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Scientific Article

Clinical Factors Associated With 30-Day Mortality Among Patients Undergoing Radiation Therapy for Brain Metastases

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Abstract

Purpose: Existing brain metastasis prognostic models do not identify patients at risk of very poor survival after radiation therapy (RT). Identifying patient and disease risk factors for 30-day mortality (30-DM) after RT may help identify patients who would not benefit from RT.

Methods and Materials: All patients who received stereotactic radiosurgery (SRS) or whole-brain RT (WBRT) for brain metastases from January 1, 2017, to September 30, 2020, at a single tertiary care center were included. Variables regarding demographics, systemic and intracranial disease characteristics, symptoms, RT, palliative care, and death were recorded. Thirty-day mortality was defined as death within 30 days of RT completion. The Kaplan-Meier method was used to estimate median overall survival. Univariate and multivariable logistic regression models were used to assess associations between demographic, tumor, and treatment factors and 30-DM.

Results: A total of 636 patients with brain metastases were treated with either WBRT (n = 117) or SRS (n = 519). The most common primary disease types were non-small cell lung (46.7%) and breast (19.8%) cancer. Median survival time was 6 months (95% CI, 5-7 months). Of the 636 patients, 75 (11.7%) died within 30 days of RT. On multivariable analysis, progressive intrathoracic disease (hazard ratio [HR], 4.67; 95% CI, 2.06-10.60; $P = .002$), progressive liver and/or adrenal metastases (HR, 2.20; 95% CI, 1.16-3.68; $P = .02$), and inpatient status (HR, 4.51; 95% CI, 1.78-11.42; $P = .002$) were associated with dying within 30 days of RT. A higher Karnofsky Performance Status (KPS) score (HR, 0.95; 95% CI, 0.93-0.97; $P < .001$), synchronous brain metastases at time of initial diagnosis (HR, 0.45; 95% CI, 0.21-0.96; $P = .04$), and outpatient palliative care utilization (HR, 0.45; 95% CI, 0.20-1.00; $P = .05$) were associated with surviving more than 30 days after RT.

Conclusions: Multiple factors including a lower KPS, progressive intrathoracic disease, progressive liver and/or adrenal metastases, and inpatient status were associated with 30-DM after RT. A higher KPS, brain metastases at initial diagnosis, and outpatient palliative care utilization were associated with survival beyond 30 days. These data may aid in identifying which patients may benefit from brain metastasis–directed RT.

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Introduction

Radiation therapy (RT) for brain metastases is commonly used to increase intracranial disease control and palliate neurologic symptoms. However, brain RT administered at the end of life (EOL) may have limited clinical utility in patients with poor prognosis, and it can contribute to adverse effects and negatively affect quality of life.[1] In other fields of oncology, the receipt of aggressive therapy such as chemotherapy at the EOL (ie, within 14 days of death) is established as an indicator of lower quality care.[2] Within radiation oncology, there are no such consensus quality utilization metrics guiding the use of RT at EOL. Consensus guidelines have proposed that 30-day mortality (30-DM) after radiation may be an indicator to judge the appropriate use of palliative RT,[3-5] but this benchmark has not been explored among patients receiving RT for brain metastases.

Accurate prognostication for patients with brain metastases is necessary to appropriately select patients who may benefit from brain RT. However, no existing brain metastasis prognostic models have identified patient or disease factors that portend very poor survival limited to 30 days.[6,7]

We conducted a large, modern, retrospective analysis at an academic medical center specializing in the care of patients with brain metastases to characterize the incidence of 30-DM after brain RT. Patient and disease characteristics (such as performance status, systemic disease, inpatient status, and intracranial disease features) associated with 30-DM were identified in this patient population.

Methods and Materials

Patient selection

This study was reviewed and approved by the Duke University Institutional Review Board (IRB #Pro00106711). All patients who received stereotactic radiosurgery (SRS) or whole-brain radiation therapy (WBRT) for brain metastases from January 1, 2017, to September 30, 2020, were identified through the radiation oncology departmental database and verified through the Duke Cancer Institute database. For the purposes of this study, SRS included both single-fraction treatments and up to 5 fractions of hypofractionated stereotactic RT. Patients were excluded if they received prophylactic cranial irradiation, had a diagnosis of lymphoma or acute lymphoblastic leukemia, or had less than 30 days of follow-up.

