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FULL PAPER

Role of extracranial stereotactic body radiation therapy in the management of Stage IV melanoma

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Objective: To investigate the role of extracranial stereotactic body radiation therapy (SBRT) in the management of oligometastatic melanoma.

Methods: Patients affected by Stage IV melanoma, with less than three extracranial metastatic lesions, who received SBRT were included in this analysis. Acute and late toxicity, local control (LC), overall survival (OS) and progression-free survival (PFS) were analysed.

Results: 31 patients were included in the study. 16 patients (51.6%) were treated for lung metastases, 8 patients for liver metastases (25.8%) and 7 (22.6%) for nodal metastases. 38 lesions were irradiated. With a median follow-up time of 13 months, 11 patients (35.4%) were still alive, in four cases (12.9%) with no evidence of disease. Median OS was 10.6 months, and

OS at 6, 12 and 24 months was 77, 41 and 21% respectively. LC at 12 and 24 months was 96.6 and 82.8%. 23 patients (74.2%) developed distant metastases. Median PFS was 5.8 months, and PFS at 6, 12 and 24 months was 48.2, 18.5 and 13.9% respectively.

Number of irradiated lesions showed a statistically significant correlation only with LC ($p = 0.03$). Response of the irradiated lesion was related to OS ($p = 0.019$). Local response showed also a borderline correlation with PFS ($p = 0.07$).

Conclusion: SBRT for extracranial metastases from melanoma is feasible and well tolerated. Response of the irradiated lesions is predictive of OS.

Advances in knowledge: SBRT for melanoma extracranial metastases is feasible and the response of the irradiated lesions is predictive of OS.

INTRODUCTION

Stage IV melanoma is characterized by poor prognosis. The presence of distant metastatic disease is associated with a 10-year survival rate of only 7%.¹

Patients with metastatic disease are often treated with various forms of chemotherapy, targeted therapy or immunotherapy. In recent years, the introduction in clinical practice of immunotherapeutic agents, such as ipilimumab,² nivolumab and pembrolizumab,^{3,4} and of targeted therapies, such as the combination dabrafenib–trametinib significantly improved OS and outcomes of patients.⁵

However, most patients ultimately experience disease progression, so that more effective approaches, may be a combination of already available therapies, are warranted. In this scenario, the role of stereotactic body radiotherapy (SBRT) is still unclear. According to the results obtained in

other forms of cancer in oligometastatic patients^{6,7} a similar use of RT is also conceivable in stage IV oligometastatic melanoma patients. This is particularly appealing, considering the well-established radioresistance of melanoma cells,⁸ which makes the typical high doses per fraction used with SBRT necessary for the ablation of metastatic deposits. However, almost all published experiences of ablative RT in metastatic melanoma focused on brain metastases, with excellent local control rates and good survival outcomes.⁹ Very few data are available regarding extracranial sites.

With this background, we performed this retrospective analysis on melanoma patients treated with SBRT for pulmonary, hepatic or nodal metastases. We analysed safety, local control (LC), overall survival (OS) and progression-free survival (PFS), with focus on the possible prognostic impact of local approaches in patients also receiving systemic treatments.

METHODS AND MATERIALS

Patients with Stage IV melanoma treated with SBRT for extracranial metastases were identified retrospectively from the institutional database. Inclusion criteria were (i) oligo-metastatic diseases (up to 3 metastatic sites); (ii) at least 6 months of follow-up for the surviving patients; and (iii) good performance status (PS): 0, 1 or 2. Patients with active cerebral disease were excluded. Any kind of previous or subsequent systemic therapy was allowed and recorded. The study was approved by the Institutional Ethical Committee. All patients were treated according to the Helsinki declaration.

