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Toxicity of combined targeted therapy and concurrent radiotherapy in metastatic melanoma patients: a single-center retrospective analysis

Johanna S. Ziegler[a], Stephanie Kroeze[b], Marie-Luise Hilbers[a], Laurence Imhof[a], Matthias Guckenberger[b], Mitchell P. Levesque[a], Reinhard Dummer[a,*], Phil Cheng[a,*] and Joanna Mangana[a,*]

The Eastern Cooperative Oncology Group consensus guidelines from 2016 recommend interruption of targeted therapy with BRAF- and MEK-inhibitors during radiotherapy with data being based mostly on BRAF monotherapy. The aim of this study is to provide data on the safety of concurrent radiotherapy and combination targeted therapy with BRAF- and MEK-inhibitors. A total of 32 patients with 51 sessions of radiotherapy from one center receiving concurrent radiotherapy and BRAF- and MEK- inhibitors were included. Radiotherapy-associated toxicities were retrospectively collected. Incidence was compared between three groups: (A) targeted therapy during radiotherapy with and, (B) without interruption, and (C) radiotherapy before the start of targeted therapy. Survival and local disease control were examined. Targeted therapy was interrupted during radiotherapy in 16, not interrupted in 14, and only started after radiotherapy in 21 sessions. Stereotactic radiotherapy was applied in 28 sessions, conventionally fractionated radiotherapy in 23. The brain was the most common site of irradiation (n=36). Radiotherapy-associated toxicities occurred in 41.2% (n=21) of sessions and did not differ significantly among the groups. Overall survival was 11.7 months and progression-free survival was 8.4 months. No increase in radiotherapy-associated toxicity was seen where combination targeted therapy was not interrupted during radiotherapy. Prospective clinical trials are warranted to support our findings. *Melanoma Res* 30: 552–561 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

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[a]Department of Dermatology, University Hospital of Zurich, University of Zurich, Gloriastrasse and [b]Department of Radiation Oncology, University Hospital of Zurich, University of Zurich, Rämistrasse, Zürich, Switzerland

Correspondence to Reinhard Dummer, MD, Dermatologische Klinik Universitätsspital Zürich Gloriastrasse 31, 8091 Zürich, Switzerland
Tel: +41 44 255 25 07; fax: +41 44 255 89 88;
e-mail: reinhard.dummer@usz.ch

*Reinhard Dummer, Phil Cheng and Joanna Mangana contributed equally to the writing of this article.

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Introduction

Novel systemic agents have revolutionized the management of advanced melanoma allowing a subset of patients to have long-term survival. Combination targeted therapy with BRAF- and MEK-inhibitors (BRAFi, MEKi) is standard of care for BRAF-mutated metastatic melanoma patients as it has considerably improved overall survival (OS) and progression-free survival (PFS) with 63–70% response rates compared to 45–51% for BRAFi monotherapy [1–6].

Interestingly, the addition of MEKi also increased the tolerability of BRAFi especially for cutaneous toxicities, known as RASopathic skin eruptions, being reported in approximately 75–100% of patients treated with BRAFi monotherapy [3,7–12]. These effects are attributed to less paradoxical activation of the MAPK pathway by addition of a MEKi to the BRAFi [13,14].

In the context of improving OS and overall responses, the combination of systemic therapies and localized therapeutic measures such as radiotherapy come into focus for the management of mono- and oligometastatic disease [15–17]. However, there are several reports on BRAFi-induced enhancement of radiotherapy-associated toxicity mostly concerning skin reactions [18–21]. Dermatitis has also been observed as a recall phenomenon at the start of BRAFi treatment several weeks after the end of radiotherapy [22]. Most toxicities were observed after the use of traditional palliative radiotherapy techniques such as whole-brain radiotherapy (WBRT), which are associated with large-volume radiotherapy exposure of normal tissue.

Radiosensitizing effects of BRAF inhibition with vemurafenib in $BRAF^{V600E}$ mutated melanoma cells have been

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shown *in vitro* [23]. An increase of chromosomal aberrations in peripheral blood lymphocytes of patients treated with BRAFi monotherapy have been reported for vemurafenib, but not for dabrafenib [24].

Based on these observations and the presumably severe toxicity under BRAFi monotherapy and concomitant radiation treatment, the current Eastern Cooperative Oncology Group (ECOG) consensus guidelines recommend holding both BRAFi and MEKi for at least 3 days before and after conventional fractionated radiotherapy and at least one day before and after stereotactic radiotherapy (SRT) [25]. However, data on combination of BRAFi/MEKi and concomitant radiotherapy are currently limited. For melanoma brain metastases (MBM), the recent ESMO consensus conference recommendations (submitted) advise to pause BRAFi/MEKi therapy during radiotherapy only in the case of WBRT but not during SRT based on expert opinion [26].

The aim of this study is to provide real-life safety and clinical outcome data on concurrent radiotherapy and combination treatment with BRAFi and MEKi. By comparing the frequency of radiotherapy-associated toxicities in different settings, we will evaluate the justification of the guidelines to interrupt combination targeted therapy during radiotherapy. We hypothesize that the addition of a MEKi 'neutralizes' the skin toxicities and radiosensitivity characterizing BRAFi monotherapy. Additionally, we hypothesize that the use of conformal radiotherapy such as SRT and radiosurgery reduces the risk of toxicity. To our knowledge, this is the largest and most well-defined study for this specific question.

Methods

Patient cohort and data collection

Data were collected retrospectively using the Melanoma Registry Database of the Department of Dermatology, University Hospital Zurich. This study was conducted in accordance with the MelProg Project (KEK-Number PB_2017-00181, 647/800). All patients have signed a general informed consent form. The study was performed in accordance with the Declaration of Helsinki.

