Re-irradiation: clinical considerations, outcomes and patient selection

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New?

First guidelines

Harms W, Budach W, Dunst J, et al, Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines for radiotherapy of breast cancer VI: Therapy of locoregional breast cancer recurrences. *Strahlenther Onkol*. 2016; 192:199-208.

Ammirati M, Cobbs CS, Linskey ME, et al. The role of retreatment in the management of recurrent/progressive brain metastases: A systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2010;96:85-96.

Nieder 201

To be considered – before decision

Previous treatment

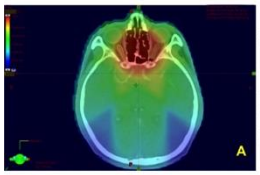
- Dose (EQD2)
- Volume
- Medical treatment

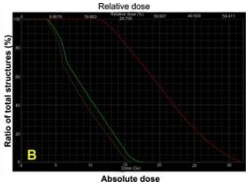
Time elapsed

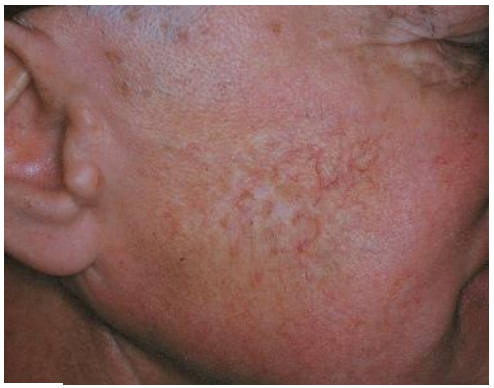
Tox after previous RT

Which organs are affected

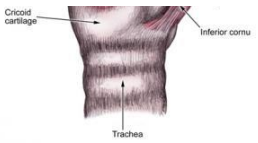
Alternative treatments

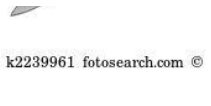






The potential advantage of re-irradiation should be weighted against the potential impact on quality of life





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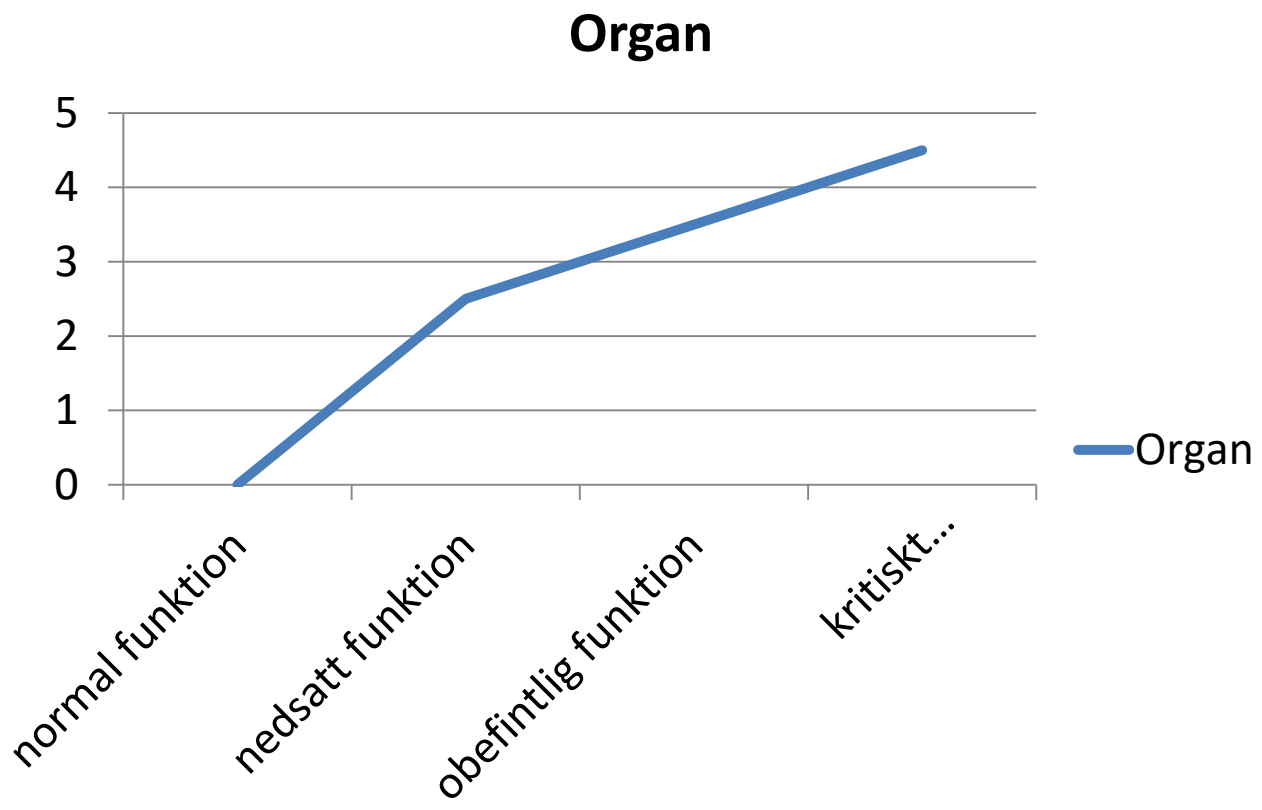
To be considered – dose plan

- Dose constraints for critical complications
- Which organs have preserved function?
- Can we perserve function in some tissues/organs?



Parotic gland

Medulla spinalis

Blood vessels

Toxicity - radiobiology

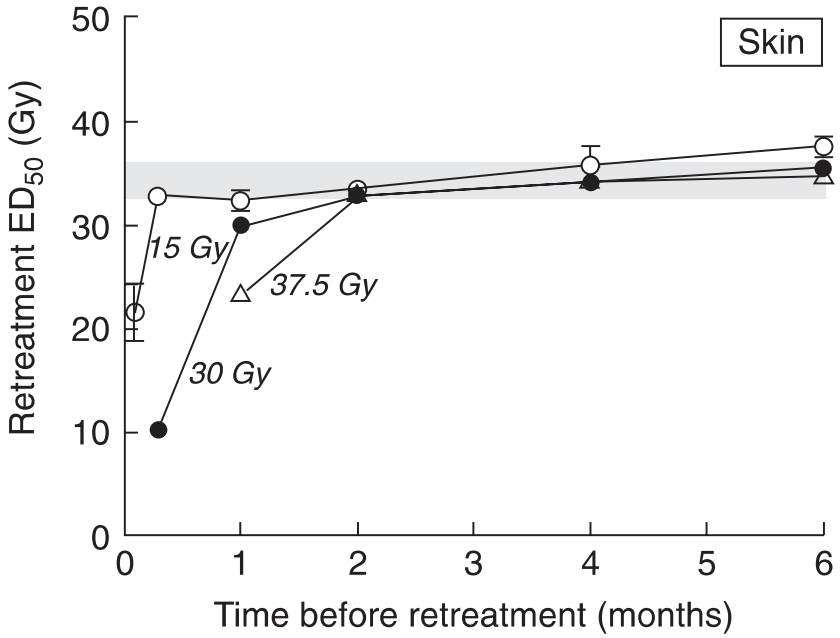
- Regeneration is mitigated by migration of stemcells from non-irradiated/low dose regions
- Tissue architechture and the supply of stem cells is important

Early toxicity

Skin

Good regeneration but dependent of initial dose

- Single fraction – allmost full regeneration after 2 months
- High initial dose – increased time to regeneration ca 6 months



Supported by later trials
De Crevoisier et al. 1998;
Montebello et al. 1993;
Harms et al. 2004;
Tada et al. 2005;
Langendijk et al. 2006;
Würschmidt et al. 2008

Terry *et al.* (1989)

Early toxicity

Oral mucosa

Like skin in low dose regions

Earlier and more pronounced toxicity (incresed grade 3-4) if high previous dose

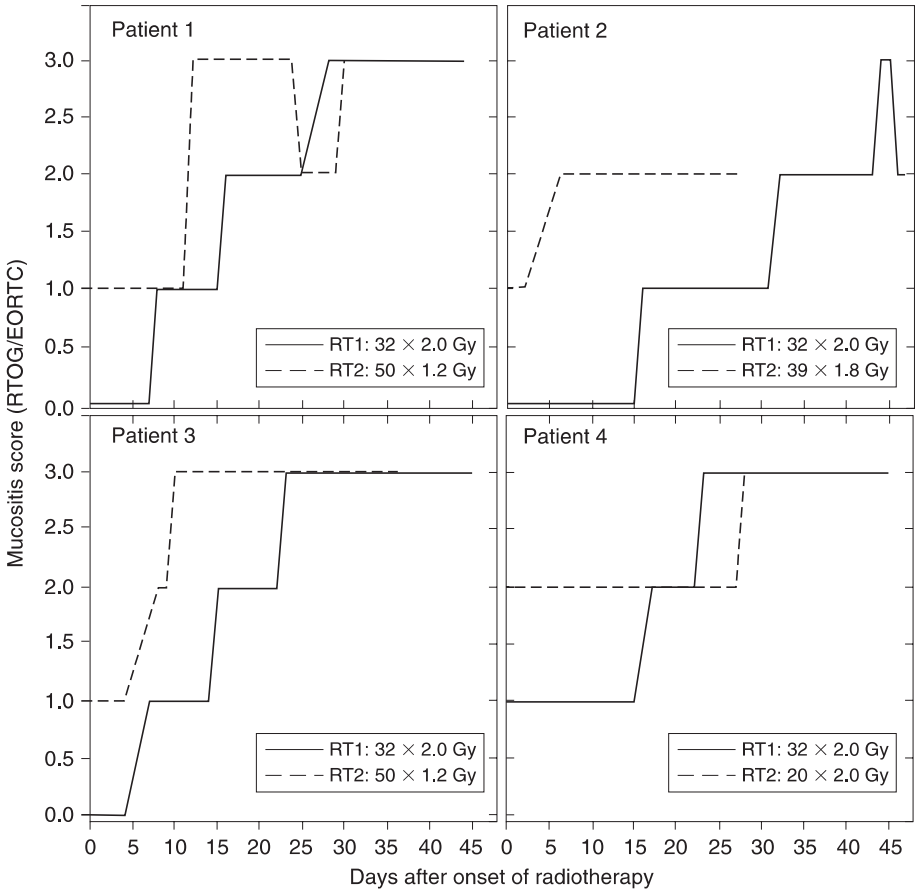


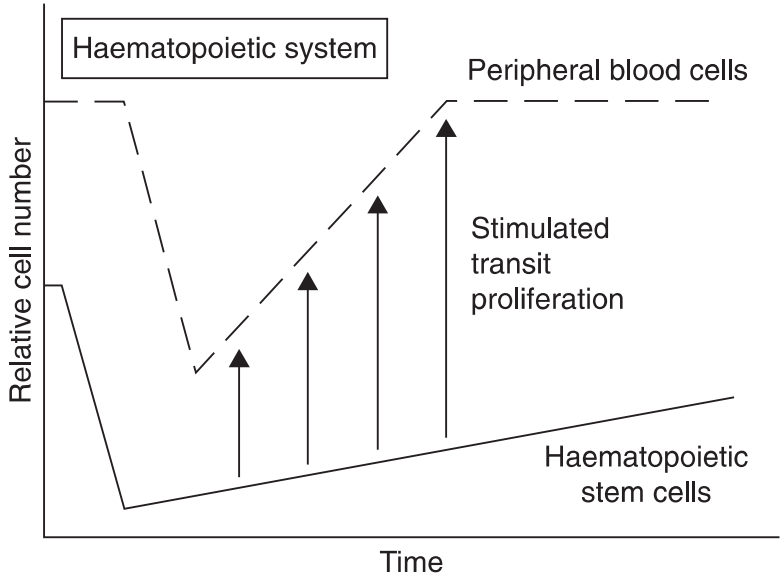
Figure 19.2 Clinical scores of oral mucositis according to Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) for four patients during their first course of radiotherapy (solid lines) and during re-irradiation (dashed lines). Dörr *et al.*, unpublished data.

