



DEUTSCHE  
KREBSGESELLSCHAFT E.V.

Interdisziplinäre Arbeitsgemeinschaft  
Tumoren der Kopf-, Halsregion



Hubertus Wald Tumorzentrum  
Universitäres Cancer Center Hamburg



Universitätsklinikum  
Hamburg-Eppendorf

# Protokolle und Indikationen für die kombinierte Radiochemotherapie

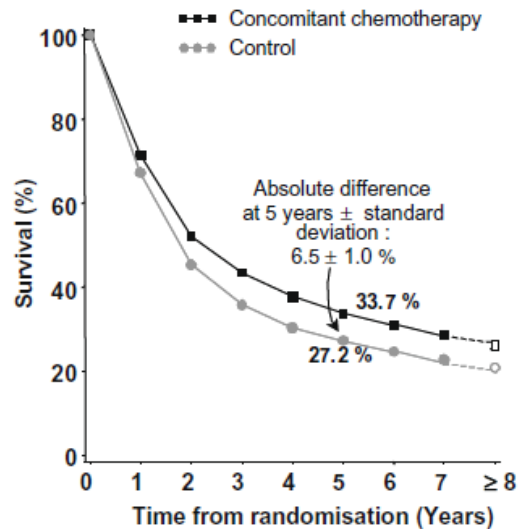
## Wilfried Budach

## Düsseldorf

# Meta-analysis of 93 randomized trials (Pignon et al. 2009)

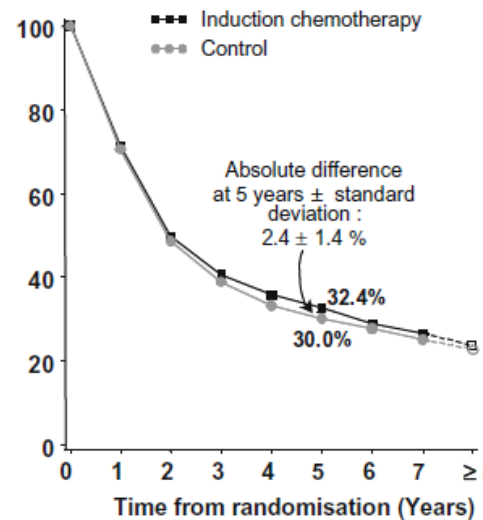
Individual data of 17,346 patients

**(a) Concomitant chemotherapy.**



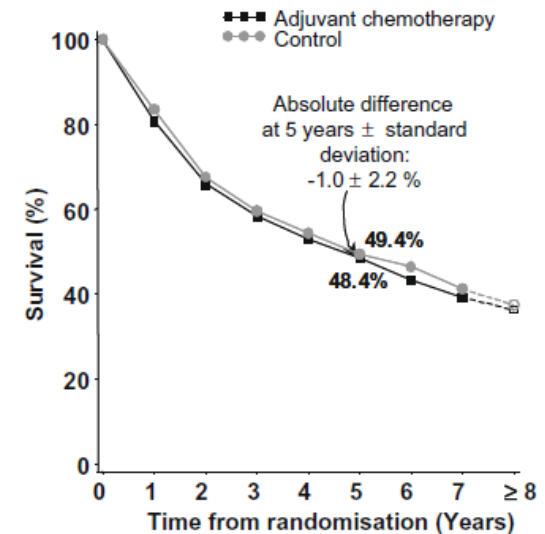
Death/person-years by period			
	Years 0-2	Years 3-5	Years ≥ 6
Control	2500/6298	672/3658	217/2487
Chemotherapy	2187/6647	706/4576	278/3194

**(b) Induction chemotherapy**



Death/person-years by period			
	Years 0-2	Years 3-5	Years ≥ 6
Control	1283/3535	393/2276	137/1417
Chemotherapy	1318/3820	392/2608	167/1530

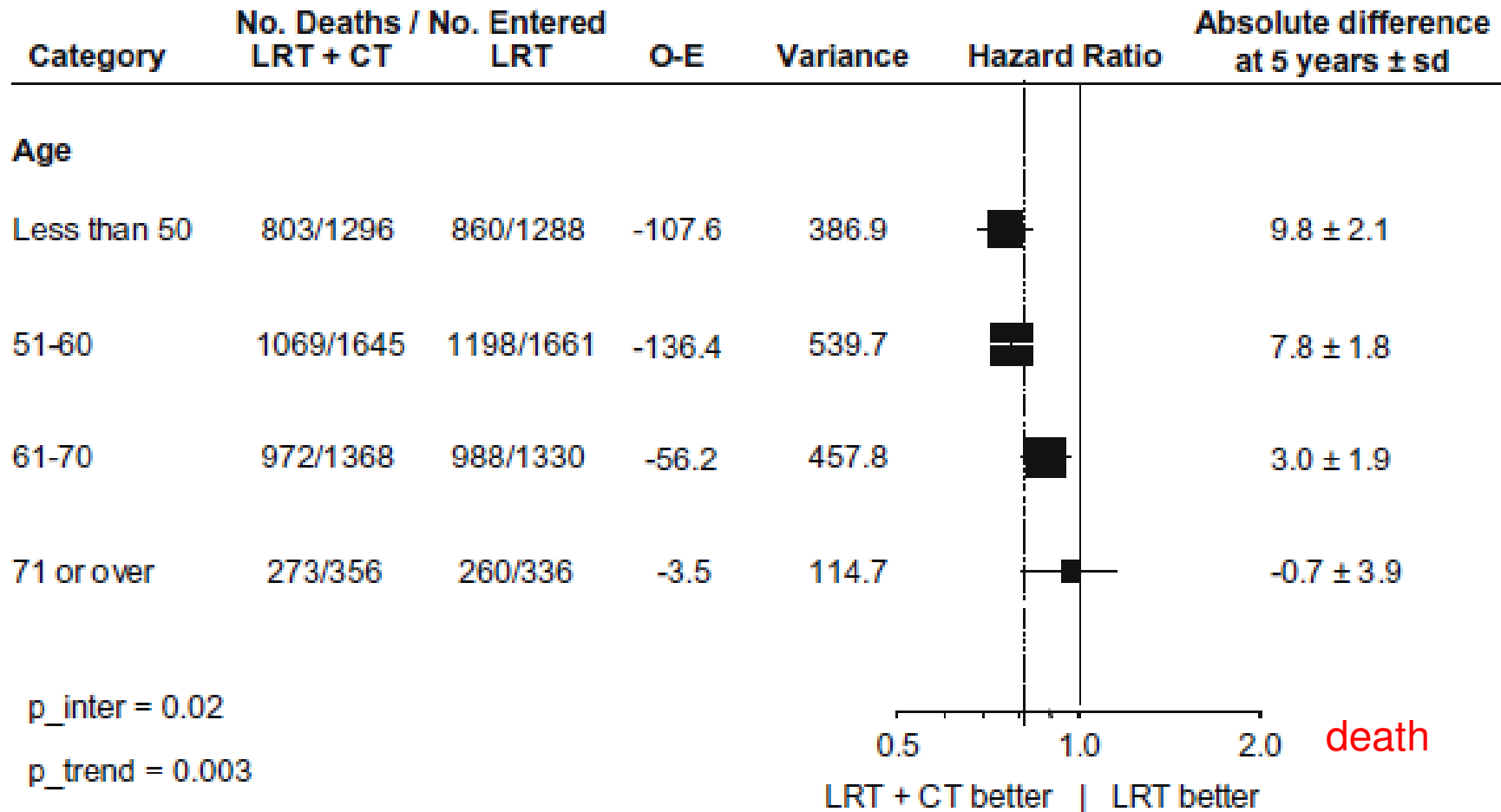
**(c) Adjuvant chemotherapy**



Death/person-years by period			
	Years 0-2	Years 3-5	Years ≥ 6
Control	417/2107	181/1653	63/729
Chemotherapy	403/1956	158/1528	70/718

