Brain metastasis is one of the most feared complications of cancer that poses significant mortality and morbidity in patients with advanced cancer. The incidence is rising because of greater use of magnetic resonance imaging and spectroscopy; and increased survival from recent advances in immunotherapy and modern radiotherapy techniques. Despite all, the prognosis remains poor. This study aimed to analyze prognostic factors and overall survival in patients with brain metastases. A total of 145 patients were analyzed from July 2014 to June 2015 for various prognostic factors prospectively. Survival analysis was done using Kaplan–Meier curve. The median overall survival was 6 months, while 1- and 2-year survival rates were 8.3% and 1.4%, respectively. Median survival was highest with surgery followed by radiotherapy (11 months). Whole-brain radiotherapy (WBRT) significantly improved the survival ($P = 0.006$). The most common primary was lung cancer (58%) and the most common histology was adenocarcinoma (36%). Most patients (38%) were diagnosed upfront with brain metastases. Most of the lesions were multiple (80%) and located in cerebrum (58%). Survival was significantly improved with female gender ($P = 0.003$), Eastern Cooperative Oncology Group performance status (PS) 0–2 ($P = 0.006$), breast primary ($P = 0.004$), time lag of >6 months ($P < 0.001$), solitary lesion ($P = 0.002$), and controlled primary ($P = 0.017$). WBRT remains the cornerstone of the management of brain metastases. The present study concludes that the survival of patients with brain metastases is significantly improved with female gender, good PS, primary breast cancer, time lag of >6 months between diagnosis of the primary tumor and development of brain metastases, solitary lesion, and controlled primary tumor.
For multiple lesions, WBRT is the only treatment option. Steroids are prescribed in almost all the patients.[13-17] The median survival is around 7 months in most of the studies for patients treated with WBRT, while <2 months for patients continued on steroids alone. Good prognostic features described in literature include age <60 years, female sex, good performance status (PS), breast as primary, controlled primary, absence of extracranial disease, ≤3 lesions, supratentorial lesions, and absence of neurocognitive abnormalities, apart from WBRT.[18-22]

**Subjects and Methods**

The present study was carried out at the department of Radiotherapy, SMS Medical College, Jaipur, from July 2014 to June 2015. A total of 152 patients presented with brain metastases, of which 7 patients having a history of previous WBRT were excluded. All patients were evaluated for histopathological confirmation of either the primary tumor or of the brain lesion itself (in case of the postoperated solitary brain lesion) and imaging of the brain, which included either CECT or MRI.

Various prognostic factors that were evaluated include baseline patient characteristics (age, gender, and Eastern Cooperative Oncology Group [ECOG] PS), tumor characteristics (site of primary tumor, histopathology, number and location of lesions), clinical characteristics (presenting sign or symptom, time lag between diagnosis of primary tumor and development of brain metastases, status of primary tumor [whether controlled or not], and presence or absence of extracranial metastasis), and treatment characteristics (treatment modality [steroids only, WBRT, or surgical excision followed by WBRT] and survival period). Out of 145 patients included in the study, 29 (20%) patients were continued on steroids only and 11 (7.6%) patients underwent surgical resection of the brain lesion followed by WBRT. WBRT was delivered over cobalt teletherapy machine (ATC-C9/Bhabhatron II) using conventional planning with dose of 30 Gy in 10 fractions with 3 Gy per fraction for 2 weeks. For survival analysis, the surviving time was the time between diagnosis of brain metastases and the death of the patient.

**Statistical analysis**

For statistical analysis, all data were recorded and analyzed on Microsoft Excel 2007 and XLSTAT software version 2017 for Windows (Addinsoft, NY, USA). Chi-square test was used for all categorical data. P value reports were two tailed and an alpha level of 0.05 was used to assess statistical significance. Survival analysis was done using Kaplan–Meier survival curve.

**Results**

The association of brain metastases with various parameters is shown in Table 1. In the present study, the most common cohort was of young male patients with primary lung adenocarcinoma presenting with headache, diagnosed upfront with more than four metastases in both cerebral hemispheres with uncontrolled primary and presence of metastases in other sites. The Kaplan–Meier survival curve of the patients is shown in Figure 1. The median survival period in our study was 6 months (range, 2 weeks–29 months), whereas 1- and 2-year survival rates were 8.3% and 1.4%, respectively.

Institution of WBRT remained the most important significant factor affecting survival of patients with brain metastases (P = 0.006). Patients with single lesion who underwent surgery followed by adjuvant WBRT had the longest survival. Other factors with which survival was found to be significantly associated in the present study were female gender (P = 0.003), ECOG PS 0–2 (P = 0.006), breast being the primary tumor (P = 0.004), infiltrating ductal carcinoma histopathology (P = 0.018), time lag of >6 months between diagnosis of the primary tumor and development of brain metastases (P < 0.001), solitary lesion (P = 0.002), and controlled primary tumor (P = 0.017).

