Radiotherapy and Oncology 136 (2019) 130–135

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Diabetes increases the risk of serious adverse events after re-irradiation of the spine

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ARTICLE INFO

Article history:
Received 28 November 2018
Received in revised form 26 March 2019
Accepted 2 April 2019
Available online 17 April 2019

Keywords:
Metastatic spinal cord compression
Radiotherapy
Palliative
Spine
Toxicity

ABSTRACT

Introduction: In this study we investigate the risk of radiation-induced serious adverse event of the spine in a large cohort of consecutive retreated patients with palliative radiotherapy (RT) for metastatic cancer in the spine.

Methods and materials: From 2010 to 2014, 2387 patients received spinal irradiation with a palliative intent for metastatic spinal cord compression at our institution. The patients were reviewed for prior RT and 220 patients had received re-irradiation of the spine. Clinical and treatment data were obtained from the patients' records and the RT planning system.

Results: Patients had metastatic disease from breast, prostate, lung, hematological or other cancers (22.7%, 21.8%, 21.4%, 3.2% and 30.9%, respectively). Median follow-up was 99 days. Median cumulative EQD2 was 57.6 Gy_2; range: 20.0–90.0 Gy. Spinal events related to re-irradiation were observed in fourteen patients; six patients were diagnosed with radiation-induced myelopathy (RIM) and nine patients with radiation-induced vertebral fracture (RIF). In a multivariate analysis, diabetes was related to increased risk of toxicity (HR = 7.9; $P = 0.003$).

Conclusion: The incidence of RIM and RIF (6 and 9 out of 220 patients, respectively) was low in our cohort of re-irradiated patients. Patients with diabetes had a higher risk of adverse events which should be considered before re-irradiation of the spine.

Radiation induced injury of the central nervous system may be difficult to characterize given the low incidence [1]. Further, the diagnosis of radiation-induced myelopathy (RIM) can be difficult to clinically separate from symptoms originating from disease progression. However, the consequences for the patients with RIM are severely debilitating and include loss of neurological function and paralysis, which makes it important to avoid. The spinal cord is generally considered a serial organ from a radiobiological standpoint and the radiation dose constraint of spinal cord dose is generally prioritized higher than the target dose in radiotherapy planning, due to the critical function of the spinal cord [2]. A reason for RIM can be re-irradiation of the spinal cord that may exceed the organ's radiation dose tolerance. In a retreatment setting, it is often challenging to estimate the actual risk of RIM, in relation to the estimated clinical benefit of radiotherapy of the symptoms at hand. Both preclinical and clinical studies show that the risk of RIM is associated with radiation dose, time between treatments and the cumulative dose [2,3].

Previous works have addressed the issue of spinal re-irradiation and provided a basis for risk estimation of myelopathy after secondary radiation of the spinal cord [3]. Samples of patients from randomized trials have confirmed the low risk of RIM, with no cases of RIM in a limited number of patients treated with re-irradiation, however the frequency of RIM in larger populations remains unknown [4,5]. Approximately half of all cancer patients should require radiotherapy in the optimal use of radiation in cancer care, with a retreatment rate of around 20% [6]. With the use of palliative radiotherapy in numerous settings, overlap with prior treatment has become a common clinical consideration. In palliation of pain from bone metastases a single fraction of radiotherapy has been recommended if re-irradiation if necessary [7]. In metastatic spinal cord compression within a prior radiotherapy field, retreatment with radiotherapy can preserve gait function in the majority of patients with a low risk of RIM during patients remaining time of life [8]. An additional complication following

Abbreviations: RT, radiotherapy; RIM, radiation induced myelopathy; RIF, radiation induced fracture; SBRT, stereotactic body radiotherapy.

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https://doi.org/10.1016/j.radonc.2019.04.002
0167-8140/

radiotherapy of the spine is radiation-induced vertebral fracture (RIF). The risk of RIF is well known for stereotactic radiosurgery of the spine, and appears to be associated with the radiation dose delivered to the bony structures [9]. Following irradiation of spinal metastases RIF is a known risk [10]. However, in terms of re-irradiation of complicated spinal metastases the incidence of RIF is not well established. Still the risk of RIF could be a possible explanation for differences in outcomes following multiple and single fraction re-irradiation schedules [11].

