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Original Research Article

Profile and outcome of treatment in non-small cell lung cancer with brain metastasis

Uzma Rehman[1], Nazir Ahmed Khan[1], Shahida Nasreen[1], Irfan Rasool Gadda[2]*

[1]Department of Radiation Oncology, Sher -I- Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India
[2]Department of Radiation Oncology, Government Medical College, Srinagar, Jammu and Kashmir, India

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***Correspondence:**
Dr. Irfan Rasool Gadda,
E-mail: docirfan2010@gmail.com

ABSTRACT

Background: Brain metastasis is a common problem in patients with NSCLC. This study was done to study the risk factors associated with the development of brain metastasis and assess treatment response in NSCLC to improve patient survival.
Methods: This was a retro-prospective study in which 126 patients with non-small cell lung carcinoma with brain metastasis were taken for the study.
Results: The mean age in study group was 56.1±12.72 years. Adenocarcinoma was found in 57.1% and squamous cell carcinoma in 41.3% patients. 65.9% patients received chemotherapy for primary disease followed by targeted therapy in 34 (27.0%) patients. 53.9% patients received WBRT after diagnosis of brain metastasis and 23% WBRT and systemic chemotherapy while as14.3% received WBRT and targeted therapy and 2.4% received WBRT, systemic chemotherapy and targeted therapy, 1.6% patients received systemic chemotherapy, WBRT and local RT to the primary site and 0.8% each was treated with gamma knife therapy; surgery, WBRT and targeted therapy; SRS and WBRT. Median overall survival of patients with brain metastasis who received WBRT was 2.5 months and patients who received WBRT and systemic chemotherapy was 9.0 months while patients with brain metastasis who received WBRT and targeted therapy was 14.3 months.
Conclusions: The median overall survival as per treatment received after diagnosis of brain metastasis was higher in patients who received WBRT and targeted therapy as compared to patients who received WBRT and systemic chemotherapy and patients who received WBRT only.

Keywords: Lung carcinoma, Brain mets, WBRT

INTRODUCTION

According to GLOBOCAN 2020, lung cancer is the 2nd most common cancer worldwide with an estimated 11.4% new cases. It is the most frequently occurring cancer and the leading cause of cancer death in men accounting for 18.0% of the total cancer deaths.[1] In the US, lung cancer is the second most common cancer and the most common cause of cancer-related death in both men and women.[2] In Kashmir, Lung cancer ranks number one among all cancers with a total of 2296 cases registered in the regional cancer centre, SKIMS from 2016 to 2020.

Lung carcinoma includes a series of different diseases which can roughly be divided into two groups based on clinical and histo-pathological features: NSCLC accounting for almost 80% of lung cancer diagnoses and SCLC responsible for the remaining 20%.[3] Among NSCLCs, Adenocarcinoma is currently the most frequent histologic type and accounts for almost half of all cases.[4]

Brain metastasis is a common problem in patients with NSCLC. About 7%-10% of NSCLC patients present with brain metastasis at the time of initial diagnosis and as many as 20-40% of patients develop brain metastasis at some point during their illness.[5,6]

The incidence of brain metastasis has been increasing due to improvements in the control of systemic extra-cranial disease and the widespread availability of imaging modalities such as magnetic resonance imaging (MRI), which has increased the detection of subclinical disease.[7,8] NSCLC with brain metastasis often has a poor prognosis, with the median survival ranging between 4 and 6 months.[9]

Many studies have been done about the risk factors and clinical factors such as age, stage, and histology which have shown association with brain metastasis in NSCLC patients.[10-14]

Historically, the survival of patients with brain metastasis has been considered very poor with the risk of death and significant impairments in quality of life being increased by a factor of 4.[15-18]

The median survival of patients with brain metastasis from NSCLC is approximately 1 month without treatment, 2-3 months when treated with steroids alone and 3-6 months when treated with whole brain radiotherapy.[19-21] WBRT has always been considered the treatment of choice for brain metastasis because it prolongs the mean survival rate from 1-6 months.[22]

While it has been recognized for decades that patients with a solitary lesion might live disease-free for many years after effective treatment, this scenario is uncommon. Among the new treatment options, apart from surgery, the last 20 years have seen the introduction of stereotactic radiosurgery in clinical practice

