



**Biology and Technology Contribution  
to clinical Advancement:  
the Case of oropharyngeal Cancer**



**Brescia – May 8<sup>th</sup>, 2009**



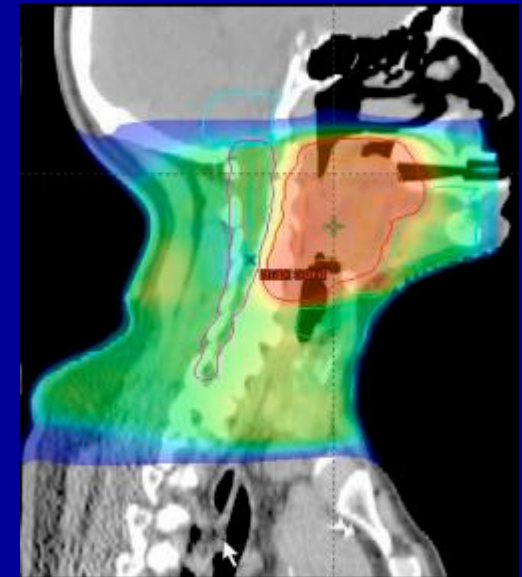
***Radiotherapy for the treatment  
of oropharyngeal cancer:  
state of the art***

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# *Goals in the management of oropharyngeal SCC*

- ? definitive cure for patients with **limited** disease
- ? survival in patients with **advanced** disease  
(improving loco-regional control,  
reducing probability of distant metastases)
- ? organ-function preservation in resectable and unresectable tumors
- ? therapeutic ratio (cure / toxicity ratio)
- ? metachronous tumor occurrence



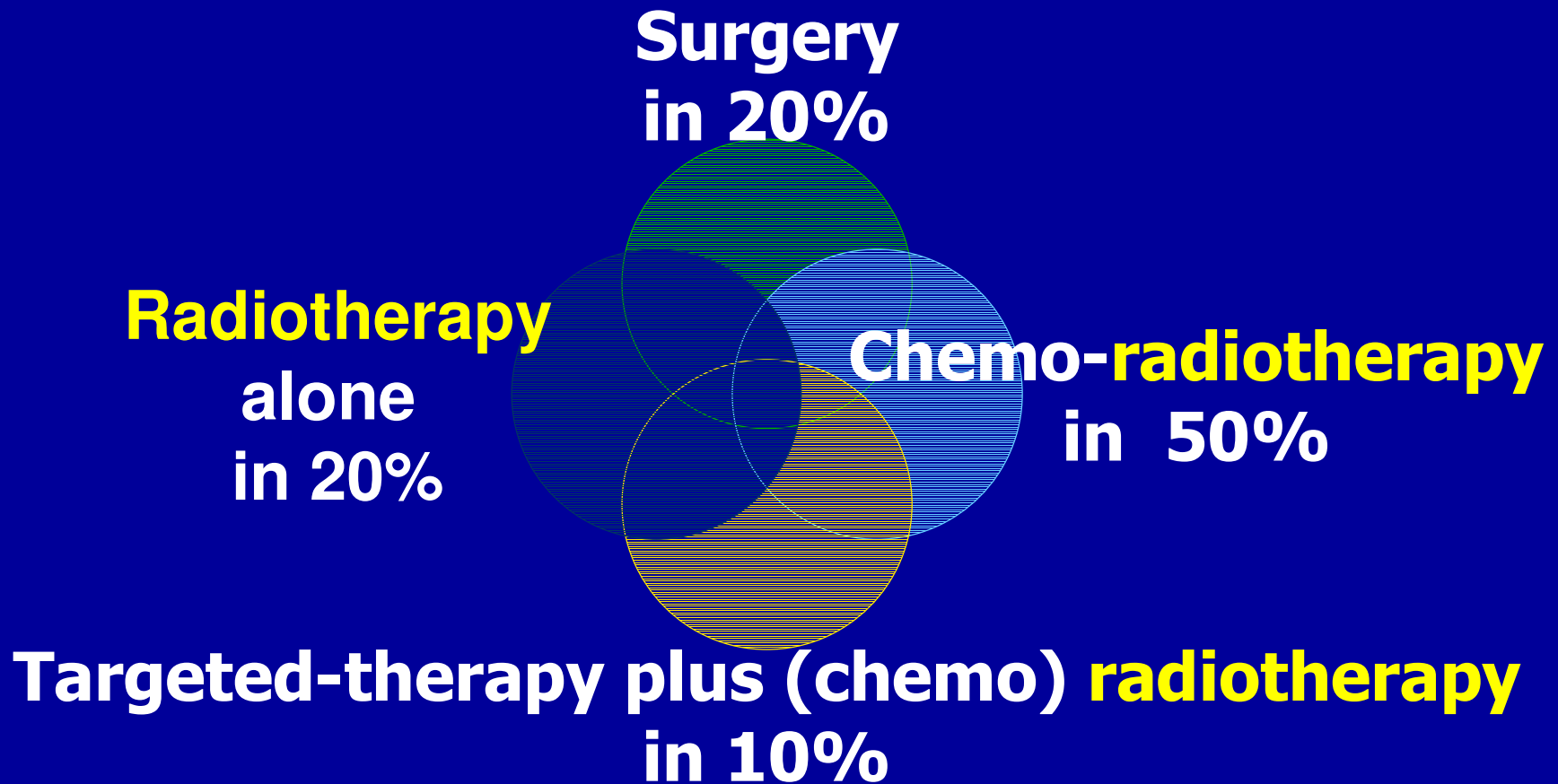
***ADJUVANT RADIOTHERAPY***  
*post-operative setting*

**THE INCREASING ROLE OF RADIOTHERAPY  
IN OROPHARYNX SCC**

***RADICAL CURE***  
*in unresectable SCC*

***RADICAL CURE  
WITH ORGAN FUNCTION  
PRESERVATION***  
*in resectable SCC*

# *Upfront treatment modalities in locally advanced oropharyngeal SCC*



# Oropharyngeal SCC

## *A Challenge for The Radiation Oncologist*

### *Tumor site*

*Total Dose Delivery Limited by Tolerance of Normal Structures (mucosa, spinal cord, brain stem, salivary gland, others)*

*• Dosimetric Challenges Due to Varying Contour/Tissue Heterogeneity*

### *Tumor biology*

*-fast cell kinetics → repopulation*

*-Hypoxia → intrinsic radioresistance*

*-High burden of clonogenic cells in advanced disease → more dose*

*-New biological constraints (EGFR overexpression, Cox-2 , others...)*

# Oropharyngeal SCC

## *A Challenge for The Radiation Oncologist*

**Tumor site → ADVANCED TECHNOLOGY**

*Total Dose Delivery Limited by Tolerance of Normal Structures (mucosa, spinal cord, brain stem, salivary gland, others)*

