radiation therapy; SFX, standard fractionation radiotherapy.
*Calculated from Fisher's exact test.

Nguyen-Tan JCO 2014

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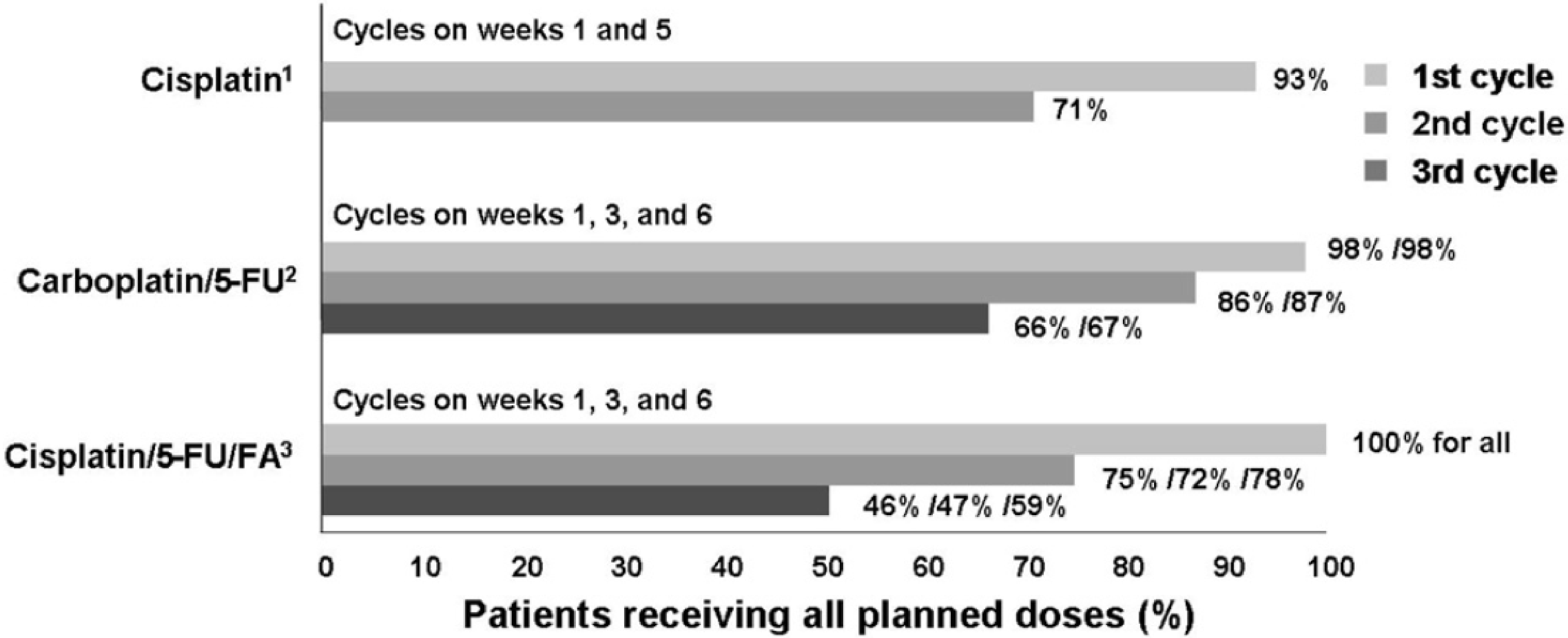
Compliance to concurrent C-RT



- 1/3 of pts. in trials do not receive the planned number of cisplatin cycles
- Compliance decreases over time
- C-RT regimens are affected by longer overall treatment times
- More frequent treatment interruptions than radiotherapy alone

Bernier J 2009

Importance of fractionation

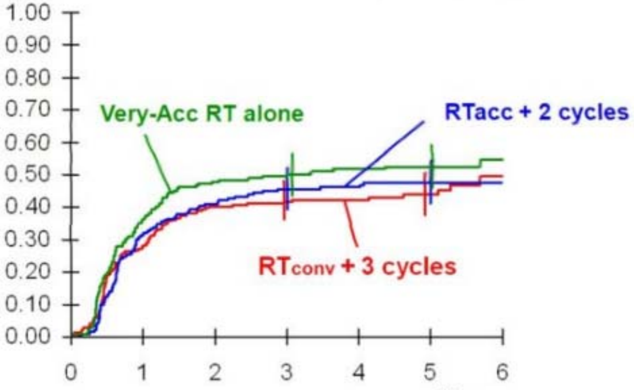
GORTEC 99-02 randomized trial

GORTEC

Randomisation

- 70 Gy / 7 weeks
  5FU / carboplatin concomitant (3 cycles)
- Accelerated concomitant boost RT
  70 Gy / 6 weeks
  5FU / carboplatin concomitant (2 cycles)
- Very accelerated RT 64.8 Gy / 3.5 weeks

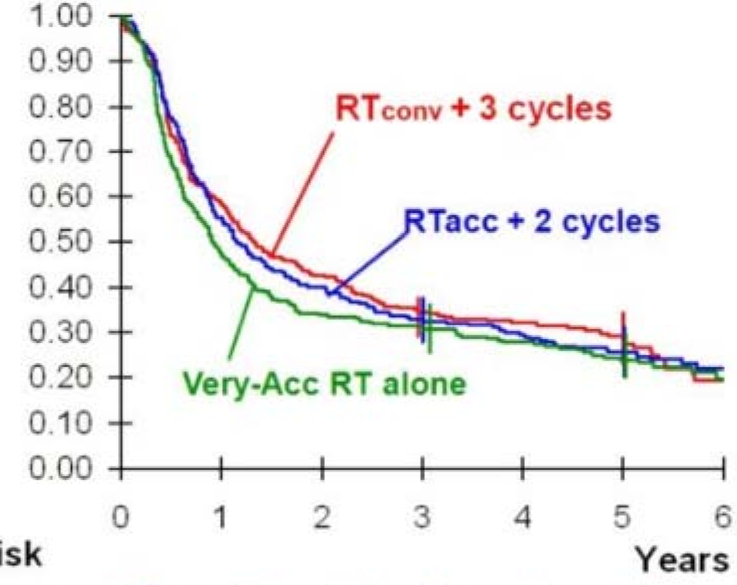
GORTEC 9902 - Locoregional progression



At risk

—278	174	127	103	81	52	17
—279	161	118	93	75	48	17
—280	140	100	91	70	55	17

Progression free survival (primary end point)



At risk

—279	163	119	92	74	46	15
—280	153	109	86	71	45	18
—281	131	92	83	63	46	13

Bourhis 2012

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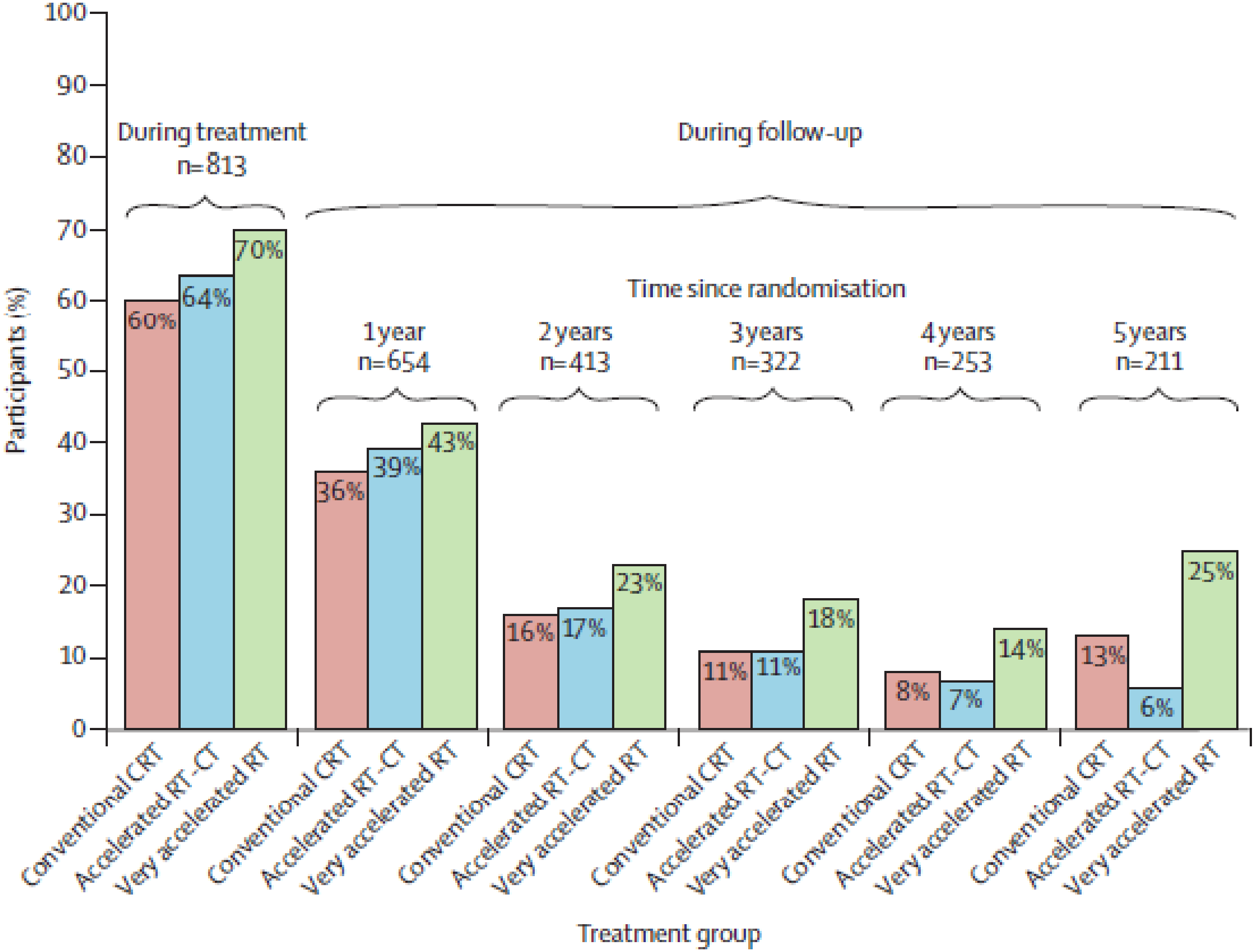
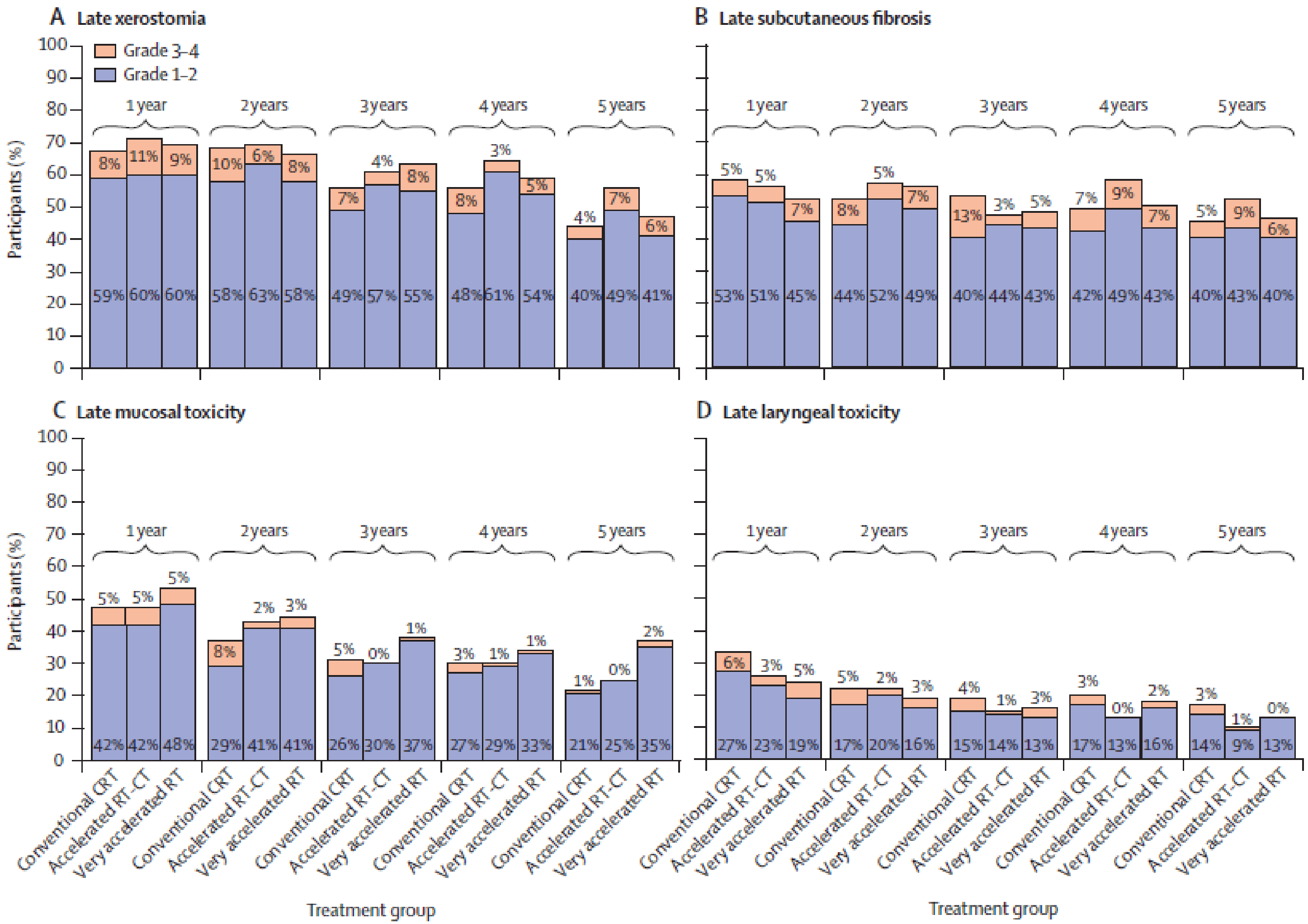
GORETEC 99-02: PEG-tube dependency



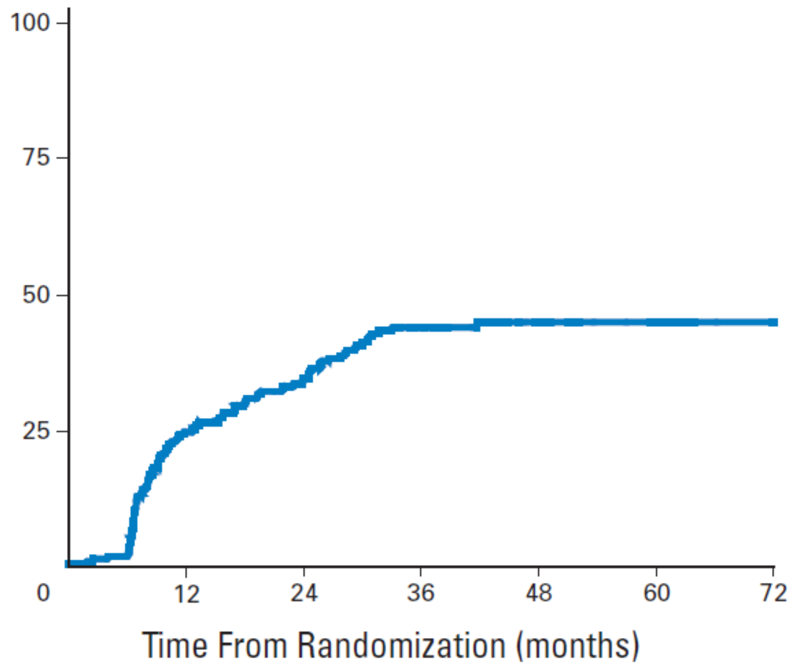
Bourhis 2012

GORETEC 99-02: Late toxicity



Bourhis 2012

Late morbidity



Analysis of 3 RTOG trial with C-RT

(RTOG 91-11, 97-03, and 99-14)

In total 230 patients

- 43% severe late morbidity
- 40% larynx/pharynx dysfunction
- 13% tube feeding >2 Y after C-RT

Machtay M 2008

DAHANCA 18 - low dose weekly cisplatin

C-RT standard in Denmark from January 1. 2007

All consecutive Danish patients from 4 of 5 National HNSCC centres from 2007-2010

Incusion criteria:
- UICC st III-IV, SCC,
- Oral cavity, larynx, oropharynx, hypopharynx
- GFR > 50mg/ml
- WHO performance 0 - 2

Treatment:
- Radiotherapy: 66-68Gy, 2Gy/F, 6 F/week, +
- Nimorazol 1200mg/m^2. +
- Cisplatin 40mg/m^2 x 1 weekly during radiotherapy

Benzten et al Acta Oncol 2015

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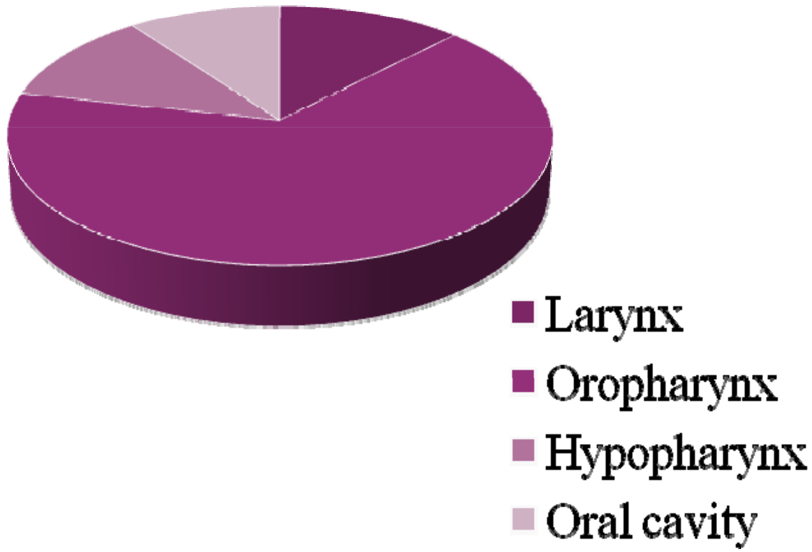
DAHANCA 18 patients

227 patients, 78% male, Median age 58 (range 32-82).

Follow-up: 46 months (range 24-73 mo)



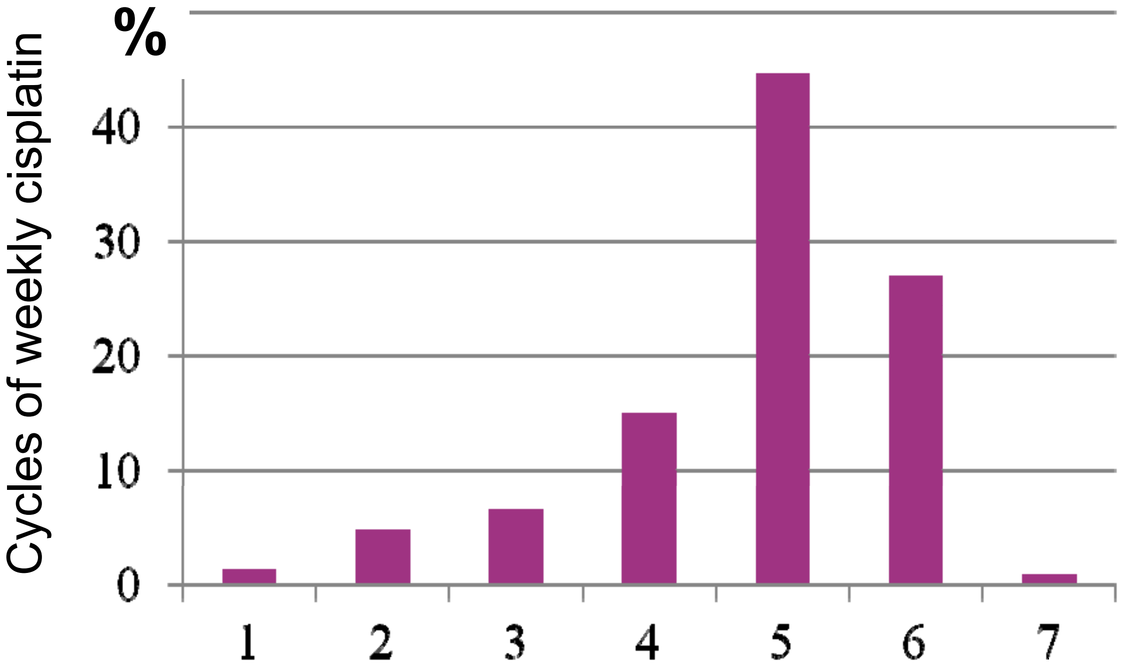
	T1	T2	T3	T4	All
N0	0	0	3	2	5
N1	14	22	10	9	55
N2	40	60	37	18	155
N3	3	5	0	4	12
All	57	87	50	33	227

Benzten et al Acta Oncol 2015

DANANCA 18: compliance

Compliance Radiotherapy and Chemotherapy

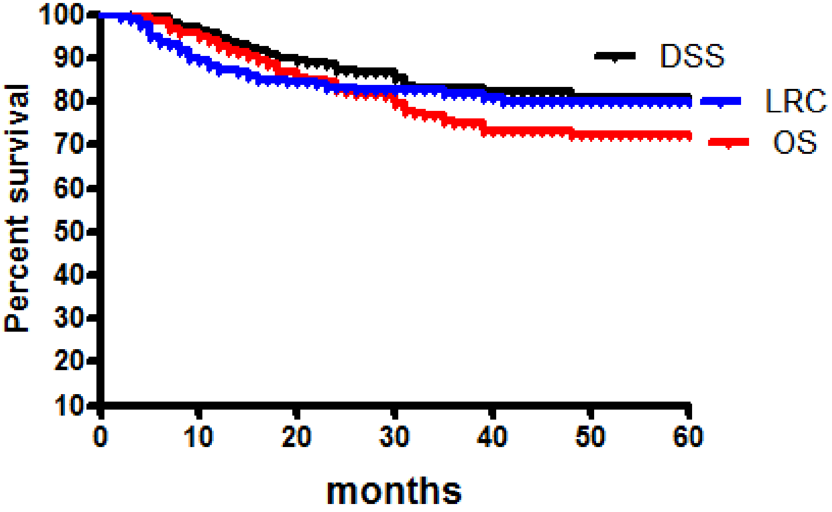
Total dose Gy	59,7	60	64	66	68
Number	1	3	1	100	122



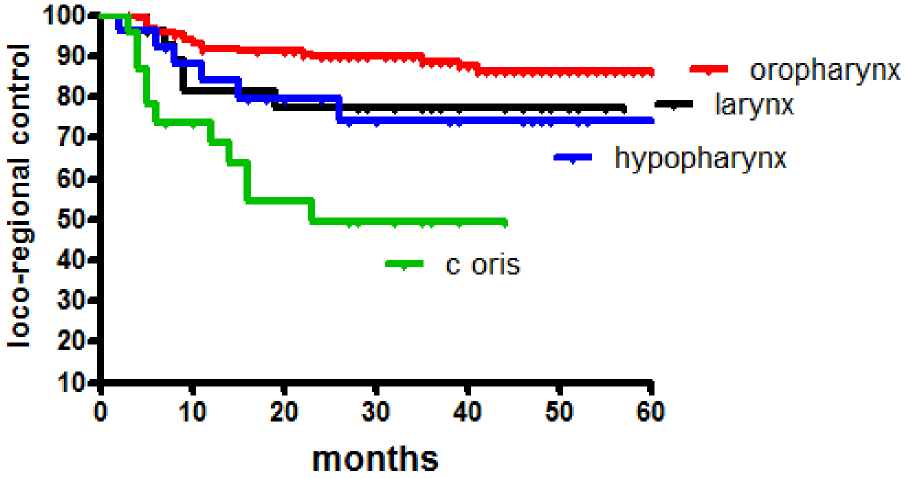
72% got 5 cycles of cisplatin or more

Benzten et al Acta Oncol 2015

DAHANCA 18: outcome



5 Year OS is 72%
5 Year DSS is 81%
5 Year LRC is 80%



5 year loco-regional contro rates is:
Larynx: 77% (n= 28)
Oropharynx: 86% (n=150)
Hypopharynx: 74% (n= 26)
Cavum oris: 49% (n=23)

Benzten et al Acta Oncol 2015

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DAHANCA 18: morbidity

Sideeffect	Acute (during treatment) (n=227)	
	n	%
Need of feeding tube	146	64
Dysphagia, only fluid nutrition	168	74

Sideeffect	Chronic 2 years after treatment (n=181)	
	n	%
Need of feeding tube	6	3
Dysphagia, only fluid nutrition	17	9
Significant dryness of mouth/throat	35	19
Significant mucousal atrophy	4	2
Pronounced fibrosis of the neck	25	14

Benzten et al Acta Oncol 2015

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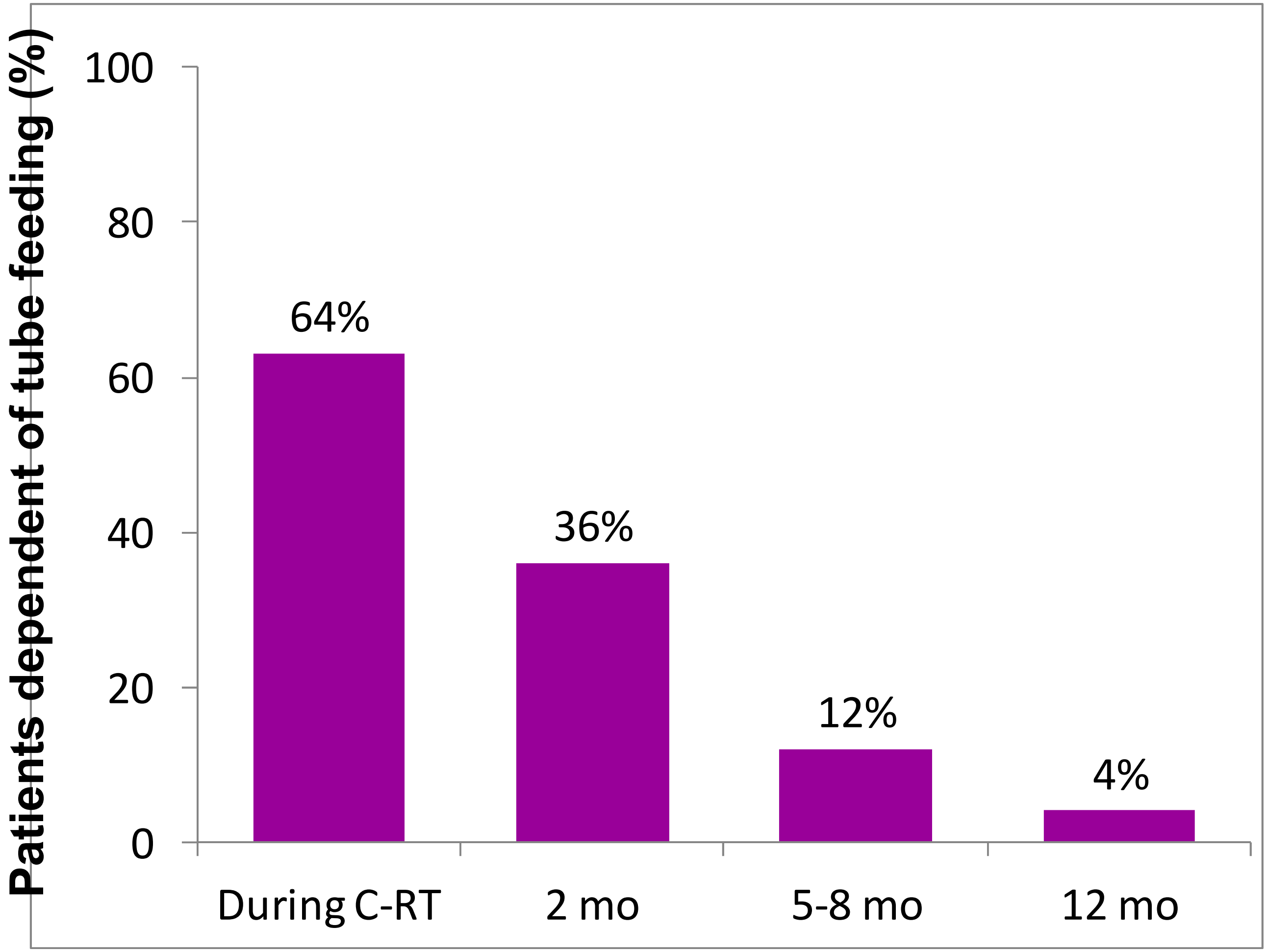
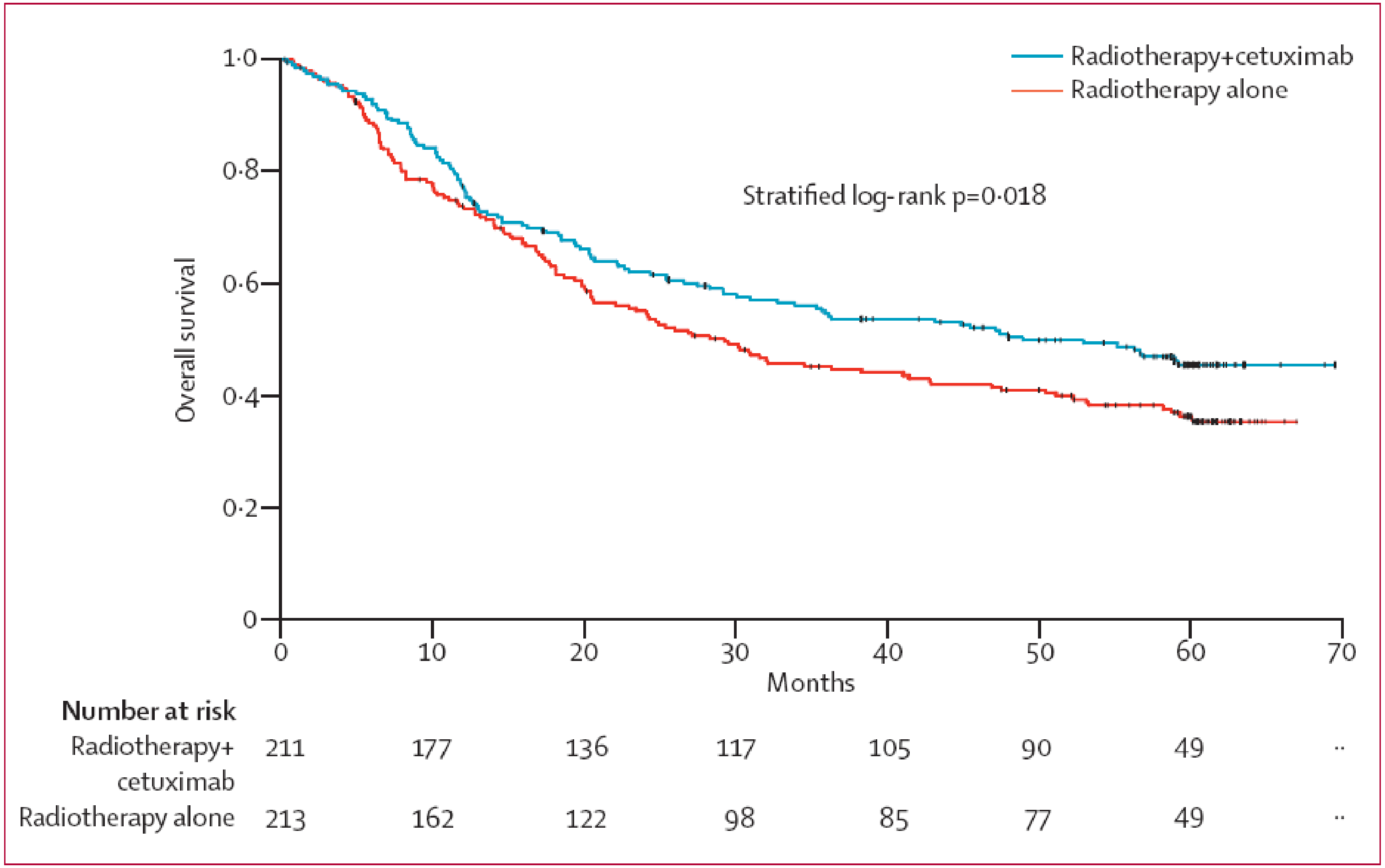
DAHANCA 18: morbidity



Benzten et al Acta Oncol 2015

Bio-radiotherapy

The “Bonner-trial”



Bonner JA Lancet Oncol 2010

Side effects to bio-radiotherapy

	Radiotherapy (N=212)			Radiotherapy plus cetuximab (N=208)		
	All grades	Grade 3/4	Grade 4	All grades	Grade 3/4	Grade 4
Skin reaction*	200 (94·3%)	45 (21·2%)	3 (1·4%)	204 (98·1%)	73 (35·1%)‖	4 (1·9%)
Mucositis/stomatitis†	199 (93·9%)	110 (51·9%)	9 (4·2%)	194 (93·3%)	116 (55·8%)	13 (6·3%)
Dysphagia	134 (63·2%)	63 (29·7%)	3 (1·4%)	136 (65·4%)	54 (26·0%)	1 (0·5%)
Xerostomia‡	150 (70·8%)	6 (2·8%)	0 (0%)	150 (72·1%)	10 (4·8%)	0 (0%)
Acneiform rash§	21 (9·9%)	3 (1·4%)	0 (0%)	174 (83·7%)‖	35(16·8%)‖	1 (0·5%)
Infusion reaction¶	4 (1·9%)	0 (0%)	0 (0%)	32 (15·4%)‖	6 (2·9%)‖	2 (1·0%)

- Grade III/IV radiation dermatitis is observed in 49-77% of HNC patients treated with cetuximab and RT
- 31% RT-pause 10 dg (9-15)

Bonner JA Lancet Oncol 2010

Pryor DL; Giro C Radiother Oncol 2009

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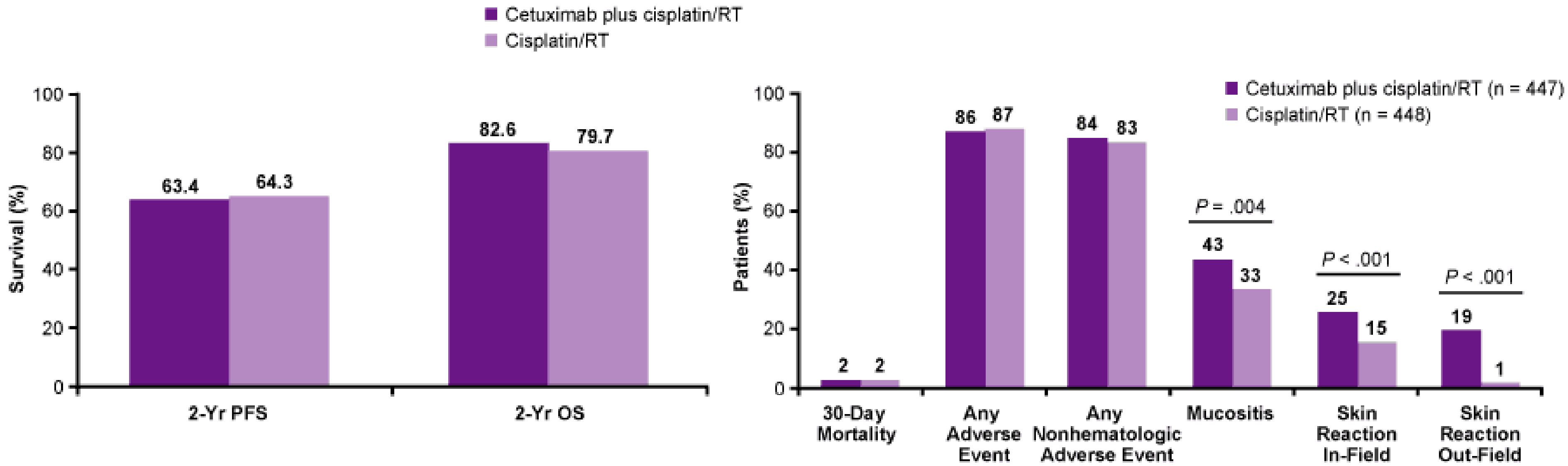
RTOG 0522: C-RT ± cetuximab for stage III-IV HNSCC

- 940 pts with stage III-IV HNSCC of the larynx and pharynx
- No significant differences in PFS or OS
- Triplet patients had higher rates of grade 3-4 mucositis and skin reactions



Ang, ASCO 2011

DAHANCA 19

Institution
T1-2 vs. T3-4
N0 vs. N+
HPV/p16-status
Site
Sex
WHO performance

Randomize

Accl. RT+(cisplatin)+nimorazole (N+)
Accl. (hyperfx.) RT+nimorazole (N0)

Accl. RT+(cisplatin)+nimorazole (N+)
Accl. (hyperfx.) RT+nimorazole (N0)
+ zalutumumab

Eriksen, ECCO 2013

DAHANCA 19 acute effects

Unpublished data

Eriksen, ECCO 2013

DAHANCA 19 acute effects

Unpublished data

Eriksen, ECCO 2013

Skin toxicity

Unpublished data

Bio-radiation toxicity

Eriksen 2009

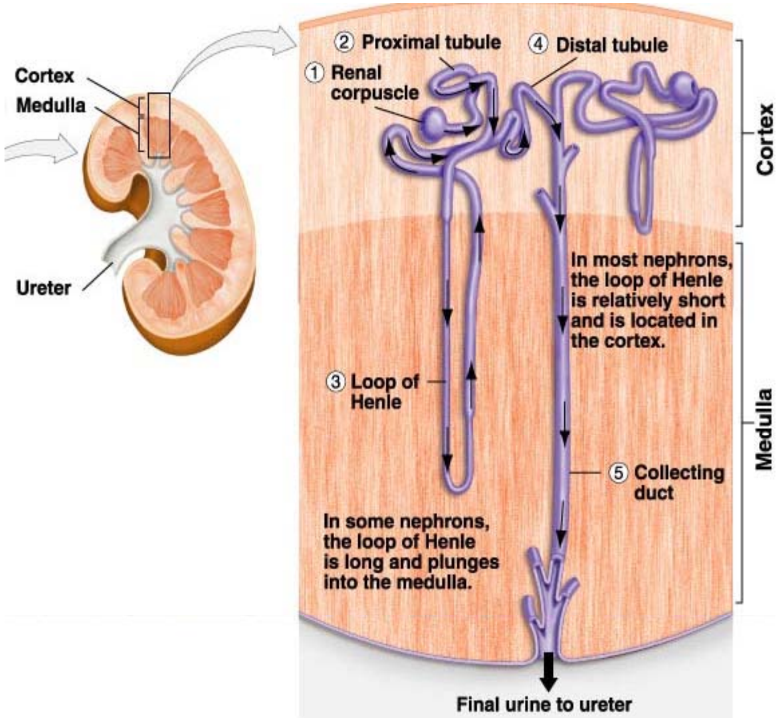
ESTRO School

Late side effects

Unpublished data

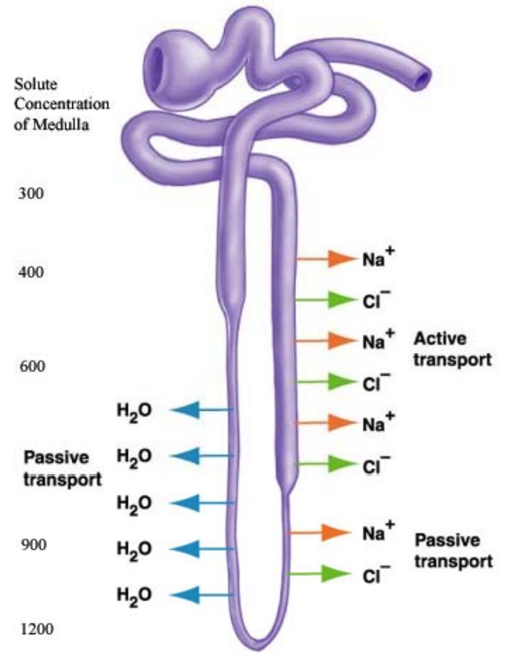
Eriksen, ESTRO Forum 2015

Kidney toxicity



- Grade 3-4 hypomagnesemia in 2-6% treated with mab's
- G3-4 in a controlled setting:
  < 3 mo. cetuximab: 0-5%
  3-6 mo. cetuximab: 3-23%
  > 6mo. cetuximab: 12-47%
- Tiredness, somnolence, seizures, cardiac arrythmias

No hypomagnesaemia during treatment



Unpublished data

Normal values: 0.67-1.10 mmol/L

Eriksen, ESTRO 2014

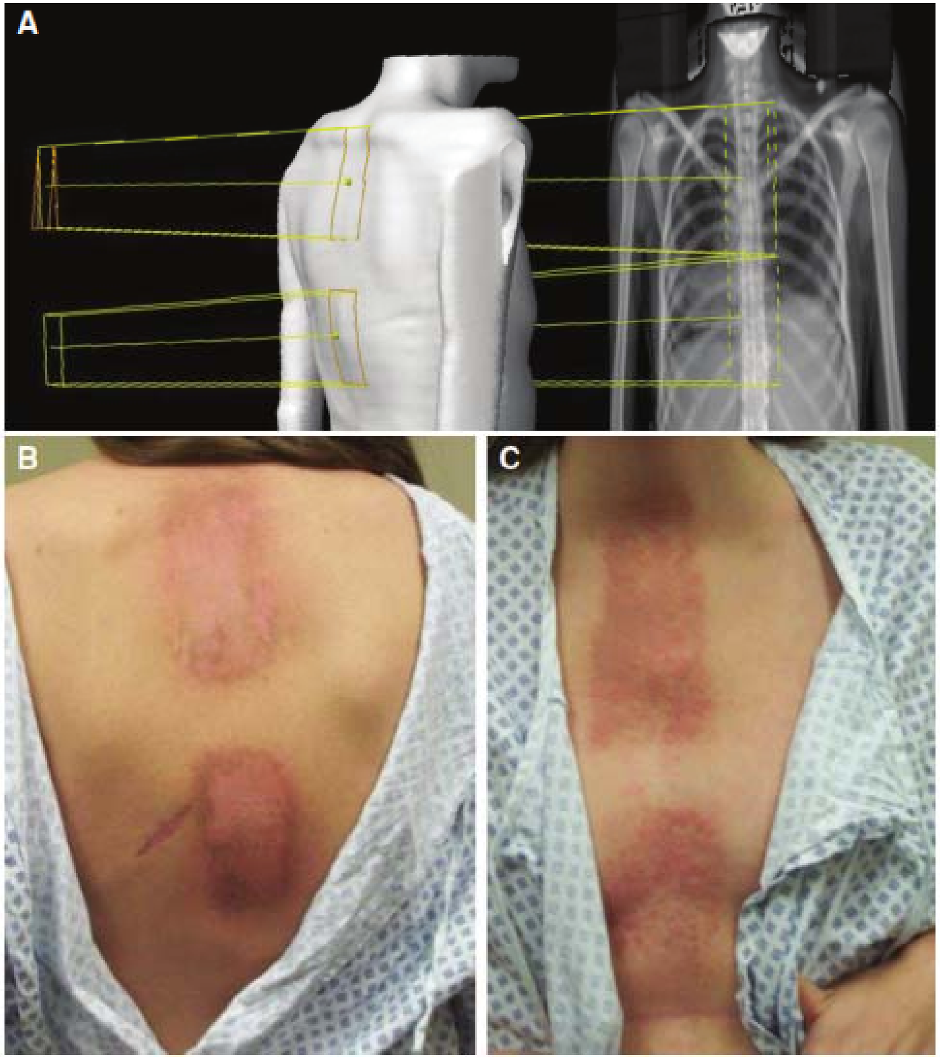
ESTRO School

Is EGFR-I and radiotherapy less toxic?

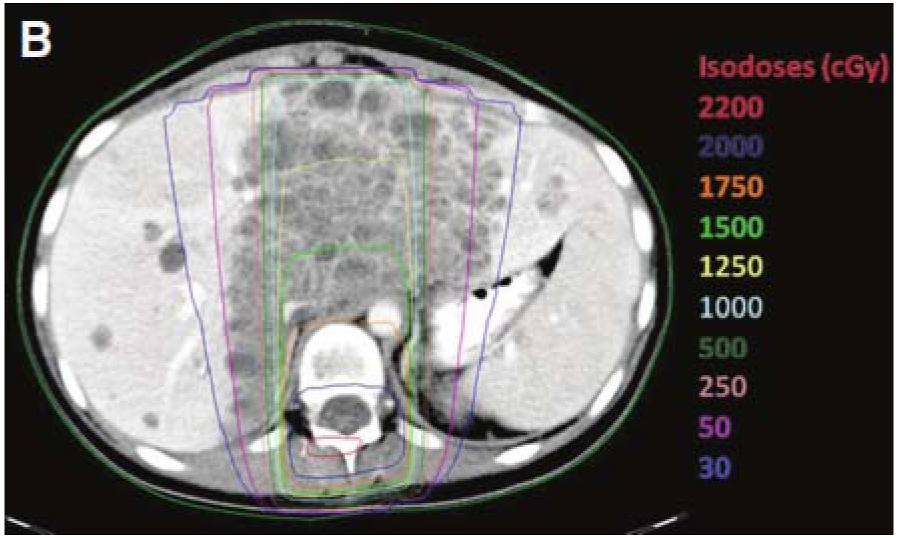
Unpublished data

Eriksen, ESTRO forum3 2015

Be alert on future combinations!



Vemurafenib + 20Gy/4fx

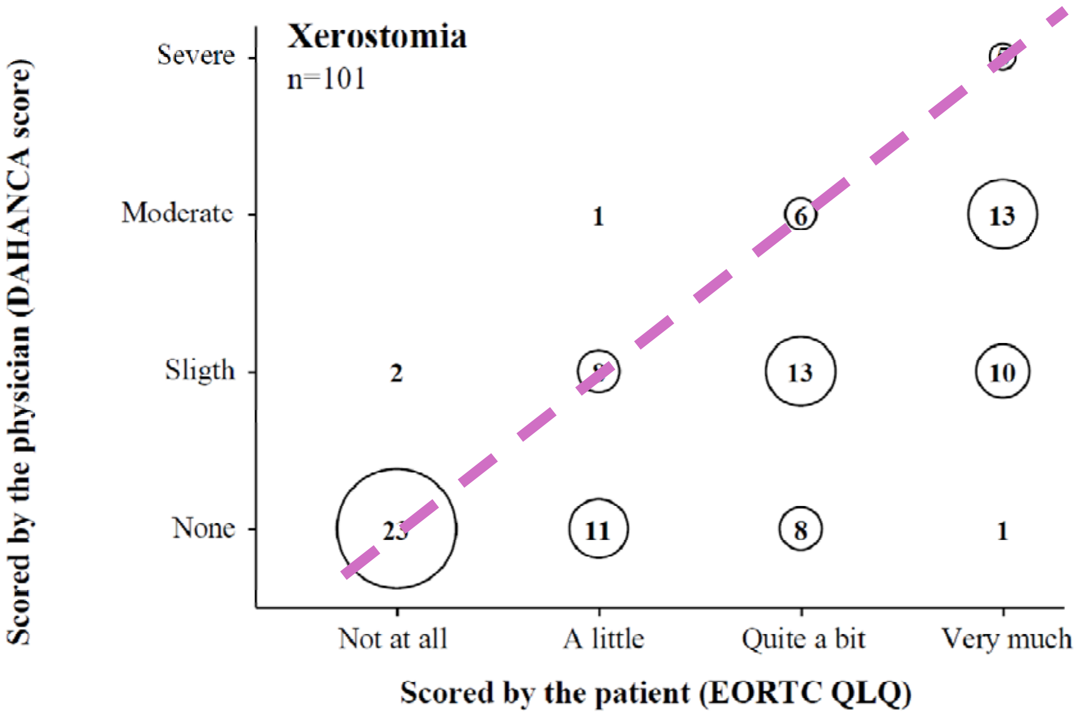


Anker, JCO 2013

Time for a paradigm shift?

- Doctor reported versus patient reported?

- EORTC QLQ-H&N35
- EORTC QLQ-C30
- PRO-CTCAE
- MDADI



Jensen, Radiother Oncol 2006

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To know To prevent To treat

- Planning of radiotherapy
- Dental prophylaxis (dental extractions)
- Avoidance of tobacco and alcohol
- Oral care
- Nutritional support
- Awareness when combining modalities
- Close monitoring during treatment

Supportive care during(chemo)radiation or anti-EGFR + radiation

Jean-Pascal Machiels

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Clinique de cancérologie cervico-maxillo-faciale

Université catholique de Louvain, Brussels, Belgium

INSTITUT ROI ALBERT II
CANCÉROLOGIE ET HÉMATOLOGIE
Cliniques universitaires SAINT-LUC I UCL Bruxelles

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The problem

Radiation

Radiation + cetuximab

Chemoradiation

The price to pay is more toxicities

The most frequent toxicities are:

- mucositis
- dermatitis
- hematological toxicities
- anti-EGFR skin toxicity

Acute mucositis

Xerostomia

Dermatitis

Anti-EGFR skin toxicity

Anemia

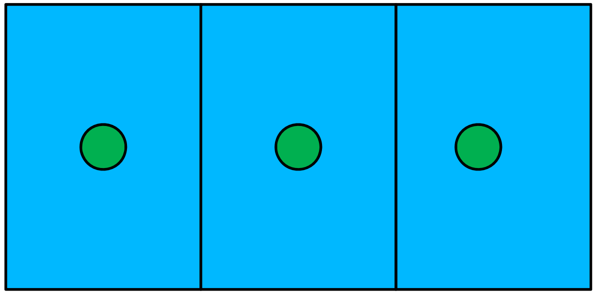
Issues related to chemotherapy

Issues related to co-morbidities and head and neck cancer

Acute mucositis: physiopathology

RT or CT

ROS



ROS

Transcriptional factors: NFκb

DNA injury and cell death

IL-1, IL-6, TNF-alpha
Cyclo-oxygenase 2, …

Reactive oxygen species = ROS

Tissue injury and apoptosis

ESTRO *School*

Acute mucositis: grading

NCI-CTC/RTOG

Grade 0	No mucositis
Grade 1	Erythema
Grade 2	Pseudomembranous ulceration < 1.5 cm and non confluent
Grade 3	Pseudomembranous ulceration > 1.5 cm and confluent
Grade 4	Ulceration with necrosis
Grade 5	Death

WHO

Grade 1	Erythema, pain
Grade 2	Ulceration and can eat solid food
Grade 3	Ulceration and can eat liquid only
Grade 4	No food intake is possible

Acute mucositis : frequency

Mucositis grade 3/4	RT	RT+CT	Chemotherapy
RTOG 95-01*	34%	77%	Cisplatin 100 mg/m2, day 1, 22, 43
EORTC 22931*	21%	41%	Cisplatin 100 mg/m2, day 1, 22, 43
GORTEC 94-01	39%	71%	Carboplatin/5-FU, three times
RTOG 91-11	24%	43%	Cisplatin 100 mg/m2, day 1, 22, 43
RTOG 0522	NA	33%	Cisplatin 100 mg/m2, day 1 & 22 86% used IMRT

* Huge variation from one study to another

Cooper et al. NEJM 2004
Bernier el. NEJM 2001
Calais et al. JNCI 1999
Forastiere et al. NEJM 2003
Ang KK et al. JCO 2014

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Acute mucositis : frequency

Side effect	RT	Cetuximab + RT	p-value
Mucositis/stomatitis	52%	56%	0.44
Dysphagia	30%	26%	0.45
Radiation dermatitis	18%	23%	0.27
Xerostomia	3%	5%	0.32
Fatigue/malaise	5%	4%	0.64
Acne-like rash	1%	17%	<0.001
Infusion-related reactions	0%	3%	0.01

Bonner J, et al NEJM 2006

Acute mucositis : frequency

Side effect	Cisplatin + RT	Cetuximab + RT	p-value
Mucositis/stomatitis	53%	59%	0.44

Low number of patients, n=70

Magrini et al JCO 2006

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Acute mucositis: risk factors

Radiation therapy field

Addition of chemotherapy

Tobacco

Alcohol

Preexisting dental disease

Change in salivary flow

Oral bacteria flora

Advanced stage

Immunosuppression due to comorbidities (diabetes, …)

Xerostomia

Low body mass index

Acute mucositis: consequences

- Pain, discomfort, dysgeusia, mouth and throat sores
- Excessive visquous secretions that may lead to nausea, vomiting, and gagging
- Impairment of the ability to eat and swallow
  Feeding tube and hospitalization
- Infection: systemic or aspiration pneumonia
- Treatment interruption: « perte de chance »

Acute mucositis: prevention

- Not enough scientific evidence to provide guidelines

- However, there is a general consensus that basic oral care is important to
  - Decrease pain
  - Avoid surinfection
  - Reduce the risks of caries and gingivitis

- Basic oral care included
  - good hygiene = dentist before treatment and mouth hygiene during treatment
  - soft tooth brush
  - mouthwash with normal saline solution and sodium bicarbonate

Kuk et al. ASCO 2011
McGuire et al Support care cancer 2013

Not recommended interventions

- Cryotherapy
- Amifostine
- Glutamine
- Steroids and anti-inflammatory drugs
- Barrier agents : Sucralfate, GelClair®, MuGard®and Mucotrol®
- Allopurinol gel, Chlorhexidine, Povidone-iodine; Triclosan mouth washes, Iseganan mouth washes, Aloe vera, Granulocyte macrophage colony-stimulating factor, Pure natural honey Misoprostol and Prostaglandin E2 Antibiotic + antifungal pastilles (containing polymixin, tobramycin and amphotericin orbacitracin, clotrimoxazole and gentamicine)

De Sanctis et al. Crit Reviews in Oncology/Hematology 2016

Acute mucositis: prevention

Mouthwash with saline solution and bicarbonate

Drug	Recommendation	
Benzydamine*	Yes	Anti-inflammatory Analgesic and anesthesic Antimicrobial
Chlorhexidine	No	Oral care protocol
Anti-fungal agents	?	
Anti-microbial agents	?	

* Similar activity mouthwash (nystatin, diphenhydramine and dexamethassone) + sucralfate (ASCO 2011)

Saunders et al Support care cancer 2013
Kuk et al. ASCO 2011
McGuire et al Support care cancer 2013
Nicolatou-Galtis et al Support care cancer 2013

Acute mucositis: prevention

Palifermin

- is a recombinant truncated form of human keratinocyte growth factor (KGF), a member of the fibroblast growth factor family, that acts on epithelial tissue to exert a cytoprotective effect against chemotherapy- and radiation therapy–induced mucosal injury

- approved for prophylaxis against severe mucositis among patients undergoing HSCT for hematologic malignancies.

Trotti et al. JCO 2009

Acute mucositis: prevention palifermin

Postoperative chemoradiation: placebo versus palifermin 120 μg/kg/week

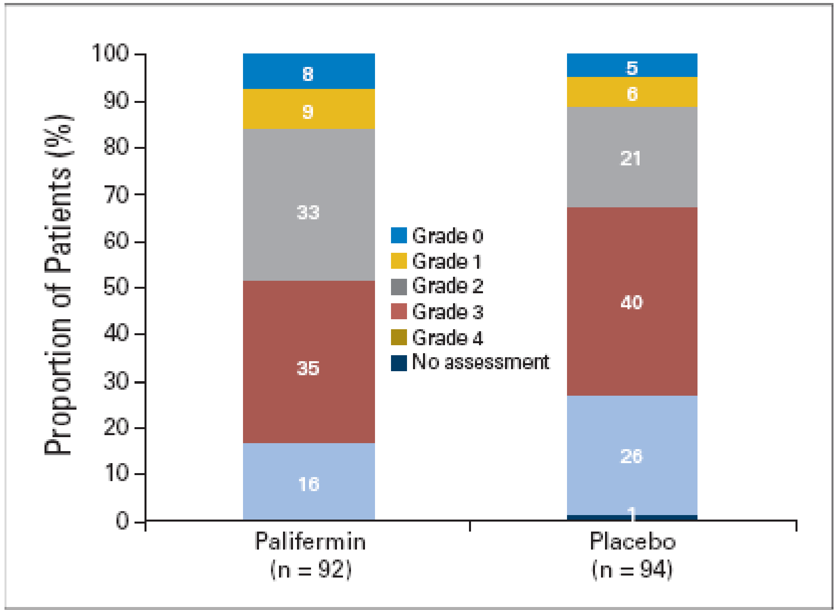

Fig 2. Distribution of maximal WHO grade oral mucositis by treatment group.

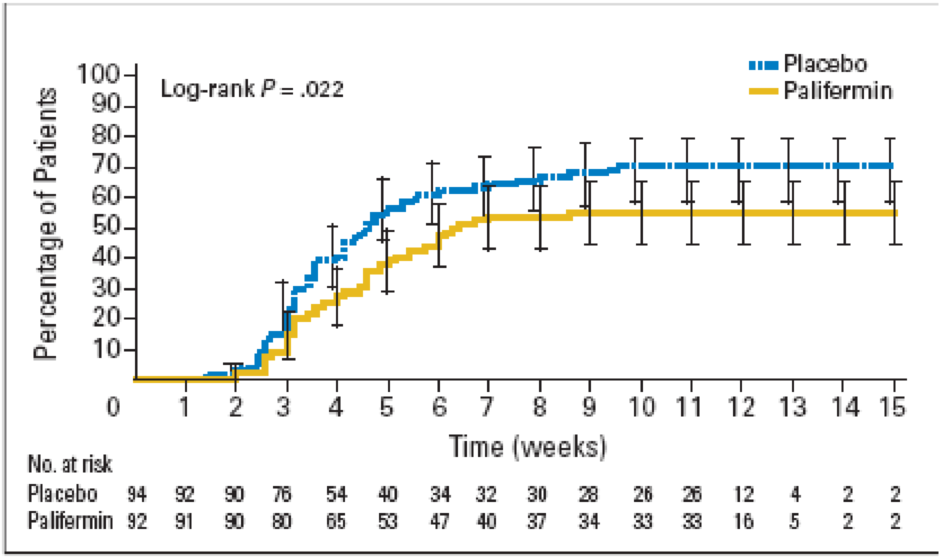

Fig 3. Kaplan-Meier plot of time to onset of severe oral mucositis (WHO grades 3 to 4) during combined postoperative radiotherapy and cisplatin-based chemotherapy for locally advanced head and neck cancer (intent to treat).

Henke et al. JCO 2011
Le et al. JCO 2011

Acute mucositis: prevention palifermin

Palifermin

- Similar study with curative definitive chemoradiotherapy (n=188)

- No impact on PFS and survival but not the primary end point

- No significant impact on pain, treatment break, and feeding tubes

Henke et al. JCO 2011
Le et al. JCO 2011

Acute mucositis: treatment

- Avoid to stop radiation and/or chemoradiation
- Treat fungal or bacterial infection (systemic)
- Analgesic: morphine
- Adequate Hydratation
- Mouthwash with analgesic
- Swallowing exercise

Guidelines:

- Multinational Association of Supportive Care in Cancer (MASCC)
- NCCN

Keefe et al. Cancer 2007

Acute mucositis: enteral feeding

- Controversial to use enteral feeding upfront
- Nasogastric tube versus gastrostomy: no difference demonstrated
- If weight loss is more than 10%: enteral feeding is indicated

Rosenthal et al. Semin Radiat Oncol 2009
Salas S et al Radioth Oncol 2009

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Acute mucositis: low level laser

N= 75 , Low-level laser versus placebo, chemoradiation

- grade ¾ mucositis not significantly decreased at week 4 ($p=0.08$)
- less treatment interruption due to mucositis: 6 vs 0 ($p= 0.02$)

N= 94 , Low-level laser versus placebo, chemoradiation

- grade ¾ mucositis decreased: 48% vs 6.4 % ($p<0.001$)
- less treatment interruption, less pain, less gastrostomia, better Q&L

N= 220 , Low-level laser versus placebo, chemoradiation

- better quality of life (FACT-HN questionnaire)
- significant reduction in severe mucositis, opoid analgesic, and parenteral nutrition

Gautam AP et al. Supportive care Cancer 2013
Gouvêa de Lima et al. Int J Radiat Oncol Biol Phys 2010
Antunes et al. Radiotherapy Oncol 2013

Acute mucositis

Xerostomia

Dermatitis

Anti-EGFR skin toxicity

Anemia

Issues related to chemotherapy

Issues related to co-morbidities

Xerostomia

Convential RT: 60-70% long term moderate/severe xerostomia

Xerostomia severity depends on the dose received by the glands, the irradiated volume, and time from RT

Consequences:

- dental caries
- oral mucosal integrity: oral pain, loss taste, difficulties in swallowing and chewing, sleep up disorders and oral infections
- problem with nutritional intake and weigh loss

Wijers et al. Head Neck 2002

Xerostomia

Amifostine recommended by ASCO for RT but not for CRT.

- reduced chronic xerostomia grade 2 from 57% to 34% (*P* = .002).

Pilocarpine approved by FDA.

- N =249
- patients randomized between placebo versus pilocarpine 5 mgr

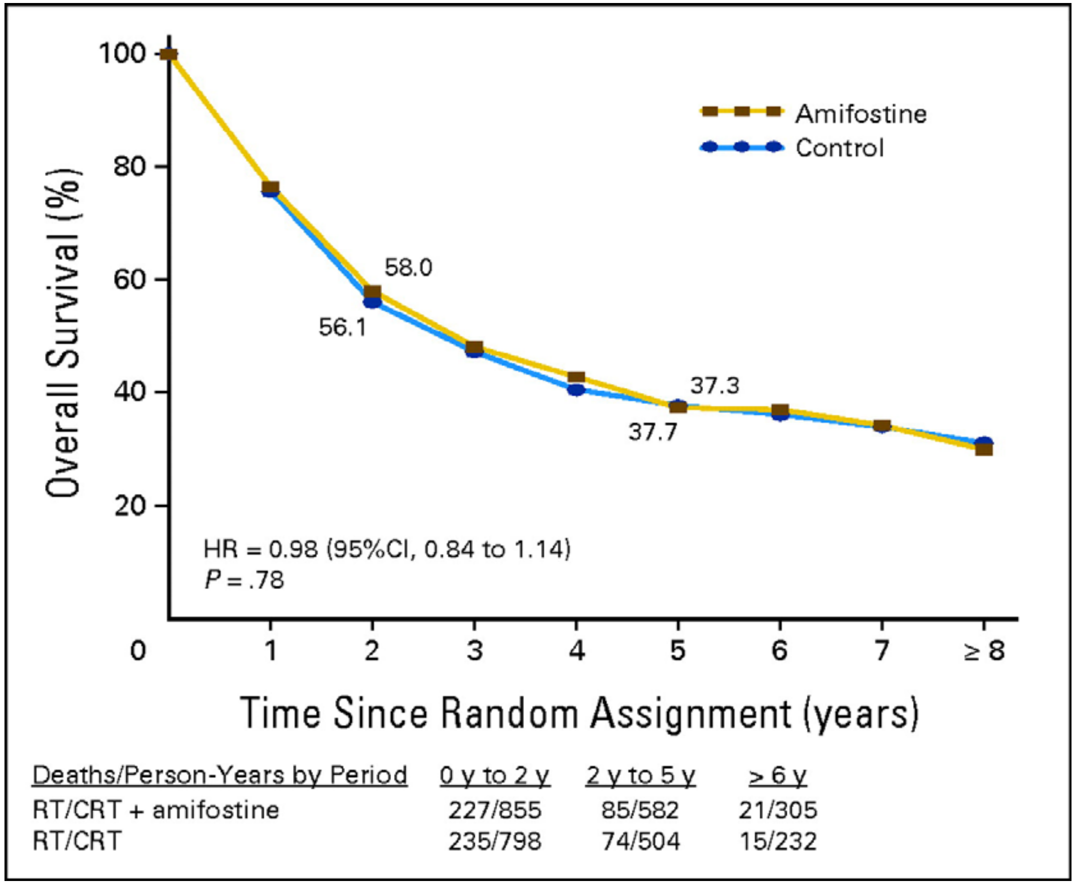
N=249	P-value
Preservation of salivary function	P< 0.05
Quality of life	P=NS

Gustatory stimuli (chewing, acid substance, saliva substitute, ..)

Buglione et al, Critical Reviews Oncology/hematology 2016
Hensley et al. JCO 2009
Fisher J Int J Radiat Oncol Biol Phys 2003

Xerostomia: amifostine tumor protection ?

12 trials: 1119 patients



Bourhis et al. JCO 2011

Xerostomia: amifostine toxicity?

