

ORIGINAL ARTICLE

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Radiotherapy with or without immunotherapy in metastatic melanoma: efficacy and tolerability

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ABSTRACT

Introduction: Radiotherapy (RT) is primarily considered as a palliative treatment in patients with metastatic melanoma. However, observations suggest that when RT is combined with immune checkpoint inhibitors (ICI), it can induce an immune response leading to an anti-tumoral effect also distant from the irradiated area – a phenomenon called ‘abscopal effect’. The frequency and circumstances of abscopal effect among metastatic melanoma patients remains uncertain and further research is necessary.

Material and method: This retrospective study included all metastatic melanoma patients who received non-stereotactic RT in Stockholm, Sweden in 2015–2020. Patients were grouped depending on if RT was given at start of ICI (RT + ICI(start)), at ICI progression (RT + ICI(salvage)) or without ICI (RT(only)). Response rates in irradiated (RR(irradiated)) and overall response rates in non-irradiated (ORR(non-irradiated)) metastases were evaluated together with survival and toxicity in each cohort.

Results: In the RT + ICI(start) ($n = 47$), RT + ICI(salvage) ($n = 41$) and RT(only) ($n = 55$) cohorts, RR(irradiated) was 70.7%, 67.5% and 43.1% ($p = 0.018$) while the ORR(non-irradiated) was 36.1%, 14.8% and 0.0% ($p = 0.003$), and the median overall survival was 18.2, 15.0 and 7.2 months, respectively ($p = 0.014$). Local response to RT was in all cohorts associated with longer survival ($p < 0.001$). The frequency of grade ≥ 3 immune-related adverse events was 17.0% and 19.5% in the RT + ICI(start) and RT + ICI(salvage) cohorts. No increased frequency of RT-related adverse events was seen in the RT + ICI cohorts, compared to the RT(only) cohort.

Conclusion: This retrospective study showed that melanoma patients receiving RT in combination with ICI had a superior antitumoral response in both irradiated and non-irradiated lesions as compared to patients receiving only RT. Additionally, a subgroup of patients receiving RT when progressing on ICI experienced tumor regression also in non-irradiated areas.

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Melanoma; abscopal effect; radiotherapy; immunotherapy; radioimmunotherapy

Background

Melanoma is a serious form of skin cancer with a steadily rising incidence in many countries [1]. Immune checkpoint inhibitors (ICIs) have greatly improved the prognosis and are now a cornerstone in the treatment of metastatic melanoma. Although ICIs have contributed to an improved prognosis, a significant number of patients do not respond to the treatment or demonstrate only a short-term benefit. With both anti PD-1 and anti PD-1/CTLA-4 treatment, approximately half of the treated patients experience progressive disease within the first 12 months [2,3]. Various strategies have been proposed to turn immunologically ‘cold’ tumors, which do not respond to ICI, into ‘hot’ immunogenic tumors. These strategies include evaluating multiple treatment modalities in combination with ICI, including cytokines, viral agents, other

novel ICIs, and radiotherapy (RT). The tumoricidal effect of RT is due to DNA damage with resultant cell death. This releases tumor neoantigens, activating signaling pathways associated with immune response [4]. When RT has triggered such an immune response, the addition of ICI could further enhance the anti-tumoral effect [5–7].

Recent observations also suggest that RT has the potential to evoke an immune response with an anti-tumoral effect distant to the irradiated area, a phenomenon also known as an abscopal effect [8]. The phenomenon ‘abscopal effect’, derived from ‘ab scopus’, meaning ‘away from target’, was first described in 1955 by Mole [9]. A systematic review identified the abscopal effect as a rare occurrence following RT alone, with only 46 reported cases between 1969 and 2014 [10]. Nevertheless, various clinical trials today are focusing on the combination of ICI and RT and its potential synergy.

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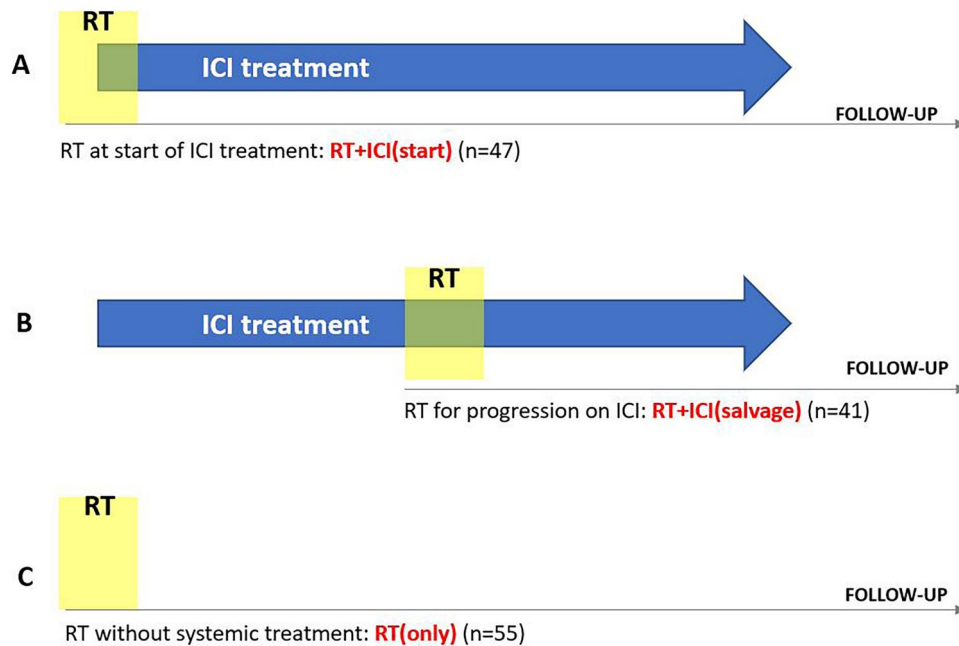


Figure 1. Summary of treatment schedules in melanoma patients receiving radiotherapy (RT) ± immune checkpoint inhibitors (ICI). Patients received radiotherapy either (A) close to the start of ICI (RT + ICI(start)), (B) when progressing in ICI (RT + ICI(salvage)) or (C) without systemic oncological treatment (RT(only)).