Data collection

Variables regarding patient demographics, disease, radiographic brain metastasis characteristics, symptoms at the time of RT consultation, radiation therapy details, and death were retrospectively recorded using the institutional Epic medical record (Epic Systems, Verona, WI) and radiation therapy planning software (ARIA, Varian Medical Systems, Palo Alto, CA). Study data were collected and stored in REDCap.[8,9]

Statistical analysis

Thirty-day mortality was defined as death within 30 days of the RT end date. All patients in the study were followed a minimum of 30 days from the end of RT.

Univariate and multivariable logistic regression models were used to assess associations between demographic, tumor, and treatment factors and 30-DM. Potential predictors included age, sex, race, lung as the primary site, presence of brain metastases at initial diagnosis, size of largest brain metastasis, number of brain metastases present, presence of hemorrhagic component, presence of leptomeningeal disease, presence of midline shift, presence of intrathoracic disease, presence of liver or adrenal metastases, presence of spinal metastases, ongoing use of systemic therapy, Karnofsky Performance Status (KPS) score, seizures, altered mentation, cranial neuropathy, motor or sensory deficit, headache, place where RT was received, palliative care utilization, steroid use, hospice use, and RT technique (WBRT or SRS).

Pretreatment patient and disease characteristics that are clinically relevant were included in the multivariable model. Logistic regression models were conducted among all patients, and secondary analyses were conducted among patients with lung and nonlung primary disease sites. The Kaplan-Meier method was used to estimate median overall survival. Cox regression was used to estimate hazard ratios and associated confidence interval estimates for overall survival. Identification of a patient subset at high risk for 30-DM was explored using recursive partitioning with cross validation (rpart and caret packages in R).[10,11] All tests were 2-tailed, and a P value of $<.05$ was considered statistically significant. All statistical analyses were performed using SAS, version 9.4 (Cary, NC).

Results

Patient, disease, and treatment characteristics

A total of 636 patients were treated with either WBRT (n = 117) or SRS (n = 519) for brain metastases in the study period. The median age of the patients was 61 years, and 56.0% were female. The most common primary types of disease were non-small cell lung (46.7%) and breast (19.8%) cancer. The median survival time for all patients

was 6 months (95% CI, 5-7 months); 75 patients (11.7%) died within 30 days of radiation treatment. Patient, treatment, and disease characteristics, overall and by those who did and did not die within 30 days of RT, are listed in Table 1. Patients who died within 30 days had worse KPS scores (median score, 50 vs 80). A higher proportion of those who died within 30 days of RT had innumerable brain metastases (45.3% vs 10.7%) and had ongoing systemic therapy at RT consultation (52.0% vs 23.5%).

Regarding disease characteristics, a higher proportion of those who died within 30 days had leptomeningeal disease (16.0% vs 5.0%), progressive intrathoracic disease (86.7% vs 49.7%), progressive liver and/or adrenal metastases (60% vs 24.2%), and progressive spinal metastases (57.3% vs 18.7%). Other characteristics of those who died within 30 days were seizure symptoms (12.0% vs 4.1%), cranial neuropathies (32.0% vs 8.7%), motor and/or sensory deficits (50.7% vs 28.9%), altered mentation (60.0% vs 26.2%), and headaches (48.0% vs 29.6%). Steroid use at radiation oncology consultation was more common in this group as well (68.0% vs 48.3%).

Regarding treatment, a higher proportion of those who died within 30 days were treated with WBRT versus SRS (46.7% vs 14.6%), were treated as inpatients (38.7% vs 3.4%), and did not complete their radiation (24.0% vs 1.2%).

