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ORIGINAL PAPER

The clinical and pathological features of 133 colorectal cancer patients with brain metastasis: a multicenter retrospective analysis of the Gastrointestinal Tumors Working Committee of the Turkish Oncology Group (TOG)

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Abstract Brain metastasis in colorectal cancer is highly rare. In the present study, we aimed to determine the frequency of brain metastasis in colorectal cancer patients and to establish prognostic characteristics of colorectal cancer patients with brain metastasis. In this cross-sectional study, the medical files of colorectal cancer patients with brain metastases who were definitely diagnosed by histopathologically were retrospectively reviewed. Brain metastasis was detected in 2.7 % ($n = 133$) of 4,864 colorectal cancer patients. The majority of cases were male (53 %), older than 65 years (59 %), with rectum cancer (56 %), a poorly differentiated tumor (70 %); had adenocarcinoma histology (97 %), and metachronous metastasis (86 %); received chemotherapy at least once for metastatic disease before brain metastasis developed (72 %), had progression with lung metastasis before (51 %), and 26 % ($n = 31$) of patients with extracranial disease at time the diagnosis of brain metastasis had both lung and bone metastases. The

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mean follow-up duration was 51 months (range 5–92), and the mean survival was 25.8 months (95 % CI 20.4–29.3). Overall survival rates were 81 % in the first year, 42.3 % in the third year, and 15.7 % in the fifth year. In multiple variable analysis, the most important independent risk factor for overall survival was determined as the presence of lung metastasis (HR 1.43, 95 % CI 1.27–4.14; $P = 0.012$). Brain metastasis develops late in the period of colorectal cancer and prognosis in these patients is poor. However, early screening of brain metastases in patients with lung metastasis may improve survival outcomes with new treatment modalities.

Keywords Colorectal cancer · Brain metastasis · Prognosis

Introduction

Metastatic brain tumors constitute 20 to −40 % of all intracranial masses, and disease is progressed in 25 to −35 % of cancer patients by brain metastasis, resulting in poor prognosis. In previous studies, median survival rates in cancer patients who developed brain metastases were reported as 4.2 months [1–3].

The rate of brain metastasis in gastrointestinal system cancers is quite low when compared with other cancers such as lung (48–60 %), breast (12–15 %), testicle (10–15 %), and melanoma (6–10 %). In previous studies, it was reported that the brain metastasis rate in gastrointestinal system cancers was lower than 4 %. The rate is 0.5–4 % in patients with colorectal cancer [2, 4, 5]. However, current improvements in treatment modalities have caused elongated survival durations, which have increased the frequency of brain metastasis. Moreover, improvements in imaging techniques have also contributed to this outcome [2, 4–6].

Brain metastasis is encountered in the late period after diagnosis in gastrointestinal system cancers, and the median survival duration is 3.8 month after the development of brain metastasis. This duration of <7 months if worse than the prognosis of similar breast and lung cancer patients with brain metastasis [4, 7, 8].

Colorectal cancer is the most frequently encountered cancer all over the world. In 2013, it was reported that the expected number of cases was 73,680 in men and 69,140 in women, and it was the third most frequently encountered cancer in both sexes [9]. It most commonly metastasizes to the liver, lungs, and the peritoneal cavity, and 30–40 % of patients have had liver metastasis, which is the predominant cause of mortality at the time of diagnosis. However, pulmonary metastasis occurs in approximately 15–20 % of cases, and peritoneal metastasis is found in ≤10 % of cases at the time of diagnosis. In addition, the probability of peritoneal carcinomatosis is 20–50 % during the recurrence [3–6]. Mean survival is approximately 21–24 months in colorectal cancer at the metastatic stage. Brain metastasis is quite rare, and the overall survival duration is quite low in these patients [1, 3–6].

In recent years, there is an increase in the number of publications in which colorectal cancer patients with brain metastasis are analyzed. However, there is still no definite predictive factor for brain metastasis in patients with colorectal cancer. In the present study, we aimed to determine the frequency of brain metastasis in colorectal cancer patients and to describe the prognostic characteristics of colorectal cancer patients with brain metastasis.

Patients and methods

Patients

In the present cross-sectional study, a total of 4,864 patients with colorectal cancer, who were diagnosed definitively by

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histopathologically between 2001 and 2012 were retrospectively reviewed.

