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Clinical study

Stereotactic radiosurgery in alveolar soft part sarcoma brain metastases: Case series and literature review

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ABSTRACT

Alveolar soft part sarcoma (ASPS) has the highest incidence of brain metastasis amongst sarcomas. There is a paucity of literature published focusing on radiation therapy for this condition. This is a single centre retrospective review of the treatment of three patients with 12 ASPS brain metastasis using single dose stereotactic radiosurgery (SRS). Five lesions were treated with low (<25 Gy) and seven with high (≥25 Gy) dose. Four lesions had a volume of >1.5 cm^3 and were defined as large, while seven had a volume of ≤0.5 cm^3 and were defined as small. The local tumor control as well as the clinical complication rates were studied. There was a statistically significant relation between treatment dose and tumor control rate. All large tumors treated with low dose recurred and required surgical removal within two months following SRS, while the large lesion treated with high dose recurred after 11 months. Five of the six small tumors treated with high doses were controlled, while the sixth required retreatment and was stable thereafter. No patient suffered from undue symptomatic radiation effects. The success rate following SRS for small ASPS metastases treated with high doses seems to be sufficient to justify the treatment. The short time for large tumor to recur, significant increase in tumor size requiring surgical removal of the tumors, makes low dose SRS unattractive. Based on this limited patient population, it seems that high dose SRS should be used for all ASPS brain metastases except for large tumors deemed surgically accessible.

1. Introduction

Alveolar soft part sarcoma (ASPS) are rare tumors, representing <1% of all soft tissue sarcomas [1]. It tends to occur with a female predisposition below the age of 20 and with a male predisposition thereafter [2,3]. ASPS metastasize frequently, but despite this the clinical course is usually indolent [3,4]. ASPS may have the highest incidence of brain metastasis amongst all sarcomas [5]. Brain metastases occur most often as part of a disseminated disease, resulting in a poor prognosis for these patients [3,5,6].

Due to the rarity of ASPS, only eight references could be found reporting brain metastases from ASPS in more than one patient [3,6–12]. Radiological findings in magnetic resonance imaging (MRI) of intra-axial brain metastases demonstrated homogenous or peripheral rim-like enhancement associated with edema and not infrequently with hemorrhage [11]. They are usually hyperintense on T2WI and hypointense on T1WI with well demarcated tumor margins on contrast enhanced T1WI images [12]. The current treatment paradigm of ASPS brain metastases is aimed at complete tumor resection. However, the tumor recurrence rate seems to be high even after complete resection [12]. Thus, additional treatments are frequently needed. Systemic treatment with different vascular endothelial growth factor receptor (VEGFR) predominant tyrosine kinase inhibitors (TKIs) has been shown to be effective [13,14].

ASPS are generally deemed to be radio-resistant [15]. The value of radiation therapy in the management of ASPS metastases is thus questionable [3,16–18]. The use of SRS for ASPS brain metastases is logical, as SRS has shown to be efficient in the management of other radioresistant brain metastases [19,20]. The literature supporting this assumption is, however, extremely limited. By describing our experience, we aim to add to the literature, and improve the understanding of ASPS brain metastasis and its response to SRS.

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2. Materials and methods

A retrospective review of all patients who underwent single session SRS for brain metastases treated in our institution 2014–2020 was performed. Inclusion criteria was previously untreated intracerebral metastasis from ASPS. Three patients with a total of 11 ASPS brain metastasis were eligible for and included in the study. Informed consent was acquired from all patients. Clinical data was acquired from the medical records and all radiological images were evaluated. The following parameters were recorded: age, gender, tumor location and volume, radiological features, and minimum dose. The minimum dose, D_{min}, was defined as the highest dose delivered to at least 95% of the tumor volume if the tumor volume was >0.1 cm^3, else as the prescription dose. D_{min} was dichotomized into low dose and high dose (<or $\geq$25 Gy).

One lesion was treated twice, and it was in the study considered being two lesions. There were seven lesions treated with high dose and five with low dose. All lesions were supratentorial with volumes ranging from 0.1 to 4.0 cm^3. A large lesion was defined as a lesion with a volume of >1.5 cm^3 and a small lesion when the lesion volume was $\leq$0.5 cm^3. All lesions were contrast enhancing with clear tumor margins without restricted diffusion. Ten lesions were isointense on T1WI, and the larger lesions had surrounding edema. One lesion showed evidence of a prior intratumoral hemorrhage.

The follow-up parameters were local tumor recurrence, defined as an increase of the tumor volume. The patients were followed up at regular intervals, initially at 6 weeks after radiation treatment, and every 3 months thereafter if it was considered clinically meaningful. The patients are described in detail below to facilitate future meta-analyses:

The Logrank (Mantel-Cox) test was used to define the impact dose and volume had on the tumor control rate. A result was considered statistically significant if $P < 0.05$. Two decimals were used when reporting the P-values.

