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Impact of Whole Cranium Radiotherapy on Survival in Patients with Brain Metastasis of Different Cancers: Descriptive Study

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Abstract

Brain metastases (BMs) are the most common intracranial brain tumor and a common complication of systemic cancer. The incidence ranges from 20% - 40% of all patients diagnosed with cancer. The most common primary site is the lung followed by breast. Metastatic brain tumors outnumber primary brain tumors by a factor of 10 - 1, The prognosis of BMs is poor and the impact on the patient's quality of life is important as a result of the functional neurologic deficits associated. The mainstay of treatment for BMs has been corticosteroids and whole brain radiotherapy. The aim of the study is to determine the impact of whole cranium irradiation gray (Gy) (2000 cGy) on median and mean survival of BMs and to analyze prognostic factors affecting survival of patients receiving whole brain irradiation. This study retrospectively reviewed the records of 80 patients with BMs who were not eligible for surgical resection and who underwent whole-brain radiation (WBRT) in Baghdad oncology teaching hospital between 1st of July 2015 and 1st of January 2017. About 47 patients were diagnosed as primary breast cancer, 20 patients as primary lung cancer and 13 patients from other site of body. All patients were treated with conventional external beam radiotherapy with a total dose of 20 Gy in five fractions over 1 week for all patients. Breast cancer represented the most common primary cancer type 47 patients (58.8%), followed by lung cancer 20 patients (25%), other types of primary care represent 13 patients (16.3%), The median survival for the total population who were receiving WBRT was 7 months, and mean survival was 9.8 months. For breast cancer the median survival time was 8 months, for lung cancer patients it was 6 months and for primary metastasis from other sites of body was 6 months. In general, the result is that patients with breast cancer had better survival than patients with other primary cancers. In regard of time to develop to BMs, median time for breast cancer, lung cancer and for other sites (22, 5, and 12 months) respectively. Breast cancer has the longest time before BMs. According to the stage of primary breast tumor. The highest frequency was seen among patients with T3A followed by T2B and T3B respectively, while the lowest frequency with T1B. Our study reported a strong correlation between the tumor stage and time to BMs with significant ($p = 0.033$). In regards of primary breast cancer metastasis, the results showed that human epidermal growth factor receptor 2 (HER2) overexpressed was 19 patients (40.4%), Triple negative were 10 patients (21.3%), luminal A-like were 9 patients (19.1%) and luminal B-like were 9 patients (19.1%). The highest frequency was seen among patients with HER2 overexpressed followed by triple negative. Our results showed a negative correlation between the molecular subtypes and time to develop of BMs with p value = 0.482 which was statistically not significant. WBRT is generally the treatment of choice, demonstrated an increase in median overall survival (OS) from 1 month with no treatment to 5 - 8 months following WBRT, primary breast cancer patients represent best OS 8 months compare to lung 6 months and other types 6 months, metastases to the brain and survivals depending on biological subtype, median survival is shortest among patients with triple-negative breast cancer. Although patients with HER2-positive tumors have higher rates of BMs.

Keywords: Brain metastasis, Overall survival, Whole brain radiotherapy, Breast cancer

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Introduction

BMs are the most common intracranial brain tumor and a common complication of systemic cancer. The incidence ranges from 20% - 40% of all patients diagnosed with cancer [1]. The most common primary site is the lung followed by breast. Metastatic brain tumors outnumber primary brain tumors by a factor of 10 - 1, with autopsy series demonstrating a 10% - 30% incidence rate for all patients with a diagnosis of cancer [2]. The most common neuroanatomical sites are the cerebral hemispheres (80%), the cerebellum (15%), and the brainstem (5%) [3].

The data showed that the distribution of intracranial metastases based solely on the model of arterial embolization and blood volume does not likely depict the full biological basis of spatial distribution of BMs. It has been found that patients with non–small cell lung cancer lesions are more likely to be located in the parieto-occipital lobes and cerebellum. Breast cancer lesions have a greater probability to be located in the cerebellum [4].

