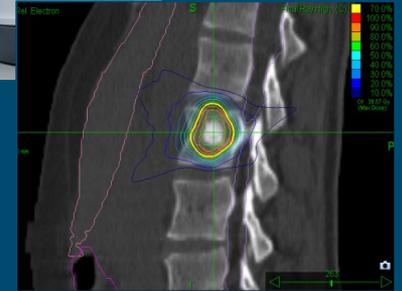


SBRT zur Re-Bestrahlung von Wirbelsäulenmetastasen

Sicher und wenn ja wie?

PD Dr. J. Hörner-Rieber
Abteilung RadioOnkologie und Strahlentherapie
Universitätsklinikum Heidelberg



Knochenmetastasen

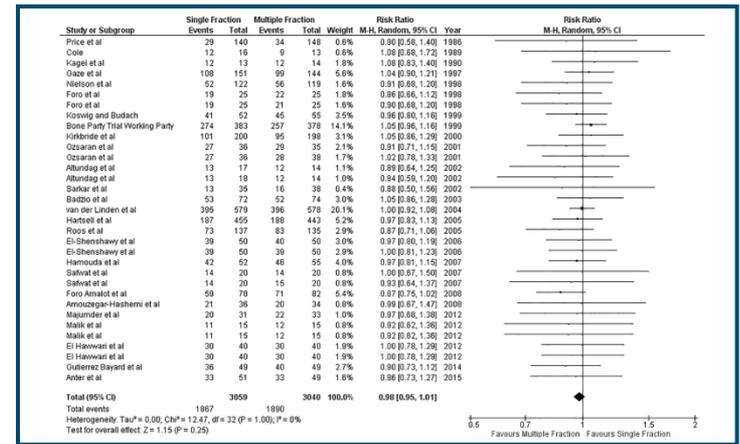
- Knochen: dritthäufigster Metastasierungsort nach Lunge und Leber
- 40% der Tumorpatienten entwickeln Knochenmetastasen
- 5 Tumorentitäten sind für 90% aller Knochenmetastasen verantwortlich (Mamma, Prostata, Lunge, Niere, Schilddrüse)
- Lokalisation 60-70% in der Wirbelsäule
- Knochenmetastasen verursachen in $\geq 75\%$ der Patienten Schmerzen



KONVENTIONELLE BESTRAHLUNG

Konventionelle Bestrahlung

- Complete response (Schmerz) auf die konventionelle EBRT nur in 0-20% der Patienten
- Partial response in 60% der Patienten
- Gleichwertiges Schmerzensprechen für Einzel- versus fraktionierte Bestrahlung
- Nach 3-6 Monaten benötigen 20% der Patienten aufgrund einer Progression der Schmerzen eine erneute RT



Rich et al. Radiother Oncol 2018

Table III: Pain status in response to the different RT fractionation schedules

	Pain status			Significance
	GP 30Gy/10fr	GP 20Gy/10fr	GP 8Gy/1fr	
Number of respondents	28/40	30/40	28/40	NS
Pain score (±SD) before RT	1.65(±0.21)	2.0(±0.26)	2.15(±0.44)	NS
Pain score (±SD) week 6 after RT	0.75(±0.08)	1.1(±0.05)	1.35(±0.1)	NS
Pain score decrease after 6 weeks RT within each group	P=.002	P=.002	P=.008	

NS: Not significant

Elhawwari et al., JRMS 2012

Table IV: Analgesia status in response to the different RT fractionation schedules

	Analgesia status			Significance
	GP 30Gy/10fr	GP 20Gy/10fr	GP 8Gy/1fr	
Number of respondents	22/40	32/40	24/40	NS
Analgesia score (±SD) before RT	1.9 (±0.17)	1.15 (±0.27)	1.15 (±0.3)	NS
Analgesia score (±SD) at week 6 after RT	0.75 (±0.11)	0.45 (±0.05)	0.65 (±0.1)	NS
Analgesia score decrease after 6 weeks of RT within each group	P=.003	P=0.008	P=0.01	

NS: Not significant

Erholungskapazität des Rückenmarks



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Biology Original Contribution

THE TOLERANCE OF PRIMATE SPINAL CORD TO RE-IRRADIATION

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 Y. FENG, M.D.,* T. E. SCHULTHEISS, PH.D.‡§ AND L. J. PETERS, M.D.*

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 PH 58360-3014(01)01599-1

BIOLOGY CONTRIBUTION

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, D.V.M.,*
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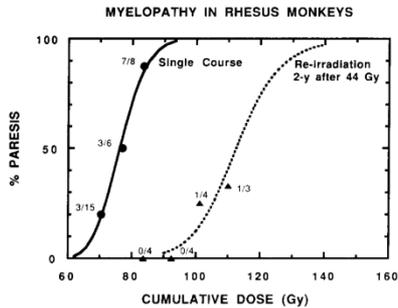


Fig. 1. Dose-incidence curves of myelopathy after a single course of irradiation and after re-irradiation.

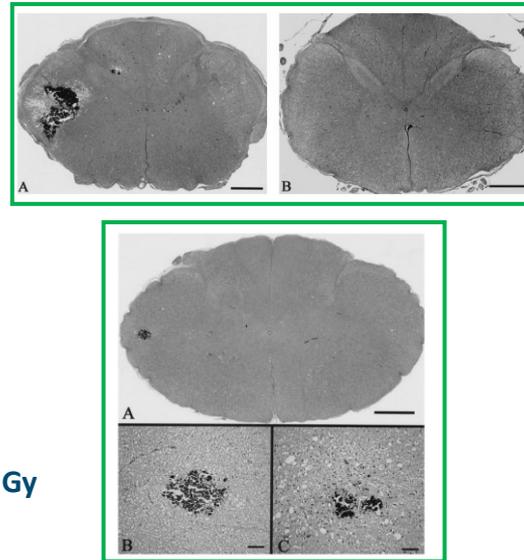


Table 2. Equivalent doses in Gy (95% confidence interval) for a 50%, 10%, or 5% incidence of myelopathy after a single course of radiation or retreatment after 44 Gy, derived using four different assumptions

Fitting data with the assumption	Effect level	Reirradiation after			
		Single course	1 year	2 years	3 years
Model 1	D_{50}	76.5 (72.2–80.8)	66.1 (57.2–75.0)	70.1 (61.7–78.5)	77.1 (65.9–88.4)
• Possible increase in recovery between Years 1 and 3	D_{10}	65.8 (58.4–73.3)	55.4 (48.5–62.3)	59.4 (54.0–64.8)	66.4 (57.8–75.1)
• All dose-response curves (reirradiations and single course) are parallel at D_{50}	D_5	62.8 (53.7–71.9)	52.4 (44.9–59.8)	56.4 (50.4–62.3)	63.4 (54.6–72.2)
Model 2	D_{50}	76.3 (72.7–79.8)	73.7 (41.0–106.5)	79.0 (41.3–116.7)	86.7 (45.6–127.8)
• Possible increase in recovery between Years 1 and 3	D_{10}	67.6 (61.6–73.7)	53.9 (39.9–67.9)	59.1 (49.5–68.7)	66.8 (50.7–83.0)
• Three reirradiation curves are parallel at D_{50} , but not necessarily parallel to the single-course curve*	D_5	65.2 (57.8–72.6)	48.3 (27.6–68.9)	53.5 (39.6–67.4)	61.2 (42.9–79.5)
Model 3	D_{50}	77.0 (71.2–82.7)	74.5 (63.1–85.8)		
• No increase in recovery after Year 1	D_{10}	62.2 (50.9–73.5)	59.7 (54.5–64.9)		
• Dose-response curve for all reirradiations combinations is parallel to the single-course curve at D_{50}	D_5	58.0 (44.0–72.1)	55.5 (49.0–62.0)		
Model 4	D_{50}	76.3 (72.7–79.8)	97.2 (9.9–184.5)		
• No increase in recovery after Year 1	D_{10}	67.6 (61.6–73.7)	58.9 (45.7–72.0)		
• Dose-response curve for all reirradiations combined is not necessarily parallel to the single-course curve at D_{50} *	D_5	65.2 (57.8–72.6)	48.0 (18.8–77.3)		

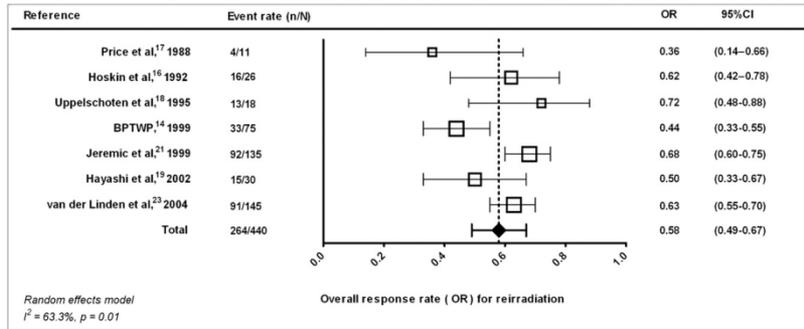
* Single-course data fitted separately.