Out of all stages, III and IV melanoma patients treated systemically with the registered BRAFi and MEKi combinations in Switzerland (vemurafenib/cobimetinib or dabrafenib/trametinib) from January 2012 to August 2019, we included patients who received concurrent radiotherapy (stereotactic or conventional fractionated radiotherapy) for any organ with a minimum follow-up of 3 months. Encorafenib/binimetinib or patients treated with a BRAFi and MEKi combination in the context of a clinical trial were excluded. The study design is shown in Fig. 1a.

The primary endpoint of this study was to assess the incidence of radiotherapy-toxicity in different groups. SRT and conventional fractionated radiotherapy (extracranial and WBRT) were conducted according to local standards. Concurrent treatment was defined as radiotherapy during or within 60 days before the start of targeted therapy to account for recall toxicity. Basic patient characteristics, radiotherapy information, and systemic therapy data were collected for all patients and all radiotherapy-modalities.

Data for response at the site of radiation and overall response were collected at 3, 6, and 12 months after the end of radiotherapy as well as at the end of treatment with targeted therapy (EOT) or last follow-up (±4 weeks) according to the (PET) Response Evaluation Criteria in Solid Tumors [(P)RECIST)], version 1.1 (1.0) with MRI, computed tomography or PET. Radiotherapy-associated toxicities were assessed and graded according to CTCAE 4.0 for the 51 courses of radiation, including acute (<90 days) and late (>90 days) reactions.

Kaplan–Meier analysis for OS and PFS were performed from the start of targeted therapy for the entire cohort of 32 patients. Local tumor control at site of radiation (LC) was assessed for all 51 radiations. The first systemic therapy for metastatic disease was counted as first-line treatment excluding adjuvant therapies. S-100, CRP, and LDH were assessed up to 4 weeks before start of radiotherapy.

Statistical analysis

Data analysis was performed using R Version 3.6. The Fisher's exact test, Mann–Whitney *U*-test and Pearson's Chi-square test were applied when appropriate to compare the incidence of radiotherapy-associated toxicity and other characteristics among the groups for all sessions of radiotherapy. A *P*-value of <0.05 was considered statistically significant. Toxicity incidence was compared using logistic regression to account for confounding factors such as age, gender, and ECOG status. The Kaplan–Meier method was applied for a total of 32 patients for OS and PFS from the start of targeted therapy. Median is indicated with the total range of values and mean is indicated with SD.

