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Palliative whole brain radiation therapy: an international state of practice※

Emily Keit[1]^, Shing Fung Lee[2,3], Melissa Woodward[4], Agata Rembielak[5,6], Kevin Shiue[7], Isacco Desideri[8], Eva Oldenburger[9], Maya Bienz[10], Dirk Rades[11], Marilena Theodorou[12], Mervin B. Agyeman[13], Joel Yarney[13,14], John Michael Bryant[1], Hsiang-Hsuan Michael Yu[1], Charles B. Simone II[15], Peter Hoskin[6,10], Peter A. S. Johnstone[1]

[1]Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [2]Department of Radiation Oncology, National University Cancer Institute, National University Hospital, Singapore, Singapore; [3]Department of Clinical Oncology, Tuen Mun Hospital, New Territories West Cluster, Hospital Authority, Hong Kong, China; [4]Department of Radiotherapy, The Christie at Oldhman, The Christie NHS Foundation Trust, Manchester, UK; [5]Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK; [6]Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK; [7]Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, IN, USA; [8]Department of Experimental Clinical and Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy; [9]Department of Radiation Oncology, University Hospitals Leuven, Leuven, Belgium; [10]Mount Vernon Cancer Centre, Northwood, UK; [11]Department of Radiation Oncology, University Medical Center Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; [12]Bank of Cyprus Oncology Center, Nicosia, Cyprus; [13]National Centre for Radiotherapy and Nuclear Medicine, Accra, Ghana; [14]University of Cape Coast, Cape Coast, Ghana; [15]New York Proton Center, New York, NY, USA

Contributions: (I) Conception and design: PAS Johnstone, E Keit; (II) Administrative support: PAS Johnstone, HM Yu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: JM Bryant, E Keit; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Emily Keit, MD. Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 USF Magnolia Drive, Tampa, FL 33612, USA. Email: emily.keit@moffitt.org.

Background: Improvements in radiation delivery and systemic therapies have resulted in few remaining indications for palliative whole brain radiation therapy (WBRT). Most centers preferentially use stereotactic radiotherapy (SRT) and reserve WBRT for those with >15 lesions, leptomeningeal presentation, rapidly progressive disease, or limited estimated survival. Despite regional differences among preferred dose, fractionation, and treatment technique, we predict survival post-WBRT will remain poor—indicating appropriate application of WBRT in this era of SRT and improved systemic therapies.

Methods: A multi-center, international retrospective analysis of patients receiving WBRT in 2022 was performed. Primary end point was survival after WBRT. De-identified data were analyzed centrally. Patients receiving WBRT as part of a curative regimen, prophylactically, or as bridging therapy were excluded. The collected data consisted of patient parameters including prescription dose and fractionation, use of neurocognitive sparing techniques and survival after WBRT. Survival was calculated via the Kaplan-Meier method.

Results: Of 29,943 international RT prescriptions written at ten participating centers in 2022, 462 (1.5%) were for palliative WBRT. Participating centers were in the United States (n=138), the United Kingdom (n=111), Hong Kong (n=72), Italy (n=49), Belgium (n=45), Germany (n=27), Ghana (n=15), and Cyprus (n=5). Twenty-six different dose regimens were used. The most common prescriptions were for 3,000 cGy over 10 fractions (45.0%) and 2,000 cGy over 5 fractions (43.5%) with significant regional preferences (P<0.001). Prior SRT was delivered in 32 patients (6.7%), hippocampal avoidance (HA) was used in 44 patients (9.5%), and memantine was prescribed in 93 patients (20.1%). Survival ranged from 0 days to still surviving at 402 days post-treatment. The global median overall survival (OS) was 84 days after WBRT [95% confidence interval (CI): 68.0–104.0]. Actuarial survival at 7 days, 1 month, 3 months, and 6 months were 95%, 78%,

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^ ORCID: 0000-0002-1646-7508.