Recovered dose after 2 years \geq 34 Gy

Im konservativsten Modell nach 2-3 Jahren Erholung bis 61% (26,8 Gy)

Re-Bestrahlung mit konv. Fraktionierung

- Nach initialem Ansprechen in rund 50 % der Pat. innerhalb 1 Jahres Progress der Schmerzen
- Höhere Re-RT Raten nach EZ-RT als nach fraktionierter RT
- Keine eindeutigen Empfehlung bezügl. der Fraktionierung
- Nur (begrenztes) Ansprechen (rund 60% overall response)



Huisman et al., IJROBP 2011

Table 3

Complete, partial and overall response rates of re-irradiation.

Author	Response rates
<i>Complete response</i>	
Mithal [13]	8/51
Jeremic [14]	31/135
BPTWP [15]	12/75
Hayashi [16]	5/30
Grosu [17]	3/4
Sayed [21]	11/60
Complete response rate	CR: 70/355 = 20%
<i>Partial response</i>	
Mithal [13]	40/51
Jeremic [14]	61/135
BPTWP [15]	21/75
Hayashi [16]	10/30
Grosu [17]	1/4
Sayed [21]	44/60
Partial response rate	PR: 177/355 = 50%
<i>Overall response</i>	
Penn [10]	5/10
Price [4]	4/11
Cole [11]	4/4
Hoskin [12]	16/26
Mithal [13]	48/51
Uppelschoten [1]	13/18
Jeremic [14]	92/135
BPTWP [15]	33/75
Hayashi [16]	15/30
Grosu [17]	4/4
van der Linden [18]	91/145
Roszkowski [19]	41/57
Hamouda [20]	6/7
Hernanz [9]	11/12
Sayed [21]	55/60
Overall response rate	OR: 438 /645 = 68%

Wong et al., Radiother Oncol 2014



Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial

Edward Chow, Yvette M van der Linden, Daniel Roos, William F Hartsell, Peter Hoskin, Jackson SY Wu, Michael D Brundage, Abdenour Nabid, Caroline J A Tissing-Tan, Bing Oei, Scott Babington, William F Demas, Carolyn F Wilson, Ralph M Meyer, Bingshu E Chen, Rebecca K S Wong

- Randomisierte Phase III-Studie (950 Pat.)
- Patienten: Schmerzhaftes Knochenmet. mit Vor-RT (Wirbelsäule nur wenn max. 5x4 Gy, Hüfte auch 10x3 Gy)
- **Randomisierung:** Re-RT mit 1x8 Gy vs. 5x4 Gy (20 Gy in 8 Fx wenn WS/Becken und Vor-RT 5x4 Gy)
- **Nicht-Unterlegenheit NUR erreicht in der ITT-Population**
ORR ca. 45-50%, CR 10-15%
Signif. weniger Diarrhoe plus Fatigue mit SF
Tendenz mehr MSCC und Frakturen mit SF

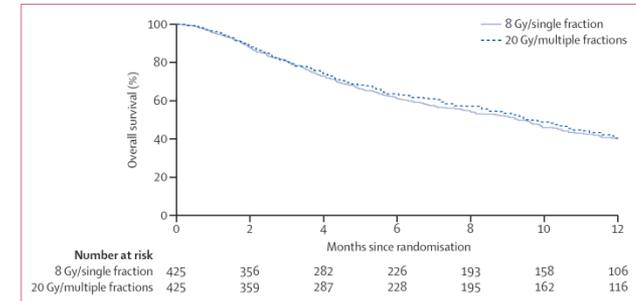


Figure 2: Kaplan-Meier curves of overall survival in the intention-to-treat population

	Intention-to-treat analysis		Per-protocol analysis	
	8 Gy/single fraction (N=425)	20 Gy/multiple fractions (N=425)	8 Gy/single fraction (N=258)	20 Gy/multiple fractions (N=263)
Overall response	118 (28%)	135 (32%)	116 (45%)	134 (51%)
Complete response	36 (8%)	30 (7%)	35 (14%)	29 (11%)
Partial response	82 (19%)	105 (25%)	81 (31%)	105 (40%)
Not assessable	162 (38%)	160 (38%)	0	0
Not defined*	92 (22%)	91 (21%)	91 (35%)	91 (35%)
No change	7 (2%)	7 (2%)	7 (3%)	7 (3%)
Pain progression	46 (11%)	32 (8%)	44 (17%)	31 (12%)

Data are number (%). *Response assessments that could not be classified as complete response, partial response, no change, or pain progression.

Table 2: Response to treatment according to Brief Pain Inventory score and daily oral morphine equivalent at 2 months in the intention-to-treat and per-protocol populations

Für Pat., die eine Re-RT aufgrund schmerzhafter Knochen-ME brauchen, scheint die SF gleich effizient wie die MF bei geringerer Toxizität zu sein

STEREOTAKTISCHE BESTRAHLUNG

Heidelberg University Hospital | November 2019 | PD Dr. Juliane Hörner-Rieber



Primäre SBRT

- 1-Jahr lokale Kontrolle 90%
- komplettes Schmerzansprechen > 50%
- Wirbelkörperfrakturen in 10%
- 0,2% neurologische Schäden (Myelopathie)

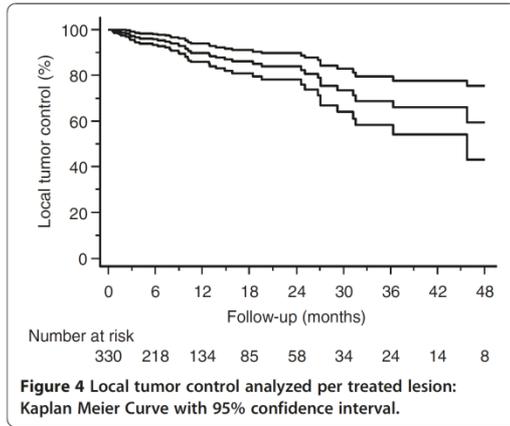
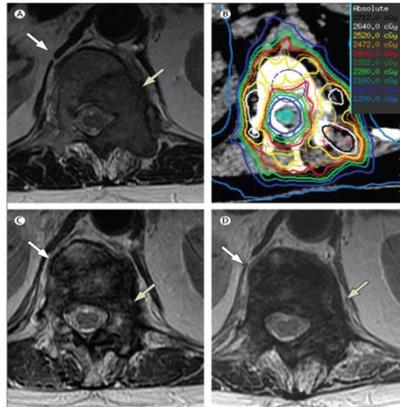


Figure 4 Local tumor control analyzed per treated lesion: Kaplan Meier Curve with 95% confidence interval.

Guckenberger et al. Radiat Oncol 2014



Thibault et al., Lancet Oncology 2015

Patientenselektion

TABLE 4. ISRS-recommended patient selection for consideration of spine SBRT outside a clinical trial*

Criteria	Rationale	Level of Evidence
Inclusion		
Oligometastasis involving the spine	These pts generally have a long expected survival & thus are most likely to benefit from radiosurgery/SBRT	V
Pts w/ radioresistant histology (RCC, melanoma, sarcoma)	Higher doses of radiation might be associated w/ improved local tumor control	IV/V
Patients with paraspinous extension contiguous to the spine	Pts w/ extrasosseous extension might experience improved soft-tissue tumor control	IV
Exclusion		
Pts w/ an expected survival time of <3 mos	Pts w/ a shorter expected survival time are less likely to benefit from SBRT	V
Mechanically unstable based on the SINS score	Pts w/ mechanical instability should be treated w/ surgical stabilization before radiotherapy	IV/V
>3 sites to be treated in a single session	For logistical reasons, it is difficult to keep a pt adequately immobilized for long enough to accurately treat more than 3 lesions in a single session	V
Spinal cord compression or cauda equina syndrome	These pts should be preferentially treated w/ up-front decompressive surgery†	I

SINS = spinal instability neoplastic score.
 * Note that these are suggestions, and patients need not meet all criteria to be considered candidates for treatment.
 † Based on the results of Patchell et al.¹¹

Dosierung

Husain et al, J Neurosurg Spine 2017

TABLE 3. Common dose and fractionation regimens used in SBRT and conventional irradiation

Total Dose (Gy)	Dose/Fx (Gy)	BED (Gy)	No. of Fx	Technique
24	24	81.6	1	SBRT
24	12	52.8	2	SBRT
27	9	51.3	3	SBRT
18	18	50.4	1	SBRT
30	6	48.0	5	SBRT
24	8	43.2	3	SBRT
30	3	39	10	EBRT
20	4	28	5	EBRT
8	8	14.4	1	EBRT

Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1-2 trial



Xin Shelley Wang, Laurence D Rhines, Almon S Shiu, James N Yang, Ugur Selekt, Ibrahim Gning, Ping Liu, Pamela K Allen, Syed S Azeem, Paul D Brown, Hadley J Sharp, David C Weksberg, Charles S Cleeland, Eric L Chang

- Phase I/II-Studie (149 Pat.), Follow up 15,9 Monate
- SBRT mit 27-30 Gy in 3 Fx
- Signifikante Schmerzreduktion und Analgetikaeinnahme
- 1-Jahres PFS 80,5%, 2-Jahres PFS 72,4%
- keine wesentliche Toxizität