Factors associated with overall survival

Among the entire cohort of 636 patients, higher KPS scores (hazard ratio [HR], 0.98; 95% CI, 0.97-0.98; $P < .001$) and synchronous brain metastases detected at time of initial diagnosis of the primary cancer (HR, 0.72; 95% CI, 0.57-0.91; $P = .006$) were associated with increased overall survival (Table E1). On multivariable analysis across all patients, older age (HR, 1.01; 95% CI, 1.00-1.02; $P = .008$), a greater number of brain metastases ($P = .02$), progressive intrathoracic disease (HR, 1.38; 95% CI, 1.11-1.71; $P = .004$), progressive liver and/or adrenal metastases (HR, 1.46; 95% CI, 1.17-1.82; $P = .001$), and inpatient status (HR, 1.77; 95% CI, 1.19-2.61; $P = .004$) were all associated with decreased overall survival. Lung versus nonlung as the primary disease site, presence of leptomeningeal disease, neurologic symptoms, and use of outpatient palliative care were not associated with overall survival.

Factors associated with death within 30 days of RT

Results of univariate analyses testing factors for associations with 30-DM are presented in Table 2. Multivariable analyses of factors associated with 30-DM are presented in Table 3, and of factors associated with overall survival, in Table E1. On multivariable analysis, progressive intrathoracic disease (odds ratio [OR], 4.67; 95% CI, 2.06-10.60; $P = .002$), progressive liver and/or adrenal metastases (OR, 2.20; 95% CI, 1.16-3.68; $P = .02$), and inpatient status (OR, 4.51; 95% CI, 1.78-11.42; $P = .002$) were all associated with dying within 30 days of radiation. Conversely, a higher KPS score (OR, 0.95; 95% CI, 0.93-0.97; $P < .001$), synchronous brain metastases detected at the time of initial diagnosis of the primary cancer (OR, 0.45; 95% CI, 0.21-0.96; $P = .04$), and outpatient palliative care utilization (OR, 0.45; 95% CI, 0.20-1.00; $P = .05$) were associated with survival past 30 days of RT. Age, lung versus nonlung primary disease site, number of metastases, presence of leptomeningeal disease, and presence of neurologic symptoms were not associated with death within 30 days (Table 3).

Thirty-day mortality after RT was further analyzed within subsets of patients with lung and nonlung histology (Table 3). For those with nonlung primary sites, synchronous brain metastases detected at the time of initial diagnosis of the primary cancer were not associated with favorable survival beyond 30 days. Additionally, progressive liver and/or adrenal metastases and inpatient status were not associated with 30-DM among those with nonlung histologies. For patients with the lung as the primary site, age, number of brain metastases, leptomeningeal disease, and presence of neurologic symptoms were not significantly associated with 30-DM.

Palliative care utilization and EOL care

Among all patients receiving RT for brain metastases, 446 had died at the time of this retrospective analysis. Characteristics regarding palliative care utilization and EOL care in these patients are presented in Table 4. A total of 122 of 446 patients (27%) had used outpatient palliative care at the time of death. A higher proportion of those who used outpatient palliative care had a hospice referral (81.1% vs 50.0%; $P < .001$). Those who used outpatient palliative care had a lower proportion of hospital or emergency room deaths (6.6% vs 15.1%) and a higher proportion of home hospice deaths (65.6% vs 39.8%). No clinically meaningful patient classification for high risk of 30-DM was found by recursive partitioning in this data set.

Discussion

In this analysis of 636 patients with brain metastases treated with SRS or WBRT, 11.7% died within 30 days of their radiation treatment. Factors associated with 30-DM included poor performance status by KPS score, progressive intrathoracic or liver and/or adrenal metastases, number of brain metastases, inpatient status, and

