Patterns of failure after stereotactic body radiotherapy (SBRT) to sacral metastases

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Abstract

Introduction: SBRT is increasingly used to treat sacral metastases. We analysed our centre's local relapse (LR) rates and patterns of failure (POF) after sacral SBRT and assessed whether using the consensus contouring recommendation (CCR) may have prevented LR.

Methods: We conducted a single-centre retrospective review of patients treated with sacral SBRT between 02/2012 and 12/2021. The cumulative incidence of local relapse, patterns of failure and overall survival were determined. Two investigators reviewed planning CT scans and imaging at relapse to determine if LR was potentially planning preventable with a larger CCR-derived radiotherapy field.

Results: 34 patients received sacral SBRT, with doses ranging from 24-40Gy over 3-5Fr. The most frequently used schedule was 30Gy in 3Fr. Common primaries treated included prostate (*n*=16), breast (*n*=6), lung (*n*=3) and renal (*n*=3) cancers. The median follow-up was 20 months (IQR 13-55 months). The cumulative incidence of LR (4/34) was 2.9% (95% CI, 0.2-13.2), 6.3% (95% CI, 1.1-18.5) and 16.8% (95% CI, 4.7-35.4) at 6 months, 1 year and 2 years, respectively. The patterns of failure were local-only (1/34), local & distant (3/34) and distant relapse (10/34). The overall survival was 96.7% (95% CI, 90.5-100) and 90.6% (95% CI, 78.6-100) at 1 and 2 years, respectively. For prostate/breast primaries, the cumulative incidence of LR was 4.5% (95% CI, 0.3-19.4), 4.5% (95% CI, 0.3-19.4), and 12.5% (95% CI, 1.7-34.8) at 6 months, 1- and 2 years, respectively. 29 cases (85.3%) deviated from the CCR. Sacral relapse was potentially preventable if the CCR was used in one patient (2.9% of the whole cohort and 25% of the relapsed cohort).

Discussion: We demonstrate excellent local control rates with sacral SBRT, which was largely planned with a target volume expansion approach.

Introduction

Spinal metastasis is a common site of metastatic spread in solid tumours.[1] Untreated, spinal metastases can be debilitating, causing significant pain and neurological damage. However, metastases to the sacrum are relatively uncommon and account for approximately 5% of spinal metastases. [2,3] The sacrum is anatomically distinct from the cervical, thoracic and lumbar spine. It lacks an intervertebral disc separating adjacent vertebral bodies and bears greater weight than other vertebral levels. [4] Traditionally, patients with symptomatic sacral metastasis were treated with conventional palliative external beam radiotherapy to improve symptoms such as pain or reduce the risk of neurological deterioration.[5,6] However, in the last decade, stereotactic body radiotherapy (SBRT) is increasingly being utilised to treat spinal metastasis. [3,7-11] SBRT has evolved as an effective treatment modality due to technological advances, inter- and intrafraction imaging, and/or rigid immobilisation. This has allowed the delivery of high biological effective doses to tumours over fewer fractions with steep dose gradients, producing excellent symptom and local control. [12-13] It is, therefore imperative that the target volume is accurately delineated to improve tumour control while minimising dose to surrounding critical structures, e.g. thecal sac, peripheral nerve roots and bowel.

Until recently, there was little guidance for target volume delineation when using SBRT for sacral metastases. However, Dunne *et al*. [14] recently published an international contouring consensus recommendation (CCR) for target volume delineation, providing a standardised framework for clinicians for clinical practice and clinical trials. [14] However, at the time of conception, there was no published pattern of failure analysis following sacral SBRT to validate this approach. Despite this, the CCR has been a vital first step in providing a standardised method for sacral tumour volume delineation and provides guidance for pattern of failure analyses in the future. Our institution has over 10 years of experience in using SBRT techniques to treat sacral metastases. In this study, we retrospectively analyse our institution's local control rate and patterns of failure after sacral SBRT, as well as our centre's implementation of the CCR. We also determine retrospectively if local failures were potentially preventable if the CCR approach had been used.