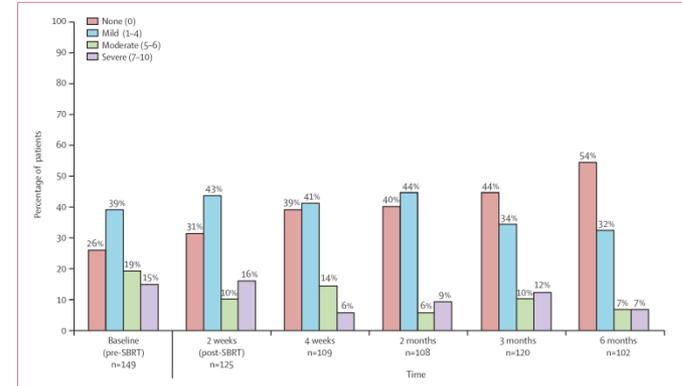
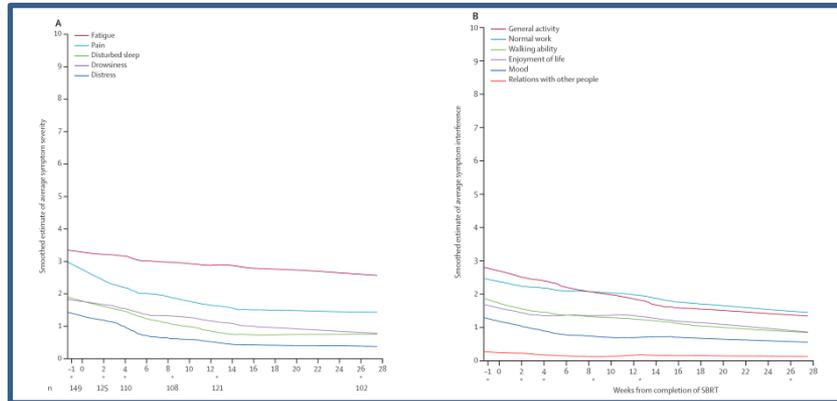


Figure 1: Percentage of patients with no, mild, moderate, or severe pain on the BPI 0-10 scale, before and after SBRT
BPI=Brief Pain Inventory. SBRT=stereotactic body radiotherapy.

	BPI pain-at-its-worst score (0-10)*		MDASI pain score (0-10)*		Strong opioid use†
	n	Mean score (SD)	n	Mean score (SD)	n (%)
Baseline	148	3.4 (2.9)	148	3.4 (3.1)	43 of 149 (28.9%)
2 weeks	124	2.9 (2.8)	124	2.9 (3.0)	34 of 121 (28.1%)
4 weeks	109	2.1 (2.4)	109	2.1 (2.6)	26 of 110 (23.6%)
2 months	108	2.3 (2.6)	108	2.3 (2.7)	23 of 105 (21.9%)
3 months	120	2.1 (2.7)	120	2.1 (2.8)	31 of 121 (25.6%)
6 months	102	1.7 (2.4)	102	1.9 (2.5)	20 of 100 (20.0%)

SBRT=stereotactic body radiotherapy. BPI=Brief Pain Inventory. MDASI=M D Anderson Symptom Inventory.
*No significant differences between BPI pain-at-its-worst mean scores and MDASI pain item mean scores (paired t tests) were found at any timepoint other than the 6-month assessment (p=0.022). †The number of patients for whom analgesia data were available differed slightly from the number of patients who provided symptom data.

Table 2: Pain severity scores and opioid use over time, before and after SBRT

Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy



Tanja Sprave^{a,c}, Vivek Verma^b, Robert Förster^{a,c,d}, Ingmar Schlamp^{a,c}, Thomas Bruckner^e, Tilman Bostel^a, Stefan Ezechiel Welte^a, Eric Tonndorf-Martini^a, Nils Henrik Nicolay^{a,c,f}, Jürgen Debus^{a,c}, Harald Rief^{a,c,*}

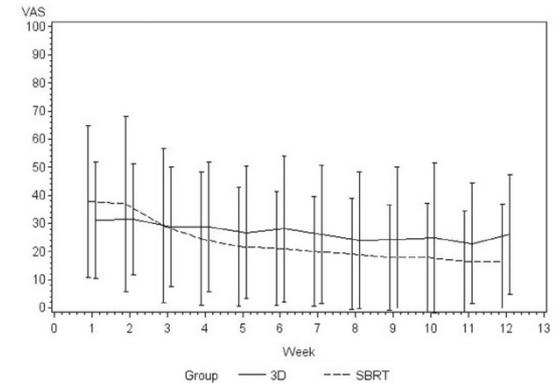
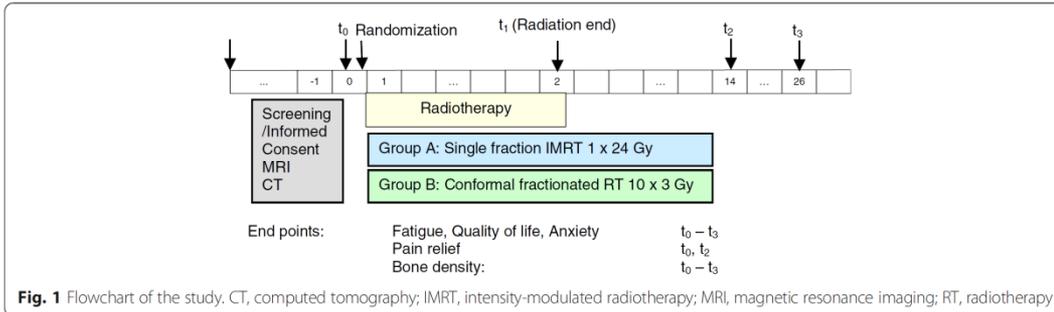
^a University Hospital of Heidelberg, Department of Radiation Oncology, Germany; ^b Department of Radiation Oncology, Allegheny General Hospital, Pittsburgh, USA; ^c Heidelberg Institute of Radiation Oncology (HIRO), Germany; ^d University Hospital Zurich, Department of Radiation Oncology, Switzerland; ^e University Hospital of Heidelberg, Department of Medical Biometry; and ^f Heidelberg Institute of Radiation Oncology (HIRO), German Cancer Research Center (DKFZ), Germany

- Randomisierte Phase II-Studie (60 Pat.)
- Schnelleres Ansprechen mit SBRT
- Signifikant bessere Schmerzkontrolle mit SBRT nach 6 Mo
- keine Toxizität ≥ CTCAE Grad 3

Table 3

Response according to Brief Pain Inventory score at 3 and 6 months in the per-protocol cohort.

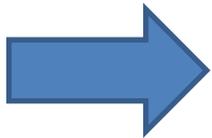
	Intervention group n = 27		Control group n = 28		p-Value
	n	%	n	%	
After 3 months					
CR	10	43,5	4	17,4	0,0568
PR	6	26,1	7	30,43	
PP	2	8,7	0	0	
IP	5	21,7	12	52,2	
Responders	16	69,6	11	47,8	
Non-responders	7	30,4	12	52,2	0,1343
After 6 months					
CR	10	52,6	2	10	0,0034
PR	4	21,1	5	25	
PP	2	10,5	0	0	
IP	3	15,8	13	65	
Responders	14	73,7	7	35	
Non-responders	5	26,3	13	65	0,0154



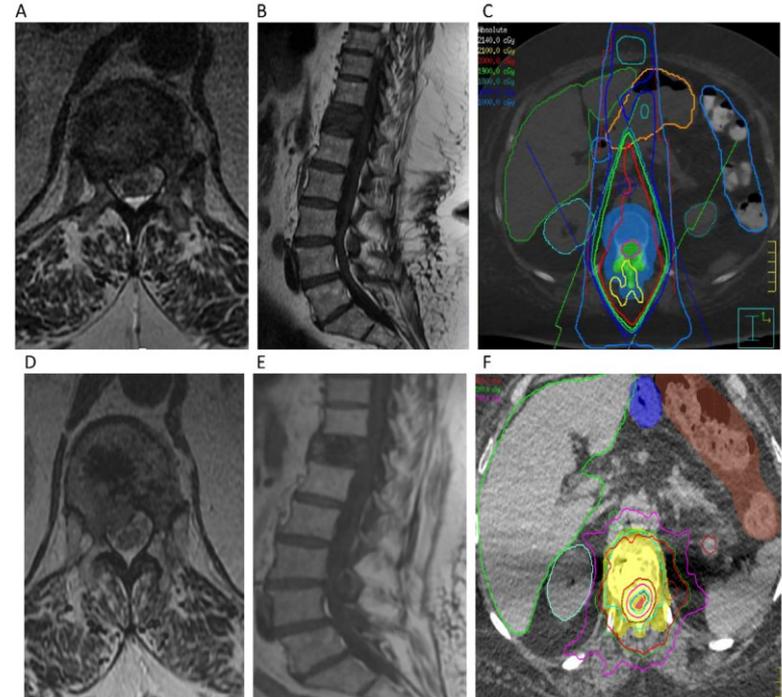
SBRT in der Re-Bestrahlung

Rationale:

- Schlechteres Ansprechen auf die konv. fraktionierte Re-RT (CR 10-15%)
- Kumulative Myelondosis ist begrenzt
- Schlechtere lokale Kontrolle nach konv. fraktionierte Radiotherapie



Bessere Schmerz- und lokale Kontrolle durch SBRT?



Myrehaug et al., Clin Oncol (R Coll Radiol). 2018

RE-BESTRAHLUNG MIT SBRT?

Erste Knochen-SBRT war eine Re-Bestrahlung...

