

Head and Neck Cancer

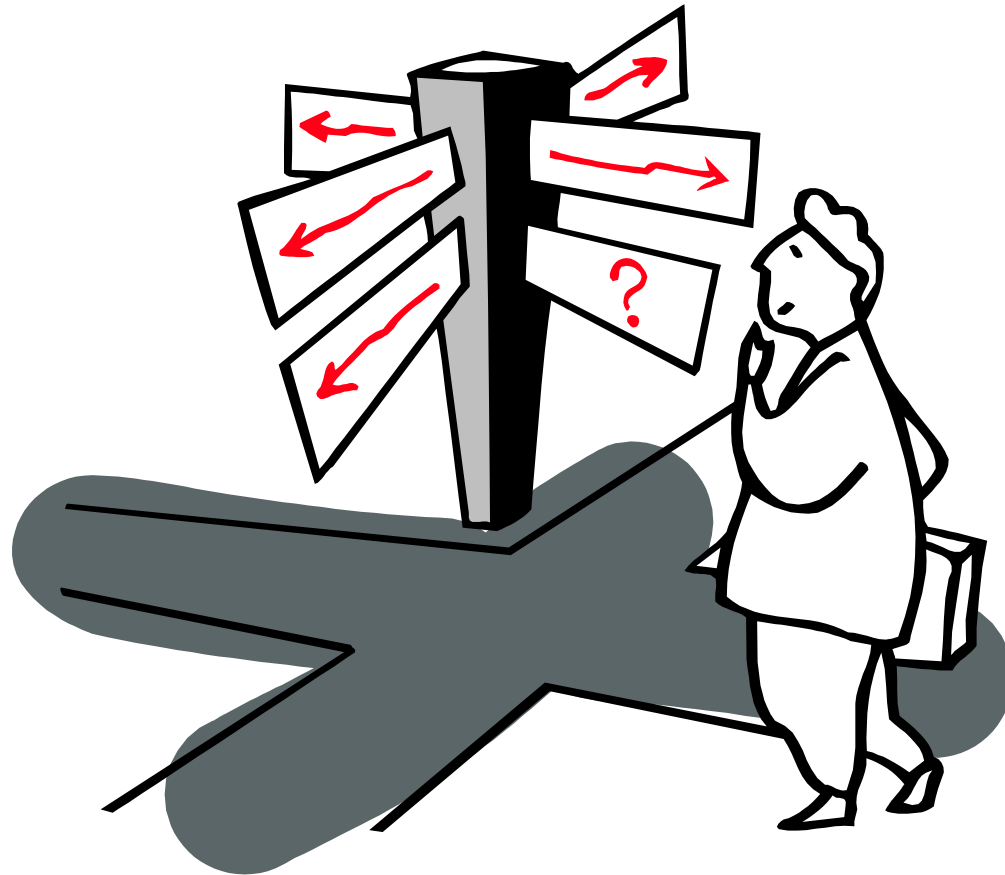
Radiation Oncology

L. Plasswilm

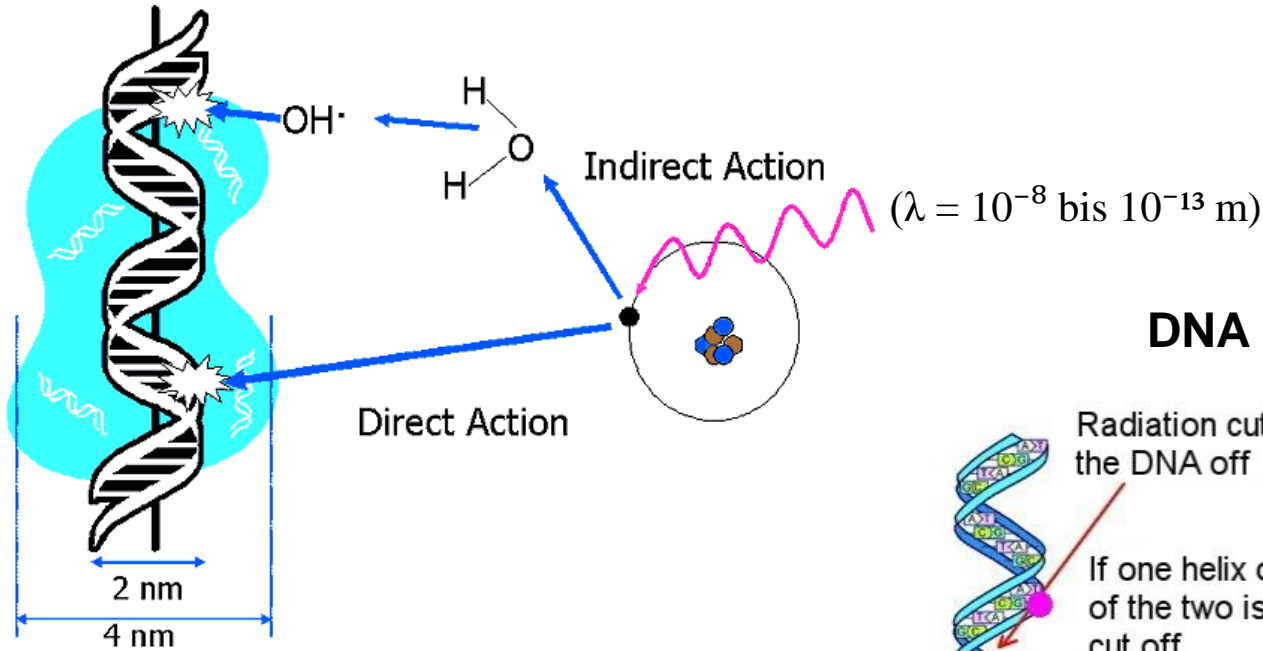
Outline

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

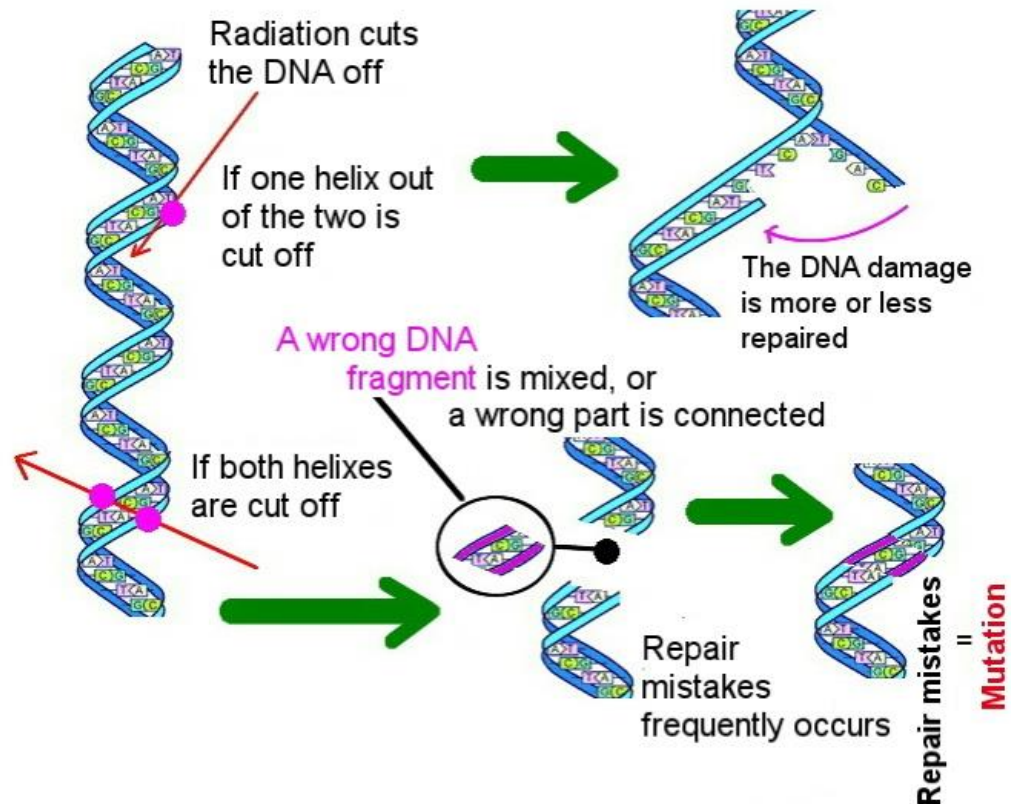
BASICS



Direct & Indirect Actions of Radiation



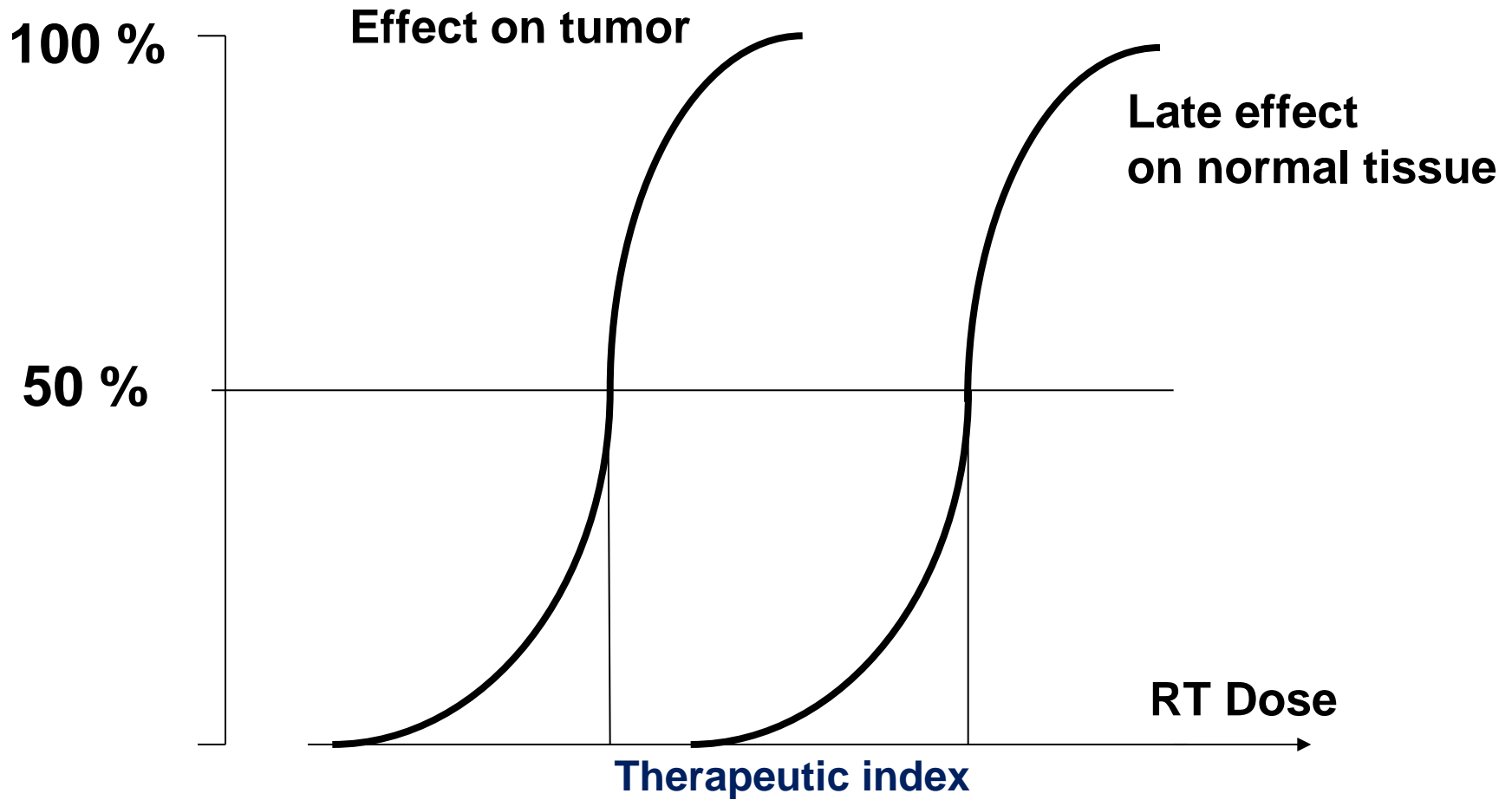
DNA cut off by radiation



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

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

Effect on tumor vs late toxicity