Addressing prognostic factors in patients with NSCLC and single brain metastasis, it was found that the only variable associated with a significantly longer survival was squamous cell histology ($p<0.02$).[23] Subsets of patients with stage IV NSCLC and one solitary brain lesion as the only site of metastatic disease have been reported to benefit from combined neurosurgery and lung surgery.[23,24]

The survival is significantly higher in patients with NSCLC and metachronous metastasis who had N0 status with respect to survival in patients with N1-2 status.[25] The discovery of the EGFR mutation and ALK rearrangement and then the introduction of first-generation tyrosine kinase inhibitors to the treatment of non-small cell lung carcinoma allowed for longer progression-free survival (PFS), higher objective response rates (ORR), and better disease control rates (DCR) in comparison with two-drug platinum-derivative-based chemotherapy.[26-28]

This study was done to study the risk factors associated with the development of brain metastasis and assess the response to treatment of brain metastasis in NSCLC and also to study the correlation of brain metastasis with clinico pathological factors in order to improve survival by early detection, prediction and treatment in these cases.

METHODS

The study was conducted in the department of radiation oncology, Sheri Kashmir institute of medical sciences, Srinagar. This was a retro-prospective study in which all patient data from 2016 to 2020 was retrieved from record files.

During this period, the total number of Lung carcinoma patients registered was 2296, out of which 126 patients with non-small cell lung carcinoma who had brain metastasis were taken for the study.

Inclusion criteria

Histologically confirmed NSCLC, imaging documented brain metastasis, (essentially); with or without visceral metastasis either at the initial presentation of disease or subsequently developing after treatment during follow-up, all age groups of patients and both genders were included in the study.

Exclusion criteria

NSCLC without brain metastasis, cases who have not received any treatment were excluded from study.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet (Microsoft excel) and then exported to the data editor of SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean ± SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar and pie diagrams. Analysis of variance (ANOVA) was employed for comparison of continuous variables. A p of less than 0.05 was considered statistically significant.

The study was undertaken only after clearance by the institutional ethical committee.

RESULTS

The most common age group affected in our study was 51-60 years i.e. 38 (30.2%) patients, 30 (23.8%) were in the age group of 61-70 years while 28 (22.2%) patients were aged between 41-50 years, 16 (12.7%) patients were aged <40 years while 14 (11.1%) patients were aged >70 years as shown in Table 1. The mean age in our study group was 56.1±12.72 years.

There was male predominance in our study with 72.2% (n=91) males versus 27.8% (n=35) females with a male-to-female ratio of 2.6:1 as shown in Table 1. There were 82 (65.1%) smokers in the present study as shown in Table 1. As per histopathology, adenocarcinoma was found in 72 (57.1%) patients, squamous cell carcinoma in 52 (41.3%) patients, large cell neuroendocrine and carcinoid in 1 (0.8%) patient each as shown in Table 1.

In our study hypertension was seen in 22 (17.5%) patients, diabetes mellitus in 9 (7.1%) patients, Hypothyroidism in 6 (4.8%) patients, BHP in 5 (4%) patients, coronary artery disease in 4 (3.2%) patients, COPD in 3 (2.4%) patients, pulmonary Kochs in 3 (2.4%) patients and bronchial asthma, RBBB and atrial septal defect in 1 (0.8%) patient as shown in Table 2.

Table 1: Clinicopathological profile of study patients.

Variables	N	Percentage (%)
Age (in years)		
≤ 40	16	12.7
41-50	28	22.2
51-60	38	30.2
61-70	30	23.8
> 70	14	11.1
Total	126	100
Mean ± SD (Range)=56.1±12.72 (20-85 years)		
Gender		
Male	91	72.2
Female	35	27.8
Total	126	100
Male: female=2.6:1		
Smoking history		
Smoker	82	65.1
Non smoker	44	34.9
Total	126	100
Histological type		
Adenocarcinoma	72	57.1
Squamous cell carcinoma	52	41.3
Large cell neuroendocrine	1	0.8
Carcinoid	1	0.8
Total	126	100

Table 2: Underlying comorbidities among study patients.

