



The Clinical Outcomes of Brain Metastasis from Colorectal Cancer: A Single Center Retrospective Study

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Abstract

Background: Brain metastasis from Colorectal Cancer (CRC) is an uncommon and late event of disease course. The prognosis becomes poor once brain metastasis occurs. This study aimed to investigate the clinical characteristics and outcomes of patients with CRC diagnosed with brain metastasis.

Methods: This study retrospectively analyzed the clinical data of patients with brain metastasis from CRC at Kosin University of Gospel Hospital from January 2018 to December 2023.

Results: This study enrolled 27 patients. The median age of patients at the time of brain metastasis diagnosis was 63 years (range, 50-80), and 37.0 % of patients demonstrated the Eastern Cooperative Oncology Group (EGOG) Performance Status (PS) (0 or 1). All patients exhibited extra cranial metastasis, and the lung was the most prevalent metastatic site (92.6%). A total of 24 patients (88.9%) received local treatment for brain metastasis and subsequent chemotherapy was administered in 12 patients. The median survival after brain metastasis diagnosis was 3.8 months (95% Confidence Interval [CI]; 3.0-4.8), and that after initial CRC diagnosis was 53.3 months (95% CI; 39.0-67.6). The multivariate analysis of prognostic analysis revealed that ECOG PS, liver metastasis, and chemotherapy after brain metastasis diagnosis were associated with survival.

Conclusion: This study revealed that brain metastasis from CRC developed in the late stage of the disease, and the prognosis brain metastasis diagnosis was dismal.

Keywords: Brain metastasis; Intra cranial tumor; Colorectal cancer; Chemotherapy

Introduction

Colorectal Cancer (CRC) is the third most prevalent cancer and the second leading cause of cancer-related deaths globally [1]. Approximately 20% to 25% of all patients are initially diagnosed with metastatic disease, and 25% will develop metastases during the course of disease. The most commonly diagnosed metastatic sites of CRC are the liver, lung, and peritoneal cavity, whereas brain metastasis is relatively uncommon [2].

Brain metastasis is the most prevalent intracranial tumor in adults, and most cases originate from lung cancer, breast cancer, melanoma, and renal cell carcinoma [3]. Brain metastasis from CRC is uncommon, with an incidence of 0.3% to 3.2%, and develops in the late stage of the disease [2,4,5]. Patients with brain metastasis exhibit a poor prognosis with a median survival of 3-7 months, despite the advances in treatment of colorectal cancer [4,6-10].

Treatment for patients with brain metastasis from colorectal cancer has no consensus, and treatment of these patients follows the approaches of brain metastasis from other solid tumors. The mainstay of brain metastasis treatment is local treatment, including surgery, stereotactic radio surgery, and whole-brain radiation therapy to control intracranial lesions [11]. Recently, systemic treatment has improved systemic and intracranial disease control for certain cancers, including non-small cell lung cancer, breast cancer, melanoma, and renal cell carcinoma, and a multi-disciplinary approach, including local treatment and chemotherapy, is the best treatment option for brain metastasis [12,13]. However, data on multi-disciplinary treatment for brain metastasis from CRC are limited.

This study aimed to investigate the clinical characteristics and outcomes of patients with CRC who developed brain metastasis.

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Materials and Methods

Subjects

This study retrospectively analyzed the clinical data of patients with brain metastasis from CRC at Kosin University Gospel Hospital from January 2018 to December 2023.

Eligible subjects included patients diagnosed with CRC who had presented brain metastasis. Radiologic studies, such as computed tomography or magnetic resonance imaging, were conducted to confirm brain metastasis. Patients' clinical features, treatment information, and outcomes were retrospectively obtained from the medical records. The Institutional Review Board of the Kosin University of Gospel Hospital approved this study (KUGH 2024-08-031).