Brain metastasis was detected in 2.7 % ($n = 133$) of all patients and these cases were included in the study. Brain metastasis was confirmed in all patients using computed tomography or/and magnetic resonance imaging.

Definitions

Patients who developed brain metastasis at the time of or within 60 days after a primary colorectal tumor diagnosis were determined to be patients with synchronous metastasis. However, patients who developed brain metastasis more than 60 days after the primary tumor diagnosis were determined to be patients with metachronous metastasis.

The time interval from primary tumor diagnosis until brain metastasis was defined as the brain metastasis-free interval.

Variables

The date of diagnosis, age, gender, disease stage at time of diagnosis, primary tumor localization, treatments for primary tumor (surgery, neoadjuvant or adjuvant radio- or/and chemotherapy), carcinoembryonic antigen (CEA) level, cancer antigen (CA)-19.9 level, diagnosis time of brain metastasis, localization in the brain, number of metastatic lesions in the brain, localization of extracranial metastases (lung, bone, liver, peritoneum, or others) before or during the brain metastasis, chemotherapy regimens used for metastatic disease, treatment options for brain metastasis, and the KRAS state were all recorded.

Statistical analyses

The data are reported as the mean ± standard deviation or the median and interquartile range (25–75 %). The distribution of study variables was expressed with the Kolmogorov–Smirnov test. Descriptive statistics were performed using the two-tailed, independent Student's *t* test, the Mann–Whitney *U* test or the chi-square test; and correlation analyses were performed using the Fisher's test, and Spearman and Pearson tests. Prognostic values of variables were assessed with logistic regression analysis according to the forward model. Kaplan–Meier curves were drawn for survival analysis. The level of significance was set at $P < 0.05$. All statistical analyses were performed using the Statistical Program for Social Sciences version 15.0 for Windows.

Ethics

The protocol for this retrospective study was compatible with the local ethical guidelines and the Declaration of Helsinki. The study was approved by the academic and administrative committees in our centers.

Results

General findings

Brain metastasis was diagnosed in 2.7 % ($n = 133$) of 4,864 patients with colorectal cancer. The mean age of patients with brain metastasis was 58 ± 16 (range 41–89) years and the median age was 51 year. Of the patients, 53 % ($n = 70$) were males and 59 % ($n = 79$) were older than 65 years. The age difference between the male and female patients was insignificant ($P = 0.194$). The demographic characteristics of the patients are shown in Table 1.

The primary tumor and the course of disease

The majority of cases involved rectum cancer ($n = 74$, 56 %); were poorly differentiated tumor ($n = 93$, 84 %); had adenocarcinoma histology ($n = 128$, 96 %); included lymphovascular invasion ($n = 71$, 53 %); had TNM stage IV disease ($n = 68$, 51 %); were operable for primary tumors at the time of diagnosis ($n = 79$, 59 %); and had extracranial disease ($n = 118$, 89 %). Additionally, the majority of patients had no received adjuvant treatment (47 %); had received chemotherapy at least once for metastatic disease before brain metastasis developed ($n = 96$, 72 %); 89 % of patients had distant metastasis before brain metastasis development, and had lung metastasis (51 %) before brain metastasis diagnosis. Of these patients, 15 % ($n = 20$) were of KRAS wild type, but the KRAS state of all patients was unknown, so it was decided that there was not enough strength for correlation and survival statistical analyses. The cohort findings were divided according to the localization of the primary tumor (colon vs. rectum) and are presented in Table 2. In addition, the correlation analysis of the brain metastasis with the study variables is shown in Table 3.

Brain lesions

Brain metastases were most commonly found to be more than three in number ($n = 77$, 58 %), in a metachronous pattern ($n = 114$, 86 %) and were located in the supratentorial ($n = 84$, 61 %) and hemispheres bilaterally (62 %). The median time interval from diagnosis of the primary tumor until brain metastasis was calculated as 32 months (range 0–84). Synchronous brain metastasis was diagnosed in 14 % ($n = 19$) of patients and 32 % ($n = 6$) of patients with synchronous metastases had isolated brain metastasis; 11 (58 %) had single lesions in the brain, 12