*• Dosimetric Challenges Due to Varying Contour/Tissue Heterogeneity*

**Tumor biology → INTENSIFIED TREATMENT**

*-Fast cell kinetics*

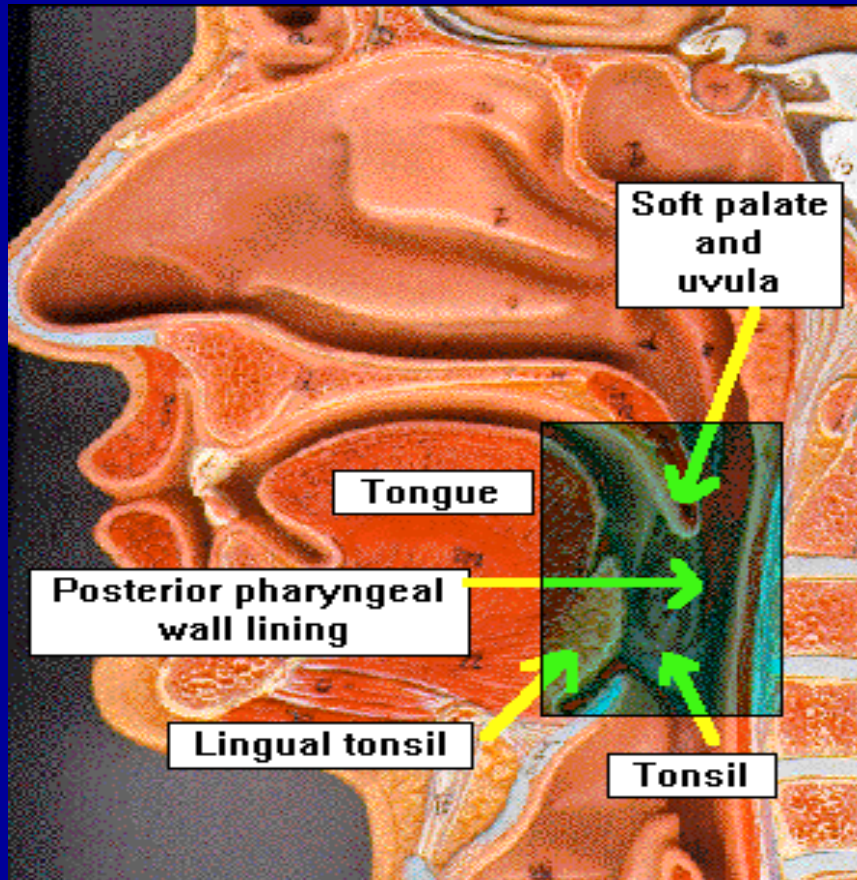
*-Hypoxia*

*-Intrinsic radioresistance*

*-High burden of clonogenic cells in advanced disease*

*-New biological constraints (EGFR overexpression, HPV -, others...)*

# Radiotherapy for Oropharyngeal SCC



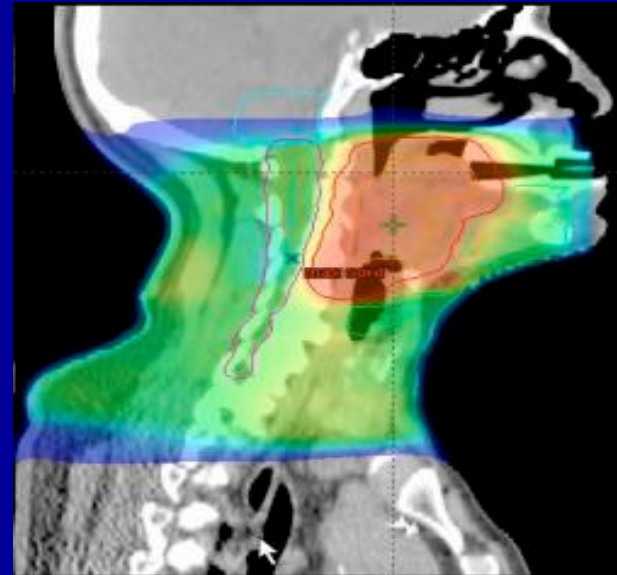
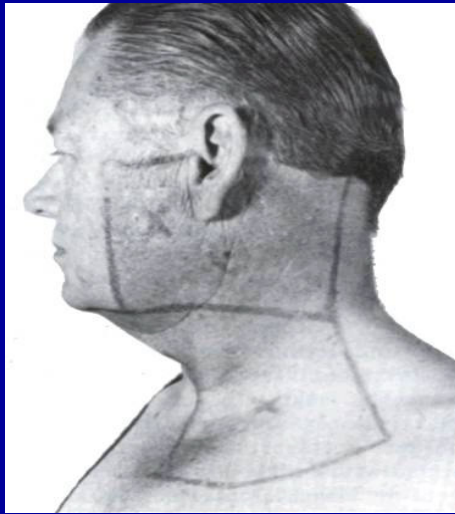
## 4 sites:

Anterior wall  
Lateral wall  
Superior wall  
Posterior wall

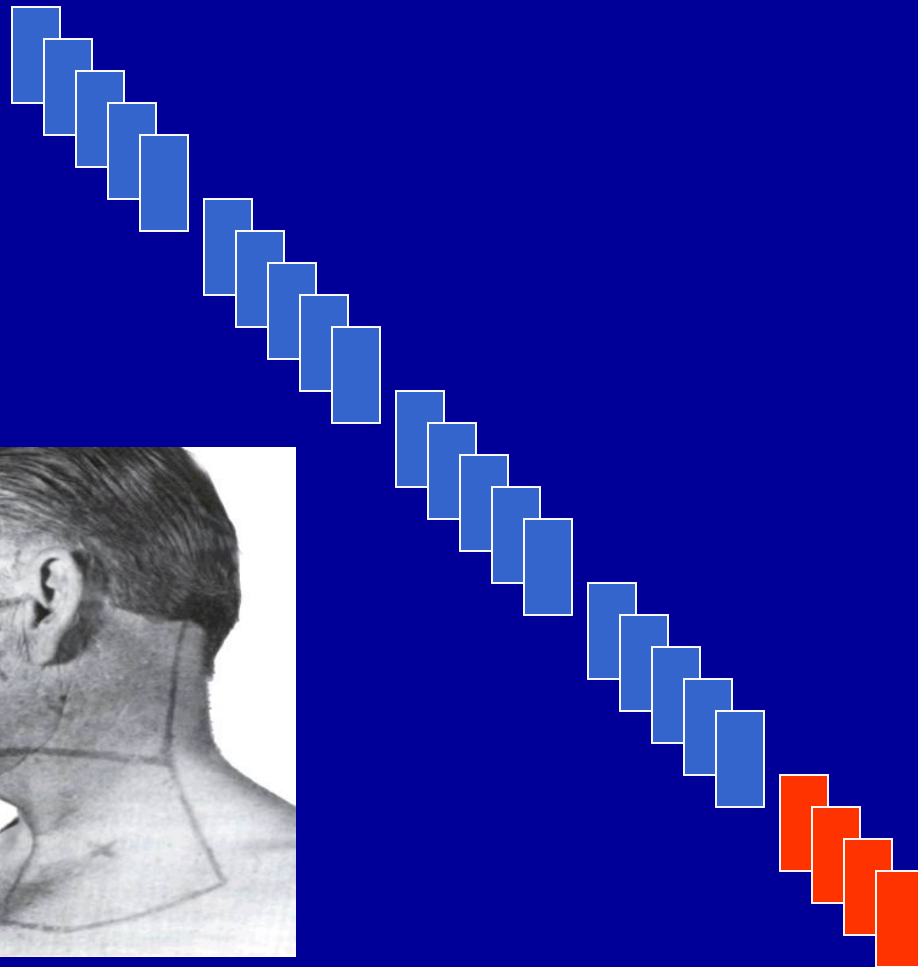
**7 subsites** each with different local spread

**STRATEGY AND  
TECHNIQUE DEPEND  
MAINLY ON PRIMARY  
TUMOR SUBSITE AND  
STAGE**

# Standard fractionation with sequential boost



**70 Gy / 35 fr / 7 w**





***Radiotherapy is a treatment option  
in oropharynx with early-stage  
tumors***

**Body of Evidence**

**There are no randomized studies in which radiation therapy was compared with conservative surgery with respect to local control or survival.**

**The recommendation to address this issue is based on evidence from prospective and retrospective cohort studies.**

# ***Outcome in oropharyngeal SCC after radiotherapy alone***

- ***Response according to clinical growth:***
  - Exophytic +++**  
(tonsillar wall, soft palate)
  - Infiltrative ++**  
(base of tongue, posterior wall)
- ***Control according to tumor stage:***
  - T1: 80%-100%**
  - T2: 70%**
  - T3: 50%-60%**
  - T4: < 30%**

# **Brachytherapy for Oropharyngeal SCC**

## **GEC-ESTRO recommendations**

**Mazeron J et al, R&O 2009**

- **Brachytherapy alone is useful for exophytic tumors measuring 10 mm or less in diameter or recurrent lesion after radiotherapy.**
- **Brachytherapy may be useful as boost for SCC measuring < 50 mm arising in the base of tongue, the soft palate, the tonsillar fossa and the vallecula.**

