

# Head and Neck Cancer

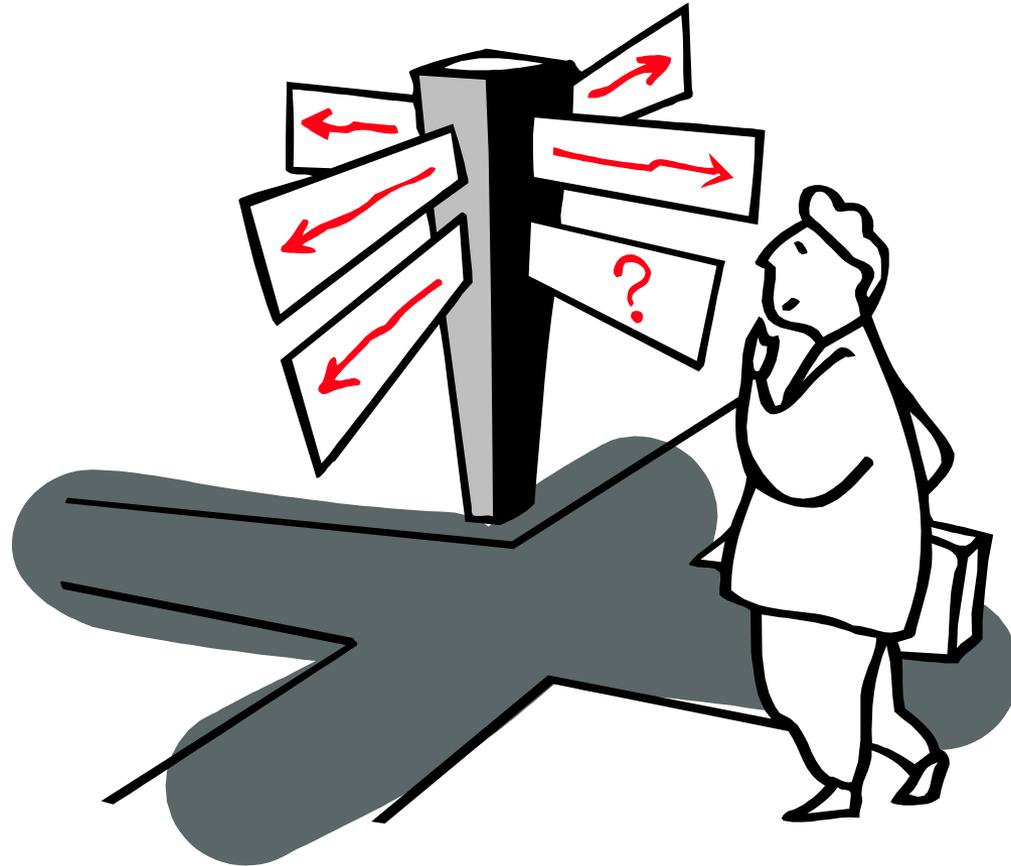
## Radiation Oncology

**L. Plasswilm**

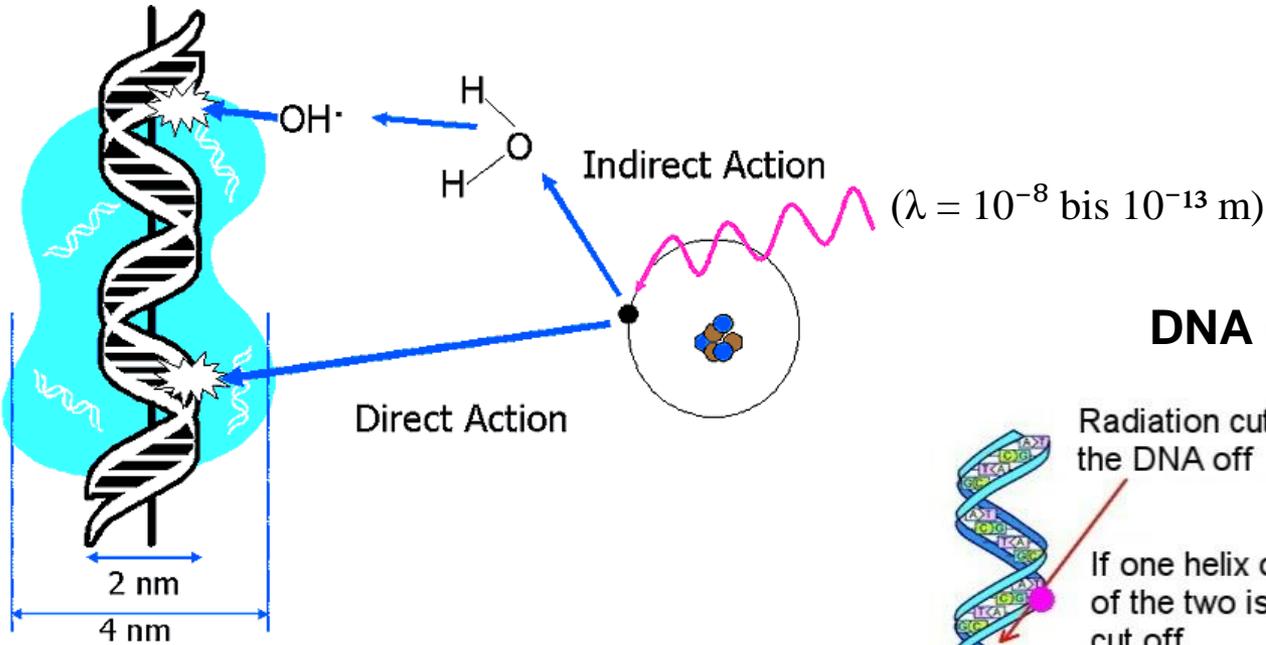
# Outline

- **Basics**
- **Technique**
- **Indication**
- **Treatment Results**
- **Toxicity**