Table 1 Patient, disease, and treatment characteristics

	Death within 30 d (n = 75)	Alive beyond 30 d (n = 561)	Total (N = 636)
Age, y*	62 (27-81)	61 (11-89)	61 (11-89)
Sex			
Female	42 (56.0%)	314 (56.0%)	356 (56.0%)
Male	33 (44.0%)	246 (43.9%)	279 (43.9%)
Other	0 (0.0%)	1 (0.2%)	1 (0.2%)
Brain metastases at initial diagnosis			
Yes	28 (37.3%)	216 (38.5%)	244 (38.4%)
No	47 (62.7%)	345 (61.5%)	392 (61.6%)
Karnofsky Performance Status*	50 (20-100)	80 (20-100)	80 (20-100)
Brain metastases, no.			
1-5	36 (48.0%)	413 (73.6%)	449 (70.6%)
6-10	1 (1.3%)	59 (10.5%)	60 (9.4%)
11-40	4 (5.3%)	29 (5.2%)	33 (5.2%)
Innumerable	34 (45.3%)	60 (10.7%)	94 (14.8%)
Size of largest brain metastasis, cm*	1.3 (0.2-6.5)	1.5 (0.1-6.3)	1.5 (0.1-6.5)
Technique			
WBRT	35 (46.7%)	82 (14.6%)	117 (18.4%)
SRS	40 (53.3%)	479 (85.4%)	519 (81.6%)
Brain metastases characteristics			
Hemorrhagic component	10 (13.3%)	44 (7.8%)	54 (8.5%)
Leptomeningeal disease	12 (16.0%)	28 (5.0%)	40 (6.3%)
Midline shift or herniation	9 (12.0%)	47 (8.4%)	56 (8.8%)
Extracranial disease at consultation			
Progressive intrathoracic disease	65 (86.7%)	279 (49.7%)	344 (54.1%)
Progressive liver or adrenal metastases	45 (60.0%)	136 (24.2%)	181 (28.5%)
Spinal metastases	43 (57.3%)	105 (18.7%)	148 (23.3%)
Systemic therapy at consultation			
Yes	39 (52.0%)	132 (23.5%)	171 (26.9%)
No	36 (48.0%)	429 (76.5%)	465 (73.1%)
Neurologic symptoms at consultation			
Seizures	9 (12.0%)	23 (4.1%)	32 (5.0%)
Cranial neuropathies	24 (32.0%)	49 (8.7%)	73 (11.5%)
Motor or sensory deficits	38 (50.7%)	162 (28.9%)	200 (31.4%)
Presence of altered mentation	45 (60.0%)	147 (26.2%)	192 (30.2%)
Headaches	36 (48.0%)	166 (29.6%)	202 (31.8%)
Steroid use at consultation			
Yes	51 (68.0%)	271 (48.3%)	322 (50.6%)
No	24 (32.0%)	290 (51.7%)	314 (49.4%)
Place of radiation			
Inpatient	29 (38.7%)	19 (3.4%)	48 (7.5%)
Outpatient	46 (61.3%)	542 (96.6%)	588 (92.5%)

(*continued on next page*)

Table 1 (*Continued*)

	Death within 30 d (n = 75)	Alive beyond 30 d (n = 561)	Total (N = 636)
Radiation completion			
Yes	57 (76.0%)	554 (98.8%)	611 (96.1%)
No	18 (24.0%)	7 (1.2%)	25 (3.9%)
Outpatient palliative care utilization			
Yes	12 (16.0%)	136 (24.2%)	148 (23.3%)
No	63 (84.0%)	425 (75.8%)	488 (76.7%)
Primary site or histology			
Breast	16 (21.3%)	111 (19.8%)	127 (19.8%)
Gastrointestinal	7 (9.3%)	32 (5.7%)	39 (6.1%)
Genitourinary	4 (5.3%)	31 (5.5%)	35 (5.5%)
Melanoma	2 (2.7%)	41 (7.3%)	43 (6.7%)
Non-small cell lung	29 (38.7%)	268 (47.8%)	297 (46.7%)
Small cell lung	8 (10.7%)	35 (6.2%)	43 (6.7%)
Other	9 (12%)	43 (7.7%)	52 (8.2%)
Primary site			
Lung	38 (50.7%)	311 (55.4%)	349 (54.9%)
Not lung	37 (49.3%)	250 (44.6%)	287 (45.1%)

Abbreviations: SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.
* Median (range).

metachronous brain metastases. Patients included in this study were evaluated and treated in the modern era, with current practices of magnetic resonance imaging and SRS treatment when appropriate, at a tertiary center specializing in the multidisciplinary care of patients with brain metastases.

Cancer treatments offered near the end of life may not appreciably improve a patient's quality of life but may contribute to toxic effects, increase time spent in medical facilities, and add costs to patients and health systems. Accordingly, the use of chemotherapy near the end of life has been a quality measure of interest proposed by the American Society of Clinical Oncology and the National Quality Forum and adopted by the Centers for Medicare & Medicaid Services for implementation.[12] Within radiation oncology, the UK Royal College of Physicians recommended a less than 20% rate of 30-DM for patients undergoing palliative RT.[3] Data detailing short-term mortality of patients undergoing brain RT is necessary to develop and implement similar radiation oncology quality metrics within the United States.

