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Retrospective Examination of Intracranial Metastasis Tumors

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Abstract

Key words: Cancer, Magnetic resonance, Metastatic brain tumours, Surgical treatment, Survival

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Introduction

Brain metastases in adults are the most common intracranial tumors, and their frequency is ten times higher than primary brain tumors(Thomas & Dunbar, 2010). As a result of improvements in systemic and local therapies, the incidence of intracranial metastases has increased due to prolonged survival in cancer patients(Lin vd., 2004). In adults, brain metastases are often caused by lung tumors (40-50%), breast carcinoma (15-25%), malignant melanoma (5-20%), renal and gastrointestinal tract carcinomas (4-6%)(Ogawa vd., 2008). Primary cancers that cause intracranial metastasis more frequently in children; leukemia and lymphoma. Germ cell tumor, osteogenic sarcoma, and rhabdomyosarcoma are tumors that tend to metastasize in children under 15 years of age(Graus vd., 1983).

The most common spreading mechanism in brain metastases is usually hematogenous spread by arterial circulation. Intracranial metastases can spread to the brain parenchyma, cranial nerves, vessels, including the dural sinuses, dura, leptomeninges, and cranium. Metastases are located 80% in the brain, 15% in the cerebellum, 3-4% in the brain stem, 1% in the meninges and cranium (Delattre vd., 1988). They most frequently involve the parietal region and the second the frontal region(Sawaya vd., 2001). Metastatic tumors can be single or multiple. In general, lung and melanomas cause multiple brain metastases, while breast, renal and colorectal cancers cause single brain metastases(Delattre vd., 1988).

If the time elapsed between the metastatic lesion and the primary tumor in diagnosis is long, it is called metachronous. If a concomitant diagnosis is made, it is called synchronous metastasis(Macchiarini vd., 1991). Intracranial metastases are diagnosed after 80% of the primary tumor(Loeffler vd., 1997). The first symptom in patients is increased intracranial pressure, and the most common headache is observed(Nutt & Patchell, 1992). Progressive neurological dysfunction usually occurs due to gradually enlarging tumor mass and edema. Common symptoms are seizures, encephalopathy, ataxia, sensory and motor impairments, aphasia, and vision loss(Kizir & Kucucuk, 2004). Computerized brain tomography (BBT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are used for diagnosis in metastatic brain tumors.

The most critical factor determining the prognosis in patients with brain metastases is systemic cancer's clinical status. In the treatment of brain metastases, surgery, radiosurgery, radiotherapy, chemotherapy, and corticotherapy are used. Treatment aims to increase survival and quality of life. While whole-brain irradiation is preferred in appropriate cases with poor prognosis and

systemic disease is not controlled, combined therapies are preferred in cases with the systemic disease under control and good prognosis(Ranasinghe & Sheehan, 2007).

In this study, 66 patients diagnosed with brain metastasis in Mersin University Faculty of Medicine Neurosurgery Clinic between 2009-2013 were retrospectively analyzed and discussed in the light of the literature.

Material and Method

1. Study Design

This is a retrospective descriptive study. It is planned to examine the data of patients with intracranial metastases who were admitted to Mersin University Faculty of Medicine, Brain and Nerve Surgery outpatient clinic and Emergency Service between 1 January 2009 and 10 November 2013. Eighty patients with intracranial metastases admitted to the neurosurgery outpatient clinic and emergency service in 58 months were evaluated. Cases with recurrence, previous operation history, missing data, preliminary imaging tests, and those who did not accept treatment were not included in the study. For this, 14 cases were excluded from the study. Sixty-six cases were included in the study.

For this research, the Ethics Committee of Mersin University Faculty of Medicine's approval, dated 20/06/2013 and numbered 2013/214, was obtained. The first applications of the cases in 58 months were considered. Age, gender, date of primary diagnosis, date of diagnosis of metastasis, date of death, complaints at admission, physical examination findings, risk factors, primary cancer diagnosis, histopathology of primary cancer, location of intracranial metastasis, histopathology, diagnostic imaging method, chemotherapy, radiotherapy, surgery treatment results were recorded. Based on these data, the survival of the patients was determined.

