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**Research Article**

# Prognostic Factors in Metastatic Brain Tumors: Study of 62 Patients

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## Summary

**Background:** Brain metastases are the major cause of morbidity and mortality in patients with cancer. Variety of clinical and autopsy studies showed that brain metastases develop at 15%-45% of all cancer patients during the course of the disease and 1/2-2/3 of them were symptomatic. Average life expectancy of cancer patients with untreated metastatic brain tumors are approximately 1-2 months.
**Methods:** We investigated the prognostic factors of removal of metastatic brain tumors in patients who admitted to neurosurgery department. Eighteen of 80 patients in the program excluded for various reasons and this study was completed with the remaining 62 cases.
**Results:** Our study showed that neurological and general status, the extension of surgical resection, presence of the extra-cranial metastases at diagnosis and localization of the primary focus affect the prognosis.
**Conclusion:** In the planning of treatment of patients with metastatic brain tumors, colleagues have to keep in mind level of neurological and general status, the extension of surgical resection, presence of the extra-cranial metastases at diagnosis and localization of the primary focus affect the prognosis. Surgical resection is beneficial for improving neurological status and survival of patients in brain metastases. Local control is essential and can be achieved with one of the adjunct therapies following the surgery.

**Key words:** Brain Metastases, Surgical Resection, Prognostic Factors

# Metastatik Beyin Tümörlerinde Prognostik Faktörler: 62 Hastalık Çalışma

## Özet

**Giriş:** Beyin metastazları, kanser hastalarında morbidite ve mortalitenin en önemli nedenidir. Klinik ve otopsi çalışmaları, beyin metastazının tüm kanser hastalarının % 15 -% 45 inde geliştiğini ve bunların 1/2-2/3'ünün semptomatik olduğunu göstermektedir. Tedavi edilmemiş metastatik beyin tümörlü hastalarının ortalama yaşam süresi yaklaşık 1-2 aydır.
**Method:** Beyin cerrahisi kliniğine başvuran 80 hastada, metastatik beyin tümörlerinin çıkarılmasını takiben prognostik faktörler araştırıldı. Çeşitli nedenlerle 18 hasta çalışma dışı bırakıldı. Çalışma geri kalan 62 olgu ile tamamlandı.
**Sonuç:** Çalışmamız, nörolojik durum, genel durum düzeyi, cerrahi rezeksiyon genişliği, tanı anında ekstrakranial metastaz varlığı ve primer tümör bölgesinin prognozu etkileyen faktörler olduğunu göstermiştir.
**Karar:** Metastatik beyin tümörlü hastaların tedavi planlamasında, nörolojik ve genel durum düzeyilerinin, cerrahi rezeksiyon genişliğinin, tanı anında ekstra kranial metastaz varlığının ve primer odak lokalizasyonunun prognozu etkileyen faktörler olduğu akılda tutulmalıdır. Cerrahi rezeksiyon hem yaşam süresi uzamasına hemde nörolojik durumun düzelmesine katkıda bulunur. Lokal kontrol, ameliyat sonrası ek tedavilerden biri ile elde edilebilir.

**Anahtar Kelimeler:** Beyin Metastazları; Cerrahi Rezeksiyon; Prognostik Faktörler

## INTRODUCTION

Brain metastases are the major cause of morbidity and mortality in patients with cancer. Brain metastases have a major impact on quality of life and median survival remains as low as 3–6 months[9]. Variety of clinical and autopsy studies showed that brain metastases develop at 15%-45% of all cancer patients during the course of the disease[5,9,18,21] and 1/2-2/3 of them were symptomatic[19]. Average life expectancy of cancer patients with untreated metastatic brain tumors are approximately 1-2 months[5,18]. Although this period is 3-6 months with steroid treatment and radiotherapy (RT)[5,18], surgical removal (SR) and RT extend this period to 9-14 months[18].