Some of the studies emphasize that RT is transforming into a treatment that enhances a systemic immune response, rather than the dogmatic view of RT being a localized treatment [7,11]. These observations have increased awareness of the topic, yet few studies focus on metastatic melanoma and many questions remain unanswered [12,13].

In this study, we report the outcome in patients with metastatic melanoma receiving RT after the introduction and approval of ICI. Our primary objective was to assess the response rates in irradiated and non-irradiated melanoma metastases, with a particular focus on investigating if an abscopal effect could be detected. Additional aims were to analyze survival and toxicity in patients receiving RT with and without concomitant ICI therapy.

Material and method

Patients

In this retrospective study, all patients with metastatic melanoma who received non-stereotactic RT at Karolinska University Hospital in Stockholm, Sweden between January 2015 and May 2020, were included. Karolinska University Hospital is the only clinic in the Stockholm region treating metastatic melanoma and the study is therefore population based. Baseline clinical data were extracted from the patients' medical records at the initiation of RT and included age, sex, Eastern Cooperative Oncology Group (ECOG) Performance status, tumor stage according to American Joint Committee on Cancer (AJCC) version 8 [14], lactate dehydrogenase (LDH) levels, *BRAF* mutations status, and previous and ongoing systemic treatments. Data were also collected on the RT fractionation schedules, total prescribed doses, target locations, presence of non-irradiated

metastases, and concomitant systemic treatment. Patients undergoing ICI treatment received approved standard regimens and dosages for metastatic melanoma. Patients receiving concomitant *BRAF* ± *MEK* inhibitors and patients treated with hypofractionated ablative RT using stereotactic (SBRT) technique were excluded. Patients were grouped depending on if RT was given at start of ICI (RT + ICI(start)), at ICI progression (RT + ICI(salvage)), or without ICI (RT(only)) (Figure 1). The RT + ICI(start) cohort included patients that had started RT within a 10-week period from the initiation of ICI treatment. A 10-week time was chosen to ensure that the initial radiological evaluation of ICI had not been performed. The RT + ICI(salvage) cohort consisted of patients that received RT after at least 8 weeks from ICI-initiation due to radiological or clinical progression. The RT(only) cohort included patients that received RT and no systemic treatment within a 10-week period from RT initiation.

Follow-up

The cohorts were evaluated until the 18 October 2022. Routine clinical follow-up typically included at least one clinical assessment during the RT treatment to monitor potential side effects. A clinical visit was scheduled 3-6 weeks after completing RT and thereafter clinical assessments and radiological evaluations every three months. Response to treatment was based on radiological investigations (computed tomography (CT) and/or 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)) evaluated retrospectively by a radiologist and assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria [15]. Response rate (RR) was defined as the frequency of patients with complete (CR) or partial response (PR) as the best

Table 1. Baseline characteristics of patients with metastatic melanoma at the start of radiotherapy.

Characteristics		RT + ICI(start) <i>n</i> = 47	RT + ICI(salvage) <i>n</i> = 41	RT(only) <i>n</i> = 55	p-value
Age, years, median (range)		64 (33–86)	66 (43–83)	75 (38–102)	0.004
Sex, <i>n</i> (%)					
Melanoma type, <i>n</i> (%)	Female	23 (48.9%)	18 (43.9%)	27 (49.1%)	0.858
	Male	24 (51.1%)	23 (56.1%)	28 (50.9%)	
Stage, <i>n</i> (%)	Cutaneous	43 (91.5%)	37 (90.2%)	51 (92.7%)	0.909
	Mucosal	4 (8.5%)	4 (9.8%)	4 (7.3%)	
LDH level, <i>n</i> (%)	Stage III	5 (10.6%)	5 (12.2%)	7 (12.7%)	0.540
	M1a	8 (17.0%)	10 (24.4%)	15 (27.3%)	
	M1b	10 (21.3%)	5 (12.2%)	6 (10.9%)	
	M1c	17 (36.2%)	16 (39.0%)	14 (25.5%)	
	M1d	7 (14.9%)	5 (12.2%)	13 (23.6%)	
BRAF status, <i>n</i> (%)	LDH ≤ ULN	16 (34.0%)	18 (43.9%)	18 (47.4%)	0.425
	LDH > ULN	31 (66.0%)	23 (56.1%)	20 (52.6%)	
	Not assessed	0	0	17	
ECOG, <i>n</i> (%)	Wild-type	27 (57.4%)	30 (73.2%)	43 (87.8%)	0.004
	V600 mutation	20 (42.6%)	11 (26.8%)	6 (12.2%)	
	Not assessed	0	0	6	
Previous lines of systemic therapies, <i>n</i> (%)	0–1	39 (83.0%)	33 (80.5%)	36 (65.5%)	0.083
	2–4	8 (17.0%)	8 (19.5%)	19 (34.5%)	
Previous therapy type, <i>n</i> (%)	0	30 (63.8%)	30 (73.2%)	38 (69.1%)	0.465
	1	14 (29.8%)	6 (14.6%)	11 (20.0%)	
	≥2	3 (6.4%)	4 (9.8%)	6 (10.9%)	
Concurrent ICI, <i>n</i> (%)	BRAF ± MEKi	13 (27.7%)	4 (9.8%)	2 (3.6%)	<0.001
	ICI	4 (8.5%)	9 (22.0%)	14 (25.5%)	
	Chemotherapy	2 (4.3%)	2 (4.9%)	6 (10.9%)	
Radiotherapy target, <i>n</i> (%)	CTLA-4	3 (6.4%)	0 (0.0%)	NA	0.071
	Anti PD-1	39 (83.0%)	40 (97.6%)	NA	
	Anti PD-1 + CTLA-4	5 (10.6%)	1 (2.4%)	NA	
Median RT dose (range)	Skin, lymph nodes or soft tissues	31 (66.0%)	28 (68.3%)	37 (67.3%)	0.995
	Lung	1 (2.1%)	2 (4.9%)	3 (5.5%)	
	Bone	8 (17.0%)	6 (14.6%)	9 (10.9%)	
	Visceral	2 (4.3%)	2 (4.9%)	2 (3.6%)	
	Brain	5 (10.6%)	3 (7.3%)	4 (7.3%)	
Metastatic lesions other than the irradiated lesions	Total dose, Gy	25 (8–35)	20 (5–30)	25 (4–30)	0.588
	Gy per fraction	6 (3–8)	6 (3–10)	6 (3–8)	0.900
	Fractions, <i>n</i>	5 (1–5)	5 (1–10)	5 (1–5)	0.497
	Yes	38 (80.9%)	32 (78.0%)	37 (67.3%)	0.247
	No	9 (19.1%)	9 (22.0%)	18 (32.7%)	

