

Re-re-irradiation

What do we know about it?

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**SWEDISH NATIONAL COMMITTEE FOR
RADIATION PROTECTION RESEARCH**
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Critical Review

Preserving the legacy of reirradiation: A narrative review of historical publications

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- **Hoffman WJ, Carver LF. Chronic myelogenous leukemia. JAMA 1931;97:836-40.**

“Remarkable symptomatic improvement lasting up to one year after repeated cycles of low doses of radiation to the spleen or spleen plus long bones”

Aus der Universitäts-Hals-Nasen-Ohrenklinik zu Jena
(Direktor: Prof. Dr. J. Zange)

**Die Komplikationen der Röntgenbestrahlung von
Kehlkopfkarzinomen durch Tumorperichondritis
und Bestrahlungserichondritis und über die Frage
der Strahlenschädigung von Knochengewebe¹**

Von
Dozent Dr. Fritz Zöllner
Oberarzt der Klinik

Published in *Strahlentherapie* 1941

- **Fatal complications after 3, 5 and 6 series for head and neck cancer**
- **Soft tissue and chondronecrosis; soft tissue & chondronecrosis plus osteomyelitis; aspiration pneumonia due to laryngeal dysfunction**

Cancer. 1974 Aug;34(2):257-61.

Rapid fractionation technique and re-treatment of cerebral metastases by irradiation.

Shehata WM, Hendrickson FR, Hindo WA.

- **WBRT, 81 patients with different primary tumors**
- **12 were retreated twice and 3 received a total of 4 series**
- **10-Gy single dose or 2-5 fractions (one week)**
- **No details reported**
- **Clinical benefit was reported after the first, second and third course in 69, 68 and 50% of the patients, respectively**
- **Mean duration of improvement was 1.8, 2.6 and 1.5 months, respectively**

From bench to beside?

- **Preclinical research**
- **Phase I clinical trial**
- **Phase II clinical trial**
- **Phase III clinical trial**
- **Evidence-based re-irradiation regimens**
- **Different EBRT fractionation concepts**
- **HDR brachytherapy, protons, carbon ions**
- **Combination with cytotoxic chemotherapy, immunotherapy, hyperthermia...**

Preclinical data – repair/recovery

Extent and kinetics of recovery of occult spinal cord injury

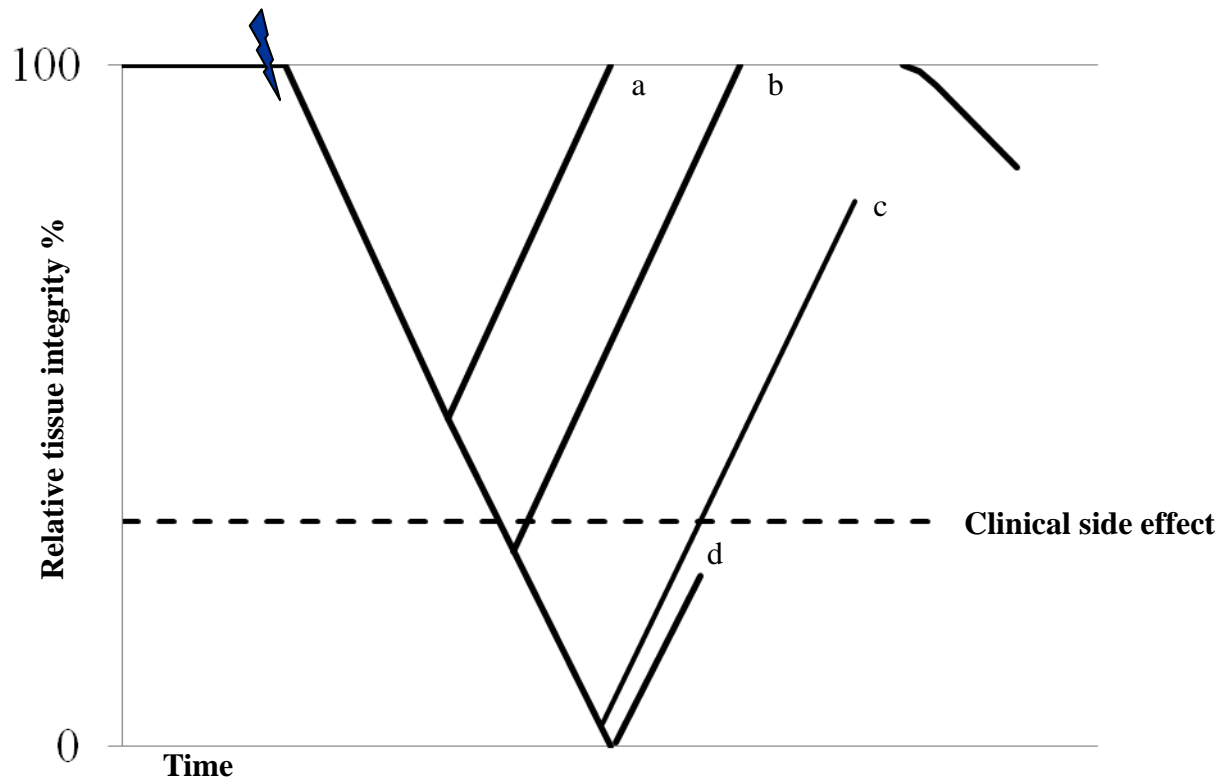
K.Kian Ang, M.D., Guo-Liang Jiang, M.D., Yan Feng, M.D., L.Clifton Stephens, Susan L Tucker, Ph.D. and Roger E Price