2.1. Case 1

A 23-year-old female who presented with a progressively enlarging left thigh lump. Histology after gross total resection revealed ASPS. Staging positron emission tomography (PET) CT scan revealed multiple bilateral pulmonary metastases and the MRI of the brain was unremarkable. The patient declined systemic therapy.

The patient developed headache and vomiting four years later. MRI demonstrated three lesions, two larger treated with <25 Gy and a smaller treated with 25 Gy. The two larger lesions progressed after two weeks and were surgically removed around one month following SRS. Histopathology showed tumor tissue for both tumors.

A follow-up scan six months following microsurgery revealed two new metastases, one smaller and one larger. Both were treated with 25 Gy. Both tumors responded well initially, but the larger recurred around one year following SRS, while the small tumor was controlled during the follow-up time of 15 months.

Another four new metastases as well as one local recurrence was diagnosed nine months after the second radiosurgical treatment. All new lesions were small as was the recurrence lesion. All new lesions were treated with 25 Gy, while the recurrence was treated with 18 Gy. All five lesions were controlled at the latest follow-up six months after the treatment.

Subsequent follow up demonstrated further progression of lung and pancreatic metastases and her chemotherapy was changed to temozolomide and bevacizumab, which was later changed to axitinib and pembrolizumab without success, and the patient opted for comfort care and passed away 11 months after the third radiosurgical treatment. The MRI images documenting her clinical course and response to SRS is demonstrated in Fig. 1.

2.2. Case 2

A 26-year-old male had a right malignant calf mass resected in another country. The completeness of the resection is unknown. The patient presented himself to us two years later with a local recurrence in the right calf as well as multiple lung metastases. A repeat resection of the calf mass and a lung biopsy were performed, and the diagnosis of metastatic ASPS was made. Staging MRI of the brain revealed a large lesion, and SRS was performed, giving 20 Gy to the lesion. Two months later, a significant growth was diagnosed, and the tumor removed, and histopathology confirmed tumor recurrence. Treatment with pazopanib was started post operatively, but with non-compliance. Routine follow up imaging three months after surgery demonstrated local recurrence. The patient declined further treatment, and he demised overseas one year later with an unknown cause of death. Fig. 2 shows the treated solitary brain metastasis and its recurrence.

2.3. Case 3

A 28-year-old female was diagnosed with a large mass in the right iliac fossa with bony metastases in L1 and L5 vertebral bodies. She underwent tumor debulking and decompression of right L5 and S1 nerve roots. Staging scans found multiple metastases in the liver, lungs, bones, and a small brain metastasis. The diagnosis of metastatic ASPS was made and adjuvant sunitinib was started. The cerebral lesion was treated with SRS with 23 Gy. The lesion hemorrhaged a month later, and the size of the hemorrhagic lesion exceeded that of the treated metastasis. Unfortunately, the systemic disease continued to progress. The patient was given pembrolizumab with sunitinib and subsequently switched to axitinib and pembrolizumab. The patient demised seven months following radiosurgery. Fig. 3 summarizes the key radiographic images of the patient.

3. Results

All four large lesions recurred, two within two weeks, one within two months, and the fourth lesion one year after SRS. Noteworthy is that all tumors recurring within two months were trea-

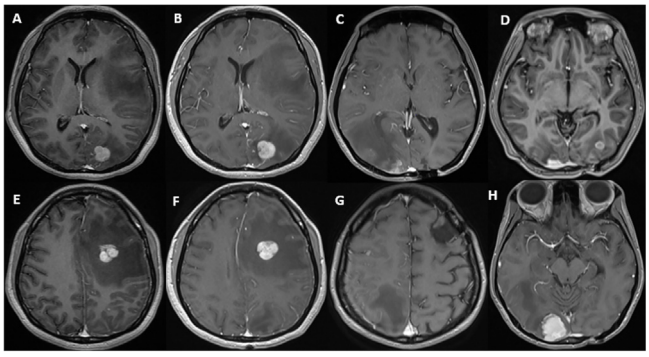

Fig. 1. Radiological Progression of Significant Brain Metastasis of Patient 1. A–C) Progression of left occipital lesion: A) Left Occipital lesion prior to GKS; B) PD two months after GKS; C) no recurrence twenty months after GTR. E–G) Progression of left frontal lesion: E) Left frontal lesion prior to GKS; F) PD two months after GKS; G) no recurrence twenty months after GTR. D, H) Progression of right occipital lesion: D) Right Occipital lesion prior to GKS; H) PD fifteen months after GKS, currently under consideration for further treatment. *GKS: gamma knife surgery; PD: Progression of disease; GTR: gross total resection.*

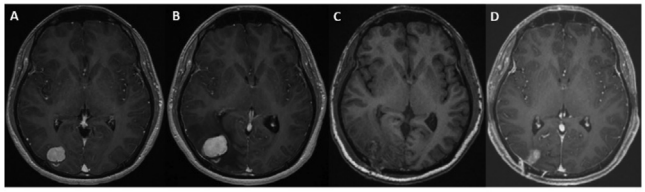

Fig. 2. Radiographic Progression of Brain Metastasis of Patient 2. A) Right occipital lesion prior to L-RS; B) PD six weeks after LINAC; C) GTR performed; D) recurrence three months after surgery. L-RS: linear accelerator radiosurgery; PD: progression of disease; GTR: gross total resection.

