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RESEARCH PAPER

Impact of hospital volume on mortality for brain metastases treated with radiation

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ABSTRACT

Background: The impact of hospital volume on cancer patient survival has been demonstrated in the surgical literature, but sparsely for patients receiving radiation therapy (RT). This analysis addresses the impact of hospital volume on patients receiving RT for the most common central nervous system tumor: brain metastases.

Materials and methods: Analysis was conducted using the National Cancer Database (NCDB) from 2010–2015 for patients with metastatic brain disease from lung cancer, breast cancer, and colorectal cancer requiring RT. Hospital volume was stratified as high-volume (≥ 12 brain RT/year), moderate (5–11 RT/year), and low (< 5 RT/year). The effect of hospital volume on overall survival was assessed using a multivariable Cox regression model.

Results: A total of 18,841 patients [9479 (50.3%) men, 9362 (49.7%) women; median age 64 years] met the inclusion criteria. 16.7% were treated at high-volume hospitals, 36.5% at moderate-volume, and the remaining 46.8% at low-volume centers. Multivariable analysis revealed that mortality was significantly improved in high-volume centers (HR: 0.95, p = 0.039) compared with low-volume centers after accounting for multiple demographics including age, sex, race, insurance status, income, facility type, Charlson-Deyo score and receipt of palliative care.

Conclusion: Hospitals performing 12 or more brain RT procedures per year have significantly improved survival in brain metastases patients receiving radiation as compared to lower volume hospitals. This finding, independent of additional demographics, indicates that the increased experience associated with increased volume may improve survival in this patient population.

Key words: brain metastases; radiation therapy; hospital volume; overall survival; national cancer database

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Introduction

The impact of hospital volume on cancer patient outcomes has been firmly established in surgical literature including nationwide analyses of brain cancer, breast cancer, lung cancer, and rectal cancer [1–5]. Recently, investigation of cancer patients receiving radiation therapy (RT) has demonstrated superior outcomes in high-volume centers for glioblastoma and cervical cancer [6, 7]. However, there has yet to be a volume-based survival analysis for the most common tumor of the central nervous system (CNS): metastatic disease. This study is the first to examine the impact of hospital volume on survival in metastatic brain disease treated with RT.

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Materials and methods

Data source

The National Cancer Data Base (NCDB) is a hospital-based cancer registry sponsored jointly by the American College of Surgeons and the American Cancer Society, and is comprised of more than 1,400 facilities accredited by the American College of Surgeons' Commission on Cancer (8). The NCDB contains de-identified data on 70% of all newly diagnosed cancers in the United States (US) and includes data on radiation therapy (i.e. dosage, technique, target) not contained in the Surveillance, Epidemiology, and End Results (SEER) database [8, 9].

Inclusion and exclusion criteria

The NCDB identified patients with metastatic brain disease from lung cancer, breast cancer, and colorectal cancer in the US from 2010 through 2015 having received brain RT (n = 4,053,146). We included only patients aged 21 and older, from a single reporting facility with a single lifetime neoplasm and whose initial diagnosis and first line of treatment occurred at that reporting facility. Radiation treatments were limited to 8–3000 cGY total dose, which was administered at the reporting facility. Patients with unknown survival status were excluded (n = 19,269, Fig. 1).

Hospital volume

The number of accredited cancer programs in the NCDB changes from one diagnosis year to the next, meaning not all facilities were accredited for each year of the study. We assessed facility accreditation using all cases in the Non-Small Cell Lung Cancer (NSCLC) database from 2010-2015 (n = 568,683), and included only facilities reporting at least one case for each year on study. Of the 1,026 originally qualified facilities, 995 (97%) reported at least 1 NSCLC case for each reporting year (n = 18,841 cases). Hospital volume for treating brain metastases was annualized as the number of cases between 2010–2015 divided by the total reporting years (n = 6). Facilities were stratified as high (12+ brain RT/year), moderate (6–11 RT/year), and low-volume (0–5 RT/year).