Comorbidity	N	Percentage (%)
Hypertension	22	17.5
Diabetes mellitus	9	7.1
Hypothyroidism	6	4.8
COPD	3	2.4
CAD	4	3.2
BHP	5	4.0
Pul Kochs	3	2.4
Asthma	1	0.8
RBBB	1	0.8
ASD	1	0.8

Table 3: Treatment modalities received for primary disease.

Treatment modality	N	Percentage (%)
Chemotherapy	83	65.9
Targeted therapy	34	27.0
No treatment received	9	7.1
Total	126	100

Most of the patients in our study i.e. 83 and (65.9%) received chemotherapy for primary disease followed by targeted therapy in 34 and 27.0 patients as shown in Table 3.

Table 4: No. of cycles of chemotherapy received.

No. of cycles	N	Percentage (%)
< 3	12	13.6
3-6	55	62.5
>6	21	23.8
Total	88	100

Table 5: Duration of intake of targeted therapy.

Duration (Months)	N	Percentage (%)
<6	7	18.4
6-12	9	23.6
12-24	11	39.4
≥24	7	18.4
Total	38	100

Mean±SD=13.6±9.97

In our study, most of the patients, 55 (62.5%) received 3-6 cycles of chemotherapy followed by >6 cycles in 21 (23.8%) patients. 12 (13.6%) patients received <3 cycles as shown in Table 4.

15 (39.4%) patients in our study received targeted therapy for 12-24 months, 9 (23.6%) patients for 6-12 months, 7 (18.4%) patients each received targeted therapy for <6 months and ≥24 months respectively as shown in Table 5.

Table 6: No. of patients who underwent surgery and radiotherapy.

Surgery	N	Percentage (%)
Yes	7	5.6
No	119	94.4
Total	126	100
Radiotherapy		
Radiotherapy only	15	48.4
Radiotherapy concurrent with chemotherapy	16	51.6
Total	31	100

Only 7 (5.6%) patients in our study underwent surgery for primary disease and 16 (51.6%) patients received

radiotherapy concurrent with chemotherapy while 15 (48.4%) patients received radiotherapy only (Table 6).

Table 7: Treatment received after diagnosis of brain METS.

Treatment	N	Percentage (%)
WBRT	68	53.9
WBRT/systemic chemotherapy	29	23.0
WBRT/targeted therapy	18	14.3
WBRT/systemic chemotherapy/ targeted therapy	3	2.4
Gamma knife therapy	1	0.8
Surgery/WBRT/targeted therapy	1	0.8
SRS/ targeted therapy	1	0.8
SRS/ WBRT	1	0.8
Systemic chemotherapy/WBRT/ Local RT	1	0.8
WBRT/ chemotherapy/ local RT	1	0.8
WBRT/ Local RT	1	0.8
WBRT/ Local RT/ targeted therapy	1	0.8
No treatment	2	1.6
Total	126	100

Treatment received was WBRT in 68 (53.9%) patients diagnosed with brain metastasis; WBRT/ systemic chemotherapy in 29 (23%) patients; WBRT/ targeted therapy in 18 (14.3%) patients; WBRT/ systemic chemotherapy / targeted therapy in 3 (2.4%) patients.

Table 8: Overall survival of study patients.

Survival (Months)	N	Percentage (%)
< 1	9	7.1
1-6	57	45.2
6-12	22	17.5
12-24	26	20.6
24-36	7	5.6
>36	5	4.0
Total	126	100

Median (Range)=5 months (7 days to 38 months)

Chemotherapy/WBRT/ local radiotherapy to the primary site in 2 (1.6%) One patient (0.8%) each was treated with gamma knife therapy; surgery/ WBRT/targeted therapy; SRS/ WBRT; WBRT/ local RT to the primary site; WBRT/ local RT to primary site/ targeted therapy as shown in Table 7.

Overall, survival of patients ranged between 7 days to 38 months with a median survival of 5 months as shown in Table 8.

Table 9: Overall survival as per treatment received after diagnosis of Brain METS.