# **Brachytherapy for Oropharyngeal SCC**

## **GEC-ESTRO recommendations**

**Mazeron J et al, R&O 2009**

- **Brachytherapy is usually delivered by Iridium LDR, HDR or PDR.**
- **After 45-50 Gy of external dose:**
- **→ 30-35 Gy for base of tongue (macroscopic site should receive up to 80 Gy)**
- **Local control: base of tongue T1-T2: 80%**
- **Late necrosis of mucosa: up to 25%**

# **Radiotherapy vs Surgery in limited disease**

- **The ultimate therapeutic choice depends on:**
  - **staging (T1 vs T2, N0 vs N1)**
  - **general physical condition**
  - **age, co-morbidity**
  - **expected functional, cosmetic and socio-economical results**
  - **emotional status**
  - **experience of the treating team**
  - **available treatment facilities**

**and why not ?..... patient preference !**

# Locally advanced disease III-IV stages

(diagnosed in 60% of patients with SCC)

With conventional-one-a-day fractionation RT:

- local recurrence up to **50%-60%** at 2 years
- metastatic disease up to **15%-20%**
- overall survival at 5 years **< 30%**

**Accelerated RT  
chemoradiation**

repopulation

**Chemoradiation  
Escalating RT dose  
(hyperfractionation,  
brachytherapy, IMRT)**

Intrinsic Radioresistance

# **RADIOBIOLOGY**

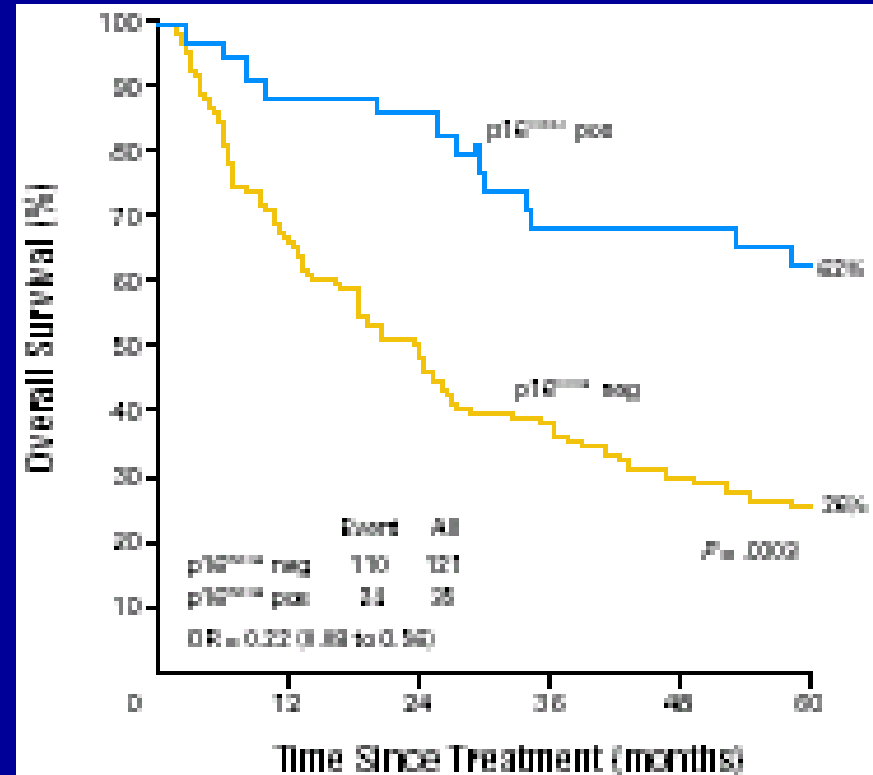
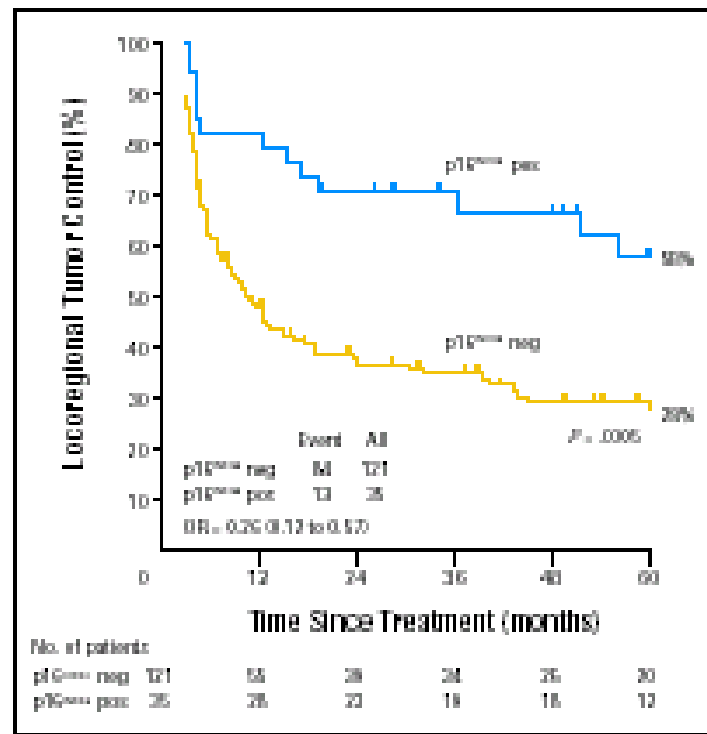
Hypoxia

EGF-R +

- Radiosensitizer
- Targeted Therapy

## Effect of HPV-Associated p16<sup>INK4A</sup> Expression on Response to Radiotherapy and Survival in Squamous Cell Carcinoma of the Head and Neck

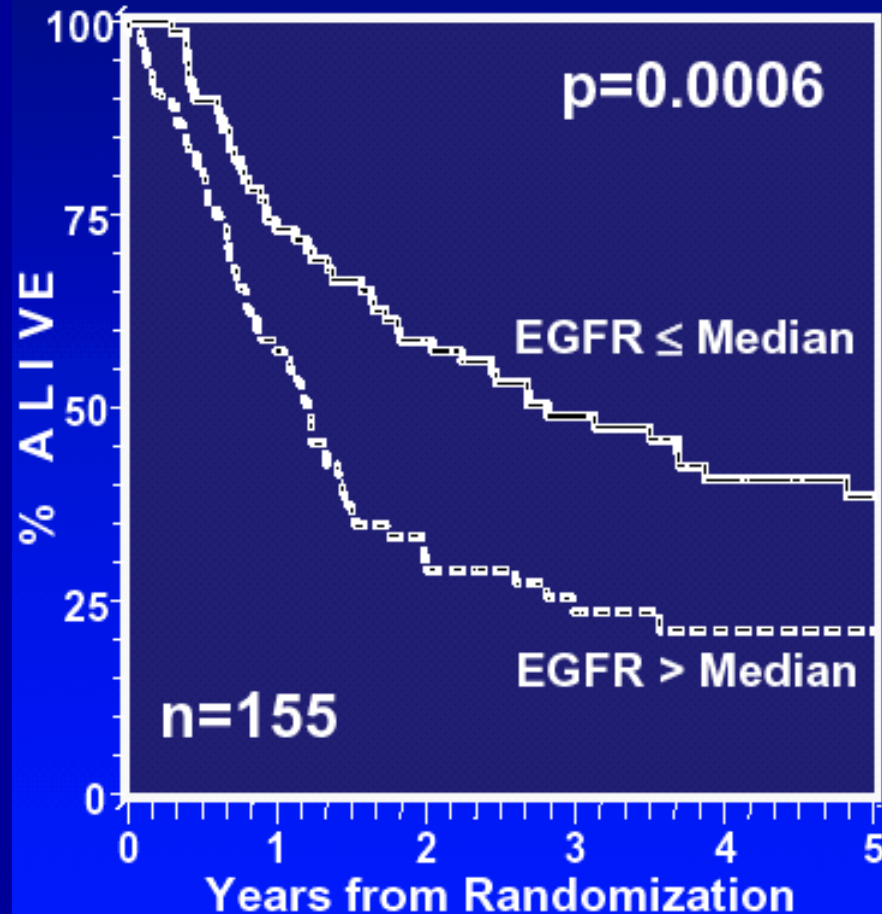
Periille Lassen, Jesper G. Bråbæk, Søren Hovfrow-Duort, Trine Thomsen, Jost Alster, and Jens Overgaard



