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Analysis of Factors Associated With Hemorrhage Post-radiotherapy for Brain Metastasis: A Population-Based Study

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Abstract

Objective: This study aimed to characterize the incidence, risk factors, and symptoms associated with intracranial hemorrhage (ICH) following radiotherapy (RT) for hemorrhage-prone brain metastases (BM).

Methods: This retrospective population-based cohort study examined all patients with BM who were treated with RT in British Columbia from 2017 to 2022. Patients were included if their primary cancers were melanoma, colorectal, renal, hepatocellular, head and neck, germ cell, or sarcoma, as such cancers are associated with a higher risk of hemorrhagic BM. Patient comorbidities and the use of blood thinners were recorded. Post-RT ICH was identified through CT or MRI reports. Cumulative incidence curves were compared using Gray's test. Fine and Gray competing risk regression models were used to evaluate factors associated with ICH.

Results: A total of 319 patients treated for 943 lesions were identified, with a median follow-up period of 4.3 months. The most common primary cancer site was melanoma (42%). Forty-one patients (13%) developed ICH, with a median time to ICH of 2.5 months. The rates of ICH pre- and post-RT were 25% and 10% at the patient level. At the lesion level, the rates of ICH pre- and post-RT were 16% and 6%, respectively. On patient-level multivariable analysis, focal RT was associated with a higher risk of ICH than whole-brain RT ($p = 0.003$). Patients with a primary cancer of melanoma were more likely to have ICH than those with primary colorectal cancer ($p = 0.008$), and those with a history of stroke were more likely to bleed than those with no history of stroke ($p = 0.05$). Older age was associated with a lower risk of ICH ($p = 0.03$). Blood thinner use was not associated with ICH. At lesion-level multivariable analysis, focal RT was no longer significantly associated with ICH. Of the 41 patients who developed ICH, 26 (63%) experienced symptoms. The most common symptoms were headache, weakness, and confusion.

Conclusions: Post-RT ICH may occur early after treatment, resulting in neurological symptoms and reduced quality of life. RT, prior hemorrhage, and the use of blood thinners were not clearly associated with an increased risk of ICH. Early and vigilant monitoring for ICH may be warranted in patients with melanoma BM.

Categories: Radiation Oncology, Oncology, Neurosurgery
Keywords: brain metastases, intracranial hemorrhages, radiation oncology, radiotherapy, survival

Introduction

Brain metastases (BM) are the leading cause of intracranial tumors, representing over one-half of all intracranial cancers in adults [1]. Approximately 10-30% of adults with systemic malignancies develop BM, which accounts for 10-26% of cancer-related deaths [2]. Partly due to advances in high-resolution imaging that facilitate early detection and improvements in treatment, patient mortality has improved [3]. However, BM continues to have significant impacts on patient morbidity secondary to neurological deficits [1]. The choice of treatment depends on factors such as the number and location of brain lesions. Common treatment modalities include whole-brain radiation (WBRT) and focal radiotherapies (RTs) such as stereotactic radiosurgery (SRS) [4].

BM can lead to an increased risk of intracranial hemorrhage (ICH), particularly in primary cancers associated with a high risk of hemorrhage such as melanoma, hepatocellular carcinoma, and renal carcinoma [3]. Hemorrhagic BM can lead to the development of new neurological deficits or the worsening of existing deficits, further reducing patients' quality of life. Furthermore, ICH can impair the quality of subsequent RT treatments, as the hemorrhage can create challenges in treatment planning [4].

RT, tumor, and patient factors may contribute to the risk of ICH. Several reports suggest that SRS may be associated with ICH following treatment [1,2,4]. In addition, tumor characteristics, such as larger lesion size

and greater number of BMs, have been associated with an increased risk of ICH [2]. Prior bleeding events have also been shown to increase the risk of post-RT ICH, particularly among patients taking anticoagulants [2]. Furthermore, comorbidities, including liver or renal disease, may contribute to an increased risk of bleeding due to pre-existing coagulopathies [5]. However, few population-based studies have examined the incidence and risk factors of post-RT ICH.

Thus, the objective of this population-based cohort study was to characterize the incidence, risk factors, and symptoms associated with post-RT ICH in patients with BM who received RT. This article was previously presented as a meeting abstract at the 2026 Canadian Association for Radiation Oncology (CARO) Conference on September 17, 2026.

Materials And Methods

Eligible patients for this retrospective study were identified through the BC Cancer registry. University of British Columbia - BC Cancer Research Ethics Board issued approval H24-00464. BC Cancer consists of six regional cancer centers, and all RT within the province is delivered and recorded by BC Cancer, enabling population-based registry analysis. Patients were eligible if they resided in BC at the time of their primary cancer diagnosis between January 1, 2017, and December 31, 2022, inclusive. Patients were included if they had BM secondary to a primary cancer histology associated with a higher risk of ICH (melanoma, renal cell carcinoma, hepatocellular carcinoma, head and neck cancer, germ cell tumor, sarcoma, colorectal cancer) and had received RT to treat their BM.

