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LONG-TERM RESULTS OF DOSE-INTENSIFIED FRACTIONATED STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR PAINFUL SPINAL METASTASES

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None

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Short running title:

Long-term results of spine SBRT.

Data sharing statement:

Research data are stored in an institutional repository and will be shared upon a reasonable request to the corresponding author.

ABSTRACT

Purpose: To report long-term outcome of fractionated stereotactic body radiotherapy (SBRT) for painful spinal metastases.

Material and Methods: This prospective single arm multi-center phase 2 clinical trial enrolled 57 patients with 63 painful, unirradiated spinal metastases between March 2012 and July 2015. Patients were treated 48.5 Gy in 10 SBRT fractions (long life expectancy [Mizumoto score ≤ 4]) or 35 Gy in 5 SBRT fractions (intermediate life expectancy [Mizumoto score 5-9]). Pain response was defined as pain improvement of minimum 2 points on a visual analogue scale (VAS) and net pain relief was defined as the sum of time with pain response (complete and partial) divided by overall follow-up time.

Results: All 57 patients received treatment per-protocol, 32 and 25 patients were treated with 10- and 5-fraction SBRT, respectively. The median follow-up of living patients was 60 months, range 33-74. Of evaluable patients, 82% had complete or partial pain response (responders) at 3 months follow-up (primary endpoint) and pain response remained stable over 5 years. Net pain relief was 74% (95% CI, 65-80%). One-, 3- and 5-year overall survival rates were 59.6% (95% CI, 47-72%), 33.3% (95% CI, 21-46%) and 21% (95% CI, 10-32%), respectively. Freedom from local spinal-metastasis progression was 82% at the last imaging follow-up. Late Grade 3 toxicity was limited to pain in 2 patients (non-responders). There was no case of myelopathy. SBRT resulted in long-term improvements of all Euro-QoL-5D-5L dimensions except Anxiety/Depression.

Conclusions: Fractionated SBRT achieved durable pain response and improved quality-of-life at minimum late toxicity.

INTRODUCTION

Advances in diagnosis, systemic therapy with targeted agents and immune checkpoint inhibition and supportive care have substantially improved survival of cancer patients with metastatic disease. This resulted in a paradigm shift of the treatment objective, from short-term palliation to durable symptom and metastatic disease control and improved quality-of-life. Conventional radiation therapy has been the standard of care for painful bone metastases with overall pain response of 60% [1], while about a half of these patients with initial pain relief develop pain relapse within 3-6 months after treatment [2]. Given non-selective dose distributions in large irradiated volumes, due to uncertainties of target volume definition and lack of image-guidance for accurate treatment delivery, conventional radiation therapy never aimed at achieving long-term local metastases and symptom control. The new objectives therefore necessitate utilization of advanced treatment technologies, which have previously been used predominantly in the curative setting [3].

Stereotactic body radiotherapy (SBRT) is characterized to precisely deliver high radiation doses to the target with minimum exposure of critical structures. SBRT for spinal metastases was observed to achieve pain relief in 80-100% of patients at a median time of 2 weeks [4] together with complete pain response rates higher than after conventional radiation therapy [5]. Pain and local metastasis control after stereotactic radiosurgery (SRS)/SBRT were reported in 80-90% of the patients lasting 13 months on average, while retreatment rates did not exceed 0-15% [6,7]. However, the evidence of SBRT in this setting is mostly based on retrospective studies and long-term data about safety and efficacy is lacking.

These promising data formed the hypothesis that fractionated dose-intensified SBRT for painful spinal metastases without instability could improve pain response at

minimum toxicity in patients with intermediate and long life expectancy that was tested in a non-randomized, single arm, multi-center phase 2 clinical trial [8]. This study reports the long-term outcome to evaluate whether improvements in pain response and quality-of-life are stable over time without late toxicity.

MATERIAL AND METHODS

The clinical trial was approved by local ethics committees, was registered at ClinicalTrials.gov (NCTXXXXXXXX), and was conducted in accordance with the ethical standards set forth by the Declaration of Helsinki. Design of the clinical trial has been reported previously [9]. In short, inclusion criteria selected patients with a maximum of 2 distinct, non-contiguous, painful or pain-free (with pain medication), unirradiated, mechanically stable spinal metastases before or after surgery from a histologically proven solid tumor. Patients with progressive neurological symptoms/deficits were excluded. The modified (hypercalcemia was not scored) prognostic Mizumoto score was used for exclusion of patients with short overall survival expectancy (score ≤ 9) [10]. We considered spinal metastases mechanically stable, if there was no radiological evidence of instability and/or symptoms indicative for instability (primarily severe pain and/or neurological deficits exacerbating by movement). The Spine Instability Neoplastic Score (SINS) score was not determined, because SINS had not been validated when the trial was designed. Stabilization or decompressive surgery if there was no progressive pain or neurological deficits after surgery, bisphosphonates and/or systemic treatment before SBRT were allowed.