	IV (%) N= 143	S/C (%) N= 148	P value
Nausea/vomiting	29%	36%	
Hypotension	20%	8%	< 0.05
Skin rash	10%	22%	< 0.05
Local pain		8%	< 0.05
Fever	2%	0%	
Asthenia	1%	6%	

Bardet et al. JCO 2011

Xerostomia

Intensity modulated radiation therapy (IMRT)

- PASSPORT phase III trial compared IMRT with to conventional RT
- n=94

	IMRT	Conventional
Grade 2 xerostomia at 12 months	37%	74%
Grade 2 xerostomia at 24 months	29%	83%

$p < 0.05$

- No difference in terms of PFS, OS, and other late toxicities

Nutting et al. Lancet Oncol 2011

Acute mucositis

Xerostomia

Dermatitis

Anti-EGFR skin toxicity

Anemia

Issues related to chemotherapy

Issues related to co-morbidities

Radiation dermatitis: grading

NCI-CTC/RTOG

Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema
Grade 3	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion
Grade 4	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site
Grade 5	Death

Skin toxicity: Radiation dermatitis

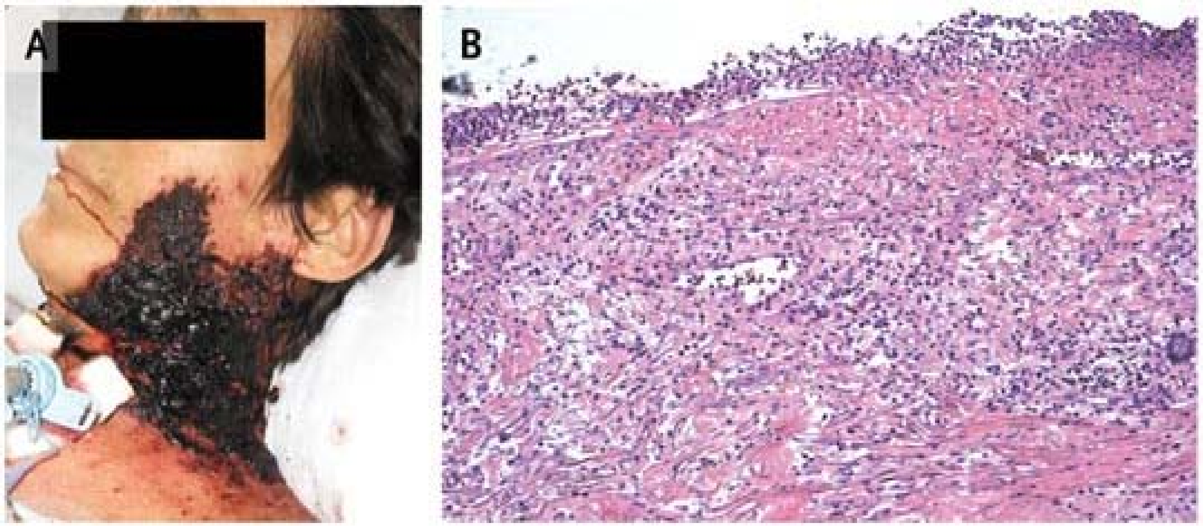
Radiation dermatitis 3/4	RT	RT+CT	Systemic treatment
RTOG 95-01	21%	14%	Cisplatin 100 mg/m2, day 1, 22,43
RTOG 91-11	9%	7%	Cisplatin 100 mg/m2, day 1, 22,43
Bonner	18%	23%	Cetuximab

Around 15-20% related to:

the total dose of RT and the RT field,
the dose per fraction,
CT or cetuximab

Cooper et al. NEJM 2004
Forastiere et al. NEJM 2003
Bonner et al. NEJM 2006

Life-threatening skin toxicity with cetuximab



Budach, et al. NEJM 2007

Management

<u>General</u>

IF YOU ARE NOT A RADIOTHERAPIST, DO NOT DO ANYTHING BEFORE ASKING HER/HIM

Maintain hygiene and gently clean and dry skin in the radiation field shortly before radiotherapy

Topical moisturisers, gels, emulsions and dressings should not be applied shortly before radiation treatment

Avoid sun and alcohol-based lotions

<u>Grade 1:</u> Use of a moisturiser is optional

Bernier et al. Ann Oncol 2008

Management

<u>Grade 2-3</u>:

One or combinations of the following topical approaches may be used:

- Drying gels, possibly with the addition of antiseptics (chlorhexidine-based creams)
- An anti-inflammatory emulsion, such as trolamine
- Hyaluronic acid cream
- Hydrophilic dressings
- Zinc oxide paste
- Silver sulfadiazine or beta glucan cream should be applied after radiotherapy (in the evening) after cleaning the irradiated area

If infection treated as indicated with topical or systemic antibiotics

Bernier et al. Ann Oncol 2008

Management

Grade 4:

Verify that radiation dose and distribution are correct

Requires specialised wound care and should be treated on a case by case basis

Acute mucositis

Xerostomia

Dermatitis

Anti-EGFR skin toxicity

Anemia

Issues related to chemotherapy

Issues related to co-morbidities

Systemic skin toxicity with anti-EGFR




60-80%
Macular, papular, pustular rash, = acne-like rash (or folliculitis)
Sometimes: severe pruritus

Segaert S, Van Cutsem E. Ann Oncol 2005

Systemic skin toxicity with anti-EGFR

35%
Dry skin, xerosis and fissure

Segaert S, Van Cutsem E. Ann Oncol 2005

Systemic skin toxicity with anti-EGFR

10-20%
Paronychia and pyogenic granuloma
Nail: discoloration and onycholysis

Segaert S, Van Cutsem E. Ann Oncol 2005

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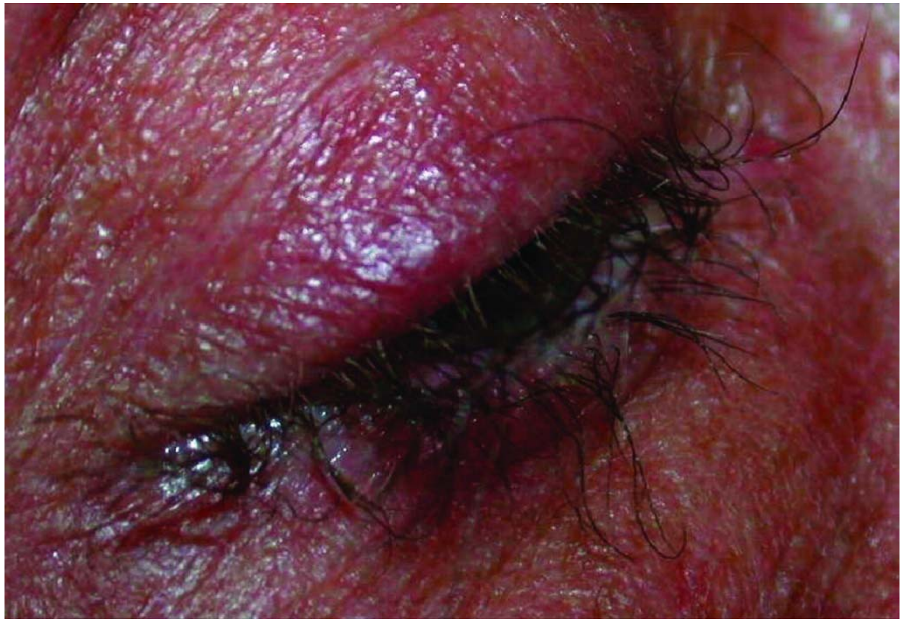
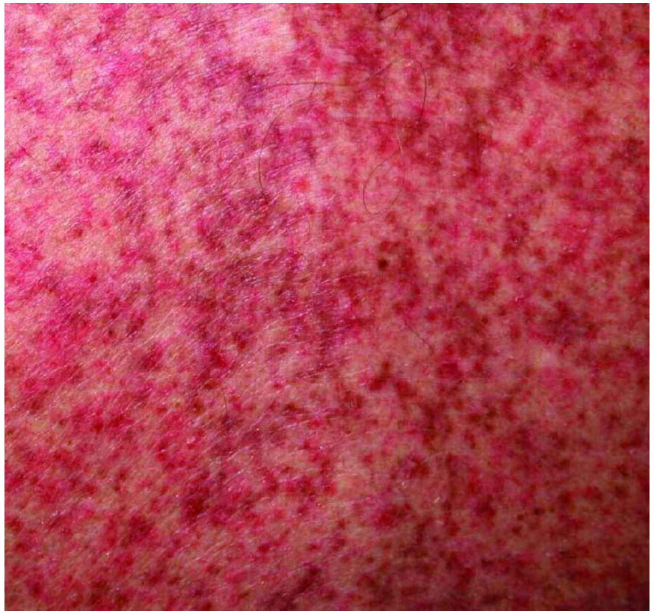
Systemic skin toxicity with anti-EGFR





Trichomegaly and hyperpigmentation

Segaert S, Van Cutsem E. Ann Oncol 2005

Systemic skin toxicity with anti-EGFR

NCI-CTC version 4.0 (acneiform rash, dry skin)

Grade 1	< 10% BSA with or without symptoms
Grade 2	10-30% BSA with or without symptoms
Grade 3	>30% BSA with or without symptoms
Grade 4	infection (AB) or life-threathening

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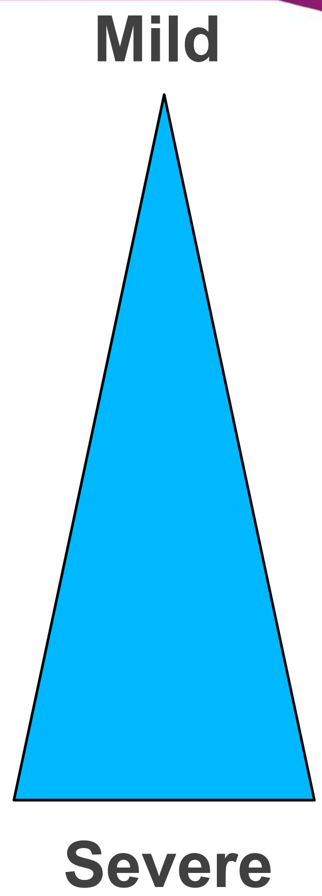
Systemic skin toxicity with anti-EGFR

Prevention

- Using sunscreens;
- Avoiding habits/products that can produce dry skin (hot water, alcohol based cosmetics);
- Enhancing skin hydration (bath oils, etc.);
- Using frequently alcohol-free moisturizing creams;
- Using tocopherol oil or gel;
- Avoiding tight shoes;
- Avoiding excessive beard growth, shaving with regular shaving razor, sharp multiblade; using pre-shaving cream emollients and moisturizing aftershave, not using alcohol and aftershave or using electric shaver.

Pinto S, et al the oncologist 2011

Systemic skin toxicity with anti-EGFR



Antiacne or antirosacea (erythromycin or clindamycin gel)

Topical corticosteroids

Antihistaminic if itching

Oral tetracycline: i.e. minocycline 100 mg/day (pustule)

Paronychia: hygiene, Potassium permanganate soak, topic steroids and antibiotics, silver nitrate

Segaert S, Van Cutsem E. Ann Oncol 2005

Diarrhea and hypomagnesemia with anti-EGFR

Diarrhea : Please inform the patient !!!

More frequent with PAN-HER inhibitor

Hypomagnesemia: please follow and correct !

Segaert S, Van Cutsem E. Ann Oncol 2005

Acute mucositis

Xerostomia

Dermatitis

Anti-EGFR skin toxicity

Anemia

Issues related to chemotherapy

Issues related to co-morbidities

Anemia

Anemia occurs frequently

Tumor response to radiotherapy in patients with pre-existing anemia is less satisfactory than in patients with normal hemoglobin

In a review of 12 studies in cervical and SCCHN, anemia was a significant predictor of negative response or poor prognosis

? correction of anemia during radiotherapy does not improve survival and local control

? smoking reduces the oxygen carrying capacity of the blood through formation of carboxyhemoglobin

Anemia and erythropoietin: Cochrane database

Meta-analysis of five studies with a total of 1397 patients

Radiation therapy versus radiation therapy + EPO

Significantly worse overall survival for RT plus EPO was observed compared to RT alone

odds ratio 0.73; (95% CI 0.58 to 0.91); p = 0.005

However, the target hemoglobin concentration was higher than recommended in four of the five trial and may have had a significant role

Lambin P Cochrane Database Syst Rev 2009

Anemia: treatment

Do not use erythropoietin outside a clinical trial

Correction of hemoglobin (HB > 11, 12-14) is appropriate with blood transfusion

Acute mucositis

Xerostomia

Dermatitis

Anti-EGFR skin toxicity

Anemia

Issues related to chemotherapy

Issues related to co-morbidities

Issues related with chemotherapy

Most frequently used cytostatics

- Cisplatin
- Carboplatin
- Docetaxel
- 5-Fluorouracil

What are the specific recommendations to use these agents?

Issues related with chemotherapy

Cisplatin

Nephrotoxicity

Peripheral neuropathy

Ototoxicity

Less hematotoxicity than carboplatin

Conditions for cisplatin administration

Creatinine Clearance > 60 ml/min

Neutrophil count > 1000/mm3

Platelet count > 75 000/mm3

Although not cardiotoxic, be sure that the patients has a heart function compatible with administration of 4 liter of saline solution in less than 24 hours

Issues related with chemotherapy

Cisplatin in the clinic

Cisplatin 100 mg/m2 in hospitalization

Be sure the patient is not dehydrated before starting

Hyperhydration to force the diuresis

When the patient start to urinate, cisplatin can be started

Monitor urine output and weight, add furosemide if needed

Highly emetogen: used apprepitant (Emend), anti-HT3, ...

Important to inform the patient to come back to the hospital rapidly if he/she cannot keep water to preserve kidney function

Issues related with chemotherapy

<u>Carboplatin</u>

More hematological toxicities

No nephrotoxicity

Less neuropathy

Ambulatory treatment

<u>5-Fluorouracil</u>

Frequently used in combination with cisplatin and carboplatin

Mucositis more frequent

Issues related with chemotherapy

Docetaxel (Taxanes)

Use with corticosteroids to avoid capillary leak syndrome

Polyneuropathy

Oedema

Docetaxel frequently used in induction approach with cisplatin and 5-FU

Issues related with chemotherapy

Grade 3/4	Vermorken PF	vs TPF	Posner PF	vs TPF
Neutropenia	52.5%	76.9%	56%	83%
Thrombopenia	17.9%	5.2%	11%	4%
Febrile neutropenia	2.8%	5.2%	7%	12%
Infection	6.1%	6.9%	5%	6%
Stomatitis	11.2%	4.6%	27%	21%

Prophylactic antibiotics, ciprofloxacine 500mg bid started day 5 for 10 days
Consider prophylactic G-CSF

Posner et al. NEJM 2007; Vermorken et al. NEJM 2007

How are you managing febrile neutropenia ?

Definition

Treatment

How are you managing febrile neutropenia ?

Definition: fever > 38.0° C and neutrophil < 500/mm3

Tricks with head and neck cancer:

- No severe neutropenia
- Fever not all time present: silent aspiration pneumonia (monitore C-reactive protein)

Treatment:

- Monotherapy, Antiobiotic IV in the hospital
- Cover anaeobic bacteria
- Tazobactam +piperacilline
- Local pathogenes (screening)

Acute mucositis

Xerostomia

Dermatitis

Anti-EGFR skin toxicity

Anemia

Issues related to chemotherapy

Issues related to co-morbidities and disease

Issues related with the co-morbidities

Alcoholic and tobacco damages

- Heart function

- Polyneuropathy

- Cirrhotic status:
  - hypersplenism and low platelet
  - oesphageal varices

- Active ethylism

Issues related with the co-morbidities

Hospital admission

- Stop drinking
- Give vitamines B1, B6 to avoid Wernicke Korsakoff
- Supplement with Magnesium, phosphorus, potassium if needed
- <u>Prevent</u> and treat the alcoholic withdrawal syndrome:
  - diazepam: 10 mgr, 3 times a day

Issues related with the disease

- Physiotherapy to avoid muscle loss
- Tracheotomy care
- Swallowing problem to diagnose to avoid aspiration pneumonia
- Nutritional counselling and oral nutritional supplements
- Pain management

Conclusions and take home mesage

The multimodal standard curative treatment of locally advanced SCCHN included radiation therapy (RT) and/or surgery and/or chemotherapy. With these classical modalities, we are at the maximal toxicity that our patients can tolerate.

Do not interrupt the RT treatment because this could impair the cancer prognosis.

Grade ¾ acute mucositis occurs in 41-73% of the patients treated with chemoradiation.

- Basic oral care, antifungal and antibiotics, enteral feeding if indicated, and adequate hydratation are the basic treatment.
- Low energy level laser could be useful.

Conclusions and take home mesage

Cetuximab does not seem to increase the risk of RT mucositis but acute grade 4 dermatitis has been described.

Systemic cutaneous toxicity of anti-Epidermal Growth Factor Receptor inhibitors can be treated depending on the symptoms with

- antiacne or antirosacea cream (erythromycin or clindamycin gel)
- topical corticosteroids,
- antihistaminic if itching,
- oral tetracycline (minocycline 100 mg/day)

Around 60% of the patients will develop long term xerostomia. The incidence of xerostomia could be reduced by IMRT.

Conclusions and take home mesage

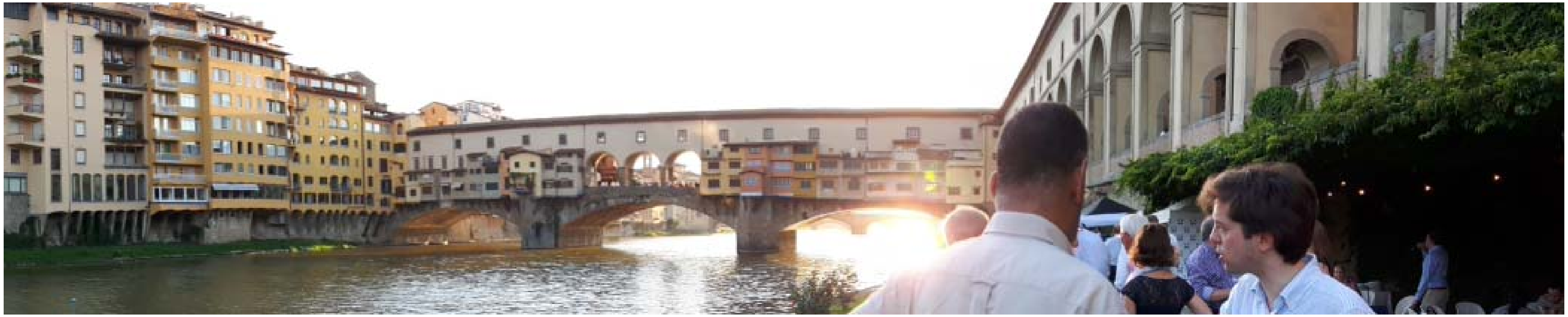
Anemia is also a frequent complication but erythropoiesis-stimulating agents should not be given outside a clinical trial.

Chemotherapy should be administered by an experimented team able to deal with chemotherapy adverse events.

The tobacco and alcoholic co-morbidities are frequent and required also an appropriate management.

MULTIDISCIPLINARY MANAGEMENT

Sino-nasal carcinoma: radiotherapy aspects



Cai Grau

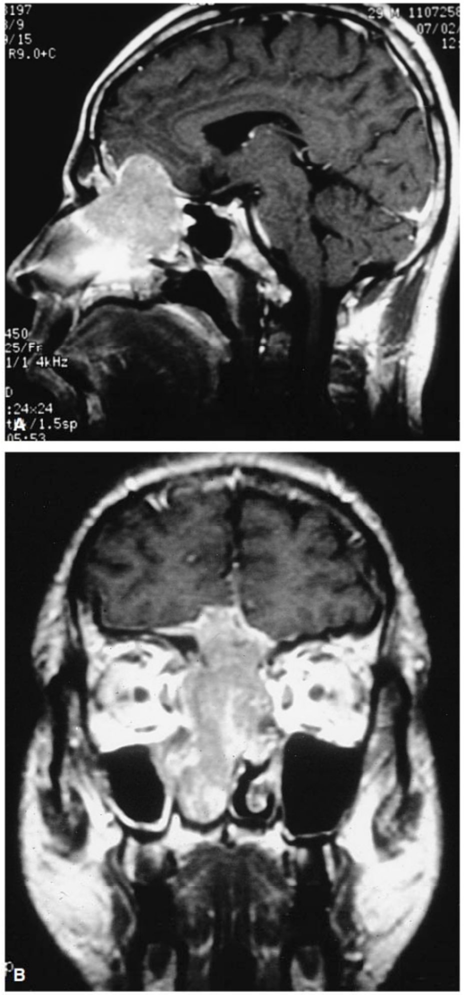
Aarhus, Denmark

June 2016
Firenze

ESTRO School

Sino-nasal carcinoma

Challenges

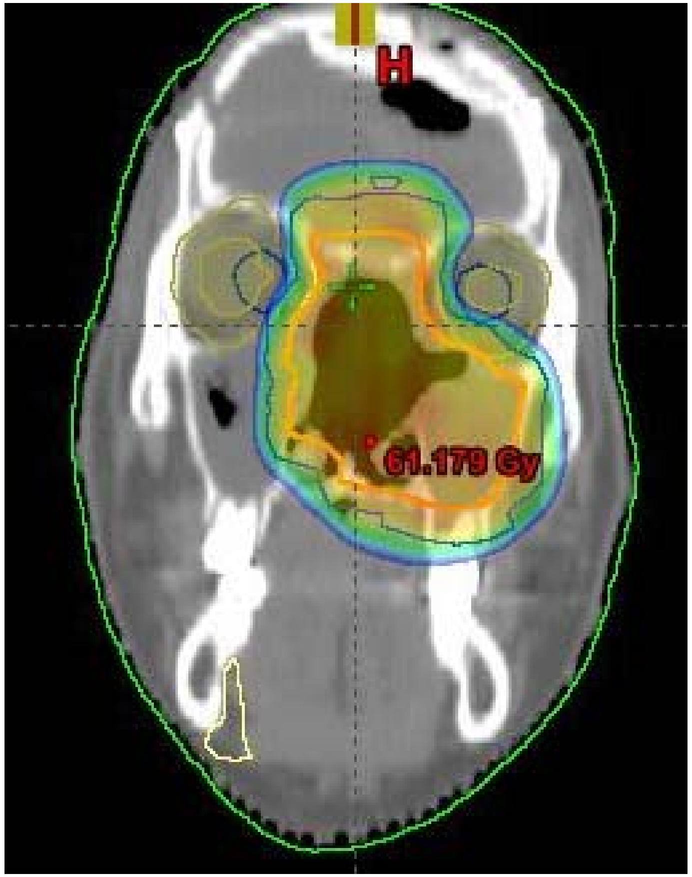


- Rare disease; small series
- Many histological types
- Complex multidisciplinary management
- Local control imperative for survival
- Surgery with secured margins is technically difficult (nerves, skull base, orbita..)
- Many critical structures surrounding the tumor
- High radiation dose needed for radical treatment

Topics

- Role of radiotherapy
- Targets, dose, fractionation
- Elective neck irradiation
- Organs at risk and constraints
- Particle therapy
- Systemic therapy

Role of radiotherapy



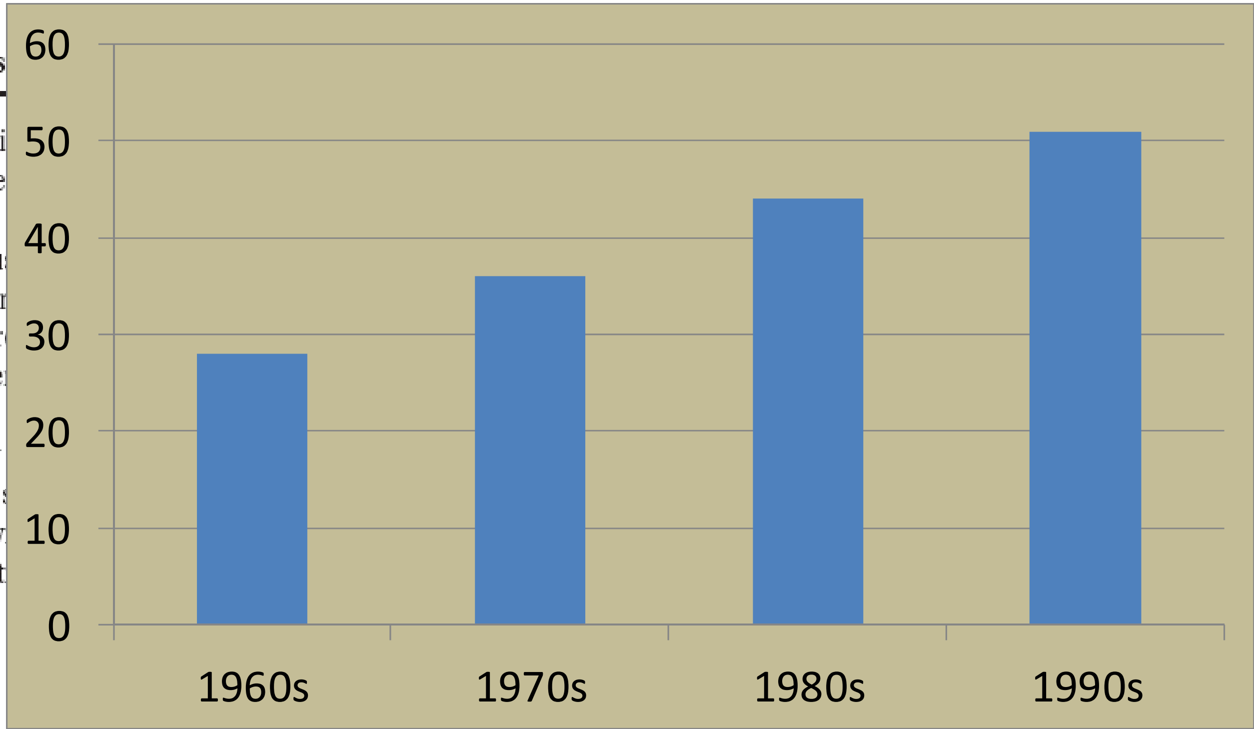
- Role of radiotherapy in sino-nasal carcinoma has never been assessed in randomized trials
- Radiotherapy alone can induce locoregional control rates of 40–50%, but high doses (66+ Gy) needed
- Postoperative radiotherapy is indicated in high risk patients
  - incomplete surgery
  - T2-T4
  - pN+
  - perineural extension

Systematic review – sino-nasal

Dulguerov et al

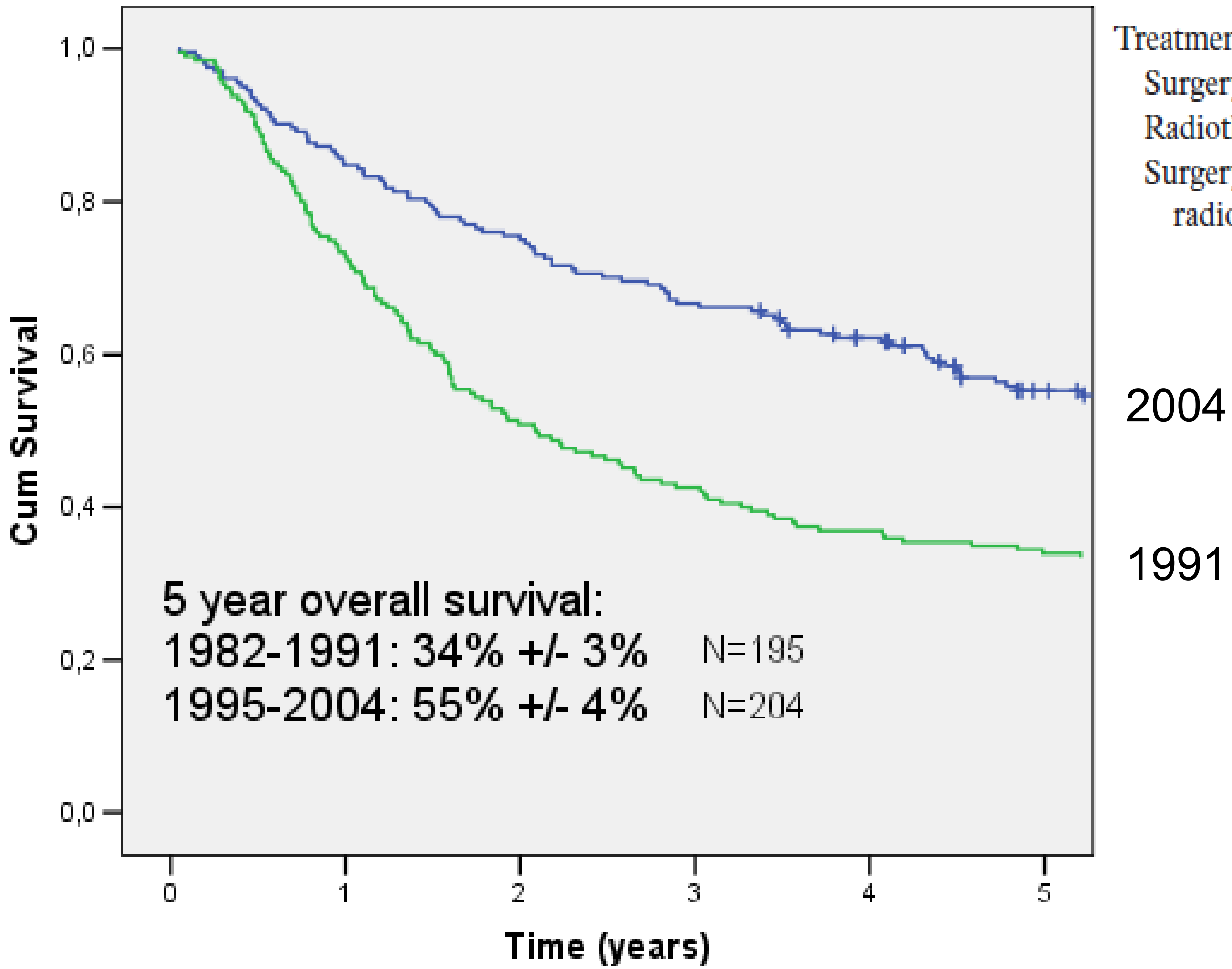
Publication CANCER December 15, 2001 / Volume 92 / Number 12

Decade (%)



Characteris					P value
No. of studi					—
No. of patie					—
Histology					
Squamou					< 0.001
Glandular					0.09
Adenocar					0.83
Undifferei					0.41
Site					
Maxillary					0.02
Ethmoid s					0.002
Nasal cav					0.71
T classificat					
T1					0.25
T2					0.28
T3					0.13
T4	0	18 ± 11	19 ± 10	28 ± 18	0.31
Treatment					
Surgery	36 ± 25	54 ± 15	57 ± 26	70 ± 20	0.034
Surgery and radiotherapy	33 ± 18	42 ± 15	54 ± 15	56 ± 13	< 0.001
Radiotherapy	21 ± 13	19 ± 17	28 ± 20	33 ± 18	0.048
Chemotherapy[b]	0[a]	21 ± 18	34 ± 24	42 ± 18	0.10
Overall	28 ± 13	36 ± 13	44 ± 15	51 ± 14	< 0.001

Sino-nasal carcinoma Denmark
1982-1991 vs. 1995-2004



Treatment	
Surgery	29 (14%)
Radiotherapy	79 (39%)
Surgery and radiotherapy	96 (47%)

Thorup et al Acta Oncologica, 2010; 49: 389–394

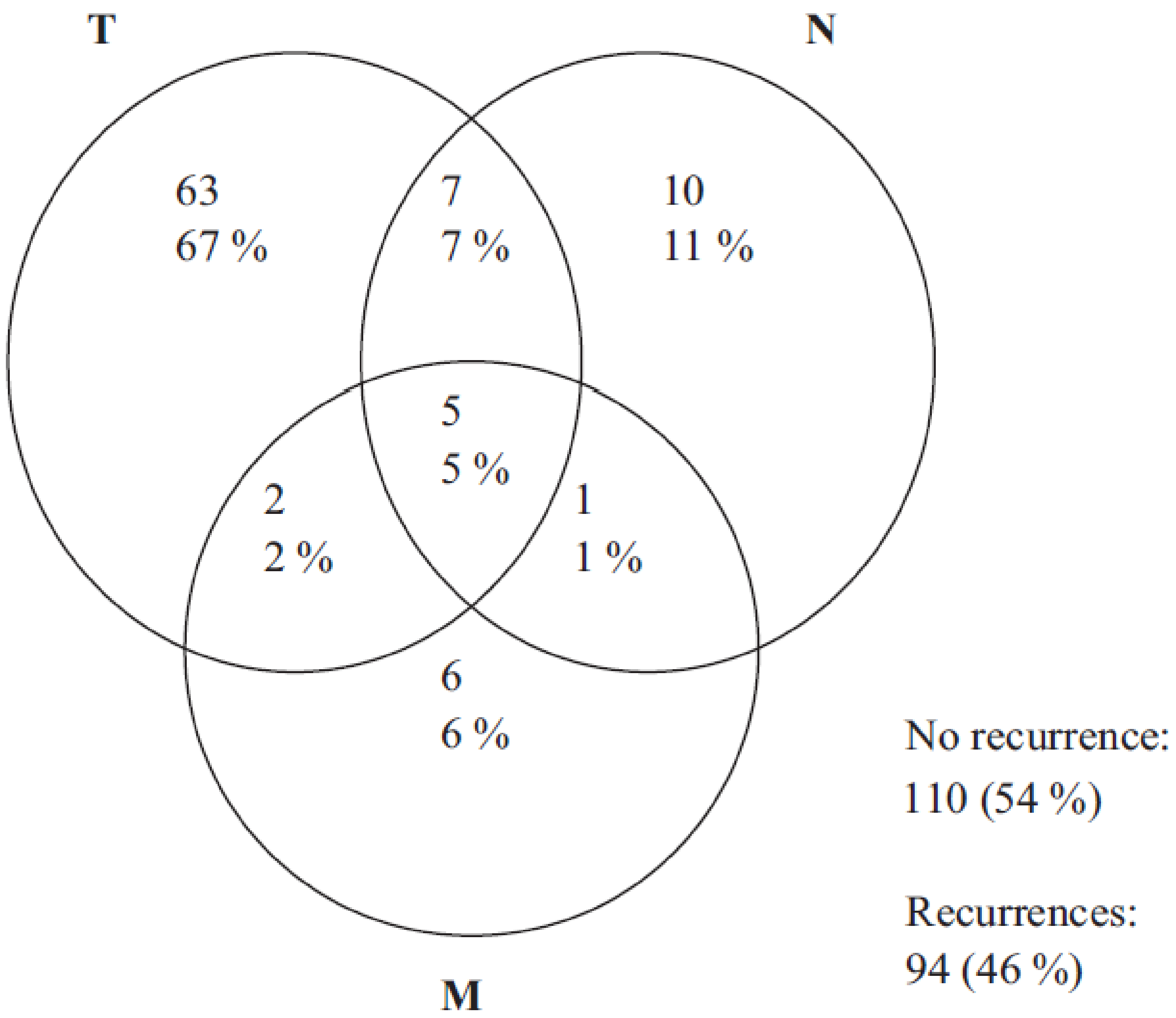
Radiotherapy techniques

Sino-nasal radiotherapy

- IMRT (or ions) !!!
- 60 Gy (R0)
- 66 Gy (R1-R2)
- 66-70 Gy (primary RT)
- Individualized margins, 0-1 cm, respect bone and other anatomical borders
- Follow route of spread, e.g. nerve (ACC, ONB)
- Involve surgeon when contouring

Elective neck irradiation?

Failure pattern



Thorup et al Acta Oncologica, 2010; 49: 389–394

Elective neck irradiation

- The risk of initial subclinical spread to neck nodes is relatively low
- Elective neck radiotherapy is recommended for
  - patients with initial N-positive disease
  - if primary tumor invades oral cavity, pharynx or skin
  - +? (emerging evidence..)
- If elective RT is indicated:
  - include levels Ib, II, and III (+facial nodes).
  - If the nasopharynx is involved, levels I–V should be included
- Unilateral neck irradiation can be used for maxillary tumors not involving the midline

Organs at risk

- Optic nerves
- Chiasm
- Temporal lobes
- Cochlea
- Nasolacrimal duct & lacrimal gland
- Lens
- Retina
- Brainstem
- Salivary glands
- ..

Constraints

www.DAHANCA.dk

	OAR (Gy)	PRV (Gy)
Spinal cord	45	50
Brainstem	54	60
Optic chiasm	54	60
Optic nerve	54	60
Posterior eye	45	50
Anterior eye	30	35
Inner ear	~~54~~ 45	~~60~~ 50

Parotid gland: mean dose ≤ 26 Gy; Larynx: 2/3 of total volume should be kept below 50 Gy


Struct
Brain
ABSOLUTE
Spinal
MUST
Anteri junctiv gland,
Chiasr nerve
Poster na)
DAHANCA
Nasal and paranasal sinus
Online Check-in - Lufthan
https://www.dahanca.oncology.dk/IndexPage
Dahanca
Til fagfolk
Organisation
Links
Bliv bruger
Login
Guidelines
Protokol
Forms
Publications
DATHYRCA
Danish Head and Neck Cancer Group
For contact and information
DAHANCA secretariat
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Fax.
+45 86197109
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Support
Aleksandar Jovanovic
E-Mail.: aleks@oncology.dk
phone.: +45 7846 2597
Næste DAHANCA møde 2-3 september - 40 års jubilæumsmøde (i trekantsområdet)
Nationale retningslinjer for mundhulekræft 2016
Opfølgningsprogram for Hoved- og Halskræft, februar 2015
Nationale retningslinjer for thyroideacancer 2016
Årsrapport 2014 (Dahanca - RKKP)
DAHANCA 32
DAHANCA 31
https://www.dahanca.oncology.dk/Brows_Web_Guidelines

Priorities and penalties

1. Critical normal tissues, potentially lethal complication

- Spinal cord
- Brain stem

2. Target coverage

- GTV
- CTV1

3. Critical serial normal tissues

- Anterior eye
- Chiasm
- Posterior eye and optic nerve
- Cochlea

4. Target coverage

- PTV1
- PTV2
- PTV3

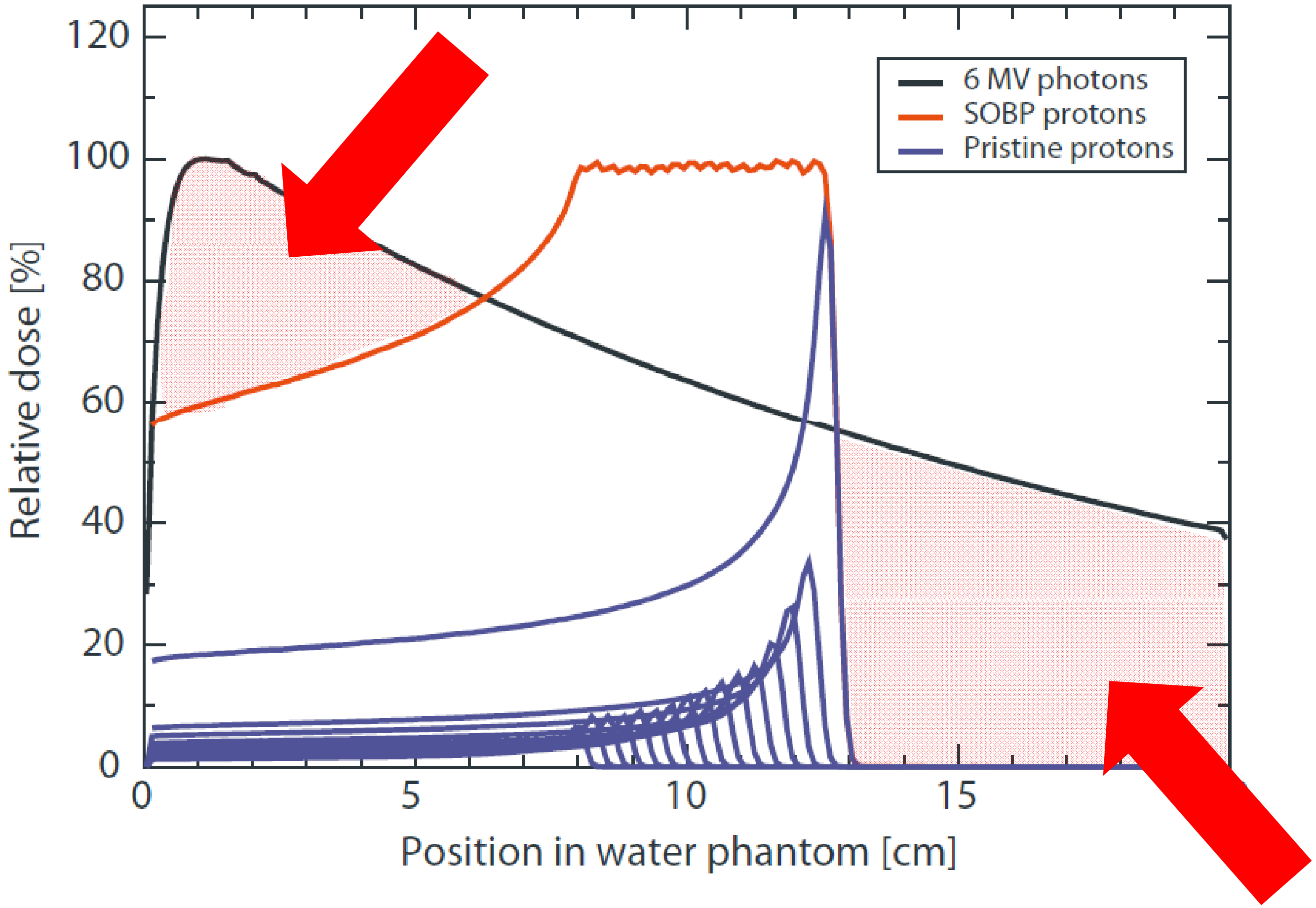
5. Sensitive normal tissues

- Brain
- Contralateral parotid
- Larynx
- Oesophagus
- Lips
- Oral cavity
- Submandibular gland
- Ipsilateral parotid gland
- Mandible
- Circumference
- Thyroid gland
- Pituitary gland

Particle therapy

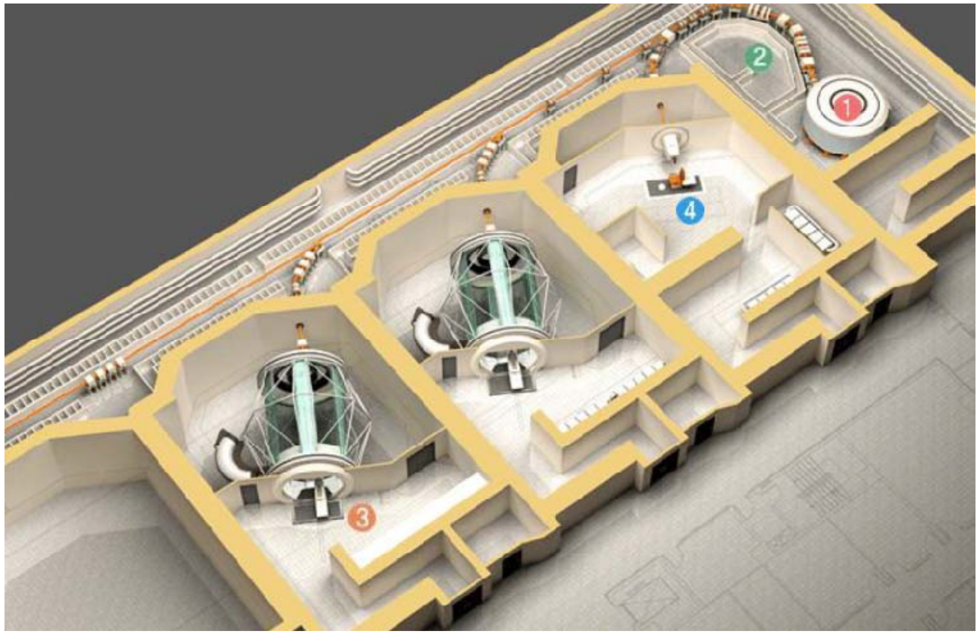
Proton, carbon

Particle therapy – Bragg Peak




IBA


DEMAG
HITACHI
Inspire the Next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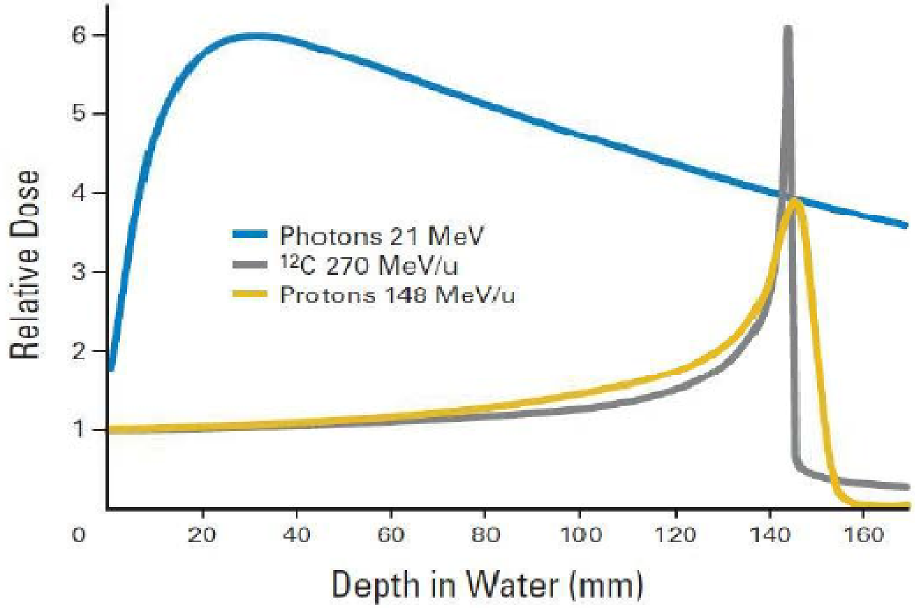
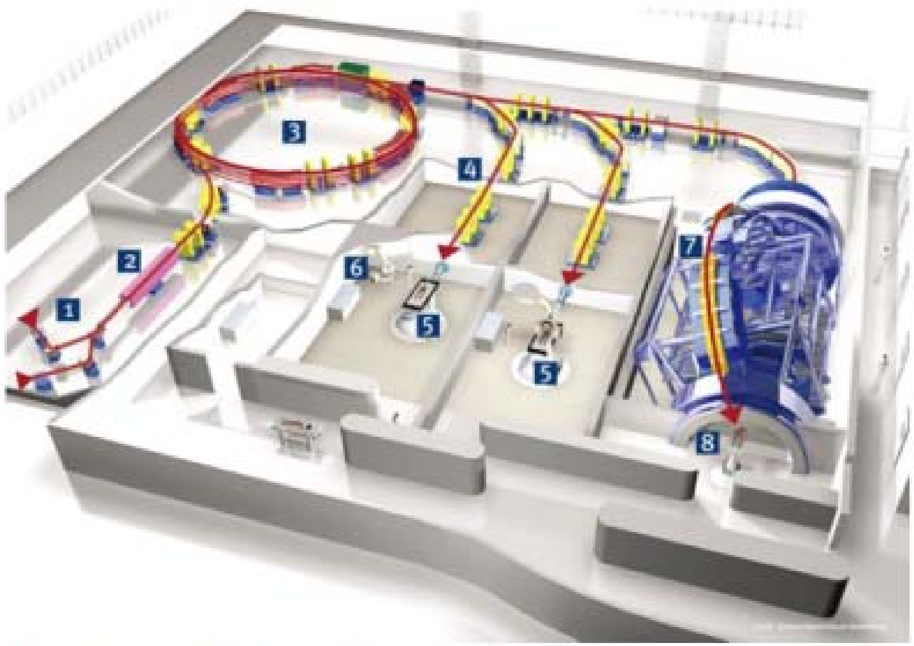
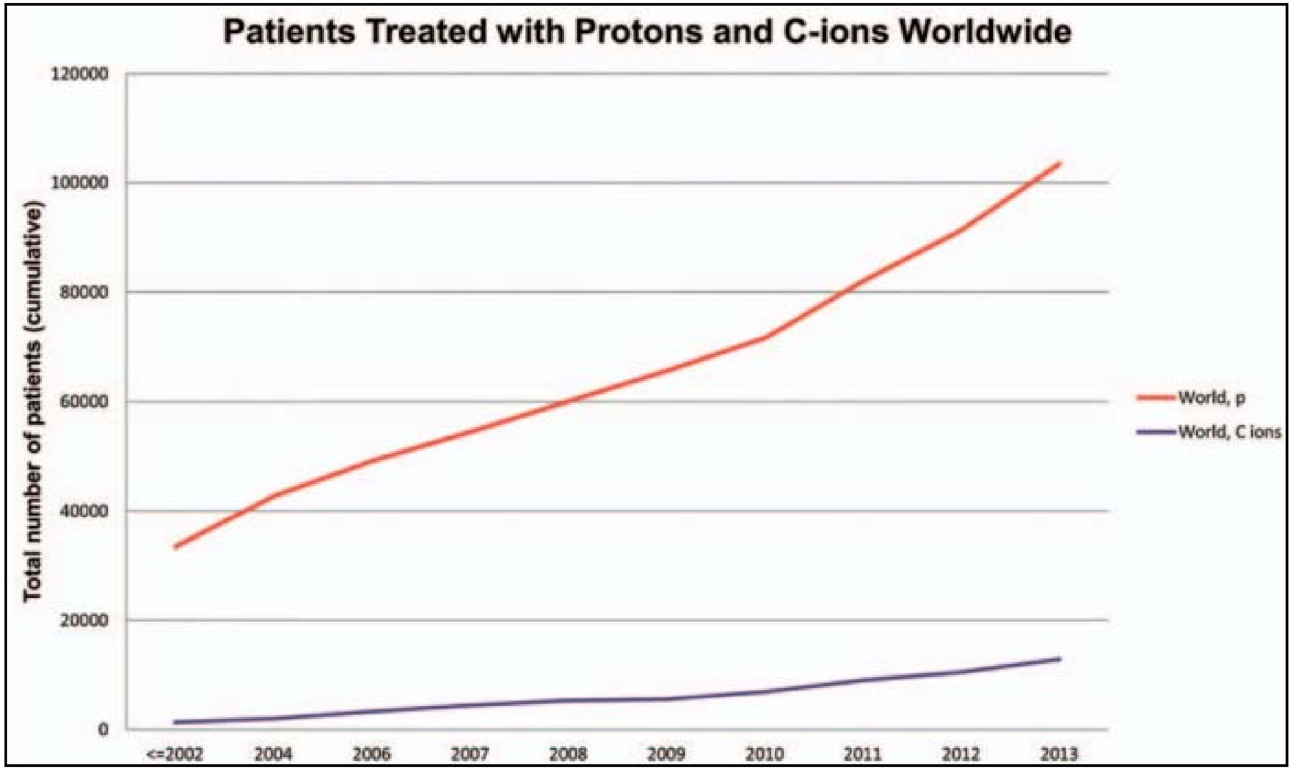




Kilde: www. www.klinikum.uni-heidelberg.de

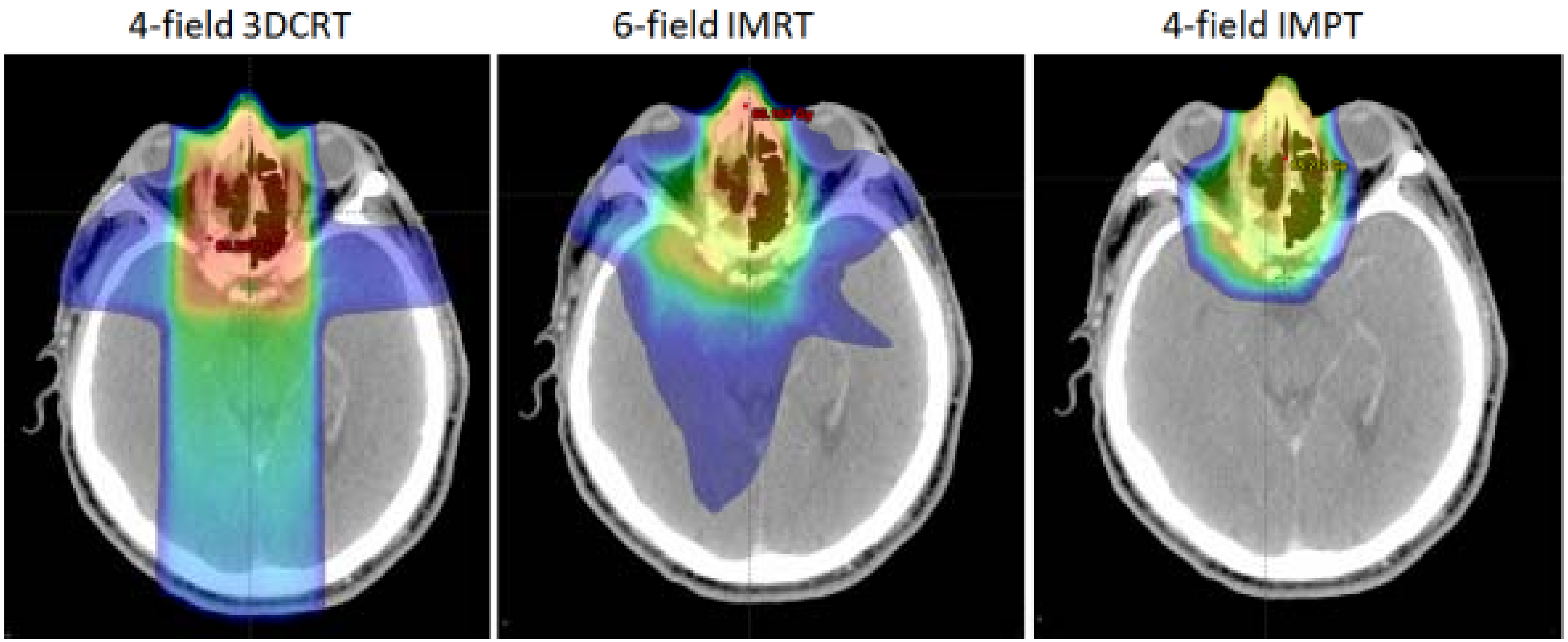
Particle therapy facilities

- 54 facilities in operation worldwide
- More than 130.000 patients treated



Indications for particle therapy

1. Reduce serious complications
   1. *especially relevant for tumours near the CNS*
   2. *reduce secondary cancer risk, especially in children and adolescents*
2. Dose escalation and increased tumor control



Patients for proton therapy - DK

Category A		**Antal**
	Intraocular melanoma	9
	Skull-base cordoma/chondrosarcoma	12
	Meningeoma	18
	AVM	12
	Medulloblastoma	12
	Reirradiation	94
	Paediatric cases (excl. medulloblastoma)	36
	Pituitary adenoma	7
	total	**200**
Category B		
	Nasopharynx/**sino-nasal cancer**	30
	Head and neck cancer (other)	100
	Sarcoma	24
	Oesophageal cancer	80
	Rectal cancer	100
	Breast cancer	100
	Thymoma	8
	Lung cancer	250
	Gynaecological cancer	30
	Glioma	30
	Liver tumours	40
	Mesothelioma	10
	Prostate cancer	86
	Malignant lymphoma	12
	Pancreatic cancer	50
	Palliation	50
	total	**1000**

J Neurosurg 70:13–17, 1989

Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull

MARY AUSTIN-SEYMOUR, M.D., JOHN MUNZENRIDER, M.D., MICHAEL GOITEIN, PH.D., LYNN VERHEY, PH.D., MARCIA URIE, PH.D., RICHARD GENTRY, M.S., STEVEN BIRNBAUM, B.S., DONNA RUOTOLO, B.S., PATRICIA MCMANUS, R.N., STEVEN SKATES, PH.D., ROBERT G. OJEMANN, M.D., ANDREW ROSENBERG, M.D., ALAN SCHILLER, M.D., ANDREAS KOEHLER, B.A., AND HERMAN D. SUIT, M.D.

Departments of Radiation Medicine, Neurosurgery, and Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, and Harvard Cyclotron Laboratory, Cambridge, Massachusetts

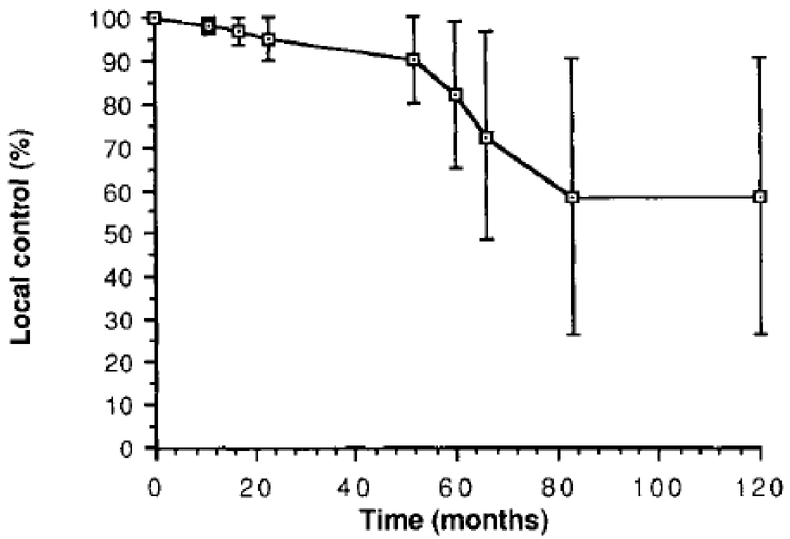


FIG. 2. Curve showing the actuarial local control rates for 68 patients with chordomas or low-grade chondrosarcomas at the base of the skull. This curve extends to 120 months.

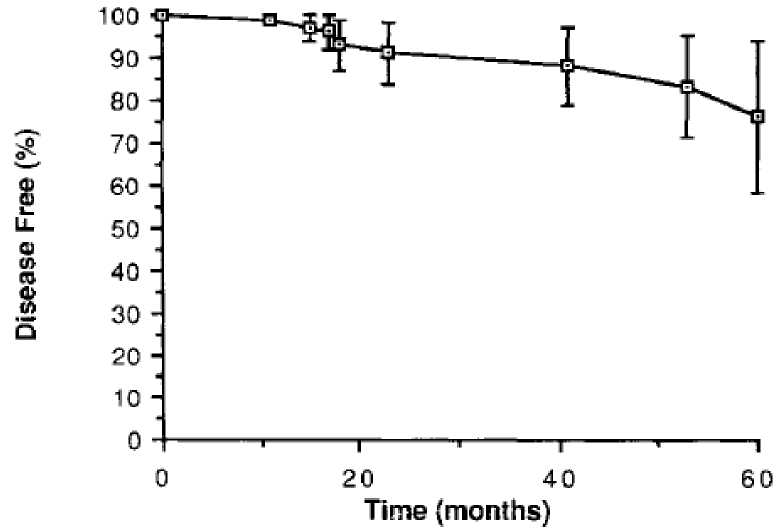
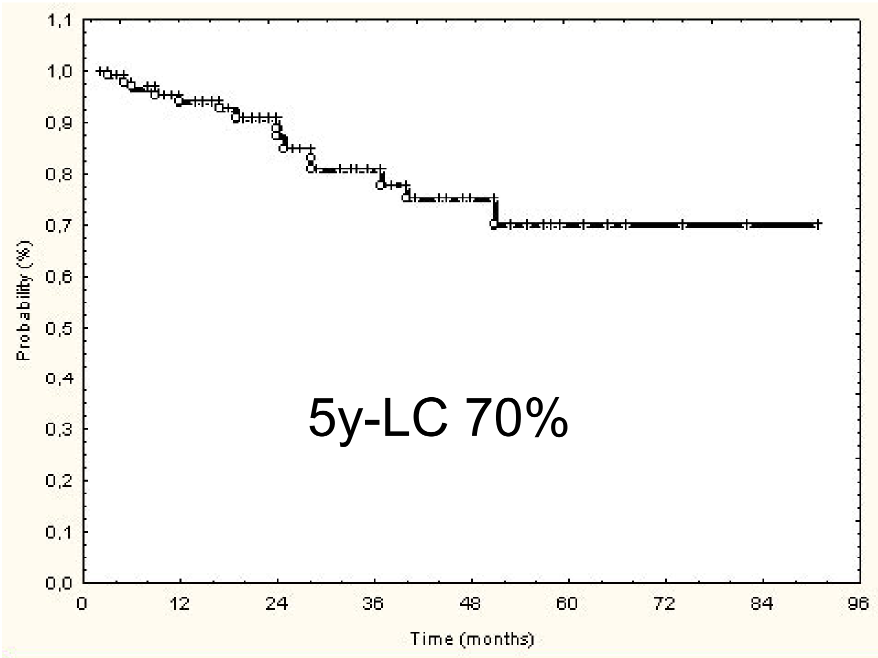
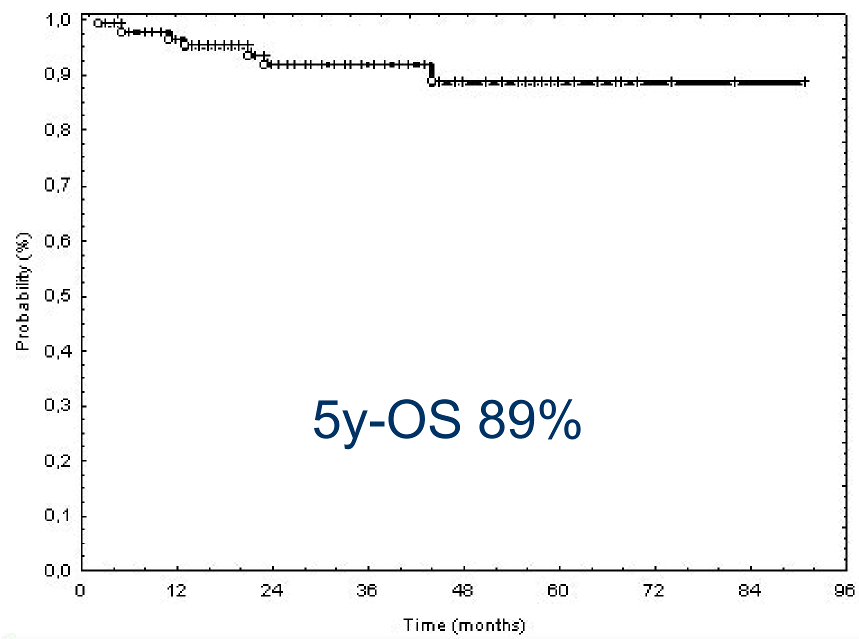


FIG. 3. Curve showing the actuarial disease-free survival rates for 68 patients with chordomas or low-grade chondrosarcomas at the base of the skull. This curve extends to 60 months.

Carbon ions in skull base chordomas

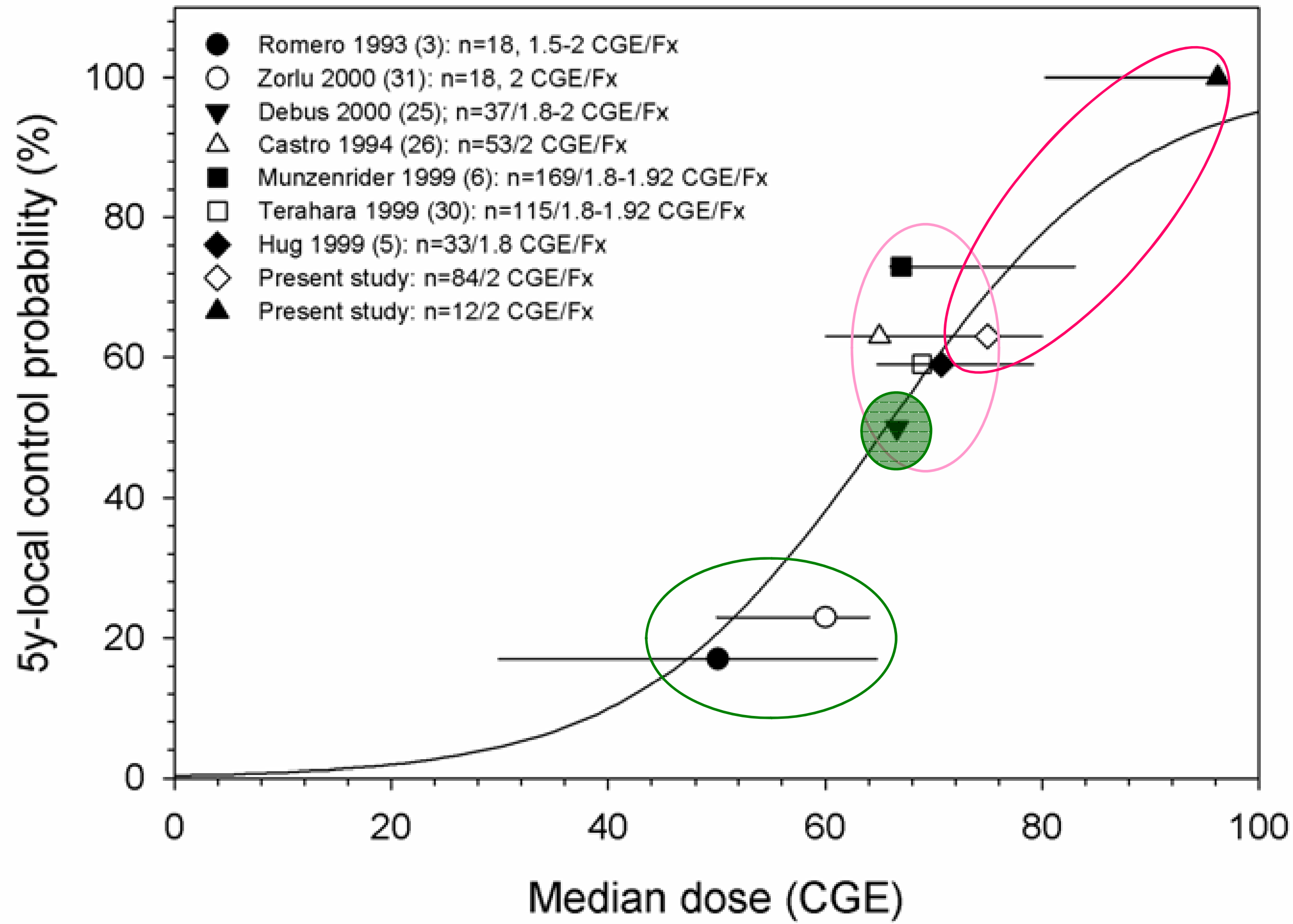
96 patients with chordomas of the skull base treated with carbon ion radiation therapy (RT) (GSI) in Darmstadt, Germany 1998-2005,





Schulz-Ertner et al. IJROBP 2007

Dose escalation with carbon ions?



[Schulz-Ertner, IJROBP 2007]

Two Phase III Randomized Studies Heidelberg

Skull Base <u>Chordoma</u> (HIT1-study):

- comparison of proton and carbon ion radiotherapy: 21 x 3GyE carbon vs 36 x 2 GyE proton

Skull Base <u>Chondrosarcoma</u> (HIT2-study):

- comparison of proton and carbon ion radiotherapy 20 x 3 GyE carbon vs 35 x 2 GyE proton

Nikoghosyan et al. BMC Cancer 2010, 10:606

Systemic therapy

- Most studies of chemotherapy are retrospective, and no randomized studies have been performed
- Response rates for induction therapy with e.g. cisplatin and 5-FU of up to 70%
- The effect of chemotherapy on locoregional control, distant metastases, and survival is still unresolved (except SNUC and SNEC)
- Systemic therapy during RT should be used with caution – unexpected toxicity and complications may occur when intensive multimodality regimens are used in this anatomical area
- Studies on the effect of other systemic therapies as antibodies, tyrosine kinase inhibitors, and radiosensitizers are ongoing and results awaited

Summary – RT key points

- Postoperative radiotherapy is indicated in
  - high risk patients, after incomplete surgery, T2-T4, pN+ or perineural extension (ACC)
- Doses of 60–70 Gy should be applied to the CTV, preferably with IMRT or particle beam, in order to reduce mean and max dose to OARs significantly.
- Carbon ion protocols are ongoing (skull base chordoma /chondrosarcomas)
- Elective nodal irradiation is indicated in N+ patients, or in case of involvement of pharynx, oral cavity, or skin
- Induction and concomitant chemotherapy should be considered in clinical trials, or in selected cases, e.g. sinonasal undifferentiated carcinoma (SNUC)

Sinonasal cancer: pathology, surgical and radiotherapy aspects

Piero Nicolai

Unit of Otorhinolaryngology - Head and Neck Surgery

University of Brescia, Italy

SINONASAL CANCER

EPIDEMIOLOGY

Review

Cancer Epidemiology
The International Journal of Cancer Epidemiology, Detection, and Prevention

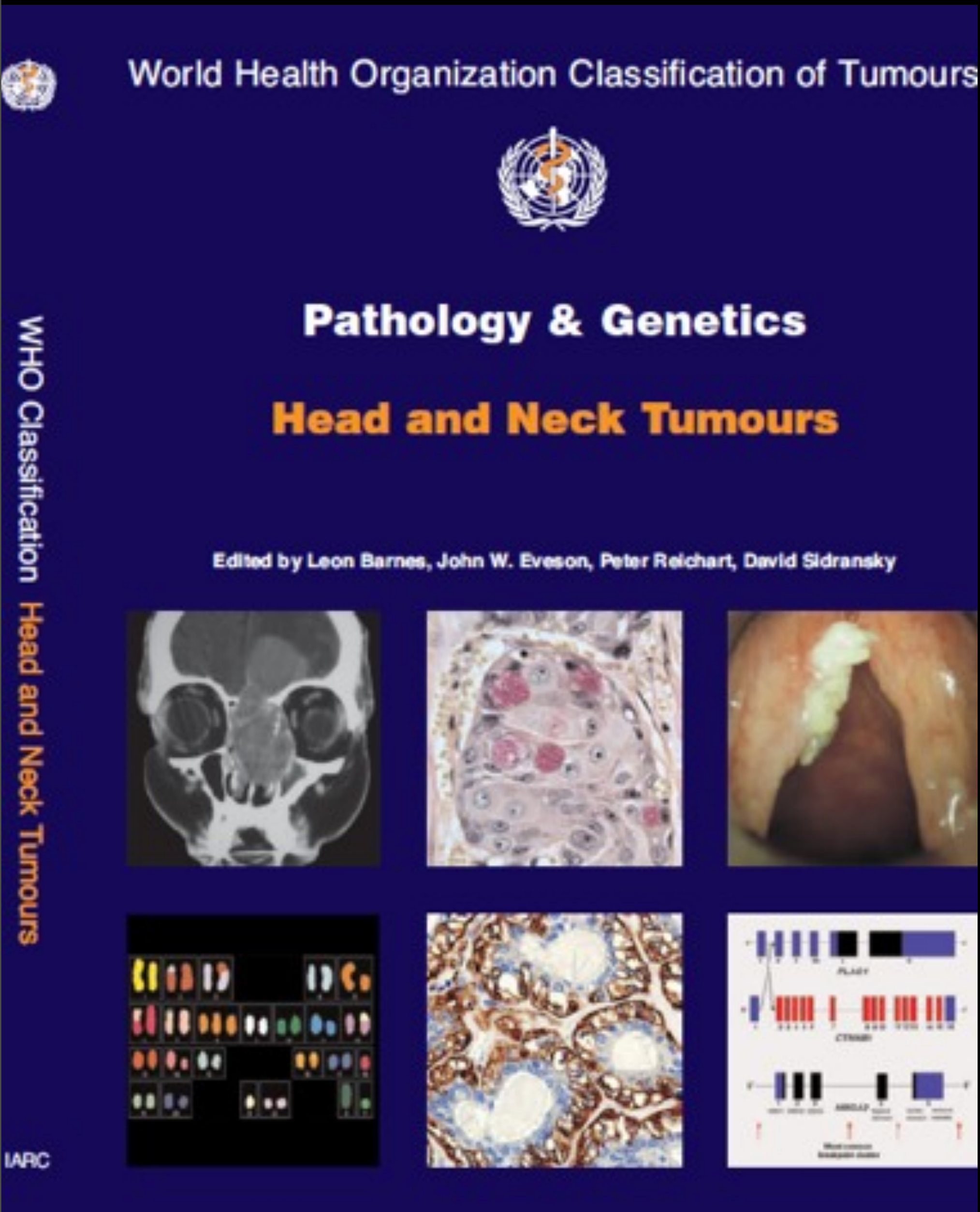
International comparisons of the incidence and mortality of sinonasal cancer

Danny R. Youlden [a,*], Susanna M. Cramb [a], Susan Peters [b], Sandro V. Porceddu [c], Henrik Møller [d], Lin Fritschi [b], Peter D. Baade [a]

2013

- 0.1-0.2% of all cancers
- Incidence: 5-9 per million for males, 2-5 per million for females
- Epithelial cancers are the commonest (SCC, ADC)
- Most frequent sites are nasal cavity and maxillary sinus
- Occupational risk factors: wood and leather dust, nickel, radium-226/228 and their decay compounds, and acids used in isopropyl alcohol production (second most important cancer site for occupational attribution after mesothelioma)
- **Mortality** rate is 0.5-3.3 per million; it **has been decreasing worldwide in the last 40 years**

SINONASAL CANCER



Malignant epithelial tumours	
Squamous cell carcinoma	8070/3
Verrucous carcinoma	8051/3
Papillary squamous cell carcinoma	8052/3
Basaloid squamous cell carcinoma	8083/3
Spindle cell carcinoma	8074/3
Adenosquamous carcinoma	8560/3
Acantholytic squamous cell carcinoma	8075/3
Lymphoepithelial carcinoma	8082/3
Sinonasal undifferentiated carcinoma	8020/3
Adenocarcinoma	
Intestinal-type adenocarcinoma	8144/3
Non-intestinal-type adenocarcinoma	8140/3
Salivary gland-type carcinomas	
Adenoid cystic carcinoma	8200/3
Acinic cell carcinoma	8550/3
Mucoepidermoid carcinoma	8430/3
Epithelial-myoepithelial carcinoma	8562/3
Clear cell carcinoma N.O.S.	8310/3
Myoepithelial carcinoma	8982/3
Carcinoma ex pleomorphic adenoma	8941/3
Polymorphous low-grade adenocarcinoma	8525/3
Neuroendocrine tumours	
Typical carcinoid	8240/3
Atypical carcinoid	8249/3
Small cell carcinoma, neuroendocrine type	8041/3
Benign epithelial tumours	
Sinonasal papillomas	
Inverted papilloma	
(Schneiderian papilloma, inverted type)	8121/1
Oncocytic papilloma	
(Schneiderian papilloma, oncocytic type)	8121/1
Exophytic papilloma	
(Schneiderian papilloma, exophytic type)	8121/0
Salivary gland-type adenomas	
Pleomorphic adenoma	8940/0
Myoepithelioma	8982/0
Oncocytoma	8290/0
Soft tissue tumours	
Malignant tumours	
Fibrosarcoma	8810/3
Malignant fibrous histiocytoma	8830/3
Leiomyosarcoma	8890/3
Rhabdomyosarcoma	8900/3
Angiosarcoma	9120/3
Malignant peripheral nerve sheath tumour	9540/3
Borderline and low malignant potential tumours	
Desmoid-type fibromatosis	8821/1
Inflammatory myofibroblastic tumour	8825/1
Glomangiopericytoma	
(Sinonasal-type haemangiopericytoma)	9150/1
Extrapleural solitary fibrous tumour	8815/1
Benign tumours	
Myxoma	8840/0
Leiomyoma	8890/0
Haemangioma	9120/0
Schwannoma	9560/0
Neurofibroma	9540/0
Meningioma	9530/0
Tumours of bone and cartilage	
Malignant tumours	
Chondrosarcoma	9220/3
Mesenchymal chondrosarcoma	9240/3
Osteosarcoma	9180/3
Chordoma	9370/3
Benign tumours	
Giant cell lesion	
Giant cell tumour	9250/1
Chondroma	9220/0
Osteoma	9180/0
Chondroblastoma	9230/0
Chondromyxoid fibroma	9241/0
Osteochondroma (exostosis)	9210/0
Osteoid osteoma	9191/0
Osteoblastoma	9200/0
Ameloblastoma	9310/0
Nasal chondromesenchymal hamartoma	
Haematolymphoid tumours	
Extranodal NK/T cell lymphoma	9719/3
Diffuse large B-cell lymphoma	9680/3
Extramedullary plasmacytoma	9734/3
Extramedullary myeloid sarcoma	9930/3
Histiocytic sarcoma	9755/3
Langerhans cell histiocytosis	9751/1
Neuroectodermal	
Ewing sarcoma	9260/3
Primitive neuroectodermal tumour	9364/3
Olfactory neuroblastoma	9522/3
Melanotic neuroectodermal tumour of infancy	9363/0
Mucosal malignant melanoma	8720/3
Germ cell tumours	
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Sinonasal yolk sac tumour (endodermal sinus tumour)	9071/3
Sinonasal teratocarcinosarcoma	
Mature teratoma	9080/0
Dermoid cyst	9084/0
Secondary tumours	

SINONASAL CANCER

Knowledge of the behaviour is the key

SINONASAL CANCER

HISTOLOGY

High-grade tumors

SNUC

SNEC

Ewing Sarcoma

Poorly differentiated carcinoma

Melanoma

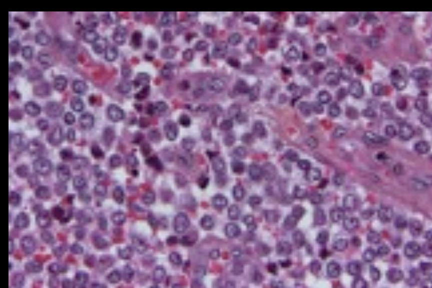
ITAC G3 / Ring cells

Adenoid cystic carcinoma G3

ONB III-IV

SNUC

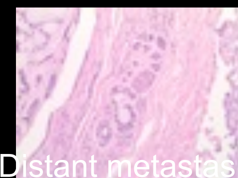
EWING SARCOMA



Intermediate-grade tumors

Adenoid cystic carcinoma G1/G2

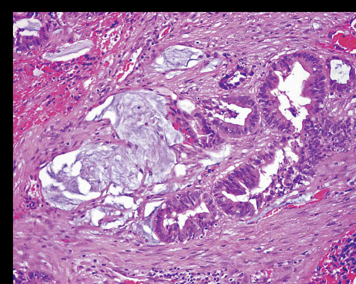
?



