

Is Whole Brain Radiotherapy Enough for Palliative Care of Patients with Infratentorial Brain Metastases from Lung or Breast Cancer?

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Short report

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Abstract

Background: Brain metastases (BM) occur in almost one third of patients with solid tumors. The aim of the study was to compare the prognosis of patients treated with whole brain radiotherapy (WBRT) among patients with supra- or infratentorial lesions.

Material and Methods: At a single center, 263 patients with either breast (BC) or lung (LC) cancer, that developed BM and received treatment with WBRT, were analyzed during an 8-year period.

Results: A total of 152 patients with BC and 111 with LC were analyzed, median age at the time of BM was 50.7 years, systemic activity other than BM was detected in 91%. Newly diagnosed BM were supratentorial and infratentorial in 133 patients (51%); exclusively supratentorial in 105 patients (40%); and exclusively infratentorial in 10%. Globally, 238 patients (90%) had supratentorial lesions, and 158 (60%) had infratentorial lesions. Median overall survival was 13 months (95%CI 11.1-14.8 months), without significant difference between supra- or infratentorial location.

Conclusion: In patients with LC or BC that develop BM, palliative WBRT is equally effective in those with supra- or infratentorial locations.

Introduction

Brain metastases (BM) are an ominous complication of cancer that develop in up to 30% of patients with solid tumors. Lately we have seen an increase in the incidence of BM, this might be due to an increased overall survival among patients with some types of solid tumors, as well as the increased use of surveillance imaging and increased awareness by oncologists.

Lung cancer (LC) and breast cancer (BC) are the tumors that most frequently develop brain metastases. (1). Up to 50% of patients with lung cancer and 15% of patients with breast cancer will develop BM at some point of their disease; due to the high incidence of the aforementioned malignancies, brain metastasis associated with either lung or breast cancer account for half of the cases of brain metastases. (2) Furthermore, the Surveillance, Epidemiology and End Results Program reported that patients with lung cancer present the highest rates of brain metastases at diagnosis. (3)

Whole brain radiation therapy (WBRT) has been a corner-stone tool for the management of BM; this therapy is primarily used for patients with BMs that are not suitable for surgical resection, and therefore this therapy is mainly used in the palliative setting (4). Although WBRT is associated with adverse effects, the effectiveness of this therapy has been validated by multiple clinical-trials, and when used in the appropriate setting the benefits outweigh the potential unwanted effects.(5) Concomitant treatment of solid tumors with WBRT along with systemic therapy has been studied elsewhere, albeit, to our current knowledge, there is no convincing evidence that simultaneous treatment with systemic therapy and WBRT significantly improves outcomes. Furthermore, it has been reported that unwanted effects increase

while using both therapies at the same time(3). Therefore, WBRT alone is currently used in many centers as the palliative treatment of choice for patients with BM (4).

Most patients that develop BM generally present with more than one BM, and the location of these metastases vary in every patient. According to their location, brain metastases are widely sub-divided as either: supratentorial metastases, which are located above the tentorium cerebelli (affecting the cerebrum); and infratentorial metastases, which are located between tentorium cerebelli and foramen magnum (affecting cerebellum and brainstem), the osseous boundaries of the infratentorial region include the clivus anteriorly, the temporal bones anterolaterally, and the occipital bone posteriorly-inferiorly, because of these osseous boundaries, the infratentorial region is considered a protective sanctuary that confers a resistance to radiation therapy in some patients, preventing them from getting the appropriate dose of radiation.

In adults most BM (80%) are located in the supratentorial compartment, however, lung and breast cancers have shown to have an increased tendency to metastasize to the infratentorial compartment (6). Owing to the cumbersome properties of this compartment, it has been proposed that patients with infratentorial metastases have worse outcome due to the fragile structures localized in this region, mainly brainstem and cerebellum, and the decreased effectiveness of radiation in this compartment(6).

The aim of the present study was to determine if WBRT is equally effective for palliating supratentorial and infratentorial BMs in patients with lung or breast cancer.

Materials And Methods

This study was designed as a retrospective, single center study; the main objective was to determine if WBRT was equally effective among patients with infratentorial BMs.

Inclusion criteria were: Patients age ≥ 18 ; received treatment with conventional WBRT for a new diagnosis of BMs between June 1, 2010 and June 30, 2018; have a confirmed primary breast or lung cancer prior to BMs; available T1-contrast (T1c) MRI obtained prior to WBRT; attended to a neuro-oncology (NeOn) consultation.

Exclusion criteria were: Incomplete medical record; neoplastic meningitis; previous treatment for BMs; alternate neurological diagnoses.

Statistical methods

Analyses comparing BC to LC were performed using χ^2 test, T test, or log-rank test according to the variable. Survival comparisons were performed using Kaplan-Meier curves with Log Rank test, a predetermined p value < 0.05 was set to be statistically significant.

