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CHARACTERISTICS AND SURVIVAL OF BRAIN METASTASIS FROM TWO RADIORESISTANT TUMORS, MALIGNANT MELANOMA AND RENAL CELL CARCINOMA: A SINGLE RADIOTHERAPY CENTER STUDY

İKİ RADYOREZİSTAN TÜMÖR OLAN MALİGN MELANOM VE RENAL HÜCRELİ KARSİNOMUN BEYİN METASTAZLARININ ÖZELLİKLERİ VE SAĞKALIMLA İLİŞKİLERİ: BİR RADYOTERAPİ MERKEZİ ÇALIŞMASI

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ABSTRACT

Objective: Malignant melanoma (MM) and renal cell carcinoma (RCC) are rare radioresistant tumors that often metastasize to the brain. Because of their rarity, studies on brain metastatic RCC and MM are limited. We aimed to outline the characteristics of brain metastasis (BM) patients from RCC and MM and analyze the potential prognostic factors for survival.

Materials and Methods: This is a retrospective-observational study using data from patients admitted to a radiotherapy (RT) center of a university hospital between 1998-2020. Clinicopathological characteristics, treatment details, and outcome results were analyzed. Univariate and multivariate survival analyses were performed.

Results: Among a total of 14,603 patients treated in our center in the study period, only 52 (0.004%) were BM cases from MM or RCC. Forty patients had complete data (median age at diagnosis of MM or RCC-related BM: 57.7; females: 25%; MM in 52.5% and RCC in 47.5%). The time between primary diagnosis and first extracranial metastases was weakly correlated with the time

ÖZET

Amaç: Malign melanom (MM) ve renal hücreli karsinom (RCC), beyne sıklıkla metastaz yapan nadir ve radyorezistan tümörlerdir. Nadir olmaları nedeniyle beyin metastatik MM ve RCC ile ilgili çalışmalar sınırlıdır. MM ve RCC kaynaklı beyin metastazı (BM) gelişen hastaların karakteristik özelliklerini ve sağkalım için potansiyel prognostik faktörleri analiz etmeyi amaçladık.

Gereç ve Yöntem: Bu çalışma, 1998-2020 yılları arasında bir üniversite hastanesinin radyoterapi (RT) merkezine başvuran hastaların verilerini kullanan geriye dönük-gözlemsel bir çalışmadır. Klinikopatolojik özellikler, tedavi detayları ve sonlanım verileri analiz edildi. Tek değişkenli analizler ve çok değişkenli sağkalım analizleri yapıldı.

Bulgular: Çalışma döneminde merkezimizde tedavi edilen toplam 14,603 hastadan sadece 52'si (%0,004) MM veya RCC ilişkili BM vakasıydı. Çalışma popülasyonunu verileri eksiksiz olan 40 hasta oluşturmaktaydı. MM veya RCC ilişkili BM tanısında medyan yaş 57,7 olup, hastaların %25'i kadındı. MM sıklığı %52,5 ve RCC sıklığı %47,5 idi. "Primer tanı ile ilk ekstrakraniyal metastazlar arasındaki

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between diagnosis of extracranial metastasis and BM (r=0.405, p=0.021). Among the potential prognostic factors on survival [age, sex, older vs younger age group, primary diagnosis (MM vs RC), presence of extracranial metastasis, number of BM, location of BM, presence of gross total resection, dose of RT, completion of prescribed RT, field of RT], none were independently associated with survival.

Conclusion: Our findings suggest that when MM or RCC patients develop brain metastasis, survival is limited without any favorable prognostic factor belonging to the patient, the tumor, or the preference of the treatment.