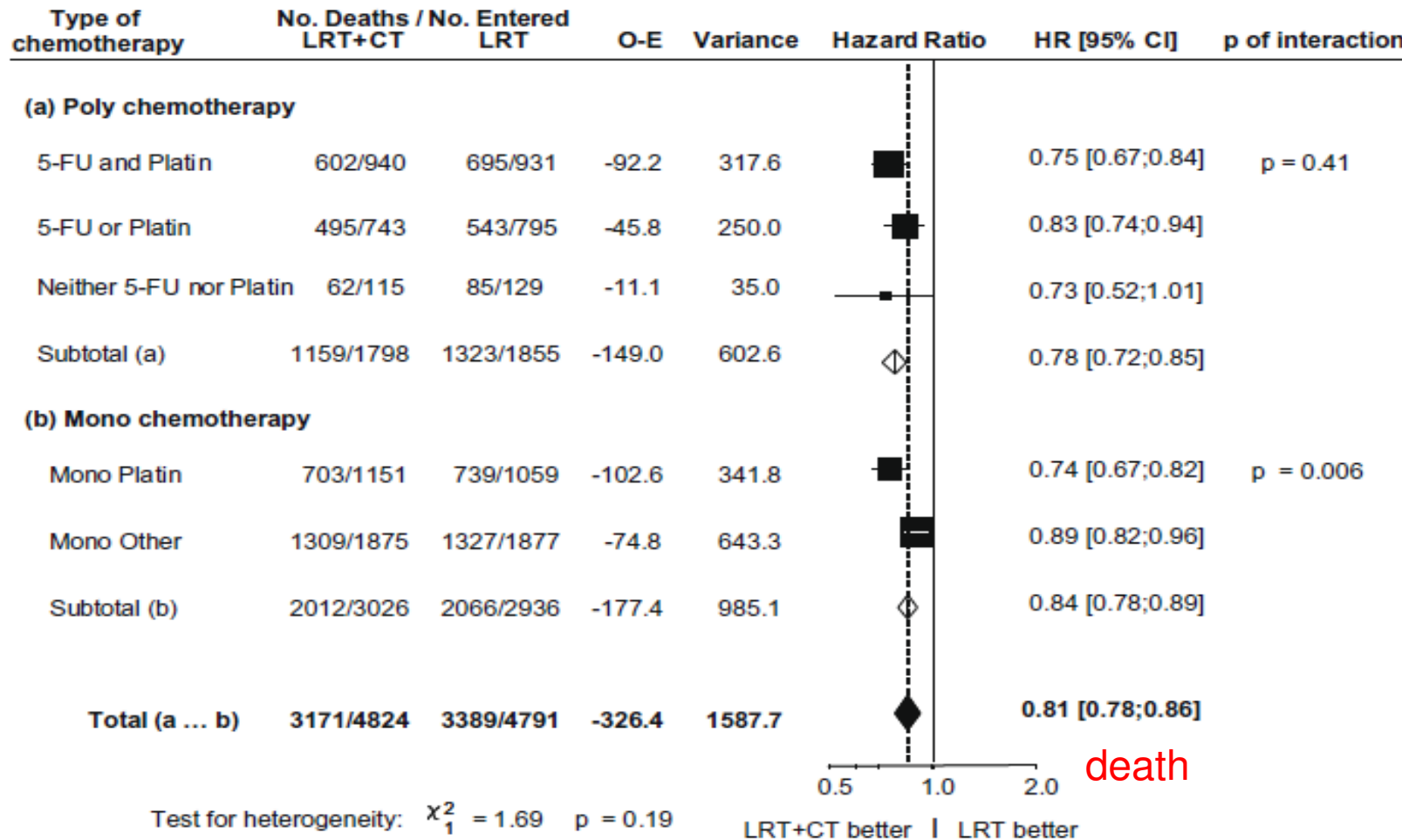
## Meta-analysis of 93 randomized trials (Pignon et al. 2009)

### Age dependence



## Meta-analysis of 93 randomized trials (Pignon et al. 2009)

(no head to head comparisons of different chemotherapy schedules)



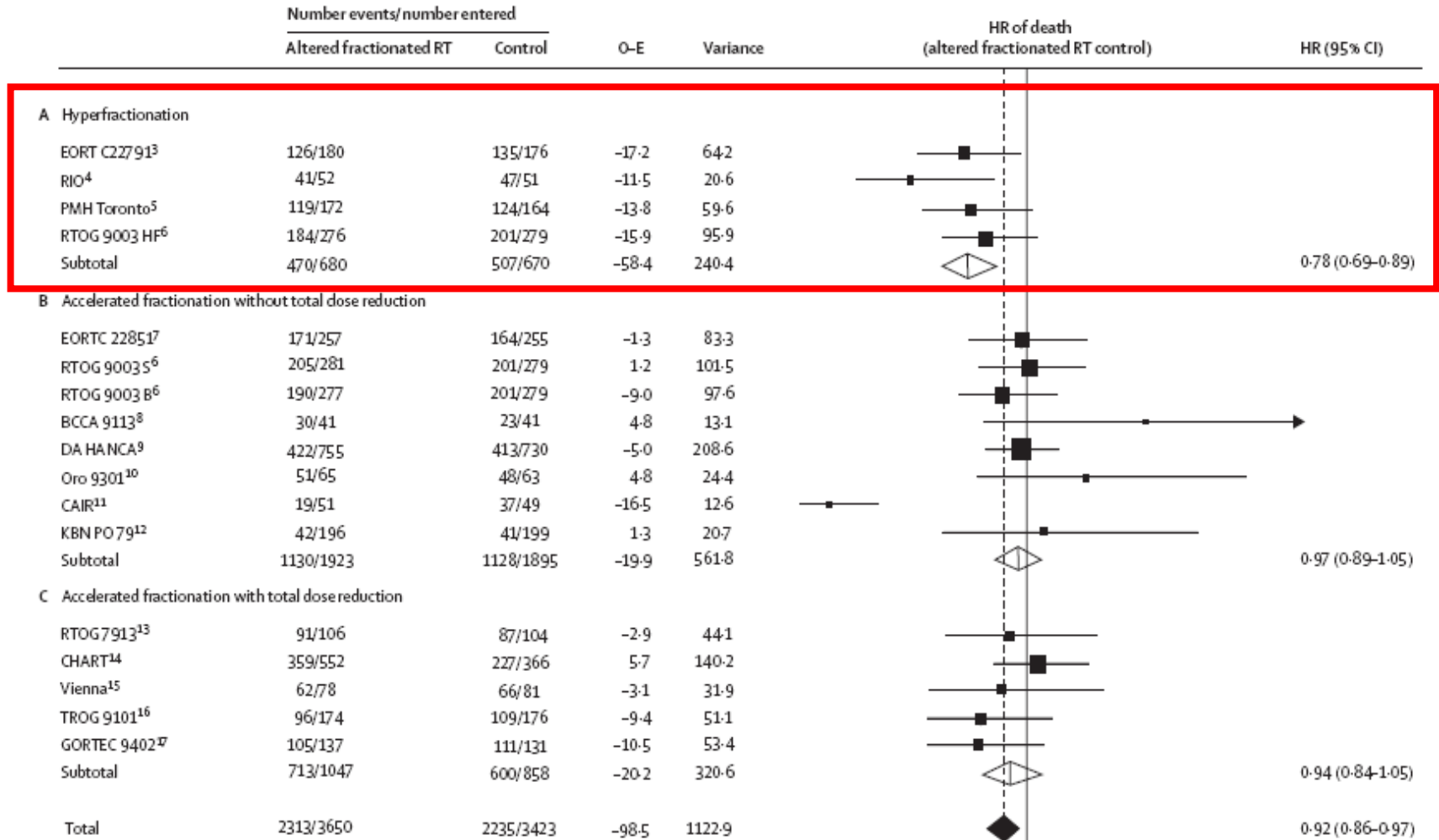
## Concomitant Chemoradiation: CHX-schedules in randomized trials (I)

