New Approach for Treatment of Vertebral Metastases Using Intensity-Modulated Radiotherapy*

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Purpose: To perform aggressive radiotherapy for vertebral metastases. Using very steep dose gradients from intensity-modulated radiotherapy (IMRT), a protocol based on the concept of partial volume dose to the spinal cord was evaluated.
Patients and Methods: 50 patients with vertebral metastases were treated using IMRT. In previously unirradiated cases, where a prescribed dose of 80 Gy (BED_{10}) was delivered, the constraint to the spinal cord should be less than 100 Gy (BED_2). For previously irradiated cases, on the other hand, the dose is the same as in the previously unirradiated case; however, constraints for the spinal cord are a cumulative BED_2 of less than 150 Gy, BED_2 of less than 100 Gy in each instance, and a treatment gap of more than 6 months. There were 6 patients considered for a partial volume dose to the spinal cord. They all received higher BED_2, ranging from 51–157 Gy of D_{1cc}.
Results: Among the 24 patients who survived longer than 1 year, there was 1 case of transient radiation myelitis. There were no other cases of spinal cord sequelae.
Conclusions: Based on the present results, we recommend a BED_2 of 100 Gy or less at D_{1cc} as a constraint for the spinal cord in previously unirradiated cases, and a cumulative BED_2 of 150 Gy or less at D_{1cc} in previously irradiated cases, when the interval was not shorter than 6 months and the BED_2 for each session was 100 Gy or less. The prescribed BED_{10} of 80 Gy could be safely delivered to the vertebral lesions.

Key Words: Radiotherapy · Intensity-modulated radiotherapy · Partial volume dose of spinal cord · Vertebral metastasis

Strahlenther Onkol 2011;187:108–13
DOI 10.1007/s00066-010-2187-1

Neue Methode für die Behandlung von vertebralen Metastasen mit intensitätsmodulierter Strahlentherapie

Hintergrund und Ziel: Aggressive Strahlentherapie bei vertebralen Metastasen. Unter Einsatz sehr steiler Dosisgradienten intensitätsmodulierter Strahlentherapie (IMRT) Evaluierung eines Therapieprotokolls basierend auf dem Konzept der partiellen Volumendosierung am Rückenmark.
Patienten und Methodik: Wir behandelten mit IMRT 50 Patienten mit Wirbelsäulenmetastasen. In Fällen ohne vorangegangene Strahlentherapie, bei denen eine verordnete Dosis von 80 Gy BED_{10} appliziert wurde, sollte die Belastung des Rückenmarks weniger als 100 Gy BED_2 betragen. In Fällen mit vorheriger Strahlentherapie wurde die gleiche Dosis appliziert, wobei allerdings die Belastung des Rückenmarks kumulativ unter 150 Gy BED_2 und in der Einzelapplikation bei weniger als 100 Gy BED_2 lag, außerdem die Behandlungspause mehr als 6 Monate betrug. Für die partielle Volumendosierung am Rückenmark kamen 6 Patienten in Frage. Alle erhielten die höhere BED_2 von mehr als 51 Gy bis zu 157 Gy D_{1cc}.
Ergebnisse: Unter 24 Patienten, die länger als ein Jahr überlebten, gab es einen Fall vorübergehender Strahlenmyelitis. Es wurden keine weiteren Fälle von Bestrahlungsfolgen am Rückenmark beobachtet.
Schlussfolgerung: Auf Basis der vorliegenden Ergebnissen würden wir eine BED_2 von 100 Gy oder weniger bei D_{1cc} am Rückenmark in Fällen ohne vorangegangene Strahlentherapie empfehlen und in Fällen mit vorheriger Strahlentherapie eine kumulative BED_2 von 150 Gy oder weniger bei D_{1cc}, wenn das Behandlungsintervall nicht kürzer als 6 Monate war und die Dosis der Einzelapplikation bei einer BED_2 von 100 Gy oder weniger lag. Die verordnete Dosis einer BED_{10} von 80 Gy bei Wirbelsäulenläsionen ließ sich sicher applizieren.