Palliative re-irradiation seems a feasible option if the benefit of treatment outweighs the risk of late toxicity. However, in light of the poorly understood risk of RIM and RIF, the clinical decision is not easy to make. With this work we intended to add to the limited information available. The aim of this study was therefore to evaluate the risk of RIF and RIM in a large consecutive cohort of patients receiving multiple courses of spinal irradiation with a palliative intent. The analysis further evaluates factors associated with increased risk of toxicity.

Methods and materials

Patients and data collection

All patients who received palliative spinal irradiation in the years 2010 until 2014 were identified in the clinical radiotherapy planning system. Staff notes from radiotherapy planning were reviewed regarding potential overlap with prior radiotherapy, at either our facility or another radiotherapy department. All previous radiotherapy plans with the spinal cord within the radiation field regardless of treatment intent or target was analyzed. For patients with overlap at the spinal cord, information on the first (any irradiation) and second irradiation (palliative spinal irradiation) was retrieved. Information on diagnosis, time of death and recorded toxicity were obtained from clinical charts. Clinical factors were obtained from patients' charts. Smoking status was registered as never, prior or active. Both type 1 and type 2 diabetes was recorded if diabetes was reported as a known diagnosis or if diabetic medicine was prescribed. Steroid induced hyperglycemia during radiotherapy was not recorded. All data were obtained with approval of the Danish Ministry of Health as required by local law. The database was approved by the Danish Data Protection Agency (2012-58-0004).

Cases of myelopathy were considered a diagnostic possibility, if the patient had lost neurologic function without evidence of progression of metastatic spinal cord compression. If the patient underwent new imaging procedures due to symptoms, the frequency of spinal fractures within the radiation field was recorded.

Biologically effective dose (BED) in 2 Gy equivalent fractions was calculated for the prescribed dose to the vertebrae as EDQ2 with an α/β of 2. In case the spinal cord was not separately delineated, the plan was reviewed and the EDQ2 was calculated from maximum prescribed dose to spinal cord by manually inspecting the dose distribution. The infield length of the spinal cord was measured on simulation CT. In case only radiographs of prior treatment fields were available according fields were extrapolated onto simulation CT and measured within these. Data on overlapping field in prior radiotherapy plans were not necessarily planned on CT or available in DICOM format. Time between treatment courses and cumulative dose was recorded [3]. Volume is a known risk factor of toxicity after radiation of the cord and therefore size of field overlap was registered [12].

Follow-up data on all patients were collected using the electronic patients charts for patients living within Denmark. Follow-up was until death or last follow-up on September 1st 2016. Patients referred from the Faroese Islands and Greenland, autonomous regions of Denmark were lost to follow-up and disregarded in this study.

Statistics

The Kaplan–Meier method was used to estimate the risk of toxicity from the date of second RT. The log-rank test was used to compare factors. For patients still alive, the last follow-up was September 1st 2016. Median follow up was calculated as inverse Kaplan–Meier. Potential independent variables that were explored as risk factors of cumulative toxicity after re-irradiation were as follows: breast cancer as primary, active smoking, gender, palliative intent of first radiotherapy course, the length of medullary field overlap, RT dose of first treatment, cumulative dose, days between first and second RT, diabetes and age. All radiation doses were recalculated to EDQ2 with an α/β of 2 and summed for cumulative RT dose. Factors significant ($p < 0.05$) in the univariate Cox analysis were included in multivariate analysis. In the multivariate analysis time between 1st and 2nd treatment course, dose of each treatment course and cumulative dose were included as variables as these are expected risk factors for myelopathy according to previous research [2,3,13]. Statistical analyses were performed using SPSS version 22 (IBM, US).