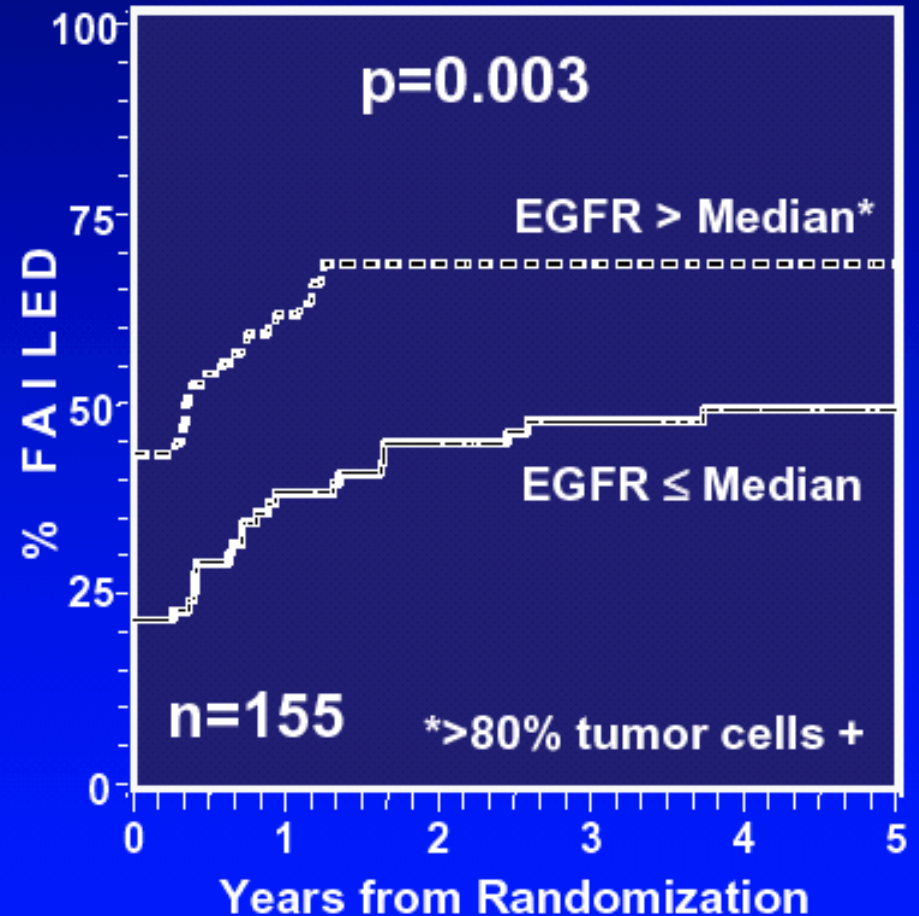


# EGFR Expression vs Radiation Response

## Overall Survival



## Local-Regional Relapse



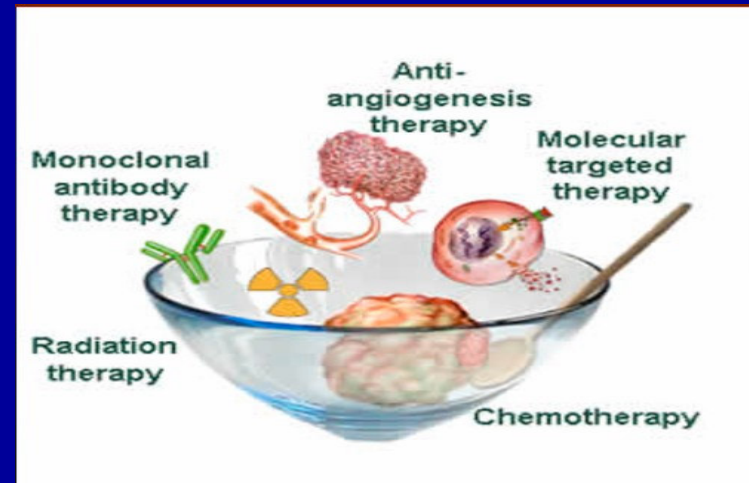
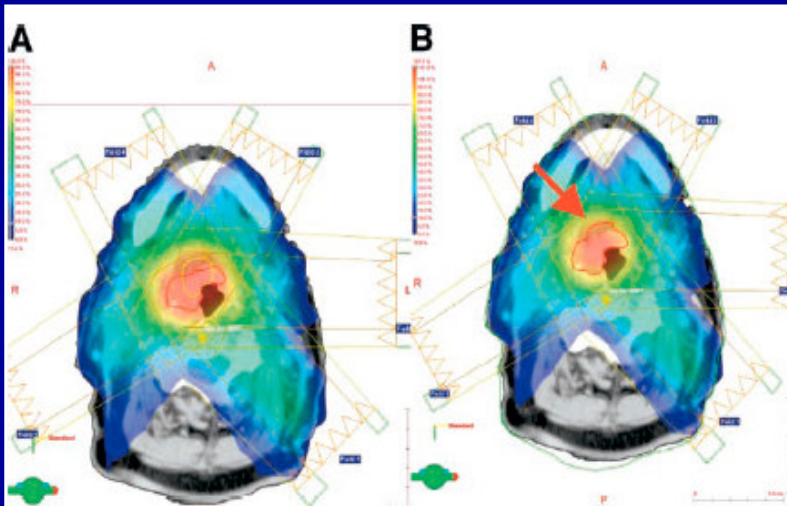
2008

HNSCC - Ang et al., Cancer Res 62: 7350, 2002 (Zymed antibody)

# ***Improving Efficacy of Irradiation.***

## ***Hypothesis: improving LRC → better OS***

- ***Dose escalation (Brachytherapy Boost, IMRT-SIB)***
- ***Altered Fractionation Schemes***
- ***Chemo-radiotherapy***
- ***Biological Therapy and Molecular Targeting + Radiotherapy***