2. Statistical analysis

In the statistical analysis, categorical data were summarized in terms of frequency and percentage, and continuous data in terms of mean ± standard deviation, min-max. Shapiro-Wilk test was used in testing the mean differences in survival between groups, depending on the shape of the distribution. Since the normal distribution assumption was not provided in comparing the two

groups, the Mann-Whitney U test was used. The Chi-Square test was used in the analysis of two categorical data. Kaplan-Meier survival analysis was used to investigate whether categorical risk factors have an impact on survival. $p < 0.05$ was accepted as the statistical significance level. Analyzes SPSS v. 11.6.0 and MedCalc 12.7.5.

RESULT

In our study, 39 (59.1%) of 66 cases were male, and 27 (40.9%) were female. The patients' mean age was 57 years, and the age range was between 3-81. Among the patients, the smoking rate was 28.8%, and alcohol use was 3%. Considering their history, 50 patients (75.8%) had comorbid diseases. It was observed that only 7 of the cases (10.6%) had a family history of cancer in their family history. No statistically significant difference was found between those with chronic diseases when compared with those without ($p = 0.185$). Of the patients with metastatic tumors, 29 (43.9%) were primarily caused by lung cancer. The second most common primary cancer was found to be breast cancer (13.6%). From other metastasizing primary cancers; 6 (9.2%) malignant melanoma, 5 (7.5%) gastrointestinal system tumors, 4 (6.1%) lymphoma, 10 (15.2%) other (renal cell cancer, testis cancer, ovarian cancer respectively), while primary tumors were not detected in 3 of them (4.5%). Among all histopathological examinations, the most common histopathological subtype was 25% adenocarcinoma. Eight of the patients (12.5%) were not diagnosed with histopathologically.

Of the patients, 21 (31.8%) were diagnosed simultaneously as the primary tumor, and 45 (68.2%) were found to have metastasis after the primary tumor diagnosis.

It was found that 36 (54.6%) metastases were solitary, and 30 (45.4%) were multiple. The most common causes of multiple metastases were found to be lung and breast cancer. Of the brain metastases, 47 (71%) were supratentorial, 12 (18%) were infratentorial, 7 (11%) were both supratentorial and infratentorial (table1).

Residential area	Count	Percent (%)
Parietal	24	36,4
Frontal	19	28,8
Cerebellar	10	15,1
Temporal	6	9,1
Occipital	3	4,6
Brainstem	2	3
Other	2	3
Total	66	100,0

Table 1: Locations of metastatic lesions

The parietal lobe is the most frequently involved localization, and in 24 (36.4%) of the cases, a metastatic tumor was found in the parietal lobe. The second most common site was the frontal lobe in 19 patients (28.8%) and metastatic involvement in the cerebellar region at the third frequency in 10 (15.1%) patients. Although 28 (42.4%) of the cases were located in the right, 20 (30.3%) in the left, and 18 (27.3%) were located in both lobes.

The number of patients with multiple metastases was found to be 26 (40%). The most common extracranial metastases were found in bone, then lung, and liver.

The patients' most common symptom at the time of admission to the emergency service and neurosurgery outpatient clinic was headache (37.8%). Of the cases, 9 (13.6%) had seizures, 7 (10.6%) had dizziness, 6 (9.1%) had confusion, 5 (7.6%) had power loss, 3 (4.5%) presented with gait disturbance and 2 (3.1%) with vision loss symptoms. In the routine examinations in asymptomatic patients, intracranial metastatic tumors were found in 5 (7.6%) patients. The symptoms of the patients at the time of application are shown in table 2.

Symptom	Count	Percent(%)
Headache	25	37,8
Epileptic seizure	9	13,6
Dizziness	7	10,6
Clouding of consciousness	6	9,1
No symptoms	5	7,6
Loss of strength	5	7,6
Other	4	6,1
Walking disorder	3	4,5
Vision loss	2	3,1
Total	66	100,0

Table 2: Patients symptoms at presentation

Neurological examinations of 29 (44%) patients at the time of admission were normal. In cases with neurological examination disorders, ataxia was detected in 11 (16.7%), hemiparesis / hemiplegia in 11 (16.7%), and confusion (with 13 or less GCS) in 9 (13.6%) patients .