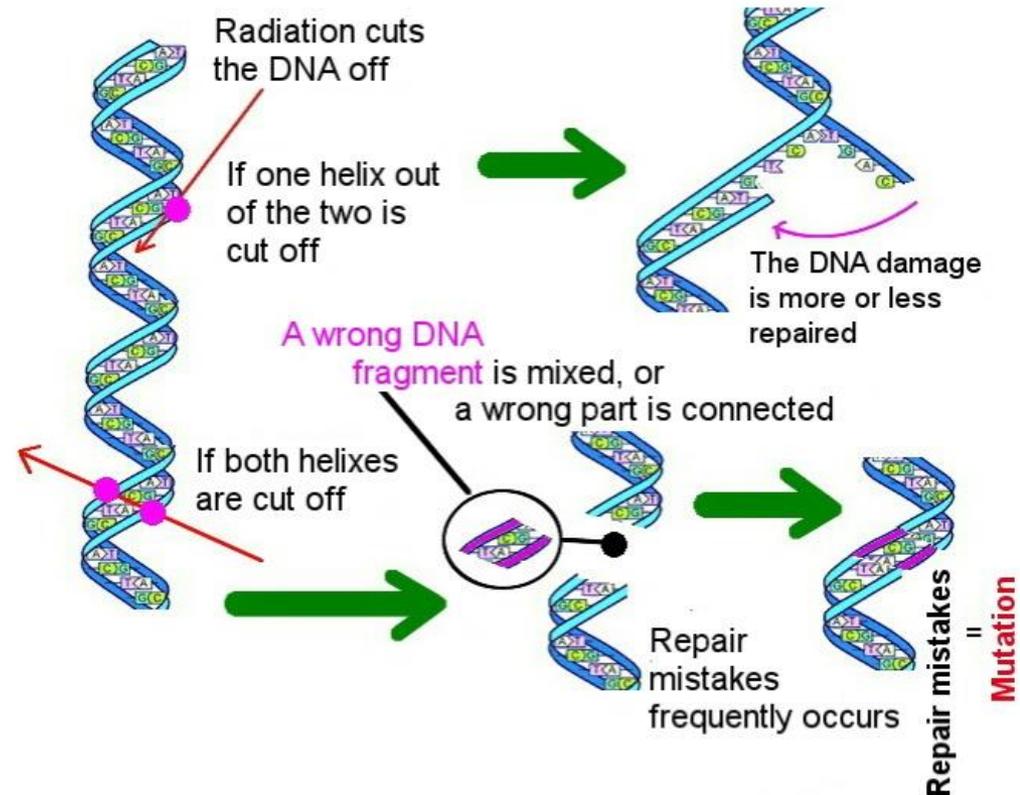
# BASICS



# Direct & Indirect Actions of Radiation



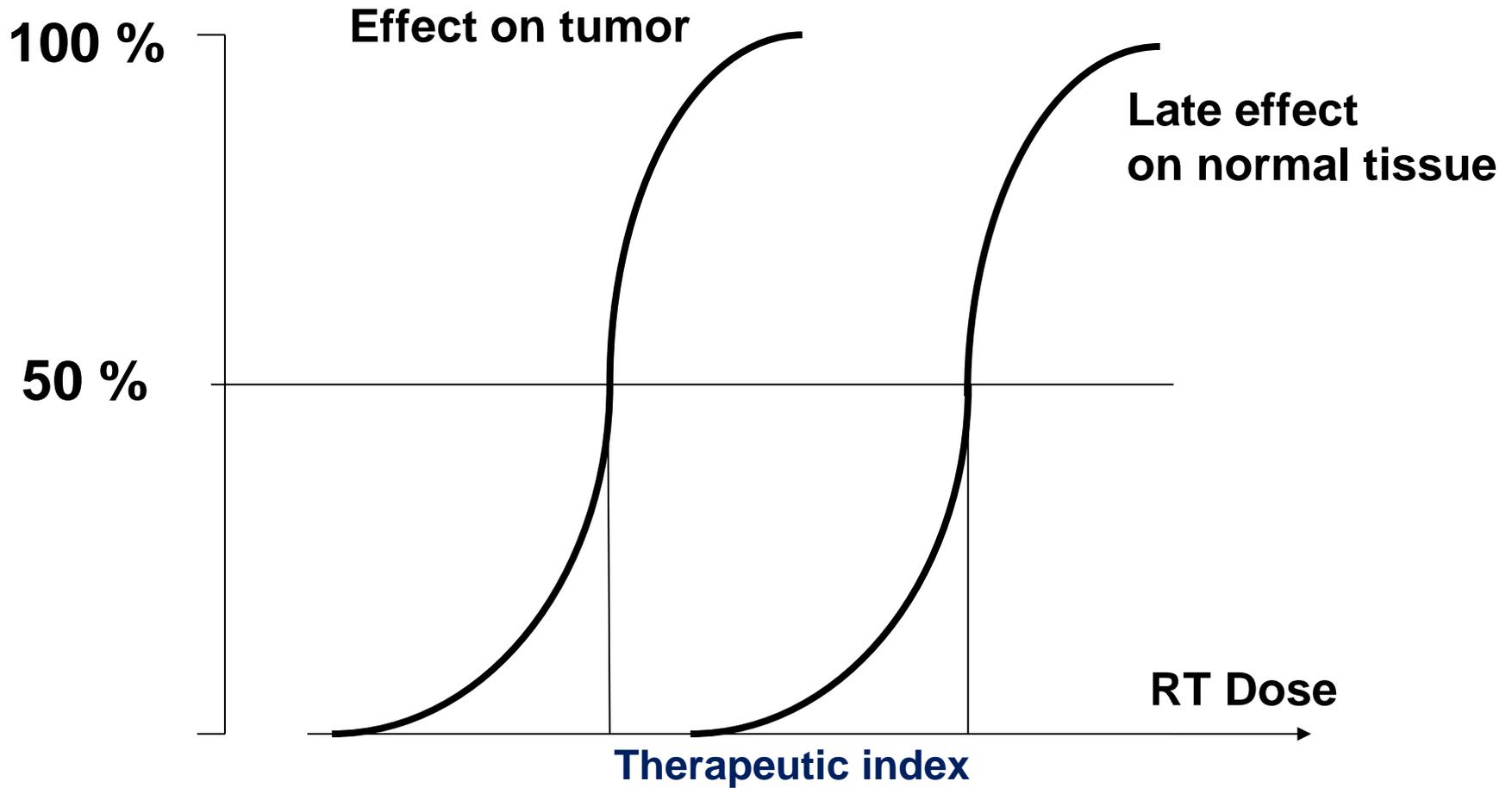
## DNA cut off by radiation



$$D = E_{\text{abs}} / M$$

$$1 \text{ Gray} = 1 \text{ Gy} = 1 \text{ J / kg}$$

# Effect on tumor vs late toxicity



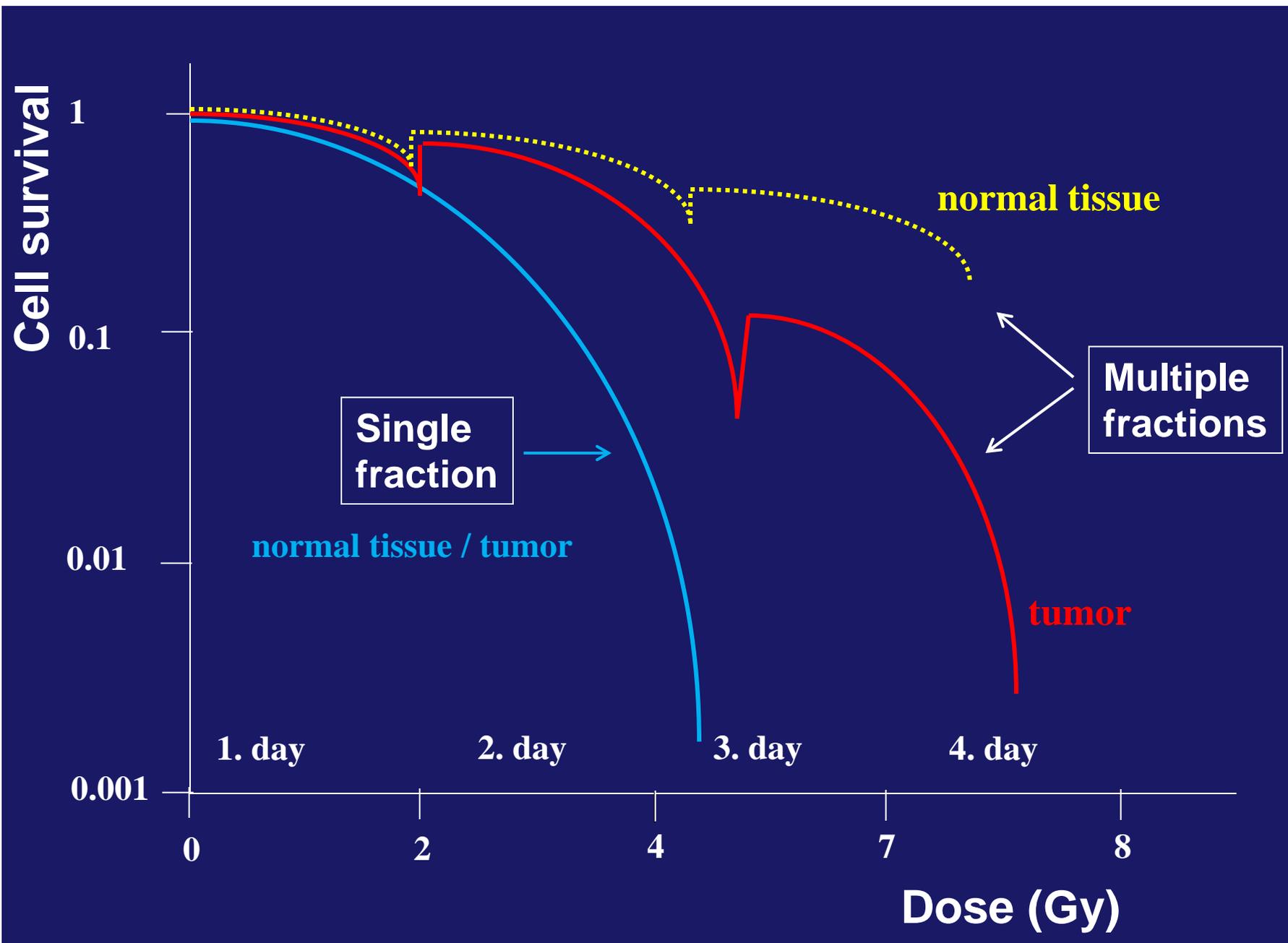
Therapeutic index  $\uparrow$   $\rightarrow$  Biology, Technique

# Dosage / Schedule

- **Total Dose**
- **Fractionation**



# Fractionation

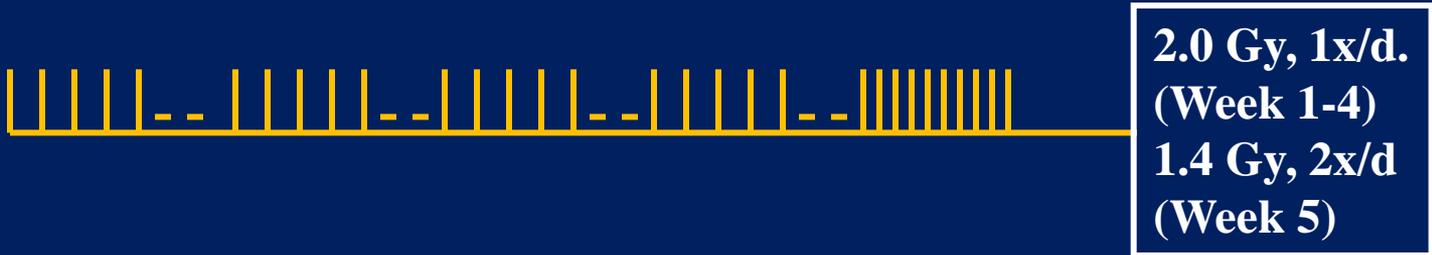


# Fractionation

## Normal



## Accelerated



## Hyperfractionated



SIB – simultan. integrated boost

# Prescribed Dose

- **Macroscopic disease (Primary-Tu / Lymphnodes):** **70 - 72 Gy\***
- **Microscopic disease (R1):** **60 - 66 Gy\***
- **Elective:** **50 - 56 Gy\***

\* 2 Gy / fraction / day

# Tolerancedose of some organs at risk (2 Gy / fraction / day)

	TD 5/5 in Gray	TD 50/5 in Gray
Spinal Cord (Myelon)	50	70 (Myelitis, Necrosis )
Parotid Gland	32	46 (Xerostomia)
Temporomandibular Joint	60	72 (Impaired Joint Function)
Larynx	70 (from 45 Gray Edema)	80 (Necrosis)
Optical Nerv	50	65 (Loss of eyesight)
Optical Lens	6-10	18 (Cataract)
Ear mid / external	30 / 55	40 /65 (acute/chronic Otitis)

TD 5/5 = Max Tolerated Dose, 5% rate within 5 years

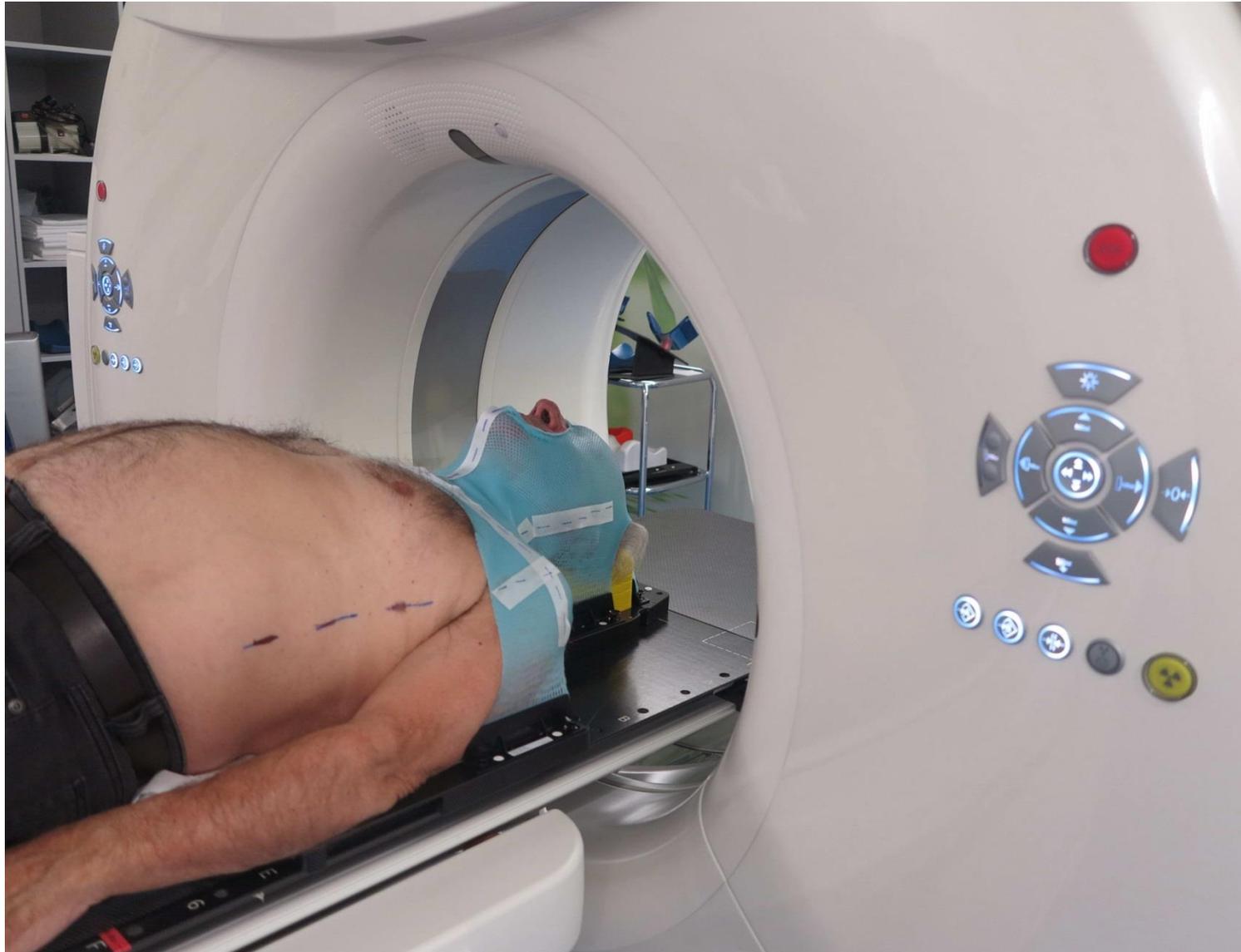
TD 50/5 = Max Tolerated Dose, 50% rate within 5 years



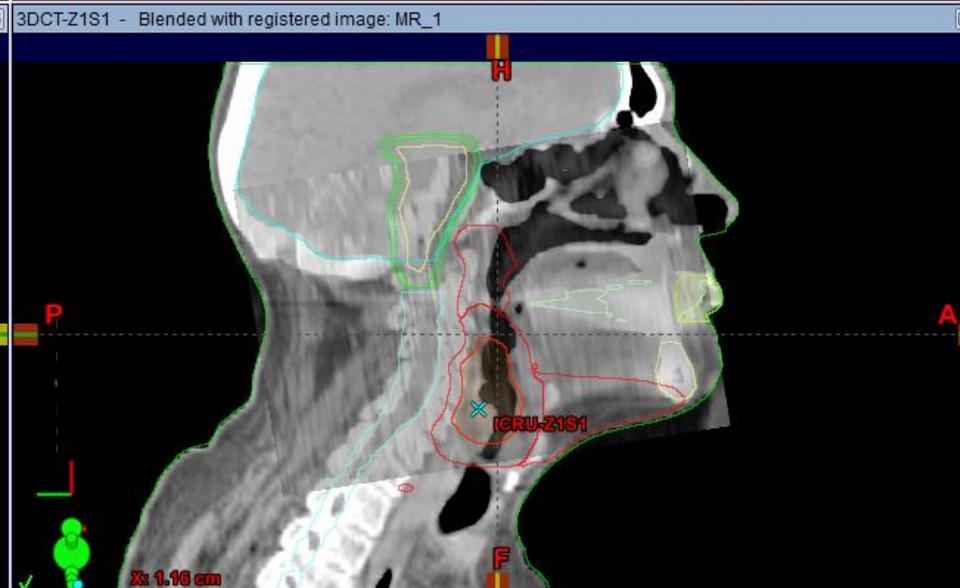
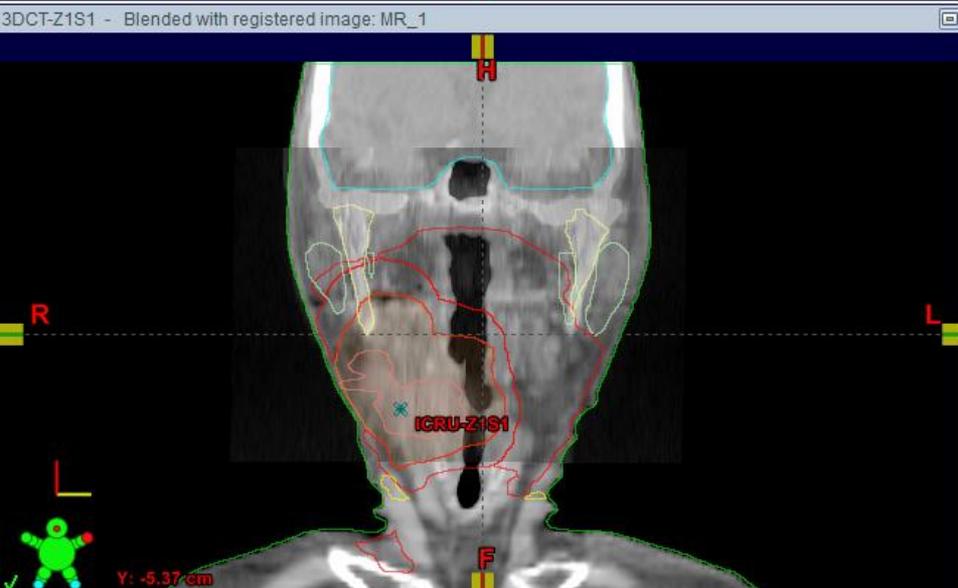
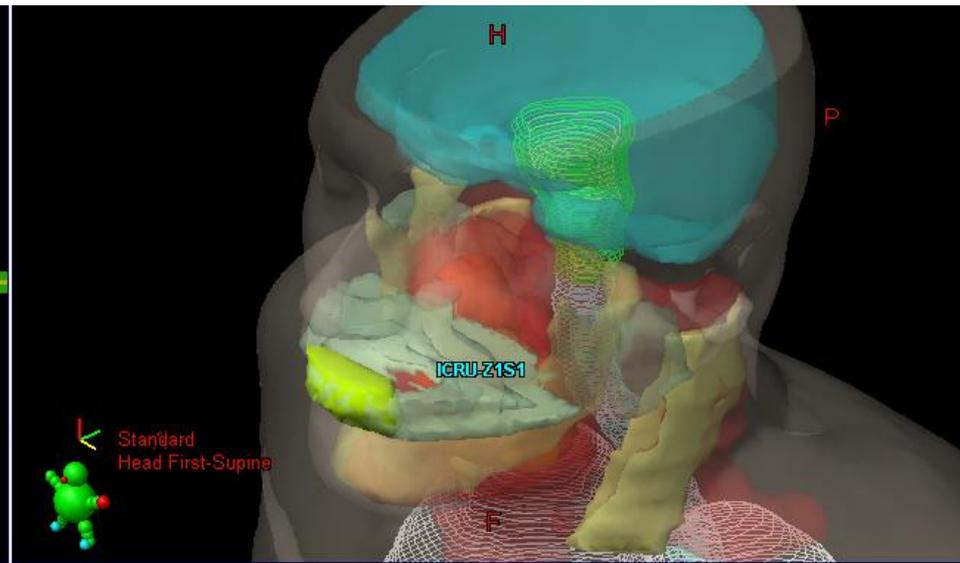
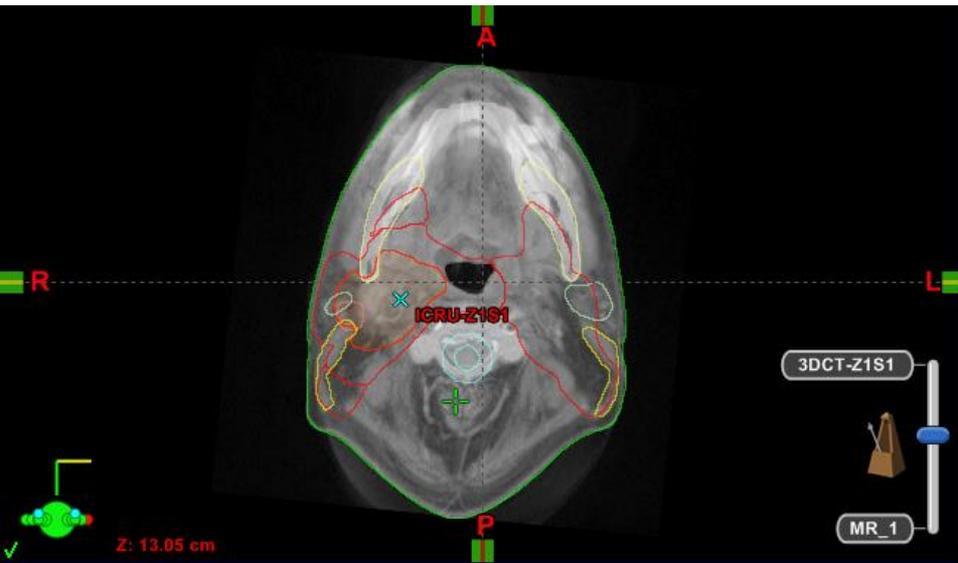
**Improving treatment quality**