Study	n	RT-Dose	RT-Fractionation	CHX	Schedule	2y OS Gain
<b>Conventional Fractionation</b>						
Browman (23)	175	66 Gy	5x 2Gy/We.	5-FU	1,2 g/m <sup>2</sup> CI d 1-3, 22-26	12%
Grau (24)	466	66 Gy	5x 2Gy/We.	MMC	15 mg/m <sup>2</sup> d 5	0%
Jeremic (10)	106	70 Gy	5x 2Gy/Wo.	Carbo	25 mg/m <sup>2</sup> d 1-49	20%
Adelstein (12)	182	66-72 Gy	5x 1,8-2,0 Gy/We.	DDP	100 mg/m <sup>2</sup> d 1, 22, 43	14%
Jeremic (10)	106	70 Gy	5x 2Gy/Wo.	DDP	6 mg/m <sup>2</sup> d 1-49	21%
Olmi (15)	127	66-70 Gy	5x 2Gy/We.	Carbo 5-FU	75 mg/m <sup>2</sup> 1-4, 29-33, 57-61 1 g/m <sup>2</sup> CI d 1-4, 29-33, 57-61	9%
Denis (14)	222	70 Gy	5x 2Gy/We.	Carbo 5-FU	70 mg/m <sup>2</sup> T d-4, 22-26, 43-47 0,6 g/m <sup>2</sup> CI T d-4, 22-26, 43-47	16%
Adelstein (25)	100	66-72 Gy	5x 1,8-2,0 Gy/We.	DDP 5-FU	20 mg/m <sup>2</sup> d 1-4, 22-26, 43-47 1 g/m <sup>2</sup> CI d1-4, 22-26, 43-47	6%

## Concomitant Chemoradiation: CHX-schedules in randomized trials (I)

Study	n	RT-Dose	RT-Fractionation	CHX	Schedule	2y OS Gain
<b>HFX / AFX</b>						
Dobrowsky (26-27)	161	<b>55,3 Gy</b> <b>70 Gy</b>	33 fx in 17 days [CHX] 5x2Gy/We. [Contr.]	<b>MMC</b>	<b>20 mg/m<sup>2</sup> d 5</b>	<b>18%</b>
Jeremic (28)	130	<b>77 Gy</b>	10x1,1 Gy/We.	<b>DDP</b>	<b>6 mg/m<sup>2</sup> d 1-49</b>	<b>22%</b>
Huguenin (11)	224	<b>74,4 Gy</b>	10x1,2 Gy/We.	<b>DDP</b>	<b>20 mg/m<sup>2</sup> d1-5, 29-33</b>	<b>9%</b>
Budach (2)	384	<b>77,6 Gy</b>	5x2 Gy/We. - 10x1,4 Gy/We. (42 d.) [CHX]	<b>MMC</b>	<b>10 mg/m<sup>2</sup> d 5+36</b>	<b>7%</b>
		<b>70,6 Gy</b>	5x2 Gy/We. - 10x1,4 Gy/We. (42 T) [Contr.]	<b>5-FU</b>	<b>0,6 g/m<sup>2</sup> CI T 1-5</b>	
Brizel (13)	116	<b>70 Gy</b>	10x1,25 Gy/We. (CHX)	<b>DDP</b>	<b>12 mg/m<sup>2</sup> d 1-5, 36-40</b>	<b>18%</b>
		<b>75 Gy</b>	10x1,25 Gy/We. (Kontr.)	<b>5-FU</b>	<b>0,6 g/m<sup>2</sup> CI d 1-5, 36-40</b>	
Wendt(5)	270	<b>70,2 Gy</b>	10x1,8 Gy/We. 1-2, 4-5, 7-8	<b>DDP</b>	<b>60 mg/m<sup>2</sup> d 1, 22, 44</b>	<b>25%</b>
				<b>5-FU</b>	<b>0,35 g/m<sup>2</sup> CI d 1-4, 22-25, 44-47</b>	
Staar (3-4)	240	<b>69,9 Gy</b>	5x1,8 Gy/We.	<b>Carbo</b>	<b>70 mg/m<sup>2</sup> d 1-5, 29-33</b>	<b>8%</b>
			concom. Boost: 1,5 Gy last 2,5 We.	<b>5-FU</b>	<b>0,6 g/m<sup>2</sup> CI d 1-5, 29-33</b>	

- No direct comparisons available
- Platin containing schedules appear more efficient
- Many consider 100 mg/m<sup>2</sup> cisplatin (d1, 22, 43) standard
- Fractionated cisplatin maybe equally effective and less toxic
- The value of additional 5-FU is unknown
- Mitomycin C + 5-FU has also been shown to be effective
- Carboplatin is also an option



$\chi^2$  test for heterogeneity p=0.001

$\chi^2$  test for interaction p=0.02

Bourhis, Lancet 2006

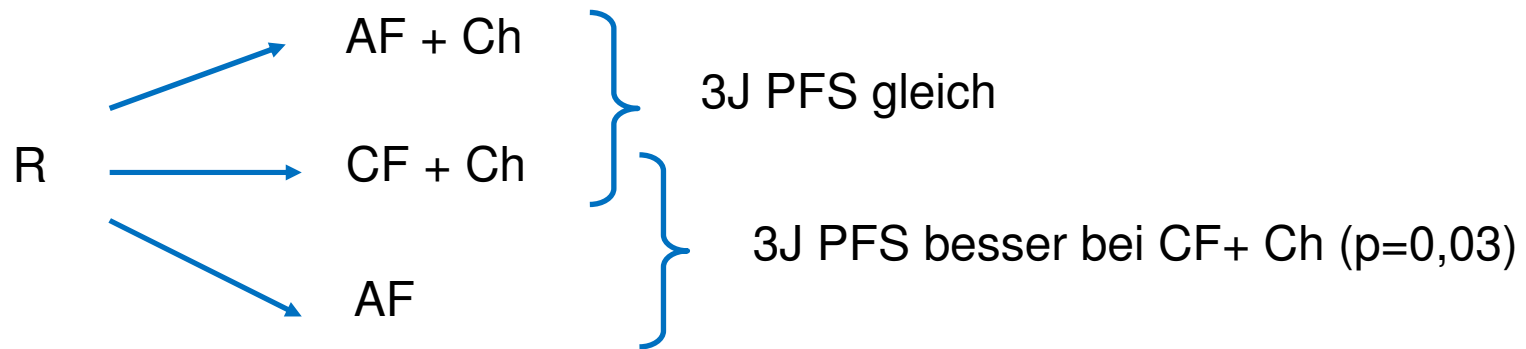
0 0.5 1.0 1.5 2.0 death

Altered fractionated RT effect with p=0.003

- Bei nicht resezierten Kopf-Hals-Tumoren (PEC) ist ab T2 (jedes N) die simultane RT-CHX die derzeitige Standardtherapie
- Wenn keine Systemtherapie appliziert werden kann, ergibt die hyperfraktionierte Strahlentherapie mit moderater Dosisescalation die besten Ergebnisse

## H&N Tumoren: Was bringt eine geänderte Fraktionierung bei RChT?

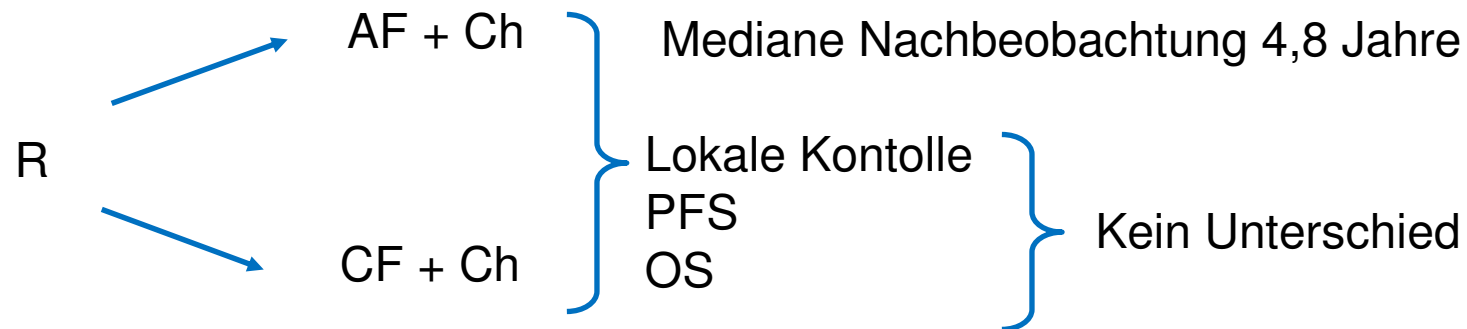
GORTEC Trial 99-02 (Bourhis): Phase III, 840 Pat. [ESTRO 2008]



⇒ Keine AF notwendig bei begleitender Chemo  
z.Zt. unklar, ob HF+ChT vs CF+ChT von Vorteil ist.