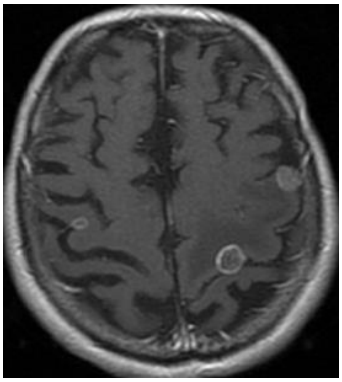

Figure1: T1 contrast-enhanced axial section; In the bilateral parietal region, masses, the largest of which is approximately 1.5x1 cm in size, with heterogeneous contrast and compatible with an edematous metastatic tumor, are seen.

Contrast-enhanced MRI was the most commonly used imaging method for the diagnosis of metastasis. The number of patients who underwent contrast-enhanced MR imaging as a diagnostic method was 26 (39.4%) (fig 1). There were 19 (28.8%) patients with only CT imaging (fig. 2). The number of patients used in both imaging methods was 21 (31.8%).

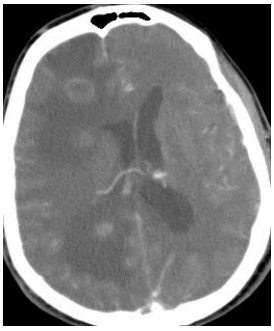

Figure2: Contrast-enhanced axial BBT; The appearance of metastatic tumors in both hemispheres, the largest of which is 2x1.5 cm in size, nodular, with dense edema around it, peripheral enhancement, and necrotic central.

		Number of patients	Male	Female	Average life expectancy
Age	0-20	3	1	2	6 month
	20-40	7	3	4	7 month
	40-60	32	17	15	6,8 month
	60+	24	18	6	4,2 month

Table3: Relationship between sex and age groups and mean survival times

Our patients' average life expectancy between the ages of 20-40 was seven months, and for those aged 60, over it was 4.8 months. Intracranial metastasis was most common in our patients between 40 and 60 (Table 3).

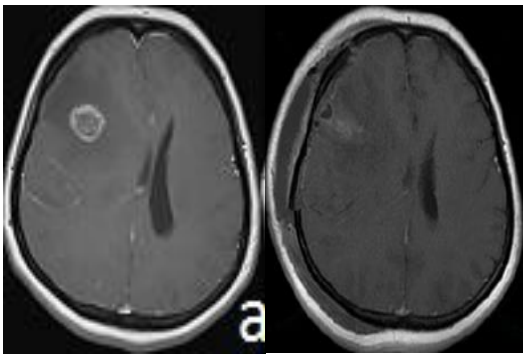

Figure 3: Cerebral MRI a) Axial contrast-enhanced section; The mass in the right frontal region is 18x15 mm in size, a nodular mass with severe edema around it, and a central necrotic mass. b) Postop cranial MR-axial contrast-enhanced section; Surgical craniotomy area, vasogenic edema, and mass in the right frontoparietal region are resected totally.

Thirty (45.5%) of the patients were treated surgically (fig 3). Surgical treatment was not applied to 36 (54.5%) patients. The histopathological diagnosis types of metastases after tumor resection are shown in table 4.

Pathological Diagnosis	**Count**	**Percent(%)**
Adenocarcinoma	13	43,3
Malignant Epithelial Tumor	7	23,3
Squamous Cell Carcinoma	3	10
Malignant melanoma	2	6,7
Small Round Cell Tumor	2	6,7
Other	3	10
Total	30	100

Table4: Histopathological subtypes of metastases

39 (59.1%) of the patients received chemotherapy. Cisplatin and Gemcitabine were the most commonly used drugs in patients with brain metastasis who received chemotherapy. 28 (42.4%) of the patients received cranial radiotherapy. Of the patients who received WBRT, 9 (32.1%) received only one day of radiotherapy, 7 (25%) patients received three days of radiotherapy. One patient with the longest WBRT received 13 days of radiotherapy. Gamma knife was applied to only 3 (4.5%) patients.