Dörr *et al.;* Nieder, Langedijk 2011

Early toxicity

Bone marrow

- Highly correlated to toxicity at first RT
- Highly correlated to volumes previously treated, caution for previous whole body radiation (!)
- Effect more pronouced the younger the patient at first RT



Clinical basic Radiobiology 2009

Late toxicity

Skin

Tolerated EQD2
lowered by ca 50- 70%

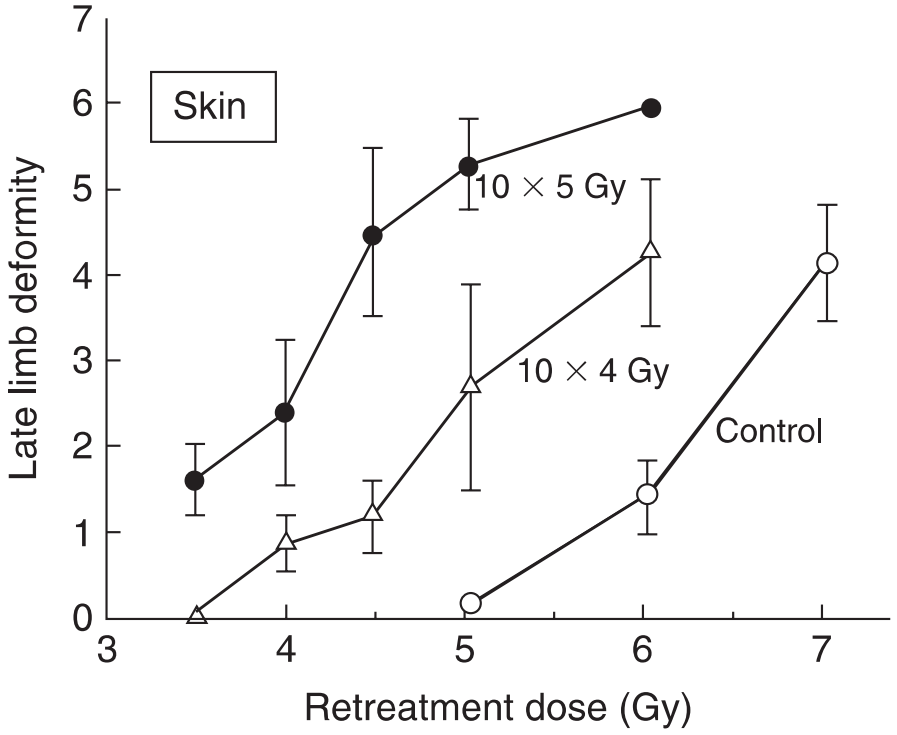


Figure 19.5 Retreatment tolerance for late hind-limb deformity in mice, as measured by fibrosis.

Brown and Probert (1975)

Late toxicity

Lung

Pneumonitis and fibrosis phase

Risk for pneumonitis reduced with lower dose per fraction

During fibrosis phase (>6mo) tendency to lower tolerance

High volume dependency for preserved function

Dose to the heart probably of importance

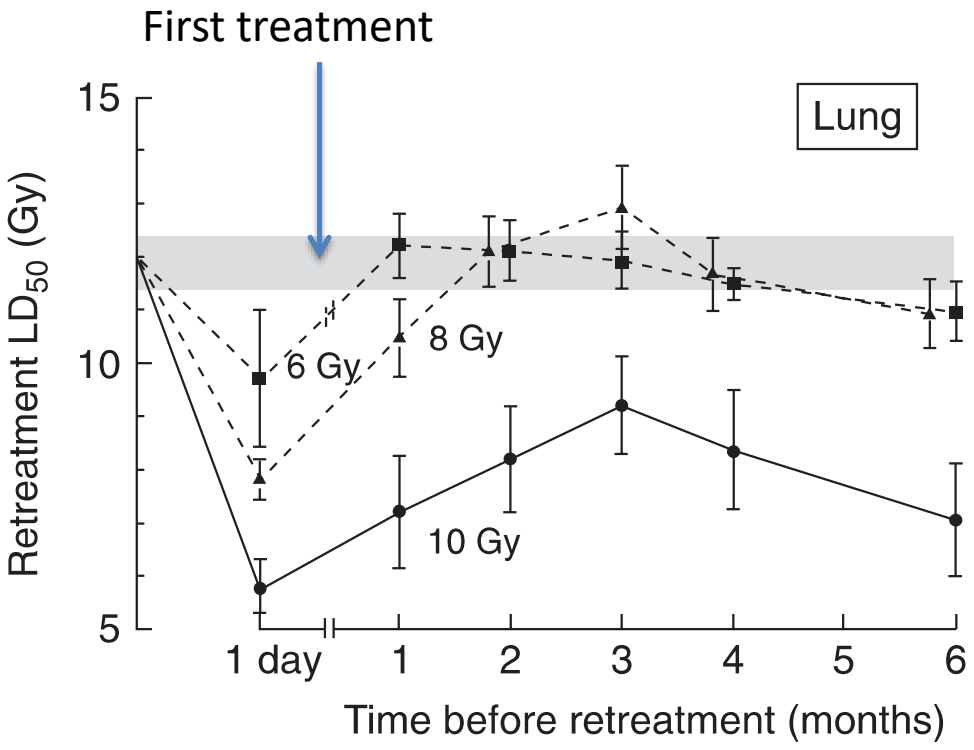


Figure 19.6 Retreatment tolerance of the mouse lung.

Terry *et al.* (1988)

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Late toxicity

Lung

The risk for pneumonitis seems to be limited at re-irradiation

Jackson and Ball 1987	22 patients, 20-30 Gy after previous 55 Gy (median) after 15 m (median) no symptomatic pneumonitis
Tada et al. 2005	15 patients, 50 Gy (median) after 50-60Gy 1 grade 3 pneumonitis, 3 grade 2 esophagitis

Late toxicity

Kidney

Very radiosensitive

Slowly progressive deterioration of function

Re-irradiation in the previous dose span of >14-18 Gy does not result in further loss of function

Significance of low doses?

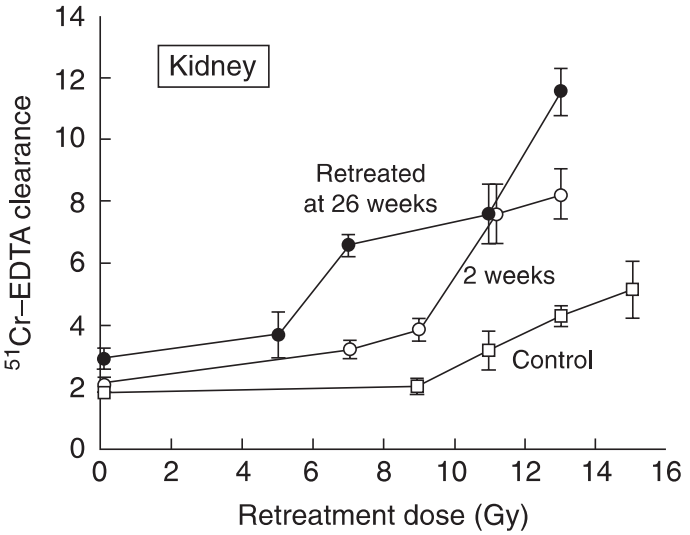

Figure 19.7 Dose–response curves for renal damage in mice at 35 weeks after re-irradiation. Retreatment was administered either 2 weeks (open circles) or 26 weeks (closed circles) after the initial treatment with 6 Gy. The response of age-matched control animals without previous irradiation (open squares) is also shown. Renal damage was worse for retreatment with the longer 26-week interval than for a shorter interval, indicating progression of subthreshold damage rather than recovery. From Stewart *et al.* (1989), with permission.

Stewart *et al.* (1989)

Late toxicity

Bladder

Mainly trials in animals – limited regeneration if symptomatic injury has occured

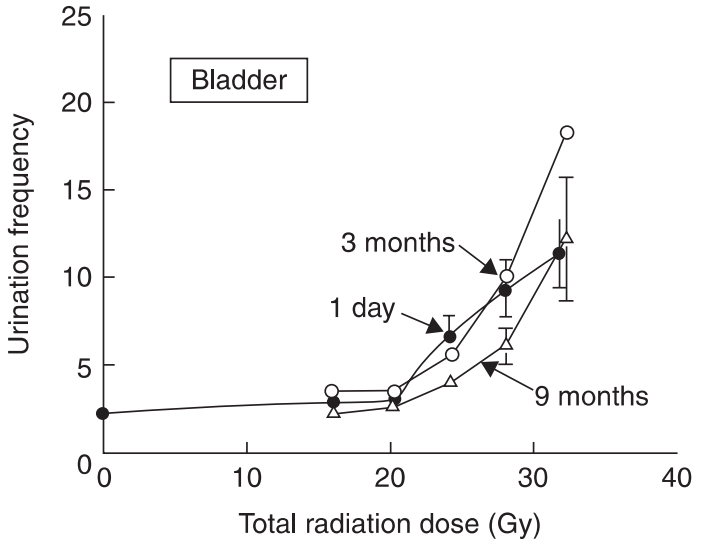

Figure 19.8 Dose–response curves for late urinary bladder damage in mice after irradiation with two doses separated by 1 day (closed circles), 3 months (open circles) or 9 months (open triangles). The total dose for a given effect did not increase with increasing time from first treatment. From Stewart *et al.* (1990), with permission.

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Late toxicity

Bowel

Lingareddy et al. 1997 — 52 pat 30 Gy after 50,4 Gy (median after 24m)+5Fu
grad 3-4 SAE: small bowel strictures 9 (17%),

cystitis

Generally good regeneration after > 6 months

Mohiu

A 50% reduction of tolerance should be considered

Haque et al. 2009 — 13 pat, 30 Gy after 45 Gy, no grade 3 SAE, 1 grade 4 bleeding

