Outcome and toxicity of hypofractionated image-guided SABR for spinal oligometastases

Charlotte Billiet [a,b,*], Ines Joye [a,b], Carole Mercier [a,b], Lieselotte Depuydt [a], Geert De Kerf [a], Peter Vermeulen [b,c], Steven Van Laere [b,c], Erik Van de Kelft [d,b], Paul Meijnders [a,b], Dirk Verellen [a,b], Piet Dirix [a,b]

[a] Department of Radiation Oncology, Iridium Kankernetwerk, Wilrijk (Antwerp), Belgium
[b] University of Antwerp, Faculty of Medicine and Health Sciences, Campus Drie Eiken, Building S, Universiteitsplein 1, 2610 Wilrijk-Antwerp, Belgium
[c] Oncologisch Centrum GZA, Translation Cancer Research Unit, Antwerp, Belgium
[d] Department of Neurosurgery, Gen Hospital Nikolaas, Sint-Niklaas, Belgium

ARTICLE INFO

ABSTRACT

Background: To investigate progression free survival (PFS), local control (LC) and overall survival (OS) outcomes for patients treated with spine hypofractionated stereotactic ablative radiotherapy (SABR) and to evaluate possible predictors of rapid progression in view of a correct patient selection for this potentially curative SABR.

Materials and methods: A cohort of 59 patients with spinal metastases were treated with SABR. Patient selection criteria were the following: histologically proven diagnosis of a solid tumor, a World Health Organization (WHO) score $\leq$ 2, life expectancy > 6 months, Spinal Instability Neoplastic Score (SINS) $\leq$ 12 points and presenting with radically treated oligometastatic disease ($\leq$5 lesions) or stable polymetastatic disease with an oligoprogressive lesion.

Results: From March 2015 to June 2019, 59 patients were treated with Linac-based SABR to 64 spinal metastases with a median follow-up of 55 months. SABR was standard delivered every other day in 3 to 10 fractions with median prescription dose of 27 Gy (range 21–49 Gy).

The 1-,2- and 5-year PFS was 98%, 85% and 75% for all patients. OS at 5 years for all patients was 92%. Metachronous lesions (p < 0.01; HR = 7.1) and oligometastatic (vs. oligoprogressive) lesions (p = 0.02; HR = 0.3) were associated with higher PFS in uni- and multivariate Cox regression analysis. No significant predictors in multivariate analysis were demonstrated for rapid progressors.

Vertebral compression fractures developed de novo in 6.3% (4/64) of cases. The median time to fracture was 11 months (range 7–15) after treatment. No other adverse events $\geq$ 3 grade were observed.

Conclusions: Tumor control and toxicity after high-dose hypofractionated SABR was evaluated in patients with spinal oligometastases. High rates of efficacy and minimal toxicity were demonstrated. Oligometastatic patients with metachronous spinal metastases seem to benefit the most from SABR.

© 2020 Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction:

Approximately one third of all cancer patients develop bone metastases in the course of their disease [1], of which 70% originate within the spine [2]. Spinal metastases often present with pain, neurological signs and symptoms, spinal instability or pathological fractures that all negatively affect patients' quality of life.

Radiotherapy (RT) plays an essential role in the multidisciplinary management of vertebral metastases.

Conventional multi- or single-fraction RT of bone metastases results in overall and complete pain responses in approximately 70% and 30% of patients respectively [3,4]. Unfortunately, about half of the patients develop progression with pain relapse within 1 year after treatment [5]. Different treatment strategies are required to provide not only durable pain control, but also long-lasting local metastatic control in selected sub-cohorts of patients with better survival prognosis. This appears to be especially true for patients with so-called "oligometastases" who clearly benefit

from the combination of radical RT with standard of care systemic therapy [6].

Dose-intensified stereotactic body radiation therapy (SABR) uses highly conformal treatment planning and image-guidance to enable precise and accurate delivery of higher radiation doses (in a single or a few fractions). Prospective (non-randomized) trials and retrospective experiences have already demonstrated SABR to be an effective tool for treating metastatic spinal disease [7–14]. However, the correct selection of patients candidates to potentially curative SABR remains challenging.