All patients were staged before SBRT, commonly with total body CT and in most cases positron emission tomography/CT. For simulation purposes, patients underwent simulation CT, with contrast medium in case of nodal or liver metastases. For lung metastases CT without medium of contrast was required, except in the case of central lesions. All patients were simulated in supine position with individualized thermoplastic mask. In case of lung or liver SBRT, in order to account for respiratory motion, 4D CT was performed. In all patients who underwent 4D CT scan, an internal target volume (ITV) was defined as the envelope of all gross tumour volumes identified in the different respiratory phases. In these cases, the treatment dose plans were optimized on the average CT. The planning target volume was generated from the ITV by adding an overall isotropic margin of 5 mm from the ITV. In all other cases, gross tumour volume was identified on simulation CT, and then a isotropic margin of 5 mm was added to obtain the planning target volume.

Treatment was performed with linear accelerator. Volumetric modulated arc therapy was utilized. One or more partial or completed arcs were used to obtain the required target coverage and to spare as much as possible the organs at risk. Daily cone-beam CT was used for treatment verification. Patients were clinically evaluated on the first and last days of treatment or more often if needed. Toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.0.

Patients were followed up at 2 months after the end of treatment and then every 3 months for the first year, every 4 months during the second year and then every 6 months. Contrast-enhanced CT scan imaging was performed within 2 months after SBRT and then for every follow-up visit. Fludeoxyglucose-positron emission tomography/CT was performed 6 months after RT.

Acute and late toxicity, LC, OS and PFS were analysed. Survival and time to LC were calculated from the date of start of the SBRT treatment. Patients were observed for LC, even if new distant lesions developed.

RESULTS

31 patients with Stage IV melanoma were treated with extracranial SBRT in our institution between 2009 and 2016. Median age at diagnosis of melanoma was 58 years (range 24–85). The main features of the enrolled patients at melanoma diagnosis are listed in Table 1. All patients underwent surgery of the primary melanoma at diagnosis. Adjuvant systemic therapies

Table 1. Patients and treatment characteristics at melanoma diagnosis

Gender	Male	18 (58.1%)
	Female	13 (41.9%)
Age at diagnosis	Median	58 years
	Mean	57.3 years
	Min	24
	Max	85
Site of primary melanoma	Trunk	14 (45.2%)
	Limbs	10 (32.2%)
	Head and neck	7 (22.6%)
Performance status at diagnosis	0	22 (71%)
	1	9 (29%)
BRAF status	Mutated	8 (25.8%)
	Not mutated	11 (35.5%)
	Unavailable	12 (38.7%)
Primary treatment	Surgery only	22 (71%)
	Surgery + adjuvant systemic therapies	8 (25.8%)
	Surgery + radiotherapy	1 (3.2%)

were administered in eight patients (interferon in four cases, and chemotherapy in the other patients). Adjuvant RT was administered just in one patient.

One patient presented with metastases at diagnosis; in all other cases the mean disease-free interval between primary diagnosis and metastases occurrence was 30.7 months (range 5.1–104.6). The more common sites of metastases were lung (13 patients), followed by lymph nodes (8 patients), skin (5 patients), liver (5 patients) and brain (4 patients).

14 patients (45.2%) underwent surgery for the metastatic disease. Systemic therapies (one or more lines) were prescribed in 23 patients (74%). Checkpoint inhibitors were utilized in nine cases, and BRAF-inhibitors or the combination MEK-inhibitor and BRAF inhibitor was prescribed in three cases. All other patients (12) received chemotherapy.

Concerning SBRT, 16 patients (51.6%) were treated for lung metastases, 8 patients for liver metastases (25.8%) and 7 (22.6%) for nodal metastases. 38 lesions were irradiated. In 11 patients (35.5%) irradiated lesions were the only site of disease; in all other cases, other metastases were under control at the time of SBRT. Mean time between diagnosis of metastases and first day of RT was 6.2 months (range 0.5–34.9). Median age at SBRT was 61 years (range 28–87). Different RT schedules were adopted according to site of disease, number and volume of metastases and proximity of organ at risk. These schedules, related patient characteristics and local outcomes are reported in Table 2. A biologically equivalent dose (BED) >100 Gy was administered in 23 patients (74%).