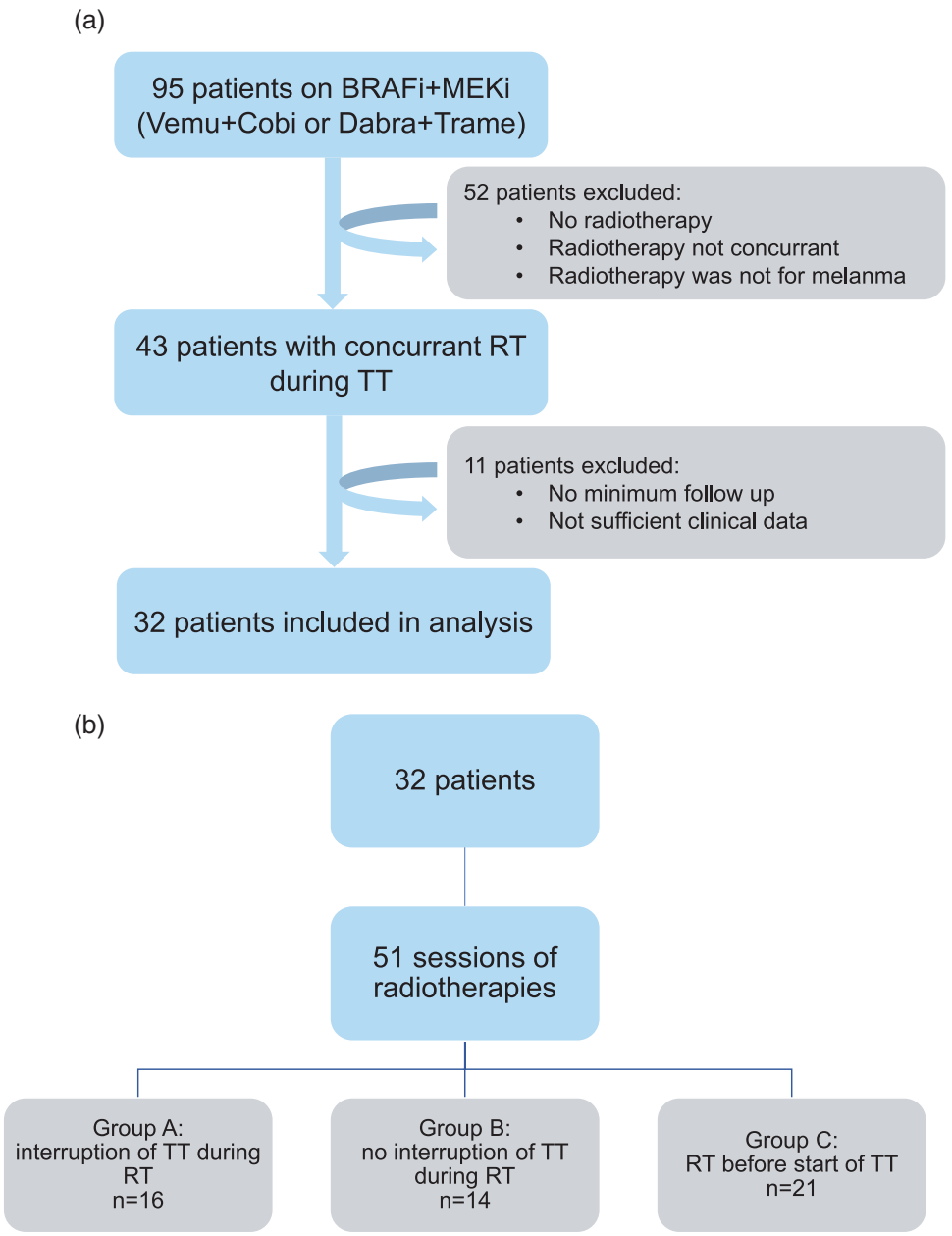
Results

In total, 32 patients receiving 51 radiotherapies were included in the analysis. The radiotherapies were divided into three subgroups: targeted therapy was initiated before radiotherapy and continued thereafter in 30 cases, out of which targeted therapy was interrupted in 16 cases (group A) and not interrupted in 14 cases (group B). Targeted therapy was initiated only after radiotherapy in 21 cases (group C). The groups are shown in Fig. 1b. The median follow-up time was 9.6 months (range 3.0–40.9 months).

Patient characteristics

Patient characteristics are summarized in Table 1. Patients were predominantly male in our cohort (71.9%).

Fig. 1



(a) Study design. This figure illustrates the workflow of patient inclusion. (b) Subgroups. This figure illustrates the division of radiotherapy sessions into subgroups.

Mean age at first diagnosis of melanoma was 48.9 (14.9) years and 53.5 (14.5) years at the start of first radiotherapy. All patients were BRAF-mutated and suffered from stage IV disease at initiation of radiotherapy. A total of 14 patients received more than one course of radiotherapy during our observation time (ranging from two to four courses of radiotherapy). About 28.1% of patients received adjuvant therapy. For 43.8% of the patients, targeted therapy was the first-line therapy. Patients were on targeted therapy for a median time of 6.2 months (range 0.4–32.8 months).

Radiotherapy-associated toxicity and local control

Interruption of targeted therapy was performed in approximately half of the patients with targeted therapy before and after radiotherapy (groups A and B) (53.3%, $n = 16$). The reason for interruption was physician's choice in 87.5% ($n = 14$) of cases. In two cases, targeted therapy was only paused on the day of radiotherapy application and not for the entire duration of radiotherapy. In 12.5% ($n = 2$) of cases, targeted therapy was already interrupted before radiotherapy due to a treatment-related adverse event. Median interruption time was 3 days (range 3–47 days).

Table 1 Patient characteristics

Number of patients	32
Sex (%)	
Female	9 (28.1)
Male	23 (71.9)
Median breslow in mm (range)	1.9 (0.3, 8.0)
Ulceration (%)	
No	16 (66.7)
Yes	8 (33.3)
Mutation status (%)	
BRAF mutation unspecified	9 (28.1)
V600E	18 (56.2)
V600K	2 (6.2)
V600R	1 (3.1)
V600 with deletion	1 (3.1)
N581S	1 (3.1)
Mean age at first diagnosis in years (SD)	48.9 (15.0)
Mean age at radiotherapy (SD)	53.5 (14.5)
Localization of primary tumor (%)	
Acral	1 (3.1)
Head/neck	6 (18.8)
Lower extremities	3 (9.4)
Melanoma of unknown primary	2 (6.2)
Neck	1 (3.1)
Trunk	15 (46.9)
Upper extremities	4 (12.5)
Type of melanoma (%)	
Superficial spreading	12 (41.4)
Nodular	7 (24.1)
Superficial spreading and nodular	4 (13.8)
Lentigo maligna melanoma	1 (3.4)
Other	5 (17.2)
Stage at initial diagnosis (%)	
IA	6 (18.8)
IB	6 (18.8)
IIA	7 (21.9)
IIB	2 (6.2)
IIC	2 (6.2)
IIIB	1 (3.1)
IIIC	5 (15.6)
IV	3 (9.4)
Median time until last follow-up or death in months (range)	9.6 (3.0, 41.0)
Adjuvant treatment before stage IV disease (%)	
Anti-PD1 monotherapy	2 (6.2)
Interferon alpha	6 (18.8)
None	23 (71.9)
Clinical trial	1 (3.1)
Median duration of targeted therapy in months (range)	6.2 (0.4, 32.8)
Line of treatment concurrent with radiotherapy (%)	
First line	14 (43.8)
Second line	10 (31.2)
Third line	5 (15.6)
Forth line	2 (6.2)
Fifth line	1 (3.1)
Survival (%)	
Alive	11 (34.4)
Dead	21 (65.6)

In group C ($n = 21$), median time to targeted therapy start after last radiotherapy was 28 days (range 2–60 days). Immunotherapy was applied concomitantly with radiotherapy in nine cases. In the remaining 12 cases, no other simultaneous systemic treatment was administered with radiotherapy before start of targeted therapy.

The timelines of the groups are illustrated in Fig. 2.