Treatment planning and delivery were described previously [8]. External patient immobilization was used in all patients. Target definition was based on high-

resolution CT and MRI imaging. The high-dose clinical target volume (CTV) included all macroscopically involved vertebral elements—body, pedicles, transverse process, and spinous process—of the involved vertebra minus the spinal cord; the low-dose CTV comprised the entire vertebrae of the involved levels. CTV-to-PTV margin was 2mm (Supplementary Fig. A1). The dose prescription involved 2 dose levels delivered simultaneously (simultaneous integrated boost) and treatment planning used volumetric modulated arc therapy or step-and-shoot intensity-modulated radiation therapy in all patients. OAR dose-volume constraints are presented in Supplementary Table A1. Patients with a long life expectancy (Mizumoto score of 0-4) were treated with 10 fractions (total dose for the high-dose PTV 48.5 Gy [biologically effective dose at $\alpha/\beta = 10$ Gy (BED_{10}), 72 Gy]; total dose for the low-dose PTV 30 Gy [BED_{10} , 39 Gy]), whereas patients with an intermediate life expectancy (Mizumoto score of 5-9) were treated with 5 fractions (total dose for the high-dose PTV 35 Gy [BED_{10} , 59.5 Gy]; total dose for the low-dose PTV 20 Gy [BED_{10} , 28 Gy]) (Supplementary Fig. A2). Mean maximum dose to 0.01 cm³ of the spinal cord expanded with a 1-mm margin was 32.9 Gy (standard deviation 6.1 Gy) with 10-fraction SBRT and 20.6 Gy (standard deviation 8.6 Gy) with 5-fraction SBRT. SBRT was delivered with a 6- to 18-MV linear accelerator; daily image-guidance was performed with online correction of set-up errors using onboard cone-beam CT.

The primary endpoint of the study was pain improvement of 2 or more points on a visual analogue scale (VAS) by 3 months after treatment at the site of the treated lesion (i.e., the overall pain response [the sum of the complete and partial responses] measured according to international consensus guidelines [11]) in at least 75% of patients [8]. Patient-rated pain and pain medication as the daily oral morphine equivalent were recorded at the baseline and each follow-up visit.

According to the international consensus guidelines [11], a complete response was defined as a VAS pain score of 0 at the treated site with no concomitant increase in the daily oral morphine equivalent. A partial response was defined as a pain score reduction of 2 or more at the treated site without an increase in daily oral morphine equivalent consumption or as no increase in pain and a reduction of 25% or more in daily oral morphine equivalent consumption. Pain progression was defined as an increase in the pain score of 2 or more at the treated site with stable oral morphine equivalent. Patients with complete or partial pain response at 3 months after treatment or any other time point thereafter were classified as responders, the rest were non-responders. Patients with a response for one lesion, but not for another were considered as non-responders.

Secondary endpoints included toxicity (late [≥ 3 months after treatment]) assessed with National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0), freedom from local spinal-metastasis progression, overall survival and patient-reported health-related quality-of-life (QoL) measured with the 5-level EuroQol 5-Dimension Questionnaire (EQ-5D-5L) [12] at the baseline and during follow-up. Each dimension of EQ-5D-5L has five response levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems. The EQ-5D-5L was used together with a 0- to 100-point VAS for rating the overall health status (EQ VAS). Follow-up visits were scheduled every week during the first 2 months and thereafter at 3-month interval.

Changes in maximum VAS pain score at the treated site and the EQ VAS at each assessment point relative to the baseline were assessed with Wilcoxon rank sum test. Fisher exact test was used to compare the distribution of patients with no problems vs. with problems in QoL dimensions relative to the baseline. We

performed repeated measures ANOVA to assess effects of total radiation dose, number of fractions, surgery before SBRT and VCF before SBRT on pain response rates during follow-up. Response duration was calculated in months in patients with overall pain response (complete and partial) as observed at 3 months follow-up (the date of primary endpoint) to the date of pain progression as compared to baseline, or in absence of relapse to the date of last follow-up visit or death [13]. Mann-Whitney U-test was used to evaluate effects of Mizumoto score, total radiation dose and number of fractions on response duration. We calculated net pain relief defined as the sum of time with overall pain response (complete and partial) divided by overall survival/follow-up time. Freedom from local spinal-metastasis progression and overall survival were estimated with Kaplan-Meier method as well as associated 95% confidence intervals (CIs). Patients were censored at the date of death or at the date of their last known follow-up, whichever came first. Local spinal metastasis progression was defined as an increase in tumor dimension in CT and / or MRI imaging by >20% in the largest dimension in the case of a partial remission initially, or the presence of measurable tumor after an initial complete remission [14]. Overall survival was defined as death from any cause calculated from the first day of SBRT. Comparisons between the variables (Mizumoto score, primary tumor histology, oligometastatic disease, type of metastasis) were performed with the two-sided log-rank test (univariate analysis). A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the BrightStat software package (version 1.2.20).

RESULTS

Between March 2012 and July 2015, 57 patients with 63 metastases were enrolled into the study (Fig. 1). The baseline information on VAS pain score and/or pain medication were missing in 3/57 patients. Six (6/57) patients had two metastases, in 3 of whom metastases were treated simultaneously. Patient and spinal metastasis characteristics are presented in Table 1. Forty-three spinal metastases (68%) had epidural spinal cord compression component (Bilsky score >0). Fifteen patients (24%) had a VCF before treatment. Twenty-five patients (44%) were treated with 5 SBRT fractions. The remaining 32 patients (56%) were treated with 10 SBRT fractions, and 4 of these patients had a Mizumoto score of 5 to 8, which was a minor violation of the study protocol. Median follow-up of living patients was 60 months (range 33-74), respectively; median imaging follow-up for living patients was 45, range 3-67 months.

