

## RESEARCH ARTICLE

# Survival of Brain Metastatic Patients in Yazd, Iran

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### Abstract

**Background:** Brain metastasis occurs when cancerous cells come from a known (or sometimes an unknown) primary tumor to the brain and implant and grow there. This event is potentially lethal and causes neurologic symptoms and signs. These patients are treated in order to decrease their neurologic problems, increase quality of life and overall survival. **Materials and Methods:** In this study we evaluated clinical characteristics of 206 patients with brain metastases referred to our center from 2004 to 2011. **Results:** The mean age was 53.6 years. The primary tumors were breast cancer (32%), lung cancer (24.8%), lymphoma (4.4%), sarcoma (3.9%), melanoma (2.9%), colorectal cancer (2.4%) and renal cell carcinoma (1.5%). In 16.5% of the patients, brain metastasis was the first presenting symptom and the primary site was unknown. Forty two (20.4%) patients had a single brain metastasis, 18 patients (8.7%) had two or three lesions, 87 (42.2%) patients had more than three lesions. Leptomeningeal involvement was seen in 49 (23.8%) patients. Thirty five (17%) had undergone surgical resection. Whole brain radiation therapy was performed for all of the patients. Overall survival was 10.1 months (95% CI; 8.65-11.63). One and two year survival was 27% and 12% respectively. **Conclusions:** Overall survival of patients who were treated by combination of surgery and whole brain radiation therapy was significantly better than those who were treated with whole brain radiation therapy only [13.8 vs 9.3 months (p=0.03)]. Age, sex, primary site and the number of brain lesions did not show significant relationships with overall survival.

**Keywords:** Brain - metastasis - survival - Yazd, Iran

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### Introduction

Metastatic brain tumors are ten times more common than primary brain tumors (Nichols et al., 2013). Although the exact incidence of brain metastases is not clear, the population based studies suggest 170000 new cases of brain metastases occur each year in US. (Kim et al., 2009; Stelzer, 2013). Brain metastatic tumors are poor prognoses and the patients survive only one month without treatment (Saito et al., 2006). Brain metastases were increased in recent years due to increase cancer patients' survival and widespread use of imaging modalities (Nichols et al., 2013). The peak of brain metastasis is between fifth and seventh decade of life and it is slightly more common in men (Winn et al., 2003). Tumors have different tendency to metastasis to brain. In adults, lung cancer, breast cancer and melanoma are the most common causes of brain metastases respectively (Nussbaum et al., 1996). In 15% of patients primary tumors remains unknown (Soffietti et al., 2002). Usually metastatic brain tumors are diagnosed using imaging studies such as CT scanning and MRI and less commonly by tissue sampling or CSF analysis. Surgery, radiation therapy and chemotherapy are used for treatment. Radiation therapy may be used as whole brain radiation therapy, stereotactic radiosurgery or

combination of these to modalities (Min Kyung Hyun et al., 2013; Duan et al., 2014). In some studies combination of whole brain radiation therapy and chemotherapy had been used with encouraging results (Wen-Jing et al., 2012; Wen-Guang et al., 2013). These days targeted therapy have been used in combination of other treatment modalities in some patients (Yong et al., 2013). We decided to evaluate clinicopathologic and survival rate of brain metastatic patients in our province.

### Materials and Methods

We evaluated the patients who referred to our center (Shahid Ramezanzadeh Radiation Oncology Center, Yazd, Iran) due to brain metastasis from September 2004 until September 2011. Imaging (CTscan and/ or MRI) had been performed for all of the patients. For 35 patients surgery was carried out. Data about age, sex, the site of primary tumors and the number of brain lesions were recorded. All of the patients received whole brain radiation therapy (WBRT). We applied the dose 30 Gy in 10 daily fractions for almost all of the patients. Overall survival was calculated from the day of diagnosis of brain metastasis (pathologically or radiologically) to death or last visit. Through coordination with The Health Center of the

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Province, data on mortality demographics of patients was obtained, however information regarding other provinces was gathered through telephone contacts.

Statistical analysis

In this study survival rate was assessed using the Kaplan-Meier curves employing Log Rank model and SPSS 15 software. Survival was estimated from the onset of WBRT. The relation between variable and survival rate was evaluated.

