Brain Metastasis: How to Predict and When not to Treat?

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Abstract

Background: Brain Metastasis (BM) is the commonest intracranial neoplasm in adults. There are different treatment approaches for BM including Whole Brain Radiotherapy (WBRT) which is used mainly for patients with multiple lesions and those unfit for Stereotactic Radiotherapy (SRS) or surgery (S). Multiple prognostic indices have been developed for better patient selection for treatment and to identify patients with very short survival. We analyzed the survival for patients with brain metastasis and investigated some predictive factors for survival and we studied a small subset of patients with lung cancer without BM to look into some predictive factors for development of BM.

Material and Methods: We retrospectively analyzed data of patients with radiologic diagnosis of brain metastasis who underwent whole brain radiotherapy either alone or with other local treatment modalities (SRS or Surgery) at our institution, looking into Overall Survival (OS) and any predictive models for prognosis and we identified a subset of lung cancer patients without brain metastasis to try to find factors associated with development of brain metastasis.

Results: The median overall survival in our study was 2.7 months and it was better for breast cancer (5.6 months) than lung cancer (3.5 months). In multivariate analysis, we found that the following factors remain the significant predictive factors for survival; use of local treatment modality (SRS or surgery), primary breast cancer, higher Radiotherapy (RT) dose (30 Gy), controlled primary, age less than 65 years, female and 2 weeks or more interval from diagnosis of BM to the start of RT. In univariate analysis, we found from our study that, age>65 years, female, smoking, weight loss, poor performance status, advanced stage at presentation and adenocarcinoma subtype were all factors associated with a higher incidence of BM in lung cancer patients. While in multivariate analysis, only age, smoking and weight loss remain risk factors for development of BM in lung cancer patients.

Conclusion: The survival after whole brain radiotherapy for BM is still poor. Our predictive models and other scoring systems have failed to identify the most important factors which can play the major role in treatment decision. We think it is worthwhile to do more studies that focus on predictive models and to develop nomograms to predict BM in asymptomatic patients, when the disease burden is low and effective local treatment whether SRS or resection could be used.

Keywords: Brain metastasis • Whole brain radiotherapy • Predictive models

Introduction

The exact incidence of brain metastasis is unknown, and the range is wide. However, it is the commonest intracranial neoplasm in adults, with a frequency between 10%-15% [1,2]. The incidence is higher in advanced stages and can reach up to 40% [3].

Lung cancer is the commonest primary (36%-40%) followed by breast cancer (15%-25%), skin melanoma (5%-20%) as sources of BM. Less commonly it can occur in colon, rectal, renal and genitourinary cancers [4]. The median age of presentation is around 60 years and this is related to primary tumor site [5,6]. Most patients have symptoms at diagnosis although in some cancers, like small cell lung cancer, a high percentage of patients with BM are asymptomatic at initial diagnosis [7,8].

Due to its availability, a computed tomography scan with contrast is the initial diagnostic modality in patients with suspected BM [9]. However, magnetic resonance is considered a better modality due to its high sensitivity and specificity in detecting small metastasis or metastasis in posterior fossa [10]. There are different treatment approaches for BM, including systemic treatment, steroids, WBRT, SRS and surgery. The choice depends on patient's performance, age, status of primary, presence of extracranial disease, number of metastases and prior treatment.

The median survival with WBRT is quoted as being between 3.2-3.6 months and 1.3 months with steroids [11,12]. The response rate for WBRT ranges from 40% to 60% [13-19]. Different fractionation schedules for whole brain radiotherapy (40 Gy/15 fractions, 30 Gy/10 and 20 Gy/5) have been used without a significant difference [13]. Generally speaking, prognosis is usually poor and estimated to be one month without treatment, prolonged to two months with steroids and 6 months with WBRT. However, a small subset might survive more than one year [20].

Accurate prognostic information is useful to optimize treatment for patients who may gain months of survival and to avoid overtreating patients who will derive little benefit. Many groups investigated different prognostic factors and tried to establish predictive models for survival. In one model, Performance Status (PS), age, extracranial metastases, and primary tumor status were crucial for the survival, in another model, neurologic impairment at the time of diagnosis and the presence of multiple brain metastases were associated with a significantly poorer survival, while solitary metastasis, gross total resection, and tumor histopathology of adenocarcinoma significantly prolonged survival. On the other hand, primary tumor site, presence of active extracranial disease, and radiation dose had no significant effect on survival [21,22]. Karnofsky Performance Status (KPS), radiation dose, solitary metastasis, and primary tumor size were good prognostic factors in a third model [23].

Multiple prognostic indices have been developed, including Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG RPA), the Rotterdam Score, the Scoring Index for Radiosurgery (SIR), the Basic Score for Brain Metastases (BSBM), the Golden Grading System (GGS), The Rades classification (RADES) [20,24-29]. Graded Prognostic Assessment (GPA) and the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) for breast and lung [30,31]. These indices had included more or less the same prognostic factors, mainly PS, age, extracranial disease, site and status of primary tumor, number of metastases and histologic subtypes.

Despite the availability of diverse scoring systems, there is still a lack of consensus regarding which clinical factors have the major impact on treatment decision-making concerning the use of WBRT in BM, especially in the light of the QUARTZ trial results which showed a lack of survival benefit adding WBRT to dexamethasone in non-small cell lung cancer patients [32].