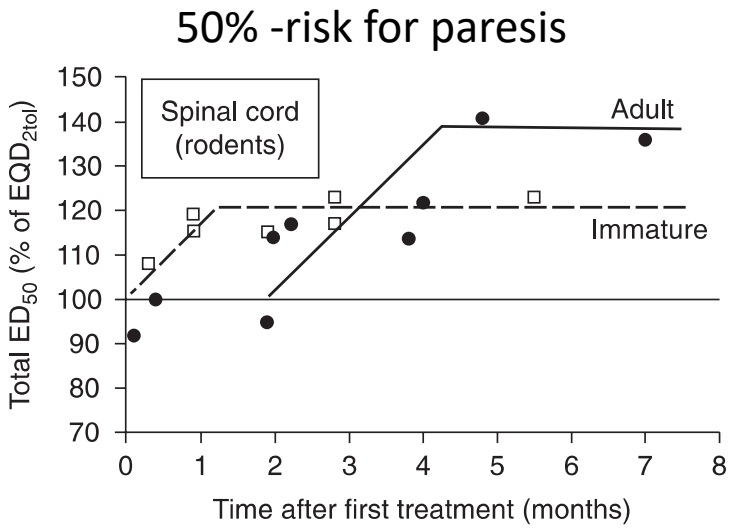
Late toxicity

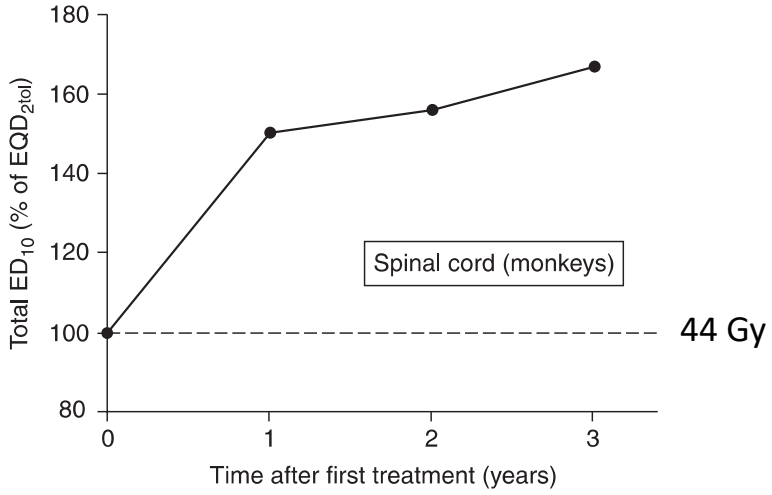
Medulla spinalis

Best studied

Data from animal- and clinical trials

Evidence of considerable long-term regeneration





Stewart *et al.* (1989); Ang *et al.* (2001)

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Late toxicity

Medulla spinalis

Data from clinical trials (man)

Kirkpatrick et al. 2010	46 Gy in 2-Gy fractions can be followed by 23–24 Gy in 2-Gy fractions (50% of tolerance dose) after 1 or 2 years

Verified by Schiff et al. 1995; Grosu et al. 2002 (palliative patients)

Magrini et al. 1990	30 Gy in 1.7 Gy fractions (plus chemo), after 1–3 years up to 40 Gy in 2 Gy fraktions (2–3 vertebral segments) – no myelopathy

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Late toxicity

Medulla spinals

Data from clinical trials (man)

Nieder et al. (2005b, 2006a) Prediction model

Damast et al. (2010)	retrospektive, pat previously recieving 30 Gy (palliative fractionated 4Gy/fr and doses of 14-16 Gy in the medulla without myelopathy (median FU 12m)

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Late toxicity

Brain

Basically no animal data

Data mainly from glioblastoma patients – short FU due to prognosis

Nieder et al. 2006b, 2008; Fogh et al. 2010	re-irradiation of glioblastoma, low toxicity
Flickinger et al. (1989)	9 patients, cumulative doses 70-89 Gy (EQD2), >5y FU, only one serious loss of vision
(Combs et al. 2005; Fogh et al. 2010)	30–40 Gy in fractions of <4 Gy low toxicity

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Late toxicity

Brain

SBRT/SRS

Shepherd et al. (1997)	5 fr/w, 5 Gy/fr after median dose of 55 Gy all total doses >40Gy Late toxicity 25% in patients with doses 30-40Gy
Shaw et al. 1996, 2000	SRS, 18 Gy for ≤20 mm, 15 Gy 21–30mm, 12 Gy för 31–40 mm, followed by dose escalation 156 pat, 36% previously 60 Gy, 64% previously 30 Gy intervall median 11 m radionecrosis in 5, 8, 9, 11% at 6, 12, 18, 24 month

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General

- Re-irradiation can be considered when the dose tolerance to the critical organs will not be exceeded
- Potential gain has to be weighted against the impact on the patients quality of life
- Re-irradiation trials – mainly heavily selected patients
- There is evidence of regeneration of several tissues after previous treatment
- Acute reacting tissues (skin, mucosa and even to some extent medulla) regenerate within months
- Late reacting tissues (kidney, heart, bladder) show little signs of regeneration
- Fibrosis, altered perfusion and late tissue damage in man can progress during years/decennia

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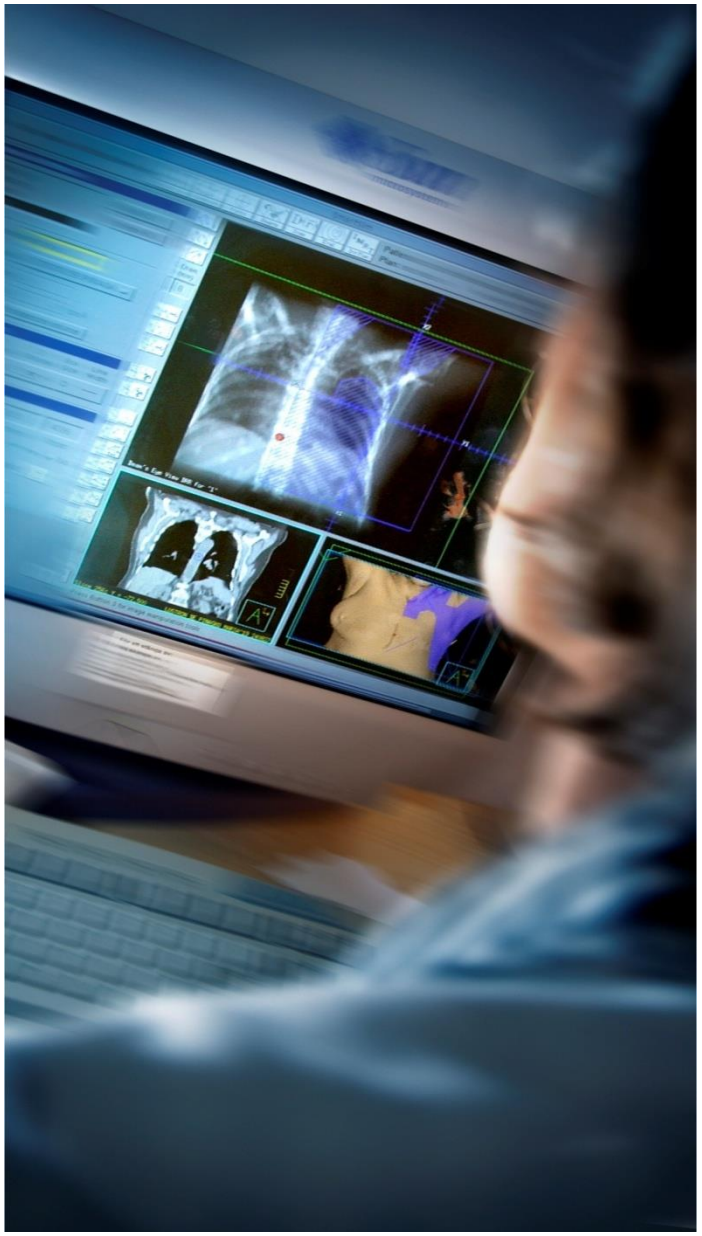
Re-irradiation

Clinical outcomes

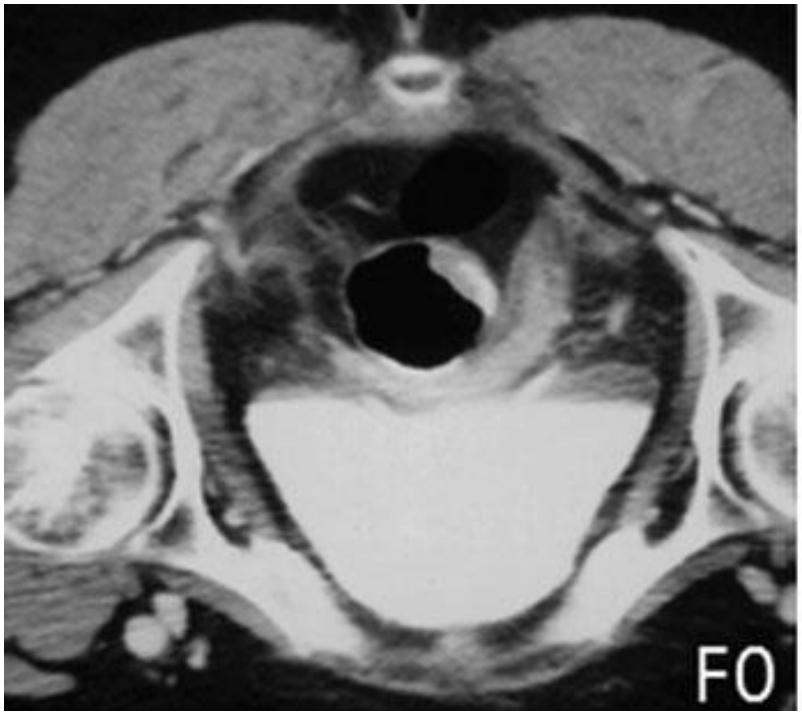


Pelvis

- Rectal cancer – local recurrence 4,4-11%
- Cervix cancer – pelvic or lymph node in up to 25%

Local recurrences – different growth pattern than primary (due to previous surgical removal of fascias) – most commonly pre-sacral growth

Restricted possibility for surgery – growth dependant



Following non-radical surgery <10% OS at 3 years and 0 at 5 (Suzuki et al. 1995)

Dresen et al. 2008

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Pelvis – rectal cancer

Table 1
Study characteristics, patient characteristics, and details of previous radiotherapy in the included studies.

Author and Publication year	Study design and Inclusion period	Reirradiat d N	Patient population	Age median, years (range)	Previous RT dose median, Gy (range)	Time since RT median, months (range)
Ng 2013 [25]	Retrospective 1997–2008	56	RC, previous pelvic RT[b] Curative $n = 13$, Palliative $n = 43$	69 (26–88)	50.4 Gy (21–64)	30 (8–176)
Sun 2012 [24]	Prospective 2004–2008	72	Recurrent irresectable RC	59 (29–78)	<50 Gy (NR)	25 (13–77)
Koom 2012 [23]	Retrospective 2000–2007	22	Recurrent RC	50 (33–64)	54 Gy (45–59.4)	26 (5–72)
Das 2010 [22]	Retrospective 2001–2005	50	RC, previous pelvic RT[c] Primary $n = 2$, Recurrent $n = 48$	60 (32–80)	47 Gy (25–70)	28 (5–354)
Valentini 2006 [21]	Prospective phase II 1997–2001	59	Recurrent RC No extrapelvic disease	62 (43–77)	50.4 Gy (30–55)	27 (9–106)
Mohiuddin 2002 [19]	NR[a] 1987–2000	103	Recurrent RC	65 (31–79)	50.4 Gy (30–74)	19 (2–86)
Valentini 1999 [20]	Prospective 1989–1997	13 (subgroup	Recurrent RC No metastases	NR	NR (27–59)	NR
Lingareddy 1997 [18]	NR[a] 1987–1993	52	Recurrent RC Palliative $n = 52$	65 (37–79)	50.4 Gy (40–70.2)	24 (3–86)
Mohiuddin 1997 [17]	NR[a] 1987–1992	39	Recurrent RC Curative $n = 39$	61 (31–77)	50.4 Gy (40–45) boost up to 66	18 (3–456)
Mohiuddin 1993 [16]	Phase I/II pilot 1987–1991	32	Recurrent RC Curative $n = 17$, Palliative $n = 15$	60 (31–79)	45 Gy (30–66)	Curative: 8 (3–456) Palliative: 27 (3–79)

NR = not reported in original publication; RC = rectal cancer; RT = radiotherapy.
[a] Reirradiation program.
[b] Previous RT for other cancer (7%); prostate $n = 3$, endometrial $n = 1$.
[c] Previous RT for other cancer (14%); cervical $n = 2$, prostate $n = 2$, bladder $n = 1$.

Ten ”reasonable” trials. Limited amount of patients. Previously mainly “long”. Both gyno- and rectal cancer patients, Ng oligometastatic patients.