## H&N Tumoren: Was bringt eine geänderte Fraktionierung bei RChT?

RTOG Trial 0129 (Kian Ang): Phase III, 721 Pat. [ASTRO 2009]



⇒ Keine AF notwendig bei begleitender Chemo  
z.Zt. unklar, ob HF+ChT vs CF+ChT von Vorteil ist.

5x2 Gy / Woche bis 70 Gy + cisplatinhaltige CHX Standard für nicht resezierte PEC

## Locally advanced head and neck cancer: RT vs. cetuximab No resection

Bonner et al. NEJM 2006

### Stratify by

- Karnofsky score:  
90-100 vs. 60-80
- Regional Nodes:  
Negative vs. Positive
- Tumor stage:  
AJCC T1-3 vs. T4
- RT fractionation\*:  
Concomitant boost  
vs. Once daily  
vs. Twice daily

\* Investigators' choice

R  
A  
N  
D  
O  
M  
I  
Z  
E

Arm 1 (RT)

**Radiation therapy**

Arm 2 (RT+E)

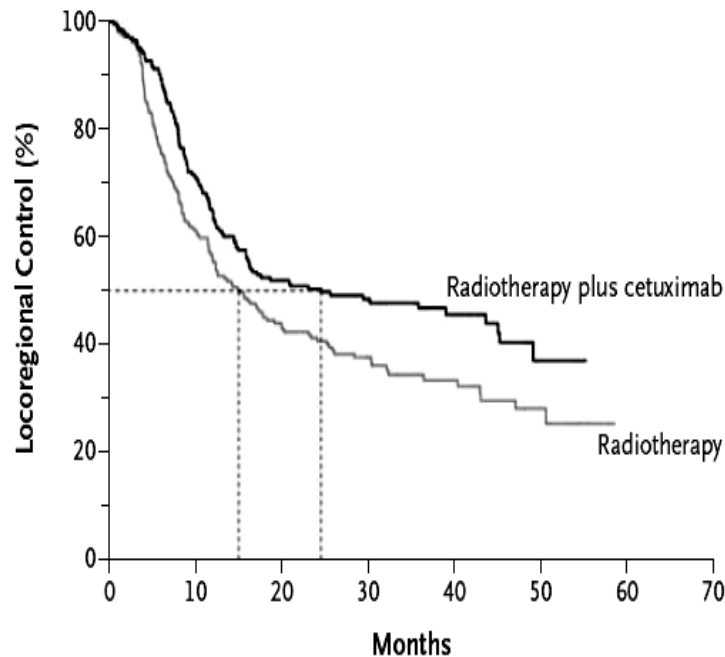
**Radiation therapy +  
Erbix, weekly\*\***

\*\* UAB regimen, Robert F:JCO

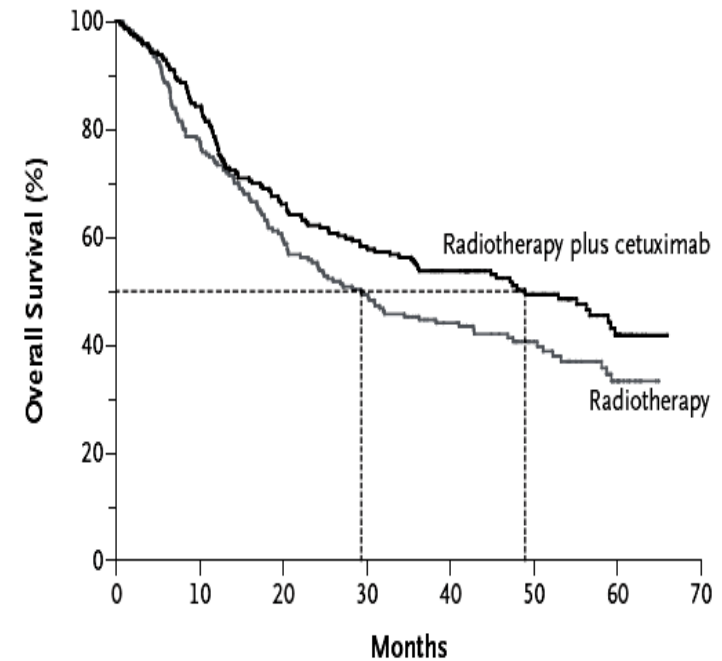
# Locally advanced head and neck cancer: RT vs. RT + cetuximab

locoregional control

overall survival



No. at Risk						
Radiotherapy	213	122	80	51	30	10
Radiotherapy plus cetuximab	211	143	101	66	35	9



No. at Risk							
Radiotherapy	213	162	122	97	73	47	22
Radiotherapy plus cetuximab	211	177	136	116	98	61	24

Bonner et al. NEJM 2006

## Recommended schedules for simultaneous chemo(bio)radiation

Best evidence (2 or more randomized trials)

- **Cisplatin 100 mg/m<sup>2</sup> d 1,22, and 43 of RT**
- **Cisplatin 12-20mg/m<sup>2</sup> + 5-FU 600 mg/m<sup>2</sup> CI d 1-5 and 29-33 of RT**

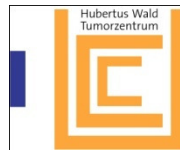
Good evidence (at least 1 large randomized trial of high quality)

- Mitomycin C 10mg/m<sup>2</sup> d 5 + 36 + 5-FU 600 mg/m<sup>2</sup> CI d 1-5 of RT**
- Carboplatin 70-75 mg/m<sup>2</sup> + 5-FU 1000 mg/m<sup>2</sup> CI d 1-4 + d29-33 of RT**
- Cetuximab 400 mg/m<sup>2</sup> d-8 + weekly Cetuximab 250 mg/m<sup>2</sup> during RT**

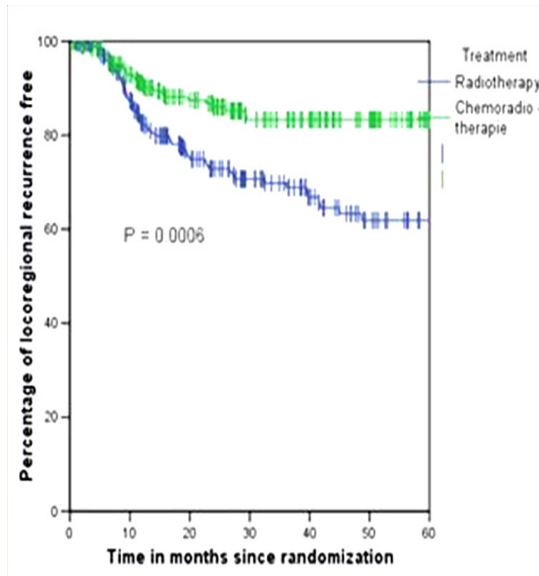
Some evidence (at least 1 randomized trial)

- Cisplatin 20mg/m<sup>2</sup> d 1-5 and 29-33 of RT**
- Cisplatin 6 mg/m<sup>2</sup> on all RT days**
- Carboplatin weekly AUC 1.5 during RT**
- Carboplatin 25 mg/m<sup>2</sup> on all RT days**
- Mitomycin 10-15 mg/m<sup>2</sup> day 1 of RT**
- 5-FU 1000 mg/m<sup>2</sup> CI d1-4 and d 29-32 of RT**