Although the surgery of the metastatic brain tumors has begun by FC Grant and other neurosurgeons in the last century, lack of the proper diagnosis and localization techniques, surgical interventions resulted in high morbidity and mortality. Therefore, surgery has not been applied to the selected cases for many years. Despite the improvement of surgery and anesthesia in the 1970s, the possibilities of SR were still limited for removal of single and preferably life-threatening metastatic lesions. Some researchers in the 1990s showed the increase in quality of life and survival with the development of microsurgery, neuroanesthesia and modern imaging methods in patients with multiple brain metastases by the SR[5]. In 1990s while there have been improvements in surgical technique and RT, also stereotactic radiosurgery (SRS) has begun to be used for treatment of brain metastases[11]. One of the developments in RT was, whole-brain radiation therapy (WBRT) accepted as a standard treatment. Also RT which focused on the lesion (boost), has a place as a method that can be added to WBRT in recurrence of brain metastases. Although there are several points to be discussed for the decision of surgical intervention, today's rapidly evolving technology has raised the idea of many alternative treatments, still there is no method to replace SR.

In this study we aimed to investigate the prognostic factors of metastatic brain tumors in 62 patients after SR.

## MATERIAL AND METHODS

We investigated the prognostic factors of removal of metastatic brain tumors in patients who admitted to neurosurgery department. Eighteen of 80 patients in the program excluded for various reasons and this study was completed with the remaining 62 cases.

In 62 patients with 80 metastatic nodules, 79 surgical interventions were done by craniotomy. There were 10 patients with 2 metastatic brain tumors at the time of diagnosis. Resections were performed by two craniotomies in one session for different localization of two tumors in 1 of 10 patients, by two craniotomies in two sessions for different localization of two tumors in 3 of 10 patients. The remaining 6 cases who had 2 metastatic nodules in different localization underwent surgery for one metastatic nodule preferably for the life threatening or symptomatic one. On postoperatively, we evaluated the extent of resection of tumor by computed tomography and magnetic resonance imaging. Tumors were named as local recurrence which was developed in operation on site and distant metastasis which were developed in other sites. Nine patients had local recurrences. While 5 of 9 patients operated for two times, 4 of 9 patients operated for three times. We accepted the postoperative mortality that occurred within 30 days of surgical intervention as surgical mortality and complications that require hospitalization more than 7 days as a surgical morbidity. Thirty-one cases received WBRT as 10x300 cGy and 2 patients received WBRT in 5x400 cGy. Remaining 29 of 62

patients did not receive RT for various reasons. Thirtyfour of 62 patients had postoperative chemotherapy for primary cancer focus.

General physical status of the patients studied according to World Health Organization (WHO) showed in Table-1.

The neurological status of the cases studied according to RTOG (Radiotherapy Oncology Group) showed in Table-2.[9].

We calculated the total survival time (TST) in living and deceased patients. In still living patients TST was the period between surgery and end of our study, in deceased patients it was the period between surgery and excitus time.

We divided causes of death into three groups; primary disease remained stable patients died of progressive neurological disease named as neurological death (ND), neurological disease remained stable systemic disease progressed as the cause of death was named as systemic death (SD) and death because of the combination of the previously mentioned factors named as combined death (CD).

We calculated duration and rate of TST with Kaplan-Meier method. We evaluated the duration and rate differentials of independent groups by Logrank test. We have accepted P=0.05 as the indicator of statistical significance.

## RESULTS

There were 62 patients in study. Forty-nine (79%) were male and 13 (21%) were female. Age distribution was between 27-75 years, median age was 57 years and the mean age was 53.4 years. The most common symptoms at diagnosis were headache (74%) and seizures (41.9%). The most common neurological signs were paresis, (43.5%) and papilledema (41.9%). Application complaints and findings of the cases are listed in Table-3 and Table-4.

We found the median levels of the general condition and neurological status of the cases as 1.

While 52 patients (83.9%) had solitary metastases, 10 cases (16.1%) had multiple brain metastases. The most commonly affected region was the parietal lobe (33.9%).

Twenty of our patients previously diagnosed with a known primary cancer, whereas 42 (67.7%) cases were admitted with neurological symptoms as the first sign of the disease. The most common primary tumor foci were lung cancer (58.1%) and breast cancer (11.3%). The rate of unknown primary tumor, in which we could not find the main culprit was 12.9%. Distribution of cases according to foci of the primary tumor are listed in Table-5.