Patient characteristics, symptoms at BM diagnosis, and comorbidities including hypertension, liver disease, kidney disease, history of stroke, excessive alcohol use, and the use of blood thinners were collected. Excessive alcohol use was defined as consumption of eight or more drinks per week for both sexes, extrapolating from the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly) major bleeding risk criteria [6]. Disease characteristics, including primary cancer histology and presence of pre-treatment ICH, were extracted. RT treatment parameters included RT modality (WBRT ± surgery, SRS ± surgery, and volumetric modulated arc therapy (VMAT) ± surgery), and equivalent dose in 2-Gy fractions (EQD2) using α/β ratio of 2 Gy. Focal RT was defined as SRS or partial VMAT RT. Since patients with BM can present with multiple lesions, lesion-specific data such as location, maximum size in centimeters, and dates of post-RT ICH were collected. In addition, symptoms and interventions associated with post-RT ICH were collected.

All analyses were conducted using R Statistical Software (v4.5.0; R Core Team 2025, R Foundation for Statistical Computing, Vienna, Austria). Descriptive analyses comparing baseline characteristics at the start of RT stratified by treatment technique were conducted using chi-square or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. The primary endpoint was post-RT ICH identified on CT or MRI reports. ICH events unrelated to RT, such as postoperative cavity hemorrhage, were not recorded. Radiologists interpreting the imaging were blinded to the RT technique. For patients who experienced the event, the time to post-RT ICH was calculated from the date of initial RT start to that of the first ICH event. In patients who did not experience post-RT ICH, follow-up time was calculated from the date of initial RT to the date of last follow-up for censored patients or the date of death for those who died before experiencing ICH. Similarly, time to death was calculated in months from the date of RT start to death or the date of last follow-up for censored patients. At the lesion level, time to post RT-ICH was calculated from the date of RT start to the date of ICH for lesions in which an ICH event occurred, or to the earliest of the last follow-up date or date of death for lesions without an ICH event.

The cumulative incidence curves of post-RT ICH stratified by primary cancer histology (colorectal cancer, melanoma, renal cell carcinoma, others) and by RT technique (focal RT ± surgery, WBRT ± surgery) over a two-year period with death before post-RT ICH as a competing event were calculated using the Aalen-Johansen approach. The overall survival (OS) was calculated with the Kaplan-Meier approach.

Univariable and multivariable Fine and Gray's regression models with deaths before post-RT ICH treated as competing events were used to investigate the relationship between post-RT ICH and baseline characteristics, including the RT technique used. Baseline characteristics were included in the multivariable model if the p-value in the univariable analyses was less than 0.1 or if the variable was deemed clinically relevant. For lesion-level analyses of post-RT ICH, mixed-effects Cox models with fixed effects for patient and lesion-level covariates and patient-level random effects to account for the nesting of lesions within patients were used. The Akaike Information Criterion (AIC) was used to assess whether variables added to the candidate model one at a time improved model fit without increasing the AIC values. Since there were no patients with missing data for the covariates of interest, the multivariable analyses included all patients included in this study.

Results

In total, 319 patients were identified in our study cohort (Table *1*). The median age of patients at the time of RT was 64 years (interquartile range (IQR), 55-73 years). Among the 136 patients who received focal RT ±

surgery, 83 (61%) received SRS, and 53 (39%) received partial VMAT. The median follow-up from RT was 4.3 months (IQR, 1.6-11). In this cohort, melanoma (133, 42%) was the most common primary cancer. Other primary cancers included colorectal cancer (81, 25%) and renal cancer (63, 20%), with the remainder (42,13%) consisting of head and neck cancers (21, 6.6%), sarcoma (17, 5.3%), hepatocellular carcinoma (2, 0.6%), and germ cell tumor (2, 0.6%). At the time of RT, 253 (79%) patients had neurologic symptoms, including nausea, weakness, numbness, vision issues, balance problems, confusion, personality change, or drowsiness. The most common pre-RT comorbidity was hypertension (134, 42%), followed by excessive alcohol consumption (38, 12%), kidney disease (22, 6.9%), and liver disease (12, 3.8%). Prior to RT, 25 (7.8%) patients had a history of stroke, and 75 (24%) were on blood-thinning medications such as antiplatelets and anticoagulants. Most patients (238, 75%) did not have ICH prior to RT.

Characteristic	Overall N (%)	Focal RT ± Surgery n (%)	WBRT ± Surgery n (%)	χ^2 values; p-value
Total	319 (100)	136 (43)	183 (57)	—
Sex	—	—	—	0.88; 0.35
Female	115 (36)	53 (39)	62 (34)	—
Male	204 (64)	83 (61)	121 (66)	—
ECOG at BM	—	—	—	3.90; 0.05
<2	277 (87)	124 (91)	153 (84)	—
2+	42 (13)	12 (8.8)	30 (16)	—
Smoker	—	—	—	0.98; 0.32
No	151 (47)	60 (44)	91 (50)	—
Yes	168 (53)	76 (56)	92 (50)	—
Histology	—	—	—	4.20; 0.24
Melanoma	133 (42)	51 (38)	82 (45)	—
Colorectal	81 (25)	32 (24)	49 (27)	—
Renal	63 (20)	33 (24)	30 (16)	—
Others	42 (13)	20 (15)	22 (12)	—
BM at diagnosis	—	—	—	4.90; 0.03
No	218 (68)	102 (75)	116 (63)	—
Yes	101 (32)	34 (25)	67 (37)	—
Neurologic symptoms	253 (79)	97 (71)	156 (85)	9.20; 0.002
Headache	113 (35)	42 (32)	71 (39)	2.10; 0.14
Seizure	50 (16)	21 (15)	29 (16)	0.01; 0.92
Dexamethasone	234 (73)	94 (69)	140 (77)	2.20; 0.14
Mass effect	119 (37)	48 (35)	71 (39)	0.41; 0.52
Hypertension	134 (42)	57 (42)	77 (42)	<0.01; 0.98
Liver disease	12 (3.8)	5 (3.7)	7 (3.8)	<0.01; 0.95
Kidney disease	22 (6.9)	12 (8.8)	10 (5.5)	1.40; 0.24
Stroke	25 (7.8)	7 (5.1)	18 (9.8)	2.40; 0.12
Alcohol use	38 (12)	11 (8.1)	27 (15)	3.30; 0.07
Blood thinners	75 (24)	30 (22)	45 (25)	0.28; 0.60
Pre-RT ICH	—	—	—	0.84; 0.36
No	238 (75)	105 (77)	133 (73)	—
Yes	81 (25)	31 (23)	50 (27)	—