We have retrospectively analyzed data of patients with radiologic diagnosis of brain metastasis who underwent whole brain radiotherapy either alone or with other local treatment modalities (SRS or Surgery) at our institution, looking into overall survival and any predictive models for prognosis and we investigated a subset of lung cancer patients without brain metastases to find factors associated with development of brain metastases.

Objectives

Primary outcome was to determine overall survival in patients with

BM after whole brain radiotherapy. Secondary outcome was to identify some predictive factors for survival, the level of concordance between CT and MRI brain and to identify predictive factors for development of brain metastasis in lung cancer patient's cohort.

Ethical considerations: This study is retrospective, all data were deidentified and most patients were expired by the time of analysis, for all those factors, this study was exempted from IBR approval.

Material and Methods

This study retrospectively reviewed the records of patients with a radiologic diagnosis of brain metastasis who underwent whole brain radiotherapy either alone or with other local treatment modalities (SRS or Surgery) at our institution. Patients with diagnosis of leukemia, lymphoma and unknown primary were excluded. Information regarding patient characteristics, disease characteristics, treatment and survival were collected.

Patient data included age, gender, smoking, Progression Free Survival (PFS), weight loss and presentation of BM. Disease variables included, primary tumor, histopathologic type, number and size of BM, method of diagnosis of BM, status of primary and its stage at initial presentations and date of diagnosis of both the primary and BM. Treatment variables included WBRT, SRS, metastatectomy, use of systemic treatment either before or after diagnosis of BM and WBRT dose.

Another cohort was patients with lung cancer without brain metastasis and their data were compared with a similar group with brain metastasis to determine predictive factors for development of brain metastasis.

Univariate and multivariate analyses were performed to determine the impact of the following parameters on Overall Survival (OS): age, gender, Eastern Cooperative Oncology Group performance status (ECOG), primary tumor, status of primary tumor control, number of intracranial metastases, different radiotherapy fractionations, time from diagnosis of the primary and development of brain metastasis.

Univariate analysis consisted of Fisher's exact tests, with the factors achieving statistical significance (defined as $p<0.05$ throughout this study in two-sided tests) entered into the multivariate analysis (Cox proportional hazards model). Actuarial survival curves were calculated by the Kaplan-Meier method, and differences were compared using the log-rank test. Overall Survival (OS) was defined as the length of time from the initiation of WBRT to death or to the last follow-up date.

Results

This study was conducted on 203 patients with radiologic diagnosis of brain metastasis who underwent whole brain radiotherapy either alone or with other local treatment modalities (SRS or Surgery).

The age ranged from 27-87 years with mean ± SD of 62.85 ± 12.26. The studied group included 116 females (57.1%) and 87 males (42.9%). The commonest primary was the lung (49.8%) and the commonest pathologic subtype was adenocarcinoma (43.3%). Half of the patients presented with stage 1V, and in 80% the primary tumor was uncontrolled and was associated with extracranial metastases. The majority had 2 or more brain lesions (70%) and most of the at patients were symptomatic presentation (88%). CT brain was the only imaging modality in 76% and the concordance between CT and MRI brain for those who had the two modalities was 50%. The vast majority were treated with whole brain radiotherapy alone (96%), two thirds received radiotherapy 2 weeks or more after initial BM diagnosis and twenty Gray regimen was utilized in 80% of patients, as shown in (Table 1).

One-way ANOVA test is used. P1 equals breast *vs* lung. P2 equals breast *vs* others. P3 equals lung *VS* others. Significance level is 0.05. Breast cancer needs a longer interval before development of BM, compared to very short interval for lung cancer (with mean of 69 months versus 5.4

Table 1. General characteristics of the studied patients.

Different Risk factors	Treatment Modalities	Number	Percent
Age (years)	Mean ± SD	62.85 ± 12.26	
	Range	27-87	
Age subgroups	<65 years	102	50.2
	>65 years	101	49.8
Gender	Female	116	57.1
	Male	87	42.9
Smoking	Yes	99	48.8
	No	-	51.2
Weight loss	Yes	25	12.3
	No	178	87.7
KPS	<70%	70	34.5
	>70%	133	65.5
Primary tumour site	Lung	101	49.8
	Breast	45	22.2
	Skin melanoma	16	7.9
	GIT-oesophagus	3	1.5
	GIT-colon	8	3.9
	GIT-rectum	7	3.4
	GIT-anal canal	1	0.5
	Genitourinary kidney	9	4.4
	Genitourinary bladder	1	0.5
	Genitourinary prostate	2	1
	Gynaecological	7	3.4
	Other	3	1.5
Primary tumour histology	Adenocarcinoma	88	43.3
	Ductal carcinoma	42	20.7
	Melanoma	18	8.9
	Squamous cell carcinoma	19	9.4
	Transitional cell carcinoma	6	3
	Small cell carcinoma	20	9.9
	Non-Small cell carcinoma	8	3.9
	Other	2	1
Primary tumour status	Controlled	10	4.9
	Uncontrolled	161	79.3
	Unknown	32	15.8
Stage at presentation	I	5	2.5
	II	37	18.2
	III	59	29.1
	IV	102	50.2
Stage IV at presentation	Yes	102	50.2
	No	101	49.8
Presence of extracranial metastasis	Yes	161	79.3
	No	10	4.9
	Unknown	32	15.8
Interval from BM diagnosis to death	Median (range)	100 (65-216)	
	Mean (SD)	200.85 (292-347)	
Number of BM	1	61	30
	2	25	12.3
	>2	117	57.6
Method of diagnosis	CT	155	76.4
	MRI	27	13.3
	CT & MRI	21	10.3
Presence of symptoms	Present	180	88.7
	Absent	23	11.3