Schlüsselwörter: Strahlentherapie · Intensitätsmodulierte Strahlentherapie · Partielle Volumendosierung am Rückenmark · Vertebrale Metastase

*This paper was presented at the 15th Workshop of German–Japanese Radiological Affiliation in Tokyo, Japan, on 23 May 2010.

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Received: June 18, 2010; accepted: November 11, 2010
Published Online: January 21, 2011

Introduction

Half of cancer patients develop distant metastases during the course of their disease with half of the lesions being osseous metastases. According to the Japanese Structure Survey of Radiation Oncology in 2007, out of 205,087 cancer patients (new + repeat) treated with radiation in 721 Japanese institutes, 27,970 (13.6%) patients underwent radiotherapy for bone metastases [6].

During the past 3 decades, results obtained from the clinical trials of the Radiation Therapy Oncology Group (RTOG) have been a golden standard of radiotherapy for painful osseous metastases [20]. Since it is a palliative treatment for pain relief, some patients develop recurrent pain at the same lesions a few months later. Because of the difficulty of reirradiation, most patients must accept their hopeless conditions and accept alternative treatments toward the end of their lives. There are currently two problems which require solving in the case of vertebral metastases. Is it possible to retreat previously irradiated lesions? Is it possible to use more aggressive treatment?

Nowadays, there are more innovative treatment methods and fine diagnostic tools for osseous metastases [7, 10]. Thus, there are more opportunities to treat oligometastases than before. In this paper, we verify a new treatment protocol of aggressive intensity-modulated radiotherapy (IMRT) for vertebral metastases with special reference of partial volume doses of the spinal cord.

Patients and Methods

Between April 2007 and December 2009, 50 patients with vertebral metastases were treated using IMRT or intensity-modulated radiosurgery (IMRS). There were 31 males and 19 females with a median age of 61 years (range, 36–93 years). The 78 lesions were divided into 17 cervical, 36 thoracic, 19 lumber, 5 sacral, and 1 coccygeal bone lesion. Of the 78 lesions, 40 (51%) were located in tissues adjacent to that which had been previously irradiated, and 20 of these 40 lesions were true in-field recurrences. Twenty of 38 lesions developed as initial vertebral metastases, while the remaining 23 lesions developed as second or third vertebral metastases, but were located separately from the previously irradiated vertebral column. According to the ECOG performance status (PS), 11 patients were classified as PS 0, 34 as PS 1, 19 as PS 2, 11 as PS 3, and 3 as PS4.

Patients were treated using a 6 MV X-ray Novalis unit® (BrainLAB AG, Germany), while BrainSCAN® and iPLAN® (BrainLAB AG Germany) were used for treatment planning. Images were obtained with a BrightSpeed® (GE, USA) CT simulator and a SIGNA HDx 1.5T® (GE, USA) MRI scanner. Movement minimization was achieved using Vac-Lok cushions and HipFix® thermoplastics (CIVCO, USA); in addition, the ExacTrac® X-ray positioning system and 6-axis robotic couch for fine localization (BrainLAB AG, Germany) were used.

The median prescribed dose was 40 Gy (range, 16–67.5 Gy), the median fraction dose was 6 Gy (range, 2.8–20 Gy), and the median fraction number was 5 (range, 1–20).

The following IMRT protocol for vertebral metastases was used. In previously unirradiated cases, when a prescribed dose of 80 Gy of the biologically effective dose of $\alpha/\beta = 10$ (BED_{10}) was delivered, the constraint for the spinal cord should be less than 100 Gy of the biologically effective dose of $\alpha/\beta = 2$ (BED_2). In previously irradiated cases, the prescribed dose is the same as in previously unirradiated cases; however, the constraints for the spinal cord are a cumulative BED_2 of less than 150 Gy, BED_2 of less than 100 Gy in each session, and a treatment gap of more than 6 months.