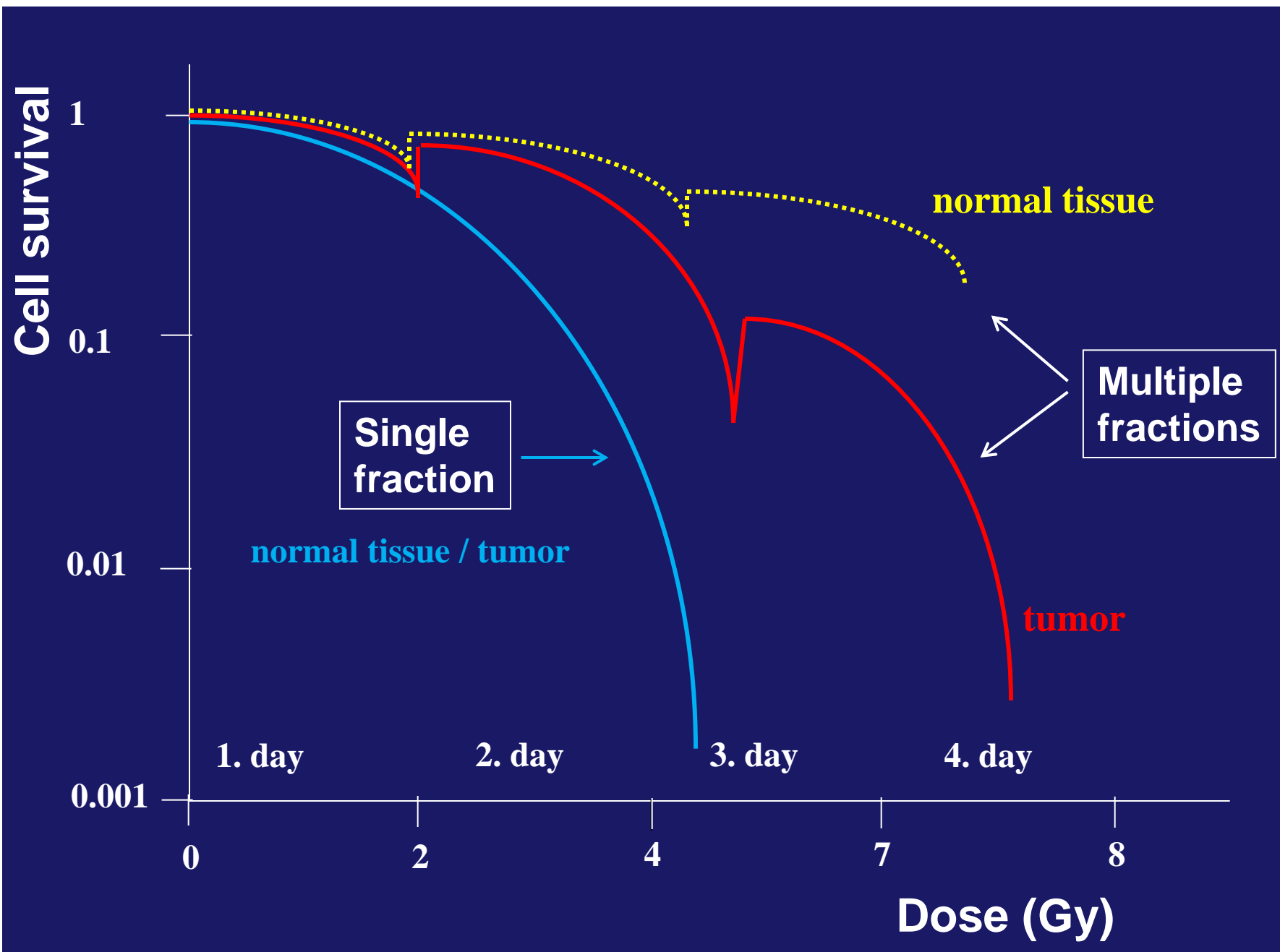
Therapeutic index   Biology, Technique

Dosage / Schedule

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



Fractionation

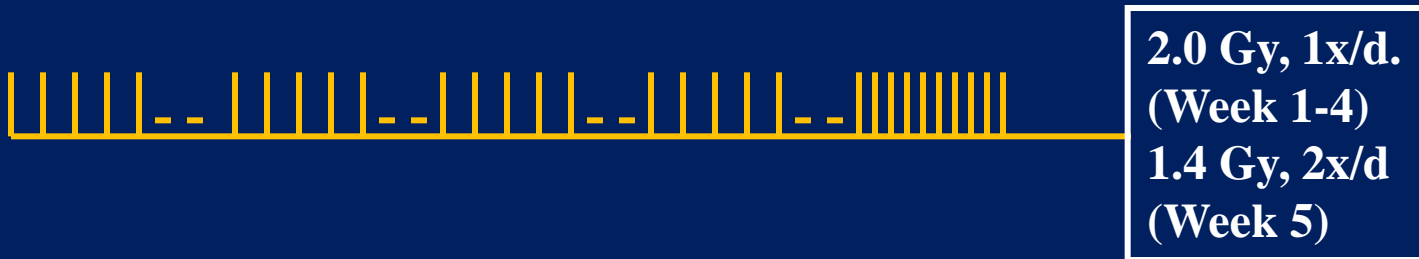


Fractionation

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

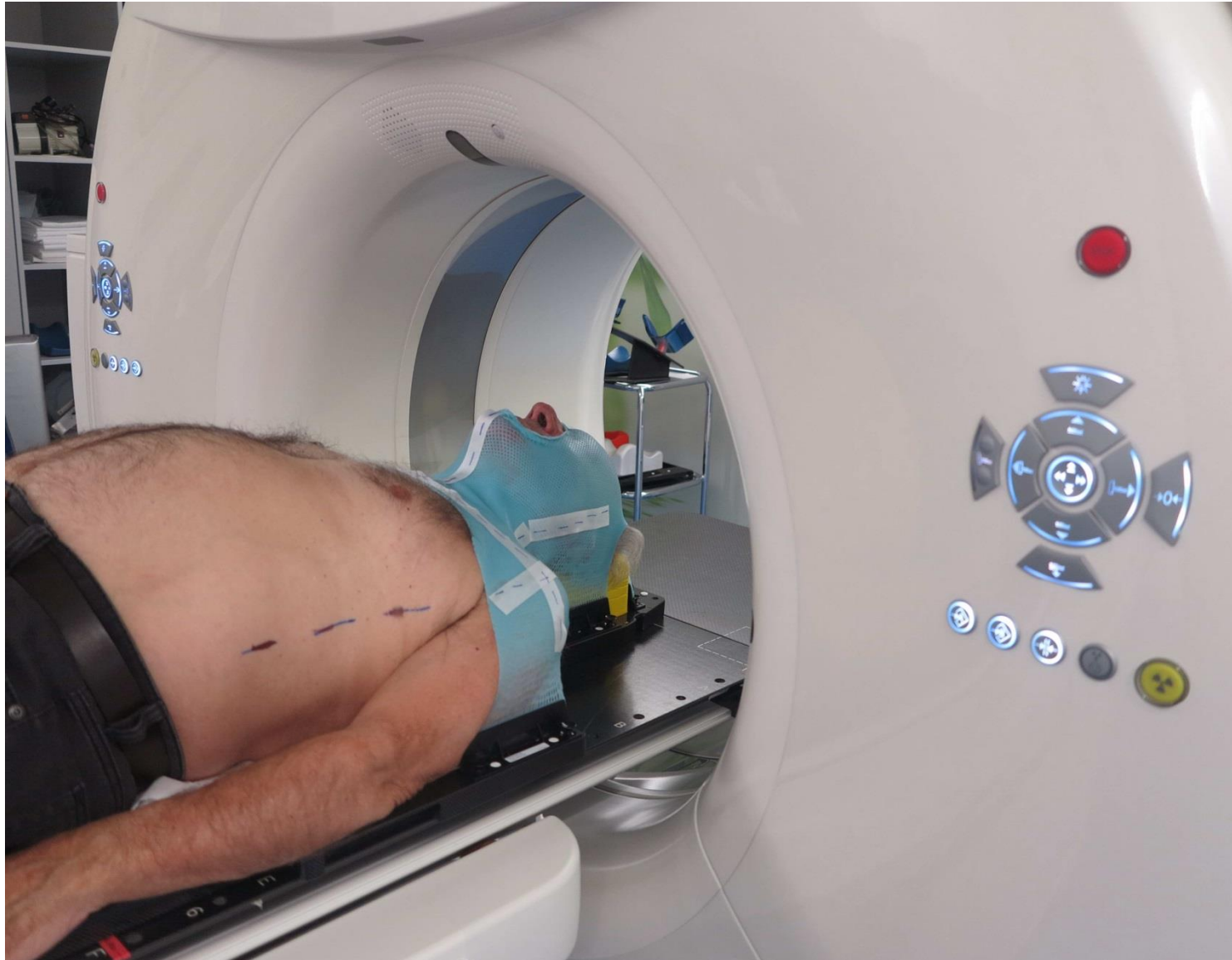


Improving treatment quality

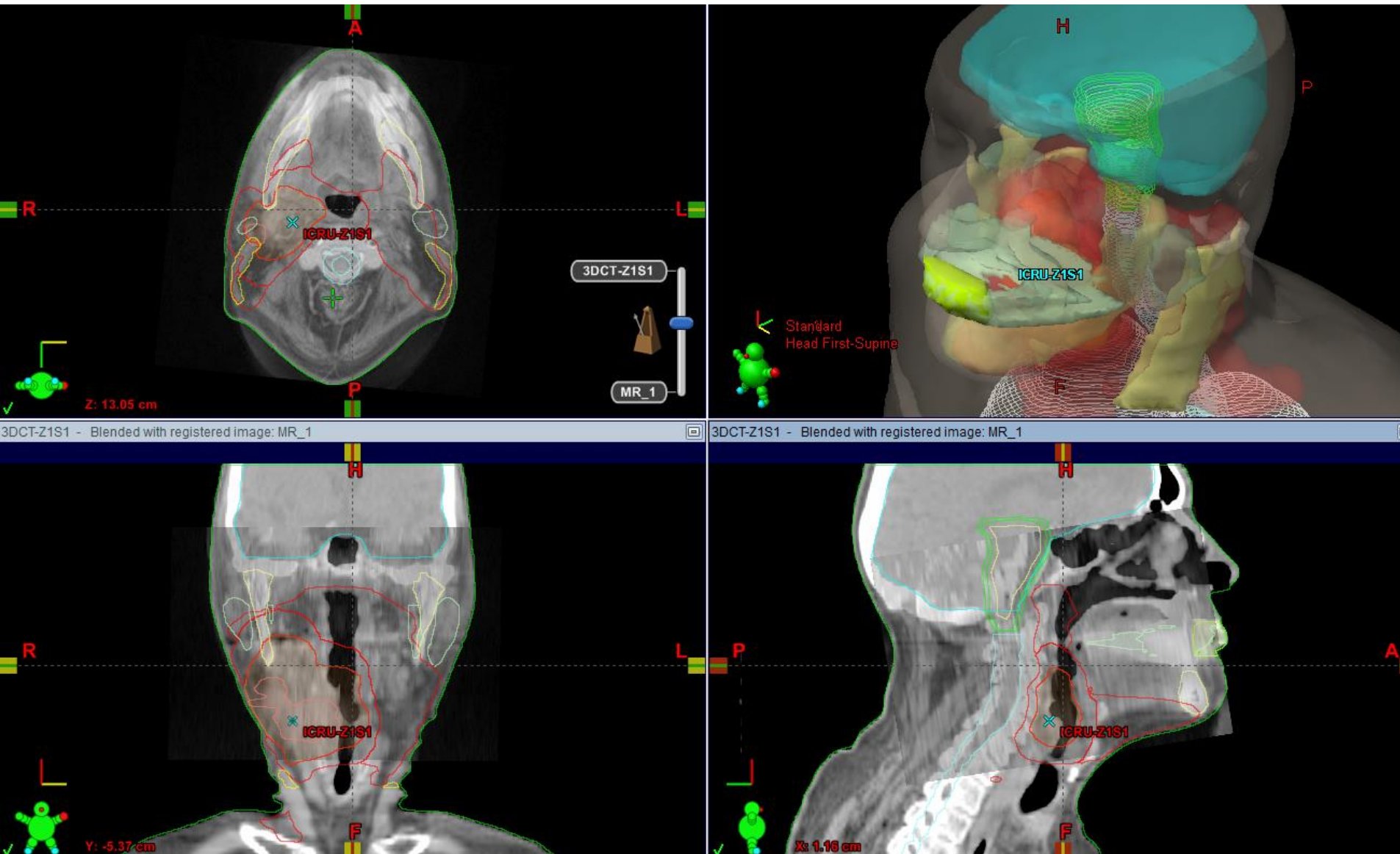
Technique

Treatment Planning

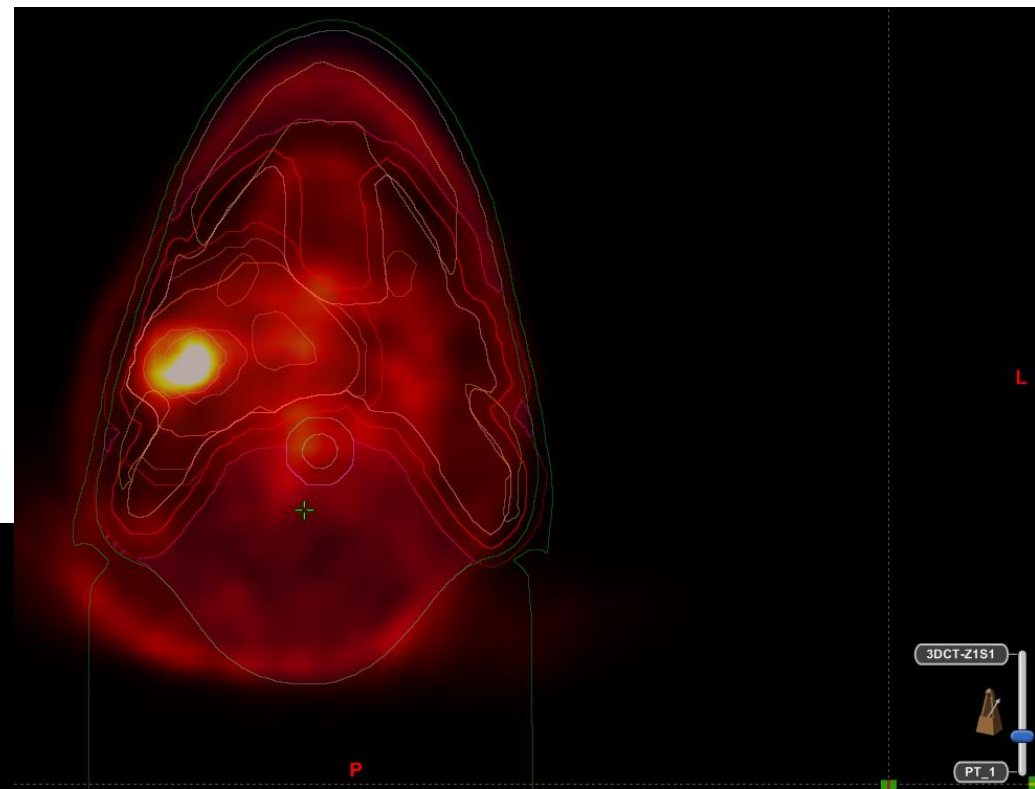
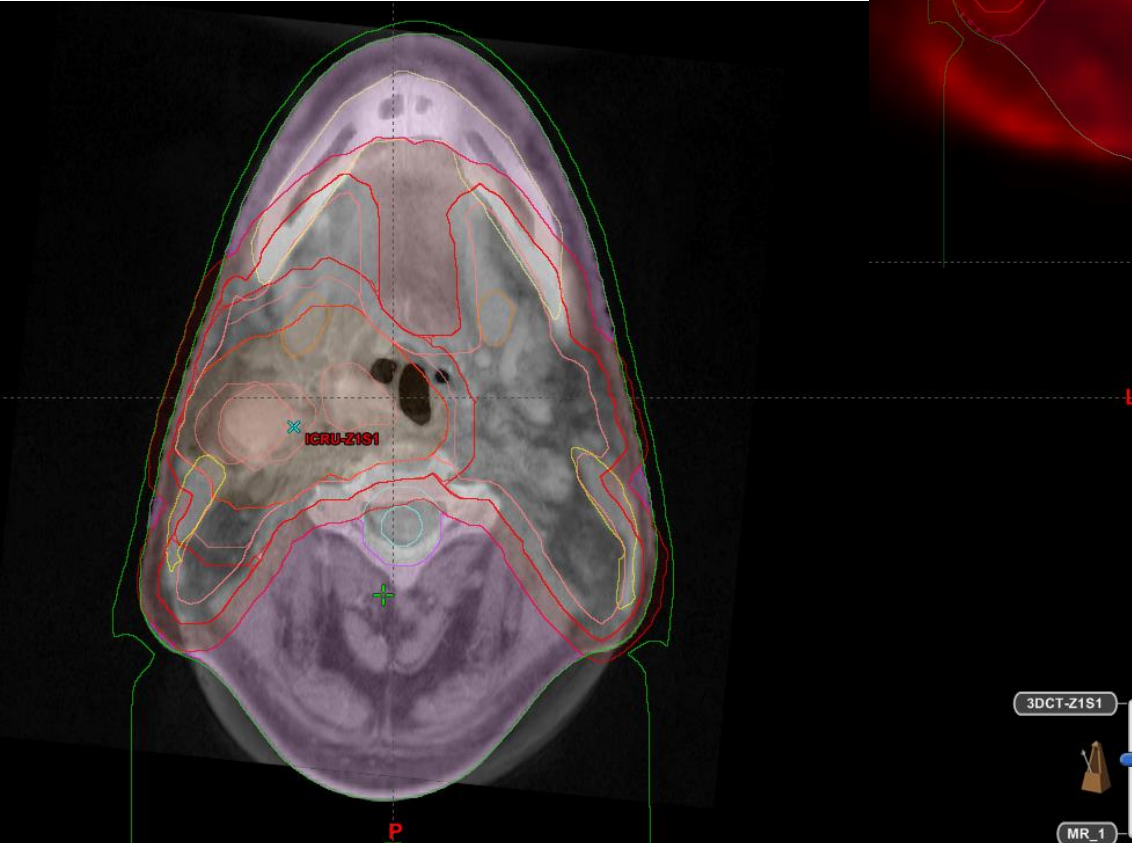
«Planning-CT»