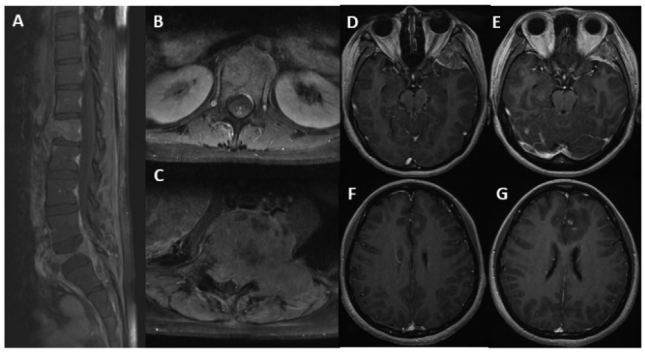

Fig. 3. Radiographic Presentation of Metastatic Lesions of Patient 3. A–C) Spinal metastasis on presentation: A) Sagittal imaging showing L1 and L5 vertebral body metastasis; B) axial image showing metastasis at L1; C) L5 vertebral metastasis with extensive bony and neural involvement. D) Left sphenoid wing bony metastasis prior to SRT; E) partial response three months after SRT. F) Left frontal lesion prior to L-RS; G) stable lesion three months after L-RS. SRT: stereotactic radiation therapy; L-RS: linear accelerator radiosurgery.

ted with <25 Gy and must be surgically removed due to the significant increase in tumor volume. Histopathology confirmed tumor recurrence in all three cases. It took one year for the lesion treated with ≥25 Gy to recur. Five of the six small lesions treated with ≥25 Gy were controlled during the whole observation time, being 22 months for one and 6 months for four lesions. The remaining sixth lesion increased in size after nine months and was retreated with 18 Gy, resulting in tumor control during the six months follow-up thereafter. The last small lesion increased in size after a hemorrhage one moths after having been treated with 23 Gy.

3.1. Statistical analyses

The outcomes for three lesions are a matter of interpretation. Is the increased tumor size one year after SRS due to tumor recurrence or radiation induced changes? Does the hemorrhage represent viable tumor and should thus be considered as treatment failure? Should the dose from the first treatment be taken into consideration when reporting the treatment dose for the retreated tumor? We assumed tumor recurrence in the first two cases and excluded the third from the dose/response analysis. When doing so, the Logrank (Mantel-Cox) test showed that the relation between tumor volume and tumor control was insignificant ($P = 0.06$), while a statistically significant relation was found between treatment dose and tumor control rate, $P < 0.01$.

3.2. Radiation induced complications

None of the patients suffered from any radiation induced complications.

4. Discussion

The scarcity of ASPS brain metastases makes publications analyzing the response to different treatments sparse, with the bulk of literature being focused on chemotherapeutics and targeted therapies. The published results following fractionated radiation for brain metastases are limited to the use of radiation as adjuvant treatment following surgical resection [12,17,21,22], and thus the role of radiotherapy for these lesions is not well documented. The good results following SRS for brain metastases from other radioresistant tumors, such as melanoma [19] and renal cell carcinoma [20], suggests that SRS may have a role in the management of ASPS brain metastases.

The most noteworthy finding in our study is the response following low dose SRS for large metastases. It is indeed rare that brain metastases increase in size within two months following SRS using a D_{min} of 20–24 Gy. In addition, it is even rarer that the growth is so significant during this short period that surgical excision is necessary. A potential contributing factor may have been interaction between the radiation and the systemic therapy. However, if so, one would have expected a similar reaction from the lesions treated with higher doses, which was not the case. Our interpretation from this small sample is a caveat to treat ASPS brain metastases with doses lower than 25 Gy.

The fact that the lesion that recurred was controlled after a second treatment using 18 Gy would imply that staged RS may be an option for large tumors. The concept of staged RS is that a low dose is given twice with an around one-month interval, during which the lesion has decreased in size. However, the patient with two large tumors treated with a low dose were scanned already two weeks after SRS, and both lesions were larger at the follow-up scan, making staged RS unattractive.

Out of the three resected lesions (all of which achieved intraoperative and radiological gross total resections), one lesion developed a recurrence three months after surgery. This is in line with the experience reported by Tao et al [12], who reported that four of eight tumors recurred after complete resection. In the Tao series, two patients were given postop RT, and none of these two tumors recurred. Bindal reported that one of two resected metastases developed a recurrence a short time after surgery in spite of RT [7]. This confirms earlier conclusions that even totally resected metastasis may recur, and thus imaging follow-up is warranted.

5. Conclusions

The main limitations of this case series are its retrospective nature, small sample size, as well as most tumors being harboured by one patient. In spite of this, awaiting larger series to be published, we believe that the data is strong enough to express a caveat for treating ASPS brain metastases with doses lower than 25 Gy.

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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.

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