In the current study we report retrospectively the treatment outcome of patients with spinal oligometastases treated with SABR using daily cone beam computed tomography (CBCT) image guidance. The main goal was to determine local control, survival and toxicity as well as to find predictors for rapid local or systemic progression (ie. within 6 months after SABR) to facilitate upfront patient selection.

2. Material/methods

2.1. Patients

Between March 2015 and June 2019, patients with spinal metastases (C1 to sacrum) were treated with stereotactic ablative radiotherapy (SABR) at the Iridium Kankernetwerk, Antwerp, Belgium. For this retrospective study, clinical data were prospectively collected, whereas data were retrospectively analyzed for the intent of the analysis.

Inclusion criteria for SABR in spinal metastases in our institute were as follows: patients with a histologically proven diagnosis of a solid tumor, a World Health Organization (WHO) classification score ≤ 2 and a life expectancy > 6 months presenting with oligometastatic disease (≤5 lesions) or stable polymetastatic disease with an oligoprogressive lesion.

The involvement of more than 3 adjacent vertebrae, previous radiation therapy at the index site or progressive neurological symptoms/deficits due to an epidural tumor component with high grade Bilsky score [15] were exclusion criteria. Patients with spinal instability (spinal instability neoplastic score (SINS) ≥ 13 based on radiological imaging) [16] were also considered not to be suitable for SABR. In case of metastatic epidural spinal cord compression, a surgical decompression treatment was offered.

2.2. Treatment

All patients underwent treatment-planning computed tomography (CT) using 1 mm slice thickness CT in treatment position: patients were immobilized in a comfortable and stable supine position to irradiate the metastatic lesion(s) using support and/or immobilization devices (e.g. knee and feet support) to increase patient comfort and to ensure set-up reproducibility. A high-definition magnetic resonance image (MRI) of the treatment region was obtained and fused with the CT simulation scan for better target and spinal cord definition.

The clinical target volume (CTV) was contoured towards the International spine radiosurgery consortium consensus guidelines for target volume definition [17], hereby including abnormal marrow signal suspicious for microscopic invasion and an adjacent normal bony expansion to account for subclinical tumor spread in the marrow space.

The high-dose planning target volume (PTV) was generated with an isotropic expansion of the CTV. Initially, this margin was 3 mm, since 2017 this was reduced to 2 mm after analysis of the set-up accuracy during treatment.

Treatment planning was initially performed using a Varian Clinac IX, and more recently, since 2017, using a Varian Truebeam STX. Volumetric modulated arc therapy (VMAT) plans were generated for 6 or 6FFF MV photons using ≥ 4 arcs with full or partial gantry rotation. Final dose calculation was performed with a collapsed cone algorithm (RayStation v7.0, RaySearch Laboratories, Sweden since 2017 and Eclipse v 13.6 AAA before) with a grid size of 1.0 mm. Immobilization material was taken into account.

The constraints of the report of the AAPM task group 101 [18] were used for treatment planning.

The recommendations of Report 91 of the International Commission on Radiation Units and Measurements (ICRU) [19] were used for prescribing, recording and reporting of the doses. The planning aim was to have 99% of the PTV receiving the prescription dose for an optimal target coverage. Because the constraints of the spinal cord (often in close proximity) prioritize over tumor coverage, covering of at least 80% to a cropped PTV (excluding spinal cord or cauda) was allowed to receive the prescribed dose. Otherwise the fractionation scheme was adapted in a more fractionated way.

Image guided treatment was performed using CBCT image-guidance and online correction of set-up errors in six degrees of freedom. An optical surface monitoring system (AlignRT, VisionRT, UK) was used since 2017 to enhance set-up accuracy during treatment.

SABR was standard delivered every other day in three fractions of 8–10 Gy, however conversion to 5 or 10 fractions was considered if necessary for adequate target volume covering and maintaining organs at risk constraints.

Regarding follow-up, clinical neurological evaluation, pain assessment (VAS score) and side effects were recorded. MR or CT based imaging of the spine was performed 3 months after treatment and further according to the physician's choice.