Table 1 Characterizations at the diagnosis of all patients in study

Characteristics	*N*	%	*P**
Patients (*n*)	133	100	–
Age (years)			
≤ 65	54	41	0.041*
≥ 65	79	59	
Gender (*n*, %)			
Male	70	53	0.265
Female	63	47	
Anatomic location of primary tumor (*n*, %)			
Rectum	74	56	0.024*
Recto-sigmoid and sigmoid colon	23	17	
Transverse colon	12	9	
Ascending colon and cecum	24	18	
Surgery of primary tumor at time of the diagnosis (*n*, %)			
Operated	79	59	0.191
Not operated	54	41	
Tumor grade (*n*, %)			
Grade 2	21	16	0.011*
Grade 3	93	70	
Unknown	19	14	
Lymphovascular invasion (*n*, %)			
Absent	35	26	0.031*
Present	71	53	
Unknown	27	21	
Previously (neo)adjuvant setting at the time of diagnosis (*n*, %)			
Neoadjuvant chemotherapy	2	2	0.125
Neoadjuvant chemo-radiotherapy	8	6	
Adjuvant radiotherapy	19	14	
Adjuvant chemo-radiotherapy	4	3	
Adjuvant chemotherapy	37	28	
Untreated	63	47	
Previously treatment for metastatic setting (*n*, %)			
Untreated	37	28	0.034*
Present, 1st line treatment	52	39	
Present, 2nd line treatment	29	22	
Present, 3rd line treatment	15	11	
Initially Stage by TNM (*n*, %)			
IIA	3	2	0.017*
IIB	9	7	
IIIA	17	13	
IIIB	36	27	
IV	68**	51	
Time of brain metastasis (*n*, %)			
Synchronous	19	14	0.006*
Metachronous	114	86	
Number of the brain metastatic lesion (*n*, %)			
1	15	11	0.029*
2–3	41	31	
>3	77	58	
Location in brain (*n*, %)			
Supratentorial	84	61	0.019*
Subtentorial	49	39	
Extracranial disease (*n*, %)			
Absent	15	11	0.025**
Present	118	89	
Extracranial disease site at diagnosis of brain metastasis (*n*, %)			
Lung	19	16	0.032*
Liver	17	14	
Lung and bone	31	26	
Liver and peritoneum	14	12	
Lung and liver	18	15	
Extensive disease (lung, liver, peritoneum and other sites)	19	17	
Progression sites of extracranial disease before diagnosis of brain metastasis (*n*, %)			
Lung	68	51	0.018*
Liver	35	26	
Peritoneum	21	16	
Lymph node	9	7	
KRAS status			
Wild type	20	15	N/A***
Mutant type	37	28	
Unknown	76	57	

* A two-tailed *P* value of <0.05 was considered statistically significant

** Metastatic stage at time of diagnosis (not operated patients + patients with palliative surgical treatment)

*** It was decided that there was not enough strength for correlation and survival statistical analyses

(63 %) had cecum cancer, and 14 (74 %) were males. Of the patients with metachronous metastasis ($n = 114$), 84 (74 %) had lung metastasis before the brain metastasis; 71 (62 %) had more than three brain lesions, 64 (56 %) were males, and in 68 (60 %) patients the metastasis originated from the rectum.

In addition, the majority of patients with isolated brain metastasis ($n = 15$, 11 %) were younger than 65-year old ($n = 11$, 73 %), were males ($n = 12$, 80 %), and 40 % ($n = 6$) of them had synchronous tumors.

Treatment modalities for primary tumor

In our study, we determined that the majority of colorectal cancer patients with metachronous brain metastasis did not have operable primary tumors at the initial diagnosis (51 % had stage IV disease). In a similar analysis; 9 % of our patients with metachronous brain metastasis had stage II disease at the time of diagnosis of the primary tumor and 40 % of them had stage III at the time of initial diagnosis. No correlation was determined between the treatment

Table 2 Results of cohort divided according to the localization of the primary tumor (colon vs. rectum)