Results

Between January 1st 2010 and December 31st 2014, 2387 patients were planned with palliative radiotherapy due to metastatic spinal cord compression. There was a potential overlap with prior RT fields in 249 patients. On review of the RT plans, 29 patients had no overlap of radiotherapy fields or did not receive the prescribed radiotherapy. The remaining 220 patients received radiotherapy with overlap of a prior field (see Fig. 1). Patients had metastatic disease from breast, prostate, lung, hematological or other cancers (22.7%, 21.8%, 21.4%, 3.2% and 30.9% respectively). Patients' characteristics are shown in Table 1. Median time from 1st irradiation to 2nd irradiation was 336 days, range 15 days-33 years. Median number of days from 2nd irradiation to death was 91 days (range 1 days-5 years). The median follow up time was 99 days. Median cumulative dose was 57.6 Gy_2 (EQD2, with $\alpha/\beta = 2$), range: 20.0–90.0 Gy_2. No patient received more than 98 Gy_2 BED to the spinal cord in a single course. Median overlap between RT fields was 6.2 centimeters (range 0.6–23.0 cm).

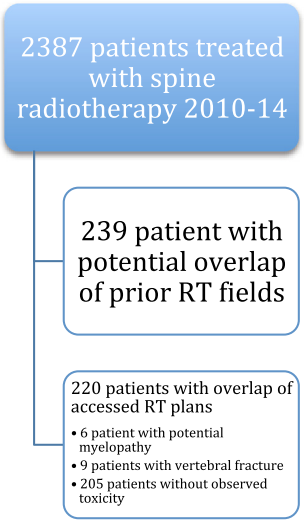

Fig. 1. Patients who received radiotherapy (RT) at Rigshospitalet, Copenhagen 2014 and reviewed for inclusion in the study.

Myelopathy or vertebral fracture likely related to re-irradiation was observed in fourteen patients. One patient developed myelopathy, for an additional five patients, myelopathy could not be ruled out from retrospective observations of declining gait function. Nine patients experienced a vertebral fracture within the treatment field, which resulted in neurological deficit in eight of these patients. One patient experienced both a vertebral fracture and possibly myelopathy. The lowest cumulative dose resulting in one event was 46.3 Gy. Example of RT plans and imaging follow-up is provided in Fig. 2. To analyze the risk of toxicity over time, we performed a Kaplan–Meier analysis of RIM, RIF and cumulative toxicity (Fig. 3). We then compared the curves with regard to time between radiotherapy, cumulative dose and size of overlapping fields and diabetes. Fig. 4 shows a Kaplan–Meier plot for cumulative toxicity of radiotherapy cumulative dose, RT field overlap more than 6.2 cm and time between treatments more than 335 days. Separation of curves is seen for overlap of more than 6.2 cm with a $P = 0.14$(log-rank test). No separation of curves is seen with cumulative dose and time between radiotherapy. Interaction between smoking status/cumulative doses and diabetes/cumulative dose was not found by visually inspection of data (not shown). In univariate cox regression analysis the diagnosis of diabetes (insulin dependent or non-insulin dependent) was significantly associated with cumulative toxicity with a hazard ratio of 5.04 (CI95% 1.51–17.0) $P = 0.009$. Univariate cox regression was for RIF and RIM respectively: RIF: HR = 2.51 (CI95% 0.52–12.12) $P = 0.25$ and RIM: HR = 10.3 (CI95% 1.46–74.3) $P = 0.02$. In multivariate Cox regression analysis diabetes was an independent risk of cumulative toxicity after re-irradiation ($P = 0.003$, HR = 7.90). Lowest dose in a patient with an adverse event and non-insulin dependent diabetes was 51.0 Gy. Additional details are available in Tables 2–4.

Discussion

In patients with neurological deterioration due to metastatic progression within a previously treated site of the spinal cord, additional radiotherapy will add an increased risk of toxicity. The consequences of omitting radiotherapy can be just as devastating with loss of gait function due to the compression of the cord. The current risk estimates of toxicity are based on published cases of RIM in the scientific literature. In this retrospective study of a consecutive cohort, 9.2% of patients treated with palliative radiotherapy of the spine had field overlap with previous radiation. As both previous curative and palliative treatments were taken into consideration, this reflects a common clinical scenario.