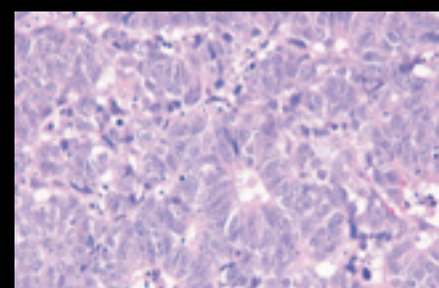
Distant metastasis

Low-grade tumors

ITAC G1-G2



ONB I-II



SINONASAL CANCER

DIAGNOSTIC WORK-UP

SINONASAL CANCER

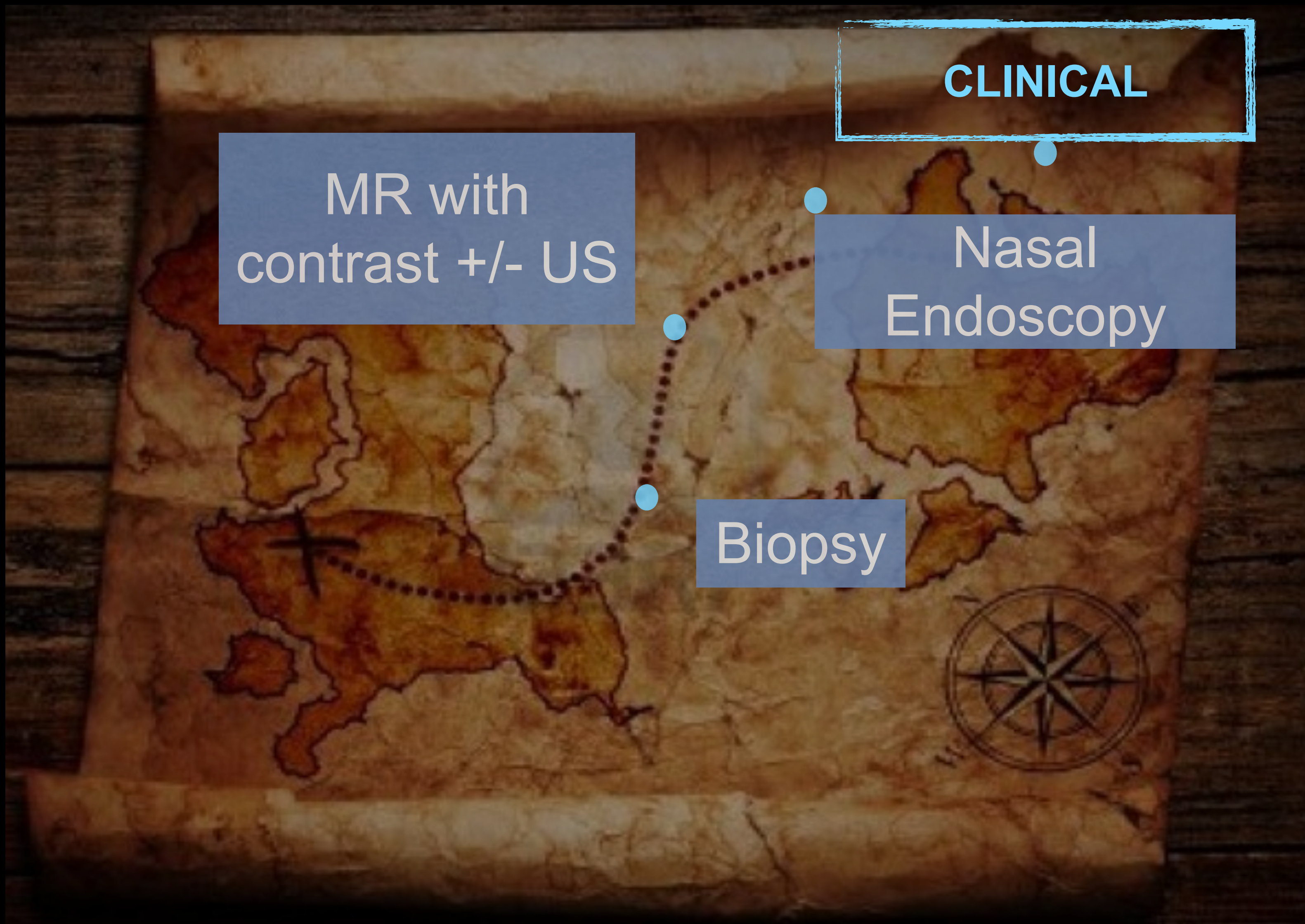
DIAGNOSTIC WORK-UP

SINONASAL CANCER

DIAGNOSTIC WORK-UP

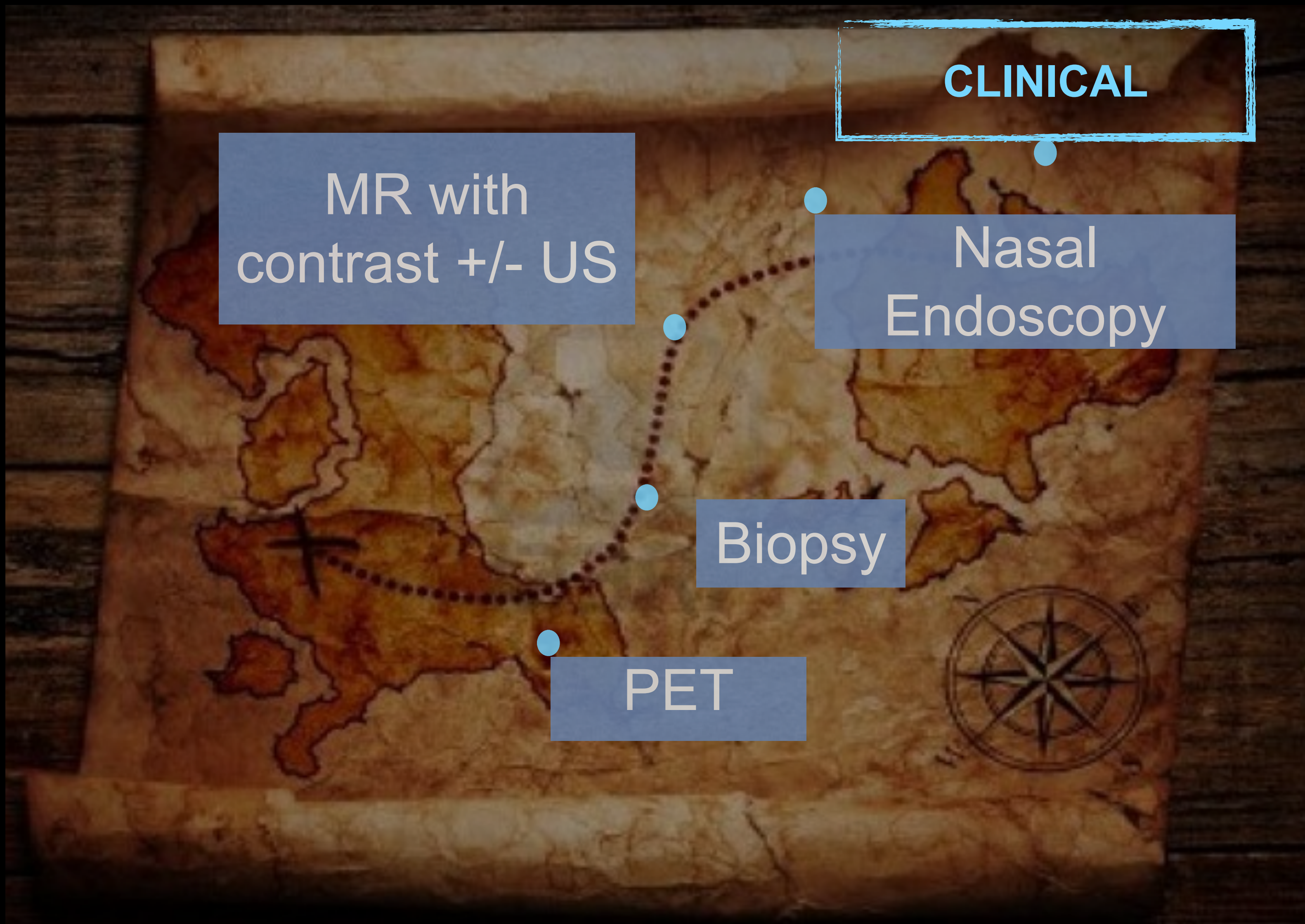
SINONASAL CANCER

DIAGNOSTIC WORK-UP



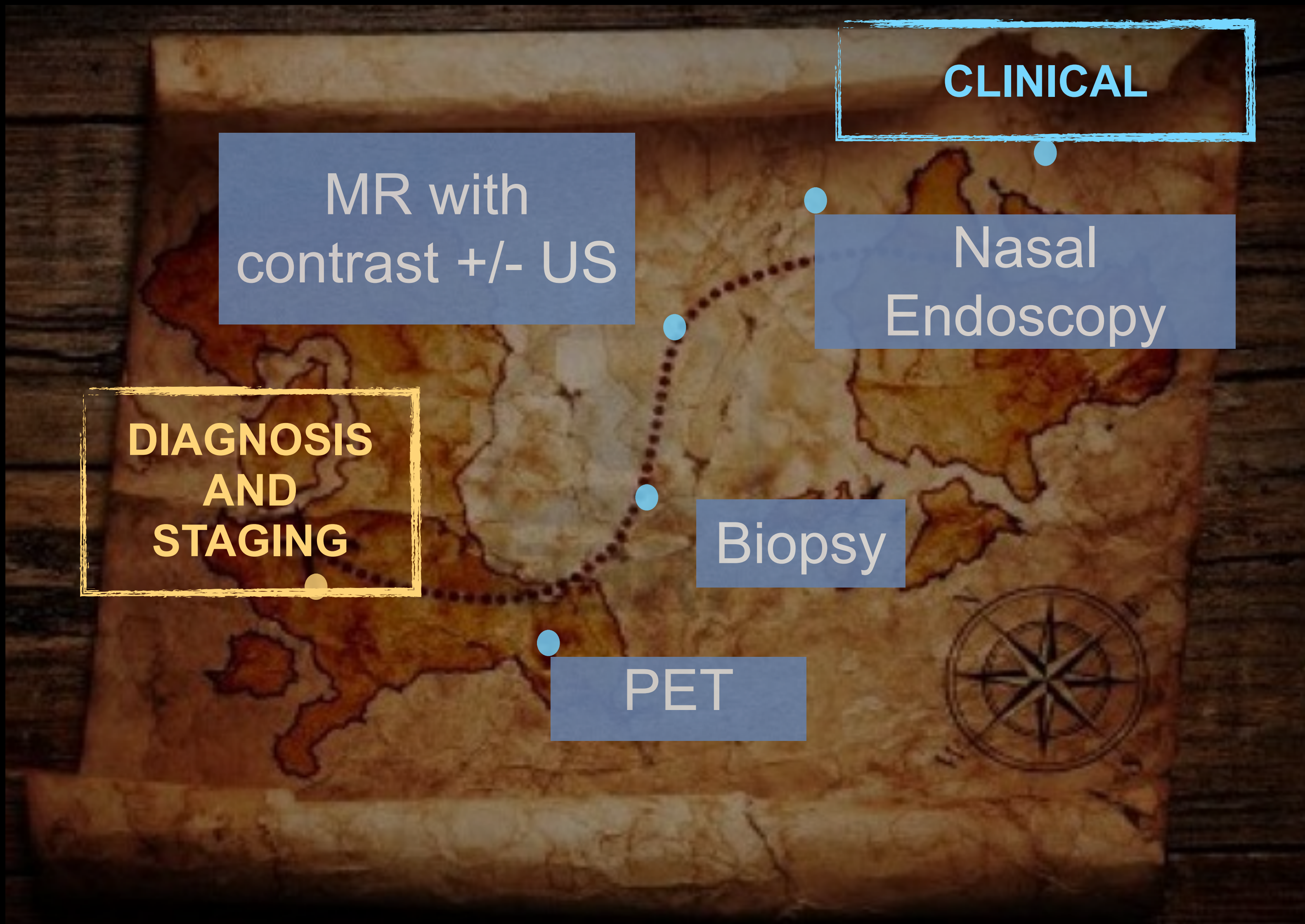
SINONASAL CANCER

DIAGNOSTIC WORK-UP



SINONASAL CANCER

DIAGNOSTIC WORK-UP

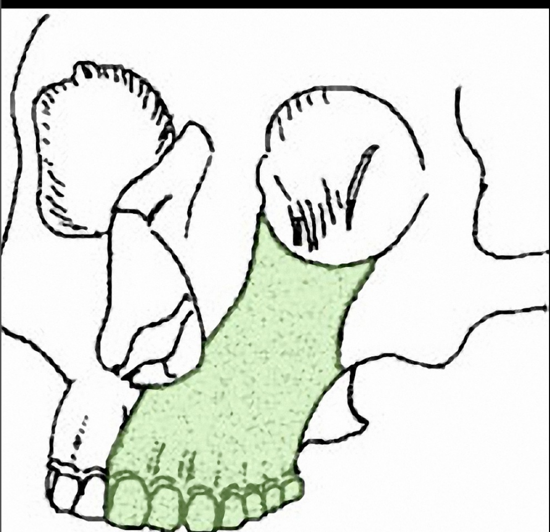
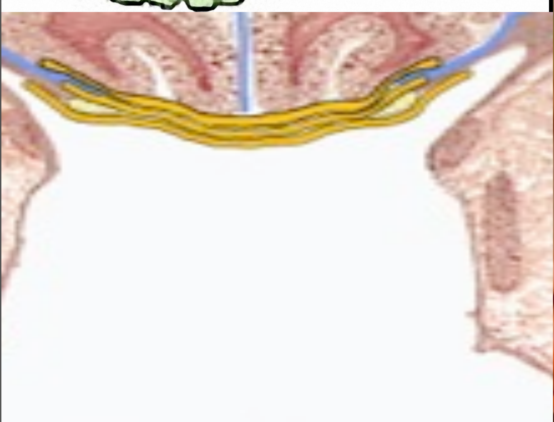


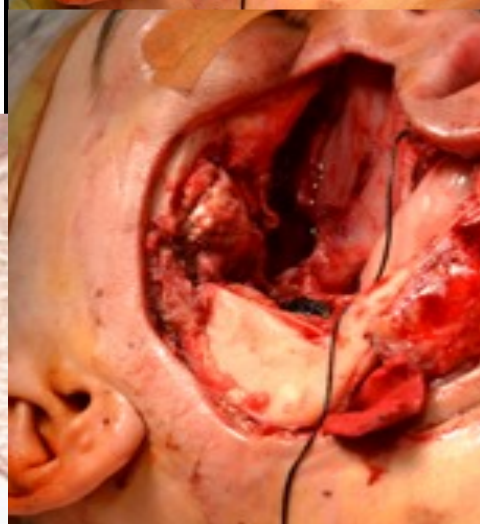
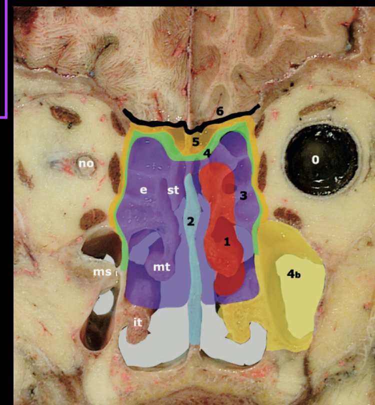
Different diseases

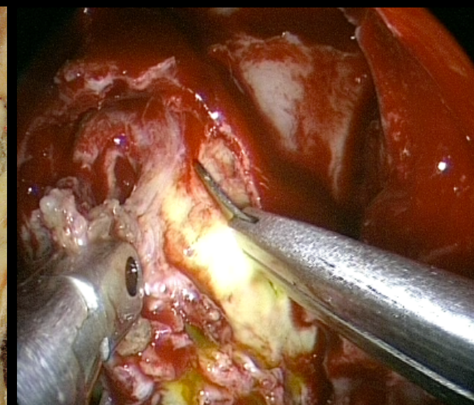
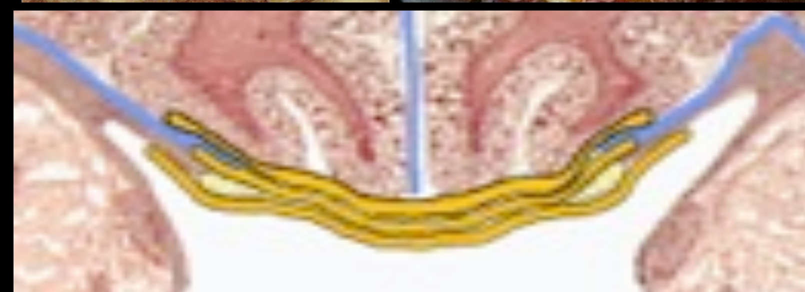
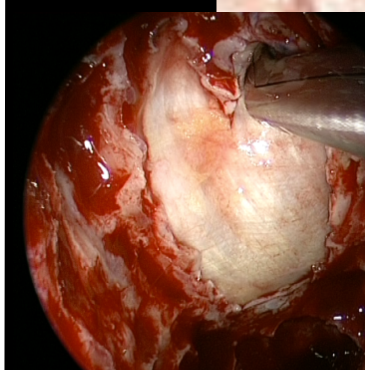
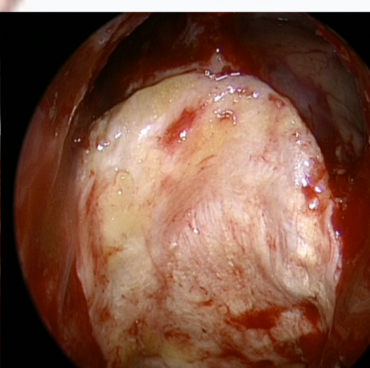
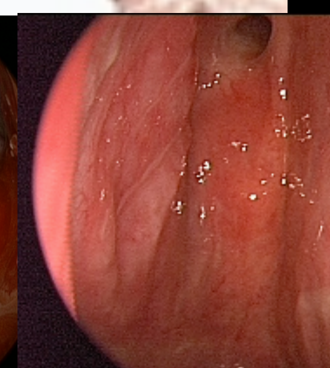
Maxillary sinus

Naso-ethmoid

Different surgical approaches

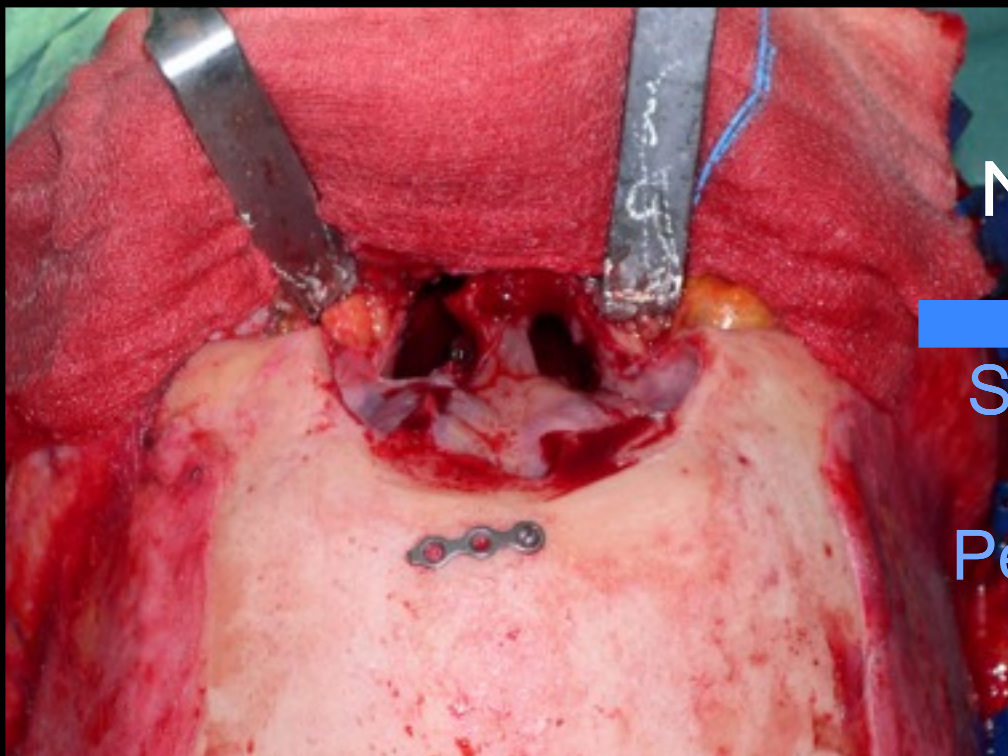



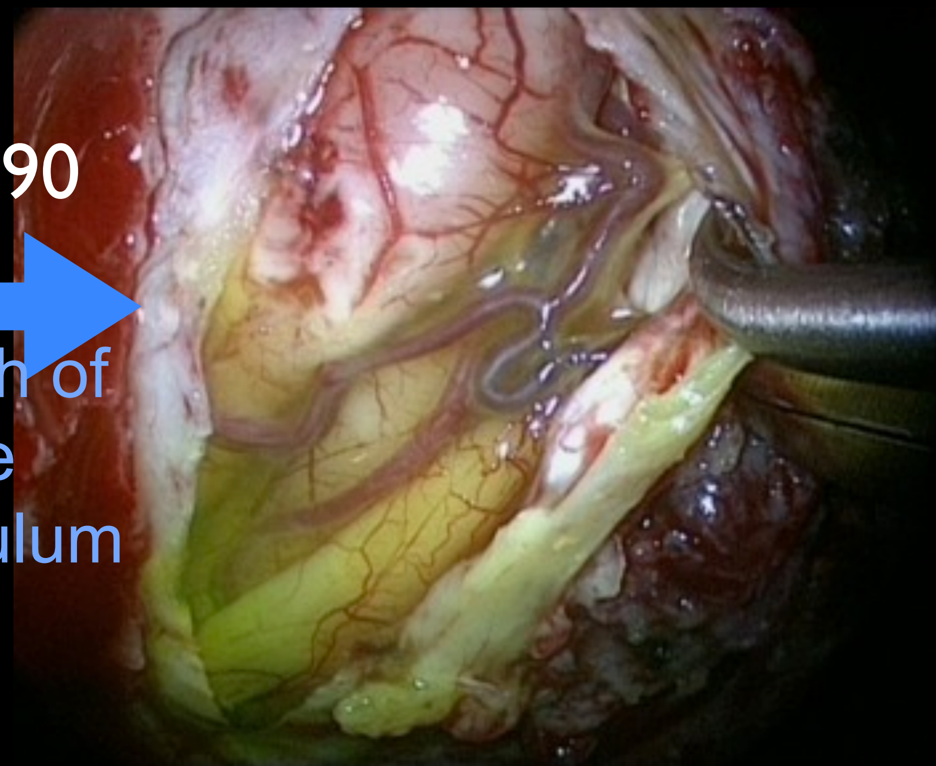
SINONASAL CANCER

Naso-ethmoidal tumors



Mid ’90

Switch of the Pendulum



SINONASAL CANCER

Naso-ethmoidal tumors

Endoscopic resection of malignant tumors of the nose and sinuses

Valerie Lund, M.S.,* David J. Howard, M.D.,* and William I. Wei, M.D.#

2007

Endoscopic surgery for malignant tumors of the sinonasal tract and adjacent skull base: A 10-year experience

Piero Nicolai, M.D.,* Paolo Battaglia, M.D.,# Maurizio Bignami, M.D.,# Andrea Bolzoni Villaret, M.D.,* Giovanni Delù, M.D.,# Tarek Khrais, M.D.,§ Davide Lombardi, M.D.,* and Paolo Castelnuovo, M.D.#

2008

Endoscopic Resection of Sinonasal Cancers With and Without Craniotomy

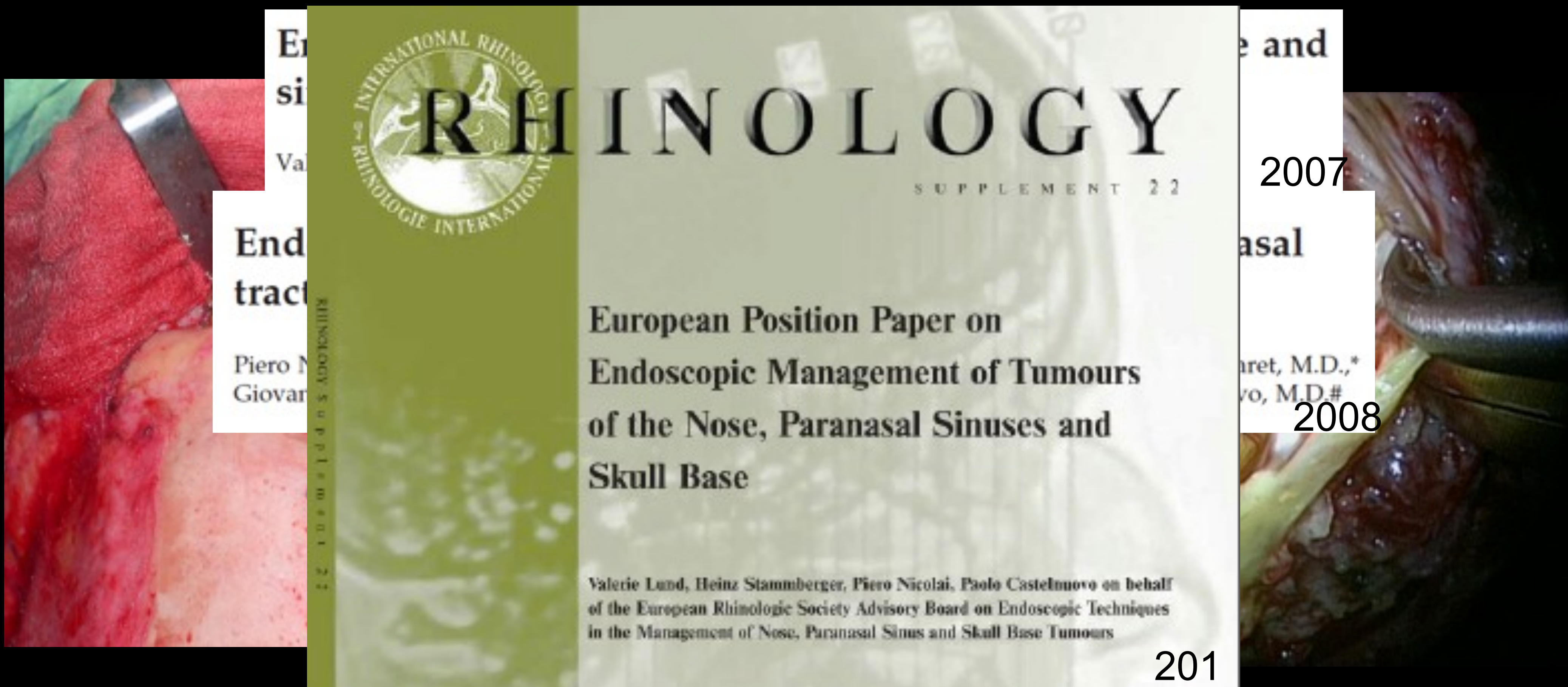
Oncologic Results

Ehab Hanna, MD; Franco DeMonte, MD; Samer Ibrahim, MD; Dianna Roberts, PhD; Nicholas Levine, MD; Michael Kupferman, MD

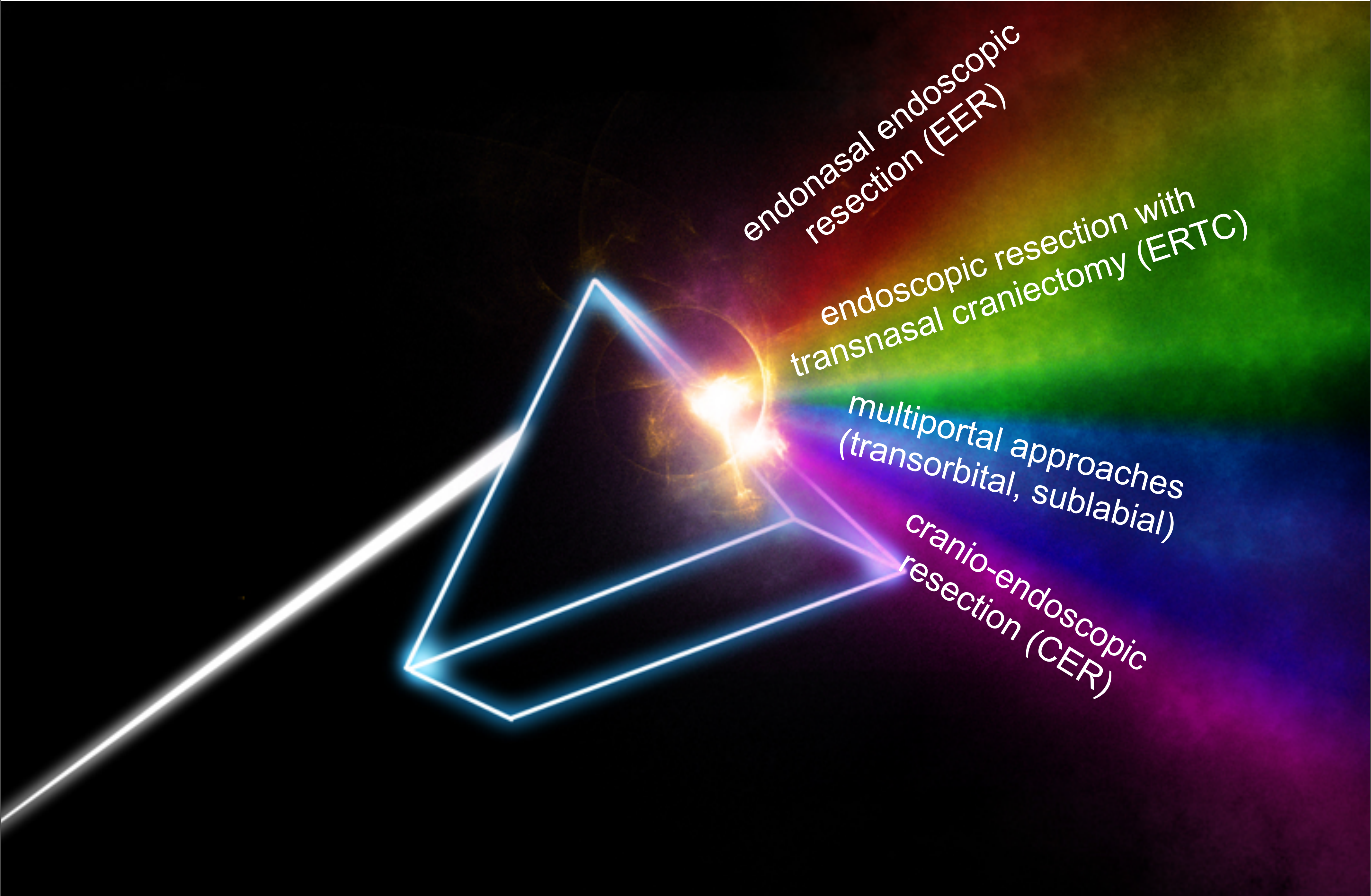
2009

SINONASAL CANCER

Naso-ethmoidal tumors



TUMORS OF THE NASO-ETHMOID

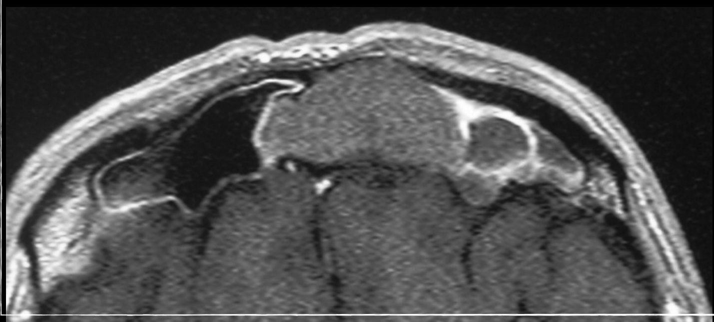


PINK FLOYD - THE DARK SIDE OF THE MOON

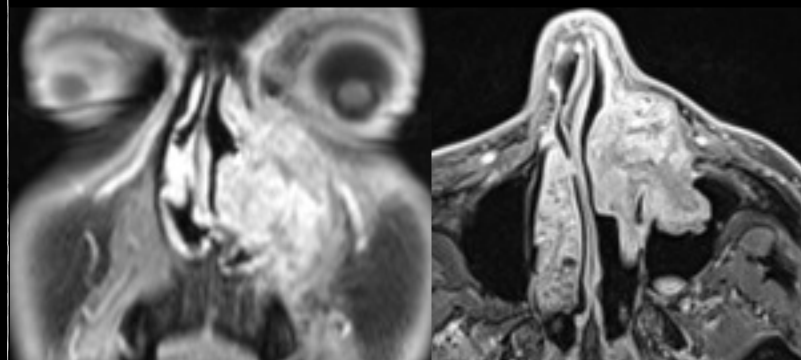
NASO-ETHMOID CANCER

Contraindications for endoscopic surgery

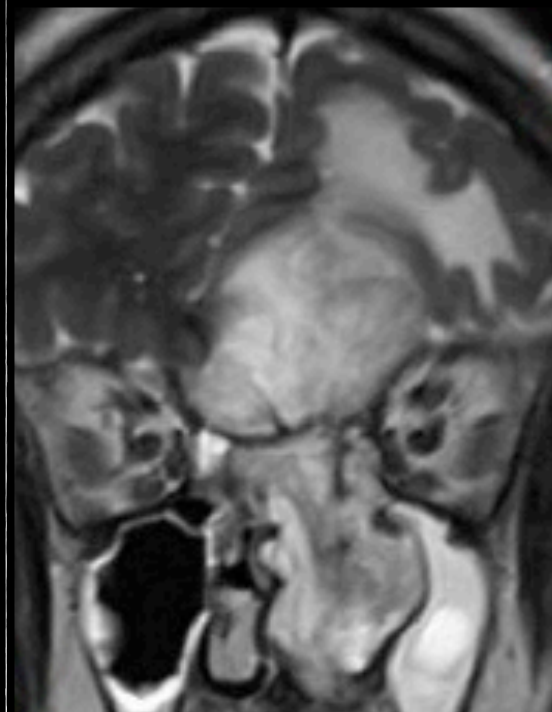
Involvement of the anterior wall/lateral portion of frontal



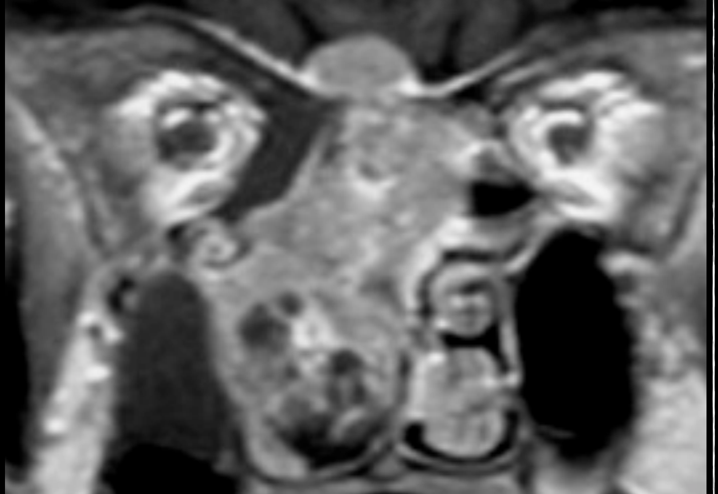
Invasion of the lacrymal



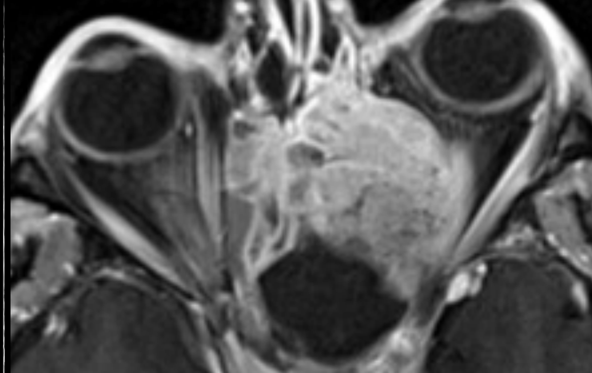
Massive transdural



Dural involvement over the



Invasion of the orbital



SURGICAL TECHNIQUE

Tumor debulking

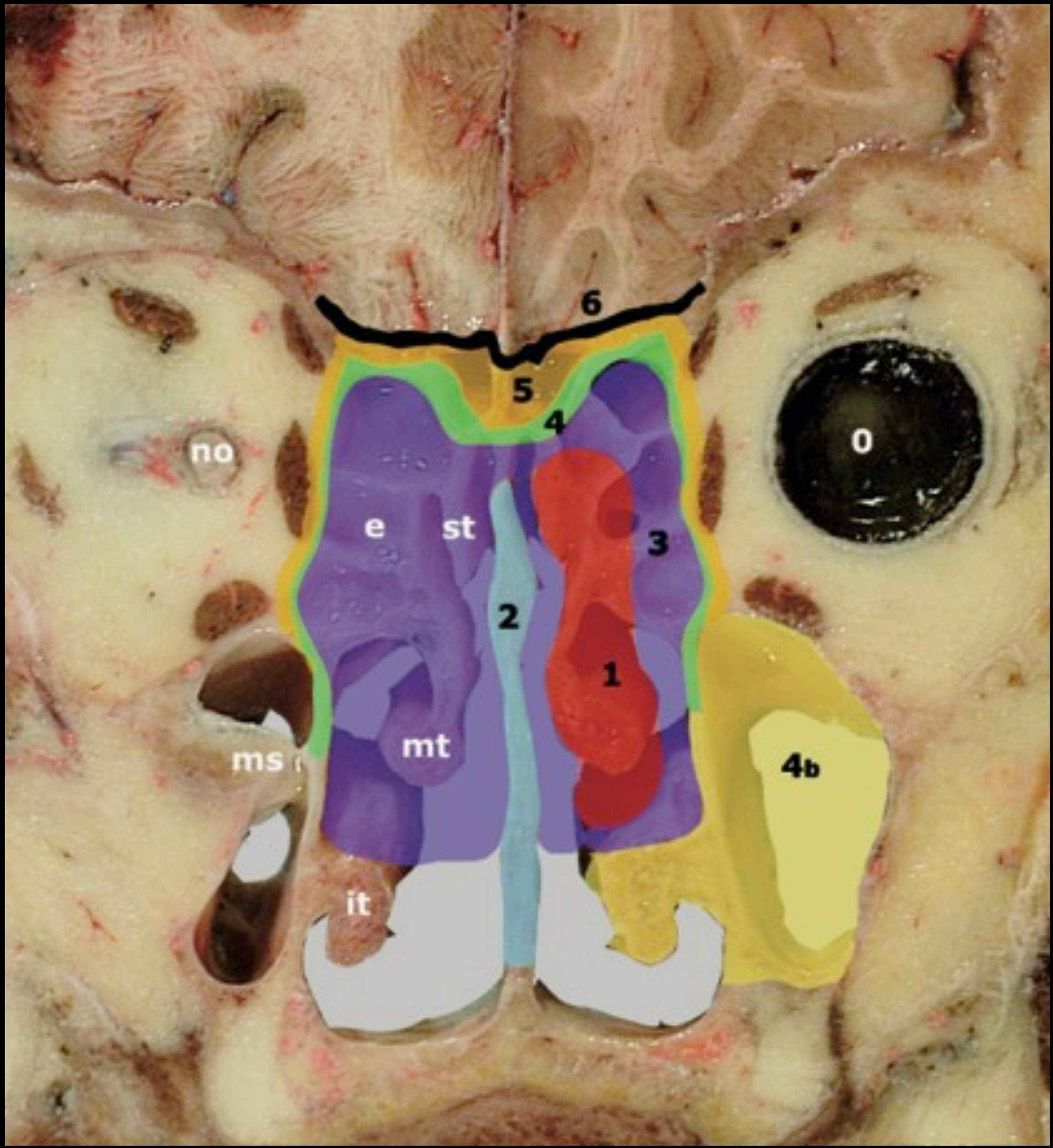
Septal resection

Centripetal removal with subperiosteal resection (Draf III + median sphenoidotomy)

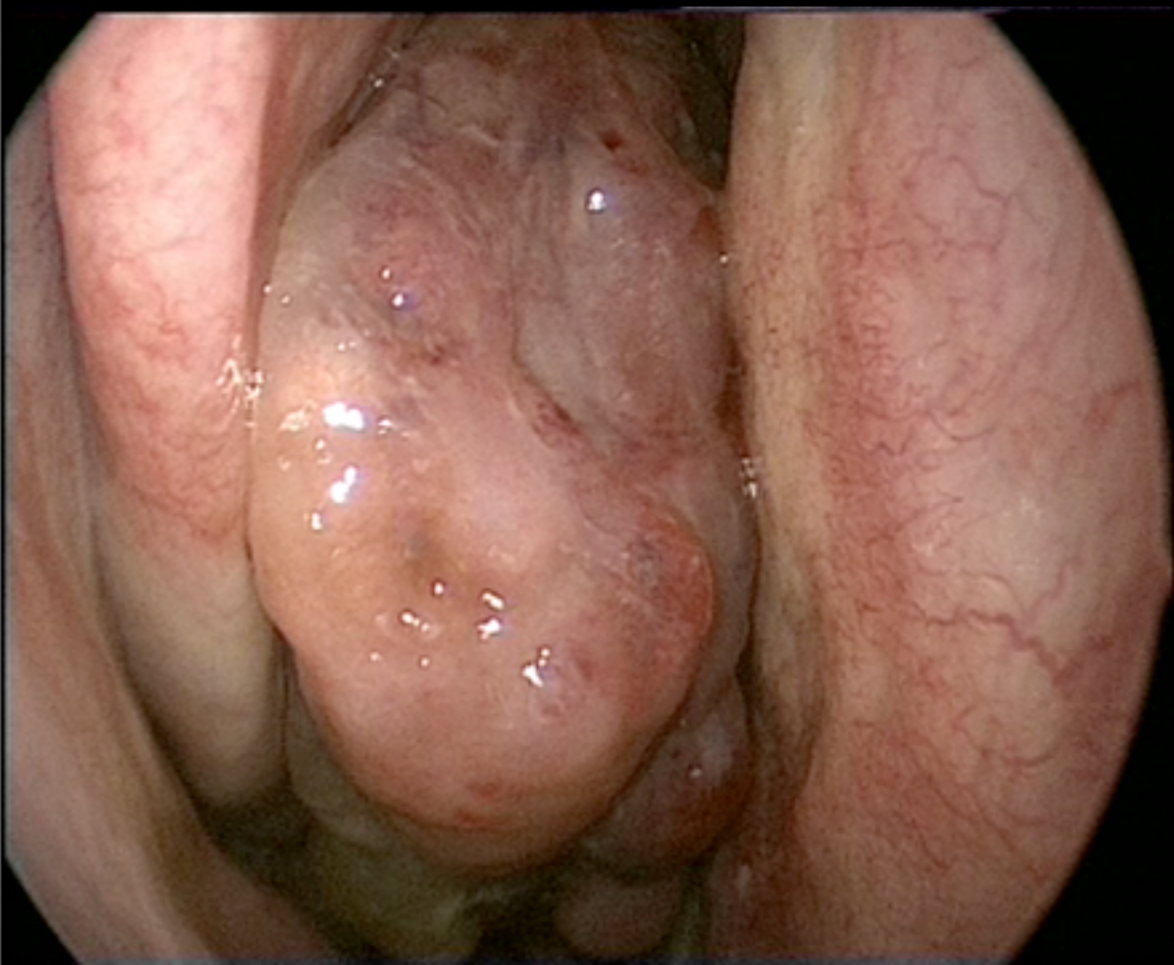
Removal of bone in contact with the tumor (skull base, lamina papyracea)

Removal of periorbita, dura, olfactory bulb(s)

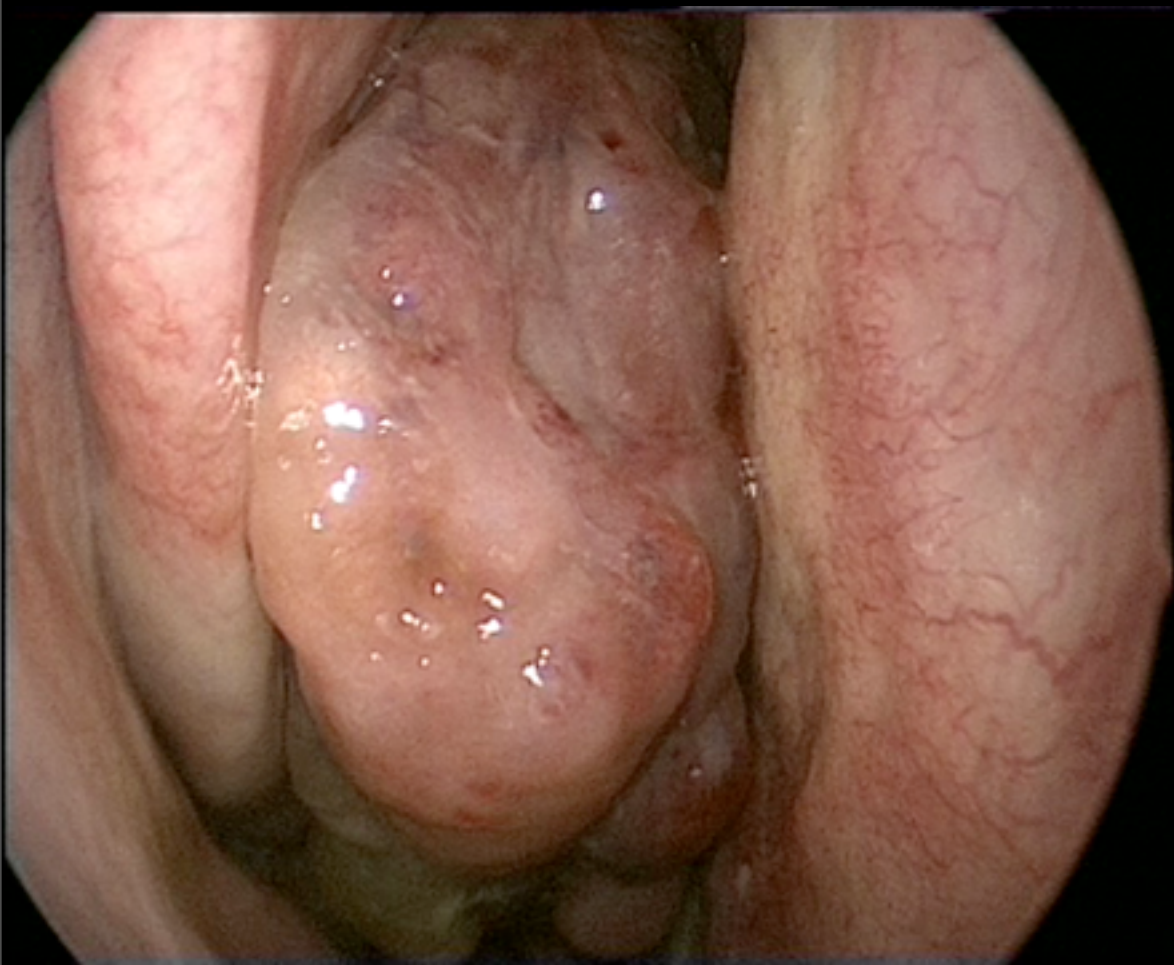
Duraplasty and skull base reconstruction



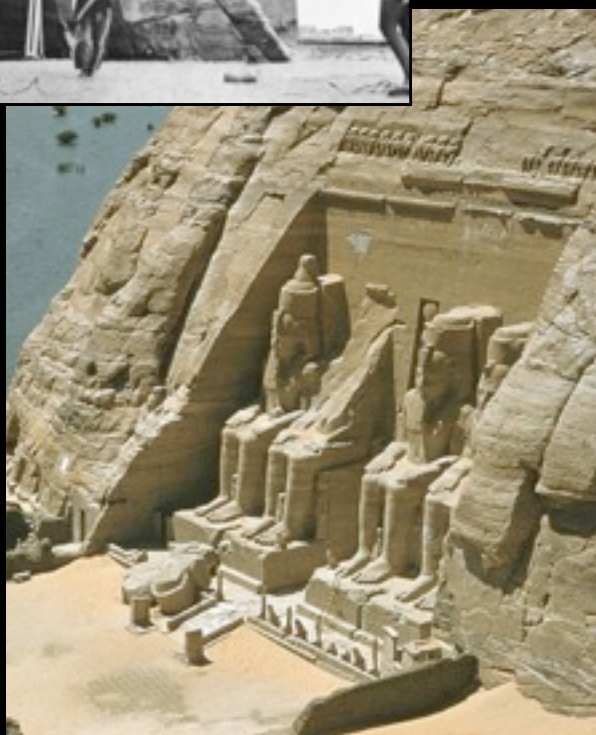
1. Debulking

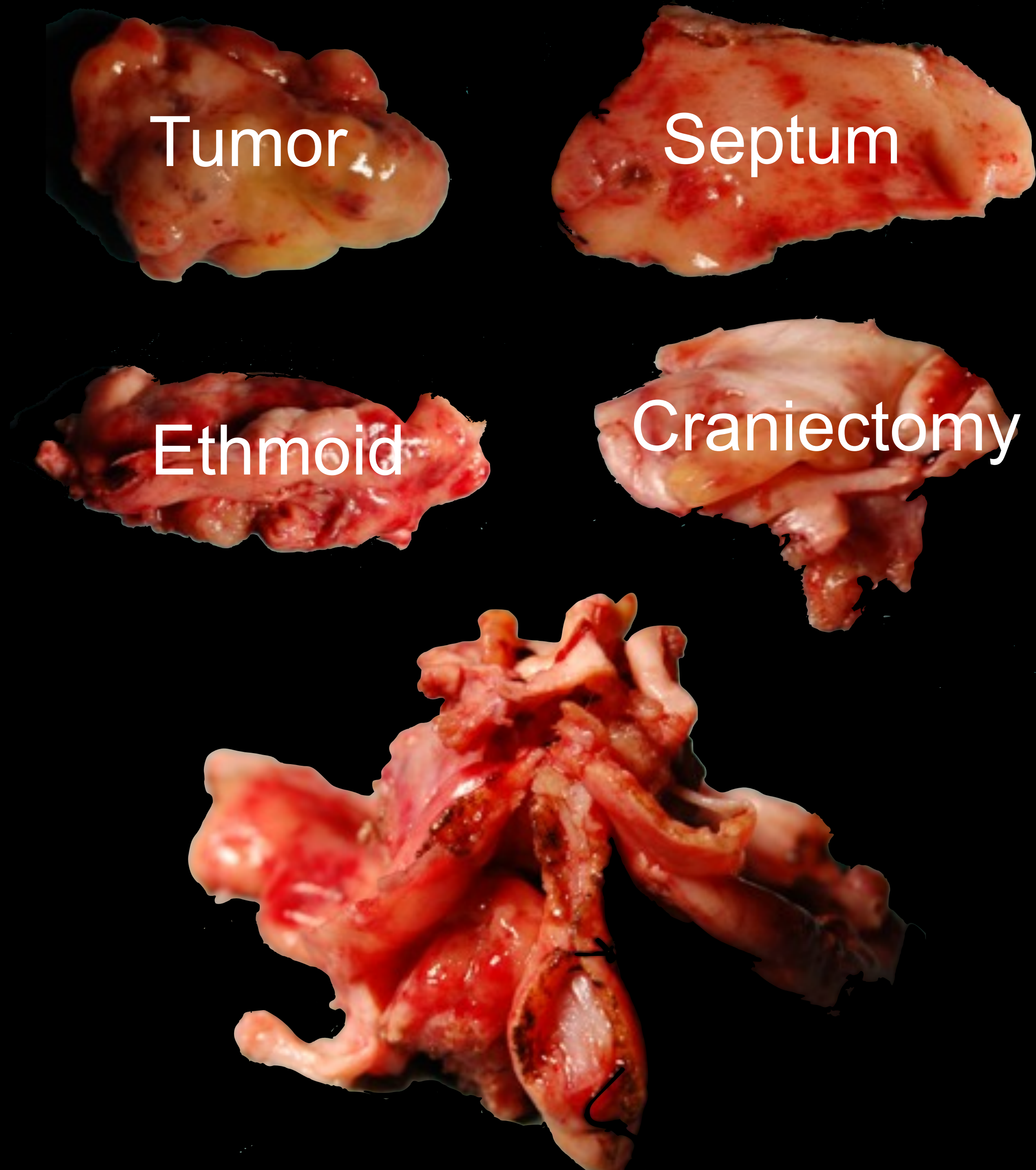


1. Debulking

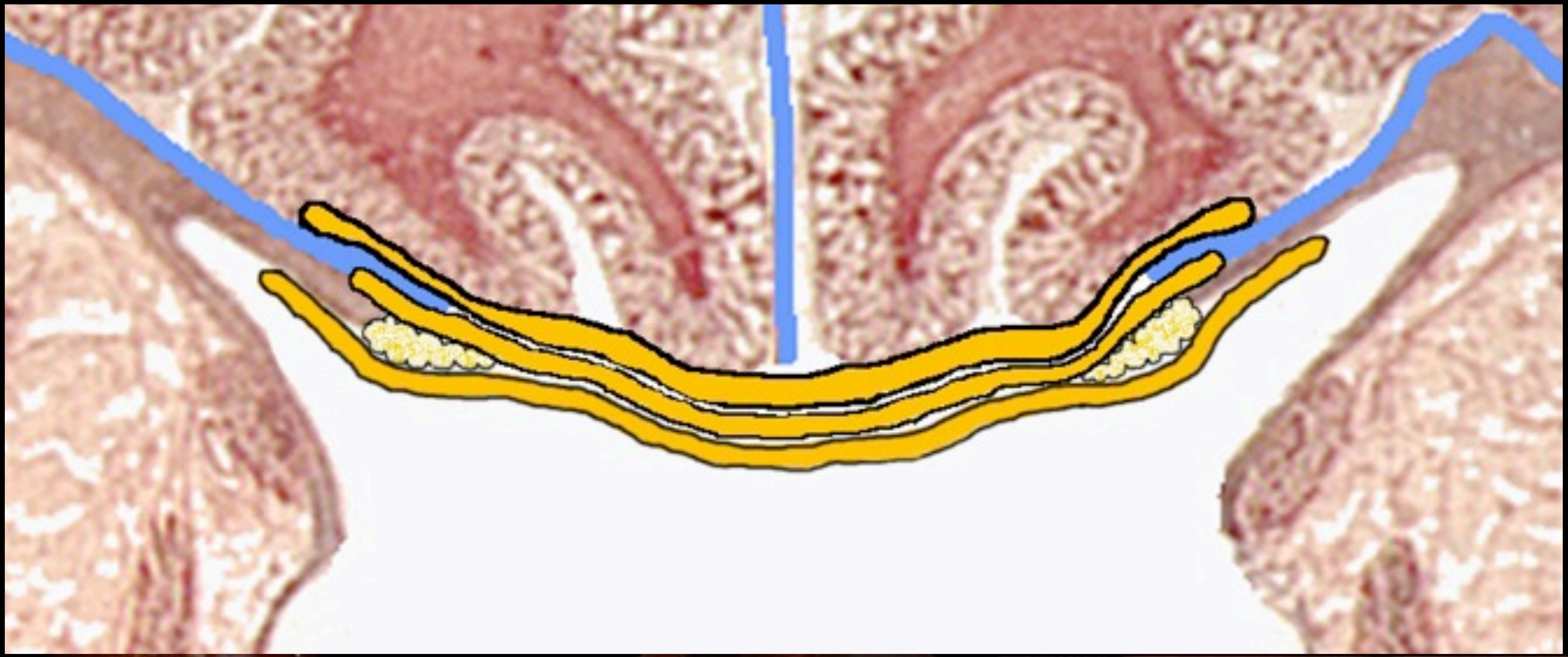


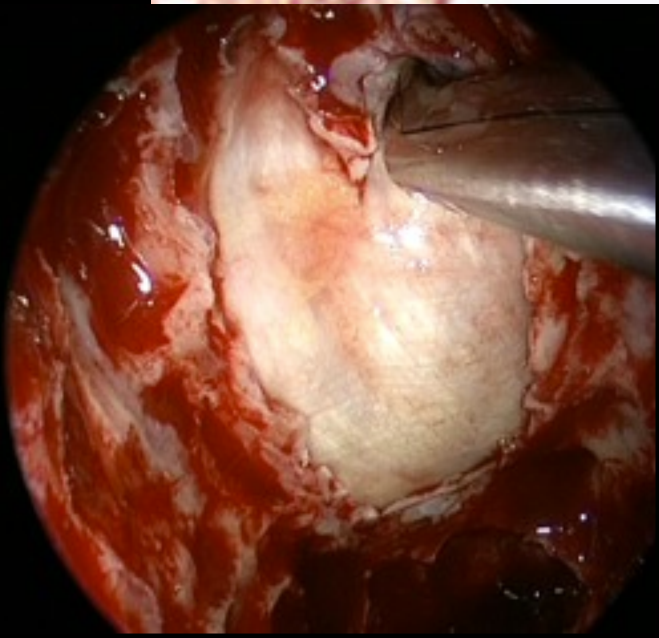
SURGICAL TECHNIQUE

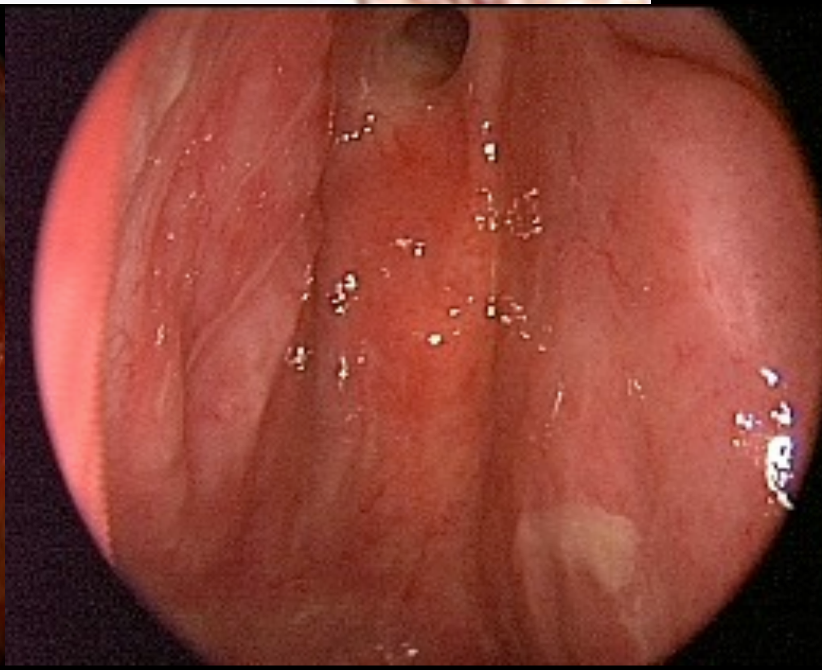




SURGICAL TECHNIQUE







RESULTS

Two surgical teams with the same philosophy

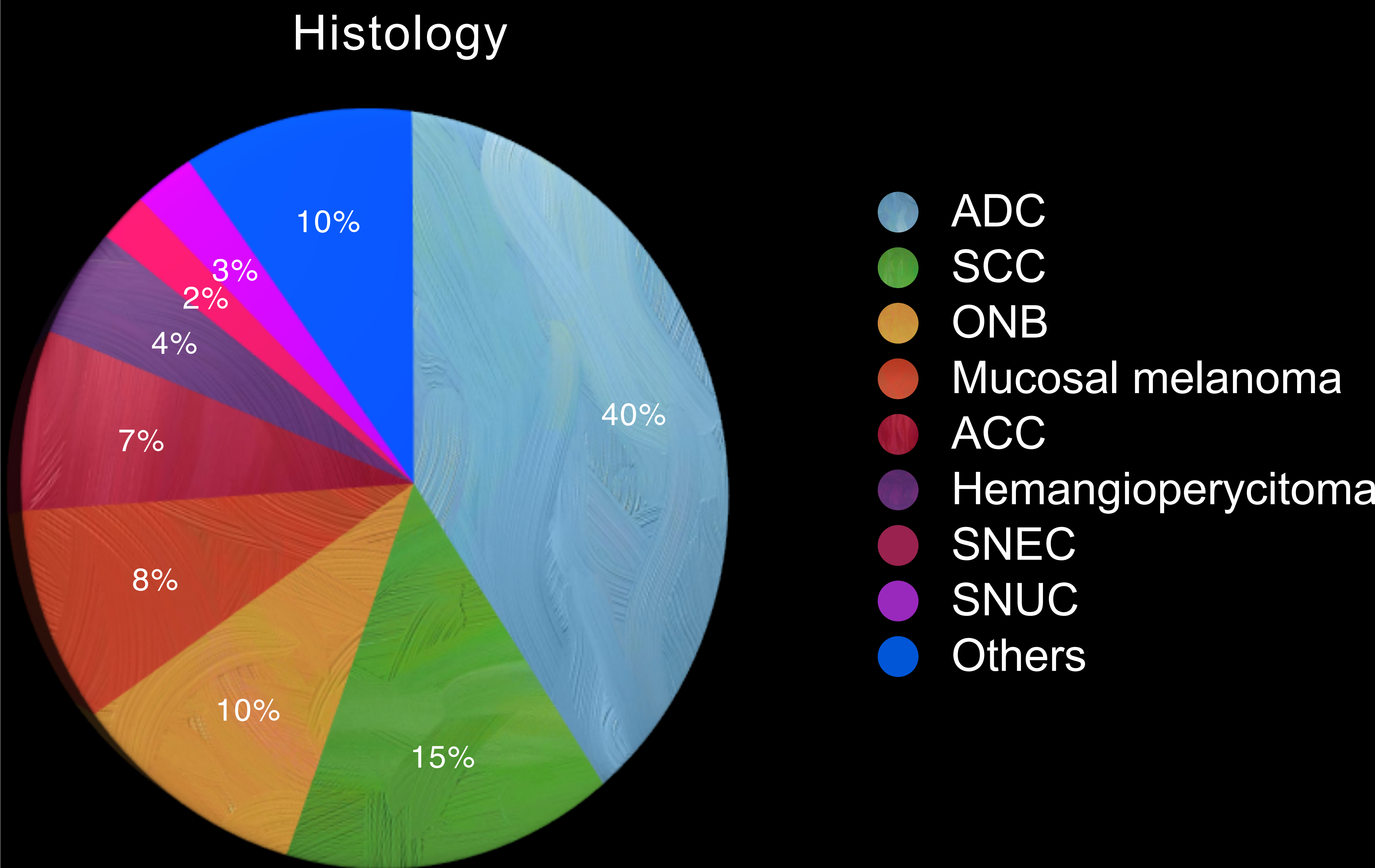
1996-2011: 387 pts

Mean age=61.1 years (range 4-89),

M/F=1.97/1

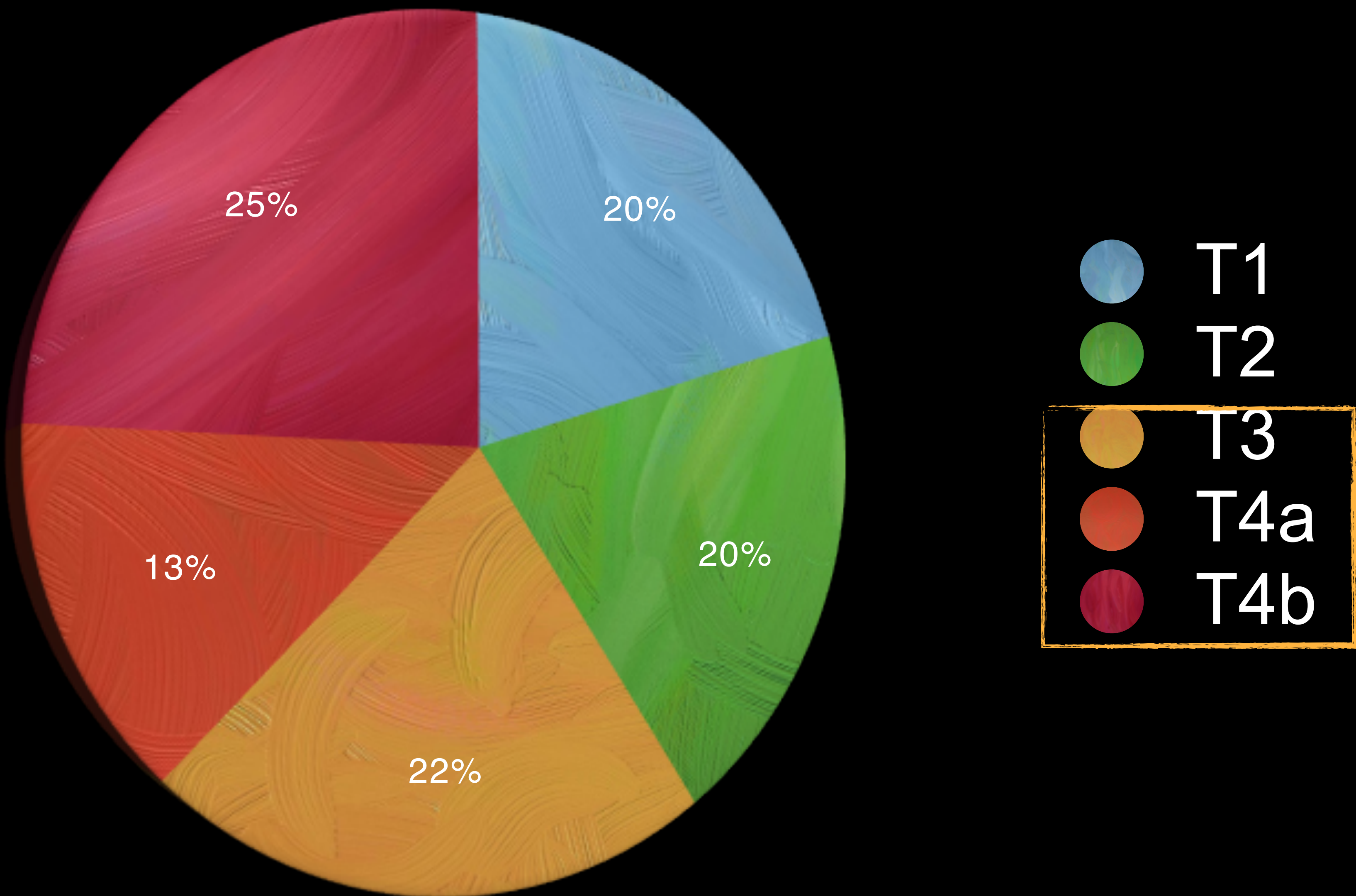
Mean follow-up=56 months (range 12-196)

RESULTS


Histology
10%
3%
2%
4%
7%
8%
10%
15%
40%
ADC
SCC
ONB
Mucosal melanoma
ACC
Hemangioperycitoma
SNEC
SNUC
Others

RESULTS

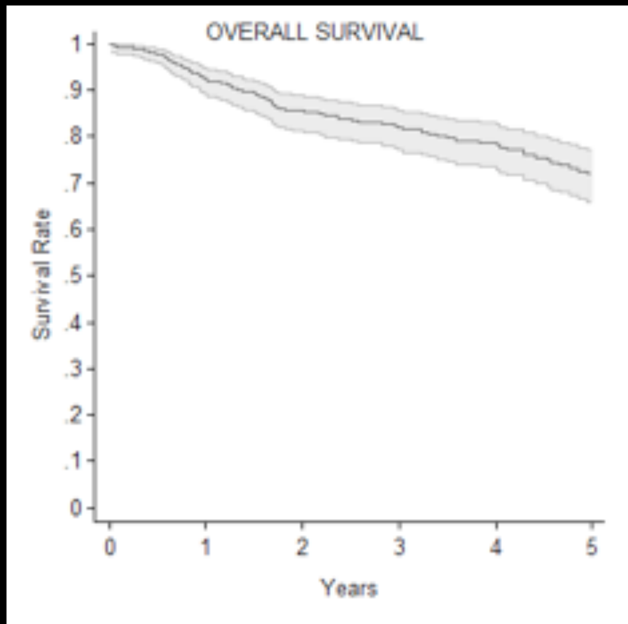
T-staging (AJCC 2010)

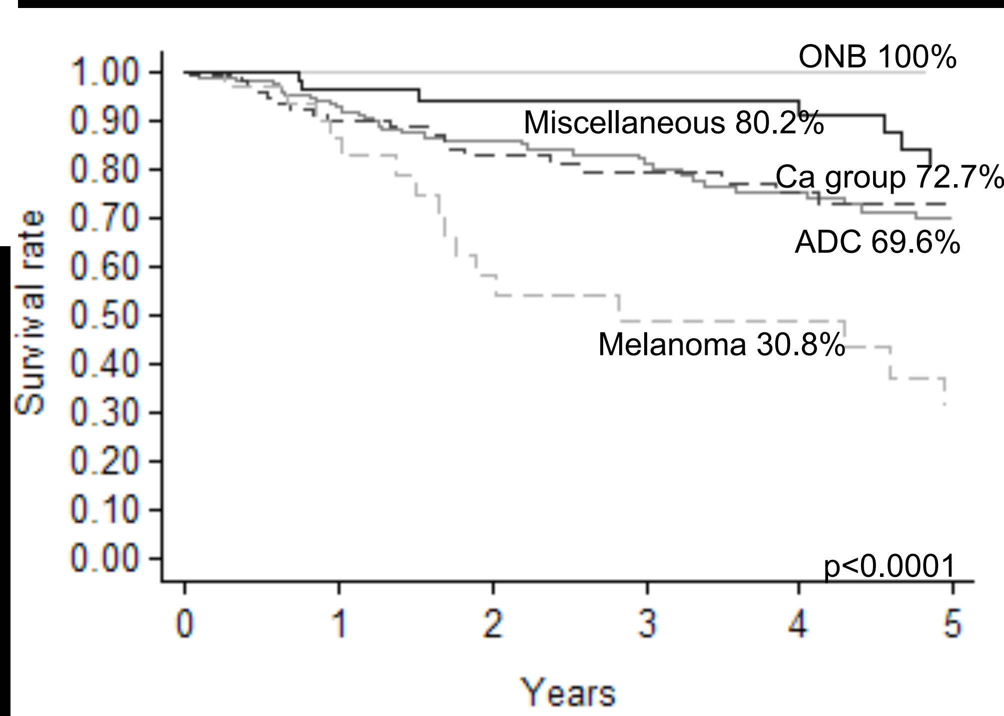


RESULTS

5-year overall survival (histology)

N= 387 pts





ADENOCARCINOMA

Intestinal type adenocarcinoma of the ethmoid: Outcomes of a treatment regimen based on endoscopic surgery with or without radiotherapy

Piero Nicolai, MD,[1*] Alberto Schreiber, MD,[1] Andrea Bolzoni Villaret, MD,[1] Davide Lombardi, MD,[1] Laura Morassi, MD,[2] Elena Raffetti, MD,[3] Francesco Donato, MD,[3] Paolo Battaglia, MD,[4] Mario Turri–Zanoni, MD,[4] Maurizio Bignami, MD[4] Paolo Castelnuovo, MD[4]

[1]Unit of Otorhinolaryngology,, University of Brescia, Brescia, Italy, [2]Unit of Pathology, University of Brescia, Brescia, Italy, [3]Unit of Epidemiology and Public Health, University of Brescia, Brescia, Italy, [4]Unit of Otorhinolaryngology, Insubria University, Varese, Italy.