Pelvis – rectal cancer

Over time

Increased dose per fraction, increased total dose, reduced volumes, kept 5-Fu

Table 2
Reirradiaton treatment.

Author and	Planned RT regimen	Reirradiation	Treatment volume	Technique	Cumulative	Concomitant
	6–20 Gy[b] (n = 43) or 1.8 Gy/30.6 Gy + boost 6–20 Gy	(15–49.2)	GTV + 2–4 cm Boost: GTV + 2 cm	3-field	(70.6–108)	
	1.8 Gy/30 Gy ± boost 10 Gy (n = 15)					

- Generally hyper fractionated, to 30-40 Gy
- R0 resection in 39–89% of operated patients
- Local recurrence in 50% of operated patients
- Median OS 39 – 60 months of operated patients, 12 - 16 months in palliative cases
- Palliative patients had good and lasting effect
- Complete or partial symptomatic control in 83% to 94%
- Rectal bleeding ceased in 100%

Bid: two fractions daily; GTV: gross tumour volume; CTV: clinical target volume; PTV: planning target volume; 3-field: 1 posterior and 2 lateral fields.
3DCRT: 3-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; 5-FU: 5-fluorouracil; MMC: Mitomycin C; NR: not reported.

[a] Total dose 39 Gy if time since previous RT ⩾ 1 year, 30 Gy if time since previous RT < 1 year.
[b] Higher boost dose if >1 year interval from initial RT.
[c] Boost if >1 year from initial RT.

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Pelvis – rectal cancer - toxicity

Toxicity decreases with volume (both grade and frequency)

Acute and late toxicity after reirradiation.

Author year	Acute toxicity[a] grade 3 or 4	Treatment break or termination (toxicity)	Late toxicity, *n*
Ng 2013 [25]	Skin 5% Gastrointestinal 9% Mucositis 2%	Termination 4%	Infection/abscess/drainage/discharge 4/12, fistula 1/12, urinary infection/retention 2/12, small bowel obstruction 1/12, delayed wound healing 1/12, skin ulceration 1/43
Sun 2012 [24]	Diarrhoea 10% Granulocytopenia 8%	Termination 4%	Skin fibrosis 4/72, urinary incontinence/dysuria 4/72, small bowel obstruction 1/72
Koom 2012 [23]	Diarrhoea 9%	–	Grade 3–4 toxicity 8/22 – small bowel obstruction, fistula, urinary stricture, haematologic
Das 2010 [22]	Nausea/vomiting 4%	–	Grade 3 toxicity 12/50 – small bowel obstruction, wound complication, abscess, fistula, ureteral stricture/leakage, haemorrhage, joint disease, nausea Grade 4 toxicity 1/50 – cystitis
Valentini 2006 [21]	Gastrointestinal 5%	Break 10% Termination 3%	Skin fibrosis 2/59, impotence 2/59, urinary incontinence/dysuria 2/59, small bowel obstruction 1/59
Mohiuddin 2002 [19]	Diarrhoea 20% Moist desquamation 8% Mucositis 4%	Break 22% Termination 15%	Diarrhoea 8/103, small bowel obstruction 15/103, fistula (recurrence) 4/103, skin ulceration 2/103
Valentini 1999 [20]	Haematologic/ diarrhoea 8% (same patient)	–	
Lingareddy 1997 [18]	Diarrhoea 19% Perineal skin breakdown 8% Mucositis 4%	Break/termination 31%	Small bowel obstruction 9/52, cystitis 3/52, fistula 4/52, skin ulceration 1/52
Mohiuddin 1997 [17]	Diarrhoea 13% Moist desquamation 10% Mucositis 5% Delayed wound healing 6%	Break 18% Termination 13%	Chronic diarrhoea 3/39, small bowel obstruction 6/39, fistula (recurrence) 3/39, coloanal stricture 2/6
Mohiuddin 1993 [16]	Diarrhoea 13% Skin reaction 13% Pelvic abscess 6%	–	Delayed wound healing 2/17, small bowel obstruction 1/17, coloanal stricture 1/5

[a] Toxicity scored by Common Toxicity Criteria (CTC) or RTOG score.

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Pelvis - gynocological

Recent trials – brachy

- Mahantshetty et al. (2014) 30 patients central recurrences, brachy alone; 76% CR och 52% OS efter 2 år; LC (52% >42Gy vs 34% < 42 Gy (P 1⁄4 0.05)); grade ≥3 SAE 20%

- Martinez-Monge et al. (2014), 2 year LC 71.5%, grade ≥3 SAE 20%

- Mabuchi et al. (2014) LC 67% in 52 patients; grade ≥3 SAE 25%

- Liu et al.(2016) Cumulative dose: median total 2cc (EQD3) bladder 86 Gy, rectum 72 Gy, sigmoid 70 Gy. Median tumour dose (EQD210) of D90 52Gy and D100 28 Gy, CR in 38% and PR in 44%

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Pelvis

Table 2 Suggested re-irradiation fractionation schedules

Location of recurrence	Radical dose/fractionation schedules (highly conformal techniques)	Palliative—high dose palliative dose/ fractionation schedules
Pelvic side-wall recurrence	EBRT 50 Gy/25 fx 45 Gy/25 fx 40 Gy/20 fx	EBRT 40 Gy/20 fx 25–30 Gy/10–15 fx
Vaginal-vault recurrence	EBRT + brachytherapy 50 Gy/25 fx 40 Gy/20 fx +brachy to total dose 65–75 Gy	EBRT 40 Gy/20 fx 30 Gy/20 fx
	EBRT alone 45 Gy/25 fx 40 Gy/20 fx	Brachytherapy alone 20–25 Gy HDR/3 fx
	Brachytherapy alone 35–50 Gy LDR over 4–6 days 20–25 Gy HDR/4–5 fx BID over 2–2.5 days	

Nieder, Langedijk 2011

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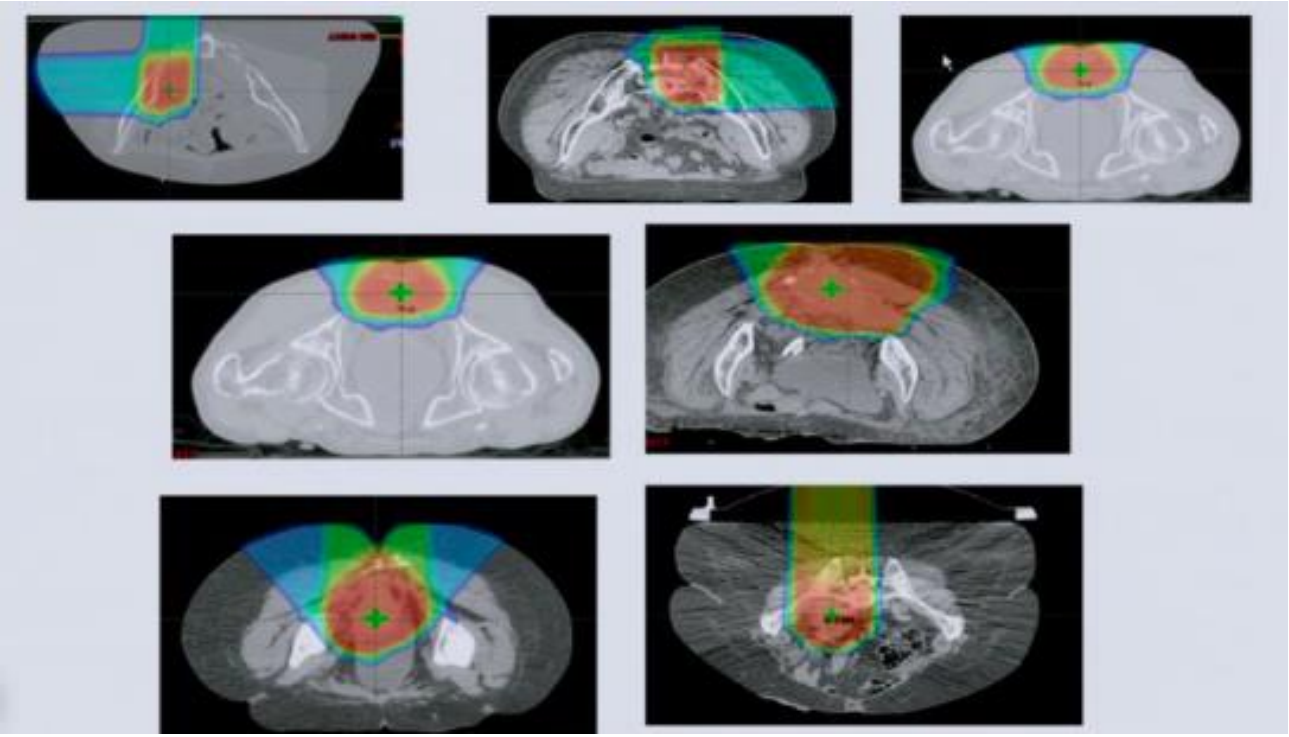
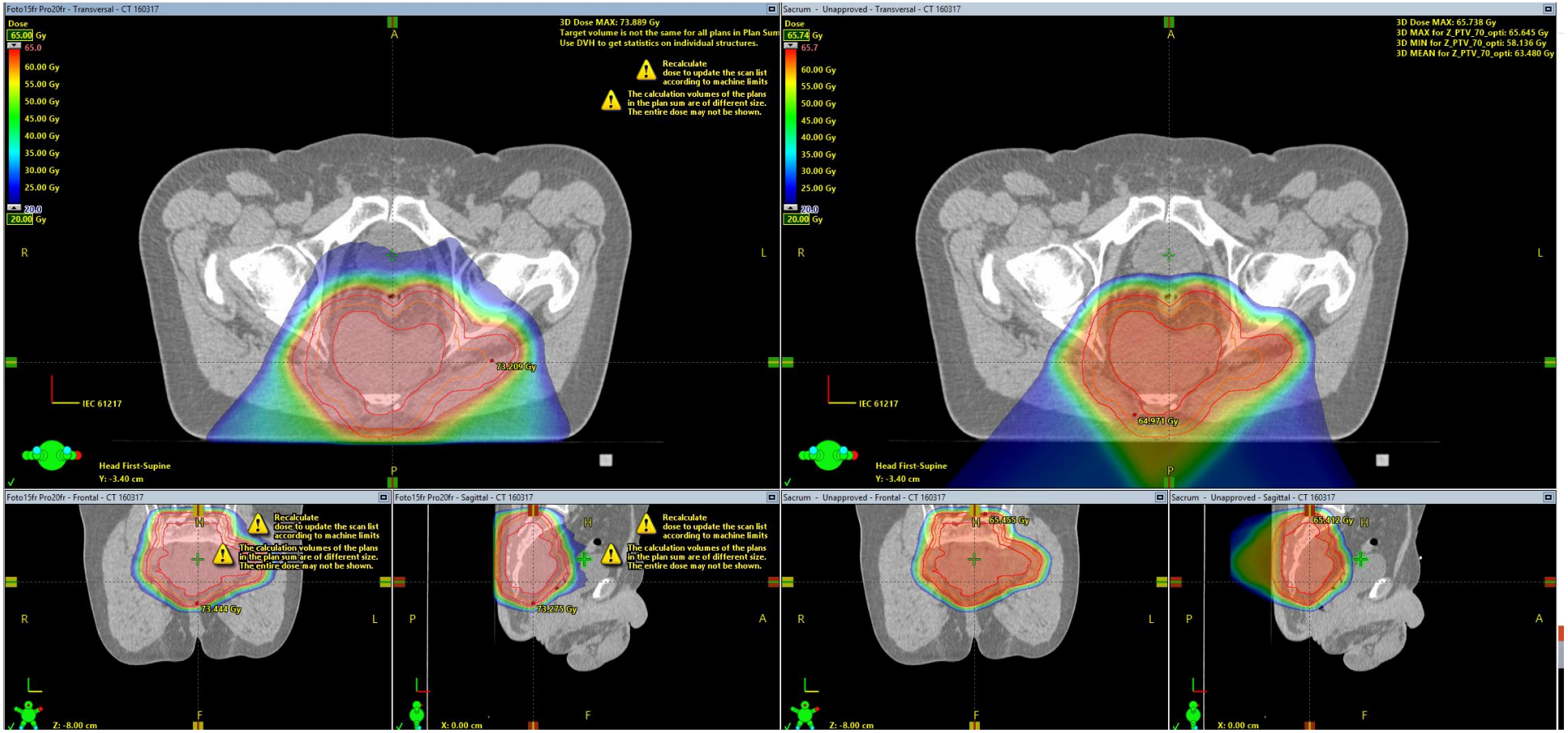
Pelvis