The Kaplan–Meier curves show the risk of toxicity over time following re-irradiation of the spine. Most importantly, by stratification of the patients into risk groups we find that diabetes substantially impacts the actuarial risk of spinal toxicity following re-irradiation, which we believe is a novel finding. Further, we find that diabetes appeared as a strong risk factor of toxicity in both univariate and multivariate Cox regression analyses. Diabetic peripheral neuropathy is a known complication of poor glycemic control. Pathological changes also appear within the spinal cord with atrophy and demyelination that could render the patient susceptible for RIM [14]. It is unknown if these changes within the spinal cord increases the radiation sensitivity. Diabetes also has an effect on bone tissue resulting in increased risk of fractures for radiotherapy patients. The contribution of diabetes to bone fragility and fracture risk in patients with diabetes and cancer is presently unclear [15]. Similarly, whether osteoporotic drugs benefit these diabetic patients with normal bone mineral density is unknown. However, diabetes is a well-known risk factor for bone fractures; both type 1 and type 2 diabetes mellitus increases the

Table 1
Patients characteristics: re-irradiation of the spinal cord.

		Count	Percentage	Mean	Median
Gender	Female	99	45.0%		
	Male	121	55.0%		
Age at 2nd radiotherapy (years)				65	
Malignancy	Prostate	48	21.8%		
	Lung	47	21.4%		
	Breast	50	22.7%		
	Hematology	7	3.2%		
	other	68	30.9%		
Surgical intervention	Yes	38	17.3%		
	No	182	82.7%		
Intent of first radiotherapy course	Palliative	170	77.3%		
	Curative	50	22.7%		
Diagnosis of diabetes	No	196	89.1%		
	IDDM	6	2.7%		
	NIDDM	17	7.7%		
	Unknown	1	0.5%		
Smoking status	Never	76	34.5%		
	Former	59	26.8%		
	Current	51	23.2%		
	Unknown	34	15.5%		
Field overlap (centimeters)					6.2
Cumulative dose (Gy)					57.59
Time between 1st and 2nd radiotherapy course (days)					336
Diagnosis of myelopathy	No	212			
	Yes	1			
	Not to be ruled out	5			
Spinal fracture after radiotherapy	Yes, symptomatic	8			
	Yes, asymptomatic	1			
	No fracture	210			
	Unknown	1			

220 cases of spinal re-irradiation, Copenhagen 2010–2014
Insulin dependent diabetes mellitus (IDDM), Non-insulin dependent diabetes mellitus (NIDDM)

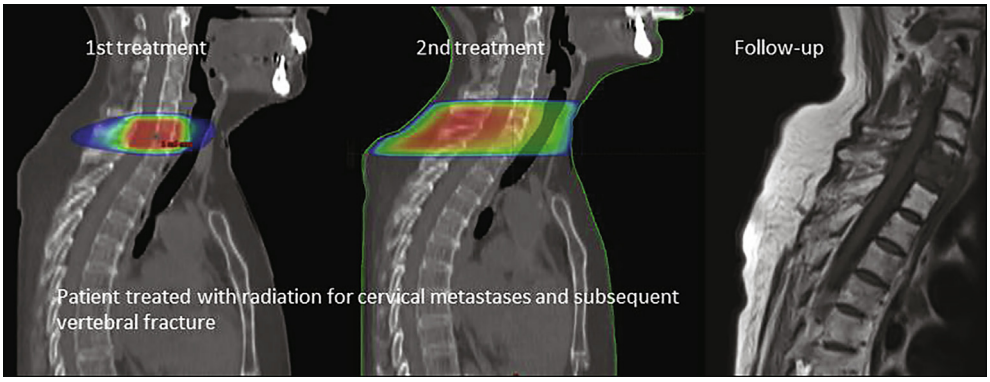

Fig. 2. Example of re-treatment.

