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**Stereotactic ablative body radiotherapy for the treatment of spinal oligometastases**

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Abstract:

Aims: To report multicenter outcomes of patients with spinal oligometastases, treated with stereotactic ablative body radiotherapy (SABR). The primary objective was to estimate the widespread failure-free survival (WFFS) at 2 years – defined as freedom from metastases not amenable to local salvage therapy and death.

Materials and methods: Patients with one to three metastases, treated with spinal SABR between January 2010 and July 2014 at four academic institutions were included in this retrospective review. The median dose/fractionation was 24 Gy (range 16 – 52.5 Gy) in 2 fractions (range 1 – 3), and the median biologically effective dose ($\alpha/\beta = 10$) was 52.5 Gy (range, 40 – 144.4 Gy). The WFFS, overall survival, freedom from local progression, and toxicity rates were described using Kaplan-Meier statistics.

Results: 60 patients with 72 spinal metastases were analyzed. The median follow-up was 21 months. Patients had a median age of 66, ECOG performance 0-1 in 97%, and metachronous oligometastases in 85%. The 1 and 2-year WFFS rates were, 67%, (95% confidence interval [CI], 55 – 80) and 59% (95% CI, 47 – 75), respectively. The 1 and 2-year overall survival rates were 90% (95% CI, 83 – 98) and 76% (95% CI, 64 – 91), respectively. The 1 and 2-year freedom from local progression were 92% (95% CI, 85 – 99) and 86% (95% CI, 75 – 99), respectively. There were 4 cases (6.7%) of vertebral compression fracture and no cases of radiation myelopathy.

Conclusion: Despite the use of relatively low biological doses respecting spinal cord constraints, SABR results in excellent 2-year local control rates with low morbidity. Through careful selection of patients with oligometastases, the majority of patients are alive and free from widespread metastases at 2 years. This cohort warrants further investigation in clinical trials of SABR.

Keywords:

Radiotherapy, intensity-modulated

Radiosurgery

Stereotactic body radiotherapy

Spine

Metastasis

## Introduction

The term oligometastases describes an intermediate state of cancer spread between localized disease and widespread metastasis [1]. When patients develop metastases from solid tumors, they are generally regarded as incurable [1]. However, long-term cures have been demonstrated in patients with limited metastatic disease in various different cancers [2-4]. An attractive consequence of the concept of oligometastases is that some patients with metastatic disease may still be curable using local therapies.

Stereotactic ablative body radiotherapy (SABR) has been shown to be an effective, non-invasive alternative to surgery for treating oligometastases [1,5,6]. SABR refers to an external beam radiotherapy treatment that delivers a high biological dose of radiation with high geometric precision to an extra-cranial target, typically using one to five fractions, delivered using highly specialized planning and treatment delivery techniques [7]. There are multiple single cohort prospective studies and retrospective reviews of using SABR for the treatment of lung metastases, showing 2-year local control rates and overall survival rates of 90 – 100% and 50 – 70%, respectively [5,6,8]. Other body sites (including lung, liver, adrenal and lymph nodes) have also been treated with SABR, with local control rates ranging from 67 – 95%, and 2-3-year survival rates in the range of 30 – 64% [1,9].

Evidence for the spine being an appropriate target for SABR is emerging. Multiple prospective cohort and retrospective studies have been performed on

SABR for spinal metastases, showing local control rates of approximately 80-90%, with low rates of toxicity [10,11]. However, most are in the context of patients with significant metastatic burden and few studies have examined the use of spinal SABR specifically in the setting of oligometastases. Spinal SABR has theoretical shortcomings compared to other body sites. Due to concerns about causing radiation myelopathy [12] and vertebral compression fractures (VCF) [13], prescribed doses for spinal SABR are typically lower than those used in other body sites such as the lung and liver. Moreover, at the interface between the planning target volume (PTV) and the spinal cord, doses are typically compromised even further below the intended prescribed dose, in order to meet dose constraints for the spinal cord [12]. An example of a typical dose distribution achieved with spinal SABR, where the dose at the interface between the PTV and the spinal cord is lowered is shown in Fig. 1. This raises the possibility that treating spinal metastases with SABR may result in inferior outcomes to those reported in other sites in the body, where higher doses can be safely employed.