Keywords: Brain metastasis, malignant melanoma, radioresistant tumor, renal cell cancer, survival

süre" ile "ekstrakraniyal metastaz tanısı ile BM arasındaki süre" arasında zayıf bir korelasyon vardı (r=0,405, p=0,021). Sağkalıma yönelik potansiyel prognostik faktörler olan "yaş, cinsiyet, yaşlı veya genç olma, primer tanı (MM veya RCC olması), ekstrakraniyal metastaz varlığı, BM sayısı, BM'nin yeri, tam yada tama yakın rezeksiyon, RT dozu, planlanan RT'nin tamamlanması, RT alanı" gibi parametrelerin hiçbiri sağkalım ile bağımsız ilişkili değildi.

Sonuç: Bulgularımız, MM veya RCC hastalarında beyin metastazı geliştirdiğinde hastaya, tümöre veya tedavi tercihine ait herhangi bir olumlu prognostik faktör olmadan sağkalımın sınırlı olduğunu göstermektedir.

Anahtar Kelimeler: Beyin metastazı, malign melanom, radyorezistan tümör, renal hücreli karsinom, sağkalım

INTRODUCTION

Brain metastasis (BM) is the most common brain tumor and about 20-40% of cancer patients develop BM eventually (1). Morbidity and mortality of BM are very high (2). BM is most seen in malignant melanoma (MM) and renal cell carcinoma (RCC) followed by lung cancer and breast cancer (3).

MM and RCC are well known for their radioresistant characteristics. As an overview, in a study that analyzed the effectiveness of whole brain radiation therapy (WBRT) of metastatic brain lesions, complete response was observed in about 40% of small cell lung cancer, 25% of squamous cell carcinoma (SCC), 15% of non-breast adenocarcinoma and 3% of breast cancer, while there was no complete response in RCC and MM cases (4).

MM and RCC have low prevalence but a high rate of BM. The prevalence of MM is about 5%, and the prevalence of BM from MM is strikingly high, being about 40-60% and 75% in the autopsy series (5, 6). If MM with BM would be left untreated, the expected survival is less than three months (5) while when treated with WBRT survival has been suggested to increase to up to eight months (7, 8). On the other hand, the prevalence of RCC has been reported as 1-2% (9, 10). Yet, the prevalence of BM from RCC is as high as %2-17 (11). If BM from RCC would be left untreated, the survival is limited to three months. If it would be treated with WBRT, survival has been suggested to improve to up to nine months (8). In case BM is operable and standard WBRT is applied, survival is suggested to be extended up to 15.5 months (9).

The prevalence of MM and RCC doubled in the last 25 years requiring increased attention to these two tumors and their associated brain metastases (7). The major treatment modality in the management of brain metastasis is still WBRT (7, 8, 12).

Clinicians need information on the characteristics of patients suffering from BM associated with MM and RCC given the increasing prevalence of both tumors and high rates of BM associated with these tumors. The analysis of various prognostic clinical factors which may aid in selecting patients for applicable treatment modalities is required as well. However, given their low prevalence so far, this information is very limited. As such, we aimed to outline the demographic and clinical characteristics of the BM patients from RCC and MM treated in our radiotherapy center over a period of 22 years and analyze the potential prognostic factors for survival.

MATERIALS AND METHODS

Population and setting

This study is a retrospective, observational study that followed the report Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (13). We analyzed the data of the patients who applied to the radiation oncology center and received radiotherapy for BM from MM or RCC (according tonternational Commission on Radiation Units and Measurements [ICRU] 83 definitions) (14) at Radiation Therapy Clinics of a tertiary health center, between January 1998 and December 2020 in 22 years. The patients with unavailable data were excluded, otherwise, the data of all patients were included. Forty [40] participants composed the study population.

All patients were applied cranial irradiation and concomitant dexamethasone treatment. WBRT was performed with 6-10 MV photon beams from a linear accelerator or cobalt 60, via parallel opposed fields (90° and 270°) with a commercial thermoplastic mask fixation. All the metastases were treated with a fractionation dose of 3Gy or 4Gy.

All procedures performed in studies involving human participants were following the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the local ethics committee (Date: 05.02.2018, Number: 2012/04). Informed consent was obtained from all of the participants included in the study.