International Journal of Radiation Oncology * Biology * Physics
[Volume 50, Issue 4, Pages 1013-1020](#) (July 2001)

- **Rhesus monkeys: 2.2 Gy per fraction, total 44 Gy, cervicothoracic cord, interval 1-3 years, cumulative dose 84-110 Gy, approximately 60% of the initial dose «disappears» within 1 year, up to 75% within 2 years**

Repair and recovery

- **Experimental animal data: certain organs „forget“ previous irradiation if this did not result in severe damage („recovery from occult damage“)**

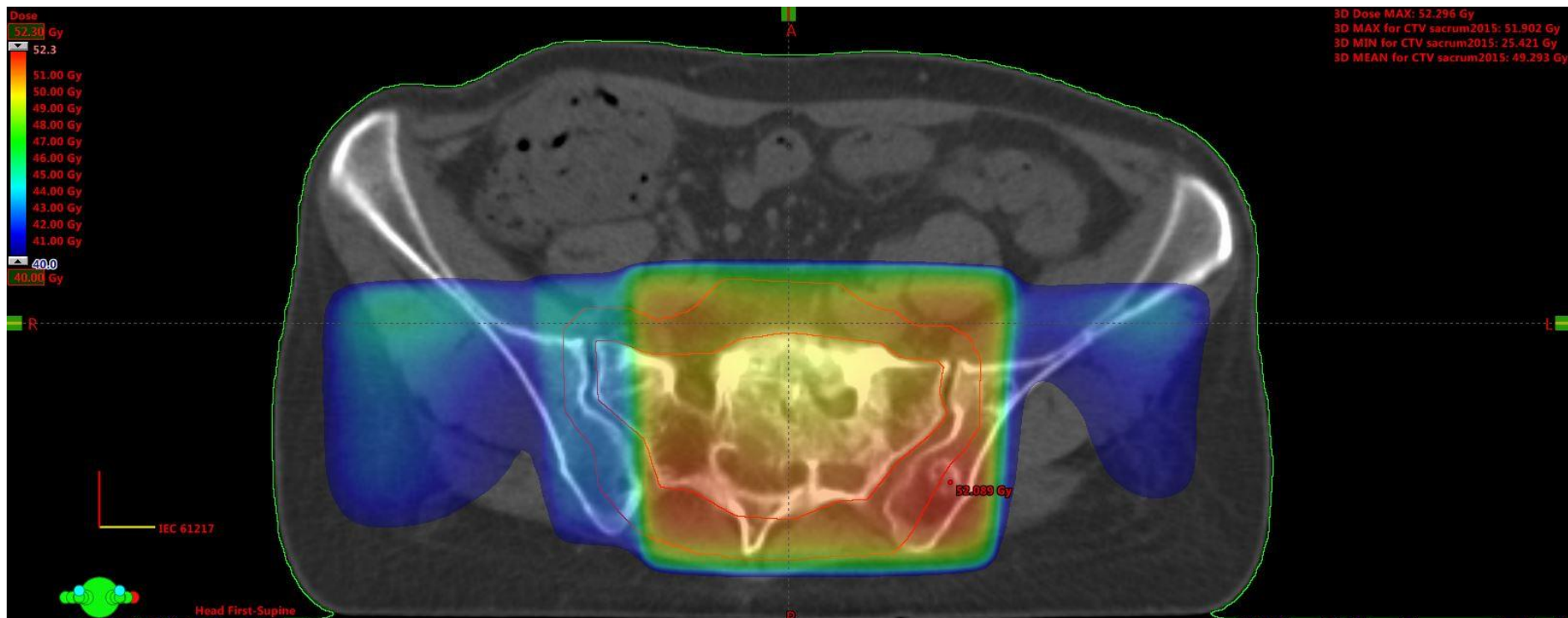


Female patient with painful sacral bone metastases from breast cancer

June 2011: single posterior field (no 3-D plan) 30 Gy in 10 fractions of 3 Gy

February 2012: 3-D conformal plan, same regimen

January 2015: 3-D conformal plan, 20 Gy in 8 fractions of 2.5 Gy



Course	Dose	EQD2 (3 Gy)	Recovery	EQD2 re
1	30 (3)	36	25% after 6-12 mo.	27
2	30 (3)	36	50% after >12 mo.	18
3	20 (2.5)	22		22