Re-irradiation in the pelvis median 66 Gy (RBE) (45-76)



Pelvis – proton/photon combined



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Lung

Recurrence site (distal, regional, local)

>6,000 patients with local recurrence, **reoperation possible 1–1.7%**

23% 2-year OS (Pairolero et al. 1984), later trials 15,5% 5-year OS (Voltolini et al. 2000)

In previously operated patients – high dose RT standard (Nieder, Langedijk 2011, Jeremic and Bamberg (2002)) OS 28.5m and 5-y survival 31.5%

RT after RT – limited amount of trials, ca 300 patients, cumulative doses 43 - 150 Gy

Palliative cases control of haemoptysis 83%, cough 65%, dyspnoea 60%, pain 64%

Table 3
Subgroup analysis according to localization of patients with grade ⩾ 2 toxicity.

	SBRT	ΔT (months)	$EQD_{2,}$ mean to CTV ($\alpha/\beta = 10$)	$EQD_{2,}$ to PTV ($\alpha/\beta = 3$)	CTV (cm^3)	PTV (cm^3)	FU (months)	Potential FU (months)
Peripheral ($n = 13$)	1		109 (56–163)	108 (78–162)	8 (1–259)	38 (15–461)		
	2	15 (5–54)	109 (84–163)	108 (52–162)	14 (1–28)	55 (16–160)	23 (4–97)	25 (6–97)
Central ($n = 8$)	1		104 (84–163)	90 (88–162)	69 (3–461)	156 (21–750)		
	2	26 (9–48)	99 (98–163)	96 (78–162)	43 (2–242)	107 (31–242)	10 (1–46)	11 (1–46)

Re-irradiation with SBRT

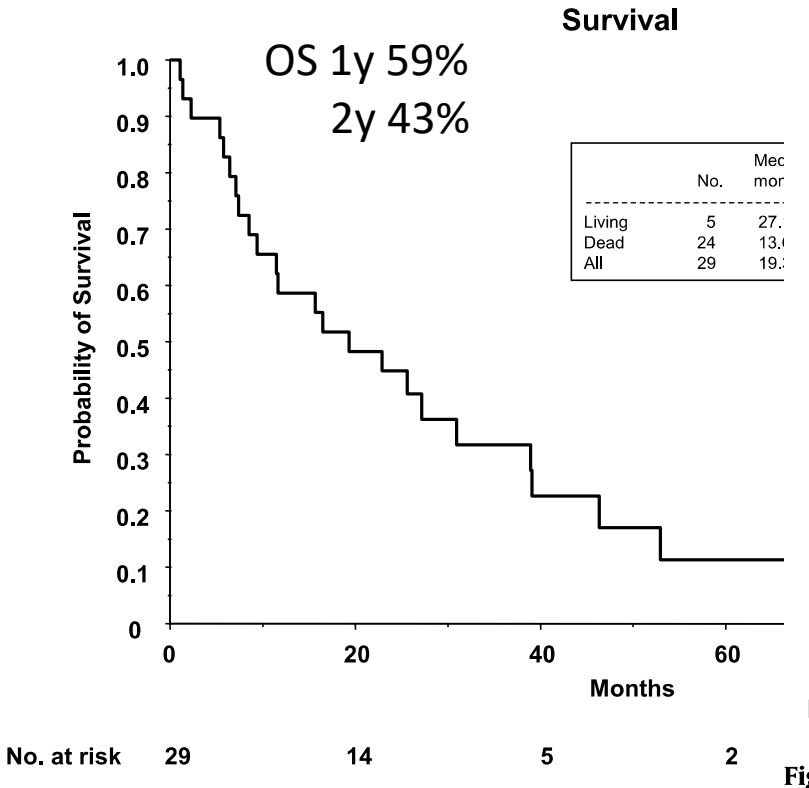

Fig. 2. Kaplan–Meier overall survival.

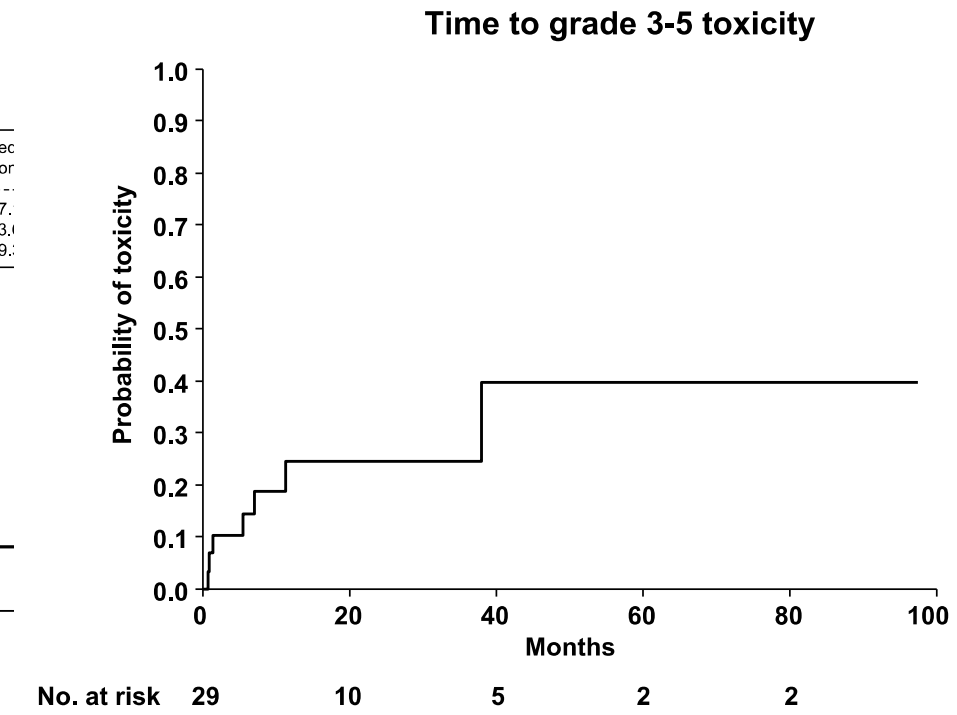

Fig. 1. Kaplan–Meier time to first occurrence of grade 3–5 toxicity after reirradiation. Patients were censored for date of death, date of third irradiation or last follow up date.

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Tolerance – plexus brachialis

Chen et al 2017

43 patients, cumulative dose to plexus 60-150 Gy

Symptoms (12 patients):

- Ipsilateral pain (54%)
- Anaesthesia (31%)
- Motor impact (15%)

1-year freedom of symptoms

67% cumulative Dmax >95 Gy

86% cumulative Dmax <95 Gy

(P=.05)

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Tolerance – esophagus

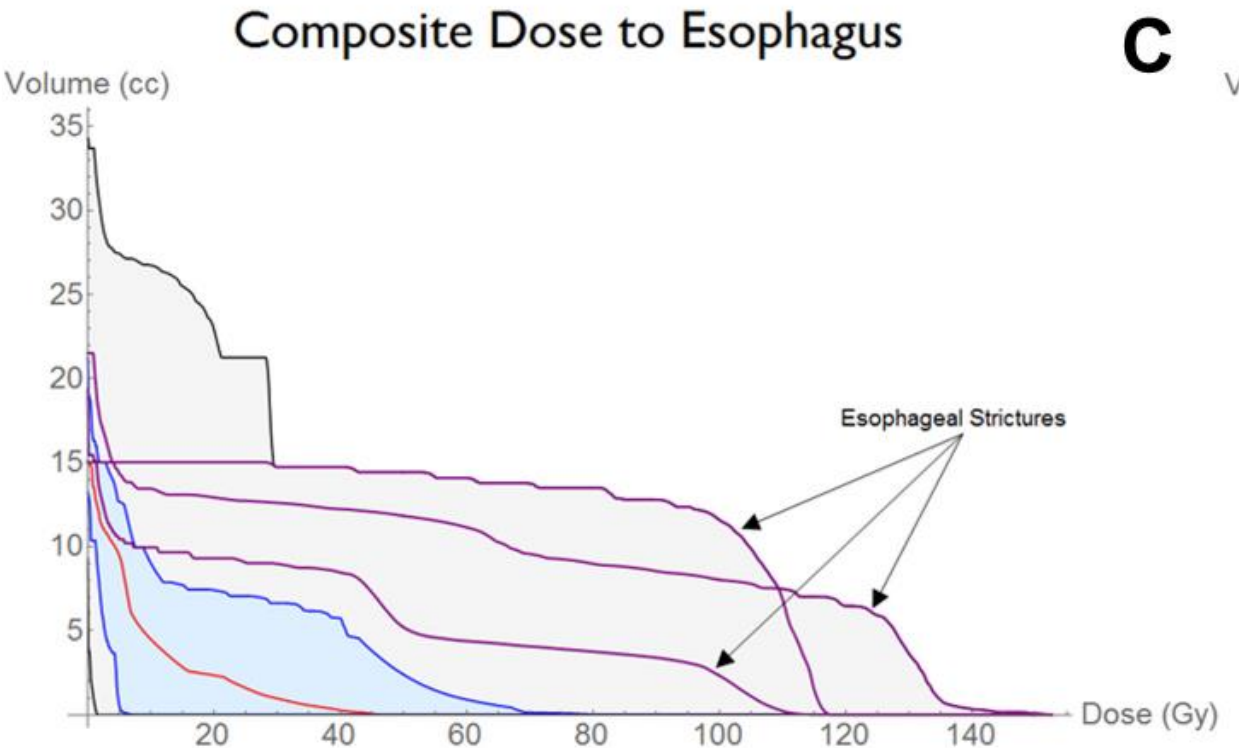
Table II. Results and adverse events in salvage radiotherapy.