Target volume & Organs at risk

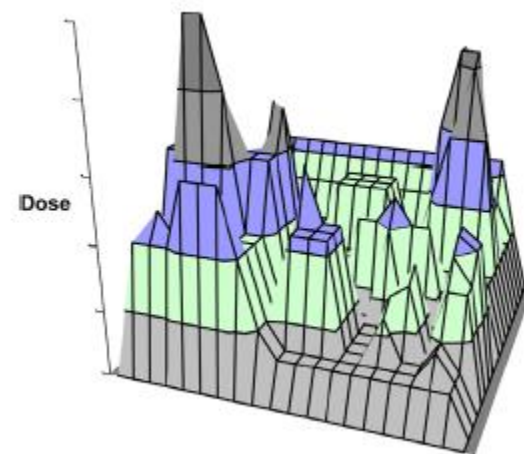
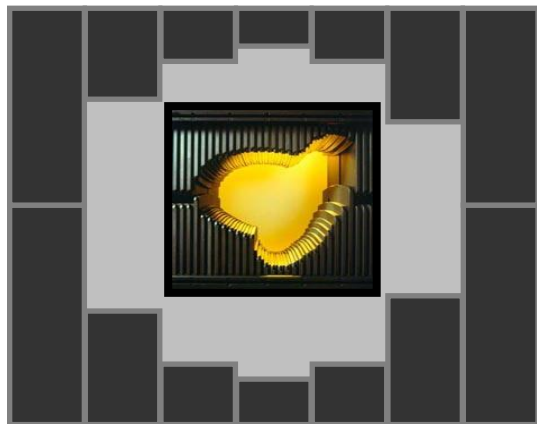


**Image fusion
+ all available information
(endoscopy, surgery,
histology, ...)**

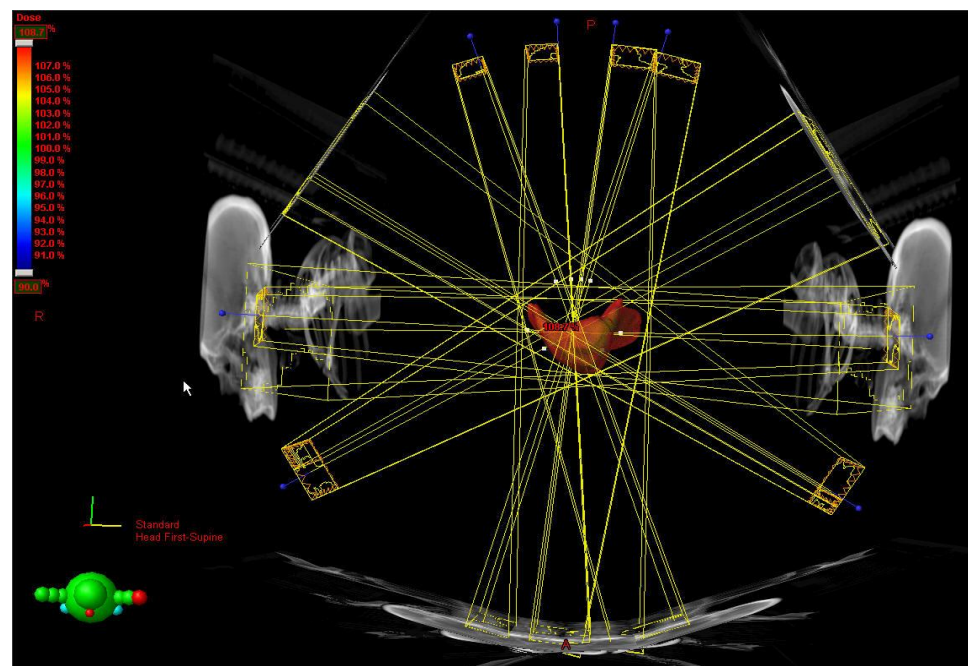
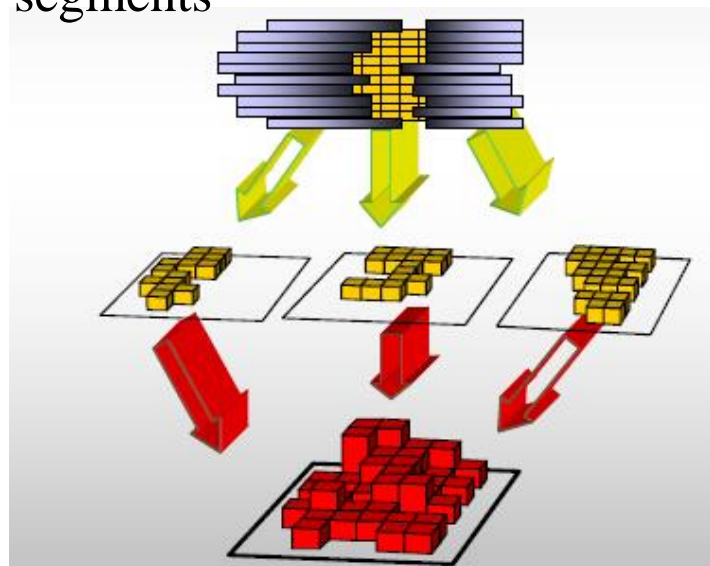


PlanningCT – MRI – PET/CT

IMRT: Intensity Modulated Radiotherapy



multiple treatment fields and segments



Intensity Modulated Radiotherapy

«Step and Shoot»

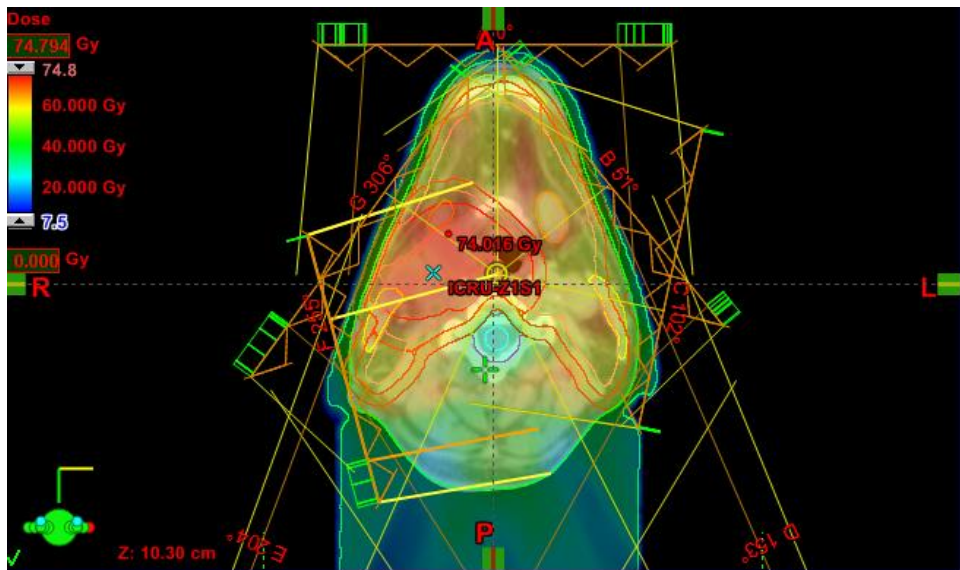
«Intensity-modulated Arc Therapy (IMAT)»