48%, and 32%, respectively. Twenty-seven patients (5.8%) were unable to complete their prescribed WBRT.
Conclusions: This moment-in-time analysis confirms that patients with poor expected survival are being appropriately selected for WBRT—illustrating the dwindling indications for WBRT—and demonstrates the variance in global practice. Since poor survival precludes patients from deriving benefit, memantine and HA are best suited in carefully selected cases.

Keywords: Whole brain radiation therapy (WBRT); palliative radiation; brain metastases

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Introduction

Background

Eventual intracranial metastases are estimated to affect up to 10–40% of all patients with malignancy (1-3). The landscape of intracranial metastasis control and palliation has undergone substantial evolution as advancements in oncology have brought about earlier detection of asymptomatic metastases, improved targeted local therapies such as gamma knife and other stereotactic radiotherapies (SRTs), better targeted systemic therapies, and an understanding of the detriment whole brain radiation therapy (WBRT) can have on quality of life (QoL) (4,5). With these advancements, the utility of WBRT in patients with limited metastases and targetable mutations has rightfully declined (6). In light of these advancements, the current role of WBRT in patients with extensive intracranial disease is now poorly defined.

Until recently, WBRT was the standard of care (SOC) for the management of intracranial metastases. Evidence of WBRT's efficacy was first published in 1954 (7). Dose escalation trials followed with RTOG 6901 and RTOG 7361 often being credited with establishing 3,000 cGy over 10 fractions and 2,000 cGy over 5 fractions as the SOC regimen (8-13). Today, there exist a multitude of different dose and fractionation regimens that may be selected depending on primary histology, disease burden and location, prior treatment, prognosis, and logistics (14).

However, as patients are living longer due to improvements in care, concerns have arisen regarding the detrimental late effects of WBRT with neurocognitive decline becoming evident after 3 to 4 months (15). More worrisome, this neurocognitive decline has been associated with worsened performance status and a detriment in QoL which conflicts with the paradigm of palliative care (16,17). This led to the introduction of intensity-modulated radiation therapy (IMRT)-based hippocampal avoidance (HA)-WBRT which has been showed to result in less cognitive decline at 4 months post-treatment (15,18). The addition of memantine to standard two-dimensional (2D) WBRT showed a trend towards slowed neurocognitive decline at 4 months post-treatment but ultimately lacked statistical significance (15). A combination of both techniques resulted in less deterioration of executive function at 4 months as well as fatigue, learning, memory, and communication at 6 months (19).

Highlight box

Key findings

- Of 29,943 international radiation prescriptions written in 2022, 462 (1.5%) were for palliative whole brain radiation therapy (WBRT).
- Twenty-six dose regimens were used with regional preferences (P<0.001). The most common were 3,000 cGy over 10 fractions (45.0%) and 2,000 cGy over 5 fractions (43.5%).
- Global median overall survival was 84 days after WBRT (95% confidence interval: 68.0–104.0).
- Twenty-seven patients (5.8%) were unable to complete their WBRT course.
- Survival at 7 and 30 days post-WBRT was 95% and 78%, respectively.

What is known and what is new?

- Stereotactic radiotherapy and improved systemic therapies often offer outcomes superior to traditional palliative WBRT.
- Here, we offer modern evidence of the dwindling use of palliative WBRT on an international scale.

What is the implication, and what should change?

- As nearly one quarter of patients (22%) received WBRT within the last month of life, we encourage Radiation Oncologists to carefully consider the risks and benefits of delivering WBRT over maximal supportive care in those with exceptionally poor performance status or very limited estimated prognosis as treatment-related stressors may have a larger impact on quality of life as patients approach end of life.

In efforts to avoid treatment of healthy brain tissue, focal therapies such as stereotactic radiosurgery (SRS) and hypofractionated courses have become attractive options for treatment of limited intracranial disease (20). In the 2000s, the development of frameless SRS led to improved access of focal therapies which has resulted in a wider adoption of targeted radiotherapy for brain metastases (21). As is stands today, it is generally deemed safe to treat up to 15 small brain metastases with SRT, either as single-fraction SRS or fractionated SRT (FSRT), in efforts to avoid irradiation of healthy brain tissue (22,23). Radiation omission in select histologic and genetic tumor profiles has also been gaining popularity as improved targeted systemic agents with central nervous system (CNS) penetration have become available (24-30). Maximal supportive care in patients who are ineligible for targeted local therapies has been shown to be noninferior to WBRT with modern trials showing a lack of survival benefit with WBRT; this has led to discussions of whether WBRT should be further limited and excluded among those near the end of life (31-33).