**Technique**

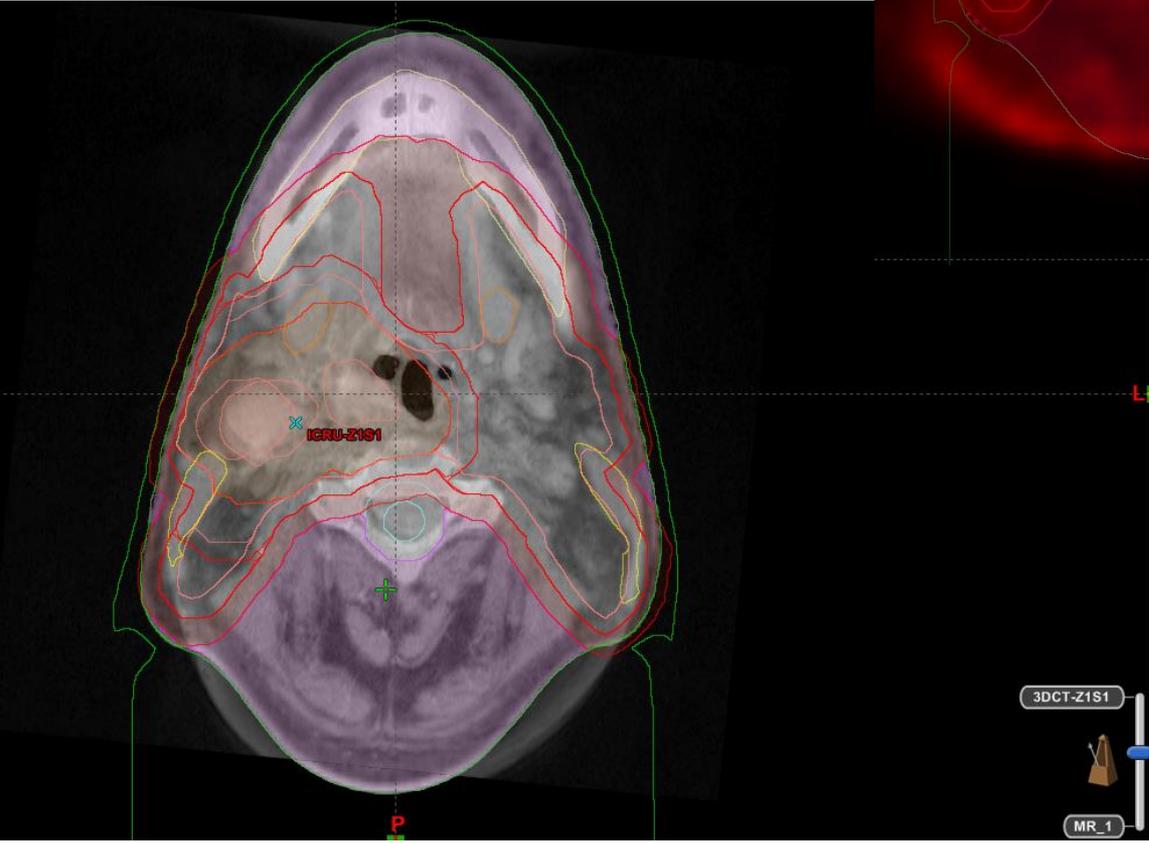
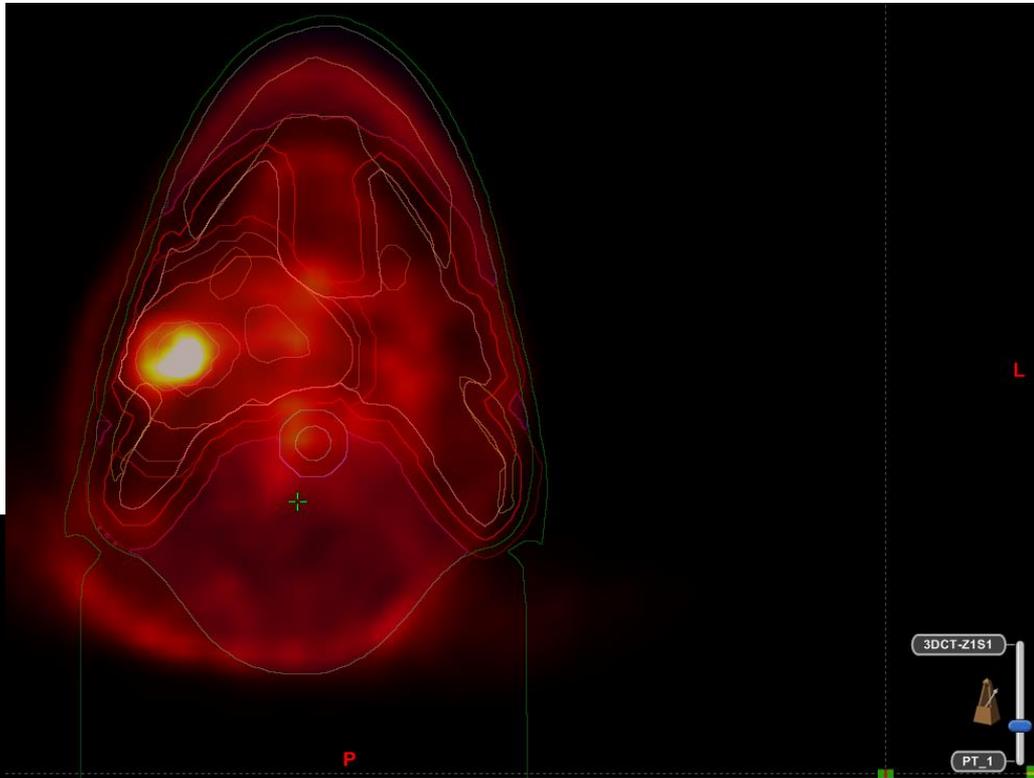
# Treatment Planning «Planning-CT»



# Target volume & Organs at risk

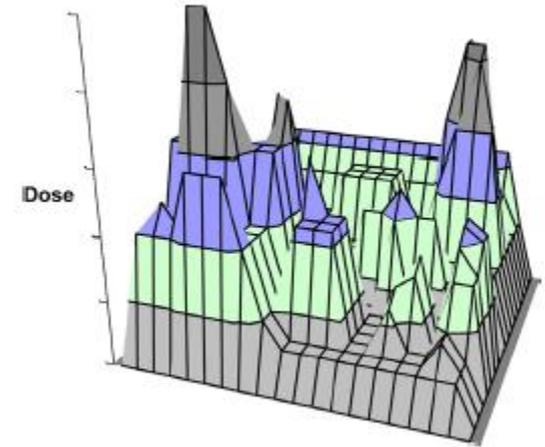
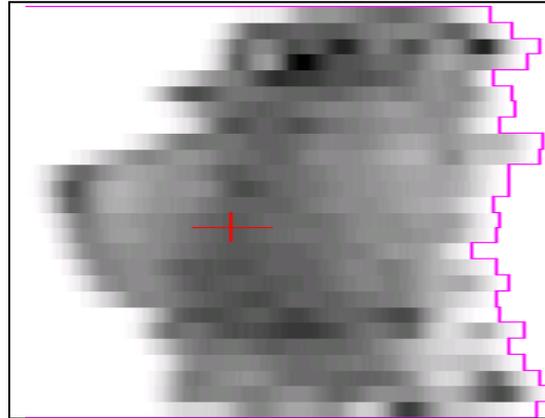
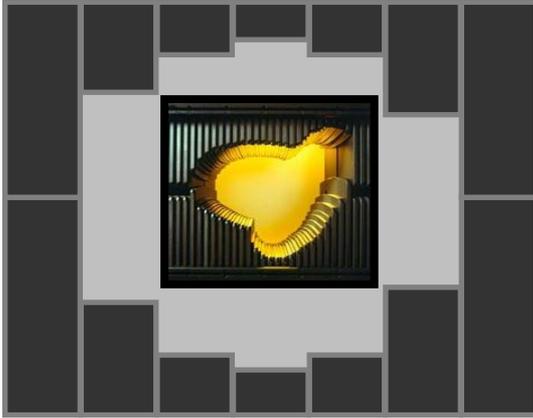


**Image fusion  
+ all available information  
(endoscopy, surgery,  
histology, ...)**

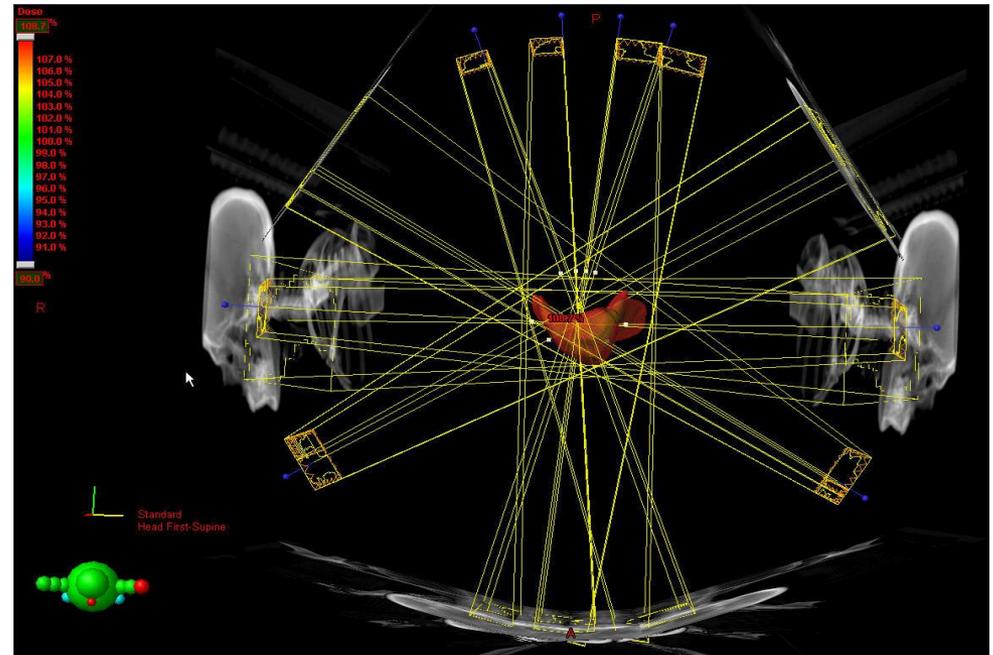
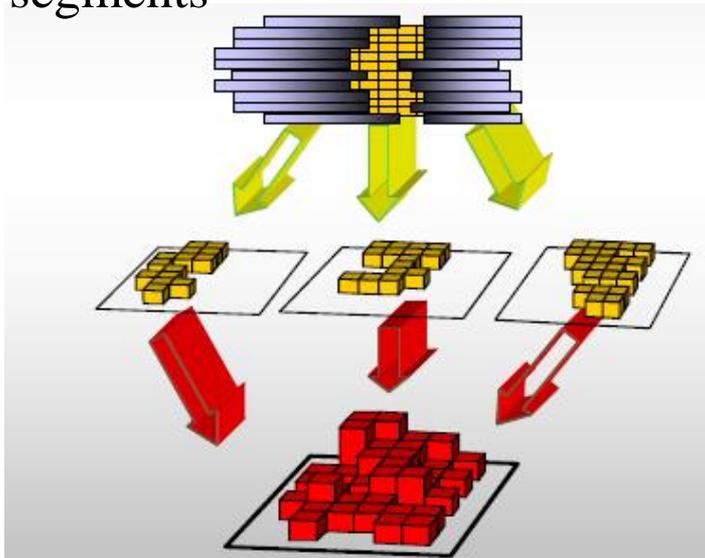