Original Article

Head Neck 2015

Accepted 31 May 2015

Treatment Strategies for Primary Early-Stage Sinonasal Adenocarcinoma: A Retrospective Bi-institutional Case-Control Study

Journal of Surgical Oncology

MARIO TURRI-ZANONI, MD,[1,2*] PAOLO BATTAGLIA, MD,[1,2] ALESSIA LAMBERTONI, MD,[1] MARTA GIOVANNARDI, MS,[3] ALBERTO SCHREIBER, MD,[4] LUCA VOLPI, MD,[1] ANDREA BOLZONI-VILLARET, MD,[4] DAVIDE LOMBARDI, MD,[4] MAURIZIO BIGNAMI, MD,[1] FRANCESCA MAGNOLI, MD,[5] CARLA FACCO, MD,[5] PAOLO ANTOGNONI, MD,[6] PIERO NICOLAI, MD,[4] AND PAOLO CASTELNUOVO, MD[1,2]

2015

169 patients

October 1997 - September 2013

100% ITAC

Mean age **66** years

Median follow-up **42.8** months (1-170)

Male **89%**

Ethmoid **100%**

Our experience

Previous treatment
(S and/or RT and/or
CHT)
25%

EER	38	(22.5%)
ERTC	103	(60.9%)
CER	28	(16.6%)

Pathological stage

pT0	1	(0.6%)
pT1	34	(20.1%)
pT2	48	(28.4%)
pT3	32	(18.9%)
pT4a	11	(6.6%)
pT4b	43	(25.4%)

Positive margins 18 (**10.6%**)

3 pT3, 1 pT4a, 14 pT4b

Adjuvant RT 99 (**58.6**%)

Nicolai et al, Head Neck 2015

ADENOCARCINOMA

Median follow-up **42.8** months (1-170)

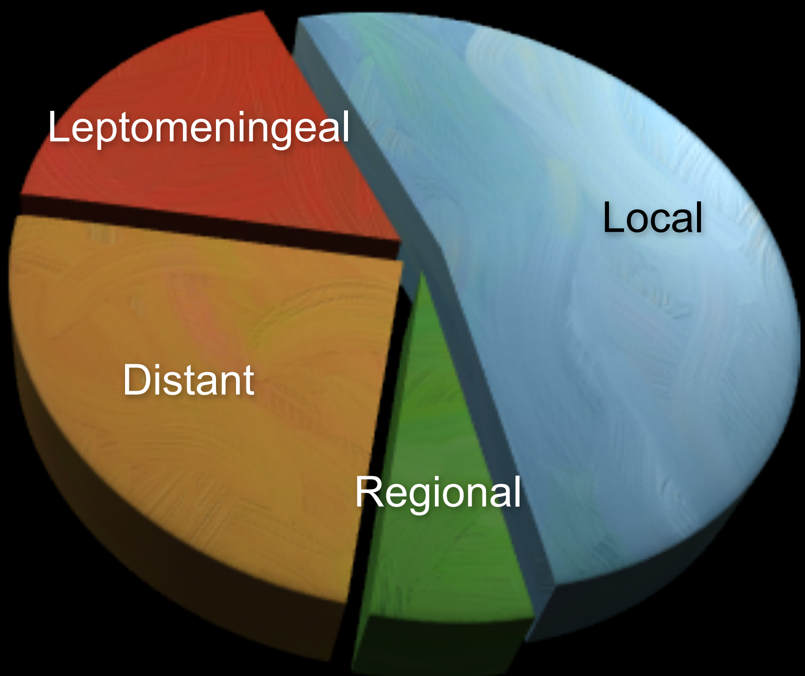
Recurrences **36/169 (21.3%)**

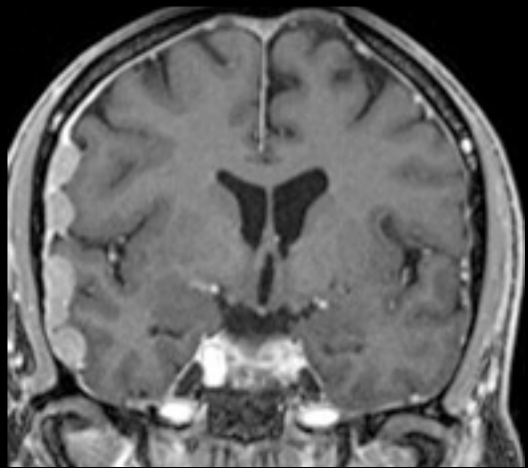
Local	**16.1%**
Distant	**7.1%**
Leptomeningeal	**5.3%**
Regional	**1.8%**

Distant metastasis:

- 6 brain
- 4 bone
- 4 lung
- 2 liver

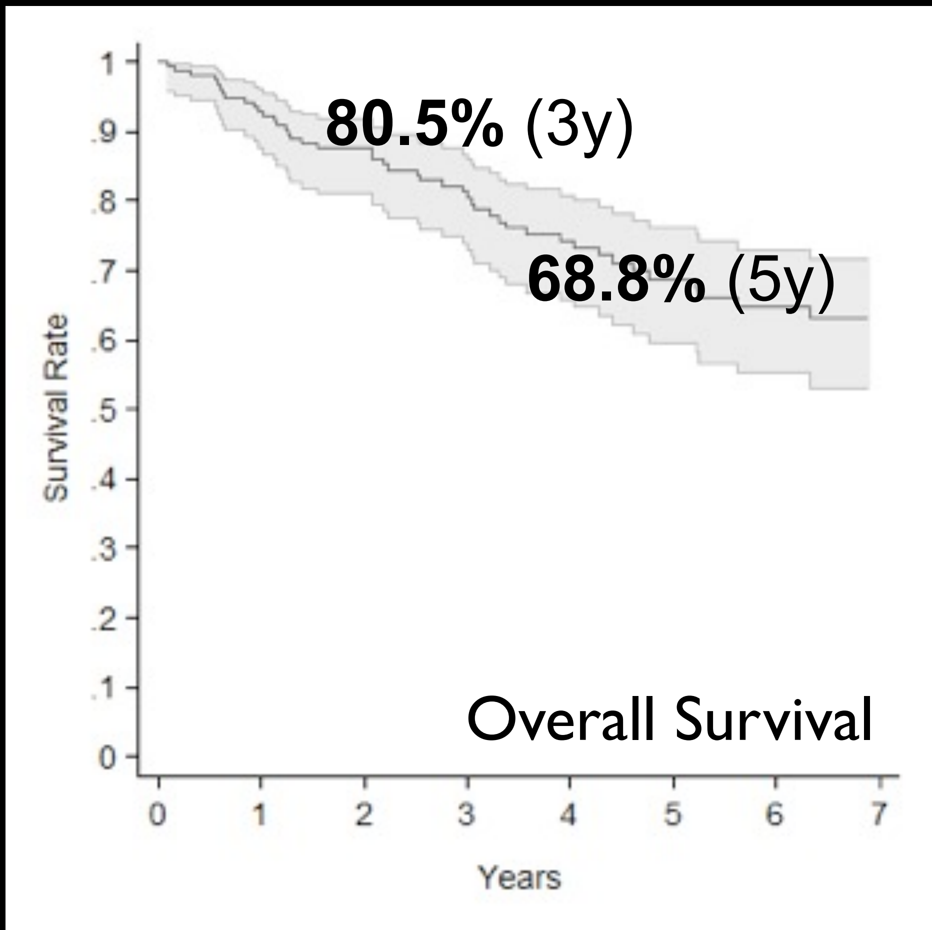
9 leptomeningeal

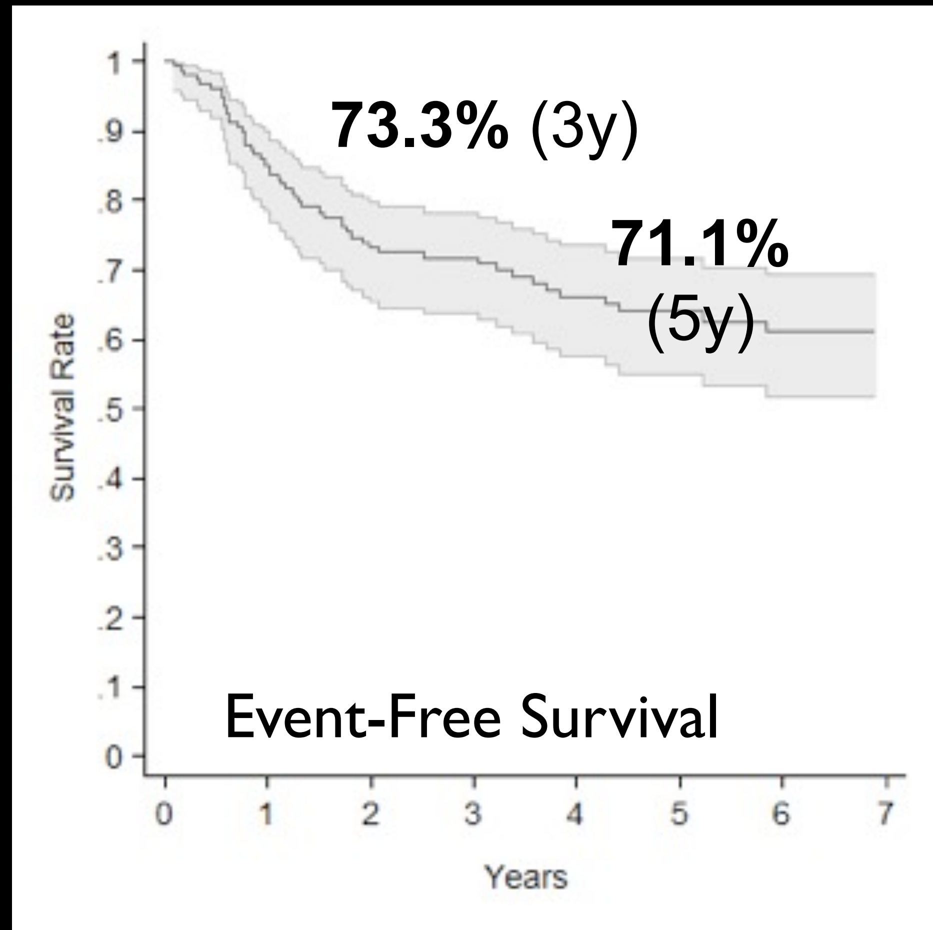




Nicolai et al, Head Neck 2015

ADENOCARCINOMA





Nicolai et al, Head Neck 2015

ADENOCARCINOMA

Variable	Category	Cox regression model Overall survival		Cox regression model Event free survival		Competing risk model	
		HR (CI 95%)*	P value	HR (CI 95%)*	P value	SHR (CI 95%)*	P value
pT stage	T1-T2	Ref.		Ref.		Ref.	
	T3-T4a	1.92 (0.85-4.34)	0.116	2.10 (1.03-4.25)	**0.040**	2.57 (0.64-10.30)	0.183
	T4b	3.15 (1.39-7.14)	**0.006**	2.35 (1.10-5.02)	**0.027**	6.24 (1.64-23.80)	**0.007**
Grading	1	Ref.		Ref.		Ref.	
	2	1.70 (0.59-4.9)	0.326	2.35 (0.82-6.71)	0.111	2.57 (0.60-11.02)	0.205
	3	3.31 (1.06-10.35)	**0.040**	4.52 (1.44-14.19)	**0.010**	5.69 (1.08-29.88)	**0.040**
Surgical margins	Positive vs Negative	3.50 (1.71-7.18)	**0.001**	3.29 (1.63-6.64)	**0.001**	5.33 (2.15-13.22)	**<0.001**

*Adjusted for all the variables in the table. HR: Hazard Ratio, SHR: Subhazard Ratio.

Stage **pT4b** (pT3-T4a for EFS), **high grading (G3)**, and **positive margins** were independently associated with a higher risk of death

Nicolai et al, Head Neck 2015

SINONASAL CANCER

Maxillary cancer

MAXILLECTOMIES

Classification

(Medial maxillectomy)

Inferior maxillectomy

Subtotal maxillectomy

Radical maxillectomy

Extended radical maxi

Surgical access

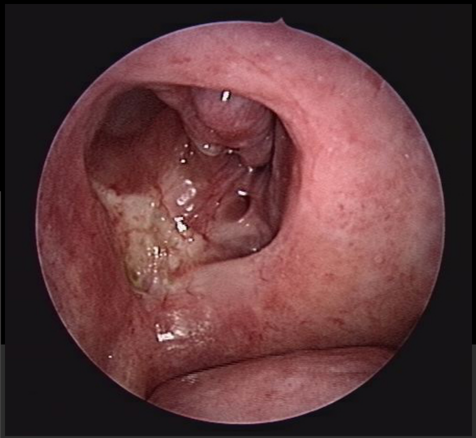
Transoral

Midfacial degloving

Lateral rhinotomy

(Weber-Ferguson

incision)



SINONASAL CANCER

Maxillary cancer

GOALS OF RECONSTRUCTION

- Separation of the sinonasal tract from the oral cavity
- Dental/Prosthetic rehabilitation
- Soft tissue and/or bony augmentation of the midfacial area to provide support to the orbital content and to re-establish facial contour
- Separation of the cranial cavity from the sinonasal tract
- Filling of the orbital cavity or its lining when an ocular prosthesis is planned

SINONASAL CANCER

Maxillary cancer

MANAGEMENT OF SURGICAL DEFECTS

Prosthesis vs. Reconstruction

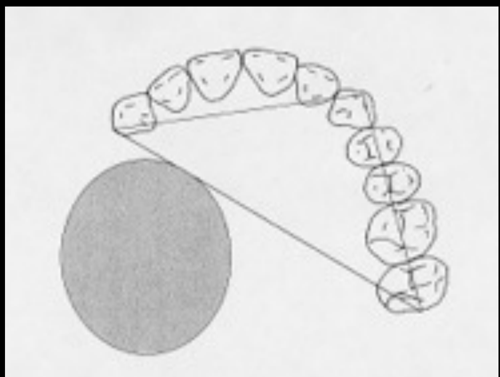
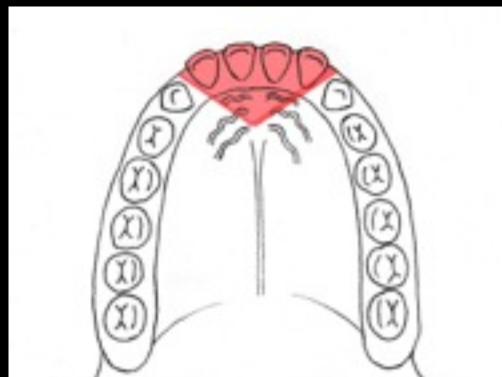
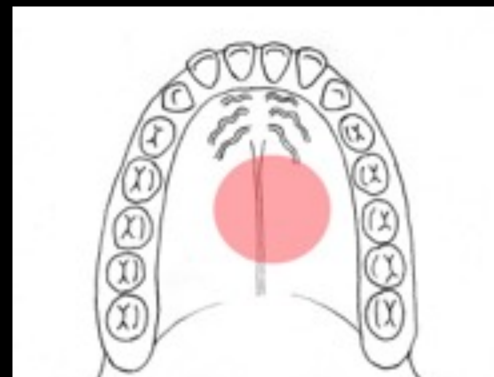
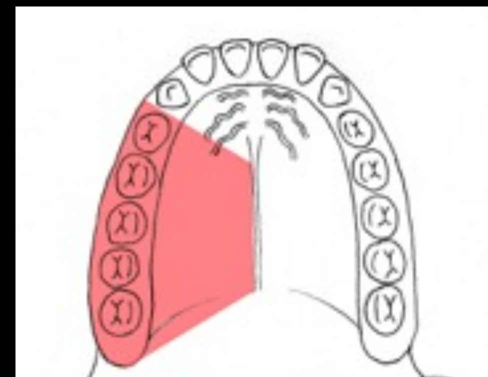
Obturator
Epithesis

Pedicled flaps
Free flaps

COMBINATION OF BOTH

PARTIAL INFERIOR MAXILLECTOMY

Obturator or buccal fat pad

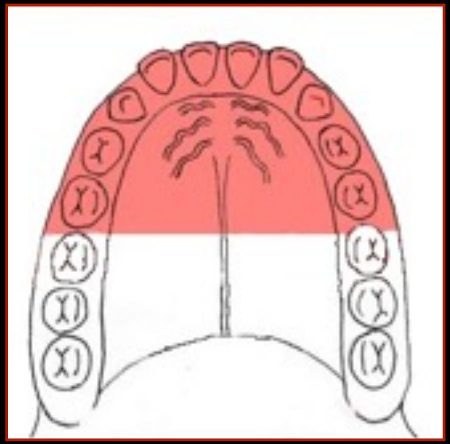





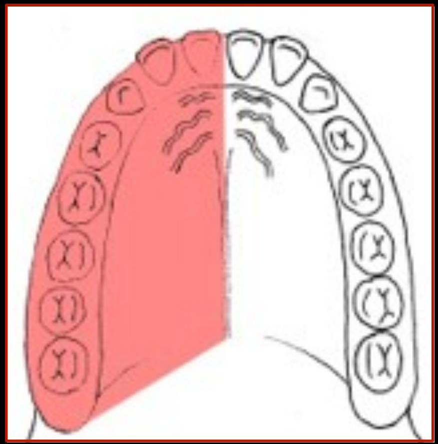




HEMI/SUBTOTAL INFERIOR MAXILLECTOMY

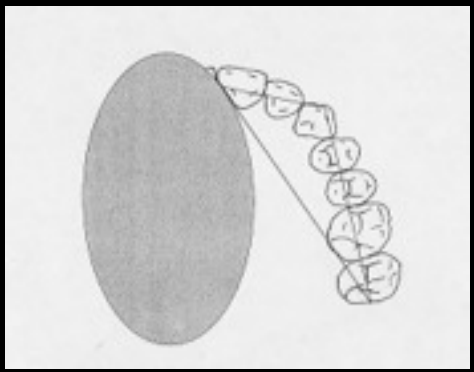
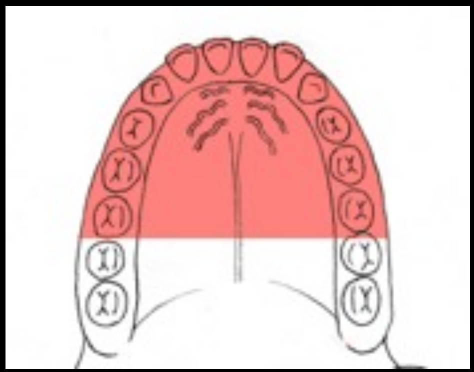
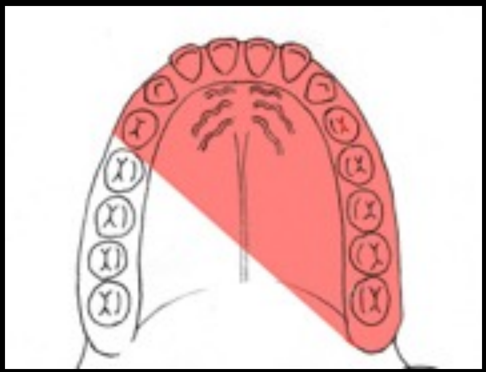
Class II - Obturator

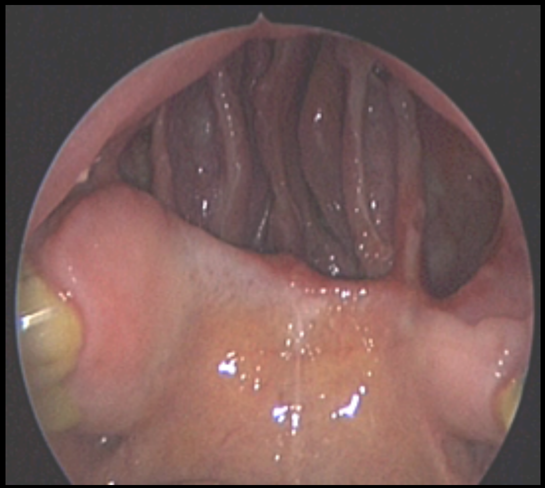
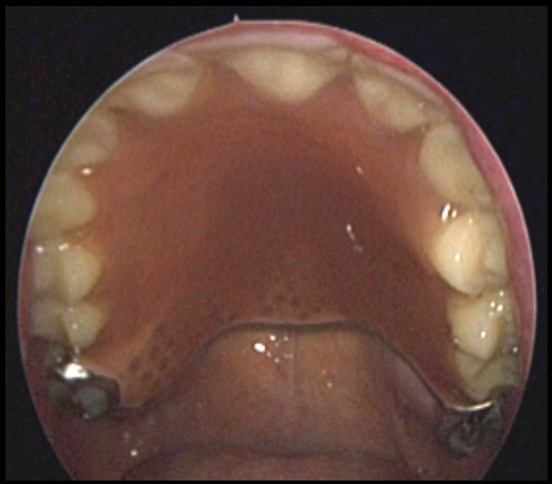




SUBTOTAL INFERIOR MAXILLECTOMY

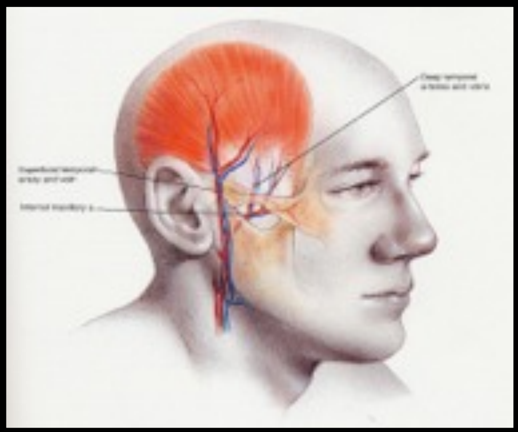
Obturator

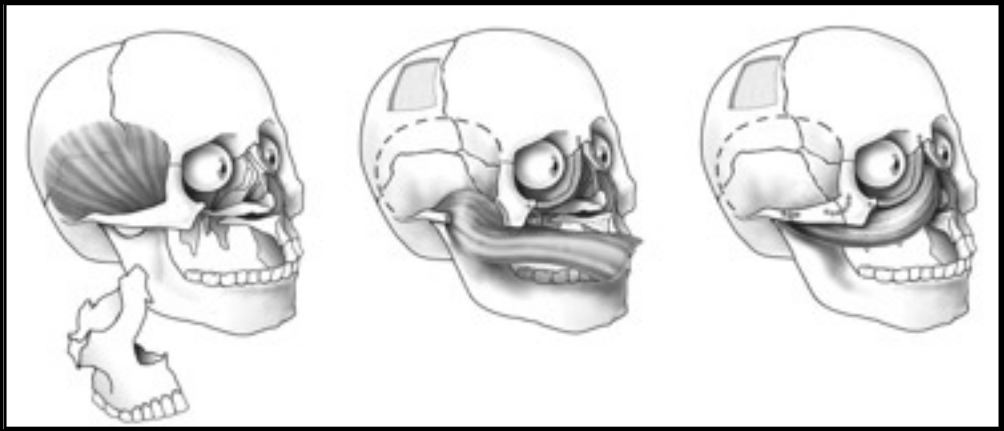




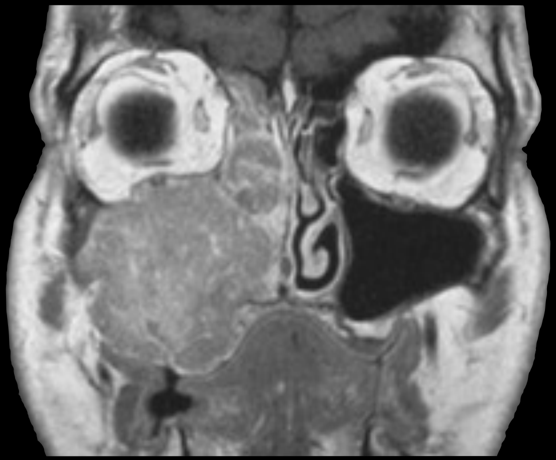



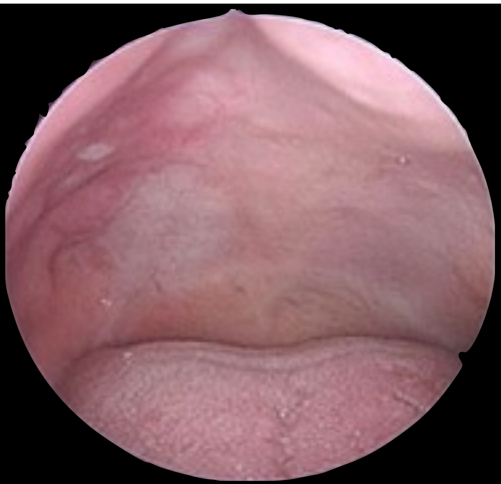
HEMI/SUBTOTAL INFERIOR MAXILLECTOMY

Temporalis muscle



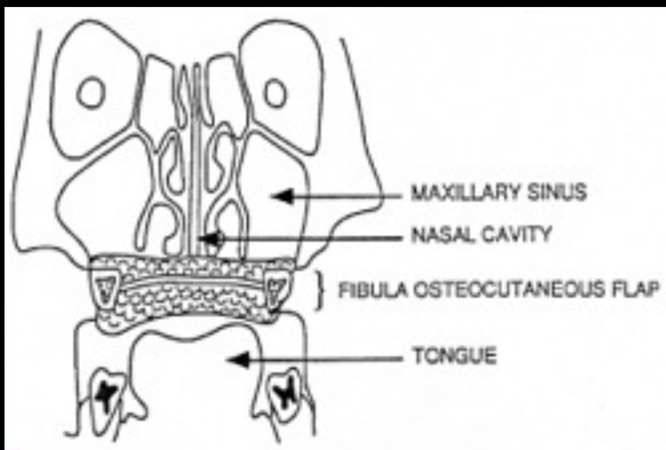


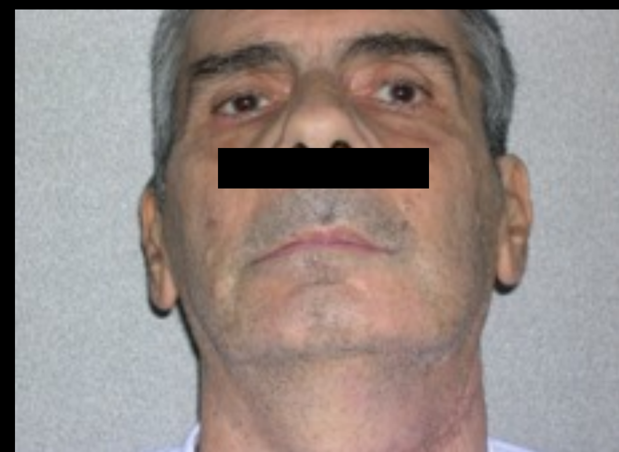




BILATERAL INFERIOR MAXILLECTOMY

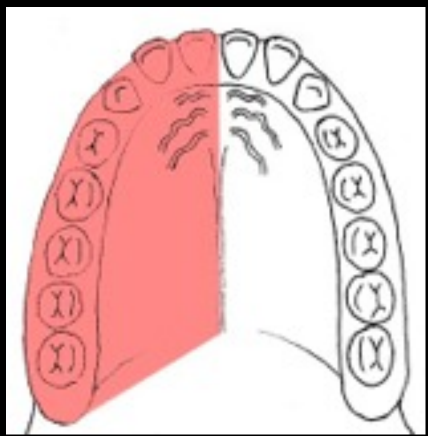
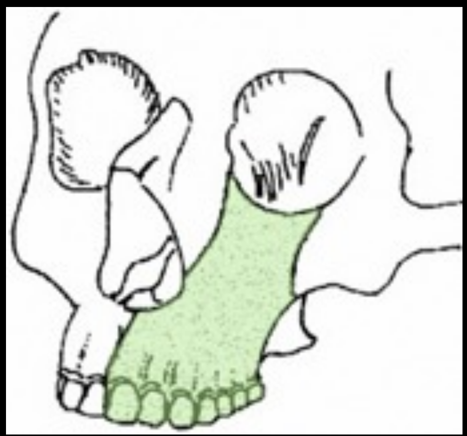
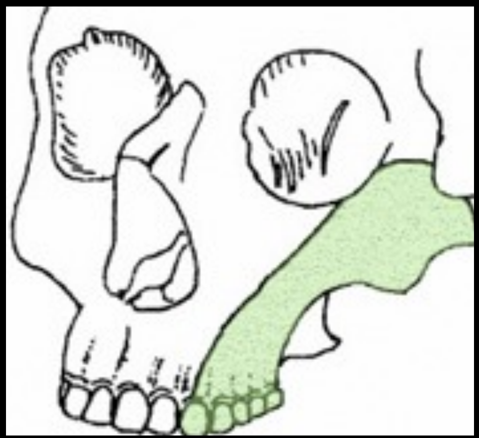
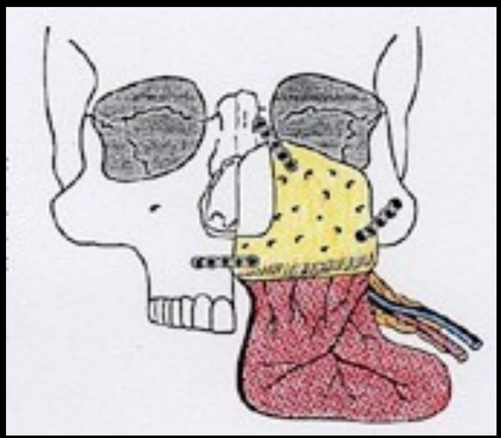
Class III - Fibula





TOTAL MAXILLECTOMY

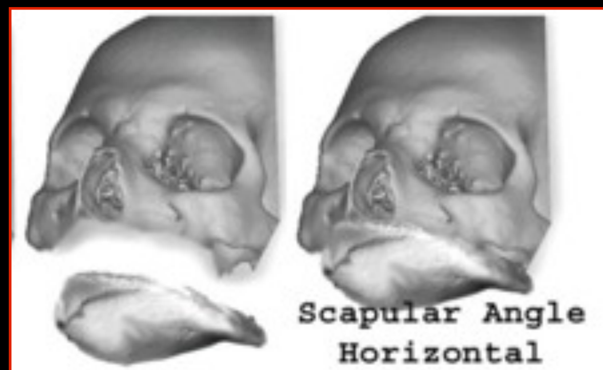
Iliac crest

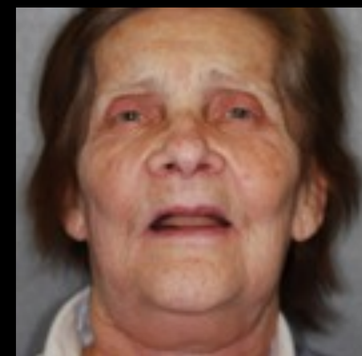





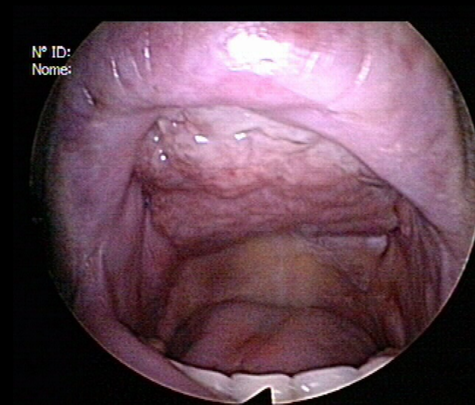


BILATERAL INFERIOR MAXILLECTOMY

Class III - Tip of scapula flap

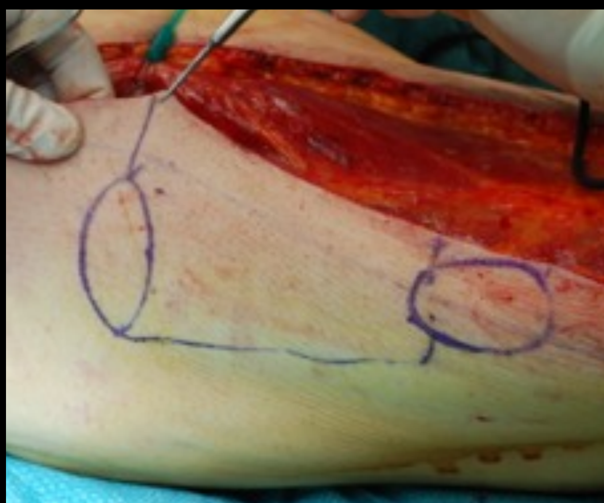






EXTENDED MAXILLECTOMY

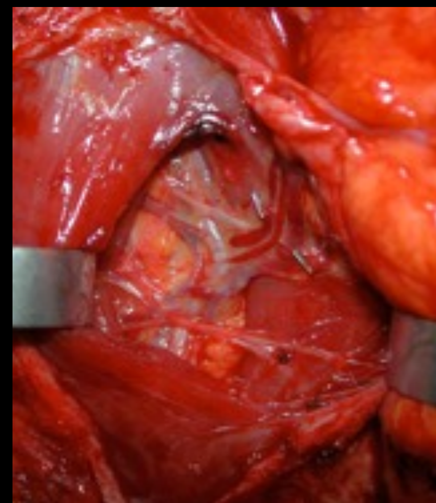
Anterolateral thigh flap

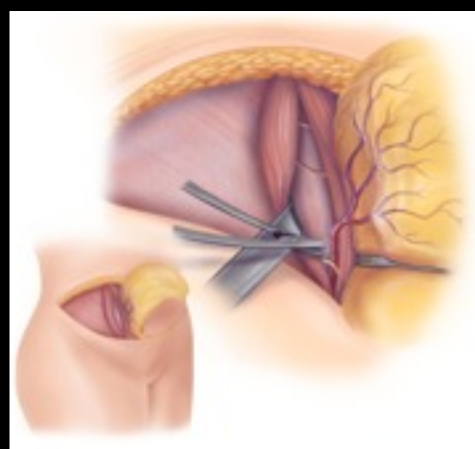


EXTENDED MAXILLECTOMY

Rectus abdominis flap

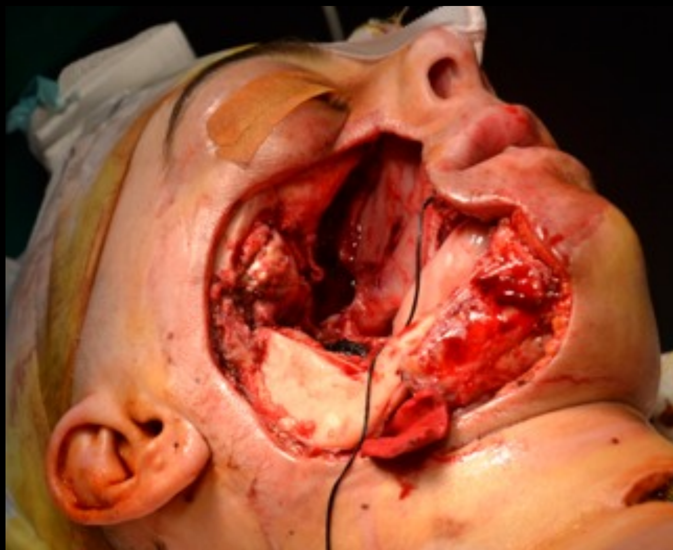


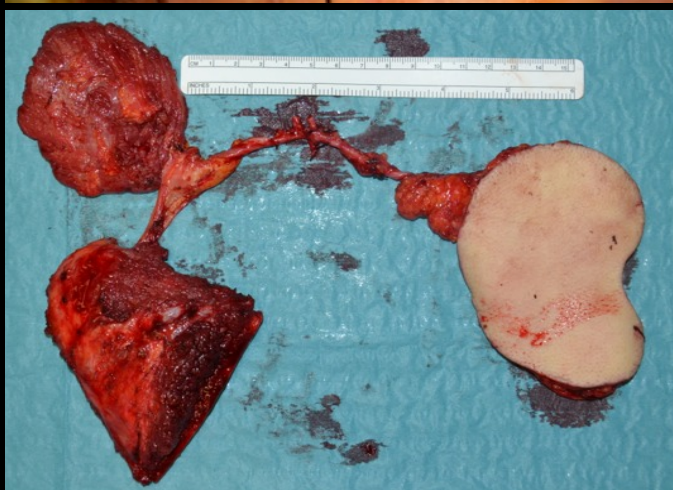


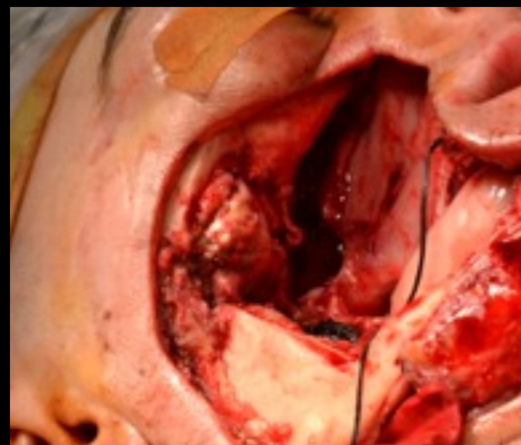


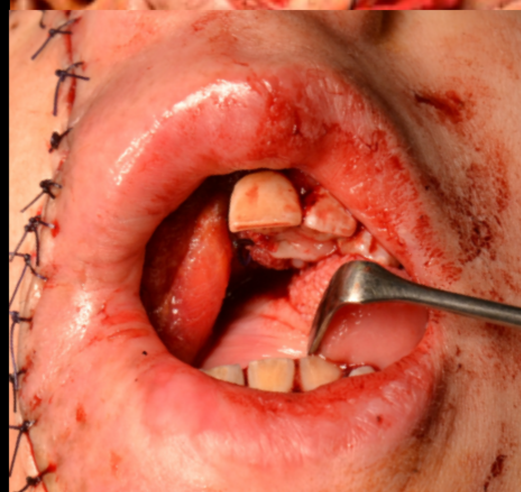
COMPLEX MAXILLOFACIAL RECONSTRUCTIONS

Chimeric flaps





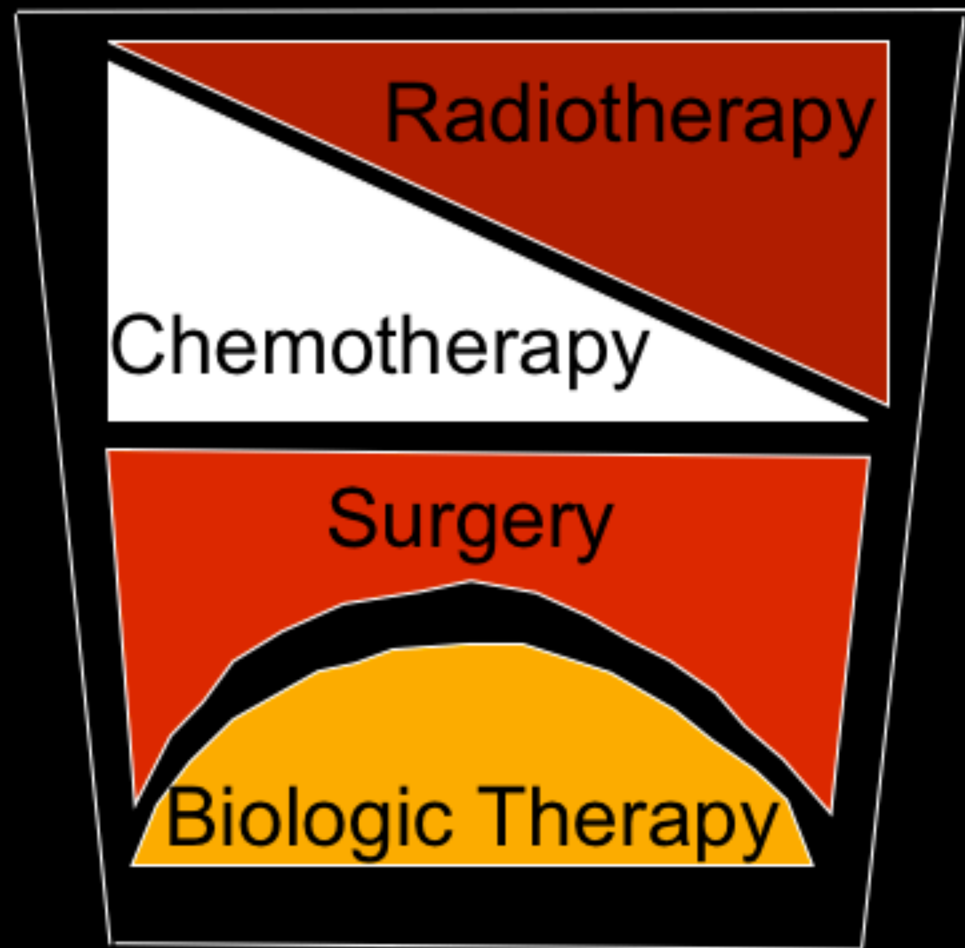




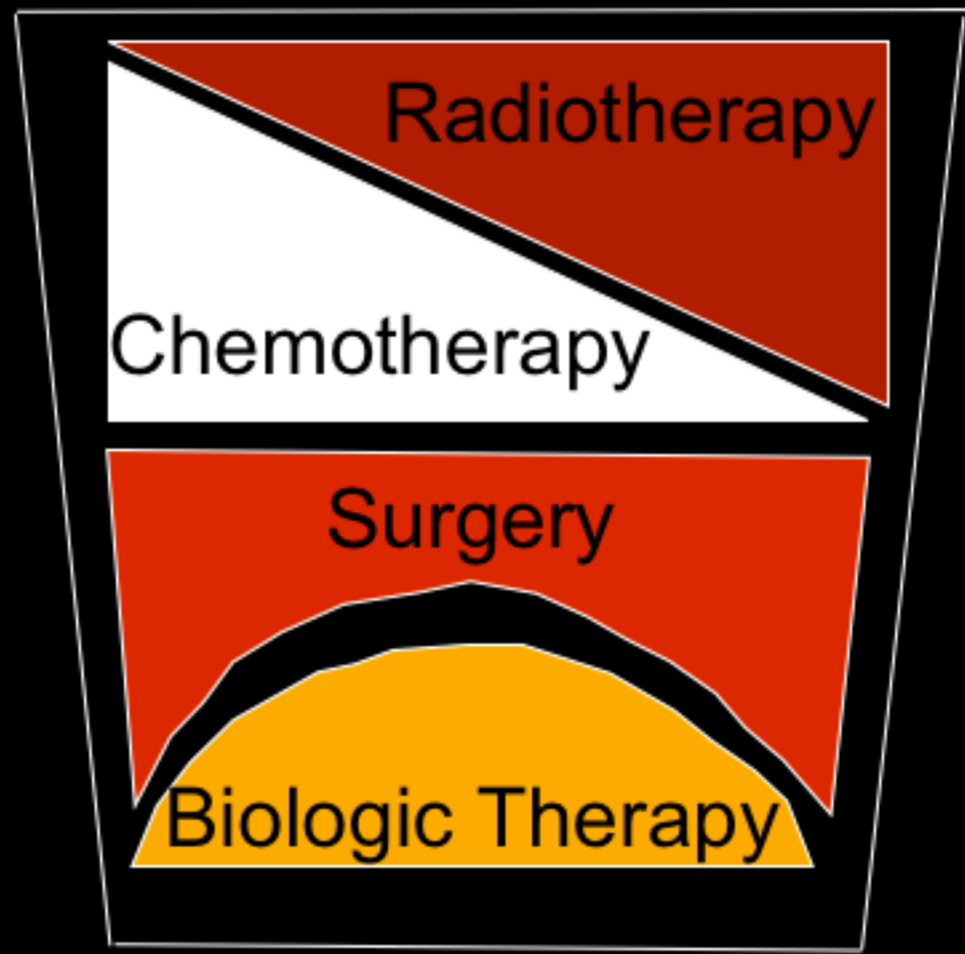
10 days after surgery

PATIENT-TAILORED TREATMENT

PATIENT-TAILORED TREATMENT



The right mixture



PATIENT-TAILORED TREATMENT

Multidisciplinary approach for poor prognosis sinonasal tumors: Phase II study of chemotherapy, surgery, photon and heavy ion radiotherapy integration for more effective and less toxic treatment in operable patients.

Protocol Code:	SINTART1
Therapeutic Area:	Oncology
Principal investigator	Lisa Licitra, MD, Fondazione IRCCS Istituto Nazionale Tumori Medical Oncology Unit Via Venezian, 1 20133 Milan Italy

RATIONALE

"...This study proposes innovative integration of ***multiple modality*** *of treatment* ***modulated by histology, molecular profile and response to induction CHT****. Moreover, heavy ion RT combined with photon RT allows the use of latest technology with greater biological effectiveness and reduction of toxicities..."*

Multidisciplinary approach for poor prognosis sinonasal tumors: Phase II study of chemotherapy, photon and heavy ion radiotherapy integration for more effective and less toxic treatment in inoperable patients.

Protocol Code:	SINTART2
Therapeutic Area:	Oncology
Principal investigator	Lisa Licitra, MD, Fondazione IRCCS Istituto Nazionale Tumori Medical Oncology Unit Via Venezian, 1 20133 Milan Italy

RATIONALE

"...Treatment outcomes for unresectable paranasal sinus carcinoma are poor, and ***combined-modality treatment*** *is needed that is both more effective and associated with less morbidity..."*

Parotid tumors: pathology, surgical and radiotherapy aspects

Piero Nicolai

Unit of Otorhinolaryngology - Head and Neck Surgery

University of Brescia, Italy

EPIDEMIOLOGY

SALIVARY GLAND TUMORS

- 3-4% of all head and neck tumors
- 70% of salivary gland tumors arises in the parotid gland
- 75% of the parotid tumors are benign

(Johnson et al. 2014)

SALIVARY GLAND MALIGNANT TUMORS

- 0.3-3% of all malignancies *(De Brito Santos 2001, Harish 2004)*
- 4-6% of all head and neck cancers *(Spiro 1986, Tran et al. 1986, Dillard et al. 2001)*
- Incidence SGMT: 4-135 / 1.000.000

HISTOLOGY

MALIGNANT TUMORS

PRIMITIVE TUMORS

Epithelial

Mesenchymal

- Hemangiopercytoma
- Malignant schwannoma
- Malignant fibrous histiocytoma

Lymphomas

- MALT
- Non-Hodgkin
- Hodgkin

LYMPH NODE METs

Head and neck skin malignancies

Nasopharyngeal carcinoma

Paranasal sinus tumors

Tumors of the conjunctiva

Tumors of the lacrimal gland

DISTANT METs

Mammary carcinoma

Renal cell carcinoma

Lung carcinoma

Sarcomas

HISTOLOGY

EPITHELIAL MALIGNANT TUMORS

LOW GRADE

MEC low grade

Acinic cell carcinoma

Polymorphus low grade ADC

Basal cell carcinoma

ADC NOS low grade

Clear cell carcinoma

Epithelial-myoepithelial carcinoma low grade

Papillary ADC

MEC intermediate grade

ACC

G1-G2 / G3

HIGH GRADE

MEC high grade

Salivary duct carcinoma

ADC NOS high grade

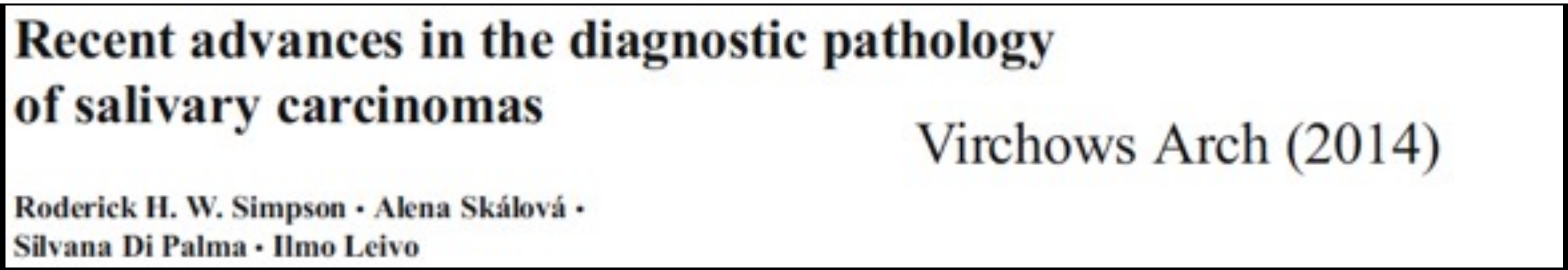
Carcinoma ex-pleomorphic adenoma

Epithelial-myoepithelial carcinoma high grade

Oncocytic carcinoma

Ellis and Auclair: "Tumors of the salivary glands", AFIP 1996

HISTOLOGY


Recent advances in the diagnostic pathology of salivary carcinomas

Virchows Arch (2014)

Roderick H. W. Simpson • Alena Skálová • Silvana Di Palma • Ilmo Leivo

NEW HISTOLOGIC ENTITIES

MAMMARY ANALOGUE SECRETORY CARCINOMA

Commonest location: parotid gland

ETV6-NTRK chromosomal translocation almost every case

Differential diagnosis: acinic cell carcinoma

High grade transformation: possible

CRIBRIFORM ADENOCARCINOMA OF THE TONGUE AND MSGs

Only minor salivary glands involved

Relatively high risk of nodal metastasis at presentation (60%)

Rearrangement of PRKD genes found in more than 80% of the cases

Differential diagnosis: polymorphus low grade adenocarcinoma

Good prognosis

HISTOLOGY

Recent advances in the diagnostic pathology of salivary carcinomas

Virchows Arch (2014)

Roderick H. W. Simpson · Alena Skálová · Silvana Di Palma · Ilmo Leivo

NEW FINDINGS IN ESTABLISHED ENTITIES

HIGH GRADE TRANSFORMATION OF ADENOID CYSTIC CARCINOMA

Chromosomal translocation leading to over expression of MYB-NFIB fusion proteins controlling proliferation apoptosis, differentiation

DUCTAL CARCINOMA

Overexpression of estrogen receptor Beta-isoform (73%)

Overexpression of androgen receptor (more than 90%)

Clinical activity of androgen deprivation therapy in patients with metastatic/relapsed ARpositive salivary gland cancers

L. Locati, F. Perrone, B. Cortelazzi, et al. Head & Neck (accepted article 2014)

2014

Biology of Human Tumors

Alterations Associated with Androgen Receptor Gene Activation in Salivary Duct Carcinoma of Both Sexes: Potential Therapeutic Ramifications

Yoshitsugu Mitani[1], Pulivarthi H. Rao[2], Sankar N. Maity[3], Yu-Chen Lee[4], Renata Ferrarotto[5], Julian C. Post[1], Lisa Licitra[6], Scott M. Lippman[7], Merrill S. Kies[5], Randal S. Weber[8], Carlos Caulin[8], Sue-Hwa Lin[4], and Adel K. El-Naggar[1,8]

DIAGNOSTIC WORK-UP

Parotid mass

US

Intraparenchymal small nodule

FNAC

Large nodule
Deep lobe
Parapharyngeal extension
Extraparenchymal extension

FNAC + MRI

Widespread increase in volume
Hypervascular lesions

No FNAC; MRI

PET for staging (high grade MT)

DIAGNOSTIC WORK-UP

A Systematic Review and Meta-Analysis of the Diagnostic Accuracy of Fine-Needle Aspiration Cytology for Parotid Gland Lesions

Am J Clin Pathol 2011

Robert L. Schmidt, MD, PhD, MMed, MBA,[1] Brian J. Hall, MD,[1] Andrew R. Wilson, MStat,[2] and Lester J. Layfield, MD[1,2]

FNAC can achieve high specificity and diagnostic accuracy (89% and 85%)

There are significant variations in the performance of FNAC within different practice settings

It is associated with high levels of inadequate diagnoses and missed malignancies especially outside specialist centers

Sensitivity for detecting malignancy has been reported between 70% and 80% and non-diagnostic rates average at 14%-56%

DIAGNOSTIC WORK-UP

FNAC

Sensitivity for MSGTs: 72%

Grading of MSGTs: 46%

Zurrida et al. 1993, Boccato et al. 1998, Stewart et al. 2000, Zbaren et al. 2004

MINIREVIEWS

Biopsy of parotid masses: Review of current techniques

World J Radiol 2016

Sananda Haldar, Joseph D Sinnott, Kemal M Tekeli, Samuel S Turner, David C Howlett

*When compared to FNAC, **Core Biopsy** showed a higher sensitivity (96%) and specificity (100%), a low complication rate (1.6% haematoma rate) and no variation in accuracy between locations (96%)*

Correlation between preoperative predictions and surgical findings in the parotid surgery for tumors

Michael Vaiman[1*], Judith Luckman[2], Tal Sigal[3] and Inessa Bekerman[3]

Head & Face Medicine (2016)

MRI

Pros:

Excellent assessment of the parotid lesion and its local extension

Evaluation of infiltration of soft tissue, cartilage, and bone

Parapharyngeal extension

Perineural spread

Cons:

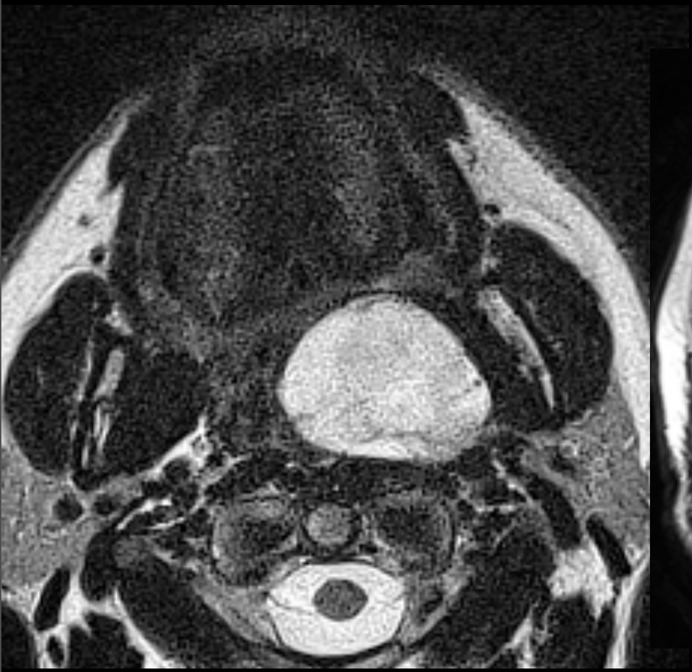
The malignant nature of a low grade lesion is not always predictable

Higher costs and more limited availability than CT

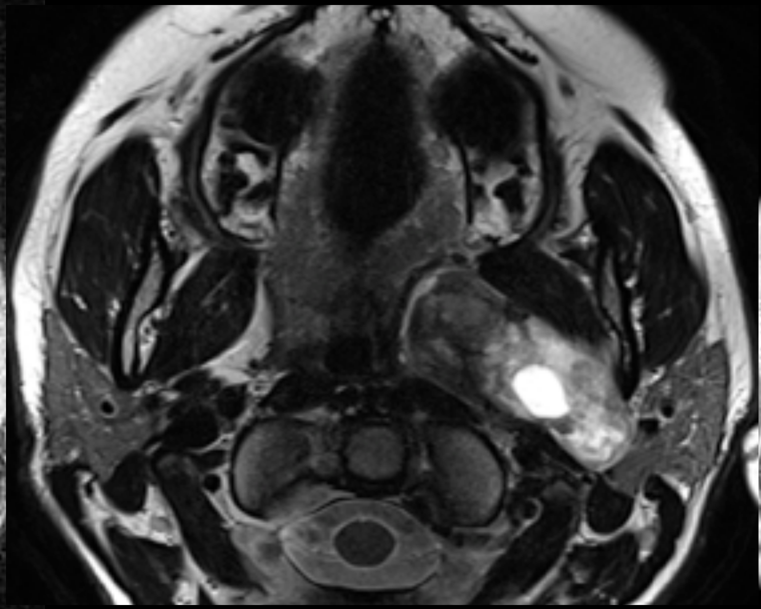
DIAGNOSTIC WORK-UP

MRI - Features of malignancy

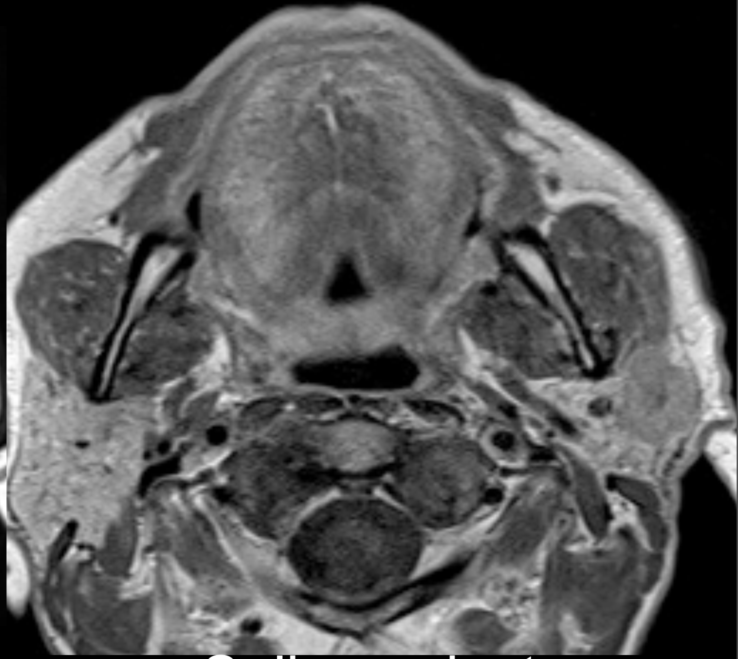
- Poorly defined margins
- Spread to surrounding structures
- Perineural spread
- Neck lymph node metastasis



Pleomorphic adenoma



Carcinoma ex-pleomorphic adenoma



Salivary duct carcinoma

DIAGNOSTIC WORK-UP

Large size is not synonymous with malignancy

STAGING SYSTEM

TNM (AJCC-UICC 2010)

Tx: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor 2 cm or less in greatest dimension without extraparenchymal extension*
T2: Tumor more than 2 cm but no more than 4 cm in greatest dimension without extraparenchymal extension*
T3: Tumor more than 4 cm and/or tumor having extraparenchymal extension*
T4a: Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b: Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

*Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic extension does not constitute extraparenchymal extension for classification purposes

Nx: Regional lymph nodes cannot be assessed
N0: No evidence of lymph node metastasis
N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but no more than 6 cm in greatest dimension
N2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c: Metastasis in bilateral or controlateral lymph nodes, none more than 6 cm in greatest dimension
N3: Metastasis in a lymph node, more than 6 cm in greatest dimension

Mx: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

TREATMENT OF THE PRIMARY

Classification of parotidectomies: a proposal of the European Salivary Gland Society Eur Arch Otorhinolaryngol

M. Quer[1] · O. Guntinas-Lichius[2] · F. Marchal[3] · V. Vander Poorten[4] · D. Chevalier[5] · X. León[1] · D. Eisele[6] · P. Dulguerov[3]

2016

Table 3 EGSG level classification (modified from Quer et al. [31])

Anatomical site	Level
Superficial superior	I
Superficial inferior	II
Deep inferior	III
Deep superior	IV
Accessory	V