**Discussion**

The baseline patient and tumor characteristics of patients with brain metastases in the present study are matched with most of the previously reported studies. Ekici et al. evaluated the clinical status, prognostic factors, and treatment modalities affecting survival in 315 patients with brain metastasis treated with WBRT in Turkey between 2004 and 2014.[23] They found that the average patient age of onset was 58 years. The primary tumor site was lung (68%) followed by breast (12%), the primary remained unknown in 4.4% of cases. Hazuka et al. have reported lung as the most common (56%) primary site and adenocarcinoma as the most common (46%) tumor histology.[24] Egawa et al. also reported lung (57.5%) as the most common primary site followed by breast (11%).[25] Saha et al. retrospectively analyzed the demographic and clinical profile of 72 patients with brain metastases and found that brain metastases were more common in males and occurred mostly in the sixth decade of life.[26] Carcinoma lung was the most common primary while adenocarcinoma was the most common histology of the primary that gave rise to metastases. However, Akhavan et al. concluded that breast cancer was the most common primary followed by carcinoma lung as...
Table 1: Univariate analysis of various baseline patient, tumor, clinical, and treatment characteristics of patients with brain metastases

| Parameters | Overall patients, n (%) | Patients with >1 year survival, n (%) | P-value |
|------------|-------------------------|---------------------------------------|---------|
| Gender     |                         |                                       |         |
| Male       | 98 (67.6)               | 3 (25)                               | 0.003   |
| Female     | 47 (32.4)               | 9 (75)                               |         |
| Age (years)|                         |                                       |         |
| ≤60        | 102 (70.3)              | 10 (83.3)                            | 0.339   |
| >60        | 43 (29.7)               | 2 (16.7)                             |         |
| ECOG performance status |               |                                       |         |
| 0-2        | 87 (60)                 | 12 (100)                             | 0.006   |
| 3-4        | 58 (40)                 | 0                                     |         |
| Primary tumor |                      |                                       |         |
| Lung       | 84 (58)                 | 2 (16.7)                             | 0.004   |
| Breast     | 26 (17.9)               | 7 (58.3)                             |         |
| Other known| 26 (17.9)               | 3 (25)                               |         |
| Unknown    | 9 (6.2)                 | 0 (0)                                |         |
| Histopathology |                   |                                       |         |
| Adenocarcinoma | 52 (36)               | 3 (25)                               | 0.018   |
| Squamous cell carcinoma | 34 (23.4)             | 2 (16.7)                             |         |
| Infiltrating ductal carcinoma | 26 (17.9)         | 7 (58.3)                             |         |
| Small cell carcinoma | 15 (10.3)             | 0                                     |         |
| Others     | 18 (12.4)               | 0                                     |         |
| Time lag between diagnosis of primary tumor and development of brain metastases (months) | |                                       | <0.001 |
| 0          | 55 (38)                 | 0 (0)                                |         |
| ≤6         | 46 (31.7)               | 1 (8.3)                              |         |
| 6-12       | 30 (20.7)               | 6 (50)                               |         |
| >12        | 14 (9.6)                | 5 (41.7)                             |         |
| Initial presentation |                   |                                       | 0.813   |
| Headache   | 87 (60)                 | 9 (75)                               |         |
| Neurological deficit | 29 (20)             | 2 (16.7)                             |         |
| Seizures   | 8 (5.5)                 | 0 (0)                                |         |
| Drowsiness | 4 (2.8)                 | 0 (0)                                |         |
| Other      | 17 (11.7)               | 1 (8.3)                              |         |
| Site of lesion |                     |                                       | 0.852   |
| Cerebrum   | 84 (58)                 | 8 (66.7)                             |         |
| Cerebellum | 15 (10.3)               | 1 (8.3)                              |         |
| Midbrain   | 3 (2)                   | 0                                     |         |
| Diffuse    | 43 (29.7)               | 3 (25)                               |         |
| Hemispherical involvement |                  |                                       | 0.800   |
| Single     | 67 (46.2)               | 6 (50)                               |         |
| Both       | 78 (53.8)               | 6 (50)                               |         |
| Number of lesions |                |                                       | 0.002   |
| 1          | 18 (12.4)               | 6 (50)                               |         |
| 2-3        | 11 (7.6)                | 1 (8.3)                              |         |
| ≥4         | 116 (80)                | 5 (41.7)                             |         |
| Extracranial metastases |                |                                       | 0.110   |
| Present    | 94 (64.8)               | 5 (41.7)                             |         |
| Absent     | 51 (35.2)               | 7 (58.3)                             |         |
| Primary tumor |                    |                                       | 0.017   |
| Controlled | 47 (32.4)               | 8 (66.7)                             |         |
| Not controlled | 98 (67.6)             | 4 (33.3)                             |         |
| Treatment  |                         |                                       | 0.006   |
| Steroids only | 29 (20)             | 0                                     |         |
| Surgery followed by WBRT | 11 (7.6)          | 4 (33.3)                             |         |
| WBRT       | 105 (72.4)              | 8 (66.7)                             |         |

EGOG: Eastern Cooperative Oncology Group, WBRT: Whole-brain radiotherapy
majority of the cases were females in their study.[27] However, adenocarcinoma remained the most common histology of the primary tumor giving rise to brain metastases.

