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CLINICAL STUDY – PATIENT STUDY

Characteristics and prognosis of patients with colorectal cancer-associated brain metastases in the era of modern systemic chemotherapy

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Abstract Brain metastases (BM) occur in approximately 20–40% of cancer patients. The present study investigated the clinical outcomes of patients with BM from colorectal cancer (CRC) to assess the benefit of systemic chemotherapy (CT) administered after surgical or radiotherapeutic control of BM and to identify independent prognostic factors associated with survival after BM. Between August 2001 and July 2009, 118 patients with symptomatic BM from CRC received either cranial irradiation or craniotomy at two large cancer centers in South Korea. Retrospective review and statistical analysis of clinical characteristics and outcomes were performed for all patients. Median time from diagnosis of metastatic CRC to detection of BM was 12.2 months (range 0–76.2 months). Thirteen patients (11%) exhibited brain involvement at initial presentation. Median survival after BM development was 4.1 months [95% confidence interval (CI) 3.3–4.9 months]. Forty-six patients (40%) had been treated previously with the chemotherapeutic agents fluoropyrimidine, oxaliplatin, and irinotecan. Patients who received CT after BM exhibited significantly improved survival compared with those who did not (12.4 versus 3.1 months, respectively; $P < 0.001$). Multivariate analysis revealed that CT intervention after presentation with BM was significantly associated with survival after BM, and the adjusted hazard ratio was 0.30 (95% CI 0.17–0.51, $P < 0.001$). Although BM is a late-stage phenomenon in CRC, approximately two-thirds of patients were still unexposed to irinotecan or oxaliplatin at the development of BM in our study. Thus, additional chemotherapeutic intervention after BM associated with CRC may be beneficial for selected patients.

Keywords Colorectal cancer · Brain metastasis · Chemotherapy · Prognostic factor · Survival

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Introduction

Brain metastases (BM) occur in approximately 20–40% of cancer patients [1–3]. Currently, the frequency of BM is increasing, probably due to longer survival resulting from earlier detection and more aggressive treatment of the primary tumor. Common primary tumors that frequently metastasize to the brain include lung and breast cancers [4, 5], and development of BM in these cancers occurs

earlier than in other cancers. In contrast, BM resulting from colorectal cancer (CRC) are uncommon (1–9%) [4–6], tend to be a late-stage phenomenon, and are an important cause of morbidity and mortality.

In the modern era, new systemic chemotherapeutics, including biologic agents for treatment of advanced CRC, have extended median survival times in CRC by almost 2 years. Additionally, a subset of CRCs presenting with isolated liver and/or lung metastases are potentially curable with surgery. In light of the many recent encouraging outcomes for multidisciplinary approach-based treatments for metastatic CRC (mCRC) that combine chemotherapy with preceding or subsequent surgery [7, 8], liver and lung metastases no longer represent incurable targets. As a result of prolonged survival times for patients with metastatic disease, incidence of BM can be expected to increase. Furthermore, management of BM has improved considerably over time, due to treatments including corticosteroids, radiotherapy, radiosurgery (RS), surgery, and chemotherapy [9]. Corticosteroids and whole-brain radiotherapy (WBRT) have been used for palliation of symptoms in the past, but in recent years, more advanced treatments have been developed, including stereotactic radiosurgery (SRS) for locoregional control of target lesions. Additionally, adjuvant WBRT or chemotherapy, administered after surgery or RS, is commonly used in practice for local and systemic control. Recently reported data suggest that chemotherapy can increase survival among patients treated with cranial irradiation for BM associated with non-small cell lung carcinoma [10] and breast cancer [11], dependent upon specific prognostic indicators and the biologic subtype of the cancer.

Few data are available regarding the optimal strategy for management of BM associated with CRC, and the lack of an adequate number of randomized trials has made assessment of definitive outcomes of chemotherapy difficult. For many years, the efficacy of chemotherapy for control of BM has been thought to be limited due to the presence of anatomic barriers such as the blood–brain and blood–tumor barriers, although the primary therapeutic approach for disseminated systemic disease is still chemotherapy. However, several new drugs, including oxaliplatin, irinotecan, bevacizumab, cetuximab, and panitumumab, have recently been identified as having great potential for treatment of mCRCs. Therefore, we hypothesized that local control combined with subsequent systemic chemotherapy can improve survival in comparison with local control alone for mCRC. In the present study, we evaluated the clinical outcomes of patients with BM from CRC to assess the benefit of systemic chemotherapy administered after surgical or radiotherapeutic control of the BM and to identify independent prognostic factors associated with survival after BM.