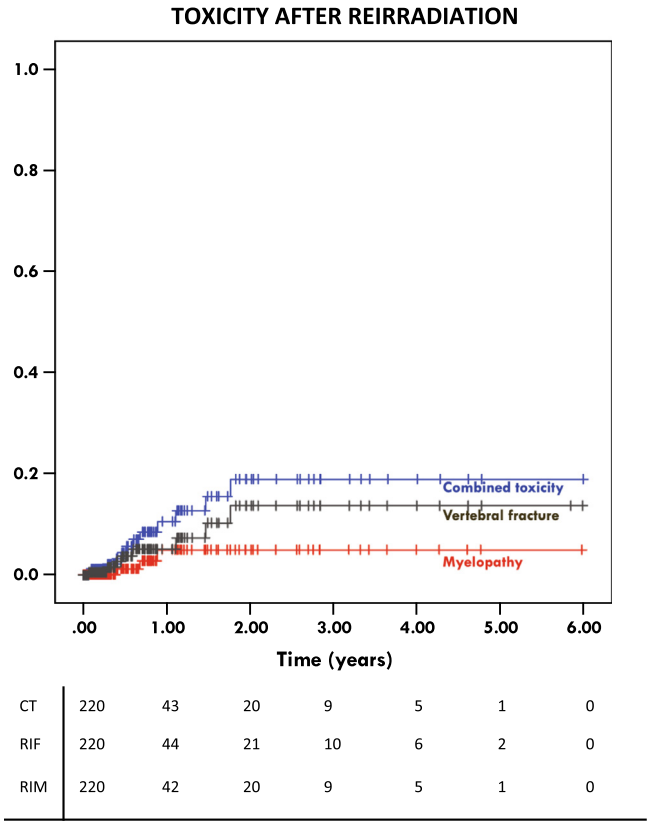

Fig. 3. Kaplan–Meier's curve of risk of toxicity censored until last follow-up or death from last radiotherapy. Number of patients at risk by CT: Cumulative toxicity, RIM: Radiation induced myelopathy, RIF: Radiation induced fracture.

risk of fractures due to multiple changes in bone turnover and bone microstructure that impair bone strength [15]. The complex underlying physiological changes affecting the risk of vertebral fractures after RT in cancer patients with diabetes is unknown and to our knowledge not described in other cohorts of adverse events after RT. The risk of fractures was somewhat higher than myelopathy in our data, which could suggest that the degree of instability of the spine is greater for patients with diabetes. In a multivariate analysis, we could not establish any correlation between any known risk factors of myelopathy and re-irradiation. This could possible be due to institution's practice of minimizing the re-irradiation dose within time intervals less than 6 months, and keeping RT course doses below 98 Gy_2 BED and cumulative doses below 135.5 Gy_2 BED [3].

To evaluate and guide treatment choices of patients on the effectiveness of re-irradiation of spinal metastasis and the risk of toxicity there is a need of more prospective data. As the median number of days from second radiotherapy to death was 91 days, some of the patients did not benefit from the 2nd course of radiotherapy. A large proportion of patients survived long enough to experience the full potential benefit from treatment but in a population with a short life expectancy the risk of treating moribund patients should be considered [16]. Re-irradiation should still be administered as a palliative measure to prevent the devastating consequences of true spinal cord compression since palliative radiotherapy may have an early effect of pain relief ten days after radiotherapy in the case of bone metastases [17]. In patient management the maintenance of neurological function is of outmost importance. Therefore treatment with a higher risk of toxicity can be clinical relevant if the neurological outcome of no intervention remains the same or worse. This study shows that the risk of death from metastatic cancer is more likely than the risk of experiencing toxicity, which concurs with previous studies [4,18]. The actuarial risk for higher risk of toxicity increases with time, up to 1–2 years at which point few patients remain alive and available for analysis. Since the risk of dying before experiencing toxicity is much higher we did not perform a competing risk analysis. We therefore investigated the risk of cumulative toxicity given that the patients are alive. Patients with spinal metastases treated with repeated radiotherapy and potential long-term survival should be considered for spinal instrumentation.

The use of stereotactic body radiotherapy (SBRT) has been occasionally advocated for re-treatment given the possibility of lowering dose to the spinal cord [19]. However, we find that the risk of RIM appears rather low in the present work. The use of SBRT does not relieve the patient from the potential risk of spinal fracture and following vertebral instability. Combined with the fact that studies on toxicity after SBRT on spine also have shown a risk of vertebral fractures with dose escalation, should the argument for the use of SBRT in spinal re-irradiation therefore be to maximize tumor control with the delivery of higher BED more than to minimize the risk of RIM [9,20,21]. However, the lack of randomized controlled trial data and the level of evidence on toxicity following re-irradiation is currently very sparse [22]. The aim of future studies should both address the need for spinal stabilization in long-term survivors but also relieve patients of burdensome treatments with no benefit.

