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Small bowel toxicity after high dose spot scanning-based proton beam therapy for paraspinal/retroperitoneal neoplasms

Paraspinal/retroperitoneal mesenchymal tumours require high target doses in close proximity to the small bowel (SB) [24, 28]. Acute and late toxicity following conventional photon irradiation are well documented and often constitute dose-limiting factors [4, 17, 18, 26, 30]. In clinical practice, SB tolerance dose constraints are based on the seminal data analysis and recommendations from Emami et al. [6] published in 1991. These authors estimated a tolerance dose (TD) 5/5 of 50 Gy for one-third of the total SB volume (approximately 1800 cm^3) and a TD50/5 of 60 Gy (same volume) for late SB toxicities. For whole-organ irradiation, TD5/5 was estimated at 40 Gy and TD50/5 at 55 Gy. These recommendations remained largely unchallenged and have represented the world-wide established consensus for 20 years.

However, radiotherapy (RT) techniques have developed dramatically during the past two decades, resulting in improved target dose conformity and significantly reduced radiation-induced acute and late sequelae [5, 12, 20]. As part of the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) study, Kavanagh et al. [11] published a comprehensive review of SB toxicities after RT. These authors recommend limiting the absolute volume of irradiated SB to <120 cm^3 for doses above 15 Gy if individual bowel loops are outlined, and a reduction of the volume receiving >45 Gy to <195 cm^3 if the entire potential peritoneal space of the bowel is outlined. In general, there is paucity of published data concerning the effects of high-dose RT to small, possibly noncircumferential volumes of SB.

Multiple preclinical comparisons of proton radiation therapy (PT) versus modern conformal RT have suggested a reduction in integral dose to normal tissues, i.e. SB, by PT [3, 14, 27].

This retrospective analysis of 31 patients with paraspinal or retroperitoneal tumours correlates target coverage with SB dose–volume histograms based on the initial treatment planning CT scans and clinical tolerance. To the best of our knowledge, this is the first evaluation of a PT-treated patient cohort that focuses on SB gastrointestinal tolerance (GI) tolerance.

Patients and methods

Between September 1997 and December 2008, 31 patients were treated with high-dose spot scanning-based PT at the Paul Scherrer Institute (PSI) Center for Proton Therapy. The mean age of the patient cohort was 52.1 years. Ages ranged from 10 to 76 years and the cohort included one child. Of the 31 patients, 12 were female and 19 were male. One patient had long-standing history of Crohn's disease.

The histological tumour diagnosis was chordoma in 81%, soft tissue sarcoma in 16% and meningioma in 3% of the patients

Tumours were located in the lumbar spine region (n=17) or confined to the sacrum (n=14). A total of 54 surgical procedures were performed in these 31 patients prior to PT; in 13 patients, surgery was performed using a posterior approach exclusively, in 5 patients, approach was exclusively anterior and in 13 patients, both posterior and anterior surgical approaches were used. No patient received concurrent chemotherapy.

Proton therapy

All patients received exclusively spot scanning PT. This technique was pioneered at PSI and has been routine clinical practice since 1996 [15]. Patients were immobilised prone in an individual vacuum mould outside the treatment room. Daily control was performed using CT scout views prior to PT to verify correct patient positioning in alignment with the planning CT. Weekly or biweekly X-ray-based position verification following PT was also performed [2].

In the majority of patients, fractionated PT was conducted without repeated soft tissue imaging (CT) and alignment was based on bony contours only. For the purpose of this retrospective study, the position of the SB was therefore based solely on the positioning information obtained at the time of the planning CT scan.

Treatment planning was based on proton beam arrangements from posterior and posterior-oblique field angles. There-