Characteristics	Colon cancer*	Rectal cancer	*P***
Patients (*n*)	59	74	0.034**
Age (years)			
≤65	23 (49)	31 (42)	0.248
≥65	36 (61)	43 (58)	
Gender (*n*, %)			
Male	29 (49)	41 (55)	0.197
Female	30 (51)	33 (45)	
Surgery of primary tumor at time of the diagnosis (*n*, %)			
Operated	34 (58)	45 (61)	0.119
Not operated	25 (42)	29 (39)	
Tumor grade (*n*, %)			
Grade 2	9 (15)	12 (16)	0.243
Grade 3	44 (75)	49 (66)	
Unknown	6 (10)	13 (18)	
Lymphovascular invasion (*n*, %)			
Absent	12 (20)	23 (31)	0.327
Present	36 (61)	35 (47)	
Unknown	11 (19)	16 (22)	
Previously (neo)adjuvant setting at the time of diagnosis (*n*, %)			
Neoadjuvant chemotherapy	0	2 (2)	0.118
Neoadjuvant chemo-radiotherapy	0	8 (11)	
Adjuvant radiotherapy	0	19 (26)	
Adjuvant chemo-radiotherapy	0	4 (5)	
Adjuvant chemotherapy	21 (36)	16 (22)	
Untreated	38 (64)	25 (34)	
Previously treatment for metastatic setting (*n*, %)			
Untreated	14 (24)	23 (31)	0.285
Present, 1st line treatment	28 (48)	24 (32)	
Present, 2nd line treatment	11 (18)	18 (24)	
Present, 3rd line treatment	6 (10)	9 (13)	
Initially Stage (*n*, %)			
IIA	1 (2)	2 (2)	0.234
IIB	4 (7)	5 (7)	
IIIA	9 (15)	8 (11)	
IIIB	14 (24)	22 (30)	
IV	31 (52)***	37 (50)***	
Time of brain metastasis (*n*, %)			
Synchronous	8 (14)	11 (15)	0.208
Metachronous	51 (86)	63 (85)	
Number of the brain metastatic lesion (*n*, %)			
1	4 (7)	11 (15)	0.297
2–3	19 (32)	22 (30)	
>3	36 (61)	41 (55)	
Location in brain (*n*, %)			
Supratentorial	38 (64)	46 (62)	0.217
Subtentorial	21 (36)	28 (38)	
Extracranial disease (*n*, %)			
Absent	7 (12)	8 (11)	0.267
Present	52 (88)	66 (89)	
Extracranial disease site at diagnosis of brain metastasis (*n*, %)			
Lung	7 (14)	12 (18)	0.127
Liver	9 (17)	8 (12)	
Lung and bone	11 (21)	20 (30)	
Liver and peritoneum	8 (15)	6 (9)	
Lung and liver	7 (14)	11 (17)	
Extensive disease (lung, liver, peritoneum and other sites)	10 (19)	9 (14)	
Progression sites of extracranial disease before diagnosis of brain metastasis (*n*, %)			
Lung	29 (49)	39 (53)	0.179
Liver	16 (27)	19 (26)	
Peritoneum	10 (16)	11 (15)	
Lymph node	4 (8)	5 (6)	
KRAS status			
Wild type	9 (15)	11 (15)	N/A****
Mutant type	13 (22)	24 (32)	
Unknown	37 (63)	39 (53)	

* Including rectosigmoid tumor

** A two-tailed *P* value of <0.05 was considered statistically significant

*** Metastatic stage at time of diagnosis (not operated patients + patients with palliative surgical treatment)

**** It was decided that there was not enough strength for correlation and survival statistical analyses

characteristics of primary tumors in 79 (59 %) of our patients who were diagnosed with non-metastatic primary tumors at baseline and the development of brain metastasis. The treatment characteristics of the primary tumors of our patients are shown in Table 1.

The serum CEA (normal range 0–6.5 ng/mL) and CA 19.9 (normal range 0–27 U/mL) values were high before the brain metastasis (58.8 ± 27.2 and 118 ± 51, respectively).

Treatment modalities for metastatic setting before brain metastasis diagnosis

During the primary tumor diagnosis, 28 % ($n = 37$) of patients with metastatic disease did not receive any treatments and were followed up with the best supportive care.

In the follow-up period, it was observed that progression with lung metastasis (68 %) was the most frequent outcome, followed by liver metastasis (26 %; Table 1). In

Table 3 Correlation analysis of the demographic, histopathological, and clinical characteristics of patients with brain metastasis of overall survival