Pain response

Mean maximum VAS pain score at the treated lesion before radiotherapy was 6.2 (standard deviation 2.4) vs. 2.2 (standard deviation 2.4) at 3 months after SBRT ($P < 0.0001$), i.e., a change in pain score -4.0 (standard deviation 2.8) (Fig. 2a). A statistically significant difference in maximum VAS pain score at the treated lesion was preserved during follow-up until 54 months ($P < 0.001$). VAS pain scores remained low at 5 years follow-up with mean 2.5 (standard deviation 2.5), the difference to pre-treatment was not statistically significant due to a smaller number of patients. We did not observe any case of pain flare defined as an increase in maximum VAS pain score ≥ 2 during treatment or at the treatment end.

Mean maximum VAS pain scores did not differ significantly between patients, who did and who did not undergo surgery before SBRT: 5.6 (2.4 standard deviation) vs.

6.4 (2.4 standard deviation) at the baseline ($P=0.87$) and 2.1 (2.2 standard deviation) vs. 2.3 (2.5 standard deviation) at 3 months after SBRT ($P=0.62$), respectively. During follow-up changes in pain score remained similar in all patients irrespectively surgery before SBRT. There were no statistically significant differences in mean maximum VAS pain scores between patients with and without VCF before (6.1 [2.9 standard deviation] vs. 6.2 [2.6 standard deviation], $P=0.8$) and 3 months after SBRT (2.4 [2.4 standard deviation] vs. 2.2 [2.4 standard deviation], $P=0.8$), respectively. The difference remained not statistically significant during follow-up. The response rates (complete and partial pain response) at 3 months were 82% (31% complete and 51% partial response) in evaluable patients (Table 2). The proportion of responders among evaluable patients remained stable (median 84%) over 5 years. SBRT fractionation did not influence pain response rates significantly ($P=0.23$). The duration of response is illustrated in Fig. 2b. There was no statistically significant difference in pain response duration between patients treated with 5- or 10-fraction SBRT ($P=0.34$). Net pain relief was 74% (95% CI, 65-80%).

Overall survival and freedom from local spinal-metastasis progression

10/57 patients registered and treated in the study were alive at the time of analysis (18%). Eight patients alive were characterized by a Mizumoto score ≤ 4 , the remaining 2 patients by Mizumoto score 5 and 6; all patients alive were treated with 10-fraction SBRT. Estimates of overall survival were 59.6% (95% CI, 47-72%), 33.3% (95% CI, 21-46%) and 21% (95% CI, 10-32%) at 1, 3 and 5 years, correspondently. The median overall survival was 19 months. The difference in overall survival in patients with a Mizumoto score ≤ 4 (long life expectancy) and 5-9 (intermediate life expectancy) was of borderline statistical significance ($P=0.054$) with

5-year overall survival rates of 24% and 11% and median survival times of 27 months and 7 months, respectively. Neither status of having oligometastatic disease at the time of study inclusion, nor primary tumor histology were found statistically significant for overall survival. There was a trend for higher survival in patients with breast cancer with a median overall survival of 38 months vs. 16 months in patients with other tumors ($P=0.07$). Freedom from local spinal-metastasis progression was 82% at the last imaging follow-up.

Late toxicity

There were neither radiation-induced myelopathy, radiation-induced plexopathy, nor any Grade 4 late toxicity. Five (9%) and 2 patients (4%) presented late Grade 2 and 3 pain, respectively, all controlled with opioid and non-opioid medication. The 2 patients with Grade 3 pain were non-responders at 3 months follow-up. Late skin toxicity was limited to 1 patient with Grade 1 skin induration. During follow-up 8 (14%) and 12 patients (21%) developed progressive and new VCF at a median time of 2 months, range 1-25 and 0-40 months, respectively. Three patients (5%) required surgery, 1 of whom with pre-existing VCF had stabilization surgery 1 month after SBRT. Two patients underwent decompressive surgery at 40- and 69-months follow-up. Because of local progression, 1 patient (1.8%) was locally re-irradiated 15 months after the 1st course of SBRT.

Quality-of-life

SBRT improved all 5 QoL dimensions and EQ VAS and improvements were stable over the time (Fig. 3). The difference relative to the baseline was statistically significant in dimensions Pain/Discomfort at 3 months ($P=0.04$), Mobility at 3

($P=0.02$), 6 ($P=0.01$) and 12 months ($P=0.001$), Usual Activities at 6 ($P=0.04$), 12 ($P=0.002$), 15 ($P=0.03$) and 30 months ($P=0.047$) follow-up. Changes in dimension Anxiety/Depression did not reach the level of significance. There was statistically significant improvement in EQ VAS score from mean 53.1 (standard deviation 19.8) to 61.8 (standard deviation 19.1) at 3 months ($P=0.008$), 6 ($P=0.009$), 12 ($P=0.004$), 15 ($P=0.009$), 18 ($P=0.002$), 21 ($P=0.03$) and 30 months ($P=0.04$). Mean EQ VAS score was 68.8 (standard deviation 4.6), range 61.9-76.3 during follow-up.

DISCUSSION

In this prospective single-arm phase 2 clinical trial we observed a strong and durable pain reduction after fractionated SBRT for painful vertebral metastases, which was associated with long-term improvements in quality-of-life. No long-term Grade 4 toxicity was observed, especially no myelopathy or nerve root damage.

