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Survival Benefit of Stereotactic Radiotherapy in the Complex Management of Metastatic Melanoma

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Abstract. *Background/Aim: Targeted therapy and immunotherapy, with additional stereotactic radiation therapy (SRT) have revolutionized the management of metastatic malignant melanoma (mMM). We aimed to analyze the effectiveness and safety of SRT and determine its role in the complex management of mMM. Patients and Methods: We treated 24 patients with solitary metastasis, 15 with oligometastatic disease and one with multiple metastases. The primary endpoint was to investigate the possible effect of stereotactic radiotherapy for metastatic lesions on patients' survival taking the systemic therapy into consideration. Results: The median overall survival (OS) for the entire group was 30.07 months; 50% of them received immunotherapy, 32% received targeted therapy. Complete remission of the irradiated lesions was observed in six patients, partial tumor response was achieved in 13, while stable disease was detected in 10; tumor progression occurred in four cases. Compartmental recurrence (recurrence in the brain in a not previously irradiated region) developed in seven patients. OS was significantly longer in those with extracranial metastases treated with stereotactic body radiotherapy in comparison to brain SRT. We found a strong correlation between tumor response and mean OS (42.5 months after complete or partial remission versus 11.8 months in those with stable or progressive disease). No OS difference was observed according to the number of irradiated lesions or type of systemic therapy before SRT (no therapy: 43.6 months, with therapy: 25.7 months). Significant OS advantage was shown when immunotherapy was administered post-SRT (mean OS: with immunotherapy: 39.6 months, no immunotherapy: 18.5 months). Conclusion: In the case of oligometastatic MM, SRT can be used safely and with good efficiency in addition to targeted therapy/anti-programmed cell death protein 1 therapy. Improved survival warrants including SRT in the complex management of mMM, however, further studies are needed for SRT optimization.*

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Malignant melanoma (MM) is the most lethal form of skin cancer (1). It has a high potential to metastasize (2). MM is one of the cancers with the highest potential to develop brain metastases (3). Introduction of B-Raf proto-oncogene serine/threonine kinase (BRAF) and mitogen-activated protein kinase kinase inhibitors and immunotherapy using cytotoxic T-lymphocyte associated protein 4 (CTLA4)/programmed cell death protein 1 (PD1)/programmed cell death 1 ligand 1 checkpoint inhibitors have remarkably increased overall survival (OS for patients with metastatic malignant melanoma (mMM). However, brain metastases occur in 10% to 60% of patients with MM, and certain cases remain resistant to treatment using novel approaches, with progression to extracranial metastases. Advancement in imaging has allowed identification of patients with a low burden of metastatic disease. There is growing evidence that local therapies for patients with limited metastatic lesions improve disease outcomes (4, 5) and maintain responses without the need for using new systemic therapeutic lines. Although MM is considered to be a relatively radioresistant tumor, high rates of local tumor control can be achieved with stereotactic radiotherapy (SRT) against both intracranial and extracranial metastatic lesions (6). In the case of oligoprogression of mMM, SRT can be useful, and may allow continuation of otherwise effective systemic therapy.

In the past, radiotherapy for mMM has encompassed large target volumes (7, 8). In these cases, a significant amount of the surrounding tissues is also inevitably irradiated with lower doses, which might cause unnecessary normal tissue complications and promote an immunosuppressive effect. On the contrary, for small target volumes, selective radiation delivery induces an immunostimulatory effect, initiating danger-associated molecular patterns, activating the production of tumor-associated antigens and antigen-presenting cells, and enhancing the migration of immunocompetent cells to the tumor (6, 9). Therefore, the combination of SRT and immunotherapy can promote improved local control and an antitumor systemic response through T-cell-mediated activation of the adaptive immune system (10). SRT could potentially help to delay the discontinuation of immune checkpoint inhibitors, with a possible effect on progression-free survival and OS without increased toxicity. Simultaneous delivery of RT with BRAF or mitogen-activated protein kinase kinase inhibitors proved to be unfavorable due to increased toxicity (11, 12). Therefore, guidelines recommend holding BRAF inhibitors at least 1 day before and after SRT and 3 days before and after radiosurgery (11, 12). The combined efficacy of systemic treatments with RT in the treatment of mMM has become evident but dosing, fractionation, and sequencing of SRT with systemic treatments remain to be defined.