Neurosurgery 1992-98

February 1995, Volume 36, Number 2

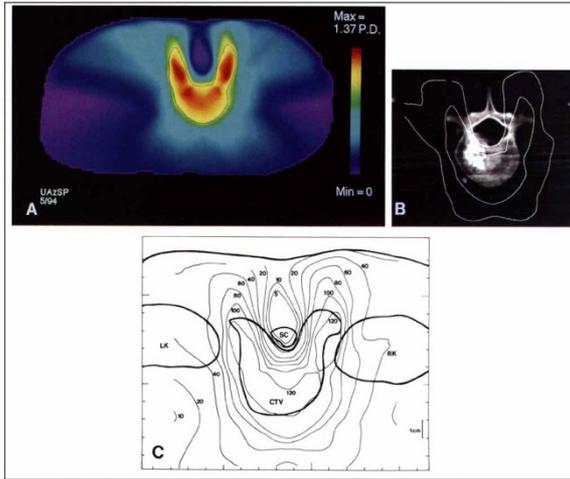
311 Preliminary Clinical Experience with Linear Accelerator-based Spinal Stereotactic Radiosurgery Technique and Application

AUTHOR(S): Hamilton, Allan J., M.D.; Lulu, Bruce A., Ph.D.; Fosmire, Helen, M.D.; Stea, Baldassarre, M.D., Ph.D.; Cassady, J. Robert, M.D.

• 5 Patienten mit ossären Metastasen

Vor-RT: mediane Dosis: 45 Gy (33-65Gy, 11-30 Fx)

- SBRT mit 1 x 10 Gy (8-10 Gy) @80%-Isodose (80-160%)
- Medianes FU: 6 Mo
- Kein Progress, 1 x Ösophagitis ansonsten keine Tox.



Patient No.	Sex/Age	Tumor	Level	Thecal Sac Compression	Prior Radiation (Gy)/No. of Fractions	Radio-surgery Dose (Gy)	No. of Isocenters	% Normalization of Maximum Dose	Follow-up (mo)	Status
1	M/13	Osteosarcoma	L1	Yes	42/21	8	5	73	14	NVR; CLR
2	M/70	Metastatic adenocarcinoma	L2-L3	Yes	46/23	10	1	74	8	NVR; CLR
3	M/71	Metastatic renal cell	T5	No	33/11	10	1	69	1	Died ~1 mo ^b
4	M/57	Adenocarcinoma lung	T3-T4	No	65/30	10	1	58	6	CLR ^c
5	F/28	Metastatic breast carcinoma	C7-T2	No	45/25	8	4	31	2	Died ~2 mo ^d

^a NVR, no radiographically visible recurrence; CLR, clinical resolution of signs/symptoms.

^b Patient pain-free at treated site; died of metastatic liver disease.

^c 50% reduction in tumor volume.

^d Died at 2 months from intracranial hemorrhage; no clinical progression of disease at treated site.

Table 1. Stereotactic Spinal Radiosurgery Patient Summary^d

SBRT in der Re-Bestrahlung

Author & Year	No. of Tumors/Pts Treated	Median Follow-up (mos)	Local control	Complete Pain Response	Overall Survival	Median Tumor dose (No. Of Fractions (previous cEBRT))
Sahgal et al., 2009	37/25	7	96%@1 yr	NA	45%@ 2 yrs	24 Gy /3 Fx (median dose 36Gy /14 Fx)
Choi et al., 2010	51/42	7	97%@6 mos / 73%@ 1 yr	65%	68%@ 1 yr	Median 20 Gy /2 Fx (median cEBRT EQD2=40Gy)
Mahadevan et al., 2011	81/60	12	93@ last follow-up	NA	Median OS: 11 mos	25-30Gy/5Fx or 24 Gy/3Fx (median dose 30 Gy/ 10 Fx)
Garg et al., 2011	63/59	17.6	76%@1 yr	NA	76%@1 yr	27 Gy/3 Fx or 30 Gy/5Fx (median dose 30 Gy)
Damast et al., 2011	97/95	12.1	66%@1yr	46%	52-59%@1yr	20 Gy/5 Fx or 30 Gy/5Fx (median dose 30 Gy)
Chang et al. 2012	54/49	17.3	81%@1yr	81% (1 yr)	Median OS: 11 mo	20.6 G/1Fx (mean cEBRT EQD2 39.2 Gy)
Thibault et al., 2015	56/40 (partially 2nd SBRT)	6.8	81.6%@1yr/71.5% @2yrs	NA	48%@1yr	30 Gy/ 4 Fx
Hashmi et al., 2016	215/247	8.1	93%@6mos/83%@ 1yr	53.9% (@ last Follow-up)	64%@6mos/48% @1yr	median SBRT dose: 18Gy/1Fx (cumulative dose 68.2Gy)

Lokale Kontrolle



Schmerzensprechen



Prospective Evaluation of Spinal Reirradiation by Using Stereotactic Body Radiation Therapy

The University of Texas MD Anderson Cancer Center Experience

Amit K. Garg, MD¹; Xin-Shelley Wang, MD²; Almon S. Shiu, PhD³; Pamela Allen, PhD¹; James Yang, PhD³; Mary Frances McAleer, MD, PhD¹; Syed Azeem, MD⁴; Laurence D. Rhines, MD⁴; and Eric L. Chang, MD¹

- Prospektive Studie, Follow up 17,6 Monate
- 59 Patienten mit 63 Knochenmetastasen
- SBRT mit 30Gy/5Fx, 27Gy/3Fx (Vor-RT mediane Dosis 30Gy, RM<45Gy)
- 1-Jahr-LC und –OS jeweils 76%
- 81% der progredienten ME lagen < 5 mm vom RM entfernt
- Gutes Schmerzansprechen, 2 Pat. mit lumbaler Plexopathie

Table 2. Tumor and Dosimetric Characteristics of the 16 Patients With Local Progression

Patient	Primary Histology	Cord Distance ^a	Dose/Fractions ^b	Cord D _{max} , cGy ^c	Tumor V80, % ^d
1	Papillary thyroid	<5 mm	27 Gy/3	1068	96
2	Lung, nonsmall cell	<5 mm	27 Gy/3	904	96
3	Renal clear cell	<5 mm	27 Gy/3	946	99
4	Chondrosarcoma	Postop	27 Gy/3	1089	94
5	Cervical	<5 mm	27 Gy/3	624	99
6	Colon	<5 mm	27 Gy/3	1261 ^e	97
7	Breast	<5 mm	27 Gy/3	951	90
8	Renal cell	<5 mm	27 Gy/3	1181	99
9	Renal cell	<5 mm	27 Gy/3	1439	99
10	Renal cell	<5 mm	27 Gy/3	982	98
11	Breast	<5 mm	27 Gy/3	1292	98
12	Renal clear cell	Postop	30 Gy/5	1150	93
13	Renal clear cell	<5 mm	27 Gy/3	1021	98
14	Myxoid liposarcoma	<5 mm	27 Gy/3	920	100
15	Renal cell	<5 mm	27 Gy/3	1153	97
16	Spindle cell sarcoma	Postop	27 Gy/3	1156	97

Postop indicates postoperative.

^aDistance of tumor to cord on initial magnetic resonance imaging.

^bTotal dose/# fractions.

^cMaximum dose to the spinal cord.

^dPercentage of gross tumor volume receiving $\geq 80\%$ of the prescription dose.

^eMaximum dose to cauda as tumor located below spinal cord at L3.

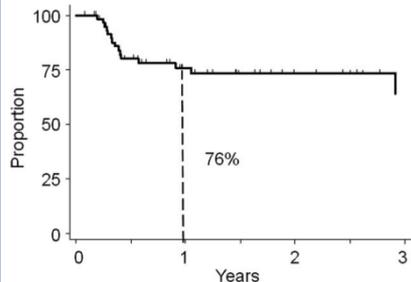


Figure 1. Tumor progression for all cases is shown.

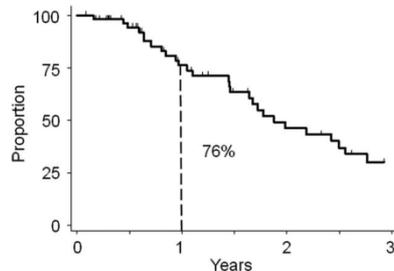


Figure 2. Overall survival for all cases is shown.

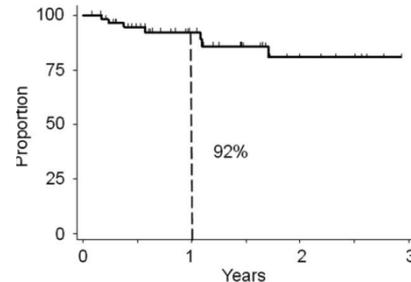


Figure 3. Neurologic progression-free survival is shown.