The prognosis of BMs is poor and the impact on the patient's

quality of life is important as a result of the functional neurologic deficits associated. Symptom management is successful in most patients and efforts can be concentrated on improving the outcome of the patients [1]. Presenting symptoms are various and require that any new neurologic symptoms be investigated in a patient known to have cancer. Symptoms reflect increasing intracranial pressure and focal neurologic deficit. Palliative treatment of BMs requires rapid control of the symptoms, which are decreasing the patient's quality of life. The mainstay of treatment for BMs has been corticosteroids (for the treatment of peritumoral edema) and whole brain radiotherapy.

Management of patients presenting with a limited number of BMs has evolved from WBRT alone to more aggressive management incorporating stereotactic radiosurgery (SRS) [5, 6]. The prognosis of patients with BMs has been considered uniformly poor, with a median survival in the 2 - 4 month range. However, it has become evident that not all patients with BMs have the same poor prognosis, and the use of an identical management strategy for all patients is no longer appropriate [7].

WBRT is the treatment of choice for many patients because of the high incidence of multiple metastatic brain sites [1, 8]. The goal of WBRT is to limit tumor progression, sterilize microscopic disease preventing future BMs [7] and to limit corticosteroid dependency. Classically, WBRT is thought to have some response in around 50% of patients and is histologically dependent on small cells and breast cancers being the most sensitive. Renal cell and melanoma histologists are thought to be the most resistant [9].

WBRT for patients with un-resected BMs results in symptomatic response in about 50% of patients and improvement in median survival from 3 - 6 months compared to historical controls. The optimal dose of radiation is unknown, but in clinical practice, the range is 20 Gy in 5 fractions over 1 week to 40 Gy in 20 fractions over 4 weeks [1].

Two studies Borgelt; Chatani provided data comparing two fractionation schedules commonly employed in Canada (2000 cGy in five fractions or 3000 cGy in ten fractions). Neither trial detected a significant difference in OS nor neurologic function between these two fractionation schemes. All trials showed no difference in symptom control with altered whole brain radiotherapy dose fractionation schedules as compared to control (3000 cGy in ten fractions) [10].

WBRT is becoming less commonly employed in patients with one to three metastatic lesions. Studies by Aoyama et al. [9] and Chang et al. [11] have shown that WBRT does not add to survival in this subset of patients and may even be detrimental, compared to SRS alone as shown in the study by Chang et al. [11] The authors attributed this finding to patients treated with WBRT receiving less salvage treatment and less systemic therapy. In the Chang et al. [11] study, there was a greater risk of significant decline in learning and memory function at 4 months in the SRS with whole brain group compared to SRS alone. Because of this association of WBRT and cognitive decline, RTOG 0933, a single-arm Phase II study, looked at hippocampal sparring WBRT, using IMRT technique, compared to historical control of WBRT without hippocampal avoidance. The dose received by the entirety of the hippocampus did not exceed 10 Gy, and the maximum dose did not exceed 17 Gy. The results showed that avoidance of the hippocampus during WBRT is associated with memory preservation at 4 months and 6 months. Only 4.5% of patients had progression in the hippocampal avoidance region [12].

Methods

This is a retrospective study that includes 80 patients who underwent WBRT in Baghdad oncology teaching hospital between July 2015 and January 2017. Of the patients enrolled in this study, 47 Patients were diagnosed as primary breast cancer, 20 patients as primary lung cancer and 13 patients from other primary cancers. The presence of BMs was defined based on appropriate computed tomography and/or magnetic resonance imaging results. Information concerning patient characteristics, treatments and survival durations was collected using treatment charts and conducting patients through phone calls, verbal consent was taken from the patients or first degree relative.

All patients were treated with conventional external beam radiotherapy using linear accelerator (Elekta Medical Systems) with a photon energy of 6 MV and opposed lateral treatment fields that encompassed the entire brain. The treatment plan included a total dose of 20 Gy in five fractions over 1 week for all patients; After treatment completion, patients were followed for 18 months. Because of the large proportion of patients with breast cancer in the patient population, the prognosis of breast cancer patients with BMs was compared by the status of molecular subtypes (ER, PR, HER2neu) and stage of breast cancer.