Sum EQD2 for all 3 courses (alpha/beta 3 Gy) = 94 Gy

Residual EQD2 taking into account recovery = 67 Gy

More than 2.5 years of follow-up without clinically evident toxicity

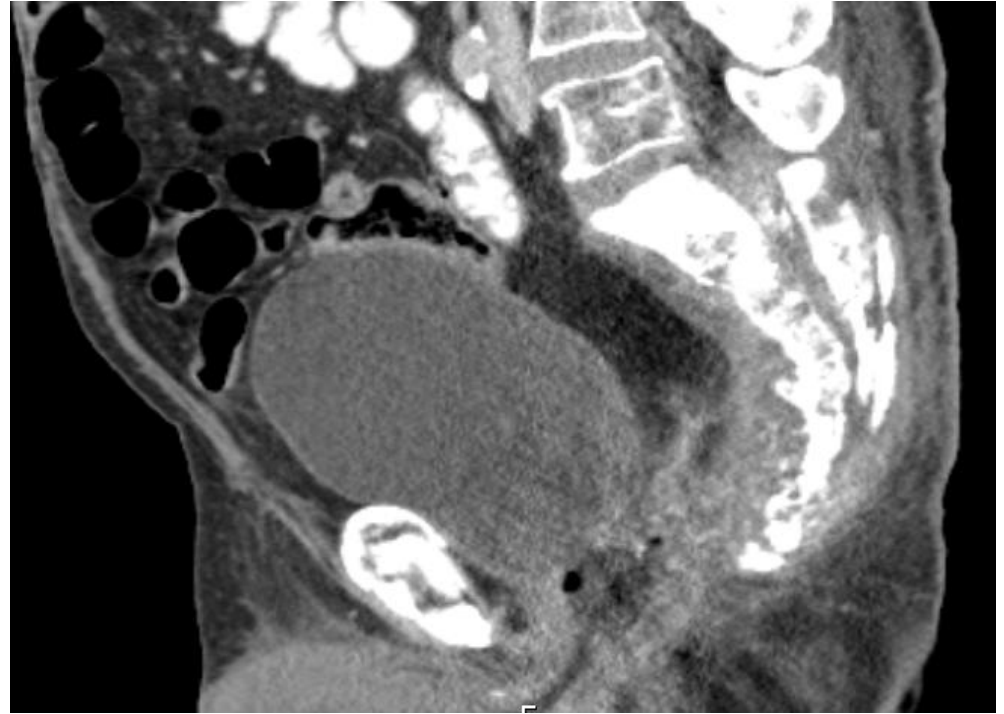
Pelvic reirradiation case (1)

- **79-year-old gentleman treated with abdominoperineal resection 4 years earlier, rectal cancer T3 N0 with lymphovascular invasion and 1mm margin to the peritoneal surface**
- **June 2008, 60 Gy in 2-Gy fractions, capecitabine**
- **Good clinical and CEA response, opted against surgery**
- **July 2009, 50.4 Gy in 1.8-Gy fractions, capecitabine**
- **Lung metastases, limited prognosis**
- **January 2012, 30 Gy in 2.5-Gy fractions**

Pelvic reirradiation case (2)



2008



2012

**Maximum dose for sacral nerves
was EQD2 142 Gy (residual
EQD2 87 Gy)**


Evidence based re-irradiation regimes

All published randomized clinical studies 2000-2017

- **Bone metastases fractionation (8 Gy vs. 20 Gy)**
- **Postoperative RCT vs. observation (H&N)**
- **Palliative RCT vs. CT (H&N), failed to accrue**
- **Nasopharynx ca fractionation (convent. vs. hypofr.)**
- **Nasopharynx ca RCT vs. RT**
- **Nasopharynx ca dose escalation (70-74-78 Gy)**
- **Breast cancer skin met. fractionation (conv. vs. hypofr.)**
- **Brachytherapy vs. EBRT (H&N), 2014 (64 pat. only)**
- **Glioblastoma RT vs. RT + APG-101**



Repeat reirradiation of the spinal cord: multi-national expert treatment recommendations

Carsten Nieder^{1,2}  · Laurie E. Gaspar³ · Dirk De Ruyscher⁴ · Matthias Guckenberger⁵ · Minesh P. Mehta⁶ · Chad G. Rusthoven³ · Arjun Sahgal⁷ · Eleni Gkika⁸

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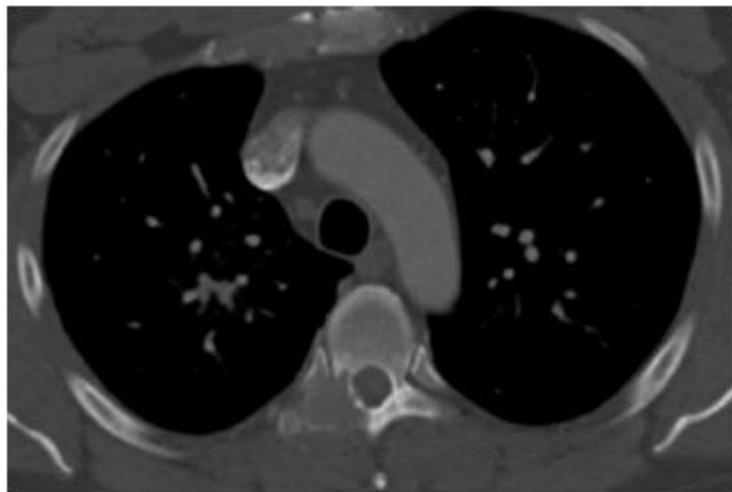


Fig. 1 Axial computed tomography (CT) imaging (2010), demonstrating a spinal metastasis in vertebra Th5 (processus transversus)