Radpid Arc

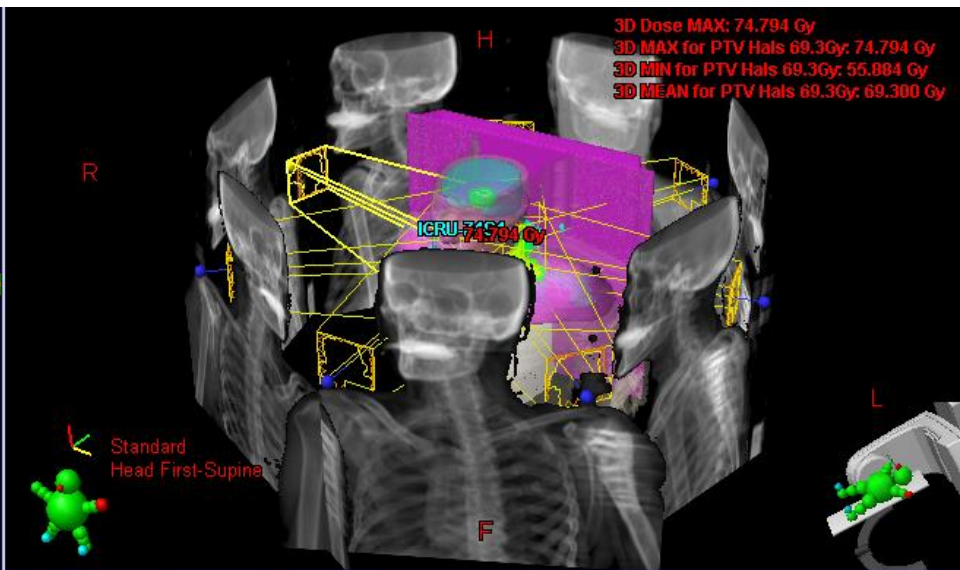
VMAT

«Tomotherapie»

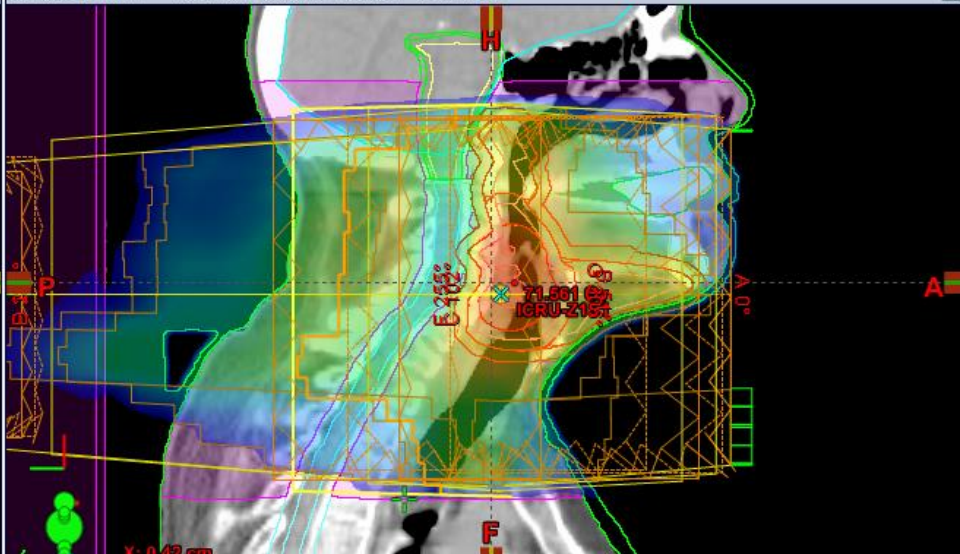
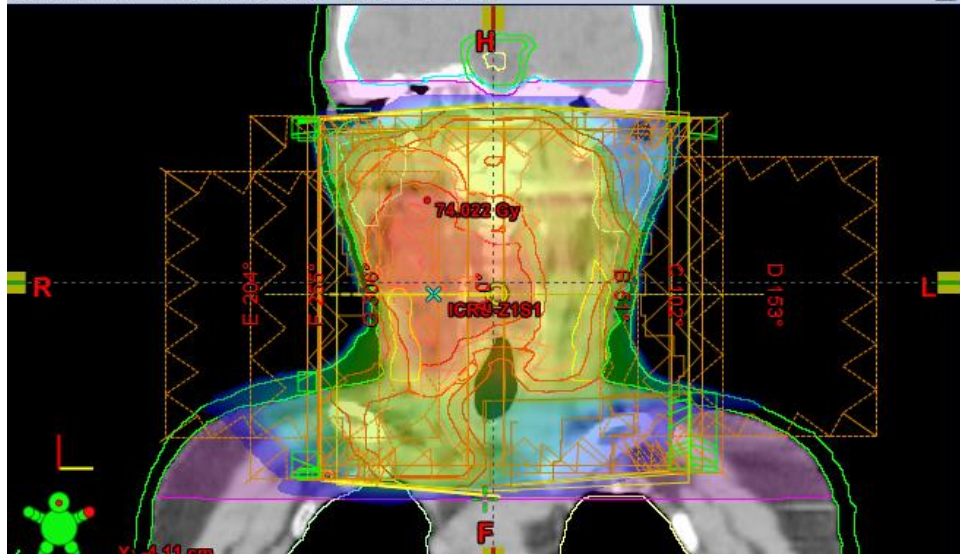
Treatment Planning: Dose Distribution



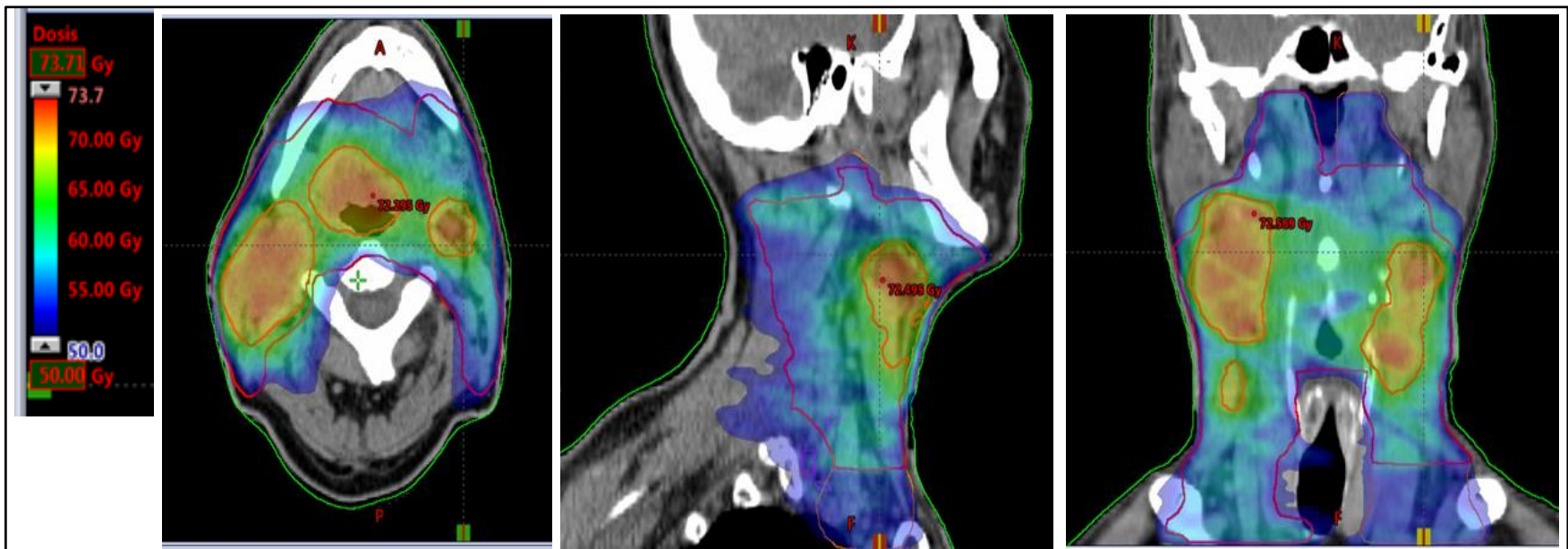
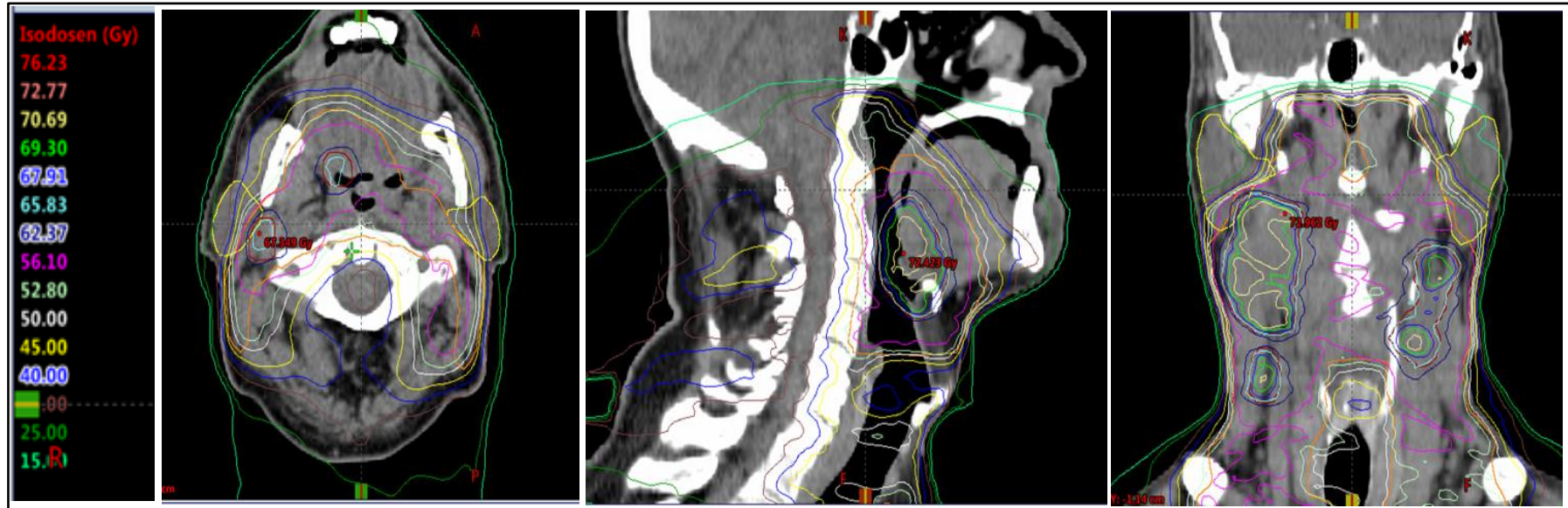
50136Z1S1IMRT - Treatment Approved - Frontal - 3DCT-Z1S1