Variables	*r*	*P**
Age (<65 vs. >65 years)	0.316	0.241
Gender (male vs. female)	0.247	0.211
Anatomic location of primary tumor (colon vs. rectum)	0.349	0.194
Surgery of primary tumor at time of the diagnosis (absence vs. presence)	0.408	0.041*
Tumor grade (2 vs. 3)	0.529	0.012*
Presence of lymphovascular invasion (absence vs. presence)	0.507	0.031*
Previously (neo)adjuvant setting at the time of diagnosis (absence vs. presence)	0.279	0.213
Previously treatment for metastatic setting (absence vs. presence)	0.645	0.009*
Initially stage (II and III vs. IV)	0.651	<0.001
Time of brain metastasis (synchronously vs. metachronously)	0.497	0.021*
Extracranial disease (absence vs. presence)	0.594	0.023*
Progression sites of extracranial disease before diagnosis of brain metastasis (lung and bone vs. other)	0.542	0.018*
Sites of extracranial disease before diagnosis of brain metastasis (lung vs. other)	0.619	0.006*

* A two-tailed *P* value of <0.05 was considered statistically significant

addition, the tumor most commonly metastasizes in the lungs and bones ($n = 31$, 26 %, $n = 0.032$) at time of the diagnosis of brain metastasis and other sites of extracranial disease as follows; the lungs ($n = 19$, 16 %), the liver ($n = 17$, 14 %), the lungs and the liver ($n = 18$, 15 %), and the liver and the peritoneum ($n = 14$, 12 %). However, 17 % ($n = 19$) of patients had extensive disease.

Among patients, who had extracranial metastasis before the development of brain metastasis or developed extracranial metastasis during follow-ups after adjuvant therapies, 39 % had at least first line chemotherapy; 22 % had second line chemotherapy, and 11 % had third line chemotherapy before the development of brain metastasis (Table 1). These results are similar with the findings of previous studies. It was also determined that a great portion of patients used oxaliplatin-containing regimens ($n = 65$, 68 %) before developing brain metastasis, but there was no difference between oxaliplatin- and irinotecan-containing ($n = 27$, 28) regimens, and also there was no prominent correlation between oxaliplatin-containing regimens and brain metastasis ($P = 0.204$). Before brain metastasis, 40 % ($n = 21$) of patients received bevacizumab in the first line; 8 % ($n = 4$) received cetuximab in the first line; 31 % ($n = 9$) received cetuximab in the second line; and 66 % ($n = 19$) received bevacizumab in the second line.

Treatment modalities for brain metastasis

All patients with brain metastasis received steroid treatment, and 74 % ($n = 98$) of patients received radiotherapy. Whole-brain radiotherapy (WBRT) with the mean of 30 Gy/10 fraction was performed in 89 % ($n = 87$) of patients, whereas stereotactic radiosurgery was performed in 11 % ($n = 11$) of patients. Curative resection was performed in 4 % ($n = 5$) of patients, who had no extracranial metastasis, and solitary and <3 metastatic lesions, and all of them had radiation therapy after the resection. Only steroids and best supportive care were performed in 26 % ($n = 35$) of patients. After brain metastasis, 8 % ($n = 11$) of 133 patients received chemotherapy, and all of them received irinotecan and cetuximab combination regimen.

Survival analysis

During the follow-up, 95 % of patients died. The mean duration of follow-up was 51 (range 5–92) months. Mean survival was 25.8 months (CI 20.4–29.3); the overall survival rate was 81 % in the first year, 42.3 % in the third year, and 15.7 % in the fifth year.

Median survival after the diagnosis of brain metastasis was 3.7 months (range 0–6). The results of the survival analyses performed according to the clinical and histological characteristics of patients are shown in Table 4.

Poor prognosis factors determined by univariate analysis are given in Table 5. The most significant independent risk factor for overall survival was defined as the absence of previous lung metastasis in the multivariable analysis (HR 1.43, 95 % CI 1.27–4.14, $P = 0.012$).

Discussion

In this multicenter retrospectively study and the first study on this topic in Turkey, we identified brain metastasis in 2.7 % of 4,864 colorectal cancer patients from 22 cancer centers and we compared the results with the literature. In the present study, we determined that metastasis from the colon to the brain did not cause significantly different results compared to metastasis from the rectum to the brain. In both conditions, the lung metastasis that developed before the brain metastasis was a poor prognostic factor for survival independently from other factors. Of the patients with extracranial disease at the time of brain metastasis, 26 % ($n = 31$) had both lung and bone metastases ($P = 0.032$).