Patients and methods

Study population

From August 2001 to July 2009, 118 patients with symptomatic BM resulting from CRC received conventional cranial irradiation, radiosurgery or surgery at either the National Cancer Center (63 patients) or Asan Medical Center (55 patients) in Korea. A retrospective analysis was conducted using the patients' medical records. CRC was confirmed histologically in all patients. Brain metastasis was diagnosed by contrast-enhanced computed tomography scans or magnetic resonance imaging (MRI) with or without pathologic confirmation. Patients who received only dexamethasone and supportive care for symptomatic BM were excluded from the present study. We obtained an institutional review board (IRB) waiver (IRB protocol number NCCNCS-10-366, AMCNCS-2010-0511) from the IRB chairperson to conduct the present study.

Treatment

All patients with symptomatic BM were treated with dexamethasone intravenously and at least one of the following treatments: WBRT, three-dimensional conformal radiotherapy (3DCRT), fractionated stereotactic radiotherapy (FSRT), radiosurgery [stereotactic radiosurgery (SRS), including gamma-knife surgery (GKS)], and surgical resection (metastasectomy). Treatment decisions were made jointly by a colorectal multidisciplinary team. Surgical resection was considered for patients with a single brain metastasis in an accessible location, particularly in cases in which the size of the metastasis was large, the mass effect was significant, and/or obstructive hydrocephalus was present. SRS was considered for patients with metastases with maximum diameter <3–3.5 cm or for patients with comorbidities that precluded surgical intervention. SRS was delivered through a single high dose of radiation using a 6-MV photon beam coupled to a micromultileaf collimator (3 mm width; National Cancer Center) or multiple cobalt sources (GKS; Asan Medical Center) through a stereotactic device (median dose 19 Gy). WBRT was performed using a dose of 30 Gy in ten fractions. Chemotherapy administered either before or after development of BM was evaluated.

Statistical analysis

Overall survival (OS) was measured from diagnosis of BM to death or to last follow-up date and was estimated using the Kaplan–Meier method and compared by log-rank analysis. *P*-values <0.05 were considered to be statistically significant. Univariate and multivariate Cox regression

analyses were performed to identify independent prognostic factors that influenced OS after diagnosis of BM.

Results

Patient characteristics

A total of 118 patients who received surgery or whole/local radiation for treatment of symptomatic BM resulting from CRC were included in the present study. Baseline characteristics of the patients are summarized in Table 1. Of the total 118 patients, 57 had synchronous metastasis, of whom 3 had brain and extracranial metastases simultaneously at diagnosis of mCRC. Sixty-one patients had metachronous metastasis. In 6 of these 61 patients, only brain metastasis was observed as a metastatic lesion. Frequent extracranial metastatic sites prior to development of the BM included lung (75%), liver (45%), and bone (36%). With regard to treatment, 86 patients (73%) were treated with either WBRT or local radiation (3DCRT, FSRT), while 32 patients (27%) received radiosurgery (SRS, GKS) or surgical resection with or without cranial irradiation. A total of 46 patients (39%) had previously been treated with fluoropyrimidine, oxaliplatin, and irinotecan, while 71 patients (60%) had not been exposed to oxaliplatin or irinotecan. The chemotherapeutic history for one patient was unknown. A total of 34 patients (29%) received systemic chemotherapy after cranial irradiation or surgery for BM. Supplementary Table 1 summarizes the details of the 34 patients who received chemotherapy after local control of BM. Of the 34 patients, 3 patients received the chemotherapy in an adjuvant manner. However, 31 patients received chemotherapy after local control of BM because BM was found when the patient already had controlled or uncontrolled extracranial metastases.