Measurements and definitions

Medical charts were reviewed systematically regarding the demographic and clinical characteristics. Age at primary diagnosis, sex, histopathology of the tumor, presence of extracranial disease at primary diagnosis, age at extracranial metastasis, age at the time of diagnosis of BM, localization of metastases, presence of single or multiple metastases, application of metastatic brain lesion surgery, type of surgery, a dose of RT for BM, implementation of the prescribed dose, the time between the initial diagnosis and BM, the time between the initial diagnosis and extracranial metastasis, the time between extracranial metastasis and BM, survival time following diagnosis, following extracranial metastasis, and BM were recorded. If the time between the primary lesion and metastasis was less than one month, these metastases were accepted *synchronous* tumors. Brain overall survival (B-OS) was defined as the time between the diagnosis of BM and death.

Outcomes

The primary outcomes were prognostic factors for MM and RCC that developed BM and received RT. We considered age, sex, age group (age>=65 vs <65), primary diagnosis (MM vs RCC), presence of extracranial metastasis, number of BM (solitary vs multiple), location of BM (cerebral vs cerebral+cerebellar), presence of gross total resection (GTR), a dose of RT, completion of prescribed RT, the field of RT (all over cranium vs all over cranium+additional RT over the specific BM location).

The secondary outcomes were clinicopathological characteristics, treatment details, and correlations between survival periods after primary diagnoses, first extracranial metastases and, brain metastases.

Statistical analysis

We examined the normality of the parameters with Shapiro Wilk test and visual histograms considering relatively low number of participants. Accordingly, non-parametric tests and parametric tests were used as appropriate. Descriptive statistics were given as percentages for categorical variables and mean, standard deviation or median, minimum-maximum for numerical data. Independent sample two test or Mann-Whitney U test was used to compare numerical variables between the group and Pearson or Spearman's correlation tests were used in correlation analyses. When the correlation was detected as significant, it was regarded strong if correlation coefficient (r) was> 0.7, moderate if between 0.5-0.7, low if between 0.3-0.5 and negligible if< 0.3. The survival analyses were performed by Log-Rank test with Kaplan–Meier survival analyses. IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. $p<0.05$ was defined as statistical significance.

RESULTS

Demographics and Baseline Characteristics (table 1)

A total of 14,603 patients were treated in our center during the study period. Among them, 52 (0.004%) patients were diagnosed as BM from MM or RCC. Twelve (12) patients' data were unavailable and therefore excluded. A flow chart on the number of patients included and excluded at different steps can be found in figure 1.

Table 1. The demographics and baseline clinical characteristic of MM and RCC patients with brain metastasis (n=40)

Parameter	
Age at primary diagnosis (years) [a]	55.9 (22.7-80.1)
Median age at the time of CNS metastasis, years[a]	57.7 (22.8-80.7)
Age group[b]	
<65	31 (77.5%)
≥65	9 (22.5%)
Primary cancer[b]	
RCC	19 (47.5%)
MM	21 (52.5%)
Sex[b]	
Women	10 (25%)
Men	30 (75%)
Extracranial metastasis[b]	
Present	32 (80%)
Absent	8 (20%)
Age at brain metastasis (years) [b]	57.7 (22.8-80.7)

MM, multiple myeloma; RCC, renal cell carcinoma
[a]Data are given as median (range, minimum-maximum)
[b]Data are given as number (percentage)

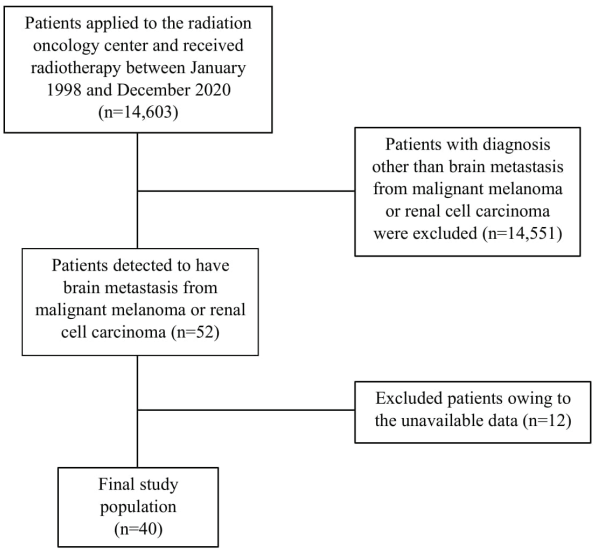

Figure 1: Flow chart on the number of patients included and excluded during the study period