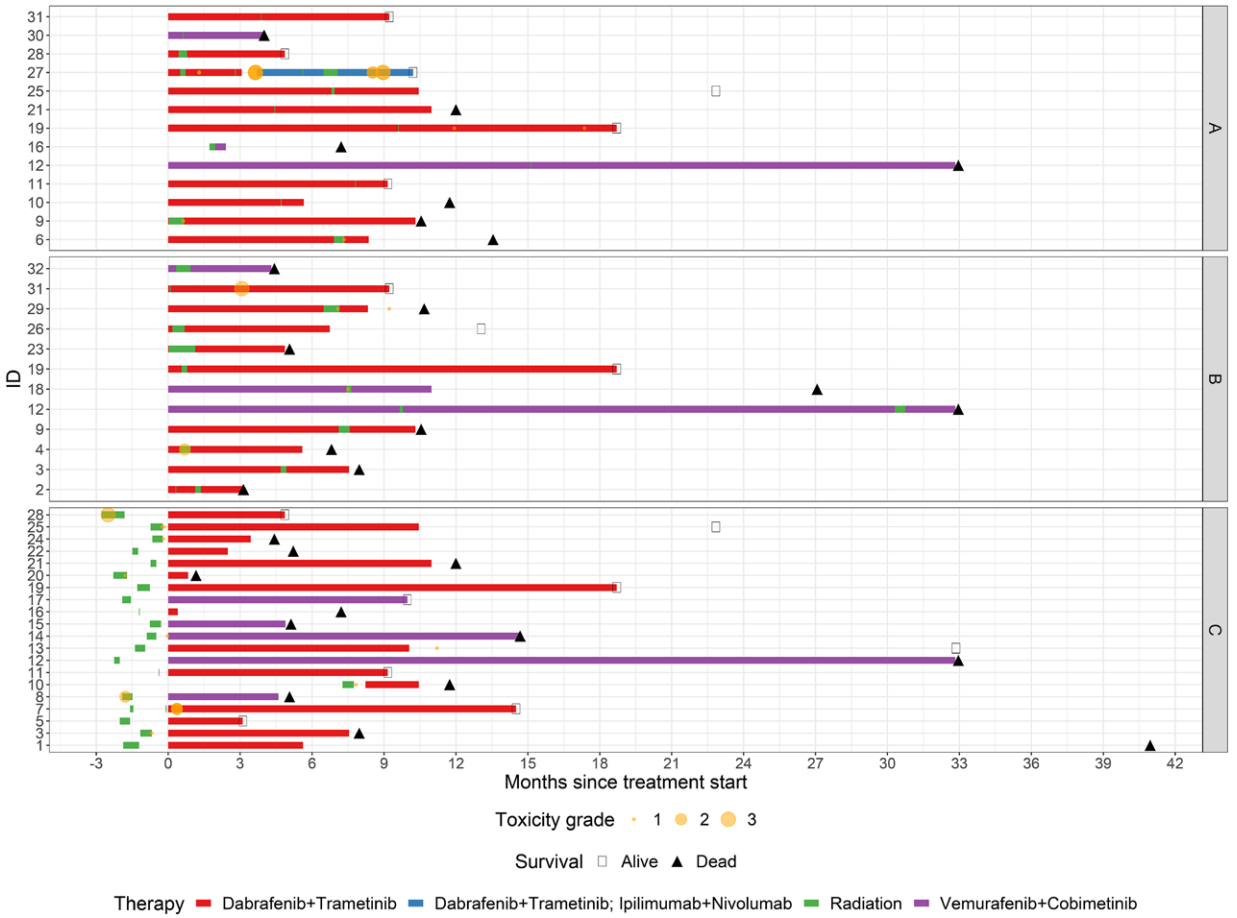
Radiotherapy characteristics were analyzed for the 51 courses of radiotherapy. Differences in radiotherapy characteristics per subgroup are shown in Table 2. MBM were present in most cases (82.4%). The brain was the most common site for radiation overall (70.6%) as well as in each group individually. The 36 brain irradiations consisted of 14 conventional WBRT (38.8%), 21 SRT (58.3%), and one conventional irradiation of the brain stem and spinal axis. With SRT, a range of one to eight brain metastases were irradiated at a time. Most of the radiotherapies were applied for polymetastatic disease (70.6%). Overall, conventional fractionated radiotherapy was applied in 45.1% of cases ($n = 23$) and SRT in 54.9% of cases ($n = 28$). Treatment with dabrafenib/trametinib was more frequent than vemurafenib/cobimetinib. One patient received both targeted therapy (dabrafenib/trametinib) and ipilimumab/nivolumab during two sessions of radiotherapy.

Groups B and C had significantly more conventional radiotherapies versus SRT compared to group A ($P = 0.038$). Additionally, group B had a higher ECOG performance status ($P = 0.016$) and they were more often polymetastatic. Group B also had higher LDH and CRP before initiation of radiotherapy without statistical significance. Cumulative dose and duration of radiotherapy were significantly lower in group A ($P = 0.024$; $P = 0.025$). All other characteristics were balanced.

Age, gender, ECOG status, type of radiotherapy, and interruption of radiotherapy did not influence the incidence of toxicity. This was analyzed with logistic regression and is shown in a forest plot as supplemental digital content in supplementary Figure 1, supplement digital content 1, *http://links.lww.com/MR/A234*.

Toxicity was assessed separately per location. Table 3 gives detailed information on the observed types and grades of radiotherapy-toxicities overall and per group. Incidence of radiotherapy-associated toxicity per session did not differ significantly between the groups ($P = 0.887$). Radiotherapy-associated toxicity of any grade occurred in 21 of 51 sessions of radiotherapy (41.2%). Higher severity of radiotherapy-associated toxicity (grades 2 and 3) was reported in 11 of 51 sessions (21.1%). A total of 38 events were noted. There was no significant difference among the groups for all events of radiotherapy-associated toxicity of any grade ($P = 0.2595$) as well as for higher grades (grades 2 and 3) specifically ($P = 0.277$). In groups A, B, and C, toxicity occurred in 43.8, 35.7 and 42.9%, respectively. We reported no grade 4 toxicities. Six grade 3 adverse events were observed in 6 of 51 sessions (11.8%), five of them being intracranial hemorrhage after SRT, and one of the uncontrollable pain of a bone metastasis requiring surgical intervention. It remained unclear, whether the latter was directly associated with radiotherapy or due to progressive disease. Grade 3 adverse events developed in 3 patients (9.4%); four of the five intracranial hemorrhages occurred in the same patient with interruption of targeted therapy for all four courses of radiotherapy. This patient did not receive anticoagulant therapy. In the other case of intracranial hemorrhage after SRT, targeted therapy was not interrupted. In the case of grade 3 bone

Fig. 2



Graphical visualization of subgroups with swimmer's plot. This figure illustrates the timelines of therapeutic interventions (systemic-targeted therapy and radiotherapy) per session of radiotherapy.

pain, targeted therapy was started only after the end of radiotherapy.