Table 2. Radiotherapy schedules and local control of the irradiated lesions

Patient	Site of irradiated metastases	Number of irradiated metastases	Size of the metastases (cm ³)	Presence of other metastatic sites	Dose/number of fractions	Systemic therapies	Best local response	Local progression
1	Lymph node	1	7	No	60/8	No	CR	No
2	Lung	1	18	Yes	60/8	Yes	CR	No
3	Lymph node	2	9/4.3	No	48/4	Yes	PD	Yes
4	Lung	1	15.8	Yes	48/4	No	SD	No
5	Lung	1	1.1	No	48/4	Yes	SD	No
6	Lung	1	74.9	No	48/4	Yes	SD	No
7	Lung	1	134.8	Yes	45/6	Yes	PR	No
8	Lung	1	22.8	No	48/4	No	PR	No
9	Lung	1	55	Yes	60/8	Yes	SD	No
10	Lung	3	0.16/9.8/8	Yes	60/3 and 60/8	Yes	PR	Yes
11	Lung	1	102.9	Yes	45/6	Yes	PR	No
12	Lung	1	6.9	Yes	60/8	No	PR	No
13	Lung	1	11.3	No	48/4	Yes	SD	No
14	Lung	1	5.3	Yes	48/4	Yes	PR	No
15	Lung	1	4.5	No	48/4	No	CR	No
16	Lung	1	14.6	Yes	45/6	Yes	CR	No
17	Lung	1	3.7	Yes	48/4	Yes	SD	No
18	Lung	1	1.4	Yes	48/4	Yes	CR	No
19	Lymph node	1	13.5	No	54/3	No	PR	No
20	Lymph node	1	13.7	Yes	30/5	Yes	SD	No
21	Lymph node	1	7.6	Yes	48/4	Yes	SD	No
22	Lymph node	1	99.6	Yes	28/4	Yes	SD	No
23	Lymph node	1	7.5	Yes	45/6	Yes	SD	No
24	Liver	1	10.6	No	75/3	Yes	PR	No
25	Liver	1	1.8	Yes	50.25/3	Yes	SD	No
26	Liver	1	620	Yes	60/6	Yes	SD	No
27	Liver	1	0.3	No	75/3	Yes	CR	No
28	Liver	1	25.7	No	75/3	No	PR	No
29	Liver	1	48.9	Yes	75/3	Yes	PR	No
30	Liver	3	7.1/9.4/14.4	Yes	75/3	Yes	SD	No
31	Liver	2	16.2/57.6	Yes	75/3	Yes	CR	No

CR, complete response; PD, progressive disease; PR, partial response. SD, stable disease.

BED calculations were performed to estimate the effective total dose if delivered in 2 Gy fractions, assuming a tumour α/β ratio of 10. Treatment was generally well tolerated. One case of G2 pneumonia and one of G1 pain were recorded during treatment. During follow-up, four patients developed pneumonia (three cases of G1, one patient of G2), one patient developed gastric ulceration and in one case G2 dyspnea was recorded.

At the time of SBRT, nine patients were being treated with systemic therapies (four cases with immunotherapy, four cases

with target therapy and one case with chemotherapy). All these patients continued their therapies after SBRT. In all other cases, non-systemic therapy was administered after SBRT during follow-up. Globally speaking, 7 patients (22.6%) did not receive any form of medical therapy during their history.

With a median follow-up time of 13 months, 11 patients (35.4%) were still alive, with 4 cases (12.9%) having no evidence of disease. One patient died of cardiovascular disease during follow-up. He was free of disease recurrence at last available follow-up. In all

Figure 1. MRI showing a liver metastasis from melanoma (a) 3-month follow-up CT scan after stereotactic body radiation therapy (75 Gy in three fractions) showing partial response (b) 6-month follow-up CT scan showing complete metabolic response (c).

other cases (61.3%) patients died owing to disease progression. Median OS was 10.6 months, and OS at 6, 12 and 24 months was 77, 41 and 21% respectively.

Concerning response to SBRT, the best local response recorded is shown in Table 2. An example of complete response is shown in Figure 1. During follow-up one patient developed progression of the irradiated lesion. LC at 12 and 24 months was 96.6 and 82.8%. 23 patients (74.2%) developed distant metastases. Median PFS was 5.8 months, and PFS at 6, 12 and 24 months was 48.2, 18.5 and 13.9% respectively. PFS, OS and LC are shown in Figure 2.