RT: radiotherapy

ICI: immune checkpoint inhibitor treatment

response observed either until a systemic therapeutic change or until the end of the study period. RRs in the irradiated tumor RR(irradiated) and overall RR in non-irradiated tumors ORR(non-irradiated) were estimated separately. Patients with no non-irradiated lesions were excluded from the ORR(non-irradiated) assessment unless they exhibited progressive disease in the subsequent tumor evaluation. Data was captured for treatment response and survival during the follow-up. Progression-free survival (PFS) was defined as the time from the start of RT until the date of confirmed progression (either irradiated or non-irradiated tumor), date of death, or censoring. Overall survival (OS) was defined as the time from initiation of RT until the date of death or censoring. Further, adverse events (AE) related to RT and ICI were

assessed in accordance with the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5) classification and registered up to 3 months after ending of RT and ICI, respectively.

Statistical analysis

The chi-square test was used to analyze patients' baseline characteristic categorical variables. PFS and OS were analyzed with Kaplan-Meier method and Cox proportional hazards regression model. Median survival, along with 95% confidence intervals (CI) were calculated. Univariate and multivariable models for the Cox regression were used to assess each predictor's association with PFS and OS. Hazard ratios (HR)

and corresponding two-sided 95% CI were estimated. P-values <0.05 were deemed statistically significant. All statistical analyses were carried out using STATISTICA (Dell Inc. (2016), version 13).

Results

Baseline characteristics

In total, 143 patients with unresectable melanoma were included, whereof 47 were in the RT + ICI(start) cohort, 41 in the RT + ICI(salvage) cohort and 55 in the RT(only) cohort (Figure 1). The median age was 64, 66 and 75 years respectively ($p=0.004$) (Table 1). The majority (>90%) of cases had metastatic cutaneous melanoma while the remaining cases had metastatic mucosal melanoma. In all cohorts approximately half of the patients had M1c-M1d disease. 23.6% of the patients in the RT(only) cohort had brain metastases, compared to 14.9% and 12.2% in the RT + ICI(start) and RT + ICI(salvage) cohorts, respectively. More than half of all patients had elevated LDH, with no significant difference between the cohorts. However, in the RT(only) cohort, a higher fraction had no baseline LDH or an unknown *BRAF* mutation status. Furthermore, in the RT + ICI(start) and RT + ICI(salvage) cohorts, 17.0% and 19.5% of patients had ECOG 2–3 compared to 34.5% in the RT(only) cohort ($p=0.083$). In the RT + ICI(start) cohort, 42.6% had *BRAF*-mutated melanoma, compared to 26.8% and 12.2% in the RT + ICI(salvage) and RT(only) cohorts ($p=0.004$). In the RT + ICI(start) cohort, 27.7% of patients had previously been treated with *BRAF*/MEK-inhibitors in comparison to 9.8% and 3.6% in the RT + ICI(salvage) and RT(only) cohorts ($p<0.001$). Moreover, 8.5% and 22.0% in the RT + ICI(start) and RT + ICI(salvage) cohorts had previously been treated with ICI (i.e., prior to the ongoing ICI treatment) compared to 25.5% in the RT(only) cohort. In terms of concurrent treatment, the majority of patients in the RT + ICI cohorts received PD-1 inhibitor monotherapy. Additionally, 93.6% and 56.1% in the RT + ICI cohorts continued with at least one course of ICI after RT ($p<0.001$), with a median treatment duration of 4.9 vs 1.9 months post-RT. In all cohorts, the majority had RT to skin,

lymph nodes or soft tissues, followed by RT to skeletal metastases. In all cohorts, the most frequent RT fraction scheme was 6 Gy x5. More details regarding radiation dosage are provided in [Supplementary Table S1](#). In the RT + ICI cohorts, 80.9% and 78.0% had non-irradiated tumor lesions compared to 67.3% in the RT(only) cohort ($p=0.247$).

Tumor evaluation and abscopal effect

In the RT + ICI(start) and RT + ICI(salvage) cohorts, RR(irradiated) was 70.7% and 67.5% compared to 43.1% in the RT(only) cohort ($p=0.018$) (Table 2). ORR(non-irradiated) was 36.1%, 14.8% and 0.0% in the RT + ICI(start), the RT + ICI(salvage) and the RT(only) cohorts, respectively ($p=0.003$). Four patients in the RT + ICI(salvage) cohort had a significant reduction in the size of non-irradiated metastases. The first patient had after four months of treatment with pembrolizumab progression of a large subcutaneous tumor mass in the left scapular region and received RT (4 Gy x5) to this area. Three months later, a reduction was observed in the irradiated lesion. Additionally, in the head and neck area, a non-irradiated metastasis that had previously been stably also significantly diminished in size (Figure 2A). The patient subsequently attained CR and discontinued pembrolizumab after 11 months of treatment. However, 4 years later, this patient had tumor relapse in the irradiated left scapular region and has resumed PD-1 inhibitor treatment. A second patient, also treated with pembrolizumab, received RT, 10 Gy x2 to a new 34 mm metastatic lesion in the right groin. A CT scan three months later demonstrated a shrinkage of the irradiated tumor and a significant anti-tumoral response in previously progressing non-irradiated liver metastases. One liver lesion shrank from 58 mm to 33 mm and another lesion from 23 mm to 15 mm (Figure 2B). After a total of 2 years of systemic treatment, pembrolizumab was ended, the patient had then attained CR and is after a follow-up of 5.5 years relapse-free. A third patient receiving nivolumab, had RT, 8 Gy x1, for a progressing and ulcerating tumor on the right leg. A CT scan three months later revealed a PR in the irradiated tumor and additionally in a previously progressing lesion within the patient's right groin (Figure 2C). The patient is still alive

Table 2. Best response after radiotherapy in patients with metastatic melanoma.