The clinical presentation of the patients in the present study is also in agreement with most of the studies cited in the literature. Ekici et al. reported in their study that 26.6% of patients had single brain metastasis, 22.5% had two or three lesions and 50.4% patients had more than three lesions. About 15.8% of patients underwent surgical resection. Akhavan et al. in their study had shown that 20.4% patients had a single brain metastasis, 8.7% had two or three lesions, while 42.2% patients had more than three lesions. Saha et al. concluded that multiple metastases were more common than the single metastasis, supratentorial lesions were more common than infratentorial lesions, and parietal lobe was the most common site of involvement. However, Delattre et al. have reported single brain metastasis in 49%, two in 21%, three in 13%, four in 6%, and five or more in 11% of the patients.[28] Posner and Chernik,[29] and Victor have reported headache as the most common symptom in 49% and 42% of the patients, respectively. Victor also had shown that the primary disease was not controlled at the time of detection of metastases in two-third of the patients.

The treatment characteristics and survival outcome of the patients in the present study also replicate the results of previous studies. Ekici et al. showed that median overall survival of patients treated with a combination of surgery and WBRT was significantly better compared with those treated with WBRT alone (13.5 vs. 5.5 months, \( P < 0.001 \)) and 1- and 2-year survival rates were 17 and 4.7%, respectively. Akhavan et al. reported an overall survival of 10.1 months and 1- and 2-year survival rates of 27% and 12%, respectively. Lagerwaard and Levendag reported the median survival of 1.6 months only in patients treated with steroids alone.[30] Lagerwaard et al. have reported an overall median survival of 3.4 months, with 6-month, 1-year, and 2-year survival rates of 36%, 12%, and 4%, respectively. Survival was statistically significantly different between treatment modalities, with median survival of 1.3 months in patients treated with steroids only, 3.6 months in patients treated with radiotherapy, and 8.9 months in patients treated with neurosurgery followed by radiotherapy (\( P < 0.001 \)). Hazuka et al. have reported the median survival of 11 months and the 1- and 2-year survival rates of 40% and 12%, respectively. Egawa et al. have reported the 50% survival period of 4.1 months for radiotherapy only, 4.2 months for radiotherapy and surgery, and 6.9 months for combined radiotherapy and chemotherapy. Sen et al. have reported the median survival of 5 months.[31] Lentsch et al. have reported the median survival of 82 weeks for 10/162 surgical patients, 26 weeks for 145/162 patients treated with radiotherapy, and 5 weeks for the 17/162 patients who received symptomatic (corticosteroid) therapy only.[32]

The factors associated significantly with survival in patients with brain metastases in the present study are more or less the same with what has been reported in the literature. Lagerwaard et al. concluded that PS, response to steroid treatment, systemic tumor activity, and serum lactate dehydrogenase were independent prognostic factors with the strongest impact on survival, second only to treatment modality. In patients with lung primaries, sex was found to have a significant impact on survival. In patients with breast primaries, interval between primary tumor and development of brain metastases appeared to be a statistically significant prognostic factor. Lagerwaard and Levendag concluded that PS, age, extracranial metastases, and primary tumor status were the major determinants of survival for patients with brain metastasis. Hazuka et al. concluded that neurologic impairment at the time of diagnosis and the presence of multiple brain metastases were associated with a significantly poorer survival; solitary metastasis, gross total resection, and tumor histopathology of adenocarcinoma significantly prolonged survival; whereas, primary tumor site, presence of active extracranial disease, and radiation dose had no significant effect on survival. Sen et al. concluded that survival was significantly decreased in the presence of symptoms related to the primary tumor (\( P = 0.001 \)). Lentsch et al. concluded Karnofsky Index, dose of radiation (\( P < 0.001 \)), solitary metastases (\( P < 0.04 \)), and primary tumor size (\( P < 0.04 \)) as significant prognostic factors for survival. Saha et al. did not find any relationship of occupation or socioeconomic status with the incidence of brain metastases.

**Conclusions**

WBRT remains the cornerstone of the management of multiple brain metastases, whereas for solitary lesion, surgical excision followed by WBRT is the preferred treatment modality. Survival of patients with brain metastases is significantly improved with female gender, good PS, primary breast cancer, infiltrating ductal carcinoma histology, time lag of >6 months between diagnosis of the primary tumor and development of brain metastases, solitary lesion, and controlled primary tumor apart from institution of WBRT.

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**Conflicts of interest**

There are no conflicts of interest.

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