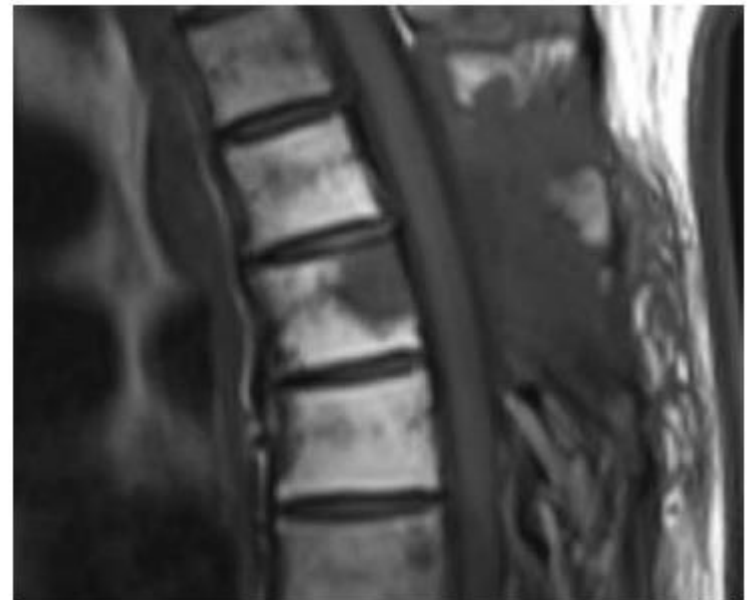


Fig. 3 Magnetic resonance imaging (MRI) obtained in 2014. Radiologically, the metastasis now involved the spinal body, too. The distance to the spinal cord was 3 mm. Postoperative changes after decompression/hemilaminectomy were present. T1 TSE sequence

Course	Dose	EQD2 (2 Gy)	Recovery	EQD2 re
1	30 (3)	37.5	50% after >12 mo.	18.75
2	30 (3)	37.5	50% after >12 mo.	18.75
3	?	?		

**Sum EQD2 for 2 previous courses (alpha/beta 2 Gy) =
75 Gy**

Residual EQD2 taking into account recovery = 37.5 Gy

Sahgal A, Ma L, Weinberg V, et al. Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;82:107-16.

- **SBRT given at least 5 months after conventional palliative radiotherapy with a reirradiation thecal sac P(max) EQD2 of 20-25 Gy appears to be safe provided the total P(max) EQD2 does not exceed approximately 70 Gy, and the SBRT thecal sac P(max) EQD2 comprises no more than approximately 50% of the total nBED**

Table 1 Treatment recommendation

Participant	Treatment concept	Total dose, dose per fraction, number of fractions, fractions per week	Dose prescription	Planning aspects	Further details	Imaging
1	No third course of radiotherapy	–	–	–	–	–
2	No third course of radiotherapy	–	–	–	–	–
3	Third course of radiotherapy	40 Gy, 2 Gy, 20, 5	D95	Eclipse™ (Varian Medical Systems Inc., Palo Alto, CA, USA); AAA dose calculation algorithm	VMAT or tomotherapy	Planning CT with vacuum cushion; MRI T1 with and w/o contrast, co-registered; daily IGRT
4	Third course of radiotherapy (SBRT)	30 Gy, 7.5 Gy, 4, 4	ICRU point, if necessary underdosage to protect spinal cord	IMRT with Pinnacle™ (Philips Healthcare, Andover, MA, USA)	CBCT and HexaPOD™ (Elekta AB, Stockholm, Sweden) immobilization in bodyfix	Daily CBCT
5	Third course of radiotherapy (SBRT)	30 Gy, 6 Gy, 5, 5	30 Gy to PTV, if necessary underdosage to protect spinal cord	VMAT, 2–3 arcs, FFF	CBCT and bodyfix	Planning CT; MRI T1 with and w/o contrast; MRI T2; daily CBCT
6	Third course of radiotherapy (SBRT)	32.5 Gy, 6.5 Gy, 5, 5	32.5 Gy to PTV, if necessary underdosage to protect spinal cord	VMAT, 2 arcs, FFF	CBCT	Planning CT; MRI T1 with and w/o contrast, daily CBCT
7	Third course of radiotherapy (robotic SBRT)	15 Gy, 5 Gy, 3, 3 ^a 30 Gy, 1.5 Gy, 20, 10 ^b	Would accept as low as 80% isodose surface covering 90% of PTV, if necessary to protect spinal cord	CyberKnife™ (Accuray, Sunnyvale, CA, USA)	Prone position, spine tracking	Planning CT; MRI T1 with contrast; repetitive intra-fraction spine imaging

RT radiotherapy, TPS treatment planning system, VMAT volumetric modulated arc therapy, IGRT image-guided radiotherapy, IMRT intensity-modulated radiotherapy, SBRT stereotactic body radiotherapy, OAR organ at risk, SIB simultaneous integrated boost, CT computed tomography, MRI magnetic resonance imaging, CBCT cone beam computed tomography, PTV planning target volume, FFF flattening-filter-free beam

^aif systemic immunotherapy would be given

- **Spinal cord EQD2: <10 Gy, 12.5 Gy, 12.5 Gy, 14 Gy, 19 Gy (maximum point dose)**
- **Sum EQD2: 94 Gy, residual EQD2: 56.5 Gy**
- **Compromise target volume coverage, however follow spine SBRT guidelines as closely as possible**
- **Different approaches to define the spinal cord PRV (cord +1 mm, cord +1.5 mm, cord +3 mm, spinal canal)**
- **With 3 courses, interfraction motion and body weight changes will probably prevent us from delivering the Dmax to the spinal cord to the exact same small volume each time**
- **Other toxicity: compression fracture, esophageal ?, lung ?, trachea ?, skin ?**