We aimed to analyze the effectiveness and safety of SRT and determine its role in the complex treatment of mMM by retrospectively analyzing patient and tumor characteristics, as well as different SRT parameters.

Patients and Methods

Patients. Patients with mMM who underwent SRT between January 2018 and August 2022 were included in our retrospective study. All patients had oligometastases and received SRT at the Department of Oncotherapy, University of Szeged, Hungary. Therapeutic decision about SRT was made by a multidisciplinary tumor board. Systemic targeted therapy, immunotherapy and chemotherapy were permitted. We performed SRT for 61 lesions in 40 cases. The study was approved by the Regional Committee for Human Medical Research Council 40/2015-SZTE).

Radiotherapeutic methods. All patients underwent planning computed tomography (CT) scanning using AIO Solution™ (ORFIT Industry, Wijnegem, Belgium) for positioning and thermoplastic mask for immobilization at each region. In the case of extracranial metastases, when relevant breathing motion was expected, 4-dimensional (4D) CT was acquired. 3D-CT treatment planning was performed with an ECLIPSE 13.6 external beam planning system (Varian Medical Systems, Inc., Palo Alto, CA, USA). The target volume encompassed the macroscopic metastases and was delineated based on the available imaging techniques (magnetic resonance imaging, 18fluorodeoxyglucose positron-emission tomography–CT) using image fusion and a safety margin according to internal protocol. The gross tumor volume (GTV) was considered equal to the clinical target volume. The planning target volume (PTV) was defined using a 2-5 mm margin around the GTV, or internal target volume developed on 4D-CT and maximum/average intensity projection. The majority of plans were generated using sliding window intensity-modulated RT or volumetric-modulated arc therapy. Two types of normalization were used for the prepared plans: for small PTVs (maximum diameter ≤3 cm), the prescribed dose was linked to the minimum dose to the PTV; for larger PTVs (maximum diameter >3 cm), the prescribed dose was linked to the mean dose the PTV. Paddick conformity index (CI) (13) and the gradient index (GI) (14) were used to analyze the SRT plans, while the homogeneity of the dose distribution was characterized by the homogeneity index (HI) calculated based on the International Commission on Radiation Units and Measurements recommendation (15). These indices were evaluated and analyzed in comparison with the number and location of irradiated metastases.

Table I. *Patient (n=40) and tumor characteristics*.

		Value
Age years	Median (range)	60.9 (29.3-83.6)
Sex, n (%)	Male	25 (63%)
	Female	15 (37%)
Location of metastases	Brain	26 (65%)
	Lung	2 (5%)
	Lymph nodes	6 (15%)
	Skin	2 (5%)
	Bone	3 (7.5%)
	Adrenal gland	1 (2.5%)
SRT	Intracranial	26 (65%)
	Extracranial	14 (35%)
Metastases irradiated, n (%)	Solitary (1)	24 (60%)
	Oligo (1-4)	15 (38%)
	Multiple (≥5)	1 (2%)
Number of sessions of RT, n (%)	1	28 (70%)
	≥2	12 (30%)

RT: Radiotherapy; SRT: stereotactic radiotherapy.

Table II. *Initial parameters of primary malignant melanoma (n=40)*.

Factor	Subgroup	Value
Location of primary tumor, n (%)	Head and neck	6 (15%)
	Ocular	2 (5%)
	Trunk	16 (40%)
	Extremities	10 (25%)
	Unknown	6 (15%)
Tumor thickness, mm	Mean (range)	3.87 (0.2-13.98)
Clark classification, n=23 (%)	I	0 (0%)
	II	3 (13%)
	III	10 (43%)
	IV	8 (35%)
	V	2 (9%)
BRAF mutation, n (%)	Negative	14 (35%)
	Positive	26 (65%)

BRAF: B-Raf proto-oncogene serine/threonine kinase.