Methods

The study was prospectively approved by The Royal Marsden Committee for Clinical Research. Electronic medical records of patients treated with SBRT were retrospectively reviewed. Patients treated with SBRT to the sacrum with a histologically proven malignancy and a minimum of 6 months of follow-up were included. Patients were excluded if they have previously received over 20Gy in 5Fr (or equivalent) to the involved sacral region. A total of 38 patients received SBRT between February 2012 and December 2021. Data including baseline characteristics such as primary tumour histology, oligometastatic disease (OMD) status (≤5 metastatic lesions), sacral compartment involved, the total number of metastatic lesions, radiotherapy treatment date, radiotherapy dose and fractionation, concurrent systemic anti-cancer treatment and previous pelvic radiotherapy were extracted. Synchronous OMD was defined as OMD at the time of primary diagnosis, while metachronous OMD was defined as OMD presentation six months or more after primary diagnosis. Oligoprogressive disease was defined as progression of a few metastatic sites while on systematic therapy with otherwise controlled disease. The local oncology team were contacted for patients followed up in external cancer centres. The SBRT treatment plans were reviewed using our institution's treatment planning system (TPS), and deviation from the CCR clinical target volume (CTV) was determined. If there was ala involvement, the superior and inferior extent of the CCR CTV was determined by the superior and inferior extent of the involved vertebral body. The margins used for target volume expansions were also measured. Electronic medical records and imaging were reviewed to assess outcomes such as death and local or distant relapse. The imaging modality of choice was based on local practice and clinician preference. Evidence of disease progression on imaging was confirmed using the RECIST 1.1 and PERCIST criteria. [15-16]

Local relapse (LR) after SBRT was defined as relapse within the sacrum irrespective of the volume of sacrum treated, while distant relapse was defined as relapse outside the sacrum. Two investigators reviewed all cases of LR to determine if using the CCR target volume could have prevented local relapse. The investigators examined the treated CTV on the TPS and imaging at relapse on the picture archiving and communication system (PACS). The investigators referred to the consensus statement to determine the CCR CTV. LR was

potentially preventable if the local failure occurred within the CCR CTV. If there was local progression within the treated PTV, this was characterised as in-field relapse.

Radiotherapy technique

Before treatment, all patients were discussed at a dedicated SBRT multi-disciplinary meeting (MDT). Patients were treated supine with knee and ankle supports, and additional immobilisation, such as a vacuum bag, was used on an individual basis. All patients underwent a CT planning scan of 1.25-1.5mm thickness, fused on the treatment planning system with an axial T1/T2 volumetric MRI. Patients were either treated on the CyberKnife platform or gantry-based SBRT. For the CyberKnife platform, X-sight spine tracking is used, while CBCT is used for image and position verification for gantry-based SBRT. The dose delivered ranged from 24Gy to 40Gy over 3 to 5 fractions. After treatment completion, patients were followed up in 3-6 monthly intervals, including regular surveillance with imaging or tumour markers.

Statistical Analysis

Descriptive statistics were used to summarise categorical and continuous variables, such as demographics, tumour type and treatment schedule. Kaplan Meier statistics were used to estimate overall survival. Competing risk analysis was performed to estimate local relapse rates with death as a competing event. For time-to-event analyses, the start time was the date of the last SBRT fraction. Patients were censored at their last hospital appointment visit. Local relapse was estimated using a cumulative incidence function at 6- months, 1- year and 2- years. Analyses were completed using R, version 4.1.3.

Results

Patient demographics

38 patients were treated with SBRT to the sacrum between June 2012 and December 2021. Three patients were excluded due to missing follow-up data (relapse outcomes) as they were followed up at external centres. One patient was excluded as the disease originated from a pre-sacral node. A total of 34 patients were included in this retrospective study. Baseline and treatment characteristics are summarised in table 1. All 34 patients had de-novo sacral SBRT, with no cases of post-operative SBRT. The median follow-up was 20 months (IQR 13-55 months). The median age of treated patients was 65 years (IQR 60-73). The most common