Size of largest BM (Median (Q1 - Q3))	2.3 (1.5 - 3.3)	1.8 (1.1 - 2.9)	2.5 (1.7 - 3.7)	8860; < 0.001*
Age at RT treatment (Median (Q1 - Q3))	64 (55 - 73)	66 (53 - 74)	63 (57 - 72)	12587; 0.86*
BM single upfront	—	—	—	8.6; < 0.01
No	205 (64)	75 (55)	130 (71)	—
Yes	114 (36)	61 (45)	53 (29)	—
Post-RT ICH	—	—	—	14.2; <0.001
No (Censored)	24 (7.5)	16 (12)	8 (4.4)	—
Yes (Post-RT ICH event)	41 (13)	25 (18)	16 (8.7)	—
Death (Competing event)	254 (80)	95 (70)	159 (87)	—
Overall survival	—	—	—	4.86; 0.027
Alive (Censored)	33 (10)	20 (15)	13 (7.1)	—
Death	286 (90)	116 (85)	170 (93)	—

TABLE 1: Baseline characteristics by radiotherapy treatment technique.

*Wilcoxon rank-sum test statistic.

RT: radiotherapy; WBRT: whole-brain radiotherapy; BM: brain metastasis; ICH: intracranial hemorrhage; ECOG: Eastern Cooperative Oncology Group

Overall, post-RT ICH occurred in 41 (13%) patients, and the median time to ICH was 2.5 months (IQR, 0.8-7.7). Among the 136 patients who received focal RT ± surgery, 25 (18%) experienced post-RT ICH, and the median time to ICH was 4.4 months (IQR, 1.9-12). In contrast, among the 183 patients who received WBRT ± surgery, 16 (8.7%) developed post-RT ICH, and the median time to ICH was 1.6 months (IQR, 0.6-5.2). The cumulative incidence of post-RT ICH at six and 12 months was 9.5% (95% confidence interval (CI), 6.6-13) and 10% (95% CI, 7.4-14), respectively. Melanoma was associated with the highest cumulative incidence of post-RT ICH (p = 0.01) (Figure *1*). The one-year cumulative incidence of post-RT ICH was 15% for melanoma, 13% for renal cancer, 3% for colorectal cancer, and 7% for others. When stratified by the type of RT technique, focal RT ± surgery (17%) was associated with a higher risk (p = 0.007) compared with WBRT ± surgery (8%) (Figure *2*). At both the patient (Figure *3*) and lesion levels (Figure *4*), hemorrhagic events were most frequent in the four weeks preceding RT.

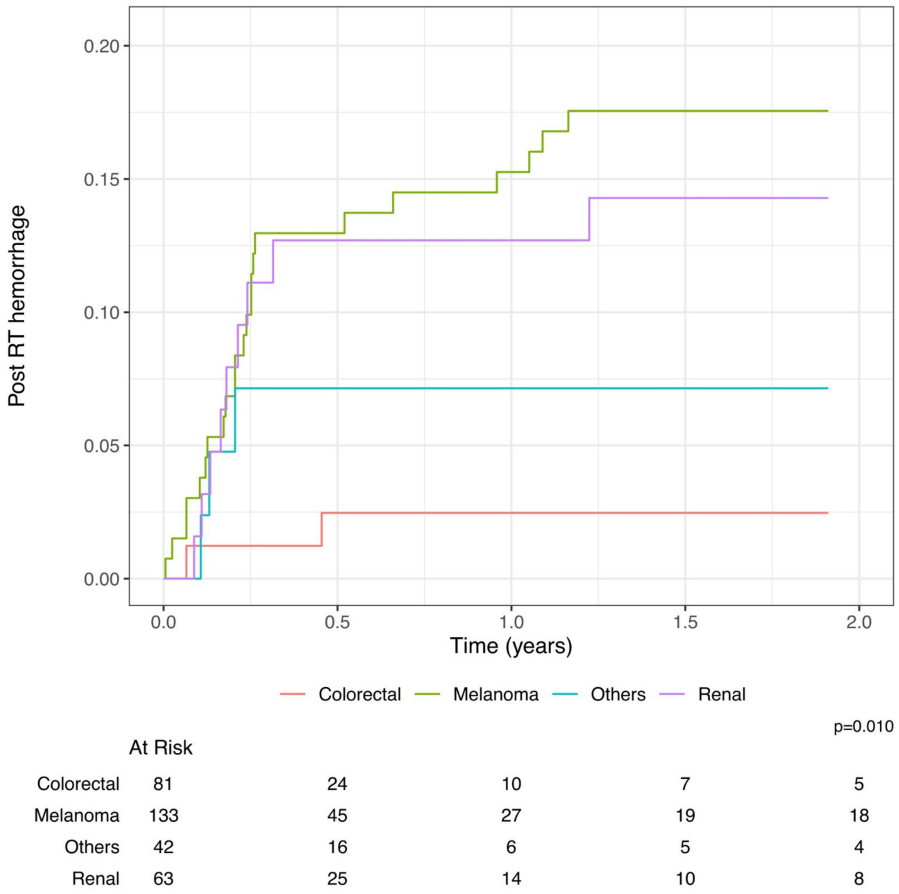


FIGURE 1: Cumulative incidence of post-RT hemorrhage over a two-year period, stratified by primary cancer histology.