Type of symptoms	Increased intracranial pressure	86	42.4
	Seizures	11	5.4
	Weakness	49	24.1
	Gait problems	40	19.7
	Visual problems	20	9.9
	Personality changes	8	3.9
Tumour size (cm)	Range	(1-8)	
	Mean (SD)	1.66 (1.06)	
	Median	1 (1.2.2)	
Interval: BM diagnosis to RT treatment start	<2 weeks	64	31.5
	≥ 2 weeks	139	68.5
Treatment modality	WBRT	195	96.1
	Surgery+WBRT	7	3.4
	SRS+WBRT	1	0.5
Radiotherapy dose	20 Gy/5 fractions	163	80.3
	30 Gy/10 fractions	40	19.7

months respectively), as illustrated in (Table 2).

The survival

The survival was very poor and about 97% of patients expired at the time of data analysis, as shown in (Table 3) and the median survival was 2.7 months as shown in (Figure 1).

The median overall survival in patients with BM after whole brain radiotherapy in this study (95% confidence interval level: 70.9-91.1 days (2.4-3 months) as shown in (Figure 1).

Factors influencing the survival

The survival was significantly better in the following groups: patients <65 *versus* ≥65, females, primary breast, with earlier stage, absence of extracranial metastases, with 1-2 brain lesions, treated 2 weeks or more after diagnosis of BM, treated with combined modality *versus* whole brain alone and those treated with 30 Gys over 20 Gys. While the following parameters did not influence the survival: KPS presence or absence of symptoms and imaging modality, as illustrated in (Table 4 and Figures 2-6).

Independent T-test. One-way ANOVA. Significance level is 0.05

Predictive factors for survival

In multivariate analysis, the use of local treatment modality (SRS or

Table 2. Relationship between primary tumor site and the interval from diagnosis of primary and the diagnosis of Brain Metastasis (BM).

Primary tumour	Interval between diagnosis of primary (staging) and diagnosis of BM					
	Mean	SD	Median	Q1	Q3	P-value
Breast	2074	1922	1217	862	3166	P< 0.001
Lung	162	305	1	0	203	P1<0.001
Other	1140	1269	775	187	1591	P2<0.001 P3<0.001

Table 3. Fate of the studied group (n=203).

Factors	Number	Percentage
Alive	7	3.4
Dead	196	96.6

Table 4. Relationship between survival and various demographic and clinical factors.

Different Risk factors	Treatment Modalities	Mean	Std. Dev.	Median	Q1	Q3	p-value
Age (yrs)	<65	248	340	138	71	270	0.028
	>65	152	225	92	50	159	
Gender	Female	245	339	138	71	249	0.018
	Male	141	203	93	53	143	
KPS	>70	211	238	143	70	232	0.079
	<70	195	317	97	55	176	
Primary tumour	Breast	314	408	169	80	285	0.007
	Lung	192	270	105	71	186	
	Other	124	169	79	55	115	
Stage	I	552	794	193	128	977	0.059
	II	233	298	116	67	276	
	III	157	258	87	63	148	
	IV	198	269	100	65	220	
Extracranial metastases	No	545.7	590.437	324	81	973	0.08
	Yes	176.18	248.924	98	64	186	
	Unknown	-	-	147	47	245	
Stage IV at presentation	No	203.12	314.752	99	65	200	0.916
	Yes	198.48	268.72	100	65	220	

Number of brain metastases	1 (61)	228.3	364	117	66	241	0.016
	2 (27)	269.4	251	94	65	173	
	>2 (115)	751	55	64	44	121	
Symptoms	No	201	302	127	55	201	0.994
	Yes	201	292	99	66	215	
BM diagnosis	CT+MRI	207	287	115	72	170	0.286
	CT	185	264	98	64	212	
	MRI	290	428	133	69	245	
Interval from BM diagnosis to RT start	<2 weeks	124.46	117.927	87	44	141	0.014
	>2 weeks	238.1	341.317	115	69	223	
Treatment modality	SRS+WBRT	302		302	302	302	<0.001
	Surgery+WBRT	892	676	586	223	1741	
	WBRT	151.1	230	81	64	174	
RT Dose	20 Gy in 5#	174	280	87	59	166	0.013
	30 Gy in 10#	308	319	191	129	299	

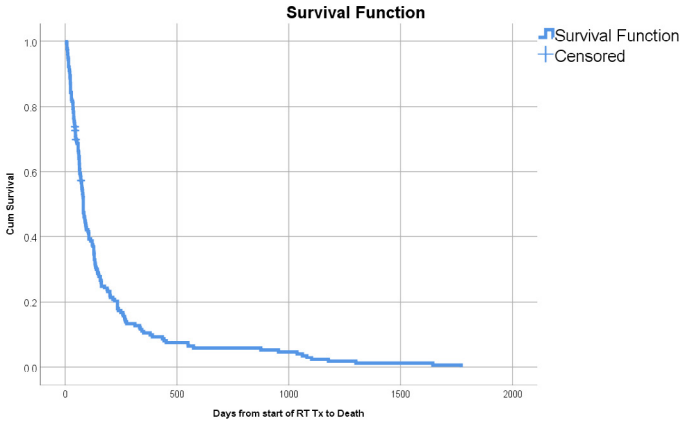

Figure 1. Kaplan-Meier survival plot of the studied patients with brain metastases demonstrating the overall survival after whole brain radiotherapy.

surgery), primary breast cancer, higher RT dose 30 Gy), controlled primary, age less than 65 years, female and 2 weeks or more interval from BM to start RT remain the significant predictive factors for survival as shown in (Table 5).