tumour types were prostate (47.1%, *n*=16), breast (17.6%, *n*=6), lung (8.8%, *n*=3), renal (8.8%, *n*=3), colorectal (5.9%, *n*=2), and other (11.8%, *n*=4). Most patients were treated using the CyberKnife platform (82.4%, *n*=28), with the remainder treated using a conventional linear accelerator. All patients had less than five metastatic lesions. The majority of patients had metachronous OMD (67.6%, *n*=23), followed by oligoprogressive OMD (20.6%, *n*=7), then synchronous OMD (11.8%, *n*=4). Twenty patients (58.8%) had a solitary oligometastatic lesion in the sacrum, while 14 patients (41.2%) had two or more (range 2-4) sites of OMD (including sacral metastasis). The dose fractionation schedules ranged from 24-40Gy over three to five fractions, with 30Gy in 3 fractions accounting for the most common schedule. The median BED10 was 60Gy (range 43.2-93.3), and the median BED3 was 130Gy (range 88-217.8).

Local Control and Overall Survival

Four (11.7%) patients had local relapses within the sacrum. The cumulative incidence of local relapse was 2.9% (95% CI, 0.2-13.2), 6.3% (95% CI, 1.1-18.5) and 16.8% (4.7-35.4) at 6 months, 1 year and 2 years, respectively. (Figure 1) Of those four patients, three (8.8%) had local and distant relapses, while one (2.9%) had a local-only relapse. Ten patients (29.4%) had distant-only relapses. The median overall survival at 1 and 2- years was 96.7% (95% CI, 90.5-100) and 90.6% (95% CI, 78.6-100), respectively. The cumulative incidence of local relapse for prostate/breast cancer patients (*n*=22) was 4.5% (95% CI, 0.3-19.4), 4.5% (95% CI, 0.3-19.4), and 12.5% (95% CI, 1.7-34.8) at 6 months, 1- and 2 years, respectively.

Deviation from the consensus statement and margins used

29 out of 34 treatment contours (85.3%) deviated from the CCR. However, 18 patients (52.9%) were treated prior to the publication of the consensus recommendations. Figures 4-5 highlights the different contouring approaches used for target volume delineation for sacral metastases. The organs at risk are not included due to variations in lumbar-sacral plexus contouring methods. 5 cases (14.7%) followed all of the CCR recommendations. Two cases (5.9%) followed part of the CCR recommendations but did not include all the recommended compartments. For example, in one case, in a lateralised lesion within the vertebral body, the ipsilateral ala was not included. In the second case, for a lesion in the vertebral body and right ala, the right lamina was not included.

In 27 (79.4%) patients, treatment was planned, using a conventional margin expansion approach (figure 6). Clinicians contoured around the GTV/CTV, using the planning CT and fused axial MRI images, followed by a GTV/CTV to PTV expansion. The total margins used are summarised in Table 3. There were 3/27 (11.1%) LR events in the duration of follow-up in those treated with a margin expansion technique and 1/5 (20%) LR event in those treated with a CCR approach.

Relapsed patients

There was a total of four local relapses after sacral SBRT. Two patients (50%) received sacral SBRT for oligoprogressive disease. Two patients (50%) had solitary oligometastatic disease in the metachronous setting. The median BED3 and BED10 were 119Gy and 55.7Gy, respectively. The clinical target volume of three cases did not follow the CCR. There were a similar proportion of patients treated with systematic anti-cancer therapy (SACT) at the time of SBRT in those without LR compared to those with LR (73.3% (22/30) vs 75% (3/4), respectively). 13 (38.2%) patients had a distant relapse, of which three patients also progressed locally. There was a greater proportion of SACT use at the time of SBRT in those without distant relapse compared to those with distant relapse (76.2% (16/21) vs 46.2% (6/13), respectively).