All the data analyzed through statistical package for social sciences, and all the quantitative variables were presented as mean and standard deviation, while qualitative variables were presented as frequency and percentages. Pearson test was used to evaluate the statistical difference. A p value <0.05 was considered significant. Univariate and multivariate analyses were performed to determine the impact of the following parameters on the OS: age, gender, primary tumor, histopathological subtype, molecular subtype, stages of primary tumor, time to develop of BMs. OS curves were calculated by the Kaplan–Meier method, and differences were compared using the log-rank test. Breslow (Generalized Wilcoxon) and Tarone-Ware (Test of equality of survival distributions for the different levels of primary cancer). OS was defined as the length of time from the initiation of WBRT to death or to the last follow-up date. with survivors having their data censored at the time they were last known to be alive.

Results

The total number of patients in this study were 80 patients with BMs. All patients were followed up for 18 months, and all died from their systemic disease progression or BMs except 18 patients who were still alive until last follow up time. with their ages ranged from 25 - 77 years with a mean age ± SD (51.3 ± 13.5) years, and the results showed the wide distribution of patient's age, with highest incidence of BMs among patients in 6^{th} (50 - 59 years) decades of life (Figure 1).

In the current study, BC represented the most common primary cancer type 47 patients (58.8%), followed by lung cancer 20 patients (25%), other types of primaries represent 13 patients (16.3%) (Figure 2).

In our 80 patients, 61 died and 19 are censored (still alive until last follow up time) as explain in the table 1.

The median survival for the total population who were receiving WBRT was 7 months (95% CI 5.4 - 8.5 months) and mean survival was 9.8 months (95% CI 7, 9 - 11.6) (Figure 3).

For breast cancer the median survival time was 8 months, for lung cancer patients it was 6 months and for other primary cancers it was 6 months. In general, the result is that patients with breast cancer had

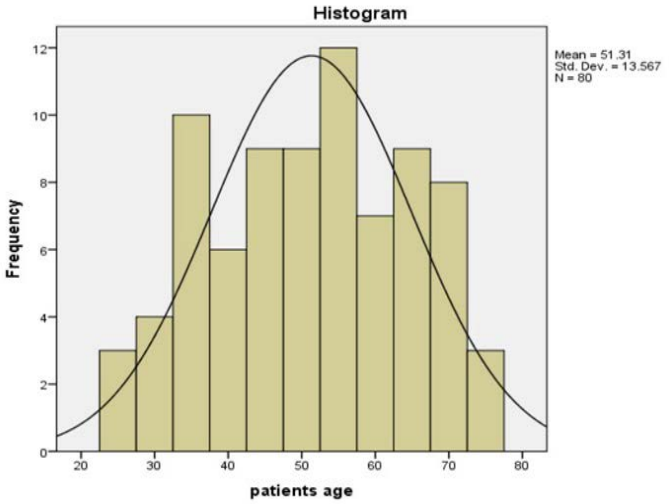

Figure 1: Histogram shows age distribution in the studied brain cancer patients (n = 80).

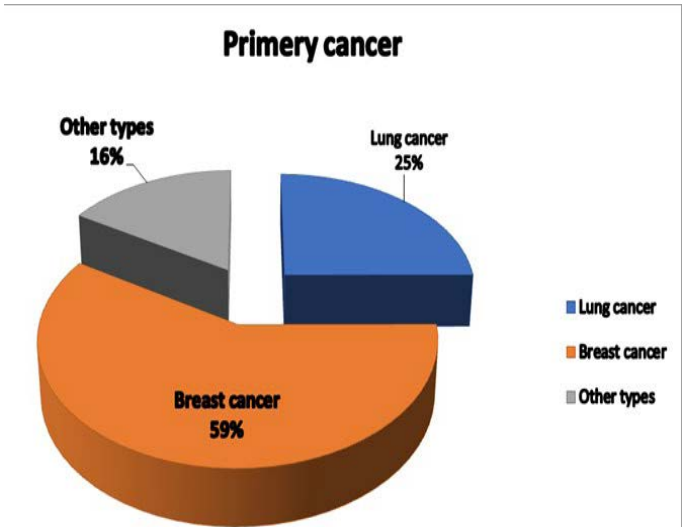

Figure 2: Primary tumor distribution in the studied BMs patients (n = 80).

Table 1: Outcome of the study.