In prior studies of patients receiving any palliative RT, rates of 30-DM ranged from 10% to 24%.[4,13-15] One recent study of patients with brain metastases from any primary site reported a 30-DM of 28%.[16] We observed a lower rate of 30-DM in our cohort, possibly owing to inclusion of those receiving SRS to limited intracranial metastases, representing a population with a better prognosis. The 30-DM rate for those receiving SRS was 7.7%, suggesting that patients are appropriately being selected for SRS at our center. Among the 117 patients receiving WBRT, however, the rate of 30-DM was considerably higher at 29.9%. The high short-term mortality in the population selected for WBRT highlights the importance of weighing the expected benefits of WBRT with the toxicity of treatment. As previously established by the QUARTZ trial, the optimal treatment for select patients with poor performance and with brain metastases ineligible for SRS or surgery may be best supportive care alone, because neither survival or quality of life were significantly improved with the addition of WBRT.[1] A patient-centered discussion of the potential benefits of brain metastasis–directed therapy, including improvement in neurologic symptoms such as headaches, weakness, dizziness, and seizures, should be balanced with possible adverse effects from the treatment, including fatigue, drowsiness, and nausea. An understanding of prognosis may help patients and their families clarify their goals of care and make these difficult treatment decisions near the end of life.

Identification of patients with brain metastases and poor prognoses, however, is an ongoing challenge. There are several prognostic models available for patients with brain metastases, including the Radiation Therapy

Table 2 Univariate analyses of clinical factors associated with 30-day mortality from last radiation therapy treatment

			Primary site			
	All patients (N = 636)		Lung (n = 349)		Not lung (n = 287)	
Factor	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.00 (0.99-1.02)	.696	1.03 (0.99-1.06)	.126	1.00 (0.97-1.02)	.796
Karnofsky Performance Status	0.93 (0.91-0.94)	<.001	0.93 (0.91-0.95)	<.001	0.93 (0.91-0.95)	<.001
Brain metastases at initial diagnosis vs metachronous presentation	0.95 (0.58-1.57)	.845	1.07 (0.54-2.11)	.849	0.99 (0.39-2.52)	.978
Primary site, lung vs not lung	0.83 (0.51-1.34)	.436	-	-	-	-
Brain metastases, no.		<.001				<.001
1-5	Reference		Reference		Reference	
6-10	0.19 (0.03-1.45)		-	-	0.67 (0.08-5.37)	
11-40	6.50 (3.78-11.17)		3.18 (1.43-7.09)		0.96 (0.12-7.85)	
Innumerable	1.58 (0.53-4.75)		2.20 (0.59-8.27)		13.06 (5.83-29.26)	
Leptomeningeal disease	3.63 (1.76-7.49)	<.001	4.36 (1.04-18.20)	.044	3.33 (1.40-7.95)	.007
Progressive intrathoracic metastases	6.57 (3.32-13.05)	<.001	6.44 (2.23-18.57)	.001	7.50 (3.02-18.62)	<.001
Progressive liver or adrenal metastases	4.67 (2.84-7.74)	<.001	5.52 (2.74-11.14)	<.001	3.91 (1.91-8.01)	<.001
Spinal metastases	5.84 (3.52-9.66)	<.001	4.59 (2.27-9.28)	<.001	7.56 (3.57-16.03)	<.001
Systemic therapy at consultation	0.28 (0.17-0.47)	<.001	0.25 (0.13-0.50)	<.001	0.31 (0.15-0.63)	.001
Neurologic symptoms						
Altered mentation	4.23 (2.56-6.96)	<.001	4.58 (2.29-9.19)	<.001	3.85 (1.87-7.95)	<.001
Seizure	3.19 (1.42-7.19)	.005	0.81 (0.10-6.53)	.846	5.03 (1.92-13.15)	.001
Cranial neuropathies	4.92 (2.79-8.67)	<.001	5.26 (2.06-13.43)	<.001	4.84 (2.30-10.19)	<.001
Motor or sensory deficit	2.53 (1.55-4.12)	<.001	1.81 (0.91-3.61)	.090	3.56 (1.75-7.24)	<.001
Headache	2.20 (1.35-3.58)	.002	1.99 (1.00-3.94)	.049	2.42 (1.20-4.86)	.013
Any neurologic symptoms	2.26 (1.27-4.02)	.006	1.79 (0.86-3.73)	.123	3.12 (1.17-8.31)	.023
Place of radiation, inpatient vs outpatient	17.98 (9.37-34.51)	<.001	16.25 (6.81-38.77)	<.001	21.13 (7.75-57-60)	<.001
Outpatient palliative care utilization	0.60 (0.31-1.14)	.116	0.68 (0.29-1.59)	.369	0.52 (0.19-1.39)	.191