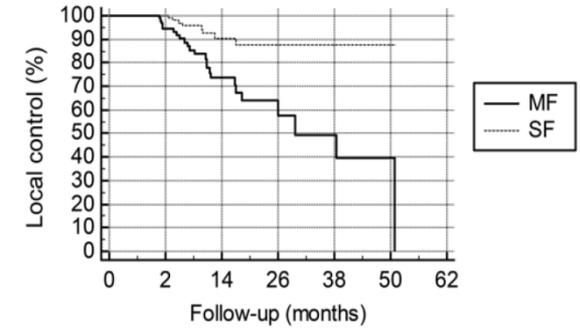
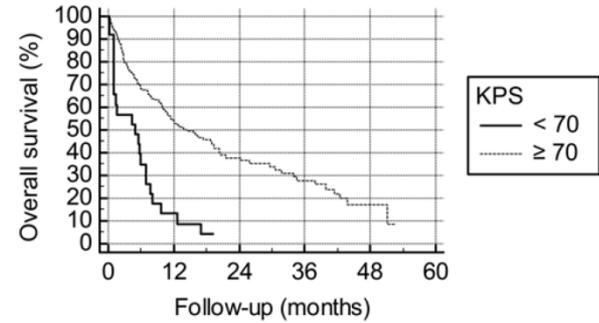
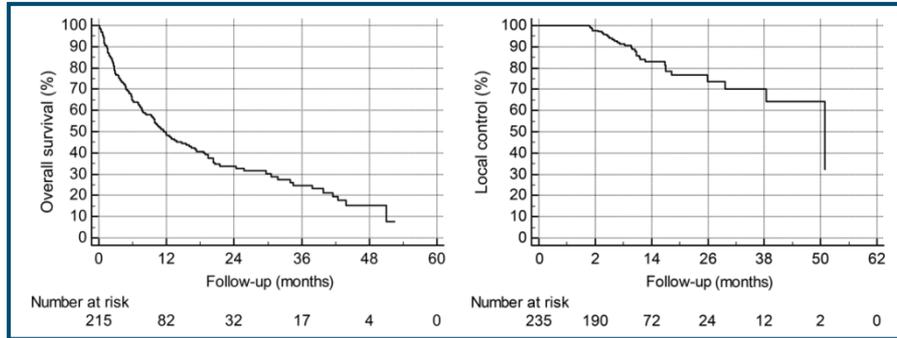
Table 3. Treatment Toxicity

Grade	Neurotoxicity	Hematologic	Gastrointestinal	Other Toxicity (worst grade)
None	44	59	44	22
Grade 1	7	0	6	19
Grade 2	4	0	6	16
Grade 3	2	0	0	0
Grade 4	0	0	0	0

Re-irradiation stereotactic body radiotherapy for spinal metastases: a multi-institutional outcome analysis

Ahmed Hashmi, MD,¹ Matthias Guckenberger, MD,^{2,3} Ron Kersh, MD,⁴ Peter C. Gerszten, MD,⁵ Frederick Mantel, MD,² Inga S. Grills, MD,⁶ John C. Flickinger, MD,⁷ John H. Shin, MD,⁸ Daniel K. Fahim, MD,⁹ Brian Winey, PhD,¹⁰ Kevin Oh, MD,¹⁰ B. C. John Cho, MD, PhD,¹¹ Daniel Létourneau, PhD,¹¹ Jason Sheehan, MD, PhD,¹² and Arjun Sahgal, MD¹

- 215 Patienten mit 247 spinalen Zielvolumina aus 7 Institutionen
- Vor-RT: mediane Dosis 30 Gy in 10Fx
- Mediane SBRT Dosis 1 x 18 Gy; 60% SF, 40% MF (med. Dosis 3 x 8 Gy)
- Mediane Zeit zw. cEBRT und SBRT 13.5 Mo
- Keine Myelopathie, 4,5 % Wirbelkörperfrakturen

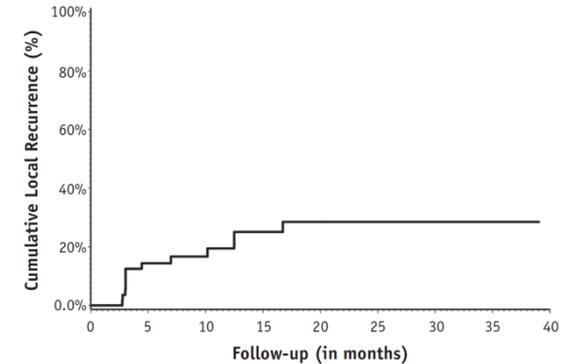
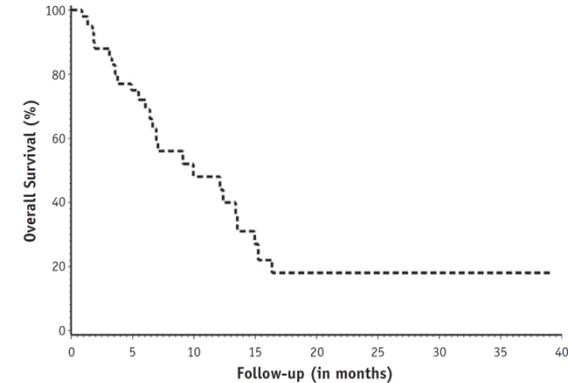


Median SBRT tumor EQD2/10 in Gy (range)†	36.0 (12.0–66.7)
Median SBRT CNT EQD2/2 D _{max} in Gy (range)†	24.6 (0–70.1)
Median cumulative tumor EQD2/10 in Gy (range)†	68.2 (33.7–116.0)
Median cumulative CNT EQD2/2 D _{max} in Gy (range)†	60.8 (14.0–107.6)

Salvage-SBRT nach primärer SBRT

Prospektive Datenbank

- 40 Patienten mit 56 spinalen Zielvolumina
- 43% der Pat. hatten zuvor cEBRT plus SBRT
- 1. SBRT mit 24 Gy in 2 Fx (20-35 Gy in 1-5Fx)
- 2. SBRT 30 Gy in 4 Fx (20-35 Gy in 2-5 Fx)
- RE-SBRT in Median nach 13 Mo
- 13 Progresse mit 85% Wachstum Spinalkanal/paraspinal



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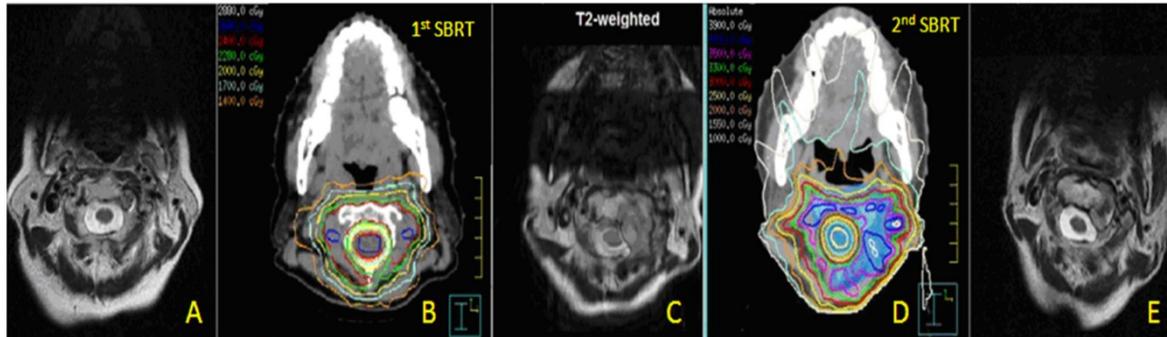
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Clinical Investigation

Salvage Stereotactic Body Radiotherapy (SBRT) Following In-Field Failure of Initial SBRT for Spinal Metastases

Isabelle Thibault, MD,* Mikki Campbell, MRT(T),*
Chia-Lin Tseng, MD,*¹ Eshetu G. Atenafu, MSc,²
Daniel Letourneau, PhD,³ Eugene Yu, MD,³ B.C. John Cho, MD,¹
Young K. Lee, PhD,* Michael G. Fehlings, MD, PhD,³ and
Arjun Sahgal, MD*¹



Salvage-SBRT nach primärer SBRT



Clinical Investigation

Salvage Stereotactic Body Radiotherapy (SBRT) Following In-Field Failure of Initial SBRT for Spinal Metastases

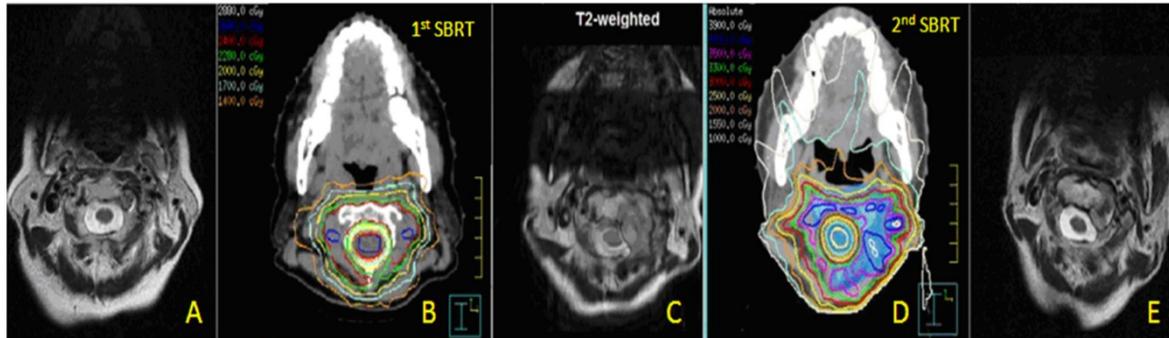
Isabelle Thibault, MD,* Mikki Campbell, MRT(T),*
 Chia-Lin Tseng, MD,*¹ Eshetu G. Atenafu, MSc,²
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 Arjun Sahgal, MD*¹