Log rank test is used. Breslow test is used. Significance level is 0.05

Factors associated with development of brain metastasis in lung cancer patients

There is a significant relationship between the occurrence of brain metastasis in lung cancer patients with the following factors; older age (≥ 65 y), females, smoking, weight loss, ECOG, advanced stage and adenocarcinoma subtype, as shown in (Table 6).

Multivariate analysis for predictive factors for development of brain metastasis in lung cancer

Age, smoking, and weight loss were the independent risk factors for occurrence of brain metastasis among lung cancer patients with odds ratio (2.80, 4.31 and 5.34 respectively) and p values: 0.031, 0.031 and <0.0001, respectively, as illustrated in (Table 7).

SE=Standard Error, CI=Confidence Interval

Discussion

Our study included 2 cohorts of patients, one with brain metastasis from a variety of primary cancers and another cohort of lung cancer patients without brain metastasis. Our department is a tertiary radiotherapy referral centre, and our patients are referred from other disciplines for radiotherapy, so we cannot comment on the true incidence of BM in our

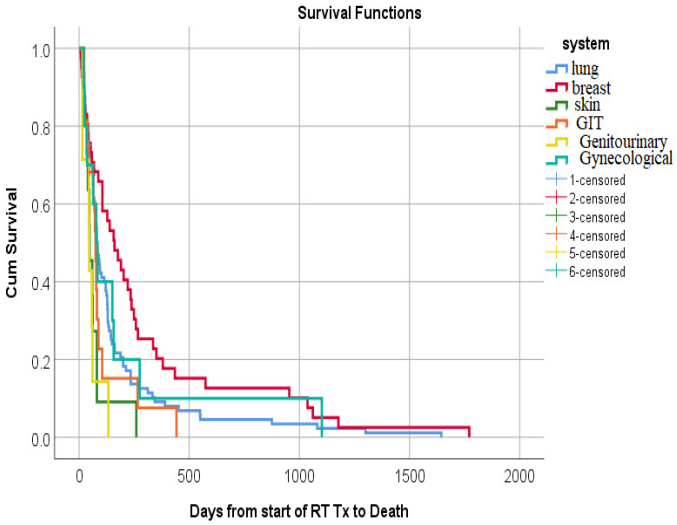

Figure 2. Kaplan-Meier survival plot of the studied patients with brain metastases demonstrating the overall survival after whole brain radiotherapy in relation to the primary tumor.

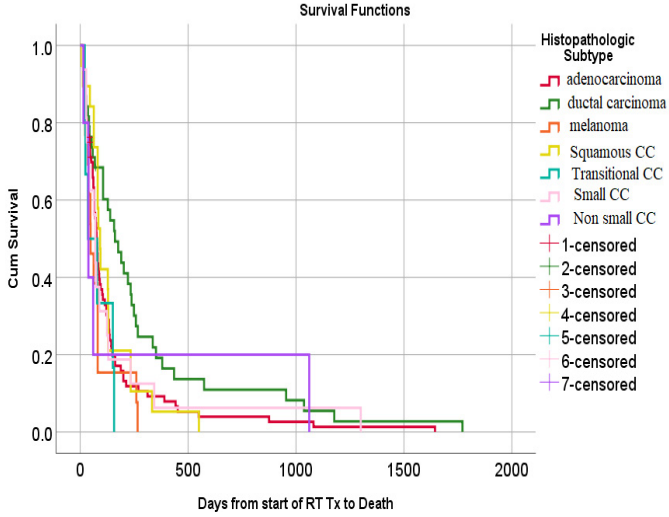

Figure 3. Kaplan-Meier survival plot of the studied patients with brain metastases demonstrating the overall survival after whole brain radiotherapy in relation to the histopathology of the primary tumor.

patient population. Half of our patients were aged 65 years or more which agrees with most trails, which quoted a median age of 60 years [5,33,34].