**PlanningCT – MRI – PET/CT**

# IMRT: Intensity Modulated Radiotherapy



multiple treatment fields and segments



# Intensity Modulated Radiotherapy

«Step and Shoot»

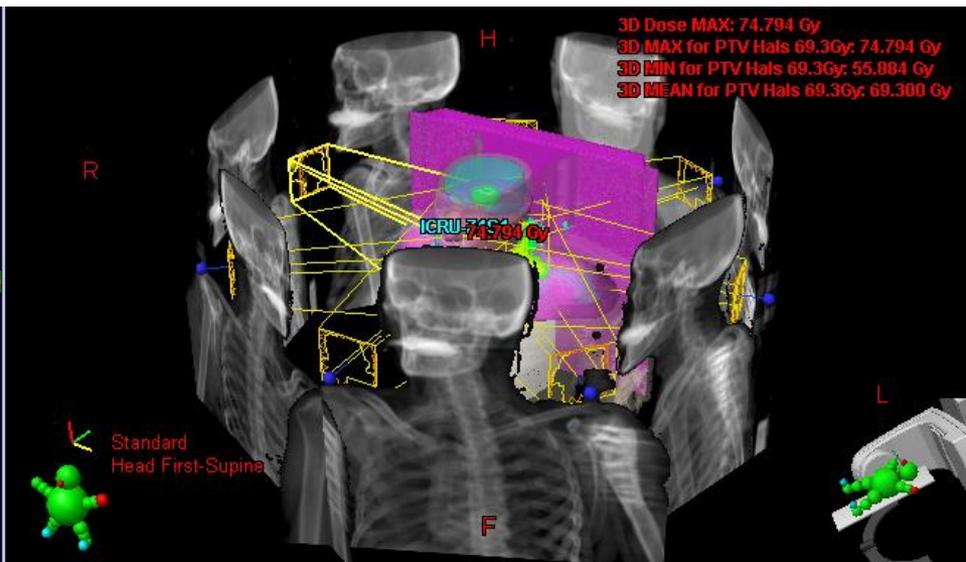
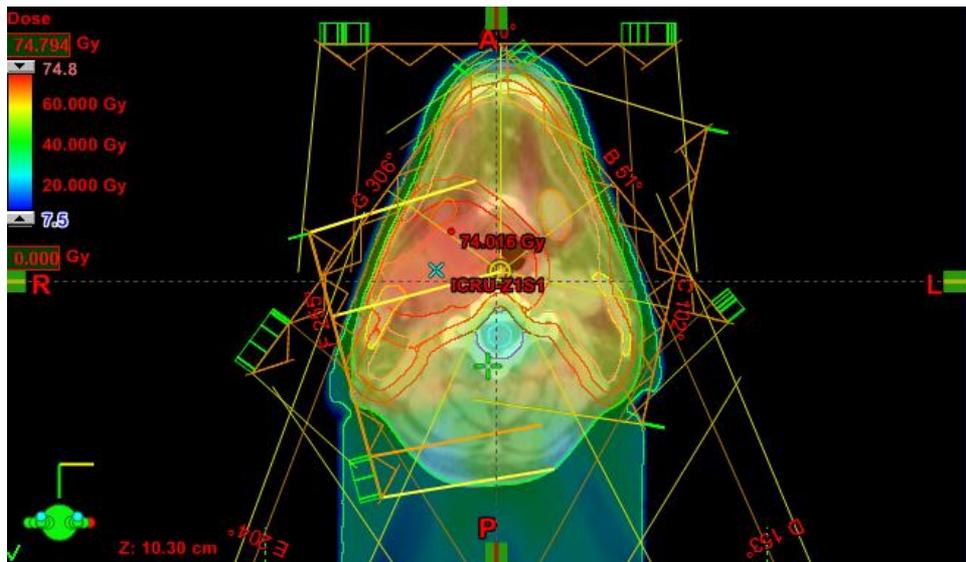
«Intensity-modulated Arc Therapy (IMAT)»

Radpid Arc

VMAT

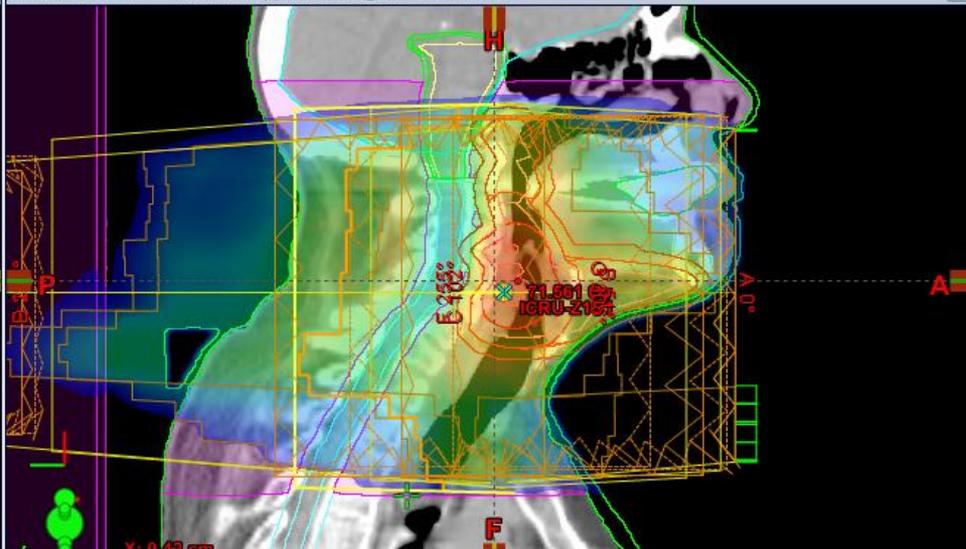
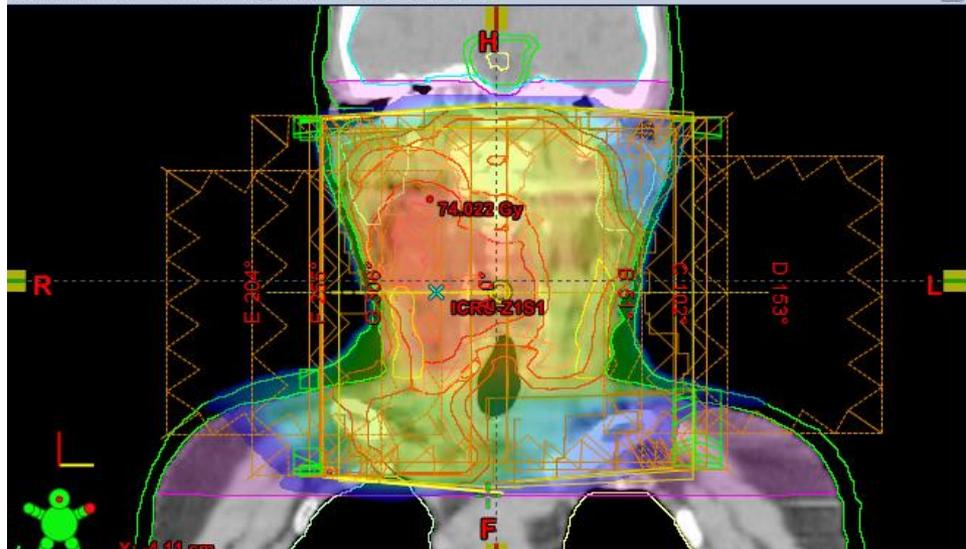
«Tomotherapie»

# Treatment Planning: Dose Distribution

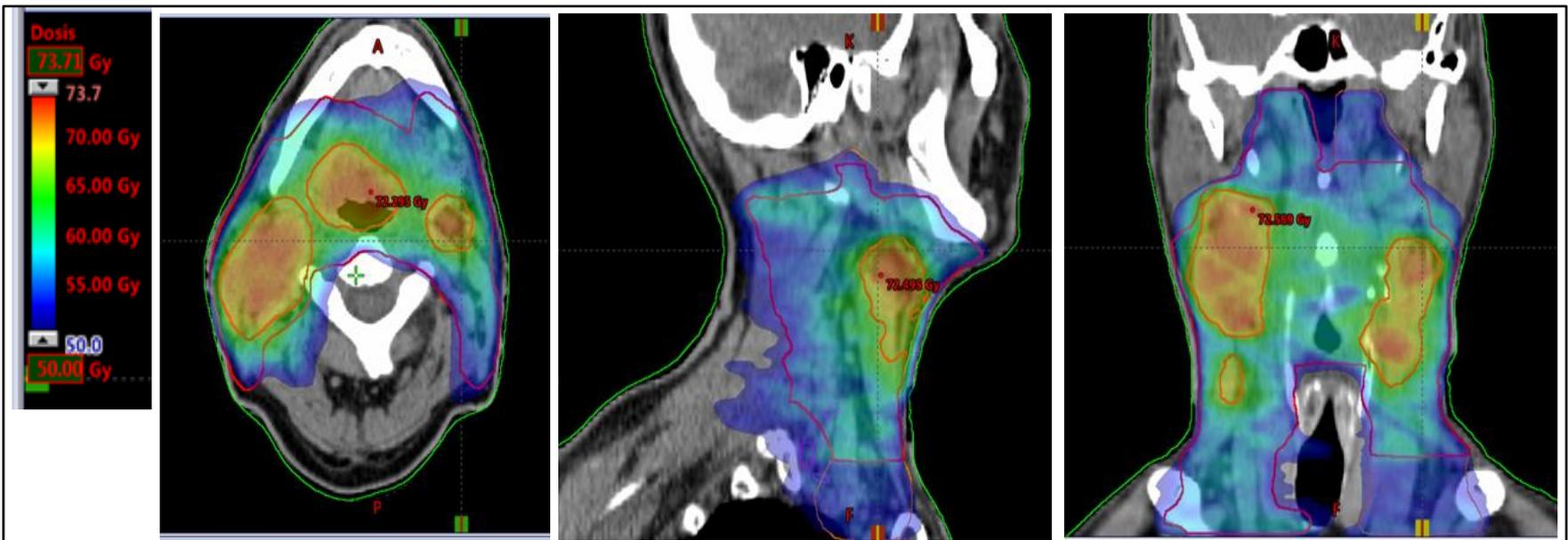
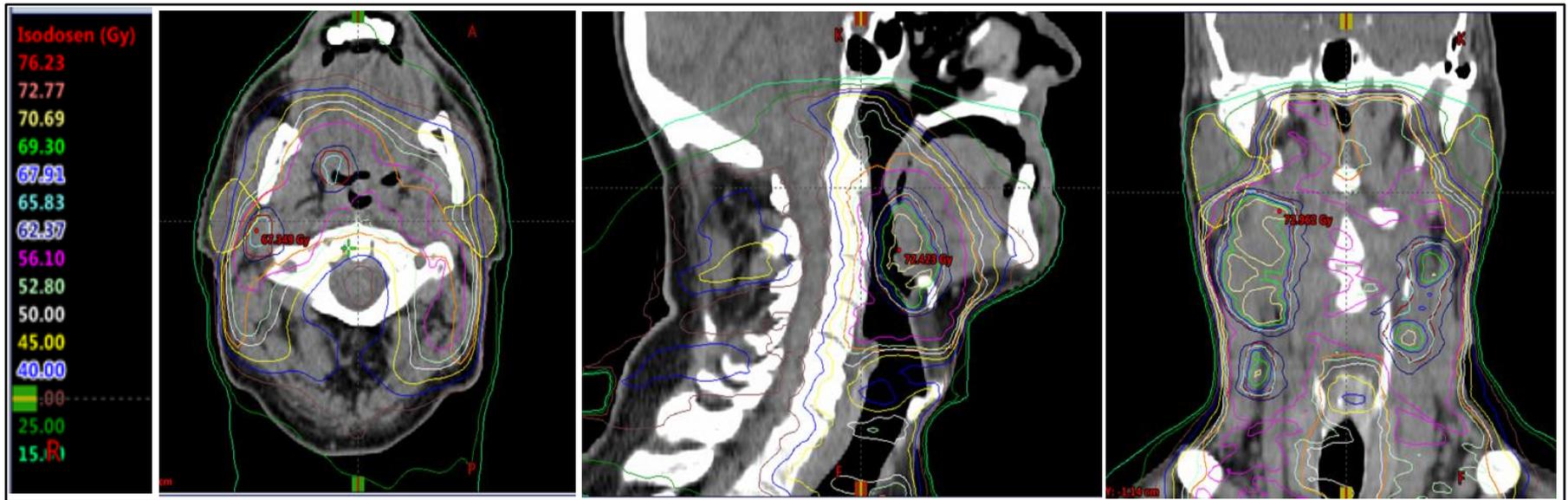