The median age at diagnosis of MM or RCC was 55.9 (22.7-80.1). The females constituted 25% (n=10) of the study population. In the total study population, 52.5% (n=21) were MM and 47.5% (n=19) were RCC. The majority of patients (80%) had extracranial metastatic disease at a median age of 56.6 (23-77). The median age at the time of BM was 57.7 years (22.9 to 80.7 years).

A total of 27.5% (n=11) patients were diagnosed with distant metastasis with BM simultaneously while 52.5% (n=21) had developed distant metastases before BM. Only 20% (n=8) of the study population were free from extracranial metastasis when BM was diagnosed. We outlined the demographics and baseline clinical characteristics of the study participants in table 1.

Data at diagnosis of metastases and treatments

Tumor histopathology was established by pathologic analysis, with biopsy either from the primary site or metastases. All patients who had BM were investigated with brain computerized tomography (CT) or magnetic resonance imaging (MRI). The time from diagnosis of the primary tumor to first extracranial metastasis was 11.3 months (0-121.7 months); the time between the diagnosis of the primary tumor to BM was 21.2 months (0-123.3 months); the time between extracranial metastases to BM was 10.1 months (0-76.9 months) (table 2). The time between primary diagnosis and first extracranial metastases correlated with the time between diagnosis of extracranial metastasis and BM (r=0.405, p=0.021).

whole Brain Radiotherapy consisted of a 30 Gy in 10 fractions in two weeks in 18 patients. A 20 Gy WBRT in five fractions in one week was applied to 15 patients. 15Gy boost irradiation for 30Gy schedule was performed up to a total dose 45Gy to single BM to four patients. Three patients were unable to receive the prescribed dose of RT.

Among the study group, 50% (n=20) had solitary brain metastasis, 45% (n=18) had multiple metastases and 5% (n=2) of patients had an unknown number of metastases. In the study population, 72.5 % (n=29) had metastasis at the cerebrum, 17.5 % (n=7) at both cerebrum and cerebellum, and 2.5% (n=1) at the cerebellum [location of metastases was unknown in 5% (n=3)]. Five patients (12.5%) had undergone gross total resection of BM (all were single metastatic), 25 % had a partial resection and 10% (n=4) had only a biopsy. A total of 30 patients (75%) had no surgery (table 3).

Survival data

Survival data of two patients was not available. All other 38 patients died within the study period. The median survival time from diagnosis of the primary tumor was 16.3 months (1.0-125.4 months). The survival time from the first extracranial metastasis was 10.2 months (1.0-87.7 months); after diagnosis of BM (Brain overall survival, B-OS) was 6.8 months (1.0-22.3 months) (table 4).

Correlation between survival periods after primary diagnoses, first extracranial metastases and brain metastases

Time from primary diagnosis to BM was weakly correlated with the time from first extracranial metastasis to death (r=0.47, p=0.007). Time from first extracranial metastasis to death and time from BM to death (B-OS) was weakly correlated as well (r=0.44, p=0.013). On the other hand, time from primary diagnosis to BM was not correlated with time from first extracranial metastasis to death, and

Table 2. Times between diagnoses of primary tumor-first extracranial metastasis and between diagnosis of extracranial metastases -brain metastasis

	Median (months)	Range
Primary diagnosis-extracranial met*	11.3	0-121.7
Primary diagnosis-BM	21.2	0-123.3
Extracranial metastasis-BM*	10.1	0-76.9