The result of the current study should be considered in the light of other factors associated with toxicity after radiotherapy of metastatic spinal cord compression. Others factors, such as single fraction palliative radiotherapy in uncomplicated spinal metastases, have been shown to be associated with increased risk of vertebral fractures [10]. Due to the retrospective nature of this study, no

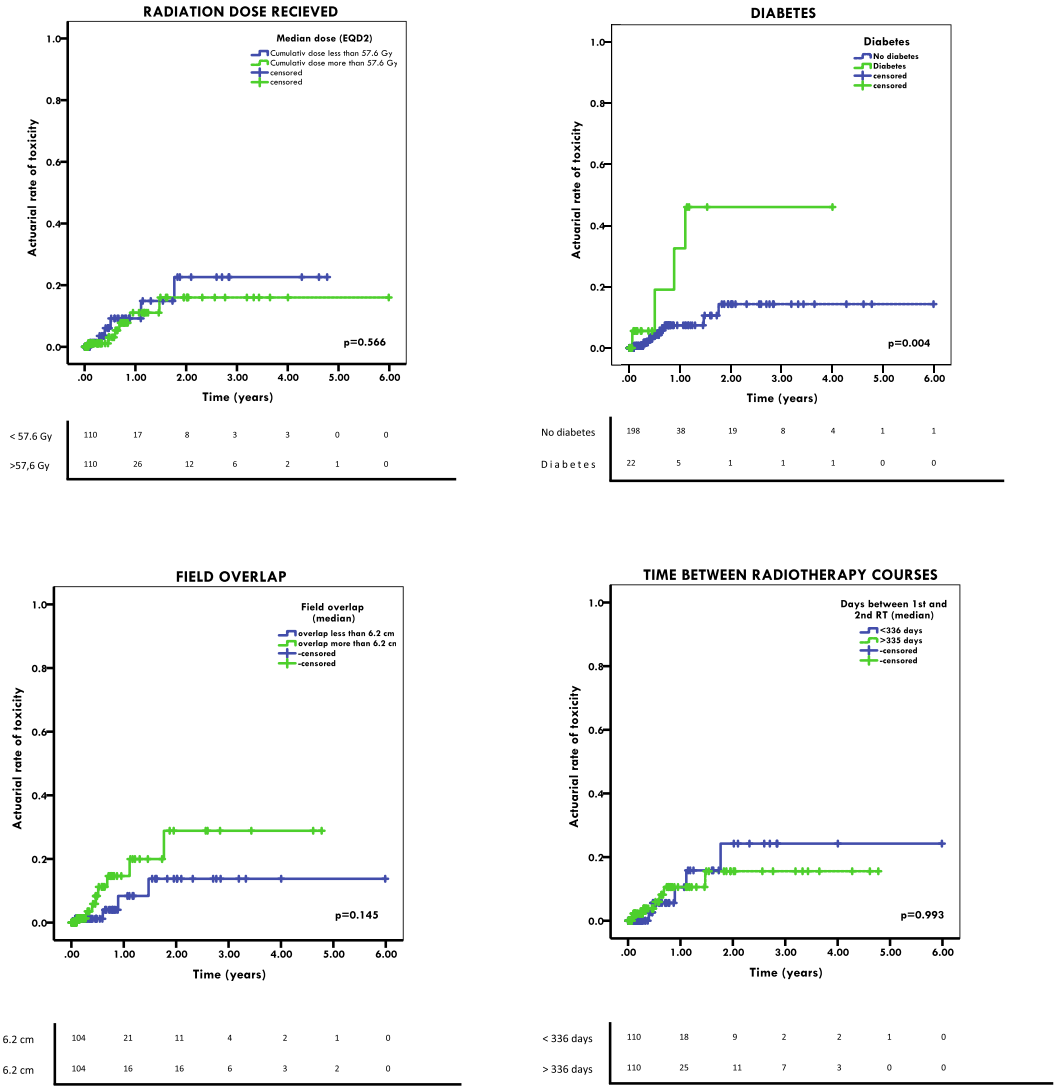

Fig. 4. Kaplan–Meier's curves of risk of toxicity for patient groups stratified by: Size of radiotherapy field overlap (log-rank, $P = 0.14$); Time between radiotherapy treatments 336 days or more (Log-rank, $P = 1.00$); Cumulative dose 57.6 Gy or more (Log-rank, $P = 0.57$); Diagnose of diabetes (Log-rank, $P = 0.004$). Number of patients at risk by stratification group.

Table 2
Cox proportional hazard regression univariate analysis of association with toxicity after re-irradiation of the spine.

Variable	HR	CI (95%)	*P*-value
Diabetes	5.04	1.50–16.93	0.01
Palliative intent of 1st RT	1.04	0.28–3.86	0.95
Breast Cancer	0.47	0.13–1.79	0.27
Active Smoker	0.37	0.05–2.91	0.34
Field overlap above 6.2 cm	2.40	0.72–8.00	0.15
Male sex	1.60	0.42–1.60	0.42
Cumulative dose above median (>57.6 Gy)	0.72	0.23–2.25	0.58
Age (years)	1.03	0.97–1.09	0.42
MSCC surgery	0.57	0.17–1.91	0.37
Days between RT treatments	1.00	0.32–3.16	1.00

Table 3
Cox proportional hazard regression multivariate analysis of association with toxicity after re-irradiation of the spine.

Variable	HR	CI (95%)	*P*-value
Diabetes	7.903	2.025–30.842	0.003
Field overlap above 6.2 cm	3.263	0.873–12.197	0.079
Days between RT treatments	1.316	0.381–4.550	0.664
Cumulative dose above median (>57.6 Gy)	1.053	0.317–3.491	0.933

standard follow-up for toxicity was applied. The true number of asymptomatic vertebral fractures is therefore unknown within this cohort. Numerous conditions can affect the ability to walk in a cohort of patients in palliative care. In some patients further diagnostic procedures is omitted due to lacking indications for treatment in end of life care.