Data collection

Patient age, sex, income, race, facility type (academic/research facility, comprehensive cancer

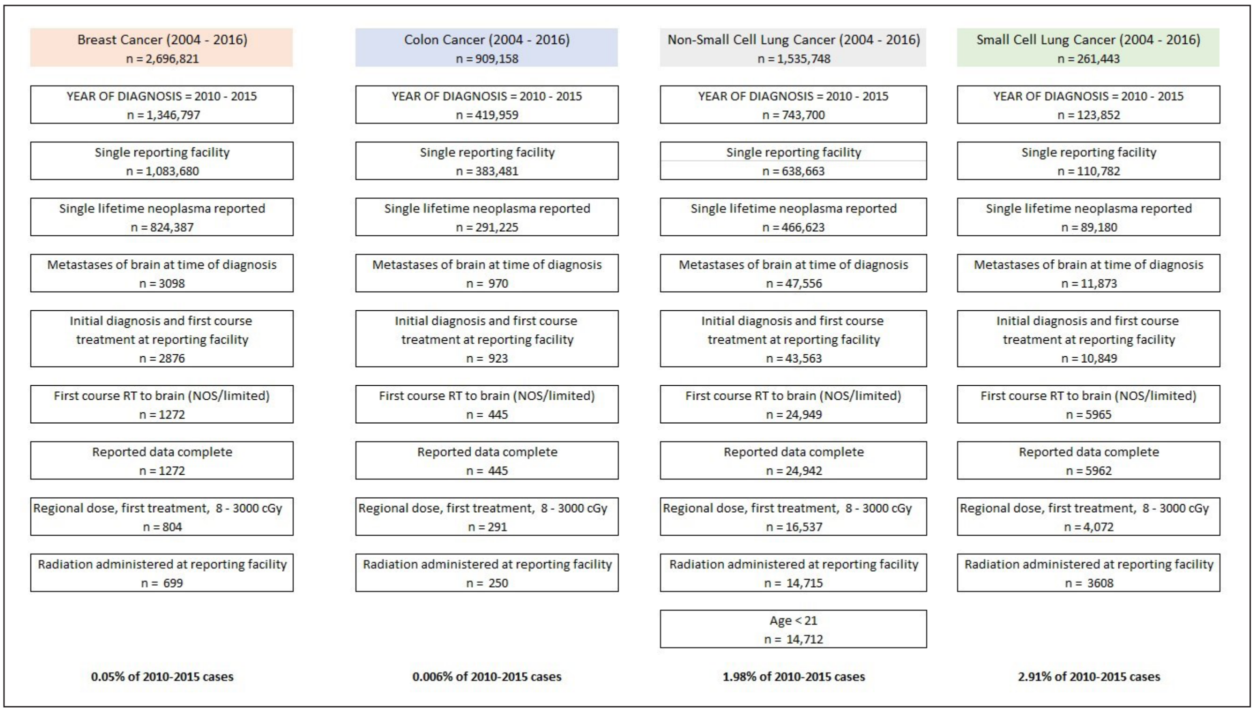

Figure 1. Schematic diagram of exclusion and inclusion criteria based on variables for patients from breast, colon, non-small cell lung and small cell lung cancer databases. Number eligible after each selection criterion is provided (n = 19,269). Final exclusion required to estimate hospital volume based on facility reporting for each study year was made after compiling the dataset. Final number eligible subjects = 18,841