The aim of this study is to evaluate the outcome of patients treated with spinal SABR in the oligometastatic setting. As patients with metastatic disease treated with local therapies are at significant risk of further distant relapse, we focus in particular on reporting patterns of failure in this cohort.

## Materials and Methods

This was a multi-institutional retrospective review of patients with oligometastases undergoing SABR. Patients were recruited from Peter MacCallum Cancer Centre, Royal North Shore Hospital, Princess Alexandra Hospital, and William Buckland Radiotherapy Centre. This study was approved by the institutional ethics committees of all four hospitals. Patients were included in this study if they were treated with spinal SABR between 1 January 2010 and 31 July 2014, and had oligometastases (defined as up to three metastases, all of which are treatable with extirpative or locally ablative treatment). Patients were excluded if they had more than 3 metastases at the time of SABR, had primary disease not treated with definitive intent, or had a hematological primary malignancy. Patient data was collected up until the study-wide closeout date of 30 June 2015.

Diagnostic MRI scans were fused to planning CT scans in all cases. Where possible, MRIs were performed on a flat tabletop to aid fusion. Clinical target volumes were defined according to consensus guidelines [14]. SABR was delivered in 1 to 3 fractions using either fixed gantry angle intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT). Prescriptions were to covering isodoses, which varied between institutions, but were generally between 70% and 80%. SABR was prescribed to no more than three metastases in any treatment episode. The techniques for patient planning and treatment delivery varied between the four different institutions, and are described in Table 1.

The primary objective was to characterize the widespread failure-free survival (WFFS). Widespread failure was defined as the development of metastatic disease not amenable to further locally ablative or extirpative therapy. WFFS was defined as the time from completion of SABR until widespread failure or death. We chose this as the primary endpoint to allow comparison to a previous study of SABR for oligometastases, which used a similar primary endpoint [15]. Secondary objectives included overall survival, freedom from systemic therapy initiation or change, progression-free survival, freedom from local progression, local progression-free survival, freedom from distant failure, distant failure-free survival, and freedom from widespread failure. Overall survival was censored either at the study-wide closeout date, or 90 days after the date of last clinical follow-up. All endpoints other than overall survival were censored either at the study-wide closeout date or the date of the last follow-up appointment.

Three outcomes (WFFS, overall survival, and freedom from local progression) were further investigated for candidate explanatory prognostic factors on univariate and multivariate analyses. Potential prognostic factors included the $BED_{10}$ (biologically effective dose, using the linear-quadratic model, assuming a tumor $\alpha/\beta$ of 10), number of metastases, primary histology (grouped into breast/prostate; sarcoma/melanoma/RCC, or other), Eastern Cooperative Oncology Group (ECOG) performance status, age, positron-emission tomography (PET) staging prior to SABR, and whether the treated lesion was a synchronous metastasis (defined as discovered within 4 months of the primary diagnosis) or metachronous (defined as discovered more than 4 months after the primary diagnosis).

Statistical analyses consisted of the production of Kaplan-Meier curves and univariate and multivariate Cox proportional hazards regression modeling, performed in the R statistical software package (R Development Core Team, 2015) [16].

## Results

A total of 60 patients with 72 treated lesions were included in this study from the four participating institutions. The baseline characteristics are listed in Table 2. The median follow-up was 21 months (range, 8 – 55). Fixed gantry angle IMRT was used for 53 patients and VMAT was used for 7 patients. The most common prescription doses for 1, 2 and 3 fractions were 20 Gy (n= 19), 24 Gy (n = 30), and 24 Gy (n = 11), respectively. The median $BED_{10}$ was 53.5 Gy (range, 40 – 144.4). Twenty six patients (43%) were staged with positron emission tomography (PET) whereas 34 patients (57%) were not (patient characteristics and specific radiotracers are listed in Table 2).