Abbreviation: OR = odds ratio.

Oncology Group's recursive partitioning analysis, the Score Index for Radiosurgery in Brain Metastases, and the diagnosis-specific Graded Prognostic Assessment.[6,7,17,18] The patients with the most unfavorable prognosis in these models are estimated to have median survival of 2 to 3 months. However, no existing brain metastasis–specific models further identify patients whose survival is limited to less than 1 month.

Prior prognostic score indices and smaller retrospective analyses have demonstrated that poor performance status and extracranial disease are important indicators of poor prognosis.[6,7,17-19] In 1 recent study inclusive of 100 patients treated with radiation for brain metastases, extracranial disease progression (measured by blood test results and imaging) was a significant predictor for 30 DM.[16] Consistent with this observation, a lower KPS score and extracranial disease were associated with 30-DM in our analysis. These factors highlight the importance of evaluating a patient's intracranial disease in the context of their systemic progression and performance status. Notably, a patient's inpatient status was significantly associated with 30-DM, suggesting that palliative brain RT, particularly WBRT, for hospitalized patients should be offered judiciously, because many may not benefit from this treatment. To our knowledge, hospitalization is not considered in any prognostic indices for those with brain metastases, and it likely should be. Although age is frequently identified as a prognostic factor for survival, older age was not associated with imminent death within 30 days in this study.

As indicated by other studies, disease histology likely influences the prognostic importance of various clinical

Table 3 Multivariable analyses of clinical factors associated with 30-day mortality from last radiation therapy treatment

			Primary site*			
	All patients (N = 636)		Lung (n = 349)		Not lung (n = 287)	
Factor	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.00 (0.98-1.03)	.75	1.01 (0.96-1.06)	.710	0.99 (0.96-1.03)	.937
Karnofsky Performance Status	0.95 (0.93-0.97)	<.001	0.96 (0.93-0.99)	.004	0.96 (0.93-0.99)	.012
Brain metastases at initial diagnosis vs metachronous presentation	0.45 (0.21-0.96)	.04	0.29 (0.11-0.75)	.01	1.23 (0.35-4.32)	.744
Primary site, lung vs not lung	1.31 (0.62-2.78)	.48	-	-	-	-
Metastases, no.		.10		.467		.017
1-5	Reference		Reference		Reference	
6-10	0.18 (0.02-1.43)		-		0.51 (0.06-4.63)	
11-40	2.05 (0.61-6.83)		3.43 (0.71-16.54)		1.13 (0.13-10.03)	
Innumerable	2.17 (1.00-4.68)		0.84 (0.25-2.77)		5.41 (1.76-16.63)	
Leptomeningeal disease	1.13 (0.35-3.68)	.83	1.23 (0.11-13.34)	.863	0.80 (0.21-3.07)	.748
Progressive intrathoracic metastases	4.67 (2.06-10.60)	.002	7.72 (2.10-27.67)	.002	4.34 (1.41-13.39)	.011
Progressive liver or adrenal metastases	2.20 (1.16-4.16)	.02	3.03 (1.25-7.38)	.014	1.69 (0.63-4.55)	.297
Any neurologic symptoms	0.73 (0.35-1.52)	.40	0.87 (0.33-2.31)	.776	0.71 (0.21-2.36)	.576
Place of radiation, inpatient vs outpatient	4.51 (1.78-11.42)	.002	10.63 (3.02-37.43)	<.001	3.27 (0.81-13.26)	.098
Outpatient palliative care utilization	0.45 (0.20-1.00)	.05	-	-	-	-

Abbreviation: OR = odds ratio.
* The model containing outpatient palliative care utilization within the lung subgroup does not converge.