	RT + ICI(start) <i>n</i> = 47	RT + ICI(salvage) <i>n</i> = 41	RT(only) <i>n</i> = 55	p-value
Irradiated lesions	41 (100%)	37 (100%)	44 (100%)	
Complete response	12 (29.3%)	12 (32.4%)	6 (13.6%)	
Partial response	17 (41.5%)	13 (35.1%)	13 (29.5%)	
Stable disease	8 (19.5%)	4 (10.8%)	16 (36.4%)	
Progressive disease	4 (9.8%)	8 (21.6%)	9 (20.5%)	
Not assessed	6	4	11	
Response rate - RR(irradiated)	70.7%	67.5%	43.1%	0.018
Non-irradiated metastasis	36 (100%)	27 (100%)	28 (100%)	
Complete response	4 (11.1%)	2 (7.4%)	0 (0.0%)	
Partial response	9 (25.0%)	2 (7.4%)	0 (0.0%)	
Stable disease	2 (5.6%)	10 (37.0%)	2 (7.1%)	
Progressive disease	21 (58.3%)	13 (48.1%)	26 (92.9%)	
Not assessed	5	7	21	
No metastasis other than the irradiated	6	7	6	
Overall response rate - ORR(non-irradiated)	36.1%	14.8%	0.0%	0.003

RT = Radiotherapy

ICI = Immune checkpoint inhibitor treatment

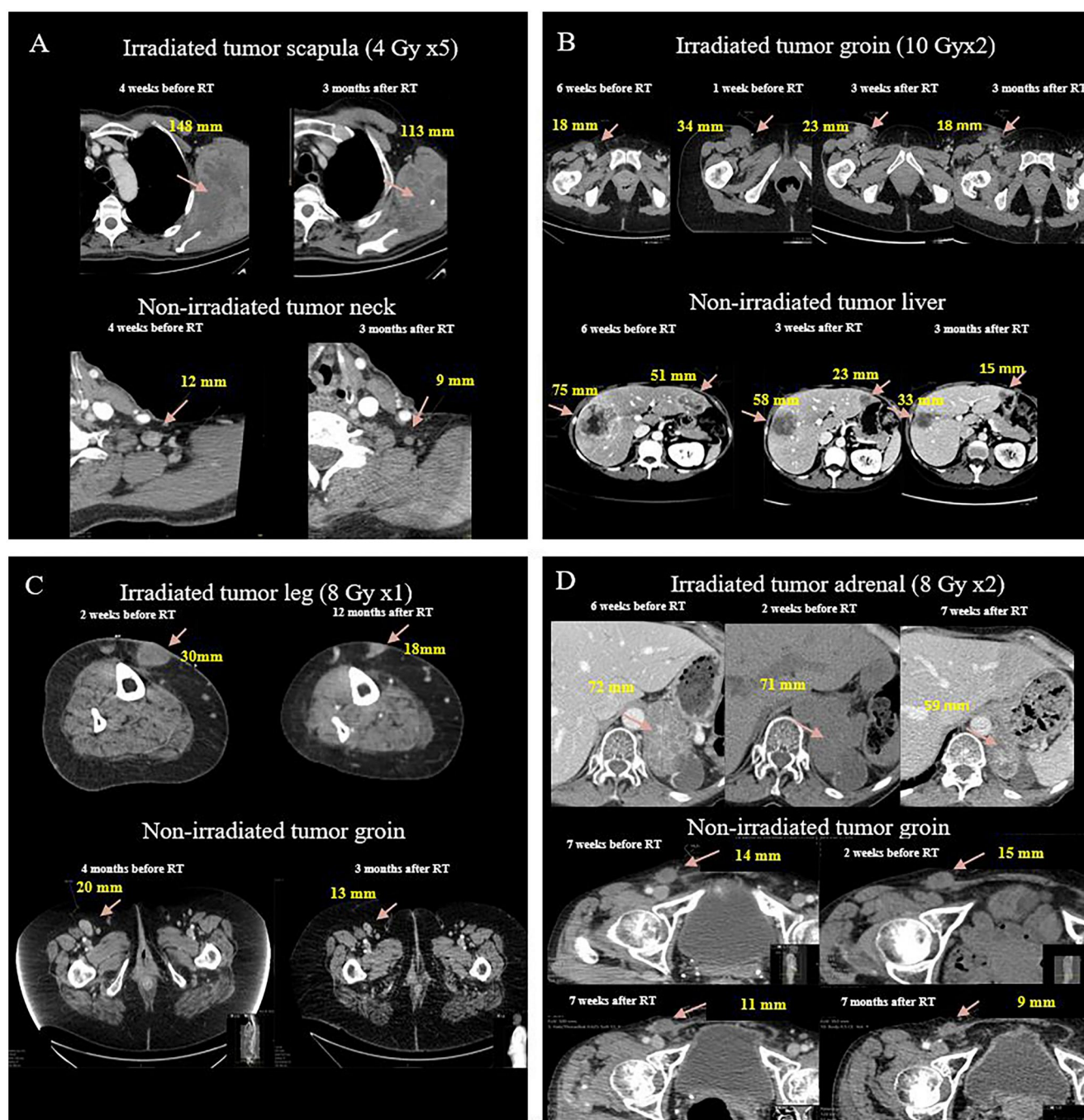


Figure 2. CT scans demonstrating the four patients (A, B, C, D) in the RT + ICI(salvage) cohort that received RT to progressing melanoma metastases and experienced tumor shrinkage in non-irradiated metastases.

and progression-free after 6.5 years of follow-up. The fourth patient receiving nivolumab had RT, 8Gy x2, to a progressing left sided adrenal metastasis. A CT scan two months later showed not only shrinkage of the irradiated tumor but also a reduction of a prior stable lymph node in the right groin from 15 mm to 9 mm (Figure 2D). Nivolumab was continued, but 11 months later, the patient again progressed and later died from the disease.