SRT was performed with a linear accelerator (TrueBeam, Varian Medical Systems, Inc.) with an integrated image-guiding system, and with motion management specific to anatomic sites, such as the lung and liver.

The patients were followed up by CT/magnetic resonance imaging/positron-emission tomography–CT imaging every 3 months to assess response to SRT. Data on toxicities were obtained via chart review and graded by Common Terminology Criteria for Adverse Events v4.0 guidelines (16).

Statistical analysis. The data were analyzed with a two-sample *t*-test or chi-square test, depending on the properties of the variables. The comparison of survival data in the different groups was analyzed using Kaplan–Meier analysis. Statistical analyses were performed using SPSS software (version 25.0; IBM Corp. Armonk, NY, USA).

Results

Different demographical data are summarized in Table I. A total of 15 and 25 female and male patients were treated, respectively. The mean age of the patients was 60.9 years (range=29.3-83.6 years) at the time of RT. We treated 24 patients with solitary metastasis, 15 with oligometastatic disease and one with multiple metastases.

Based on initial MM parameters (Table II), the majority of patients were at high risk of recurrence (40% of the cases were metastatic at diagnosis). In six cases, the primary tumor was unknown. Primary tumor location was on the trunk, extremities, and in the head and neck region in 16, 10 and six cases, respectively. Two patients had ocular melanoma. The mean tumor thickness was 3.87 mm (range=0.2-13.98 mm). Almost half of the cases (46%) were BRAF-positive.

The treatments were performed intracranially in 26 cases and extracranially in 14 cases. In the cases in which brain metastases were irradiated, we calculated the Graded Prognostic Assessment (GPA) index (17). It was below 2 and ≥2 for 30 and 10 patients, respectively.

In cases with brain metastases, RT was performed in 3 fractions with a fractional dose of 7-9 Gy (Table III). The dose was determined based on the tumor location and previous brain irradiation, as seven (26.9%) patients had undergone whole-brain irradiation before. In the case of intracranial metastases, the mean GTV was 7.0 cm^3 (range=0.3-26.6 cm^3), the mean PTV was 14.4 cm^3 (range=1.1-47.5 cm^3) (Table IV).

In cases with extracranial metastasis, treatment was carried out in 1-8 fractions with a fractional dose of 5.2-10 Gy (Table III). The irradiated lesions were the following: lymph node in 50%, lung in 14.3%, skin in 14.3%, bone in 14.3 and adrenal gland in 7.1%. The mean GTV of the irradiated metastases was 22.6 cm^3 (range=2.0-83.1 cm^3) and the mean PTV was 48.3 cm^3 (range=6.6-127.2) cm^3 (Table IV).

Local tumor responses are summarized in Table V. Complete remission of the irradiated lesion on imaging was observed in six patients whose systemic treatment continues to this day. Partial tumor response was observed in 13 patients, while stable disease was observed in 10. Tumor progression occurred in four cases. Compartmental recurrence (recurrence in the brain in a not previously irradiated region) was observed in seven patients.

Table III. *Radiotherapy doses and fractionation of stereotactic radiation therapy (SRT) in study patients*.

SRT	Dose scheme	BED, Gy	n (%)
Intracranial (n=26)	3×7 Gy	35.70	3 (11.5)
	3×8 Gy	43.20	4 (15.4)
	3×8.5 Gy	47.18	2 (7.7)
	3×9 Gy	51.30	17 (65.4)
Extracranial (n=14)	1×7 Gy	11.90	1 (7.1)
	5×6 Gy	48.00	1 (7.1)
	2×7 Gy	23.80	1 (7.1)
	3×9 Gy	51.30	3 (21.4)
	4×10 Gy	80.00	2 (14.3)
	4×5.2 Gy	31.62	1 (7.1)
	4×6.4 Gy	41.98	1 (7.1)
	5×8 Gy	72.00	1 (7.1)
	6×6 Gy	57.60	1 (7.1)
	7×7 Gy	83.30	1 (7.1)
	8×7.5 Gy	105.00	1 (7.1)

BED: Biologically equivalent dose.