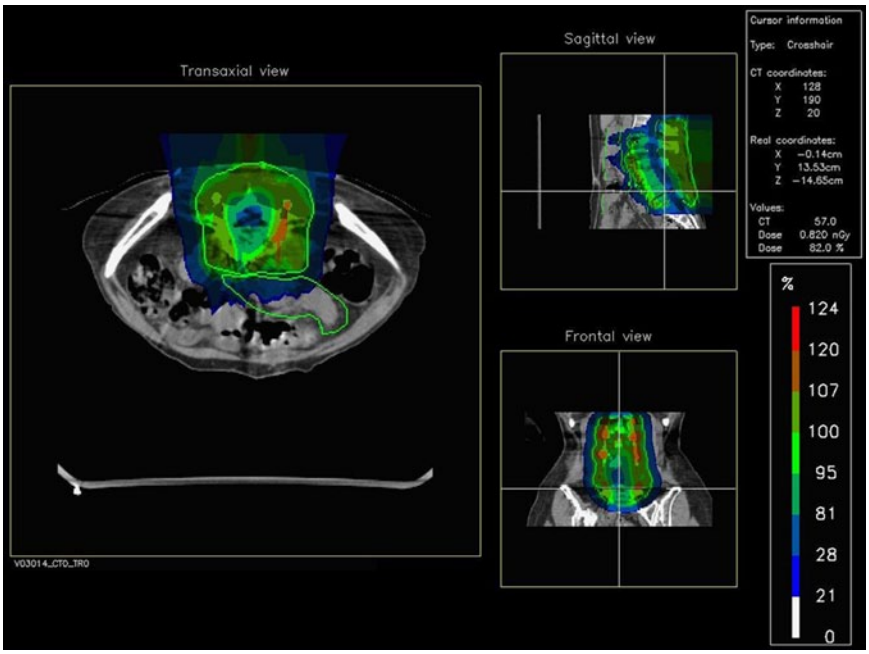

Fig. 1 ▲ The composite dose fall-off of a proton beam arrangement from 60 (~81%) to 20 Gy (RBE) (~28%) at the distal target edge with a prescribed dose of 72.0 Gy (RBE) (100%). Delineation of small bowel and high-dose planning target volume. Field arrangements included combinations of posterior and posterior-oblique angles

fore, bowel filling-dependent beam range uncertainties did not generally influence the planning procedure. A relative biologic effectiveness (RBE) factor of 1.1 for protons versus photons was assumed, consistent with previous reports [7, 19]. The prescribed and applied total PT dose ranged from 64 to 76 Gy (RBE), with a mean total dose of 72.3 Gy (RBE). The dose per fraction was standard at a value of 1.8–2.0 Gy (RBE).

Gross tumour volume (GTV) and clinical target volume (CTV) had been defined for each patient at the time of PT planning and delivery. CTVs/GTVs were expanded by 5 to 7 mm to generate the respective planning target volumes (PTVs). Review of patient records revealed that organ at risk (OAR) constraints for SB were not defined in the majority of cases; otherwise these ranged from a maximum dose of 64 to 76 Gy (RBE).

Project

Based on the original planning CT scans, the treatment plans of the 31 patients were reanalysed. SB was defined on axial CT levels as the volume extending from 2 cm above to 2 cm below the PTV. The thickness of the original CT slices ranged between 2.0 and 3.0 mm. Contours of small bowel loops were outlined. All delineations were retrospectively performed by one physician and independently verified by a second.

Dosimetric indices showing the SB volumes treated to doses of 5, 20, 30, 40, 50, 60, 70, 75 and 80 Gy (RBE) were calculated to give V5, V20, V30, V40, V50, V60, V70, V75 and V80 values, respectively. Late SB toxicity was reviewed as recorded during follow-up and correlated to dosimetric parameters.

Toxicity analyses

Acute and late toxicities were defined or retrospectively redefined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Patients were regularly (generally weekly) examined during their treatment procedure. Late toxicities were evaluated by annual follow-up examinations at our institute, or alternatively, by contacting the responsible physician or individual patient by telephone and e-mail/post.

Statistical analysis

Local control (LC) and overall survival (OS) rates were calculated from the PT start date using Kaplan–Meier estimates [10]. Censored events were death (all causes) for OS and local failure for LC.

Results

The follow-up period for the entire patient cohort ranged from 1.6 to 10.4 years. Mean follow-up time was 4.9 years, with a minimum follow-up after PT of ≥2 years in 29/31 patients (94%).

Local control and survival

LC rate was obtained in 16/31 patients (52%) and resulted in 3- and 5-year actuarial LC rates of 68.2±8.9 and 52.3±10.6%, respectively. Overall, 21/31 patients (68%) survived, resulting in 3- and 5-year actuarial OS rates of 83.7±6.7 and 72.1±8.5%, respectively.