Analysis of survival and prognostic factors

Median OS after diagnosis of BM was 4.1 months [95% confidence interval (CI) 3.3–4.9 months], and the estimated 1-year survival rate was 19.1% (Fig. 1). Results from univariate analyses of the predictive factors for survival after diagnosis of BM are shown in Table 2. No significant differences in survival were observed for the following variables: age, sex, primary tumor site (colon or rectum), location, or size of BM. Significant differences in median OS were observed for several variables, including Eastern Cooperative Oncology Group performance status (ECOG PS) score, recursive partitioning analysis (RPA; Fig. 2a), initial disease status, histologic grade, number of

Table 1 Characteristics of 118 patients with brain metastases from colorectal cancer

Characteristic	No. of patients	%
Age at initial diagnosis, years		
Median (range)	54 (19–77)	
Sex		
Male	63	53
Female	55	47
Primary site		
Ascending colon	19	16
Transverse colon	6	5
Descending colon	5	4
Sigmoid colon	17	14
Rectum	72	61
Histologic grade		
Favorable (W/D, M/D)	89	75
Unfavorable (P/D, mucinous, SRCC)	15	13
Unknown differentiation	14	12
Systemic chemotherapy before BM		
No	21	18
Fluoropyrimidine only	20	17
Fluoropyrimidine + oxaliplatin	13	11
Fluoropyrimidine + irinotecan	17	15
Fluoropyrimidine + oxaliplatin + irinotecan	46	39
Missing	1	0
Age at BM, years		
Median (range)	58 (23–81)	
<65 years	78	66
≥65 years	40	34
ECOG PS at BM		
ECOG 0–1	55	47
ECOG 2–4	61	53
Missing	2	0
Metastatic status		
Metachronous	61	52
Synchronous	57	48
Location of BM		
Supratentorial	55	48
Infratentorial	23	20
Both	36	32
Missing	4	0
Size of BM, maximal diameter, cm		
Median (range)	2.8 (0.7–8)	
≤3 cm	51	54
>3 cm	44	46
Missing	23	0
No. of BM		
1	58	50
2–3	31	26
>3	28	24
Missing	1	0

Table 1 continued

Characteristic	No. of patients	%
Extracranial metastatic site		
Lung	89	75
Liver	53	45
Intraabdominal LN	42	36
Intrathoracic/neck LN	31	26
Bone	43	36
Peritoneum	21	18
Sum of extracranial metastatic sites		
≤2	60	51
>2	58	49
RTOG RPA prognostic class		
Class I	6	5
Class II	58	50
Class III	52	45
Missing	2	0
Local control modality of BM		
WBRT only	74	63
Local RT (3DCRT, FSRT)	12	10
Radiosurgery (SRS, GKS)	8	7
Surgical resection ± RT	24	20
Systemic chemotherapy after control of BM		
No	84	71
Yes	34	29
Interval between diagnosis of mCRC and BM		
Median (range), months	12.2 (0–76.2)	
<1 year	58	49
≥1 year	60	51

BM brain metastases, *W/D* well differentiated, *M/D* moderately differentiated, *P/D* poorly differentiated, *SRCC* signet ring cell carcinoma, *ECOG PS* Eastern Cooperative Oncology Group performance status, *RTOG RPA* Radiation Therapy Oncology Group recursive partitioning analysis, *WBRT* whole-brain radiotherapy, *3DCRT* three-dimensional conformal radiotherapy, *FSRT* fractionated stereotactic radiotherapy, *RS* radiosurgery, *SRS* stereotactic radiosurgery, *GKS* gamma-knife surgery, *mCRC* metastatic colorectal cancer

BM, sum of extracranial metastatic sites, number of drugs used prior to BM, modality of local control for BM (Fig. 2b), and treatment with systemic chemotherapy after local control for BM. Based on univariate analysis, when seven significant variables (initial disease status, RPA class, number of chemotherapeutics before brain metastasis, systemic chemotherapy after local control for BM, histologic grade, number of BM, and sum of extracranial metastatic sites; Table 3) for survival after diagnosis of BM were included in the multivariate Cox regression model, initial disease status, RPA classification, number of chemotherapeutic drugs administered prior to BM, and use of systemic chemotherapy after BM were independent factors for survival after diagnosis of BM.