2.3. Statistical analysis

Following factors associated with progression-free survival (PFS), local recurrence (LR), overall survival (OS) and rapid progression were retrospectively investigated by uni- and multivariate analysis: Primary tumor, RPA class, delivered dose and timing and number of metastases. Patients having local and/or systemic progression within 6 months after the end of the treatment were defined as rapid progressors. The oncological outcome analysis was evaluated for 2 subgroups: the rapid progressors and the prostate cancer only patients.

Concerning toxicity, an uni- and multivariate analysis was performed for following factors: PTV dose and volume, pain, Bilsky and SINS score and presence of an osteolytic component.

3. Results

3.1. Patients and treatment

We identified 59 patients receiving SABR to a total of 64 vertebral metastases and they were followed for at least 6 months. In 4 patients, 2 separate lesions were treated simultaneously while one other patient received SABR for 2 metachronous lesions with a 10-month time interval. Patient and tumor characteristics are depicted in Table 1a. Prostate cancer was the predominant primary tumor site (58%).

The majority of patients (89%) presented with synchronous or metachronous oligometastatic disease (OMD) (defined as ≤ 5 lesions). All oligometastatic patients were treated radically (52.6% with single metastasis and 47.4% with multiple metastases). Following the recent ESTRO/EORTC consensus recommendation of

Table 1a
Patient and tumor related characteristics.

Patient related factors (N = 59)		
Sex		
Male	38	64.4%
Female	21	35.6%
Performance status		
WHO 0	42	71.2%
WHO 1	17	28.8%
WHO 2	0	0%
Median age (start treatment)	68	[28,29]
Primary tumor		
Prostate	34	57.6%
Breast	15	25.4%
Other	10	17.0%
RPA class		
1	23	39.0%
2	28	47.5%
3	8	13.5%
Tumor related factors (N = 64)		
Solitary lesion		
Yes	30	46.9%
No	34	53.1%
Extent of disease		
Oligometastatic (n $\leq$ 5)	57	89.1%
Oligoprogression	7	10.94%
Location		
Cervical	3	4.7%
Thoracic	31	48.4%
Lumbar	27	42.2%
Sacral	3	4.7%
Imaging at diagnosis		
MR	51	79.7%
PET/PSMA/choline scan	35	54.7%
Bone scan +/− SPECT	24	37.5%
Timing		
Synchrone	18	28.1%
Metachrone	45	70.3%
Primary	1	1.6%
Time interval (mean)	56	(0–228)
Bilsky score/ECSC		
0	51	79.7%
1a	7	10.9%
1b	3	4.7%
1c	3	4.7%
SINS score		
<7	60	93.7%
7–10	4	6.3%

Abbreviations WHO: World health organization; RPA: Recursive partitioning analysis; MR: magnetic resonance; PET: Positron emission tomography; PSMA: Prostate-specific membrane antigen; SPECT: Single Photon Emission Computed Tomography; ESCC: epidural spinal cord compression score; SINS: Spinal Instability Neoplastic Score.

Table 1b
Treatment related characteristics.

Treatment related factors (N = 64)		
Dose prescription (Gy)		
21–30 Gy in 3 fractions	56	88.0%
30–40 Gy in 5 fractions	7	11.0%
48.5 Gy in 10 fractions	1	1.0%
Median dose PTV near max (BED, Gy)	74	(28–106)
Median dose PTV D50% (BED, Gy)	65	(28–85)
Median dose PTV near min (BED, Gy)	32	(17–103)
Systemic treatment		
No	18	30.5%
Hormonal therapy	37	62.7%
Chemotherapy	2	3.4%
Immunotherapy	1	1.7%
Targeted therapy	1	1.7%

Abbreviations PTV: planning target volume: BED: biological effective dose.

Forty-five lesions were osteoblastic (70%), 17 were osteolytic (27%), and 2 were mixed (3%); all patients had a SINS score of $\leq$ 10 [15] based on the available medical imaging and no patients had upfront vertebral compression fracture (VCF).