Statistical analysis

Overall survival was defined as the time from the date of confirming brain metastasis to the date of death. The Kaplan-Meier method was utilized to estimate survival, and differences between groups were analyzed with the log-rank test. Prognostic factors associated with survival were assessed using a Cox proportional hazard model. Statistical Package for the Social Sciences version SPSS 23.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis that were performed using, and p-values of <0.05 indicated statistical significance

Results and discussion

Patient's characteristics: A total of 27 patients with CRC were diagnosed with brain metastasis from January 2018 to December 2023 in Kosin University Gospel Hospital. Synchronous brain metastasis was diagnosed in six patients. Among the patients who developed synchronous brain metastasis, four had brain metastasis at the time of the initial CRC diagnosis, and 2 relapsed with metastatic disease, including brain metastasis, after surgical resection. Twenty-one patients had already had other extra cranial metastatic lesions when brain metastasis was presented. No patient had brain-only metastasis. Table 1 summarizes the patient characteristics. The median age of patients at the time of brain metastasis diagnosis was 63 years (range, 50-80), and 37.0 % of patients demonstrated a good the Eastern Cooperative Oncology Group (EGOG) Performances (PS) (0 or 1). Half of the patients (13 [48.1%]) had localized disease at the time of initial CRC diagnosis (\leq stage III), and the median time of initial diagnosis to metastatic disease of these 13 patients was 23.4 months (range; 3.0-86.1). Twenty-one patients (77.8%) had left-sided CRC, and the majority of the patients (25[92.6%]) had lung metastasis at the time of brain metastasis diagnosis.

Time interval to diagnosis of brain metastasis: The median time interval from initial CRC diagnosis to brain metastasis development was 42.6 months (95% Confidence Interval [CI]; 24.5-57.0), and the median time interval from metastatic disease diagnosis to brain metastasis was 30.2 months (95% CI; 18.5-45.6). Twenty-five patients had lung metastasis at the time of brain metastasis diagnosis, and the median time interval from lung metastasis to brain metastasis diagnosis was 24.3 months (95% CI; 7.0-34.9) (Table 2).

Treatment after diagnosis of brain metastasis: Table 3 presents treatment ment for brain metastasis. Three patients underwent surgical resection of brain lesions, and they received radiotherapy postoperatively. Twenty-one patients received radiotherapy without surgical resection. Eight patients received whole-brain radiotherapy.

Table 1: Patients characteristics at diagnosis of BM from CRC (n=27).

	Number of patients [n (%)]
Age, median (range) (years)	63 (50-80)
Gender	
Male	13 (48.1)
Female	14 (51.9)
ECOG PS	
0-1	10 (37.0)
≥ 2	17 (60.9)
Primary tumor location	
Left-sided	21 (77.8)
Right-sided	6 (22.2)
RAS mutation	
Yes	13 (48.1)
No	10 (37.0)
Unknown	4 (14.8)
Resection of primary tumor	
Yes	22 (81.5)
No	5 (18.5)
Stage at initial diagnosis	
\leq III	13 (48.1)
IV	14 (51.9)
Number of brain metastasis	
Single	17 (63.0)
Multiple	10 (37.0)
Synchronous brain metastasis	
Yes	6 (22.2)
No	21 (77.8)
Liver metastasis	
Yes	15 (55.6)
No	12 (44.4)
Lung metastasis	
Yes	25 (92.6)
No	2 (7.4)
Bone metastasis	
Yes	6 (22.2)
No	21 (77.8)

BM: Brain Metastasis; CRC: Colorectal Cancer; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status

Stereotactic radio surgery and partial brain radiotherapy were conducted in 3 and 13 patients, respectively. Subsequent chemotherapy was applied in 12 patients and 1 patient continued chemotherapy without regimen change after brain metastasis diagnosis.

Survival and prognostic factors: The median survival after initial CRC diagnosis of 27 patients with brain metastasis was 53.3 months (95% CI; 39.0-67.6), and the median survival after metastatic disease diagnosis was 46.9 months (95% CI; 29.0-64.8). The median survival after brain metastasis diagnosis was 3.8 months (95% CI; 3.0-4.8) (Figure 1). The 6-month and 12-month survival rates after brain metastasis diagnosis were 34.3% and 17.1%, respectively.

Table 2: Time interval to at BM diagnosis.