The current study has no standardized outcome data and therefore cannot guide on efficacy of re-irradiation in palliative setting. The effect on pain relief after re-irradiation has been shown to be around 60% in bone metastases [23]. Whether this can be translated into an effect of the same magnitude in spinal cord compression is unknown. We are currently investigating the proportion of patients who remain ambulatory after re-irradiation of spinal cord compression in a prospective study.

Table 4
Cases with radiation-induced myelopathy (RIM).

Malignancy	Status	Field overlap	Diabetes	RIM	RIF	Gender	Age	Time between RT	1st dose (Gy)	2nd dose (Gy)	3rd dose (Gy)	Σ dose (Gy)
NSCLC	Dead	7.1 cm	No	Possibility	Yes, neuro deficit	Male	75	15	20.00	26.25	0.00	46.25
NSCLC	Alive	8.8 cm	No	Possibility	No fracture	Female	43	820	43.75	30.00	0.00	73.75
Colon	Dead	5.3 cm	NIDDM	Possibility	No fracture	Male	51	220	37.50	12.00	12.00	61.50
Breast	Dead	11 cm	No	Possibility	No fracture	Female	60	3020	48.00	20.00	0.00	68.00
Astrocytoma	Dead	9 cm	No	Possibility	No fracture	Male	34	91	37.50	18.75	0.00	56.25
SCLC	Dead	7.1 cm	NIDDM	Yes	No fracture	Female	53	669	38.95	12.00	0.00	50.95

Radiation induced myelopathy (RIM), Radiation induced fracture (RIF), Radiotherapy (RT), Cumulative (Σ).

In conclusion, we find that diabetes is a pronounced risk factor for serious adverse events in the spine following re-irradiation of the spine. For the few patients with long-term survival, the risk of experiencing spinal toxicity from re-irradiation was relatively pronounced. For patients with a long life-expectance, the risk of spinal toxicity has to be considered when planning repeated radiotherapy of the spine.

Conflict of interest

None.

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