Table 2 summarises further details on the local relapses and highlights if LR was potentially preventable if the CCR was used. In case one, SBRT was delivered to the S3-S5 vertebral body, bilateral lamina and posterior ala using a margin expansion approach. However, there was subsequent infield and distant progression- therefore, local relapse was considered unavoidable even if the CCR were followed. In case two, the S1 right anterior ala lesion was treated using a margin expansion approach, with subsequent relapse outside the PTV but within the S1 right ala compartment and in the S4 region. The S1 relapse was potentially preventable with the CCR approach; however, the S4 relapse was deemed not preventable. In case three, the patient received SBRT to S2/3 lesion (vertebral body and posterior ala) using a margin expansion approach, with subsequent relapse in S3/4. The CCR recommends including the entire vertebral body at the involved level and ipsilateral ala and lamina; therefore, relapse was deemed potentially preventable. Case four followed the CCR, the CTV

included S1 vertebral body and right ala and lamina. However, the patient relapsed in the left sacral ala compartment and at distant sites.

Discussion

Our single-centre experience demonstrates excellent rates of local control after sacral SBRT. The cumulative incidence of LR (4/34) was 2.9%, 6.3% and 16.8% at 6 months, 1 year and 2 years, respectively. Our study shows lower rates of LR in patients with prostate/breast cancer at 1 and 2 years. The slightly better outcomes could be due to less aggressive tumour biology, relative radiosensitivity, and the vast array of systemic treatment options available for these patients. [17-18]

We present one of the largest single-centre outcome datasets for sacral SBRT. Zeng *et al*. published their outcomes for sacral SBRT in 22 patients, with a median follow-up of 19.5 months. [19] Local control rates were 86.5% and 78.7% at 1 and 2 years, respectively. Interestingly, only two patients (9.1%) had prostate cancer, with breast cancer being the most common primary (40.9%), followed by renal cancer (22.7%). Ten (45.4%) patients in their study did not have OMD. [19] Kowalchuk *et al*. published single-centre outcomes for sacral SBRT in 28 patients, with a median follow-up of 15.8 months. [20] The authors report a local control rate of 63%, with multi-variate analysis demonstrating a large PTV >50cc and epidural involvement associated with decreased local control. [20] The most common histology type was breast cancer, with no prostate cancer patients included in the study. In this study, 49% had previous sacral radiotherapy, and only one patient had solitary OMD, compared with 21 (58.3%) in our study. The median BED10 was lower at 35.7Gy (range 16-60), explaining the lower local control rates. [20] Thiagarajan *et al*. report 1-year local control rate of 91.7% in a population of 43 patients treated with sacral SBRT in a single centre with a median follow-up of 17 months. Prostate cancer was the most common primary malignancy accounting for 28% of the population, followed by renal cell carcinoma (16%) and sarcoma (12%). [21] Compared to other published studies, our high local control rates could be attributed to a greater proportion of patients with prostate cancer and a relatively high BED to the treated lesion.

The CCR often produces larger treatment volumes (Figure 4), which could cause difficulties in achieving dose constraints and increase toxicity. [22] Therefore, even since the CCR

publication, several patients were planned with a margin expansion approach. In terms of other studies' contouring approaches, Zeng et al. use similar principles to the CCR, and Kowalchuk *et al*. used a margin expansion approach. [19,20] In Kowalchuk et al., local failure occurred in the treated vertebrae (54%), paraspinal soft tissue (23%), epidural space (15%), and adjacent vertebrae (8%). However, lower doses were used, and nearly half of the population had previous sacral radiotherapy.

One out of the four local relapses were due to in-field progression. Using the CCR approach would not have impacted this, as in-field progression is often caused by inadequate dose or intrinsic tumour radiosensitivity. Despite mostly using a margin-expansion approach, we report excellent local control outcomes in our follow-up period. A recent study by Chen *et al.* has shown that deviating from the CCR in spinal SBRT is associated with worse outcomes.[23] After adjusting for confounding factors, deviation from consensus guidelines was associated with a 2.5-fold risk of progression (HR 3.52, 95% CI 2.11-5.86, P<0.001). [23] The authors demonstrate that local failures in cases which deviate from consensus guidelines are attributed to mainly marginal misses within the diseased and adjacent vertebral compartments. However, this study only included 19 (5.3%) with sacral metastases, and patients with prostate cancer were excluded from the analysis.