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Factor	Prior conventional EBRT (n=24)			No prior conventional EBRT (n=32)			
	EBRT	Initial first SBRT course	Salvage second SBRT course	Median total nBED	Initial first SBRT course	Salvage second SBRT course	Median total nBED
Median prescription total dose nBED (Gy ₁₀) and range	23.3 (22.7-32.5)	42.0 (27.8-44.0)	43.8 (31.3-50.0)	111.1	44.0 (33.3-68.0)	43.8 (25.0-49.6)	87.8
Cord PRV nBED (Gy ₂)*							
Median Pmax and range	30.0 (16.9-37.5)	20.8 (12.5-29.9)	21.9 (17.5-26.7)	73.9	31.8 (18.1-40.1)	21.9 (12.4-25.0)	51.3
Median D _{0.1cc} and range	30.0 (16.9-37.5)	17.2 (8.6-21.8)	18.1 (12.4-21.4)	66.8	21.7 (13.2-30.0)	17.7 (8.6-21.7)	40.0
Thecal sac nBED (Gy ₂) [†]							
Median Pmax and range	37.5 (30.0-37.5)	19.7 (14.3-24.7)	24.5 (19.4-32.9)	80.4	33.4 (14.0-67.4)	23.5 (8.8-34.6)	54.6
Median D _{0.1 cc} and range	37.5 (30.0-37.5)	15.3 (11.8-19.4)	20.9 (17.7-25.8)	71.5	25.0 (11.9-60.5)	20.6 (8.4-29.5)	43.6

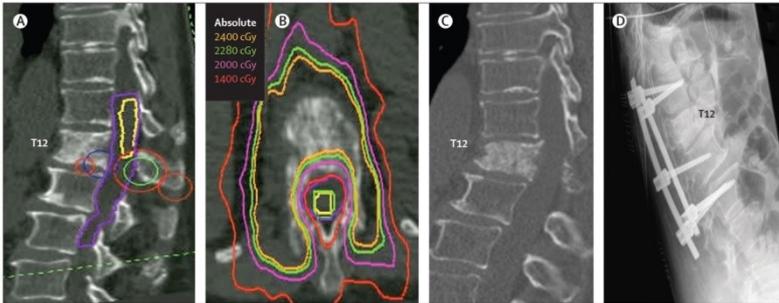


- Keine Myelopathie
- Keine Frakturen

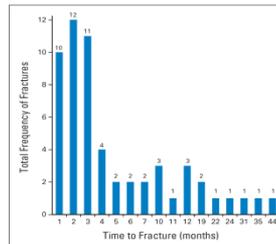
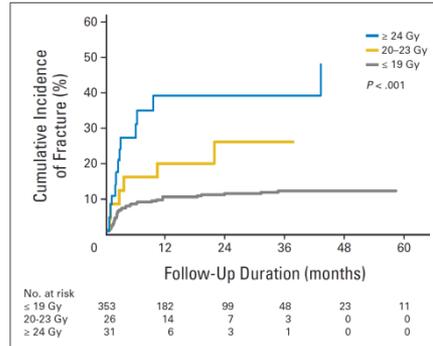
- **Wirbelkörperfrakturen?**
- **Radiogene Myelopathie?**

ERNSTHAFTHE NEBENWIRKUNGEN

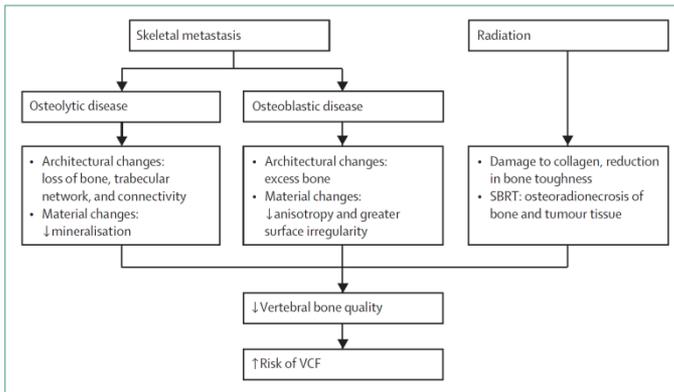
Wirbelkörperfrakturen nach primärer SBRT



11-39% nach spinaler SBRT



Sahgal et al., Lancet 2013



Sahgal et al., JCO 2013

Table 3. Significant Predictors of VCF on Univariate and Multivariate Analysis

Factor	Univariate P	Multivariable Fine and Grey Model		
		P	HR	95% CI
Vertebral body collapse	< .001	Global, < .001		
≥ 50% VCF		.0189	6.92	1.38 to 34.77
< 50% VCF		< .001	8.98	4.48 to 18.00
No VCF but > 50% of vertebral body involved		< .001	4.46	2.08 to 9.57
Dose/fraction, Gy	< .001	Global, < .001		
≥ 24		< .001	5.25	2.29 to 12.01
20-23		< .001	4.91	1.96 to 12.28
Alignment	.0027	< .001	2.99	1.57 to 5.70
Bone lesion type	< .001	.0022	3.53	1.58 to 7.93
Paraspinal/epidural extension	.0036	NS		

NOTE. For vertebral body collapse, the reference is no VCF and less than 50% vertebral body involvement; for dose/fraction, the reference is ≤ 19 Gy/fraction; for alignment was normal, and yphosis/scoliosis and subluxation/translation were grouped as only one patient had subluxation; and the reference for bone lesion was grouped according to mixed and osteoblastic tumor versus osteolytic, given that the majority of VCFs occurred in lytic tumors.

Abbreviations: HR, hazard ratio; NS, not significant; VCF, vertebral compression fracture.

Sahgal et al., JCO 2013

Risikofaktoren:

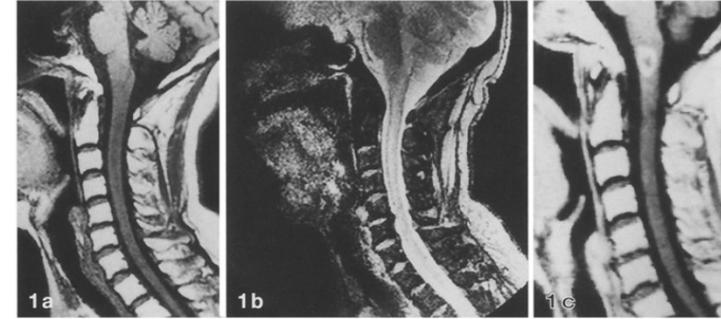
- SF ≥ 20 Gy
- Osteolyse
- Bestehende VCF
- Histologie Lunge oder Leber
- Kyphose/Sklerose
- Alter ≥ 55 Jahre
- 41-60% Beteiligung des Wirbelkörpers

Myelopathie nach primärer SBRT

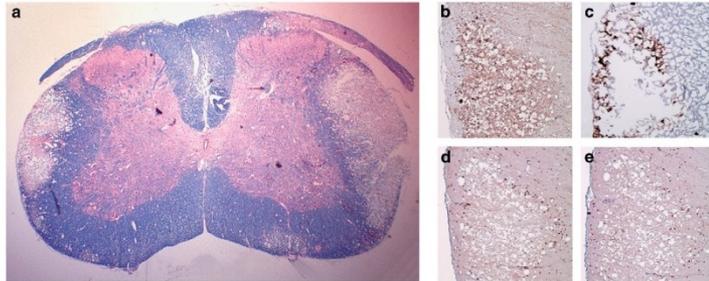


Wong et al., Spinal Cord 2015

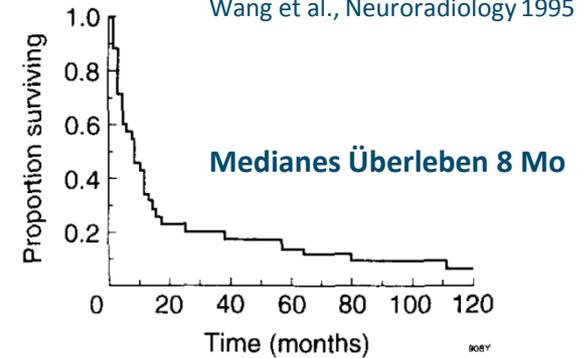
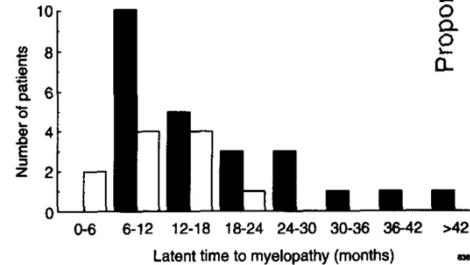
- **Häufigkeit:** äußerst selten nach konv. Fraktionierung mit GD <50 Gy (0.2%) oder SF 8-10Gy
- **Auftreten:** im Median 18 Mo nach RT
im Median 11 Monate nach RE-RT
- **MRT:** niedriges Signal in T1
hohe Intensität in T2
fokale KM-Aufnahme
- **Histologie:** reaktive Gliose, Demyelinisierung
Nekrose der weißen Substanz
vaskuläre Veränderungen in weißer und grauer Substanz



Wang et al., Neuroradiology 1995



Wong et al., Spinal Cord 2015



Wong et al., IJROBP 1994

Myelopathie primäre SBRT: ab welcher Dosis?