<u>Comparison</u>	<u>HR</u>	<u>p</u>	<u>comment</u>
AFX-RT (mod acc. same dose) vs. CF-RT	0.97	<0.01	Meta-analysis
AFX -RT (very acc. dose reduced) vs. CF-RT	0.92	<0.01	Meta-analysis
HFX-RT vs. CF-RT	0.75	<0.0001	Meta-analysis
RT-CHX (concom.) vs. RT	0.81	<0.0001	Meta-analysis
RT-CHX (cisplatin) vs. RT-CHX (others)	0.75	<0.05	Meta-analysis
RT+ Cetuximab vs. RT	0.74	0.03	Bonner 2006
Neo. CHX (all old studies) → RT vs. RT	0.95	n.s.	Meta-analysis
Neo. CHX (PF) → RT vs. RT	0.88	<0.05	Meta-analysis
Neo. TPF → RT vs. Neo. PF → RT	0.73	0.005	EORTC 2005
Neo. PPF → RT-CHX vs. Neo. PF → RT-CHX	0.75	0.035	Hitt 2005
Neo. TPF → RT-CHX vs. Neo. PF → RT-CHX	0.70	0.006	TAX 234 2006



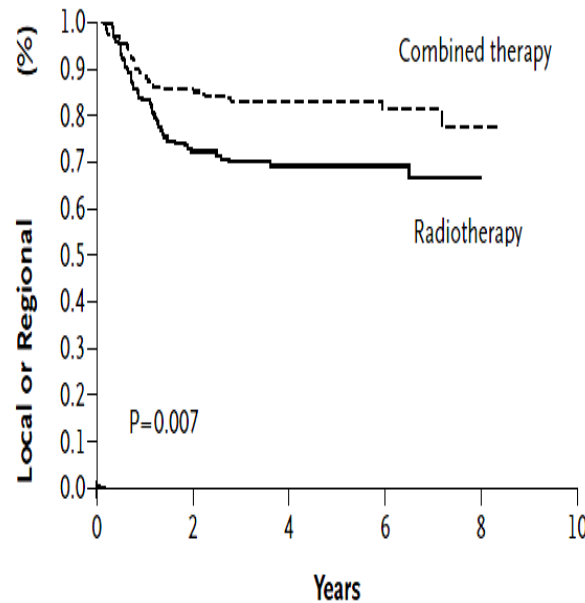
## Locoregional tumor control



pT3 R1 or pT4 or ECE or  $\geq 3$  LN+

45% ECE  
Close margin ?