We observed a significant reduction in pain score by -4.0 (standard deviation 2.8) on a VAS at 3 months after SBRT that was maintained over 5 years. A randomized phase 3 clinical trial of NRG Oncology/Radiation Therapy Oncology Group (ROG) 0631 on 339 patients reported a 3-month change in pain score of -3 (standard deviation 3.34) on a Numerical Rating Pain Score with single-fraction SBRT [15], which appears smaller compared to our results, given similarities between the two pain score scales [16]. However, pain reduction was similar with -3.83 [standard deviation 2.97] by conventional single-fraction external radiation therapy in the control arm of the NRG Oncology/ROG 0631 study. In another randomized phase 2 clinical trial from Heidelberg on 55 patients comparing single-fraction SBRT vs. fractionated 3-dimension (3D) conformal radiotherapy (CRT), changes in pain scores on a VAS did not significantly differ between treatments by 3 months [17]. Similar

improvements in pain score were observed in a non-randomized single-arm phase 1-2 clinical trial: using Brief Pain Inventory, baseline pain was 3.4 (standard deviation 2.9), which improved to 2.1 (standard deviation 2.7) at 3 months and became statistically significant at 6 months with 1.7 (standard deviation 2.4) post-treatment [18]. We observed a pain response rate of 82% at 3 months. This pain response of multiple-fraction SBRT in our study appears higher compared to the NRG Oncology/ROTG 0631 study reporting 40.3% after single-fraction SBRT vs. 57.9% after external radiation therapy ($P=0.99$) and also higher compared to the Heidelberg experience, which reported a 69.6% pain response rate after single-fraction SBRT vs. 47.8% after 3DCRT ($P=0.13$). In a phase 2 clinical trial on single-fraction SBRT followed by prophylactic vertebroplasty 95.2% of patients were responders 3 months after treatment [19] (Table 3). Overall, early pain response appears higher after multiple-fraction SBRT compared to single-fraction SBRT.

On a long-term scale, VAS pain scores remained low at a VAS score of 2.5 over a 5-year period in our study. Approximately 80% of evaluable patients maintained a pain response over 5 years. These data suggest that the benefit of SBRT becomes especially apparent with longer follow-up, aiming for durable pain response. SBRT for pain relief might therefore be justified in particular in patients with longer life expectancy, while (single-fraction) external radiation therapy might be sufficient in patients with (very) short life expectancy. The Mizumoto score was used in our study to exclude patients with short life expectancy from SBRT. Although this prognostic score proved to be relatively reliable, it has not been validated and needs to be revised considering the recent developments in cancer care, e.g., immune checkpoint inhibition [20].

Long-term pain response was associated with long-term improvements of quality-of-life in our study. Of the 5 QoL dimensions, 4 improved after SBRT and remained stable during the follow-up. EQ VAS was significantly improved beyond 2 years. Neither of the two randomized trials described above observed a difference in QoL after SBRT vs. external radiation therapy at 3 months [15,21], though results of the NRG Oncology/ROTG 0631 study were published as an abstract without details on QoL changes and follow-up. This again indicates an advantage of multiple-fraction SBRT compared to single-fraction SBRT.

The observed long-lasting effects of multiple-fraction SBRT might be attributed to durable local control observed in our study that was comparable to results reported by others [19, 22-24] (Table 3). No randomized trial investigated single-fraction versus multiple-fraction SBRT. In a retrospective study comparing single- and multi-fraction (3, 4 or 5 fractions) robotic SBRT in 228 patients, the fractionated approach was associated with improved local metastasis control (at 2 years 96% vs. 70% [P=0.001]), improved overall survival (at 1 year 63% vs. 46% [P=0.002]) and with lower retreatment rates (1% vs. 13% [P<0.001]) compared single-fraction treatment [25]. Experimental data on mechanisms of radiotherapy-induced tumor immunity may suggest higher effects of fractionated irradiation of a selected dose in individual patients [26]. Another potential explanation for the favorable results observed in our study is the elective irradiation of the whole vertebra with conventional doses of 30 Gy in 10 fractions or 20 Gy in 5 fractions. These doses might be sufficient for sterilization of microscopic spread and thereby contribute to long-term local and pain control. More experimental and clinical studies are warranted.

High rates of long-term local spinal metastasis control were achieved despite 68% of the spinal metastases in our study were characterized by a pre-treatment epidural

disease component (Bilsky score >0). These patients are more difficult to treat due to the radiosensitivity of the spinal cord and presence of epidural disease was consequently among the exclusion criteria of the NRG Oncology/RTOG 0631 study. Simultaneously, patients with epidural disease are at increased risk for metastatic spinal cord compression if local disease control is not achieved. Consequently, patients with epidural disease represent a high-risk patient population benefiting the most from fractionated SBRT. Pre-SBRT decompressive surgery or separation surgery are alternative treatment strategies [27,28], which is an established standard of care in patients with symptomatic spinal cord compression [29].

With long-term follow-up SBRT maintained its favorable toxicity profile. None of our patients developed radiation-induced myelopathy, radiation-induced plexopathy, or late Grade 4 toxicity. This is in agreement with published data [30]. Late Grade 3 toxicity was limited to pain controlled with medication in 2 non-responders. In a retrospective study on 54 patients with a minimum 5-year follow-up by Ling et al., 3 patients (5.6%) developed late Grade 3 painful sensory neuropathy, though all 3 patients had been treated with external radiation therapy followed by 3-5 courses SBRT [31]. Previously we reported a relatively high rate of VCF: 35% of the patients developed progressive or new VCF in our study [32]. However, this needs to be put into the context that almost one quarter of the patients had VCF before SBRT. Additionally, fractures were asymptomatic in most patients although 2 patients required stabilization surgery after SBRT.