RT: radiotherapy

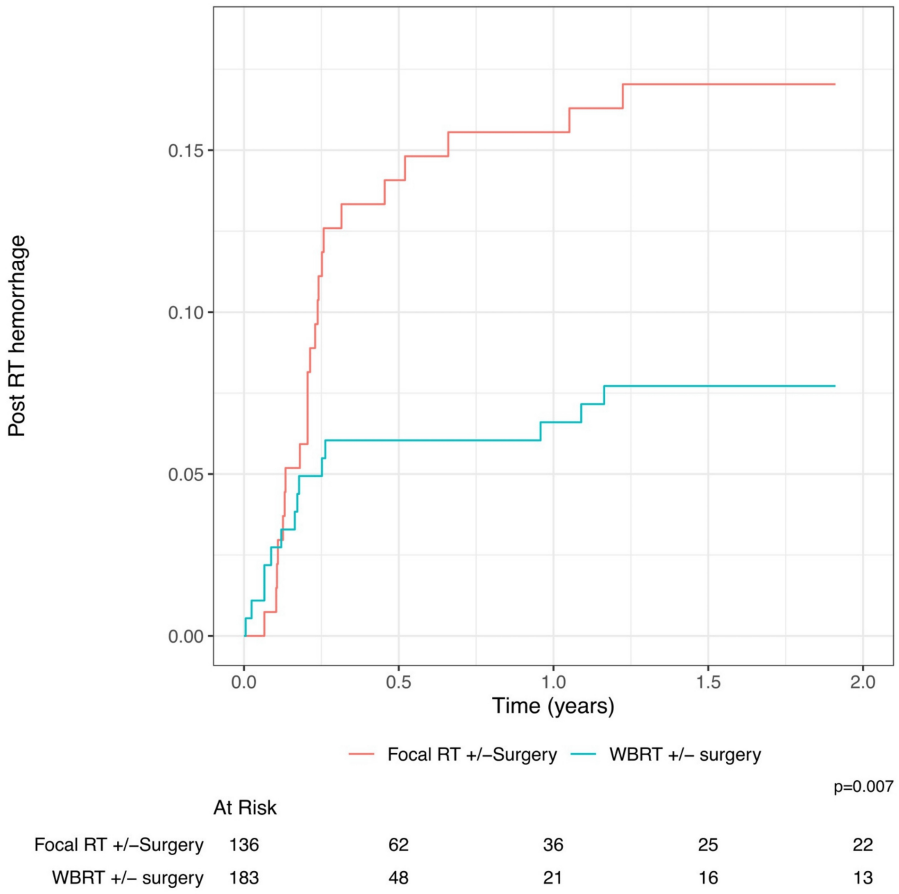


FIGURE 2: Cumulative incidence of post-RT hemorrhage over a two-year period, stratified by the type of RT treatment received.

RT: radiotherapy; WBRT: whole-brain radiotherapy

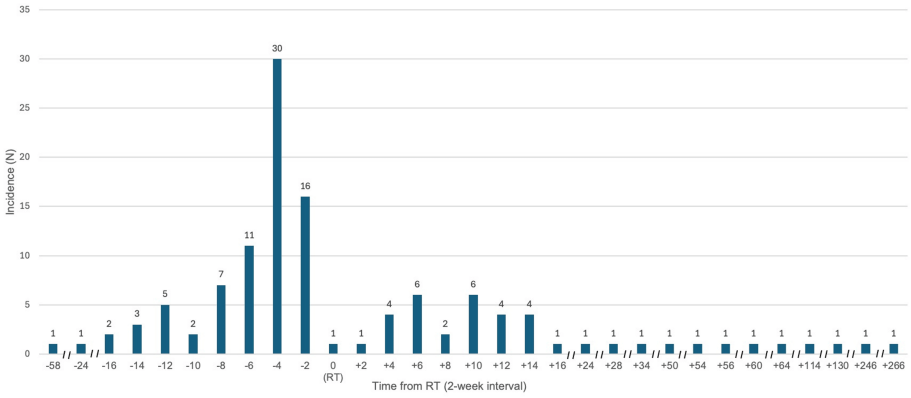


FIGURE 3: Timing of ICH relative to RT at the patient level.

Distribution of hemorrhagic events according to time from RT, shown in two-week intervals. Negative values indicate ICH before RT, and positive values indicate ICH after RT. The y-axis represents the incidence (N) of hemorrhagic events. The x-axis is not to scale; // indicates omitted intervals with no events.