Most patients (88%) were treated with 3 fractions of 8 to 10 Gy. The remaining patients (11%) were treated with 40 Gy in 5 fractions and 1 patient with 48.5 Gy in 10 fractions (Table 1b). The mean GTV volume was 8.7 cc (range 0.5–58 cc) and mean PTV volume was 52.3 cc (range 2.7–150 cc). Biological effective dose (BED) was calculated assuming an α/β-ratio of 10 Gy for spinal metastases. Median dosimetric parameters PTV D98%, D50% and 2% were 32 Gy, 65 Gy and 74 Gy BED respectively.

3.2. Oncologic outcomes

Mean follow-up was 55 months for all patients. The 1-,2- and 5-year PFS was 98%, 85% and 75% for all patients (Fig. 1); for prostate cancer patients only, the 5-year PFS was 81%. OS at 5 years for all patients was 92%.

In six patients (9.3%) a local recurrence was observed with a mean time interval of 11 months (range 3–22 months) after start of SABR. Concerning these 6 patients, 3 were having prostate cancer with high Gleason score (8or9); 2 patients had a colorectal tumor and 1 patient had a follicular thyroid carcinoma. All 6 metastases were diagnosed in metachronous setting and the recursive partitioning analysis (RPA) class was 1 or 2 in respectively 2 and 4 patients [21]. There was no spinal cord compression (ESCC), 2 lesions were osteolytic and all 6 patients received SABR in 3 fractions with a median PTVD98%, 50% and 2% of 29, 49 and 55 Gy BED respectively. Mean GTV volume of these 6 lesions was 19 cc and mean PTV 57.8 cc.

In uni- and multivariate Cox regression analysis, metachronous (vs. synchronous) lesions (p < 0.01; HR = 7.1) and oligometastatic (vs. oligoprogressive) lesions (p = 0.02; HR = 0.3) were correlated with higher PFS (Table 2a). In subgroup analysis of prostate cancer patients, four variables were significantly associated with PFS in univariate analysis: RPA class, Gleason score, metachronous lesions and oligometastases (Table 2b). In multi-variate analysis, the presence of metachronous lesions and oligometastatic disease remained marginally associated with better PFS (p = 0.05). Finally, we performed a subgroup analysis for rapid progressors- i.e., patient with systemic and/or local progression within 6 months after SABR treatment. Results from univariate analysis demonstrated Gleason score (p = 0.05), (cervical location (p < 0.01) and number of fractions (p < 0.01) as significant variables, however none of the parameters remained significant after multivariate analysis.

oligometastatic disease [20], all oligometastatic patients were classified as follows: 32% with synchronous OMD and 47% with metachronous OMD (42% metachronous oligorecurrence and 5% metachronous oligoprogression); 20% repeat OMD of which 11% repeat oligorecurrence and 9% repeat oligoprogression.

On the other hand, there were 11% (7/64) of cases with polymetastatic disease having oligoprogression of a spinal metastasis. Towards, the ESTRO/EORTC recommendation the polymetastatic patients were categorized as induced oligoprogression (6/64) and in one patient as induced oligopersistence.

Regarding systemic therapy, 18 patients (30.5%) were not treated with systemic treatment, while regarding the other patients: 37 (62.7%) were treated simultaneously with hormonal therapy, 2 (3.4%) with chemotherapy and 2 (3.4%) with targeted or immunotherapy (Table 1b).