Table 4 Outpatient palliative care utilization

	Outpatient palliative care use			
	Yes (n = 122)	No (n = 324)	Total (N = 446)	*P* value
Hospitalization within 30 d of death				
Yes	38 (31.1%)	119 (36.7%)	157 (35.2%)	.045*
No	78 (63.9%)	170 (52.5%)	248 (55.6%)	
Missing	6 (4.9%)	35 (10.8%)	41 (9.2%)	
Referral to hospice				
Yes	99 (81.1%)	162 (50.0%)	261 (58.5%)	<.001*
No	23 (18.9%)	159 (49.1%)	182 (40.8%)	
Missing	0 (0.0%)	3 (0.9%)	3 (0.7%)	
Place of death				
Hospital or emergency room	8 (6.6%)	49 (15.1%)	57 (12.8%)	<.001*
Inpatient hospice	12 (9.8%)	26 (8.0%)	38 (8.5%)	
Home hospice	80 (65.6%)	129 (39.8%)	209 (46.9%)	
Home without hospice	17 (13.9%)	102 (31.5%)	119 (26.7%)	
SNF	3 (2.5%)	8 (2.5%)	11 (2.5%)	
Unknown	2 (1.6%)	10 (3.1%)	12 (2.7%)	
Days from RT completion to death†	128.5 (8.0-654.0)	101.0 (3.0-1248.0)	110.0 (3.0-1248.0)	.216‡

Abbreviations: RT = radiation therapy; SNF = skilled nursing facility.
* Chi-square.
† Median (range).
‡ Where applicable, missing data were not used when generating *P* values.

factors.[17] Among patients with metastatic lung cancer, synchronous brain metastases were associated with survival beyond 30 days. Innumerable brain metastases were associated with 30-DM among patients with nonlung histologies but not with lung histologies. These differences may reflect relative improvements in prognoses for patients with lung cancer who have brain metastases resulting from emerging systemic therapies. This also highlights the continued need to revisit prognostic factors in the modern era, given evolving diagnostic and therapeutic advances in the management of brain metastases.

Use of outpatient palliative care (OPC) was associated with significantly decreased mortality in the 30-day post-RT period. This finding reflects the results of several studies that demonstrated that early palliative care utilization in patients with advanced cancer was associated with improved survival.[20-22] Another possibility is that patients engaging with OPC services may be more appropriately selected for RT intervention. We observed that OPC was infrequently used (27%) in this population of patients with brain metastases. A higher proportion of those who used palliative care were referred to hospice and died on home hospice. A lower proportion of those who used OPC died in the hospital, emergency room, or at home without hospice. Although the correlation of these EOL outcomes is difficult to assess in a retrospective study, it is likely that early OPC influences care delivery at the end of life, and this should be the topic of further investigation in patients with brain metastases.[23]

One of the strengths of this study is that it was conducted at a multidisciplinary center in the modern era (2017-2020), incorporating common utilization of immune-checkpoint and molecularly targeted therapies—likely making these data more generalizable than older studies. Given robust follow-up and consistent documentation at our center, we detailed several clinical factors, including extracranial disease, intracranial disease features, and hospitalization, which may influence mortality in this population. Limitations of this study include the retrospective nature, selection bias, heterogeneity of the population given inclusion of multiple primary disease sites, and the small number of deaths within 30 days. Additionally, patients who were considered for but did not receive RT were not included in this study. Molecular profiling of tumors has been used in prior prognostic brain metastasis models; however, it was not available in this study.[18]

Conclusion

In summary, we identified multiple factors, including performance status, extracranial disease, metachronous metastases, inpatient status, and outpatient palliative care utilization, that were associated with 30-DM after brain RT. The importance and interaction of these individual factors, particularly in relation to the primary disease site, are unknown. Although the recursive partitioning analysis in this study was underpowered, future analyses including validation among a larger data set across multiple centers will be useful to more precisely risk stratify patients who have a high likelihood of 30-DM.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101211.

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