Twenty patients (32.2%) had one or more extra-cranial organ metastasis at the time of surgery and 42 patients (64.4%) had no other organ metastasis at the time of cranial intervention. Eighteen of 42 patients developed other organ metastases during follow-up. Twenty-four of 42 patients (% 38.6) remained with their primary tumor during follow-up. The extent of surgical resection was complete in 43 patients (69.4%) and was partial in 19 cases (30.6%). Postoperative complications developed in eight cases (12.9%). Three cases (4.8%) had CSF fistula, 4 cases (6.5%) had paresis and 1 case (1.6%) had lung infection. Postoperative deaths occurred in 2 cases (3.2%) in first 30 days. Thirty-three cases (53.2%) received postoperative RT, 34 patients received postoperative chemotherapy for the primary cancer and 24 patients (38.6%) received postoperative both chemotherapy and RT. Brain metastases recurred in 22 patients (35.5%) during follow-up period. Nine of 22 were (40.9%) local recurrence, and 13 (59.1%) had distant metastasis. Postoperatively follow-up time was minimum 7 months and maximum 57 months. Median follow up time was 43.5 months. Fiftysix cases (88.7%) died during follow-up period. In 33 patients (53.2%) systemic death (SD),

in 14 patients (22.6%) neurological death (ND) and in 9 patients (14.5%) combined deaths (CD) occurred in the follow-up period. Six patients (11.3%) were still live at the end of the study.

The mean survival time for TST was 9 months and the median was 6 months for all patients. Advanced age (60 years and over) had negative impact on the TST. While mean and median TST was 6 months and 4 months respectively in patients over 60 years, it was 11 months 8 months respectively in patients under 60 years (p=0.024). Good general physical status was significantly increased the TST (p=0.016). Mean and median TST was 12 months and 7 months respectively when overall status level was ≤1. These values were both 6 months when overall status level was >1. Also good neurological status was a positive effect on TST (p=0.035). Mean and median TST was 11 months and 7 months respectively when neurological status was ≤1. These values were both 6 months when neurological status was >1. The number of metastatic foci in the brain had no statistically significant effect on TST. While mean and median TST was 7 months and 6 months respectively multiple brain metastases, these values were 9 months and 6 months respectively with single brain metastases (p=0.428). Localization of primary cancer focus was one of the factors which affected the prognosis. When compared the patients who had primary lung cancer and other localization of primary cancer for TST, is the end value that we have found statistically significant results in favor of non-lung cancer patients (p=0.073). The most important indicator for poor prognosis was presence of extra-cranial metastasis. Mean and median TST was 4 months and 3 months respectively in patients who had extra-cranial organ metastases during surgery. These values were 8 months and 12 months respectively in patients who had only brain metastases. The difference was statistically significant between two groups. Comparison of the extent of surgical resection for complete resection and partial resection was also statistically very highly significant (p=0.000). While the mean and median TST were 11 months and 8 months respectively in complete resection, these values were 4 months and 3 months respectively for partial resection. The mean and median TST were 13 months and 10 months for patients who received postoperative RT. This duration was longer than other patients who did not receive postoperative RT ($p<0.05$). Cases who received postoperative chemotherapy (mean and median TAS was 11 months and 8 months respectively) lived longer than non-receiving chemotherapy (mean and median TAS were 5 months and 3 months respectively) (p=0.001). Location of metastatic brain tumor (lobe localization) (p=0.854), on the right or the left (p=0.362), infratentorial or supratentorial settlement (p=0.920) had not a significant impact for TST. Also the time between diagnosis of brain metastasis and primary cancer did not affect TST. Prognostic factors for TST were summarized in Table 6.

**Table 1-**Level of general physical status (WHO scale)

| |
|---|
| 0-Independent |
| 1-There are symptom, but independent |
| 2- Spends in bed less than 50% of day |
| 3- Bedridden more than 50% of the day |
| 4-Bed-ridden all day |

**Table 2-**Neurological function status according to RTOG (9)

| |
|---|
| 0 -No neurologic Sx; fully active at home/work without assistance |
| 1 -Minor neurologic Sx; fully active at home/work without assistance |
| 2 -Moderate neurologic Sx; fully active at home/work but requires assistance |
| 3 -Moderate neurologic Sx; less than fully active at home/work and requires assistance |
| 4 -Severe neurologic Sx; inactive and unable to work; requires complete assistance |