ICH: intracranial hemorrhage; RT: radiotherapy

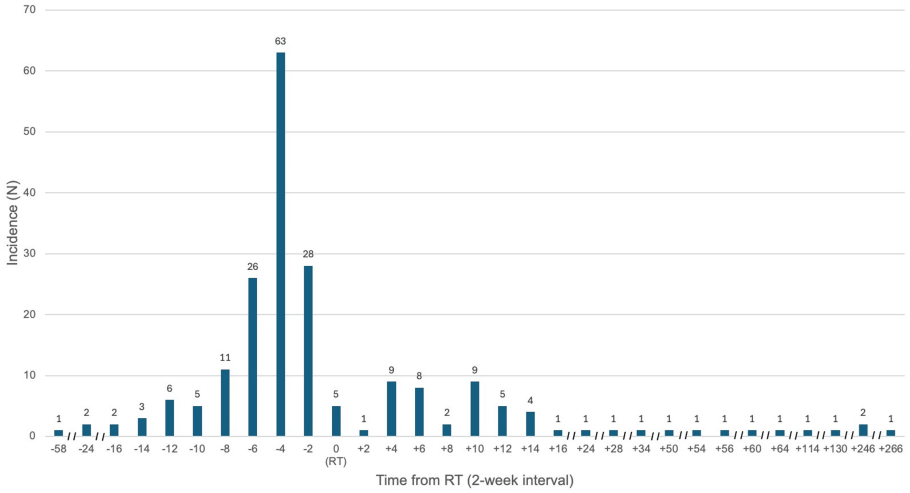


FIGURE 4: Timing of ICH relative to RT at the lesion level.

Distribution of hemorrhagic events according to time from RT, shown in two-week intervals. Negative values indicate ICH before RT, and positive values indicate ICH after RT. The y-axis represents the incidence (N) of hemorrhagic events. The x-axis is not to scale; // indicates omitted intervals with no events.

ICH: intracranial hemorrhage; RT: radiotherapy

The analysis of variables associated with post-RT ICH for patients is summarized in Table 2. On univariable analysis, a higher Eastern Cooperative Oncology Group (ECOG) score was associated with a lower risk of post-RT ICH (hazard ratio (HR), 0.65 (95% CI, 0.46-0.92), p = 0.01). On multivariable Fine and Gray's regression, there was a lower risk of post-RT ICH in patients with primary colorectal cancer compared with melanoma (HR, 0.1 (95% CI, 0.03-0.5), p = 0.01), while the other histologies showed no significant differences in post-RT ICH rates. Patients diagnosed at an older age were less likely to experience post-RT ICH (HR, 0.98 (95% CI, 0.96-1.0), p = 0.01). Patients with a history of stroke prior to RT had a higher risk of post-RT ICH (HR, 2.6 (95% CI, 0.97-7.2), p = 0.05). There were significant differences in post-RT ICH risk between RT modalities in the multivariable analysis (p = 0.003). Compared with focal RT ± surgery, patients who received WBRT ± surgery had a lower risk of post-RT ICH (HR, 0.4 (95% CI, 0.2-0.7), p = 0.003). No significant associations were observed for the remaining variables examined in this analysis, including use of blood thinners (p = 0.77), hypertension (p = 0.91), kidney disease (p = 0.42), and liver disease (p = 0.70).

	Univariable analysis			Multivariable analysis		
Characteristic	HR	95% CI	Z/ χ^2 values; p-value	HR	95% CI	Z/ χ^2 values; p-value
Sex	—	—	0.42; 0.52	—	—	—
Female	—	—	—	—	—	—
Male	1.2	0.65, 2.4	0.65; 0.52	—	—	—
ECOG at BM (cont.)	0.65	0.46, 0.92	-2.46; 0.01	0.70	0.50, 1.0	-1.97; 0.05
Smoker	—	—	2.06; 0.15	—	—	—
No	—	—	—	—	—	—
Yes	0.64	0.35, 1.2	-1.44; 0.15	—	—	—
Histology	—	—	9.31; 0.03	—	—	9.3; 0.03
Melanoma	—	—	—	—	—	—
Colorectal	0.12	0.03, 0.52	-2.84; < 0.01	0.12	0.03, 0.5	-2.79; < 0.01
Renal	0.94	0.47, 1.9	-0.91; 0.85	0.83	0.39, 1.7	-0.5; 0.62
Others	0.50	0.18, 1.4	-1.29; 0.20	0.42	0.15, 1.2	-1.62; 0.11
BM at diagnosis	—	—	0.12; 0.73	—	—	—