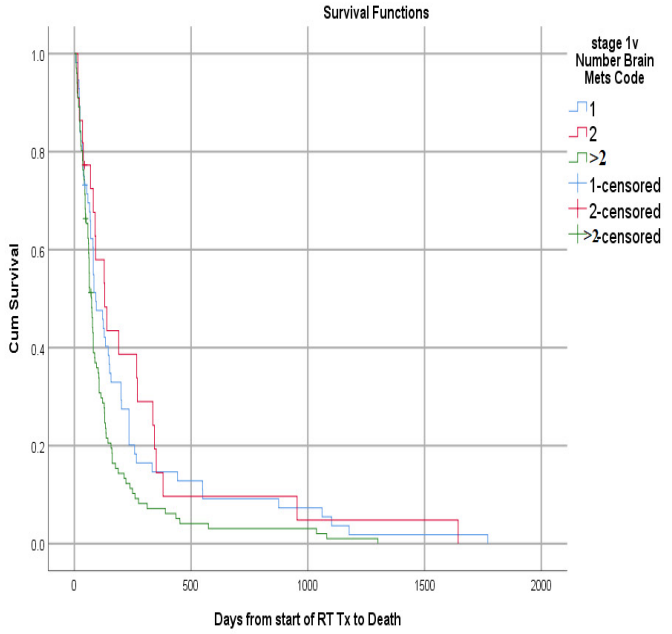

Figure 4. Kaplan-Meier survival plot of the studied patients with brain metastases demonstrating the overall survival after whole brain radiotherapy in relation to the number of BM.

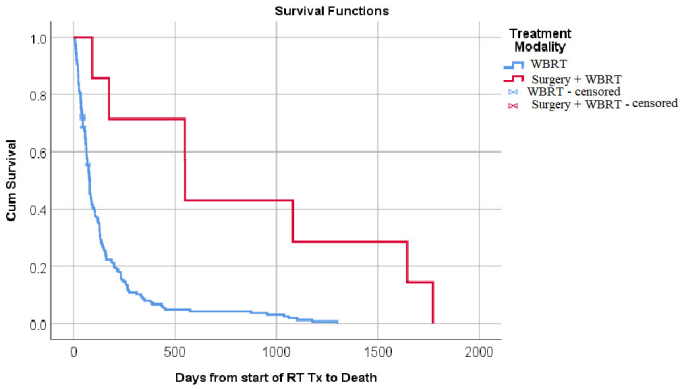

Figure 5. Kaplan-Meier survival plot of the studied patients with brain metastases demonstrating the overall survival after whole brain radiotherapy in relation to the treatment modality of BM.

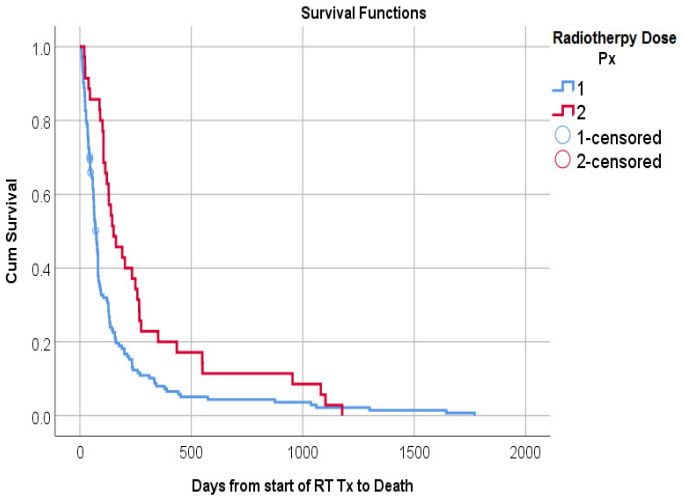

Figure 6. Kaplan-Meier survival plot of the studied patients with brain metastases demonstrating the overall survival after whole brain radiotherapy in relation to the radiotherapy dose.

The effect of gender on BM incidence is unclear, some reported higher incidence in females, others reported higher incidence in males, while some others did not report any impact [35-37]. We found that BM was higher in women than men, but this could be due to inclusion of more female patients in our study; about 22% of our patients were diagnosed with breast cancer.

Table 5. Survival analysis (Kaplan Meier curve for predictive model).

Different Risk Factors	Treatment Modalities	Median survival	95% confidence interval		p-value
Treatment modality	SRS+WBRT	302			0.001
	Surgery+WBRT	586	519.278	652.722	
	WBRT	81	85.793	110.207	
	Overall	100	83.396	116.604	
Primary tumour	Breast	169	83.685	254.315	0.001
	Lung	105	74.508	135.492	
	Others	77	70.07	83.93	
	Overall	100	83.396	116.604	
Radiotherapy dose	20 Gy in 5#	87	74.506	99.494	0.002
	30 Gy in 10#	170	81.8	258.2	
	Overall	100	83.396	116.604	
KPS	>70%	143	108.015	177.985	0.083
	<70%	97	83.021	110.979	
	Overall	100	83.396	116.604	
Number of brain metastases	Single	143	108.015	177.985	0.112
	Multiple	97	83.021	110.979	
	Overall	100	83.396	116.604	
Status of primary Tumour	Controlled	202	0	756.727	0.0044
	Uncontrolled	98	84.633	111.367	
	Unknown	147	57.786	236.214	
	Overall	100	83.396	116.604	
Age (years)	<65 years	138	100.626	175.374	0.006
	>65 years	92	75.36	108.64	
	Overall	100	83.396	116.604	
Gender	Female	138	101.848	174.152	0.002
	Male	93	78.382	107.618	
	Overall	100	83.396	116.604	
Interval from diagnosis of BM to RT start	<2 weeks	87	71.964	102.036	0.005
	>2 weeks	115	81.832	148.168	
	Overall	100	83.396	116.604	

In our cohort, BM was more frequent among lung cancer patients compared with breast cancer and melanoma patients (50%, 22% and 8% respectively), which is concordant with other studies, which reported an incidence of 56% and 57.5% for lung cancer, while others reported an incidence of 50% and 20% for lung and breast cancers respectively [15,22,31,38]. A few trials reported higher incidence in breast cancer than lung cancer, but the majority of their patient population were females [39].