Primary cancer	Total	No. of death	Censored
Lung cancer	20	17	3 (15%)
Breast cancer	47	32	15 (31.9%)
Other primary cancers	13	12	1 (7.7%)
Total	80	61	19 (23.8%)

better survival than patients with other primary cancers (Figure 4).

On the following figure 5 of the 80 patients with BMs. About 6 patients were presenting with BMs from the start. The median and mean time of progress from primary cancer (lung, breast, other cancers) to brain secondaries is 13 (±1.118) months, 17.93 (±1.58) months, respectively.

In regard of time to develop to BMs, median time for breast cancer, lung cancer and other primary cancers (22, 5, and 12 months) respectively. Breast cancer has the longest time before progress to BMs (Figure 6).

According to the stage of primary breast tumor, in this study it

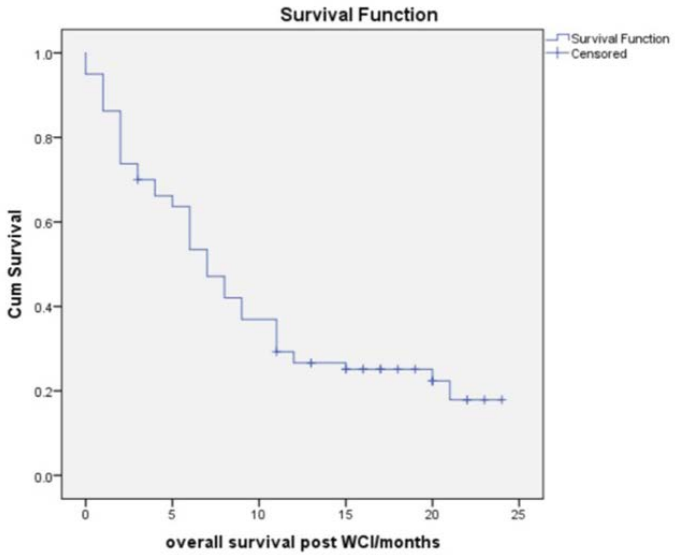

Figure 3: Kaplan-Meier OS estimate for all patients posts WBRT.

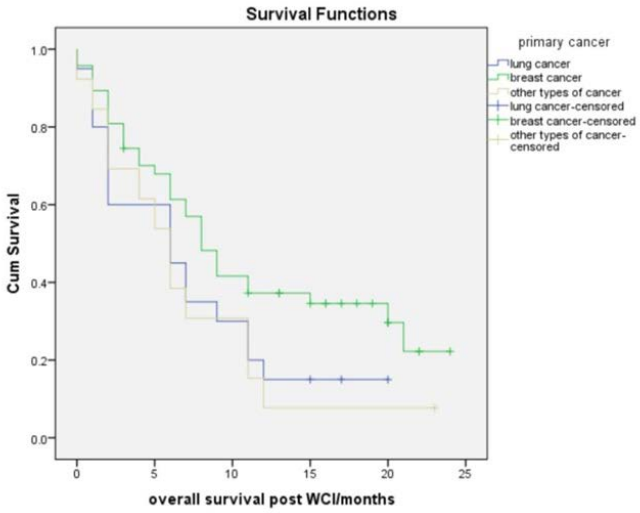

Figure 4: Kaplan-Meier of patients with BMs, survival curve according to primary cancer (n = 80).

was divided according to the seventh edition of the American Joint Committee for Cancer Staging Manual. The results revealed that T1B was (6.4%), T2A was (8.5%), T2B was (19.1%) and T3A was (40.4%), T3B was (10.6) and T3C was (14.9). The highest frequency was seen among patients with T3A followed by T2B and T3B respectively, while the lowest frequency with T1B (Figure 7).

Our current study reported a strong associated between the tumor stage and time to BMs with significant (p = 0.033), so the locally advance tumor of breast has shortest time to BMs than early staged tumor. In regards of primary breast cancer metastasis, the results showed that HER2 overexpressed were 19 patients (40.4%), triple negative were 10 patients (21.3%), luminal A-like were 9 patients (19.1%), and luminal B-like were 9 patients (19.1%). The highest frequency was seen among patients with HER2 overexpressed followed by triple negative, while the lowest frequency was seen among patients with luminal A and luminal B (Figure 8).