Currently, the risk of brain metastasis is increased in colorectal cancer patients because of the elongated duration

Table 4 Overall survival of patients as study variables

Study variables	Overall survival; months (range)	Log rank	*P* value*
Tumor grade			
Grade 2	34.4 (24.6–42.7)	9.3	0.038*
Grade 3	31.3 (22.8–34.8)		
Presence of lymphovascular invasion			
Presence	31.7 (29.4–41.7)	0.34	0.345
Absence	34.4 (31.3–42.7)		
Previously treatment for metastatic setting			
Presence	34.2 (23.7–39.9)	9.7	0.045*
Absence	24.7 (21.3–32.4)		
Initially Stage			
II	31.4 (24.1–42.7)	4.7	0.041*
III	29.7 (21.7–38.4)		
IV	19.4 (11.9–24.7)		
Time of brain metastasis			
Synchronously	26.4 (20.0–32.9)	0.21	0.643
Metachronously	25.0 (21.5–28.4)		
Extracranial disease			
Presence	21.7 (18.7–33.1)	11.3	0.021*
Absence	26.5 (19.7–38.2)		
Sites of extracranial disease before diagnosis of brain metastasis			
lung + brain	24.4 (19.3–29.5)	14.66	0.012*
liver + brain	33.6 (25.3–41.9)		
Other sites + brain	25.3 (22.6–42.7)		
Localization of primary tumor			
Rectum	25.1 (21.1–29.1)	1.63	0.443
Colon	26.4 (19.6–33.2)		

* A two-tailed *P* value of <0.05 was considered statistically significant

Table 5 Univariate and multivariate analysis of the factors for poor survival in colorectal cancer patients with brain metastasis

	Hazard ratios (95 % CI)	*P* value
Univariate factors		
Surgery of primary tumor at time of the diagnosis (absence vs. presence)	1.44 (0.65–3.11)	0.214
Tumor grade (2 vs. 3)	1.59 (1.24–4.84)	0.031*
Presence of lymphovascular invasion (absence vs. presence)	2.11 (1.94–3.93)	0.024*
Previously treatment for metastatic setting (absence vs. presence)	1.74 (1.39–6.13)	0.021*
Initially stage (II and III vs. IV)	1.94 (1.78–3.46)	0.033*
Time of brain metastasis (synchronously vs. metachronously)	1.14 (1.27–4.13)	0.018*
Extracranial disease (absence vs. presence)	2.04 (1.34–4.37)	0.008*
Extracranial disease site (lung and bone vs. other)	2.18 (1.47–6.13)	0.011*
Sites of extracranial disease before diagnosis of BM (lung vs. other)	2.84 (1.96–4.81)	0.014*
Multivariate factors		
Sites of extracranial disease before diagnosis of BM (lung vs. other)	1.43 (1.27–4.14)	0.012*

CI Confidence intervals, *BM* brain metastasis

* A two-tailed *P* value of <0.05 was considered statistically significant

of survival. However, no predictive risk factors have been clearly defined. Additionally, a prospective trial has yet to be performed, which is necessary to defines predictive and prognostic factors in colorectal cancer for brain metastasis in the literature.

In previous studies, the performance state of solid tumors in brain metastasis, extracranial disease state, and age were reported as significant prognostic factors [10]. In later studies, results related to these factors were unclear and even contradictory in patients with colorectal cancer. Jung et al. [11] reported in their study in 2011 that chemotherapy administration before brain metastasis diagnosis was an independent risk factor for colorectal cancer patients with brain metastasis.

The median age of our colorectal cancer patients with brain metastasis was 58 years. The majority of our patients were males, but there was no difference between the ages of the males and females. In previous studies, the median age range was reported to be 55–68 years, but it was not significant as an independent prognostic risk factor [4–11]. Similarly, male predominance was reported in the previous studies, but no effect of this condition was shown on survival [6–10].

Studies that included colorectal cancer patients with brain metastasis found that patients had tumors predominantly in the left colon including the rectum, or the rectum, rectosigmoid, and sigmoid colon [12]. The primary tumor was reported to be originated from the rectum in 17 out of 29 patients in the study by Noura et al. [13]; in 48 % of patients in the study by Damien et al. [4]; in 85.5 % of 41 patients in the study by Magni et al. [6]; and in 17 out of 39 patients in the study by Mongan et al. [14]. However, the most common localization was reported to be colon ($n = 88$) in the study by Matsunaga et al. [15], which was performed on 152 colorectal cancer patients with brain metastasis, and operated on by gamma knife surgery. In the present study, we determined that the primary localization was the rectum in 56 % of colorectal cancer patients with brain metastasis. Moreover, we found that similar to previous studies, brain metastasis was more common in the left colon cancer cases including the rectum. It was frequently emphasized in previous publications that this might be related to the characteristics of rectal blood supply [13, 15].