Treatment	N	Median	95% CI	P value
WBRT	66	2.5	2.1-2.8	<0.001*
WBRT/ systemic chemotherapy	29	9.0	8.4-10.1	
WBRT/ targeted therapy	18	14.3	12.5-17.2	

The 66 patients diagnosed with Brain metastasis who received WBRT survived for a median time of 2.5 months. 29 patients with brain metastasis who received WBRT/systemic chemotherapy survived for a median time of 9.0 months while 18 patients with brain metastasis who received WBRT/targeted therapy survived for 14.3 months (Table 9). A statistically significant association ($p<0.05$) was observed with overall survival as per treatment received after diagnosis of brain metastasis and treatment received.

DISCUSSION

The mean age of our patients was 56.1±12.72 years with a male predominance of 72.2% versus 27.8% female with a male-to-female ratio of 2.6:1which is comparable with the study done by Antuna et al who observed that 58.8 years was the average age of their patients with a range of 43-82 years and men constituted 63.4% of the study population compared to 36.6% women in their study.[28]

In our study, the most common underlying comorbidity was hypertension 17.5% followed by diabetes mellitus 7.1% and Hypothyroidism in 4.8% of patients which is comparable to the study conducted by Lee et al.[29]

There were 65.1% smokers and 34.9% non-smokers in our study which was comparable to a study conducted by Chawla et al.[30]

In our study, adenocarcinoma was found in 57.1% of patients, squamous cell carcinoma in 41.3% of patients, large cell neuroendocrine and carcinoid in 0.8% patients each, which is consistent with a study conducted by He et al in which adenocarcinoma was found in 51.43%, squamous cell carcinoma in 44.29% and large cell neuroendocrine in 1.14% patients.[31]

In our study, most of patients, 62.5% received 3-6 cycles of chemotherapy followed by >6 cycles in 23.8% of patients. 13.6% of patients received <6 cycles which.is comparable with Soon et al who in their study identified 13 trials which included patients with stage III to IV non-small cell lung cancer and found that extending chemotherapy was associated with clinically modest, but statistically significant 8% reduction in hazard of death as compared with standard duration of chemotherapy.[32]

There was no statistically significant heterogeneity in HRs for overall survival from individual trials.

Further in our study, 31 patients received radiotherapy for primary disease out of which 51.6% patients received radiotherapy concurrent with chemotherapy while 48.4% patients received radiotherapy alone which is comparable with a study conducted by O'Rourke et al who in their study included nineteen randomized studies of concurrent chemoradiotherapy versus radiotherapy alone and found that chemoradiotherapy significantly reduced overall risk of death, overall progression-free survival at any site.[33]

Treatment received after diagnosis of brain metastasis was WBRT in 52.4% of patients, WBRT and systemic chemotherapy in 23%, WBRT and targeted therapy in 14.3%, WBRT, systemic chemotherapy and targeted therapy in 2.4% while as systemic chemotherapy, WBRT and local RT to primary site in 2 (1.6%) and each 0.8% patients were treated with gamma knife therapy alone; surgery, WBRT and targeted therapy; SRS and targeted therapy; SRS and WBRT; WBRT and local RT to primary site; WBRT, local RT to primary site and targeted therapy

In our study, the median overall survival of patients was 5 months. However, in a study conducted by Ali et al the median overall survival of NSCLC patients with brain metastases was 7.8 months.[34]

Further in our study, median overall survival of patients who received WBRT after diagnosis of brain metastases was 2.5 months, it was 9 months in patients who received WBRT and systemic chemotherapy and 14.3 months in patients who received WBRT and targeted therapy. However, in a study conducted by Chen et al the median overall survival of patients who received systemic medication plus brain localized treatment-15.3 months to systemic medication only which was 11.1 months and brain localized treatment only which it was 7 months.[35]

Limitations

Our study highlights the risk profile and survival of non-small cell lung cancer patients with brain metastasis in this part of the country. Consequently, early detection and use of novel treatment strategies may modify the natural progression of brain metastases, improve progression-free survival and quality of life. It is therefore important to carry out further studies in a large independent cohort.

CONCLUSION

Adenocarcinoma was the most common histological type followed by squamous cell carcinoma in our study. The median overall survival as per treatment received after diagnosis of brain metastasis was higher in patients who received WBRT and targeted therapy as compared to patients who received WBRT and systemic chemotherapy and patients who received WBRT only. Thus, clearly proving the survival benefit of combined modality i. e., WBRT and targeted therapy.

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