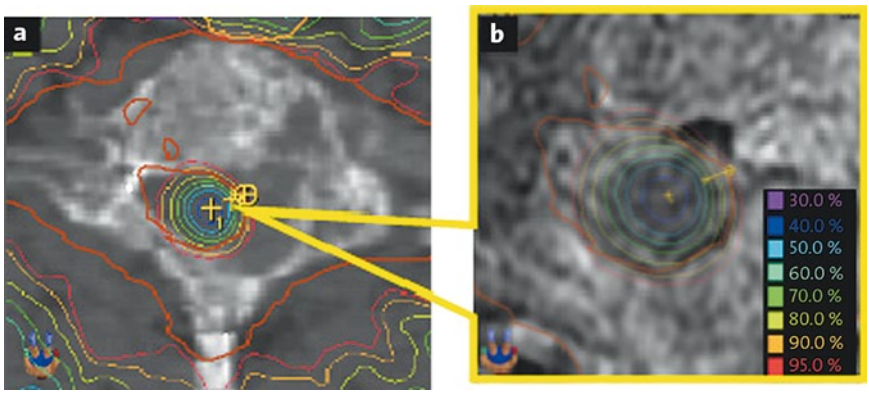
The radiotherapy treatment planning for all the patients in the present study was performed on the basis of CT and MRI results. The fusion of MRI and CT images was achieved by means of iPlan RT Image 4.1.1® (iPlan RT Dose 4.1.2®, since August 2010) and treatment planning was made using BrainSCAN 5.31® (BrainLAB AG Germany).

In this series, 24 of 50 patients were followed for more than 1 year. Among these 24 patients, MRI studies were performed regularly in 7 lesions of 6 patients. Accordingly, 6 patients were candidates to consider the partial volume dose to the spinal cord (Table 1).

Table 1. Seven vertebral lesions to assess radiation myelitis.

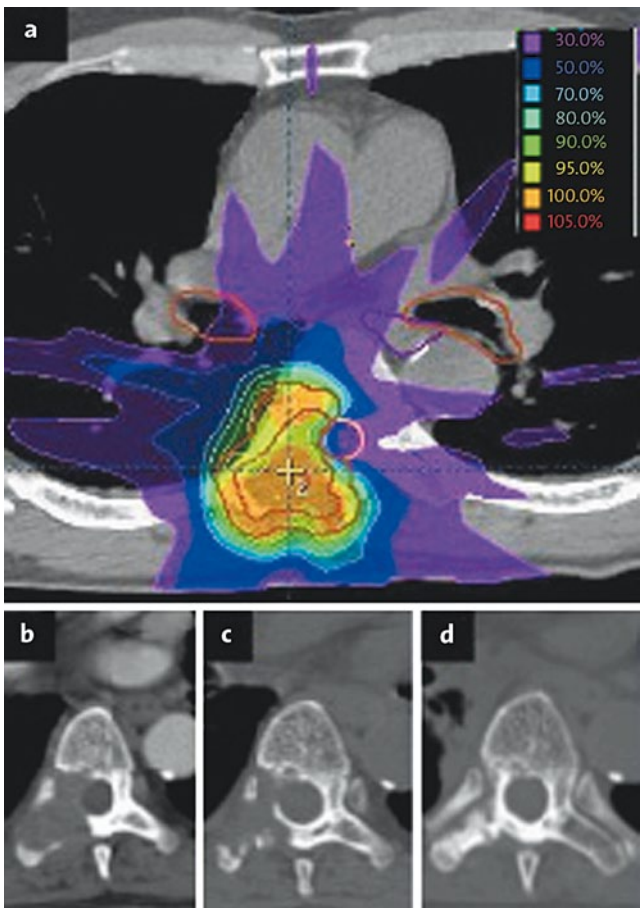
Tabelle 1. Strahlenmyelitis bei sieben vertebralen Läsionen.