Patients receiving chemotherapies and targeted therapy interrupted the medical treatment during SABR, while hormonal therapy and immunotherapy was continued.
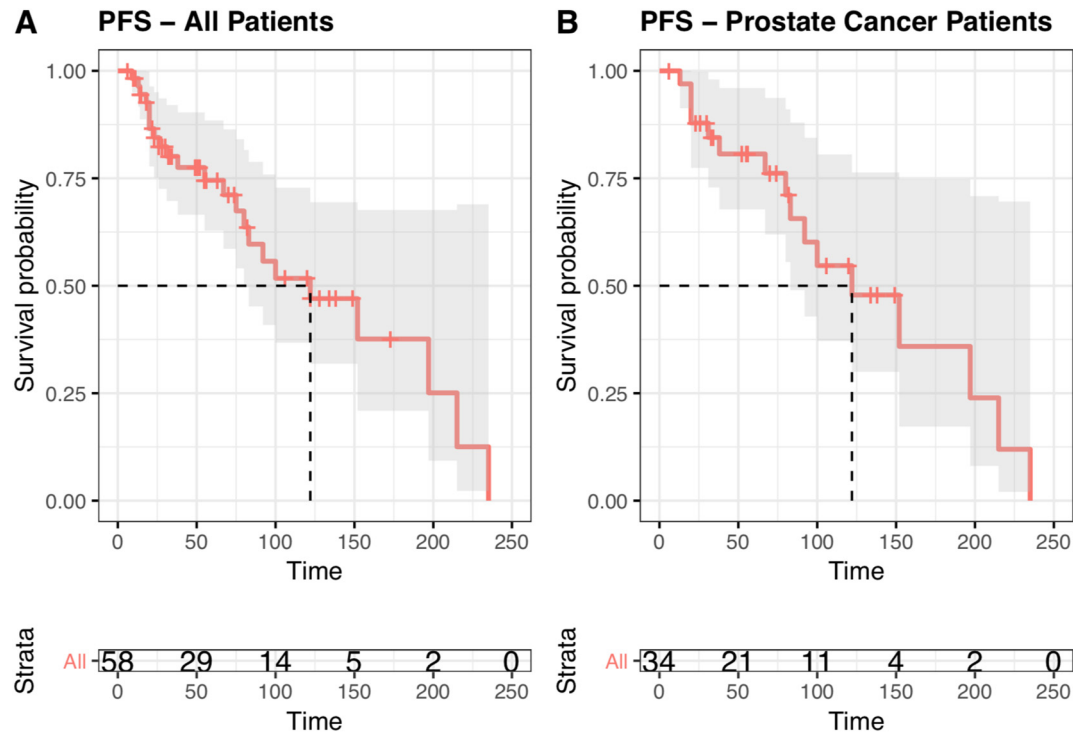
Fig. 1. Progression free survival (time in months) for all patients and for prostate cancer patients only.

Table 2a
Univariate and multivariate analysis of factors influencing PFS, LR and OS for all patients.

Variable	Progression Free survival				Local Recurrence free survival		Overall Survival	
	Univariate analysis		Multivariate analysis		Univariate analysis		Univariate analysis	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Primary tumor (prostate vs other)	0.39(0.12–0.28)	0.12			0.08(0.01–0.49)	**0.007**	5.37(0.06–5.18)	0.59
RPA (2 vs 1)	1.95(0.76–5.02)	0.17			2.91(0.48–17.7)	0.25	1.70(0.24–12.14)	0.60
RPA (3 vs 1)	3.12(0.59–16.56)	0.18			0(0–inf)	0.99	1.38(0–inf)	0.99
Synchronous vs metachronous metastasis	7.08(1.95–25.67)	**0.003**	8.25(2.21–30.88)	**0.002**	0(0–inf)	0.99	1.87(0–inf)	0.99
Solitary metastasis (yes vs no)	0.92(0.38–2.23)	0.85			0.23(0.03–2.09)	0.19	2.52(0.03–2.29)	0.22
Oligometastasis (yes vs no)	0.26(0.08–0.83)	**0.02**	0.22(0.07–0.70	**0.001**	0.33(0.04–2.97)	0.32	1.10(0.02–0.78)	**0.03**
PTV D2%	1(1–1)	0.27			1(1–1)	0.93	1(1–1)	0.39
PTV D50%	1(1–1)	0.36			1(1–1)	0.98	1(1–1)	0.41
PTV D98%	1(1–1)	0.87			1(1–1)	0.58	1(1–1)	0.51

Significant p-values (<0.05) are marked in bold Abbreviations: HR:hazard ratio; CI:confidence interval; RPA:recursive partitioning analysis; PTV:planning target volume.

Table 2b
Univariate and multivariate analysis of factors influencing PFS, LR and OS for prostate cancer patients only.