Adenocarcinoma is the commonest pathologic subtype that metastasizes to the brain according to many studies and this was confirmed in our study (43%) and in another study which reported 46% [22,40,41].

BM is more common in advanced stages, and it was 50% in our patients and 40% in others studies [3,35,42]. Half of the patients in our cohort presented with stage 1V cancer, which is alarming and needs an intervention like adoption of screening programs specially for lung cancer.

Some studies have reported a higher incidence of BM in the presence of extracranial metastases [43]. We found about 80% of our patient had extracranial disease which is comparable to incidences of 85% and 60% reported in two other studies [44,45]. We think that the presence of extracranial metastases at the initial diagnosis or its development during the course of disease, is a clear risk factor for the development of brain metastasis. Most patients present with multiple lesions as documented in

Table 6. Relationship between the occurrence of Brain Metastases and the studied parameters among lung cancer patients (n=96).

Different Risk Factors	Treatment Modalities	Brain metastases	No Brain metastases	p value
Age	<65 (32)	21 (43.8%)	11 (22.9%)	0.03
	>65 (64)	27 (56.2%)	7 (77.1%)	
Gender	Male (58)	23 (47.9%)	35 (72.9%)	0.012
	Female (38)	25 (52.1%)	13 (27.1%)	
Smoking	Yes (79)	32 (66.7%)	47 (97.9%)	<0.0001
	No (17)	16 (33.3%)	1 (2.1%)	
Weight loss	No (51)	9 (18.8%)	42 (87.5%)	<0.0001
	Yes (45)	39 (81.2%)	6 (12.5%)	
ECOG PS	0 (5)	2 (4.2%)	3 (6.3%)	0.016
	1 (24)	7 (14.6%)	17 (35.4%)	
	2 (48)	32 (66.7%)	16 (33.3%)	
	3 (17)	7 (14.6%)	10 (20.8%)	
	4 (2)	0	2 (4.2%)	
Tumour stage	I (2)	1 (2.1%)	1 (2.1%)	0.016
	II (5)	2 (4.2%)	3 (6.3%)	
	III (32)	9 (18.7%)	23 (47.9%)	
	IV (57)	36 (75%)	21 (43.8%)	
Tumour histology	AdenoCa (28)	22 (45.8%)	6 (12.8%)	<0.0001
	Squamous (39)	11 (22.9%)	28 (59.6%)	
	Small cell (26)	13 (27.1%	13 (27.7%)	

Table 7. Binary logistic regression analysis (inter method) for independent risk factors for occurrence of brain metastasis among lung cancer patients (n=96).

Different Risk Factors	S.E.	Wald X^2	p Value	Odds ratio	95% CI.	
					Lower	Upper
Age	1.3	4.68	0.031	2.8	1.3	208.74
Sex	1.07	0.03	0.858	0.19	0.148	9.9
Smoking	1.74	6.12	0.013	4.31	2.45	2279.04
Weight loss	1.48	12.99	<0.0001	5.34	11.41	3791.38
ECOG	40193.08	7.81	0.099	17.92	-	-
Stage of primary tumour	1.134	4.8	0.187	2.26	0.011	0.963
Tumour histopathology	22887.01	0.019	0.999	22.124	-	-

our cohort (70%) and others [1,46-48], while some authors have reported higher incidence of solitary metastasis [49,50].

Seventy-five percent of our patients had CT scan as their only investigation for BM. It was noted that patients who had both CT and MRI, the concordance rate was only 52%. Forty percent of our patients with a solitary lesion on CT scan were found to have multiple lesions on MRI, which is in agreement with some studies, but lower than others which reported 80% [4,51]. It is worthwhile to mention that in 20% of our cases, CT scan was negative while MRI was positive for brain metastasis. We think it is an acceptable practice to start with CT brain with contrast if BM is suspected, however MRI should be considered if CT scan is negative, in the face of a high level of suspicion, as well as for exclusion of BM in certain high risk cancers, such as lung cancer.

Ninety percent of our patients were symptomatic at time of diagnosis, which in agreement with Tsakonas, et al who reported 93% and Cairncross, et al. who reported 66% in their patients. Only trials utilized MRI reported higher percentage of asymptomatic patients like Hjorthaug, et al. who detected BM in 50% of asymptomatic patients [7,52,53].

The median size of BM was 1 cm in our patients; however, some trials reported a larger median size of 2.1 cm [43]. Whole brain radiotherapy as a sole modality was utilized in 96% of our patients, although 30% of them presented with a solitary metastasis and this highlights the underutilization of local treatment whether surgery or SRS. Most of our patients treated with 20 Gy over 5 fractions (80%).

Breast cancer typically shows a longer interval before the development of BM compared with relatively very short interval for lung cancer. In our group, the mean duration was 69 months for breast cancer versus 5.4 months for lung. An interval of 2.6-7 months for the lung was reported in some studies [35,54,55] and an interval of 39-47 months for the breast in other studies [56-58].