Volume coverage

The mean volume of the high-dose PTV (GTV +5–7 mm) was 560.22 cm^3 (range 6.3–1720 cm^3). In 20/31 patients, planning aimed to deliver 95% of the prescribed dose to 90% of the PTV. This resulted in a mean of 87% (range 55.5–99.9) of the PTV receiving at least 95% of the prescribed dose, whereas a mean of 93.2% of the PTV was covered by at least 90% of the prescribed dose. OAR constraints for SB did not influence coverage of the high-dose areas in the treatment planning process. However, high-dose PTV coverage was affected by dose constraints to the following OARs: kidneys, generally 30/23 Gy (RBE) to 33/66% of the organ, respectively; spinal cord, 63–64 Gy (RBE) to the surface and 53–54 Gy (RBE) to the centre; cauda equine, below L4 no constraints, otherwise 70 Gy (RBE); nerve roots, generally 70 Gy (RBE) except for areas in direct contact with residual tumour.

Acute and late small bowel toxicity

Two patients (6%) experienced grade 1 acute toxicity. No acute higher grade (≥2) toxicities were recorded.

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Small bowel toxicity after high dose spot scanning-based proton beam therapy for paraspinal/retroperitoneal neoplasms

Abstract

Purpose. Mesenchymal tumours require high-dose radiation therapy (RT). Small bowel (SB) dose constraints have historically limited dose delivery to paraspinal and retroperitoneal targets. This retrospective study correlated SB dose–volume histograms with side-effects after proton radiation therapy (PT).
Patients and methods. Between 1997 and 2008, 31 patients (mean age 52.1 years) underwent spot scanning-based PT for paraspinal/retroperitoneal chordomas (81%), sarcomas (16%) and meningiom (3%). Mean total prescribed dose was 72.3 Gy (relative biologic effectiveness, RBE) delivered in 1.8–2 Gy (RBE) fractions. Mean follow-up was 3.8 years. Based on the pretreatment planning CT, SB dose distributions were reanalysed.
Results. Planning target volume (PTV) was defined as gross tumour volume (GTV) plus 5–7 mm margins. Mean PTV was 560.22 cm^3. A mean of 93.2% of the PTV was covered by at least 90% of the prescribed dose. SB volumes (cm^3) receiving doses of 5, 20, 30, 40, 50, 60, 70, 75 and 80 Gy (RBE) were calculated to give V5, V20, V30, V40, V50, V60, V70, V75 and V80 respectively. In 7/31 patients, PT was accomplished without any significant SB irradiation (V5=0). In 24/31 patients, mean maximum dose (Dmax) to SB was 64.1 Gy (RBE). Despite target doses of >70 Gy (RBE), SB received >50 and >60 Gy (RBE) in only 61 and 54% of patients, respectively. Mean SB volumes (cm^3) covered by different dose levels (Gy, RBE) were: V20 (n=24): 45.1, V50 (n=19): 17.7, V60 (n=17): 7.6 and V70 (n=12): 2.4. No acute toxicity ≥ grade 2 or late SB sequelae were observed.
Conclusion. Small noncircumferential volumes of SB tolerated doses in excess of 60 Gy (RBE) without any clinically-significant late adverse effects. This small retrospective study has limited statistical power but encourages further efforts with higher patient numbers to define and establish high-dose threshold models for SB toxicity in modern radiation oncology.

Keywords

Organ at risk · Radiation therapy · Follow-up · Chordoma · Sarcoma

Hochdosis-Spot Scanning basierte Protonen-Strahlentherapie von paraspinalen/retroperitonealen Tumoren und Dünndarm-Toxizität