Patient No.	Age/Sex	Primary site	Pathology	Vertebral metastasis	Prior in-field RT (months)	Prescribed dose (BED_{10})
1	61/F	Unknown	Failed	C-7	None	54 Gy/9 fx (86 Gy)
2	72/M	Hard palate	Adenoid cystic carcinoma	C-5–C-7	None	60 Gy/10 fx (96 Gy)
2	72/M	Hard palate	Adenoid cystic carcinoma	Th-4–Th-5	None	60 Gy/10 fx (96 Gy)
3	45/F	Breast	Adenocarcinoma	Th-11–Th-12	None	35 Gy/5 fx (60 Gy)
4	67/M	Oropharynx	Squamous cell carcinoma	Th-7	None	50 Gy/10 fx (75 Gy)
5	62/M	Kidney	Renal cell carcinoma	C-2	40 Gy/20 fx (31)	45 Gy/10 fx (65 Gy)
6	59/F	Thyroid	Papillary carcinoma	C-7	I-131	40 Gy/5 fx (72 Gy)



Figures 1a and 1b. When a BED_{10} of 80 Gy (EQD_2 = 67 Gy) is delivered to the spine (**a**), a BED_2 of 100 Gy (EQD_2 = 50 Gy) can be delivered to the spinal cord due to the rapid dose fall-off from 95% to 65% within only 2 mm using the IMRT hollow-out technique (**b**).

Abbildungen 1a und 1b. Bei Applikation einer BED_{10} von 80 Gy (EQD_2 = 67 Gy) an der Wirbelsäule (**a**), kann bei Einsatz der IMRT-Technik wegen des steilen Dosisabfalls von 95% auf 65% innerhalb von 2 mm eine BED_2 von 100 Gy (EQD_2 = 50 Gy) am Rückenmark angewendet werden (**b**).



Figures 2a to 2d. Patient 4 underwent IMRT (BED_{10} = 75 Gy; EQD_2 = 63 Gy) at Th-7 (**a, b**). Tumor regression was found 4 months later (**c**). Recalcification was observed after 14 months (**d**).

Abbildungen 2a bis 2d. Patient 4 erhielt IMRT (BED_{10} = 75 Gy; EQD_2 = 63 Gy) an Th-7 (**a, b**). Tumorregression zeigte sich 4 Monate später (**c**); Rekalzifizierung wurde nach 14 Monaten festgestellt (**d**).

When a curative BED_{10} of 80 Gy, or biologically equivalent dose in 2 Gy fractions (EQD_2) of 67 Gy, was delivered to the spinal column with IMRT using the Novalis unit®, the spinal cord is protected due to a rapid dose fall-off from the 95% to the 65% level within only 2 mm. Accordingly, the dose to the spinal cord was restricted to a BED_2 of 100 Gy (EQD_2 of 50 Gy) (Figure 1). The median follow-up time was 5 months (range, 0.5–23 months).

Results

In-field recurrences were recognized in 4 lesions (5%), including 2 adenocarcinoma of the lung, 1 squamous cell carcinoma of the uterine cervix, and 1 lymphoepithelioma of the nasopharynx. The former 3 were located at previously irradiated spine. The doses were 50 Gy/25 fractions, 40 Gy/20 fractions, and 29.7 Gy/9 fractions, respectively. Accordingly, these 4 lesions did not receive sufficient dose because of the constraint for spinal cord. Sites of relapse received the dose of 32.4 Gy/12 fractions, 40 Gy/5 fractions, 25 Gy/5 fractions, and 30 Gy/3 fractions with IMRT, respectively.

An osteolytic vertebral lesion was successfully treated with locally curative IMRT as in the following. Patient 4 underwent IMRT of 50 Gy/10 fractions/12 days (BED_{10} = 75 Gy or EQD_2 = 63 Gy) at the 7th thoracic vertebra. Tumor regression was observed 4 months later, while recalcification of the right transverse process and right 7th rib were recognized 8 months and 14 months later, respectively (Figure 2). He is still doing well at the 22-month follow-up.