Among the operated and non-operated patients, 13 (44.8%) of lung-derived brain metastatic tumors were adenocarcinoma, followed by 10 (34.5%) small cell carcinoma, 5 (17.2%) squamous cell carcinoma, respectively. 1 (3.5%) was found to be large cell carcinoma. While 19 (65.5%) of metastatic tumors were metachronous, 10 (34.5%) of them were found synchronous. Surgical treatment was performed in 9 (31%) cases, and total resection was performed. Chemotherapy and radiotherapy treatments were applied during follow-up. Eight of the patients who underwent surgery were solitary, and one was multiple. Surgical treatment was not applied to 20 (69%)

patients with lung-related brain metastases. Of the patients who did not undergo surgery, seven had solitary, and 13 had multiple metastases. The average survival of patients who underwent surgery + RT + chemotherapy was 10.7 months in patients with cranial metastases with primary lungs. The average life expectancy in patients receiving only RT + chemotherapy was 6.1 months. When lung and extrapulmonary cancers were compared in terms of survival, no statistically significant relationship was found between metastatic lung cancer and mean survival ($p = 0.449$). There was no statistically significant relationship between lung cancer being single or multiple in terms of metastasis number ($p = 0.506$).

Histological diagnosis of 9 patients with brain metastases caused by breast cancer was invasive ductal carcinoma. All of these tumors were metachronous metastases. Solid lesions were detected in 3 of the cases, and multiple lesions in 6 of them. Tumors of three operated cases were solid. Postoperative RT and KT treatments were applied. One patient who underwent surgery died immediately after the operation. RT + chemotherapy was applied to six patients with multiple lesions. The average life expectancy was 3.5 months.

Of the five patients with malignant melanoma, three had solid masses, and surgery was performed. The average survival of patients who underwent surgery + RT + KT was 18 months. Two patients who did not undergo surgery had multiple metastatic tumors. These two patients received only RT + chemotherapy. The average life expectancy was 11 months.

Surgery was performed on 3 of 4 patients originating from the gastrointestinal system. While the tumor was solid in 2 of these 3 cases, there were multiple lesions in 1 case. These patients who underwent surgery + RT + KT lived an average of 9 months. One patient had multiple brain metastases. RT was applied, and the survival time was seven months.

	Surgical	Non-surgical
Number of patients	23 (%45.1)	28 (%54,9)
Average life expectancy	8,7 ay	5,6 ay

Table5: Relationship between surgical treatment and mean survival time

The cause of metastasis in four patients was lymphoma. 2 of these cases were operated. Surgery + KT + RT was applied. The average life span was 15 months. Two patients did not undergo surgery, and RT + chemotherapy was given. These cases lived for an average of 2 months.

In patients with intracranial metastases who did not undergo surgery, an average survival time of 5.6 months was found with RT + chemotherapy. It was found that the average survival time of patients who were given the combined surgery + KT + RT therapy was 8.7 months (table 5).

	Synchronous	Metachronous
Number of patients	16 (%31,4)	35 (%68,6)
Average life expectancy	6,3 month	8,2 month

Table 6: Intracranial metastasis diagnosis time and its effect on average life expectancy

The average survival of patients with metachronous tumors was 8.2 months and for synchronous tumors 6.3 months (table 6). A statistically significant difference was found in terms of mean life span ($p = 0.042$). The majority of metachronous tumors were lung, breast, and malignant melanoma cases. Surgery was performed on 24 patients with solid tumors, while surgery was performed on only six patients with multiple tumors. Combined chemotherapy and RT were used after surgery. The distribution of patients, according to treatment groups, is shown in table 7.