Although numerous agencies have put forth guidelines for the treatment of brain metastases, all have nuanced differences (34-37). There continues to be a lack of international SOC guidelines for management of such patients which could streamline treatment approaches and ensure consistent patient care. However, with regional differences in cancer histologies, healthcare systems, and access to care, international standardized guidelines may not be feasible.

Objective

This report serves to provide a moment-in-time analysis of current global practices in palliative WBRT. By reporting international palliative brain metastasis treatment trends, the authors hope there will be continued promotion of knowledge exchange among different regions and healthcare systems, and further discussion can be fostered regarding the future utility of palliative WBRT in the global context. We present this article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-448/rc) (38).

Methods

Patient selection

A multi-center, international retrospective analysis of patients receiving palliative WBRT in the calendar year 2022 was performed. Participating centers were located in the United States, the United Kingdom, Germany, Belgium, Italy, Cyprus, Hong Kong, and Ghana. Patients with WBRT courses overlapping a new year were included if part of the treatment occurred in 2022. Those receiving WBRT as part of a curative regimen (e.g., primary CNS lymphomas), prophylactically in small cell lung cancer or leukemia, as bridging prior to chimeric antigen receptor (CAR)-T, or under the age of 18 were excluded. Patient follow up was performed per individual center's standard practices.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) (39). Institutional Review Board approval was obtained from participating centers as required by respective national guidelines. The de-identified data were analyzed centrally; the study was approved by the University of South Florida/Moffitt Cancer Center Institutional Review Board MCC 17324, and individual consent for this retrospective analysis was waived.

Statistics and end points

The primary end point was overall survival (OS). Other collected data included prescription dose and fractionation, and use of cognitive-sparing techniques such as HA and memantine, prior SRS, and primary tumor site. All statistics were performed with SPSS software (IBM Corp., released 2021, IBM SPSS Statistics for Macintosh, version 28.0, Armonk, NY, USA). Time to event analysis was conducted from last day of treatment. Survival was calculated via the Kaplan-Meier method (40). Patients were censored at last follow up. Multivariate analysis was conducted via Cox regression, and independent variables were assessed via the chi-squared method (41). The threshold for significance was $P \leq 0.05$.

Results

Ten participating centers were located across four continents and represented patients in the following countries and region: United States (n=138), the United Kingdom (n=111), Hong Kong (n=72), Italy (n=49), Belgium (n=45), Germany (n=27), Ghana (n=15), and Cyprus (n=5). Of 29,943 international radiation therapy (RT) prescriptions written at these centers in 2022, 462 (1.5%) were for palliative WBRT. Each institution's palliative WBRT prescriptions

Table 1 Continental differences among primary cancer sites

Primary site	Global	North America	Europe	Asia	Africa	P value
Most common	Lung (41.8%)	Lung (49.3%)	Lung (36.7%)	Lung (52.8%)	Breast (93.3%)	<0.001
Second most common	Breast (28.4%)	Breast (22.5%)	Breast (32.5%)	GI (15.3%)	GU (6.7%)	
Third most common	GI (7.4%)	Melanoma (9.4%)	GI (7.6%)	Breast (12.5%)	N/A	

GI, gastrointestinal; GU, genitourinary; N/A, not applicable.

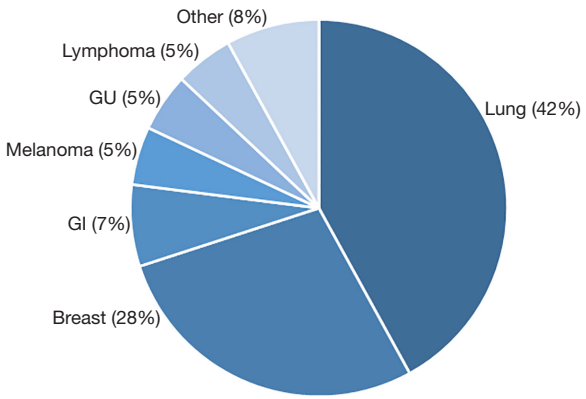

Figure 1 Primary cancer type. GI, gastrointestinal; GU genitourinary.