50136Z1S1IMRT - Treatment Approved - Frontal - 3DCT-Z1S1

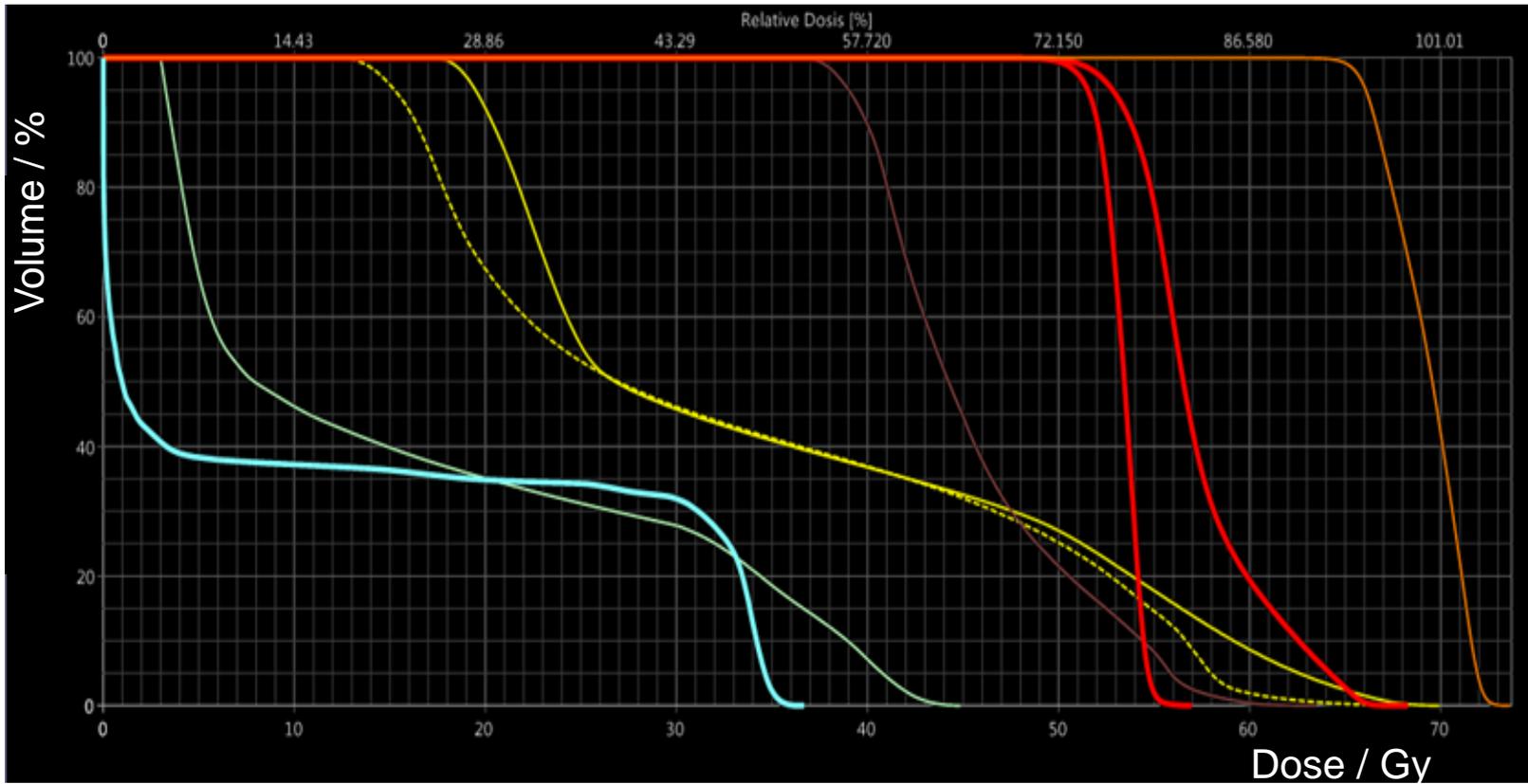
50136Z1S1IMRT - Treatment Approved - Sagittal - 3DCT-Z1S1



# Treatment Planning: Dose Distribution

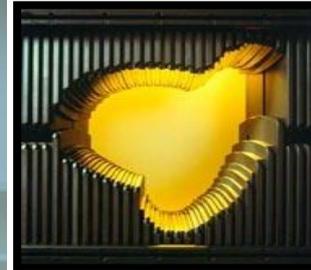
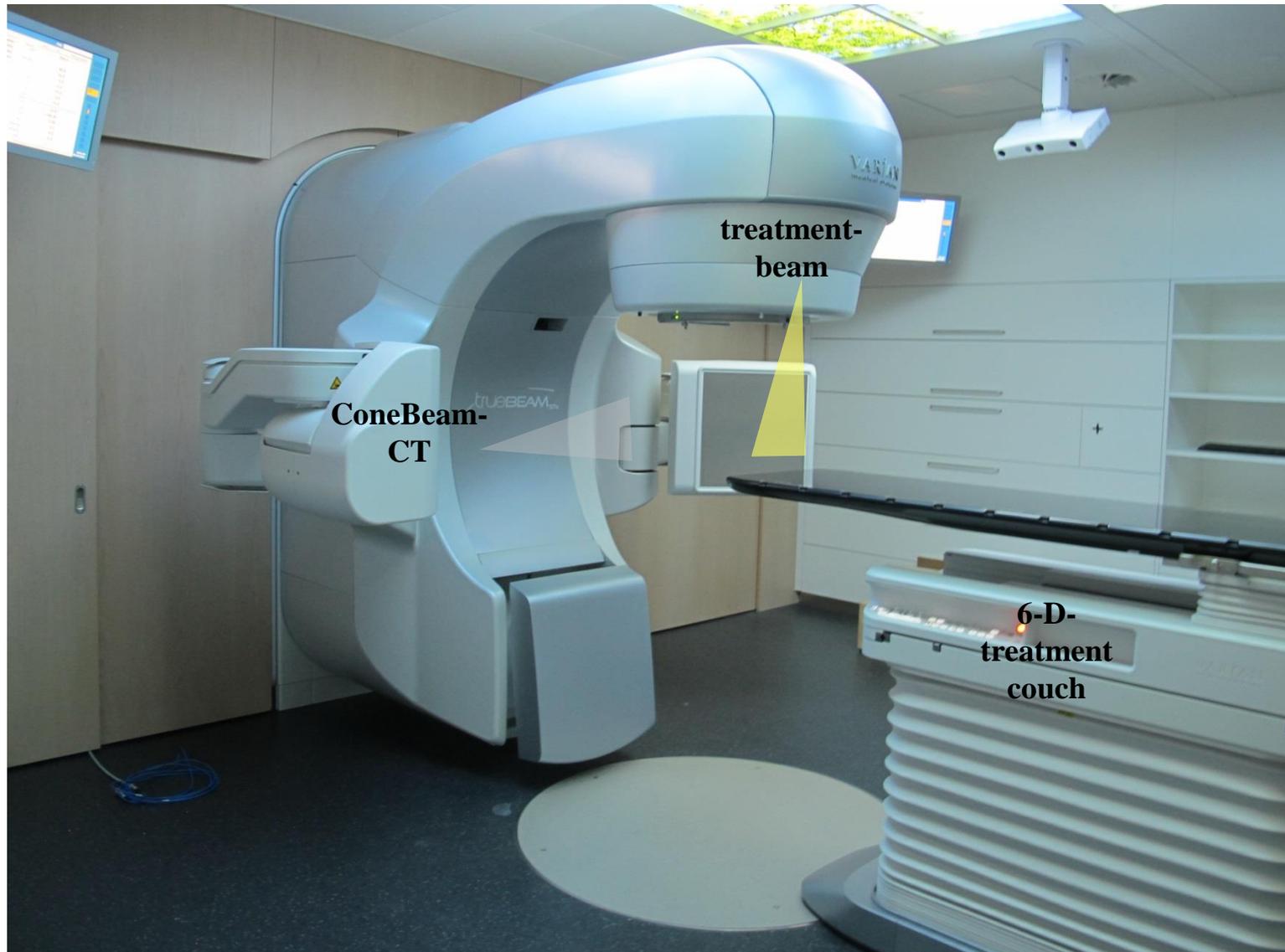


# Treatment Planning: Dose Volume Histogram (DVH)



DVH anzeig...	Struktur	Volumen [cm <sup>3</sup> ]	Max Dosis [Gy]	Mittel Dosis [Gy]
<input type="checkbox"/>	prox. Esophagus			
<input checked="" type="checkbox"/>	BrainStem	26.3	44.931	16.367
<input checked="" type="checkbox"/>	Glottis	19.8	63.499	45.612
<input checked="" type="checkbox"/>	Myelon	71.1	36.711	12.271
<input checked="" type="checkbox"/>	PTV Hals 52.8Gy	99.8	56.980	53.317
<input checked="" type="checkbox"/>	PTV Hals 56.1Gy	715.1	68.344	57.276
<input checked="" type="checkbox"/>	PTV Hals 69.3Gy	154.2	73.708	69.297
<input checked="" type="checkbox"/>	Parotid_L	21.4	68.265	33.227
<input checked="" type="checkbox"/>	Parotid_R	19.8	70.007	35.507

# Linear accelerator (LINAC)



# Tomo-Therapie





# Indication

**Radiotherapy (RT)**

**Radiochemotherapy (RCT)**

**Primary operated**



**Post Operative RT / RCT ? !**

# Post Operative RT / RCT

**Primary tumor:**

- R1 / R2
- pT3 / pT4

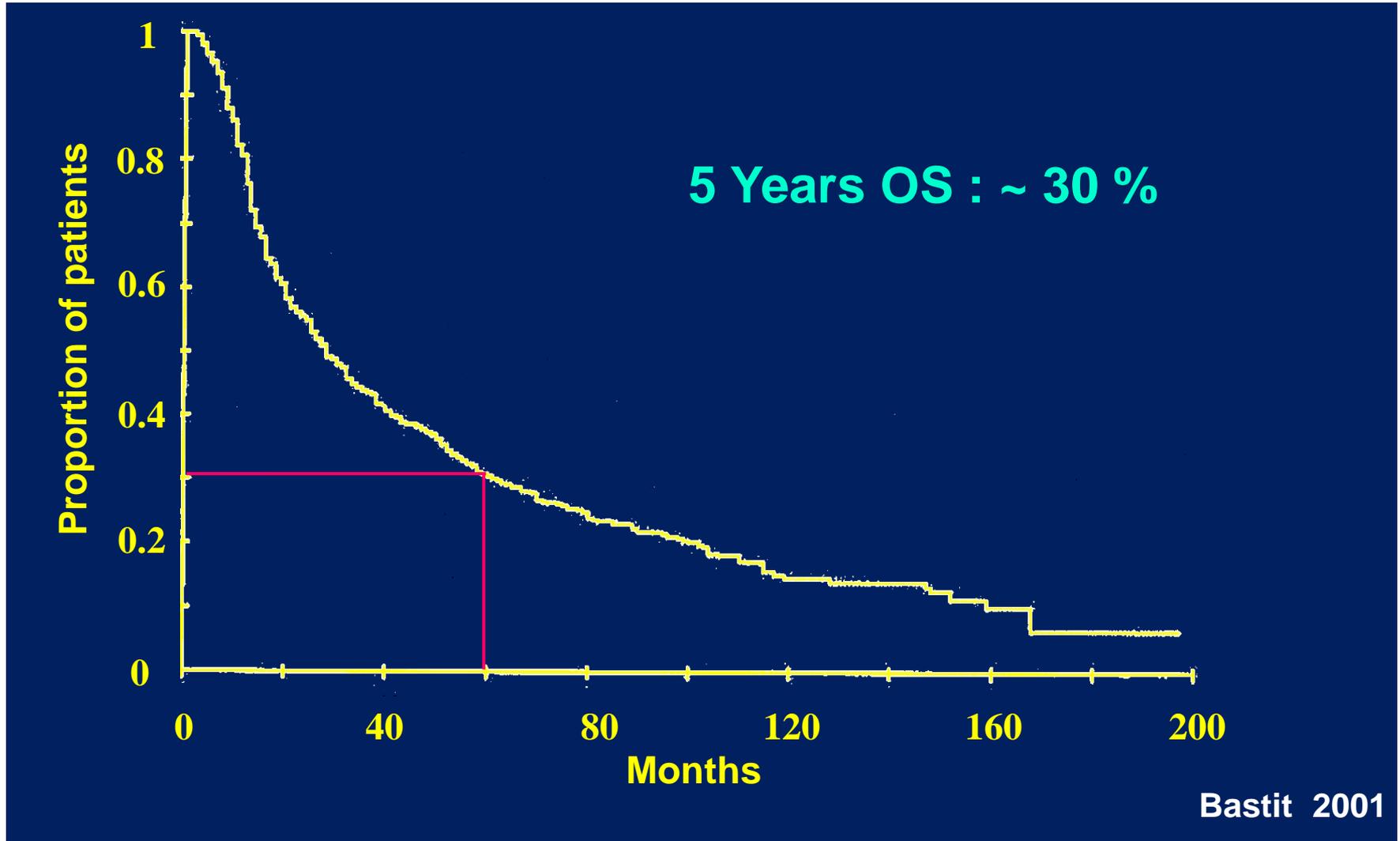
**Lymphnodes:**

- R1 / R2
- N involvement

but: 1-2 involved nodes ?  
( $< 3.0\text{cm}$ )

# Postoperative Radiation Therapy

Survival (01/81 - 12/92; n=420)



RT only ?