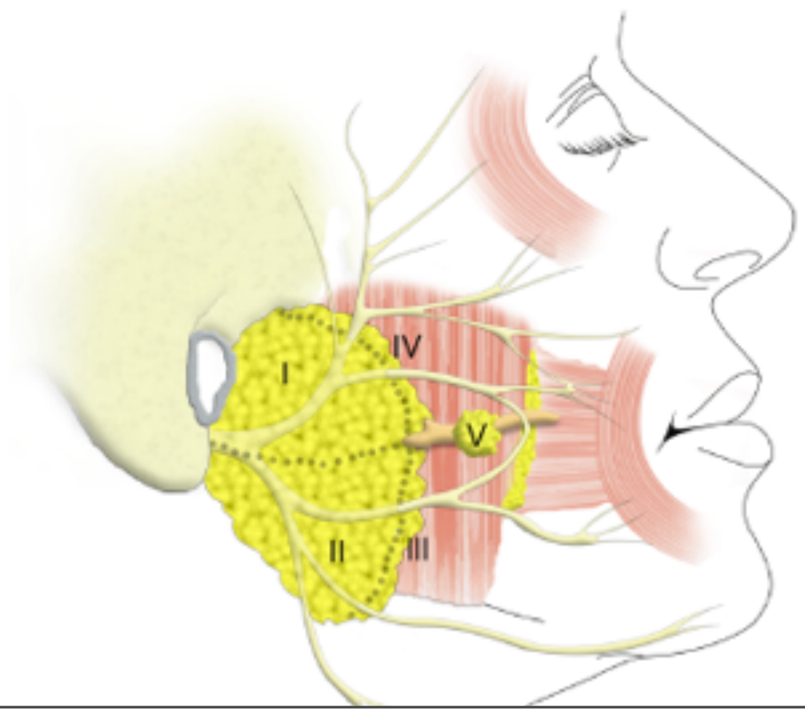


Table 6 Comparison of the new proposed classification and classical terms

ESGS proposal	Classical classifications
Parotidectomy I–IV (VII)	Total parotidectomy with facial nerve resection
Parotidectomy I–IV	Total parotidectomy with facial nerve preservation
Parotidectomy I–IV (VII, S, MM)	Extended total parotidectomy with facial nerve resection plus skin and masseter muscle resection
Parotidectomy I–II	Superficial parotidectomy
Parotidectomy III–IV	Deep lobe parotidectomy
Parotidectomy I	Partial superficial parotidectomy
Parotidectomy II	Partial superficial parotidectomy
Parotidectomy I–II–III	Superficial parotidectomy extended to the inferior deep lobe
Parotidectomy V	Accessory lobe removal
ECD I	Extracapsular dissection with tumor in level I
ECD II	Extracapsular dissection with tumor in level II
ECD V	Extracapsular dissection with tumor in level V

TREATMENT OF THE PRIMARY

SURGICAL OPTIONS

SUPERFICIAL PAROTIDECTOMY	T1-T2 Low grade
TOTAL PAROTIDECTOMY	T3 low grade T1-T3 high grade Tumors involving deep lobe
EXTENDED TOTAL PAROTIDECTOMY	Tumors involving soft tissues, masseter, skin, EEC, mandible
RADICAL PAROTIDECTOMY	Tumors involving the facial nerve
EXTENDED RADICAL PAROTIDECTOMY	Tumors involving the facial nerve and other structures

LYMPH NODE METASTASIS

Overall prevalence of nodal metastasis: 25-38%

Overall prevalence of occult metastasis: 18-49%

Overall prevalence of nodal recurrence: 12-14%

Presence of nodal metastasis: 10-y overall survival decreses more than 50%

RISK FACTORS

Histologic type (SDC, ADC)

T Stage and dimension (>3 cm)

Grading

Age

Pain

Facial nerve palsy

Extraparenchymal extension

Poulsen et al. 1992, Kelley and Spiro 1996, De Brito-Santos et al. 2001, Harish 2004, Zbaren et al 2005, Chen et al 2007

NECK MANAGEMENT

High risk of occult metastasis

Risk of occult mets preop unpredictable

Low risk of occult metastasis

PORT on T and N

1) Elective neck dissection (levels Ib-II-III-Va)
2) Frozen sections on level IIA and ND in case of N+
3) If the patient needs PORT on T the neck can be included in the field

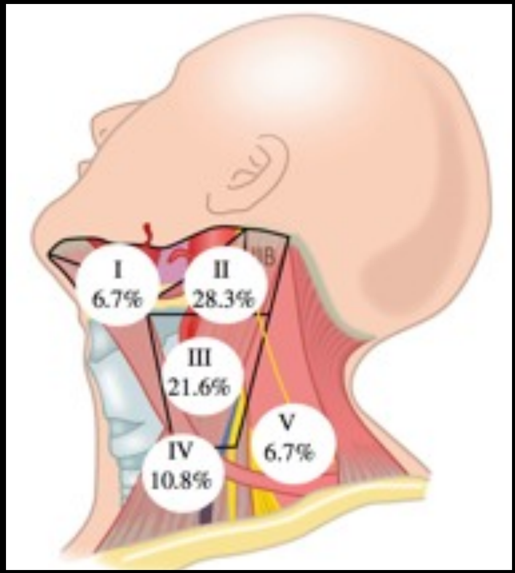
"Wait and see"

NECK MANAGEMENT

Elective ND

Neck level dissected	No of patients (%) (n=74)	Pathological positivity (%)
1	53(72%)	6.7%
2	74(100%)	28.3%
3	74(100%)	21.6%
4	47(64%)	10.8%
5	43(58%)	6.7%

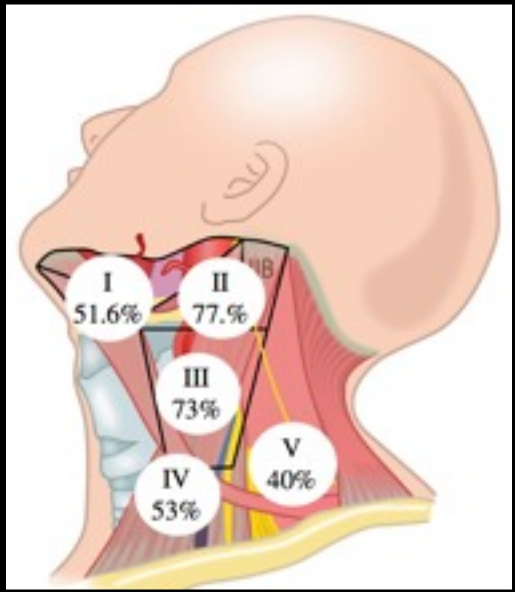
Neck levels dissected in patients having END



Therapeutic ND

Neck level dissected	No of patients (%) (n=31)	Pathological positivity (%)
1	26(86%)	51.6%
2	31(100%)	77.0%
3	31(100%)	73.0%
4	29(94%)	53.0%
5	27(87%)	40.0%

Neck levels dissected in patients having TND



Ali et al. "Treatment of the Neck in Carcinoma of the Parotid Gland" Ann Surg Oncol 2014

OUR INDICATIONS FOR ADJ RT

ACC

EVERY PATIENT WITH EXCLUSION OF:

pT1 WITHOUT HISTOLOGICAL RISK FACTORS:

- Perineural spread
- Endovascular invasion
- Solid variant

non-ACC

HIGH GRADE TUMORS

LOW GRADE pT3-pT4

LOW GRADE pT2 in presence of “aggressive” features:

- Involved margins
- Close proximity to the nerve

PENDING PROBLEMS: HIGH GRADE MALIGNANCIES

Frozen sections

MINIREVIEWS

Biopsy of parotid masses: Review of current techniques

World J Radiol 2016

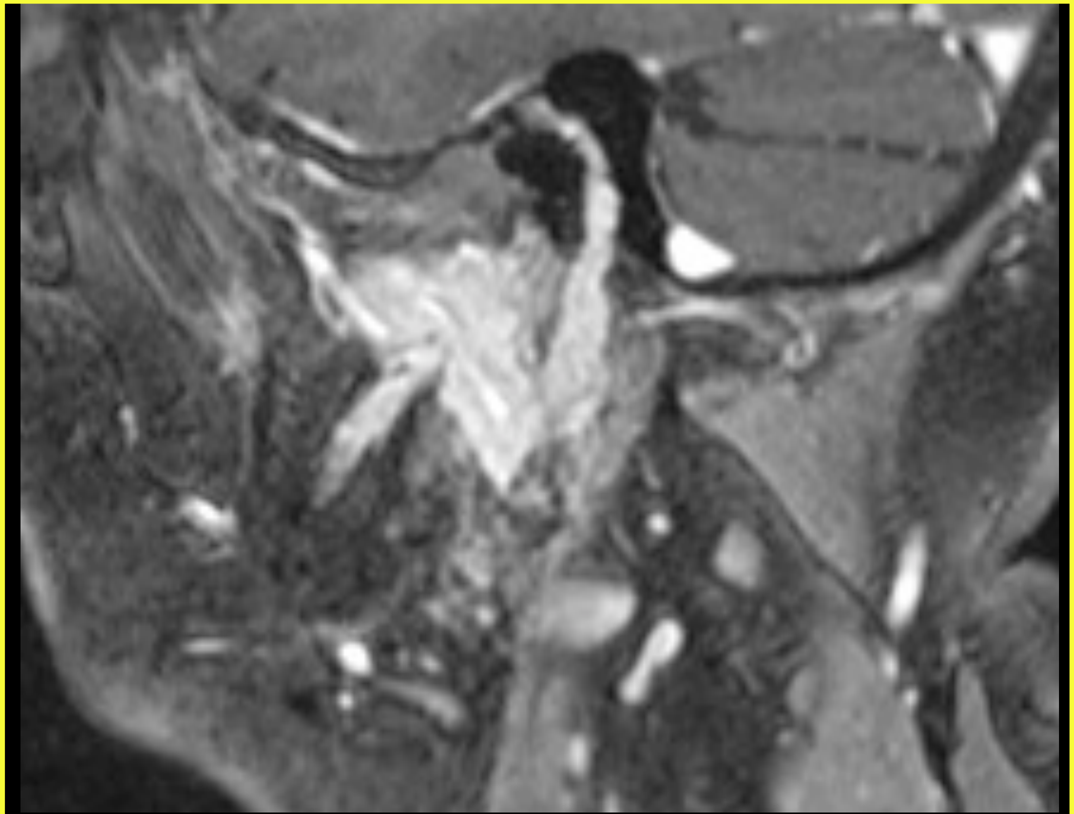
Sananda Haldar, Joseph D Sinnott, Kemal M Tekeli, Samuel S Turner, David C Howlett

"IOFS can be employed to guide further surgical management while the patient is still on the operating table. A meta-analysis published in 2011 (Schmidt et al.) looking at data from 13 studies over a 25-year period describes 90% sensitivity, 99% specificity and good consistency of results across study centres"

"In general, IOFS can be used as an adjunct to the less invasive options where diagnostic suspicion and uncertainty remain"

PENDING PROBLEMS: ACC

- Insidious growth
- Perineural spread
- Periosteal/perichondral spread
- Low rate of nodal metastases (G1/G2)
- Aggressive behavior of G3 (Solid component)
- High rate of distant metastases
- Multiple local and distant relapse



Facial nerve (retrograde and anterograde)
Masticator space and muscles and V3

LYMPH NODE METASTASIS

FUTURE TRENDS

Clinical activity of androgen deprivation therapy in patients with metastatic/relapsed ARpositive salivary gland cancers

L. Locati, F. Perrone, B. Cortelazzi, S. Lo Vullo, P. Bossi, G. Dagrada, P. Quattrone, C. Bergamini, P. Potepan, E. Civelli, C. Fallai, S. Pilotti, L. Licitra

Head & Neck 2015

17 pts with relapsing and/or metastatic SGCs AR-expressing: SDC (N=8), adenocarcinoma NOS (N=7), cystadenocarcinoma (N=1) and poorly differentiated carcinoma originated from SDC (N=1)

All pts were homogeneously treated with ADT (*Bicalutamide + decapeptyl)*

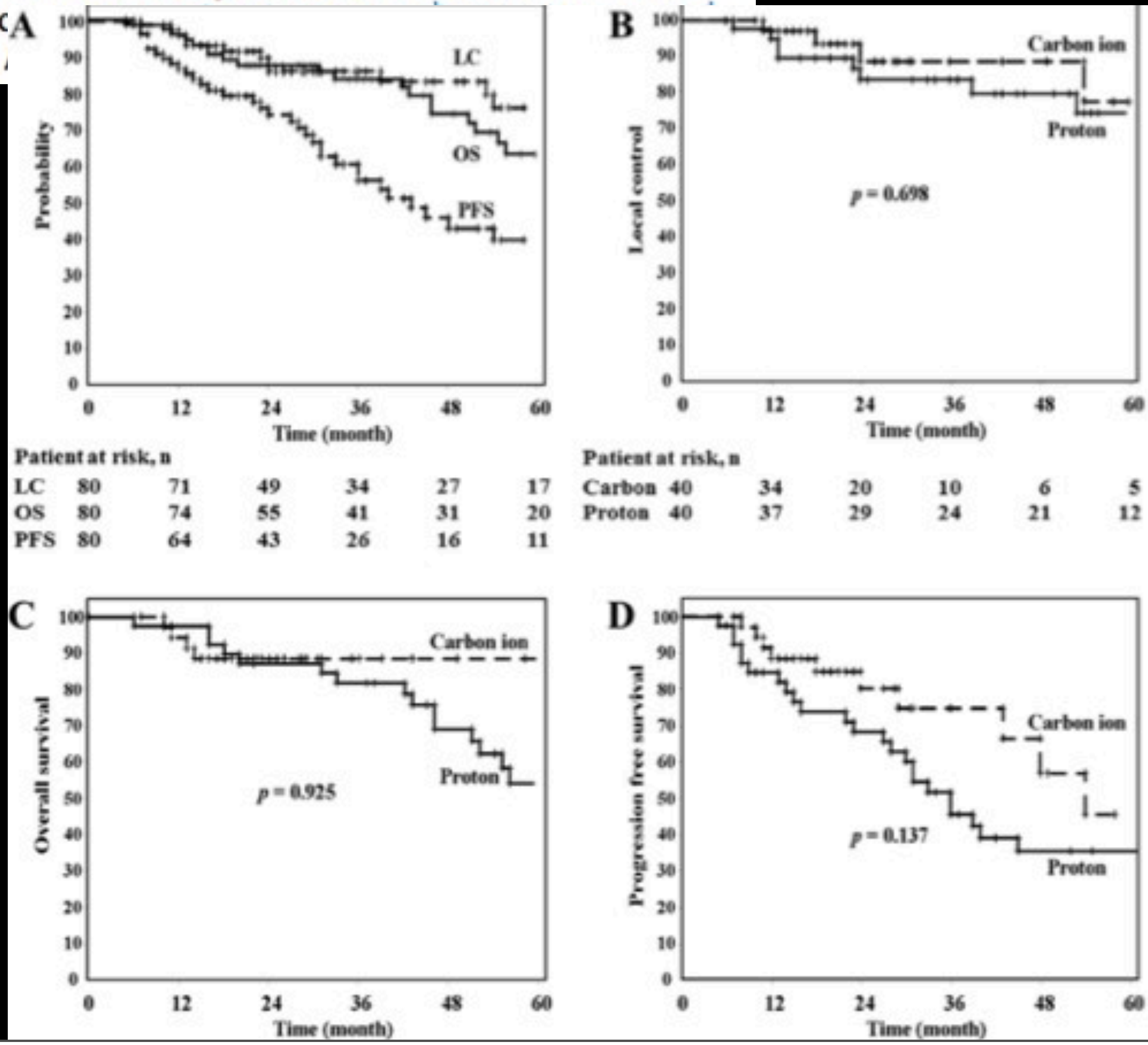
No significant toxicities were reported. Overall response rate was 64.7%; three−year PFS and 5−year OS were 11.8% and 19.3%, respectively

FUTURE TRENDS

Treatment outcomes of particle radiotherapy using protons or carbon ions as a single-modality therapy for adenoid cystic carcinoma of the head and neck ☆

Radiotherapy and Oncology 2014

Masaru Takagi [a,*], Yusuke Demizu [a], Naoki Hashimoto [a], Masayuki Mima [a], Kazuki Terashima [a],
Osamu Fujii [a], Dongcun Jin [a], Yasue Niwa [c], Koic
Ryohei Sasaki [f], Yoshio Hishikawa [g], Mitsuyuki



80 patients with ACC

- no lymph node or distant metastasis
- no previous treatment
- radical intent; treated with proton therapy or carbon ion therapy

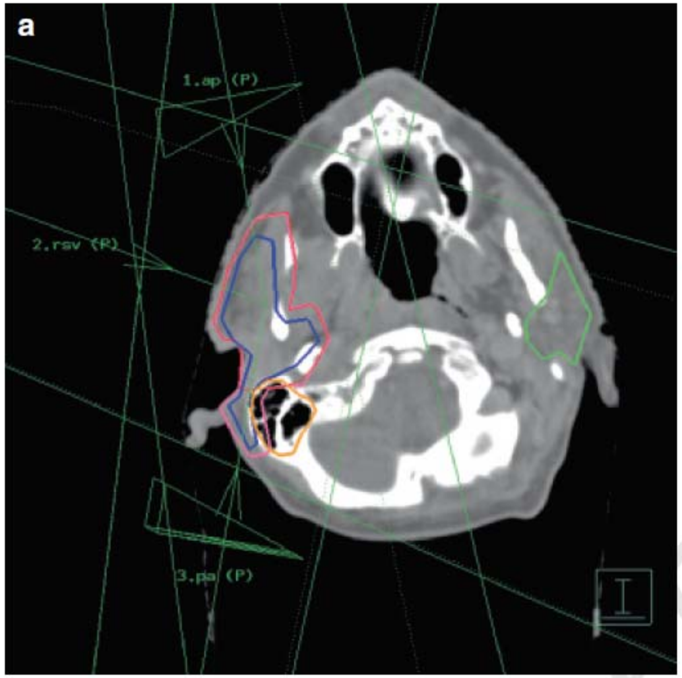
Higher local control than XRT in large or inoperable ACC

Salivary gland carcinoma non-surgical aspects

Cai Grau

Aarhus, Denmark

Role of radiotherapy



- Role of radiotherapy in salivary gland carcinoma has never been assessed in randomized trials
- Radiotherapy alone can induce locoregional control rates of 40–50%, but high doses (66+ Gy) needed
- Postoperative radiotherapy is indicated in high risk patients
  - incomplete surgery
  - T3-T4
  - pN+
  - perineural extension
  - adenoid cystic carcinoma and other high risk histologies

Low risk

- Acinic cell carcinom
- Polymorphous low-grade adenocarcinoma
- Basal cell adenocarcinoma
- Epitelial-myoepitelial carcinoma
- Well / moderately differentiated mucoepidermoid carcinoma
- Adenocarcinoma NOS well differentiated
- Non-invasive and minimally invasive carcinoma in pleomorph adenoma
- Clear celle carcinoma
- Sialoblastoma

DAHANCA guidelines for management of salivary gland tumours 2010

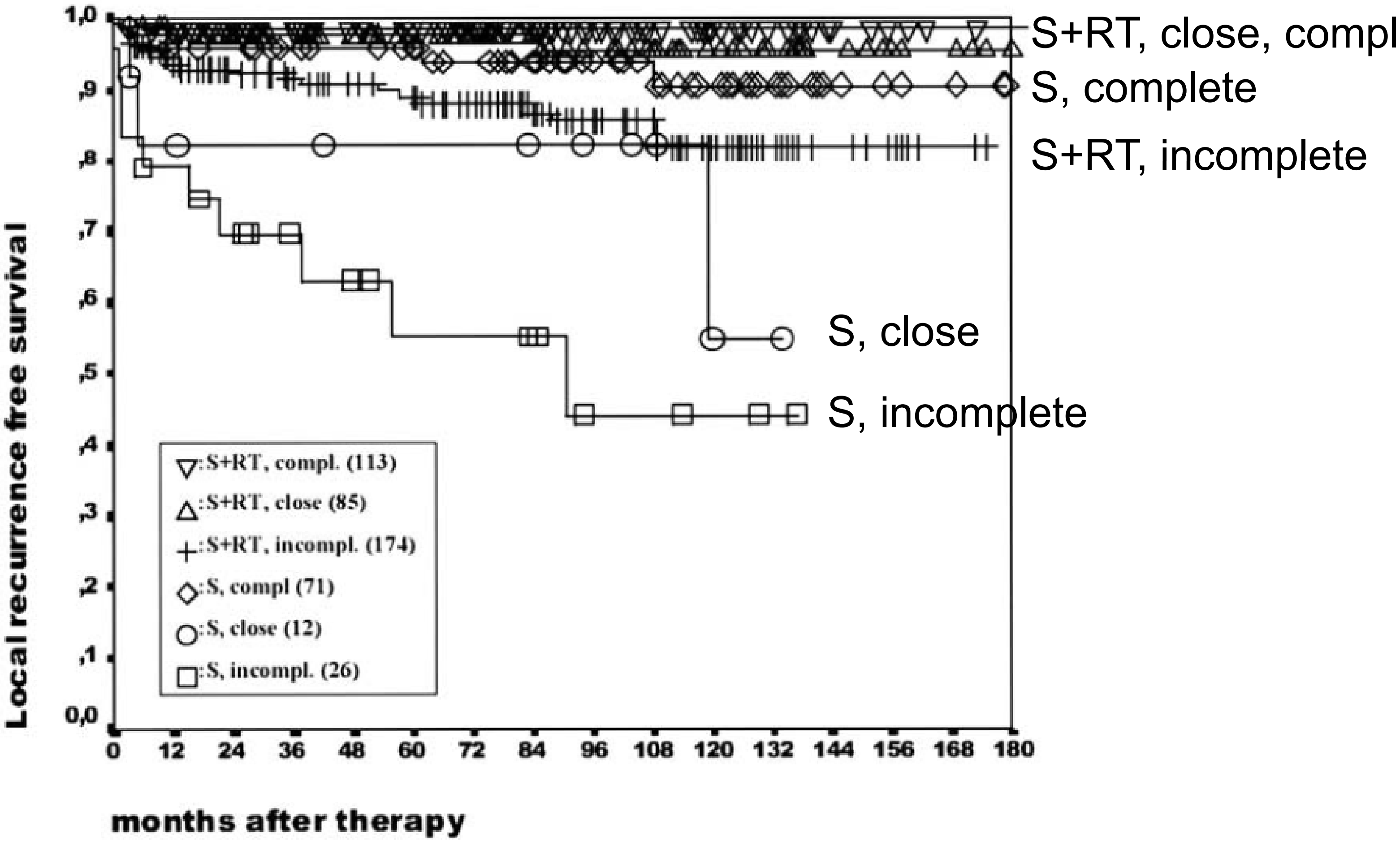
www.DAHANCA.dk

High risk

- Adenoid cystic carcinoma
- Adenocarcinoma NOS moderate-poorly differentiated
- Carcinoma in pleomorph adenoma, invasion >1.5 mm
- Poorly differentiated mucoepidermoid carcinoma
- Salivary duct carcinoma
- Primary squamous cell carcinoma
- Undifferentiated carcinoma (lymphoeptelial carcinoma)
- Large cell carcinoma
- Mucinous adenocarcinoma
- Oncocytary carcinoma
- Carcinosarcoma
- Small cell carcinoma
- Myoepitelial carcinoma

Salivary glands - surgical margins

Dutch HN Oncology Cooperative Group (n=538)



Terhaard et al. IJROBP 61:103–111, 2005

Adjuvant RT - major salivary gland tumors

SEER population-based study - ASTRO 2009 (n=3,714)

“Multivariate analysis revealed a significant association between adjuvant radiation and decreased mortality (HR = 0.76, 95% CI: 0.65–0.89, p = 0.0008).

…

…

In the absence of randomized data, our results support the role of adjuvant radiation for high-grade and locally advanced major malignant salivary gland tumours”

2683 … **nant**

U. Mahmo…

University…

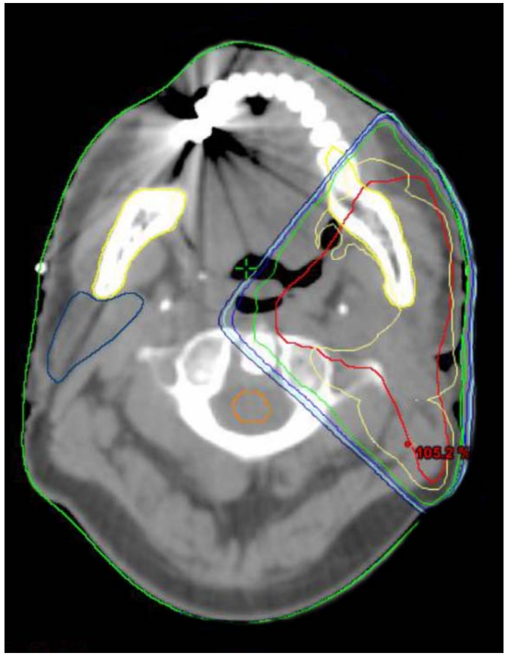
Purpose/… …tment of high-grade… …mine the effect of a… …tabase.

Materials… …patients 18 years a… …(T3/4 or N+) non-m… …ed using year of dia… …ce or absence of a…

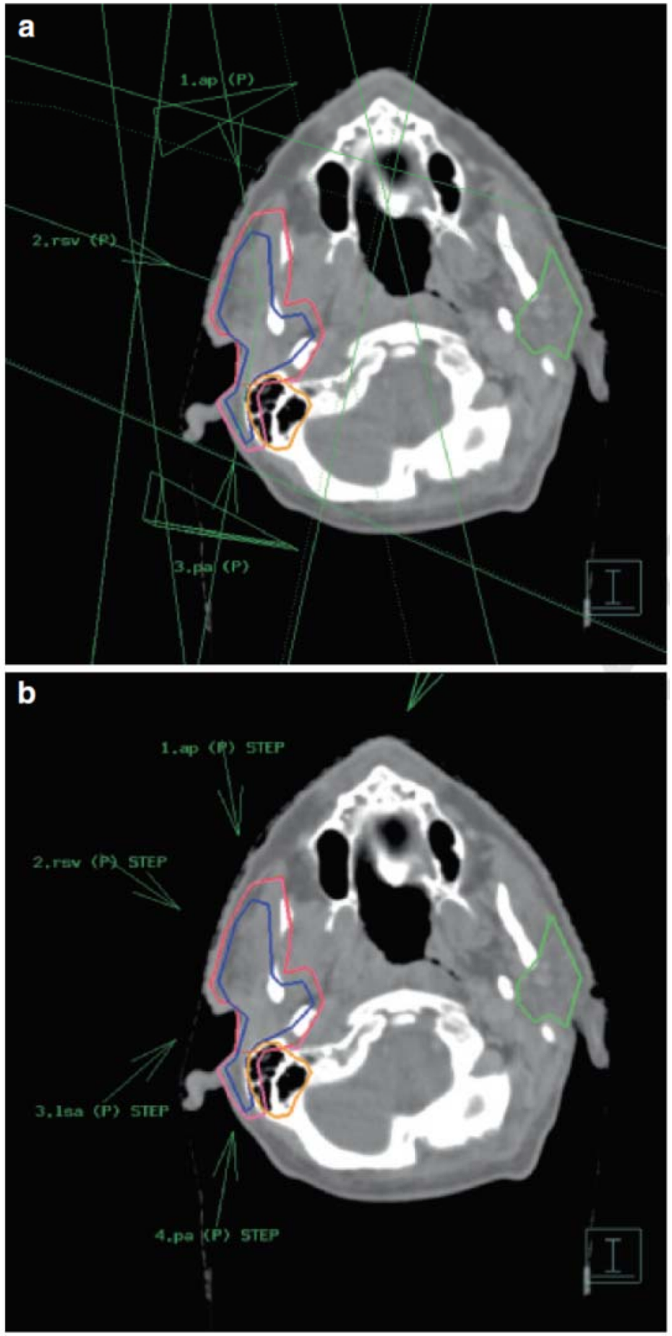
Results: A… …ed) were identified … …tion: parotid 80%,… …rentiated 36%, undi… …phic adenoma/mi… …1– 10%, 2– 31%, 3… …uvant radiation 30… …ecreased mortality (… …younger age at diag… …T-Stage ($p < 0.000$… …radiation and decrea… …77, 95% CI: 0.66–…

Conclusions: Adjuvant radiation was associated with improved survival for high-grade and locally advanced MMSGT based on analysis of this large, population-based database. In the absence of randomized data, our results support the role of adjuvant radiation for high-grade and locally advanced MMSGT.

Radiotherapy



- Ipsilateral tumor(bed) +/-N
- 60 Gy (R0)
- 66 Gy (R1-R2)
- 66-70 Gy (primary RT)
- OAR: Cochlea, spinal cord/brainstem, salivary glands
- 3DCRT (wedge pair) or IMRT



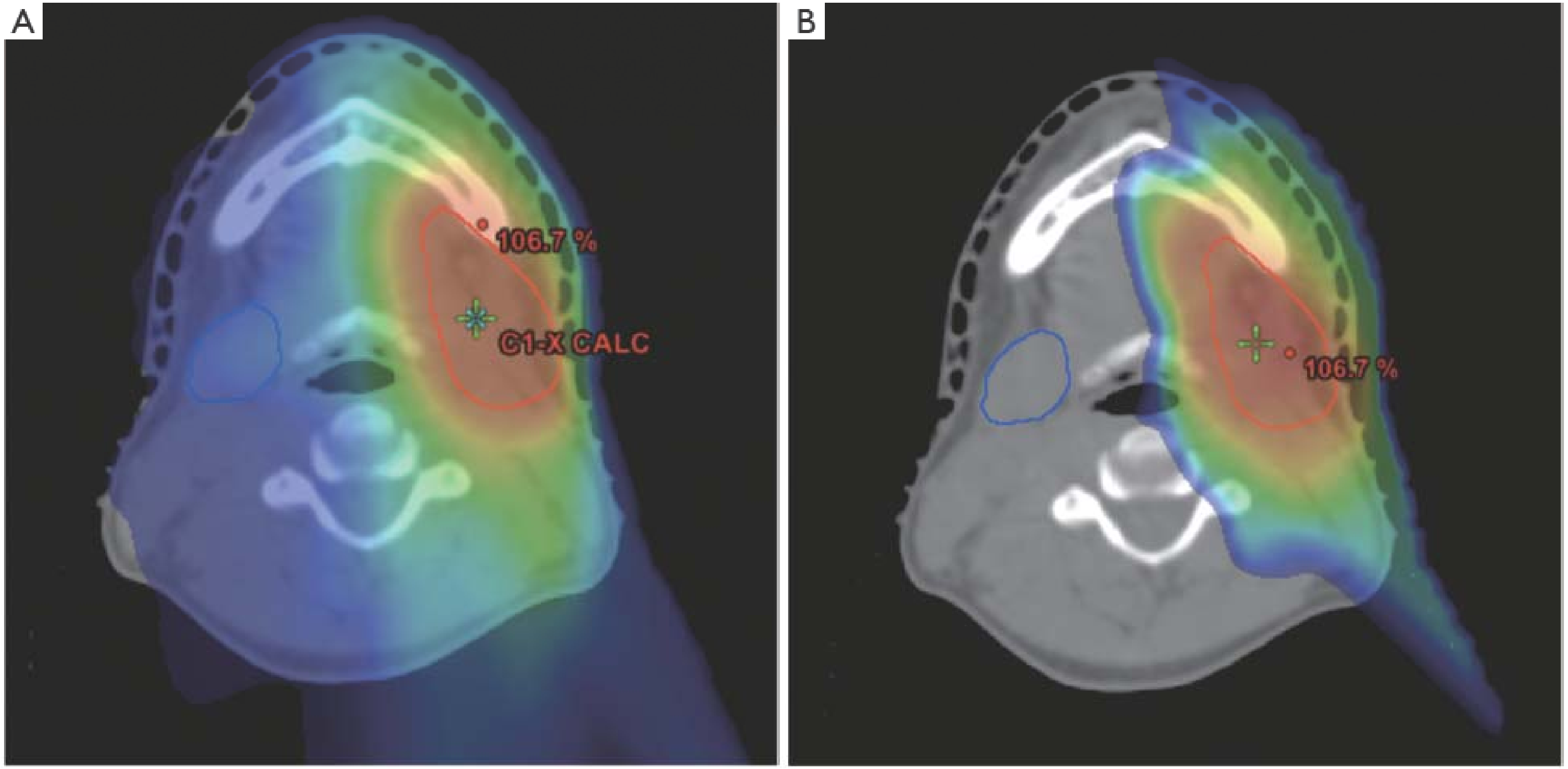
Parotid RT:
3DCRT or IMRT

	3D conventional	IMRT
PTV: mean/max (Gy)	65.6/68.2	66.9/69.9
Ipsilat. cochlea: mean/max (Gy)	23.4/44.6	18.9/35.2
Ipsilat. mastoid: mean/max (Gy)	53.7/66.5	48.8/68.7
Contralat. subm: mean/max (Gy)	9.2/10.4	4.0/6.8
Contralat. parotid: mean/max (Gy)	7.6/8.9	2.8/7.5
Ipsilat. eye: mean/max (Gy)	6.3/19.0	3.9/11.6

From Chris Terhaard

Protons?

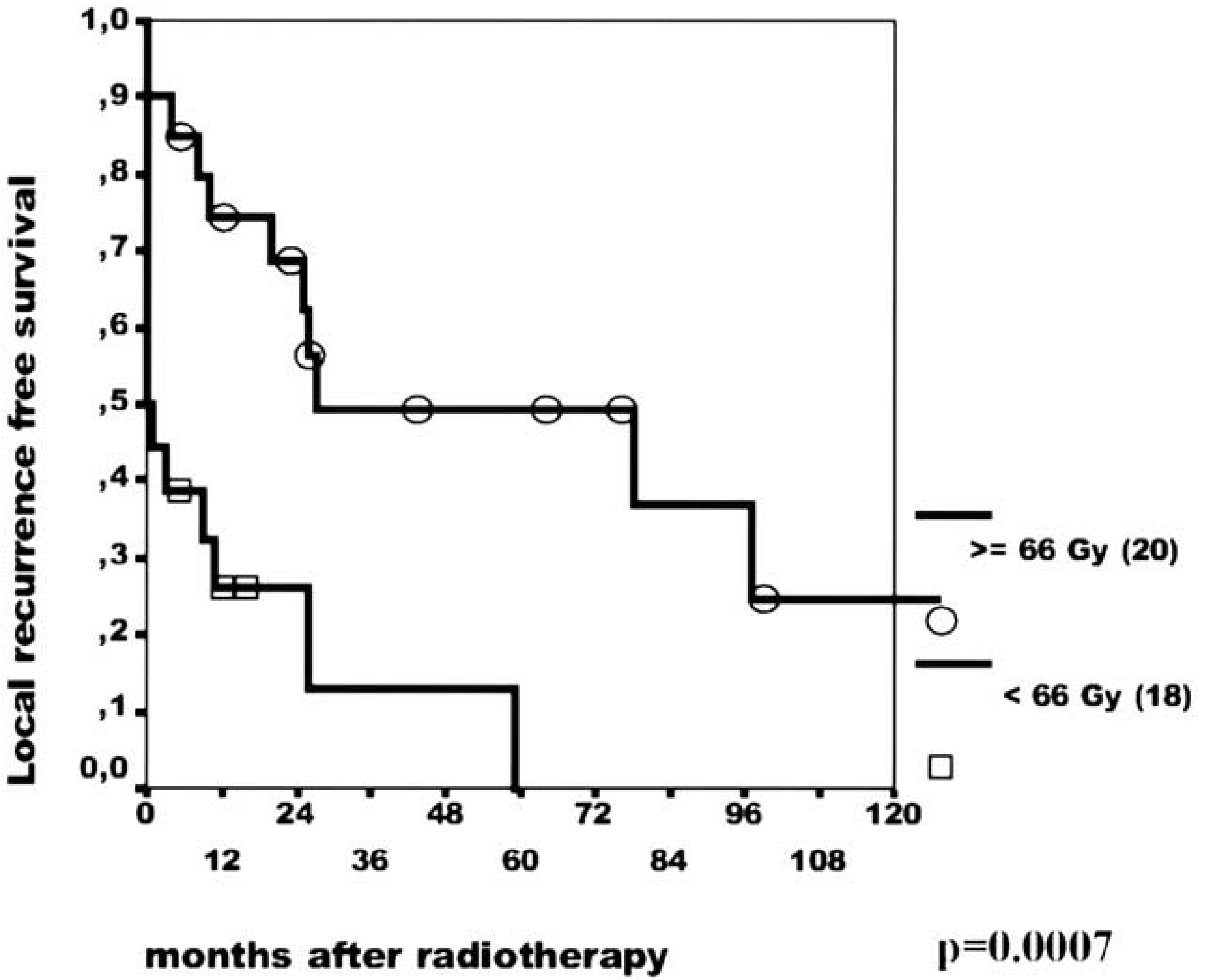
IMRT | Proton (DS)



Linn, Upenn, Translational Cancer Research 2012

Primary radiotherapy - dose?

Dutch HN Oncology Cooperative Group



Terhaard et al. IJROBP 61:103–111, 2005

	Structure	Dose constraint OAR [Gy]	Dose constraint PRV [Gy]	Comments and organ definition	References
ABSOLUTE	Brain stem	$D_{max} \leq 54Gy$	$D_{max} \leq 60Gy$	Treating ≤10 cm^3 of OAR to a maximum of 59 Gy results in a very low risk of neurological damage. If it is necessary for target coverage it can be done after thorough patient information and consent. Delineation: From the top of dens (in order to avoid overdosing medulla) to the bottom of 3rd ventricle (since cranial border is difficult to identify on CT).	Mayo et al. IJROBP vol 76 (3) S36-S41, 2010
	Spinal cord	$D_{max} \leq 45Gy$	$D_{max} \leq 50Gy$	Risk for neurological damage is estimated to 6 % for doses at 60 Gy. Limited overdosage may therefore be allowed in order to achieve target coverage after thorough patient information and consent. Delineation: Spinal cord *not* spinal canal.	Kirkpatrick et al. IJROBP 76 (3) s42-9, 2010
MUST	Anterior eye (conjunctiva, lacrimal gland, cornea, iris)*	$D_{max} \leq 30Gy$	$D_{max} \leq 35Gy$	Even if constraints are not met for other parts of the optic pathways the anterior eye may be worth sparring in order to preserve the eye in situ. In case of severe dry eye syndrome the eye must often be removed. *The lenses have been removed from the list of OAR since it is contained in the anterior eye OAR and side effects may be treated.	Jeganathan et al. IJROBP 79 (3) 650-9, 2011 DAHANCA 2004
	Chiasm and optic nerve	$D_{max} \leq 54Gy$	$D_{max} \leq 60Gy$	$D_{max} \leq 55$ Gy leads to a very low risk of side effects. Doses above 60 Gy leads to above 7% estimated risk. Dose constraint can be violated in order to achieve target coverage after thorough patient information and consent.	Mayo et al IJROBP 76 (3) S28-35, 2010 RTOG0615
	Posterior eye (retina)	$D_{max} \leq 45Gy$	$D_{max} \leq 50Gy$	Retinopathy is seen after doses as low as 30 Gy, and doses must be kept as low as possible. There is a volume effect and eg. Lateral retina can be spared separately.	DAHANCA 2004 Jeganathan et al. IJROBP 79 (3) 650-9, 2011
SHOULD	Cochlea	$D_{mean} \leq 45Gy$ og $D_{95\%} \leq 55Gy$		Cochlea is delineated (hypodense area in the temporal bone anterior of the internal auditory canal). Risk of clinical relevant hearing loss may be as high as 15% at mean doses of 47 Gy when using concomitant cisplatin.	Bhandare et al. IJROBP 76 (3) S pp S50-57, 2010; Chan et al IJROBP 73, (5) 1335-1342, 2009; Hichcock et al IJROBP 73 (3) 779-88, 2009
	Parotid gland	1) Contralateral parotid: $D_{mean} \leq 20Gy$ 2) Both parotids: $D_{mean} \leq 26Gy$		A gradual reduction of function is seen from 10-40 Gy. Mean doses should be kept as low as possible.	DAHANCA 2004 Deasy et al IJROBP 76 (3) S58-63, 2010
	Mandible	Hotspots in the mandible should be avoided			*Int J Radiat Oncol Biol Phys*. 2010 April ; 76(5): 1333–1338
MAY	Pituitary gland	$D_{mean} \leq 30Gy$		No observed threshold. Hormonal changes may occur after >30 Gy and may require follow up by endocrinologist	Darzy et al. Pituitary (2009) 12;40-50
	Brain	$D_{max} \leq 60Gy$		At D_{max}=72 Gy the risk of necrosis is 5% after 5 years. Cognitive disturbances may be seen after lower doses. The entire brain is delineated.	Lawrence et al. IJROBP vol 76 (3) S20-27, 2010
	Submandibular gland	$D_{mean} \leq 35Gy$		The submandibular gland is a part of level Ib and should only be spared if level I or II are not parts of the target	Deasy et al IJROBP 76 (3) S58-63, 2010
	Oral cavity	$D_{mean} \leq 30Gy$ for non-involved oral cavity		Delineation: Mobile tongue, floor of mouth cheeks and hard palate.	RTOG 1016
	Lips	$D_{mean} \leq 20Gy$			RTOG 1016
	Larynx	$D_{mean} \leq 44$ Gy		Delineation: larynx including arytenoidea from the hyoid bone to cricoid cartilage	Rancanti et al. IJROBP 76 (3) s64-69, 2010
	Thyroid gland	$D_{mean} \leq 40$ Gy		No specific threshold has been identified and the endpoint is uncertain in the literature. Thyroid stimulating hormone should be controlled at doses above constraint according to local guidelines	Garcia-Serra AJCO 28, (3) June 2005 p 255-8 Boomsma R&O 99(2011)1-5
	Oesophagus	$D_{mean} \leq 30Gy$		Delineation: Below the cricoid cartilage to the top of the manubrium	RTOG 1016

Absolute: Organs of critical importance that must be prioritized over target coverage as a rule.

Must: Serial organs that must be delineated but not necessarily prioritized over target coverage.

Should: Parallel organs with good evince for sparing or serial organs with severe side effects if damaged.

May: Poor evidence, uncertain endpoints or manageable toxicity. Organs may be delineated according to local guidelines/research projects. Swallowing structures may be included here.

Priorities and penalties

1. Critical normal tissues, potentially lethal complication

- Spinal cord
- Brain stem

2. Target coverage

- GTV
- CTV1

3. Critical serial normal tissues

- Anterior eye
- Chiasm
- Posterior eye and optic nerve
- Cochlea

4. Target coverage

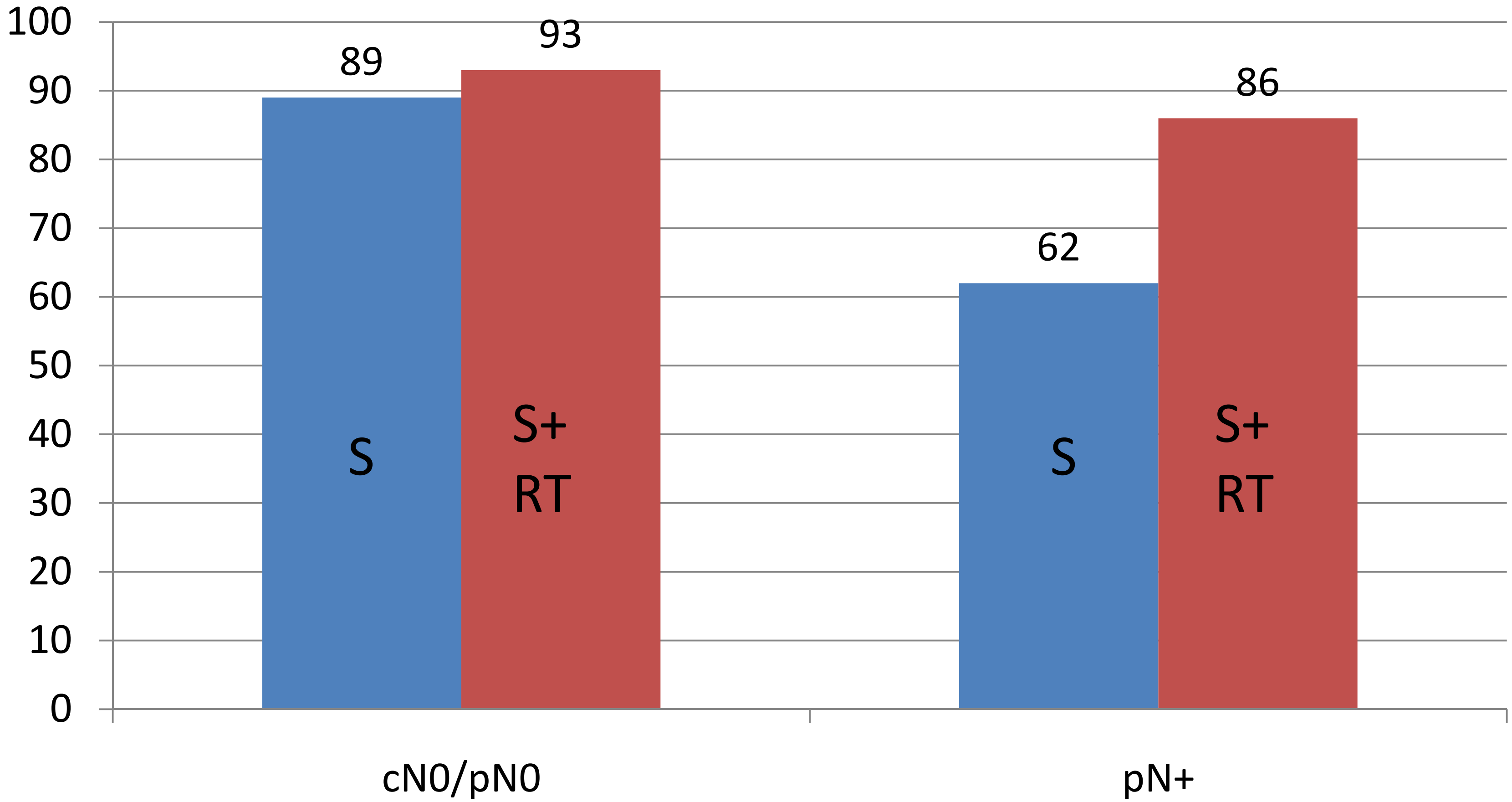
- PTV1
- PTV2
- PTV3

5. Sensitive normal tissues

- Brain
- Contralateral parotid
- Larynx
- Oesophagus
- Lips
- Oral cavity
- Submandibular gland
- Ipsilateral parotid gland
- Mandible
- Circumference
- Thyroid gland
- Pituitary gland

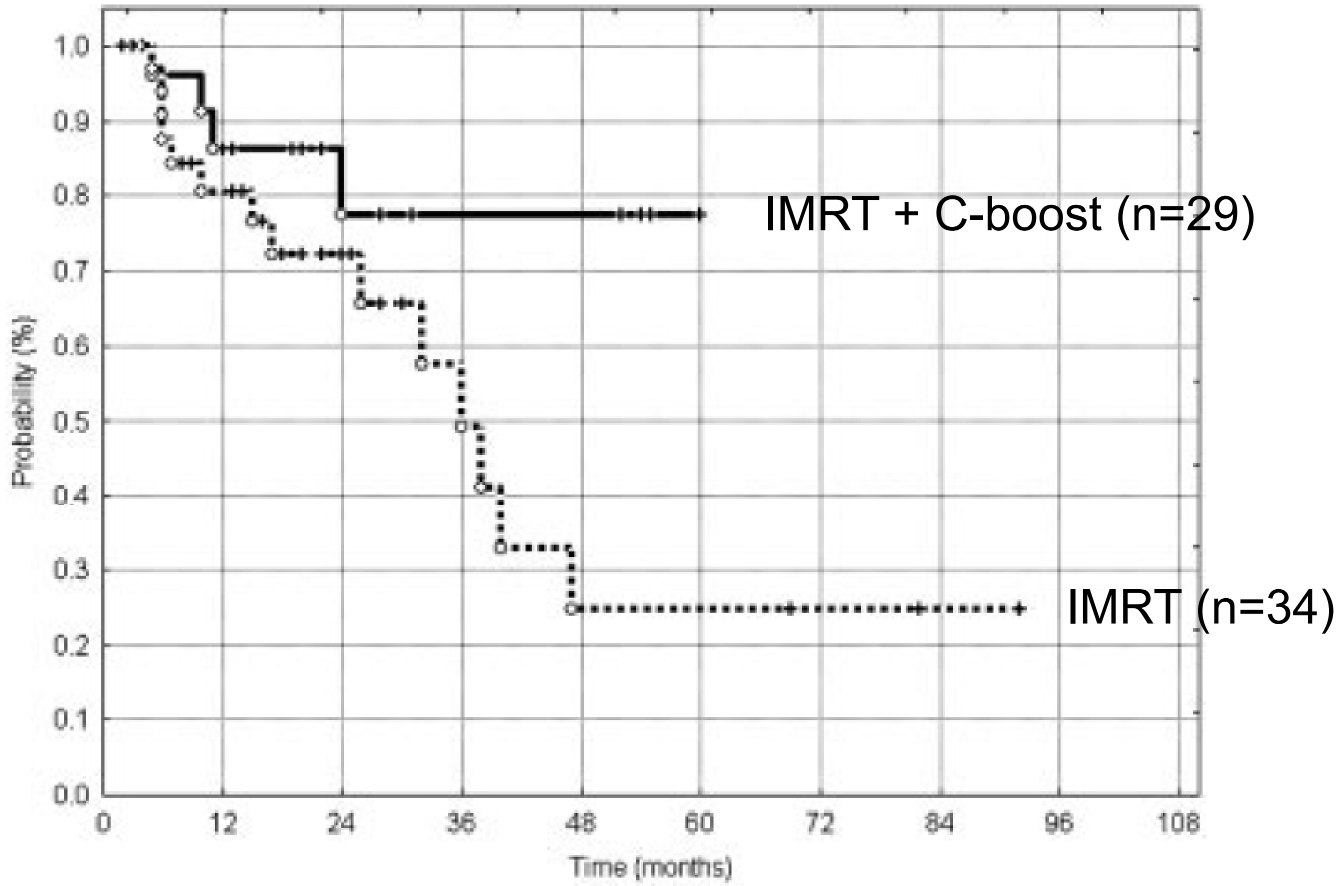
Elective neck irradiation?

+/- Neck RT in salivary gland RT



Terhaard et al. IJROBP 61:103–111, 2005

Adenoid cystic ca – carbon ion boost Heidelberg



Schulz-Ertner et al. Cancer 104:338–44, 2005

Summary – key points

- Primary management is surgery; radical RT can be used in inoperable cases
- Postoperative radiotherapy is recommended in cases of
  - incomplete surgery, T3-T4, pN+, perineural extension, ACC and other high risk pathologies
- Doses of 60–70 Gy should be applied to the CTV
- Ipsilateral RT; wedge pair 3DCRT or IMRT
- Isolated neck recurrences or distant metastases are rare and elective nodal irradiation is only indicated in N+ patients
- Protons, carbon ions and systemic therapy are still experimental

Recurrent/metastatic squamous cell carcinoma of the head and neck

Jean-Pascal Machiels
Department of Medical Oncology
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Université catholique de Louvain, Brussels, Belgium

INSTITUT
ROI ALBERT II
CANCÉROLOGIE ET HÉMATOLOGIE
Cliniques universitaires SAINT-LUC | UCL Bruxelles

ESTRO School

Recurrent and/or metastatic non-curative disease

- **Squamous cell carcinoma of the head and neck**

- Salivary gland tumor

- Nasopharyngeal

- **Diagnosis**
- Prognosis
- Lung metastases: surgery ?
- Re-irradiation and salvage surgery
- Chemotherapy
- Molecular biology and targeted therapies
- Immunotherapy

Diagnosis

- Between 40-60% of patients will relapse in the head and neck area without distant metastases.
- Imaging sometimes difficult due to the morphological modification of the local tissues induced by previous surgery and/or (chemo)radiation.
- The differential diagnosis includes radionecrosis, infection,and scar from previous treatment(s).
- **Effort should be made to obtain pathological confirmation**
- **PET/scan**

- Diagnosis
- **Prognosis**
- Lung metastases: surgery ?
- Re-irradiation and salvage surgery
- Chemotherapy
- Molecular biology and targeted therapies
- Immunotherapy

Prognosis

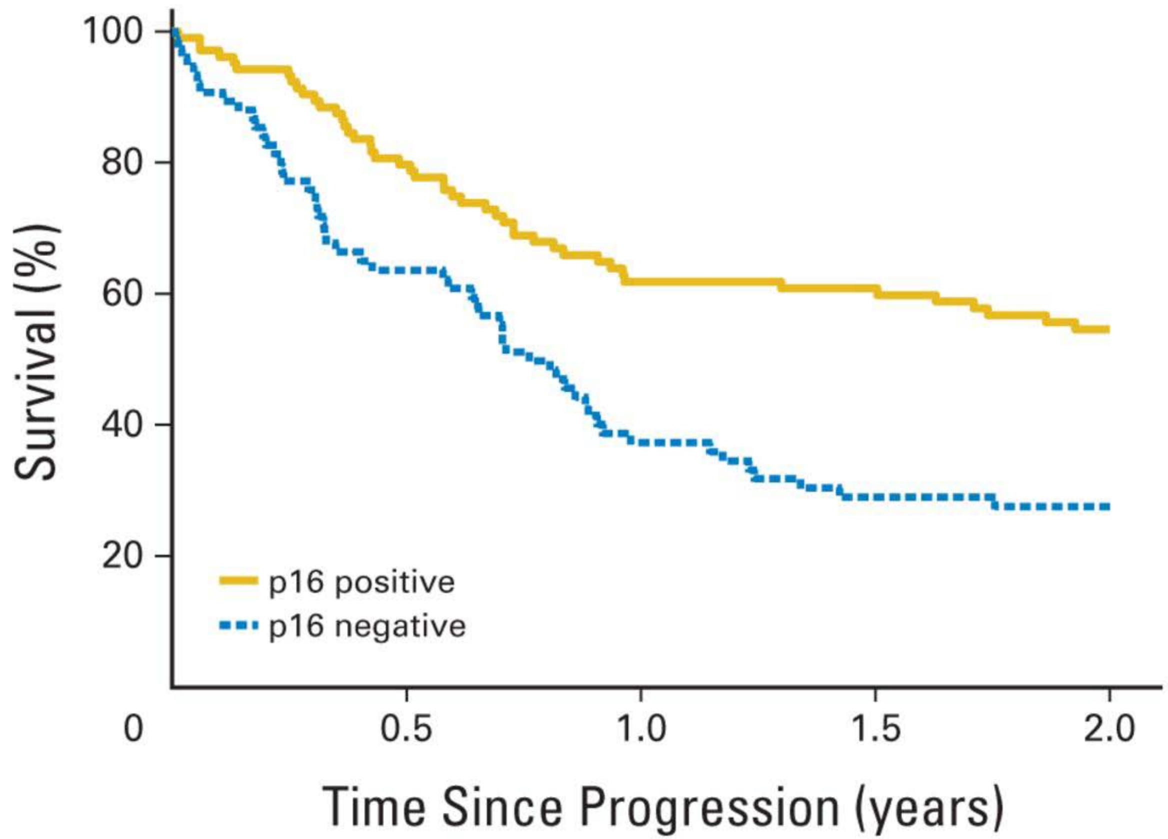
Prognostic factors in patients with recurrent or metastatic SCCHN treated with cisplatin-based chemotherapy in two phase III trials (E1393 and E1395)

Prognostic factors for poor survival in the multivariate analysis (n=399)	p
Weight loss > 5%	0.0004
ECOG 1 vs 0	0.0016
Well and moderate differentiation	0.028
Primary tumor oral cavity or hypopharynx	0.011
Prior radiation therapy	<0.0001

- 0-2 unfavorable prognostic factors: median OS = one year.
- 3-5 unfavorable prognostic factors: median OS = six months ($p < 0.0001$)

Argiris et al Cancer 2004

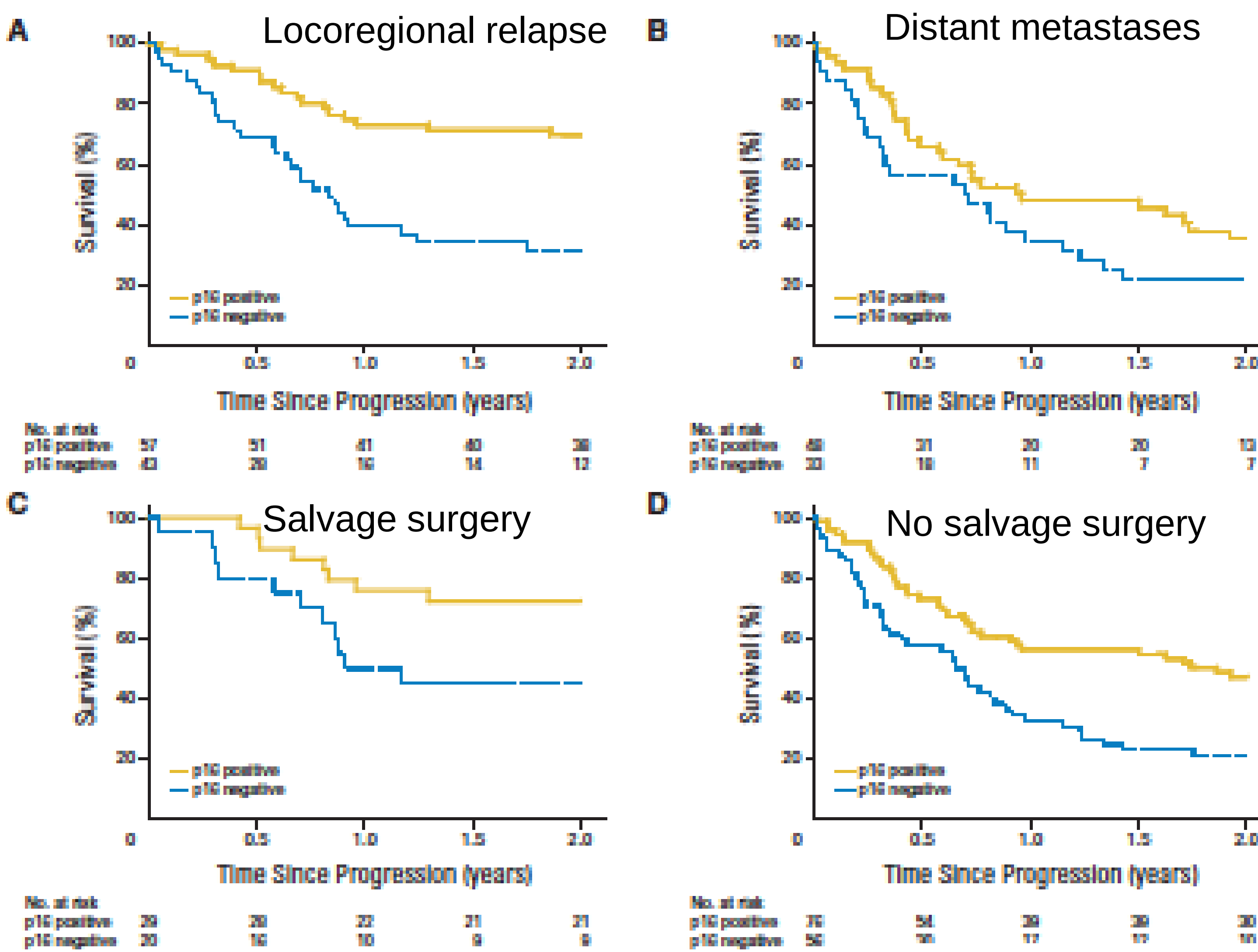
Prognosis: p16 and recurrent disease



No. at risk	0	0.5	1.0	1.5	2.0
p16 positive	105	82	61	60	51
p16 negative	76	46	27	21	19

Carole Fakhry et al. JCO 2014;32:3365-3373

Prognosis: p16 and recurrent disease



Fakhry et al. J Clin Oncol 2014

ESTRO

Prognosis

Other prognostic factors included:

- comorbidity
- ongoing tobacco and alcohol use
- hypercalcemia
- response to prior treatment
- social support

Colevas AD, JCO, 2006

- Diagnosis
- Prognosis
- **Lung metastases: surgery ?**
- Re-irradiation and salvage surgery
- Chemotherapy
- Molecular biology and targeted therapies
- Immunotherapy

Lung metastases: surgery ?

- The differential diagnosis must be made taking with a second primary cancer, particularly if curative treatment can be proposed.
- The rate of synchronous pulmonary tumors is around 4%
- The overall incidence of metachronous second primary cancers is 2% per year.

Ghosh et al Head Neck 2009, Laccourreye et al Ann Otol Rhinol Laryngol. 2002

Lung metastases: surgery ?

- The 5-year survival after pulmonary metastasectomy: 26.5-59.5%
- It is reasonable to recommend lung resection

  - for a single cancerous lung nodule.

- For two or more lung metastases: to be discussed within a multidisciplinary team.

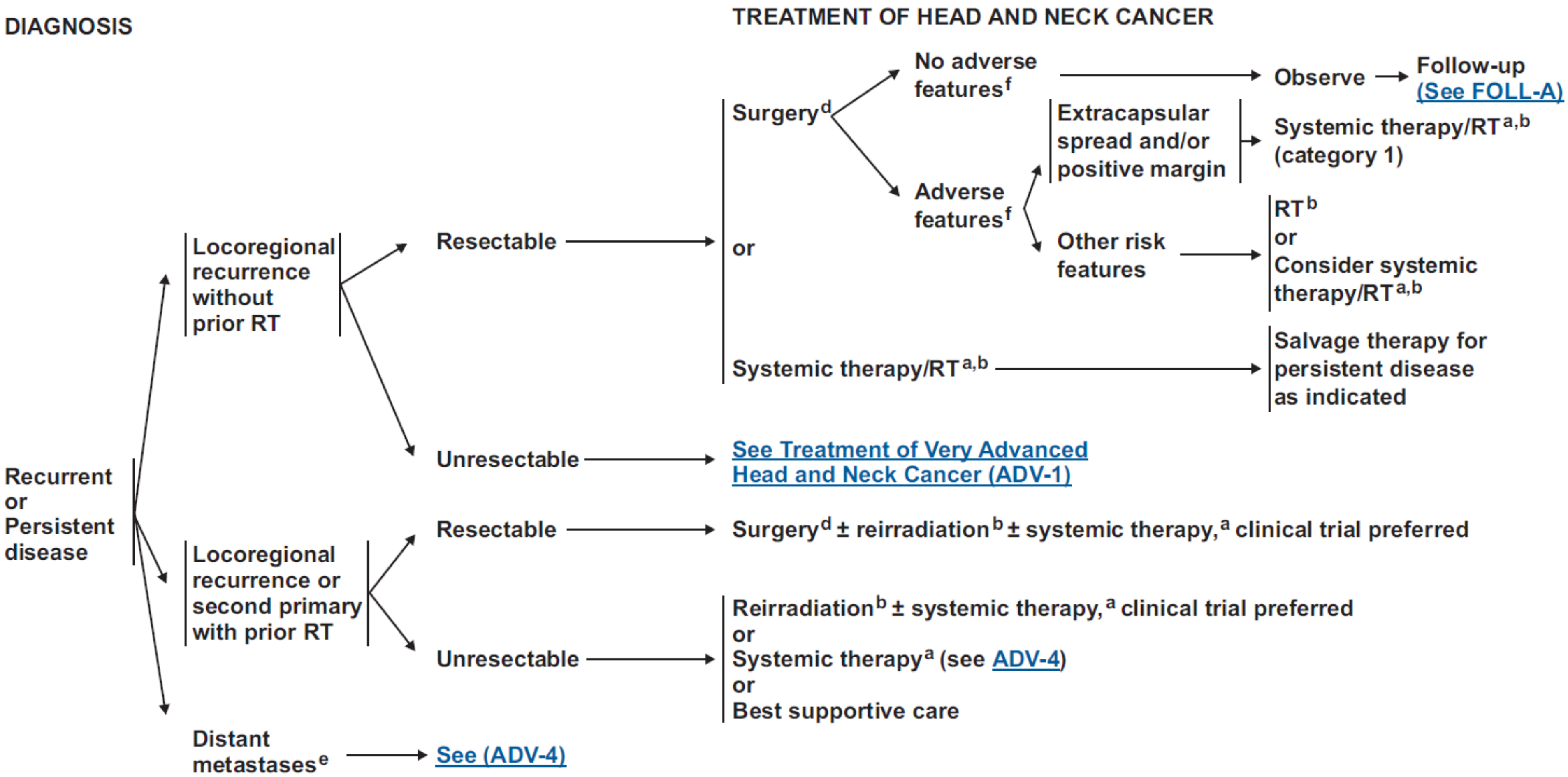
- Diagnosis
- Prognosis
- Lung metastases: surgery ?
- **Re-irradiation and salvage surgery**
- Chemotherapy
- Molecular biology and targeted therapies
- Immunotherapy

(Re)irradiation or salvage surgery

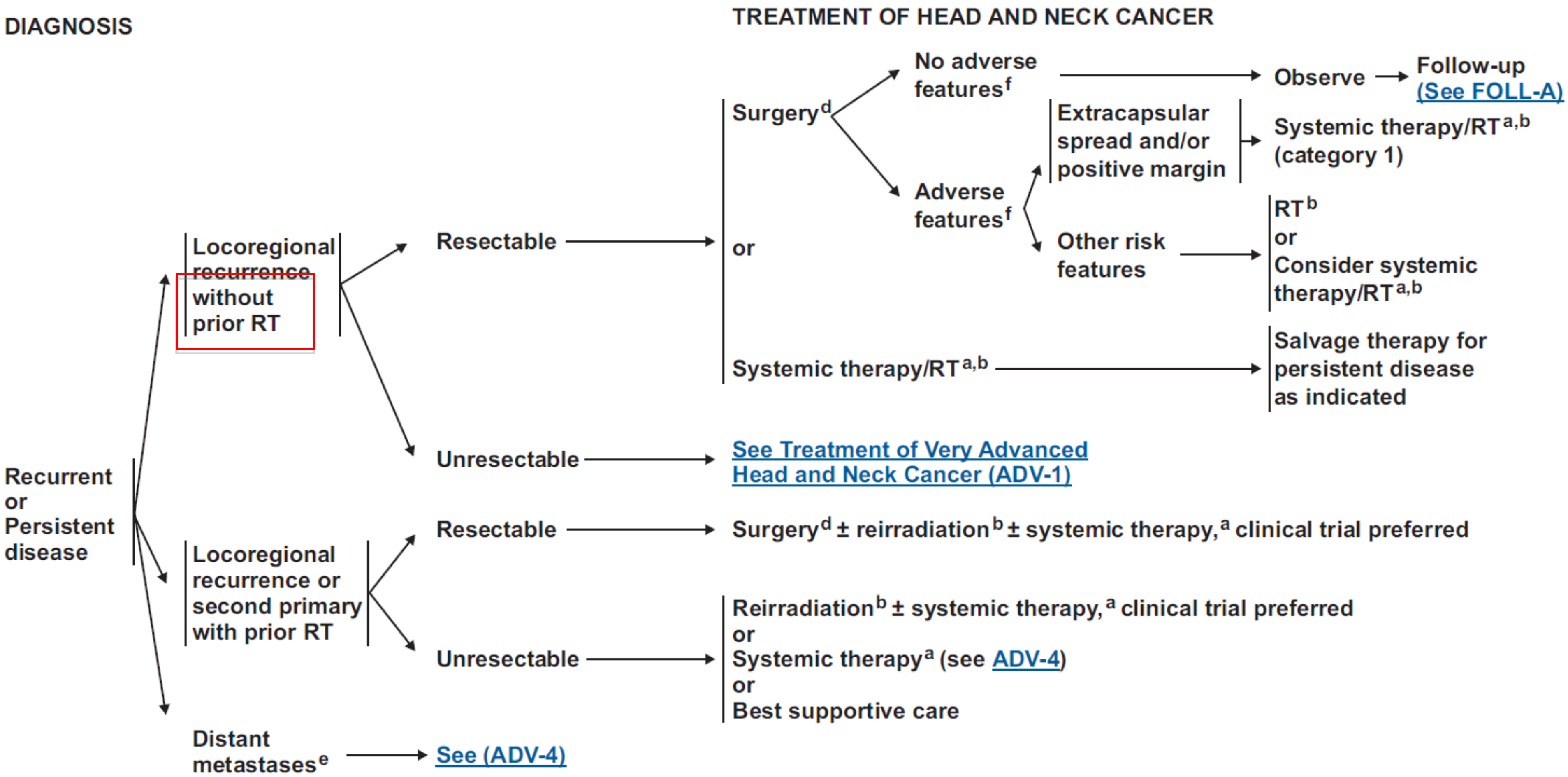
- Between 20-57% of patients treated with radiation therapy will develop local and/or regional relapse

- Re-irradiation and salvage surgery: discuss within the multidisciplinary team

(Re)irradiation or salvage surgery



(Re)irradiation or salvage surgery



(Re)irradiation or salvage surgery

DIAGNOSIS

TREATMENT OF HEAD AND NECK CANCER

Recurrent or Persistent disease

- Locoregional recurrence without prior RT
  - Resectable → Surgery[d]
    - No adverse features[f] → Observe → Follow-up (See FOLL-A)
    - Adverse features[f]
      - Extracapsular spread and/or positive margin → Systemic therapy/RT[a,b] (category 1)
      - Other risk features → RT[b] or Consider systemic therapy/RT[a,b]
  - or
    - Systemic therapy/RT[a,b] → Salvage therapy for persistent disease as indicated
  - Unresectable → See Treatment of Very Advanced Head and Neck Cancer (ADV-1)
- Locoregional recurrence or second primary with prior RT
  - Resectable → Surgery[d] ± reirradiation[b] ± systemic therapy,[a] clinical trial preferred
  - Unresectable → Reirradiation[b] ± systemic therapy,[a] clinical trial preferred or Systemic therapy[a] (see ADV-4) or Best supportive care
- Distant metastases[e] → See (ADV-4)

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- **Diagnosis**
- Prognosis
- Lung metastases: surgery ?
- Re-irradiation and salvage surgery
- **Chemotherapy**
- Molecular biology and targeted therapies
- Immunotherapy

Single-agent response rate

	Response rate (%)
Cisplatin	14-41%
Carboplatin	20-30%
Oxaliplatin	10%
Methotrexate	8-77%
5-Fluorouracil	15%
Capecitabine	8%
Docetaxel	21-42%
Paclitaxel	13-40%

Randomized trials chemotherapy versus BSC

- One trial:
  - BSC (n=26) versus bleomycin (n=22) versus cisplatin (n=38) versus cisplatin plus bleomycin (n=30).