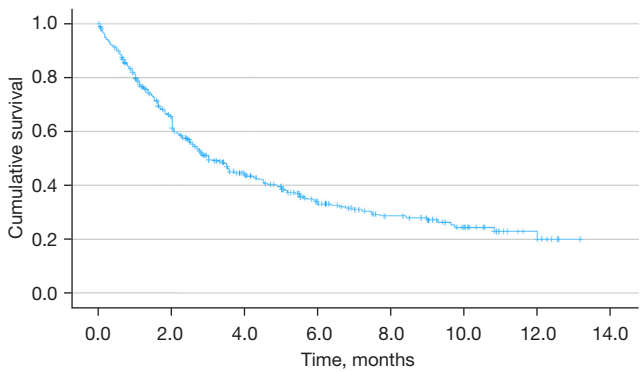

Figure 2 Global survival after WBRT. WBRT, whole brain radiation therapy.

accounted for 1–3% of their total RT scripts. Continent-specific data is described in Table S1. Globally, the most common primary cancers were lung (41.8%), breast (28.4%), and gastrointestinal (GI) (7.4%) with variations among continents (P<0.001) (*Table 1*, *Figure 1*). GI primary cancers were more common in Europe, and Asia, whereas melanoma was more common in North America, and genitourinary (GU) malignancies were more common in Africa.

Survival ranged from 0 days post-WBRT to still surviving at 402 days post-WBRT. The global median OS was 84 days after completion of WBRT [95% confidence interval (CI): 68.0–104.0] (*Figure 2*). Actuarial survivals at 7 days, 1 month, 3 months, and 6 months were 95%, 78%, 48%, and 32%, respectively.

Twenty-six different dose and fractionation regimens were used globally with each continent preferring different regimens (P<0.001) (*Table 2*). The two most common prescriptions were for 3,000 cGy over 10 fractions (45.0%) and 2,000 cGy over 5 fractions (43.5%) with a median OS of 2.8 and 3.0 months, respectively (P=0.519). The third most common WBRT regimen varied among continents: 6.4% of Europe's WBRT scripts were for 3,600 cGy with a 900 cGy simultaneous integrated boost (SIB) over 18 fractions, 3.6% of North American's scripts were for 2,500 over 10 fractions, and 2.8% of Asia's scripts were for 1,000 cGy over 5 fractions. SIB regimens were used exclusively in Europe, specifically Germany, where an 18 fractions regimen accounted for 55.6% of German WBRT scripts.

Neurocognitive-sparing techniques were uncommonly used worldwide, with 74.8% of patients receiving neither memantine nor HA. Memantine was used in 93 patients (20.1%), and HA was used in 44 patients (9.5%). Memantine alone was prescribed in 72 patients (15.6%) globally and accounted for 75% of WBRT scripts in Asia. HA alone was prescribed in 23 patients (5.0%). The combination of HA and memantine was prescribed in 21 patients (4.5%) (*Table 2*). North America contributed 75.0% of the world's HA use despite contributing only 29.9% of the cohort. There was a trend towards higher OS among those who received HA (P=0.052): without neurocognitive-sparing techniques, OS was 2.6 months, whereas survival exceeded 4.0 months with HA (*Table 3*, *Figure 3*). Prior CNS SRS was delivered in 32 (6.7%) patients.