Local control at site of radiation remained balanced between the groups at months 3, 6, and 12 but diverged significantly at EOT or last follow-up ($P=0.032$). Complete remission was achieved in 12 sessions of radiotherapy (23.5%) at EOT or last follow-up. Patients with radiotherapy applications before initiation of targeted therapy (group C) experienced a higher rate of complete remission at the radiation site.

Progression-free survival and overall survival

At the end of our observation period, 21 patients (65.6%) had died. Median PFS calculated from start of targeted therapy was 8.4 months (Fig. 3a). Median OS calculated from start of targeted therapy was 11.7 months (Fig. 3b).

Discussion

To our knowledge, this retrospective, real-life, single-center analysis is the largest study to investigate radiotherapy-associated toxicity in the context of the interruption of combined targeted therapy during radiotherapy. To this day, data on concurrent combined targeted therapy and radiotherapy are extremely limited and the implementation of the recommended guidelines are inconsistent [27]. The recommendation of the ECOG Consensus guideline to hold BRAFi and MEKi during radiotherapy is mostly based on reports with BRAFi monotherapy and use of non-SRT. These data do not represent the current clinical standards sufficiently, since combination targeted therapy treatment has almost entirely replaced BRAFi monotherapy and SRT has replaced conventional radiotherapy in many situations, especially brain metastases.

According to the recent ECOG consensus guidelines, a review of 27 publications on potential dermatologic, pulmonary, neurologic, gastrointestinal, and hepatic toxicities of concurrent BRAFi and radiation treatment, cutaneous reactions are the most frequent. No fatal reactions occurred with a radiation fraction dose of ≤4 Gy [25].