# Locally advanced H&N Evidence Based Medicine

## Phase III trials and meta-analyses

*(pts with oropharynx SCC: near to 50%)*

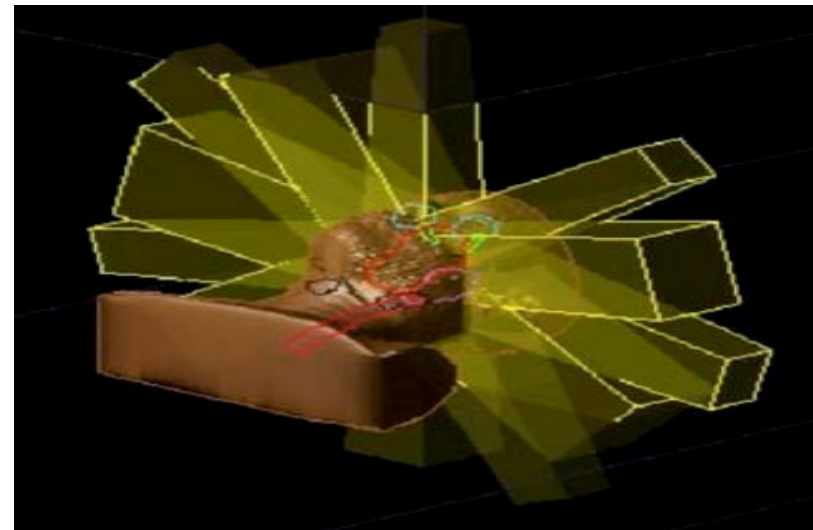
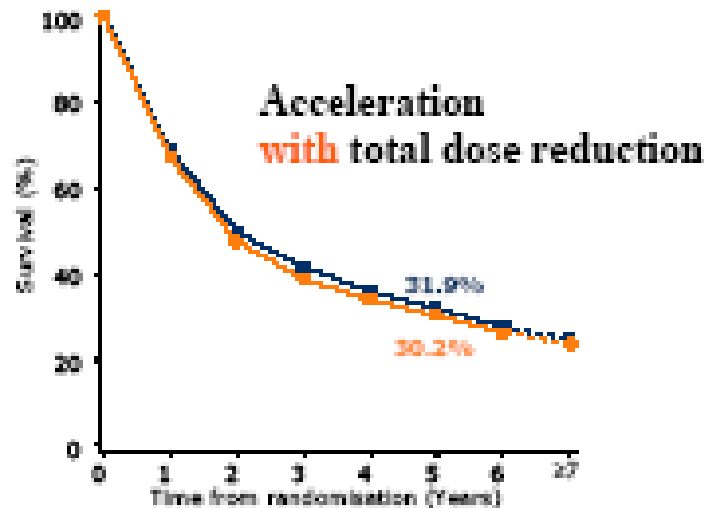
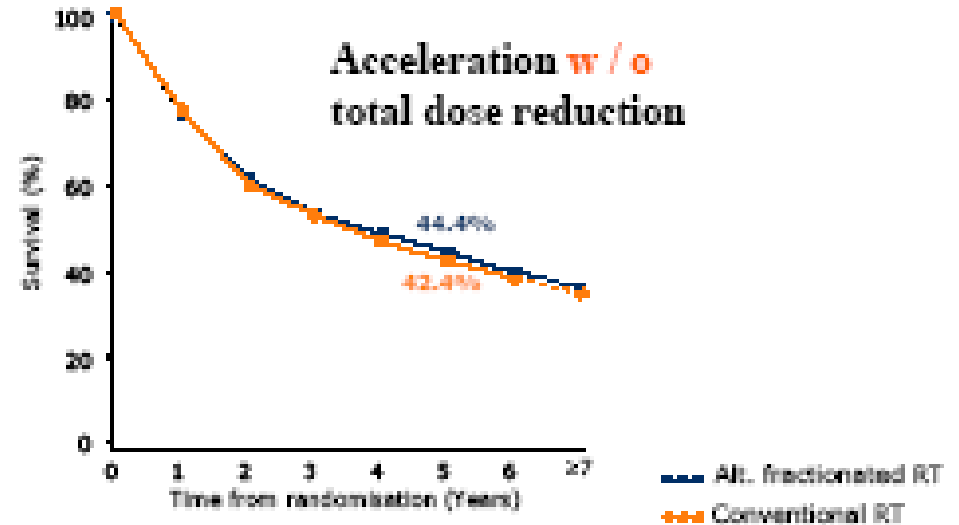
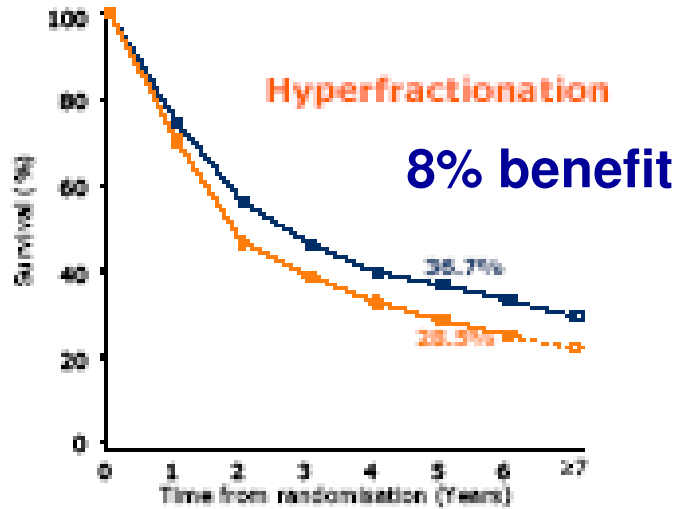
- **CT-RT > conventional RT** (level 1)
- **Hyperfractionated or accelerated radiotherapy > conventional RT**  
(RTOG/ EORTC trials - level 1)



Meta-Analysis of  
Chemotherapy  
in Head & Neck Cancer

# Overall survival

## MARCH Meta-analysis



<b>Chemo-radiotherapy trials META-ANALYSES</b>	<b>No of Trials</b>	<b>No of patients</b>	<b>Benefit in overall survival</b>	<b>p value</b>
<b><i>1. Chemoradiotherapy vs RT MACH-NC- Pignon et al, 2000</i></b>				
<b>Overall results</b>	<b>63</b>	<b>10741</b>	<b>4% at 5 years</b>	<b>0.0001</b>
<b>-Neoadjuvant chemotherapy</b>	<b>31</b>	<b>5269</b>	<b>2% at 5 years</b>	<b>0.10</b>
<b>-Concomitant chemoradiotherapy</b>	<b>26</b>	<b>3727</b>	<b>8% at 5 years</b>	<b>0.0001</b>
<b>-Adjuvant chemotherapy</b>	<b>8</b>	<b>1054</b>	<b>1% at 5 years</b>	<b>0.74</b>
<b><i>2. Chemoradiotherapy vs RT Updated MACH-NC- 2004</i></b>	<b>87</b>	<b>16000</b>	<b>5% at 5 years</b>	<b>0.0001</b>

## Evidence-based Radiation Oncology in locally advanced OROPHARYNX SCC

→ ***Improved loco-regional control***  
(with respect to conventional RT)

- hyperfractionation with increased total dose
- accelerated RT (without total dose reduction)
- concurrent chemo-radiotherapy
- radiosensitizer (?) – radiotherapy
- EGFR-inhibitors + radiotherapy
- **Reduced rate of distant metastases?**  
chemo-radiotherapy (doubtful evidence)

# Evidence-based Radiation Oncology in locally advanced OROPHARYNX SCC

→ ***Improved overall survival***

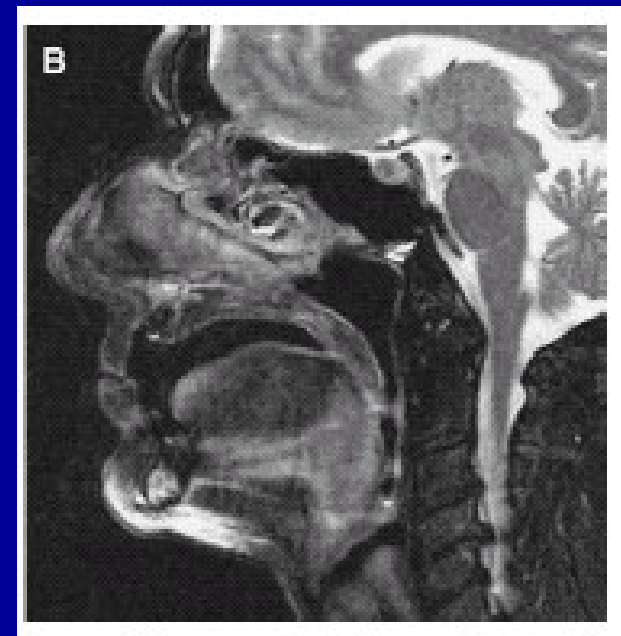
(with respect to conventional RT)

- **concurrent chemo-radiotherapy \***
- **hyperfractionated RT with ? total dose\***
- **accelerated RT** (at lower level of evidence)
- **EGFR-inhibitors –RT** (at lower level of evidence)
- 