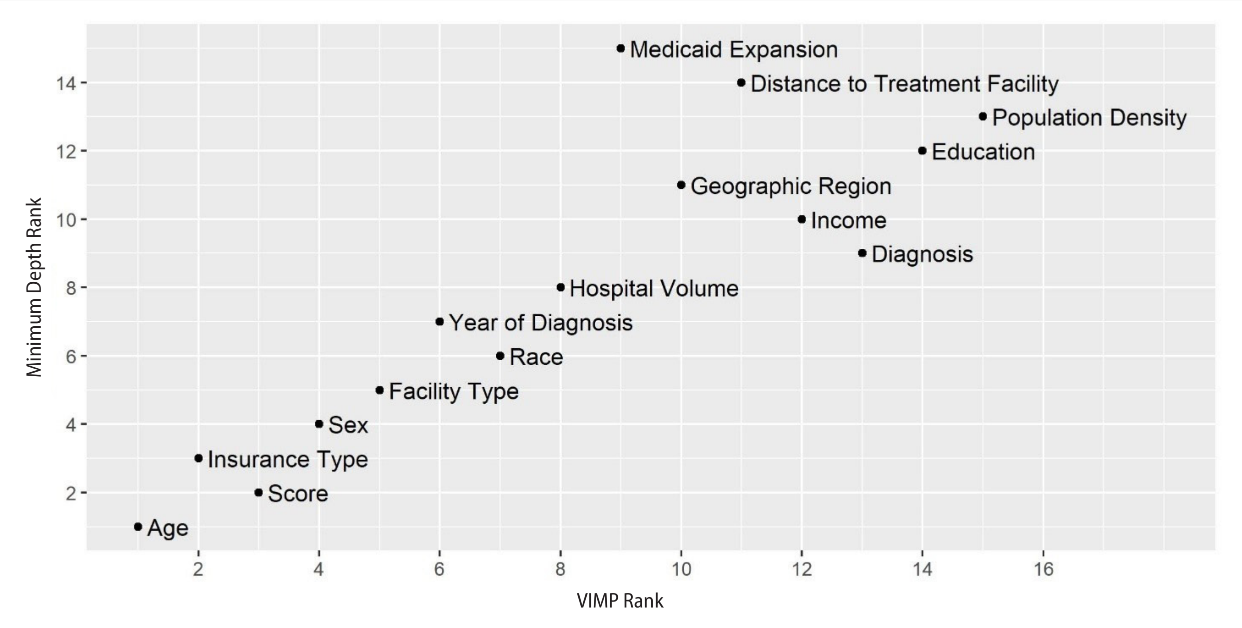

Figure 2. Variable rank by VIMP and Minimal Depth averaged across 2,000 Random Survival Forest simulations. X-axis: selection ranked by variable importance (average change in prediction error in the presence or absence of each variable); Y-axis: selection ranked by minimal depth (average split distance from the terminal node)

center, community, integrated network), primary payer (Medicare, Medicaid, other government, private, no insurance), education (% high school graduates in the region), geographic region of the US (Northeast, South, Midwest, West), income, distance to the treatment facility, primary diagnosis, year of primary diagnosis and medical comorbidities (the overall comorbidity burden was calculated using the Deyo comorbidity index, an adapted Charlson comorbidity index) were analyzed in this study [10, 11].

Statistical analysis

R version 3.4.4 (R Foundation; Vienna, Austria) was used to perform statistical analyses. Descriptive statistics were used to compare demographic and healthcare characteristics of eligible subjects based on hospital volume at the primary site, using Kruskal-Wallis Test for categorical variables and the Mantel-Haenszel Test for Trend for ordinal variables. Univariate logistic regression was used to identify demographic and disease characteristics associated with risk of death from metastatic brain disease. Due to the size of the dataset all covariates achieved a p-value < 0.0001, with several variable violating the proportions hazard assumption. Because of this, we applied the random survival forest algorithm (R package random ForestSRC) to a subset of the data (no missing values, n = 19,452) to select variables most strongly associated with survival based on variable importance (VIMP) and Minimal Depth calculated over 2000 simulations. Variables selected by random survival forest were entered into the multivariable model in a stepwise fashion first entering hospital volume and then adding subsequent variables based on their strength of association (proximity to origin, Fig. 2). Variable selection was based on Bayesian Information Criterion (BIC) and Akaike's Information Criterion (AIC).

Results

A total of 18,841 patients (50.3% men, 49.7% women; median age 64) met the final inclusion criteria. 16.7% were treated at high-volume hospitals, 36.5% at moderate-volume, and the remaining 46.8% at low-volume centers. Patients who identified as Black were more likely to be treated at a high- or moderate-volume facility than a low-volume facility (15.8 or 15.1% *vs.* 11.7%, respectively). High-volume facilities were more likely to be located in the Northeast (38.8% high-volume *vs.* 21.6% moderate volume vs 18.8% low volume). Based on our criteria, no high-volume facilities were identified in the West. High-volume centers are more likely to be academic (74.0% high-volume, 49.1%

moderate-volume, 19.1% low-volume). Twice as many patients traveled over 50 miles to be treated at a high-volume vs low-volume facility (18.2% *vs.* 9.0%). There was little change in proportion of patients treated by hospital volume facilities over the 6-year period (Tab. 1).