Table 2 Radiotherapy characteristics

	Level	Overall	Group A	Group B	Group C	*P* value
Number of radiotherapy sessions		51	16	14	21	
Stage at start of radiotherapy (%)	M1a	1 (2.0)	0 (0.0)	0 (0.0)	1 (4.8)	0.748
	M1c	8 (15.7)	2 (12.5)	3 (21.4)	3 (14.3)	
	M1d	42 (82.4)	14 (87.5)	11 (78.6)	17 (81.0)	
Disease burden at start of radiotherapy (%)	Oligometastatic	15 (29.4)	7 (43.8)	4 (28.6)	4 (19.0)	0.262
	Polymetastatic	36 (70.6)	9 (56.2)	10 (71.4)	17 (81.0)	
Median S-100 level at start of radiotherapy (range)		0.2 (0.0, 18.7)	0.2 (0.0, 11.0)	0.2 (0.1, 18.7)	0.2 (0.1, 1.8)	0.094
Median LDH level at start of radiotherapy (range)		426.0 (257.0, 4716.0)	410.0 (296.0, 748.0)	494.5 (257.0, 4716.0)	356.0 (270.0, 543.0)	0.212
Median CRP level at start of radiotherapy (range)		5.0 (0.4, 134.0)	4.8 (0.7, 53.0)	20.5 (0.4, 134.0)	3.1 (0.5, 33.0)	0.293
ECOG performance status (%)	0	35 (68.6)	14 (87.5)	5 (35.7)	16 (76.2)	0.016
	1	10 (19.6)	0 (0.0)	7 (50.0)	3 (14.3)	
	2	5 (9.8)	2 (12.5)	2 (14.3)	1 (4.8)	
	3	1 (2.0)	0 (0.0)	0 (0.0)	1 (4.8)	
Type of radiotherapy (%)	Conventional	23 (45.1)	3 (18.8)	8 (57.1)	12 (57.1)	0.038
	Stereotactic	28 (54.9)	13 (81.2)	6 (42.9)	9 (42.9)	
Location of radiotherapy (%)	Bone	8 (15.7)	0 (0.0)	3 (21.4)	5 (23.8)	0.327
	Brain	36 (70.6)	13 (81.2)	9 (64.3)	14 (66.7)	
	Other	7 (13.7)	3 (18.8)	2 (14.3)	2 (9.5)	
Subdivision of type of radiotherapy per location (%)	Brain conventional[a]	15 (29.4)	2 (12.5)	4 (28.6)	9 (42.9)	0.132
	Brain stereotactic	21 (41.2)	11 (68.8)	5 (35.7)	5 (23.8)	
	Bone conventional	4 (7.8)	0 (0.0)	2 (14.3)	2 (9.5)	
	Bone stereotactic	4 (7.8)	0 (0.0)	1 (7.1)	3 (14.3)	
	Other conventional	4 (7.8)	1 (6.2)	2 (14.3)	1 (4.8)	
	Other stereotactic	3 (5.9)	2 (12.5)	0 (0.0)	1 (4.8)	
Median cumulative dose of radiotherapy in Gy (range)		30.0 (6.0, 56.0)	20.0 (6.0, 45.0)	30.0 (16.0, 37.5)	30.0 (16.2, 56.0)	0.024
Toxicity of radiotherapy (%)	No	30 (58.8)	9 (56.2)	9 (64.3)	12 (57.1)	0.887
	Yes	21 (41.2)	7 (43.8)	5 (35.7)	9 (42.9)	
Median time until onset of toxicity in days (range)		17.0 (2.0, 381.0)	62.0 (13.0, 235.0)	44.5 (2.0, 91.0)	14.5 (4.0, 381.0)	0.186
Median duration of interuption of targeted therapy in days (range)		3.0 (3.0, 47.0)	3.0 (3.0, 47.0)	Not applicable	Not applicable	
Median duration of radiotherapy in days (range)		8.0 (1.0, 34.0)	1.5 (1.0, 20.0)	11.0 (1.0, 34.0)	14.0 (1.0, 30.0)	0.025
Median time between end of radiotherapy and start of targeted therapy in days(range)		28.0 (2.0, 60.0)	Not applicable	Not applicable	28.0 (2.0, 60.0)	
Type of targeted therapy (%)	Dabrafenib + trametinib	37 (72.5)	11 (68.8)	10 (71.4)	16 (76.2)	0.313
	Dabrafenib + trametinib; Ipilimumab + nivolumab	2 (3.9)	2 (12.5)	0 (0.0)	0 (0.0)	
	Vemurafenib + cobimetinib	12 (23.5)	3 (18.8)	4 (28.6)	5 (23.8)	
Intention of radiotherapy (%)	Kurativ	9 (17.6)	5 (31.2)	2 (14.3)	2 (9.5)	0.273
	Palliative	38 (74.5)	9 (56.2)	11 (78.6)	18 (85.7)	
	Postoperative	3 (5.9)	2 (12.5)	1 (7.1)	0 (0.0)	
	Postoperative/palliative	1 (2.0)	0 (0.0)	0 (0.0)	1 (4.8)	
Previous radiotherapy (%)	No	30 (58.8)	7 (43.8)	9 (64.3)	14 (66.7)	0.332
	Yes	21 (41.2)	9 (56.2)	5 (35.7)	7 (33.3)	
Concurrent steroid administration during radiotherapy (%)	No	18 (35.3)	6 (37.5)	5 (35.7)	7 (33.3)	0.965
	Yes	33 (64.7)	10 (62.5)	9 (64.3)	14 (66.7)	
Response at site of radiation at month 3 (%)	CR	9 (17.7)	1 (6.2)	3 (21.4)	5 (23.8)	0.482
	PD	14 (27.5)	5 (31.2)	5 (35.7)	4 (19.0)	
	PR	16 (31.4)	6 (37.5)	4 (28.6)	6 (28.6)	
	SD	10 (19.6)	2 (12.5)	2 (14.3)	6 (28.6)	
	NA	2 (4.0)	2 (12.5)	0 (0.0)	0 (0.0)	
Response at site of radiation at month 6 (%)	CR	14 (27.5)	2 (12.5)	3 (21.4)	9 (42.9)	0.216
	PD	6 (11.8)	2 (12.5)	1 (7.1)	3 (14.3)	
	PR	7 (13.7)	3 (18.8)	3 (21.4)	1 (4.8)	
	SD	3 (5.9)	1 (6.2)	0 (0.0)	2 (9.5)	
	NA	21 (41.2)	8 (50.0)	7 (50.0)	6 (28.5)	
Response at site of radiation at month 12 (%)	CR	10 (19.6)	2 (12.5)	2 (14.3)	6 (28.6)	0.569
	PD	3 (5.9)	1 (6.2)	0 (0.0)	2 (9.5)	
	PR	2 (3.9)	0 (0.0)	1 (7.1)	1 (4.8)	
	SD	1 (2.0)	1 (6.2)	0 (0.0)	0 (0.0)	
	NA	35 (68.6)	12 (75.0)	11 (78.6)	12 (57.1)	
Response at site of radiation at end of treatment or last follow-up (%)	CR	12 (23.5)	1 (6.2)	2 (14.3)	9 (42.9)	0.032
	PD	22 (43.1)	8 (50.0)	8 (57.1)	6 (28.6)	
	PR	6 (11.8)	5 (31.2)	0 (0.0)	1 (4.8)	
	SD	4 (7.8)	1 (6.2)	1 (7.1)	2 (9.5)	
	NA	7 (13.7)	1 (6.2)	3 (21.4)	3 (14.3)	

The radiotherapy characteristics are shown for all sessions of radiotherapies overall as well as per group *P*-values <0.05 were considered to be statistically significant. CR, complete remission; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NA, not applicable; PD, progressive disease; PR, partial remission.

[a]The 15 conventional brain irradiations consisted of 14 WBRT and 1 conventional radiation of the brain stem (group B).

Table 3 Toxicity characteristics

	Level	Overall	Group A	Group B	Group C	*P* value
Number of radiotherapy sessions		51	16	14	21	
Number of sessions with radiotherapy-toxicity (%)	No (all grades)	30 (58.8)	9 (56.2)	9 (64.3)	12 (57.1)	0.887
	Yes (all grades)	21 (41.2)	7 (43.8)	5 (35.7)	9 (42.9)	
Number of sessions with high-grade radiotherapy-toxicity (%)	Grades 2 and 3 toxicity	11 (21.1)	4 (25.0)	2 (14.2)	5 (23.8)	0.277
Number of absolute radiotherapy-toxicity events (all grades)		38	15	5	18	0.2595
Grade of toxicity (% of absolute events)	1	24 (63.2)	7 (46.7)	4 (80.0)	13 (72.2)	
	2	8 (21.0)	3 (20.0)	1 (20.0)	4 (22.2)	
	3	6 (15.8)	5 (33.3)	0 (0.0)	1 (5.6)	
Location of toxicity (% of absolute events)	Abdomen	5 (13.15)	1 (6.7)	1 (20.0)	3 (16.7)	
	Bone	2 (5.26)	0 (0.0)	1 (20.0)	1 (5.6)	
	Central nervous system	20 (52.63)	12 (80.0)	1 (20.0)	7 (38.8)	
	Head and neck	2 (5.26)	1 (6.7)	0 (0.0)	1 (5.6)	
	Skin	9 (23.68)	1 (6.7)	2 (40.0)	6 (33.3)	
Type of toxicity	Alopecia	4	1	0	3	
	Anorexia	2	0	1	1	
	Cerebral edema	1	0	0	1	
	Dysphagia	1	0	0	1	
	Emesis	1	0	0	1	
	Fatigue	5	2	0	3	
	Headache	3	2	0	1	
	Intracranial Hemorrhage	7	5	1	1	
	Mucositis	1	1	0	0	
	Nausea	2	1	0	1	
	Pain	2	0	1	1	
	Acute radiation dermatitis	5	0	2	3	
	Radionecrosis	1	1	0	0	
	Seizure	2	1	0	1	
	Vertigo	1	1	0	0	