We determined that colorectal cancer patients with brain metastasis were mainly operable (59 %) at the time of primary tumor diagnosis. In our analysis, at the time of primary tumor diagnosis 9 % of the patients had stage II disease; 40 % had stage III; and 51 % had stage IV diseases according to the TNM. Noura et al. [13] reported from their study including 29 patients who five had stage II; 12 had stage III; and 12 had stage IV diseases according to the TNM staging. In a previously study by Magni et al. [6], according to Duke's classification at the time of diagnosis, the ratios were reported as 19.5 % for stage II, 39 % for stage III, and 39 % for stage IV in a sample of 41-patients. In the analysis performed by Magni et al. [6], it was reported that Duke's stage II disease had a positive effect on overall survival in the univariate analysis, but no effect on overall survival in the multivariate analysis. We reached similar conclusions using TNM staging at our analysis and decided that TNM staging had no independent effect on overall survival in brain metastasis.

No correlation was observed between treatment characteristics and the development of brain metastasis for adjuvant and neoadjuvant settings for primary tumor therapy in 49 % ($n = 65$) patients with non-metastatic colorectal cancer (stages II and III) at the time of diagnosis. Magni et al. [6] reported that 91.7 % of 24 patients without metastasis received adjuvant chemotherapy, and 18 of them received an oxaliplatin-containing regimen. It was shown in the study of Magni et al. [6] that adjuvant chemotherapy had no significant effect on the survival durations related to brain metastasis.

However, the incidence of brain metastasis was determined to be higher in patients with stage IV disease at the time of primary tumor diagnosis [16]. In 89 % of patients, we determined that extracranial metastatic disease appeared before the development of brain metastasis. We determined that lung metastasis developed in 51 % of patients before the brain metastasis, which was consistent with the results of previous studies. There was a significant correlation found in previous studies between brain metastasis and extension of extracranial disease. However, Damien et al. [4] reported in their 48-disease series that 90 % of the extracranial disease was present at the time of brain metastasis diagnosis; 64 % had metastasized to the lungs, and 50 % to the liver. Similarly, Magni et al. [6] reported that 95 % of their 41 patients had extracranial disease, and the lungs were the metastatic site in 87.8 % of patients. Noura et al. [13] reported that 20 out of 29 of their patients had lung metastasis before the brain metastasis. However, Noura et al. [13] also reported that 11 out 29 patients had distant metastasis other than in the brain at the time of the primary tumor resection, and they listed places of synchronous metastasis including the liver ($n = 8$), lungs ($n = 5$), and peritoneum ($n = 1$).

In our study, the time interval between the primary colorectal tumor diagnosis and brain metastasis was 32 months (range 0–84). In previous studies, the time intervals were reported as a mean of 24 months by Damien et al. [4]; a median of 34 (range 0–116) months (95 % CI 27–45) by Magni et al. [6]; a mean of 38.4 (median = 38.4) months by Noura et al. [13]; and a median of 27 (range 0–180) months by Matsunaga et al. [15]. In contrast to all of these studies, the study by Jung et al. [11] included a similar number of patients compared to our study ($n = 126$), and they reported the time interval as nine (range 0–85) months.

In the present study, the metachronous type of brain metastasis was prominent, and it constituted 86 % of the cases. In previous studies, metachronous brain metastasis was reported as 77 % by Damien et al. [4]; 83 % by Magni et al. [6]; and 96 % by Noura et al. [13]. Jung et al. [11] determined brain metastasis at the initial presentation in 11 out of 126 of their patients.

In the present study, the majority of patients with isolated brain metastasis ($n = 15$, 11 %) were younger than 65 years old ($n = 11$, 73 %), were males ($n = 12$, 80 %), and 40 % ($n = 6$) of had synchronous tumors. The number of brain lesions was fewer than three in these patients, and they were frequently located in the cerebellum. In previous studies, the proportions of patients with isolated brain metastasis were reported to be 63 % by Damien et al. [4]; 53 % by Magni et al. [6]; and 31 % by Noura et al. [13]. Surgical resection and radiotherapy after surgical resection are the most commonly performed treatment modalities. Patients with >3 lesions were reported to have worse survival rates than the patients with 1–2 lesions [17, 18]. Auchter et al. [19] reported that <3 lesions and good performance status were ideal for SRS, and WBRT was preferred widely in patients with multiple brain metastasis. It was also reported that radiotherapy had a positive effect on survival after the surgical resection, but neither WBRT nor SRS had significant different effects on overall survival [6].