Zusammenfassung

Hintergrund. Paraspinale und retroperitoneale mesenchymale Tumoren benötigen hohe strahlentherapeutische Dosen. Der Dünndarm ist ein dosislimitierendes Risikoorgan. In dieser retrospektiven Studie verglichen wir Dosis-Volumen-Histogramme des Dünndarms mit Nebenwirkungen nach Protonenstrahlentherapie (PT).
Material und Methode. Zwischen 1997 und 2008 erhielten 31 Patienten (Durchschnittsalter: 52,1 Jahre) mit paraspinalen/retroperitonealen Chordomen (81%), Sarkomen (16%) und einem Meningeom (3%) eine Spot-Scanning-basierte PT. Die verschriebene Gesamtdosis betrug im Mittel 72,3 Gy (RBE) mit Fraktionierungsdosen zwischen 1,8 und 2 Gy (RBE). Die durchschnittliche Nachbeobachtungszeit betrug 3,8 Jahre. Basierend auf dem initialen Planungs-CT wurde die Dosisverteilung am Dünndarm reanalysiert.
Ergebnisse. Gemittelte 93,2% des PTVs (GTV +5–7 mm) mit durchschnittlich 560,22 cm^3 wurden von mindestens 90% der verschriebenen Dosis erfasst. Bei 7 von 31 Patienten wurden keine wesentlichen Dünndarmdosen (V5=0) appliziert. Die Maximaldosis am Dünndarm der übrigen 24 Patienten betrug durchschnittlich 64,1 Gy (RBE). Trotz üblicher Zieldosen von >70 Gy (RBE) erhielt der Dünndarm nur bei 61/54% der Patienten >50/60 Gy (RBE). Das durchschnittlich belastete Dünndarmvolumen (cm^3) innerhalb unterschiedlicher Dosisstufen [Gy (RBE)] betrug V5 (24 Patienten): 86,5, V20 (24 Patienten): 45,1, V50 (19 Patienten): 17,7, V60 (17 Patienten): 7,6, V70 (12 Patienten): 2,4. Es traten keine Akut- oder Spättoxizitäten ≥Grad 2 am Dünndarm auf.
Schlussfolgerung. In dieser retrospektiven Untersuchung an 31 Patienten wurden Dosen von mehr als 60 Gy (RBE) an nichtzirkumferenziellen kleinen Dünndarmvolumina ohne signifikante Spätnebenwirkungen toleriert. Bei entsprechend limitierter statistischer Aussagekraft sollten weitergehende Untersuchungen mit höheren Patientenzahlen durchgeführt werden, um Hochdosisschwellen-Modelle für akute und späte Dünndarmtoxizitäten in moderner Strahlentherapie zu definieren und zu etablieren.

Schlüsselwörter

Risikoorgan · Strahlentherapie · Nachbeobachtung · Chordom · Sarkom

Only one patient reported grade 1 late toxicity. No patient experienced grade ≥2 late adverse events. This included 18 patients with transabdominal surgical resection.

The composite dose fall-off from 60 to 20 Gy (RBE) at the distal target edge was accomplished within a maximum distance of 2 cm in this patient cohort. This was dependent on the location of the PTV and the beam arrangements (**Fig. 1**).

Dosimetric analysis of small bowel

Dosimetric analysis revealed that in 7 out of 31 patients (23%), spot scanning-based PT to total target doses ranging between 70 and 74 Gy (RBE), with a mean dose of 73 Gy (RBE), were delivered without significant dose deposition to SB. The dose to V5 was 0%, despite the fact that SB was present anteriorly. In these patients, the approximately 3-cm distance between anterior paraspinal PTVs to the most posterior SB wall was sufficient to reduce the dose levels to below 5 Gy (RBE).

In the remaining 24/31 patients (77%), the mean maximum dose (Dmax) to SB was 64.1 Gy (RBE) at prescribed target doses >70 Gy (RBE). SB received >50 Gy (RBE) in 61% of patients and >60 Gy (RBE) in 54%. For these 24 patients, average values of calculated dosimetric indices are presented in **Fig. 2**; mean values, ranges and the maximum doses to SB ≥ V75 (10/31 patients) are given in **Tab. 1**.

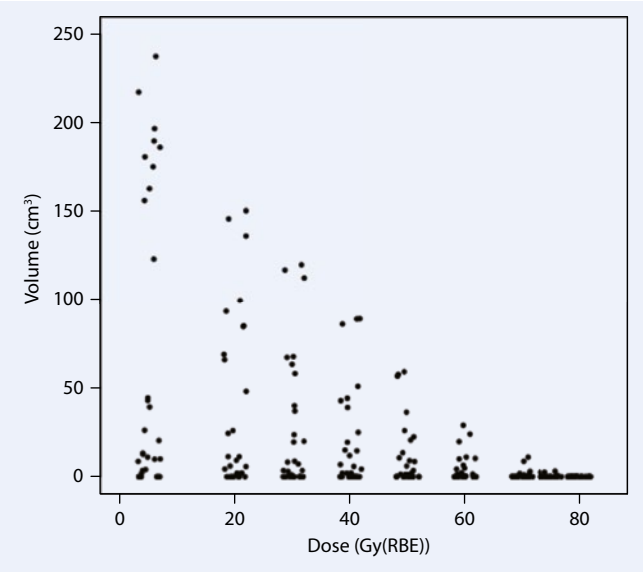

Fig. 2 ◀ Small bowel dose–volume distribution. Small bowel volumes treated to maximum doses of 5, 20, 30, 40, 50, 60, 70, 75 and 80 Gy (RBE; V5, V20, V30, V40, V50, V60, V70, V75 and V80, respectively) are plotted