CI, HI, and GI indices were analyzed in comparison with the number and location of irradiated metastases (Table VI). HI was significantly better (*i.e.* lower) in cases receiving intracranial SRT. CI and GI were similar in different localizations. Regarding the number of metastases, we found that with similar HI, CI was better (*i.e.* higher), and GI was more favorable (*i.e.* lower) in cases with a solitary metastasis.

The median OS for the entire group was 30.07 months (95% confidence interval=5.41-54.73 months). Median OS was significantly longer (40.9 months) in patients whose extracranial metastasis was irradiated in comparison with those receiving brain SRT (24.1 months) (p=0.028). We found a strong correlation (p<0.001) between tumor response and OS, which was a median of 42.5 months for the group with complete remission, partial response, and compartmental recurrence, while it was 11.8 months for those in which the local tumor response was stable or progressive disease.

Regarding those patients whose metastasis was intracranial, OS was 13.5 and 41.9 months for those with GPA index <2 and ≥2, respectively (p=0.017).

The OS was not significantly correlated with the number of lesions irradiated, nor to the dose fraction or the GTV. Although not significant, a tendency for better OS was noted when the biologically equivalent dose (BED) was above 51 Gy (32.47 *vs*. 25.09 months, respectively; p=0.403).

Different systemic therapies are summarized in Table VII. 50% of the patients received immunotherapy while 32%

Table IV. *Target definition for stereotactic radiation therapy.*

Target	Imaging modality	Mean GTV (range), cm^3	Mean PTV (range), cm^3
Intracranial	MRI	7.0 (0.3-26.6)	14.4 (1.1-47.5)
Extracranial	^{18}FDG-PET/CT	22.6 (2.0-83.1)	48.3 (6.6-127.2)

GTV: Gross tumor volume; ^{18}FDG-PET/CT: positron-emission tomography with 2-deoxy-2-^{18}F-D-glucose integrated with computed tomography; MRI: magnetic resonance imaging; PTV: planning target volume.

Table V. *Local response of irradiated lesions in patients (n=40).*

Best response	Frequency, n (%)	IC (n=26)	EC (n=14)	BED mean±SD, Gy
Complete response	6 (15)	2	4	42.63±15.49
Partial regression	13 (32.5)	5	8	57.35±21.89
Stable disease	10 (25)	10	0	45.81±7.41
Progressive disease	4 (10)	2	2	57.28±17.77

BED: Biologically equivalent dose; EC: extracranial; IC: intracranial; SD: standard deviation.

Table VI. *Conformity (CI), homogeneity (HI) and gradient (GI) indices regarding the number and location of irradiated metastases. Data are the mean±standard deviation.*

		n	CI	*p*-Value	HI	*p*-Value	GI	*p*-Value
All plans		40	0.715±0.118	-	0.070±0.023	-	3.647±0.810	-
SRT	Intracranial	26	0.711±0.108	0.755	0.058±0.010	**0.001**	3.722±0.767	0.432
	Extracranial	14	0.723±0.138		0.092±0.024		3.508±0.897	
Irradiated metastases	Solitary	24	0.743±0.135	**0.044**	0.073±0.028	0.283	3.394±0.826	**0.014**
	Oligo/multiple	16	0.674±0.071		0.066±0.014		4.026±0.636	

Statistically significant *p*-values are shown in bold.

received target therapy. There was no difference in median OS when we examined the kind of systemic therapy before SRT (no therapy: 43.6 months, with therapy: 25.7 months, p=0.156). When we examined only those patients who received immunotherapy, no correlation was found between OS and previous immunotherapy, but OS was significantly higher in those patients who received immunotherapy after SRT (39.6 months *vs*. 18.5 months without immunotherapy, p=0.003).

Acute and late toxicities are summarized in Table VIII. The most common acute toxicity was nausea. As late side-effect, asymptomatic lung fibrosis, was observed in one patient. Brain necrosis developed in three cases; necrosis needed to be surgically removed due to novel neurological symptoms in one patient.

Discussion

Introduction of immune checkpoint inhibitors and targeted therapies in the treatment of mMM has resulted in a significant improvement in the survival of patients. The effectiveness of these methods can be increased with different local modalities, such as electrochemotherapy and SRT (18, 19). Nowadays, immunological irradiation plans are at the forefront of treatment (20, 21).