- The conclusions were
  - cisplatin improved survival compared with BSC by 10 weeks
  - cisplatin was better than bleomycin or methotrexate
  - cisplatin monotherapy (median survival: 160 days) was at least as effective as the platinum-based combinations.

Campbell JB et al Acta Otolaryngol 1987
Morton et al Cancer Chemother Pharmacol.1985

Randomized trials chemotherapy versus BSC

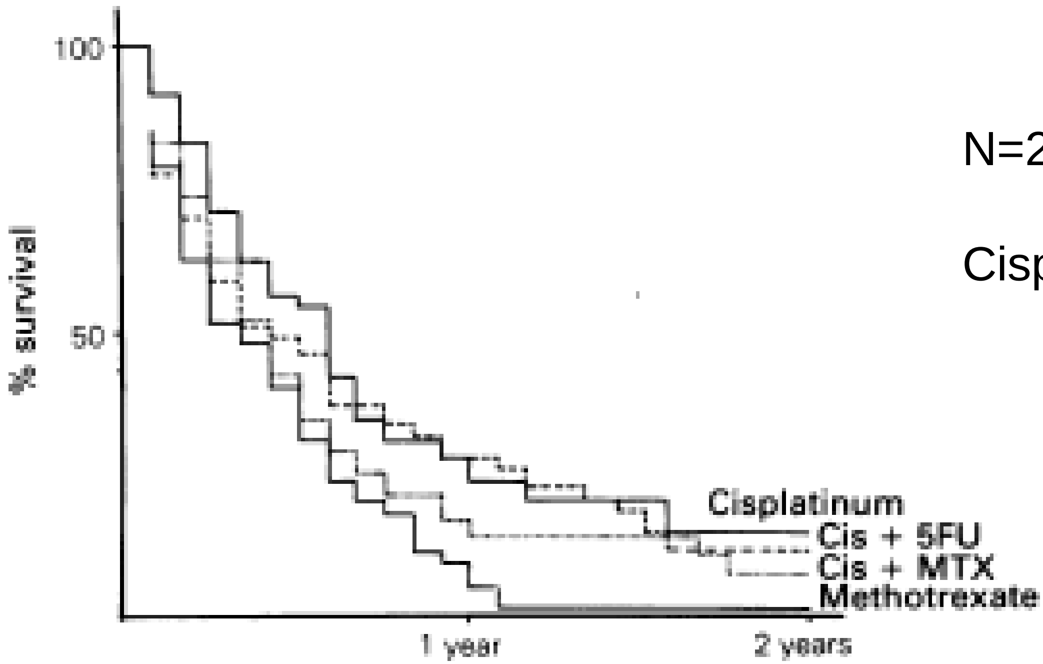


Figure 1 Survival curves of all four groups.

N=200

Cisplatin vs methotrexate (p=0.025)

The Liverpool head and neck oncology group. BJC 1990

Randomized trials mono vs polychemotherapy

Regimens	N	ORR (%)	Median survival (months)
Cisplatin/5-FU *vs* Cisplatin *vs* 5-FU	249	32% 17% 13%	5.5 5 6.1
Cisplatin/methotrexate/ bleomycine/vincristine *vs* Cisplatin/5-FU *vs* Cisplatin	382	34% 31% 15%	8.2 6.2 5.3

Jacobs et al JCO 2002, Clavel et al Ann Oncol 1994, Forastiere et al JCO 1992

Randomized trials mono vs polychemotherapy

Regimens	N	ORR (%)	Median survival (months)
Cisplatin/5-FU *vs* Carboplatin/5-FU *vs* Methotrexate	277	32% 21% 10%	6.6 5 5.6
Cisplatin/pemetrexed *vs* Cisplatin	795	12.1% 8.%	7.3* 6.3 p= 0.082

* ECOG 0-1: OS (8.4 vs 6.7 months; p=0.026)
Oropharyngeal: OS (9.9 vs 6.1 months; p=0.002)

Jacobs et al JCO 2002, Clavel et al Ann Oncol 1994, Forastiere et al JCO 1992, Urba et Cancer 2012

Randomized trials with taxanes

Regimens	N	ORR (%)	Median survival (months)
Cisplatin/5-FU	**218**	**27%**	**8.7**
versus			
Cisplatin/paclitaxel		**26%**	**8.1**

- Cisplatin (100 mg/m2, day 1)/5-FU (1000 mg/m2/d, day 1-4), every 3 weeks
- Cisplatin (75 mg/m2, day 1)/paclitaxel (175 mg/m2, day 1), every 3 weeks

Gibson et al JCO 2005

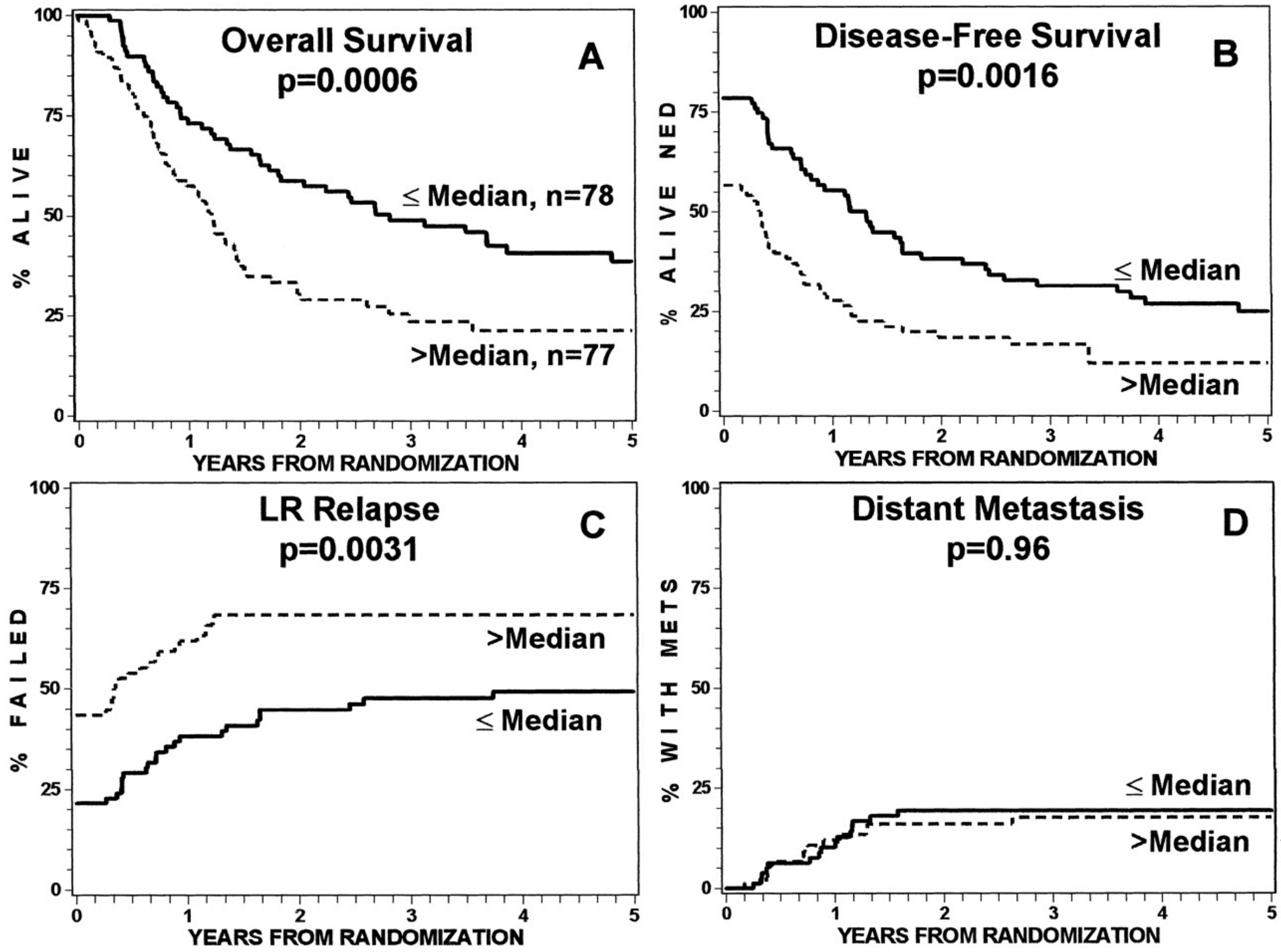
Chemotherapy: conclusions

- Median survival of patients is 6-8 months
- No evidence that chemotherapy prolongs survival
- Polychemotherapy versus monochemotherapy:
    - Higher response rate
    - More toxic
    - No improvement in survival

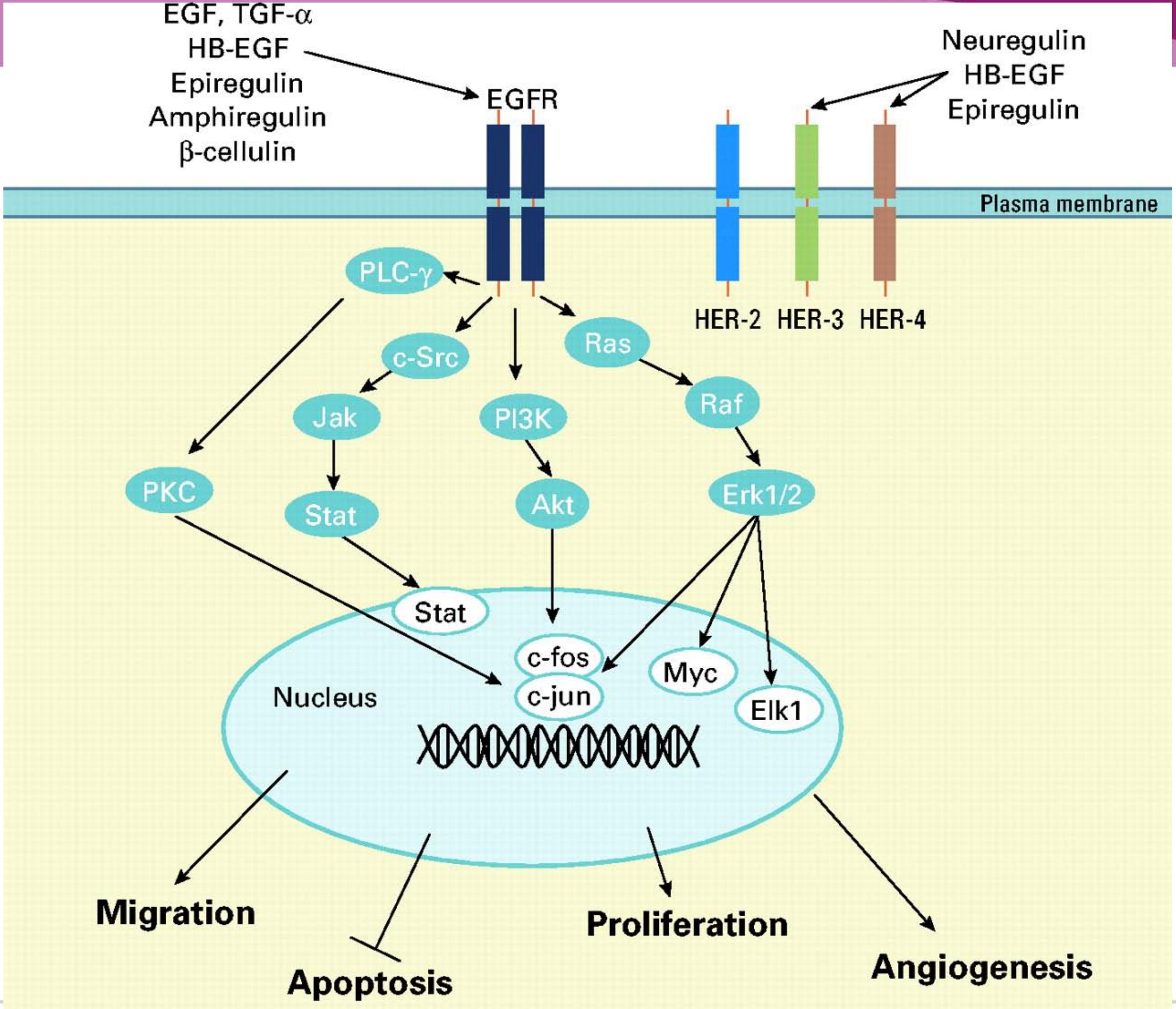
- Cisplatin /5-FU
- Cisplatin /paclitaxel
- Methotrexate (40 mg/m2/every week)

- Diagnosis
- Prognosis
- Lung metastases: surgery ?
- Re-irradiation and salvage surgery
- Chemotherapy
- **Molecular biology and targeted therapies**
- Immunotherapy

EGFR overexpression and prognosis



Ang, K. K. et al. Cancer Res 2002;62:7350-7356



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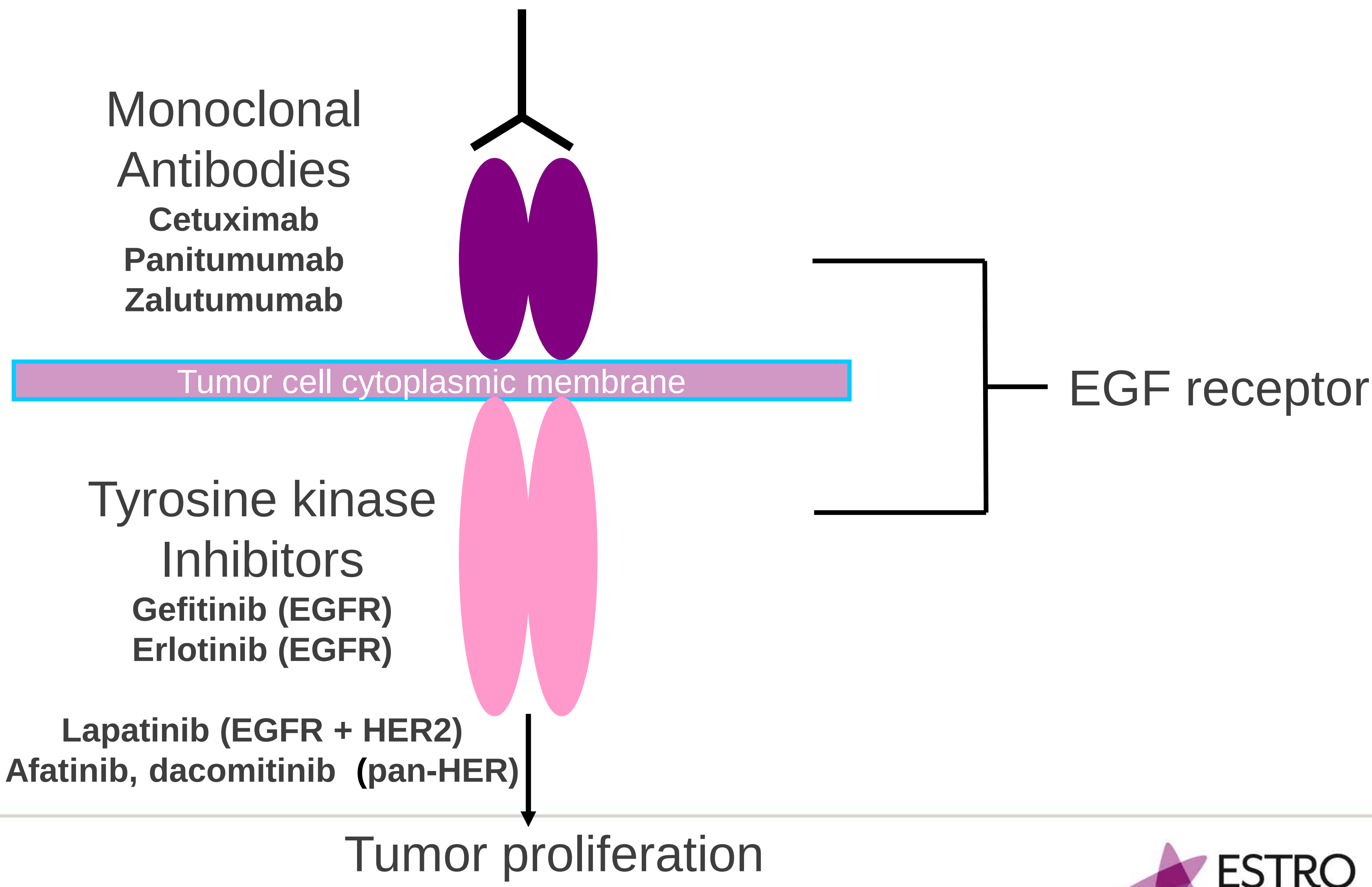
HER1 or EGFR targeting



Recurrent and/or metastatic non-curative disease

- **Anti-EGFR first-line palliative treatment: mAbs**

- Anti-EGFR second line: mAbs and TKIs

Recurrent/metastatic: first-line

Study	N	Regimens	Median PFS	Median Survival
Vermorken NEJM 2008	220 222	Platin/5-Fluorouracil *versus* Platin/5-FU/cetuximab	3.3 months* 5.6 months*	7.4 months* 10.1 months*
Vermorken Lancet Oncol 2013	330 327	Cisplatin/5-Fluorouracil *versus* Cisplatin/5-FU/panitumumab	4.6 months* 5.8 months*	9 months 11.1 months

Platin/5-FU vs platin/5-FU plus cetuximab

EXTREME Trial: first line palliative treatment

R

Platinum-5FU

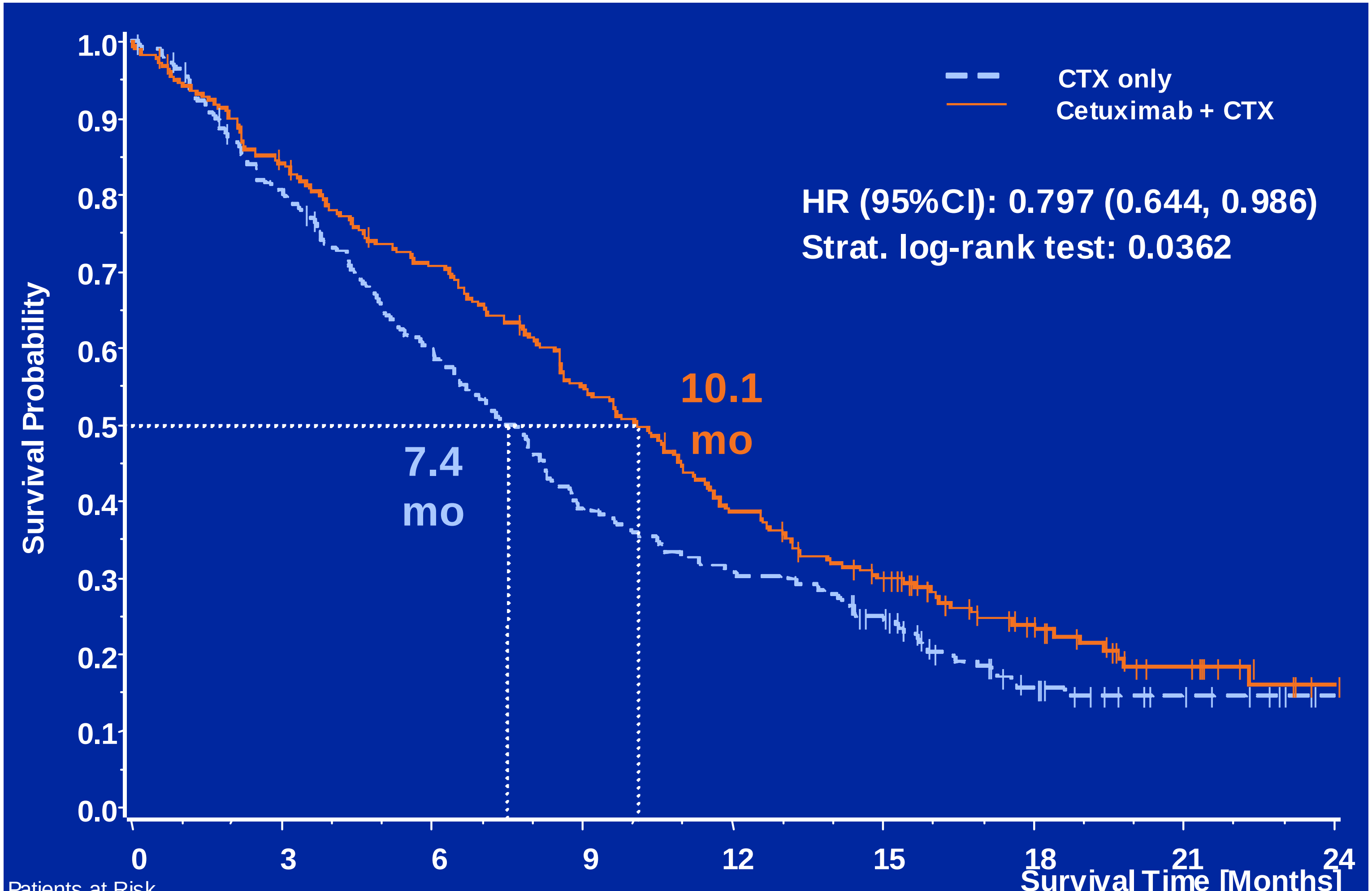
Platinum-5FU + cetuximab → Cetuximab monotherapy
6 chemotherapy cycles until PD or toxicity

N= 442

Primary endpoint: survival

Vermorken et al, NEJM, 2008

Extreme trial



Patients at Risk	0	3	6	9	12	15	18	21	24
CTX only	220	173	127	83	65	47	19	8	1
CET + CTX	222	184	153	118	82	57	30	15	3

Vermorken et al, NEJM 2008

These regimens can be TOXIC

Table 3. Grade 3 or 4 Adverse Events in the Safety Population.*

Event	Cetuximab plus Platinum–Fluorouracil (N=219) Grade 3 or 4	Cetuximab plus Platinum–Fluorouracil (N=219) Grade 4	Platinum–Fluorouracil Alone (N=215) Grade 3 or 4	Platinum–Fluorouracil Alone (N=215) Grade 4	P Value†
	number of patients (%)				
Any event	179 (82)	67 (31)	164 (76)	66 (31)	0.19
Neutropenia	49 (22)	9 (4)	50 (23)	18 (8)	0.91
Anemia	29 (13)	2 (1)	41 (19)	2 (1)	0.12
Thrombocytopenia	24 (11)	0	24 (11)	3 (1)	1.00
Leukopenia	19 (9)	4 (2)	19 (9)	5 (2)	1.00
Skin reactions‡	20 (9)	0	1 (<1)	0	<0.001
Hypokalemia	16 (7)	2 (1)	10 (5)	1 (<1)	0.31
Cardiac events§	16 (7)	11 (5)	9 (4)	7 (3)	0.22
Vomiting	12 (5)	0	6 (3)	0	0.23
Asthenia	11 (5)	1 (<1)	12 (6)	1 (<1)	0.83
Anorexia	11 (5)	2 (1)	3 (1)	1 (<1)	0.05
Hypomagnesemia	11 (5)	8 (4)	3 (1)	1 (<1)	0.05
Febrile neutropenia	10 (5)	2 (1)	10 (5)	4 (2)	1.00
Dyspnea	9 (4)	2 (1)	17 (8)	5 (2)	0.11
Pneumonia	9 (4)	3 (1)	4 (2)	1 (<1)	0.26
Hypocalcemia	9 (4)	5 (2)	2 (1)	0	0.06
Sepsis (including septic shock)	9 (4)	6 (3)	1 (<1)	1 (<1)	0.02
Tumor hemorrhage	3 (1)	2 (1)	6 (3)	4 (2)	0.33
Decreased performance status	2 (1)	1 (<1)	4 (2)	4 (2)	0.45
Respiratory failure	1 (<1)	0	5 (2)	4 (2)	0.12

Recurrent and/or metastatic non-curative disease

- Anti-EGFR first-line palliative treatment: mAbs

- **Anti-EGFR second line: mAbs and TKIs**

Anti-EGFR monoclonal antibodies

Platinum-5FU + anti-EGFR
6 chemotherapy cycles

→

anti-EGFR moAbs monotherapy
until PD or toxicity

Platinum-based CT
6 chemotherapy cycles

→

anti-EGFR moAbs monotherapy
at PD

What is the best option ?

Anti-EGFR monoclonal antibodies after platinum

Pooled of three prospective phase II trials with cetuximab monotherapy or with platin (N=278)

Retrospective study of patients who received various second-line treatments (N=194)

5.2 - 6.1 months

3.4 – 3.6 months

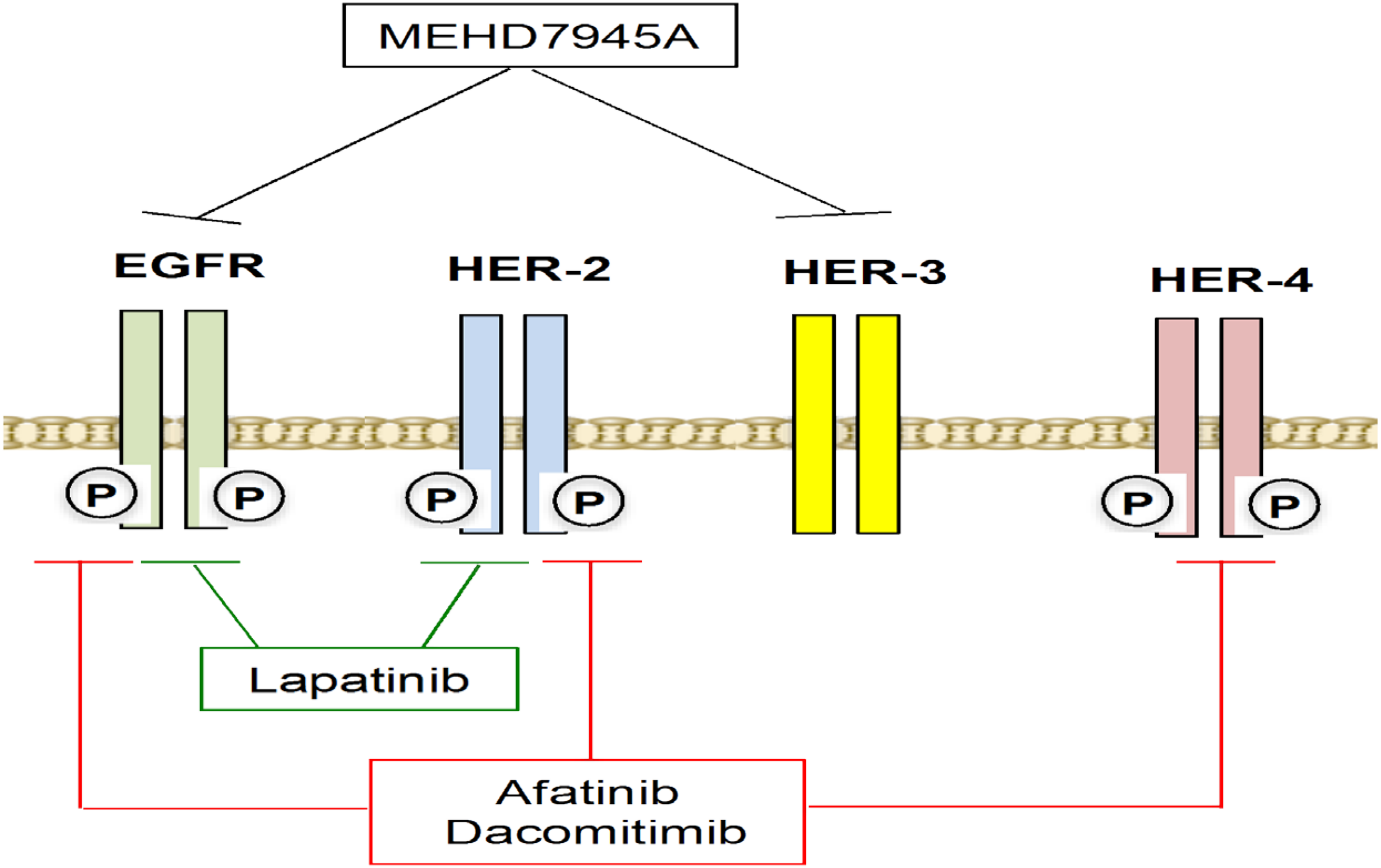
FDA approval

Vermorken et al. Cancer 2008

Anti-EGFR failed in second-line

Study	N	Regimens	ORR	Median PFS	Median Survival
Stewart JCO 2009	161 158 167	Methotrexate *versus* Gefitinib 250 mg/day *versus* Gefitinib 500 mg/day	3.9% 2.7% 7.6%	NA	5.6 months 6 months 6.7 months
Argiris JCO 2009	136 134	Docetaxel + placebo *versus* Docetaxel + gefitinib	6.2% 12.5%	NA	6 months 7.3 months
Machiels Lancet Oncol 2011	95 191	BSC or methotrexate *versus* Zalutumumab	1.1% 6.3%	8.4 weeks 9.9 weeks*	5.2 months 6.7 months

* Statistically signi


MEHD7945A
EGFR
HER-2
HER-3
HER-4
P
P
P
P
P
P
Lapatinib
Afatinib
Dacomitimib

EGFR/HER3 or pan-HER inhibition

Study	N	Regimens	ORR	Median PFS	Median Survival
Fayette ESMO LBA 2014	62 59	Cetuximab *versus* MEHD7945A	14.5% 11.9%	4 months 4.1 months	8.5 months 7.2 months
Machiels** Lancet Oncol 2015	161 322	Methotrexate *versus* Afatinib	5.6% 10.2%	1.7 months 2.6 months*	6 months 6.8 months

* Statistically significant
** Previous used of cetuximab allowed

Who is going to response ?

EGFR overexpression:	NO
EGFR polysomy or amplification:	NO
K-ras mutations	Rare in H&N
P16 or HPV	?

Licitra et al, Annals of Oncology 2010

Who is going to response ? HPV or p16 no clear answer

Study	N	N	Population	Benefit
Rosenthal ASCO 2014	Radiotherapy/ cetuximab Radiotherapy	p16+ = 44; p16- = 109 p16+ = 39; p16- = 120	Stage III/IV	p16- : HR: 0.9 (0S) p16+: HR: 0.45
Vermorken Ann Oncol 2014	Platin/5-FU/Cetuximab Platin/5-FU	p16+ = 18; p16- = 178 p16+ = 23; p16- = 162	Recurrent/metastatic: first-line	p16- : HR: 0.82 (0S) p16+: HR: 0.63
Vermorken Lancet Oncol 2013	Platin/5-FU/Panitumumab Platin/5-FU	p16+ = 57; p16- = 179 p16+ = 42; p16- = 165	Recurrent/metastatic first-line	p16- : HR: 0.73 (0S) p16+: HR: 1
Machiels Lancet Oncol 2015	Afatinib Methotrexate	p16+ = 31; p16- =141 p16+ = 11; p16- = 42	Recurrent/metastatic second-line	p16- : HR: 0.69 (PFS) p16+: HR: 0.95

Who is going to response ? HPV or p16 no clear answer

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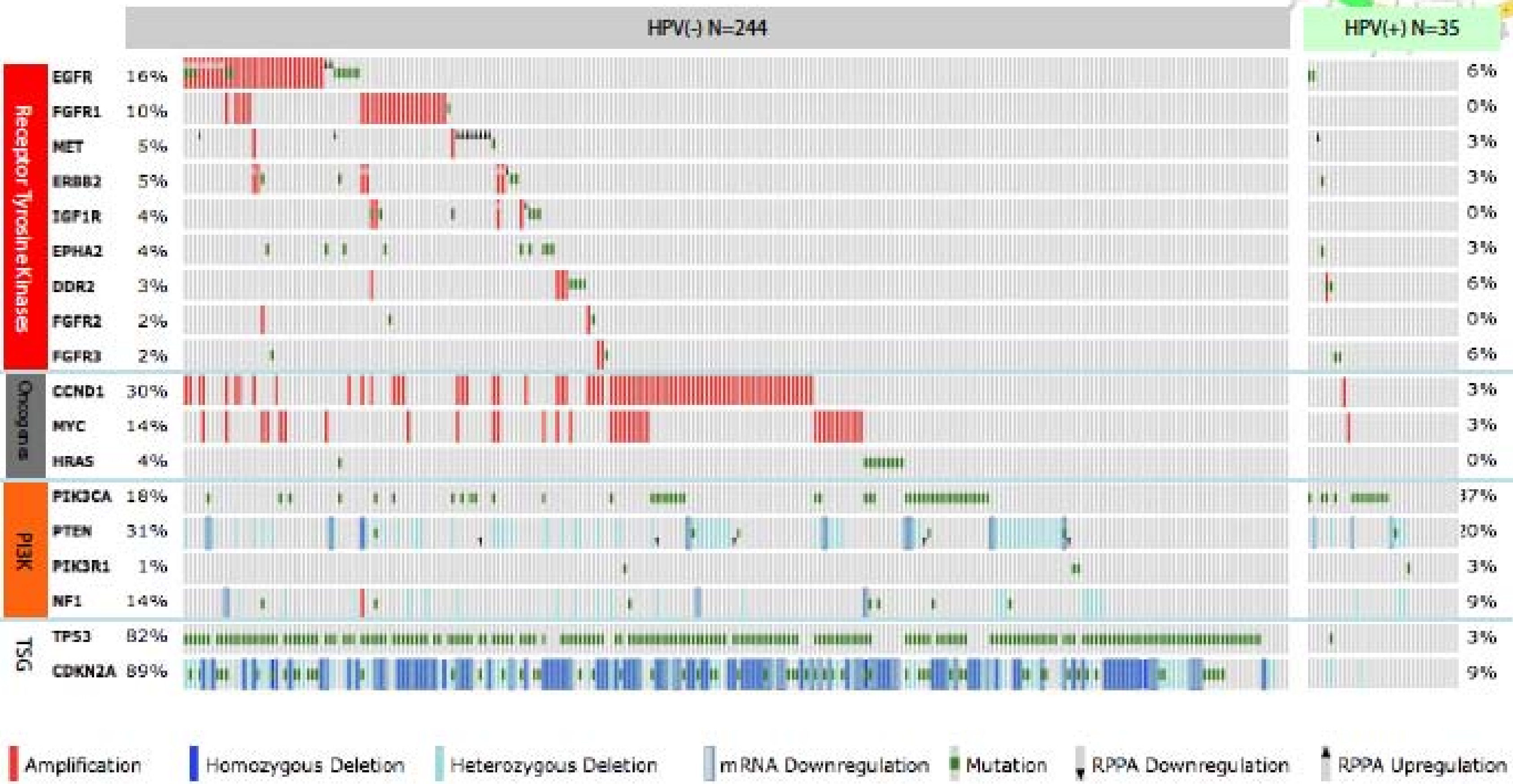
Who is going to response ? HPV or p16 no clear answer

- Very low number of patients in the p16 positive group
- p16 positive group included non-oropharyngeal sites
- p16 cut-off different in the EXTREME (10%)

Study	N	N	Population	Benefit
				.9 45
				.82 .63
				.73
Machiels Lancet Oncol 2015	Afatinib Methotrexate	p16+ = 31; p16- =141 p16+ = 11; p16- = 42	Recurrent/metastatic second-line	p16- : HR: 0.69 (PFS) p16+: HR: 0.95

Candidate Therapeutic Targets

Analysis – Tanguy Seiwert, Niki Schultz



BERIL-1: A Phase II, Randomized, Placebo-controlled Study of Buparlisib and Paclitaxel In Platinum-pretreated Advanced SCCHN

Recurrent or metastatic SCCHN
Failure of one prior platinum-based therapy

↓

Randomization (1:1)
Stratification by prior lines of treatment (1 vs 2) and study site (North America vs rest of world)

↓ ↓

Buparlisib (100 mg/day) + paclitaxel (80 mg/m^2/week)	**Placebo** + paclitaxel (80 mg/m^2/week)

Primary endpoint
- PFS (local assessment, RECIST v1.1)

Key secondary endpoint
- OS

Secondary endpoints
- ORR, DCR, DoR
- Safety/tolerability
- Pharmacokinetics
- HRQoL

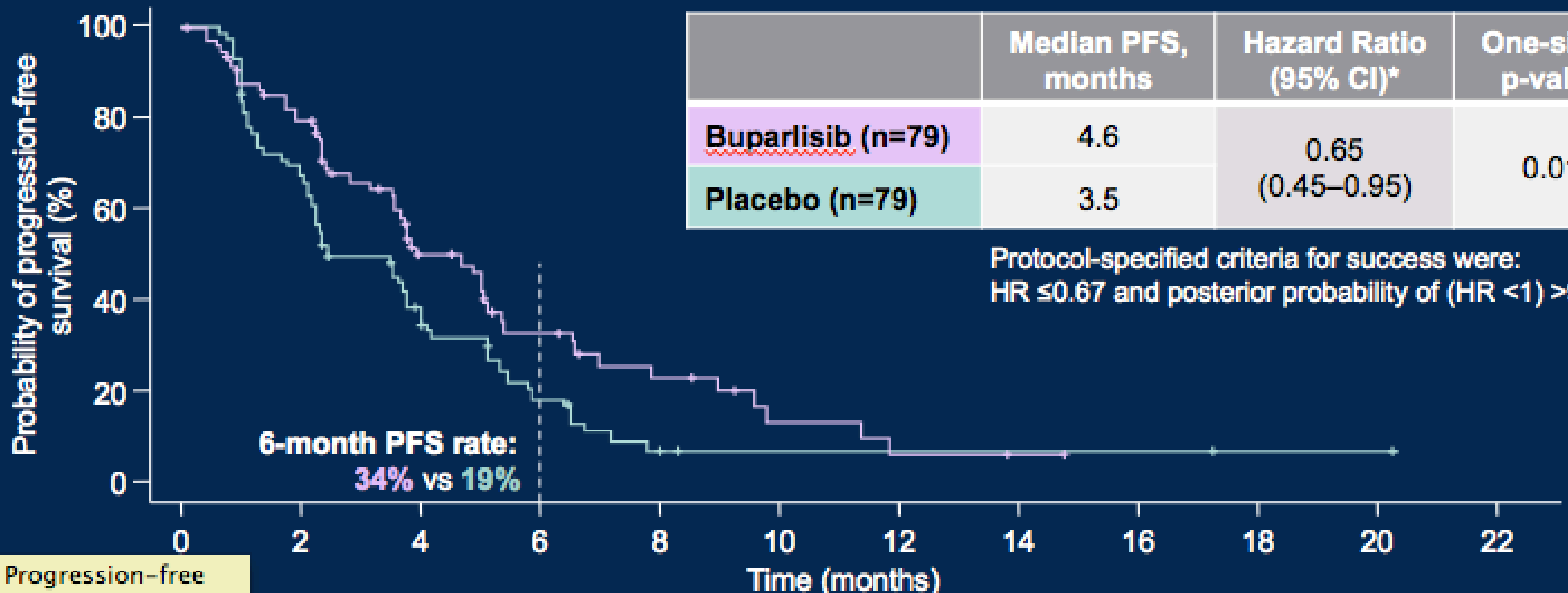
Exploratory biomarker assessments
- PI3K pathway activation status
- HPV status
- Molecular alterations in ctDNA/tumor tissue

ctDNA, circulating tumor DNA; DCR, disease control rate; DoR, duration of response; HPV, human papillomavirus; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.
BERIL-1 (ClinicalTrials.gov NCT01852292) involved 58 trial sites in 18 countries.

Soulières D *et al.* ASCO 2016:Abstract 6008

BERIL-1 Primary Endpoint: Progression-free Survival

BERIL-1 Primary Endpoint: Progression-free Survival



	Median PFS, months	Hazard Ratio (95% CI)*	One-sided p-value†
Buparlisib (n=79)	4.6	0.65 (0.45–0.95)	0.011
Placebo (n=79)	3.5		

Protocol-specified criteria for success were:
HR ≤0.67 and posterior probability of (HR <1) >97.5%

dpoint: Progression-free

Number of patients at risk

	0	2	4	6	8	10	12	14	16	18	20	22
Buparlisib	79	57	26	15	9	4	2	1	0	0	0	0
Placebo	79	51	22	11	3	2	2	2	2	1	1	0

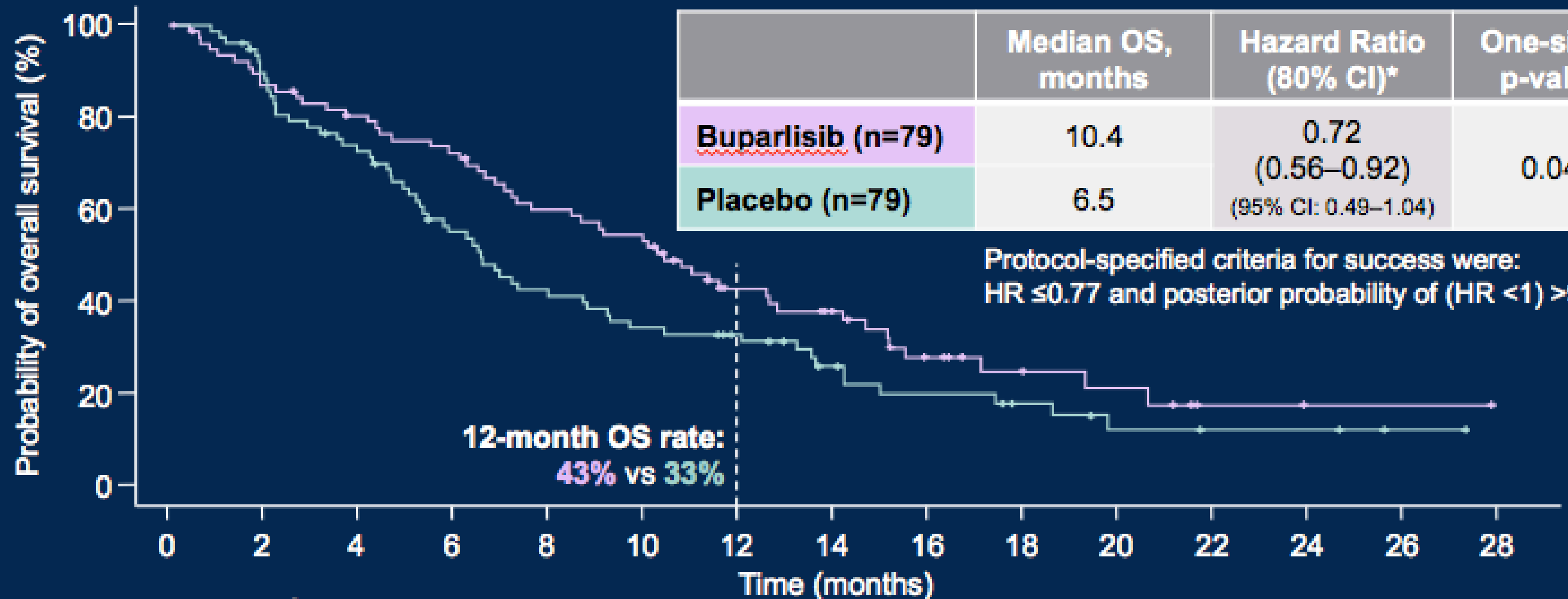
CI, confidence interval.
*The 97.5% Bayesian posterior probability criteria is equivalent to a 95% CI being <1; †Nominal p-value, not adjusted for multiple testing.

CI, confidence interval.
*The 97.5% Bayesian posterior probability criteria is equivalent to a 95% CI being <1; †Nominal p-value, not adjusted for multiple testing.

Soulières D *et al.* ASCO 2016:Abstract 6008

BERIL-1 Key Secondary Endpoint: Overall Survival

BERIL-1 Key Secondary Endpoint: Overall Survival



	Median OS, months	Hazard Ratio (80% CI)*	One-sided p-value†
Buparlisib (n=79)	10.4	0.72 (0.56–0.92) (95% CI: 0.49–1.04)	0.041
Placebo (n=79)	6.5		

Protocol-specified criteria for success were:
HR ≤0.77 and posterior probability of (HR <1) >90.0%

Number of patients at risk

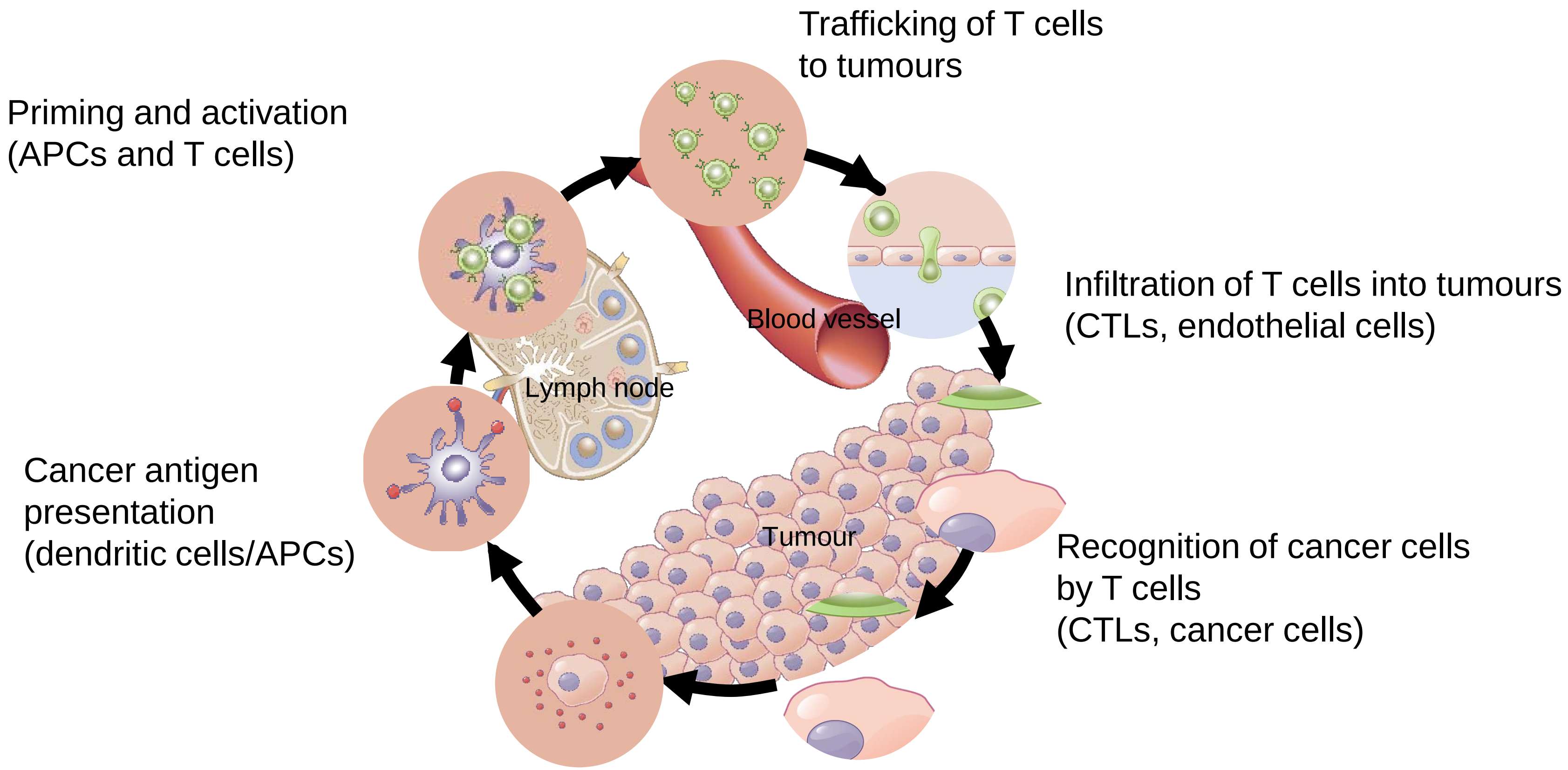
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Buparlisib	79	67	60	54	44	39	26	20	12	7	6	2	1	1	0
Placebo	79	68	55	40	30	25	21	14	10	7	4	3	3	1	0

*The 90% Bayesian posterior probability criteria is equivalent to a 80% CI being <1; †Nominal p-value, not adjusted for multiple testing.

Soulières D *et al.* ASCO 2016:Abstract 6008

- Diagnosis
- Prognosis
- Lung metastases: surgery ?
- Re-irradiation and salvage surgery
- Chemotherapy
- Molecular biology and targeted therapies
- **Immunotherapy**

The cancer-immunity cycle

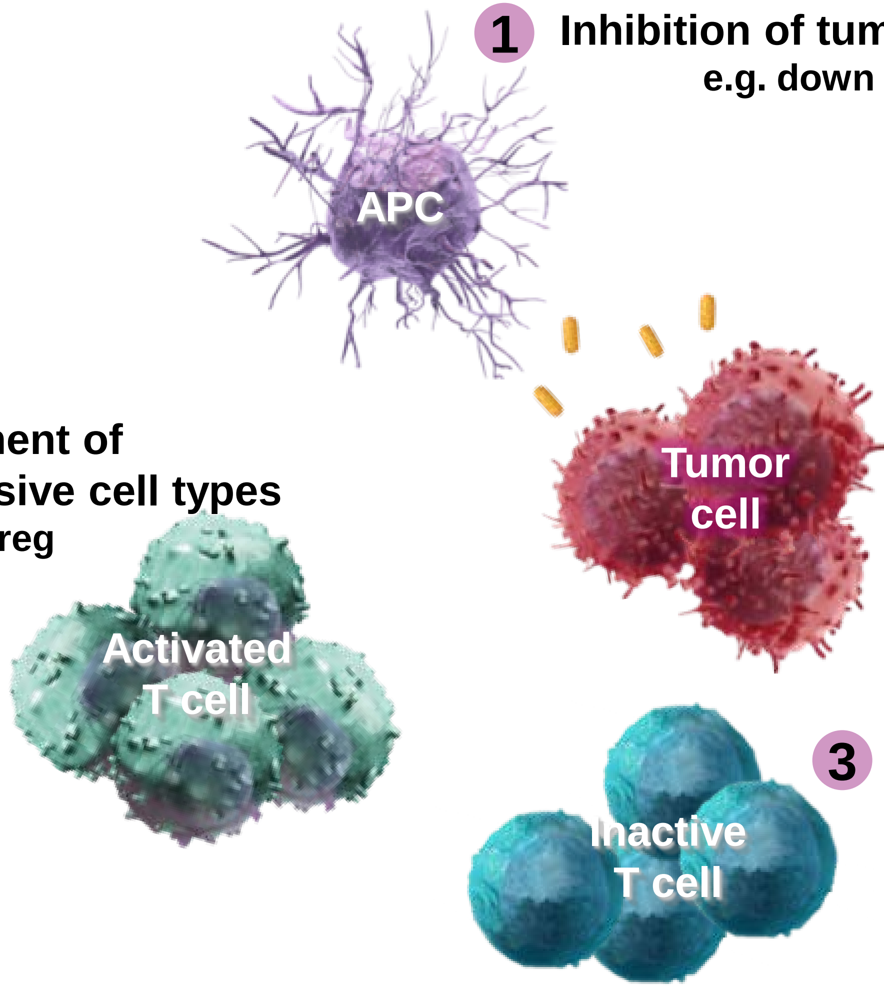


CTL = cytotoxic T cell.

Chen DS, Mellman I. *Immunity* 2013;39.

Tumors use complex, overlapping mechanisms to evade and suppress the immune system

1 **Inhibition of tumor antigen presentation**
e.g. down regulation of MHC I



2 **Secretion of immunosuppressive factors**
e.g. TGF-ß

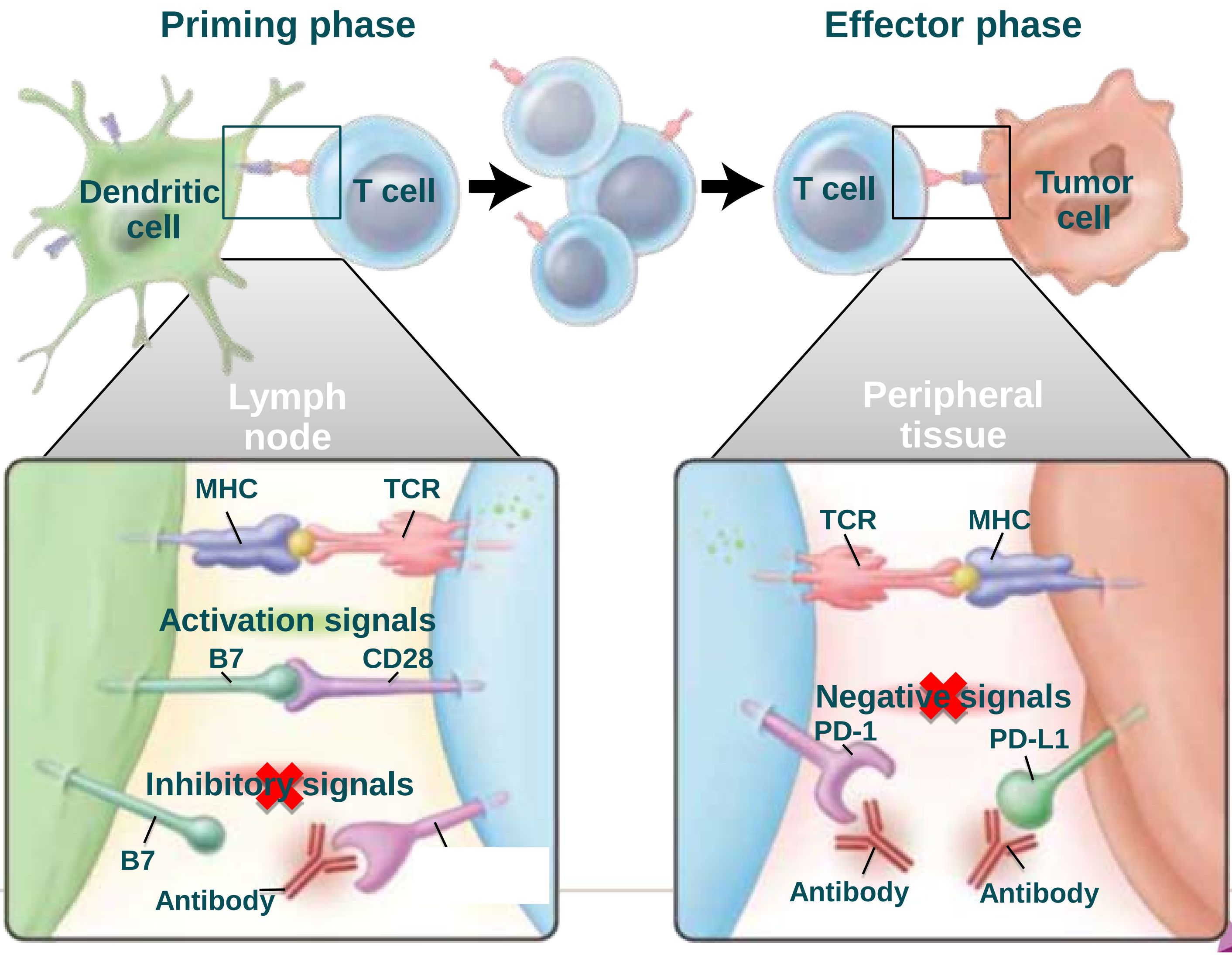
3 **Inhibition of attack by immune cells**
e.g. through T-cell checkpoint pathways

4 **Recruitment of immunosuppressive cell types**
e.g. T-reg

MHC = major histocompatibility complex; TGF-ß = tumor growth factor-ß.

Drake CG, et al. *Adv Immunol.* 2006;90:51–81; Vesely MD, et al. *Annu Rev Immunol*. 2011;29:235–271.

The role of immune checkpoint pathways in the immune response



TCR = T-cell receptor; PD-L1 = programmed death-ligand 1.

Ribas A. *N Engl J Med*. 2012;366:2517–2519.

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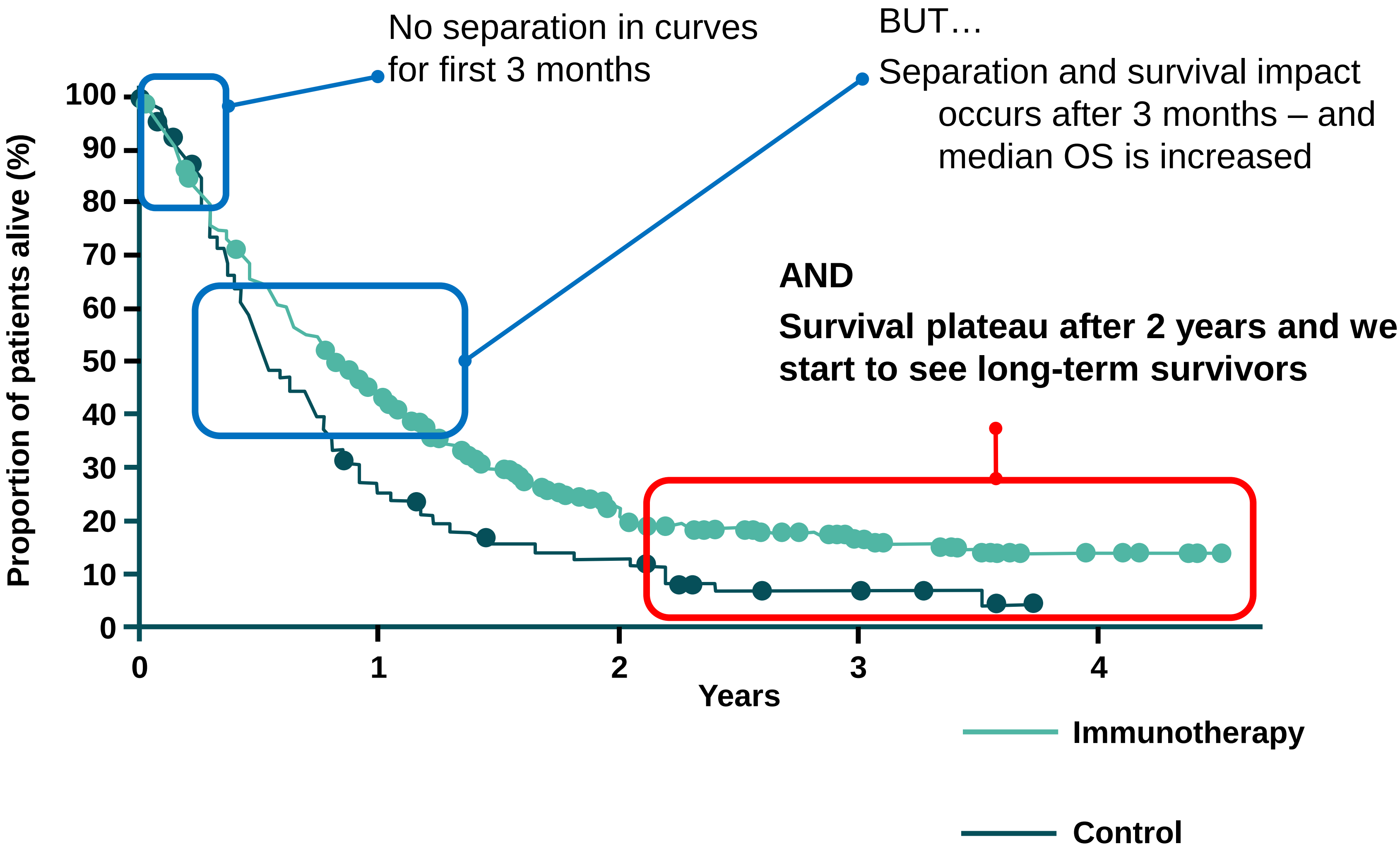
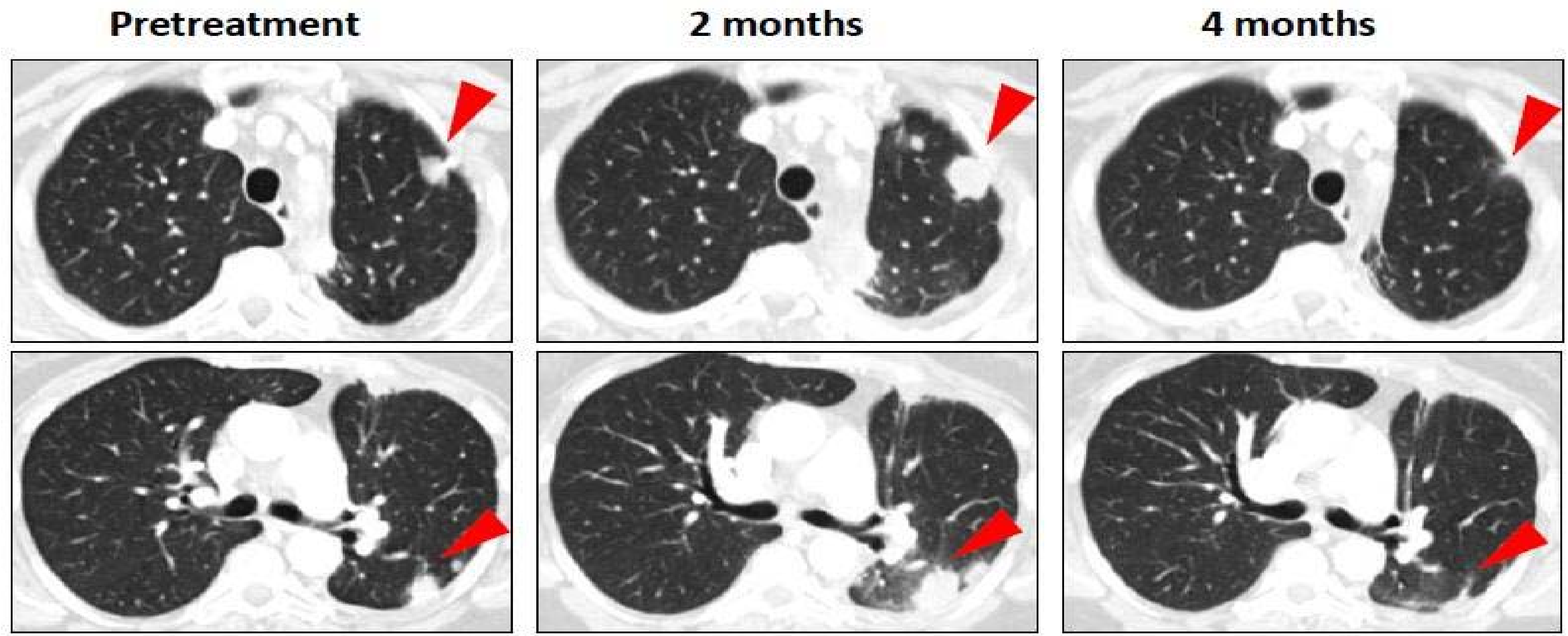
Overall survival



OS = overall survival.

Hodi FS, et al. *N Engl J Med.* 2010;363:711–723.

Pseudoprogression during nivolumab treatment of NSCLC



Topalian S, et al. *N Engl J Med*. 2012;366:2443–2454.

Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression

Pembrolizumab Anti-PD-1	Total N=117	HPV+ N=34	HPV- N=81
ORR	24.8%	20.6%	27.2%

MEDI4736 Anti-PD-L1	Total N=62	PD-L1+ N=22	PD-L1- N=37
ORR	11%	18%	8%

Toxicity with Immuno-Oncology agents

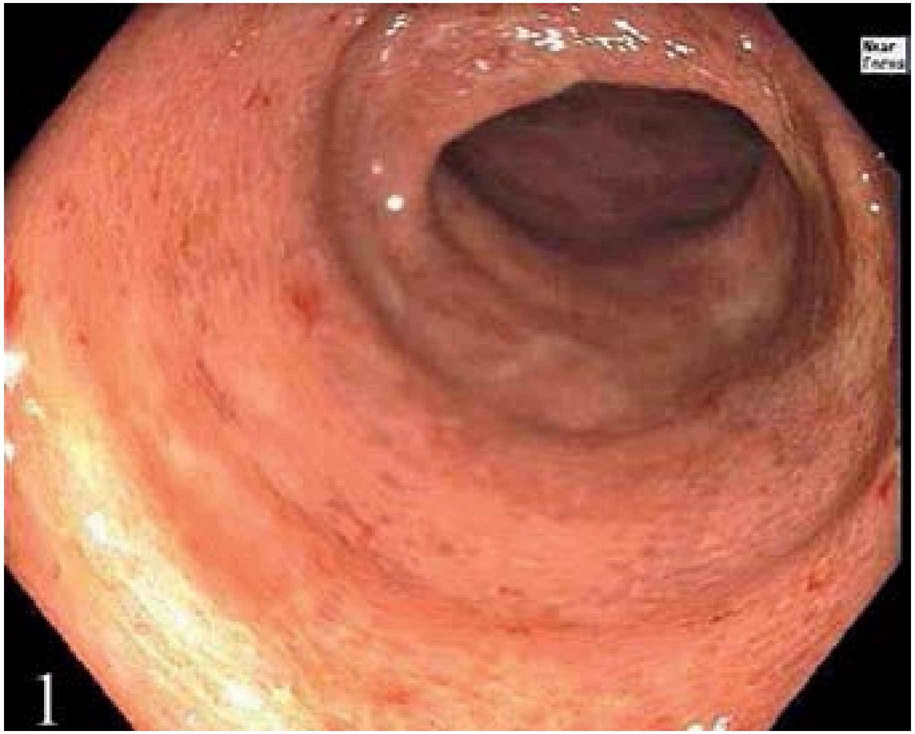
Activation of the immune system against tumors can result in a novel spectrum of Adverse events

AEs occur in certain organ systems:

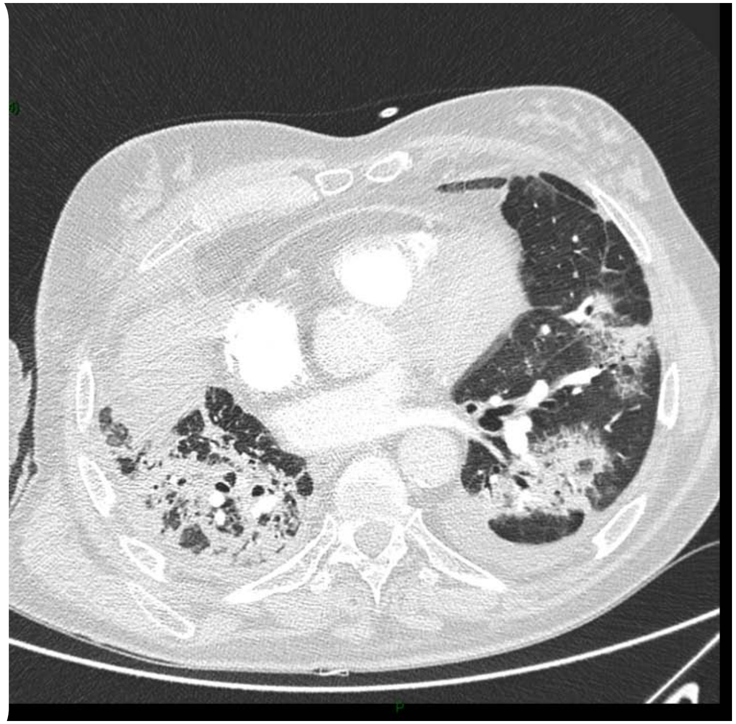
- Skin
- Endocrine system
- Liver
- Gastrointestinal tract
- Nervous system
- Eyes
- Respiratory system
- Hematopoietic cells

- Can be serious
- Requires prompt recognition and treatment
- Requires patient and health care professional education

Patient with diarrhea



Patient with dyspnea



CheckMate 141 Study Design

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab versus investigator's choice in patients with R/M SCCHN

Key Eligibility Criteria

- R/M SCCHN of the oral cavity, pharynx, or larynx
- Not amenable to curative therapy
- Progression on or within 6 months of last dose of platinum-based therapy
- ECOG PS 0–1
- Documentation of p16 to determine HPV status
- No active CNS metastases

Stratification factor
- Prior cetuximab treatment

R
2:1

Nivolumab
3 mg/kg IV q2w

Investigator's Choice
- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly)

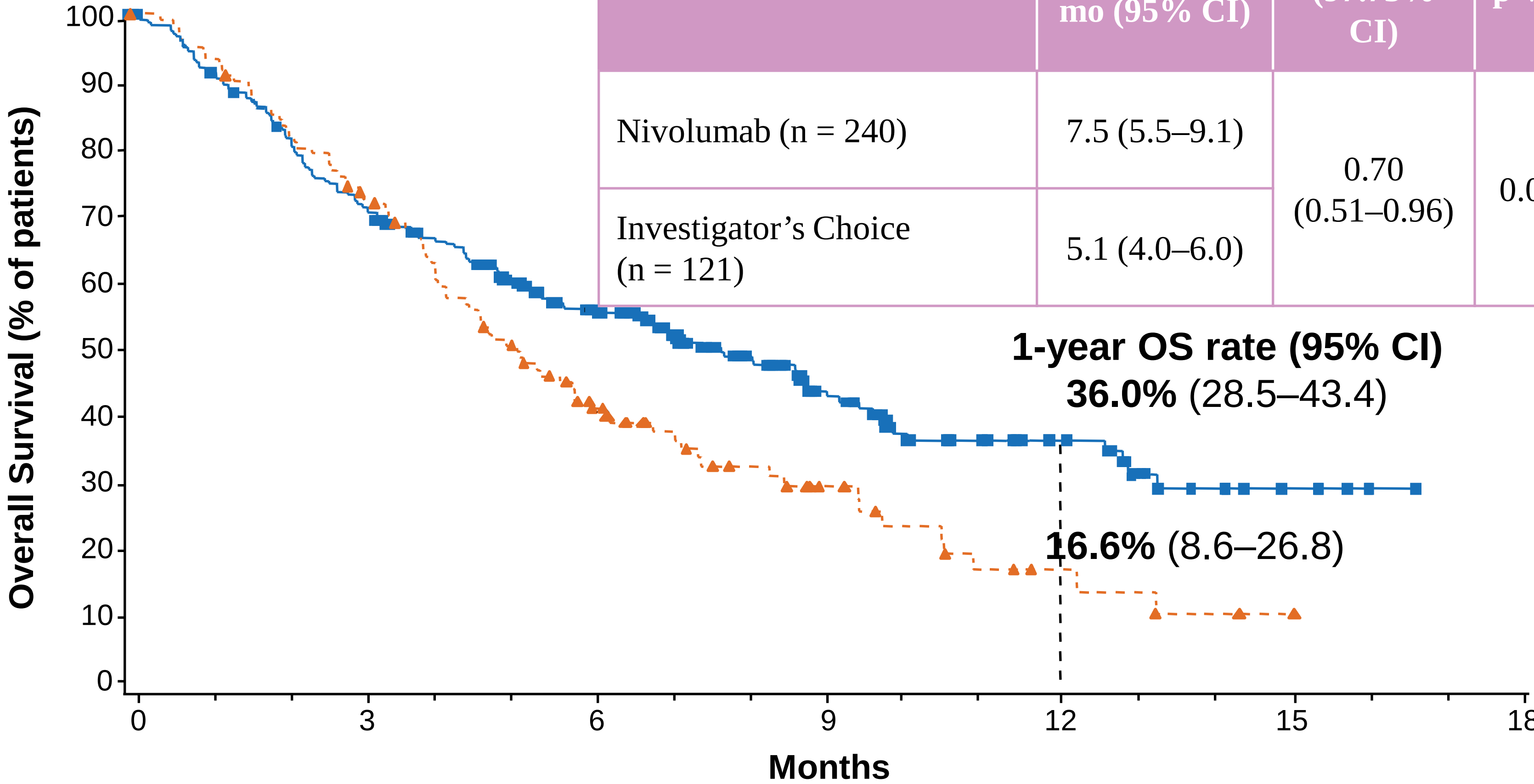
Primary endpoint
- OS

Other endpoints
- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomized; R/M, recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck; Clinicaltrials.gov. NCT02105636.

