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ORIGINAL ARTICLE

Survival and prognostic factors in patients with brain metastasis: Single center experience

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Summary

Purpose: *The purpose of this study was to evaluate the clinical status, prognostic factors and treatment modalities affecting survival in patients with brain metastasis. We aimed to evaluate the whole brain radiation therapy (WBRT) outcomes of patients with brain metastasis in our center.*

Methods: *Clinical data of 315 patients referred to our center between 2004 and 2014 with metastatic brain cancers were collected and analysed for possible relationships between survival time, age, gender, Karnofsky performance status (KPS), recursive partitioning analysis (RPA), primary tumor, number of brain lesions, surgery, radiation therapy scheme, extracranial metastatic status and primary disease control status.*

Results: *The average patient age of onset was 58 years. The primary tumor site was lung (68%), breast (12%), melanoma (4%), colorectal (1.6%), sarcoma (1.3%) and unknown primary disease (4.4%). The rest of the patients had other primary sites. Eighty four (26.6%) patients had single brain metastasis, 71 (22.5%) had 2 or 3 lesions, and 159 (50.4%) patients had more than 3 lesions. Leptomeningeal involvement was seen in combination of paranchymal involvement in 11 (3.5%) patients. Fifty patients had undergone surgical resection. WBRT was delivered to all of the patients. Median overall survival was 6.7 months (95% CI, 5.80-7.74). Median overall survival of patients treated with combination of surgery and WBRT was significantly better compared with those treated with WBRT alone (13.5 vs 5.5 months, p=0.0001). One- and 2- year survival was 17 and 4.7%, respectively.*

Conclusions: *The present study concludes that brain metastasis is common in cancer patients. The best overall survival was obtained by surgery+NBRT in good-condition patients. Treatment should be tailored on an individual basis to all these patients.*

Key words: *brain metastatic cancers, prognosis, radiotherapy, survival*

Introduction

Brain metastases are the most common (15-40%) intracranial tumors in adults [1]. In patients with systemic malignancies, brain metastases occur in 10-30% of adults and 6-10% of children [2]. Brain metastases increased in recent years due to increase of cancer patients' survival and widespread use of imaging modalities [3]. There are about 200,000 new cases in only one year in USA, which is 10-fold higher than primary intracranial tumors [4]. The peak of brain metastasis is between the fifth and seventh decade of life and it is slightly more common in men [5]. The majority of patients who develop brain metastases have a known primary cancer (metachronous presentation). Most brain metastases originate from lung (40-50%), breast (15-25%), melanoma (5-20%) and kidney (5-10%).

No primary site of cancer is detected in 5-10% of patients with brain metastases [6].

Usually metastatic brain tumors are diagnosed using imaging studies such as computed

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tomography (CT) and magnetic resonance imaging (MRI) [5]. Brain metastasis is the most important cause of morbidity and mortality in cancer patients [7]. The prognosis of patients with brain metastases is generally poor, and survival is about 4 weeks, if untreated [8].

Radiation therapy, surgery and chemotherapy are used for treatment. Radiation therapy may be used as WBRT, stereotactic radiosurgery or combination of these modalities. WBRT has always been considered as the standard treatment of brain metastases [9].

The purpose of this study was to retrospectively evaluate the clinicopathologic characteristics and survival outcome of patients with brain metastatic patients in our province.

Methods

Three hundred and fifteen patients with brain metastasis who referred to our clinic from November 2004 and February 2014 (Inonu University, Department of Radiation Oncology, Malatya, Turkey) were retrospectively evaluated. Data about sex, age, KPS, RPA, primary tumor, number of cranial lesions, surgery, radiation therapy, extracranial metastasis status and primary disease control status were evaluated. Imaging of the brain (CT scan or MRI) had been performed in all patients. RPA of our patients was assessed to classify brain metastases, adapted from Gaspar et al. [1] and Lutterbach et al. [10]. Patients who had less than 3 lesions and suitable for surgery were referred to surgery. All of our patients received WBRT. We applied 2-D conventional or 3-D conformal radiotherapy to all patients. Patients were simulated in a supine position with their heads fixed with thermoplastic head masks. The target volume consisted of all the intracranial contents with at least a 1 cm margin around the bony skull at each margin. The inferior border at the cervical vertebral bodies was the C1 interspace. Patients were treated on a megavoltage linear accelerator (LINAC) with 6 MV photons or on Cobalt 60 with gamma rays. According to the dose-fraction scheme for WBRT a median dose of 30 Gy (range 20-39) was delivered in 5 or 13 fractions. To prevent the development of edema during radiation therapy, the patients were administered dexamethazone 8-16 mg/d.