Limitations

There are several limitations to this study. This data is confined to a single centre's experience with sacral SBRT, and pooling data from other centres' experiences is warranted. We did not examine toxicity outcomes due to heterogeneity in imaging/surveillance post-SBRT. Most patients had PET imaging at surveillance, however, as per the SPINO group recommendations, MRI is preferred for local response assessment after spinal SBRT. [24] Given the study's retrospective nature and imaging modalities used for response assessment, we cannot guarantee that all sacral relapses were captured. Also, we could not perform multi-variant analyses due to the small number of local relapse events. The study's retrospective nature could introduce selection bias, though this is limited by our centre's prospective data collection for patients treated with SBRT. The strengths of this study are that this is one of the largest datasets for sacral SBRT from a single centre, with all patients reviewed at a specialist MDT.

Further work

Longer follow-up is required to exclude future marginal failure events. Our data must also be validated with other centres' experiences. Pooling data from other centres is an essential next step due to the relative rarity of sacral SBRT, and this could contribute to validating and expanding the current CCR. Future work could also focus on assessing the feasibility of meeting dose constraints and toxicity events when the CCR approach is used.

Conclusion

This study demonstrates a high local control rate after sacral SBRT, which was mostly planned using a margin expansion approach. Further collaboration with other centres is necessary to validate and improve the current CCR.

Figures and Tables

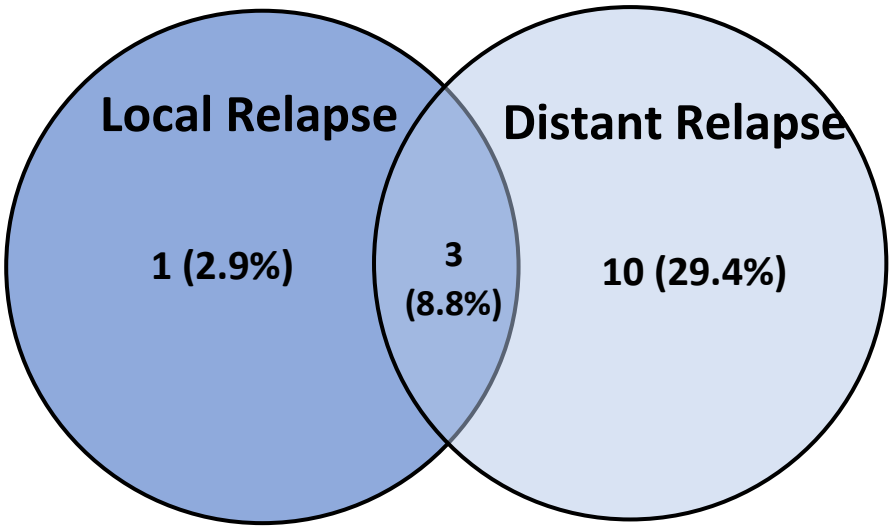

Figure 1: Venn Diagram summarising local and distant failure rates after sacral SBRT.