Results

A total of 296 patients were sent to the NeOn of which 263 were included in this analysis, of the 33 excluded patients, 16 had WBRT after surgical resection, and 17 stereotactic radiosurgeries. Female gender predominated with 221(84%) patients; at the time the analysis was performed 21 (8%) patients were still alive. The primary tumor was BC in 152 (58%) patients and LC in 111 patients (42%), the most frequent histological types being HER2+ and non-small cell (NSCLC) respectively; general characteristics of the population are described in Table 1.

Median time from the diagnosis of primary cancer to diagnosis of BM was 13 months (Range 0-354 months), most patients had systemic metastases other than BM (91%). Treatment of BM was WBRT alone in 208 patients (79%) and WBRT followed by chemotherapy in 55 (21%). Median overall survival (OS) after diagnosis of BM was 13 months (95% CI 11-14 months) for all patients; 14 months for those with supratentorial lesions only; 14 months for those with infratentorial lesions only and 13 months for patients with supra- and infratentorial BM (p 0.19) as seen in Table 2 and Figure 1.

Discussion

In our sample of 263 patients, the median OS was not statistically different between patients with infratentorial BMs than in patients with supratentorial BM. Furthermore, we did not identify significant difference in OS according to affected hemisphere, number of BMs, or affected lobe.

OS of our patients with infratentorial BM was similar to those reported previously – even in those treated previously with SRS or surgery(7) – suggesting that WBRT might be considered a palliative treatment modality for these patients. Previous reports have considered radiobiological models to provide with non-uniform irradiation compared to the integral whole-brain dose delivered uniformly(5), but our study provides information suggesting this approach might not be needed when an homogeneous dose is planned. The historic affirmation that infratentorial BM have a worse prognosis than those with supratentorial(8) could be reconsidered in the palliative setting in the modern era, probably due to advances in systemic treatments and the technology and planning of the WBRT.

The retrospective design of this study confers some limitations to the collected data; to address this limitation, every electronic medical chart and imaging studies were reevaluated by an experienced neuro-radiologist and a neuro-oncologist, and variable definitions were established *a priori*. Beside this caveat, the study was performed by collecting data from a single center, therefore a selection bias should also be considered.

Our results clearly suggest that WBRT continues to be a useful tool in the management of patients with brain metastasis, and that its effectiveness in the palliative setting is similar for patients with infratentorial BMs; we consider that these results should be corroborated by future prospective studies.

Conclusion

In patients with lung or breast cancer with brain metastases not candidates for surgical resection, WBRT is effective for the palliation of brain metastases, irrespective of their supra or infratentorial location.

Abbreviations

BM= Brain metastases

WBRT= whole brain radiation therapy

LC= lung cancer

BC= breast cancer

OS= overall survival

NeOn= Neuro Oncology

Declarations

Ethical Approval and Consent to participate: This study was an observational retrospective study that did not jeopardize patients clinical management or identity. Therefore, ethical approval and consent to participate were not required

Consent for publication: All authors approved the final version of this manuscript

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Author contributions: BCD designed the protocol, wrote the original version of this manuscript, , analyzed data and recruited patients; AAA and KSM developed the dataset and assisted with study conceptualization and writing; ORM BGSC assisted in analyzing data, provided data of patients and assisted in study writing; OA wrote the original version of this manuscript, provided data of patients and assisted in study conceptualization and design.

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Tables

Table 1. General characteristics of 263 patients with breast or lung cancer who had brain metastases.

	Breast cancer n = 152	Lung cancer N = 111	Total N = 263	<i>p</i>
Gender				
· Women	152 (100%)	69 (62%)	221 (84%)	* <0.0001
· Men	-	42 (38%)	42 (16%)	
Median age at cancer diagnosis, years (Min-Max)	46.9 (25-75)	57.4 (31-85)	50.7 (25-85)	** <0.0001
Median age at BM, years (Min-Max)	53.9 (30-79)	58.1 (31-85)	55.1 (30-85)	** 0.008
Median time from cancer to BM, months (Min-Max)	33.5 (0-354)	1 (0-100)	13 (0-354)	** <0.0001
Median survival after BM, months (95%CI)	13 (10.7-15.2)	13 (9.9-16.1)	13 (11.1-14.8)	***0.6
Systemic activity	144 (95%)	95 (86%)	239 (91%)	*<0.01
Lung metastases / contralateral lung, n (%)	68 (45%)	21 (19%)	89 (34%)	* <0.0001
Liver metastases, n (%)	52 (34%)	25 (23%)	77 (29%)	0.027
Bone metastases, n (%)	88 (58%)	69 (62%)	157 (60%)	0.28

Pvalue was calculate with the following statistical tests: * χ^2 , **T test, ***Log-rank