At univariate analysis, various parameters were analysed for OS, LC and PFS. Number of irradiated lesions showed a statistically significant correlation only with LC ($p = 0.03$), with an LC of 100% at 12 months in patients with a single irradiated lesion to be compared with 66.7% for patients with two or three irradiated lesions. Response of the irradiated lesion was related to OS ($p = 0.019$); patients having a complete or partial response had a median OS of 23.1 vs 8.9 months in patients with SD or PD (Figure 3). Local response showed also a borderline correlation with PFS ($p = 0.07$). Patients with CR or PR had a median PFS of 7.6 vs 3.2 months. None of other parameters was correlated with any of the analysed outcomes. BRAF mutation showed a borderline correlation with PFS ($p = 0.07$). Patients with BRAF mutation had a median PFS of 10.2 vs 2.6 months. This advantage is probably attributable to the availability of efficient target therapies more than to the SBRT itself.

Considering the RT dose delivered to the tumour, no statistically significant difference resulted in terms of LC, PFS and OS between patients treated with a BED $<$ or ≥ 100 . Particularly, at 12 months LC was 100 vs 95.2% ($p = 0.46$), PFS was 12.5 and 20.1% ($p = 0.57$) OS was 20.0 and 47.0% ($p = 0.4$).

DISCUSSION

To our knowledge, this is the largest collected series of extra-cranial SBRT in oligometastatic melanoma patients. On the

contrary, much experience regarding stereotactic radiotherapy for brain metastases has included or focused specifically on melanoma patients. This is probably due to the high proclivity of melanoma for the development of cerebral disease and also to the radioresistance of this disease, which rendered radiosurgery very fashionable for these patients. Results in this setting are encouraging. In selected patients with one to four metastases measuring less than 3–4 cm, radiosurgery yields a good LC (more than 85%) and median survival of 5–11 months.⁹

Despite the increasingly available data on local ablative therapies for oligometastatic patients, reports on melanoma are still rare. Some of the published series do not specifically address the primary histology;¹⁰ some others specifically focus on other types of cancer, such as breast^{11,12} or colorectal cancer.¹³ Most of the available literature includes also melanoma patients, but in very small proportions. For instance, a Phase I/II clinical trial by Rusthoven *et al*¹⁴ enrolled 38 patients with one to three lung metastases, 7.9% of whom had melanomas. None of the melanoma patients in this series had local progression, but the very small number of patients does not allow to draw any conclusion specifically for this subset. A larger number of melanoma patients was included in the retrospective analysis on lung SBRT published by Guckenberger *et al* recently.¹⁵ In this series, 15 lesions out of 525 were melanoma metastases. Two (13.3%) cases of local progression were reported in this subset of patients. One of the two local progression cases in our series concerned a patient treated for lung metastases.

Stinauer *et al* in 2011¹⁶ collected a small series of oligometastatic patients affected by renal cell carcinoma or melanoma treated with SBRT. Focusing on melanoma, they treated 28 lesions in 17 patients, mostly lung and liver lesions. Apart from G3 pulmonary toxicity in two, treatment was well tolerated also in their patients. Median OS in melanoma patients was 22.2 months and LC was 82% at 1 year. Compared to our experience, overall survival is significantly longer (22.2 vs 10.6 months), while LC is inferior (82 vs 96.6%). These apparently contradictory results are

Figure 2. Local control, progression-free survival and overall survival.

difficult to explain. The better LC in our series implies that the inferior OS is not related to the local effectiveness of RT. Probably a better and careful selection of patients and the smaller number of them in the series by Stinauer et al translated in a long median OS.

Figure 3. Overall survival according to local response of irradiated lesion.