Primary tumors (renal cell carcinoma or malignant melanoma)
Met: Metastases; BM: Brain metastasis, *The data from 32 patients that developed extracranial metastases before BM

Table 3. The characteristics of brain metastasis of MM and RCC (n=40)

Characteristic	
Site of brain metastasis[a]	
Only cerebrum	29 (72.5%)
Only cerebellum	1 (2.5%)
Cerebrum and cerebellum	7 (17.5%)
Not recorded	3 (7.5%)
Number of brain metastasis[a]	
Single	20 (52.6%)
Multiple	18 (47.4%)
Not recorded	2 (5.0%)
Surgery[a]	
Gross total resection	5 (12.5%)
Partial resection	1 (2.5%)
Only biopsy	4 (10%)
No surgery	30 (75%)
RT[a]	
<prescribed RT dose	3 (7.5%)
20Gy	15 (37.5%)
30Gy	18 (45%)
45Gy	4 (10%)

CNS: Central nervous system, MM: Multiple myeloma, RCC: Renal cell carcinoma, RT: Radiotherapy
[a]Data are given as number (percentage)

Table 4. Survival data of the patients with MM and RCC related brain metastasis (n=38)

	Median (months)	Range (months)
Survival time after primary diagnosis (OS)	16.3	1.0-125.4
Survival after first extracranial metastasis	10.2	1.0-87.7
Survival after brain metastasis (B-OS)	6.8	1.0-22.3

B-OS: Brain overall survival, MM: Multiple myeloma, OS: Overall survival, RCC: Renal cell carcinoma

time from primary diagnosis to BM was not correlated with time from BM to death (brain overall survival, B-OS).

B-OS was not correlated with the completion of the prescribed RT dose in the study population. However, when the patients were grouped as older (aged >=65) vs younger (aged<65) patients, in the younger group, B-OS was significantly correlated (r=0,42, p=0,02) with failure in receiving the prescribed RT dose while in an older group, it was not.

Examining the potential prognostic factors associated with brain overall survival (B-OS)

We grouped the patients as those that had B-OS time equal to or longer vs shorter than the median B-OS (6.8 months). Consequently, we examined the association between B-OS and potential prognostic factors. The studied prognostic factors were as follows: age (p=0.31), sex (p=0.82), age group (>=65 years vs <65 years of age) (p=0.67), primary diagnosis (RCC vs MM) (p=0.29), presence of extracranial metastasis (p=0.91), number of BM (solitary vs multiple) (p=0.23), location of BM (cerebral vs cerebral+cerebellar) (p=0.76), presence of gross total resection (GTR) (p=0.82), a dose of RT (p=0.69), completion of prescribed RT (p=0.40), the field of RT (all over cranium vs all over cranium+additional RT over the specific BM location) (p=0.62); hence, neither was associated with B-OS. We examined the relationship between B-OS and potential prognostic factors with multivariate analyses as well. We studied different models by including different independent parameters. In *model 1*, we included age at BM, sex, completion of RT, and presence of brain surgery in *model 2*, we included age at BM, sex, completion of RT, and time between primary diagnosis and first extracranial metastasis, in *model 3* we included age, sex, primary diagnosis, number of BM, completion of prescribed RT and in *model 4*, we included age group, sex, primary diagnosis, number of BM, completion of prescribed RT. In none of the models, there was an association between the B-OS and the potential prognostic factors.

DISCUSSION

In this study, we have reported the experience of a single tertiary radiotherapy center on BM of two most common radioresistant tumors, MM and RCC collected over a period of 22 years. We considered a wide range of potential prognostic factors on survival including age, sex, older vs younger age group, primary diagnosis (MM vs RC), presence of extracranial metastasis, number of BM, location of BM, presence of gross total resection, a dose of RT, completion of prescribed RT, the field of RT and found that none of these parameters were independently associated with B-OS. Hence, our findings suggest that when a MM or RCC patient develops brain metastasis, survival is limited without any favorable prognostic factor belonging to the patient, the tumor, or the preference of the treatment. Another explanation may be that competing factors for mortality (other than the tumor itself) might have been effective in the death of older tumor patients, which is a frequent issue and practice in older patients (15, 16).