No	—	—	—	—	—	—
Yes	1.1	0.60, 2.1	0.35; 0.73	—	—	—
Neurologic symptoms	—	—	0.07; 0.80	—	—	—
No	—	—	—	—	—	—
Yes	0.91	0.44, 1.9	-0.26; 0.80	—	—	—
Headache	—	—	0.85; 0.36	—	—	—
No	—	—	—	—	—	—
Yes	1.3	0.72, 2.4	0.92; 0.36	—	—	—
Seizure	—	—	2.59; 0.11	—	—	2.9; 0.09
No	—	—	—	—	—	—
Yes	1.8	0.89, 3.4	1.61; 0.11	1.8	0.91, 3.6	1.7; 0.09
Dexamethasone	—	—	<0.01; 0.97	—	—	—
No	—	—	—	—	—	—
Yes	0.99	0.50, 1.9	-0.04; 0.97	—	—	—
Mass effect	—	—	0.27; 0.61	—	—	—
No	—	—	—	—	—	—
Yes	1.2	0.64, 2.1	0.52; 0.61	—	—	—
Hypertension	—	—	0.01; 0.91	—	—	—
No	—	—	—	—	—	—
Yes	0.96	0.53, 1.8	-0.12; 0.91	—	—	—
Liver disease	—	—	0.15; 0.70	—	—	—
No	—	—	—	—	—	—
Yes	1.3	0.34, 5.1	0.39; 0.70	—	—	—
Kidney disease	—	—	0.64; 0.42	—	—	—
No	—	—	—	—	—	—
Yes	1.5	0.56, 4.0	0.80; 0.42	—	—	—
Prior stroke	—	—	1.40; 0.24	—	—	3.61; 0.05
No	—	—	—	—	—	—
Yes	1.7	0.70, 4.3	1.18; 0.24	2.6	0.97, 7.2	1.9; 0.05
Alcohol use	—	—	0.22; 0.64	—	—	—
No	—	—	—	—	—	—
Yes	0.79	0.29, 2.2	-0.47; 0.64	—	—	—
Blood thinners	—	—	0.08; 0.77	—	—	—
No	—	—	—	—	—	—
Yes	0.90	0.44, 1.8	-0.29; 0.77	—	—	—
Pre-treatment ICH	—	—	2.92; 0.09	—	—	0.53; 0.47
No	—	—	—	—	—	—
Yes	1.7	0.93, 3.1	1.71; 0.09	1.3	0.68, 2.3	0.73; 0.47
Size of BM (Max)	1.0	0.84, 1.2	0.19; 0.85	—	—	—
Age at RT treatment (cont.)	0.98	0.96, 1.0	-1.74; 0.08	0.98	0.96, 1.0	-2.15; 0.03

RT technique	—	—	11.98; 0.04	—	—	—
SRS	—	—	—	—	—	—
VMAT	0.54	0.22, 1.3	1.35; 0.18	—	—	—
WBRT	0.28	0.13, 0.61	-3.21; 0.001	—	—	—
SRS + surgery	0.63	0.20, 2.0	-0.79; 0.43	—	—	—
VMAT + surgery	0.89	0.13, 6.1	-0.11; 0.91	—	—	—
WBRT + surgery	1.2	0.41, 3.2	0.26; 0.80	—	—	—
RT technique combined	—	—	6.39; 0.01	—	—	8.72; < 0.01
Focal RT ± surgery	—	—	—	—	—	—
WBRT ± surgery	0.45	0.25, 0.84	-2.53; 0.01	0.39	0.21, 0.73	-2.95; < 0.01

TABLE 2: Fine and Gray univariate and multivariable model results for post-radiotherapy intracranial hemorrhage.

CI: confidence interval; HR: hazard ratio; RT: radiotherapy; SRS: stereotactic radiosurgery; VMAT: volumetric modulated arc therapy; WBRT: whole-brain radiotherapy; ICH: intracranial hemorrhage; BM: brain metastasis

We identified 943 BM lesions in our study cohort (Table *3*). The most common lesion locations were the frontal lobe (309, 33%), parietal lobe (149, 16%), and the cerebellum (122, 13%). At the time of RT, the median size of the brain lesions was 1.2 cm (IQR, 0.6-2.1 cm). Prior to RT, 147 (16%) lesions already had ICH. During the study period, most lesions (568, 60%) were treated with WBRT ± surgery. The median EQD2 was 30 Gy (IQR, 30-60 Gy). Overall, 56 (6%) lesions developed post-RT ICH. On univariable mixed-effects Cox regression, there was a higher risk of post-RT ICH (HR, 2.8 (95% CI, 1.2-6.8), p = 0.02) in lesions with ICH prior to RT (Table *4*). However, this association was not significant on multivariable analysis (p = 0.12). No other variables, such as primary cancer histology or lesion location, showed statistically significant associations.

Characteristic	Overall N (%)	WBRT ± Surgery n (%)	Focal RT ± Surgery n (%)
Total	943 (100)	568 (60)	375 (40)
Location	—	—	—
Frontal	309 (33)	175 (31)	134 (36)
Parietal	149 (16)	81 (14)	68 (18)
Cerebellar	122 (13)	69 (12)	53 (14)
Temporal	96 (10)	53 (9.3)	43 (11)
Occipital	95 (10)	43 (7.6)	52 (14)
Deep Cerebral Structures	64 (6.8)	43 (7.6)	21 (5.6)
Brainstem	26 (2.8)	22 (3.9)	4 (1.1)
Undocumented	82 (8.7)	82 (14)	0 (0)
Size of BM (cm) (Median (Q1 - Q3))	1.2 (0.60 - 2.1)	1.3 (0.60 - 2.2)	1.1 (0.60 - 1.9)
Post-RT ICH	—	—	—
No (Censored)	886 (94)	543 (96)	343 (91)
Yes (Post-RT ICH event)	57 (6.0)	25 (4.4)	32 (8.5)
Follow-up duration (months) (Median (Q1 - Q3))	3 (2 - 8)	2 (1 - 4)	7 (3 - 17)
Pre-RT ICH	—	—	—
No	796 (84)	480 (85)	316 (84)
Yes	147 (16)	88 (15)	59 (16)
RT received	—	—	—
WBRT	547 (58)	547 (96)	0 (0)
SRS	232 (25)	0 (0)	232 (62)
VMAT	111 (12)	0 (0)	111 (30)
WBRT + surgery	21 (2.2)	21 (3.7)	0 (0)
SRS + surgery	25 (2.7)	0 (0)	25 (6.7)
VMAT + surgery	7 (0.7)	0 (0)	7 (1.9)
Radiation dose (Gy) (Median (Q1 - Q3))	20 (20 - 30)	20 (20 - 20)	25 (20 - 35)
Fractionation (Median (Q1 - Q3))	5 (5 - 5)	5 (5 - 5)	5 (1 - 5)
EQD2 (Median (Q1 - Q3))	30 (30 - 60)	30 (30 - 30)	79 (44 - 100)

TABLE 3: Lesion characteristics by radiotherapy treatments received in all patients.