Sx: Sign

**Table 3-**Application complaints

| **Complaint** | **Number** | **%** |
|---|---|---|
| Headache | 46 | 74.1 |
| Seizures | 26 | 41.9 |
| Paresis | 25 | 40.3 |
| Nausea and vomiting | 21 | 33.8 |
| Dizziness | 13 | 20.9 |
| Visual impairment | 9 | 14.5 |
| Speech impairment | 8 | 12.9 |
| Imbalance | 8 | 12.9 |
| Impairment of consciousness | 6 | 9.6 |
| Mental disorder | 3 | 4.8 |
| Incontinence | 3 | 4.8 |
| Loss of sensation | 2 | 3.2 |

**Table 4-**The findings of the cases

| **Neurological sign** | **Number** | **%** |
|---|---|---|
| Paresis | 27 | 43.5 |
| Papilledema | 26 | 41.9 |
| Seizures | 23 | 37 |
| Ataxia | 13 | 20.9 |
| Cerebellar signs | 13 | 20.9 |
| Cranial nerve involvement | 10 | 16.1 |
| Visual impairment | 9 | 14.5 |
| Impairment of consciousness | 6 | 9.6 |
| Aphasia | 6 | 9.6 |
| Mental disorder | 3 | 4.8 |
| Sensory impairment | 3 | 4.8 |

**Table 5-**Distribution of cases according to foci of the primary tumor

| Primary | Number | % |
|---|---|---|
| Lung | 36 | 58.1 |
| Breast | 7 | 11.3 |
| Malignant Melanoma | 3 | 4.8 |
| Colorectal | 2 | 3.2 |
| Thyroid | 2 | 3.2 |
| Urinary Tract | 2 | 3.2 |
| Nasopharynx | 1 | 1.6 |
| Primary unknown | 8 | 12.9 |
| **Total** | **62** | **100** |

**Table 6-**Prognostic factors for Total Survival Time (TST)

| Variable | TST (month) | "p" value' |
|---|---|---|
| **Age** | | 0.024 |
| ≥60 | 6 | |
| <60 | 11 | |
| **Genus** | | 0.616 |
| male | 8 | |
| women | 11 | |
| **Level of the general status** | | 0.016 |
| ≤1 | 12 | |
| >1 | 6 | |
| **Level of neurological status** | | 0.035 |
| ≤1 | 11 | |
| >1 | 6 | |
| **Extent of the resection** | | 0.000 |
| total | 11 | |
| subtotal | 4 | |
| **Postoperative chemotherapy** | | 0.001 |
| there | 11 | |
| none | 5 | |
| **Postoperative radiotherapy** | | 0.000 |
| there | 13 | |
| none | 5 | |
| **The primary tumor site** | | 0.073 |
| lung | 7 | |
| extrapulmonary | 13 | |
| **Localization** | | 0.920 |
| supratentorial | 9 | |
| infratentorial | 8 | |
| **Peroperative extra cranial metastases** | | 0.000 |
| there | 4 | |
| none | 12 | |
| **The number of metastases in the brain** | | 0.428 |
| single | 9 | |
| multiple | 7 | |
| **Side** | | 0.362 |
| right | 9 | |
| left | 8 | |
| mid-line | 12 | |
| **Interval between diagnosis of primary tumors and brain metastases** | | 0.167 |
| ≤12 months | | |
| >12 months | 6 | |
| | 10 | |
| **Cause of death** | | 0.001 |
| systemic | 7 | |
| neurological | 6 | |
| combined | 7 | |

## DISCUSSION

Tumor invasion and metastasis are the most important cause of failure in the treatment of cancer. In these patients, development of brain metastases can be fatal in a short time despite effective treatment of primary focus[18]. Development of brain metastases during the course of the disease was 15-45% all of cancer patients[3,9,18,19]. Prolongation of life expectancy as a result of advances in the treatment of cancer increases the rate of brain metastases[9,19] so treatment of brain metastases became the focus of many researchers. Treatment of metastatic tumors has various difficulties for a long time. Time of the operation or necessity of operation is still discussed. In recent years, with the development of diagnostic and treatment techniques, surgical morbidity and mortality rates were reduced and importance of surgery in the treatment of metastatic brain tumors was increased.