Overall Survival

	Median OS, mo (95% CI)	HR (97.73% CI)	p-value
Nivolumab (n = 240)	7.5 (5.5–9.1)	0.70 (0.51–0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0–6.0)		



No. at Risk

	0	3	6	9	12	15	18
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

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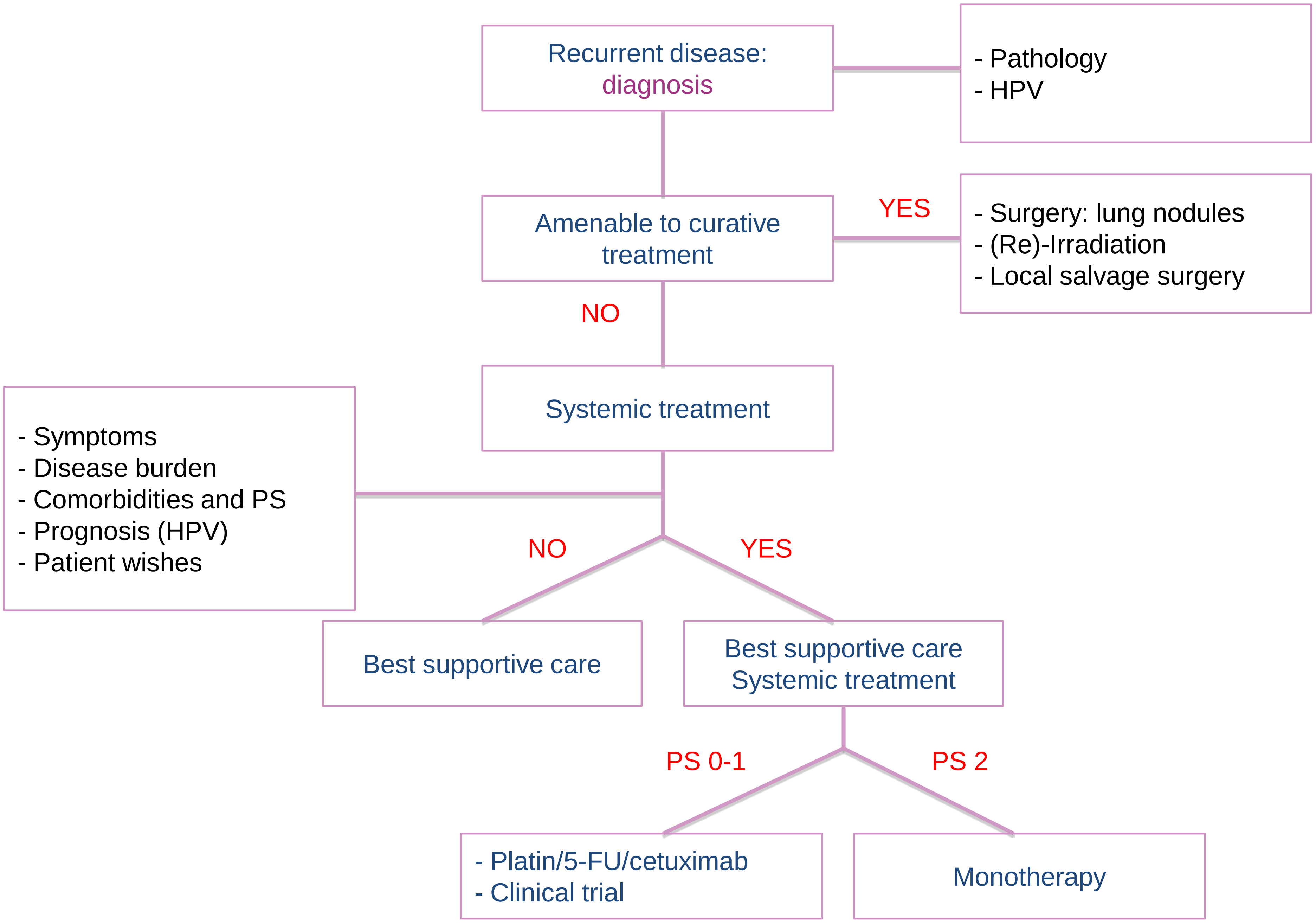
Treatment-Related AEs in ≥ 10% of Patients

Event	Nivolumab (n = 236)		Investigator's Choice (n = 111)	
	Any grade n (%)	Grade 3–4 n (%)	Any grade n (%)	Grade 3–4 n (%)
Any[a]	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
Fatigue	33 (14.0)	5 (2.1)	19 (17.1)	3 (2.7)
Nausea	20 (8.5)	0	23 (20.7)	1 (0.9)
Diarrhea	16 (6.8)	0	15 (13.5)	2 (1.8)
Anemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)
Asthenia	10 (4.2)	1 (0.4)	16 (14.4)	2 (1.8)
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Alopecia	0	0	14 (12.6)	3 (2.7)

Treatment-Related Select AEs

Event	Nivolumab (n = 236)		Investigator's Choice (n = 111)	
	Any grade n (%)	Grade 3–4 n (%)	Any grade n (%)	Grade 3–4 n (%)
Skin	37 (15.7)	0	14 (12.6)	2 (1.8)
Endocrine	18 (7.6)	1 (0.4)	1 (0.9)	0
Gastrointestinal	16 (6.8)	0	16 (14.4)	2 (1.8)
Hepatic	5 (2.1)	2 (0.8)	4 (3.6)	1 (0.9)
Pulmonary	5 (2.1)	2 (0.8)	1 (0.9)	0
Hypersensitivity/Infusion reaction	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal	1 (0.4)	0	2 (1.8)	1 (0.9)

Select AEs: AEs with potential immunologic etiology that requires monitoring/intervention


Recurrent disease: diagnosis
- Pathology
- HPV
Amenable to curative treatment
YES
- Surgery: lung nodules
- (Re)-Irradiation
- Local salvage surgery
NO
Systemic treatment
- Symptoms
- Disease burden
- Comorbidities and PS
- Prognosis (HPV)
- Patient wishes
NO
YES
Best supportive care
Best supportive care
Systemic treatment
PS 0-1
PS 2
- Platin/5-FU/cetuximab
- Clinical trial
Monotherapy

- Median survival of patients is 10-12 months (? Immunotherapy)

- First-line: Cisplatin /5-FU/cetuximab: standard of care
- Second-line: nivolumab

- Options: Platin/paclitaxel, taxanes, methotrexate

Recurrent and/or metastatic non-curative disease

- Squamous cell carcinoma of the head and neck
- **Salivary gland tumor**
- Nasopharyngeal

Salivary gland: metastatic disease

- Cisplatin
- Adriamycine
- 5-FU
- Cyclophosphamide
- Vinorelbin
- Taxanes

Rare disease: no randomized trials !!!

Salivary gland: metastatic disease

- Adenoid cystic carcinoma
  - indolent: follow-up
  - surgery
  - Chemotherapy: RESISTANT
    - adriamycine monotherapy,
    - cisplatine/adriamycine,
    - mitoxantrone, vinorelbin
    - taxanes: NO activity

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Salivary gland: metastatic disease

- Adenocarcinoma/salivary duct: rare
- Higher prevalence in men, > 50 years old
- Mainly in parotid gland
- Agressive with median survival: 3 years

- Histologically resemblance to invasive ductal carcinoma
- ER and PR rarely positive
- Androgen receptor present in 30-40%

Salivary duct carcinoma

Table 1. Characteristics of Patients With AR-Positive SDC Treated With Androgen Deprivation Therapy

Age (years)	Sex	Location	Prior Treatment	Recurrence/Metastasis	First-Line Antiandrogen	Second-Line Antiandrogen	RR	PFS (months)	OS (months)
57	M	Parotid	None	Locoregional lymph node, bone	Bicalutamide 150 mg	None	SD	14	14*
50	M	Submandibular	Surgery, radiation	Cerebral, bone	Bicalutamide 150 mg	None	PR	8	11
83	F	Parotid	None	None	Bicalutamide 50 mg	None	PR	26	56
56	M	Parotid	None	Locoregional lymph node, lung	Bicalutamide 150 mg	Bicalutamide 50 mg + goserelin 3.6 mg for 4 weeks†	SD	12‡	17
73	M	Parotid	Surgery, radiation	Locoregional lymph node, cerebral, skin	Bicalutamide 150 mg	Bicalutamide 50 mg + goserelin 3.6 mg for 4 weeks	PD	0	4
68	M	Parotid	None	Locoregional lymph node, lung	Bicalutamide 150 mg	Bicalutamide 50 mg + goserelin 10.8 mg for12 weeks§	PD	1	8
67	M	Parotid	Surgery, radiation	Local recurrence, locoregional lymph node, lung	Bicalutamide 50 mg + goserelin 3.6 mg for 4 weeks	None	SD	8‖	16
64	F	Parotid	Surgery, radiation	Locoregional lymph node, bone, lung	Bicalutamide 50 mg	None	PD	0	12
39	M	Parotid	None	Locoregional lymph node, liver	Bicalutamide 150 mg	None¶	PD	0	5*
73	M	Submandibular	None	Locoregional lymph node, cerebral	Bicalutamide 150 mg	None	PD	0	5*

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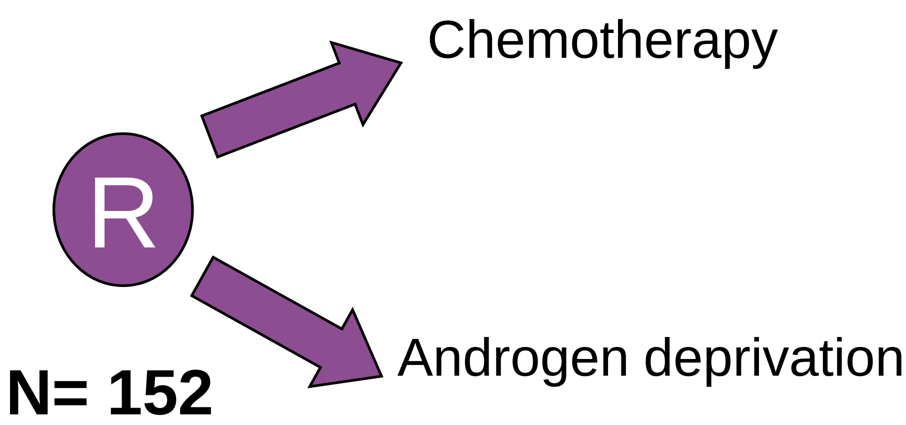
EORTC 1206

A randomised phase II study to evaluate the efficacy and safety of Chemotherapy (CT) vs androgen deprivation therapy (ADT) in patients with recurrent and/or metastatic, androgen receptor (AR) expressing, salivary gland cancer (SGCs)



Primary endpoint: Progression-free survival

Vermorken et al, NEJM, 2008

Recurrent and/or metastatic non-curative disease

- Squamous cell carcinoma of the head and neck
- Salivary gland tumor
- **Nasopharyngeal**

Metastatic nasopharyngeal carcinoma

1016 patients

16.15% had a solitary metastasis

Distant metastases:

Bones :	53.35%
Lung:	41.34%
Liver:	29.72%

Pan et al Experimental and therapeutic Medicine 2012

Metastatic nasopharyngeal carcinoma

FDG-PET: 20% distant metastases

ORR with platinum-based chemotherapy: 40-70%

Considered incurable but occasional long-term survivors have been described

In the largest series of long-term survivors, they were treated with CT followed by consolidation RT to the bone metastases

Liu et al. J Nucl Med 2007
Fandi et al. J Clin Oncol é000
Hui et al. Cancer 2004
Chan SL BMC cancer 2006
Lim et al. J Clin Oncol 2011

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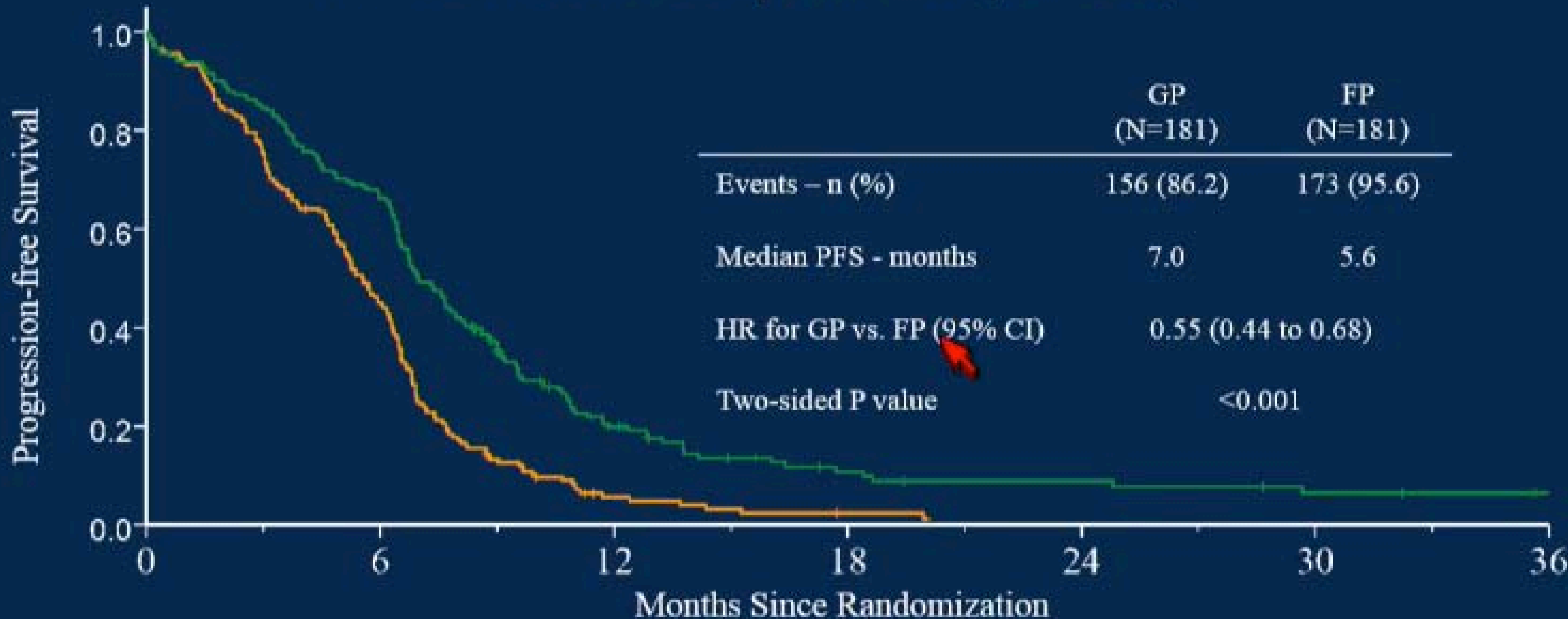
Trial design – *Randomized, open-label, multi-center, phase III*

NPC, nasopharyngeal carcinoma; RESIST, Response Evaluation Criteria In Solid Tumors; PS, performance status; ECOG, Eastern Cooperative Oncology Group; G, gemzar; P, cisplatin; F, 5-FU; civ, continuous infusion; PFS, progression-free survival; OS, overall survival; ORR, objective response rate.

Primary End Point: PFS by independent imaging-review committee

Intent-to-Treat Population (N=362)



	GP (N=181)	FP (N=181)
Events – n (%)	156 (86.2)	173 (95.6)
Median PFS - months	7.0	5.6
HR for GP vs. FP (95% CI)	0.55 (0.44 to 0.68)	
Two-sided P value	<0.001	

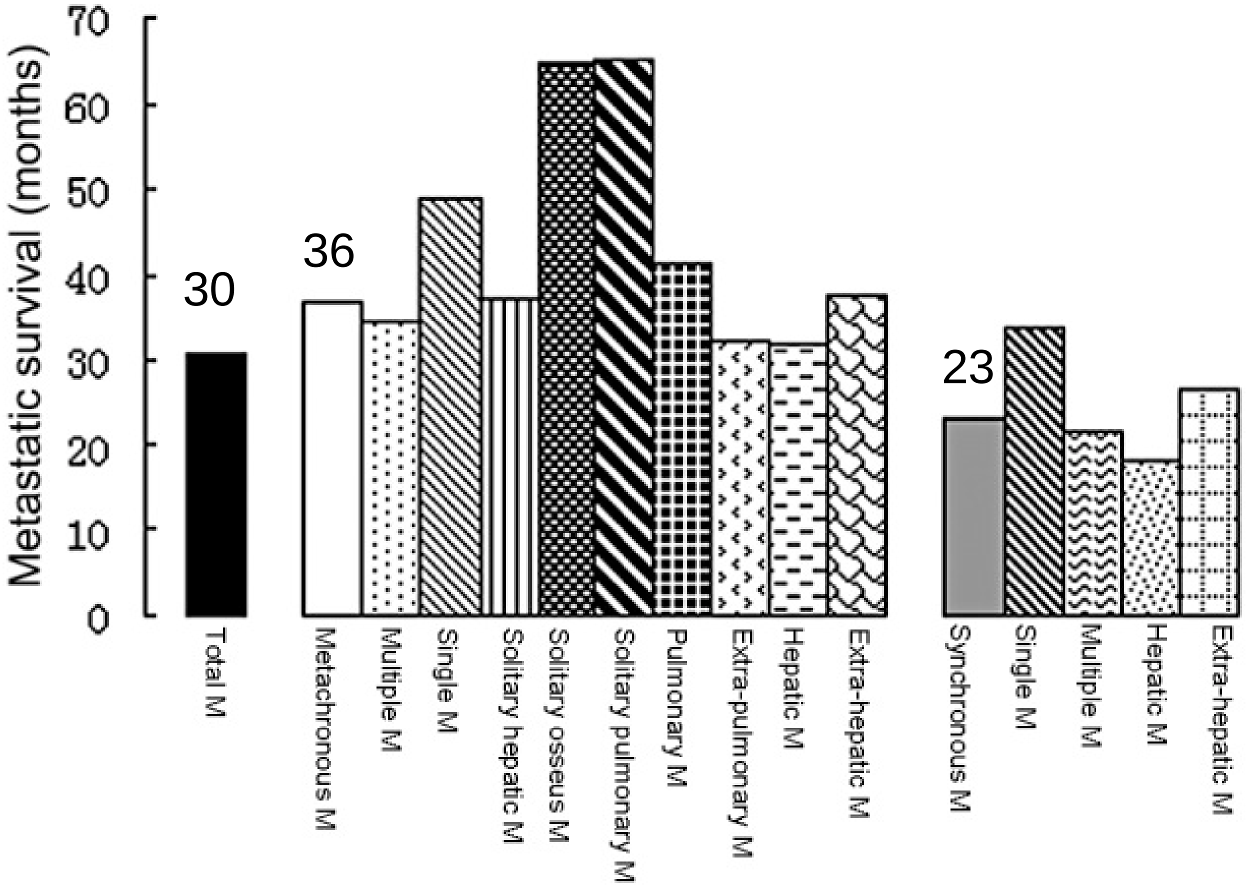
Risk of progression or death decreased by 45% with GP vs. FP

Secondary End Point: OS (*N=362*)

	GP (N=181)	FP (N=181)
Deaths – n (%)	66 (36.5)	95 (95.6)
Median OS - months	29.1	20.9
HR for GP vs. FP (95% CI)	0.62 (0.45 to 0.84)	
Two-sided P value	0.002	

OS data was immature; study will continue until the final OS analysis is performed

Metastatic nasopharyngeal carcinoma



Survival in 1016 patients with metastatic nasopharyngeal carcinoma according to subdivisions of metastatic status

Pan et al Experimental and therapeutic Medicine 2012

Thank you

INSTITUT
ROI ALBERT II
CANCÉROLOGIE ET HÉMATOLOGIE
Cliniques universitaires **SAINT-LUC** | **UCL** Bruxelles

Recurrent Tumours after Chemoradiation

C. René Leemans, MD, PhD
Professor and Chair

Otolaryngology-Head and Neck Surgery
VU University Medical Center
Amsterdam, The Netherlands

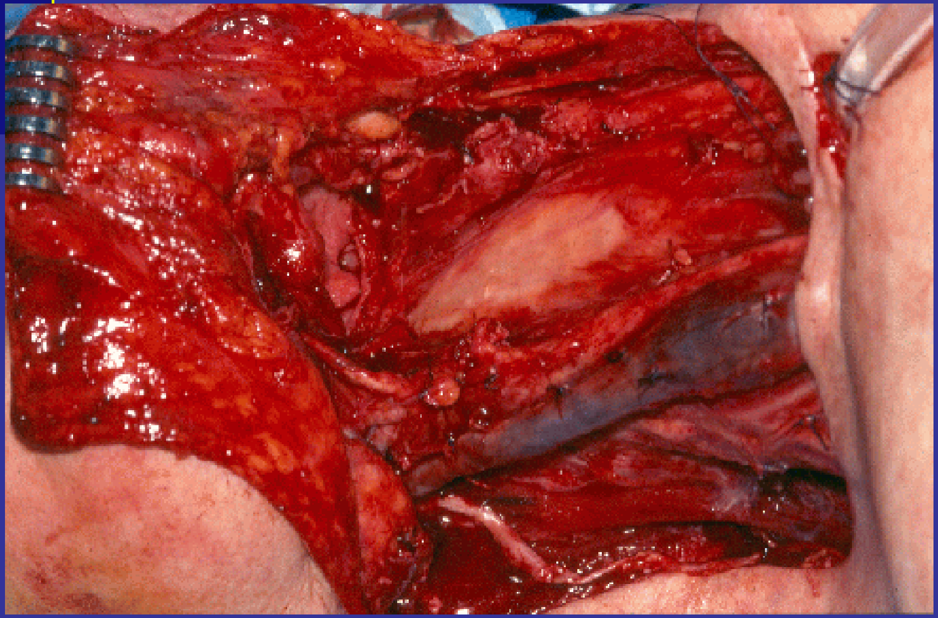
MULTIDISCIPLINARY MANAGEMENT
OF HEAD AND NECK ONCOLOGY
Florence, Italy. June 26-29, 2016

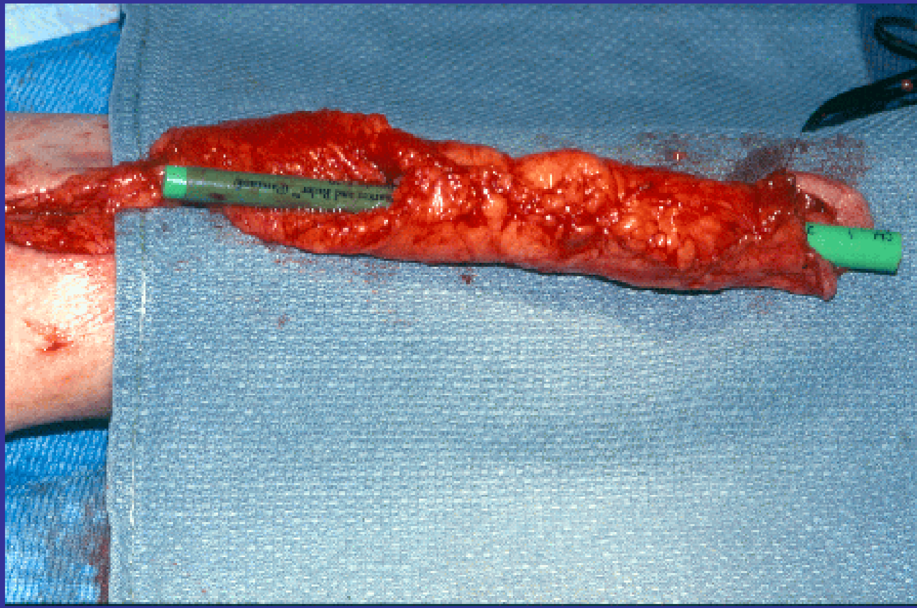
Pharyngo-esophagus Resection and Reconstruction

- Female 65 years
- Previous neck irradiation for TBC
- T3N0 hypopharynx carcinoma
- Total laryngopharyngectomy + neck dissection
- Tubed RFFF with monitor
- 60 months NED

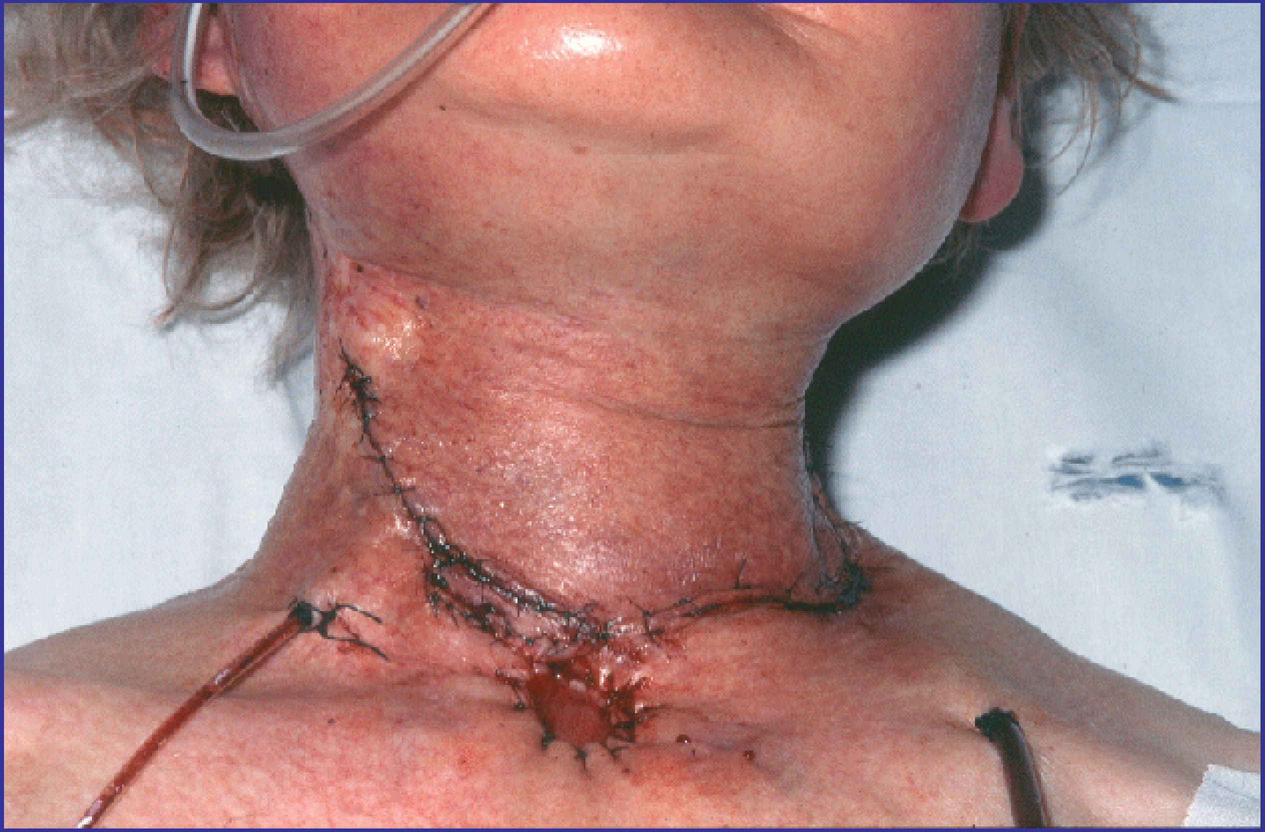
Surgical Salvage

Pharyngo-esophagus Resection and Reconstruction





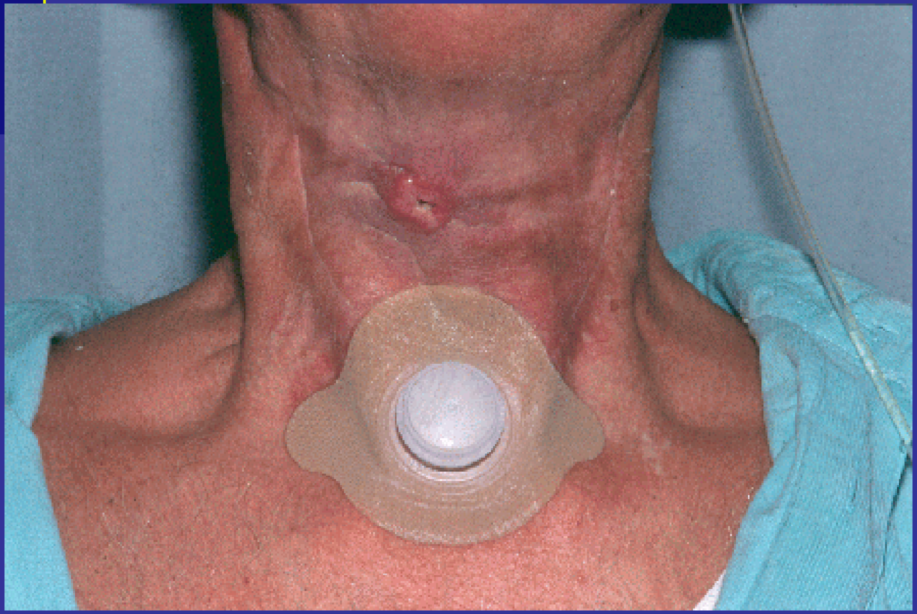
Pharyngo-esophagus Resection and Reconstruction

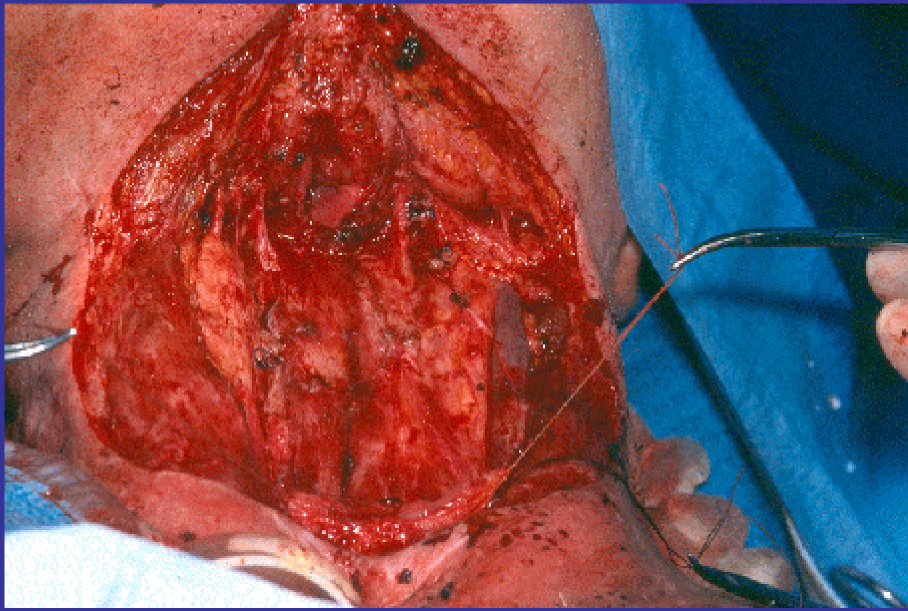


Complex Pharyngo-esophagus Resection and Reconstruction

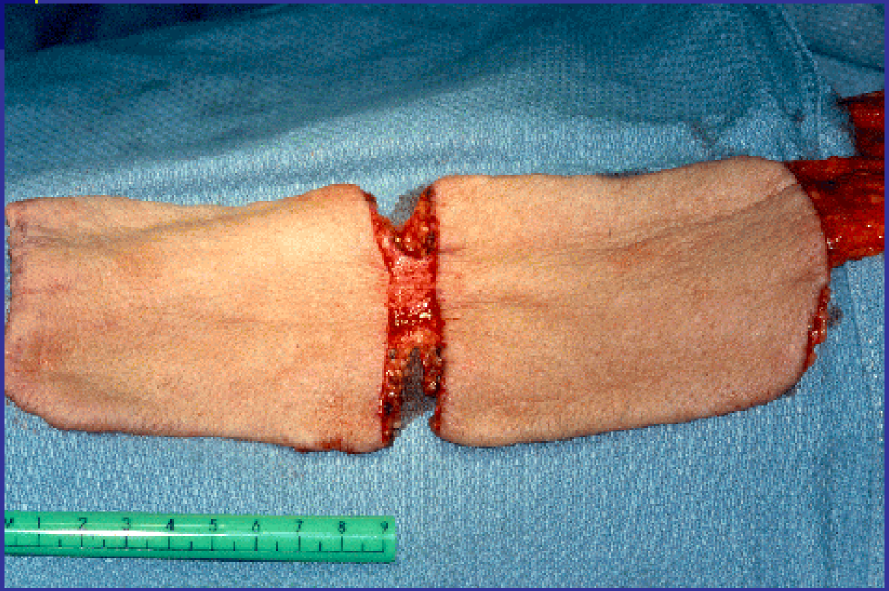
- Male 69 years
- Previous radiotherapy and total laryngecomy
- Recurrence in neopharynx with skin involvement
- Neopharyngectomy with skin
- Double-paddle RFFF with tube
- 47 months NED

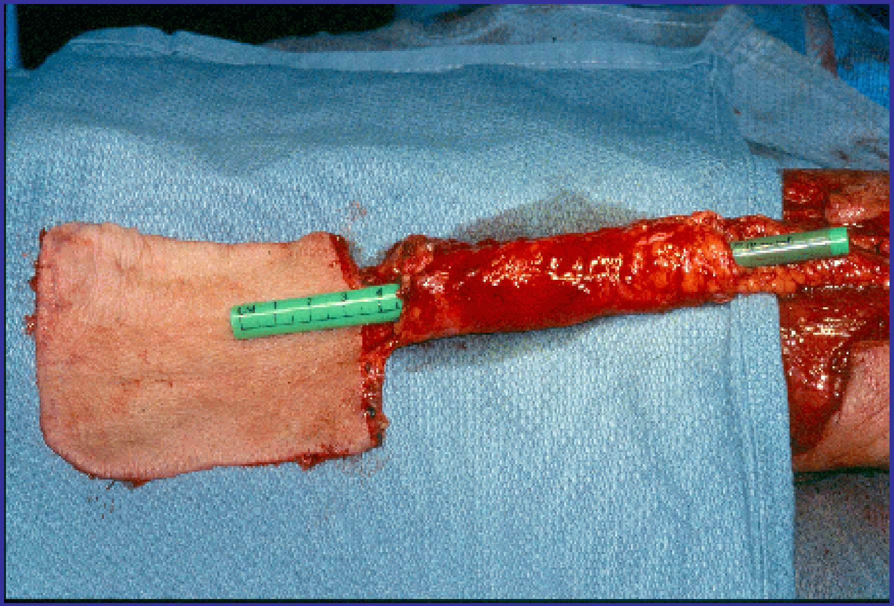
Complex Pharyngo-esophagus Resection and Reconstruction



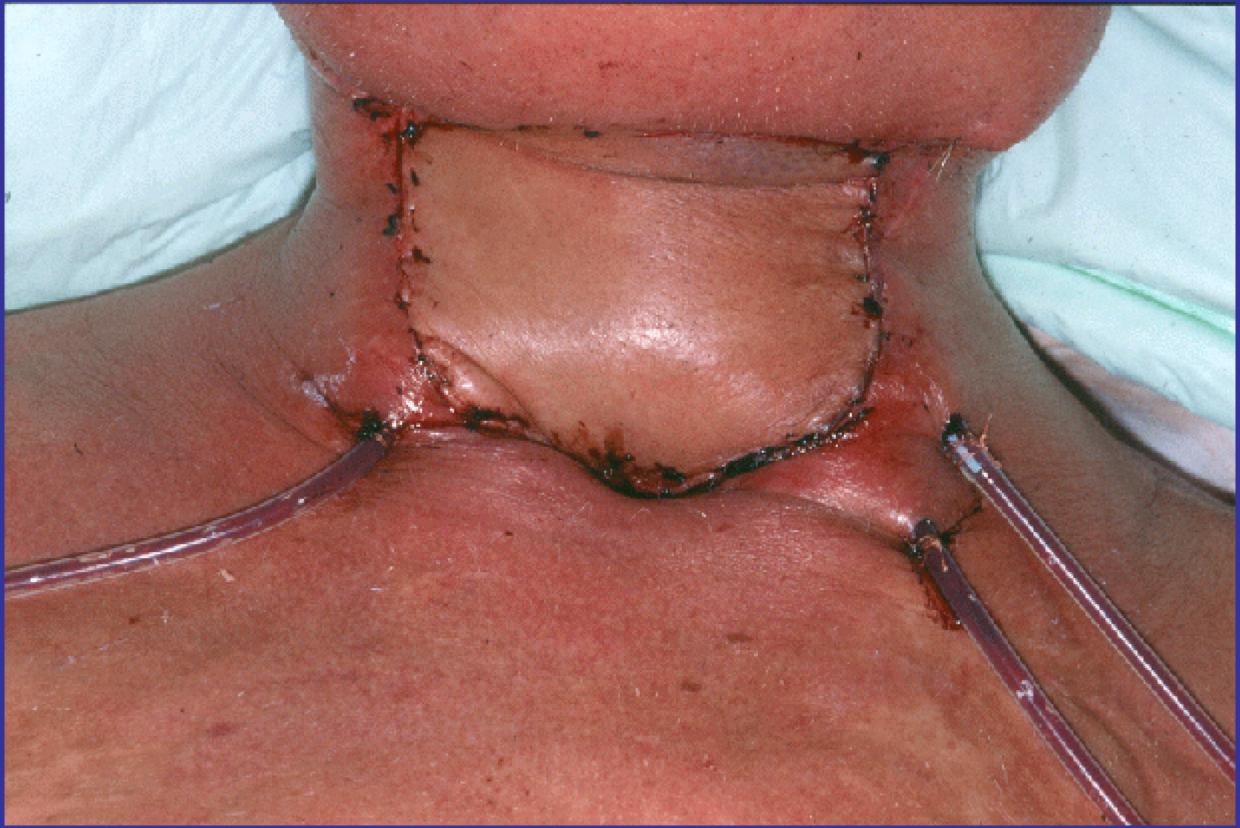


Complex Pharyngo-esophagus Resection and Reconstruction





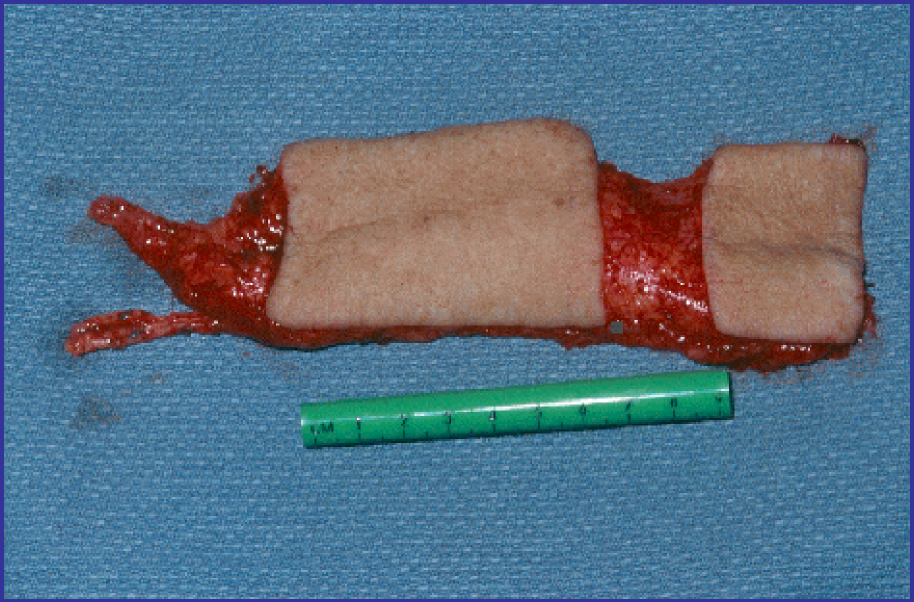
Complex Pharyngo-esophagus Resection and Reconstruction



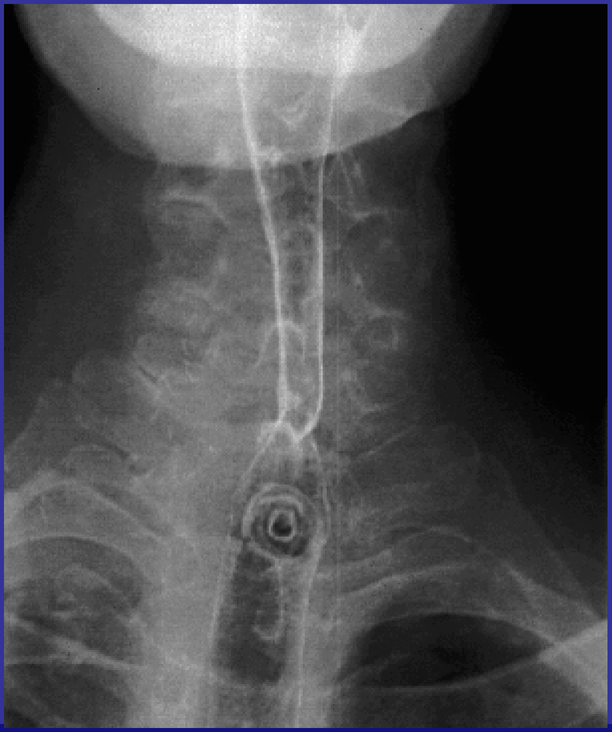
Palliative Salvage Surgery

- Male 55 years
- Previous total laryngectomy and neck dissections
- Local recurrence and pulmonary metastases, for which chemotherapy
- Large pharyngocutaneous fistula
- Double-paddle RFFF
- Palliation 24 months (without PEG)

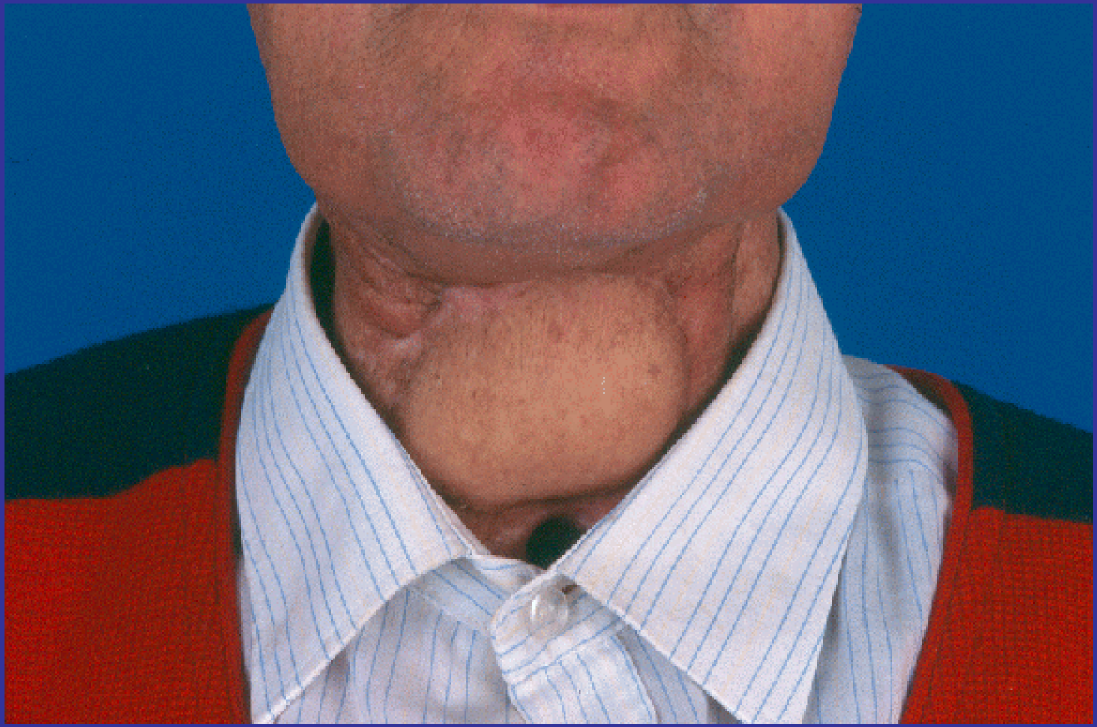
Palliative Salvage Surgery



Palliative Salvage Surgery



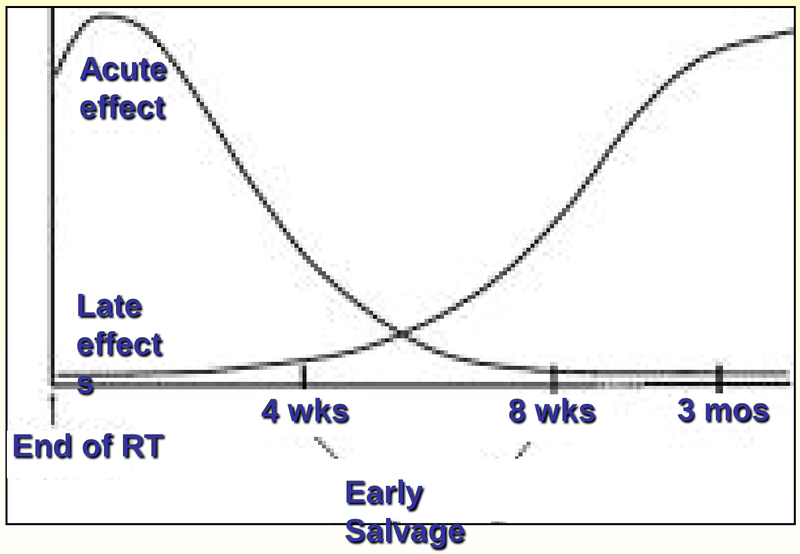
Palliative Salvage Surgery



Background

- Chemo-radiotherapy is increasingly applied in head and neck cancer to preserve function
- The role for surgery is evolving, with increased salvage for chemoradiation failures
- Not all recurrent disease is operable
- Early detection and salvage yields improved control and survival
- Reliable diagnostics are essential

Time Window Response Evaluation



Window for response evaluation, when acute inflammatory reactions subside and before long-term soft tissue damage is maximal

Dilemma: early diagnostics less reliable

Yom SS *et al*. Am.J.Clin.Oncol. 2005;28:385-92.

MRI and CT

Problems:

- Oedema at least 4-6 weeks after (chemo)radiation
- Volume reduction often delayed
- CT/MRI artefacts by dental filling

Accuracy after (chemo)radiation for head and neck carcinoma:

	Sensitivity	Specificity
CT	63% - 92%	47% - 80%
MRI	92% - 100%	41% - 86%

Lack of specificity

FDG-PET

Problems:

- <3-4 months after (C)RT high incidence equivocal and inaccurate interpretation (local and regional)
- Problems:
  - False-positive: inflammatory effect
  - False-negative: tumors < 0.5 cm

Accuracy after (chemo)radiation for head and neck carcinoma:

Local	Sensitivity	Specificity
PET	50% - 100%	64% - 93%

Regional	Sensitivity	Specificity
PET	40% - 100%	25% - 100%

Negative predictive value at 3 months in general very reliable

FDG-PET: Regional Control

Accuracy PET for detection of lymph node metastases is interval dependent:

Author	Interval after chemoradiation	Negative Predictive Value	
Rogers	4 weeks	14%	(95%CI: 3%-45%)
McCollum	4-12 weeks	73%	(95%CI: 46%-99%)
Yao; Porceddu	> 8 weeks	97% - 100%	(95%CI: 87%-99% en 96%-100%)

Rogers JW *et al*. Int.J.Radiat.Oncol.Biol.Phys. 2004;58:694-7.
McCollum *et al*. Head Neck 2004;26:890-6.
Porceddu SV *et al*. Head Neck 2005;27:175-81.

Diagnostic Accuracy USgFNAC

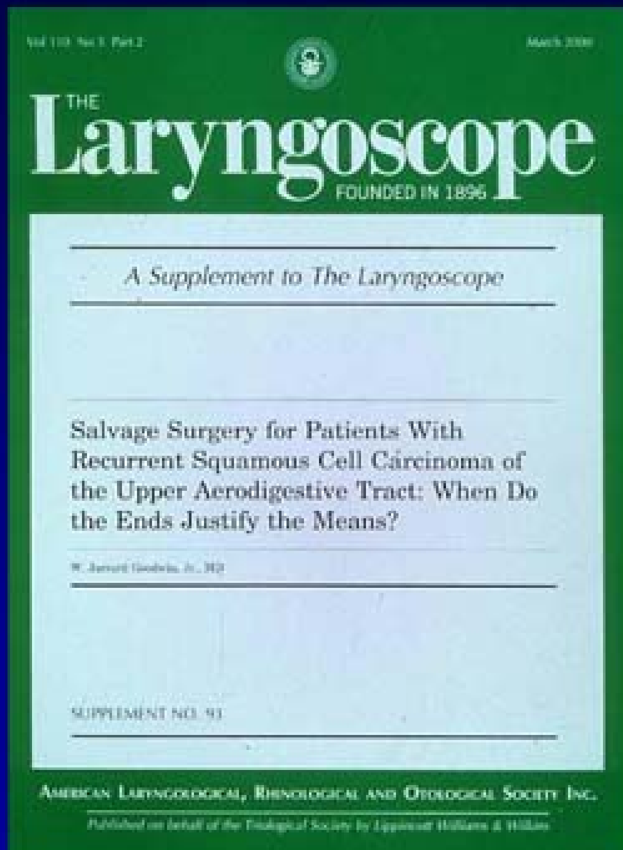
Accuracy	%
Sensitivity	80
Specificity	42
PPV	40
NPV	81
Overall accuracy	57%

Salvage Surgery

- Salvage surgery for a limited number of patients
- High complication rate
- High rate of locoregional recurrences after salvage surgery, distant metastases and second primaries

- What is the outcome?

Salvage Surgery


THE Laryngoscope
FOUNDED IN 1896

A Supplement to The Laryngoscope

Salvage Surgery for Patients With Recurrent Squamous Cell Carcinoma of the Upper Aerodigestive Tract: When Do the Ends Justify the Means?

SUPPLEMENT NO. 93

American Laryngological, Rhinological and Otological Society Inc.

Jerry Goodwin

Goodwin WJ. Laryngoscope 2000;110(3 Pt 2 Suppl 93):1-18

Outcomes of Salvage Surgery for Recurrent Squamous Cell Carcinoma of the Upper Aerodigestive Tract

Stage I & II

• 2-Years Survival	> 70%
• Good Quality of Life	60 – 85%
• Surgical Complications	6%
• Death Related to Surgery	Rare

Outcomes of Salvage Surgery for Recurrent Squamous Cell Carcinoma of the Upper Aerodigestive Tract

Stage III

• 2-Years Survival	33%
• Good Quality of Life	40%
• Surgical Complications	30%
• Death Related to Surgery	< 2%

Outcomes of Salvage Surgery for Recurrent Squamous Cell Carcinoma of the Upper Aerodigestive Tract

Stage IV

• 2-Years Survival	< 25%
• Good Quality of Life	30%
• Surgical Complications	30%
• Death Related to Surgery	< 2%

Conclusions Goodwin

- Weighted average of 5-year survival was 39% in 1,080 patients from 28 different institutions
- Median DFS of 17.9 months in 109 patients, correlated strongly with recurrent stage, weakly with recurrent site, and not at all with time to recurrence
- Noneconomic costs for patients and economic costs correlated with recurrent stage, but not with site

Goodwin WJ. Laryngoscope 2000;110(3 Pt 2 Suppl 93):1-18

Conclusions Goodwin (cont'd)

- Success was limited and costs were great in stage III and, especially, in stage IV recurrences
- The decision to undergo salvage surgery should be a personal choice made by the patient after honest and compassionate discussion with his or her surgeon

Goodwin WJ. Laryngoscope 2000;110(3 Pt 2 Suppl 93):1-18

Salvage Surgery

- Salvage surgery for a limited number of patients
- High complication rate
- High rate of locoregional recurrences after salvage surgery, distant metastases and second primaries

- What is the outcome in VU University medical center series?

Patient Population n=503 (1993-2012) Chemoradiation (Surgically Potentially Salvageable)

Reasons	Excluded (#)
NPC	61
Other Sites	12
Non-curative Intent	29
Non-cisplatin based	4
Other	65
Study Population	331

Primary Tumor Site

Site	N	%
Oral Cavity	35	11
Oropharynx	160	48
Hypopharynx	72	22
Larynx	64	19

Patient Population
Chemoradiation (n=331)

	N	%
Control	200	60
Residual	41	12
Recurrent	87	27
Dead	3	1

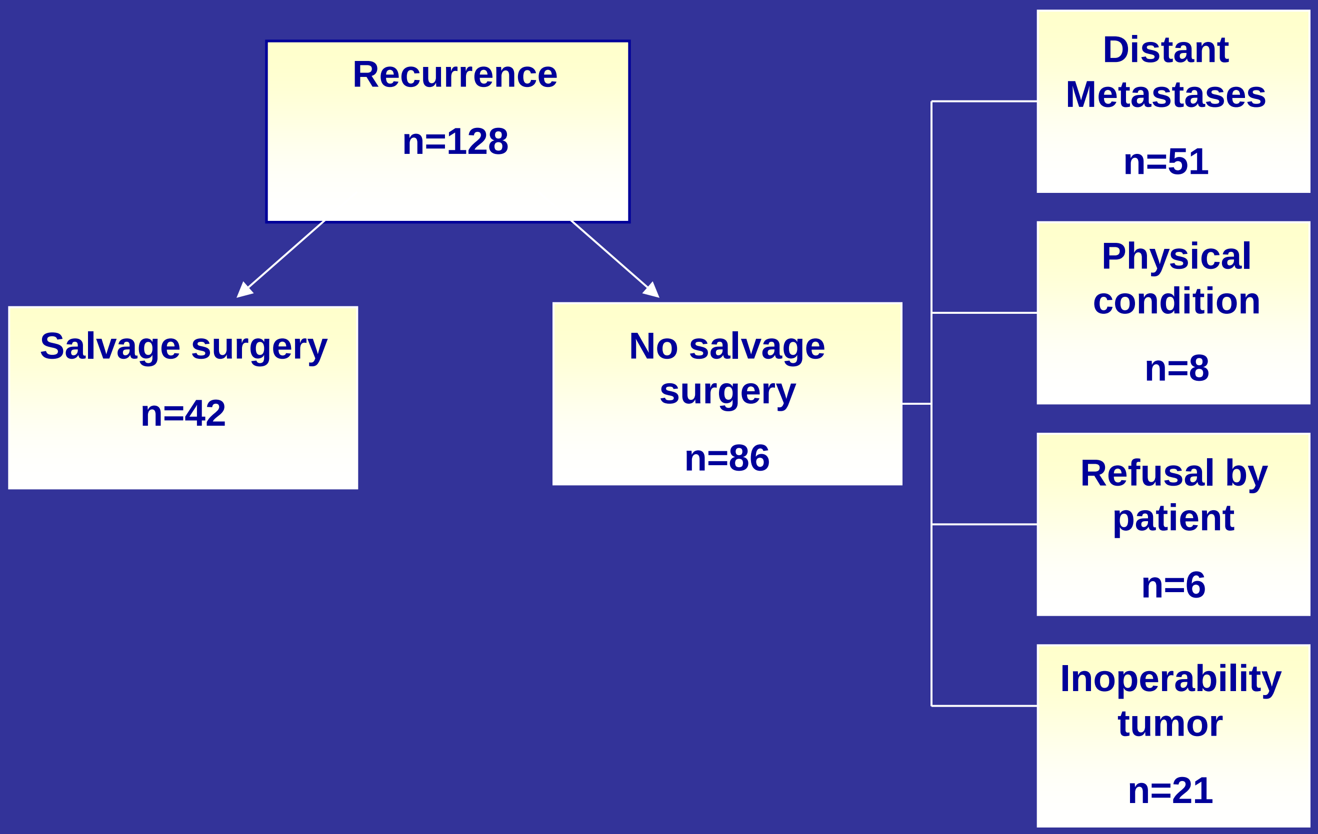
First Recurrence after Chemoradiation (n=128)

	N	%
Local *	45	35
Regional	27	21
Loco-regional	10	8
Distant	46	36

* Exclusion of 4 local recurrences > 3 years after primary tumor

Salvage surgery

Recurrence after chemoradiation



Salvage Surgery

This is:

51 % Locoregional Recurrence (n=82)

33 % Recurrence (n=128)

13 % Total Population Chemoradiation (n=331)

Salvage Surgery
Relative to Tumor site

Site	Salvage (%)
Oral Cavity	9
Oropharynx	11
Hypopharynx	10
Larynx	24

Details of Surgery

Characteristics	All patients (n=42)	Hypopharynx Larynx (n=18)	Oral cavity Oropharynx (n=3)	Neck dissection (n=21)
Type of reconstruction				
No	11 (26%)	1 (6%)	0 (0%)	10 (48%)
Pedicled Flap	26 (62%)	14 (78%)	1 (33%)	11 (52%)
Free Flap*	5 (12%)	3 (17%)	2 (66%)	0 (0%)
Lymph node dissection				
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unilateral	24 (57%)	3 (17%)	1 (33%)	20 (95%)
Bilateral	18 (43%)	15 (83%)	2 (67%)	1 (5%)
Re-operation with flap				
No	37 (88%)	16 (89%)	2 (67%)	19 (90%)
Pedicled Flap	5 (12%)	2 (11%)	1 (33%)	2 (10%)

*Incl. Forearm, Rectus, Fibula, Gracilis

Complications of Surgery

Group	Complications	Pharynx Open (n=18)	Pharynx Closed (n=24)
I	No	5 (28%)	9 (38%)
II	Fistula	6 (33%)	2 (8%)
III	Infection Delayed wound healing	5 (28%)	13 (54%)
IV	Systemic	2 (11%)	0 (0%)
	Patients with one or more complications	13 (72%)	15 (62%)

Histopathology

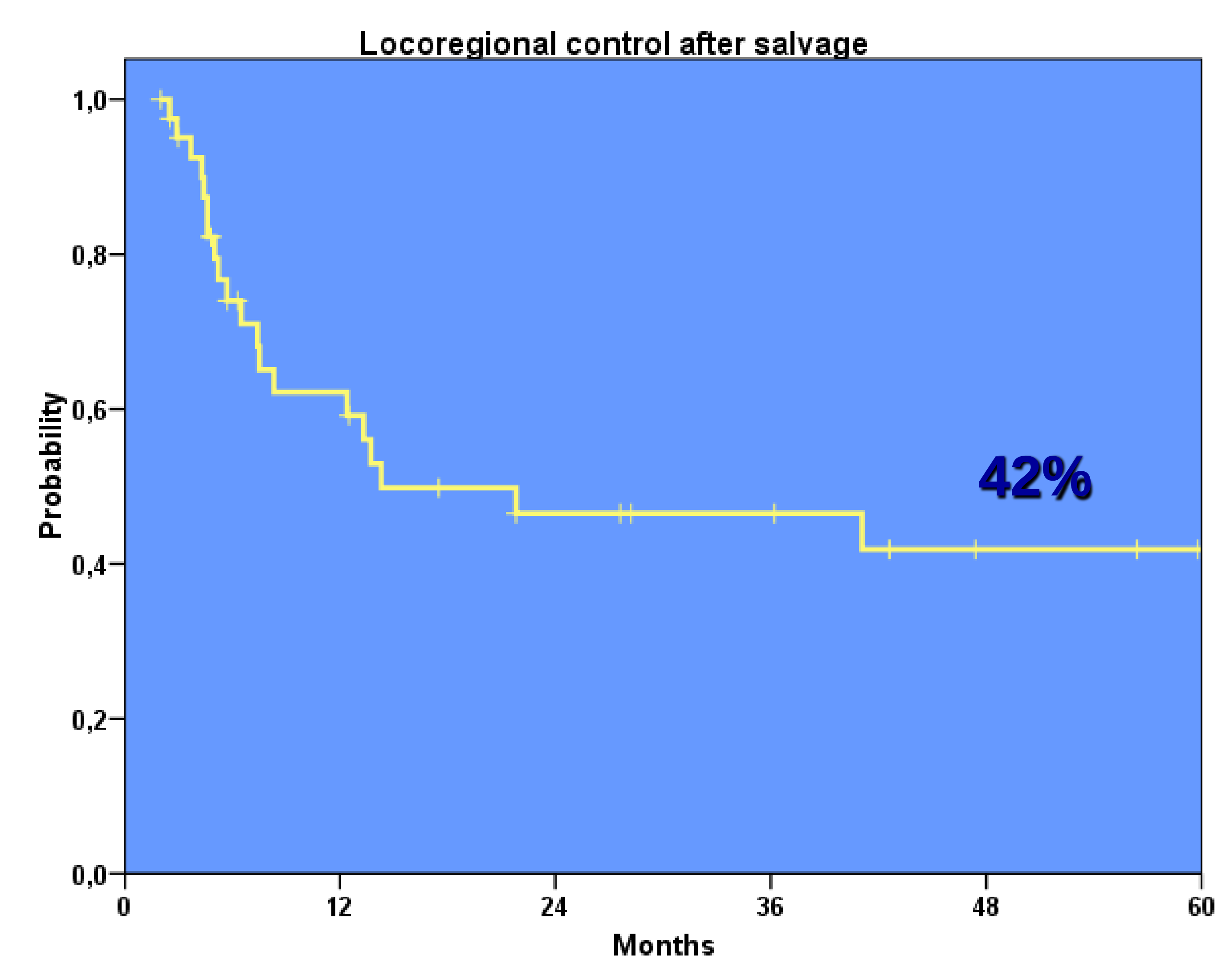
Margins	N	%
R0	32	76
Close	4	10
R1	6	14
R2	0	0

Recurrence after Salvage Surgery

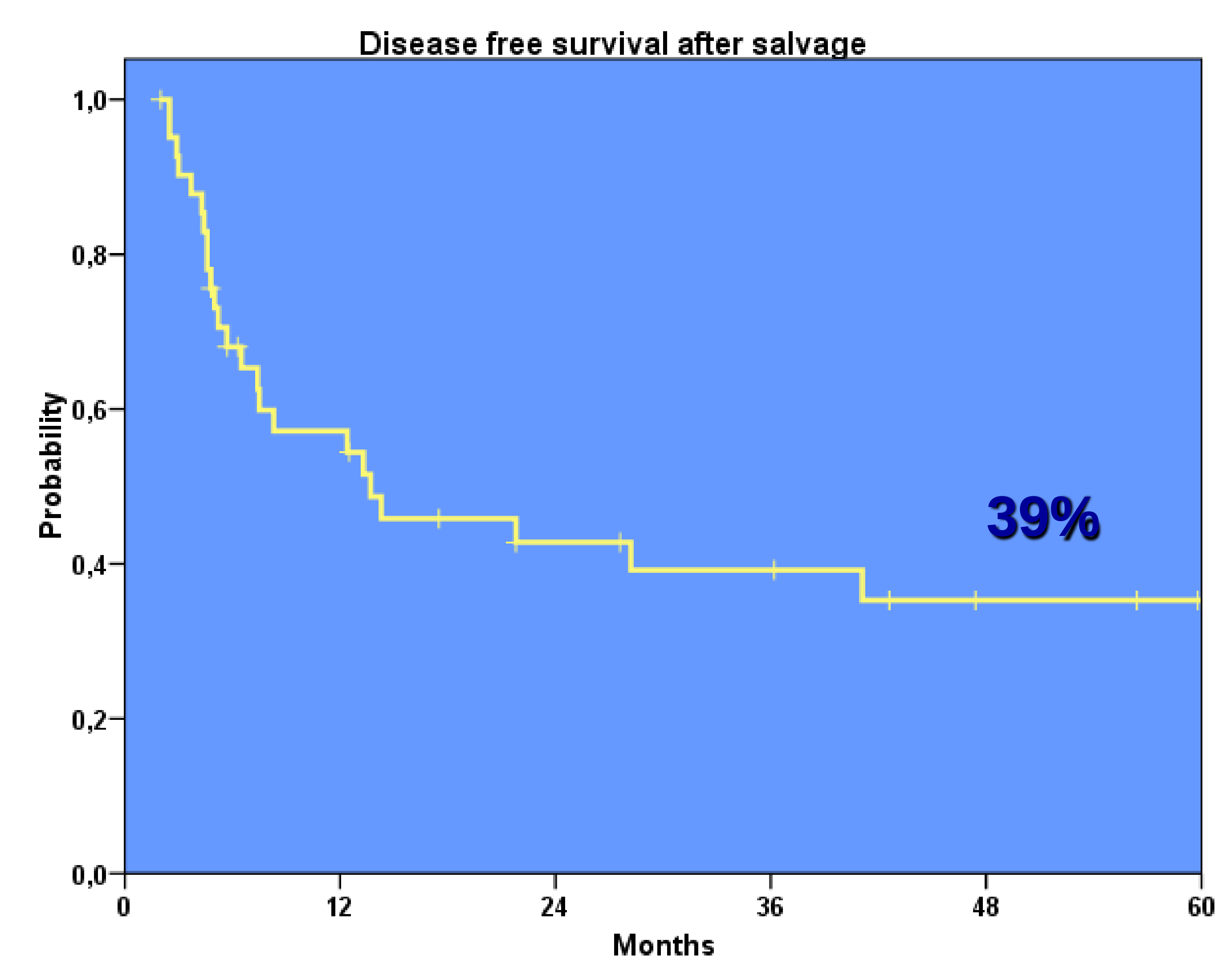
Recurrence *	24	57
Loco-regional	20	48
Distant	7	17

*Follow-up 2 - 118 months

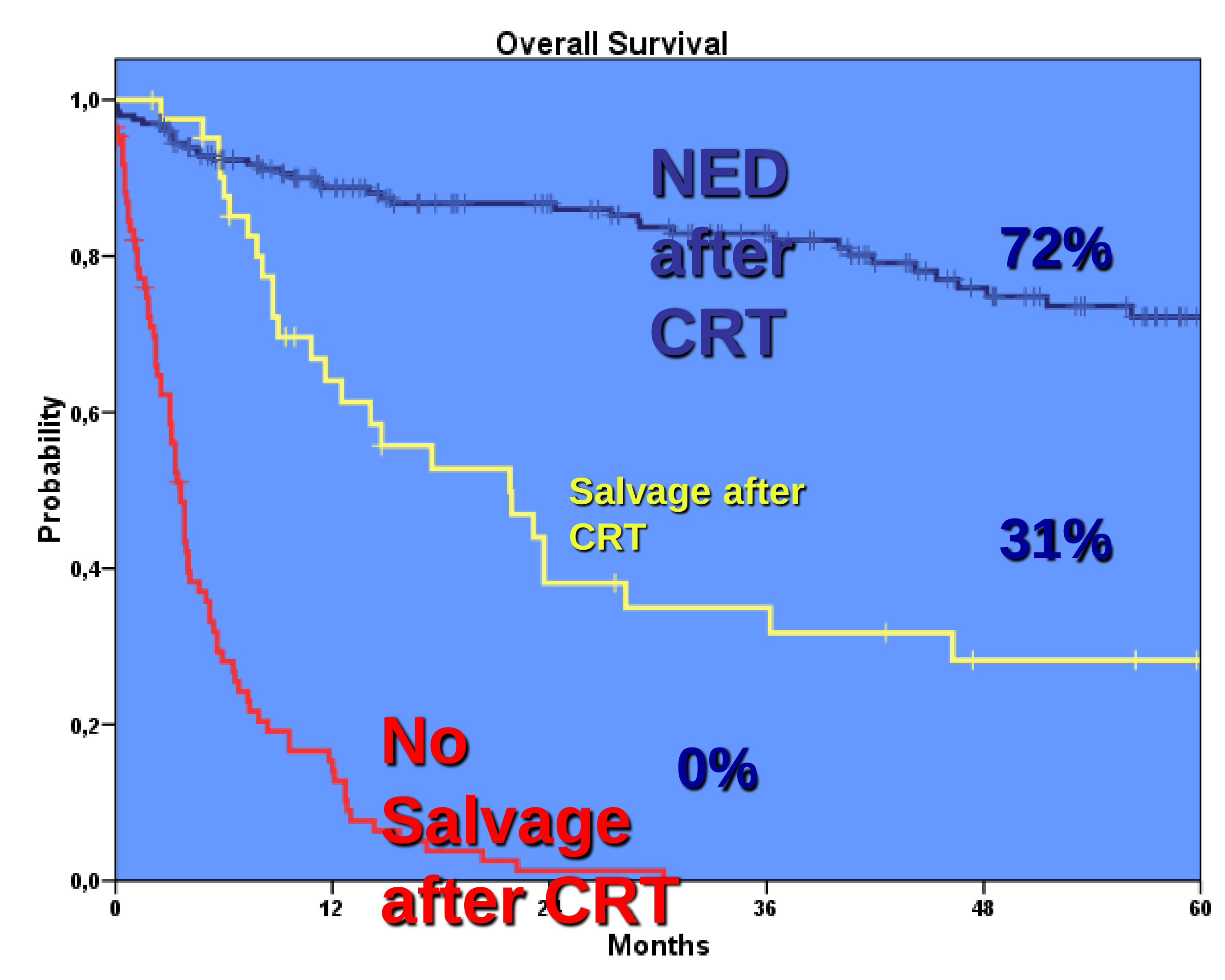
Salvage Surgery



Salvage Surgery



Salvage Surgery



Salvage Surgery

Overview Literature

Authors	Year	N	LR control	DFS	OS	RT/CRT	
Oropharynx							
Yom *	2005	14	86% (2 year, +/- salvage)		82% (2 year, +/- salvage)	CRT	6/54 hypopharynx
Nichols	2010	29			65%(2 year), 43%(5 year)	(C)RT	
Kostrzewa	2010	72			77%(2 year), 44%(5 year)	(C)RT	
Bachar	2010	175		40% (5-year)	23% (5 year)	RT	
Larynx/Pharynx							
Paleri (syst. rev)	2011	>350	87% (2 year)	91%(2 year)	83% (2 year)	(C)RT	Partial laryngectomy
vd Putten	2011	120	70% local, 79% regional (5 year)	58% (5 year)	50% (5 year)	(C)RT	Total laryngectomy
Neck							
vd Putten	2007	61	79% regional (5 year)		36% (5 year)	CRT	
Head and neck							
Gleich	2004	48	20% local, 30% regional (5 year)		15% (5 year)		OC/OP/L/HP
Taussky	2005	17			46%(3 year),13%(5 year)		OC/OP/L/HP/NP
Tan	2010	38			43%(2 year), 37%(5year)	CRT	OC/OP/L/HP/UP

* Survival rates of all patients (with and without salvage/recurrence)

Summary

- Retrospective, skewed towards larynx
- Mixed bag of salvage procedures

- Careful indication
- High morbidity - Vigilance as to complications
  - Liberal use of flaps
- In selected patients feasible with reasonable survival

Acknowledgements

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Marije Vergeer, MD

Hans Langendijk, MD PhD

Medical Oncology

Jan Buter MD, PhD

Henk Verheul MD, PhD

ESTRO school

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

EHNS www.ehns.org

JOINT EHNS-ESMO-ESTRO MULTIDISCIPLINARY TEACHING COURSE ON HEAD AND NECK ONCOLOGY

26-29 June
Florence, Italy

Carcinoma of unknown primary

Piero Nicolai, MD

Department of Otorhinolaryngology – Head and Neck Surgery

University of Brescia, Italy

UNIVERSITY OF BRESCIA - HEALTH & WEALTH - UNIVERSITAS·STUDIORUM·BRIXIAE

INTRODUCTION

Presence of malignancy in one or more lymph nodes within the head and neck region that are ***not solely*** in the *supraclavicular region, without an identifiable primary tumor*

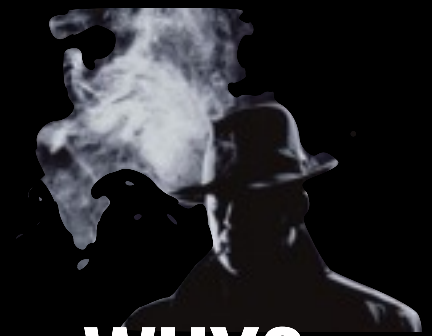
WHY?