Results from the univariate analysis are shown graphically (Fig. 3). Variables associated with decreased risk of death from brain metastases include moderate and high hospital volumes (10% and 18%, respectively), female sex (18%), receiving palliative care (26%), and primary diagnosis of breast

Table 1. Patient demographic and healthcare system characteristics by Hospital Volume (n = 18,841)

Level	Overall	Low volume	Moderate Volume	High volume
N	18841	8824	6869	3148
Age [median (IQR)]	64.00 [56.00, 71.00]	65.00 [57.00, 72.00]	63.00 [56.00, 71.00]	62.00 [55.00, 70.00]
Sex (%)				
Male	9479 (50.3)	4470 (50.7)	3443 (50.1)	1566 (49.7)
Female	9362 (49.7)	4354 (49.3)	3426 (49.9)	1582 (50.3)
Race/Hispanic (%)				
NH White	14826 (78.7)	7110 (80.6)	5279 (76.9)	2437 (77.4)
NH Black	2565 (13.6)	1028 (11.7)	1039 (15.1)	498 (15.8)
Hispanic	630 (3.3)	331 (3.8)	208 (3.0)	91 (2.9)
Asian/Pacific Islander	608 (3.2)	270 (3.1)	273 (4.0)	65 (2.1)
Other/Unknown	212 (1.1)	85 (1.0)	70 (1.0)	57 (1.8)
Annual income (%)				
≥ 46,000 USD	6219 (33.0)	2944 (33.4)	2260 (32.9)	1015 (32.2)
36,000–45,999 USD	5261 (27.9)	2535 (28.7)	1834 (26.7)	892 (28.3)
30,000–35,999 USD	3631 (19.3)	1719 (19.5)	1315 (19.1)	597 (19.0)
< 30,000 USD	3204 (17.0)	1385 (15.7)	1231 (17.9)	588 (18.7)
(Missing)	526 (2.8)	241 (2.7)	229 (3.3)	56 (1.8)
Percent no. High School (%)				
< 14%	5418 (28.8)	2541 (28.8)	1994 (29.0)	883 (28.0)
14–19.9%	4448 (23.6)	2183 (24.7)	1560 (22.7)	705 (22.4)
20–28.9%	4852 (25.8)	2269 (25.7)	1732 (25.2)	851 (27.0)
≥ 29%	3595 (19.1)	1589 (18.0)	1353 (19.7)	653 (20.7)
(Missing)	528 (2.8)	242 (2.7)	230 (3.3)	56 (1.8)
Population (%)				
Metropolitan, > 250,000 population	14592 (77.4)	6730 (76.3)	5336 (77.7)	2526 (80.2)
Urban	3300 (17.5)	1650 (18.7)	1168 (17.0)	482 (15.3)
Rural/Other	533 (2.8)	243 (2.8)	256 (3.7)	34 (1.1)
Missing	416 (2.2)	201 (2.3)	109 (1.6)	106 (3.4)
Charlson-Deyo Score (%)				
0	11853 (62.9)	5516 (62.5)	4261 (62.0)	2076 (65.9)
1	4749 (25.2)	2231 (25.3)	1793 (26.1)	725 (23.0)
2	2239 (11.9)	1077 (12.2)	815 (11.9)	347 (11.0)
Facility type (%)				
Academic	7392 (39.2)	1689 (19.1)	3372 (49.1)	2331 (74.0)
Integrated Network Cancer	2487 (13.2)	1211 (13.7)	745 (10.8)	531 (16.9)
Comprehensive Cancer Center	7610 (40.4)	4667 (52.9)	2657 (38.7)	286 (9.1)
Community Cancer Center	1352 (7.2)	1257 (14.2)	95 (1.4)	0 (0.0)

→

Table 1. Patient demographic and healthcare system characteristics by Hospital Volume (n = 18,841)