Twenty-seven patients (5.8%) were unable to complete their prescribed WBRT course. Among these patients, 15 (55.6%) were prescribed 3,000 cGy in 10 fractions, 11

Table 2 Outcomes by geographical region

Outcomes	Global	North America	Europe	Asia	Africa	P value
Dose and fractionation regimens (%)						<0.001
3,000 cGy in 10 fx	45.0	88.4	33.3	8.3	6.7	
2,000 cGy in 5 fx	43.5	4.3	51.1	83.3	93.3	
3,600 cGy in 18 fx (900 cGy SIB)	3.2	0.0	6.3	0.0	0.0	
2,500 cGy in 10 fx	1.5	3.6	0.8	0.0	0.0	
1,000 cGy in 5 fx	0.4	0.0	0.0	2.8	0.0	
Cognitive-sparing techniques (%)						<0.001
WBRT alone	74.8	63.8	94.9	25.0	100.0	
Memantine only	15.6	12.3	0.4	75.0	0.0	
HA only	5.0	10.9	3.4	0.0	0.0	
Combination	4.5	13.0	1.3	0.0	0.0	
Prior SRS (%)	6.7	13.8	5.5	0.0	0.0	–

fx, fractions; SIB, simultaneous integrated boost; WBRT, whole brain radiation therapy; HA, hippocampal avoidance; SRS, stereotactic radiosurgery.

Table 3 OS stratified by neurocognitive sparing techniques

Technique	OS (months)	P value
WBRT alone	2.6	0.052
Memantine only	3.6	
HA only	4.9	
Memantine + HA	5.9	

OS, overall survival; WBRT, whole brain radiation therapy; HA, hippocampal avoidance.

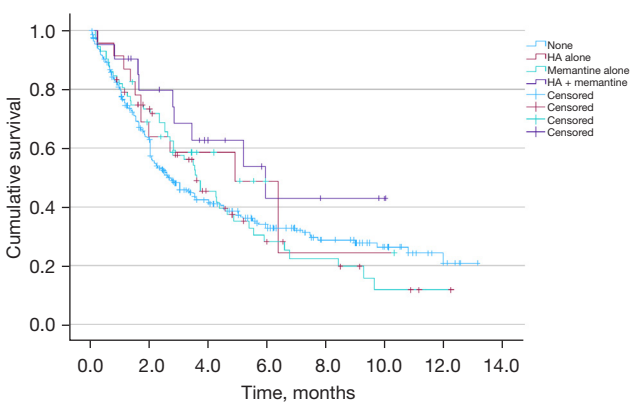

Figure 3 Survival by neurocognitive sparing technique. HA, hippocampal avoidance.

(40.7%) were prescribed 2,000 cGy in 5 fractions, and 1 (3.7%) was prescribed 3,000 cGy in 12 fractions. Six patients (22.2%) received memantine, and 3 (11.1%) received HA.

Discussion

Explanations of findings

WBRT accounted for 1.5% of global RT prescriptions written in 2022, illustrating the current limited use of whole-brain treatment. Twenty-six different dose regimens were used with regional preferences (P<0.001). The most common regimens were 3,000 cGy over 10 fractions (45.0%) and 2,000 cGy over 5 fractions (43.5%). The global median OS was poor at 84 days after completion of WBRT (95% CI: 68.0–104.0).

For intracranial metastatic disease, the purpose of treatment is to palliate symptoms, prevent further neurological sequelae, and provide local control of disease. With this aim, the field of oncology has witnessed shifts in the management of metastatic brain tumors due to the introduction of better targeted local and systemic therapies (4-6). Improved imaging has also allowed for earlier detection of intracranial disease resulting in treatment prior to symptomatic presentation with large or diffuse

intracranial disease (42).

As such, WBRT appropriately is in decline and is reserved for patients with poor expected survival or a large burden of intracranial disease. This is evident by WBRT prescriptions accounting for only 1.5% of RT courses despite estimates of up to 10–40% of patients with cancer eventually developing intracranial disease (1-3). While 26 different dose regimens were used globally, 3,000 cGy over 10 fractions and 2,000 cGy over 5 fractions remain the most commonly used palliative WBRT regimens accounting for 45.0% and 43.7% of scripts in 2022, respectively. North America appears to prefer the more extended 10-fraction regimen, which accounted for 88.0% of their WBRT prescriptions. Asia and Africa preferred the shorter 5-fraction regimen, which accounted for 83.3% and 93.0% of their WBRT prescriptions, respectively. Europe was more divided, with 51.1% of their WBRT being over 5 fractions and 33.3% being over 10 fractions. The German site was the only country to employ SIB WBRT, which accounted for the majority of their WBRT scripts with most SIB scripts being for 36 Gy with a 9 Gy SIB over 18 fractions. Despite regional differences existing within WBRT prescription patterns, patients are nevertheless being appropriately selected for WBRT as evident by a notably low median OS of 84 days.