Our study has several limitations due to its design as a multi-center, non-randomized trial running over 3 years on the small number of patients. Although we applied selection criteria for patients in our study, e.g., a good performance status, long and intermediate life expectancy using the non-validated prognostic scoring system, we

could not avoid heterogeneity in the patient population. Another limitation of our study was availability of CT vs. MRI for follow-up imaging, which might have influenced consistency of the definition of local metastasis control. Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 was used for assessment of local progression, which is not a bone-specific criterion [14]. Finally, we did not formally consider pseudoprogression. However, freedom from local progression was only a secondary endpoint of this study whereas pain response as the primary endpoint of this study was not influenced by these limitations.

In conclusion, we demonstrated that dose-intensified multiple-fraction SBRT safely achieved durable pain response and improved QoL, as a result of long-term local metastasis control. Multiple-fraction SBRT might therefore be considered especially in patients with favorable life expectancy, which is currently being tested in a randomized trial design (NCTXXXXXXXXX).

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32. XXXXXXXX

FIGURE CAPTIONS

Fig. 1. Consort diagram.

Fig. 2a. Individual and mean of maximum pain score on the Visual Analogue Scale (VAS) at the treated lesion before and after treatment.

Fig. 2b. Follow-up in pain responders and non-responders (▲ = pain recurrence; x = death).

Fig. 3. Proportion of patients reporting no problems using EuroQol 5-Dimension Questionnaire during follow-up. The number (n) of the reporting patients are within parentheses.

Table 1. Patient and metastasis characteristics.

Parameter	No. (%)
Treated spinal metastases	63
Age at diagnosis, year	
Mean \pm SD	62 \pm 12
Median (range)	64 (25-84)
Sex	
Male	31 (54)
Female	26 (46)
Karnofsky performance status	
\geq 70%	46 (81)
\leq 70%	11 (19)
Primary tumor site	
Breast	12 (21)
Non-small cell lung cancer	11 (19)
Prostate	11 (19)
Colorectal	5 (9)
Kidney	4 (7)
Melanoma	1 (2)
Other	13 (23)
Oligometastatic disease	32 (56)
Surgery before SBRT	
Stabilization surgery	6 (11)
Decompressive surgery	10 (18)
Analgesics at the baseline	
Opioid medication	18 (32)
Non-opioid medication	31 (54)
Site of treated metastasis	
Cervical	6 (10)
Thoracic	36 (57)
Lumbar	19 (30)
Sacral	2 (3)
Maximum pain score on VAS at the site of spinal metastasis at baseline	
0-1	1 (2)
2-4	15 (24)
5-6	12 (19)
7-10	32 (51)
Missing	3 (5)
Grade of epidural spinal cord compression (Bilsky score) at the site of spinal metastasis	
0	17 (27)
1a	9 (14)
1b	4 (6)
1c	4 (6)
2	22 (35)

3	4 (6)
Missing	3 (5)
Mizumoto score	
0-4	28 (49)
5-9	27 (47)
10	2 (4)
SBRT fractions	
5	25 (44)
10	32 (56)

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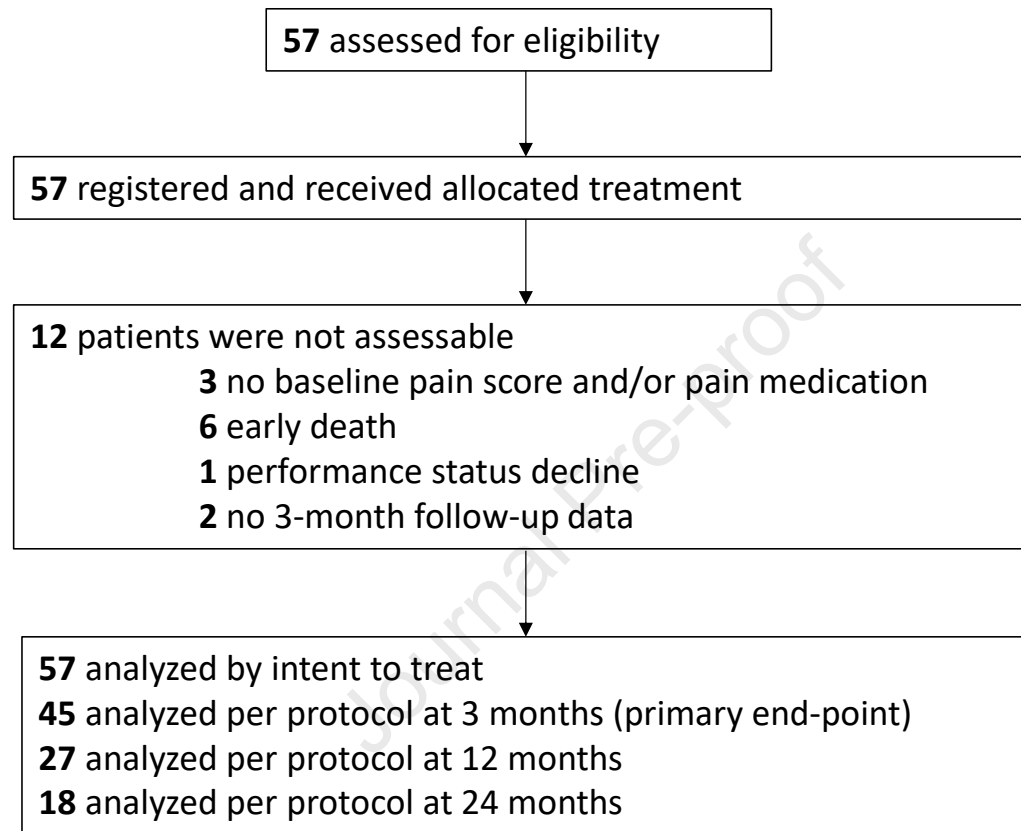
Table 2. Pain response over time by evaluable patient population.