Variable	Progression Free survival				Local Recurrence free survival		Overall Survival	
	Univariate analysis		Multivariate analysis		Univariate analysis		Univariate analysis	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
RPA (2 vs 1)	0.70(0.17–2.8)	0.61			0(0–inf)	0.99	1.14(0.1–12.96)	0.91
RPA (3 vs 1)	8.91(1.41–56.3)	**0.02**	5.0(0.42–60.34)	0.20	NA	NA	2.69(0–inf)	0.99
Synchronous vs metachronous metastasis	7.59(1.25–46)	**0.03**	13.23(0.95–184.93)	0.05	NA	NA	3.92(0–inf)	0.99
Solitary metastasis (yes vs no)	0.98(0.32–3)	0.98			0.83(0.05–13.67)	0.9	3.3(0.03–3.17)	0.34
Oligometastasis (yes vs no)	0.11(0.03–0.44)	**0.002**	0.17(0.03–1.07)	0.06	0.08(0–1.22)	0.07	5.9(0–0.65)	**0.02**
PTV D2%	1(1–1)	0.48			1(1–1)	0.56	1(1–1)	0.28
PTV D50%	1(1–1)	0.71			1(1–1)	0.77	1(1–1)	0.34
PTV D98%	1(1–1)	0.51			1(1–1)	0.91	1(1–1)	0.61
Gleason score	0.04(0–0.75)	**0.03**	0.07(0.00–3.53)	0.19	0(0–inf)	1	0(0–inf)	0.98
PSA	1(0.97–1.05)	0.75			0(0–2373)	0.35	1.06(1–1.1)	**0.02**
Systemic therapy (no vs yes)	1.1(0.3–4.1)	0.88			2.14(0.13–34.23)	0.59	0(0–inf)	0.99

Significant p-values (<0.05) are marked in bold
Abbreviations: HR:hazard ratio; CI:confidence interval; RPA:recursive partitioning analysis; PTV:planning target volume; PSA = Prostate specific antigen.

3.3. Toxicity

No clinically radiation-induced myelopathy was observed. Vertebral compression fractures developed de novo in 6.3% (4/64) of patients. The median time to fracture was 11 months (range 7–15) after receiving SABR. The mean SINS score was 2.7, only 1 lesion was described as lytic and involved the posterior wall of the vertebral body. Mean GTV volume of these 4 lesions was 5.1 cc and mean PTV 58.1 cc. In three patients the lesion was located lumbar and in one thoracic. No spinal deformity of pre-existing VCF was seen before treatment. All 4 patients received SABR in 3 fractions with a median PTVD98%, 50% and 2% of 34, 560 and 71 Gy BED respectively. Three out of four patients received hormonal therapy concomitant and 1 patient had no concomitant systemic treatment.

Additionally, 67% of the patients were asymptomatic before SABR (median baseline pain score (VAS) was 0). Only 4 patients (6%) developed a pain flare-up during SABR treatment, of which 2 required corticoid treatment. During follow-up, a pain response was seen in 16% of the only 19 symptomatic patients, the other patients reported stable symptoms. Of all patients, five (8%) reported higher pain scores compared to baseline (due to VCF or degenerative reasons) during the first 6 months after treatment.

4. Discussion

SABR is an innovative approach capable of delivering high radiation doses that potentially improve local control rates in the treatment of vertebral metastases. In this study, we report high rates of local control and minimal toxicity in patients treated with high-dose stereotactic hypofractionated RT for spinal metastases. Metachronous lesions and oligometastatic patients were identified as variables associated with better PFS rates in multivariable analysis. No clinically significant predictors for rapid progression could be retrieved.

Our high local control rates are consistent with LR described in the literature; different systematic reviews report similar high rates of local control (90% at 1 year) [14,22]. Subgroup analysis of the patient cohort suffering local recurrences showed larger mean GTV volumes and inferior PTV covering compared to the whole cohort. These two factors may be correlated with a higher local recurrence risk.