Recently, interest towards the possible synergism of immunotherapy and radiotherapy increased, especially in melanoma patients. Preclinical data strongly support the role of immunotherapy in generating and strengthening the “abscopal effect” of RT.¹⁷⁻¹⁹

Blanchard et al recently generated a model of oligometastatic melanoma in C57BL/6 immunocompetent mice and then used a combination of SBRT and systemically administered VSV-TAA (vesicular stomatitis virus expressing defined tumour-associated antigens) viral immunotherapy. The authors reported that local SBRT combined with systemic viral immunotherapy cured (long-term survival with local tumour eradicated) more than 80% of mice with oligometastatic disease when treatment was administered with a low initial tumour burden. On the contrary, RT or immunotherapy alone failed because of distant (RT) or local (immunotherapy) failure.²⁰

There are also some clinical suggestions supporting the combination of RT and immunotherapy. Apart from the most famous case report published by Postow et al in 2012²¹ some retrospective experiences also pointed out some possible advantages from this combination. For instance, Kiess et al reported a series of 45 patients treated with ipilimumab and brain RT. In multivariable analysis,

prolonged survival was associated with the delivery of RT during ipilimumab.²² On the other hand, recent reports in the literature have suggested the possibility of an increase in toxicity, particularly radiation necrosis in patients receiving stereotactic radiosurgery and newer systemic therapies such as immunotherapy agents, and patients should be closely monitored for these side effects when receiving these therapies in combination.^{23,24}

An interesting approach was adopted by Kropp et al. Patients being treated with ipilimumab who received RT to all sites of limited melanoma progression were analysed. 16 patients were analysed. The results were excellent; the median LC was 31.4 months, the median disease control was 18.7 months and the OS at 1 and 2 years was 87 and 61%, respectively. Seven patients had no evidence of disease, with a median follow-up of 29.5 months.²⁵ In our series, probably owing to the small number of patients, immunotherapy combined with radiotherapy did not translate in a significant benefit for any outcome, when compared with patients receiving other types of systemic therapies or no medical treatment at all. We also did not observe any abscopal effect in our study; however, the present analysis was not specifically focused on this issue.

We are aware of the limitation of the present series, but we think this work could represent a first attempt at better identification of the role of RT in the management of patients with metastatic melanoma. Of course, the number of patients is small; however, this represents to our knowledge the largest experience focused on extracranial SBRT in melanoma. The limited number of patients did not allow us to identify precisely the predictive and prognostic factors that could allow a better identification of patients who can benefit from local treatments.

From the data of the present series, we must admit that survival outcomes are still unsatisfactory. Median OS was 10.6 months, OS at 6, 12 and 24 months was 77, 41 and 21% respectively. The

most relevant issue in our experience was the high rate of distant failure. More than two-third of patients developed further distant metastases during follow-up. In our opinion, this high rate, which surely had a really negative impact on OS, can be partly related to the significant proportion of patients not receiving any kind of systemic therapies, because of age and/or comorbidities. A prospective study comparing patients receiving RT to metastatic sites and patients treated just with systemic therapies is advisable, in our opinion, to assess the real impact, if there is, of local ablative therapies in this setting of patients. The model should be the study recently published by Gomez et al in Stage IV lung cancer patients. In that study, patients were randomized to systemic therapies plus local ablative therapies or systemic therapies alone. PFS in the patients receiving both treatments was significantly higher, supporting the role of local ablation also in metastatic patients.²⁶ On the contrary, LC rates in our experience are high and comparable with the results obtainable with metastatic lesion from more radiosensitive histology. LC at 12 and 24 months was 96.6 and 82.8%. Lastly, there is data in the present series that deserves to be highlighted, because it supports the use of SBRT for extracranial metastases in melanoma. Indeed, the local response of the irradiated lesion was strongly related to OS ($p = 0.019$); patients having a complete or partial response had a median OS of 23.1 vs 8.9 months in patients with SD or PD. Local response also showed borderline correlation with PFS ($p = 0.07$).

CONCLUSIONS

SBRT for extracranial metastases from melanoma is feasible and well tolerated. Survival outcome remained quite unsatisfactory, suggesting the need for prospective and larger studies to identify prognostic and predictive factors to select patients for local ablative therapies. Moreover, more data are needed to clarify how SBRT and systemic therapies can synergize to improve patients' outcome. Response of the irradiated lesions had a significant impact on OS, suggesting that ablation of metastatic deposits can improve patients' prognosis.

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