	Number of patients (n)	Patient Percentage (%)	Average life expectancy
KT+RT	31	47	5,1 ay
KT + RT + Surgery	24	36,3	8,9 ay
RT + Surgery	6	9,1	7,1 ay
RT only	3	4,6	4,2 ay
KT only	2	3	3,1 ay

Table 7: Distribution of patients with intracranial metastatic tumors by treatment groups

Discussion

Intracranial metastases; These are the lesions with high mortality and morbidity, recurrent, and sometimes diagnosed with the diagnosis of primary cancer. Clinical signs can be masked and delayed due to the accompanying symptoms of chemotherapy's primary cancer and complications. Primary tumors that most commonly cause brain metastases in adults are lung, breast, malignant melanoma, renal and colorectal cancers. Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, and osteosarcoma are the most common tumors in the pediatric age group that causes brain metastasis. In the autopsies of those who died of cancer, 25% of intracranial metastases were found(Mehta & Tremont-Lukats, 2002). Advances in diagnosis and treatment in recent years have played a role in the increase in intracranial metastasis incidence.

While the incidence of brain metastasis in stage 1-2 lung cancers is between 12-18%, in postoperative primary lung tumors, this rate is around 1-15% depending on the stage and histological type. The average time to develop brain metastasis is reported to be two years after diagnosis in 50% of patients treated for lung cancer(Yokoi vd., 1999). Brain metastases can be single or multiple. Colon, breast, and renal cell cancer usually develop single, malignant melanoma, and lung cancer multiple metastases. The rate of multiple metastases in patients with brain metastasis is 33-75%. Solitary metastases are seen in 40-50% and are often located in the supratentorial(Mehta & Tremont-Lukats, 2002). Spread is usually via the middle cerebral artery. Therefore approximately 80% of metastases are located in the cerebral hemispheres, 15-17% in the cerebellum, and 3-5% in the basal nuclei and brainstem(Bergqvist vd., 1998). In our study, 47 (71%) of the cases with brain metastases were detected in the supratentorial region. In a study of

28 cases by Kula et al., 54% of solitary type metastases were found, and the most common localization was reported as the frontal lobe(Kula vd., 1995). In Hsiung et al.'s study, Brain metastasis was most frequently detected in the parietal lobe(Hsiung vd., 1998). In our study, solitary type brain metastasis was detected with a rate of 54.6%, and the most common localization was the parietal lobe.

With the widespread use of magnetic resonance imaging (MRI), especially contrast-enhanced MRI, the metastasis detection rate increases. 30-50% of brain metastases are candidates for surgical treatment(Olak & Ferguson, 2000). In our study, 30 (45.5%) of the patients were surgically resected. Conditions, where surgical resection cannot be performed are the presence of multiple intracranial metastases that cannot be removed with a single craniotomy, the presence of extracranial metastases, general medical problems, and survival of fewer than three months(Pachell, 2002).

Brain metastases in lung cancer are usually detected months after a primary cancer diagnosis. In the study of Mehta et al., The average time between lung cancer diagnosis and brain metastasis diagnosis was found to be approximately eight months(Ferrigno & Buccheri, 1994). In some studies, metastases developing within two to three months after lung cancer diagnosis have been defined as synchronous brain metastasis(Bonnette vd., 2001). Although %22-30 of solitary brain metastases are synchronous, only %1 of patients diagnosed with lung cancer have synchronous brain metastasis. Metachronous metastases are seen more commonly. The average time between resection of the primary tumor and brain metastasis development is 12 months(Olak & Ferguson, 2000). In our study, synchronous brain metastasis rate was %31.5, and metachronous metastasis rate was %68.2 among cases with brain metastasis. The frequency of brain metastasis is higher in adenocarcinoma, which is a histopathological subtype of lung cancer. In the study of Ferrigno and Buccheri, it was observed that the most common lung cancer type that developed brain metastasis was adenocarcinoma with a rate of %20.8(Ferrigno & Buccheri, 1994). In our study, adenocarcinoma was found in %25 of the cases.