Patient ID	KPS score at re-RT (%)	Prescription dose and fractionation	Chemotherapy, no. of cycles	Response to re-RT	Acute hematological AEs, grade	Acute non-hematological AEs, grade	Late AEs	Time to second recurrence from re-RT (months)	Site of second recurrence
A	90	45 Gy, 1.8 Gy/fr (once daily)	NDP 64 mg/m^2+ S-1 100 mg/body, 4	PR	Leukopenia G4, anemia G3, thrombocytopenia G3	Mucositis G1	Dysphagia G1, pleural effusion G1, pneumonitis G1	6	Mt
B	90	50.4 Gy, 1.2 Gy/fr (twice daily)	NDP 80 mg/m^2+ S-1 120 mg/body, 4	CR	Leukopenia G3, anemia G2, thrombocytopenia G1	Dermatitis G1 dysphagia G1	Dysphagia G1, pleural effusion G2	15.6	SMLN, thoracic vertebra (T9)
C	90	50.4 Gy, 1.2 Gy/fr (twice daily)	NDP 64 mg/m^2+ S-1 100 mg/body, 4	CR	Leukopenia G2, anemia G2, thrombocytopenia G2	Mucositis G1 fatigue G2	Pneumonitis G1	30.4	Ut
D	90	50 Gy, 2 Gy/fr (once daily)	NDP 80 mg/m^2 + S-1 120 mg/body, 4	PD	Leukopenia G3, anemia G3, thrombocytopenia G1	Mucositis G1 fatigue G1	NE	NE	NE
E	90	30 Gy, 1.5 Gy/fr (twice daily)	None	PR	Leukopenia G1, anemia G2, thrombocytopenia G1	Mucositis G1 dysphagia G1	Hypothyroidism G2 dysphagia G3, pleural effusion G1	11.5	Lung
F	80	30 Gy, 1.2 Gy/fr (twice daily: Total 18 Gy) + 2 Gy/fr (once daily: Total 12 Gy)	NDP 80 mg/m^2 + S-1 100 mg/body, 1	PD	Leukopenia G1, anemia G2, thrombocytopenia G1	Mucositis G1 nausea G2	NE	NE	NE

Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; DWD, dead with disease; re-RT, re-irradiation; SMLN, superior mediastinal lymph node; AEs, adverse events; NE, not evaluable; KPS, Karnofsky Performance Status; CR, complete response; PR, partial response; PD, progressive disease.

Katano et al. 2017

Tolerance – esophagus



Garg et al. 2016

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Head-neck

>30 000 patients with HN-tumours

20% second cancer

80% in HN, lung or esophagus

Hashibe *et al.*, 2005

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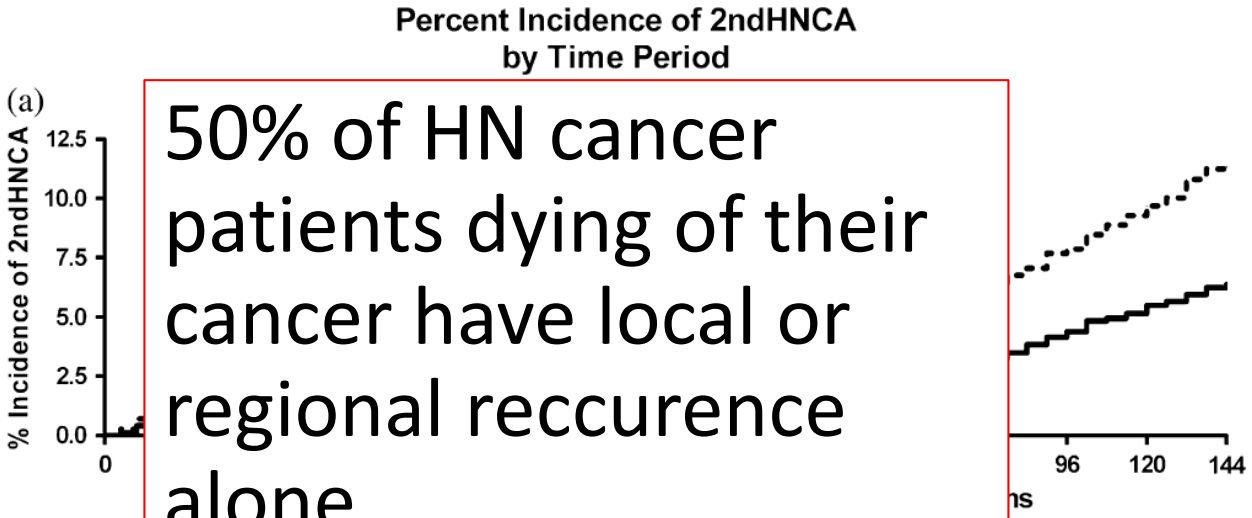
Head-neck



50% of HN cancer patients dying of their cancer have local or regional reccurence alone

Fig. 2. Percent incide … omparing patients treated with and without radiothe… from 1988 to 1997.

Rusthoven *et al.*, 2008

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Head-neck

Taussky et al. Head and Neck 2005

Retrospective analysis 75 patients with locoregional reccurrence after RT +/- chemo for H&N cancer.

- 17(23%) salvage surgery
- Median survival after reccurrence 44 months efter salvage surgery vs. 11 months if no surgery (p=0.001)

Table 2. Reasons for not operating (*n* = 58, multiple answers possible).

Reasons for not undergoing salvage surgery	No. (%)
Unresectable disease	25 (43%)
Poor health status/age	21 (30%)
Patient refusal	6 (8%)
Metastasis and simultaneous local recurrence	6 (8%)
Rapid disease progression/intercurrent death	3 (5%)
Not clear	8 (11%)

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Head-neck – salvage surgery

Temam et al.

- 16/69 recurrence of oropharyngeal cancer after RT had surgical salvage.
- 3-year OS 20%, 5-year OS 11% for those with surgery

McLaughlin et al. Head and Neck 1996.

- 23/26 LR Laryngeal cancer after RT for T1-2 SCC glottic larynx.
- 59% had no recurrent cancer for at least 2 years after surgery.

Parsons et al. IJROBP 1995.

- 30/46 LR after RT for SCC of the SGL had salvage surgery. 50% with no recurrence in first 2 years.
- 5-year OS 20% for all LR, 29% for those with salvage surgery.

Generally DFS ≈36% after 2 years and OS ≈36% after 5 years

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Head-neck – re-irradiation

Salama et al. IJROBP 2006 (Chicago)

- 115 patients with loco regional recurrences after RT
- 49 surgery followed by CRT
- 66 CRT only
- Large variation in doses and volumes
- Spinal cord och brainstem dose max 50 Gy from both treatments
- No constraints to soft tissue, bone and vessels
- 2Gy/d or 1.5 Gy BID

Head-neck – re-irradiation

Salama et al. IJROBP 2006 (Chicago)

Outcomes

- Median composite RT dose 131 Gy
- Median FU 67.4 months
- Median OS 11 months, 3-year OS 22%
- 3-year LR controll 51%

Toxicity

- 19 patients died due to treatment induced toxicity (median 7 months efter treatment)
- 9 patients died during CRT and 10 after completing

Table 7. Grade 4–5 complications*

Complication	*n*
Carotid hemorrhage	6
Osteoradionecrosis	13
Brain necrosis	0
Myelopathy	1
Peripheral neuropathy	1

* Using common terminology criteria for adverse events.

Head-neck

Langer et al. JCO 2007
RTOG 99-11

- 105 patients (23% second primary, 40% oropharynx). Median previous dose 65.4 Gy, median RT interval 40 months
- 1.5 Gy BID till 60 Gy med Cisplatin/Taxol
- Median FU 23.6 months
- Median Survival 12.1 months
- 2-y OS 25.9%
- Grad >= 4 toxicity 28%
- osteoradionekrosis 4%
- 8 Grad 5 tox (5 acute and 3 late – 2 carotid blowout)

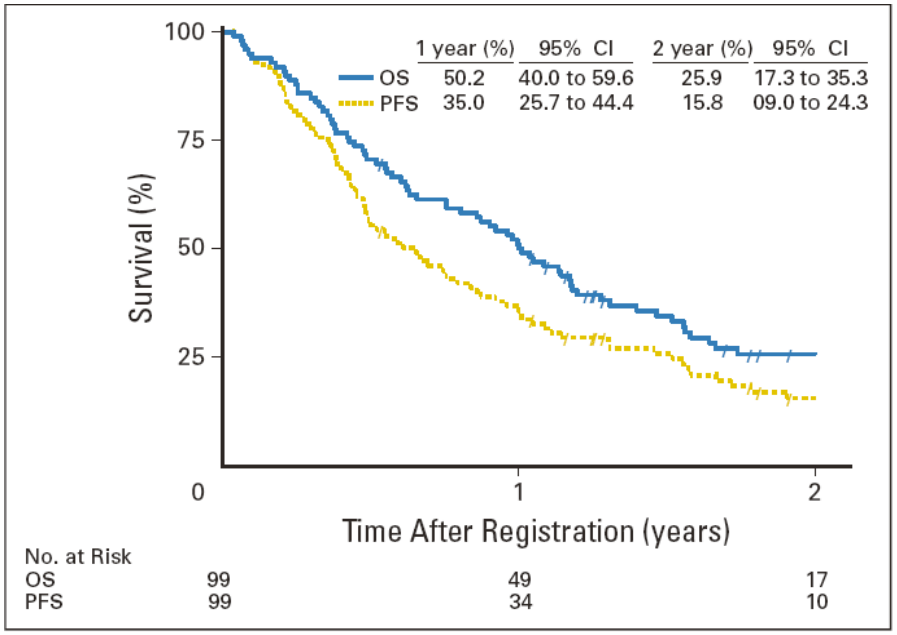


Fig 1. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) for Radiation Therapy Oncology Group protocol 9911.

RTOG 04-21 attempt to randomise patients between chemo alone and CRT failed due to poor recruitment

Tolerans – carotis

Risk for blow-out

6 months

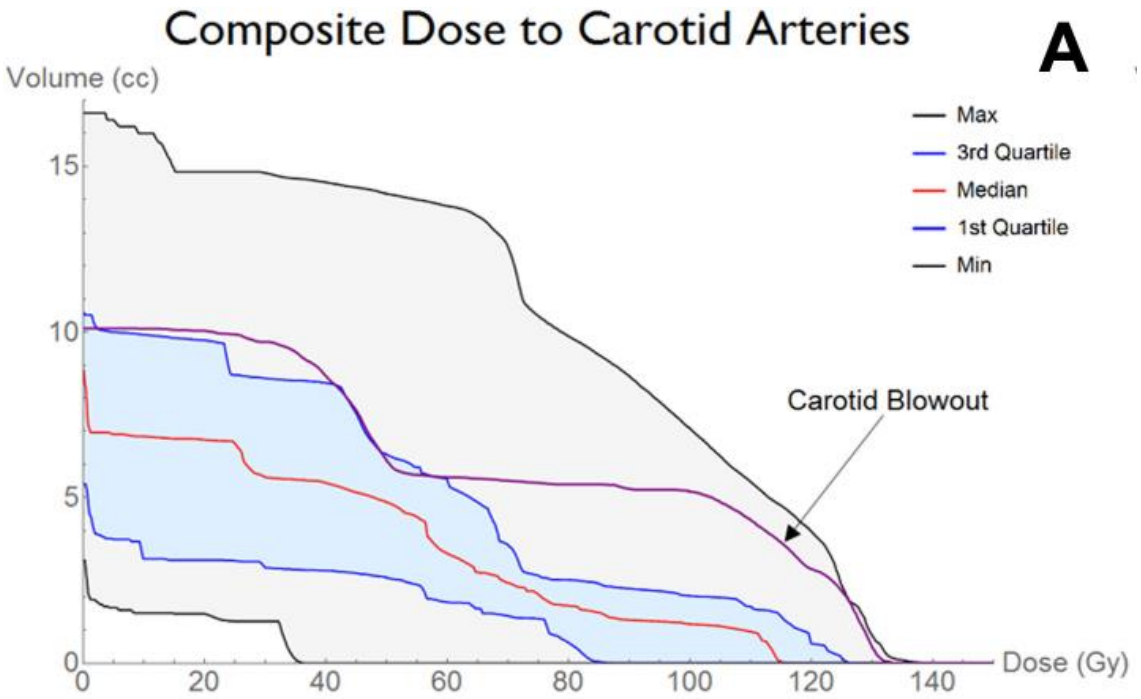
4,6% < 120 Gy

13,3%>120 Gy

12 moths

5,9% < 120 Gy

25% > 120 Gy



Garg et al. 2016

Head-neck

Janot et al. JCO 2008

CRT vs. BSC/other medical treatment

Significant advantage in DFS and LC, but not OS

- 28% Grade 3-4 acute tox (RT-arm)
- 3 early and 2 late treatment related deaths

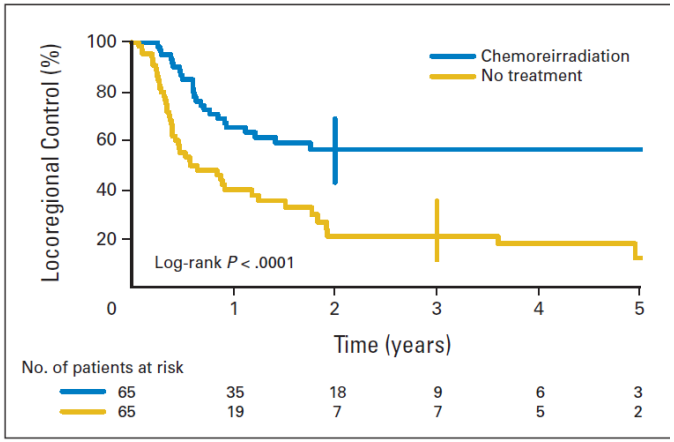


Fig 2. Locoregional control. Large tick marks represent the 95% CI of the point estimates. Chemoirradiation, reirradiation plus concomitant chemotherapy.