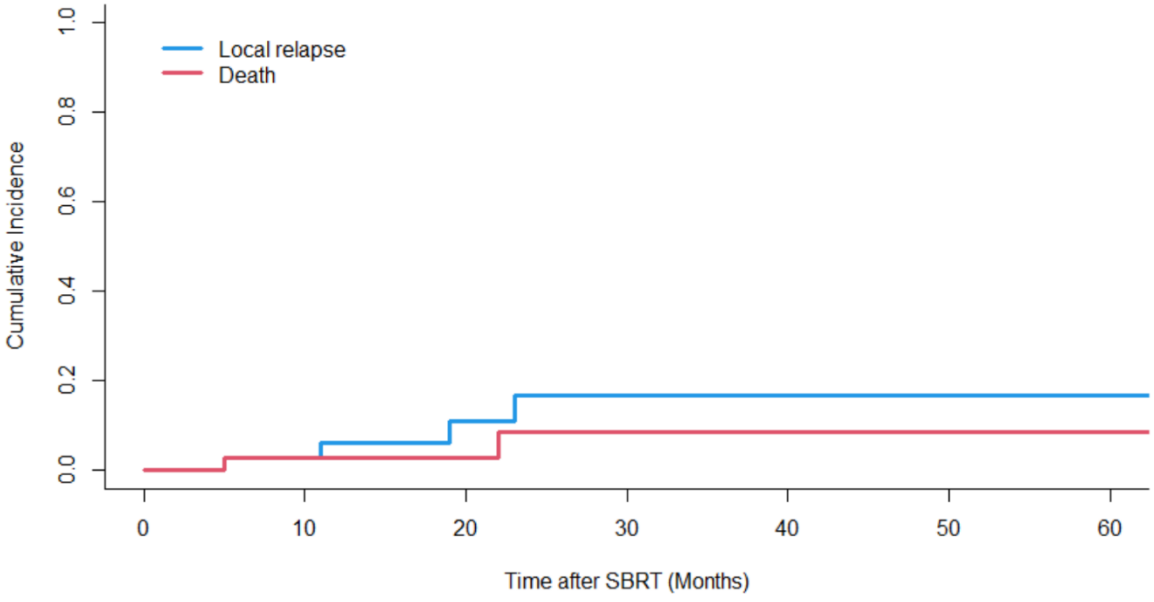

Figure 2: Cumulative incidence curve for local relapse and death after SBRT to the sacrum.

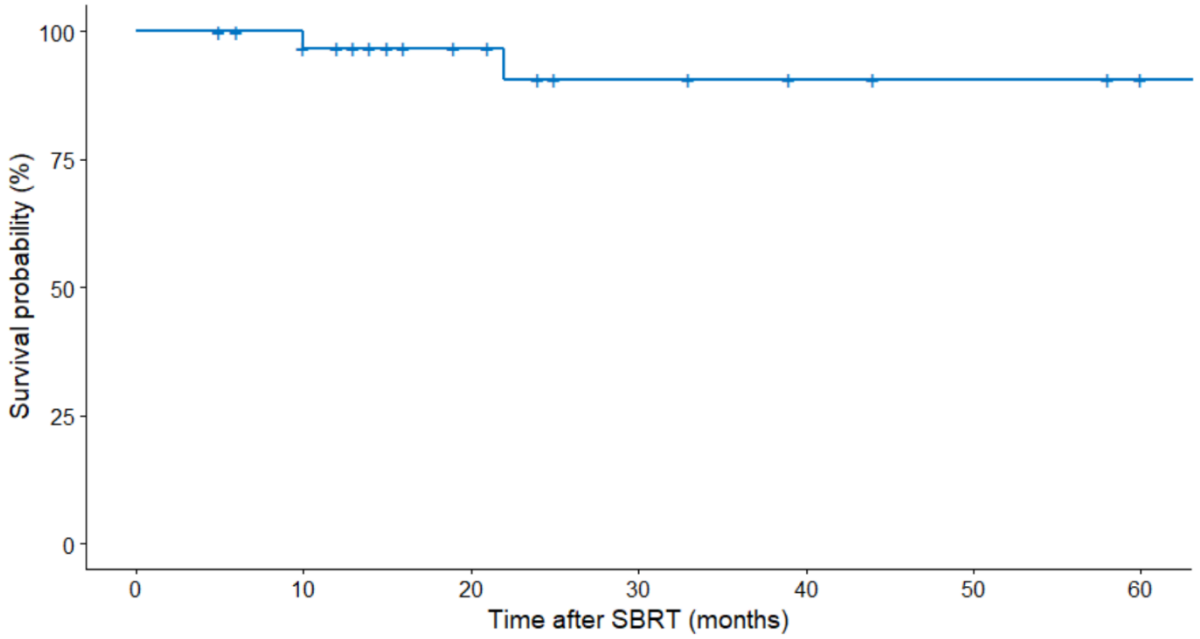

Figure 3: Kaplan Meier curve for overall survival after SBRT to the sacrum.