Second re-irradiation: spine

Thibault I. et al. *Int J Radiat Oncol Biol Phys* 2015

- **Toronto group: 24 spinal segments**
- **Conventional RT 20-30 Gy in 5-40 fractions**
- **Than 2 series of SBRT 20-30 and 24-35 Gy in 2-5 fractions**
- **Individual sum doses and time intervals not reported**
- **Median spinal cord PRV EQD2: 30, 20.8, 21.9 Gy maximum point dose**
- **Median cumulative EQD2: 73.9 Gy**
- **Median EQD2 to 0.1 cc: 30, 17.2, 18.1 Gy (cum. 66.8 Gy)**
- **Regarding thecal sac (repr. cauda equina PRV), median cumulative EQD2 was higher: 80.4 Gy (max), 71.5 Gy (0.1 cc)**

Second re-irradiation: spine

Thibault I. et al. *Int J Radiat Oncol Biol Phys* 2015

- **Median follow-up from 2nd SBRT: 6.8 months**
- **No compression fracture in patients who were surgery-naïve (not stabilized before)**
- **No radiation myelopathy**
- **No toxicity grade 3+**
- **Crude local control 77%**
- **Most often prescribed 30 Gy in 4 fractions of 7.5 Gy (identical to the recommendation in the previously presented case scenario)**

Second re-irradiation: spine

Katsoulakis E. et al. *J Neurosurg Spine* 2013

- **MSKCC group: 10 patients, IG-IMRT**
- **Initial course: 9 different dose/fractionation regimes**
- **Median time interval 1: 18.5 mo (3-6 in 2 cases)**
- **Second course: 30 Gy in 5 fractions (n=6), 25/5 (n=2)**
- **Median time interval 2: 11.5 mo (minimum 2, in the 2 cases with short interval 1 minimum 9 mo)**
- **Third course: often 30 Gy or 25 Gy in 5 fractions**

Second re-irradiation: spine

Katsoulakis E. et al. *J Neurosurg Spine* 2013

- **Median follow-up from 2nd Re-RT: 12 months**
- **Crude rate of local control: 80%**
- **Median true spinal cord (CT myelogram) maximum EQD2: 70.7 Gy**
- **Three patients had >75 Gy (2/3 to the lumbar spine)**
- **No high-grade toxicity, however one grade 2 neuropathy after 101.7 Gy EQD2 to segment L3**

Second re-irradiation: bone mets

Jeremic B. et al. *J Pain Symptom Manage* 2002

- **25 patients, first RT: 4, 6 or 8 Gy single fraction**
- **Second & third RT: 4 Gy each**
- **Median time interval to third RT: 20 weeks**
- **80% overall response rate, 64% palliated until death**
- **Median OS 7 weeks**
- **As expected with low dose RT, no serious toxicity**

Peulen H, Karlsson K, Lindberg K, Tullgren O, Baumann P, Lax I, Lewensohn R, Wersäll P. Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy. *Radiother Oncol* 2011;101:260-6.

- **All patients re-irradiated with SBRT in the period 1994–2004, for stage II–III lung tumors or lung metastases, at Karolinska University Hospital, Sweden**
- **n=29, 4 had 3 courses (1 even 4), mean EQD2 for each course was 109 Gy, 10 Gy x3 and 8 Gy x5 were common regimens**
- **Higher risk in central tumors (tracheal fistula, stenosis of superior vena cava), larger clinical target volumes; no grade 4 or 5 toxicity in peripheral tumors**

Second re-irradiation: pelvis

Feddock J. et al. *Int J Radiat Oncol Biol Phys* 2017

- **Permanent interstitial brachytherapy, mostly uterine cancer after previous pelvic RT**
- **9 patients with re-implant to vaginal lesions**
- **Median cumulative EQD2 was 152 Gy**
- **Only 3/9 tumors controlled at last follow-up or death**
- **Median time to failure was 7.7 months**
- **All patients developed soft tissue necrosis (symptomatic in 2/9)**

Second re-irradiation: pelvis

Abusaris H. et al. *Radiother Oncol* 2011

- **Rotterdam group: 23 patients with dose summation after 2nd re-irradiation, 14 treated to pelvic target volumes (often rectal cancer), 6 to thoracic wall target volumes**
- **For re-irradiation of the organs at risk, the maximum dose was set as 50% more than the normal constraint if the interval was ≥ 12 mo (maximum allowed dose for spinal cord, sacral nerves (cauda equine) was EQD2 75 Gy, 105 Gy (alpha/beta 3 Gy))**
- **A dose adjustment of 25% was allowed for re-irradiation after 6–12 months. No recovery was used when re-irradiation was done within 6 months**

Second re-irradiation: pelvis

Abusaris H. et al. *Radiother Oncol* 2011

- **Individualized technique and fractionation**
- **32 Gy/4, 20 Gy/4, 30 Gy/2...**
- **Median interval 15 and 7 mo (f/u 7 mo, OS 7 mo)**
- **71% experienced pain reduction**
- **No grade 4 acute or late toxicity**
- **<10% each acute grade 3 dysuria or pain**
- **1 grade 3 late skin toxicity**