Ferrel et al. reported that a higher number of brain metastases (>5) and lower performance scores were statistically significant predictors of a lower B-OS prognosis (8). A correlation between B-OS and gross total resection (GTR) has been reported in some studies (17). In our series, we were not able to reach this correlation. Although the exact data about the performance status of the participants was not available in our study, an assumption of the study group demonstrating a poor performance status would not be wrong, since we have been applying a lower dose of radiation to the patients with poor performance. Our findings showed that half of them got a radiation dose of ≤30 Gy. Hence, a factor underlying the lack of such association might be the lower performance status of the patients in our study group. However, we cannot comment more on this point.

When we consider the overall characteristics of the patients, the median age at primary diagnosis was 56 which is compatible with the literature reporting median age of 55-66 years (12, 18, 19). In the study population, 78.4% had metastasis at the demographic and clinical characteristics of the BM patients from RCC and MM treated in our radiotherapy center over 22 years period and analyze the potential prognostic factors for survival. cerebrum, 2.7% at the cerebellum, and 17.5% at both the cerebrum and cerebellum pointing out a significant predilection of metastases at the cerebrum. This feature is also in line with the literature findings reporting a predominance of cerebral metastases in BM cases (5).

Stereotactic radiotherapy (SRT) has become a standard of care for patients with a limited number of brain metastases (18). However, during the study period, we lacked an SRT facility in our center. Hence we applied WBRT and consequently a total of 15 Gy boost irradiation to the solitary BM reaching a total dose of 45Gy. Also in our series, 47.4% of the patients had multiple metastases. For extensive BM, WBRT was the gold standard in line with our application of WBRT in the study patients (12).

The time between radioresistant cancer diagnosis and first extracranial metastasis was correlated with the time between diagnosis of extracranial metastasis and BM (p=0.021). The sooner an extracranial metastasis occurred, the sooner BM occurred after extracranial metastasis. This is somewhat an expected finding as it shows clinical aggressiveness and metastatic capacity of the primary tumor but we did not find any article researching this point. Our results suggest that if there is an extracranial metastasis, it is logical to screen for a BM with cranial magnetic resonance imaging.

This study has its limitations and strengths. First, this is a retrospective study suffering from the shortcomings of such studies. Confounding factors which have not potentially been considered might be related to the survival of the patients. Although SRT is used as a standard treatment in patients with limited metastases, SRT was not performed as an RT technique in our study. This is a single-center study; however, the center was a tertiary referral serving a population of about 1,600,000 people pointing out the quality of data derived from the present data. Our other strengths are we reported our data on BM of the two most common radioresistant tumors and considered several potential prognostic factors on survival over a considerably long period. Our patient number was somewhat limited to 38 and 40 patients, however, these are rare tumors, and it is difficult to have extensive related data. Similarly, a significant study included only 122 MM and RCC BM cases, which includes about three times the present patients but is still limited (8). Another such study included only 27 such patients which is lower than the number in this study (7). Overall, these reports suggest that meta-analyses type studies are needed on this issue.

In conclusion, our findings suggest that when a MM or RCC patient develops brain metastasis, survival is limited without any favorable prognostic factor belonging to the patient, the tumor, or the preference for the treatment. Due to limited data in the literature, meta-analysis-type studies are needed to make more comments on this subject.

Ethics Committee Approval: This study was approved by Karadeniz Technical University Faculty of Medicine Clinical Research Ethics Committee (Date: 05.02.2018, No: 24237859).

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retation- Z.B., S.Ö.; Drafting Manuscript- Z.B., Ö.A., M.K.; Critical Revision of Manuscript- V.A.Ç., E.Ç., S.Ö.; Final Approval and Accountability- Z.B., Ö.A., V.A.Ç., E.Ç., M.K., S.Ö.

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