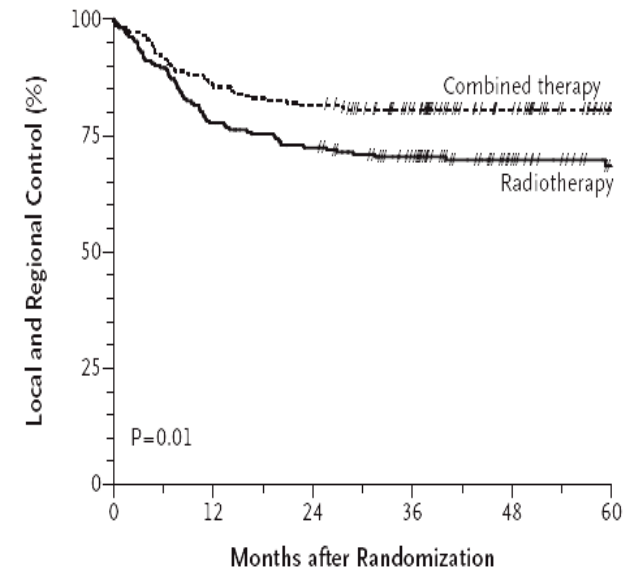
ARO 96-03  
Fietkau et. al. ASCO 2006



pT3 or pT4 or LN+

57% ECE  
Close margin: 29%

EORTC  
Bernier et. al. NEJM 2004

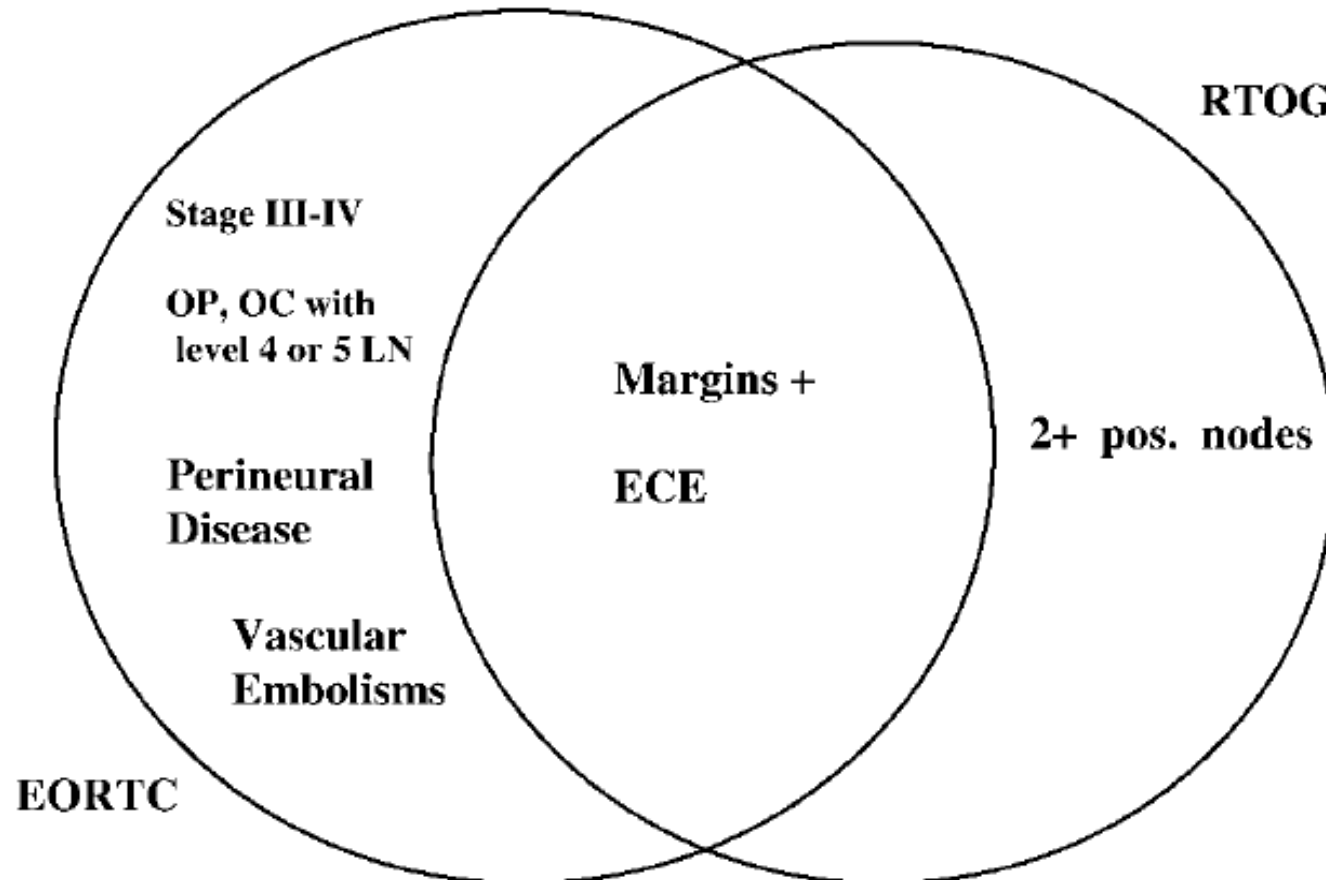


R1 or  $\geq 2$  LN+ or ECE

55% ECE  
Close margin 10%

RTOG  
Cooper et. al. NEJM 2004

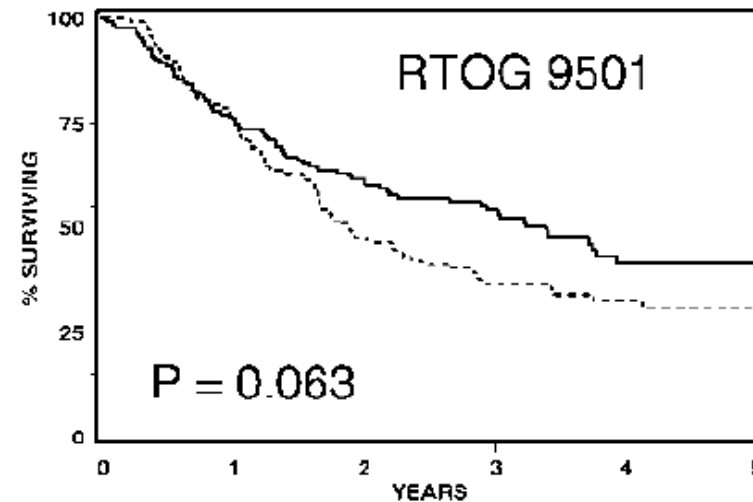
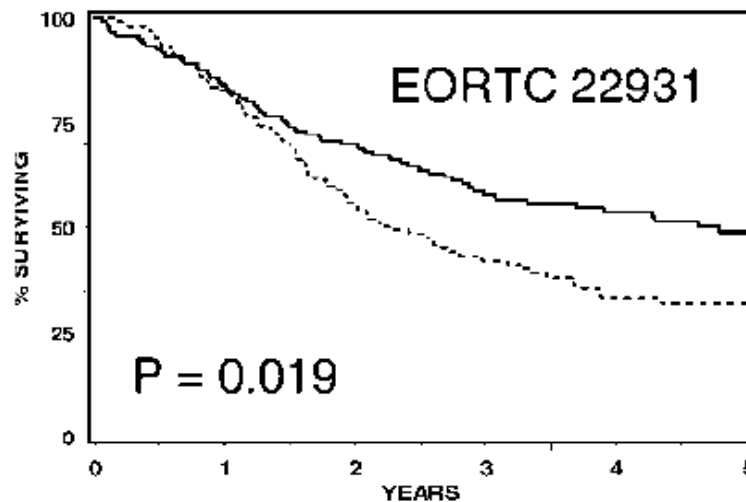
## Meta-analyses: EORTC and RTOG studies



J. Bernier et al. 2005

# Subgroup: R1 (<5 mm) or extracapsular extension

## Overall survival



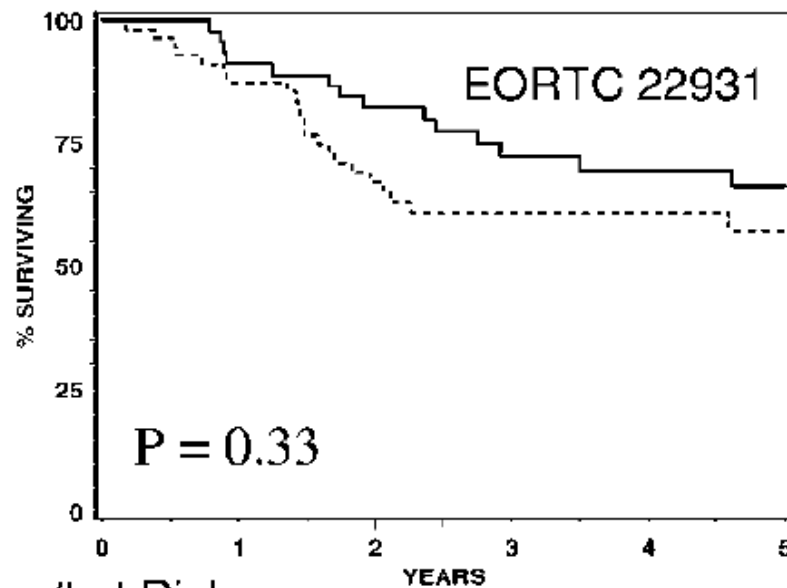
J. Bernier et al. 2005

# at Risk

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

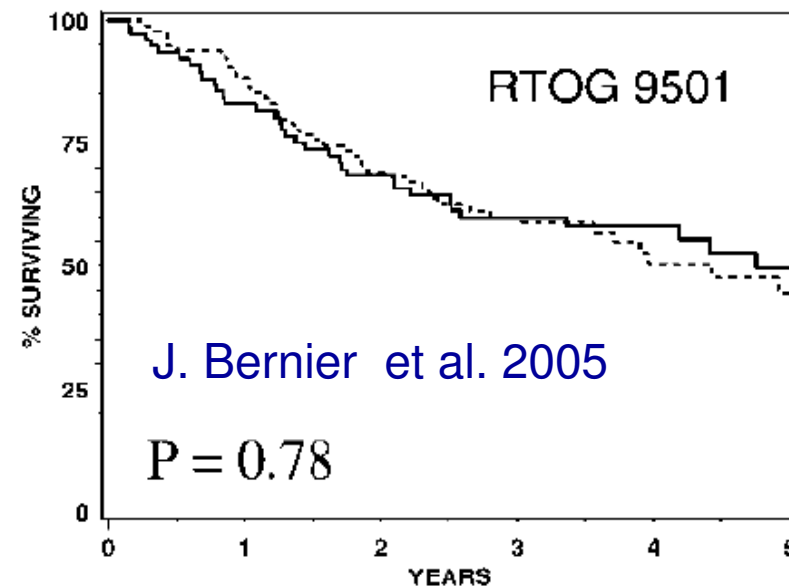
# Subgroup: R0 (>5 mm) and no extracapsular extension

## Overall survival



# at Risk

Year	0	2	5
RCT —	45	36	16
RT ---	56	34	15



Year	0	2	5
RCT —	76	52	11
RT ---	94	65	14

**Concurrent chemoradiation ist standard of care for  
high risk patients**

**(ECE or close margin [ $<5$  mm])**

**Overall survival in this high risk group is still below  
50% at 5 years. DFS at 5 years is 36%**

EGFR antagonist have not been show to be effective in  
the adjuvant setting

## How much surgical safety margin is needed?

Variable	No. of patients (%)	LRC at 5 yrs (%)	Uncorrected OR	95%CI
Wide margins	519 (65)	82	1.00	
Close margins (1-5 mm)	110 (14)	65	2.13	1.40-3.22
Positive margins (< 1 mm)	170 (21)	66	1.93	1.34-2.79
Extracapsular lymph node extension				
No	391 (49)	83	1.00	
Yes	410 (51)	70	1.94	1.40-2.68

LRC: locoregional control; OR: odds ratio; 95%CI: 95% confidence interval.

Langendijk et al. Cancer 2005

## Chemotherapy schedules in combination postoperative radiotherapy

**EORTC**      **Cisplatin 100 mg/m<sup>2</sup> days 1,22, and 43** of radiotherapy

**RTOG**      **Cisplatin 100 mg/m<sup>2</sup> days 1,22, and 43** of radiotherapy

**ARO**      **Cisplatin 20mg/m<sup>2</sup> days 1-5 and 29-33** of radiotherapy  
+ **5-FU 600 mg/m<sup>2</sup> CI days 1-5 and 29-33** of radiotherapy

Radiotherapy: 5x2 Gy per week to 64 Gy (ARO) - 66 Gy (RTOG /EORTC)