HA was utilized more in the United States which contributed 75% of the global use. Memantine use with 2D treatment was popular in Asia, with 75% of these patients receiving this treatment. OS among those receiving HA with (5.9 months) and without (4.9 months) memantine was higher than for those without any neurocognitive-sparing technique (2.6 months) (P=0.052). This likely indicates selection bias rather than a superior treatment. As 4 months is regarded as the post-radiation interval required to see neurocognitive benefit from HA, this implies patients with longer estimated survivals are being preferentially selected for the more expensive, labor intensive, and extended treatment times required for IMRT-based HA. The OS among those with memantine use without HA was 3.6 months. While 4 months is again considered the timepoint at which benefit may be detected, memantine is a relatively benign drug with minimal side effects and cost (15). It is, therefore, likely reasonable to continue these prescription patterns as physicians cannot always predict which patients will be outliers surviving at least 4 months beyond WBRT.

Implications and actions needed

When providing palliative radiation at the end of life, reducing the number of treatments may be important for patients as longer treatment can cause discomfort with treatment positioning and immobilization, anxiety, logistical burdens with travel, financial implications, and time spent away from loved ones. Therefore, it is important to consider these factors when choosing a fractionation regimen and select a shorter course when appropriate. Although SRT may be appealing from a logistical perspective due to fewer fractions, such advanced techniques are not suitable for patients with numerous or bulky metastases, hemorrhagic metastases, uncontrolled systemic disease, poor performance status, or limited access to surveillance imaging (36,37,43).

It is also important to carefully consider whether any radiation treatment should be preferred over maximal supportive care as radiation within the last month of life is unlikely to provide meaningful palliation and may result in side effects such as profound fatigue (32,44-48). Here, survival at 1 week and 30 days was 95% and 78%, respectively. Twenty-seven patients (5.8%) were unable to complete their prescribed WBRT course, of which 15 patients (55.6%) received a 10-fraction regimen and 3 patients (11.1%) received HA. With nearly a quarter of patients (22%) receiving WBRT within the last month of life, there is potential to better select patients for WBRT; maximal supportive care over WBRT has shown QoL and OS non-inferiority among those with multiple non-small cell lung cancer brain metastases ineligible for SRT or surgery, with both groups surviving a median of approximately 9 weeks (32).

Granted, physician estimates of survival can often be incorrect, and we acknowledge the multifaceted and nuanced discussions that occur prior to delivering radiation in those with extensive metastatic burden (49). Prognostic nomograms and survival scores such as the Rades Score, WBRT-30, and Graded Prognostic Assessment (GPA) Index should be considered for assistance in estimating prognosis and guiding treatment when appropriate (50-54). Certain patient factors have also been significantly associated with 30-day mortality including those receiving palliative treatment to multiple locations, primary site melanoma, mesothelioma, and hepatobiliary cancers, presence of liver metastases, inpatient status, and an Eastern Cooperative Oncology Group (ECOG) performance status of 3–4 (55). We encourage Radiation Oncologists to continue to

carefully consider the risks and benefits of delivering WBRT to those with exceptionally poor performance status and an estimated prognosis of less than 1 month as the aforementioned treatment-related stressors and side effects may have a larger impact on QoL as patients approach the end of life. If palliative WBRT is thought to improve QoL in these settings, the number of fractions should also be considered to potentially minimize patient time within treatment facilities at the end of life.