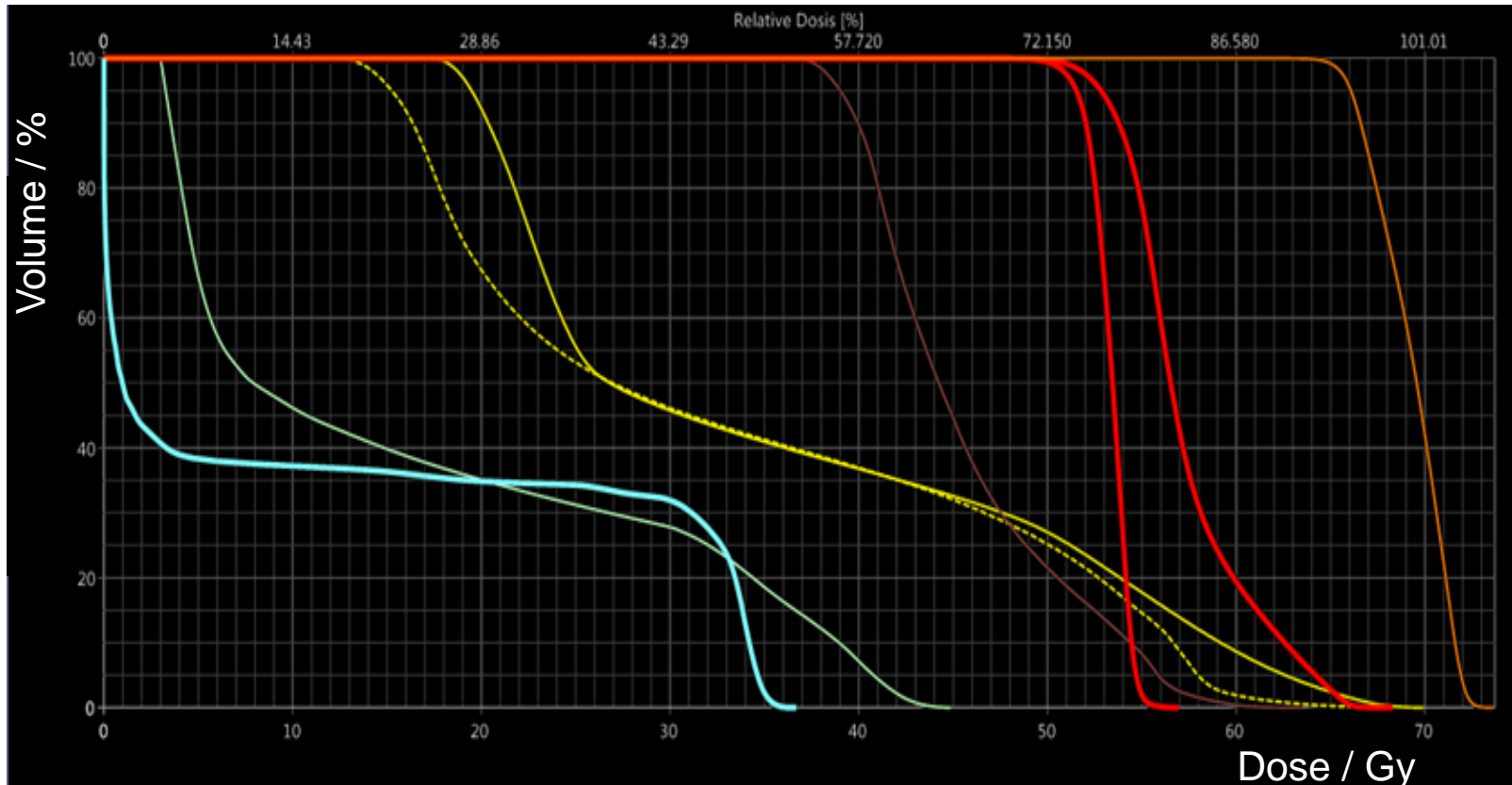
50136Z1S1IMRT - Treatment Approved - Sagittal - 3DCT-Z1S1



Treatment Planning: Dose Distribution

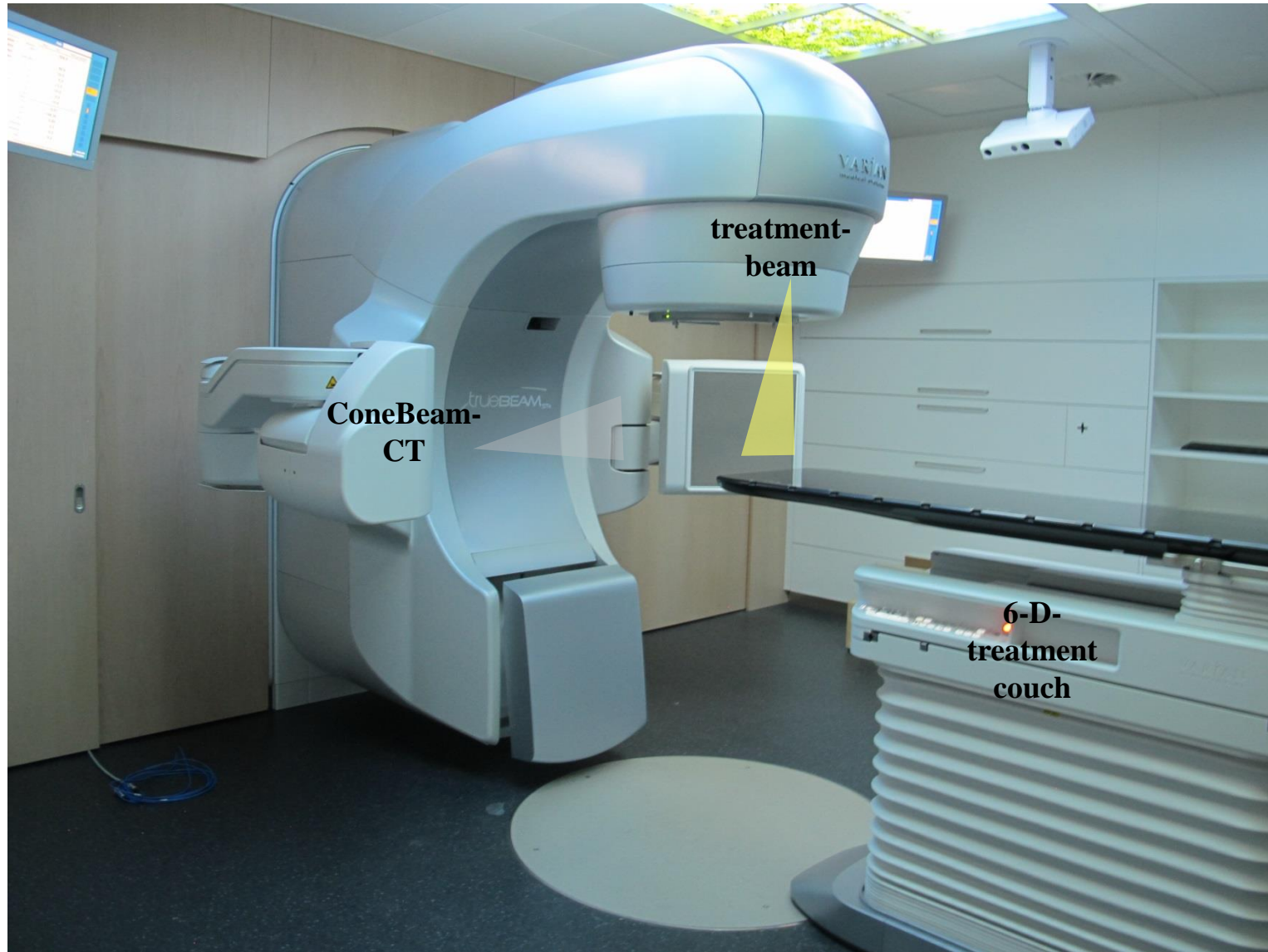


Treatment Planning: Dose Volume Histogram (DVH)

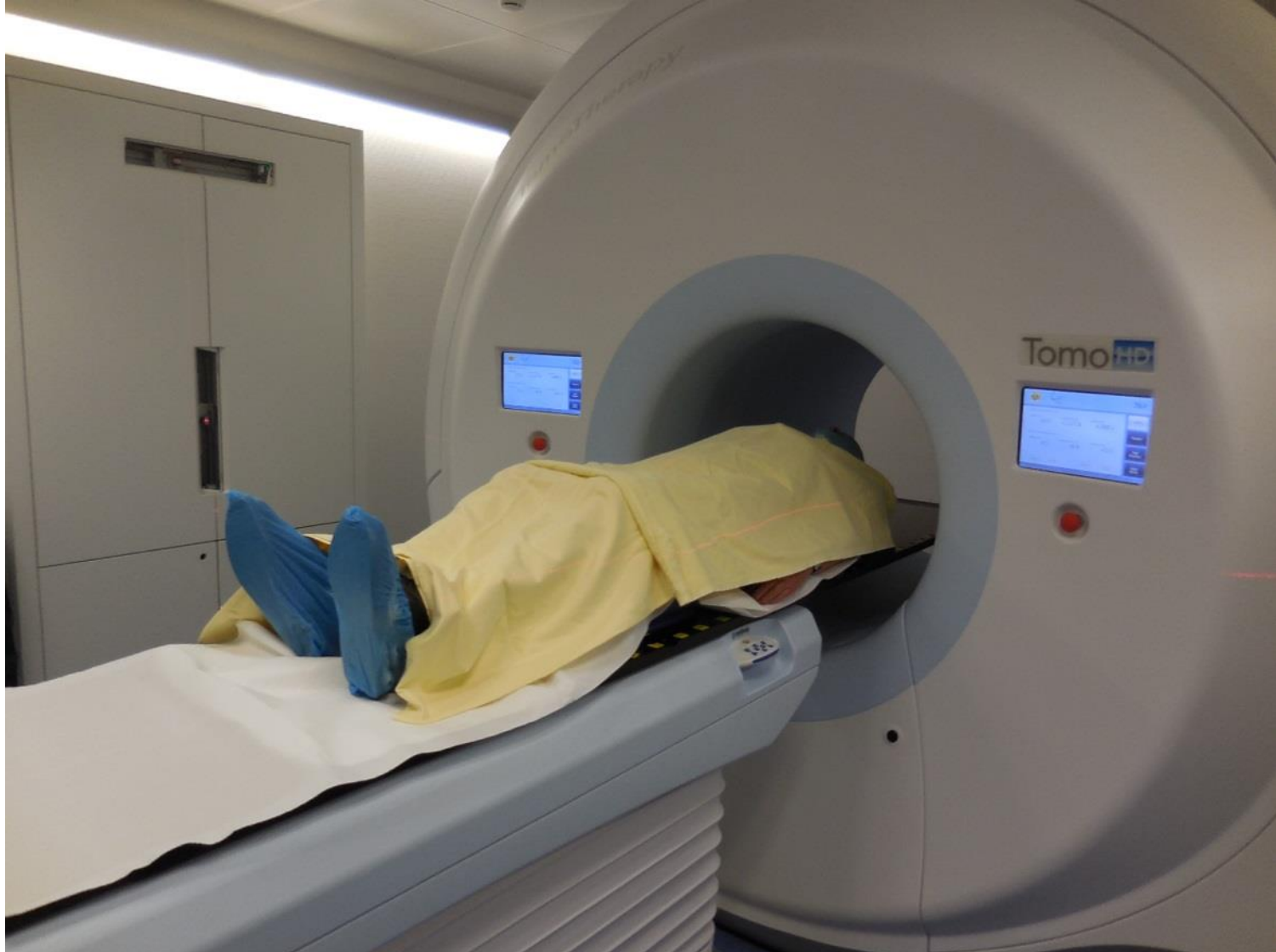


DVH anzeig...	Struktur	Volumen [cm³]	Max Dosis [Gy]	Mittel Dosis [Gy]
<input type="checkbox"/>	prox. Esophagus			
<input checked="" type="checkbox"/>	BrainStem	26.3	44.931	16.367
<input checked="" type="checkbox"/>	Glottis	19.8	63.499	45.612
<input checked="" type="checkbox"/>	Myelon	71.1	36.711	12.271
<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)