Partial volume dose of the spinal cord indicated that all of these patients received very high doses (Table 2). However, the volume was very small. Patient 5 had had a history of radiotherapy of 40 Gy/20 fractions/28 days 31 months before; he underwent a second treatment for a recurrent 2nd cervical vertebral lesion with a locally curative dose of 45 Gy/10 fractions/16 days. The cumulative dose was high. However, he has not developed any sign of radiation myelitis during the 19-month observation period.

Patient 1 received IMRT for a metastatic 7th cervical vertebra. A BED_{10} of 88 Gy (EQD_2 of 72 Gy) was delivered to the 7th cervical vertebra, but the D_{1cc} of the spinal cord was only 51 Gy (BED_2) due to the rapid dose fall-off using IMRT (Figure 3). She has not developed any side effects of the spinal cord during the 15-month follow-up.

Patient 6 received IMRT at the 7th cervical vertebra and developed transient radiation myelitis 16 months later. Her partial volume dose to the spinal cord was extremely high with a D_{max} = 191 Gy (BED_2) and $D_{0.5cc}$ = 127 Gy (BED_2). Moreover, she had had a history of radiotherapy to

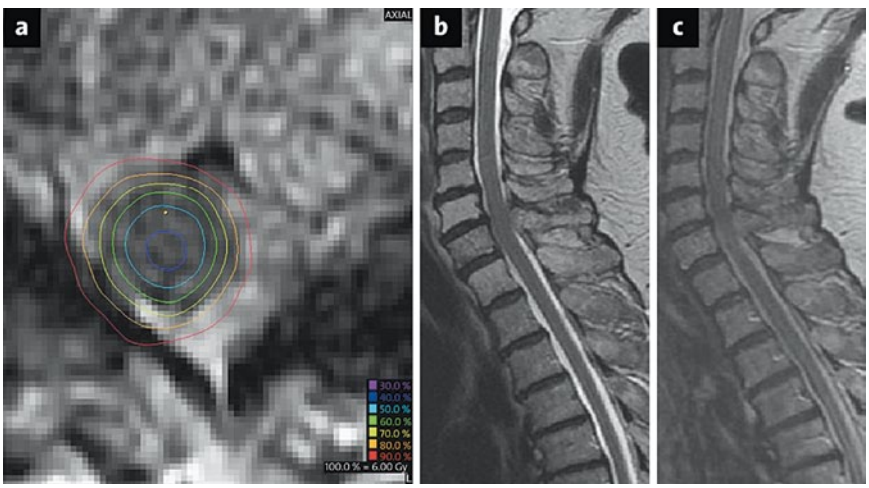
adjacent 2nd–8th thoracic vertebrae 31 months previously and had also received ^{131}iodine treatment. This history was also estimated to add to the above partial volume dose to the spinal cord. She developed hypesthesia in both arms 16 months later; she also reported weakness of the left 5th finger, and abnormal heat sensation in the right half of her body 19 months later. However, symptoms improved after 23 months without any treatment, and no particular side effects were detected in the spinal cord after 26 months (Figure 4). Accordingly, it is likely that this partial volume dose is estimated as an upper limit of the spinal tolerance dose.

Table 2. Partial volume dose of the spinal cord and radiation myelitis.

Tabelle 2. Strahlenmyelitis bei partieller Volumendosierung am Rückenmark.

Patient No.	Dmax	D0.1cc	D0.5cc	D1cc	Radiation Myelitis (months)	Follow-up (months)
		BED_2 (Gy)				
1	170	132	75	51	no	14
2	219	193	175	157	no	20
2	206	187	157	135	no	20
3	113	88	76	65	no	29
4	141	115	101	87	no	23
5[a]	205	181	155	140	no	19
6[b]	191	182	127	70	yes	31
					16[c]	

[a]Cumulative dose (prior RT 31 months ago + present RT);
[b]prior RT (Th-2–Th-8 35 months ago and I-131 treatment);
[c]transient radiation myelitis (healed 23 months later).