Brain metastasis is symptomatic regardless of the type of primary cancer. In cases without neurological symptoms, when the staging screening is performed, the chance of detecting brain metastasis with computed tomography is 3%, and studies are suggesting that this examination with a high-cost rate should be performed in patients with symptoms(Spiro & Porter, 2002). In a study conducted by Ferrigno and Buccherin, 63% of patients with brain metastases were found to be asymptomatic, and the place of the symptom in the diagnosis was not significant(Ferrigno & Buccheri, 1994). Contrast-enhanced brain MRI is more sensitive than computed tomography in

detecting brain metastases. In a study, the rate of asymptomatic brain metastasis detection was found to be 17% in contrast-enhanced MRI(Spiro & Porter, 2002). Headache was detected in approximately 50% of cases with brain metastases. In the study of Yılmaz et al., headache (35.7%) was the most common symptom in cases with brain metastasis, and 50% of cases were found to be asymptomatic(Yılmaz vd., 1998). The most common symptoms in our cases were headache (38.7%) and dizziness (10.6%), and the rate of our asymptomatic cases was 7.6%.

Factors claimed to be useful in survival; age, other organ metastasis, lymph node involvement, tumor status, cancer type, metastasis type, presence of neurological symptoms, and chemotherapy(Penel vd., 2001; Rodrigus vd., 2001). The most decisive prognostic factors determined by Lagerwaard et al. Karnofsky performance status, response to steroid therapy, and whether there are signs of systemic disease. Histopathological diagnosis and localization of brain metastases have no prognostic effect(Lagerwaard vd., 1999). In our study, the neurological condition at presentation was among the factors affecting survival.

In the treatment of cranial metastatic tumors, RT and CT treatments are combined with surgery. Side effects of RT and KT are disadvantageous in these treatments. The average life span with cranial RT is three to six months. Late complications of RT are brain atrophy and necrosis, endocrine dysfunction, and dementia(Kelly & Bunn, 1998; Shahidi & Kvale, 1996). Dementia due to radiation; is characterized by memory loss, attention deficit, emotional lability, and within a few weeks or months, patients become bedridden and die within 1-48 months of the onset of symptoms(Keime-Guibert vd., 1998). In the study conducted by Lee et al. In 72 patients, necrosis due to radiation was treated with dexamethasone at a rate of 35 % (Lee vd., 2002). Since RT contributes to treatment and survival, it is essential to add it to treatment. Combining the treatment of radiation necrosis by adding dexamethasone will contribute to survival.

The ideal chemotherapy treatment choice should be of a type that can affect both systemic disease and brain metastasis. The most successful results can be obtained in patients with chemosensitive tumors (such as SCLC, breast cancer, and germ cell tumors). Response rates to chemotherapy are 56-82% in primary lung and breast cancers(Pachell, 2002). The disadvantage of these chemotherapeutic agents is that they cannot cross the blood-brain barrier and increase the possibility of metastasis by disrupting the blood-brain barrier (Kelly & Bunn, 1998).

Brain metastases are known as the last stage of malignant disease, and temporary and short-term treatments are applied because survival is short at the time of diagnosis (Yılmaz vd., 1998). Currently, the recommended treatment options for brain metastases are corticosteroids,

chemotherapy, RT, surgical intervention, stereotactic radiosurgery techniques, and chemotherapy. In the patient who was not given any treatment, the survival time was four weeks, two to three months with steroid therapy, three to six months with chemotherapy and RT, and 3.5-8 months with the addition of metastasis surgery to the combined treatment. In one study, death in untreated cases is thought to develop secondary to brain metastasis(Ranasinghe & Sheehan, 2007). In our study, the average life expectancy of patients who received only chemotherapy and radiotherapy was 5.1 months; for patients who received only surgery and radiotherapy, 7.1 months, and for patients who underwent chemotherapy and RT together with surgery, the mean life expectancy was 8.9 months.

Conclusion

Life expectancy in patients with brain metastases is low. The patient's general condition, the condition of the comorbidities, the number of metastases, the size and location of the metastases should be evaluated, and individual treatment should be planned for the patient. Our study observed that the average life expectancy increased in patients with early diagnosis, solitary metastasis, and surgery. It has been observed that combined chemotherapy and RT combined with surgery contribute more to survival than other treatment combinations. It was observed that patients did not die due to neurological deficits but died due to primary tumor and other organ failures.

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