Second re-irradiation: brain mets

Six small datasets

- **WBRT + SRS + SRS (and 2 studies WBRT x2 + SRS)**
- **Balermipas et al., n=5 (1 radiation necrosis)**
- **Koffer et al., n=8, compared to SRS + SRS higher rate of local failure (37.5 vs. 12.5%, p=0.15) and of radiation necrosis (37.5% vs. 6.3%, p=0.05). 75% experienced failure or necrosis**

Second re-irradiation: brain mets

Rana N. et al. *Frontiers in Oncology* 2017

- **10 patients: WBRT + SRS + SRS**
- **Median 10.7 mo between WBRT and SRS1, 9.7 mo between SRS1 and 2 (all 28 patients with SRS x2)**
- **Includes SRS to surgical cavities and SFRT**
- **Prior WBRT not sign. associated with local failure, no further details reported**
- **The same is true for radionecrosis**
- **Overall rate of radionecrosis: 19% (1 patient needed surgery)**

Second re-irradiation: brain mets

Moreau J. et al. *PLOS One* 2018

- **22 patients: WBRT + SRS + SRS**
- **All without neurological deficit and with KPS 70+**
- **Minimum 10 mo between SRS 1 and 2**
- **>5 mm to brain stem/optic nerve/chiasm**
- **Outside motor area**
- **Another 2 patients had SRS + SRS + WBRT**
- **WBRT standard regimen was 30 Gy in 10 fr.**
- **SRS 2 was 12-20 Gy (median 18) at the isocenter**

Second re-irradiation: brain mets

Moreau J. et al. *PLOS One* 2018

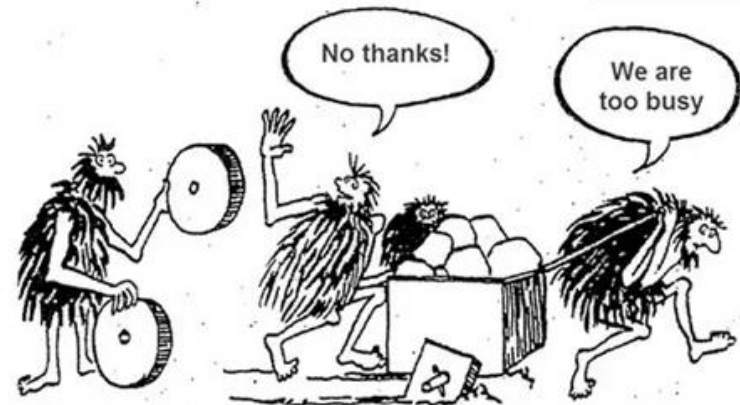
- **Results unfortunately reported in 30 patients (some had SRS + SRS without any WBRT)**
- **LC after SRS 2: 68% at 12 months**
- **1-year OS: 65.5%**
- **If previous WBRT, better LC (similar OS)**
- **All adverse effects were RTOG grade 1 or 2 and did not cause neurologic deficit**
- **All were observed in patients with WBRT + SRS x2**
- **5 local edema, 5 hemorrhage, 4 radionecrosis (18%)**
- **Less adverse effects if BM was <7 ccm**

Conclusions (1)

- **Some centers offer re-re-irradiation, resulting in increasing numbers of publications**
- **Due to small retrospective datasets, the level of evidence is limited and the number of open questions is high**
- **Highly selected patients who tolerated prior RT and were willing to provide informed consent**
- **Typically, individually tailored approaches, which might result in clinical benefit and acceptable risk of complications in bone metastases and pelvic targets**
- **Tissue necrosis and fatal outcomes have been reported**

Conclusions (2)

- **Research into recovery processes**
- **Starting point for clinicians 25% (6 mo) and 50% (12 mo)?**
- **No established dose constraints**
- **Image registration, assessment of true cumulative life time dose**
- **The impact of different fractionation regimens is not clear**
- **Emerging strategy in palliative scenarios**