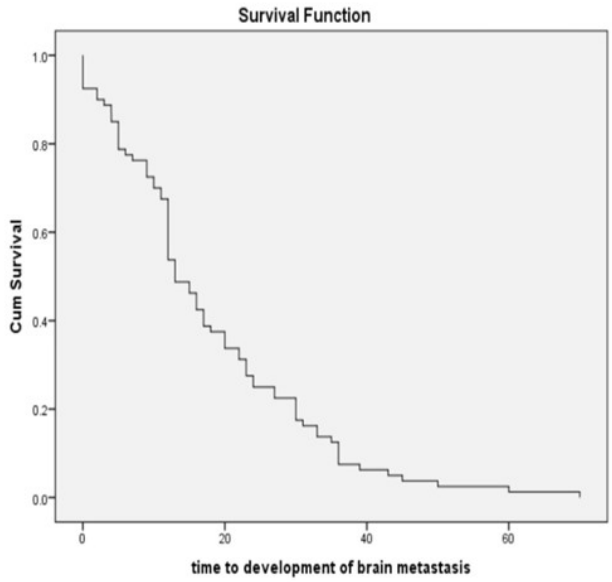

Figure 5: Kaplan-Meier, survival curve estimates by time to development of BMs.

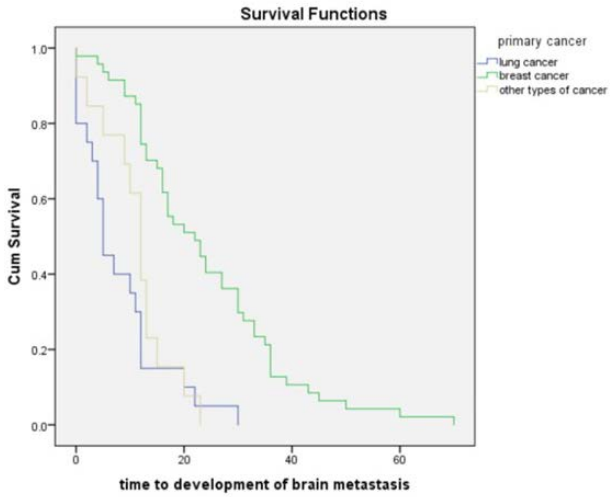

Figure 6: OS curve estimates by time to development of BMs from primary cancer.

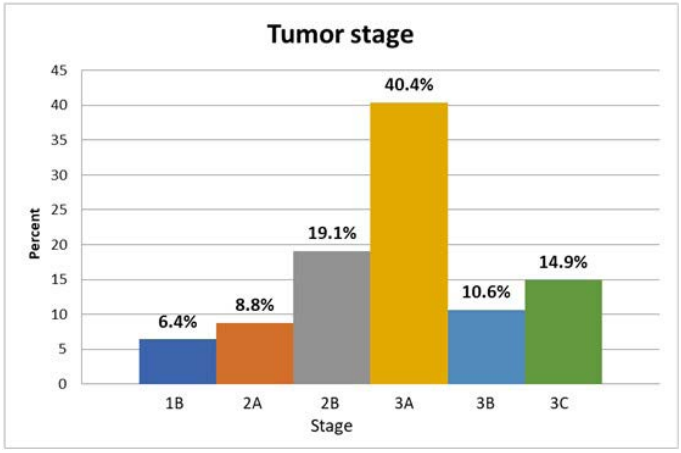

Figure 7: Par chart shows percentage of primary breast cancer stages in women with BMs (n = 47).

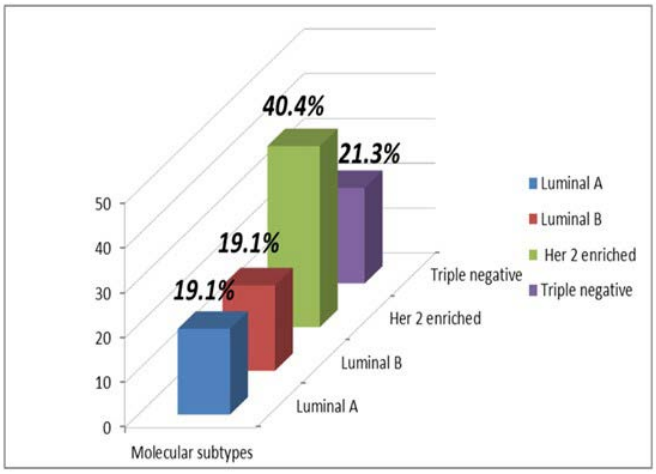

Figure 8: Par chart shows the percentage of primary breast cancer stages in women with BMs (n = 47).