Limitations

The continental trends described are greatly generalized and subject to selection bias. For example, only one African and one Asian country were represented here. Africa and Asia are large, diverse regions consisting of over 100 countries—all with different cultural and socio-economic groups, healthcare payment structures, and standards of care. Notably, different countries' healthcare structures may prefer shorter treatment regimens and 2D planning to maximize cost-effective care and patient access to care.

The continent with the most countries represented was Europe, with seven institutions across six countries participating in this study. This is the likely reason for the greater diversity amongst European dose regimens; different countries and healthcare systems practice differently, which was more adequately captured in this part of the world. Despite a greater representation of European countries, only one to two centers from each country were sampled which may be insufficient to represent the entire region. Prior surveys of Italian and German centers have revealed more complete country-specific data than could be collected here (56,57). In the Italian survey, the majority (>90%) of brain metastases treated with palliative intent utilized non-IMRT and non-SRT which is congruent with our findings; however, the survey revealed larger variations in dose regimens (range, 4–45 Gy) (57). In the German study, high-volume centers more frequently used targeted radiation over WBRT and employed more IMRT relative to low-volume centers (56). The participating high-volume center in the present study used SIB approaches 78% of the time, confirming this survey's findings of frequent IMRT-based WBRT in this region. However, potential differences among high and low-volume centers were unable to be assessed.

Access to care and clinic workflow are also varied across countries. The most notable difference from American oncologic care is the presence of rapid-access palliative radiation clinics that exist in the United Kingdom. The required credentials of practitioners present are different from what is required in the USA, which offsets the burden imposed by physician presence during radiation simulations and treatment delivery in cases that require quick turnaround. Differences in global Radiation Oncology logistics is beyond the scope of this manuscript and deserving of a separate discussion.

Data regarding all institutional SRT use and resulting survival was not consistently available among centers which limits our ability to comment on whether patients are being appropriately selected for focal palliation of brain metastases. As SRT continues to become more accessible and offers the potential for neurocognitive protection, exploring palliative SRT trends and survival outcomes is deserving of future investigation.

Conclusions

Despite regional differences among national healthcare structures, primary cancer types, dose regimens, and neurocognitive-sparing techniques, this international moment-in-time analysis illustrates the dwindling indications for palliative WBRT which, as expected, appears reserved for those with limited survival in this era of SRT. As 22% of patients received WBRT within the last month of life, and 6% were unable to complete their radiation, we encourage Radiation Oncologists to continue to carefully consider the risks and benefits of delivering WBRT over maximal supportive care or consider shorter treatment courses in those with very limited estimated prognosis as treatment-related stressors may have a larger impact on QoL as patients approach the end of life.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional Review Board approval was obtained from participating centers as required by respective national guidelines. The de-identified data were analyzed centrally; the study was approved by the University of South Florida/Moffitt Cancer Center Institutional Review Board MCC 17324, and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 All collected parameters among those receiving palliative WBRT by continent