The median WFFS was 25.4 months (95% confidence interval [CI], 20.4, upper limit undefined due to insufficient events). The 1 and 2-year WFFS were 67% (95% CI, 55 – 80%), and 59% (95% CI, 47 – 75%), respectively. The median freedom from systemic therapy initiation or change was 24.1 months (95% CI, 15.1, upper limit undefined due to insufficient events). The 1 and 2-year freedom from systemic therapy initiation or change were 72% (95% CI, 61 – 85%) and 51% (95% CI, 38 – 69%), respectively.

The 1-year, 2-year and median (where defined) outcomes for overall survival, freedom from systemic therapy initiation or change, progression-free survival, freedom from local progression, local progression-free survival, freedom from distant failure, distant failure-free survival, freedom from widespread failure, and WFFS are listed in Table 3. The Kaplan-Meier curves for WFFS, DFFS, overall survival and freedom from local progression are shown in Fig. 2.

On univariate analysis of WFFS, the ECOG performance status ($p < 0.001$) and synchronous vs metachronous metastases ($p = 0.026$) were significantly prognostic. On multivariate analysis of WFFS, the ECOG performance status ($p = 0.001$) and synchronous vs metachronous ($p = 0.043$) remained significantly prognostic. The hazard ratios (HR) for ECOG 0, 1 and 2 on multivariate analysis were 1, 4.11 (95% CI, 1.7 – 10.1), and 6.76 (95% CI, 1.4 – 33.3), respectively. The HR for metachronous and synchronous were 1 and 2.70 (95% CI 1.11 – 6.59), respectively. On univariate analysis of overall survival, the primary group ($p = 0.001$) and ECOG performance status ($p = 0.003$) were significantly prognostic. On multivariate analysis, the primary group ($p = 0.008$) and ECOG performance status ($p = 0.041$) remained significant. The HR for breast / prostate, other, and sarcoma / melanoma / renal cell carcinoma were 1, 5.95 (95% CI, 1.2 – 29.9) and 7.66 (95% CI, 1.8 – 32.3), respectively. On univariate analysis of freedom from local progression, only the ECOG performance status ($p = 0.016$) was significantly prognostic. The HR for ECOG 0, 1 and 2 were 1, 7.37 (95% CI, 0.8 – 66.6) and 21.31 (95% CI, 1 – 348), respectively.

Ten patients developed grade 1 acute toxicity (including fatigue, nausea, pain flare and esophagitis), and three patients experienced acute grade 2 toxicities (transient radiculitis and diarrhea). No patients experienced grade 3 or higher acute toxicities. Three patients developed grade 2 late toxicity (VCF causing pain) and one patient developed grade 3 late toxicity (VCF requiring a stabilization procedure). This corresponds to a crude rate of VCF of 6.7%. The median time until VCF was 15.4 months (range 1.1 to 24.6 months). No patients developed grade 4 or higher late toxicity. There were no cases of radiation myelopathy.

## Discussion

In this study of 60 patients with oligometastases treated with spinal SABR, we found excellent 2-year freedom from local progression of 86%, with low toxicity rates including 6.7% VCF and no cases of radiation myelopathy. These findings are consistent with previous studies of SABR for non-spine sites in the setting of oligometastatic disease. Furthermore, overall survival in our cohort at 2-years was excellent at 76%, reflecting careful patient selection, limitation of definition of 'oligometastases' as 1-3 sites of disease, and utilization of PET screening.

Our outcomes compare favorably with other extracranial oligometastatic cohorts of mixed histology. In our study we demonstrated a 2-year WFFS of 59% and a 2-year overall survival of 76%. Milano et al. performed a prospective study of 121 patients with five or fewer metastatic lesions, metastatic to one to three organ sites, treated with SABR. Multiple sites were treated including lung, liver, brain

and bone [15]. The preferred treatment schedule was 50 Gy in 10 fractions. The 2-, 4- and 6-year WFFS rates were 35%, 26%, and 21%, respectively. The 2-, 4-, and 6-year overall survival rates were 50%, 28%, and 20%, respectively. These outcomes are poorer than those found in our study, possibly because of our use of three metastatic lesions as a cut-off as compared with five metastatic lesions in this study.