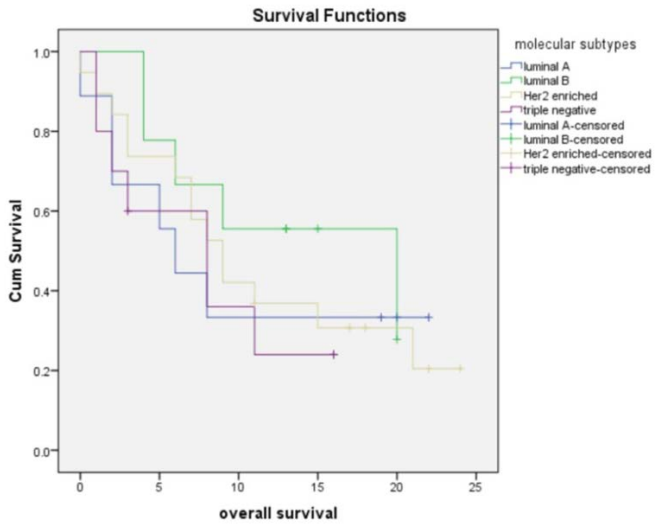

Figure 9: Kaplan-Meier, survival curve for BMs in four biological subgroups.

Median OS in subgroup of triple-negative, HER2-positive luminal A and B breast cancer patients was 8, 9, 6, 20 months, respectively (p = 0.728). We conclude that the median survival is shortest among patients with triple-negative breast cancer and luminal A. Median survival calculated from BMs in the entire molecular subtypes were 8 months (95% CI 6.1 - 9.8) (Figure 9).

Our results showed a negative correlation between the molecular subtypes and time to develop of BMs with (p = 0.482) which was statistically not significant.

Results and Discussion

Until the past few years, the most common primary tumors responsible for BMs reported in adults were lung and breast cancer. Recently, however, two large studies found that the incidence of intracranial metastasis has shifted with (in descending order) lung cancer, malignant melanoma, renal cell carcinoma, breast carcinoma, and colorectal carcinoma which now represent the most common

tumors associated with BMs [13]. This shift might be explained by improved treatments in breast cancer, resulting in fewer patients with metastatic disease, coupled with the rising incidence and more common screening for intracranial disease.

In this study, the breast cancer is the most common primary tumor which consisted (58.8%) followed by lung cancer (25%) and other primaries tumor (16.3%). As our results were compactable to Witzel et al. [14] in which the incidence of BM in breast cancer patients is rising, probably because many patients survive longer due to the improvement of systemic therapies to control extracranial disease; thus, patients can experience BM before dying from other manifestations. This reflects insufficient control of cerebral tumors spread by current treatment strategies and also supports our study about the longest time that breast cancer takes before developing brain secondary (22 months) as comparison with time of progression for lung cancer and other sites (5 and 12 months) respectively. Interval time to BCBM was defined as date of pathologic breast cancer diagnosis to date of radiographic evidence of BMs.

The observed 7 month overall median survival for patients receiving whole cranium irradiation in the present study is nearly identical to Sneed et al. [15] showed WBRT for patients with un-resected BMs results in improvement in median survival from 5 - 8 months compared to historical controls.

In an earlier study by Sneed et al. [16] on the University of California, San Francisco, SRS experience, patients who were initially treated with SRS alone without WBRT experienced worse freedom from new BMs, although the OS was not different. Furthermore, brain failure can lead to unacceptable consequences. Furthermore, in several published reports, local treatment of these neoplasms with surgical resection or SRS alone or in combination with WBRT has proven to be a more effective management approach for select patients when compared to WBRT alone [17].