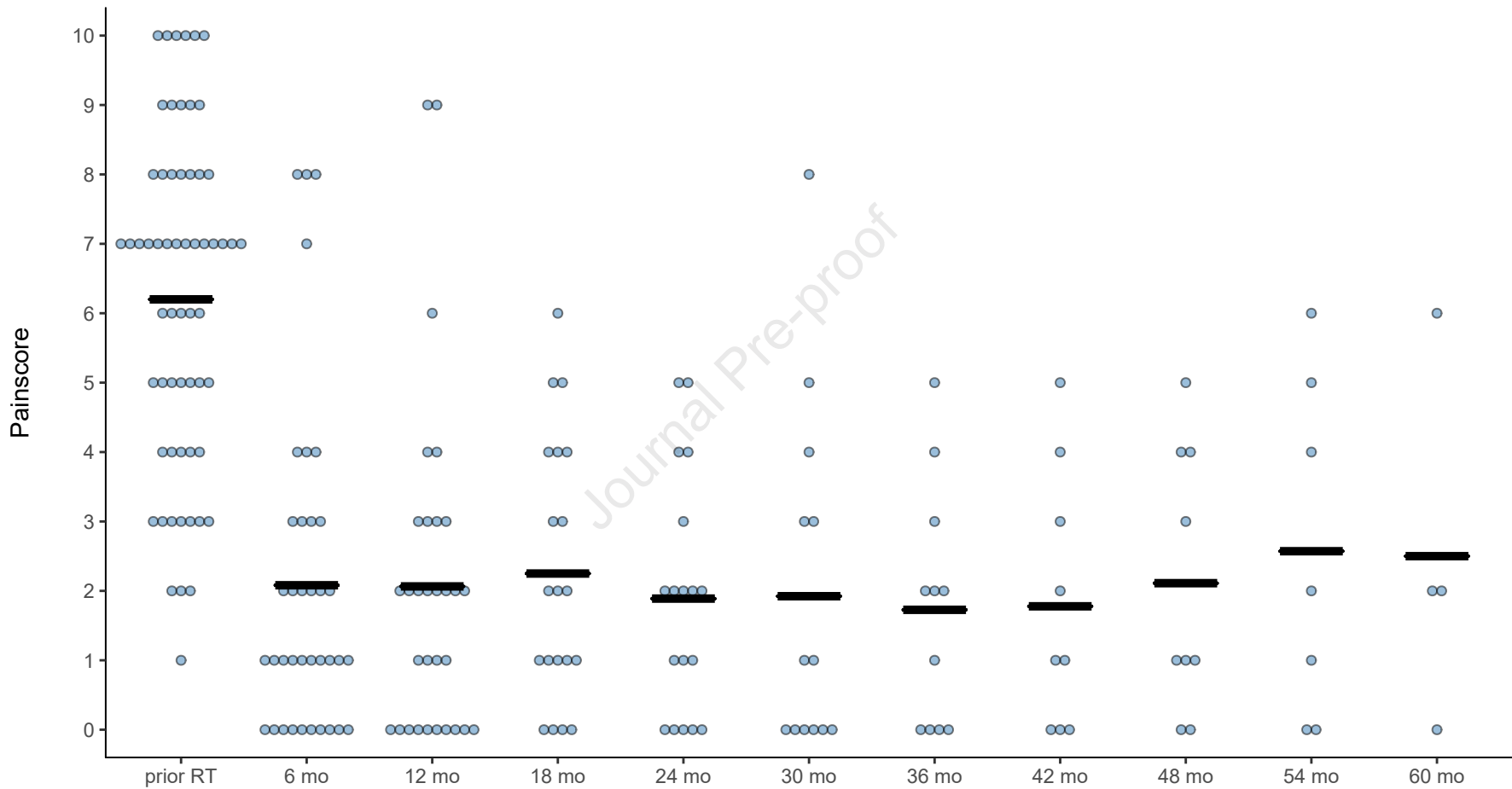
	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months	60 months
Responders, No. (%)	29 of 35 (83)	23 of 27 (85)	17 of 19 (89)	17 of 18 (94)	14 of 15 (93)	9 of 11 (82)	7 of 9 (78)	8 of 9 (89)	3 of 7 (43)	3 of 4 (75)
Non- responders, No. (%)	6 of 35 (17)	4 of 27 (15)	2 of 19 (11)	1 of 18 (6)	1 of 15 (7)	2 of 11 (18)	2 of 9 (22)	1 of 9 (11)	4 of 7 (57)	1 of 4 (25)

Table 3. Selected studies reporting treatment outcome after SBRT for unirradiated spinal metastases.