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Clinical Investigation: Central Nervous System Tumor

Probabilities of Radiation Myelopathy Specific to Stereotactic Body Radiation Therapy to Guide Safe Practice

Arjun Sahgal, MD,^{*,1} Vivian Weinberg, PhD,¹ Lijun Ma, PhD,¹ Eric Chang, MD,³ Sam Chao, MD,¹ Alexander Muacevic, MD,³ Alessandra Gorgulho, MD,^{**,4} Scott Soltys, MD,¹ Peter C. Gerszten, MD,^{1,4} Sam Ryu, MD,^{1,5} Lilyana Angelov, MD,¹ Iris Gibbs, MD,¹ C. Shun Wong, MD,¹ and David A. Larson, MD, PhD¹

Vergleich der DVH-Parameter von 9 Pat. mit Myelopathie nach spinaler SBRT mit 66 Pat. ohne Myelopathie

Logistic Regression Model zur Abschätzung der Wahrscheinlichkeit für das Auftreten einer Myelopathie

Table 4 Calculated nBED ($Gy_{2/2}$) for 1%, 2%, 3%, 4%, and 5% predicted probabilities of RM based on logistic regression models for various spinal cord volumes (max point, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7 and 0.8 cc)

Volume	nBED ($Gy_{2/2}$): 1% probability	nBED ($Gy_{2/2}$): 2% probability	nBED ($Gy_{2/2}$): 3% probability	nBED ($Gy_{2/2}$): 4% probability	nBED ($Gy_{2/2}$): 5% probability	AUC
Pmax	25.68	33.78	38.56	41.99	44.68	0.87
0.1 cc	12.88	20.79	25.46	28.81	31.44	0.83
0.2 cc	9.29	17.20	21.87	25.22	27.85	0.81
0.3 cc	6.08	14.14	18.90	22.32	25.00	0.79
0.4 cc	3.52	11.74	16.61	20.09	22.83	0.78
0.5 cc	0.76	9.26	14.28	17.89	20.71	0.77
0.6 cc	N/A	6.78	12.02	15.78	18.73	0.76
0.7 cc	N/A	4.00	9.53	13.50	16.60	0.73
0.8 cc	N/A	1.41	7.23	11.40	14.67	0.72

Note: In regard to nBED 1% probability at volumes 0.6 cc or larger, algebraically they are negative doses and therefore left as not applicable (N/A). The area under the curve (AUC) for each model calculated for each volume indicates the fit of the logistic regression model.

Table 3 Comparison of median and mean nBED between the radiation myelopathy (RM) and no-RM cohorts

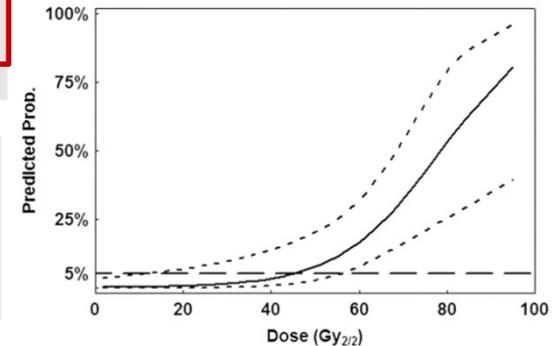
	No-RM cohort (n=66) ($Gy_{2/2}$)	RM cohort (n=9) ($Gy_{2/2}$)	Mann-Whitney/ t test (P value)
Median/mean Pmax volume nBED	35.69/38.82	73.69/70.60	.0003/.0006
Median/mean 0.1 cc nBED	28.32/29.28	56.20/56.63	.001/.006
Median/mean 0.2 cc nBED	27.65/26.89	54.08/52.53	.003/.008
Median/mean 0.3 cc nBED	26.34/25.10	52.46/49.32	.005/.01
Median/mean 0.4 cc nBED	24.36/23.87	49.85/46.69	.006/.01
Median/mean 0.5 cc nBED	20.35/22.64	47.45/44.30	.01/.02
Median/mean 0.6 cc nBED	21.20/22.08	41.86/41.75	.01/.02
Median/mean 0.7 cc nBED	20.54/21.32	39.75/39.44	.02/.03
Median/mean 0.8 cc nBED	19.91/20.69	38.30/37.24	.03/.04
Median/mean 0.9 cc nBED	19.13/20.12	36.55/35.12	.04/.05
Median/mean 1 cc nBED	17.63/19.51	35.05/33.68	.08/.05
Median/mean 2 cc nBED	13.48/16.07	22.15/23.44	.35/.14

Table 5 Predicted Pmax volume absolute doses in Gy for 1 to 5 SBRT that result in 1%-5% probability of radiation myelopathy (RM)

	1 fraction Pmax limit (Gy)	2 fractions Pmax limit (Gy)	3 fractions Pmax limit (Gy)	4 fractions Pmax limit (Gy)	5 fractions Pmax limit (Gy)
1% probability	9.2	12.5	14.8	16.7	18.2
2% probability	10.7	14.6	17.4	19.6	21.5
3% probability	11.5	15.7	18.8	21.2	23.1
4% probability	12.0	16.4	19.6	22.2	24.4
5% probability	12.4	17.0	20.3	23.0	25.3



Algami et al., Adult CNS Radiation Oncology pp 533-547



SBRT in der Re-Bestrahlung

Author & Year	No. of Tumors/Pts Treated	Median Follow-up (mos)	Local control	Complete Pain Response	Overall Survival	Median Tumor dose (No. Of Fractions (previous cEBRT))
Sahgal et al., 2009	37/25	7	96%@1 yr	NA	45%@ 2 yrs	24 Gy /3 Fx (median dose 36Gy/14 Fx)
Choi et al., 2010	51/42	7	97%@6 mos / 73%@ 1 yr	65%	68%@ 1 yr	Median 20 Gy /2 Fx (median cEBRT EQD2=40Gy)
Mahadevan et al., 2011	81/60	12	93@ last follow-up	NA	Median OS: 11 mos	25-30Gy/5Fx or 24 Gy/3Fx (median dose 30 Gy/ 10 Fx)
Garg et al., 2011	63/59	17.6	76%@1 yr	NA	76%@1 yr	27 Gy/3 Fx or 30 Gy/5Fx (median dose 30 Gy)
Damast et al., 2011	97/95	12.1	66%@1yr	46%	52-59%@1yr	20 Gy/5 Fx or 30 Gy/5Fx (median dose 30 Gy)
Chang et al. 2012	54/49	17.3	81%@1yr	81% (1 yr)	Median OS: 11 mo	20.6 G/1Fx (mean cEBRT EQD2 39.2 Gy)
Thibault et al., 2015	56/40 (partially 2nd SBRT)	6.8	81.6%@1yr/71.5% @2yrs	NA	48%@1yr	30 Gy/ 4 Fx
Hashmi et al., 2016	215/247	8.1	93%@6mos/83%@ 1yr	53.9% (@ last Follow-up)	64%@6mos/48% @1yr	median SBRT dose: 18Gy/1Fx (cumulative dose 68.2Gy)

SBRT in der Re-Bestrahlung: Toxizität

Author & Year	No. of Tumors/Pts Treated	Median Follow-up (mos)	Local control	Complete Pain Response	Overall Survival	Median Tumor dose (No. Of Fractions (previous cEBRT))	VCF	No. Of Neurological adverse events
Sahgal et al., 2009	37/25	7	96%@1 yr	NA	45%@ 2 yrs	24 Gy /3 Fx (median dose 36Gy/14 Fx)	NR	0
Choi et al., 2010	51/42	7	97%@6 mos / 73%@ 1 yr	65%	68%@ 1 yr	Median 20 Gy /2 Fx (median cEBRT EQD2=40Gy)	NR	1
Mahadevan et al., 2011	81/60	12	93@ last follow-up	NA	Median OS: 11 mos	25-30Gy/5Fx or 24 Gy/3Fx (median dose 30 Gy/ 10 Fx)	NR	4
Garg et al., 2011	63/59	17.6	76%@1 yr	NA	76%@1 yr	27 Gy/3 Fx or 30 Gy/5Fx (median dose 30 Gy)	NR	2
Damast et al., 2011	97/95	12.1	66%@1yr	46%	52-59%@1yr	20 Gy/5 Fx or 30 Gy/5Fx (median dose 30 Gy)	9	0
Chang et al. 2012	54/49	17.3	81%@1yr	81% (1 yr)	Median OS: 11 mo	20.6 G/1Fx (mean cEBRT EQD2 39.2 Gy)	12	0
Thibault et al., 2015	56/40 (partially 2nd SBRT)	6.8	81.6%@1yr/71.5% @2yrs	NA	48%@1yr	30 Gy/ 4 Fx	0	0
Hashmi et al., 2016	215/247	8.1	93%@6mos/83%@ 1yr	53.9% (@ last Follow-up)	64%@6mos/48% @1yr	median SBRT dose: 18Gy/1Fx (cumulative dose 68.2Gy)	11 (5 de novo/ 6 fracture progression)	0

WENN JA, WIE?

Wenn ja, wie? Welche Patienten?