Level	Overall	Low volume	Moderate Volume	High volume
Geographic region (%)				
Northeast	4361 (23.1)	1655 (18.8)	1484 (21.6)	1222 (38.8)
South	6646 (35.3)	2996 (34.0)	2647 (38.5)	1003 (31.9)
Midwest	5403 (28.7)	2642 (29.9)	1838 (26.8)	923 (29.3)
West	2431 (12.9)	1531 (17.4)	900 (13.1)	0 (0.0)
Insurance (%)				
Private	6028 (32.0)	2694 (30.5)	2228 (32.4)	1106 (35.1)
Medicare	8696 (46.2)	4324 (49.0)	3069 (44.7)	1303 (41.4)
Medicaid	2369 (12.6)	1011 (11.5)	884 (12.9)	474 (15.1)
Uninsured	1096 (5.8)	510 (5.8)	417 (6.1)	169 (5.4)
Other/Missing	652 (3.5)	285 (3.2)	271 (3.9)	96 (3.0)
Distance to facility (%)				
< 10 miles	9444 (50.1)	5004 (56.7)	3051 (44.4)	1389 (44.1)
10–19 miles	3860 (20.5)	1771 (20.1)	1488 (21.7)	601 (19.1)
20–49 miles	3044 (16.2)	1239 (14.0)	1225 (17.8)	580 (18.4)
≥ 50 miles	2454 (13.0)	796 (9.0)	1085 (15.8)	573 (18.2)
Unknown	39 (0.2)	14 (0.2)	20 (0.3)	5 (0.2)
Diagnosis (%)				
Breast cancer	683 (3.6)	357 (4.0)	222 (3.2)	104 (3.3)
NSCLC	14384 (76.3)	6597 (74.8)	5293 (77.1)	2494 (79.2)
SCLC	3533 (18.8)	1757 (19.9)	1254 (18.3)	522 (16.6)
Colon cancer	241 (1.3)	113 (1.3)	100 (1.5)	28 (0.9)
Year of diagnosis (%)				
2010	2723 (14.5)	1323 (15.0)	993 (14.5)	407 (12.9)
2011	2852 (15.1)	1340 (15.2)	1034 (15.1)	478 (15.2)
2012	2994 (15.9)	1342 (15.2)	1143 (16.6)	509 (16.2)
2013	3264 (17.3)	1493 (16.9)	1189 (17.3)	582 (18.5)
2014	3460 (18.4)	1607 (18.2)	1271 (18.5)	582 (18.5)
2015	3548 (18.8)	1719 (19.5)	1239 (18.0)	590 (18.7)
Palliative care (%)				
Palliative care	7287 (38.7)	3488 (39.5)	2644 (38.5)	1155 (36.7)
No palliative care	11,552 (61.3)	5336 (60.5)	4224 (61.5)	1992 (63.3)

cancer (18% compared to NSCLC). Distance from the treatment facility did not follow an ordered protective effect and observed decreased risk of death by race may be related to the small sample size.

Variables associated with increased risk of death from brain metastases include treatment at a non-academic center (41% increase, Community Cancer Center, 27% increase for comprehensive cancer center). The 10% increase observed at integrated cancer networks is unclear, given this is a mixture of academic and non-academic environments. Subjects with Medicare see a 47% increased risk of death compared to those with private insurance, although much of this difference is likely attributable to age; those 65 years of age and older are at 43% increased risk of death compared to those younger than 65 years. As expected, those with increased Charlson-Deyo score are at increased risk of death (22% for score = 1, 39% for score at least 2, as compared to 0). Subjects living in smaller communities are at higher risk, most likely due to limited access to treatment (8% for urban centers, 19% for rural/other, compared to metropolitan centers) and those from the South and Midwest are at great-