Discussion



Disclaimer

I am
not
YOUNG
ENOUGH
to know
EVERYTHING
OSCAR WILDE

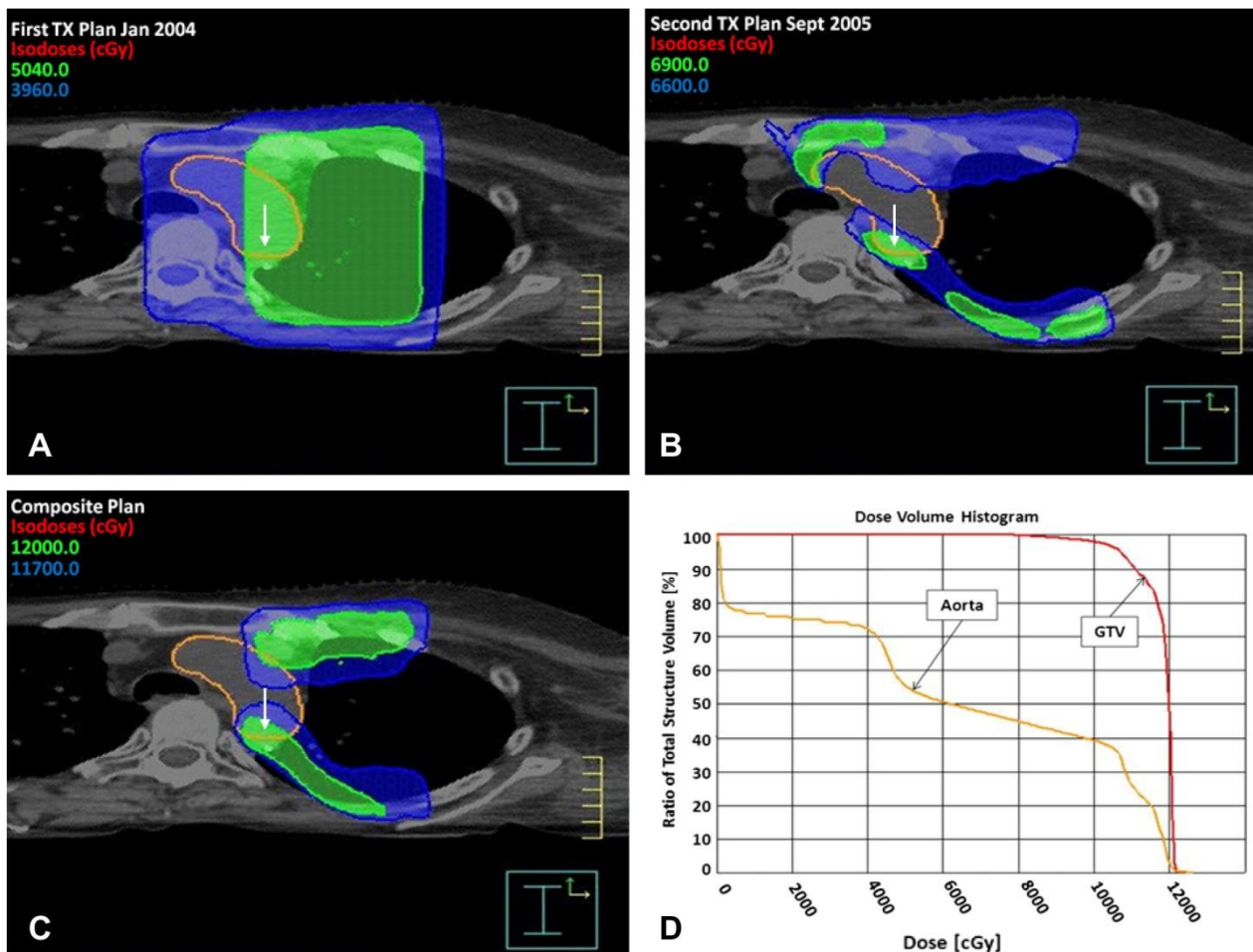
**Any fool can know.
The point is to
understand.**

Visit www.brainiac.com For More Quotes.



Albert Einstein

Evans JD et al. Thorakale Aorta: <math><120\text{ Gy}</math> (



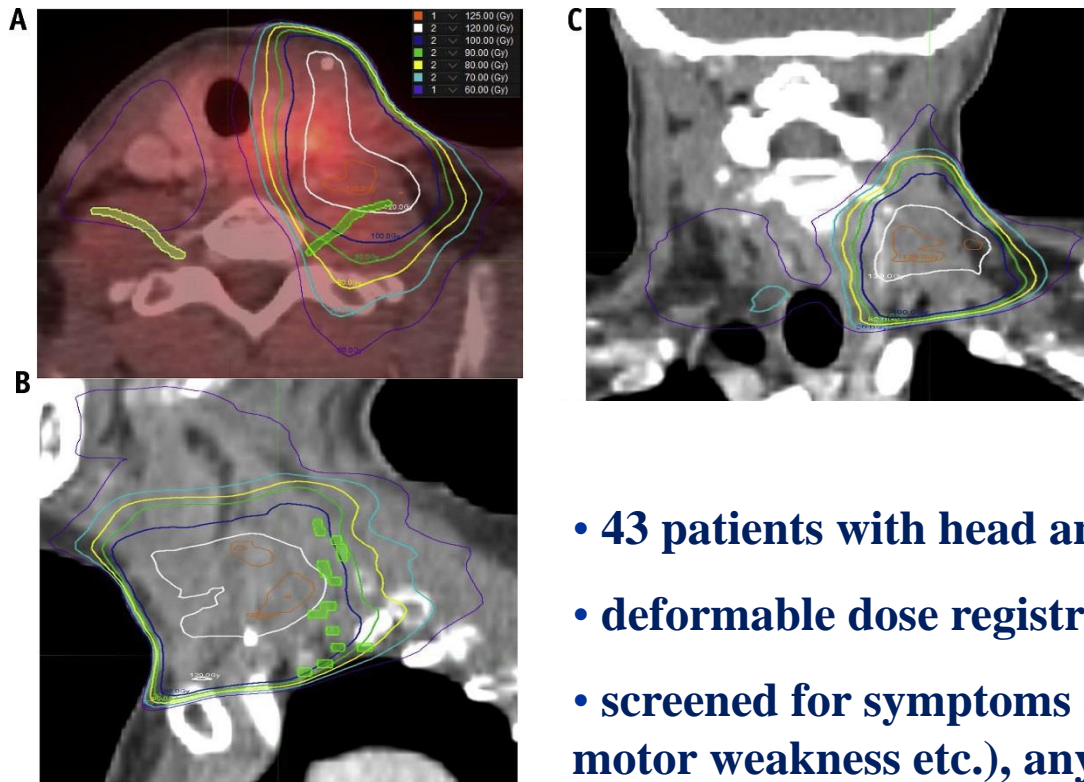
Tolerance of the Brachial Plexus to High-Dose Reirradiation