In addition, the treatment was well tolerated: toxicity in general was low, with vertebral compression fractures in 6% of all patients and no neurologic adverse events. A multi-institutional spine analysis based on 410 spinal segments reported a 14% risk of development of VCF [23]. A large systematic review reported VCF occurring in 9.4% of the patients [23]. Baseline VCF, lytic lesions, spinal deformity and high SINS score [7–12 24] have been identified as significant predictors of VCF. However, no clear association with these risk factors was seen in our subgroup. Our only finding was a predominance of lumbar locations (3/4) in the patients with VCF.

The combination of modern RT techniques with novel systemic agents was reported in a recent Italian AIRO review [25], the tolerability profile of the association between various tyrosin-kinase inhibitors and RT seemed to be acceptable. In our patient cohort the association of systemic therapies other than hormonal treatment was limited. Only 4 patients received systemic therapy and no excess toxicity was seen.

Concerning pain response, a recent prospective phase II trial demonstrated that the use of hypofractionated SABR for painful spinal metastases was associated with a rapid and durable pain response combined with improved quality of life [26]. A randomized phase II trial demonstrated faster and improved pain response compared to conventional fractionated palliative radiotherapy [27]. In contrary, the preliminary results of the ROTG 0631 could not demonstrate better pain response at 3 months with SABR (1x16 Gy) compared to palliative external beam radiotherapy (1x8 Gy) [28]. In the current study, we retrieved pain scores retrospectively and non-standardized. Moreover, the majority of patients (67%) were baseline asymptomatic, so limited conclusions can be drawn for pain response in general.

Finally, we evaluated possible predicting factors for rapid progression, because correct selection of patients for potentially curative but costly SABR is of high importance. It is crucial to identify patients who would really benefit of more intensive treatment versus those who are rather candidate for a palliative intent. A prognostic index for OS using an RPA index has been developed in 2012 [21] using 3 factors: time from primary diagnosis (<>30 months), Karnofsky performance status (<> 70) and age (<> 70 years). After retrospective analysis, the majority of our patient cohort (86.5%) consisted of RPA group 1 or 2, reflecting already a rather correct upfront patient selection. Our univariate analysis demonstrated also the number of fractions and cervical location as significant variables. However, these results were not retained in multivariate analysis so we assume no clinical significance and maintain meanwhile the RPA classification as prognostic for patient selection.

There are certain limitations of this study worth mentioning: the retrospective nature, the relative small sample size and follow-up time; the heterogeneity of the cohort with different primary tumor types and lack of uniform fractionation regimen.

Strengths are the uniform dose reporting towards ICRU recommendations [19] and a uniform contouring and planning system. A dedicated contouring and planning system for this high innovative treatment can lead to high local control rates and safety profiles [29].

In conclusion, our results are consistent with those reported by others, indicating that SABR is an effective and safe treatment option for selected cases with spinal metastases, with a limited risk of complications. Oligometastatic patients with metachronous lesions seem to benefit the most from SABR for spinal metastases. Probably, these metachronous lesions are the main reflection of a true oligometastatic state. Obviously, these findings need to be investigated further in larger and prospective trials.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Wong DA, Fornasier VL, MacNab I, et al. Spinal metastases: the obvious, the occult, and the impostors. Spine 1990;15:1–4.
[2] Ecker RD, Endo T, Wetjen NM, et al. Diagnosis and treatment of vertebral column metastases. Mayo Clin Proc 2005;80:1177–86.
[3] Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25:1423–36.
[4] van der Linden YM, Steenland E, van Houwelingen HC, et al. Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study. Radiother Oncol 2006;78:245–53.
[5] Steenland E, Leer JW, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiother Oncol 1999;52:101–9.
[6] Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers

　　　　　　　　　　　　　　　　　C. Billiet et al. / Clinical and Translational Radiation Oncology 24 (2020) 65–70

(SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019;10185:2051–8.

[7] Yamada Y, Bilsky MH, Lovelock DM, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. Int J Radiat Oncol Biol Phys 2008;71:484–90.

[8] Gerszten PC, Burton SA, Ozhasoglu C, et al. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. Spine 2007;32:193–9.

[9] Gerszten PC, Mendel E, Yamada Y, et al. Radiotherapy and radiosurgery for metastatic spine disease: what are the options, indications, and outcomes?. Spine 2009;34:S78–92.