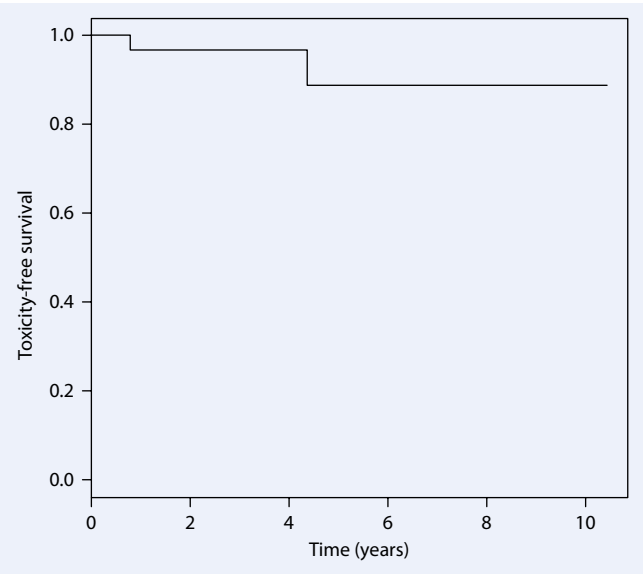

Fig. 3 ◀ Non-GI-related late toxicities. Actuarial 5-year grade ≥2 toxicity-free overall survival rate of 88.7±8.3% in 31 patients with paraspinal/retroperitoneal and sacral neoplasms treated with spot scanning proton beam therapy

Non-GI-related acute and late adverse effects

Overall, treatment was well tolerated by all patients. Non-GI-related grade 2 late adverse events were observed in 7 out of 31 patients (22.6%) and 2 patients (6.4%) experienced grade 3 toxicities. No grade ≥4 toxicity was observed. The majority of patients (71%) did not experience any significant long-term side effects. Overall, the actuarial 3- and 5-year non-GI-related grade ≥2 toxicity-free survival rates were 96.8±3.2 and 88.7±8.3%, respectively (**Fig. 3**).

Skin toxicity

The preference for posterior beam approaches (resulting in maximum sparing capability of internal organs) largely resulted in the same skin area being within the entrance path of all fields. Furthermore, surgical pathways and scars were generally part of the PTV. The majority of patients (n=25, 80.6%) experienced acute grade ≤2 skin erythema. In 4 patients (12.9%), acute skin toxicity was scored as grade 3. Late toxicities comprised grade 2 skin fibrosis in 5 out of 31 patients (16.1%) with one grade 3 adverse event (3.2%).

Neurotoxicity

Chronic grade 2 pain occurred in 3 out of 31 patients (9.7%). Two patients developed grade 2 functional neuropathies (6.4%), resulting in sexual dysfunction in one patient and sphincter dysfunction in the second.

Other toxicities

Bone necrosis (grade 3) was diagnosed in one patient.

Discussion

Our study raises questions about the relevance and applicability of photon-based and largely historical OAR constraints for SB in PT and modern RT techniques. Present SB OAR dose definitions and threshold-type models are generally based on percentage-of-entire-organ–volume parameters [1, 8, 13, 22, 23]. They do not address the issue of OAR dose definition based on partial-volume tolerance and/or non-circumferential versus circumferential dose distribution. Both issues are well accepted concepts for other organs—spinal cord, brainstem etc., and notably, for rectum. Our results indicate that SB tolerance concepts warrant further investigation and should follow more sophisticated OAR concepts as already in place for other systems [21, 25]. Additional contouring of bowel loops in close proximity to target volumes may help to define high-dose thresholds.

Due to their physical characteristics, protons have the potential to reduce both irradiated SB volumes in general and the high-dose volumes of moving loops in close proximity to the distal edge of the beam. SB loops with potentially significant interfractional and intrafractional variability may not receive high doses at identical locations and volumes. Mean or low doses to the bowel wall will also differ (**Fig. 1**).