Number of sessions of radiotherapy, where radiotherapy-associated toxicity was observed are shown for all grades and for grades 2 and 3 only. Since some sessions evoked several toxic events, the absolute number of radiotherapy-toxicities is higher than the number of sessions with radiotherapy-toxicity. The toxicity grades, location, and types are analyzed according to number of total events.

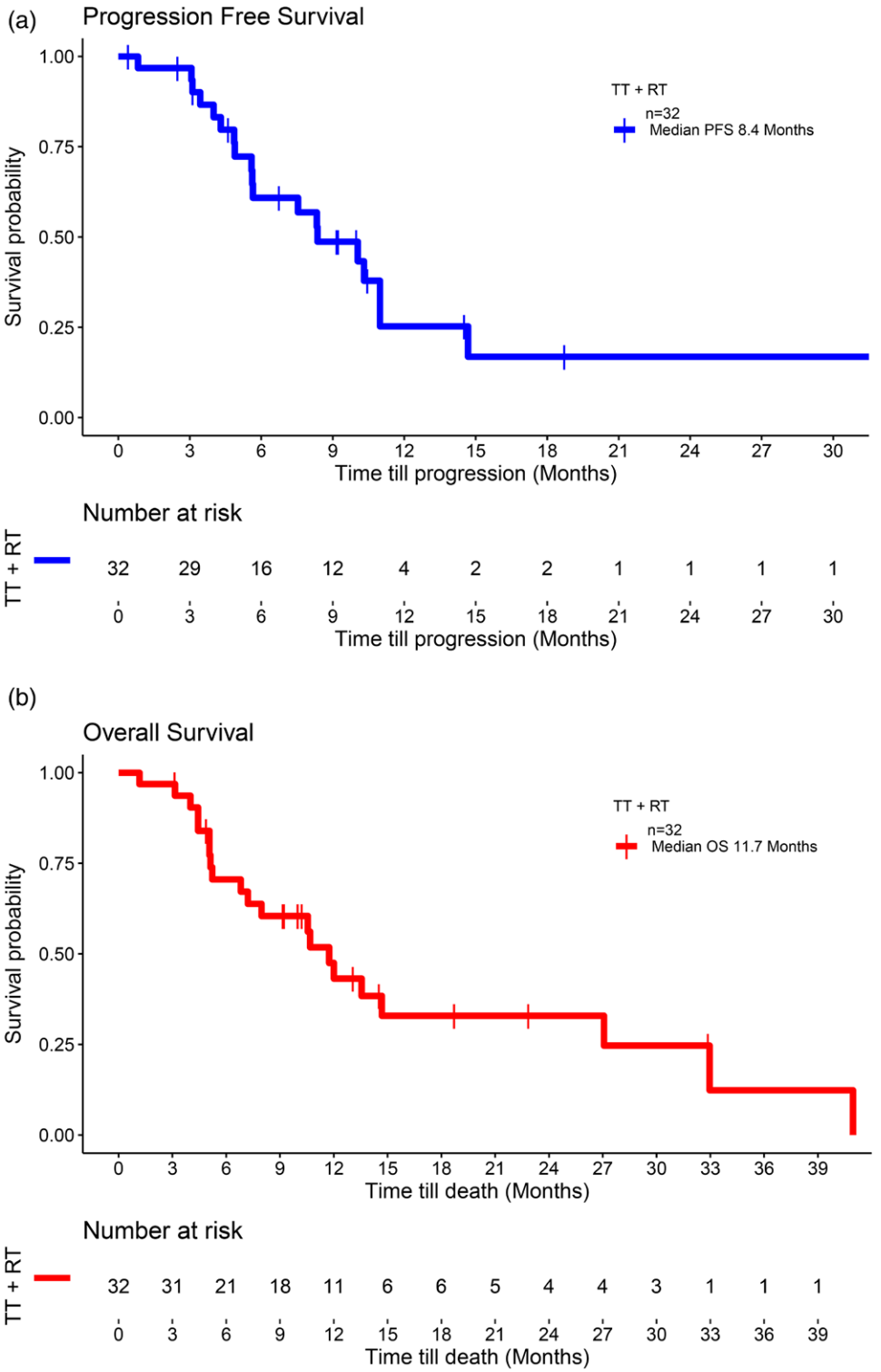
Initial experience with concurrent SRT for metastatic melanoma to the brain and BRAFi and MEKi combination in six patients reported no increase in toxicity [28]. This investigation does not account for the effects of concurrent radiotherapy and combined targeted therapy on the skin because SRT affects a much smaller surface than conventionally fractionated radiotherapy.