Patients with MM have a high incidence of cerebral metastases, both at diagnosis and during the course of the disease, and the brain is the main site of progression. The blood–brain barrier limits the usefulness of otherwise effective systemic treatment. Consequently, in our patient population treated by SRT, brain metastases dominated. Intracerebral radiosurgery with SRT was established decades ago and can be delivered consistently. Recent advances in the management of mMM has also resulted in prolonged survival of patients with brain metastasis. Prognosis of patients not treated for brain MM is poor, with a median survival of 3-5 months (22, 23); if the metastatic lesion is treated locally, the median OS ranges between 6 and 10 months (24). We reported on the results of simultaneous

Table VII. *Different systemic therapies before and after stereotactic radiation therapy (SRT).*

Systemic therapy		
Before SRT	Chemotherapy	1 (2%)
	Targeted therapy (BRAF-MEK inhibitor)	12 (30%)
	Immunotherapy (PD1, CTLA4 inhibitor, combined immunotherapy)	20 (50%)
	None	7 (18%)
After SRT	Remained the same	18 (45%)
	Changed	9 (23%)
	None	8 (20%)
	Started systemic therapy	5 (12%)

BRAF: B-Raf proto-oncogene serine/threonine kinase; CTLA4: cytotoxic T-lymphocyte associated protein 4; MEK: mitogen-activated protein kinase kinase; PD1: programmed cell death protein 1.

integrated boost whole-brain RT (15×2.2 Gy plus boost of 15×2.9 Gy) for brain metastases of MM, with survival of 6.5 months compared with 3.2 months by whole-brain RT alone (25). In recent years, our practice has changed, as we now apply SRT as first-line treatment for single and oligometastatic brain lesions. In the present analysis, OS of 24.1 months was achieved for patients with brain mMM with a range of 13.5-41.9 months depending on the GPA status. Our result is in good concordance with other reported series, where the OS after radiosurgery was 15.7 months (95% confidence interval=11.4-27.7 months) prior to targeted and immunotherapy, and 25 months in patients managed since 2015 (26). The improvement of mMM outcome in our study was even more enhanced in the case of SBRT for extracranial oligoprogressive sites in addition to novel systemic treatments. In the past, expected OS for patients with mMM (with brain metastasis or not) was around 6 months (27). In the past decade, retrospective studies confirmed survival benefit in patients who received SRT combined with immunotherapy compared to immunotherapy or RT alone (28, 29).

Even if resistance occurs during anti-PD1 therapy, the addition of SRT for oligoprogressive metastases of non-small cell lung cancer or melanoma showed high rates of response and extended the clinical benefit of immunotherapy by delaying further progression (30).

The optimal timing and dosing for SRT in this setting of anti-PD1 therapy remain unknown, and clinical data related to this combination are inconsistent (31-33).

In our study, 50% of the patients received immunotherapy with immune checkpoint inhibitors (PD1 inhibitor alone or CTLA4 inhibitor plus PD1 inhibitor in combination). There was no difference in OS when the patients received immunotherapy before SRT, but OS was significantly improved when patients received immunotherapy after SRT, which is consistent with the literature. Retrospective analyses revealed an advantage of applying immunotherapy in combination or after SRT in comparison to immunotherapy before SRT (34, 35). Only a few prospective studies provide data on SRT-immunotherapy combination. Seung *et al*. reported a phase I study combining SRT and interleukin-2 in patients with mMM or metastatic renal cell carcinoma and found that eight out of 12 patients had a complete or partial response by Response Evaluation Criteria in Solid Tumors in unirradiated lesions after treatment (36). In the PEMBRO-RT study, 92 patients with advanced non-small-cell lung cancer treated with pembrolizumab with or without SBRT were analyzed. Patients who were treated with SRT received 24 Gy in 3 fractions to a single site of metastasis, followed by pembrolizumab. The primary goal of the trial was to determine whether SRT improved the objective response rate (ORR) at 12 weeks relative to pembrolizumab alone. They found an improvement in ORR from 20% to 50% with the addition of SRT. At 12 weeks, the ORR was doubled in patients who received SRT, at 36% in the investigational arm in comparison with 18% in the control arm (p=0.07) (37). Ongoing trials will provide further data on sequencing of the local and systemic therapies in the management of mMM (NCT03313206, NCT03842943). However, large variation exists in dosing and fractionation of SRT, in particular for extracranial SRT (38). Shibamoto *et al*. recommended the