Figures 3a to 3c. Patient 1 received IMRT (BED_{10} = 88 Gy; EQD_2 = 72 Gy) at C-7 (**a, b**). However, D_{1cc} of the spinal cord was 51 Gy (BED_2) due to the rapid dose fall-off using IMRT. She had no indications of radiation myelitis after 15 months (**c**).

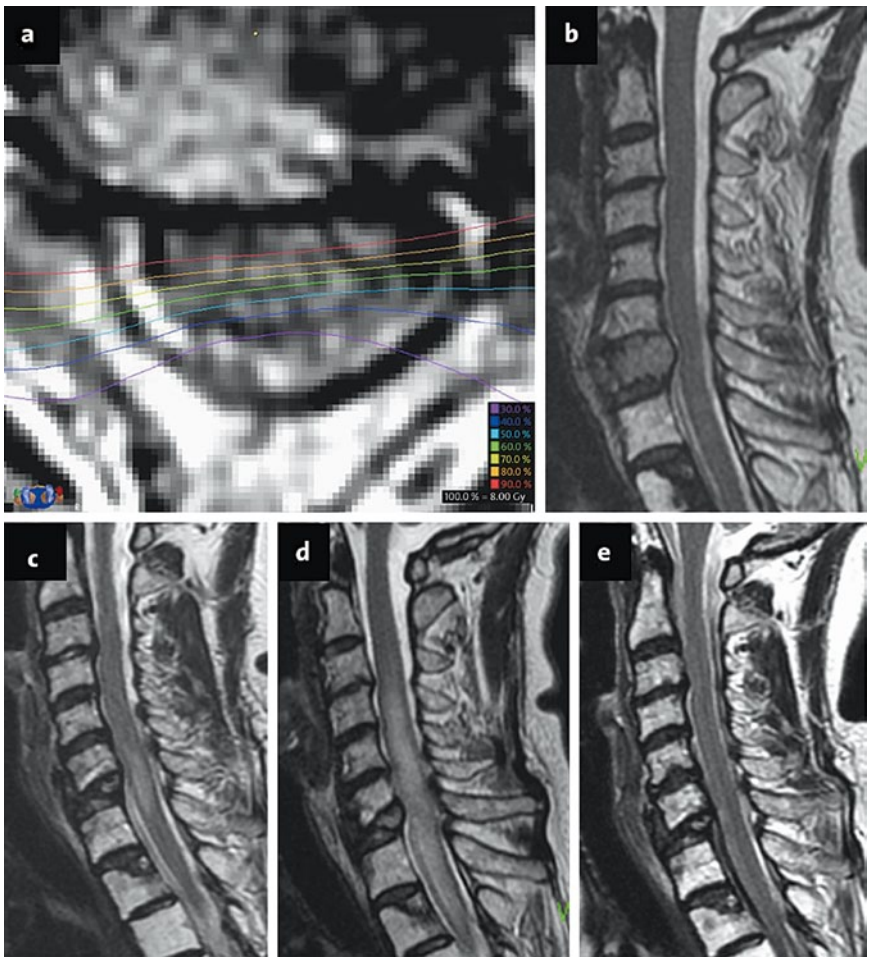
Abbildungen 3a bis 3c. Patientin 1 erhielt IMRT (BED_{10} = 88 Gy; EQD_2 = 72 Gy) an C-7 (**a, b**). Allerdings lag D_{1cc} wegen des steilen Dosisabfalls durch die IMRT-Technik am Rückenmark bei 51 Gy (BED_2). Die Patientin wies nach 15 Monaten keine Anzeichen von Myelitis auf (**c**).

Discussion

Radiotherapy is generally considered for painful osseous metastases. During the past 3 decades, a variety of moderate dose schedules have been used based in RTOG trials [20]. A schedule of 30 Gy/10 fractions/2 weeks is popular for painful osseous metastatic lesions. In Canada, the most common fractionation for bone metastases is 20 Gy in 5 fractions compared with 30 Gy in 10 fractions in the US. Nearly 70% use a standard dose fractionation to palliate localized painful metastasis by radiotherapy, independent of the site of involvement or tumor type [3].