RT: radiotherapy; WBRT: whole-brain radiotherapy; BM: brain metastasis; ICH: intracranial hemorrhage; WBRT: whole-brain radiotherapy; SRS: stereotactic radiosurgery; VMAT: volumetric modulated arc therapy; EQD2: equivalent dose in 2 Gy fractions

	Univariable analysis			Multivariable analysis		
Characteristic	HR	95% CI	Z values; p-value	HR	95% CI	Z values; p-value
Pre-treatment ICH	—	—	—	—	—	—
No	—	—	—	—	—	—
Yes	2.8	1.2, 6.8	2.32; 0.02	2.3	0.80, 6.5	1.54; 0.12
Histology	—	—	—	—	—	—
Melanoma	—	—	—	—	—	—
Colorectal	0.19	0.03, 1.4	-1.64; 0.10	0.21	0.04, 1.2	-1.76; 0.08
Renal	0.91	0.23, 3.7	-0.13; 0.90	0.79	0.23, 2.7	-0.37; 0.72
Others	0.34	0.04, 2.6	-1.04; 0.30	0.35	0.06, 2.1	-1.15; 0.25
Location	—	—	—	—	—	—
Frontal	—	—	—	—	—	—
Parietal	1.0	0.42, 2.5	0.05; 0.96	—	—	—
Occipital	0.64	0.20, 2.0	-0.77; 0.44	—	—	—
Temporal	0.57	0.21, 1.6	-1.08; 0.28	—	—	—
Cerebellar	0.78	0.22, 2.7	-0.39; 0.70	—	—	—
Brainstem	0.40	0.05, 3.1	-0.88; 0.38	—	—	—
Deep Cerebral Structures	1.5	0.38, 6.1	0.60; 0.55	—	—	—
Size of BM (cm)	1.2	0.91, 1.5	1.26; 0.21	1.1	0.84, 1.5	0.77; 0.44
RT received	—	—	—	—	—	—
WBRT ± Surgery	—	—	—	—	—	—
Focal RT ± Surgery	0.94	0.39, 2.3	-0.14; 0.89	0.99	0.37, 2.7	-0.02; 0.99
EQD2	1.0	0.99, 1.0	-0.52; 0.60	—	—	—

TABLE 4: Univariable and multivariable fixed effects cox model results for post-radiotherapy intracranial hemorrhage in all lesions.

CI: confidence interval; HR: hazard ratio; RT: radiotherapy; WBRT: whole-brain radiotherapy; ICH: intracranial hemorrhage; BM: brain metastasis; EQD2: equivalent dose in 2 Gy fractions

Of the 41 patients who developed post-RT ICH, 21 (51%) were monitored without any intervention, whereas 20 (49%) received dexamethasone. Twenty-six (26/41, 63%) patients experienced symptoms, with the most common symptoms being headache (10/26, 39%), weakness (10/26, 39%), and confusion (7/26, 27%). Eleven of these patients (11/26, 42%) had their symptoms resolved at last follow-up, with a median time of one month from symptom onset to resolution.

Overall, 286 (90%) patients died. For patients treated with focal RT ± surgery or WBRT ± surgery, the median OS was 7.3 (95% CI, 5.3-9.8) and 2.9 months (95% CI, 2.2-3.6), respectively. The median OS for the cohort was 4.4 months (95% CI, 3.6-5.2), and the two-year OS rate was 14% (95% CI, 10%-18%).

Discussion

This is the first population-based study to characterize the incidence, symptoms, and risk factors for post-RT ICH in patients with hemorrhage-prone BM. The development of post-RT ICH differed significantly by primary cancer histology, ranging from 3% in colorectal cancers to 18% in melanoma. This difference is consistent with the current literature and may be explained by the high angiogenic and proliferative activity of melanoma, resulting in a higher risk of bleeding [2,7,8]. These findings highlight melanoma as an important risk factor for post-RT ICH. The median time from RT to ICH was 2.5 months, highlighting the

importance of early and vigilant clinical monitoring.

Patients who received focal RT, including SRS, had a higher risk of post-RT ICH than those who received WBRT. However, at the lesion level, neither the RT technique nor EQD2 was associated with an increased risk of ICH (Table *4*). Despite attempts to account for demographic and disease characteristics, including the patients' ECOG score in the multivariable analysis, it is possible that patients who received WBRT may not have lived long enough to develop post-RT ICH compared to patients who received focal RT, as patients who received WBRT had shorter life expectancies in our cohort. The relationship between SRS and post-RT ICH is debated in the literature [9-11], and there is an ongoing phase II trial investigating the safety and efficacy of fractionated stereotactic radiotherapy for hemorrhagic BM.