Allen M. Chen, Taeko Yoshizaki, Maria A. Velez, Argin G. Mikaeilian, Sophia Hsu, Minsong Cao

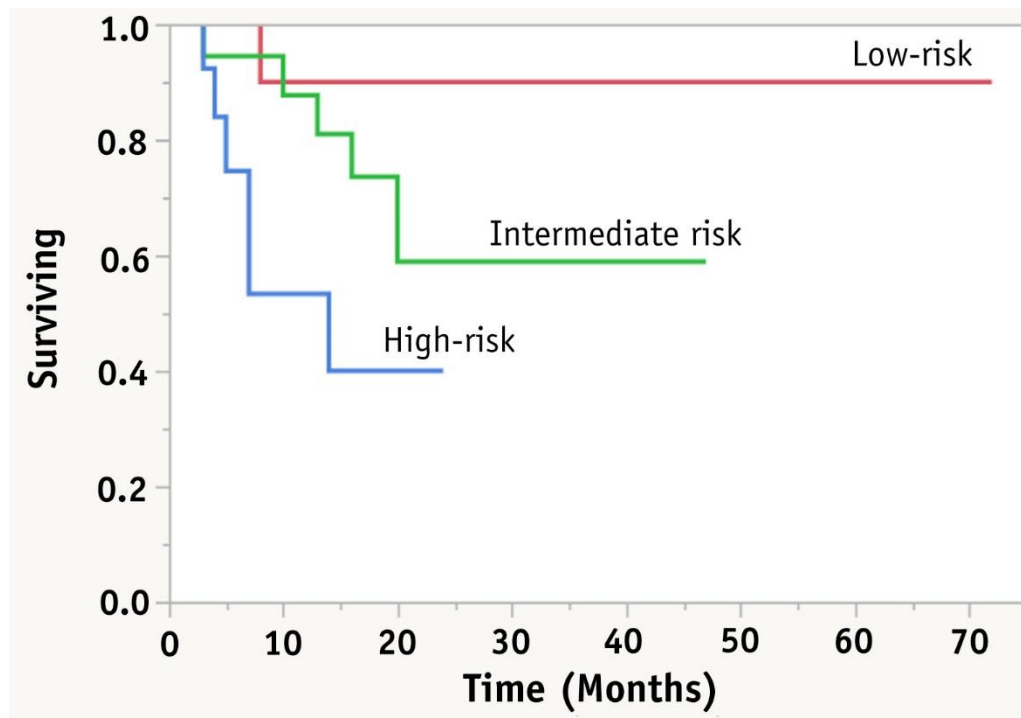
International Journal of Radiation Oncology • Biology • Physics

Volume 98, Issue 1, Pages 83-90 (May 2017)

DOI: 10.1016/j.ijrobp.2017.01.244



- 43 patients with head and neck cancer
- deformable dose registration
- screened for symptoms of neuropathy (pain, motor weakness etc.), any grade
- 12 patients had self-reported symptoms



Low:	12	12	12	12	9	6	5	4
Intermediate:	18	13	9	5	5	5	3	3
High:	13	7	3	0	0	0	0	0

- **Low risk of neuropathy if >2 years between courses and Dmax <95 Gy (EQD2)**
- **High risk if <2 years and Dmax >95 Gy**
- **Even with 120 Gy or more 8/13 patients (62%) remained free from symptoms**



Key questions

- **How radiosensitive is the tumor?**
- **Relapse within the previous target volume shortly after correctly administered accurate treatment?**
- **Relapse in a low-dose or adjuvant region?**
- **Second primary tumor, e.g., in the head & neck region?**
- **Curative vs. palliative treatment, other options?**
- **Tolerance of normal tissues/organs at risk at the site of reirradiation? (volume, dose/fractionation, interval, toxicity of the previous treatment)**

Future trends

- **More data about QoL**
- **NTCP models, risk scores**
- **Reliable data about total accumulated dose (IGRT, 4-D imaging, deformable image registration)**
- **MR Linac**
- **Protons and Carbon ions**
- **Multimodal concepts**
- **Diseases such as pancreatic, esophageal, HC cancer**
- **Three courses of radiation treatment**

Published re-irradiation concepts

Head & neck, lung and brain tumors

Regimen	HN tumors	Lung tumors	Brain tumors
External beam, conventional fractionation 1.8-2 Gy	x	x	x
External beam, hyperfractionation, twice daily	x		x
External beam, hypofractionation 2.2-2.5 Gy	x	x	x
External beam, hypofractionation 3-4 Gy		x	x
External beam, hypofractionation 5-7 Gy	x	x	x
External beam, hypofractionation 3 Gy twice daily	x		
External beam, RTOG quad shot, 3.7 Gy twice daily	x		
External beam, two fractions of 8 Gy		x	
External beam, severely hypofractionated SABR		x	
External beam, single dose radiosurgery			x
High dose rate brachytherapy	x	x	x
Pulsed dose rate brachytherapy	x		x