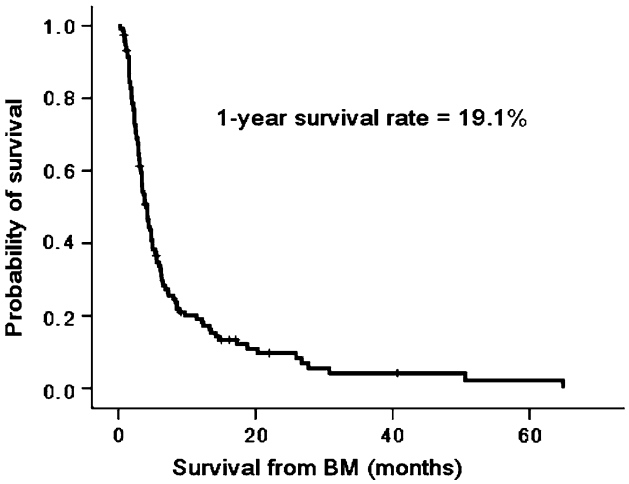

Fig. 1 Kaplan–Meier survival curves for 118 patients with brain metastases (BM) derived from colorectal cancer

Impact of chemotherapy on survival after brain metastases

Systemic chemotherapy after local control of BM was an independent prognostic factor for survival after BM [hazard ratio (HR) 0.30; 95% CI 0.17–0.53; $P < 0.001$; Table 3 and Fig. 3a]. As shown in Table 4, the proportions of patients per treatment group who received chemotherapy were as follows: WBRT (9/70, 13%), local RT (6/10, 60%), radiosurgery (5/8, 63%), and surgery (7/19, 37%). In patients who died due to progression of BM among the patients who received WBRT treatment, the survival rate was low regardless of whether chemotherapy was or was not administered (1.9 versus 2.3 months, $P = 0.155$), whereas in the patients who died due to extracranial metastases, administration of chemotherapy tended to increase the survival rate (4.2 versus 3.2, $P = 0.053$). Although among the patients who underwent surgery, the group that received chemotherapy showed a high survival rate regardless of cause of death, the low number of patients who received chemotherapy limited the interpretation of the results. In addition, it was difficult to analyze the effects of administration of chemotherapy according to local control of BM after local RT and radiosurgery. When patients were grouped based on ECOG PS score, median survival time with and without administration of systemic chemotherapy for the ECOG PS 0–1 subgroup was 14.6 and 3.5 months, respectively ($P < 0.001$). In the ECOG PS 2–4 subgroup, median survival time with and without systemic chemotherapy was 4.8 and 2.9 months, respectively ($P = 0.126$; Fig. 3b). When patients were grouped based on the number of systemic chemotherapy drugs administered prior to BM, in the subgroup that received 0–2 drugs, median survival time with and without systemic chemotherapy was 13.5 and 3.7 months, respectively

Table 2 Univariate predictors of survival after diagnosis of brain metastases

Variable	No. of patients	Median OS (months)	95% CI	*P*-value
Age				
<65 years	78	4.6	3.8–5.4	0.051
≥65 years	40	2.8	2.2–3.4	
ECOG PS				
0–1	55	6.3	3.9–8.7	**<0.001**
2–4	61	3.0	2.4–3.6	
Missing	2			
RTOG RPA prognostic class				
Class I	6	30.8	24.1–37.5	**<0.001**
Class II	58	5.4	3.78–7.0	
Class III	52	2.9	2.1–3.7	
Missing	2			
Histologic grade				
Favorable (W/D, M/D)	89	4.3	3.4–5.4	**0.027**
Unfavorable (P/D, mucinous, SRCC)	15	2.8	2.2–3.4	
Unknown differentiation	14	3.5	0.0–8.6	
Metastatic status				
Metachronous	61	4.6	3.3–5.9	**0.021**
Synchronous	57	3.4	2.5–4.3	
No. of BM				
1	58	4.6	3.9–5.3	**0.031**
2–3	31	4.2	2.5–5.9	
>3	28	2.9	2.2–3.6	
Missing	1			
Extracranial metastatic site				
Lung				
No	29	5.4	2.9–9.7	**0.030**
Yes	89	3.8	3.1–4.6	
Liver				
No	65	5.6	4.2–6.5	**<0.001**
Yes	53	2.8	2.0–3.7	
Bone				
No	75	3.5	2.8–4.8	0.715
Yes	43	4.4	3.4–5.6	
Sum of extracranial metastatic sites				
≤2	60	4.9	3.5–6.3	**0.033**
>2	58	3.1	2.0–4.2	
Systemic chemotherapy before BM				
≤2 drugs	72	5.6	4.2–7.1	**<0.001**
≥3 drugs	46	3.0	2.0–4.1	
Missing	1			
Local control modality for BM				
WBRT only	74	3.0	2.5–3.5	**0.002**
Local RT (3DCRT, FSRT)	12	4.9	3.7–6.1	
RS (SRS, GKS)	8	6.1	0.0–15.1	
Surgical resection ± RT	24	7.2	2.0–12.4	
Systemic chemotherapy after control of BM				
No	84	3.1	2.7–3.5	**<0.001**
Yes	34	12.4	9.7–15.1	
Interval between diagnosis of mCRC and BM				
<1 years	58	4.2	2.4–6.0	0.493
≥1 years	60	3.7	2.8–4.6	