The survival of patients with brain metastasis, especially If multiple, is poor, regardless the treatment modality used. In our study, 97% of our patients demised, while only 3% were alive when censored to last follow up at the time of data collection. In a group of more than 900 patients with BM, Wong, et al. reported that 94% of their patients were deceased [59].

The median overall survival for our patients was 2.7 months which was identical to Wong, et al. and similar to Periestman, et al. who reported 2.6 months. While Fleckenstein, et al, Lagerwaard et al. and Silva et al reported a higher median survival of 3.8 months and 3.4 and 4.5 months respectively [24,59-62]. On the other hand, Chan et al reported a shorter median survival of 2.3 months. Although there are some differences in the median survival among different trials, for those short- lived patient cohort, the direct comparison between different trails, considering the heterogeneity of the patient populations and different methods for survival calculation (calculated form date of diagnosis versus date of treatment), is difficult, although it did confirm a poor survival [63].

In our study and in that of Wong, et al patient's ≥ 65 years had a poorer survival compared with a younger group, while Jakhar, et al failed to show

any impact of age on the survival. When we categorized patients into ≤ 60 years and >60 years, the difference in survival was highly significant and this coincide with Jeene et al. who reported a significant difference between different age groups (<50, 50-59,60-69 and ≥ 70 years) [59,64,65].

Females had a better survival than males as documented in our study and in others, while other studies did not demonstrate any gender difference. Performance status did not affect the survival in our patients and this is in accordance with some studies while in contradiction to others who reported a better survival among patients with good performance status [59,64-68].

In our cohort, the survival was significantly better for patients with breast rather than lung cancer (median survival 5.6 months and 3.5 months respectively), and it was lowest in skin cancer where melanoma was the predominant subtype. A median survival of 8 months for breast cancer patients was reported in one study and a median survival of 2.7-6.3 months for lung cancer patients reported in some studies [35,57,69,70]. Jeene et al reported a median survival for the breast and lung cancer patients of 3.7 months and 2.7 months respectively and Wong et al reported a median overall survival of 4.3 months, 2.2 months, 2.1 months and 2.7 months, in breast, GIT, GU and lung cancers patients respectively [59,65].

In our study there was a marginally significant survival advantage for those presented with early stage compared to those presented with advanced stage. We have found that the presence of extracranial disease was associated with a poor survival. In a study by Wang, et al for non-small cell lung cancer patients with brain metastases, not just the presence or absence of extracranial disease has affected the survival, but the number of extracranial disease has also influenced outcome as well. This result was reproduced by Gerdan, et al. in a similar cohort with non-small cell lung cancer and second cohort of small cell lung cancer patients and also in a third cohort of patients with breast cancers [71-74].

In our cohort, patients presented with a fewer number of brain metastases (1-2) had a better survival when compared with patients with multiple brain metastases and this is in agreement with most publications [31,75,76,66], while Fleckenstein, et al. was unable to demonstrate any significant difference. Although 48% of our patient cohort had 1-2 lesions, only 4% had local treatment (surgery or SRS) which highlights underutilization of local treatment modalities [61].

Patients who are asymptomatic from brain metastases is associated with a better survival when compared with symptomatic counterparts as reported in most trials, however we found the survival was not adversely affected with symptoms and this could be due to the fact that almost 90% of our patient cohort were symptomatic at time of diagnosis [77-80].

Brain metastasis imaging modality whether MRI or CT scan did not affect the survival as per our study, however we cannot make any conclusion as the number of patients who had MRI was low.

We found the survival was better if the interval between BM diagnosis and initiation of radiotherapy was more than 2 weeks rather than less 2 weeks. Mehta, et al. and Hansen et al. did not show any impact and Nieder et al. concurred except in those patients without extracranial disease where the survival was better if this interval was less than 2 weeks compared to poorer survival if it was more than 2 weeks [81-83].

In our study the median survival was 19 months,10 months and 2.7 months for S+WBRT, SRS+WBRT and WBRT alone, respectively and this was statistically significant. Lentzsch, et al. reported a median OS of 20 months,6.5 months and 1.25 respectively for patients treated with surgery, WBRT or steroids and Ekici et al. reported a median survival of 13.5 months for S+WBRT and 5.5 months only for WBRT alone, while Hazuka et al. reported 11 months' median survival with S+WBRT. There is general agreement in most trials that the inclusion of a local treatment modality is associated with a better survival [22,23,34].

It is unclear if higher doses of WBRT would improve the survival or not. Twenty Grays in 5 fractions achieved similar survival as 30 Gy in 10 fractions, with a better toxicity profile, as reported in 2 studies [13,84]. However, we found 30 Gy was associated with a significantly better survival when compared with 20 Gy and this is in agreement with Wong et al. and Thakur et al. [59,66].

In our study, adenocarcinoma of the lung was associated with a significantly poorer survival when compared to non-adenocarcinoma and this was reported by Harada et al [85]. We also found that the survival was significantly better for infiltrating ductal carcinoma of the breast when compared with lung cancer; both non-small and small cell cancer, and this was in agreement with Jeene et al. and Wong et al [59,65]. Other studies have found no prognostic significance of histology [86-88]. Tumor size did not seem to influence the survival in our group, and this is concordant with Staudt el al. who reported no significant effect of the size on survival. Thakur et al. on the other hand, reported a better survival for lesions<3 cm when compared with those ≥ 3 cm [66,88].