Re-irradiation SBRT

TABLE 3. Summary of the current literature specific to re-irradiation SBRT

Authors & Year	No. of Tumors/Pts Treated	Median Follow-Up (mos)	Local Control	Complete Pain Response	OS	Median Tumor Dose/ No. of Fractions (previous cEBRT)	Significant Predictors of Local Control	Significant Prognostic Factors for OS
Sahgal et al., 2009	37/25	7	96% @ 1 yr	NA	45% @ 2 yrs	24 Gy/3 Fx (median dose 36 Gy/14 Fx)	Distance btwn GTV & CNS <1 mm	NA
Choi et al., 2010	51/42	7	87% @ 6 mos/73% @ 1 yr	65%	68% @ 1 yr	Median 20 Gy/2 Fx (median cEBRT EQD2 = 40 Gy)	<12-mo time interval btwn cEBRT & SBRT; presence of epidural disease	NA
Mahadevan et al., 2011	81/60	12	93% @ last follow-up	NA	Median OS: 11 mos	25–30 Gy/5 Fx or 24 Gy/3 Fx (median dose 30 Gy/10 Fx)	NA	NA
Garg et al., 2011	63/59	17.6	76% @ 1 yr	NA	76% @ 1 yrs	27 Gy/3 Fx or 30 Gy/5 Fx (median dose 30 Gy/NA Fx)	NA	Prior cEBRT dose >35 Gy, trend for time interval to re-treat >12 mos (p = 0.05) on univariate analysis
Damast et al., 2011	97/95	12.1	66% @ 1 yr	46%	52–59% @ 1yr	20 Gy/5 Fx or 30 Gy/5 Fx (median dose 30 Gy/NA Fx)	30 Gy/5 Fx associated w/ better local control vs 20 Gy/5 Fx	KPS, radiosensitive histology; time interval to re-treat >12 mos
Chang et al., 2012	54/49	17.3	81% @ 1 yr	81% (1 yr)	Median OS: 11 mos	20.6 Gy/1 Fx (mean cEBRT EQD2 39.2Gy)	Presence of epidural disease	NA
Thibault et al., 2015	56/40 (24/56 cEBRT followed by 2 courses SBRT; 32/56 SBRT & a 2nd course SBRT)	6.8	81.6% @ 1 yr/71.5% @ 2 yrs	NA	48% @ 1 yr	Median 30 Gy/4 Fx (24/56, median cEBRT = 22.5 Gy/5 Fx & 1st course SBRT = 24 Gy/2 Fx; 32/56 median 1st course SBRT = 24 Gy/2 Fx)	Presence of paraspinal soft tissue disease	Time interval btwn 1st SBRT & 2nd SBRT

Hashmi et al.,
J Neurosurg Spine 2016

GTV = gross tumor volume; NA = not available; OS = overall survival; pts = patients.

PRO:

- Keine epidurale Ausbreitung/spinale Kompression
- Abstand zwischen GTV und RM > 1mm
- >12 Mo zw. cEBRT und SBRT
- Kein paraspinaler Tumoranteil
- KPS ≥ 70%
- Radiosensible Tumoren
- Eher Einzeit-SBRT?

Wenn ja, wie? Welche Dosis?



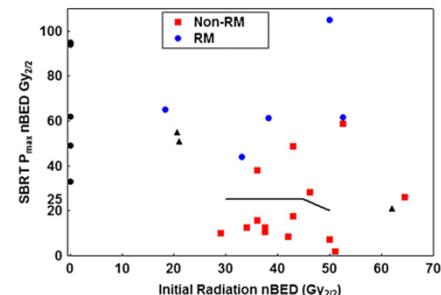
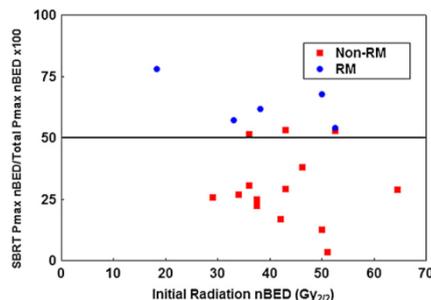
Vergleich der DVH-Parameter von 5 Pat. mit Myelopathie nach cEBRT sowie Re-RT mit spinaler SBRT mit 14 Pat. ohne Myelopathie

Analyse der Maximumdosis, $D_{01.cc}$, $D_{1.0cc}$ und $D_{2.0cc}$ im Spinalkanal und Berechnung der EQD2

Table 4. Comparison of total nBED at each specified thecal sac volume between the RM and no-RM groups

	Median RM (Gy _{2/2})(range)	Median No-RM (Gy _{2/2})(range)	Mann-Whitney prob.	Mean RM (Gy _{2/2})(95% CI)	Mean No-RM (Gy _{2/2})(95% CI)	ANOVA prob.
Total	99.6	52.4	0.01	105.8	62.3	0.001
P _{max} nBED	(77.2–154.9)	(39.1–111.2)		(84.3–127.4)	(50.3–74.3)	
Total	92.8	49.9	0.01	94.7	55.8	0.001
0.1 cc nBED	(70.3–145.6)	(36.5–98.1)		(75.8–113.6)	(45.2–66.4)	
Total	69.3	46.8	0.03	77.6	50.4	0.01
1.0 cc nBED	(52.3–132.6)	(34.0–79.7)		(60.1–95.2)	(40.5–60.2)	
Total	63.3	45.6	0.08	68.6	48.1	0.03
2.0 cc nBED	(43.0–120.4)	(32.8–67.6)		(52.5–84.7)	(39.1–57.2)	

Abbreviations: ANOVA = analysis of variance; CI = confidence interval; nBED = normalized biologically effective doses; prob. = probability; RM = radiation myelopathy; SBRT = stereotactic body radiotherapy.



Re-RT mit SBRT nach **mindestens 5 Mo** nach cEBRT mit einer **Dmax am Spinalkanal von 20-25 Gy EQD2 (SBRT)** und einer **Gesamtmaximumsdosis am Spinalkanal von rund 70 Gy EQD2 (SBRT+cEBRT)** sowie einer **Dmax SBRT am Spinalkanal von maximal 50%** der **Gesamtmaximumsdosis am Spinalkanal** scheint sicher

Wenn ja, wie? Welche Dosis?

Table 6. Reasonable reirradiation SBRT doses to the thecal sac P_{max} following common initial conventional radiotherapy regimens

Conventional Radiotherapy (nBED)	1 fraction: SBRT dose to thecal sac P_{max}	2 fractions: SBRT dose to thecal sac P_{max}	3 fractions: SBRT dose to thecal sac P_{max}	4 fractions: SBRT dose to thecal sac P_{max}	5 fractions: SBRT dose to thecal sac P_{max}
0*	10 Gy	14.5 Gy	17.5 Gy	20 Gy	22 Gy
20 Gy in 5 fractions (30 Gy _{2/2})	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
30 Gy in 10 fractions (37.5 Gy _{2/2})	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
37.5 Gy in 15 fractions (42 Gy _{2/2})	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
40 Gy in 20 fractions (40 Gy _{2/2})	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
45 Gy in 25 fractions (43 Gy _{2/2})	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
50 Gy in 25 fractions (50 Gy _{2/2})	N/A	11 Gy	12.5 Gy	14 Gy	15.5 Gy

Abbreviations: N/A = not applicable; nBED = normalized biologically effective doses; SBRT = stereotactic body radiotherapy.

* These dose limits are based on our prior publication for spinal cord tolerance in patients treated with SBRT and no prior history of radiation (7).

Sahgal et al., IJROBP 2012

Leitlinien (International stereotactic radiosurgery society)

TABLE 6. ISRS recommendations

Recommendation	Level of Evidence
Following cEBRT, retreatment w/ SBRT is a recommended therapeutic option in suitable patients based on multidisciplinary assessment	III
Following SBRT, retreatment w/ SBRT is a treatment option in suitable patients based on multidisciplinary assessment	III
For patients w/ clinical features concerning for malignant epidural spinal cord compression, mechanical instability, or baseline vertebral body compression fracture, the radiation oncologist should consult a spine surgeon before the patient undergoes SBRT	II

- **Aufgrund der geringen Datenlage keine klaren Empfehlungen zur Dosierung**
- **Sorgfältige Konturierung der neuralen Risikostrukturen**
- **Bezüglich Rückenmarksdosis Verweis auf die Arbeiten von Sahgal et al. (IJROBP 2012, 2013)**

Zusammenfassung

Bisher nur begrenzte Datenlage zur Re-RT mittels SBRT, allerdings.....

- **Bessere Ansprechraten (Schmerzen!) und höhere lokale Kontrolle im Vergl. zur cEBRT**
- **Zur primären SBRT vergleichbare Raten an Wirbelkörperfrakturen**
- **Bei Einhaltung der Dosisgrenzwerte scheint das Risiko für eine Myelopathie nur gering erhöht** (Sahgal et al. IJROBP 2012 + 2013)
- **(Nur) Indikation für klar selektionierte Patienten** (KPS, Abstand zur primären RT, kein paraspinaler Anteil, Abstand GTV zu RM, Oligometastasierung?, Oligoprogression?)
- **Bei spinaler Kompression, Instabilität oder bestehender Wirbelkörperfraktur interdisziplinäre Diskussion des Falls mit den Kollegen der Neurochirurgie dringend indiziert**

Vielen Dank für die Aufmerksamkeit!

Fragen.....?