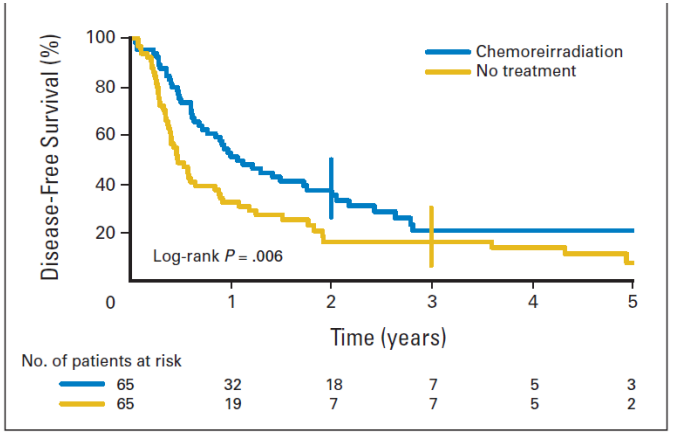


Fig 3. Disease-free survival. Large tick marks represent the 95% CI of the point estimates. Chemoirradiation, reirradiation plus concomitant chemotherapy.

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Head-neck

Table 2 IMRT Reirradiation Studies for Recurrent Second Primaries in the Head and Neck

Study	Number of Patients	RT Regimen (Chemotherapy)	Median OS (Median Follow-Up) in Months	1-Year Survival (%)	Toxicity, % (Number of Patients)
Sulman et al[13]	78	Median RT dose 60 Gy (49% CT)	28 (NR)	75	Acute + late: 20 (15) grade 3-5 Deaths:1 (1) unspecified
Lee et al[14]	105 (74 IMRT)	Median RT dose 59.4 Gy (74% CT)	25 (35)	56	Acute Gr (3) 23 (24) Late Gr ¾: 11 (12)
Popovtzer[15]	66	Median RT dose 64 Gy (71% CT)	(42)	40%; 2-year OS	Acute ≥3: 6 (4); 2 deaths Late ≥3: 29 (19)
Zwicker et al[16]	38	Median RT dose 49 Gy (50% concurrent CT)	17 (NR)	63	Acute: 6 (2) grade 4 Late: 21 (8) grade 0-3 Deaths: 0
Sher et al[17]	35	Median RT dose 60 Gy	23 (28)	59	Acute: 91 (32) grade 3-4 and 14 (5) grade 4 Late: 46 (16) grade 3-5
Goldstein et al[18]	41	Median RT dose 61.1 Gy (curative) 54.5 Gy (palliative)			l fatal bleed ade 3 or 4:
Chen et al[19]	21	Median RT dose 66 Gy			ity: NR

Lee et al. IJROBP 2007

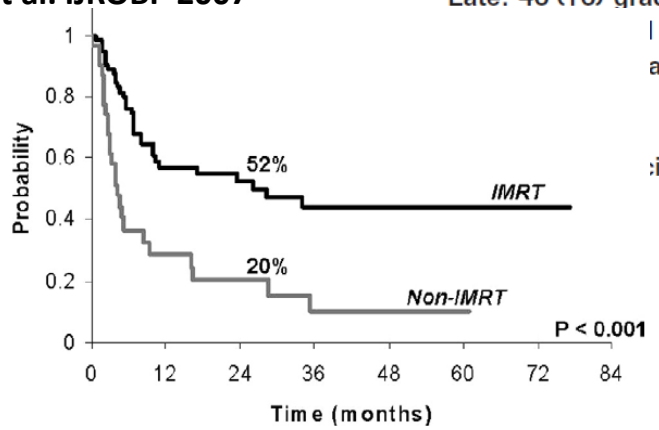

Fig. 3. Kaplan-Meier estimate of 2-year locoregional progression-free probabilities for intensity-modulated radiation therapy (IMRT) vs. nonintensity-modulated radiation therapy patients.

Wang et al. Seminars in Radiation Oncology 2012

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Head-neck

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

Refining Patient Selection for Reirradiation of

- 7 centres - 412 patients
- Median dos re-IMRT 60 Gy (overlap with previous >40Gy), concomitant chemo 44%
- Median RT-interval 2.4 years
- Grade ≥3 19%, grade ≥4 4,4% and grade 5 1,2% (acute toxicity)
- 2-års cumulative incidence of grade ≥3 late toxicity 14.2%

Table 2 Toxicity

Acute events*	n	% Yes	First late event	n
Grade 2 aspiration	17	5	FT dependence >1 year	15
Grade 3 aspiration	12	3	Esophageal stricture dilation	14
Tracheostomy use†	2	1	Aspiration pneumonia	11
Feeding tube‡	23	11	Osteoradionecrosis	8
Stricture	2	1	Carotid blowout	3
Neutropenic fever	6	2	Other late toxicity	2
Wound/soft tissue necrosis	13	4	New feeding tube placement	2
Other grade ≥3	19	5	Fistula	1
Overall grade ≥3 acute	68	19.1	Total	56
Overall grade ≥4 acute	18	4.4	Cumulative incidence late toxicity at 2 years§	14.2%
Overall grade 5 acute	5	1.2	Multiple late events	7 of 56 (13%)

Abbreviation: FT = feeding tube.

* Acute rates calculated as a crude proportion of patients with complete toxicity data available on all endpoints (n=358).

† In patients who did not undergo laryngectomy and a tracheostomy was not placed prior to re-irradiation.

‡ Omitting pre-existing feeding tube dependence.

§ Cumulative incidence of late toxicity calculated using Gray's method accounting for competing risks of recurrence or death.

Head-neck

Most common causes of death

- Loco regional and distal progression 70%
- 14 carotid blowout of which 9 due to tumour progression
- Time to blowout median 2,4 years (4mån-11,7 years)

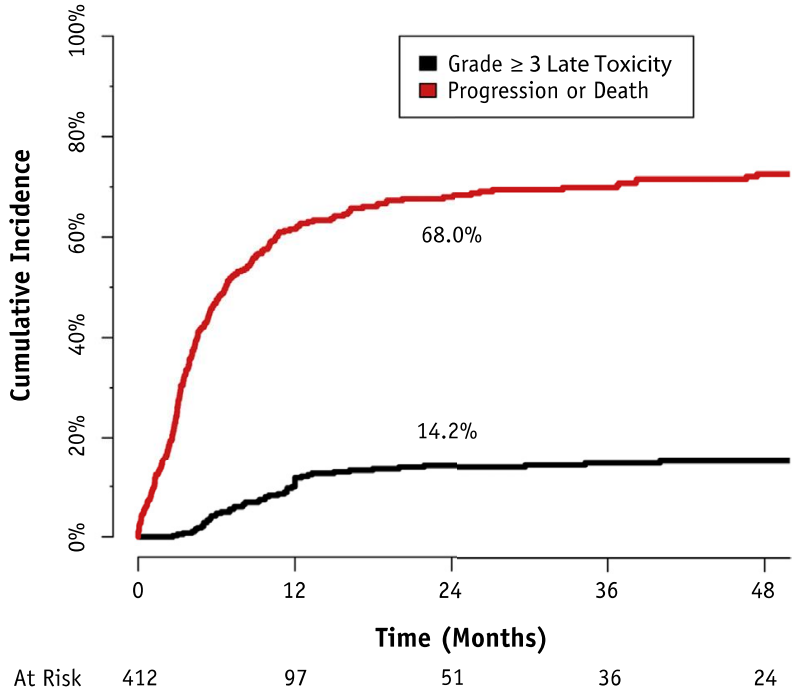

Fig. 2. Cumulative incidence of grade ≥3 late toxicity.