Results

Two hundred and six patients were evaluated. Mean age of the patients was 53.6 years. We divided the patients into four age groups. Group 1: 20 years and less group 2: 21-50 years, group 3: 51-70 years and group 4: more than 70 years. Figure 1 shows frequency of each primary site in different age groups and Figure 2 shows more frequent primary sites that metastasis to the brain in different age groups. One hundred and eleven (57.8%) patients were female and 87 (42.2%) were male. The primary site of the tumor was breast (32%), lung (24.8%), lymphoma (4.4%), sarcoma (3.9%), melanoma (2.9%), colorectal (2.4%) and renal cell carcinoma (1.5%). In 16.5% of the patients, brain metastasis was the first presenting symptom and the primary site had not been found (unknown primary disease). The rest of patients had other primary sites. Forty two (20.4%) patients had single brain metastasis, 18 patients (8.7%) had two or three lesions, 87 (42.2%) patients had more than three lesions. Leptomeningeal involvement was seen exclusively in 23 (11.2%) patients and in combination of parenchymal involvement in 26 patients (12.6%). In 10 (4.9%) patients

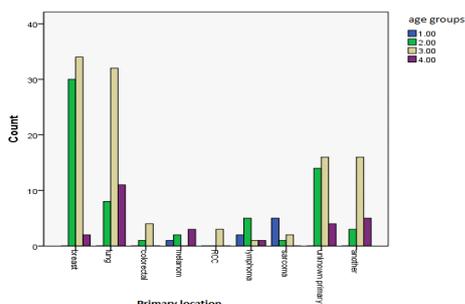


Figure 1. Frequency of Primary Locations in Each Age Groups

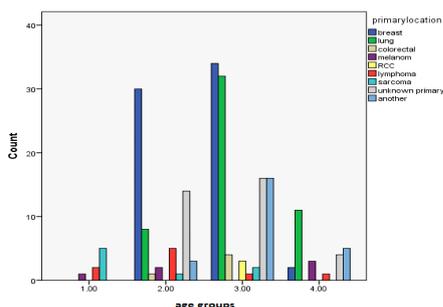


Figure 2. More Frequent Primary Locations in Each Age Groups

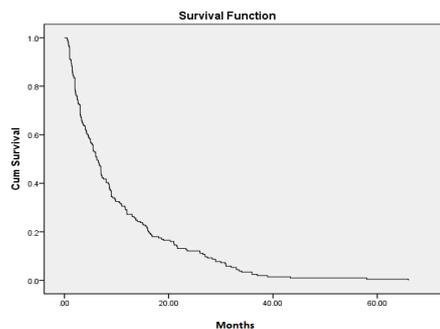


Figure 3. Overall Survival

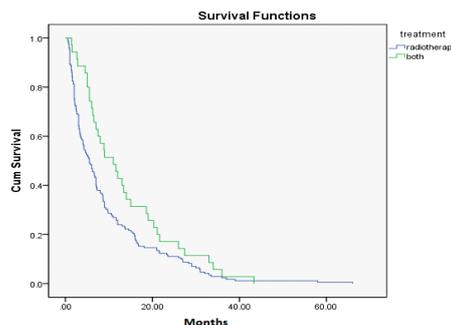


Figure 4. Overall Survival in Each Treatment Groups. (only WBRT vs surgery+WBRT)

Table 1. Overall Survival According to Primary Site

Primary site	Overall survival (months)
Breast	10.5
Lung	9.03
Melanoma	7.77
Colorectal	7.57
Lymphoma	15.31
Sarcoma	6.5
Renal cell carcinoma	3.73
Unknown primary	10.71

the number of lesions was not recorded in their documents. In September 2013 from 206 patients, 197 (95.6%) patients were deceased and only 9 (4.4%) were alive. Mean overall survival was 10.14 months (95%CI; 8.65-11.63) (Figure 3). One and two year survival was 27% and 12% respectively. Overall survival was 10.17 months in male and 10.12 months in female. Overall survival was 11.8, 8.8, 9.9, 9.8 and 10.1 months in patients with single, 2-3 and more than 3 lesions, leptomeningeal involvement and parenchymal and leptomeningeal involvement respectively. Overall survival of patients who were treated by combination of surgery and WBRT was significantly better than those were treated with WBRT only. [13.8 vs 9.3 months (p=0.03)] (Figure 4). Age, sex, primary site (Table 1) and the number of brain lesions did not show significant relationship to overall survival.