The development of BMs severely impairs quality of life and is associated with poor patient survival. In the current study, better OS has been achieved in BC patients with BMs who were treated with WBRT with median survival 8 months, we show best results as compare with Mahmoud-Ahmed et al. [10] of whole brain radiotherapy in patients with BMs from breast cancer: a retrospective study which identified 116 women with breast cancer who were treated with WBRT. Results in the median survival from the start of WBRT were 4.2 months. The 1-year survival rate was 17%, and the 2-year survival rate was 2%.

Also, because the BC represents more than half of population in our study is another reason explaining why breast cancer has better survival rate than other sites of body.

The group of 47 breast cancer patients with BMs was divided into four biological subgroups, luminal A (19.1%), luminal B (19.1%), triple negative (21.3%), HER2-positive (40.4%), and from our data, we concluded higher percentage of patients with HER2-positive metastasis to brain which is compatible with results of Niwińska et al. [18]. The group of 222 breast cancer patients with BMs was divided into three biological subgroups. metastases to the brain and survival depend on biological subtype. The rate of patients with triple-negative, HER2-positive and luminal breast cancer with BMs was 28%, 53%, and 19%, respectively.

The median survival of luminal A (6 months), luminal B (20 months), triple negative (8 months) and for HER2-positive subtype (9 months), we noticed the OS was longer among patients with luminal B and compared with those with luminal A and HER2-negative disease, patients with a triple-negative tumor have the worst prognosis that consistent with Niikura et al. [19]. In a retrospective study with 1256 patients diagnosed with BM, the cohort was stratified according to tumor subtype. Median OS after the development of BMs was 9.3 months for the luminal type, 16.5 months for the luminal-B type, 11.5 months for the HER2 type, and 4.9 months for the triple-negative type. Luminal B type patients had significantly longer OS than patients with the luminal A type (hazard ratio (HR) = 1.50, $p < 0.0001$) and triple-negative type (HR = 1.97, $p < 0.0001$); no significant differences were noted compared to HER2-type patients (HR = 1.19, $p = 0.117$). According to the previous studies which showed that median survival is shortest among patients with triple-negative breast cancer. Although patients with HER2-positive tumors have higher rates of BMs, median survival for these patients is longer than it is for patients with triple-negative. The prognosis and clinical course of patients with BMs from breast cancer before and after developing BMs vary according to subtype.

In the current study the demonstrating tumor stage of the studied breast cancer patients were 6.4%, 8.5%, 19.1%, 40.4%, 10.6%, and 14.9% for stage 1B, 2A, 2B, 3A, 3B, 3C, respectively. The highest recorded frequency was displayed for 3A patients (locally advanced), Our results were consistent with Gil-Gil et al. [20]. Only 2.5% of patients who were initially presented with localized disease ultimately developed central nervous system (CNS) disease, whereas 7.6% of patients diagnosed with regional disease, and 13.4% of patients presenting with stage IV disease were eventually found to have CNS involvement.

The typical dose and fractionation schedule for WBRT is 30 Gy in 10 fractions. If patients have a short life expectancy, WBRT could also be delivered in 5 fractions with 20 Gy in total as we see in our study, compared with the typical schedule (30 Gy in 10 fractions daily), RTOG 6901 study demonstrated that altered dose-fractionation schedules of WBRT do not show any improvement in OS, neurologic function, or symptom control. According to hormonal status our results showed a weak correlation between molecular subtype and time of develop to BMs within significant p value < 0.482, conflicting with Saraf et al. [21]. Also, the current study presented a strong correlation between tumor stage and time of progression to BMs significant p value = 0.031 which was agree with Aria et al. [22].

Conclusion

In patients with multiple cerebral metastases, WBRT is generally the treatment of choice, demonstrated an increase in median OS from 1 month with no treatment to 5 - 8 months following WBRT. Primary breast cancer patients represent best OS compared to lungs and other types. There was strong correlation between time to develop BMs with tumor stage of primary breast cancer p value > 0.033. There was negative correlation between time to develop BMs and molecular subtype $p < 0.482$. Primary breast cancer takes longer before progression to brain secondary than lung and other cancer types. Metastases to the brain and survivals depending on biological subtype, HER2/neu-positive represents the largest percentage. Median survival is shortest among patients with triple-negative breast cancer. Although patients with HER2-positive tumors have higher rates of BMs.

Acknowledgements

None.

Conflicts of Interest

None.

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