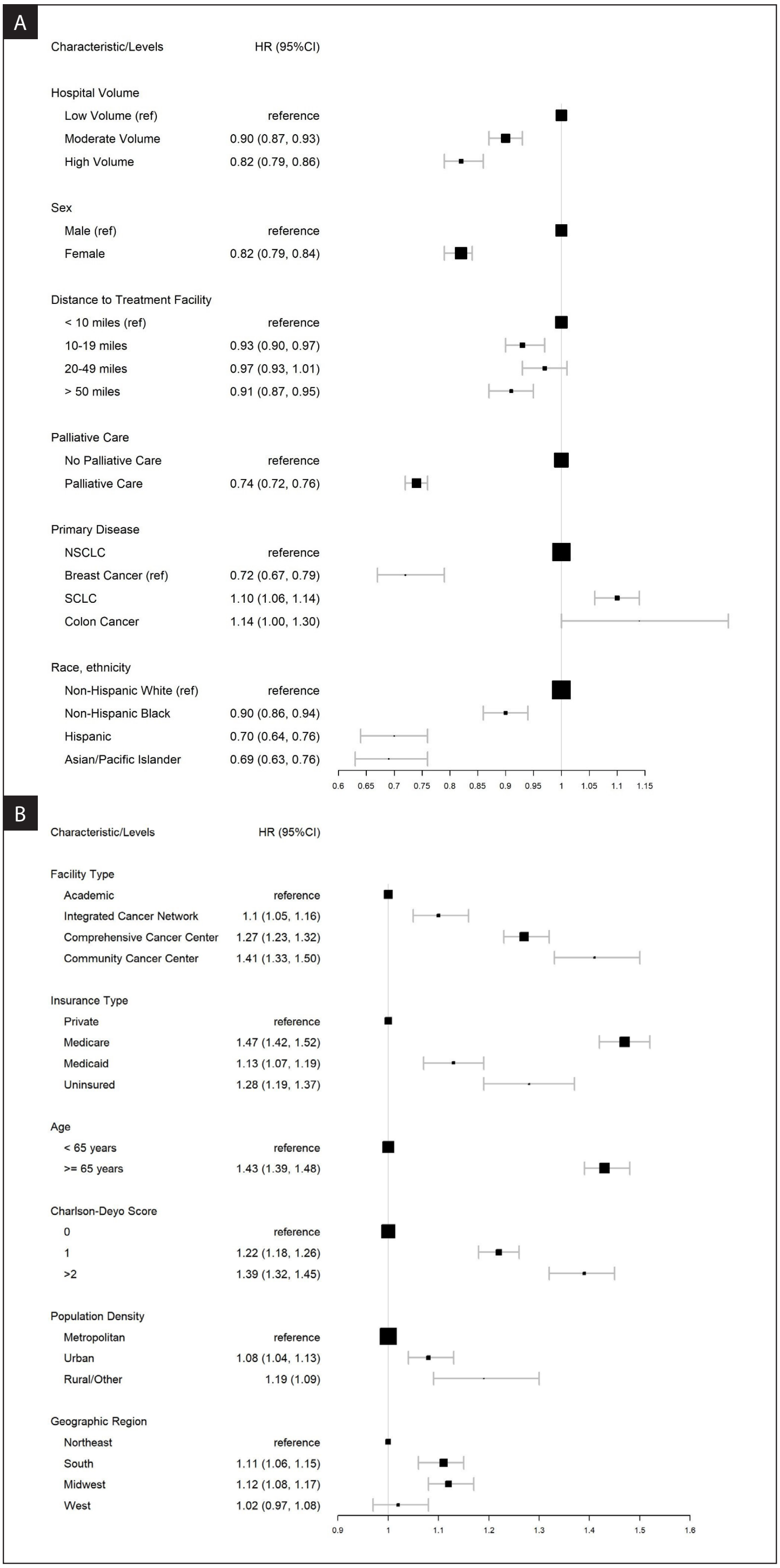

Figure 3. Forest Plots, Risk of Death from Brain Metastases. Hazard ratio for risk of death in the univariate cox models. Box size is proportional to population in each group. **A.** Variables associated with decreased risk of death relative to the reference level. **B**. Variables associated with increased risk of death relative to the reference level

er risk than those in the Northeast and West (11% and 12%, respectively, compared to Northeast).

We used a random survival forest approach to determine variables most influential on survival. After entering hospital volume, we sequentially tested variables with the strongest association with survival (Fig. 2) to generate a multivariable model including Hospital volume, age (continuous), insurance type, Charlson-Deyo score, sex, facility type, race, receipt of palliative care and income. Mortality was 5% lower in high-volume centers (p = 0.039) compared with low-volume centers, after adjusting for the effects of sex, race, insurance status, income, facility type, Charlson-Deyo score, and receipt of palliative care (Tab. 2). In the final multivariable model subjects treated in community cancer centers were at 29% increased risk of death compared to those treated at academic centers and

Table 2. Multivariable Model for factors associated with risk of death from brain metastases (n = 18,841)

Term Levels	N	HR (95% CI)	p-value
Hospital volume			
Low volume (ref)	8824		
Moderate volume	6869	0.97 (0.94 ,1.01)	0.162
High volume	3148	0.95 (0.91 ,10)	0.039
Facility type			
Academic (ref)	7392		
Integrated Network Cancer	2487	1.06 (1.01 ,1.12)	0.014
Comprehensive Cancer Center	7610	1.17 (1.13 ,1.22)	< 0.001
Community Cancer Center	1352	1.29 (1.21 ,1.38)	< 0.001
Age	18841	1.02 (1.02 ,1.02)	< 0.001
Insurance type			
Private (ref)	6028		
Medicare	8696	1.09 (1.05 ,1.14)	< 0.001
Medicaid	2369	1.19 (1.13 ,1.26)	< 0.001
Uninsured	1096	1.30 (1.21 ,1.39)	< 0.001
Other/Missing	652	1.20 (1.1 ,1.31)	< 0.001
Charlson-Deyo score			
SCORE 0 (ref)	11853		
SCORE1	4749	1.13 (1.09 ,1.17)	< 0.001
SCORE2	2239	1.25 (1.19 ,1.31)	< 0.001
Sex			
Male (ref)	9479		
Female	9362	0.83 (0.8 ,0.85)	< 0.001
Race/hispanic			
NH White (ref)	14826		
NH Black	2565	0.93 (0.89 ,0.98)	0.004
Hispanic	630	0.74 (0.68 ,0.81)	< 0.001
Asian/Pacific Islander	608	0.73 (0.66 ,0.80)	< 0.001
Other/Unknown	212	0.87 (0.75 ,1.01)	0.067
Annual income			
> 46,000 USD (ref)	6219		
30,000–45,999 USD	8892	1.11 (1.07 ,1.15)	< 0.001
< 30,000 USD	3204	1.10 (1.05 ,1.16)	< 0.001
Missing	526	0.92 (0.83 ,1.01)	0.072