Survival

The median follow-up was 60 months in all three cohorts. In the RT + ICI(start), RT + ICI(salvage) and RT(only) cohorts, the

median PFS (95% CI) from RT initiation was 4.0 (2.4–10.3), 5.4 (3.3–13.6), 3.2 (2.0–4.4) months ($p=0.047$) (Figure 3A) and the median OS (95% CI) was 18.2 (9.3–31.3), 15.0 (8.4–31.8), and 7.2 (3.8–9.7) months, respectively ($p=0.014$) (Figure 3B). Improved PFS and OS was seen among patients treated with ≥ 6 Gy per fraction compared to lower fractional doses, $p=0.025$ (PFS) and $p=0.014$ (OS) (Figure 3C,D). Patients who underwent RT to the central nervous system (CNS (majority having whole brain RT)) had significantly poorer PFS and OS compared to those receiving RT to other organs, $p=0.011$ (PFS) and $p<0.001$ (OS) (Figure 3E, F). Of the 12 patients receiving RT to the CNS ($n=5$, $n=3$, $n=4$ in the RT + ICI(start), RT + ICI(salvage) and RT(only) cohorts,

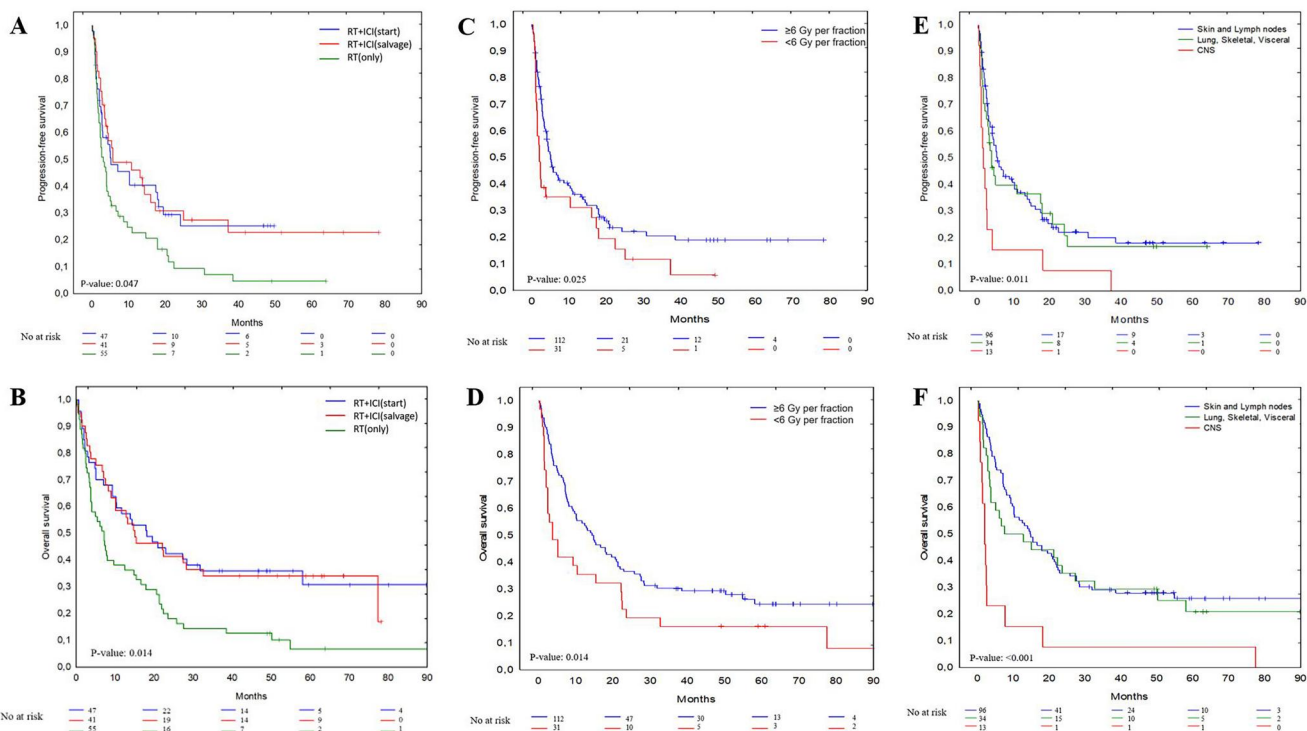


Figure 3. Kaplan-Meier curves illustrating progression-free survival and overall survival in metastatic melanoma patients treated with radiotherapy (RT) ± immunotherapy (ICI). Section A and B presents survival in the RT + ICI(start)-cohort (RT at start of ICI), RT + ICI(salvage)-cohort (RT at progression on ICI) and RT(only)-cohort (RT without ICI). Section C and D shows survival in patients treated with ≥ 6 or < 6 gray (Gy) per fraction (all RT/ICI cohorts combined). Section E and F shows survival dependent on which organ was irradiated, skin and lymph nodes or lung, skeletal and visceral or central nervous system (CNS) (all RT/ICI cohorts combined).

Table 3. Cox regressions for survival in metastatic melanoma patients treated with radiotherapy (RT) ± immunotherapy (ICI).