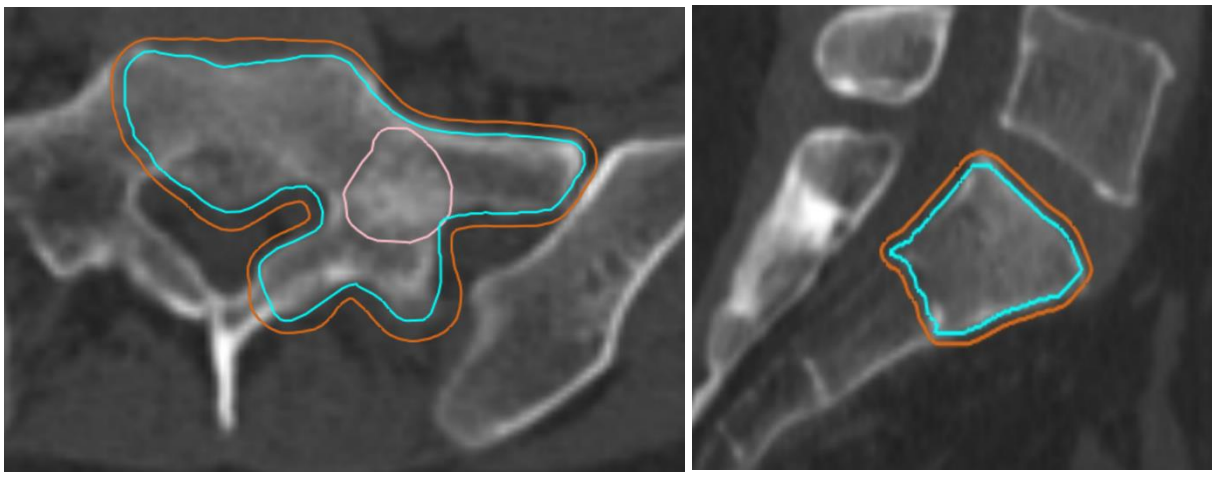

Figure 4: Example of a CCR approach for target volume delineation for a vertebral body and right ala metastasis. The GTV (pink) is contoured, with a CTV (blue) which follows the CCR approach, however, the CTV is not expanded to adjacent vertebral levels. The PTV (brown) is created with a 2mm CTV expansion.

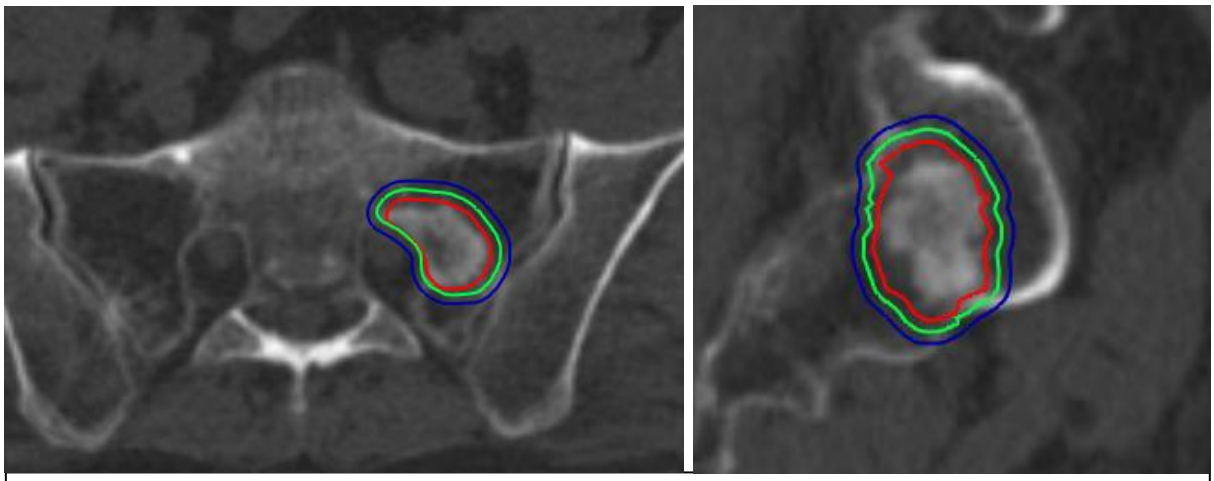

Figure 5: Example of margin expansion approach for target volume delineation for an S1/2 ala metastasis. The clinicians contoured the GTV (red), followed 3mm CTV (green) expansion and a 2mm PTV (blue).