Statistics

SPSS software package, version 17.0.0, was used for the statistical analyses (SPSS Inc., Chicago, Ill, USA). Overall survival was defined as the time between the date of diagnosis (pathologically or radiologically) to the date of death or lost to follow-up. The Kaplan–Meier method was used to calculate survival and differences in survival between two groups were assessed by the log-rank test. A p value less than 0.05 was deemed to indicate statistical significance.

Results

Three hundred and fifteen patients were evaluated and 5 (1.5%) of them are alive. The mean age of the patients was 58 years (range 20-87). Two hundred and thirty (73%) patients were male and 85 (27%) female. The primary site of the tumor was lung (68%), breast (12%), melanoma (4%), colorectal (1.6%), sarcoma (1.3%) and unknown primary disease (4.4%). The rest of the patients had other primary sites. Eighty four (26.6%)

Table 1. Clinicopathological and therapy characteristics

Characteristics	*N*	*%*
Gender		
Male	230	73
Female	85	27
Age, years		
≤65	240	76
>65	75	24
Primary tumor		
Lung	214	68
Breast	38	12
Melanoma	12	4.0
Colorectal	5.0	1.6
Primary unknown	14	4.4
KPS		
<70	57	18
≥70	258	82
Extracranial metastasis		
No	108	34
Yes	207	66
Surgery		
No	265	84
Yes	50	16
Primary disease control*		
No	252	80
Yes	63	20
Number of metastases		
1	84	26.5
2	52	16.5
3	19	6.0
≥4	160	51
Radiation therapy dose		
300*10	254	80.5
Other	61	19.5
Leptomeningeal involvement		
No	304	96.5
Yes	11	3.5
RPA class		
1	16	5.0
2	243	77
3	56	18

KPS: Karnofsky performance status, RPA: Recursive partitioning analysis
*No disease except brain

Table 2. Median patient survival (Kaplan-Meier) according to several parameters

Parameters	*Overall survival (months, median)*	*p value*
Gender		
Male	6.64	0.867
Female	6.91	
Age, years		
≤65	6.8	0.683
>65	6.5	
Primary site		
Lung	7.2	0.016
Breast	5.02	
Melanoma	6.36	
Colorectal	10.14	
Unknown prim. disease	4.07	
KPS		
<70	3.48	0.0001
≥70	7.49	
Extracranial metastasis		
No	9.49	0.0001
Yes	5.30	
Surgery		
No	5.52	0.0001
Yes	13.47	
Primary disease control		
No	5.95	0.016
Yes	9.71	
Number of metastases		
1	9.69	0.002
2	6.56	
3	6.84	
≥4	5.11	
Radiotherapy schema		
300*10	7.14	0.003
Other	1.25	
Leptomeningeal involvement	6.95	0.0001
No	1.15	
Yes		
RPA class		
1	13,43	
2	6.89	0.0001
3	4.23	

For abbreviations see footnote of Table 1

had single brain metastasis ,71 (22.5%) had 2 or 3 lesions, and 159 (50.4%) patients had more than 3 lesions. Leptomeningeal involvement was seen in combination of parenchymal involvement in 11 (3.5%) patients. The median overall survival was 6.7 months (95 CI%, 5.80-7.74). One- and 2-year survival were 17 and 4.7% respectively. The median overall survival of patients who were suitable for surgery and treated with combination of surgery and WBRT was significantly better than those treated with WBRT alone (13.5 vs 5.5 months respectively, p=0.0001). These patients had a good PS and had less than 3 metastastic lesions. Median overall survival of patients who had KPS ≥ 70 was significantly higher compared to those with KPS <70 (7.5 vs 3.5 months respectively, p=0.0001). Patients with extracranial metastasis had significantly lower overall survival than patients with only brain metastasis (5.3 vs 9.5 months, p=0.0001). When the single metastasis group of patients was compared to the patient group with more than 2 metastases, overall survival was significantly higher in the single metastasis group (p=0.0002). The median survival of patients with leptomeningeal involvement (N=11) was significantly lower compared to the patients without leptomeningeal involvement (1.1 months vs 7 months respectively, p=0.0001). Patients with primary disease control (PDC) (no disease except brain) had significantly higher overall survival when compared with those without PDC (6 vs 9.7 months respectively, p=0.016). Univariate analysis results of patient survival are shown in Table 2. Leptomeningeal involvement decreased survival. Also, patients treated with 10x300 cGy and who had PDC, single metastasis, RPA class I, surgery, without extracranial metastasis and KPS ≥70 showed significant relationship with overall survival.