Table VIII. *Acute and late toxicities due to stereotactic radiation therapy.*

Toxicity		Grade, n				
		1	2	3	4	5
Acute	Pain	3	4	0	0	0
	Nausea	4	6	0	0	0
	Fatigue	5	0	0	0	0
	Pneumonitis	1	0	0	0	0
Late	Brain necrosis	0	2	1	0	0
	Lung fibrosis	1	0	0	0	0

number of fractions to be between 6 and 8 (39). Dewan *et al*. examined mice that were randomly assigned to eight groups receiving no RT or to three distinct regimens of radiotherapy (1×20 Gy, 3×8 Gy, 5×6 Gy on consecutive days). Fractionated but not single-dose RT led to increased antitumor effects (40). Model simulations suggest that the optimal radiation dose per fraction to maximize antitumor immunity is between 10 and 13 Gy (41). We applied SRT of 21-27 Gy in 7-9 Gy/fraction for brain metastases, but quite a large range of fractionation schemes and fraction doses were applied in the treatment of extracranial metastasis. In another retrospective analysis (42), although no significant relationship was proven, a tendency was observed for better response to higher BED. This suggests that a higher administered dose may contribute to better survival. This is in good agreement with published results of dose-finding studies. Stinauer *et al*. found that a higher dose per fraction ($p<0.01$) and a higher BED ($p=0.05$) were correlated with better local control of the irradiated lesion (43). Another recent multi-institutional phase I/II trial demonstrated that high-dose SRT (3×16-20 Gy) was safe and effective for the treatment of patients with one to three lung metastases (44).

In our study, complete response by imaging of the irradiated lesion was observed in 15% of patients, which contributed to continuation of systemic therapy. Hinkler *et al*. prospectively tested patients with mMM who received immunotherapy and SRT and experienced a systemic complete response (45). By effective local treatment of metastasis, OS may increase. Our data show that the achieved response has a high impact on the outcome of the disease. When complete or partial response occurred, the OS proved to be more favorable. Among the irradiation parameters, the HI exhibited significant correlation with local tumor response.

For our patients, it was possible to administer SRT safely with moderate side-effects. Acute toxicities were easily managed. Most of the observed late side-effects were asymptomatic. Brain necrosis developed in about 7% of patients who received brain SRT, which is in accordance with the published data (46, 47).

Conclusion

Our study has several limitations due to its retrospective nature: The patient population was quite inhomogeneous from the point of view of metastatic disease, and treatment parameters; in particular, the RT dose and fractionation varied highly for SRT. Selection bias may have also existed for SRT, hence patients with favorable characteristics were most probably treated with extracranial SRT.

In spite of the potential uncertainties, important conclusions can be drawn from careful analysis of real patient data on outcome in patients with mMM treated with SRT in the modern era of availability of advanced systemic therapies. In the case of brain or extracranial progression of mMM, SRT can be used safely and with good efficiency, prolonging survival. In the scope of the impact of local response on OS, BED escalation should be considered in everyday practice. In our study, the effect of immunotherapy was more favorable when applied after SRT, but this finding has to be confirmed by further studies, which are also needed to optimize SRT parameters.

Conflicts of Interest

There are no conflicts of interest.

Authors Contributions

G. Kelemen: Writing – review and editing. Z. Együd, Á. Dobi, A. Nikolényi, L. Varga, R. Kószó, E. Borzási, V. Paczona and Z. Végváry: Project administration. F. Borzák and E. Fodor: Visualization. H. Ócsai and E. Baltás: Writing – review and editing. J. Oláh: Supervision. K. Hideghéty: Writing – review and editing, supervision.

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