Parameters	North America		Europe		Asia		Africa		Cumulative	
	N	%	N	%	N	%	N	%	N	%
Total RT scripts	6,272		19,248		2,225		2,198		29,943	
Total WBRT scripts	138	2.2	237	1.2	72	3.2	15	0.7	462	1.5
Primary site										
Lung	68	49.3	87	36.7	38	52.8	0	0.0	193	41.8
Breast	31	22.5	77	32.5	9	12.5	14	93.3	131	28.4
GI	5	3.6	18	7.6	11	15.3	0	0.0	34	7.4
GU	4	2.9	17	7.2	0	0.0	1	6.7	22	4.8
Lymphoma	5	3.6	10	4.2	7	9.7	0	0.0	22	4.8
Melanoma	13	9.4	8	3.4	0	0.0	0	0.0	21	4.5
GYN	2	1.4	6	2.5	2	2.8	0	0.0	10	2.2
Unknown primary	3	2.2	4	1.7	1	1.4	0	0.0	8	1.7
CNS	2	1.4	3	1.3	0	0.0	0	0.0	5	1.1
Liver	0	0.0	0	0.0	3	4.2	0	0.0	3	0.6
Pancreas	2	1.4	1	0.4	0	0.0	0	0.0	3	0.6
Thyroid	0	0.0	2	0.8	1	1.4	0	0.0	3	0.6
Sarcoma	2	1.4	2	0.8	0	0.0	0	0.0	4	0.9
Head/neck	0	0.0	1	0.4	0	0.0	0	0.0	1	0.2
Leukemia	1	0.7	1	0.4	0	0.0	0	0.0	2	0.4
All dose regimens (cGy/fx)										
3,000/10	122	88.4	79	33.3	6	8.3	1	6.7	208	45.0
2,000/5	6	4.3	121	51.1	60	83.3	14	93.3	201	43.5
3,600/18 (900 cGy SIB)	0	0.0	15	6.3	0	0.0	0	0.0	15	3.2
2,500/10	5	3.6	2	0.8	0	0.0	0	0.0	7	1.5
3,000/15	0	0.0	4	1.7	0	0.0	0	0.0	4	0.9
2,000/10	0	0.0	3	1.3	0	0.0	0	0.0	3	0.6
1,000/5	0	0.0	0	0.0	2	2.8	0	0.0	2	0.4
4,000/20	0	0.0	2	0.8	0	0.0	0	0.0	2	0.4
1,200/2	0	0.0	2	0.8	0	0.0	0	0.0	2	0.4
3,000/5	0	0.0	1	0.4	0	0.0	0	0.0	1	0.2
2,400/12	1	0.7	0	0.0	0	0.0	0	0.0	1	0.2
2,340/13	1	0.7	0	0.0	0	0.0	0	0.0	1	0.2
2,340/14	1	0.7	0	0.0	0	0.0	0	0.0	1	0.2
2,160/12	1	0.7	0	0.0	0	0.0	0	0.0	1	0.2
3,500/18	0	0.0	1	0.4	0	0.0	0	0.0	1	0.2
1,500/10	0	0.0	0	0.0	1	1.4	0	0.0	1	0.2
1,500/5	0	0.0	1	0.4	0	0.0	0	0.0	1	0.2
1,750/5	0	0.0	0	0.0	1	1.4	0	0.0	1	0.2
1,800/20	0	0.0	0	0.0	1	1.4	0	0.0	1	0.2
3,500/20	0	0.0	0	0.0	1	1.4	0	0.0	1	0.2
1,800/10	0	0.0	1	0.4	0	0.0	0	0.0	1	0.2
3,750/15 (750 cGy SIB)	0	0.0	1	0.4	0	0.0	0	0.0	1	0.2
2,800/14 (700 cGy SIB)	0	0.0	1	0.4	0	0.0	0	0.0	1	0.2
3,000/12 (600 cGy SIB)	1	0.7	1	0.4	0	0.0	0	0.0	2	0.4
3,000/13 (900 cGy SIB)	0	0.0	1	0.4	0	0.0	0	0.0	1	0.2
3,500/14 (700 cGy SIB)	0	0.0	1	0.4	0	0.0	0	0.0	1	0.2
Neurocognitive sparing technique										
Prior SRS	19	13.8	13	5.5	0	0.0	0	0.0	32	6.9
No HA (total)	105	76.1	221	93.2	72	100.0	15	100.0	413	89.4
HA (total)	33	23.9	11	4.6	0	0.0	0	0.0	44	9.5
Memantine (total)	35	25.4	4	1.7	54	75.0	0	0.0	93	20.1
HA + memantine	18	13.0	3	1.3	0	0.0	0	0.0	21	4.5
HA alone	15	10.9	8	3.4	0	0.0	0	0.0	23	5.0
Memantine alone	17	12.3	1	0.4	54	75.0	0	0.0	72	15.6

All collected parameters: i.e., radiation perscription number, primary cancer, fractionation regimens, and neurocognitive sparing techniques. WBRT, whole brain radiation therapy; RT, radiation therapy; GI, gastrointestinal; GU, genitourinary; GYN, gynecologic; fx, fractions; SIB, simultaneous integrated boost; SRS, stereotactic radiosurgery; HA, hippocampal avoidance.

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