Patients with metastatic brain tumors, should be investigated for the prognostic factors such as, patient's age, level of neurological and general status, systemic involvement, single or multiple foci and localization of the brain metastasis. Postoperative RT should be applied in eligible patients and chemotherapy should be added to treatment in sensitive tumors[30]. In metastatic brain tumors which are requiring emergency treatment, addition of steroid administration to surgery and RT is also effective in relieving symptoms[19]. Brain metastasis is the major reason of death, if presence of controlled systemic cancer. Therefore, the most important factor affecting the survival in patients is the treatment of brain metastases. In this group of patients, surgical intervention is become more important. Some of the developments such as more reliable anesthesia, the widespread use of corticosteroids, developments of non-invasive cranial imaging technology and innovations in stereotactic surgeries reduced the risk of surgical intervention in the last 10-20 years[19].

Two prospective randomized trials[21,31] demonstrated the importance of surgical resection in single brain metastasis. In a prospective randomized study, Patchell et al.[21] evaluated 48 cases in two groups. In first group patients had suspicious lesions. Other group included patients with metastatic brain lesions. They performed WBRT after brain biopsy and complete resection to first and second group respectively. Total radiation doses were the same in both groups. While TST was 40 weeks in second group, it was 15 weeks in biopsy group and there was a statistically significant difference between two groups. Determined mortality rate in 30 days as 4% in both groups as mentioned above. In another prospective randomized study Vecht et al. reported 63 patients in two groups[31]. While they performed complete resection and WBRT to the first group, second group had only WBRT and they found significant elongation for TST when compared each group. TST was 10 months and 6 months in first and second group respectively. They reported mortality rates of 30-days as 9% in the surgical group and 0% in RT group. These two prospective randomized studies showed clearly that SR is useful in selected patients. Combined SR and RT should be the treatment modality, if brain metastasis is single and appropriate for surgery. Rosenstein et al.[23] reported a retrospective study for the treatment of brain metastases in patients with bladder cancer. The mean TST was 11 months and 4 months in surgery plus RT group and only RT group respectively. Mandell et al,[14] reported a retrospective study for the treatment of brain metastases with lung cancer in 109 cases. They found median TST was 16 months and 4 months in surgery plus RT group and only RT group respectively. In our study, mean and median TST were13 months and 10 months respectively in patients who underwent surgery with RT in 33 of 62

patients. We did not apply only RT without SR so we could not compared surgery with RT and only RT groups.

In various studies, SR has been reported as the most important factor affecting TST[22]. Delarive and Tribolet[5] reported the mean of TST was 10.2 months in retrospective analysis of a surgical series, which include 71 of 81 patients whom applied RT. Ferrara et al. reported the median of TST was 13 months in a study, which included 100 patients whom had surgical intervention for single brain metastasis[6]. In our study that included 62 patients with surgical interventions, mean and median TST were 9 months and 6 months respectively.

In old series, operative mortality remained about 10-34%[21]. Advancement of surgical techniques, using of steroid has reduce the surgical mortality rate below 10% in recent years[4,5,6,17,18,20,21]. While Patchell[22], Ferrara[6] and Delarive[5] reported operative mortality rate as 4%, 6% and 7.4% respectively Mut reported surgical mortality is around 0.7-1.9% in her literature review[17]. In our study group, we have found mortality rate of 3.2%.

In several series, early postoperative complication rates were reported as 7-13.9% and these complications included wound infection, hematoma, hydrocephalus, deep vein thrombosis, urinary infections and pulmonary infection[3,18]. Also neurological morbidity was 3.9-6%[17,18]. In our study, early postoperative complications were, lung infection in 1 case (1.6%), paresis in 4 cases (6.4%) and CSF fistula in 3 cases (4.8%) and complication rate was calculated in 8.8% per each craniotomy.