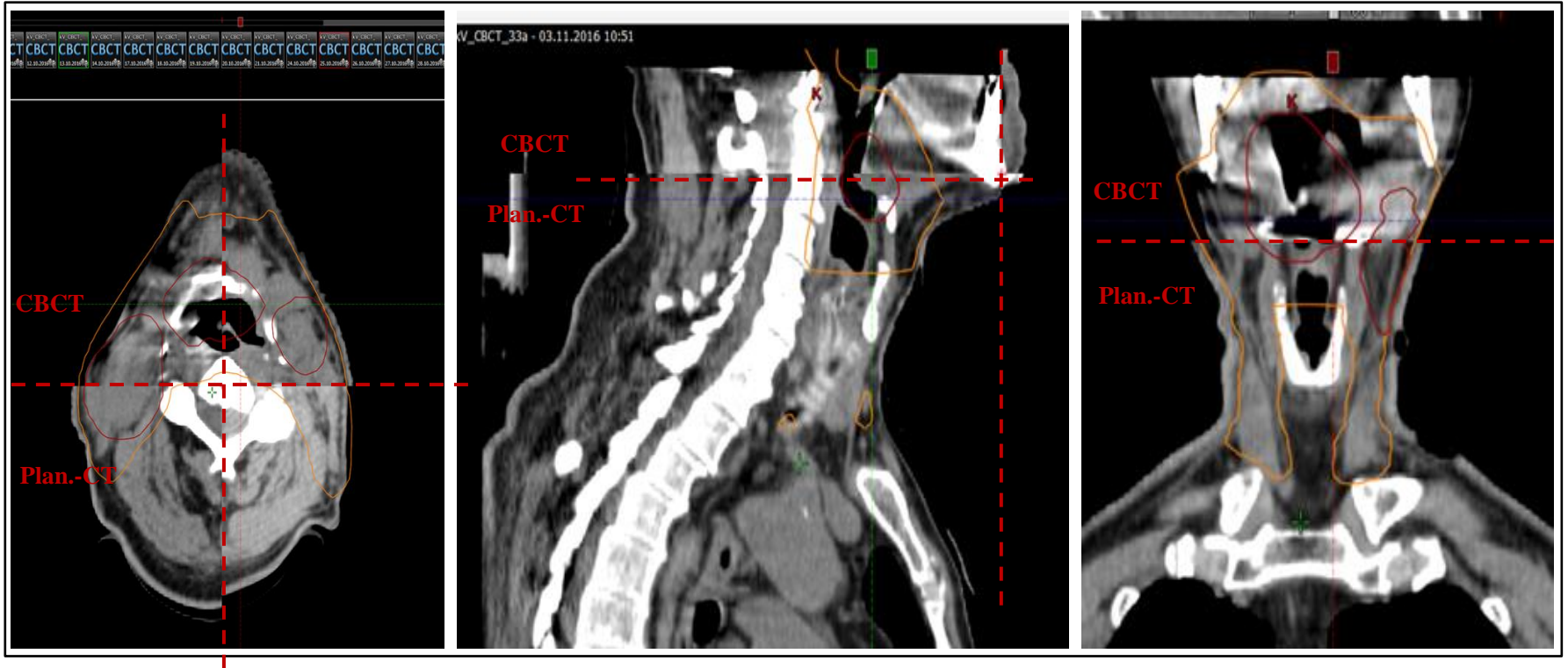


Tomo-Therapie



Treatment Precision

IGRT: Image Guided Radiation Therapy



immobilization device;
on board imaging

Indication

Radiotherapy (RT)

Radiochemotherapy (RCT)

Primary operated



Post Operative RT / RCT ? !

Post Operative RT / RCT

Primary tumor:

- R1 / R2
- pT3 / pT4

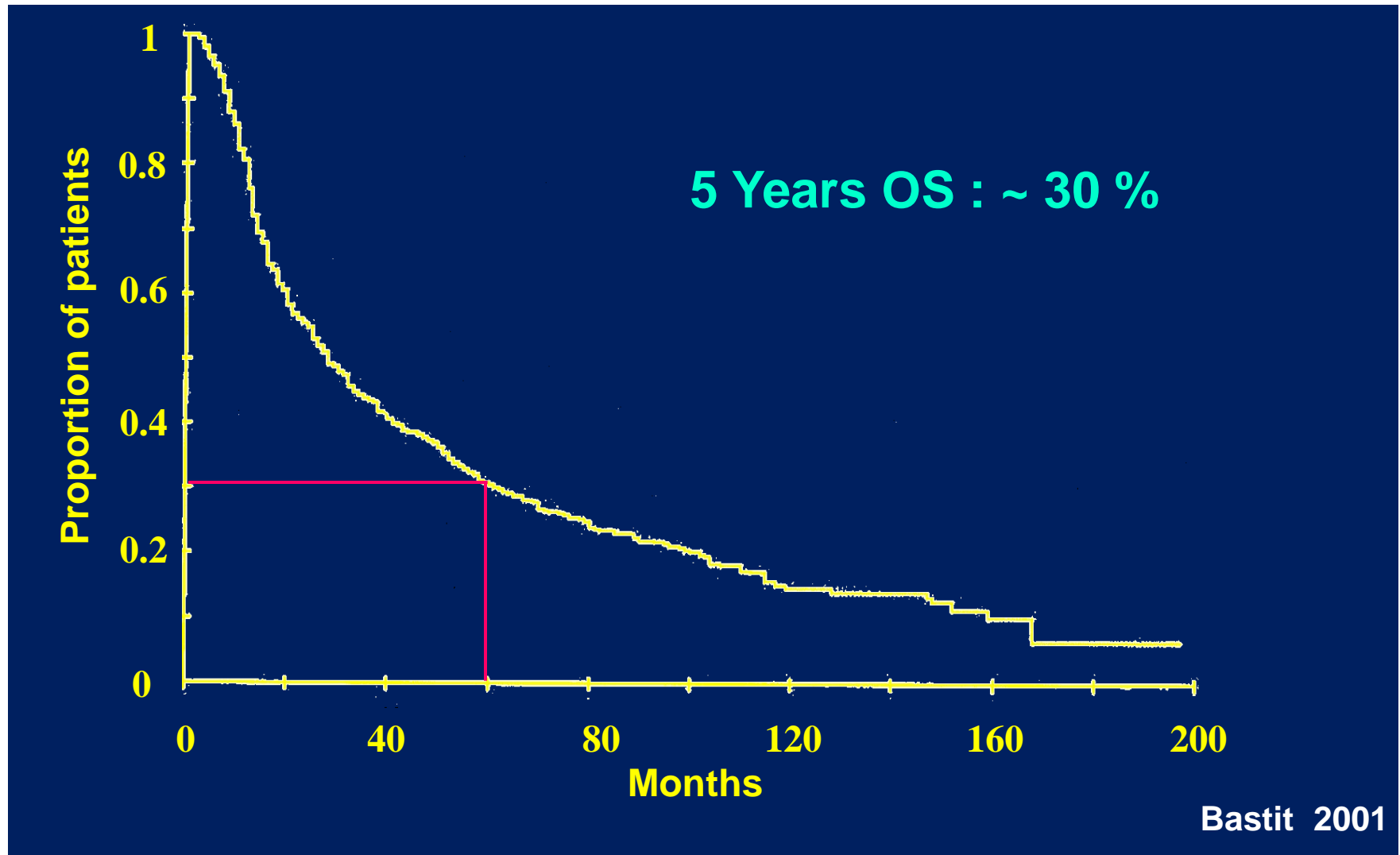
Lymphnodes:

- 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

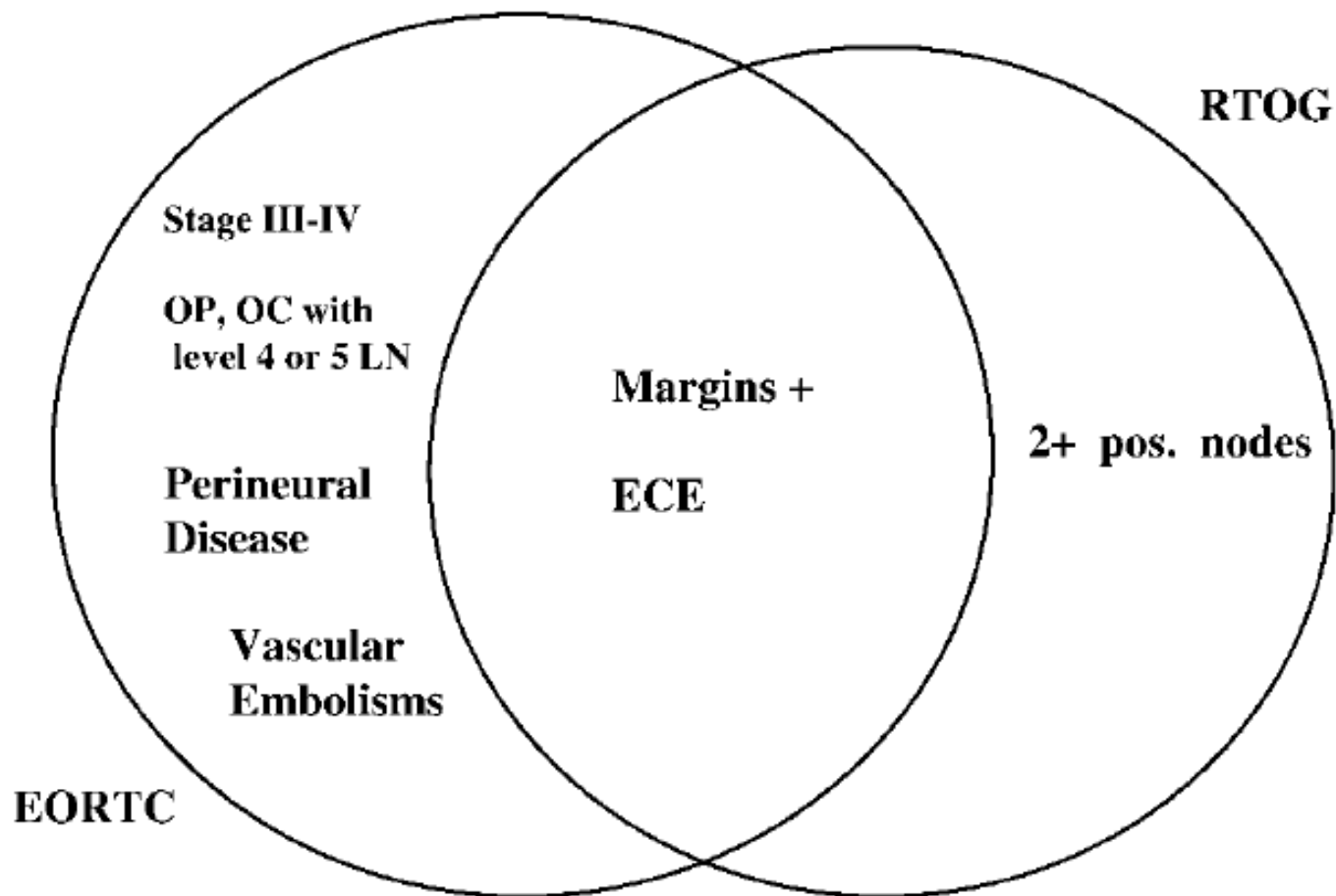
**5years

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“)



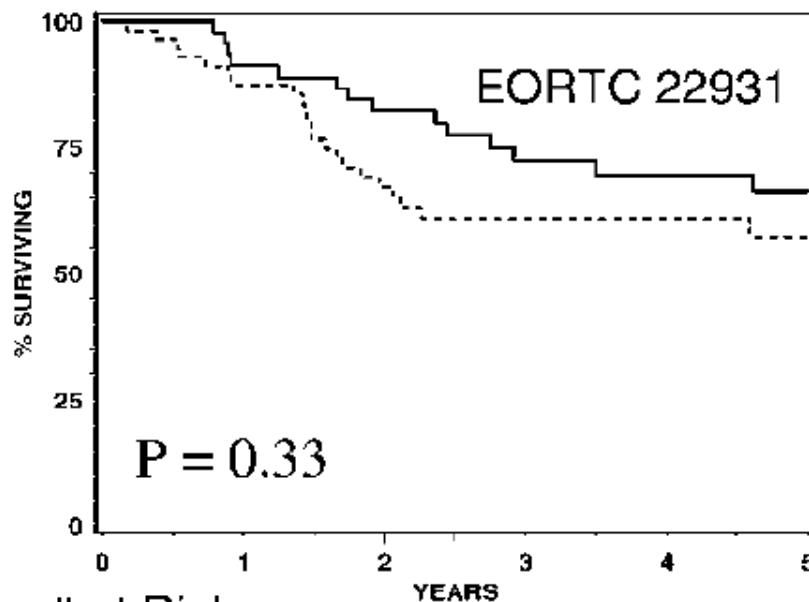
Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.