Salama et al. performed a prospective dose escalation study of 61 patients with five or fewer metastatic lesions treated with SABR [17]. Patients were treated in 3 fractions, starting at 24 Gy, with subsequent patients treated at escalating doses up to 48 Gy. Multiple sites were treated including lung, liver, adrenals, pancreas, and bone (including vertebrae). The 2-year progression-free survival, overall survival, and freedom from local progression were 22.0%, 56.7%, and 52.7%, respectively. These outcomes are poorer than that found in our study, again possibly reflecting the greater number of metastases treated in this cohort.

Another important finding in our study was a median time until systemic therapy initiation or change of 24.1 months. This is longer than expected in a group with metastases. A prolonged interval before systemic therapy change or initiation is required may reduce side effects associated with systemic therapy initiation or change, which may have an impact on quality of life [18,19]. Decaestecker et al. performed a study of 50 patients with prostate primaries, with three or fewer metastatic lesions, all treated with SABR [19]. Multiple sites were treated including lymph nodes, liver, and bone (22% of which involved lesions in the axial skeleton). Patients were treated with either 50 Gy in 10

fractions or 30 Gy in 3 fractions. Similar to our result for systemic therapy initiation or change, they reported a median androgen deprivation therapy free survival of 25 months. The 2-year progression-free survival and freedom from local progression were also similar to our study at 35% and 100%, respectively.

It is important to note that none of these aforementioned oligometastases studies looked specifically at spinal metastases. One of the few such studies by Gill et al. performed was a retrospective review of 20 patients with single vertebral body oligometastases treated with SABR [20]. The most common primary histology was sarcoma, comprising 35% of treated patients. The 2-year overall survival and freedom from local progression were 57% and 73%, respectively, with inferior local control possibly related to relatively gentle median dose / fractionation schedule of 30Gy in 5 fractions as compared to our 24Gy in 2 fractions, as previously described by Saghal et al. [21]

It is interesting that outcomes achieved in our study were similar to those achieved with SABR for other body sites where much higher doses are usually required. A threshold dose of $BED_{10}$ > 100 Gy is often quoted as being required to achieve optimal local control in lung and liver metastases [22,23], which is much higher than the doses employed in this cohort. This is an important consideration in this patient cohort because it is speculated that the close proximity of spinal SABR target volumes to the spinal cord may restrict the dose that can be safely delivered, and may therefore have inferior outcomes compared to sites where higher doses are typically delivered. Our comparable outcomes despite lower doses may be due to the intrinsically different natural histories of

primary cancers that typically metastasize to the spine as the first site of oligometastases compared to other organs. Furthermore, there is also emerging evidence that different anatomical sites of metastasis (from the same primary histology) may have differing radiosensitivities [24].

The treatment of oligometastases is an area of intense international scientific activity, with multiple clinical trials currently underway. The Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET) trial is a randomized phase 2 trial of patients with controlled primary tumors, with maximum three metastases in any single organ system [25]. Patients are randomized to standard of care versus SABR to all sites of metastases. Their target accrual is 99 patients. The Stereotactic Ablative Radiotherapy for Oligometastatic Non-small Cell Lung Cancer (SARON) trial is a phase 3 randomized controlled trial of patients with non-small cell lung cancer with one to three metastases at any site in the body, randomized to either palliative chemotherapy alone, or to chemotherapy and radical radiotherapy (conventional radiotherapy and SABR) [26]. Their target accrual is 340 patients. These studies will help to define the role of local intervention with SABR in patients with oligometastatic disease.