In our cohort, whether targeted therapy was interrupted or not, no significant difference in overall radiotherapy-toxicity was seen. This was overserved for any grade of toxicity as well as severe toxicity (grades 2 and 3).

Radiation dermatitis is a common side effect of radiotherapy, affecting up to 95% of patients [29,30]. Hecht *et al.* found acute radiation dermatitis ≥2° to occur in 36% of patients with concomitant BRAFi (40% with vemurafenib, 26% with dabrafenib) [24]. Similarly, a later work found radiation dermatitis ≥2° in 21% of patients treated with dabrafenib and in 35% with vemurafenib, suggesting vemurafenib to be the more potent radiosensitizer than dabrafenib. They also showed a significant increase in radiation dermatitis ≥2° in patients without interruption of BRAFi compared to those with interruption. A total of 15 patients with combination targeted therapy were included in their study; however, potential differences in radiotherapy-toxicity between the groups were not analyzed [31]. We observed acute radiation dermatitis in five cases (four with dabrafenib/trametinib and one with vemurafenib/cobimetinib). All dermatitis reactions were mild (grade 1) and well controllable by topical emollients. Two cases of radiation dermatitis occurred in group B and three cases in group C, thus not hinting towards any correlation with simultaneous combination targeted therapy and radiotherapy. No acute radiation dermatitis was seen in group A. All five cases of acute radiation dermatitis were reported in patients receiving conventional radiotherapy (WBRT = 3, bone = 2). This could be explained by the fact that conventional radiotherapy affects a much larger skin surface that SRT, thus increasing the risk of developing radiation dermatitis. Indeed, 81.2% of the radiotherapies in group A consisted of SRT. No recall dermatitis or non-dermatitis skin reactions such as cutis verticis gyrata or folliculitis were observed.

Various data on radiotherapy-associated toxicities in patients treated with BRAFi and SRT simultaneously is available for MBM [17]. Ly *et al.* reported a significant increase in brain metastasis hemorrhage after SRT; others report an increased risk of radionecrosis and several cases of cerebral edema and headache [32–37]. However, intracranial radionecrosis and hemorrhage rates did not appear to be increased for both SRT and WBRT with concurrent or sequential administration of BRAFi in the ECOG consensus guideline review, amongst others [16,25,38]. Hemorrhage rates for BRAFi monotherapy and SRT have been reported between 17.9 and 29.2% [16,32]. In our study, intracranial hemorrhage occurred in 7 of 51 sessions (13.7%). We saw one case of radionecrosis, diverging from results found by Patel *et al.* [37]. However,

Fig. 3



(a) Kaplan–Meier analysis of PFS calculated from the start of targeted therapy. PFS was calculated from the start of targeted therapy for all patients. PFS, progression-free survival. (b) Kaplan–Meier analysis of OS calculated from the start of targeted therapy. OS was calculated from the start of targeted therapy for all patients. OS, overall survival.

radionecrosis might occur months or even years after radiotherapy, possibly leading to a detection bias [39].

Reported PFS in patients treated with combination targeted therapy ranges between 9.3 and 12.3 months [1,3,4]. However, patients with active brain metastases were excluded from these phase III trials. MBM were present in 82.4% of our cases, possibly explaining the lower PFS with 8.4 months. OS in MBM patients treated with concurrent targeted therapy and SRT ranges from 12.7 months to 19.7 months for combination targeted therapy [40–42]. The lower OS in our cohort could be explained by the fact that many patients suffered from a high disease burden in the brain, which requires WBRT as opposed to conformal radiotherapy such as SRT and radiosurgery (38.8% of cases of brain irradiation).

The interpretation of our results is limited due to the retrospective nature of the study. Patients were included regardless of previous and subsequent therapies, type, or location of radiotherapy, resulting in a heterogeneous population. Worse prognostic factors in group B might have led to a selection bias. The limited patient number allows no final statement on the justification of interruption of targeted therapy during radiotherapy and is not sufficient to find any associated factors influencing the incidence of radiotherapy-associated toxicity or local control at EOT or last follow-up.

However, this study provides important data on a topic where few data are available yet and the clinical need is high, showing real-life results for patients treated with targeted therapy for metastatic melanoma undergoing concomitant radiotherapy.

In line with our clinical experience, we did not see an increase in radiotherapy-associated toxicity if targeted therapy was continued during radiotherapy. Studies performed with large cohorts on this topic do not exist. This study could be used by clinicians to aid in the decision-making process. To confirm our findings and make a definite recommendation on targeted therapy interruption during radiotherapy, a controlled, blinded, prospective clinical trial is warranted.

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Data are available in the Melanoma Registry Database of the Department of Dermatology, University Hospital Zurich.

J.Z., R.D., P.C., and J.M. developed the study concept and design. J.Z. and S.K. collected the clinical data. P.C. performed statistical analysis. J.Z., J.M., and P.C. interpreted the data. J.Z. and J.M. wrote the manuscript with the help of P.C., M.H., R.D., and S.K. L.I. and M.G. were responsible for performing the radiotherapy and provided data. M.L. and R.D. provided funding for the personnel involved, and M.L., R.D., and M.G. reviewed and edited the manuscript.

Conflicts of interest

R.D. has intermittent, project-focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, Alligator outside the submitted work. M.P.L. also has intermittent, project-focused research funding from Novartis and Roche. J.M. has intermittent project focused consultant or advisory relationships with Merck/Pfizer, Merck Sharp & Dohme, Amgen, Novartis and Pierre Fabre and has received travel support from Ultrasun, L'Oreal, Merck Sharp & Dohme, Bristol Myers and Squibb und Pierre Fabre outside of the submitted work. For the remaining authors, there are no conflicts of interest.

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