BM brain metastases, *ECOG PS* Eastern Cooperative Oncology Group performance status, *W/D* well differentiated, *M/D* moderately differentiated, *P/D* poorly differentiated, *SRCC* signet ring cell carcinoma, *RTOG* RPA Radiation Therapy Oncology Group recursive partitioning analysis, *WBRT* whole-brain radiotherapy, *3DCRT* three-dimensional conformal radiotherapy, *FSRT* fractionated stereotactic radiotherapy, *RS* radiosurgery, *SRS* stereotactic radiosurgery, *GKS* gamma-knife surgery, *mCRC* metastatic colorectal cancer

($P < 0.001$). However, in the subgroup that received ≥3 drugs, median survival time with and without systemic chemotherapy was 4.8 and 2.9 months, respectively ($P = 0.044$; Fig. 3c). Table 5 summarizes the median survival of patients with BM from CRC in each subgroup. In analysis stratified by ECOG PS score and the number of chemotherapy drugs administered prior to development of BM, a longer median survival after BM that was dependent on administration of chemotherapy after brain metastasis was significantly associated with good PS (ECOG PS 0–1) and administration of few (≤2) chemotherapy drugs before BM ($P = 0.003$).

Discussion

BM from CRC are uncommon (1–9%) [4–6] and are often a late-stage phenomenon. However, incidence of BM is increasing due to earlier detection of subclinical disease and prolonged survival of patients with metastatic disease because of better systemic disease control. The occurrence of BM affects patient quality of life and leads to poorer prognosis. In the present study, we assessed the clinical features of 118 patients with symptomatic BM associated with CRC and identified prognostic factors for survival after diagnosis of BM by retrospective analysis of data from these patients.

It was previously shown that lung metastases commonly occur before development of BM from CRC [12–15]. In the present study, we found that the lungs (75%), liver (45%), bones (36%), and lymph nodes [intraabdominal (36%) and intrathoracic (26%)] were common extracranial

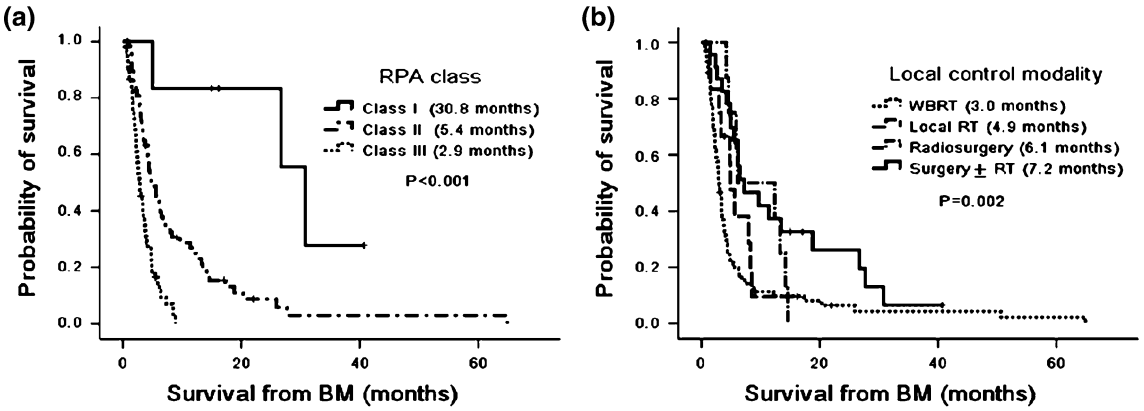

Fig. 2 Kaplan–Meier curves for survival after diagnosis of brain metastases (BM) stratified according to **a** recursive partitioning analysis (RPA) class and **b** local control modality for BM