**\* benefit of 8 % at 5 yrs in meta-analyses**



## **HYPERFRACTIONATION OR ACCELERATED RADIOTHERAPY**



## **CHEMO-RADIOTHERAPY**



## Potential indications for altered fractionation radiotherapy in oropharyngeal SCC

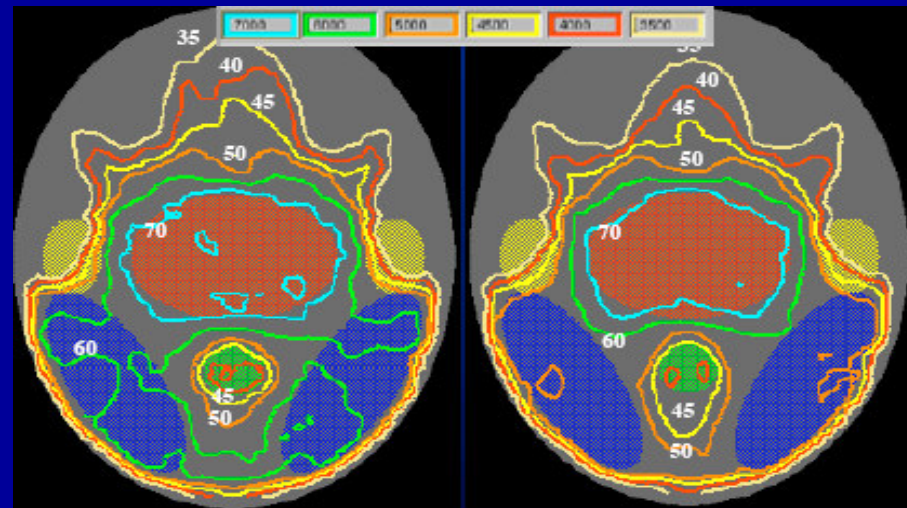
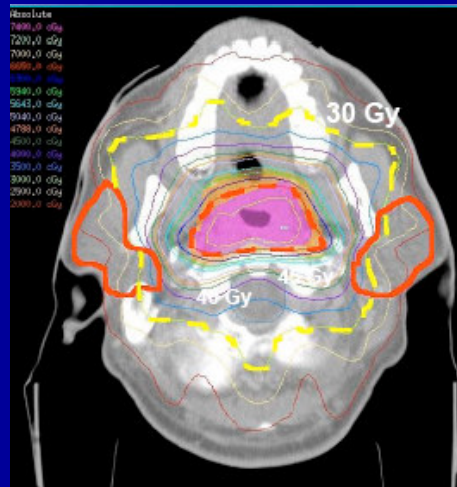
- Good performance status
- Age < 70 yrs
- Intermediate stage:

Stage III: T1 N1- T2 N1 – T3 N0- T3 N1

**→chemotherapy-induced toxicity may be avoided !**



# Adjuvant (chemo) radiotherapy in oropharyngeal SCC



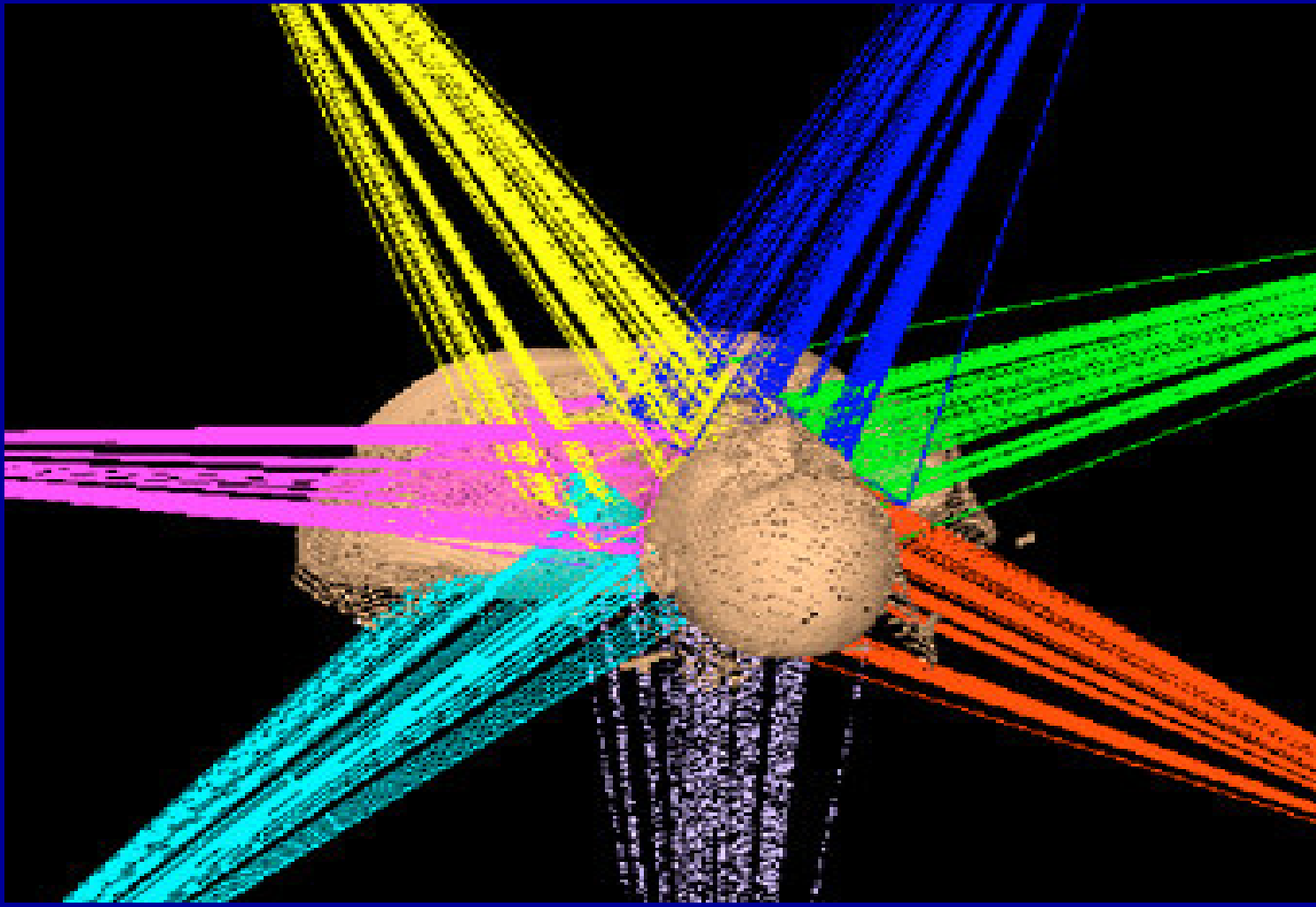
# Post-operative score of failure risk after surgery

- **Low-risk:**  
pT1-pT2 N0 with clear margins
- **Intermediate risk:**  
pT3-pT4 pN0 with clear margins  
pN+ (without ECE)  
close margins (not involved)
- **High risk:** extracapsular invasion  
involved margins

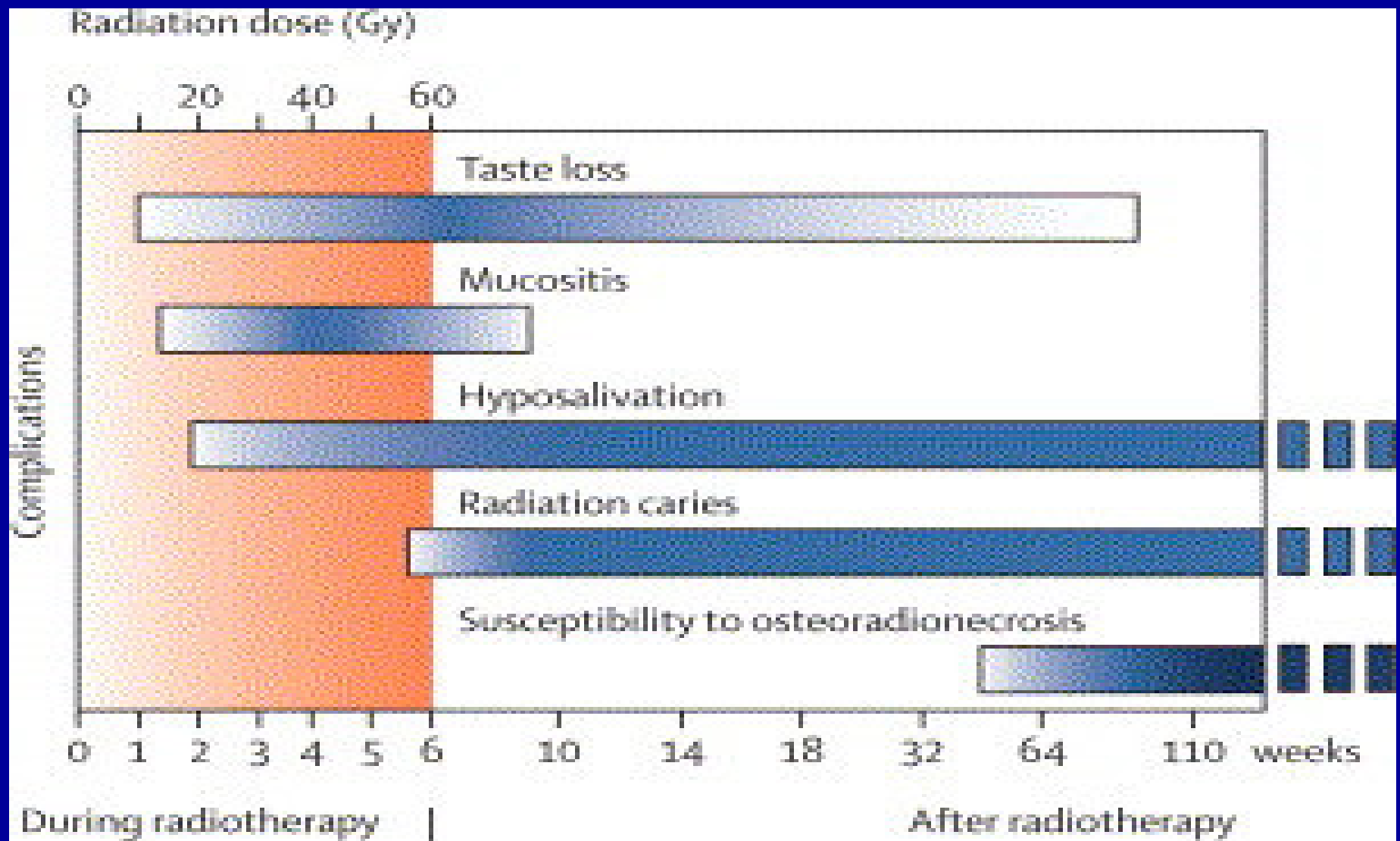
# Post-operative score of failure risk after surgery