A single dose or fractionated half-body irradiation has been applied for widespread metastatic bone lesions [17, 19, 21]. On the other hand, a surgical procedure should be considered whenever cortical erosion of a weight-bearing area may cause a pathologic fracture. However, the surgical approach to vertebral lesions carries a heavy burden for cancer patients. Recently vertebroplasty has developed as a minimally invasive surgical technique to provide rapid pain relief and stabilization for metastatic vertebral lesions [1, 4]. ^{89}Strontium is also applicable for pain relief for widespread metastatic bone lesions [12, 14].

When more intensive treatment (surgery, high-precision radiotherapy) were not available, dose escalation beyond 30 Gy in 10 fractions did not improve motor function, local control, or survival in metastatic spinal cord compression patients with oloigometastatic disease (no visceral or other bone metastases, involvement of only 1–3 vertebrae) from relatively radioresistant tumors (e.g., renal cell carcinoma, colorectal cancer, malignant melanoma) [5]. Concerning metastatic spinal cord compression (MSCC) in colorectal cancer patients, no significant difference was observed between short-course and long-course radiotherapy with respect to functional outcome. In the clinical situation, short-course radiotherapy may be considered preferable, because it means less patient discomfort [13]. According to DEGRO (German Society of Radiation Oncology) practice guidelines, different therapeutic goals (e.g., pain relief, local tumor control, prevention of motor deficits, and stabilization of the spine or other bones) require complex approaches considering individual factors (i.e., life expectancy and tumor progression at other sites). An optimal dose fractionation schedule or optimal standard dose for treatment of bone metastases has not been established. With regard to different therapeutic goals, the dose concepts and fractionation schedules should be adapted individually [18].



Figures 4a to 4e. Patient 6 received IMRT (BED_{10} = 72 Gy; EQD_2 = 60 Gy) at the 7th cervical vertebra and developed transient radiation myelitis 16 months later (**c**). The patient reported weakness of the left 5th finger and abnormal heat sensation in the right half of her body after 19 months (**d**). After 26 months, symptoms had improved and no particular side effects remained in the spinal cord (**e**).

Abbildungen 4a bis 4e. Patientin 6 erhielt IMRT (BED_{10} = 72 Gy; EQD_2 = 60 Gy) am 7. Halswirbel und wies 16 Monate später vorübergehende Strahlenmyelitis auf (**c**). Die Patientin berichtete 19 Monate spatter über eine Schwächung des 5. Fingers links und über abnorme Hitzewahrnehmung in der rechten Körperhälfte (**d**). Nach 26 Monaten hatten sich die Symptome gebessert, und das Rückenmark blieb frei von Nebenwirkungen (**e**).

In this study, the median prescribed dose was 40 Gy (range, 16–67.5 Gy), the median fraction dose was 6 Gy (range, 2.8–20 Gy), and the median fraction number was 5 (range, 1–20). Based on each patient condition, we decided the treatment schedules adjusted by BED_{10} and BED_2. In fact, the most popular dose schedule in this study was 40 Gy/5 fractions, which was used for 18 cases. The following dose schedules of 30 Gy/3 fractions, 40 Gy/4 fractions, 45 Gy/5 fractions, 50 Gy/10 fractions, and 60 Gy/10 fractions were applied for 4 cases, respectively.

During the past 10 years, diagnostic tools, such as PET-CT and diffusion MRI, have also progressed rapidly. Thus it is possible to treat asymptomatic patients with vertebral metastases using a painless method. A total of 35 (58%) patients with a PS of 0–1 were treated in this series. Accordingly, the philosophy for treating vertebral metastases should be changed. As far as oligometastases, the treatment goal of the vertebral column is not only pain relief but also stability of the metastatic vertebral lesion.