In the early 1990s because of low morbidity and mortality rates, surgical intervention to multiple metastases come into question and studies has begun on this issue but two contrasting results have been reported in two different retrospective study[3,7]. Bindal et al. compared two groups of patients with multiple metastases. In first group all brain metastases removed surgically and in second group one or more lesions left unresected. While median TST was 14 months for first group, it was 6 months for second group. Mortality rate of 30-day for the group of multiple metastases have been reported as 4% and 3% respectively[3]. Hazuka et al reported comparison results of, 18 patients with multiple metastases and 28 patients with single metastasis. Median TST was 5 months and 12 months in multiple metastases and single metastases groups respectively. The complete resection rate of whole group was 50% (in multiple metastases group complete resection rate did not reported) and in both groups, mortality rate of 30 day was 0%[7]. Also Mut reviewed the literature and reported that in selected patients with a limited number of multiple brain metastases may benefit from resection of all lesions or the dominant lesion[17]. In our series 10 patients (16.1%) had multiple cerebral metastases. Mean and median TST was 7 months and 6 months respectively. These values were 9 months and 6 months respectively in single metastases groups. There was no statistically significant difference between two groups (p=0.428). While mortality rate was 0%, morbidity rate was 20% in multiple brain metastases group.

Brain metastases are easily separate and resectable lesions. Administration of RT after complete resection of single metastasis is still a moot point. There is no doubt that implementation of RT as the only treatment extended TST. It is believed that postoperative RT (WBRT) is beneficial in the treatment of residual tumor[19]. Non-randomized retrospective studies have been reported postoperative WBRT does not benefit[14]. De Angelis et al.[4] compared 98 cases in two groups. First group had postoperative RT after for single metastases. Second group had only surgery. They reported increase of TST and reduction rate of recurrence in first group. In our study mean TST was 13

months for patients who received postoperative RT. This value was 5 months for non-receiving postoperative RT group. TST was longer in postoperative RT group and it was statistically significant (P=0.000).

In several series, the rate of local recurrence was lower in surgery plus RT group than only RT group[4]. Similarly the rate of local recurrence was lower in surgery plus RT group than only surgery group[27]. In various studies these ratios have been reported as 20-35% in surgery plus RT group, 40-50% in surgery group and 50% in only RT group[27]. Relapses developed 62% local and 38% in other regions[2]. In our study, the rate of local recurrence was 15.1% in patients who underwent surgery plus RT. Local recurrence and distant metastasis rates were 16.2% and 23.2% respectively in patients who underwent complete resection.

Surgical intervention can be selected as a treatment method for single metastases if presence of controlled systemic cancer[19]. Experience in re-operation is limited[19]. Sundaresan et al[29], applied second surgery to 21 cases for recurrence. They reported 2/3 of patients had improvement in neurological symptoms and TST was 9 months after second operation. Patchell et al.[20], applied surgery for recurrence tumor after inefficient initial WBRT and reported median TST was 5 months in these patients. Arbit et al. analyzed retrospectively 214 cases who had primary non-small cell lung cancer plus surgical intervention for brain metastases. They reported median TST as 11.3 months in 109 patients who reoperated due to recurrence. This value was 9.5 months in non-relapsing group[2]. In our study, while mean and median TST were 13 months and 8 months respectively in patients with recurrence, these values were 7 months and 5 months respectively in non-recurrence patients. The difference was statistically significant between two groups (p=0.012).

Also in recent years SRS has begun to be used for treatment of brain metastases[10,11,16,26]. Muacevic et al. compared the effects of Gamma Knife surgery (GKS) alone versus microsurgery plus whole brain irradiation in 64 patients who had single metastases to the brain. Thirty three patients underwent surgery plus WBRT and 31 patients underwent radiosurgery. They concluded Gamma Knife surgery alone is less invasive and local tumor control seems to be as high as after surgery plus WBRT. They also reported patients of the radiosurgery group experienced more often distant recurrences[16]. Kano et al. reported selected patients can attain a survival benefit after resection of brain metastasis despite prior radiosurgery[10]. Karlsson et al. reported as a result of 30 years experienced that repeated GKS is more effective than the addition of WBRT and control of the primary disease is much more important than the number of metastases[11]. Samlowski et al. applied SRS to 32 patients who had clear cell renal cancer and brain metastases. One year and 3 year survival rates were 43% and 16% respectively. They demonstrated that SRS based treatment of patients with up to 5 brain metastases from clear cell renal cancer is feasible results in excellent CNS control[26]. But Mut reported surgery seems to be superior to SRS in terms of the survival and the rates of local recurrence and neurological death[17]. Sperduto et al. reported that SRS with combined modality therapies were statistically superior to WBRT alone. But for melanoma, breast cancer and small cell lung cancer SRS alone was not statistically significantly superior to WBRT alone[28]