- **Low-risk:** → no radiotherapy  
pT1-pT2 N0 with clear margins
- **Intermediate risk:** → radiotherapy alone ?  
pT3-pT4 pN0 with clear margins  
pN+ (without ECE)  
close margins (not involved)
- **High risk:** extracapsular invasion  
involved margins → chemo-RT

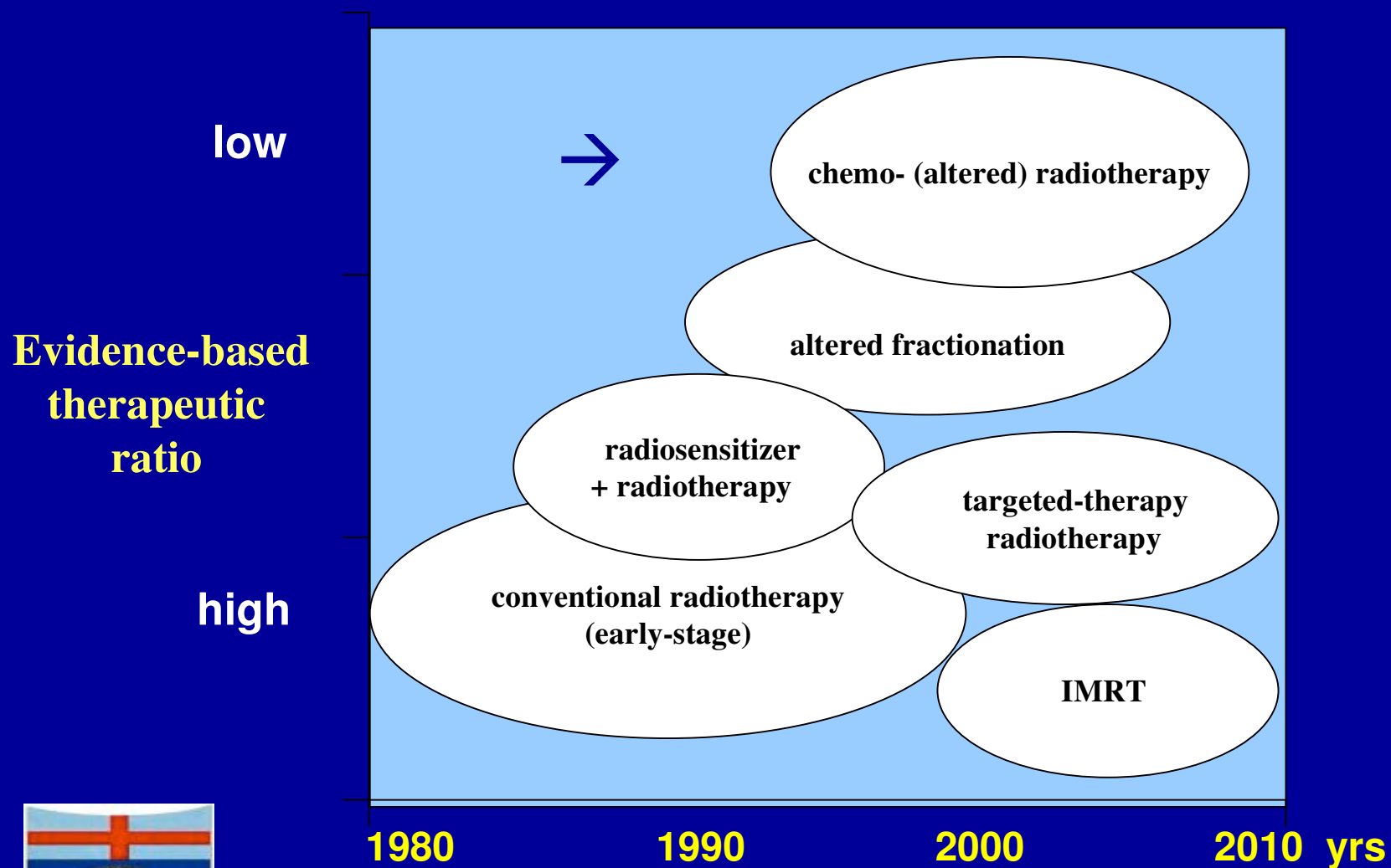
# *How to reduce toxicity ?*



# RADIO-INDUCED TOXICITY



# EVOLVING STRATEGIES in HNSCC

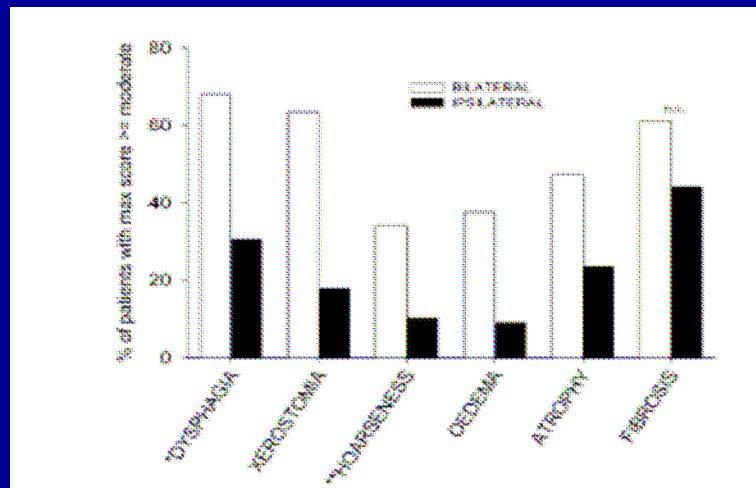


# Concerns with 3-D RT: OARs

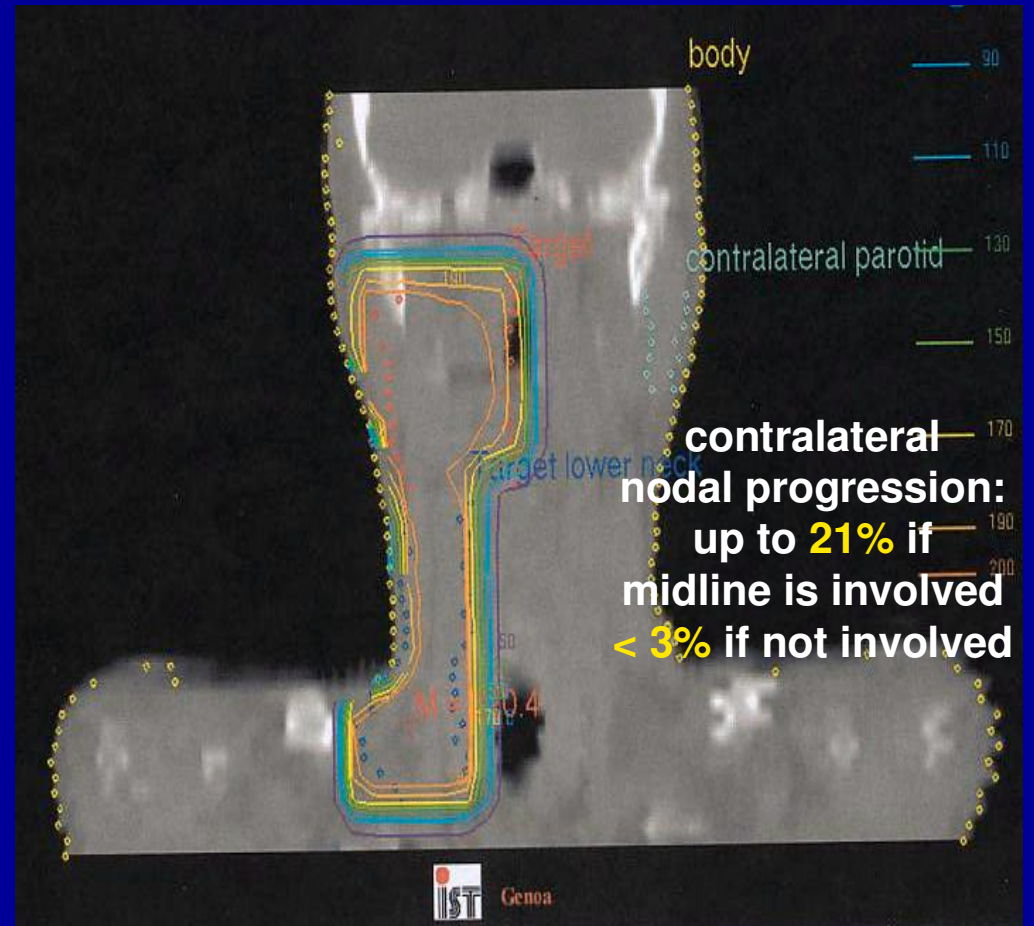
OARs	incidence/ prevalence of severe effects with 3-D RT
mucosa	mucositis 3+ up to 70%
parotid gland	severe xerostomia up to 82% ? stimulated parotid flow rate
larynx	hoarseness up to 30%
pharynx constrictor muscles	chronic dysphagia / aspiration: 35-76%
cochlea	sensor-neural hearing loss up to 68% with doses > 45 Gy



# UNILATERAL 3-D RADIO THERAPY for oropharynx SCC

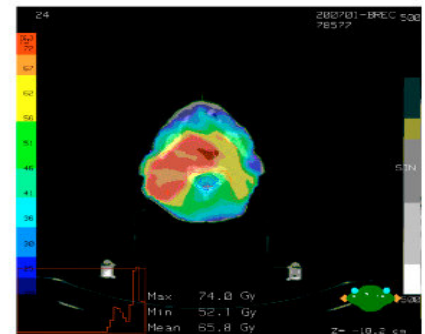
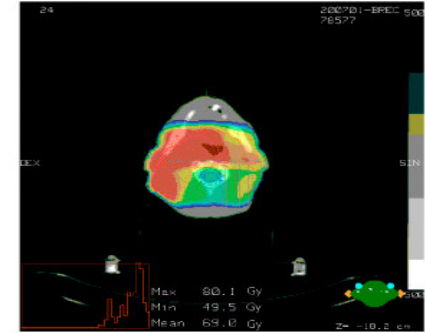
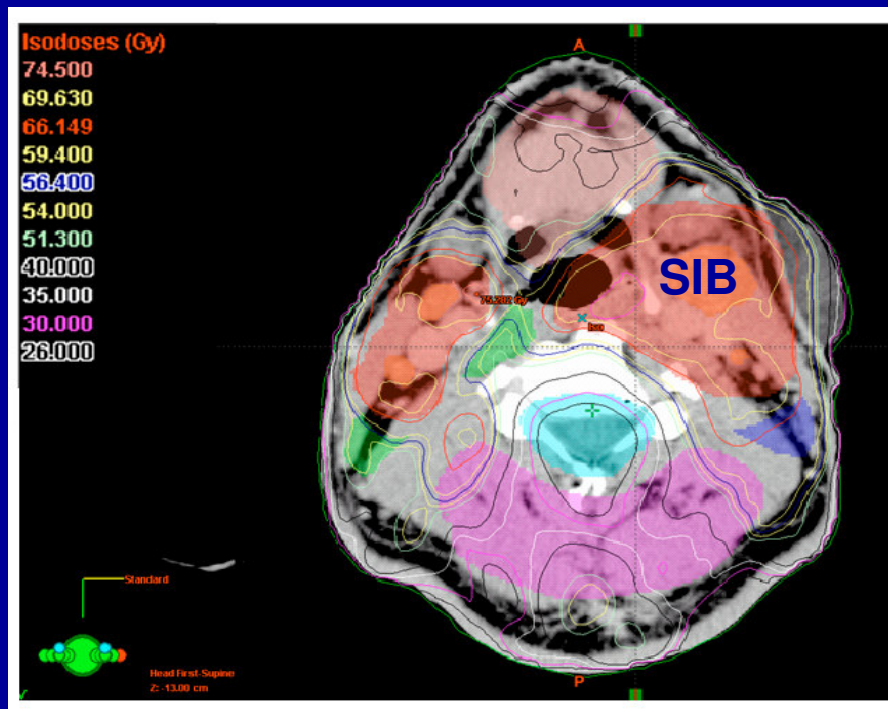


Jensen K. et al, R&O 2007



IST- Genoa, Tumori 2004

→ **LEVEL OF EVIDENCE IN 2009:**  
**IMRT offers effective local control with lower**  
*late toxicity rates* **than historical data.**



**IMRT for oropharynx SCC**

<b>Prognostic subgroup</b> <b>5-yr survival</b> <b>estimation</b>	<b>TNM features</b>	<b>Stage classification</b> <b>2002</b> <b>6th edition</b>
<b>Low-risk subgroup</b> <b>75%-90%</b>	<b>T1- T2 N0</b>	<b>I-II</b>