# Radiotherapy vs. Radiochemotherapy post-OP

## Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer (EORTC)

*“Postoperative concurrent administration of high-dose cisplatin with radiotherapy is more efficacious than radiotherapy alone“*

Bernier 2004

## Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck (RTOG)

*“Among high-risk patients with resected head and neck cancer, concurrent postoperative chemotherapy and radiotherapy significantly improve the rates of local and regional control and disease-free survival. However, the combined treatment is associated with a substantial increase in adverse effects“*

Cooper 2004

# Locoregional Control

	<u>OP + RT</u>	<u>OP + RCT</u>	
EORTC 22931	69%**	82%**	p=0.007
RTOG 9501	72%*	82%*	p=0.01

\*2years

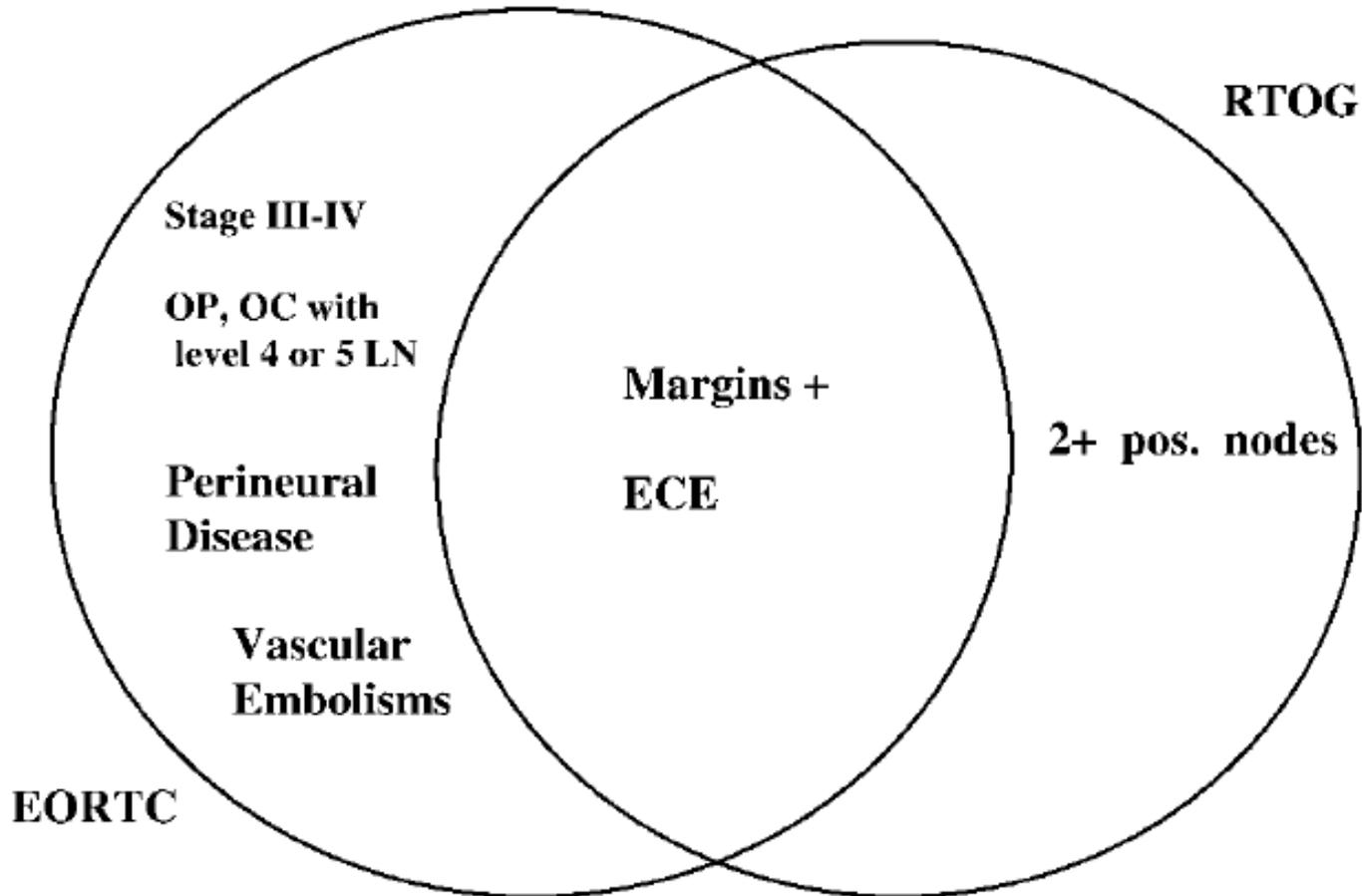
\*\*5years

# Progression-Free Survival

	<u>OP + RT</u>	<u>OP + RCT</u>	
EORTC 22931	36%	47%	p=0.04
RTOG 9501	25%	35%	p=0.04

# Radiotherapy vs. Radiochemotherapy post-OP

## EORTC versus RTOG Eligibility (“high risk“)



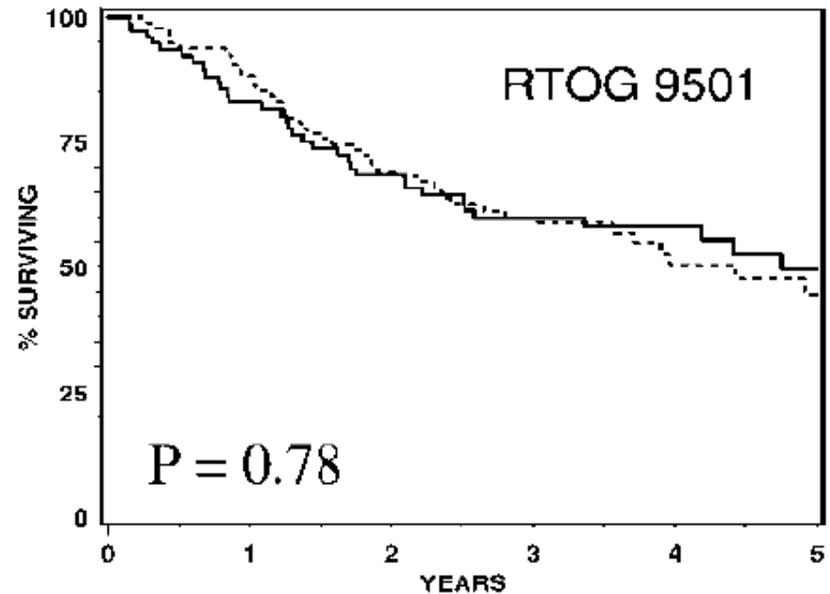
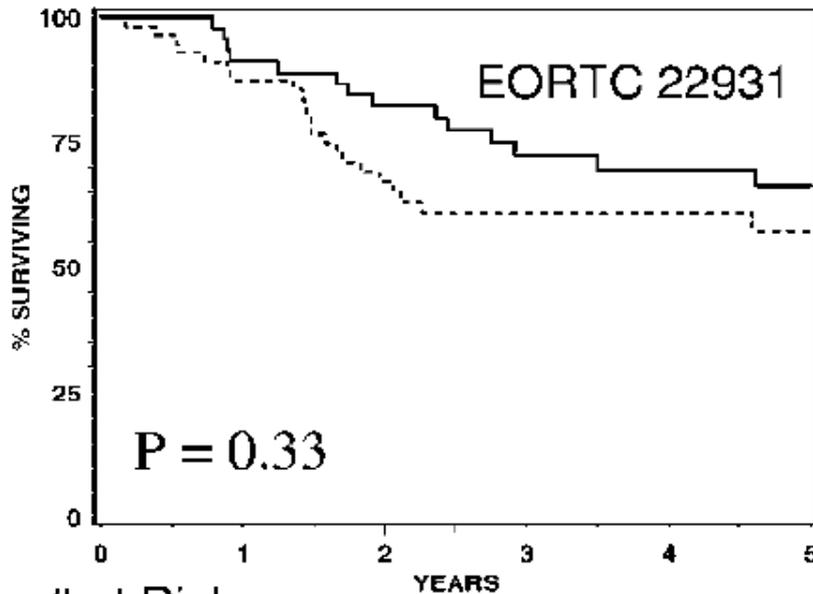
Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.

# A COMPARATIVE ANALYSIS OF CONCURRENT POSTOPERATIVE RADIATION PLUS CHEMOTHERAPY TRIALS OF THE EORTC (#22931) AND RTOG (#9501)

Impact of adjuvant chemoradiation on overall survival according to the presence of extracapsular extension (ECE) and/or positive surgical margins in the EORTC and RTOG trials

## Overall Survival

Patients without positive margin and/or ECE



# at Risk

Year	0	2	5
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RCT —	45	36	16
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RT ---	56	34	15
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Year	0	2	5
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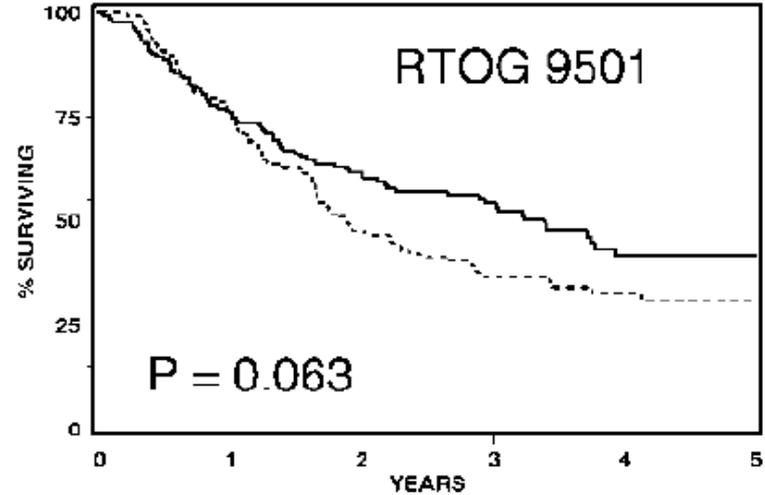
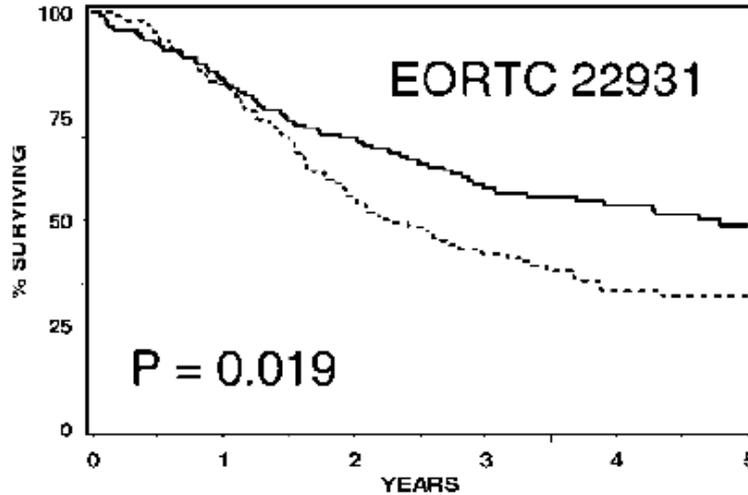
RCT —	76	52	11
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RT ---	94	65	14
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# A COMPARATIVE ANALYSIS OF CONCURRENT POSTOPERATIVE RADIATION PLUS CHEMOTHERAPY TRIALS OF THE EORTC (#22931) AND RTOG (#9501)

Impact of adjuvant chemoradiation on overall survival according to the presence of extracapsular extension (ECE) and/or positive surgical margins in the EORTC and RTOG trials

## Overall Survival Patients with positive margin and/or ECE



# at Risk

Year	0	2	5
RCT —	122	82	31
RT ---	111	59	16

Year	0	2	5
RCT —	130	80	16
RT ---	116	55	11

**➔ R1 or ECE !**

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

**median follow-up of 9.4 years**

- **no significant differences in outcome were observed in the analysis of all randomized eligible patients**
- **patients who had either microscopically involved resection margins and/or extracapsular spread of disease showed improved local-regional control and disease-free survival with concurrent administration of chemotherapy**
- **the remaining subgroup of patients who were enrolled only because they had tumor in 2 or more lymph nodes did not benefit from the addition of CT to RT**