Table 3 Multivariate predictors of survival after diagnosis of brain metastases

Variable	Hazard ratio	95% CI	*P*-value
Initial disease status (metastatic)	1.86	1.18–2.92	**0.007**
RPA class III	2.64	1.56–4.47	**<0.001**
No. of chemotherapeutics before BM (≥3 drugs)	2.38	1.46–3.89	**0.001**
Systemic chemotherapy after local control for BM	0.30	0.17–0.53	**<0.001**
Histologic grade (unfavorable)	0.85	0.71–1.02	0.075
No. of BM (>3)	1.04	0.52–2.09	0.918
Sum of extracranial metastatic sites (>2)	1.45	0.92–2.30	0.113

BM brain metastases, *CI* confidence interval, *RPA* recursive partitioning analysis

metastatic sites, consistent with previous reports, indicating that lung metastases commonly precede cranial metastases [16]. The location of the primary tumor was the distal colon in 89 cases (75%), sigmoid colon in 17 cases, and rectum in 72 cases, indicating that primary tumors in the distal colon are more frequently associated with BM [12, 16].

Brain metastasis occurs in approximately 25% of all cancer patients, and the median survival rate has been reported to be 4–6 months, although many studies have been conducted to improve the treatment outcome [17]. In clinical practice, it is not easy to decide whether to perform chemotherapy for patients with a relatively short life expectancy, and to judge which patients can obtain benefits from chemotherapy treatment. The lack of prospective randomized trials has made it difficult to make definitive conclusions about the role of chemotherapy after BM. However, BM from several cancers, including lung cancer, breast cancer, germ cell tumors, and choriocarcinoma, have been reported where chemotherapy has survival benefit [9]. However, the direct effect of chemotherapy for BM is limited.

It was recently suggested that systemic control after BM could be beneficial for selected patients with breast or lung cancer [10, 18] because not only complications of BM but also systemic disease progression affected survival or the quality of life of patients whose BM had been treated with local modalities. In the present study, 34 patients (29%) were treated with systemic chemotherapy after local control of BM. Their median survival was as long as 12.4 months, while the median survival of all 118 patients was 4.1 months (95% CI 3.3–4.9 months). The prominent better survival outcome of the chemotherapy-treated patients could be attributed to the selection of medically fit patients for chemotherapy; this possible selection bias is a weakness of the present retrospective study. However, even among those patients exhibiting good PS (ECOG PS 0–1), the survival difference between chemotherapy-treated and untreated patients was significant (14.6 versus 3.5 months; $P < 0.001$). Conversely, in the poor PS subgroup (ECOG PS 2–4), no significant difference in median survival dependent on systemic chemotherapy after BM was demonstrated (4.8 versus 2.9 months; $P = 0.126$), indicating that the clinical benefit of systemic chemotherapy after BM could be limited in those with good PS. Another significant finding of the present study is that only 39% of patients with BM from CRC were heavily treated with oxaliplatin, irinotecan, and fluoropyrimidine. Although BM are a late-stage phenomenon in CRC, the actual proportion of chemorefractory patients was less than half of the patients with