Reference	Patients (No. metastases)	Dose, Gy (No. fractions)	Median follow-up, mo.	Pain response	Local control	Overall survival (OS)	VCF
Ryu 2019 [15] RCT phase 2-3	SBRT 209 ERT 130	SBRT 16-18 (1) ERT 8 (1)	NR	NPRS change (3 mo.): -3±3.34 (SBRT) vs. -3.83±2.97 (ERT), NS Responders (3 mo.): 40.3% (SBRT) vs. 57.9% (ERT), NS	NR	NR	NR
Sprave 2019 [17] RCT phase 2	SBRT 30 ERT 30	SBRT 24 (1) ERT 30 (10)	8.1 (mean)	VAS change (3mo.): SBRT vs. ERT, NS VAS change (6 mo.): SBRT vs. ERT, SS Responders (3 mo.): 70% (SBRT) vs. 48% (ERT), NS	NR	Mean OS 7.9 mo. (SBRT) Mean OS 7.9 mo. (ERT)	Prior treatment 29% After treatment 27.8%
Tseng 2019 [22] Prospective	145 (279)	24 (2)	17	NR	90.3% (1 y.) 82.4% (2 y.)	73.1% (1 y.) 60.7% (2 y.) Median OS 33.3 mo.	Cumulative risk 8.5% (1 y.) 13.8% (2 y.)
Wardak 2019 [19] Single arm phase 2	29 (35)	20 (1)	7	Responders (3 mo.): 95.2%	92% (1 y.)	Median OS 9 mo.	10.3%
Garg 2012 [23] Single arm phase ½	61 (63)	16-24 (1)	17.8	No pain: 21% (baseline) vs. 30% (3 mo.), NS	88% (1.5 y.)	64% (1.5 y.) Median OS 30 mo.	26% Neurologic toxicity Grade 3-4: 3.3%
This study Single arm phase 2	57 (63)	48.5 (10) 30 (5)	19	VAS change (3 mo.): -4.0±2.8 Responders (3 mo.): 82%	82% at the last imaging follow-up	59% (1 y.) 48% (2 y.) Median OS 19 mo.	Prior treatment 24% After treatment 21%
Guckenberger 2014 [24] Retrospective	301 (387)	24 (3)	11.8	No pain: 18.2% (baseline) vs. 76.8% (last follow-up)	89.9% (1 y.) 83.9% (2 y.)	64.9% (1 y.) 43.7% (2 y.) Median OS 19.5 mo.	7.8%

No. = number; mo. = months; VCF = vertebral compression fracture; SBRT = stereotactic body radiation therapy; VAS = visual analogue scale; y. = year; RCT = randomized clinical trial; ERT = external radiation therapy; NPRS = numerical pain rating scale; NS = not statistically significant; NR = not reported; SS = statistically significant; SABR = stereotactic ablation body radiation therapy.