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Table 2. Multivariable Model for factors associated with risk of death from brain metastases (n = 18,841)

Term Levels	N	HR (95% CI)	p-value
Palliative care			
Palliative (ref)	7287		
Not palliative care	11552	0.75 (0.73 ,0.78)	< 0.001

those treated in comprehensive cancer centers were at 17% increased risk of death. After multivariable adjustment, uninsured were at 30% increased risk of death, while those on Medicaid were at 19% increased risk. After adjusting for age, those with Medicare were at 9% increased risk of death (compared with 47%, unadjusted risk). Those who did not receive palliative care were at 25% decreased risk of death compared with those receiving palliative care.

Discussion

The role of hospital and provider volume as a pre-treatment predictor of post-treatment morbidity and mortality has become increasingly important due to the unsustainable growth in healthcare costs. Over the past decade, such investigation has expanded from the surgical realm (where for example it has been established that surgeons performing fewer than three acoustic neuroma surgeries annually yield significantly increased in-hospital operative morbidity and mortality) to radiation therapy, where hospitals treating fewer than six cervical cancer cases with RT annually yield inferior survival [1, 7]. The goal of this study was to expand this important aspect of patient care investigation to brain metastases, the most common central nervous system malignancy, by examining patients with primary tumors comprising some of the most common cancer site causes of brain metastases (lung, breast, colorectal).

Our findings indicate that brain metastases patients receiving RT from hospitals performing fewer than 12 brain RT per year (fewer than one per month) have inferior survival compared to those treated at hospitals performing at least one brain RT per month. While certain patient characteristics were predictably associated with survival (race, income and comorbidities), most striking was that hospital volume itself remained significantly predictive of survival even after all of these characteristics were accounted for. Such a result only highlights the necessity of ensuring that any patient with metastatic brain disease is appropriately triaged to high-volume centers. Noteworthy is that there is a substantial overlap between hospital volume and academic centers; as demonstrated in Table 1, academic centers were more likely than non-academic centers to be moderate-volume (45.7% *vs.* 30.1%) or high-volume (31.5% *vs.* 3.2%), and survival rates were significantly higher in academic centers ($p < 0.001$ on univariate and multivariable analysis).

Limitations of this study include the possibilities of incomplete/biased data reporting and/or miscoding during data submission to NCDB, and its retrospective nature. While NCDB contains several important details, important treatment variables, such as Karnofsky performance status or delineation of comorbidities beyond the Charlson/Deyo score, were unavailable; these represent limitations of the source data, in addition to the absence of melanoma and renal cell cancer patients in this analysis. As with all work derived from the NCDB, this study is derived from predominantly Commission on Cancer-approved hospitals; this skews the data towards hospitals more likely to be affiliated with a medical school/residency program, more likely to offer oncology-related services (chemotherapy, radiation therapy, screening programs, hospice/palliative care), less likely to be critical access hospitals, more frequently located in urban locations, and more likely to have more total beds than non-approved hospitals comprising more than 70% of hospitals in the American Hospital Association Annual Survey Database [12].

Conclusion

Hospitals performing on average one brain RT procedure per month show increased survival for brain metastases patients receiving radiation than those treated in lower volume hospitals. This finding, independent of additional demographic and disease characteristics, suggests the increased experience associated with increased volume improves patient survival. Patients with brain metastases should be strongly considered by their providers for referral to high-volume centers in order to optimize their care.

Conflict of interest

Dr. McClelland receives research support from the Indianapolis Public Transportation Corporation. No author has any conflict of interest.

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