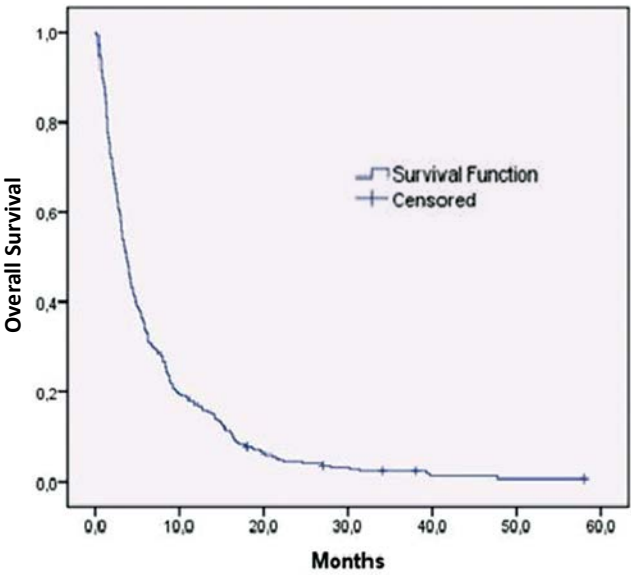

Figure 1. Kaplan-Meier overall survival (median 6.7 months).

Discussion

Brain metastases are the most common type of intracranial neoplasms, outnumbering primary brain tumors by a ratio of 10:1 and occur in about 25% of all patients with cancer. Conservative estimates suggest that about 200,000 new cases of brain metastases are diagnosed every year in the

USA [4]. Advances in neuroradiology have contributed greatly to the diagnosis and management of patients with suspected neoplastic diseases of the central nervous system (CNS). Contrast-enhanced computed tomography (CT) is used widely because of its easy accessibility and low cost. Contrast-enhanced magnetic resonance imaging (MRI) is more sensitive than enhanced CT scanning in detecting brain metastases, particularly small lesions or metastases situated in the posterior fossa [11]. Clinical symptoms or presentation of a patient with brain metastases have been described by Posner et al. In their series, headache was the most common clinical symptom, observed in 49% of the patients, followed by mental changes in 32%, focal weakness in 30% and seizures in 18% of the patients [12]. Headache, vomiting, and neurological symptoms were predominant clinical presentations in our patients. Approximately 80% of brain metastases are located in the cerebral hemispheres, 15% in the cerebellum and 5% in the brainstem [13]. A study by Victor et al. [14] showed that about 60% of the patients with brain metastasis are between 50 and 70 years of age. Out of 62 patients treated in southeast Turkey and reported by Yilmazer et al, their mean age was 57 [15]. The mean age of our patients was 58.

Brain metastasis is not common in children; it accounts for 6% of all central nervous system (CNS) tumors in children. Leukemia accounts for most metastatic CNS lesions in young patients, followed by germ cell tumors, lymphoma, osteogenic sarcoma and rhabdomyosarcoma. Lassman and De Angelis reviewed 9 studies and found the following variations in reported percentages of patients developing brain metastases for specific primary histologies: 18-64% in lung cancer, 2-21% in breast cancer, 2-12% in colorectal cancer, 4-16% in melanoma, 1-8% in kidney, 1-10% in thyroid and 1-18% in unknown primaries [16]. In 2700 cases from the Memorial Sloan-Kettering Cancer Center in New York, Victor et al. reported that the distribution of primary cancers was as follows: 48% lung, 15% breast, 9% melanoma, 1% lymphoma, 3% gastrointestinal, 11% genitourinary, 10% osteosarcoma, 5% neuroblastoma and 6% head and neck cancer [15] . In the present study the primary tumor site was lung (68%), breast (12%), melanoma (4%), colorectal (1.6%), sarcoma (1.3%) and unknown primary cancer (4.4%).