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

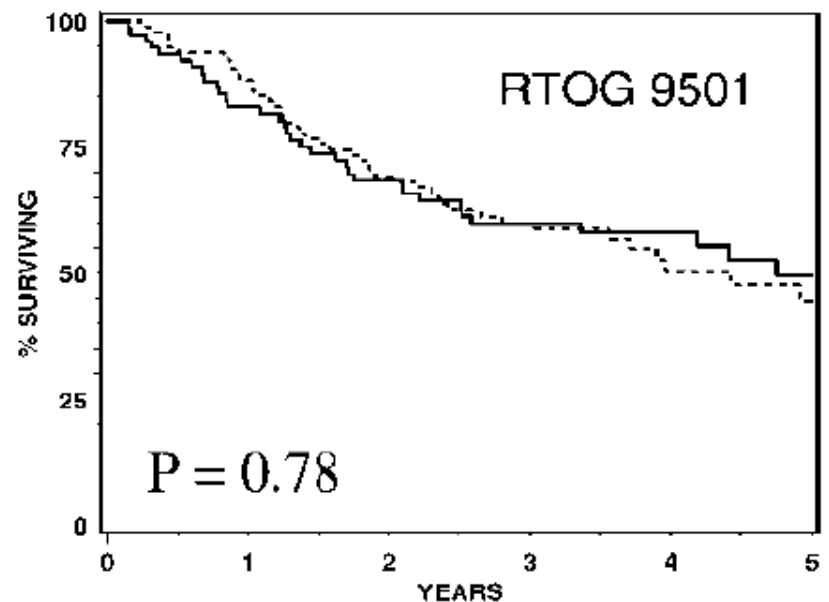


at Risk

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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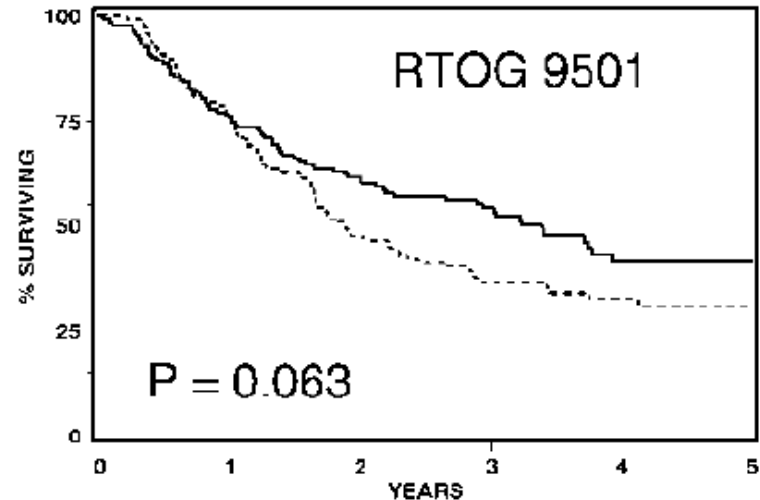
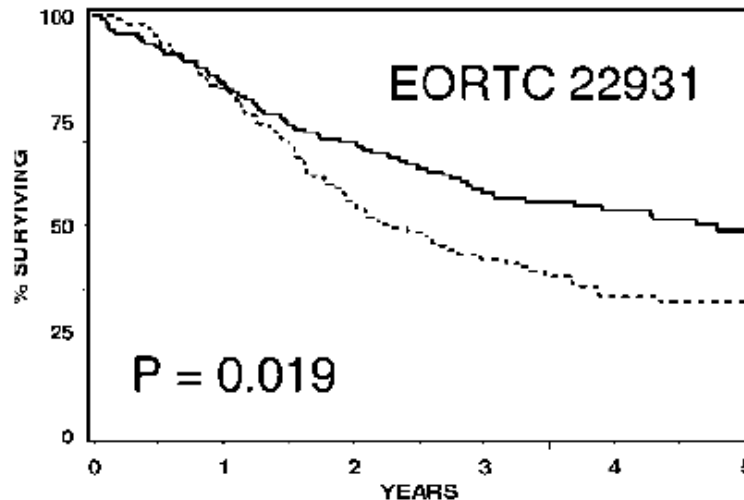
RCT —	76	52	11
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RT ---	94	65	14
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A COMPARATIVE ANALYSIS OF CONCURRENT POSTOPERATIVE RADIATION PLUS CHEMOTHERAPY TRIALS OF THE EORTC (#22931) AND RTOG (#9501)

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Overall Survival Patients with positive margin and/or ECE



at Risk

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

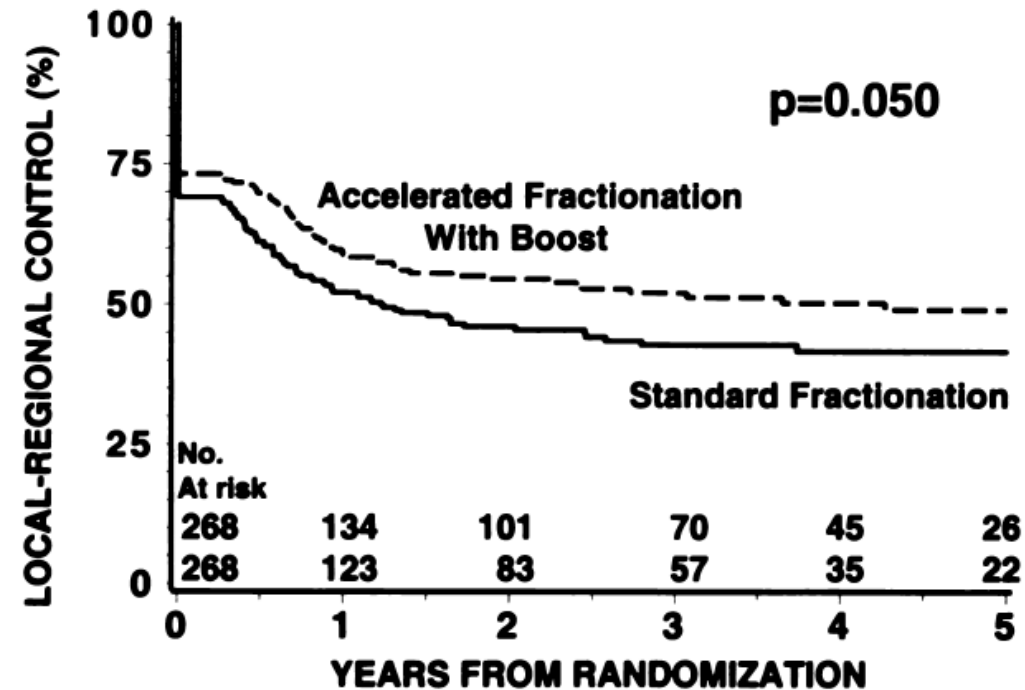
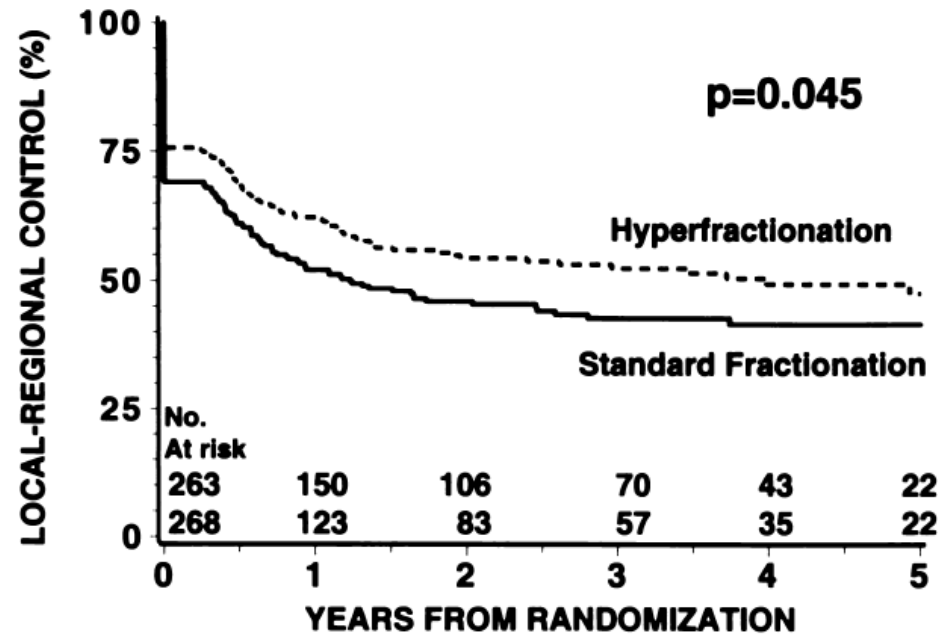
1.8 Gy/fract./day to large field

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

72 Gy / 42 fract. / 6 weeks

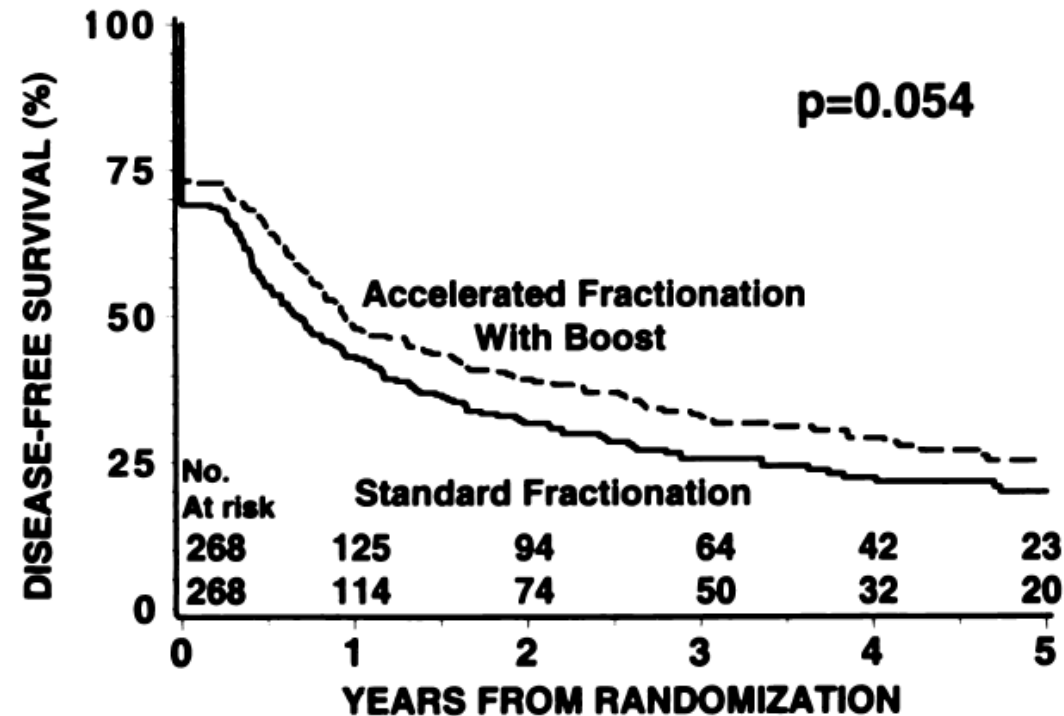
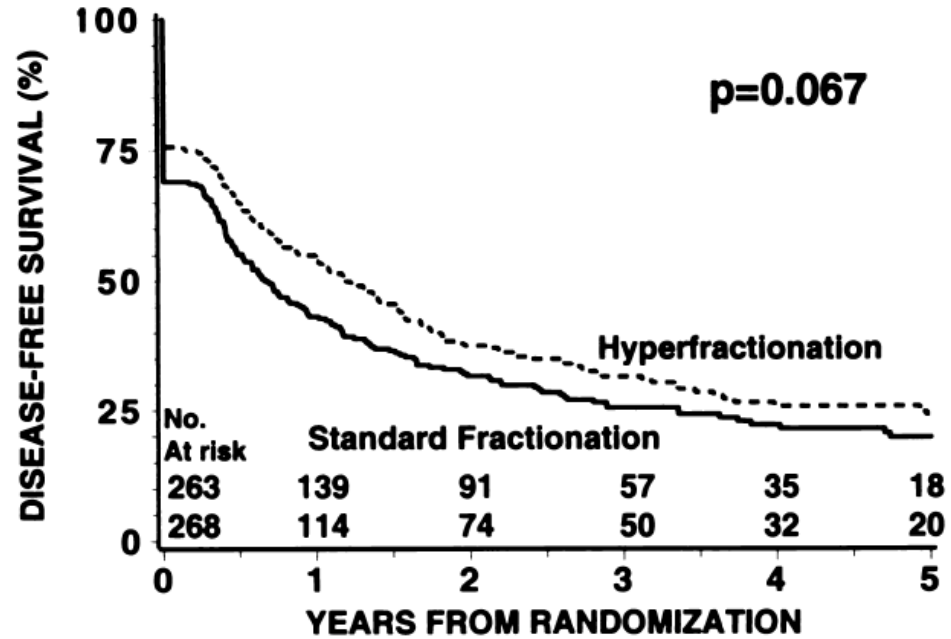
RTOG 9003