[10] Chang EL, Shiu AS, Mendel E, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. J Neurosurg Spine 2007;7:151–60.

[11] Ryu S, Jin JY, Jin R, et al. Partial volume tolerance of the spinal cord and complications of single-dose radiosurgery. Cancer 2007;109:628–36.

[12] Sahgal A, Weinberg V, Ma L, et al. Probabilities of radiation myelopathy specific to stereotactic body radiation therapy to guide safe practice. Int J Radiat Oncol Biol Phys 2013;85:341–7.

[13] Amdur RJ, Bennett J, Olivier K, et al. A prospective, phase II study demonstrating the potential value and limitation of radiosurgery for spine. Am J Clin Oncol 2009;32:515–20.

[14] De Bari B, Alongi F, Mortellaro G, Mazzola R, Schiappacasse L, Guckenberger M. Spinal metastases: is stereotactic body radiation therapy supported by evidences?. Crit Rev Oncol Hematol. 2016;98:147–58. https://doi.org/10.1016/j.critrevonc.2015.11.002.

[15] Bilsky MH, Laufer I, Fourney DR, et al. Reliability analysis of the epidural spinal cord compression scale. J Neurosurg Spine 2010;13:324–8.

[16] Fisher CG, DiPaola CP, Ryken TC, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine 2010;35:E1221–9.

[17] Cox BW, Spratt DE, Lovelock M, et al. International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 2012;83:e597e605.

[18] Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 2010;37:4078–101.

[19] Wilke L, Andratschke N, Blanck O, et al. ICRU report 91 on prescribing, recording, and reporting of stereotactic treatments with small photon beam: statement from the DEGRO/DGMP working group stereotactic radiotherapy and radiosurgery. Strahlenther Onkol 2019;195:193–8.

[20] Guckenberger M, Lievens Y, Bouma A, et al. Characterization and classification of oligometastatic disease: an ESTRO and EORTC consensus recommendation. Accepted for publication in the Lancet.

[21] Chao ST, Koyfman SA, Woody N, et al. Recursive partitioning analysis index is predictive for overall survival in patients undergoing spine stereotactic body radiation therapy for spinal metastases. Int J Radiat Oncol Biol Phys 2012;82:1738–43.

[22] Zain A, Husain MD, Sahgal A, et al. Stereotactic body radiotherapy for de novo spinal metastases: systematic review. J Neurosurg Spine 2017;27:295–302.

[23] Sahgal A, Atenafu EG, Chao S, et al. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi- institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. J Clin Oncol 2013;31:3426–31.

[24] Lee SH, Tatsui CE, Ghia AJ, et al. Can the spinal instability neoplastic score prior to spinal radiosurgery predict compression fractures following stereotactic spinal radiosurgery for metastatic spinal tumor? A post hoc analysis of prospective phase II single- institution trials. J Neurooncol. 2016;126:509–17.

[25] Arcangeli S, Jereczek-Fossa BA, Alongi F, et al. Combination of novel systemic agents and radiotherapy for solid tumors – Part II: an AIRO (Italian association of radiotherapy and clinical oncology) overview focused on treatment toxicity. Crit Rev Oncol Hematol. 2019;134:104–19.

[26] Guckenberger M, Sweeney RA, Hawkins M, et al. Dose-intensified hypofractionated stereotactic body radiation therapy for painful spinal metastases: results of a phase 2 study. Cancer 2018;9:2001–9.

[27] Sprave T, Verma V, Förster R, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three- dimensional conformal radiotherapy. Radiother Oncol. 2018;128:274–82.

[28] RTOG 0631 Phase II/III Study of Image-Guided Stereotactic Radiosurgery for Localized (1-3) Spine Metastases. Published abstract IJROBP Sept 2019, Vol 105 Sup.

[29] Giaj-Levra N, Niyazi M, Figlia V, et al. Feasibility and preliminary clinical results of linac-based Stereotactic Body Radiotherapy for spinal metastases using a dedicated contouring and planning system. Radiat Oncol 2019;184.