## Grade III/IV mucositis

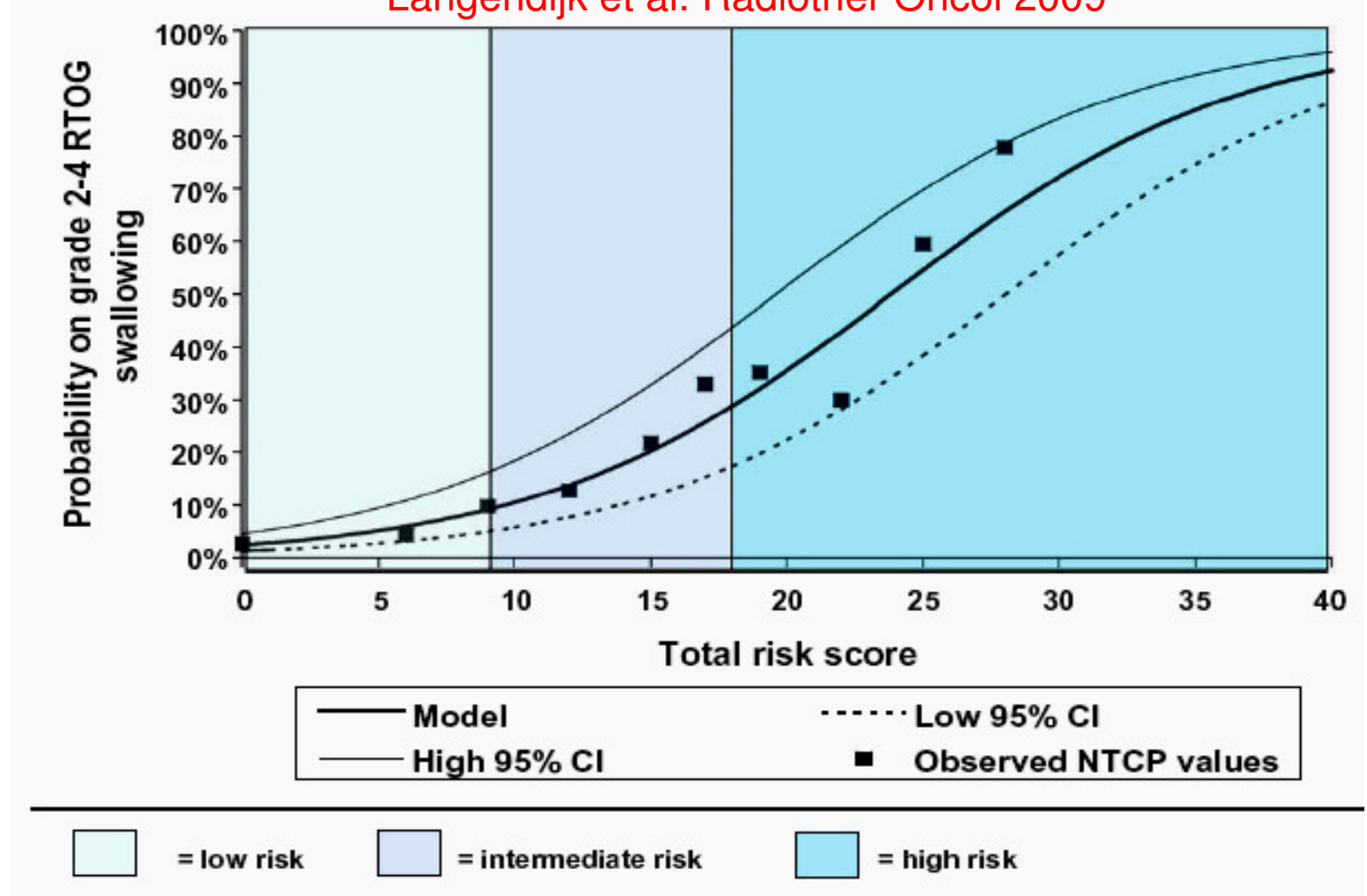
	RT+ Cisplatin	RT	p
EORTC post -OP	41%	21%	0.001
RTOG post -OP	30%	18%	0,003
ARO* post -OP	21%	13%	0.038

Spätnebenwirkungen Grad III/IV jeweils tendenziell erhöht (nicht signifikant)

\*Cisplatin + 5FU

# Prediction of swallowing dysfunction 6 months after RT

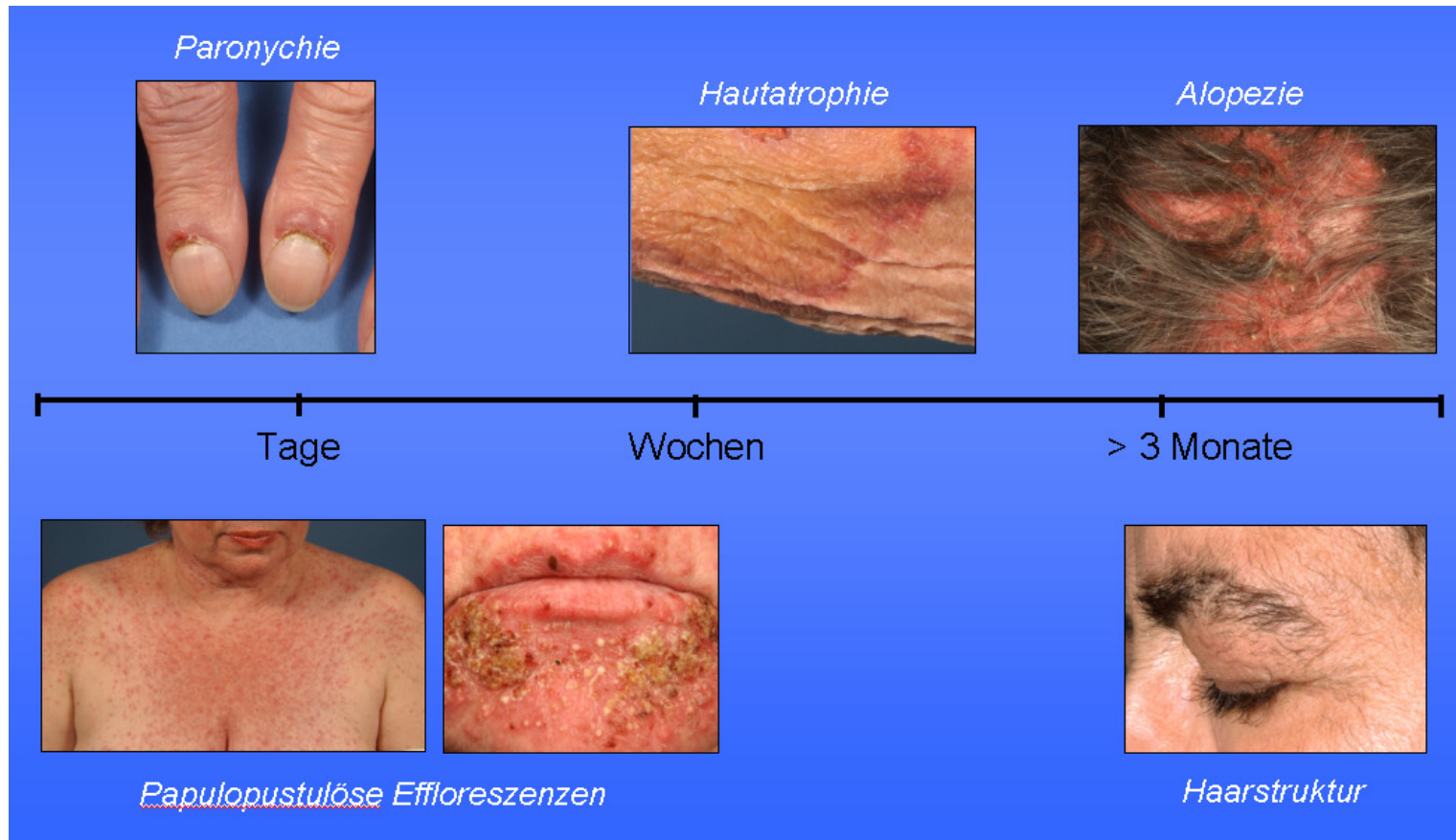
Langendijk et al. Radiother Oncol 2009



## Multivariate analysis with grade 2–4 RTOG swallowing dysfunction at 6 months as primary endpoint

Variable	B	OR	95% CI (OR)	P-value	Risk points
T-classification	<b>n=529</b>				
T1-T2		1.00			0
T3-T4	0.868	2.38	(1.36–4.19)	<i>p</i> = 0.003	4
Neck irradiation					
Primary alone ± ipsilateral neck		1.00			0
Primary + both necks	1.715	5.55	(2.52–12.2)	<i>p</i> < 0.001	9
Weight loss (baseline)					
No weight loss		1.00			0
1–5%	0.981	2.67	(1.41–5.03)	<i>p</i> = 0.002	5
6–10%	1.053	2.87	(1.27–6.49)	<i>p</i> = 0.012	5
>10%	1.324	3.76	(1.29–10.9)	<i>p</i> = 0.015	7
Primary tumour site					
Larynx		1.00			0
Oropharynx	1.376	3.96	(2.03–7.70)	<i>p</i> < 0.001	7
Nasopharynx	1.816	6.15	(1.89–20.0)	<i>p</i> = 0.003	9
Treatment modality					
Conventional radiotherapy		1.00			0
Accelerated radiotherapy	1.170	3.22	(1.56–6.67)	<i>p</i> = 0.002	6
Concomitant chemoradiation	0.975	2.65	(1.17–5.98)	<i>p</i> = 0.019	5