Akhavan et al. reported leptomeningeal involvement with parenchymal involvement with a ratio of 12.6% [5]. In our study 3.5% of the patients had leptomeningeal involvement with parenchymal involvement. The median survival of patients with leptomeningeal involvement was significantly lower compared to patients without leptomeningeal involvement.

Currently, treatment of brain metastasis has no fixed therapeutic approach. All of the factors that follow should be taken into consideration: the patient's general condition, the site of primary disease and the pathological type of brain metastasis, the number of metastases and the presence of PDC. Traditionally, WBRT is the preferred treatment for brain metastases.

The role of chemotherapy in the treatment of brain metastases is controversial because of the blood-brain barrier. Most authors maintain that most chemotherapeutic drugs cannot pass through the blood-brain barrier hence the chemotherapy efficacy in brain metastatic disease is low or absent [17]. Surgery is an effective treatment option but it is only suitable for very few patients with single brain metastasis and good general condition [18]. There are many studies comparing WBRT to more aggressive combined therapies in the treatment of oligometastatic brain tumors. In the study reported by Patchel et al., 95 patients with solitary brain metastasis were subjected to surgery alone or to surgery+WBRT. Comparison of the two groups showed that postoperative WBRT decreased brain recurrence significantly, however, no significant difference was found regarding survival rates [19]. Our patients who were treated with surgery had increased survival, however, these patients had good performance status and less than 3 lesions.

Stereotactic radiosurgery (SRS) is a non-invasive treatment technique, which enables single-fraction high-dose of ionizing radiation delivery within the target, while minimizing damage to the surrounding normal tissues. SRS attains survival rates similar to surgery [19]. Aoyama et al. compared SRS alone with SRS+WBRT in 132 patients with oligometastatic brain tumors (the number of metastases in the brain was 1-4) and stated that adding WBRT to SRS significantly decreased local recurrence and distant relapse risk with no significant effect on overall survival [21].

In the EORTC 22952-26001 study, the results of adding WBRT to local treatment (surgery or SRS) were evaluated in 359 patients with 1-3 brain metastases. Adjuvant WBRT following surgery decreased significantly local relapse (27 vs 59%, $p<0.001$) and development of new brain metastases (23 vs 42%, $p=0.008$). Similarly, adjuvant WBRT following SRS also significantly decreased

local recurrence (19 vs 31%, p=0.04) and development of new brain metastases (33 vs 48%, p=0.02) [22].

RPA classes are valid and reliable for historical comparisons. Both the RTOG and other clinical trial organizers should currently utilize this RPA classification as a stratification factor for clinical trials. According to the literature, the best survival was observed in RPA class I [1,23]. In the current study, patients who had RPA class I had 13.4 months survival.

Recent studies reported that there is neither improvement in symptom control nor neurologic improvement among the different dose-fractionation schemes as compared to 3000 cGy in 10 daily fractions of WBRT. Also, no survival advantage with the use of different radiotherapy schemes was noted [24-26]. In the present study, survival advantage was registered in the 10x300 cGy scheme but in other schemes, we included the patients who had poor PS and shorter survival expectation.

Nieder and Mehta compared different prognostic indices and analyses of prognostic factors based on a systematic literature search on Medline. They identified 6 different prognostic indices and one of them was RPA and analysed and compared the prognostic indices with each other in studies with more than 20 patients. The authors concluded that they could not find an ideal pognostic index [27].

In conclusion, to our knowledge this study is one of the largest evaluations of metastatic brain tumors in our country. The best overall survival was obtained by surgery/SRS+WBRT. Especially, adding surgery or SRS in good-condition patients could lead to beneficial effects on their survival. We maintain WBRT is still the most important treatment option for all patients with brain metastasis.

Conflict of interests

The authors declare no confict of interests.

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