	Number of patients	Median time interval, month (95% CI)
Time to initial diagnosis of CRC to BM	27	42.6 (24.5-57.0)
Time to metastatic disease to BM diagnosis	27	30.2 (18.5-45.6)
Time to liver metastasis to BM diagnosis	15	24.1(1.0-49.2)
Time to lung metastasis to BM diagnosis	25	24.3 (7.0-34.9)
Time to bone metastasis to BM diagnosis	6	0.7 (0.7-10.4)

BM: Brain Metastasis; CRC: Colorectal Cancer; CI: Confidence Interval

Table 3: Treatment modalities of BM (n=27).

	Number of patients [n(%)]
Local therapy	24 (88.9)
Surgery alone	0
Surgery + radiotherapy	3 (11.1)
Radiotherapy alone	21 (77.8)
Chemotherapy	12 (44.4)
Local therapy + Chemotherapy	12 (44.4)
Best supportive care alone	3 (11.1)

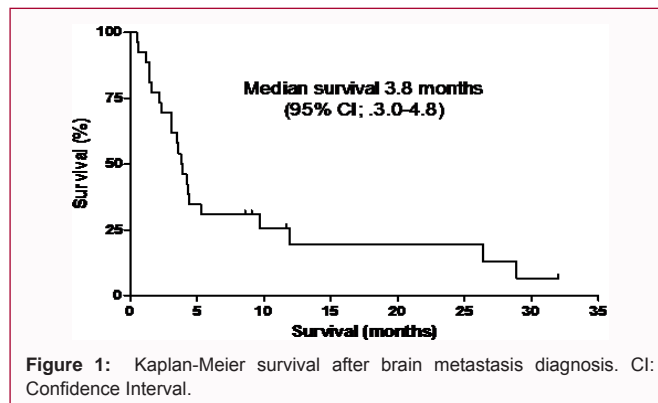
BM: Brain Metastasis

Table 4 shows the univariate and multivariate analysis of potential prognostic factors associated with survival in patients with brain metastasis from CRC. The univariate analysis revealed that good ECOG PS (0 or 1) at the time of brain metastasis, a prior history of primary tumor resection, no liver metastasis, and chemotherapy after brain metastasis diagnosis were associated with longer survival. In the multivariate analysis, ECOG PS, liver metastasis, and chemotherapy after brain metastasis exhibited statistical significance.

Discussion

Brain metastasis from CRC is an uncommon and late event of the entire course of disease [11]. In several previous retrospective studies about patients with brain metastasis from CRC, the time interval from initial CRC diagnosis to brain metastasis development has been reported to be 20 to 36 months [9,10,14,15]. The present study revealed that the median time interval from initial CRC diagnosis to brain metastasis development with 42.6 months seemed to be relatively longer. The time interval between primary tumor diagnosis and brain metastasis development was reported significantly longer in patients with CRC compared with non-gastrointestinal tumor (35.4 vs. 6-8 months) [11,16].

Longer survival is considered one of the risk factors for brain metastasis development in CRC [11]. Christensen et al. [17] reported that patients developing brain metastasis had a longer overall survival from metastatic disease diagnosis, compared with those without brain metastasis (median survival 32 vs. 28 months) [17]. Considering the median overall survival of metastatic colorectal cancer has steadily improved, recently reaching approximately 30 months, it is likely that the patients who developed brain metastasis had a prolonged disease course [18]. However, once brain metastasis occurred, the disease progressed rapidly. This study revealed that a relatively longer median survival after metastatic disease diagnosis with 46.9 months, but the median survival after brain metastasis development was only 3.8 months. The survival after brain metastasis diagnosis was consistent with results of other retrospective studies (3-7 months) [4,6-10].



Brain metastasis from CRC is predominately metachronous developed, and most patients have extra cranial metastasis at the time of brain metastasis diagnosis [19]. Several retrospective studies reported that approximately 80% of patients were diagnosed with metachronous brain metastasis and approximately 85% had extra cranial metastasis [4,7,8]. Consistent with these studies, this study demonstrated that brain metastasis was metachronous in 77.8% of patients, and all patients had extra cranial metastasis at time of brain metastasis diagnosis. The lung was the most prevalent among extra cranial metastatic sites. Lung metastasis is associated with an increased risk of brain metastasis. Sundermeyer, et al. revealed that patients with lung metastasis were more likely to have brain metastasis than those without lung metastasis (6.2% vs. 1.2%) [20]. A systemic review by Christensen, et al. indicated that approximately 70% of patients had lung metastases at brain metastasis diagnosis and approximately 40% had liver metastases [2]. It is well known that liver is the most common metastatic site in colorectal cancer. However, considering that lung metastasis is more frequent in patients with brain metastasis, lung and brain metastasis appeared to demonstrate an association. Riihimäki, et al. reported that lung metastasis occurred frequently together with nervous system metastasis in a population-based study to assess metastatic patterns in CRC [21].