Our study has a number of limitations. The retrospective nature of this study limits the accuracy of data collection. Because there is no control arm, it is difficult to determine whether our favorable outcomes are due to patient selection. Our results should be carefully considered before extrapolation into clinical practice, as they are only generalizable when using similar patient

selection criteria. In particular, a large proportion of our patients had prostate and breast primary histology (68%), and application of this data to a local practice with a different patient mix is cautioned against. Despite these limitations, these findings are still of significance as this is one of the few studies to look specifically into the subgroup of patients with spinal oligometastases.

## Conclusion

SABR for spinal oligometastases results in excellent local control with low morbidity at 2-years. With careful patient selection, the majority of patients were alive and free from widespread metastases at 2 years. These results are consistent with studies of SABR for oligometastases at other body sites where higher radiotherapy doses are employed; indicating that SABR for spinal oligometastases is a promising strategy that should be further explored in prospective clinical trials.

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Fig. 1. An example of a typical dose distribution achieved in a spine stereotactic ablative body radiotherapy plan prescribed to 24 Gy in 2 fractions with a spinal cord planning organ-at-risk limit of 17 Gy maximum point dose. The plan is demonstrated on a CT scan, zoomed in on the target T8 vertebra, shown in axial (a), sagittal (b), and coronal (c) planes. The planning target volume is shown in pink color wash, and the spinal cord PRV is shown in green color wash. The isodose lines are shown with dose legend on the right.

Fig. 2. Kaplan-Meier curves for widespread failure-free survival (a), distant failure free survival (b), overall survival (c), and freedom from local progression (d)

Table 1. Treatment protocols for the different institutions participating in this study

| | PMCC | RNSH | PAH | WBRC |
|---|---|---|---|---|
| PTV margin | 2 mm | 3 mm | 2-3 mm | 1 mm |
| CNT at level of spinal cord | Spinal cord | Spinal cord | Spinal cord | Thecal sac |
| PRV margin | 3 mm | 2 mm | 2-3 mm | 0 mm |
| CNT at level of cauda equina | Thecal sac | Nerve roots inside thecal sac | Thecal sac | Thecal sac |
| PRV margin | 0 mm | 2 mm | 2-3 mm | 0 mm |
| CNT PRV constraint for 1 fraction | D0.035cc < 12Gy | V10Gy < 0.35cc, V14Gy < 0.03cc | Dmax <11-12Gy | D0.35cc < 10Gy |
| CNT PRV constraint for 2 fractions | | V10Gy <1.2cc, V14.5Gy <0.035cc | Dmax <14-16Gy | |
| CNT PRV constraint for 3 fractions | | | | D0.35cc <18-20Gy |
| Treatment planning system | Eclipse, iPlan | Eclipse | Eclipse, Pinnacle | iPlan |
| Immobilisation for | BodyFIX | BodyFIX | BodyFIX | none |

| | | | | |
|---|---|---|---|---|
| thoracic/lumbar spine | | | | |
| On-board imaging | CBCT, ExacTrac | CBCT, ExacTrac | CBCT | CBCT, ExacTrac |
| Timing of imaging | CBCT initially, for verification, and mid-treatment. ExacTrac every 1-2 beam angles | CBCT initially and for verification; ExacTrac with each couch rotation | CBCT initially, for verification, and mid-treatment (for long duration treatments) | CBCT initially. ExacTrac for verification, and every 1-2 beam angles |
| Patient repositioning | 6 DOF couch with manual repositioning | 6 DOF robotic couch | 6 DOF robotic couch | 6 DOF robotic couch |
| Linear accelerator | Varian Trilogy / Truebeam sTx 2.0 | Varian Truebeam sTx 2.0 | Elekta Axesse | Novalis Classic |
| MLC leaf thickness | 5 mm, 2 mm | 5 mm | 4 mm | 3 mm |

PMCC, Peter MacCallum Cancer Centre; RNSH, Royal North Shore Hospital; PAH, Princess Alexandra Hospital; WBRC, William Buckland Radiotherapy Centre; PTV, planning tumor volume; CNT, critical neural tissue; PRV, planning organ at

risk volume; CBCT, cone beam CT; DOF, degrees of freedom; MLC, multileaf collimator