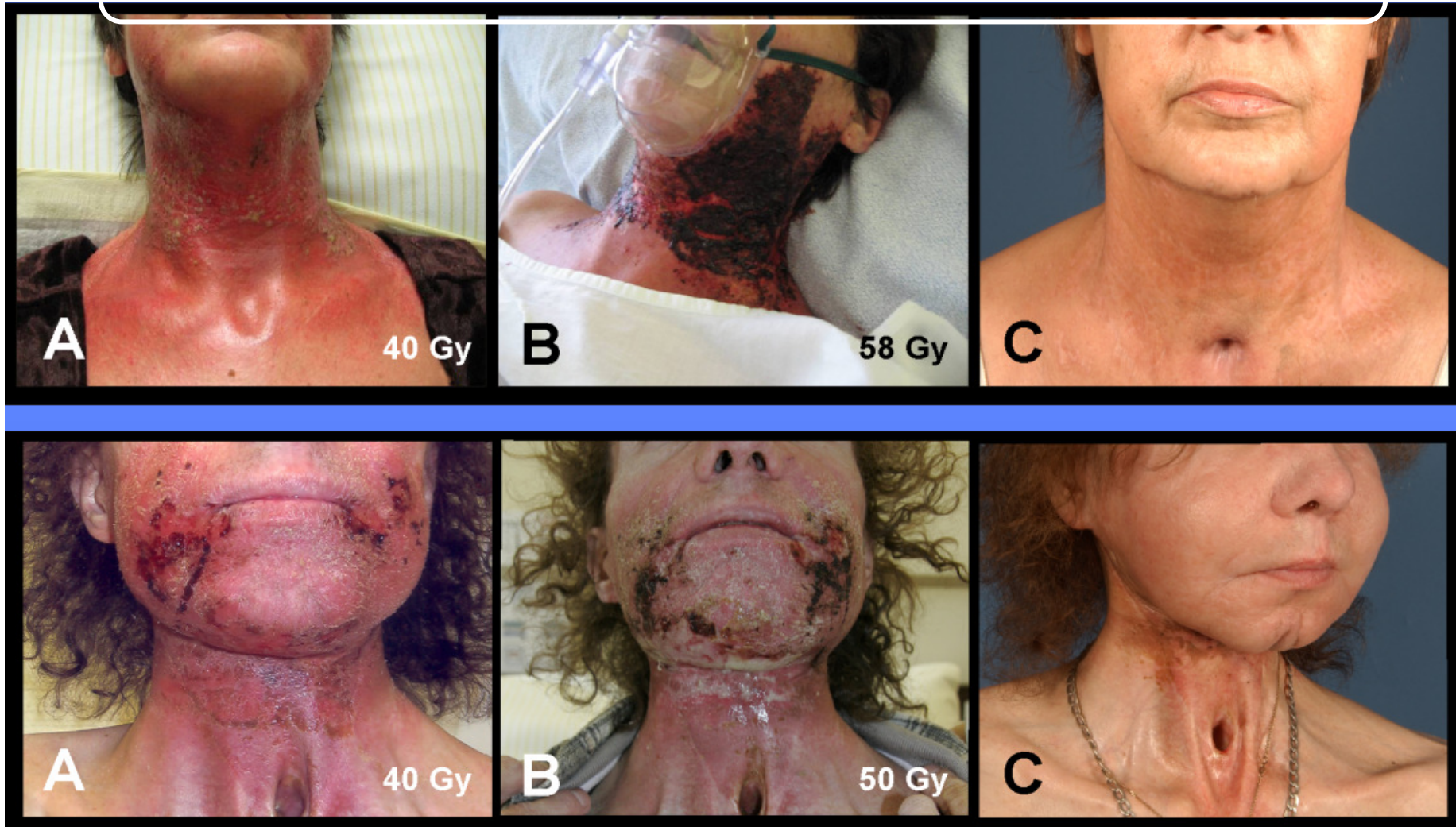
## H&N Tumoren: Cetuximab NW => zeitl. Verlauf

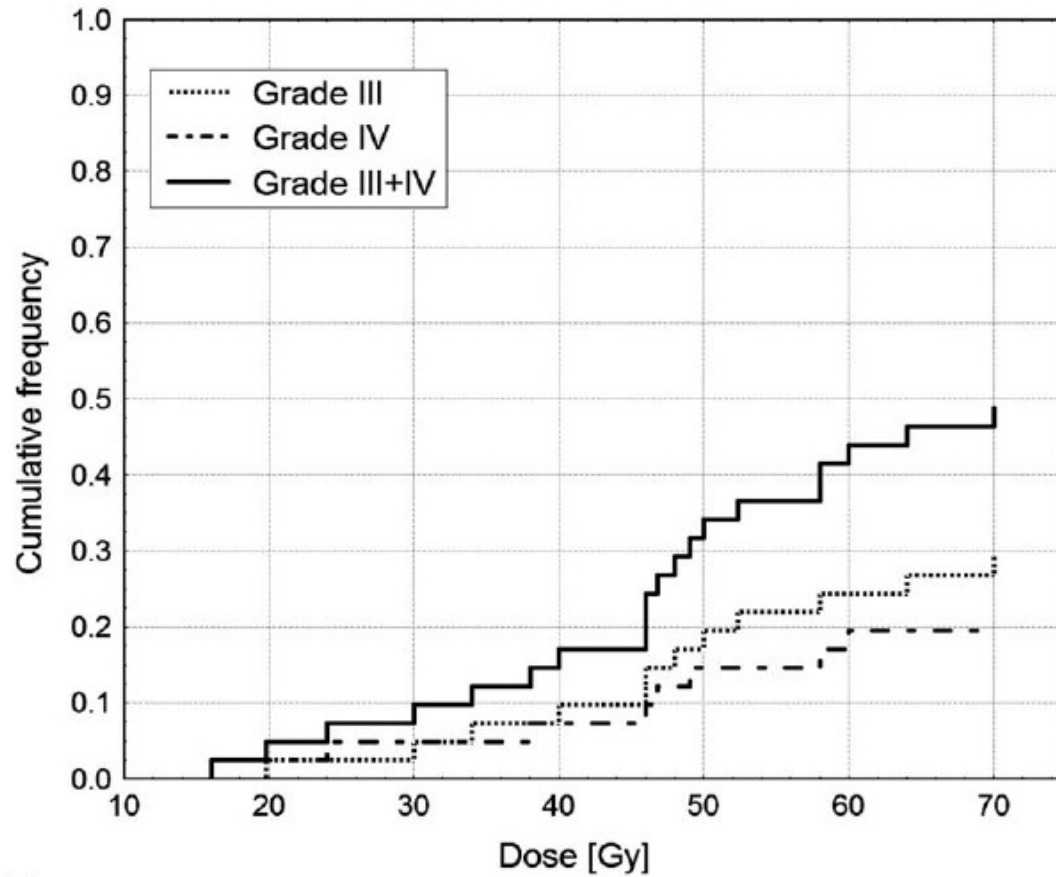


### Behandlung:

Rückfettende Pflege  
Schutz vor mechanischen Reizen  
Schutz vor UV-Exposition

H&N Tumoren: Cetuximab NW => Sepsis möglich!





EORTC Umfrage  
(Giro, Radiotherapy  
and Oncology 2009)

# at risk:	10	20	30	40	50	60	70
Grade III	41	40	39	37	34	31	29
Grade IV	41	40	39	38	35	33	33
Grade III+IV	41	39	37	34	27	23	21

## H&N Tumoren: Cetuximab NW => Behandlung