Several retrospective studies have revealed prognostic factors of survival in patients with brain metastasis from CRC. PS, extra cranial metastasis, number of metastatic brain lesions, and treatment modality for brain metastasis were associated with survival in patients with brain metastasis from colorectal cancer in these studies [7-10,15,22]. The present study demonstrated that PS, liver metastasis, and chemotherapy after brain metastasis diagnosis were associated with survival in the multivariate prognostic analysis. The prognostic factors of survival of patients with brain metastasis from colorectal cancer have not been established, considering that most studies had retrospective design and small sample sizes.

PS was the most common prognostic factor in patients with brain metastasis from CRC among several variables [7-10,15,23]. Consistent with previous studies, patients with good PS (ECOG PS of 0 or 1) in this study had longer survival. Patients with good PS may be offered intensive therapy, including local treatment for intracranial lesions and systemic treatment for extra cranial lesions. Chemotherapy after brain metastasis diagnosis was an independent prognostic factor for survival in this study. Systemic chemotherapy might be beneficial to control extra cranial disease because most patients had extra cranial metastasis at the time of brain metastasis diagnosis. Gao, et al. reported that combination therapy with chemotherapy and local

Table 4: Prognostic factor analysis of OS in patients with BM from CRC.

Variable	Median OS (months)	Univariate	Multivariate	
		p value	HR (95% CI)	p value
Age (years) ^{a)}				
≤ 63	4.2	0.707		
> 63	3.4			
Gender				
Man	3.6	0.580		
Women	4.3			
ECOG PS ^{a)}				
0-1	11.9	0.003	3.362 (1.098–10.291)	0.034*
≥ 2	3.1			
Tumor location				
Left-sided	3.6	0.159		
Right-sided	11.3			
RAS mutation				
No	5.6	0.559		
Yes	3.1			
Unknown	3.8			
Resection of primary tumor				
Yes	4.2	0.010	1.424 (0.357–5.671)	0.616
No	1.6			
Initial CRC stage				
≤ III	4.2	0.298		
IV	3.5			
Number of brain metastasis				
Single	4.2	0.076		
Multiple	2.2			
Synchronous brain metastasis				
Yes	4.3	0.089		
No	3.8			
Liver metastasis ^{a)}				
Yes	3.4	0.018	5.166 (1.600–16.679)	0.006*
No	5.3			
Local therapy after BM diagnosis				
Yes	3.8	0.141		
No	1.6			
Chemotherapy after BM diagnosis				
Yes	5.7	0.029	5.102 (1.423–18.290)	0.012*
No	3.1			
Treatment of BM				
Local therapy+CTX	5.6	0.071		
Local therapy only	3.1			
No treatment	1.6			

OS, overall survival; BM, brain metastasis; CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

* $p < 0.05$

treatment improved survival in patients with brain metastasis from CRC, similar to this study [23].

Patients with certain cancer types at high risk of brain metastasis, such as lung cancer and melanoma, routinely undergo brain imaging studies [13]. However, brain imaging studies to screen brain metastasis are not recommended in CRC [24]. The diagnosis may be delayed because patients with CRC are tested when they have symptoms suggesting brain metastasis. A screening strategy is required in patients at a risk of developing brain metastasis, knowing that early brain metastasis diagnosis provides aggressive treatment options, and this improves survival outcomes [25].

Conclusion

Brain metastasis from CRC was developed in the late stage of the disease course. The median time interval from the initial CRC diagnosis to brain metastasis development appeared to be relatively longer, but survival after brain metastasis diagnosis was poor. All patients had extra cranial metastasis upon brain metastasis diagnosis,

and lung metastasis was most prevalent. ECOG PS, liver metastasis, and chemotherapy after brain metastasis diagnosis were independent prognostic factors associated with survival.

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