The prevalence of patients with multiple brain lesions was 89 % ($n = 118$) in the present study (31 and 58 % for 2–3 lesions and >3 lesions, respectively). There was no correlation between brain metastasis with multiple lesions and gender, the metastasis pattern, the stage at onset, and adjuvant treatments (Table 3). In previous studies, it was reported that WBRT had a significant effect on overall survival duration when compared to only steroids or the best supportive care in the treatment of patients with multiple metastasis [20]. While Noura et al. [13] reported that 20 out of 29 patients had multiple brain lesions; Mongan et al. [14] reported that 60 % of 39 patients had solitary lesions. These findings may be due to the retrospective design of the studies, which included select patient groups. As a matter of fact, when other studies are

considered, brain metastasis was generally caused in colorectal cancer cases with multiple lesions [6, 11, 21].

Significant elevations in CEA and CA 19.9 levels were determined before brain metastasis. During the follow-up after primary tumor resection, it was shown that CEA was the better predictor of liver and lung metastases [22–25]. Noura et al. [13] reported that CEA levels were related to brain metastasis in their study (20/29, 69 %). Additionally, when the cut-off value was accepted as 50 ng/ml, 1-year survival was reported as 0 % by >50 ng/ml, whereas the 1-year survival was reported as 38.9 % by <50 ng/ml ($P = 0.0205$).

As previously reported, brain metastatic lesions were most commonly located in the cerebrum [6, 11]. Although metastatic lesions were rarely located in the cerebellums of colorectal cancer patients, the majority of cerebellar lesions were solitary. In the present study, the most common localization of metastatic lesions was in the hemispheric cerebrum [6, 11]. In our study, no patient had brainstem localization, although other studies have reported the rare metastasis of this region [11].

In previous studies, the median survival duration was reported as 4–8 months after the brain metastasis. The durations were reported as a median of 4 months (range 1–13 months) by Damien et al. [4]; 5 months (95 % CI 3–12 months) by Magni et al. [6]; 5.4 months (95 % CI 3.9–6.9 months) by Jung et al. [11]; 7.4 months by Noura et al. [13]; and 8 months (95 % CI 4.2–11.8 months) by Jiang et al. [21]. In the present study, the median survival duration after brain metastasis was 3.7 months (range 0–6) with 51 months (range 5–92) of follow-up.

Some studies in the literature found that the administration of chemotherapy before the metastasis had favorable effects on survival, whereas treatments before brain metastasis did not show any significant effects. However, it could not be clearly shown which chemotherapeutic or targeted treatment-containing regimens had clear effects on survival. This may be due to the variety of regimens used in different sequences during chemotherapy, and also to the inadequate number of patients sampled. Moreover, the effects of chemotherapy administration have not been clearly defined among treatment modalities used after the brain metastasis. Our results indicated that 39 % of our patients received at least the first line of chemotherapy before the development of brain metastasis. However, the effects of chemotherapy given before the brain metastasis on survival could not be shown because of the heterogeneity of the treatment options, and the relatively low number of patients. Similarly, no significant difference was detected between a single use of oxaliplatin or irinotecan and combined uses with cetuximab or bevacizumab.

Factors affecting survival duration have been discussed with variable results in different studies. In those studies, brain metastasis, extracranial metastatic disease, bad performance status, the presence of extracranial metastatic disease before the brain metastasis, and the development of lung metastasis before the brain metastasis were reported to be poor prognostic factors. However, there is currently no consensus on a definite prognostic factor for brain metastasis in colorectal cancer patients. This may be due to the small samples size of the studies and the heterogeneity of the treatment modalities.

In conclusion, longer survival durations of colorectal cancer patients may lead to an increase in the number of patients with brain metastasis. Determining the predictive factors associated with brain metastasis and improving our understanding of the variable factors related to patient prognosis will affect treatment success. Therefore, while randomized, controlled, large sample size studies are being designed; retrospective studies, descriptive trials, and meta-analyses should also be included in the literature to define patient characteristics.

Conflict of interest We certify that all of our affiliations without financial involvement, within the past 5 years and foreseeable future and, any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, and royalties).

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