Table 1 Baseline Characteristics

	n (%)
Tumour Type	
Prostate	16 (47.1)
Breast	6 (17.6)
Lung	3 (8.8)
Renal	3 (8.8)
Colorectal	2 (5.9)
Other*	4 (11.8)
Oligometastatic Disease Type	
Metachronous	23 (67.6)
Synchronous	4 (11.8)
Oligoprogression	7 (20.6)
Previous EBRT to the pelvis	
Yes	8 (23.5)
No	26 (76.5)
Dose/Fractionation	
24Gy 3Fr	3 (8.8)
27Gy 3Fr	3 (8.8)
30Gy 3Fr	18 (52.9)
30Gy 5Fr	8 (23.5)
36Gy 3Fr	1 (2.9)
40Gy 3Fr	1 (2.9)
Total Number of Oligometastatic Lesions	
One	20 (58.8)
Two	9 (26.5)
Three	4 (11.8)
Four	1 (2.9)
Concurrent Systemic Therapy	
Yes	22 (64.7)
No	12 (35.3)
Surveillance imaging	
PET	16 (47.1)
MRI	8 (23.5)
CT	7 (20.6)
NM bone scan	1 (2.9)
None**	2 (5.9)

Table 1: Baseline characteristics. EBRT= external beam radiotherapy. *other tumour types include melanoma, sarcoma, myeloma and thyroid cancer. ** tumour marker surveillance instead.

Table 2: Local Relapse events after sacral SBRT

Case	Background	Site of disease	Fractionation Schedule	BED 10/BED 3 (Gy)	CTV	Contouring strategy	Site of relapse	Would have following the CCR prevented relapse to date?
1	Metachronous oligometastatic colorectal cancer (Previous pelvic radiotherapy)	S3-S5 VB and bilateral lamina and posterior ala	30Gy in 5Fr	48/90	S3-S5 VB, bilateral lamina and posterior ala	Margin expansion approach	Infield relapse and distant site (pelvic lymph node and lung)	No (in-field relapse)
2	Metachronous oligometastatic prostate cancer	S1 right anterior ala	30Gy in 3Fr	60/130	S1 right anterior ala lesion	Margin expansion approach	Marginal relapse (right S1 anterior ala), non-adjacent uninvolved sacral compartment (S4) and distant site (right iliac bone)	Right S1 anterior ala relapse preventable S4 relapse was not preventable.
3	Oligoprogressive castrate-resistant prostate cancer	Left S2/S3 VB and S2 posterior ala	30Gy in 3Fr	60/130	Left S2/S3 VB lesion and left S2 posterior ala lesion	Margin expansion approach	The previously uninvolved S3 VB, left ala and left lamina.	Yes
4	Oligoprogressive non-small cell lung cancer	S1 VB (lateralised) and right anterior ala	27Gy in 3Fr	51.3/108	S1 VB, right ipsilateral ala, and lamina	CCR	Non-adjacent uninvolved sacral compartment and distant sites (liver, pleural, peritoneal and bone)	N/A

Table 2 summarises local Relapse events after sacral SBRT including the site of disease and site of relapse, and if the CCR approach could have prevented local relapse. CCR= consensus contouring recommendations; VB= vertebral body; CTV= clinical target volume.

Table 3: Summary of margins used

Total margin used* (mm)	CCR/part CCR approach, (*n*=7) (%)	Margin expansion approach, (*n*=27) (%)
2	2 (28.6)	2 (7.4)
3	2 (28.6)	8 (29.6)
5	3 (42.8)	13 (48.1)
7	0	3 (11.1)
Missing	0	1 (3.7)

Table 3 summarises the margin used for the CCR and margin expansion approach.
*total margin is a combination of GTV>CTV>PTV expansion or CTV>PTV expansion (if GTV is not contoured).

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