Pawlita, Clin Exp Metastasis, 2015

INTRODUCTION

Presence of malignancy in one or more lymph nodes within the head and neck region that are ***not solely*** in the *supraclavicular region, without an identifiable primary tumor*

Pawlita, Clin Exp Metastasis, 2015



WHY?

SMALL SIZE AND ANATOMICAL POSITION

OR

CANCER CONFINED TO LYMPHOEPITHELIAL TISSUE OF THE OROPHARYNX (CRYPT ARE CHARACTERIZED BY INCOMPLETE BASEMENT MEMBRANE)

OR........

INTRODUCTION

INTRODUCTION

2-5 % OF HEAD AND NECK CANCERS

SUBSEQUENT MANIFESTATION OF THE PRIMARY SITE
OCCURS IN A PERCENTAGE OF PATIENTS RANGING FROM 1.4% TO 54%

“TRUE” CARCINOMA OF UNKNOWN PRIMARY ACCOUNTS OF
ONLY 1-2% OF HEAD AND NECK CANCER…

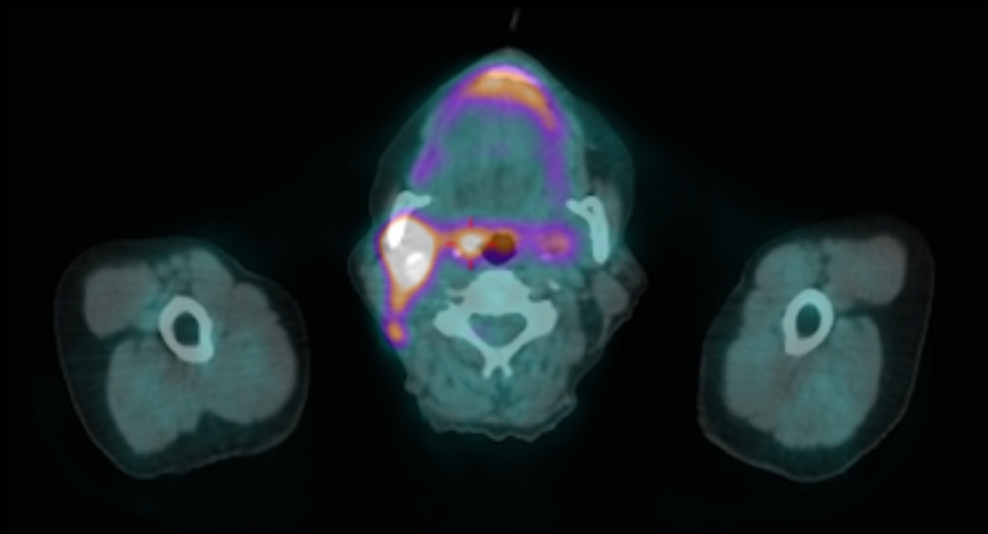
… AND MAY BE DECREASING DUE TO IMPROVED DETECTION
METHODS

PRESENTATION OF DISEASE

Nguyen C et al., Head Neck 1994
Grau C et al., Radiother Oncol 2000
Aslani M et al., Head Neck 2007
Waltonen JD et al., Arch Otolaryngol Head Neck Surg 2009
Chen AM et al., In J Radiat Oncol Biol Phys 2010

PRESENTATION OF DISEASE

MASS IN THE NECK

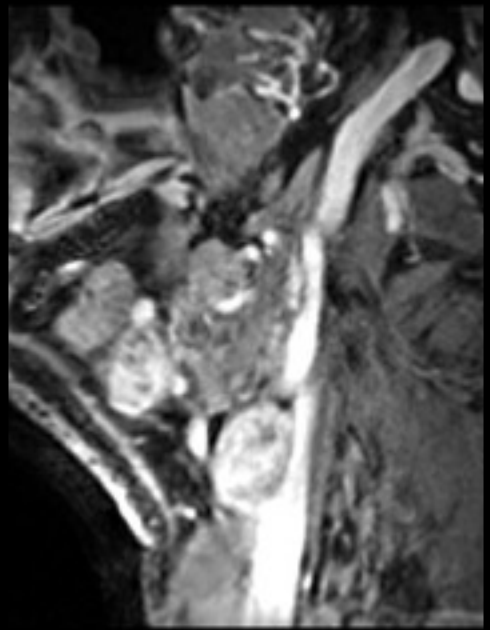


PAIN AND WEIGHT LOSS

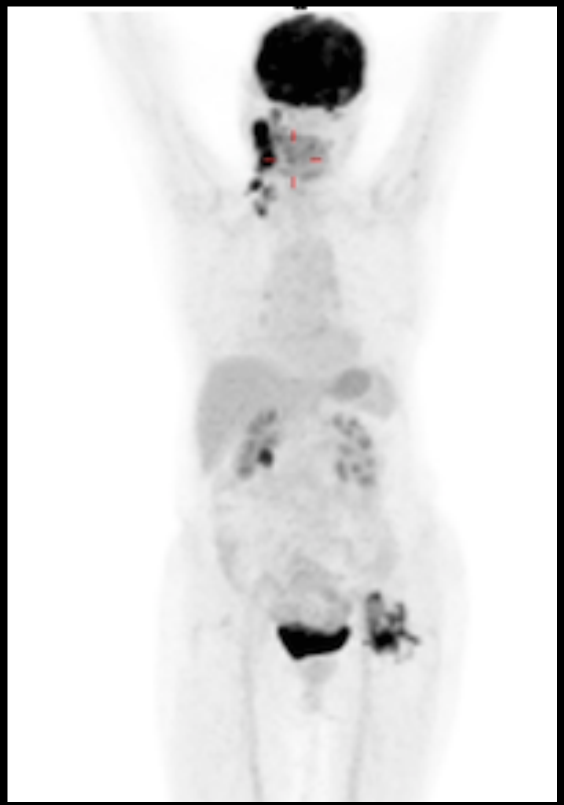
N CLASSIFICATION IN MAJORITY OF CASES: N2 (A,B OR C)

MEDIAN NODE SIZE IS RANGING FROM 3.5 TO 5 CM

INVOLVEMENT OF LEVEL II FOLLOWED BY LEVEL III



BILATERAL INVOLVEMENT IN LESS THAN 10%



DESPITE AN ADEQUATE DIAGNOSTIC WORK-UP, THE PRIMARY TUMOR CANNOT BE DETECTED IN APPROXIMATELY 2-3% OF PATIENTS

Nguyen C et al., Head Neck 1994
Grau C et al., Radiother Oncol 2000
Aslani M et al., Head Neck 2007
Waltonen JD et al., Arch Otolaryngol Head Neck Surg 2009
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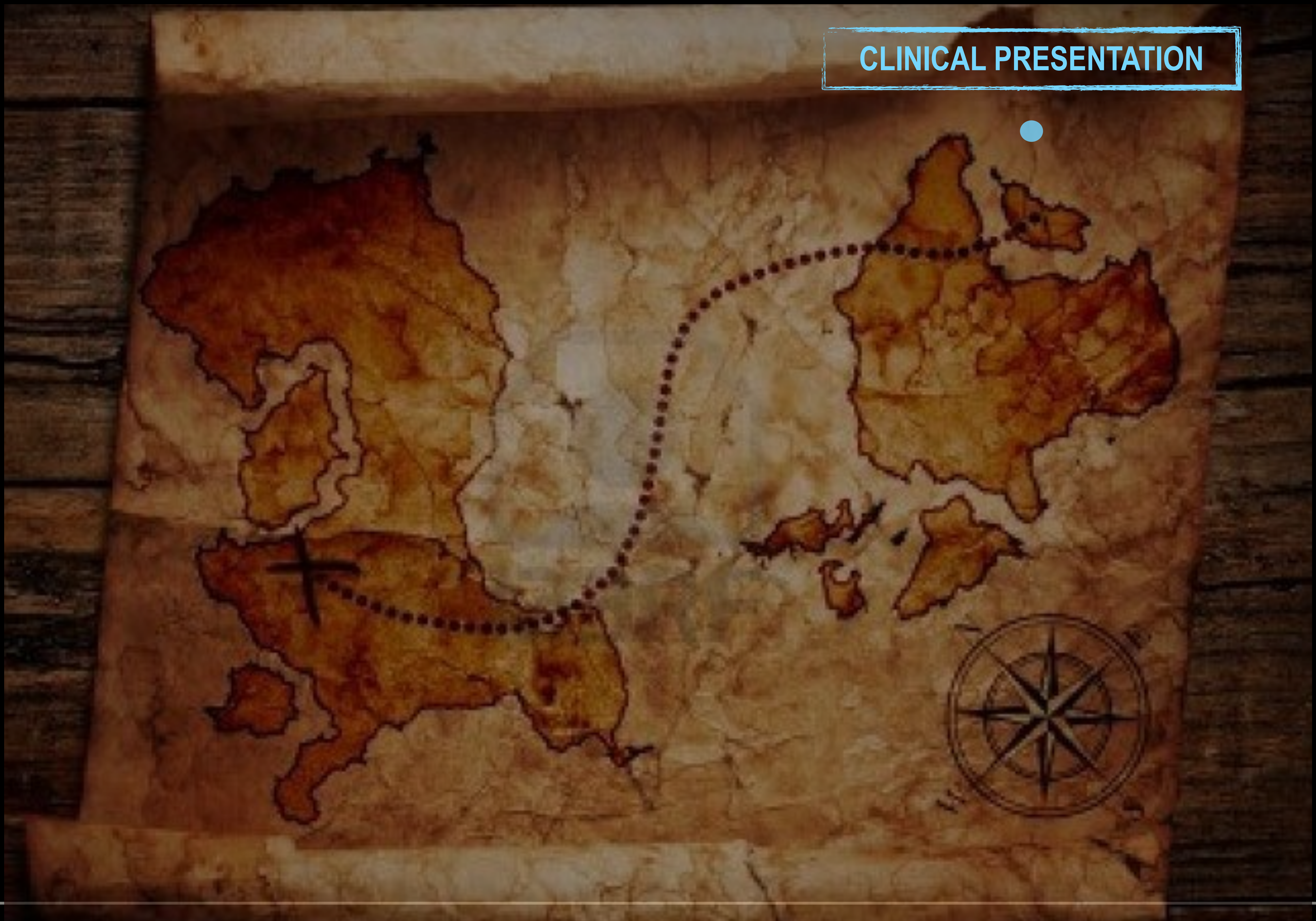
IDENTIFICATION OF THE PRIMARY TUMOR



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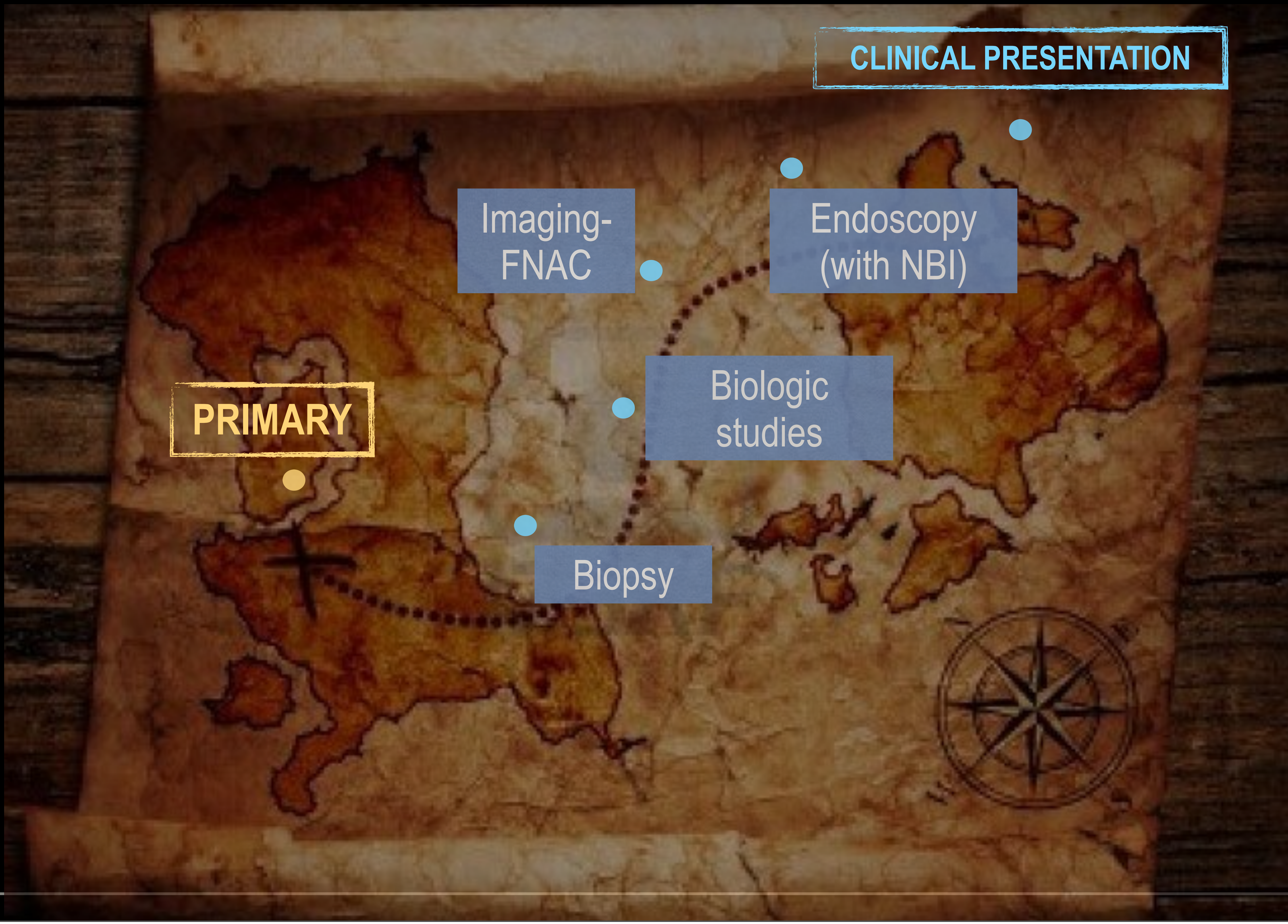
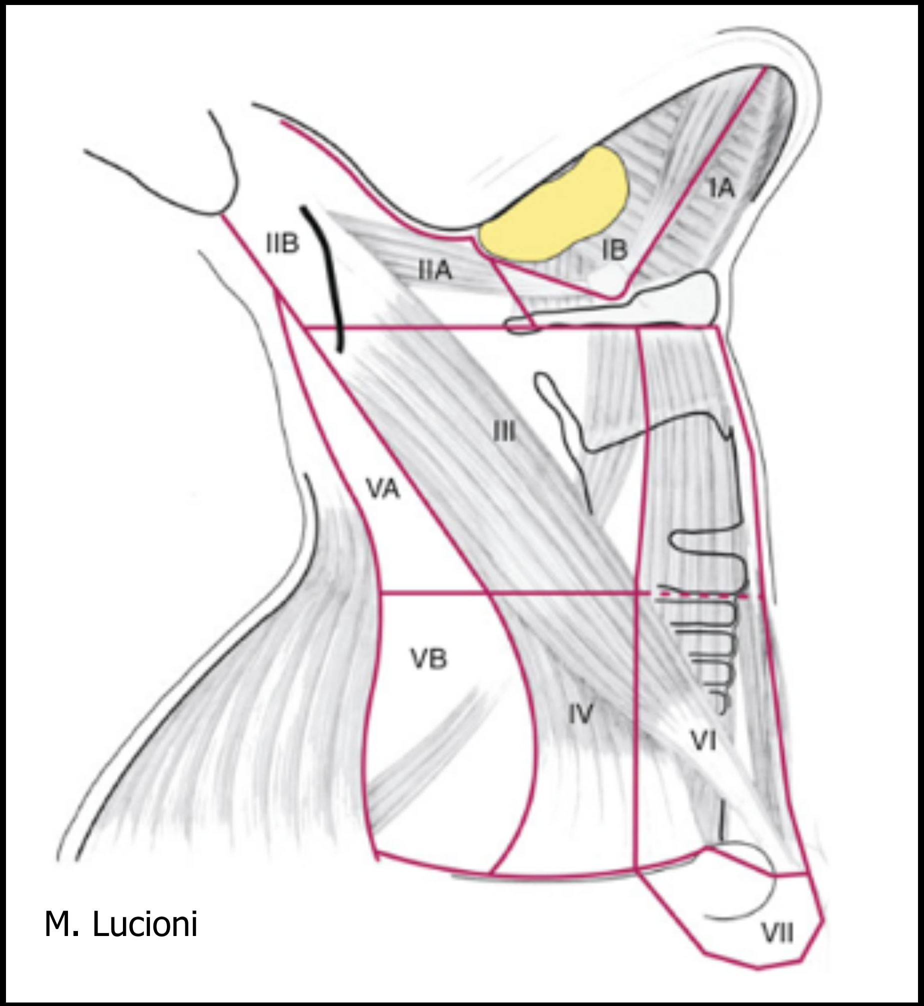


IDENTIFICATION OF THE PRIMARY TUMOR

LOCATION OF CERVICAL LYMPHONODE



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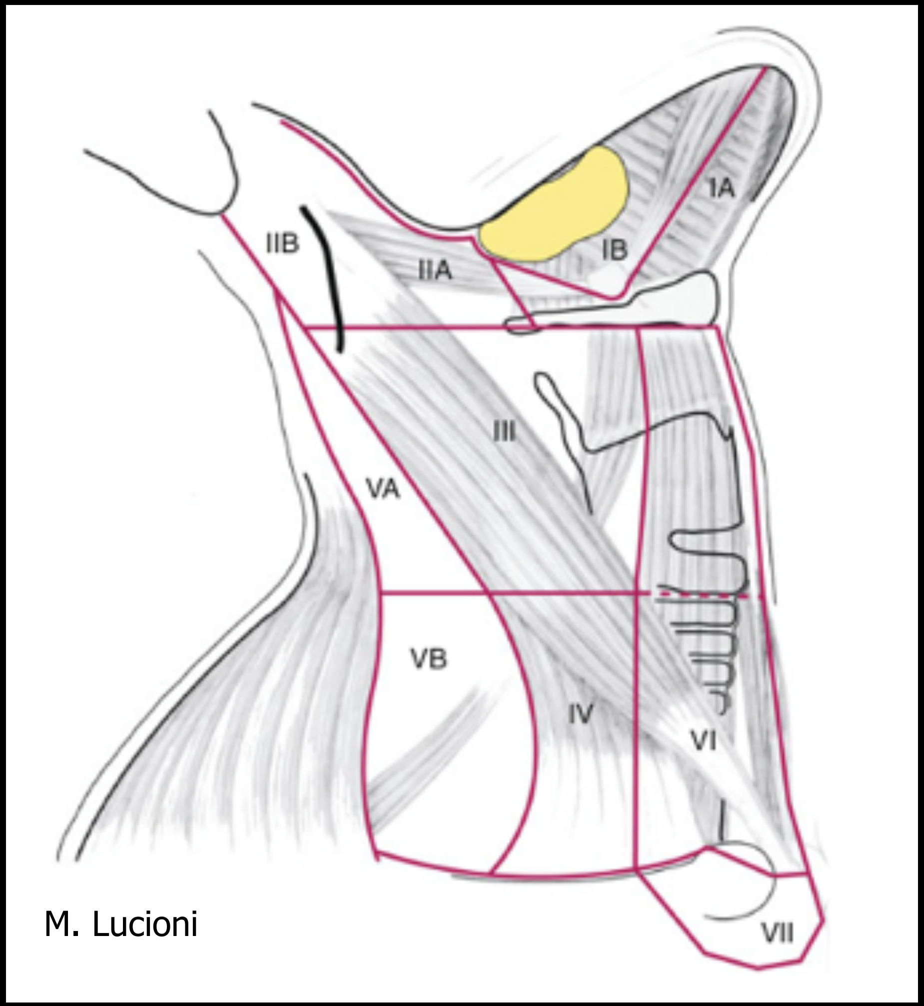


LEVELS I-III
ORAL CAVITY
LIP

LEVELS II-IV
OROPHARYNX
HYPOPHARYNX
LARYNX
THYROID

INTRAPAROTID LYMPHNODES
SKIN
SALIVARY TUMORS

LEVEL V
NASOPHARYNX

50% OF MASSES LIMITED TO LEVEL IV AND/OR SUPRACLAVICULAR FOSSA
ARE FROM PRIMARY TUMOR ARISING BELOW THE CLAVICLE
(I.E. LUNG, BREAST, GASTROINTETINAL TRACT, KIDNEY, AND OVARY)

IDENTIFICATION OF THE PRIMARY TUMOR

PANENDOSCOPY

Cianchetti M et al., Laryngoscope 2009

IDENTIFICATION OF THE PRIMARY TUMOR

PANENDOSCOPY

EVALUATION OF THE UADT

(NASOPHARYNX, ORAL CAVITY, OROPHARYNX, LARYNX, HYPOPHARYNX AND CERVICAL ESOPHAGUS)

DIRECT BIOPSIES OF SUSPICIOUS AREAS
(NO RANDOM BIOPSIES!!)

PATIENT UNDER GENERAL ANESTHESIA - IF REQUIRED

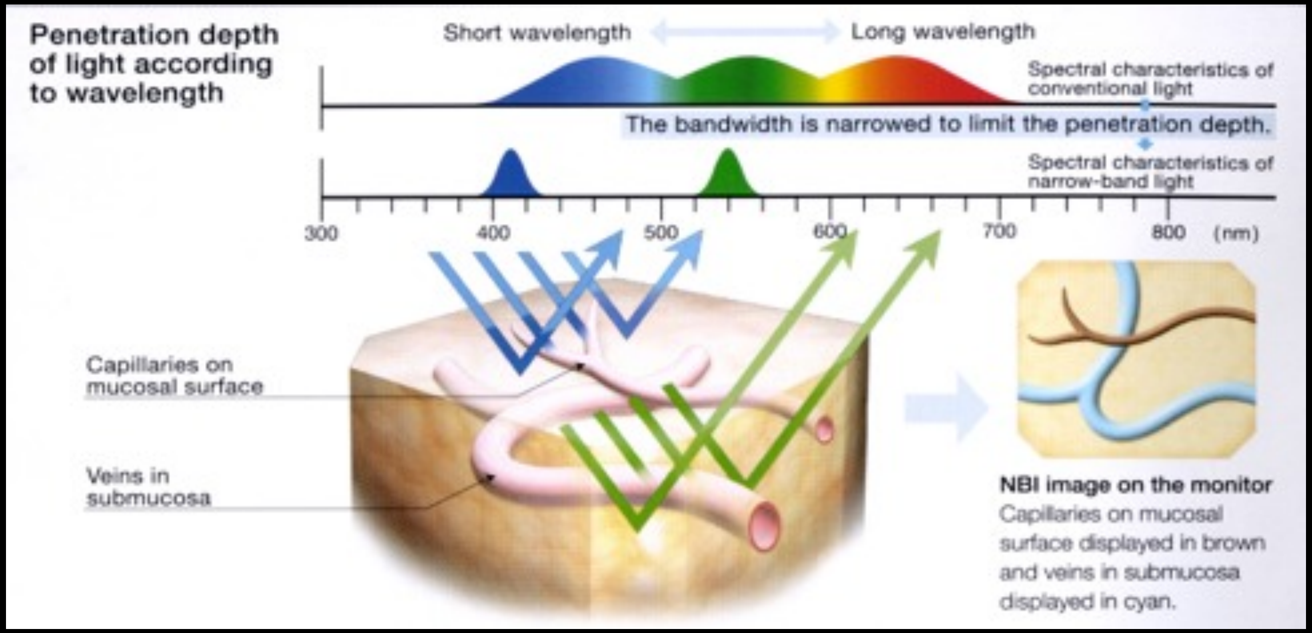
WHEN ROUTINE DIAGNOSTIC WORK-UP FAILED TO IDENTIFY THE PRIMARY SUBSEQUENT PANENDOSCOPY HAD SUCCESS IN 29.2%

BRONCHOSCOPY IS WARRANTED WHEN THERE IS AN ABNORMALITY OF THE LUNG ON CHEST IMAGES

Cianchetti M et al., Laryngoscope 2009

IDENTIFICATION OF THE PRIMARY TUMOR

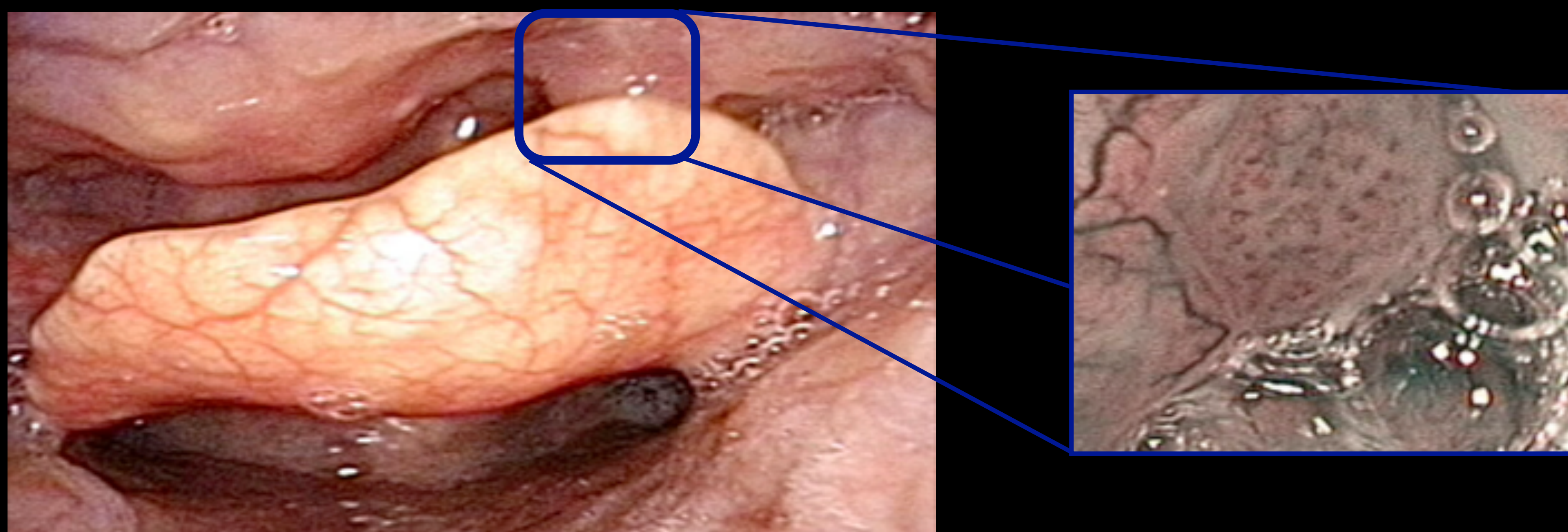
NARROW BAND IMAGING



CLINICAL PRESENTATION
RIGHT N1 LEV II-III

IDENTIFICATION OF THE PRIMARY TUMOR

NARROW BAND IMAGING



PATTERN NBI +
BASE OF THE TONGUE

CLINICAL PRESENTATION
RIGHT N1 LEV II-III

HAYASHI ET AL. WERE ABLE TO IDENTIFY **16 PRIMARY CANCERS** (10 IN THE HYPOPHARYNX AND 6 IN THE OROPHARYNX) BY **NBI ALONE** IN 46 PATIENTS WITH TX PREVIOUSLY EVALUATED BY CT, MRI, PET, LARYNGOSCOPY, AND GASTROINTESTINAL ENDOSCOPY

SAKAI ET AL REPORTED A DETECTION RATE OF TX **IMPROVED FROM 40%** BY WL ENDOSCOPY IN A CONVENTIONAL STRAIGHT HEAD POSITION **TO 71%** BY NBI WITH ADJUNCTIVE MANOEUVRES (HEAD TORSION, KILLIAN POSITION AND VALSALVA)

Hayashi T et al., Jpn J Clin Oncol 2010
Sakai A et al., Laryngoscope 2010

IDENTIFICATION OF THE PRIMARY TUMOR

FNAC

EFFICIENT, MINIMALLY INVASIVE, AND COST-EFFECTIVE DIAGNOSTIC METHOD WITH NEGLIGIBLE RISK OF SEEDING TUMOR CELLS ALONG THE NEEDLE TRACK

Gourin et al., Laryngoscope 2000
Layfield, Diagn Cytopathol 2007
Cianchetti et al., Laryngoscope 2009

IDENTIFICATION OF THE PRIMARY TUMOR

FNAC

EFFICIENT, MINIMALLY INVASIVE, AND COST-EFFECTIVE DIAGNOSTIC METHOD WITH NEGLIGIBLE RISK OF SEEDING TUMOR CELLS ALONG THE NEEDLE TRACK

FOR METASTATIC LESIONS:
SENSITIVITY: 83-97%
SPECIFICITY: 91-100%

SCC ACCOUNTS FOR **53-77%**

THE REMAINING ARE ADENOCARCINOMA AND UNDIFFERENTIATED CARCINOMA

BUT....IN **CYSTIC METASTASES**, A FALSE-NEGATIVE RATE OF 42% WITH FNAC IS REPORTED WITH SENSITIVITY RANGING FROM 33% TO 50%, BECAUSE IT CAN BE DIFFICULT TO DISTINGUISH CYSTIC METASTASES FROM BENIGN BRANCHIAL CYSTS, ABSCESS, OR TUBERCULOSIS

Open cervical lymphnode biopsy is indicated ***only when*** repeated FNAC followed by a core-needle-biopsy are nondiagnostic or in patients with masses clinically and histologically suspicious for lymphoma

Gourin et al., Laryngoscope 2000
Layfield, Diagn Cytopathol 2007
Cianchetti et al., Laryngoscope 2009

IDENTIFICATION OF THE PRIMARY TUMOR

BIOLOGICAL STUDIES

Lewis et al, Head and Neck Patol, 2015
Pawlita et al, Clin Exp Metastasis, Sept 2015

Lee et al.,Head Neck 2000
Gillison et al., J Natl Cancer Inst 2008
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Pavlidis et al., Oral Oncology 2015
von Buchwald C et al, 2014

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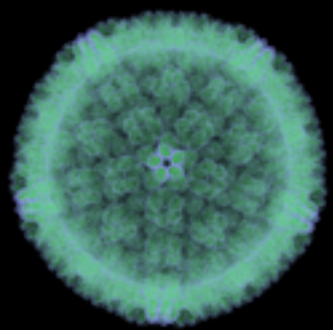

EBV

DETECTION OF EPSTEIN-BARR VIRUS IN A LYMPH NODE BIOPSY IS USEFUL TO DETECT NASOPHARYNGEAL CARCINOMA IN THE AREAS WHERE THE DISEASE IS ENDEMIC, OTHERWISE, ITS VALUE IS LIKELY LIMITED

Lewis et al, Head and Neck Patol, 2015
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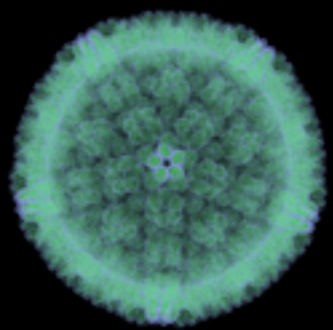

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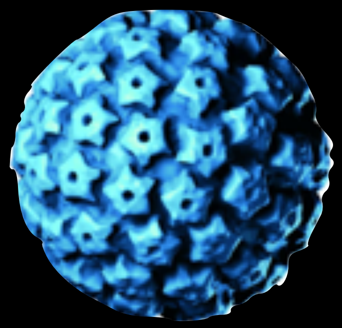

HPV

92% TYPE 16 (FOLLOWED BY TYPE 18, 33 AND 58)

STRONGLY ASSOCIATED
WITH THE PRESENCE OF CYSTIC CERVICAL METASTASIS

DETERMINATION OF HPV STATUS CAN BE OBTAINED BY FNAC

95% OF SCC HPV+ ARE NON KERATINIZING
85% OF SCC KERATINIZING ARE HPV -

HPV RELATED SCC ARE GENERALLY DIAGNOSED WITH EARLIER T CATEGORY AND MORE ADVANCED N CATEGORY

Lewis et al, Head and Neck Patol, 2015
Pawlita et al, Clin Exp Metastasis, Sept 2015

Lee et al.,Head Neck 2000
Gillison et al., J Natl Cancer Inst 2008
Desai et al., Exp Mol Pathol 2009
Vent el al., Head Neck, 2013
Pavlidis et al., Oral Oncology 2015
von Buchwald C et al, 2014

IDENTIFICATION OF THE PRIMARY TUMOR

DIFFERENT PATIENTS

IDENTIFICATION OF THE PRIMARY TUMOR

DIFFERENT PATIENTS

DIFFERENT DISEASE ?

MALE
55-65 YEAR-OLD
TOBACCO AND/OR ALCOHOL ABUSE

MIDDLE AGE
NON SMOKER
HPV-RELATED CANCER

HPV AND NECK METASTASIS FROM UNKNOWN PRIMARY

Can HPV positivity or overexpression of p16 be used as surrogate markers guiding the localization of the primary tumor???

Fotopoulos et al, Oral Oncology (2015)

Bussu et al, Ann Surg Oncol (2015)

Dixon et al, Head Neck (2016)

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Can HPV positivity or overexpression of p16 be used as surrogate markers guiding the localization of the primary tumor???

…HPV is a probable causative agent

1. etiological association
2. ICH staining for HPV in every biopsy

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p16-positive status

Associated with younger age, nonsmoker status, and lower disease burden at presentation

↓

Low-risk UP patients for potential treatment de-escalation

Dixon et al, Head Neck (2016)

HPV AND NECK METASTASIS FROM UNKNOWN PRIMARY

Impact of p16 expression, nodal status, and smoking on oncologic outcomes of patients with head and neck unknown primary squamous cell carcinoma

Dixon et al, Head Neck (2016)

n=73

HPV AND NECK METASTASIS FROM UNKNOWN PRIMARY

Impact of p16 expression, nodal status, and smoking on oncologic outcomes of patients with head and neck unknown primary squamous cell carcinoma

Dixon et al, Head Neck (2016)

n=73

63%
p16-positive

less advanced nodal status

N1–N2b: 52% vs 89%
p=0.035

less aggressive treatment

p16-positive tumors had improved 3-year DFS
79% vs 56%
p=0.012

p16-positive status is an independent predictor of DFS, but not of OS

IDENTIFICATION OF THE PRIMARY TUMOR

IMAGING: MRI OR CT SCAN

PATIENTS WITH SUSPICIOUS FINDINGS ON PHYSICAL EXAM AND/OR CT AND/OR MRI HAD A HIGHER PROBABILITY OF PRIMARY SITE DETECTION THAN THOSE WITHOUT SUSPICIOUS FINDINGS

CT PRIOR TO PANENDOSCOPY LIKELY SIGNIFICANTLY INCREASED THE PROBABILITY OF DETECTING THE PRIMARY SITE

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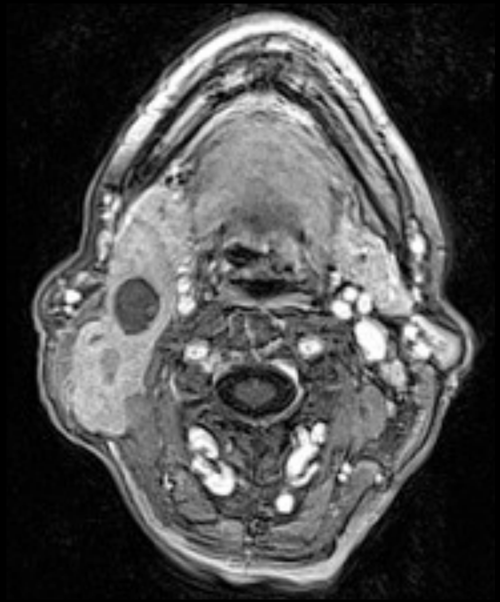
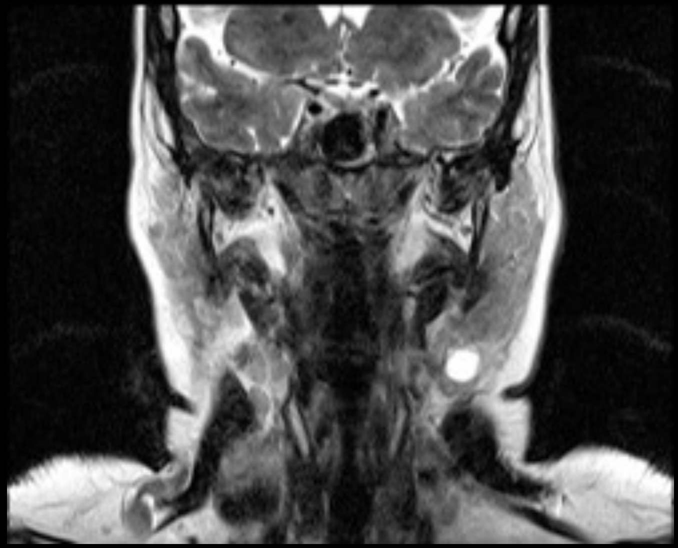
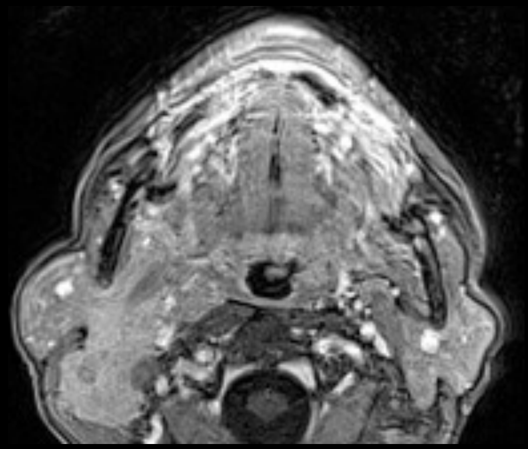
THE POTENTIAL OF **CT, MR, OR BOTH TO DETECT A PRIMARY TUMOR IS IN THE RANGE OF** 9.3% TO 23%, **RISING 60% WHEN SUSPICIOUS RADIOLOGIC FINDINGS DIRECT SUBSEQUENT ENDOSCOPIC BIOPSIES**







Cianchetti M et al., Laryngoscope 2009
Strojan P et al., Head Neck 2013

IDENTIFICATION OF THE PRIMARY TUMOR

IMAGING: PET-CT / FDG-PET

PET-CT DETECTION RATE **OF THE PRIMARY TUMOR:** 24.5% **(**SENSITIVITY 88.3%, SPECIFICITY 74.9%, DIAGNOSTIC ACCURACY 78.8%**)**

TONSILS: HIGHEST FALSE-POSITIVE (39.3%), THE LOWEST SENSITIVITY RATE WAS FOR THE BASE OF THE TONGUE (80.5%)

Rusthoven KE et al., Cancer 2004

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Rusthoven KE et al., Cancer 2004

FDG-PET/CT ON THE LOCATION OF THE PRIMARY SITE:
TONSIL 6.9%, BASE OF TONGUE 9.8%, AND PHARYNX 13.7%.
FALSE-POSITIVE: 41.6%, 16.7%, AND 12.5%, RESPECTIVELY
SENSITIVITY: 87.5%, 83.3%, AND 87.5%, RESPECTIVELY

Zhu et al., Surg Oncol 2013

COMPARISON BETWEEN FDG-PET AND FDG-PET/CT: THE LATTER HAD A HIGHER SENSITIVITY AND SPECIFICITY

Dong et al.,Nucl Med Commun 2008

IDENTIFICATION OF THE PRIMARY TUMOR

TONSILLECTOMY

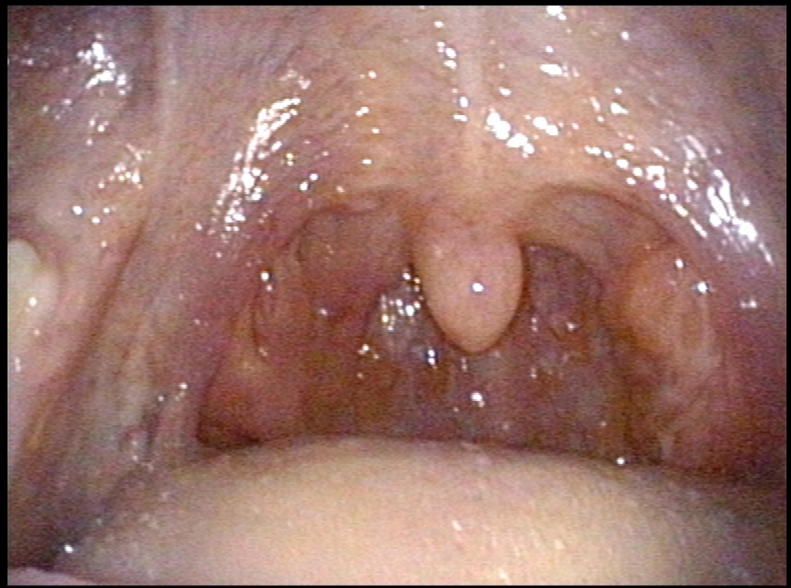
Tonsillectomy has a role in the diagnostic work-up of CUP

IT IS ESPECIALLY USEFUL WHEN LYMPH NODES ARE LOCATED IN THE UPPER AND/OR MIDDLE JUGULAR GROUP WITH A CYSTIC ASPECT

Righini C.-A. et al Eur Ann Otol, 2014

IPSILATERAL TONSILLECTOMY **IS WARRANTED AND YIELDS AN** 18% TO 44.6% PRIMARY TUMOR DETECTION RATE**.**

Strojan et al., Head Neck 2013



OTHER STUDIES RECOMMEND TO PERFORM BILATERAL TONSILLECTOMY IF THERE IS NO EVIDENCE OF A PRIMARY SITE ON PHYSICAL AND RADIOGRAPHIC EXAMINATION (CONTROLATERAL TUMORS IN 10-23%)

BILATERAL TONSILLECTOMY AVOID THE UPTAKE OF NORMAL TONSILLAR TISSUE DURING FOLLOW-UP

Lewis et al, Head and Neck Patol, 2015

Kothari et al., Br J Oral Maxillofac Surg 2008

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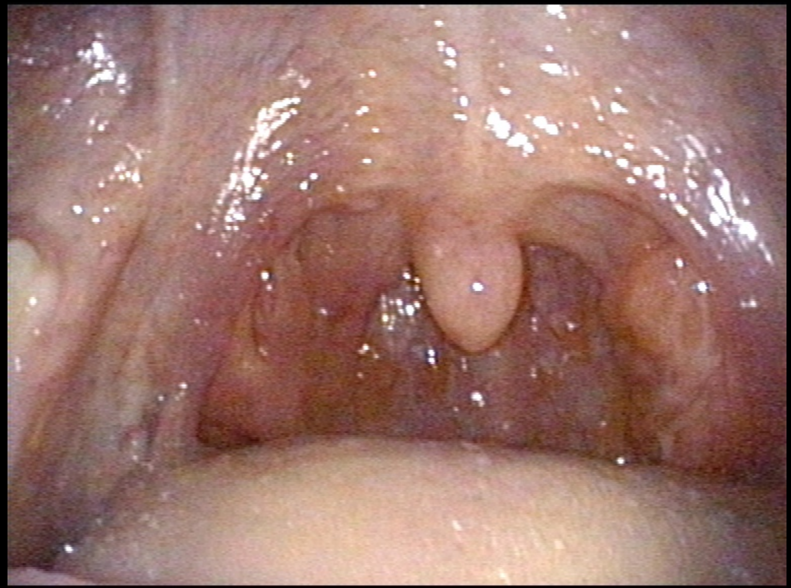

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Lewis et al, Head and Neck Patol, 2015

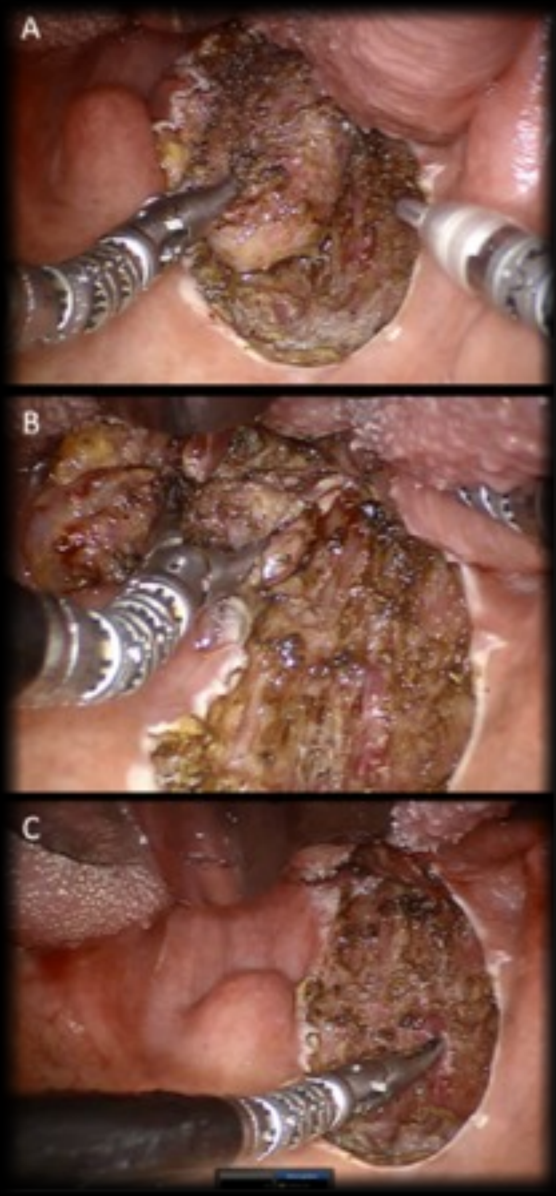
Kothari et al., Br J Oral Maxillofac Surg 2008

RANDOM BIOPSIES OF NASOPHARYNX AND HYPOPHARYNX ARE **NOT NECESSARY** IN THE WORK-UP OF CUP

Mendenhall W. M. et al., Head Neck 2015

IDENTIFICATION OF THE PRIMARY TUMOR

TORS FOR TONSILS AND BOT



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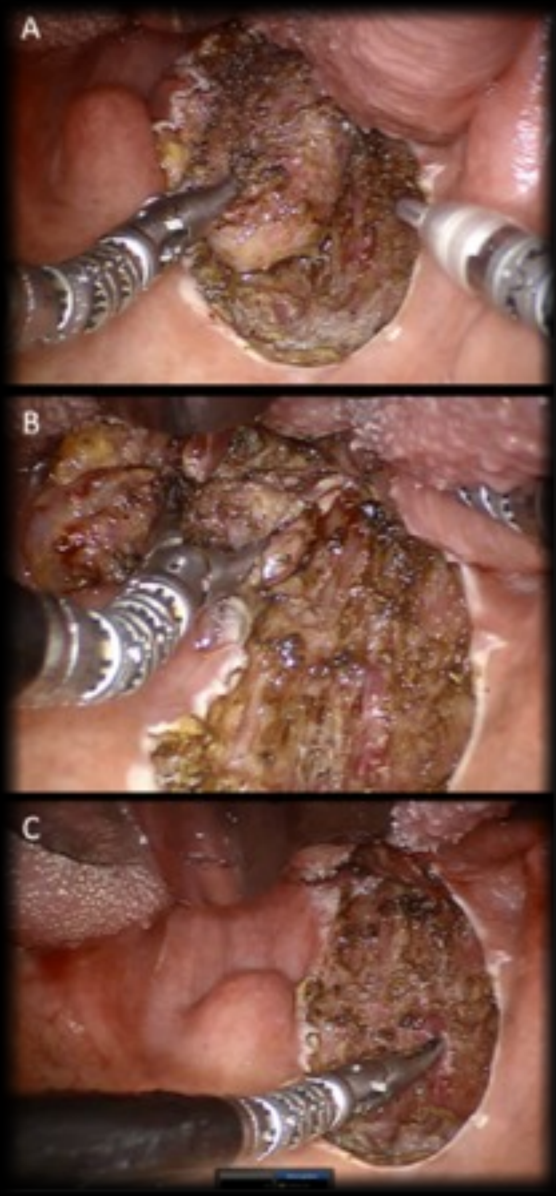


PRIMARY REVEALED IN 77%

SCC OF PALATINE TONSIL IN 59%

SCC OF BOT TONSIL 18%

NO GASTROSTOMY TUBE NEITHER TRACHEOTOMY WERE NECESSARY AFTER TORS
ADJUVANT THERAPY: RT ALONE 59.1%, RT-CHT 40.9%

Durmus K, Head Neck 2013

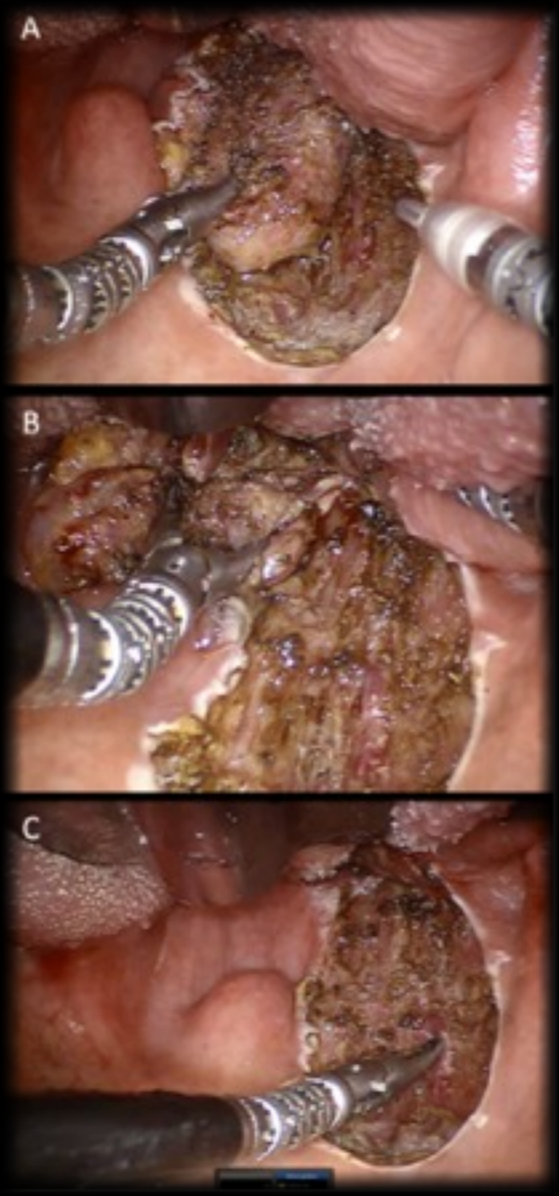
OVERALL IDENTIFICATION PRIMARY (PRE-OP WORK-UP + TORS): 34/47 : 72.3%
TORS IDENTIFICATION PRIMARY: 13/18: 72.2% (PALATIN TONSIL AND BOT)

PRIMARY TUMOR SIZE: 0.2 - 2CM
NO ADJUVANT THERAPY FOR PT1N1

Patel S, JAMA Otolaryngol Head Neck Surg 2013

IDENTIFICATION OF THE PRIMARY TUMOR

TORS FOR TONSILS AND BOT



TORS is associated with an incremental cost-effectiveness ratio of $8619 compared with traditional EUA alone

JK Byrd, Otolaryngol Head Neck Surg 2014

THERAPEUTIC OPTIONS

Treatment options are usually based on **non-randomized data** and **institutional polices** that incorporate the same principles of aggressive multimodality therapy that are used in cases of head and neck SCC in which the primary site is known.

CERVICAL LYMPH NODE METASTASES FROM OCCULT SQUAMOUS CELL CARCINOMA: CUT DOWN A TREE TO GET AN APPLE?

CARSTEN NIEDER, M.D.,* VINCENT GREGOIRE, M.D., PH.D.,† AND K. KIAN ANG, M.D., PH.D.‡

- **RT ALONE**
- **NECK DISSECTION ALONE OR IN COMBINATION WITH RADIOTHERAPY FOR THE TREATMENT OF IPSILATERAL CERVICAL LYMPH NODES**
- **RT ALONE OR IN COMBINATION WITH NECK DISSECTION FOR THE TREATMENT OF THE MUCOSAL SITES AND BILATERAL CERVICAL AND SUPRACLAVICULAR LYMPH NODES**

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THERAPEUTIC OPTIONS

MOST OF THE GUIDELINES ON CUP TREATMENT ARE BASED ON DATA AND CONCEPTS DERIVING FROM THE EXPERIENCE IN THE MANAGEMENT OF NECK METASTASIS IN THE PRESENCE OF A PRIMARY TUMOR

EARLY STAGE NECK DISEASE

IN LOW-VOLUME NECK DISEASE
(N1 AND EARLY N2A)
WITHOUT EXTRACAPSULAR SPREAD **(ECS)**

EXCELLENT REGIONAL CONTROL WITH EITHER SURGERY OR RT ALONE

NECK LEVELS DISSECTION AS APPROPRIATE OR RT OF THE INVOLVED NECK.

ADVANCED STAGE NECK DISEASE

ADVANCED NECK DISEASE
EXTRACAPSULAR SPREAD

A COMBINED TREATMENT IS STRONGLY RECOMMENDED: IN SOME SERIES OMISSION OF RADIOTHERAPY RESULTS IN 75% OF RECURRENCE

AN IMPROVEMENT RANGING FROM 67.3% TO 93% FOR NECK CONTROL AND FROM 40.9% TO 78.9% FOR OVERALL SURVIVAL AT 5 YEARS IS EXPECTED

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NOT CLEAR WHAT IS THE OPTIMAL THERAPY…

SURGERY WITH POSTOPERATIVE RT

VS

(CHEMO) RADIOTHERAPY FOLLOWED BY NECK DISSECTION ONLY IN THOSE PATIENTS WHO DO NOT ACHIEVE A COMPLETE CLINICAL OR METABOLIC PET RESPONSE TO IRRADIATION

ADVANCED STAGE NECK DISEASE

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EXTRACAPSULAR SPREAD

A COMBINED TREATMENT IS STRONGLY RECOMMENDED: IN SOME SERIES OMISSION OF RADIOTHERAPY RESULTS IN 75% OF RECURRENCE

AN IMPROVEMENT RANGING FROM 67.3% TO 93% FOR NECK CONTROL AND FROM 40.9% TO 78.9% FOR OVERALL SURVIVAL AT 5 YEARS IS EXPECTED

Shumann, J Cranio Max Fac Surg 2015

THERAPEUTIC OPTIONS

NECK DISSECTION + TOTAL MUCOSAL IRRADIATION + BILATERAL NECK IRRADIATION
ONCOLOGIC RESULTS AND TREATMENT MORBIDITY

Total Mucosal Irradiation with Intensity-modulated Radiotherapy in Patients with Head and Neck Carcinoma of Unknown Primary: A Pooled Analysis of Two Prospective Studies

2016

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PATIENTS (N=36) RECEIVED IMRT TO THE POTENTIAL PRIMARY TUMOUR SITES AND ELECTIVE CERVICAL NODES. CONCOMITANT CHEMOTHERAPY WAS USED IN PATIENTS WHO RECEIVED PRIMARY RADIOTHERAPY OR THOSE WITH NODAL EXTRACAPSULAR EXTENSION.

FUNCTIONAL OUTCOMES

GRADE 3 DYSPHAGIA AT 1 YEAR: 33%

G-TUBE DEPENDANCY AT 1 YEAR: 2.7%

HIGH-GRADE XEROSTOMIA AT 2 YEARS: 15%

SURVIVAL OUTCOMES

Survival	2 year survival rate (95% confidence interval)
Overall survival	81.3% (67.6–95.0)
PFS	77.6% (62.5–92.7)
Locoregional (lymph node and mucosa) PFS	89.8% (78.4–100)
Primary mucosal PFS	97.1% (91.4–100)
Cervical lymph node PFS	89.8% (78.4–100)

THERAPEUTIC OPTIONS

OPEN QUESTIONS

THERAPEUTIC OPTIONS

OPEN QUESTIONS

NO FIRM CONCLUSIONS CAN BE DRAWN ON SOME ISSUES BASED ON THE AVAILABLE LITERATURE

CONTRALATERAL NECK RECURENCE ARE RARE...

CANDIDATES FOR BILATERAL NECK RT:
SUSPECTED MIDLINE PRIMARY
EXTENSIVE NODAL DISEASE

→

MORBIDITY
LIMITATIONS FOR SALVAGE SURGERY

RADICAL NECK DISSECTION IS RARELY INDICATED AS IT IS COMPREHENSIVE (LEVELS I–V) NECK DISSECTION

Galloway TJ et al, J Clin Oncol, 2015
Nieder C et al., On J Radiat Oncol Biol Phys, 2001
Jereczek-Fossa BA et al., Cancer Treat Rev 2004
Strojan P et al., Head Neck 2013

THERAPEUTIC OPTIONS

OPEN QUESTIONS

PATTERNS OF FAILURE AFTER RT

FACTORS, OTHER THAN RT DOSE, INCLUDING HPV STATUS, MAY ULTIMATELY DICTATE LOCOREGIONAL RECURRENCE RISK IN PATIENTS WITH HEAD NECK CANCER OF UNKNOWN PRIMARY

CONTRALATERAL NECK FAILURE IS RARE

THERAPEUTIC OPTIONS

OPEN QUESTIONS

PATTERNS OF FAILURE AFTER RT

FACTORS, OTHER THAN RT DOSE, INCLUDING HPV STATUS, MAY ULTIMATELY DICTATE LOCOREGIONAL RECURRENCE RISK IN PATIENTS WITH HEAD NECK CANCER OF UNKNOWN PRIMARY

CONTRALATERAL NECK FAILURE IS RARE

Lee N. et al., Head Neck, 2015

Galloway TJ et al, J Clin Oncol, 2015

SYSTEMIC THERAPY

INTENSIFICATION OF (LOCO)REGIONAL TREATMENT: IMPROVING NECK CONTROL

PALLIATE THE SYMPTOMS OF REGIONALLY ADVANCED DISEASE OR SYSTEMIC METASTASES

IMPACT OF IMMUNOTHERAPY WAS NOT DESCRIBED IN LITERATURE

Nieder C et al., J Radiat Oncol Biol Phys, 2001
Jereczek-Fossa BA et al., Cancer Treat Rev 2004
Strojan P et al., Head Neck 2013
P Shumann, J Cranio Max Fac Surg 2015

THERAPEUTIC OPTIONS

OPEN QUESTIONS

Galloway TJ et al, J Clin Oncol, 2015

THERAPEUTIC OPTIONS

OPEN QUESTIONS

IS DEINTENSIFICATION A SAFE PROGRAM ?

SURVIVAL FOR PATIENT WITH RECURRENCE IS POOR

NO DATA AVAIABLE IN LITERATURE ABOUT IPSILATERAL IRRADIATION VS MORE EXTENSIVE FIELD
(EVEN IF BILATERAL NECK RT PRODUCE GRATIFYING RESULTS)

Galloway TJ et al, J Clin Oncol, 2015

THERAPEUTIC OPTIONS

OPEN QUESTIONS

Bilateral neck radiation

Author, Yera	n[a]	Years	Prior EUA (with Biopsy), %	Prior CT or MRI, %	Prior PET, %	Chemo RT, %	Neck Dissection, %	Mucosal Emergence, %	Ipsilateral Neck Failure, %	Contralateral Neck Failure, %	Distant Failure,[b] %
Wallace[44]	179	1964–2006	87 (—)	74 CT 8 MRI	9	1 IND 5 CRT	61	8 actuarial rate at 5 y	19 actuarial rate at 5 y		14 actuarial rate at 5 y
Colletier[43]	136 (120)	1968–1992	96 (83)	45	0	0	71 29 ExBx	8 actuarial rate at 5 y	8	1	15 actuarial rate at 5 y
Reddy[41]	36	1974–1989	All	All after 1978	0	0	63	8	31	14	15
Grau et al,[3] 2000	224	1975–1995	94 (55)	30 CT 7 MRI	1	0	9 45 ExBx	8[c]	Not Reported LRC: 48	2	7
Perkins[42]	25	1989–2008	100 (100)	100 CT or MRI	36	28	68 8 ExBx	4	0	0	22
Ligey et al,[10] 2009	36	1990–2007	— (19)	Use of CT 'Varied' 2 MRI	17	6 IND 39 CRT	83	6	19	19	30
Keller et al,[4] 2013	35	1990–2010	100 (100)	100 CT or MRI	40	11	89 11 ExBx	3	0	0	8
Demiroz[45]	41	1994–2009	100 (100)	100 CT or MRI	66	61	54 ExBx:29	5	5	0	19.50
Frank[37]	52 (46)	1998–2005	100 (—)	100 CT or MRI	50	15 IND 12 CRT	50 27 ExBx	2 actuarial rate at 5 y	4	2	8.3 actuarial rate at 5 y
Klem[46]	21	2000–2005	—	100 CT and/or MRI	95	67	62 14 ExBx	0	10	0	10
Chen[47]	60	2001–2009	100 (100)	100 CT	32	53	70 5 ExBx	3	5	2	16 actuarial rate at 2 y
Sher[48]	24	2004–2009	100 (100)	100 CT	100	29 IND 100 CRT	25 33 ExBx	0	0	0	4
Mourad[49]	68	1998–2010	All	—	—	56	44	2	3	0	0

Galloway TJ et al, J Clin Oncol, 2015