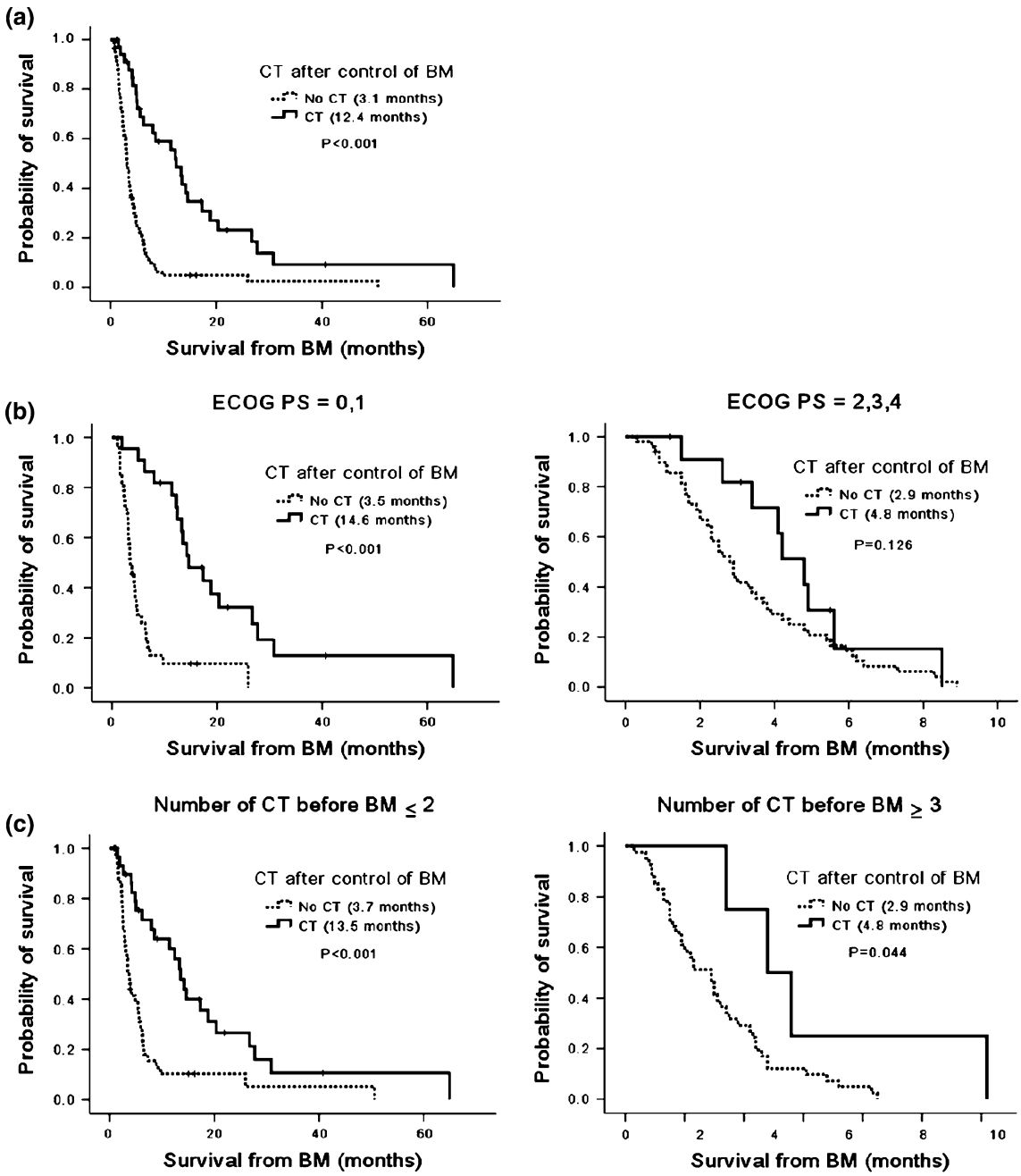

Fig. 3 Kaplan–Meier curves for survival after diagnosis of brain metastases (BM) stratified according to administration of systemic chemotherapy (CT) after presentation with BM for: **a** all patients, **b** Eastern Cooperative Oncology Group performance status (ECOG PS) subgroups 0–1 and 2–4, and **c** patients treated with 0–2 and ≥3 drugs prior to BM

BM. In addition, regardless of whether cause of death was progression of brain or extracranial metastases, survival time after BM in the group that received chemotherapy after BM was significantly extended (Supplementary Table 2). This implies that further palliative chemotherapy could be considered for those patients who maintain good PS after local control for BM.