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Head-neck

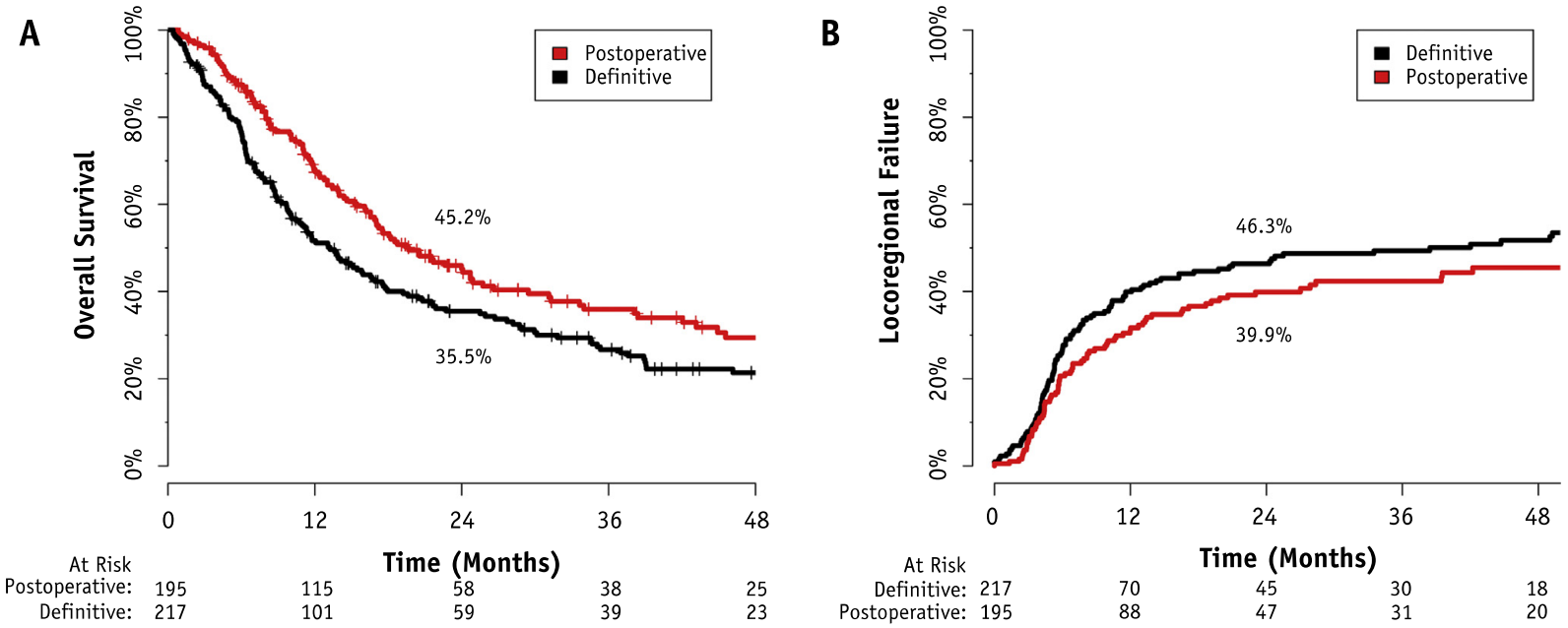
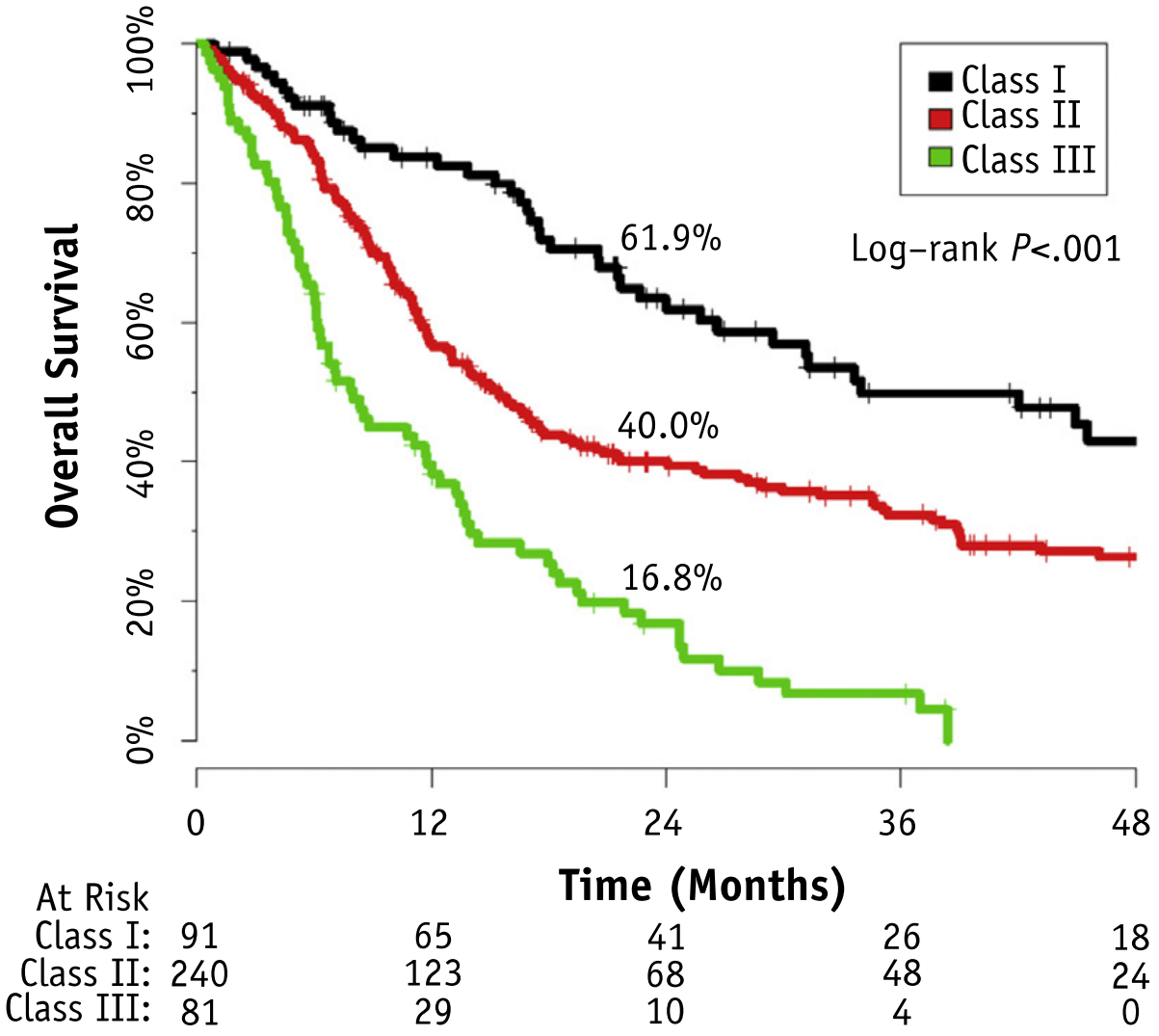


Fig. 1. (A) Overall survival and (B) locoregional failure stratified by use of surgery.

Median OS all patients 16.5 months and 2-year OS 40.0%


Overall Survival
100%
80%
60%
40%
20%
0%
Class I
Class II
Class III
61.9%
40.0%
16.8%
Log–rank P<.001
0
12
24
36
48
Time (Months)
At Risk
Class I: 91 65 41 26 18
Class II: 240 123 68 48 24
Class III: 81 29 10 4 0

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Head-neck

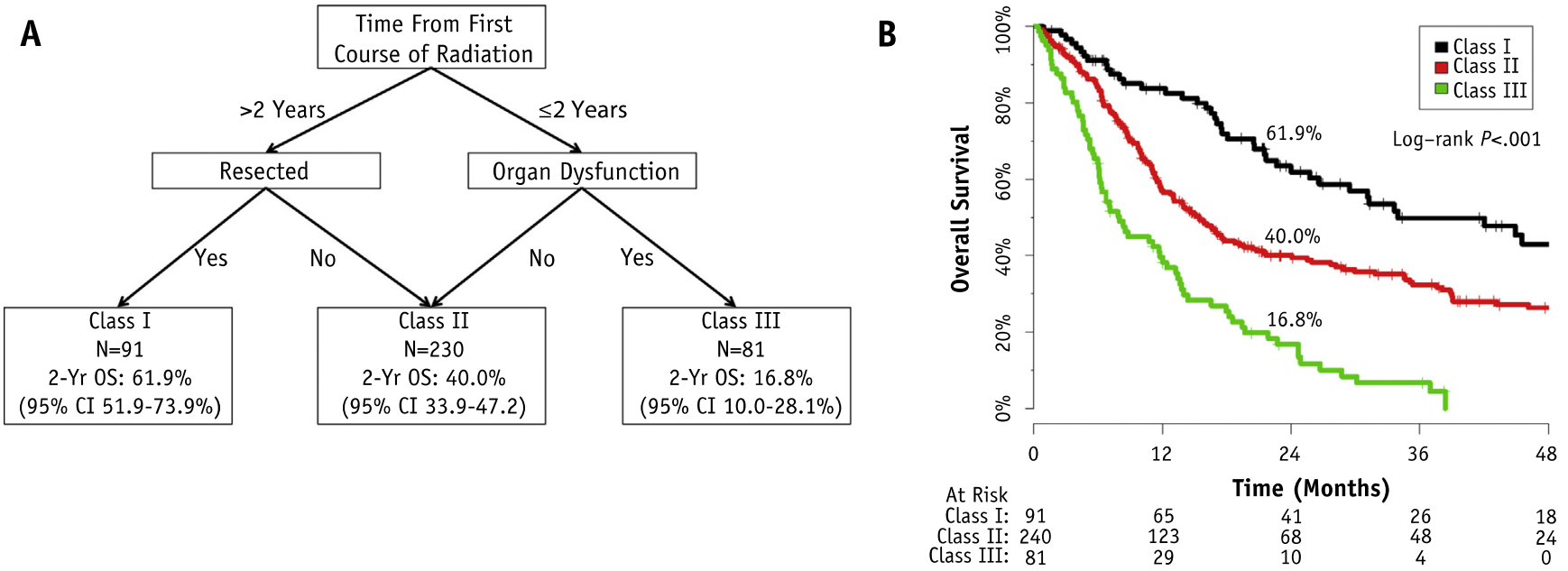
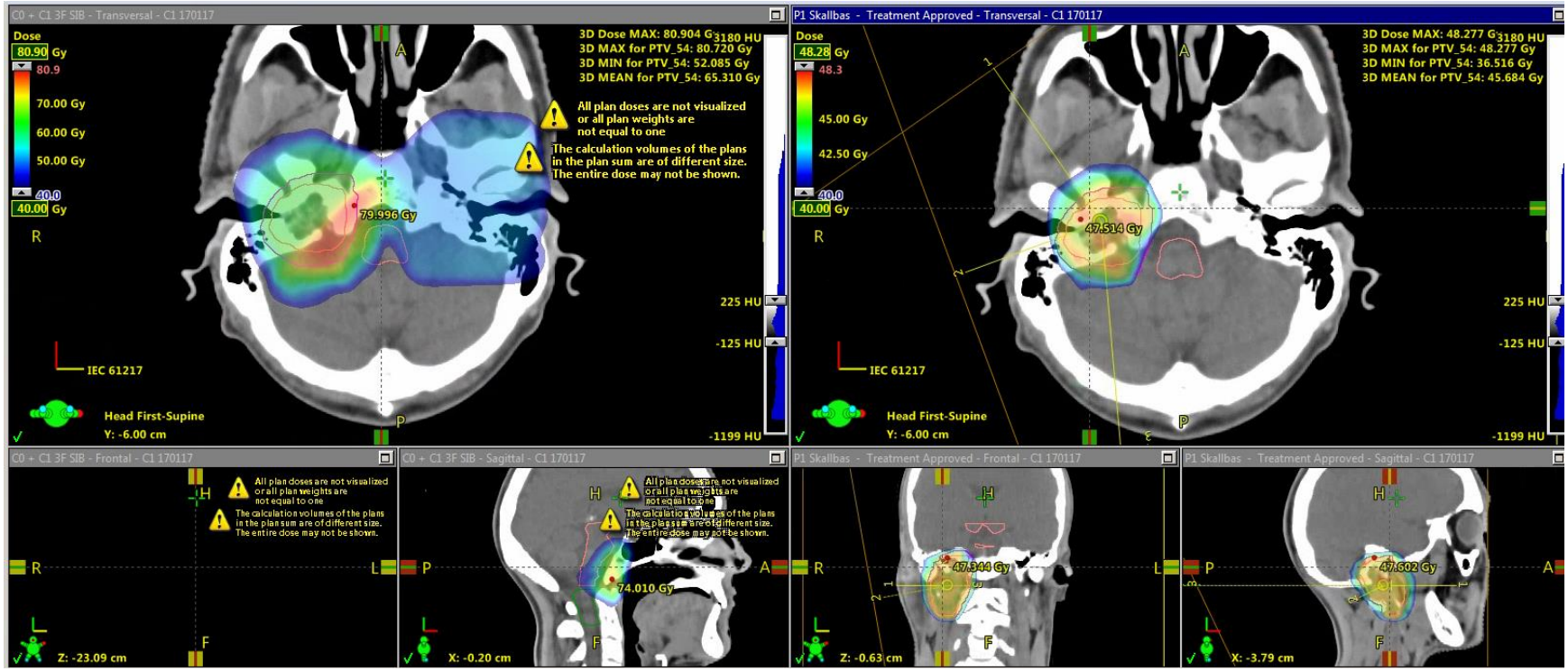


Fig. 3. (A) Recursive partitioning analysis (RPA) for overall survival. *Abbreviations:* OS = overall survival; CI = confidence interval. Organ dysfunction defined as pretreatment dependence on a feeding tube or tracheostomy. (B) Kaplan-Meier curves for overall survival separated by RPA class.

Head-neck - protons



Thank you