<b>Intermediate-risk</b> <b>subgroup</b> <b>60%</b>	<b>T3 N0</b> <b>T1-3 N1</b>	<b>III</b>
<b>High-risk subgroup</b> <b>32%</b>	<b>T4a N0-N1</b> <b>T1-T4 N2</b>	<b>IVA</b>
<b>Very-high risk</b> <b>25%</b>	<b>T4b any N</b> <b>Any T N3</b>	<b>IVB</b>

# Radiotherapy for oropharyngeal SCC: old and new investigations

- Conventional radiotherapy
- Brachytherapy alone
- External RT plus brachytherapy
- Hyperfractionation/accelerated RT
- Concurrent chemo-radiotherapy
- Concurrent radiotherapy with cetuximab
- **Induction CT → concurrent CT-RT**
- **Intensified Radiotherapy (SIB-IMRT) +/-CT**

# Practice recommendation

for the population with locally advanced  
oropharyngeal SCC disease  
**participation in clinical trials**  
is emphasized  
as a preferred or recommended treatment  
option”

Head & Neck Cancer Practical Guidelines – v.1-2008  
National Comprehensive Cancer Network- NCCT

# Radiotherapy for Oropharyngeal SCC

Multi-modality Strategy

Team expertise-based Strategy

Technology-based Strategy



# Radiotherapy: guidelines

Stage	NCCN	recommendation	PDQ-NCI	recommendation
<b>I</b>	RT	2B ++	RT for tongue base and tonsil	2A ++
<b>II</b>	RT	2B ++	RT for tongue base and tonsil	2A ++
<b>III early (T2N1)</b>	CT-RT	3 +	HF-RT (tonsil)	1iiA +++
<b>III-IVA</b>	Concurrent CT-RT	1 +++	HF-RT (tonsil)	1iiA +++
	Induction CT → CT-RT	3 +	Concurrent CT-RT	1iiA +++
			Induction CT → CT-RT	2A ++