In the present study, Cox multivariate regression analysis revealed that independent prognostic factors for survival after BM from CRC included initial disease status, RPA class, number of chemotherapy drugs administered prior to BM, and systemic chemotherapy after BM (Table 3). Interestingly, those patients with an initial diagnosis of mCRC exhibited poor survival after BM, implying that a higher metastatic potential in synchronous disease affects the control of BM. RPA class is considered to be a useful approach for determining the prognostic classification of patients with BM [17]. Median survival after diagnosis of BM for RPA classes I, II,

Table 4 Survival after diagnosis of brain metastasis, dependent on administration of chemotherapy according to cause of death

Local control modality of BM	Cause of death	CT after control of BM	No. of patients (107)	Median survival (95% CI)	*P*-value
WBRT	Brain	No	20	2.3 (1.4–3.2)	0.155
		Yes	2	1.9 (NA)	
	Extracranial	No	28	3.2 (2.7–3.7)	0.053
		Yes	5	4.2 (2.5–5.9)	
	Others	No	13	2.2 (1.3–3.1)	0.392
		Yes	2	4.1 (NA)	
Local RT (3DCRT, FSRT)	Brain	No	1	3.0 (NA)	
		Yes	0		
	Extracranial	No	3	3.3 (0.6–6.0)	0.343
		Yes	3	5.6 (4.3–6.9)	
	Others	No	0		
		Yes	3		
Radiosurgery (SRS, GKRS)	Brain	No	1	6.2 (NA)	0.083
		Yes	3	14.6 (9.5–19.7)	
	Extracranial	No	0		
		Yes	1	12.4 (NA)	
	Others	No	2	4.2 (NA)	0.225
		Yes	1		
Surgery ± RT	Brain	No	4	5.9 (2.1–9.7)	0.007
		Yes	4	18.8 (4.9–32.7)	
	Extracranial	No	7	4.2 (2.4–6.0)	0.115
		Yes	1	13.3 (NA)	
	Others	No	1	5.5 (NA)	0.808
		Yes	2	5.0 (NA)	

Brain progression of brain metastases, *Extracranial* progression of extracranial metastases, *Others* infection, unknown, etc

Table 5 Survival after diagnosis of brain metastasis, dependent on administration of chemotherapy after control of BM, grouped by ECOG PS score and number of chemotherapy drugs administered prior to development of BM

ECOG PS	No. of CT drugs before BM	CT after control of BM	No. of patients	Median survival (95% CI)	*P*-value
0–1	≤2	No	16	4.2 (1.0–7.4)	**0.003**
		Yes	21	17.3 (10.9–23.7)	
		Overall	37	12.4 (7.1–17.7)	
0–1	≥3	No	17	3.2 (2.7–3.7)	0.070
		Yes	1	12.2 (NA)	
		Overall	18	3.2 (2.6–3.8)	
2–4	≤2	No	25	2.9 (1.9–3.9)	0.318
		Yes	9	4.2 (4.0–4.5)	
		Overall	34	3.4 (2.1–4.7)	
2–4	≥3	No	23	4.8 (2.6–7.0)	0.358
		Yes	3	4.2 (3.4–5.0)	
		Overall	26	2.3 (1.2–3.4)	

BM brain metastases, *ECOG PS* Eastern Cooperative Oncology Group performance status, *CT* chemotherapy, *CI* confidence interval

and III differed significantly, with durations of 30.8, 5.4, and 2.9 months, respectively ($P < 0.001$; Fig. 2a). Risk of death in the RPA class III subgroup was 2.6 times that for the other subgroups. The number of chemotherapy drugs administered prior to BM was also an independent prognostic factor in the present study (HR 2.38; $P = 0.001$), in agreement with previous studies [15, 16, 19]. Additionally, administration of systemic chemotherapy after control of BM prolonged survival (HR 0.30; $P < 0.001$) and was the most powerful prognostic factor for survival after BM. However, not all patients were candidates for chemotherapy after BM, due to poor PS or chemorefractoriness. Thus, identifying patients who may benefit from systemic chemotherapy after BM remains an important issue.

In conclusion, survival after BM from CRC is poor, despite the development of multidisciplinary modalities, including local RT, RS, and surgery. Our results show that initial disease status, RPA class, number of chemotherapy drugs administered before BM, and chemotherapy after BM are independent prognostic factors, and a subset of patients could obtain clinical benefit from systemic chemotherapy and survive >1 year after development of BM. Thus, we expect that treatment with additional chemotherapeutics after diagnosis of BM from CRC could be an option for consideration to prolong survival of selected patients.

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Competing interests The authors declare that they have no competing interests.

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