Table 2. Baseline patient characteristics

| Variable | | Median (range) |
|---|---|---|
| Age | | 66 (23-84) |
| Maximum dimension of treated lesion (cm) | | 2.5 (0.1-6.3) |
| GTV volume | | 8.5 (0.1-193.2) |
| CTV volume | | 44.1 (5.9-273.1) |
| Prescribed dose | | 24 (16-52.5) |
| Fractions | | 2 (1-3) |
| $BED_{10}$ | | 53.5 (40-144.4) |
| $BED_{1.5}$ | | 230.2 (152-665) |
| CTV median dose | | 26.1 (15.6-50.3) |
| | | |
| Variable | Statistic | n (%) |
| Sex | Male | 49 (82%) |
| | Female | 11 (18%) |
| ECOG PS | 0 | 35 (58%) |
| | 1 | 23 (38%) |
| | 2 | 2 (3%) |
| Number of vertebrae treated | 1 | 49 (82%) |
| | 2 | 10 (17%) |
| | 3 | 1 (2%) |
| Location of lesions | C1-C7 | 6 (10%) |
| | T1-T12 | 45 (75%) |
| | L1-L5 | 20 (33%) |
| | S1-S5 | 1 (2%) |
| SINS score | 0-6 | 45 (75%) |

| | | |
|---|---|---|
| | 7-12 | 9 (15%) |
| | 13-18 | 0 (0%) |
| | Surgical stabilisation prior to SABR | 6 (10%) |
| Timing of treated spinal metastasis | Synchronous | 9 (15%) |
| | Metachronous | 51 (85%) |
| Primary histology | Prostate | 35 (58%) |
| | Breast | 6 (10%) |
| | Melanoma | 6 (10%) |
| | Sarcoma | 4 (7%) |
| | Kidney | 1 (2%) |
| | Lung | 4 (7%) |
| | Gastroesophageal | 1 (2%) |
| | H&N | 1(2%) |
| | Unknown primary | 2 (3%) |
| PET staging | FDG PET | 15 (25%) |
| | NaF PET | 9 (15%) |
| | CHOL PET | 2 (3%) |
| | No PET | 34 (57%) |
| Prostate cancer patients on androgen deprivation therapy at the time of SABR | Yes | 26 (43%) |
| | No | 34 (57%) |

GTV, gross tumor volume; CTV, clinical tumor volume; $BED_{10}$, biologically effective dose with $\alpha/\beta = 10$; $BED_{1.5}$, biologically effective dose with $\alpha/\beta = 1.5$; ECOG PS, Eastern Cooperative Oncology Group Performance Status; SINS, spinal instability neoplastic score; PET, positron emission tomography; FDG, $^{18}$F-

fluorodeoxyglucose; NaF, $^{18}$F-sodium fluoride; CHOL, $^{11}$C-choline; SABR. stereotactic ablative body radiotherapy

Table 3. Summary of outcomes

| Outcome | 1 yr. outcome (%) [95% CI] | 2 yr. outcome (%) [95% CI] | Median outcome (months) [95% CI] |
|---|---|---|---|
| Overall survival | 90 [83, 98] | 76 [64, 91] | NA |
| Freedom from systemic therapy initiation or change | 72 [61, 85] | 51 [38, 69] | 24.1 [15.1, NA] |
| Progression free survival | 59 [47, 73] | 37 [25, 55] | 18.1 [11.6, 25.4] |
| Freedom from local progression | 92 [85, 99] | 86 [75, 99] | NA |
| Local progression free survival | 85 [76, 94] | 66 [52, 83] | NA |
| Freedom from any distant failure | 63 [51, 77] | 44 [32, 62] | 19.0 [12.1, NA] |
| Distant failure free survival | 60 [49, 74] | 43 [30, 60] | 18.1 [11.9, NA] |
| Freedom from widespread failure | 69 [58, 83] | 65 [53, 79] | 28.3 [24.7, NA] |
| Widespread failure free survival | 67 [55, 80] | 59 [47, 75] | 25.4 [20.4, NA] |

CI = confidence interval