Chemotherapy applications in the treatment of brain metastases, has increased particularly in recent years. It has been reported the effects of chemotherapy, in sensitive systemic tumors and brain metastases were similar[13]. Lange applied combine treatment chemotherapy and WBRT simultaneously to 61 patients with

primary breast cancer and brain metastases and found median survival time as 8 months[12]. Also Lange reported that 20% of patients achieved a complete remission of intracranial lesions median TST was 12 months. Rosner reported median survival as 29.5 months in 10 of 100 patients whom received a complete response with chemotherapy in primary breast cancer. In the same study median survival was 10.5 months in 40 of 100 patients whom received partial response with chemotherapy[24]. Markulin-Grigic applied RT and RT plus chemotherapy into two groups of 110 patients which was brain metastases of lung, breast, melanoma and renal origin. Survival was longer in second group which include RT plus chemotherapy[15]. Rustin reported median survival of 32 months in 10 patients with germ cell tumors which was sensitive to chemotherapy[25]. Hwu et al. treated 26 patients with temozolomide plus thalidomide who had recurrent or progressive brain metastases from melanoma. They reported median duration of response or stable disease in brain was 4 months after retreatment[8]. Iwamoto et al. applied temozolomide plus vinorelbine to 38 patients who had recurrent or refractory brain metastases. Median progression free survival was 1.9 months after retreatment[9]. Ammirati et al. reviewed the literature and concluded that some patients with recurrent or progressive brain metastases will have an objective radiographic response and/or improvement in functional status after treatment with chemotherapy and the median time to recurrence after retreatment with chemotherapy was ranged from 2 to 4 months[1]. In our study we found mean TST was 11 months and 5 months respectively in postoperative chemotherapy receiving group and non-receiving group. In first group TST was statistically significant longer (p=0.001).

In the planning of treatment of patients with metastatic brain tumors, prognostic factors were investigated in several studies. It has been identified that some factors such as, controlled or uncontrolled of systemic cancer[3,4,7,14,22] the extent of the SR[7], neurological status[7] and the general status[14,31] of the patient, histopathology[3,7] and region[17,27] of the primary tumor, patient age[4,31] and gender[19], formation of single or multiple brain metastases[7] and localization[4,14], duration of between diagnosis of the primary tumor with the development of brain metastases[4], were significantly altered the prognosis. In an another study, Sperduto et al. investgated the prognostic factors of brain metastases in different cancers. They concluded that Karnofsky performance status, age, presence of extracranial metastases and number of the brain metastases are the significant prognostic factors for non-small cell lung cancer and small cell lung cancer. For melanoma and renal cell cancer the significant prognostic factors were Karnofsky performance status and the number of the brain metastases. For breast and gastrointestinal cancer the only significant prognostic factors was Karnofsky performance status[28]. Also in our study, we investigated the possible prognostic factors. We found some factors such as age (p=0.024), general status level (p=0.016), level of neurological status (p=0.035), the extension of surgical resection (p=0.000), presence of the extra-cranial metastases at diagnosis (p 0.000) changed the prognosis significantly.

Also in our study we examined primary cancer in two groups as well as pulmonary and extrapulmonary. We found TST was longer in second group. The difference between two groups was not statistically significant but “p” value was very close to the border of significance (p=0.073).

We examined the interval between diagnosis of primary disease and the development of metastatic brain tumor in two groups. First group was 0-12 months, second group was over of 12 months. Mean TST was 6 months and 10 months

respectively in first and second group. In our study group the time of between primary diagnosis of cancer and development of the brain metastasis did not create statistically significant difference for TST.

## CONCLUSION

1-In the planning of treatment of patients with metastatic brain tumors, colleagues have to keep in mind level of neurological and general status, the extension of surgical resection ,presence of the extra-cranial metastases at diagnosis and localization of the primary focus affect the prognosis.

2-Surgical resection is beneficial for improving neurological status and survival of patients in brain metastases.

3-Local control is essential and can be achieved with one of the adjunct therapies following the surgery.

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