	Univariate		Multivariate*	
Progression-free survival	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (≥ 65 vs. < 65 years)	1.36 (0.91–2.03)	0.137	1.11 (0.72–1.70)	0.643
Sex (Male vs. Female)	1.01 (0.69–1.47)	0.967	1.03 (0.70–1.51)	0.882
ECOG (≥ 2 vs. 0–1)	3.67 (2.38–5.66)	< 0.001	3.35 (2.12–5.30)	< 0.001
Stage (M1c-d vs. III-M1a-b)	1.20 (0.82–1.75)	0.343	1.37 (0.93–2.02)	0.113
Cohort (RT-only vs. RT + ICI)	1.74 (1.19–2.54)	0.004	1.39 (0.93–2.09)	0.112
Overall survival				
Age (≥ 65 vs. < 65 years)	1.38 (0.92–2.06)	0.117	1.10 (0.72–1.70)	0.671
Sex (Male vs. Female)	0.91 (0.62–1.33)	0.625	0.95 (0.65–1.39)	0.787
ECOG (≥ 2 vs. 0–1)	4.57 (2.96–7.06)	< 0.001	4.46 (2.81–7.07)	< 0.001
Stage (M1c-d vs. III-M1a-b)	1.33 (0.91–1.94)	0.136	1.57 (1.07–2.31)	0.022
Cohort (RT-only vs. RT + ICI)	1.95 (1.33–2.86)	< 0.001	1.57 (1.04–2.36)	0.030

*All variables adjusted for the other four covariabels in the table.

respectively), only 2 patients were alive after 6 months, and they were in the two RT + ICI cohorts.

The uni- and multivariate analysis (Table 3) demonstrated that ECOG performance status (≥ 2) and M1c-d disease were both independently associated with significantly worse PFS and OS. Patients in the RT + ICI cohorts had a significantly better PFS (univariate analysis) and OS (univariate and multivariate analyses), compared to those in the RT(only) cohort. Additionally, a multivariate analysis was performed, showing that ≥ 6 Gy per fraction was not significantly associated with improved PFS or OS when adjusted for other factors HR = 1.09, 95% CI (0.68–1.73) and HR = 1.06, 95% CI (0.67–1.68), respectively).

Further, survival analyses were performed based on the best response in the irradiated tumor. Patients who experienced shrinkage of their irradiated metastases (CR or PR) had improved survival compared to patients without local response to RT ($p < 0.001$) (Figure 4).

Tolerability of ICI and RT

In the RT + ICI(start) and RT + ICI(salvage) cohorts, 51.1% and 68.3% experienced ICI related AEs, of which 17.0% and 19.5% were grade 3, respectively (Table 4). There were no grade 4–5 AEs. A higher frequency of patients in the RT + ICI(salvage) cohort needed oral glucocorticoids or hospitalization due to AEs. No increased frequency was seen in RT-related AE in the RT + ICI cohorts, compared with the RT(only) cohort.

Discussion

In this retrospective study, we examined the impact of RT when given as monotherapy and in combination with ICI in patients with metastatic melanoma. Our results demonstrated that melanoma patients receiving RT in combination with ICI experienced better RR in both irradiated and non-