Local control



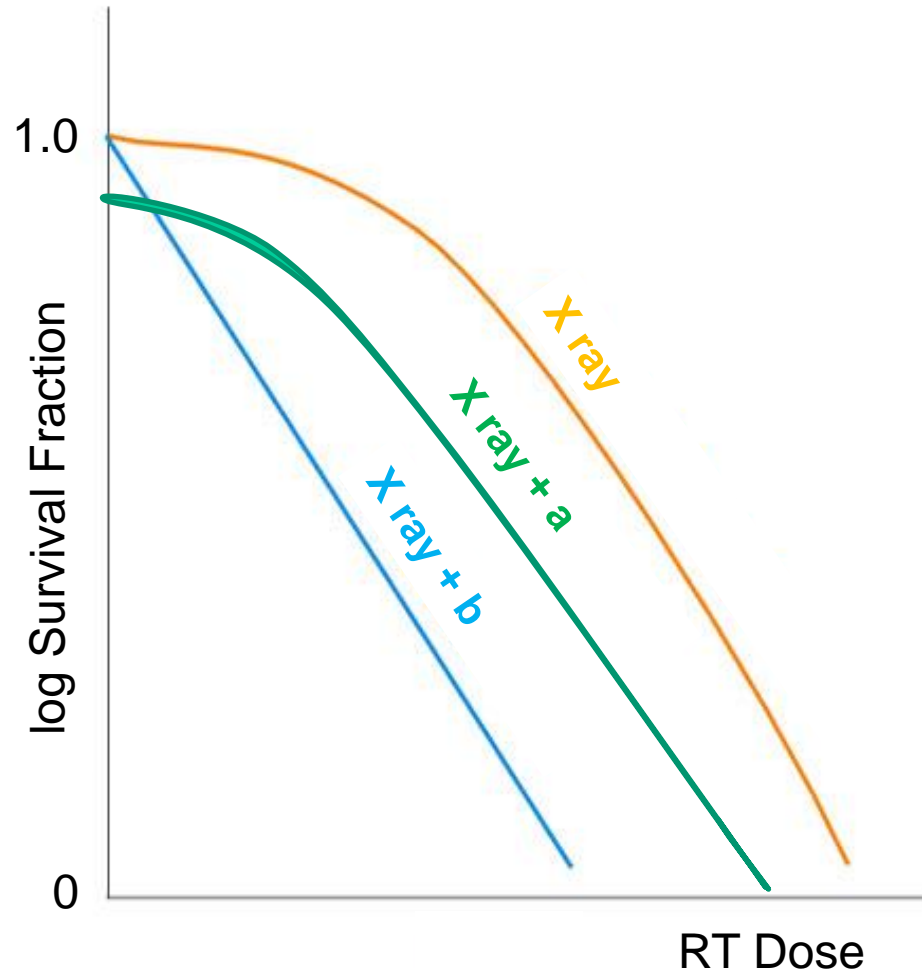
RTOG 9003

Survival



Radiochemotherapy

in vitro



RT plus «Chemo»

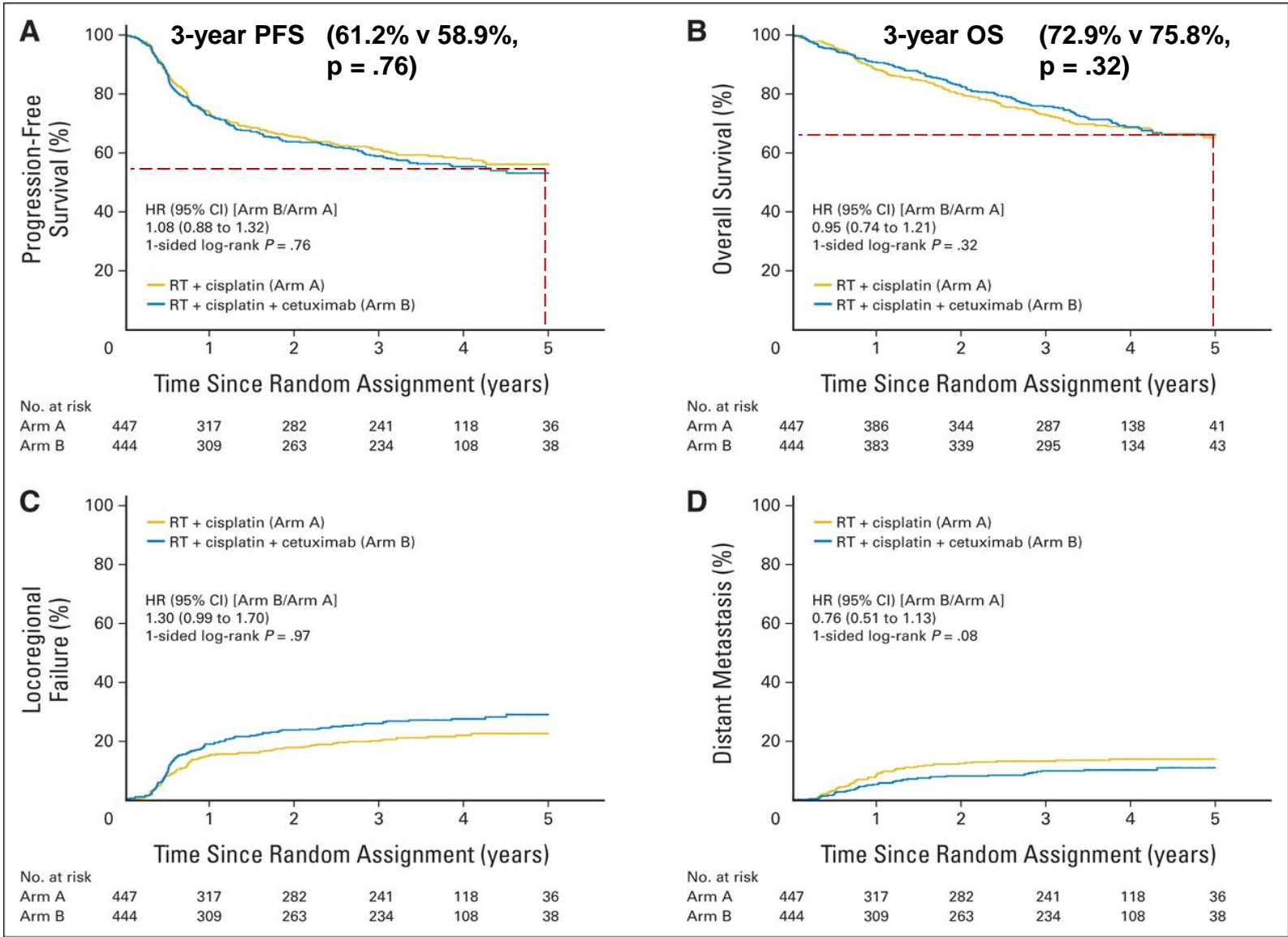
Radio-Chemotherapy

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)	Hetero- geneity	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%
! Concomitant	0.81 (0.76-0.88)	<0.0001	<0.0001	7%	8% !
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



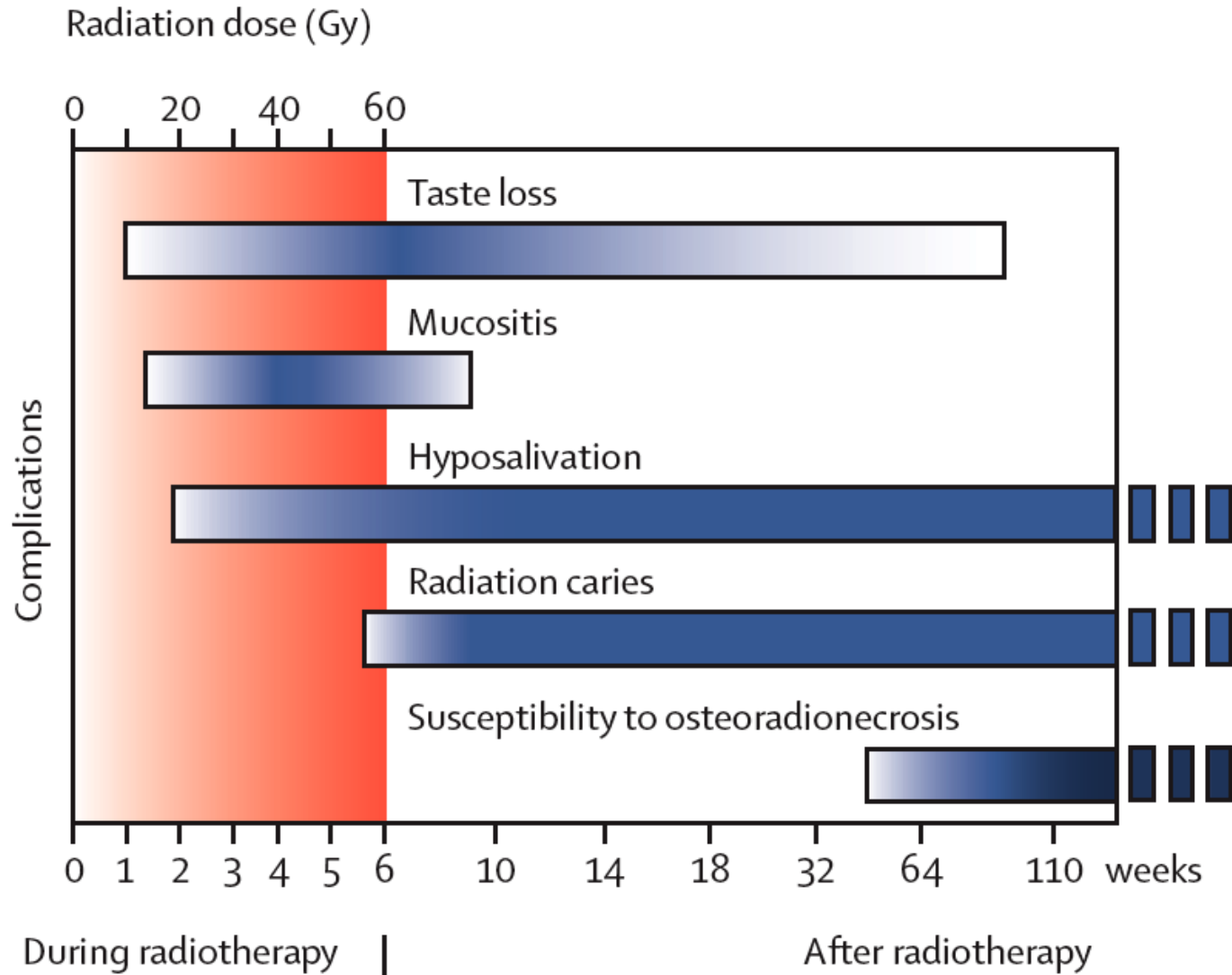
891 analyzed patients, stage III or IV (M0), median follow-up 3.8 years

Possible adverse effects

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

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

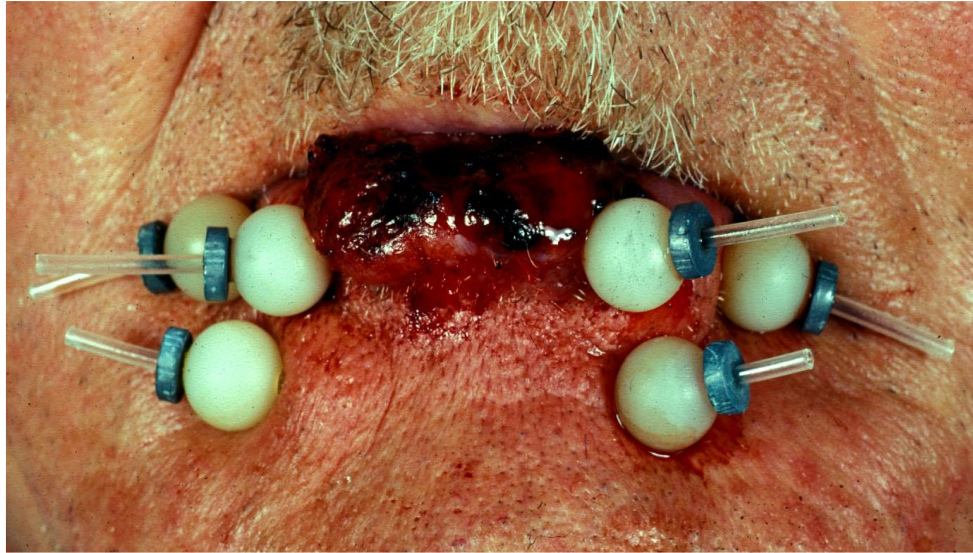
Treatment-Related Adverse Events by Assigned Treatment % of Patients

<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

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UNIVERSITÄT
BERN



«After-Loading»

„take home“

Indication:

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

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