In multivariate analysis, we found that the use of a local treatment modality (SRS or surgery), primary breast cancer, higher RT dose (30 Gy), controlled primary, age less than 65 years, female and 2 weeks or more interval from BM to start RT remain the most significant predictive factors for survival. In a study for survival among breast and lung cancer patients treated with WBRT by Jeene et al. they reported that primary site age and sex were the predictive factors. According to Wong et al. primary tumor site still stands as a significant predictive factor in addition to age and KPS, while Thakur et al. reported that number and size of BM in addition to RT dose were the most predictive factors for survival [59,65,66]. Patil et al. reported that number of BM and KPS were significant predictive factors, while Saito et al. found that high KPS and resection status were the significant predictive factors for survival. It is therefore evident from trials that have been conducted, that there is no consistency demonstrable among the predictive factors for the survival [89,90].

Many scoring systems or predictive models for better selection of patients have been assessed. In 1997 The Radiation Therapy Oncology Group (RTOG) developed the Recursive Partitioning Analysis (RPA) and the Grading Prognostic Assessment (GPA) was developed in 2008 and more recently, disease specific GPAs were developed mainly for lung and breast in 2012 [20,70,91]. RTOG RPA classified patients into 3 classes; Class One, those who have Karnofsky Performance Score (KPS) of ≥ 70, age <65, and controlled primary tumour without extracranial metastases, Class 3 patients have KPS <70, all other patients fall into Class 2, including those with KPS ≥ 70 but other unfavorable characteristics, such as uncontrolled primary tumor, extracranial metastases, or age ≥ 65. The median survival for classes 1,2 and 3 were 7.1,4.2 and 2.3 months respectively [20,43,92]. GPA classification excluded the status of extracranial disease acknowledging only its presence or absence; it kept age and KPS and added number of brain metastases and each factor was given values of 0,0.5 and 1. Four prognostic groups were created and the median survival was 2.6 months,3.8 months, 6.9 months and 11 months for GPA scores of 0-1,1.5-2.5,4 and 3.5-4 respectively [91].

Diagnosis-specific graded prognostic assessment was developed after the primary tumour site was shown to be an important prognostic factor in some studies [30]. Despite the availability of diverse scoring systems, there is still a lack of consensus regarding which clinical factors have the major impact on treatment decision-making concerning the use of WBRT and making a clinical decision based on them is still a challenge as it is difficult to identify patients with very short survival (<2 months) after WBRT and the survival for groups with poor prognostic score based on RPA or DS GPA is still heterogonous.

Quartz trial which is the only randomized trial that investigated the benefit of WBRT in non-small lung cancer patients with multiple brain metastases. In this trail, patients were prospectively randomized into best supportive care including dexamethasone plus WBRT or best supportive care and dexamethasone alone. This trail confirmed that WBRT does not significantly improve quality of life or overall survival, except for young patients [32]. Although this trail was criticized in relation to its protracted recruitment period and its inclusion of patients with multiple poor prognostic factors, yet it still quires the role of WBRT in non-small cell lung cancer.

In an attempt to find predictive factors for the development of BM among lung cancer patients, we collected data for 48 patients with lung cancer without BM and compared with same number of patients from our study group with BM. In univariate analysis, we found from our study that, age >65 years, female, smoking, weight loss, poor performance status, advanced stage at presentation and adenocarcinoma subtype were all factors associated with higher incidence of BM in lung cancer patients. While with multivariate analysis, only age, smoking and weight loss remain risk factors for development of BM in lung cancer patients. Different studies have investigated alternative predictive factors for development of BM in lung cancer patients. In a study by Waqar et al. it was found, on multivariate analysis, that younger age, adenocarcinoma or large cell histology, tumor size >3 cm, tumor grade ≥ II and node positive disease

were all factors associated with brain metastases and they created a scoring system to predict the development of BM [93].

Zhang et al. managed to gather data for 26, 154 patients with lung squamous cell carcinoma. After doing multivariate cox regression, they found that age at the time of diagnosis, tumor grade and stage, the number of extracranial metastatic sites, the use of chemotherapy, surgery, and radiation were independent factors for predicting BM. Then they developed a nomogram using those factors to predict BM [94].

In an interesting study by Yokoi et al. who investigated the value of intensive follow up with brain CT scan in early-stage lung cancer patients treated with surgery, they detected BM in 11/128 patients, of which 7/11 were asymptomatic and 5/11 had a single metastatic lesion. Even in this group with early lung cancer about 9% developed brain metastasis and the majority were asymptomatic, so it is probably reasonable to expect a higher incidence of BM among asymptomatic patients who presented with advanced disease [95].

Conclusion

The role of whole brain radiotherapy in the management of multiple brain metastases is still a challenge. Despite the availability of diverse prognostic scoring systems, there is still a lack of consensus regarding which clinical factors have the major impact on treatment decision-making. However, it is reasonable not to offer WBRT for patients with multiple brain metastases, if the patients are elderly, have poor performance status, uncontrolled primary and have multiple extracranial metastases. We believe that it would probably be worthwhile to investigate predictive models and nomograms which might be able to predict BM in asymptomatic patients, when the disease burden is low and there is effective local treatment available possibly in the form of SRS or resection.

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