Discussion

Brain metastasis is one of the worst scenarios in cancerous patients. By improving imaging techniques and modalities and increasing patients' survival, brain metastasis is detected more easily than before brain

metastasis is diagnosed in a patient with a known cancer, however in some cases brain metastasis is the first presentation of cancer. Approximately 8.5% of cancer patients develop brain metastasis (Larson et al., 2011). Tumors have different tendencies for brain metastasis. Different studies reported various incidence of brain metastasis, however it seems lung cancer, breast cancer, melanoma and colorectal cancer are the most common causes of brain metastasis (Nichols et al., 2013) There is no widespread study in metastatic brain tumors in our country, however Miabi et al. reported that breast, lung, kidney and colorectal are the most common primary tumors that metastasis to brain in East Azarbyjan (Miabi, 2011). In this study breast and lung cancer were the most common primary sites, too. Wolf et al. (2013), Windsor (Windsor et al., 2013) et al and Saha et al. (2013) in the US, Australia and India respectively showed that lung cancer is the most common primary site. This discrepancy maybe due to the fact that breast cancer is more prevalent in our country and in our province, too. According to the last available national cancer registry program (Ministry of Health and Medical Education; 2006) breast cancer is the most common cancer in our country and our province (without considering skin tumor), however lung cancer is the 7th common cancer in males and in Iranian female, it is not considered among the ten common cancers. Overall survival did not have significant relation with primary tumors' site. ( $p=0.47$ ) such as the results of Schackert et al. (Schackert et al., 2013) and Hazuka et al. (1993) studies and no with gender. ( $p=0.946$ ). Schackert et al, also did not show survival advantage between the two genders (Schackert et al., 2013), however Wolf et al. and Wen-Guang Song et al. show significantly better survival in female (Wolf et al., 2013; Wen-Guang et al., 2013).

The mean age of the patients in this study was 53.6 year. Miabi et al. (2011) did not report this item. Out of 54 patients treated in Tehran and reported by Yousefi Kashi et al. (2010) 72.3% of the patients were <65 years. Schackert et al. (2013) and Wolf et al. (2013) reported a mean age of 67 and 60 years respectively in Germany and the US. It is clear that mean age of the patients in developing countries is lesser than patients in developed countries. For example mean age of breast cancer patients in our country is 47.1 year that about 10 years lesser than the patients of developed countries (Harirchi et al., 2000). As we showed in Figure 2 in children and young adults, sarcoma is the most common primary tumor that metastasis to the brain such as that showed by Kebudi et al. (2005). On the other hand in elderly patients lung cancer is the most common primary. Overall survival was 15.5, 11.5, 8.9 and 9.8 months for patients 20 years old and less 21-50, 51-70 and above 70 years respectively. The difference of overall survival between age groups was not significant. ( $p=0.297$ ). Overall survival in patients under 65 years and above, was better in Wolf et al. (2013) study however, it did not show significantly difference in the same groups in the study of Schackert et al. (2013). In this study 20.4% of patients had single brain lesion. In two other studies in Iran 16.3% (Miabi, 2011) and 29.4% (Yousefi Kashi et al., 2010) of patients had single lesion. However in neither of these two studies leptomeningeal involvement

was reported. In our study 11.2% and 12.6% of patients had only leptomeningeal involvement and leptomeningeal and parenchymal involvement respectively. In a large study that was carried out by Wolf et al. (2013) in the US 35.6% of 1263 patients had single lesion, however the study of Saha et al. (2013) which was performed in India 22.2% of the patients had single lesion. Maybe availability of more imaging facilities in the US and performing radiological studies earlier in cancerous patients could explain this difference. Our study did not show significant relationship between the number of lesions and overall survival. ( $p=0.727$ ). Wolf et al. and Wen-Guang Song et al. showed overall survival decreased when more than 3 lesions existed (Wen-Guang et al., 2013; Wolf et al., 2013). Schackert et al. evaluated patients with multiple metastases and the number of lesions did change overall survival (Schackert et al., 2013). To our knowledge this study is one of the largest evaluations of metastatic brain patients in our country. Overall survival of the patients was 10.17 months and similar to the results of other studies or even better than them (10, 15). Using WBRT with and without surgery seems effective.

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