For example, if 50% of the bowel circumference were to be inside a high-dose area on the initial planning CT, this might be increased to 100% (compared to treatment planning CT) by intra-/interfraction variability, but may also receive greatly reduced doses. Therefore, one-time deter-

Tab. 1 Small bowel dose–volume distributions in 24 patients. Small bowel volumes treated to maximum doses of 5, 20, 30, 40, 50, 60, 70, 75 and 80 Gy (RBE) were defined as V5, V20, V30, V40, V50, V60, V70, V75 and V80, respectively. In 7 patients, dose to small bowel was reduced to a maximum below 5 Gy (RBE). Maximum doses to small bowel ≥ V75 (10/31 patients) in patients undergoing proton beam therapy for paraspinal/retroperitoneal neoplasms are given

Dose volumes Gy (RBE)	Mean (cm^3)	Range (cm^3)	Max. RBE doses to small bowel ≥ V75 (Gy)
V5 (n=24, 77.4%)	86.5	2.0–238	
V20 (n=24, 77.4%)	45.1	0.2–151	
V30 (n=24, 77.4%)	35.5	0.1–120	
V40 (n=20, 64.5%)	27.5	0.2–89.0	
V50 (n=19, 61.3%)	17.7	0.2–59.0	
V60 (n=17, 54.8%)	7.6	0.4–29.0	
V70 (n=12, 38.7%)	2.4	0.1–11.0	
V75 (n=10, 32.3%)	1.9	<0.1–3.1	75.5, 76.0, 76.4, 77.4, 78.3, 79.0
V80 (n=4, 12.9%)	0.2	<0.1–0.5	81.3, 81.5, 84.8, 86.0

RBE relative biologic effectiveness.

mination of bowel position during treatment planning can only serve as guide of approximate location and thus significantly limits the conclusions to be drawn from this retrospective review. Daily confirmation of bowel loop position using image-guided RT (IGRT) could determine the true SB dose.

However, this report documents that patients tolerated high-dose PT to targets in close proximity to SB exceedingly well. Additionally, it shows that treatment plans suggested that in a large number of patients, SB received noncircumferentially higher radiation doses than presently recommended for conventional photon therapy [21, 25]. Neither history of extensive transabdominal surgery nor long-standing Crohn's disease resulted in a higher toxicity rate in our patient cohort.

The two advantages of PT, namely high-dose target coverage and increased normal tissue tolerance contribute to the favourable toxicity profile in our patient cohort. This effect will likely be of specific clinically-relevant benefit for patients:

a) with paraspinal/retroperitoneal disease entities requiring high-dose (>70 Gy) irradiation,
b) with pre-existing bowel damage or chronic inflammatory conditions of intra-abdominal organs [29]. (for which subgroup of patients a safe bowel tolerance level has never been established),
c) with a history of extensive transabdominal surgery resulting in a higher risk of acute and chronic SB toxicity, presumably due to adhesions [9] and those patients
d) undergoing combined chemoradiotherapy at risk for severe acute and chronic grade I side effects.

For technical reasons, all patients with (para)spinal or sacral tumours were treated in the prone position without use of any other bowel-displacing measures, e.g. a belly board or internal surgical displacement. Further investigation with a larger patient cohort should include a discussion of the risk factors [16] and expected changes in SB location associated with using prone or supine positioning for PT.

In our patient cohort, all entrance fields were directed from posterior or posterior-oblique, thereby "ranging out" into SB in many patients and all patients had doses to SB ≥60 Gy (RBE). No specific considerations were given to issues of proton range uncertainty or the presence of a high linear energy transfer (LET) component at the end of range. It is therefore of interest that we have not observed any toxicity that could possibly be related to these issues.

Conclusion

Our data demonstrate the ability of PT to deliver curative doses in excess of 70 Gy (RBE) to paraspinal and retroperitoneal tumours (sarcomas) without any higher-grade SB adverse events. Retrospective SB dose calculations based on the initial treatment planning CT scans of 31 patients indicated radiation doses to small noncircumferential volumes of SB well exceeding 60 Gy (RBE) and ≥70 Gy (RBE). This experience encourages further efforts to define and establish high-dose threshold models for acute and late SB toxicity in modern radiation oncology.

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Compliance with ethical guidelines

Conflict of interest. R.A. Schneider, V. Vitolo, F. Albertini, T. Koch, C. Ares, A. Lomax, G. Goitein and E.B. Hug state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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