Table 2. Localization of BM and survival

	N (%)	Median overall survival months (95%CI)	Log - Rank P
Total	263 (100)	13 (11.1 – 14.8)	
Primary tumor	111	13 (10.7-15.2)	0.64
· Lung	152	13 (9.9-16.1)	
· Breast			
Number of BM			0.31
· 1	73 (28)	14 (10.7 – 17.3)	
· 2-3	67 (26)	11 (6.9 – 5)	
· >3	123 (47)	13 (10.3 – 15.7)	
Hemisphere			0.66
· Left	48 (18)	14 (9.0 – 18.9)	
· Right	51 (19)	12 (8.1 – 15.8)	
· Both	159 (61)	13 (10.6- – 5.3)	
· Middle line	5 (2)	13 (10.8 – 15.1)	
Location			0.19
· Supratentorial only	105 (40)	14 (10.5 – 17.4)	
· Infratentorial only	25 (10)	14 (9.1 – 18.8)	
· Both	133 (51)	13 (10.6 – 15.3)	
Supratentorial yes	238 (90)	13 (11.0 – 14.9)	0.29
Infratentorial yes	158 (60)	13 (10.8 – 15.1)	0.29
Frontal lobe	154 (59)	13 (10.9 – 15.0)	0.46
Parietal lobe	151 (57)	13 (10.2 – 15.7)	0.54
Temporal lobe	101 (38)	13 (10.7 – 15.2)	0.28
Occipital Lobe	126 (48)	15 (12 – 17.9)	0.59
Cerebellum	143 (54)	13 (10.7 – 15.2)	0.10
Brainstem	31 (12)	9 (5.5 – 12.4)	0.44
Basal ganglia	33 (13)	12 (8.6 – 15.3)	0.41

95%CI = 95% confidence interval.

Figures

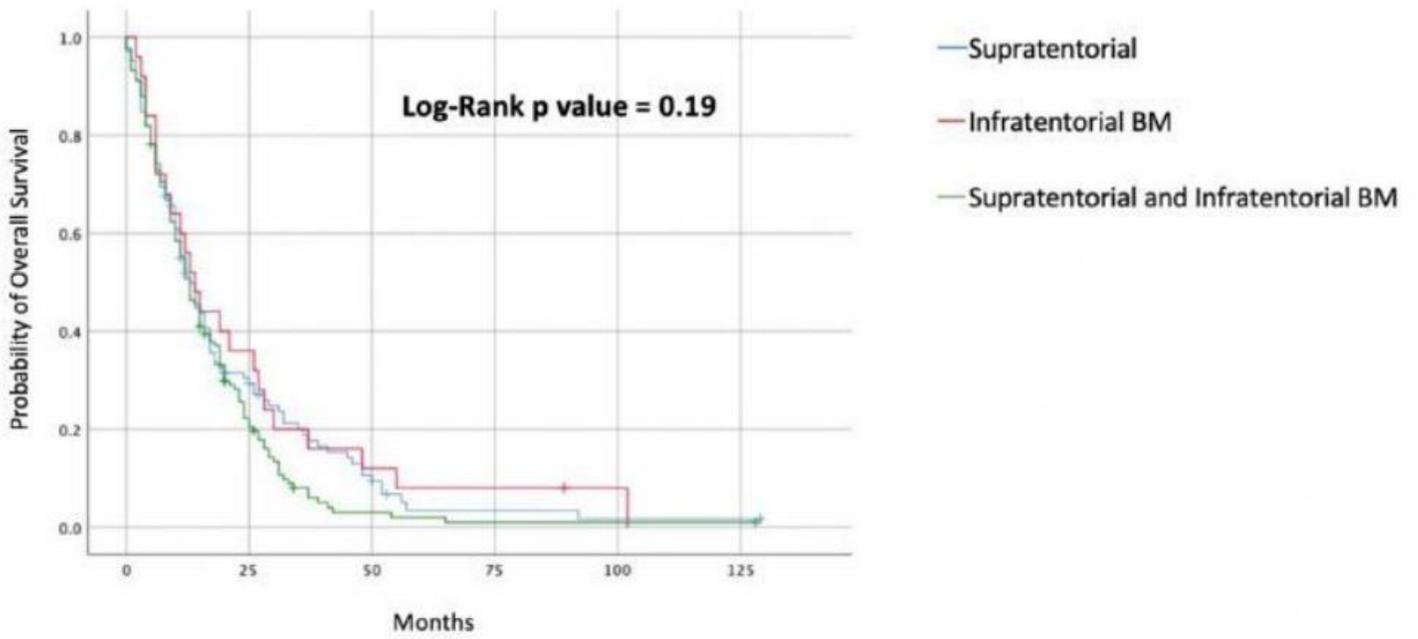


Figure 1

Kaplan Meyer curves for overall survival according to brain metastases location