**Primary not operated**

**Radiotherapy**

**Radiochemotherapy**

# Radiotherapy

## RTOG 9003

**Standard fractionation:**

**2 Gy/fract., 70 Gy / 35 fract./ 7weeks**

**Hyperfractionation:**

**1.2 Gy/fract., twice daily, 81.6 Gy / 68 fract. / 7weeks**

**Accelerated fractionation with split:**

**1.6 Gy/fract., twice daily, 67.2 Gy / 42 fract. / 6weeks**

**2-week rest after 38.4 Gy**

**Accelerated fractionation with concomitant boost:**

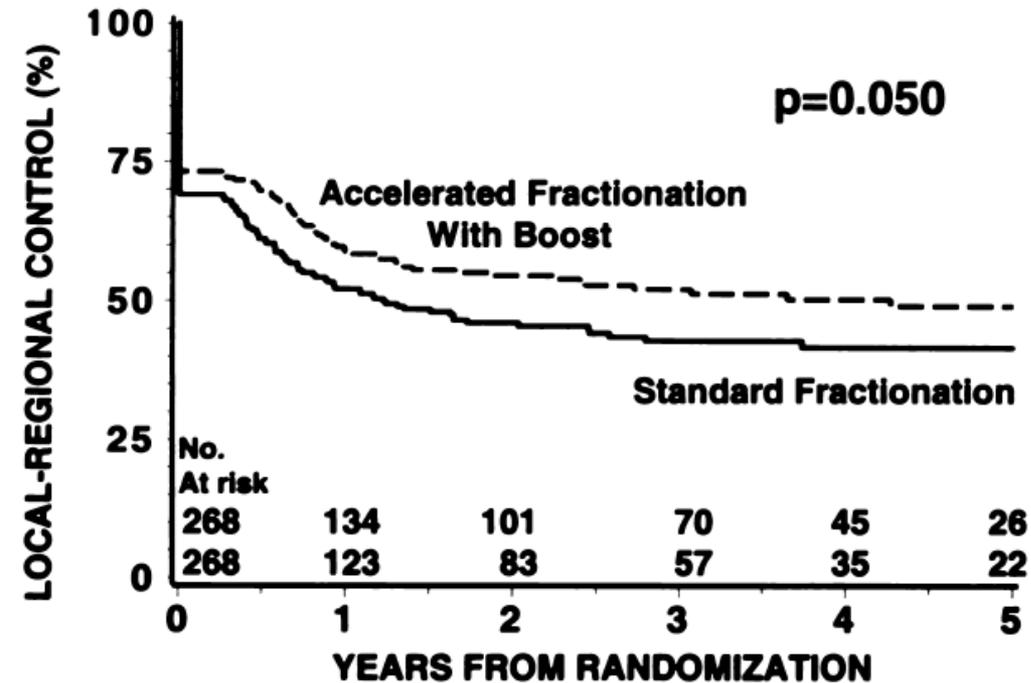
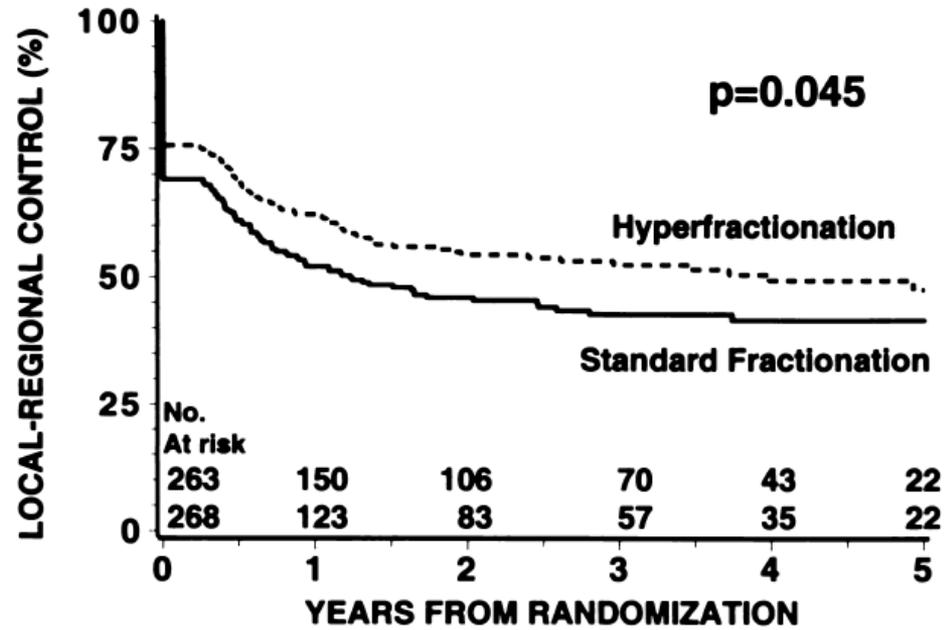
**1.8 Gy/fract./day to large field**

**+ 1.5 Gy/fract./day to boost for the last 12 treatment days**

**72 Gy / 42 fract. / 6 weeks**

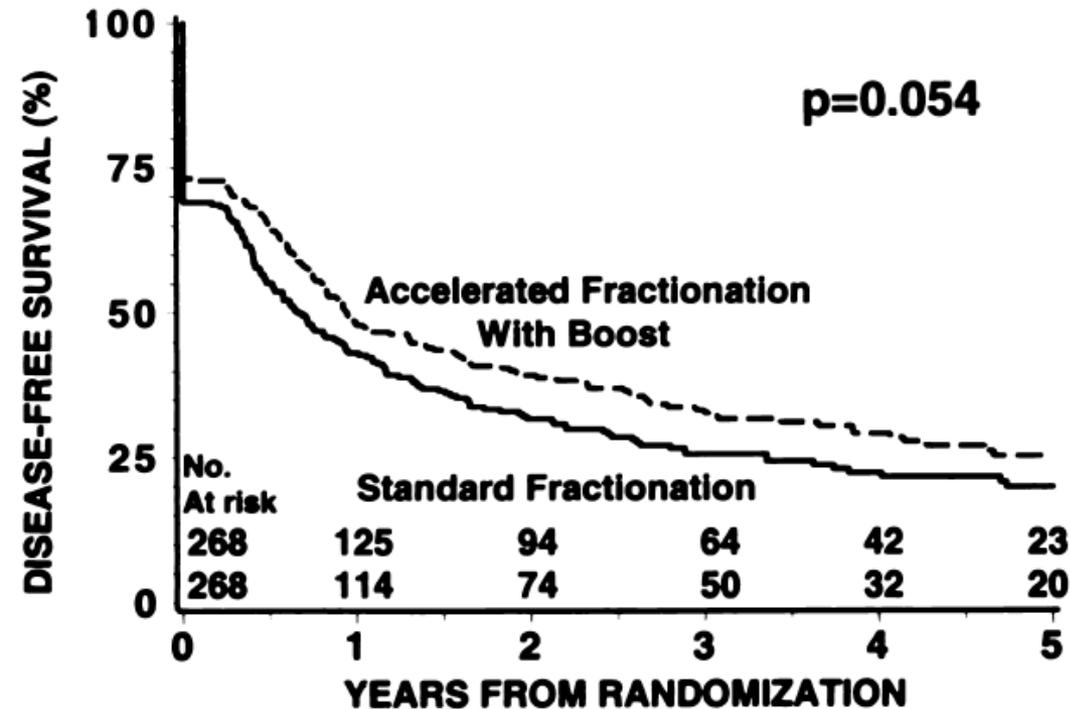
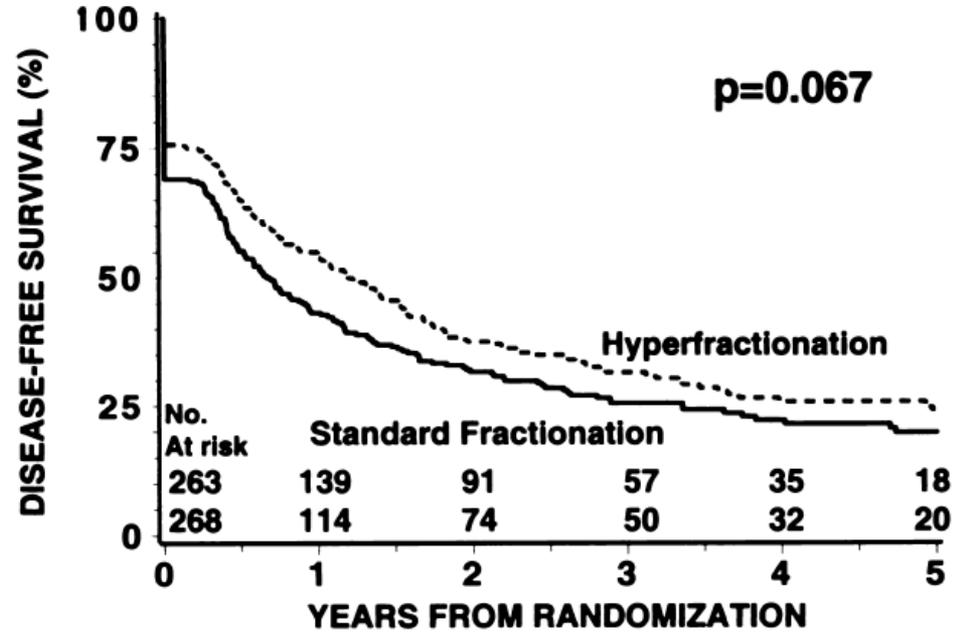
# RTOG 9003

## Local control



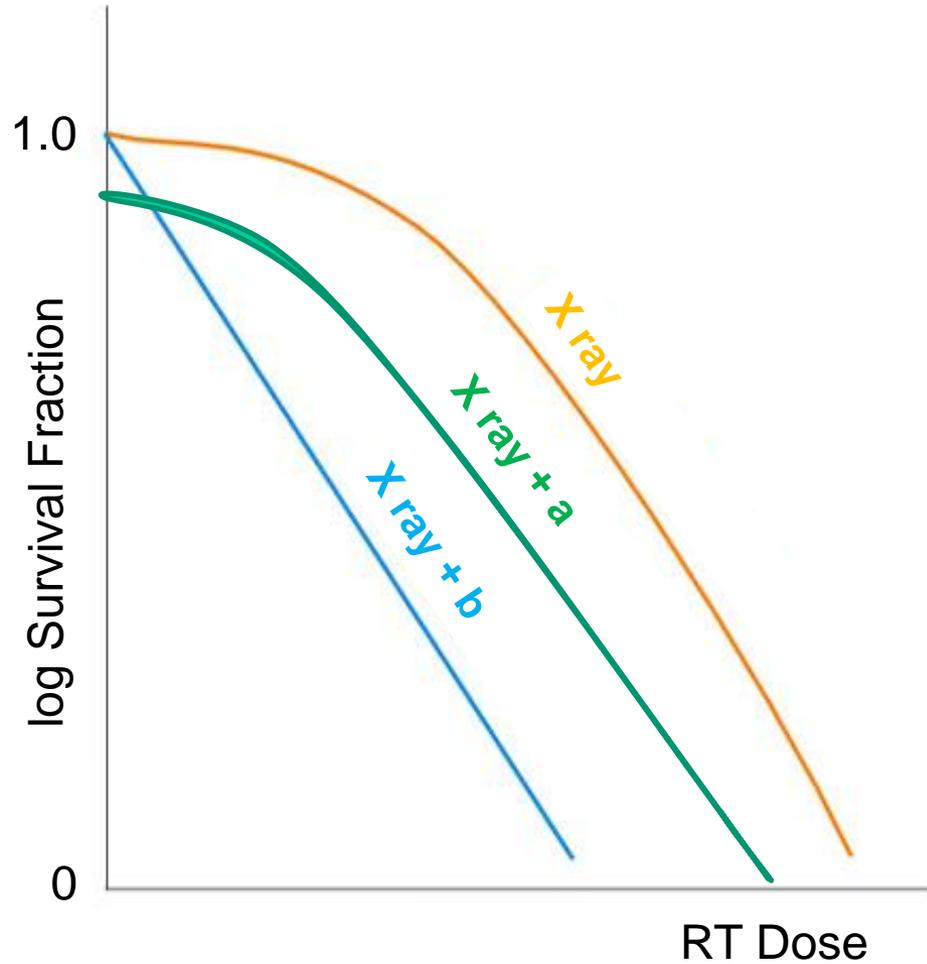
# RTOG 9003

## Survival



# Radiochemotherapy

in vitro



RT plus «Chemo»

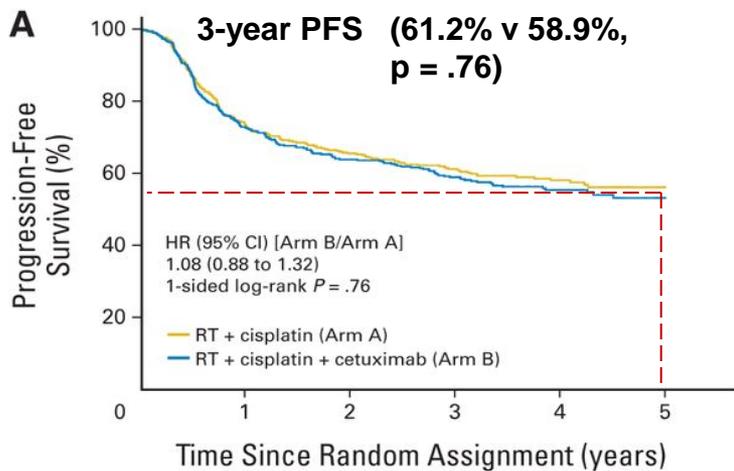
# Radio-Chemotherapy

## Chemotherapy Added to Locoregional Treatment for Head and Neck Squamous-cell Carcinoma: Meta-Analyses of Updated Individual Data (n=10741)