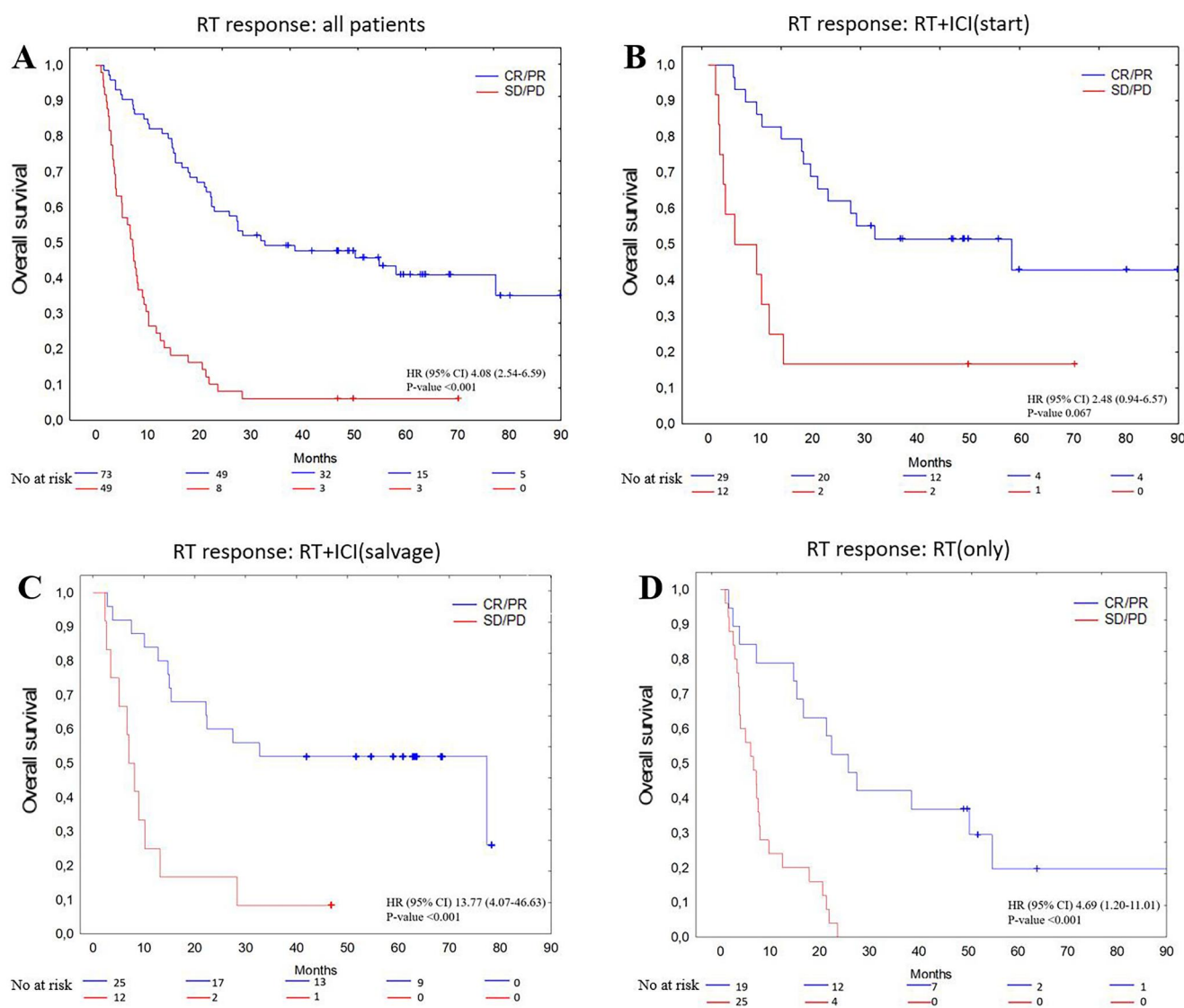


Figure 4. Kaplan-Meier curves illustrating survival depending on tumor shrinkage of irradiated melanoma metastases. Overall survival (OS) was here assessed from the timepoint of radiotherapy (RT). Patients were grouped for complete to partial response (CR/PR) or stable to progressive disease (SD/PD) in their irradiated metastases. Section (A) shows all the included patients with significantly worse OS in patients with no shrinkage in irradiated metastases (hazard ratio 4.08 (2.54-6.59), HR adjusted for age, sex, AJCC tumor stage, cohort (RT(only) vs RT + ICI), and ECOG. Section (B), (C) and (D) demonstrate OS for the specific cohort, RT + ICI(start)-cohort (radiotherapy at start of immunotherapy), RT + ICI(salvage)-cohort (radiotherapy at progression of immunotherapy), and RT(only)-cohort (radiotherapy without immunotherapy).

Table 4. Adverse events in the patients with metastatic melanoma receiving radiotherapy .

		RT + ICI(start)	RT + ICI(salvage)	RT(only)
		<i>n</i> = 47	<i>n</i> = 41	<i>n</i> = 55
Immunotherapy related AE	Total n, all grade	24 (51.1%)	28 (68.3%)	NA
	Total n, grade 3	8 (17.0%)	8 (19.5%)	NA
Immunotherapy side effects leading to	Supportive treatment, hormone substitution, <i>n</i> (%)	5 (10.6%)	4 (9.8%)	NA
	Oral glucocorticoids, <i>n</i> (%)	12 (25.5%)	17 (41.5%)	NA
	Hospitalization, <i>n</i> (%)	1 (2.1%)	5 (12.2%)	NA
	Cessation of immunotherapy, <i>n</i> (%)	4 (8.5%)	5 (12.2%)	NA
Radiotherapy related AE	Radiation dermatitis, <i>n</i> (%)	9 (19.1%)	10 (24.4%)	16 (29.1%)
	Fatigue, <i>n</i> (%)	0 (0.0%)	2 (4.9%)	4 (7.3%)
	Diarrhea, <i>n</i> (%)	1 (2.1%)	0 (0.0%)	2 (3.6%)
	Radiation pneumonitis, <i>n</i> (%)	0 (0.0%)	0 (0.0%)	3 (5.5%)
	Nausea, <i>n</i> (%)	0 (0.0%)	0 (0.0%)	3 (5.5%)

RT: radiotherapy.

ICI: immune checkpoint inhibitor treatment.

irradiated lesions compared to patients receiving RT only. Additionally, we observed suggestions of an abscopal effect among a subgroup of patients that received RT after progressing on ICI. Moreover, our results demonstrated that RT can be safely administered during concurrent ICI (majority PD-1 inhibitor monotherapy).

Overall response rate

In the patients that received RT at start of ICI treatment, we observed an ORR(non-irradiated) of 36.1%. This response is not superior to the reported RR in large studies using ICI without RT, with reported ORR in patients receiving PD-1 monotherapy ranging from 33–43% [2,3,16]. Further, 11.1% of patients experienced CR in non-irradiated lesions, consistent with clinical studies of PD-1 inhibitor monotherapy, where CR rates typically range from 3% to 9% [2,16,17]. It should be noted that our study cohort had more patients with brain metastases and elevated LDH and worse performance status than the patients included in the clinical trials.

In the RT + ICI(salvage) cohort, four patients (ORR(non-irradiated) 14.8%) showed signs of abscopal effect, with shrinkage of non-irradiated metastases when RT was given due to progression on ICI. This is a lower fraction than what has been reported in three retrospective melanoma studies with different RT strategies reporting an ORR from 23 to 32% [18–20]. Likewise, a retrospective study showed that treatment with ICI beyond progression improved OS if given concurrently with RT compared to ICI alone [21]. Furthermore, a meta-analysis performed by Yin et al. reported an ORR of 34% (range 17.9–64.7%) but included studies regardless of whether RT was administered when progressing on ICI or not. Hence, the reported ORR may thus reflect the systemic effects of ICI rather than the abscopal effect [12]. In the RT(only) cohort, no abscopal case was presented which is coherent with the rarity of the phenomenon if RT is given without ICI.

The definition of abscopal effect is not well-established, as some authors report an abscopal effect if a single lesion shrinks while others define it as the overall response of the disease. This makes comparison between studies somewhat challenging. Our intention was to evaluate the clinical benefit of adding RT to ICI and we have thus assessed abscopal response as a global response including all non-irradiated tumor sites. Chicas et al. performed a prospective study with lung and melanoma patients treated with SBRT. ORR was 42%, defined as the response among all sites of the disease, including the irradiated ones. In addition, an abscopal effect, defined as $a \geq 30\%$ reduction in a preciously selected nonirradiated lesion, was seen among 65% after SBRT [22]. In our study, the irradiated lesion was excluded in the ORR assessment and patients with no non-irradiated lesions were excluded unless they exhibited progressive disease in the subsequent tumor evaluation, leading to a possible underestimation in our study. However, we believe that the most reliable way to determine radiologically if an abscopal effect really has occurred, is to estimate ORR of non-irradiated metastases in patients receiving RT after an established PD on ICI treatment. The ORR of 14.8% in the RT + ICI(salvage)

cohort is however closely comparable to Topp et al.'s finding that melanoma patients that experienced PD in Keynote 001 later presented a RR of 13.7% despite discontinuing pembrolizumab. It is hence plausible that our ORR is a late effect of ICI rather than abscopal effects [23].