RT was not clearly associated with an increased risk of ICH at the patient level, where the rates of ICH before and after RT were 25% and 10%, respectively, and at the lesion level, where the corresponding rates were 16% and 6%, respectively. The temporal distribution of ICH relative to RT (Figures *3*, *4*) further suggests that RT may not substantially influence ICH risk. At both the patient and lesion levels, ICH events clustered in the weeks leading up to the date of RT, peaking approximately four weeks before RT, while post-RT events were less frequent and more dispersed. However, this should be interpreted cautiously, as only patients who received RT were included, which introduces selection bias. Pre-RT ICH may be overrepresented because a bleed often prompts imaging and treatment, whereas post-RT events are subject to limited follow-up and competing risk of death, particularly in the WBRT cohort. Therefore, the difference in bleeding rates between the two periods should be interpreted with caution, as they reflect different observation processes, and these findings cannot exclude a modest effect of RT on ICH risk.

Among the patients who developed post-RT ICH, almost half were treated with dexamethasone, suggesting a substantial proportion of these patients required medical management for associated symptoms or cerebral edema. Consistent with previous literature [11,12], ICH was clinically significant in a substantial proportion of patients, with headache, weakness, and confusion among the most common symptoms, indicating that post-RT ICH can manifest with a range of neurologic symptoms that may impact patients' quality of life and functional status. Importantly, symptom resolution was not universal. Literature suggests that hemorrhagic lesions may be less likely to respond to radiation, potentially compromising local control and worsening prognosis; this outcome was not assessed in our study but is worth further investigation [13]. Thus, post-RT ICH may lead to prolonged or persistent neurologic morbidity in a notable subset of patients, highlighting its clinical significance beyond a purely radiographic finding.

HAS-BLED is a validated scoring system used clinically to estimate bleeding risk in patients with atrial fibrillation [14-17]. Since no validated bleeding risk scores exist for localized intracranial pathology, we used factors from HAS-BLED to evaluate the risk of post-RT ICH. Many of the factors were not significantly associated with ICH risk in our cohort (Table *2*). This may reflect the distinct mechanisms underlying ICH in patients with BM. For instance, degenerative changes to the penetrating arterioles in the brain can result in fragile aneurysms in the deep cerebral structures that are prone to rupture and subsequent bleeding [18]. Furthermore, the local inflammatory environment of BMs may disrupt the vascular integrity, a phenomenon that may not be captured by established scoring systems. These findings suggest that generalized bleeding scores may be insufficient for this population, highlighting the need for risk models specific for localized intracranial pathology.

Antiplatelets and anticoagulants are frequently used for the prevention of conditions such as venous thromboembolism, which is common among patients with BM [12,19]. Given that bleeding is a common adverse effect of blood thinners, it is plausible that they may increase the risk of ICH following focal RT. As such, this relationship is commonly examined in the literature, but the findings are often mixed [1,8]. For instance, Zoga et al. [8] found that the use of anticoagulants significantly increased the risk of bleeding. In contrast, both Ehret et al. [1] and Donato et al. [12] reported no correlation, even in patients with primary cancers such as melanoma and renal cell carcinoma that carry a high risk of bleeds. In our study, the use of blood thinners was not associated with an increased risk of post-RT ICH, contributing to the ongoing debate in the literature.

Multivariable analysis indicated that a history of stroke was associated with an approximately three-fold increase in the risk of post-RT ICH (Table *2*). This could be explained by underlying vascular pathology as a common risk factor for cerebrovascular disease, increasing patients' susceptibility to subsequent RT-associated vascular damage. Pollock et al. [20] noted that aneurysms, more commonly seen in patients with a history of stroke, were associated with a significantly higher risk of post-RT ICH. This suggests that a history of stroke may be an important clinical factor to consider when evaluating ICH risk in patients receiving RT for BM. However, this result should be interpreted with caution, as the relationship between history of stroke and post-RT ICH was of borderline significance.

Several limitations of this study should be acknowledged. Given the retrospective nature of our study, causality cannot be established. Furthermore, only selected primary cancer histologies associated with a higher risk of ICH were included. Therefore, the findings may not be generalizable to the broader population of patients with BM treated during the same period. ICH is a complex phenomenon with a multifactorial

etiology; our study may not have fully captured all of the underlying patient and disease characteristics that contribute to bleeding risk. Moreover, many patients in this cohort had a shorter survival time following RT. As death served as a competing risk in these patients, the estimated associations between baseline factors and post-RT ICH may differ in populations with longer survival. Additional limitations include the potential for incomplete ascertainment of post-RT ICH events and a limited number of events relative to the number of candidate predictors, which yielded wide confidence intervals for certain estimates and warrants cautious interpretation of the multivariable findings. Future studies should account for systemic therapies, which are commonly used as part of the treatment for BM and may contribute to the risk of post-RT ICH [21,22].

Conclusions

This population-based study demonstrates that the risk of post-RT BM ICH may be elevated in select histologies, particularly melanoma. At patient level, association between focal RT and higher risk ICH compared to WBRT was noted. However, this association was not observed at the lesional level, suggesting presence of confounders including differences in life expectancy. Post-RT ICH was also found to be associated with prior stroke history, although this relationship was of borderline significance and should be interpreted cautiously. Conversely, blood thinner use was not significantly associated with post-RT ICH risk. These findings highlight potential clinical factors associated with the risk of post-RT ICH and underscore the importance of careful monitoring in high-risk patients following RT, particularly in the first three months.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: William Lee, Katherine Feng, Michael Zhang, Justin Oh

Acquisition, analysis, or interpretation of data: William Lee, Richard Musoke, Justin Oh

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