The spinal cord is the OAR in curative radiotherapy for the vertebral column. In the classic literature, Rubin et al. [15] stated the tolerance dose of the spinal cord to be 50 Gy/25 fractions /5 weeks for minimal injurious dose (TD5/5) and less than 60 Gy/30 fractions/6 weeks for maximal injurious dose (TD50/5) using 1–6 MeV supervoltage therapy. In the new era of 3D treatment planning, Emami et al. [4] updated the information on tolerance of normal tissues with a special emphasis on partial volume effects. Nieder et al. [11] updated the new tolerance dose for spinal cords with special reference to reirradiation. They concluded that the risk of radiation myelopathy appeared small after cumulated BED_2 of 135.5 Gy, when the interval was not shorter than 6 months and the dose of each course was BED_2 of 98 Gy or less. They commented that the influence of very steep gradients from stereotactic irradiation and IMRT approaches required further evaluation.

Marks et al. [8] reported in 2010 that there is a lack of data for advanced precision radiotherapy of IMRT for the vertebral column; therefore, up-to-date information is necessary to establish the new tolerance dose level for the spinal cord. The relatively small number of vertebral metastases in this report treated with IMRT is, thus, an important contribution of the new technology for aggressive treatment in the future.

IMRT can deliver a near-uniform dose to the target volume. However, the dose distribution in the surrounding normal tissues is more variable [2]. In this case, the target volume is a vertebral body, and surrounding normal tissue (OAR) is the spinal cord. The spinal cord is protected due to a rapid dose fall-off from 95% to 65% within only 2 mm. Accordingly, we can restrict the dose to the spinal cord to a BED_2 of 100 Gy (EQD_2 of 50 Gy). Moreover, the dose distribution is not uniform over the cross section of the spinal cord. Thus, the late

damage might be limited in the unilateral spinal cord. Nowadays, we are faced with the new situation of late damage to the spinal cord.

IMRT is also challenging with respect to treatment planning for advanced vertebral lesions or local recurrences after previous moderate-dose palliative treatment. We intended to consider the partial volume dose of the spinal cord. Ryu et al. [16] stated that rapid dose fall-off from 90% to 50% is obtained within 5.24 mm $\pm$ 0.92 mm in the spinal cord. We also indicated the successful dose fall-off from 95% to 65% within only 2 mm using the Novalis® IMRT hollow-out technique.

Based on our present data, it is likely that the partial volume dose of case 6 is estimated as an upper limit of spinal tolerance. In the previously unirradiated case, we propose a BED_2 of 100 Gy or less at D_{1cc} as a constraint for the spinal cord. In this situation, we can deliver prescribed curative dose of 80 Gy (BED_{10}) to the vertebral lesion. In previously irradiated cases, we propose a cumulative BED_2 of 150 Gy or less at D_{1cc} when the interval was not shorter than 6 months and the dose of each session was a BED_2 of 100 Gy or less. In this situation, we can also deliver the prescribed curative dose of 80 Gy (BED_{10}) to the vertebral lesion.

Conclusion

The spinal cord is a typical OAR. However, it is possible to treat complex lesions with sharp dose fall-off using IMRT. Thus, we adopted the concept of partial tolerance as a treatment strategy in such cases. In spite of the relatively small number of patients and nonuniform dose schedules, the present conclusion drawn from aggressive treatment for vertebral metastases is reasonable using the analysis of partial dose volume to the spinal cord. In this study, only 24 patients were followed for 12 months or longer; however, the present data do not lose their importance in establishing the tolerance dose level to the spinal cord when using modern IMRT technology.

Based on the present results, a BED_2 of 100 Gy or less at D_{1cc} is proposed as a constraint for the spinal cord in previously unirradiated cases, and a cumulative BED_2 of 150 Gy or less at D_{1cc} in previously irradiated cases, when the interval was not shorter than 6 months and the dose of each session was 100 Gy or less (BED_2). In both situations, the prescribed curative dose of 80 Gy (BED_{10}) could be delivered to the vertebral lesion.

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