Local response rate

We observed that approximately 2/3 of the patients treated with RT and concurrent ICI showed tumor shrinkage of the treated lesion. These findings are similar to the result of Chicas et al. that showed a RR of 70% when combining SBRT and ICI [22]. Our study presented a higher RR in irradiated lesions compared to a retrospective study published in 2022 that showed an RR of 52% among patients who received hypofractionated RT or stereotactic radiosurgery when progressing on anti-PD1 treatment [20]. However, in the RT(only) cohort RR(irradiated) was 43.1% which is inferior to an older study from 1999 that presented a local response rate of 66% with RT as monotherapy [24] and another retrospective study that demonstrated a response of 84% in melanoma patients receiving palliative RT [25]. Hence, our study showed that patients receiving RT in combination with ICI had superior tumor response and survival compared to those receiving RT only. Interestingly, in our study, the response in irradiated metastases and survival duration was comparable for patients receiving RT either at start or upon ICI progression. This result contradicts the expectation that patients starting ICI would have better a outcome than those progressing on ICI. One interpretation is that RT is a good salvage treatment, potentially reversing tumor progression in patients already on ICI. However, considering the retrospective nature of this study, the skewed distribution of baseline characteristics between the cohorts, and different eligibility factors for RT at each time point, one need to be cautious to make any assumptions.

We also observed that a shrinkage of irradiated melanoma tumors was associated with improved OS, in all cohorts and irrespectively of concomitant ICI in univariate analysis. Local response, CR/PR vs SD/PD, to RT treatment, remained significant for OS, even after adjusting for age, sex, tumor stage and ECOG status in all cohorts except for the RT + ICI(start) cohort. Another study showed superior survival among patients having CR after RT compared to PR, SD and PD, but this was without ICI [24]. Tumor shrinkage in the irradiated tumor at the start of ICI can be associated with improved survival since it also mirrors the ICI response. To our knowledge, it has previously not been reported that in patients progressing on ICI, a response in the irradiated tumor is also predictive of a better OS. Collectively, this suggests that patients with radiosensitive melanoma metastasis have tumors that biologically are less prone to progress and are possibly more responsive to ICI.

Radiation dose

There are varying perspectives regarding the most suitable radiation dosage for inducing an immune response through

RT. This is partially from preclinical research on how RT, besides the capacity to kill tumor cells, can elicit both immune-stimulatory and inhibitory effects depending on the radiation dosage administered [26]. Poleszczuk et al. formulated a thesis, using a mathematical model, which indicated that the optimal radiation dose required to trigger an immune response was between 10 and 13 Gy [27]. Other preclinical studies also support an increased immune response when treated with high-dose radiation [28,29]. Additional studies that support a higher dose per fraction are from clinical observations, including a large retrospective study that showed superior response among melanoma patients receiving ICI combined with ≥ 5 Gy per fraction compared to conventional dosage with < 5 Gy per fraction [30]. Further, a case report showed an abscopal effect in a patient receiving 8 Gy x3 after progression on pembrolizumab [31]. Additionally, a phase 1 trial showed long-lasting effects when combining 8–17 Gy per fraction after progression on ICI in patients with different solid tumors [32]. There have also been studies showing the opposite result, including a study demonstrating improved response rates with radiation fraction sizes ≤ 3 Gy when combining RT with ipilimumab and another study demonstrating abscopal effect in patients progressing on ipilimumab, majority receiving ≤ 4 Gy [19,33]. In our study, patients received hypofractionated RT doses, most commonly 6 Gy x5. Interestingly, the patients treated with ≥ 6 Gy per fraction had improved PFS and OS, however not independent of other covariables. This indicates that caution is needed when evaluating the effect of different doses in a retrospective setting, since the dose chosen can be dependent on the tumor site, symptoms etc. The clearest example from our study are the patients receiving RT to CNS metastases (majority whole brain RT, 4 Gy x5), that had a particularly poor prognosis with a median OS of only 2 months. This finding is in agreement with previous studies reporting poor survival after whole brain radiotherapy, and our study shows that this is the case, also when combining with ICI [34].

Tolerability

Our study supports already published data that RT and ICI is a well tolerable combination [35,36]. Remarkably, the RT(only) cohort presented a higher incidence of RT-related AE, likely due to the study's retrospective nature and recall bias. Hence, patients and clinicians are possibly more likely to place greater emphasis on RT side effect in the absence of concurrent systemic therapy.

Conclusion

Our findings suggest that RT in combination with ICI can have an additive antitumoral effect in metastatic melanoma, however separating an abscopal effect from a late response to ICI remains a challenge. Additionally, RT can be safely administered combined with ICI. A strength of this study is the population-based setting, including all melanoma patients receiving non-stereotactic RT in the largest health care region in Sweden and this in the era of 'modern ICI

treatment'. To our knowledge, this study includes one of the largest cohorts of melanoma patients receiving ICI together with RT and it also has a unique comparison with patients who have received RT only. A weakness is the retrospective nature with all the pitfalls associated with that study design. We believe that this study nevertheless closely reflects the real-life setting and outcome for patients with metastatic melanoma receiving RT with or without ICI. However, further clinical trials are necessary to gain a comprehensive understanding of the extent to which the abscopal effect can be observed. Currently, we are conducting a phase 2 trial (PROMMEL study) investigating the use of SBRT in metastatic melanoma patients who have progressed on ICI [37].

Ethical approval

This study was approved by the Swedish Ethical Review Authority (Dnr 2020-04163). The Ethical Board approved this retrospective analysis, without collecting informed consent from each patient, which was justified by the fact that most of the included patients were deceased when the study was performed.

Authors contributions

E.B writing manuscript, data analysis, investigation, V.G RECIST assessment, H.H methodology, analysis, supervision, writing, reviewing, and editing manuscript. S.E.B, K.L and R.L supervision, reviewing and editing manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability statement

The data that support the findings of this study are available from the corresponding author E.B and specific data will be available on reasonable request.

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