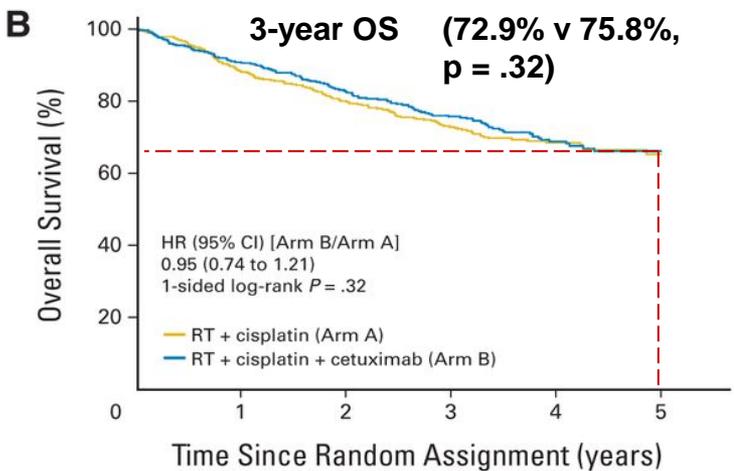
### Meta-analysis of locoregional treatment with and without chemotherapy: effects on survival

Trial category	Hazard ratio (95% CI)	Chemotherapy effect (p)	Heterogeneity	benefit	
				At 2 years*	At 5 years*
Adjuvant	0.98 (0.85-1.19)	0.74	0.35	1%	1%
Neoadjuvant	0.95 (0.88-1.01)	0.10	0.38	2%	2%
<b>Concomitant</b>	0.81 (0.76-0.88)	<0.0001	<0.0001	7%	<b>8%</b>
Total	0.90 (0.85-0.94)	<0.0001	<0.0001	4%	4%

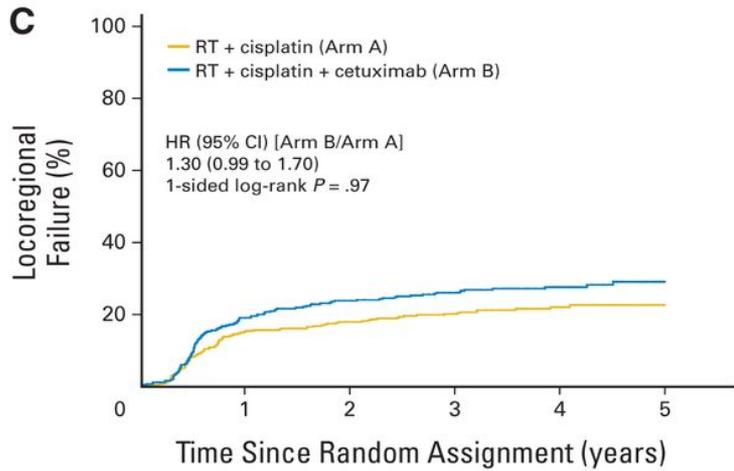
# Randomized Phase III Trial of Concurrent Accelerated Radiation Plus Cisplatin With / Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522



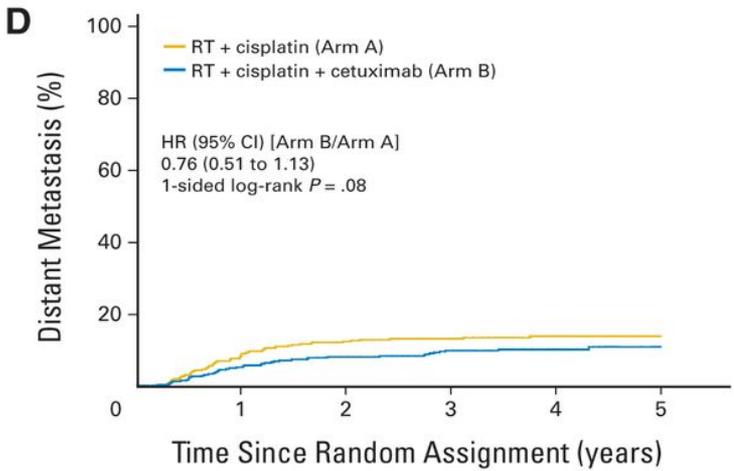
No. at risk						
Arm A	447	317	282	241	118	36
Arm B	444	309	263	234	108	38



No. at risk						
Arm A	447	386	344	287	138	41
Arm B	444	383	339	295	134	43



No. at risk						
Arm A	447	317	282	241	118	36
Arm B	444	309	263	234	108	38



No. at risk						
Arm A	447	317	282	241	118	36
Arm B	444	309	263	234	108	38

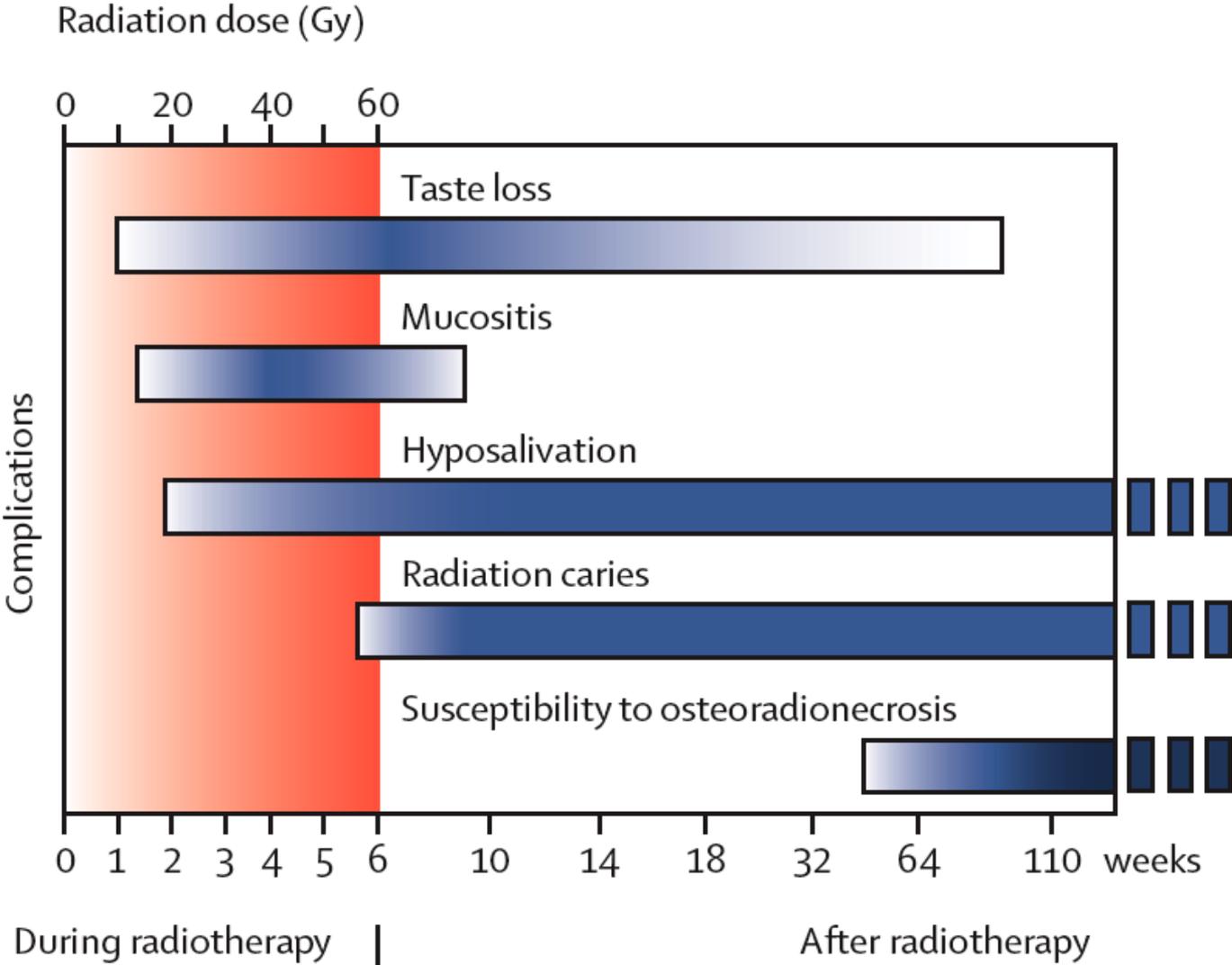
891 analyzed patients, stage III or IV (M0), median follow-up 3.8 years

# Possible adverse effects

<b>Scin</b>	<b>Inflammation, Fibrosis</b>
<b>Mucosa</b>	<b>Mucositis</b>
<b>Salivary gland</b>	<b>Xerostomia</b>
<b>Larynx</b>	<b>Edema, Necrosis</b>
<b>Thyroid gland</b>	<b>Hormon. dysfunction</b>
<b>Ear</b>	<b>Ototoxicity</b>
<b>Spinal cord</b>	<b>Paralysis</b>
<b>Bone</b>	<b>Osteonecrosis</b>
<b>Pharyngeal constrictor muscle</b>	<b>Dysphagia</b>

# Possible adverse effects

## Overview clinical course



# RT: Adverse effects

## RTOG 9003

### Incidence (%) of grade 3 or worse

	acute adverse effects	late adverse effects
Standard fractionation	35	28
Hyperfractionation	55	28
Accel. fract. with split	51	28
Accel. fract. with boost	59	38



**Supportive treatment !!!**

# RCT: Adverse effects

## RTOG 0522

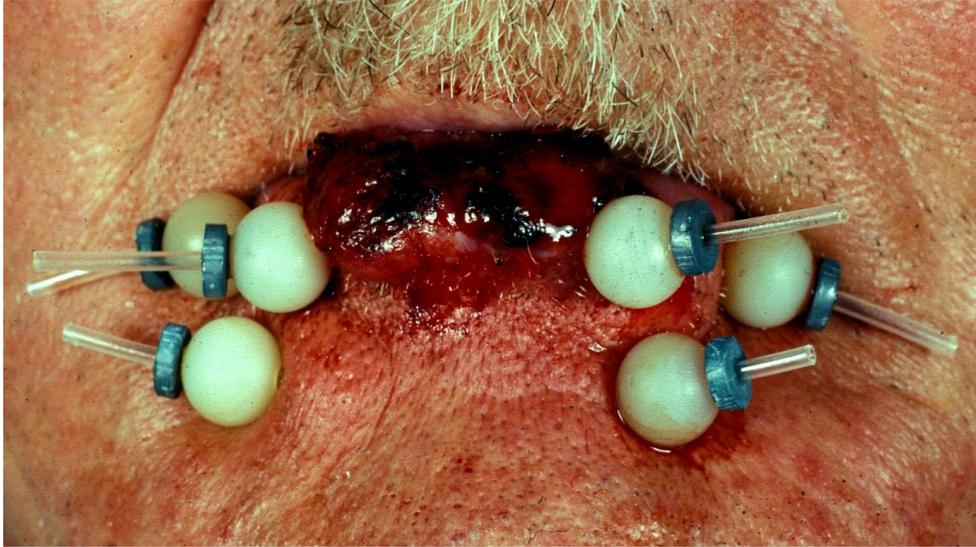
### Treatment-Related Adverse Events by Assigned Treatment % of Patients

<u>Arm A: RT + Cisplatin</u>		<u>Arm B: RT + Cisplatin + Cetuximab</u>	
Adverse Event	Grades 3-4	Adverse Event	Grades 3-4
<u>Acute period</u>		<u>Acute period</u>	
No. of patients	447	No. of patients	444
	%		%
Any event	87	Any event	89
Dysphagia	57	Dysphagia	53
Radiation mucositis	33	Radiation mucositis	43
<u>Late period</u>		<u>Late period</u>	
No. of patients	432	No. of patients	415
	%		%
Any event	54	Any event	60
Dysphagia	36	Dysphagia	37
Dry mouth	4	Dry mouth	5

# BRACHYTHERAPY

$u^b$

<sup>b</sup>  
UNIVERSITÄT  
BERN



«After-Loading»

# ***„take home“***

## **Indication:**

<b>No OP:</b>	<b>Radiochemo., RT/EGFR-I, RT only (altered fractionated)</b>	
<b>Post OP:</b>	<b>low risk of recurrence</b>	<b>→ no RT</b>
	<b>intermediate risk of recurrence</b>	<b>→ RT</b>
	<b>high risk of recurrence</b>	<b>→ RCT</b>

## **Technique:**

**IMRT / IMAT (CT-Planning, MRI, PET); IGRT**

## **Dose:**

**TD: 50 – 56 – 64 - > 70 Gy; SD: 1.2 – 2.0 / > 2,0 Gy**

## **Treatment duration:**

**5½ - 7½ weeks**

## **Treatment results (Stage III to IV/M0):**

**curative intention, 5 years OS : 35 - 65 %**

## **Adverse effects:**

**Inflammation (mucosa, skin), Xerostomia, Fibrosis, Nerosis, Dysphagia**