at risk

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37

31

20

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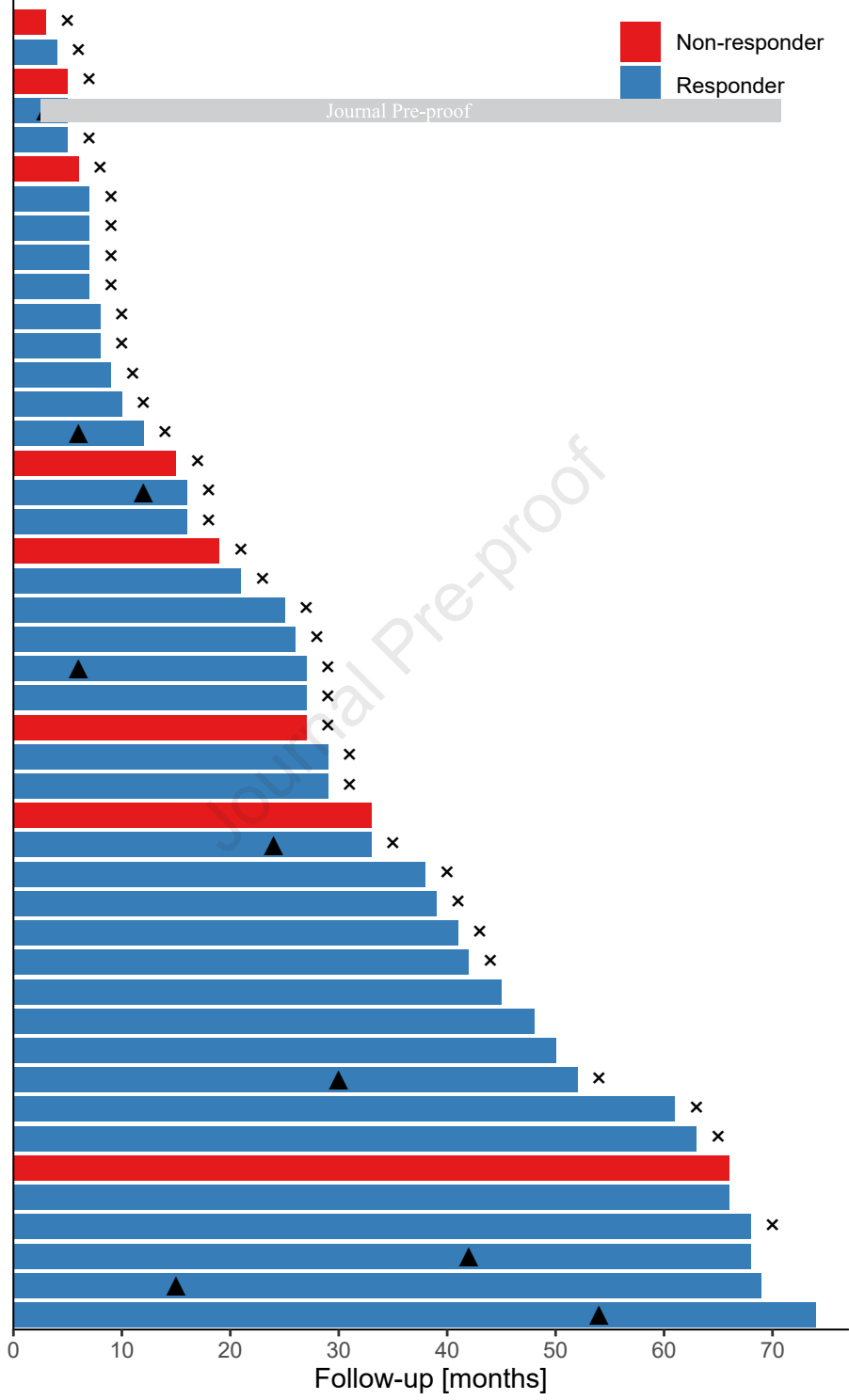
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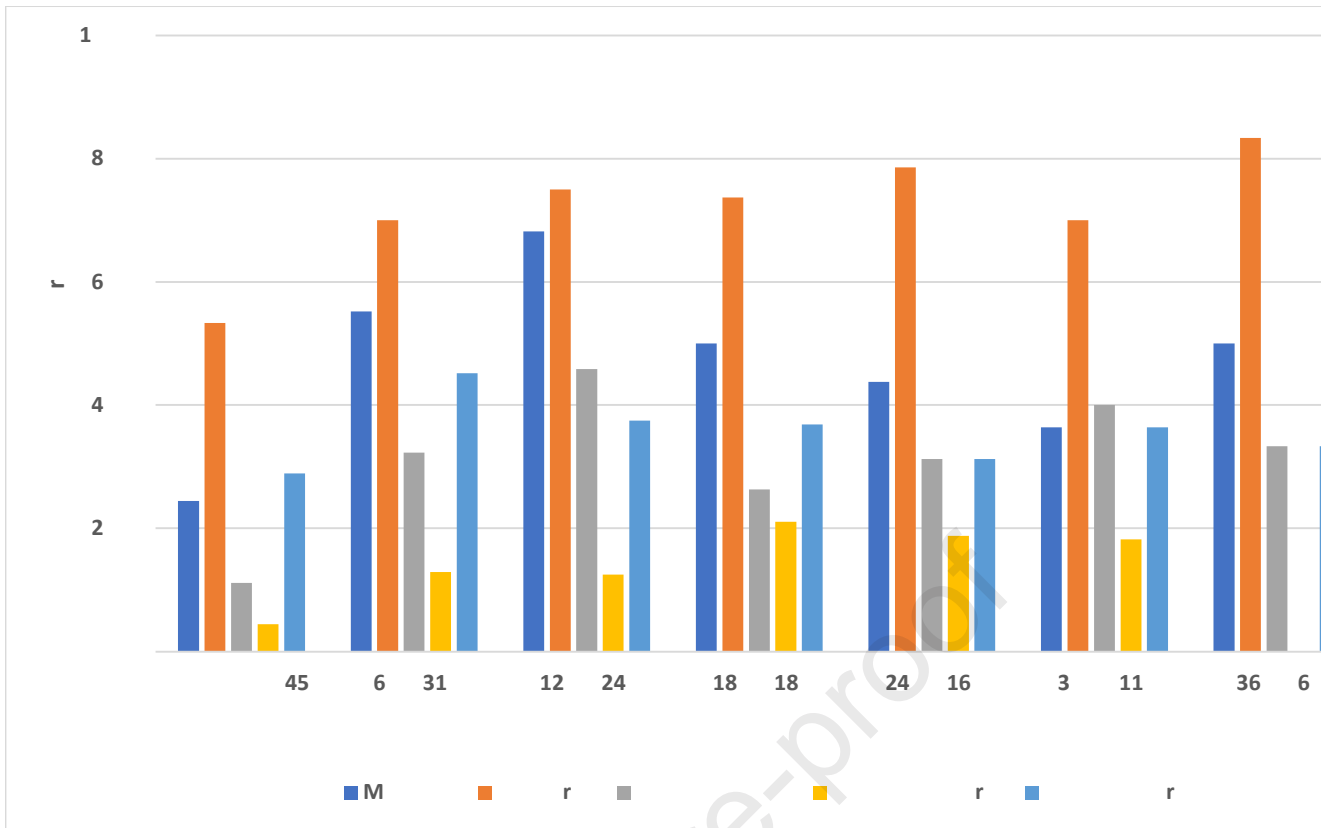
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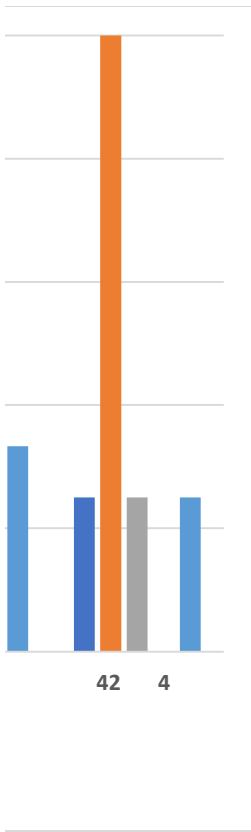
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4

Non-responder
Responder







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