Original Article

Prognosis for Patients with Peritoneal Metastases-only Colorectal Cancer after Systemic Therapy: An Institutional Experience

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Purpose. Prognosis of metastatic colorectal cancer (mCRC) differs by metastatic site. We present our preliminary treatment result for patients with peritoneal metastases-only colorectal cancer (pcCRC).
Methods. For this study, 11 patients diagnosed as having pcCRC who had received systemic therapy from January 2014 to December 2017 were recruited. They received follow-up until April 2019. Patients' characteristics including gene mutation profiles, regimens of therapy, and clinical outcomes were evaluated.
Results. The median age was 65 years (37-71 years). The primary tumor was located in the right colon (4 patients) or left colon (7 patients). Ten patients underwent primary tumor resection, and all patients received systemic therapy. Of the 11 patients, 1 exhibited a *KRAS* codon 12 mutation, 1 exhibited a *KRAS* codon 13 mutation, 1 exhibited a *BRAF* codon V600E mutation, and 9 exhibited epidermal growth factor receptor overexpression. The median progression-free survival was 10.6 months (3.7-19.8 months), and overall survival was 13.8 months (5.1-19.8 months).
Conclusions. Although chemotherapy regimens with new chemotherapeutic and molecular targeting agents improved the mCRC outcome, our research suggested that the pcCRC might be associated with poor clinical outcomes among patients with mCRC. Further comparison studies and prospective randomized trials based on carcinomatosis status should be considered.
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Key Words
Prognosis;
Metastatic colorectal cancer;
Peritoneal carcinomatosis

Colorectal cancer (CRC) is a major cause of cancer-related deaths worldwide, with over 1 million new cases diagnosed annually.[1] Approximately 20% of patients with CRC present with metastases at the time of initial diagnosis. Furthermore, in almost 40% of the remaining patients, the initially limited diseases progress to metastases during treatment.[2] Prognosis of metastatic colorectal cancer (mCRC) differs by specific metastatic sites; a combination of systemic therapy and metastasectomy provides the best survival rate.[3]

Peritoneal metastases colorectal cancer (pcCRC)

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has a poor prognosis and often considered to be a terminal condition. The reported median overall survival (OS) after 5-fluorouracil-only systemic chemotherapy without aggressive cytoreduction is 5 to 7 months.[4,5] Patients presenting with malignant bowel obstruction due to peritoneal carcinomatosis have worse prognoses, with a median OS of approximately 3-4 months.[6]

The association between clinical outcome and the gene mutation of the *KRAS*, *NRAS*, and *BRAF* genes has become more clearly understood. Treatment of mCRC has significantly improved in terms of progression-free survival (PFS) and OS due to new chemotherapeutic and molecular target agents. In this study, we present our current results for patients with peritoneal metastases-only mCRC who received systemic therapy.

Materials and Methods

Patients' characteristics

From a single institution, 518 patients with stage IV CRC who had received treatment between January 2014 and December 2017 were selected. Patients with record duplications (N = 5) or neuroendocrine tumors (N = 1) were excluded, and those with liver, lung, or other sites metastases were also excluded. For this study, 11 (11/518, 2%) patients consecutively diagnosed with pcCRC were recruited, and the flow diagram of patient selection is presented in Fig. 1. In this study, a case series analysis was performed using a routinely updated and maintained electronic medical record database. Demographic data included age at diagnosis, sex, location of primary tumor, and gene mutation. All aspects of this study were approved by the institutional review board of our hospital. This study is a retrospective review of 11 patients with pcCRC, and written informed consent was obtained from all patients.

Oncological follow-up

These patients were followed up for a median of 13.8 months (range, 5.1-19.8 months). Follow-up included a physical examination and carcinoembryonic antigen measurements every 3 months for 2 years, twice a year afterward. A computed tomography (CT) scan of the abdomen and thorax was arranged every 3-6 months for the first 2 years and yearly after that. We performed colonoscopy within 1 year after surgery. Magnetic resonance imaging and positron emission CT are not routine imaging tools and are only used when necessary.

Statistical analysis

Data were analyzed using SPSS Version 19.0 (SPSS, Inc., Chicago, IL, USA). PFS and OS rates were plotted using the Kaplan-Meier method. PFS was defined as the time from the start date of treatment until the date of any type of progression or the final follow-up, whereas OS was defined as the time from the beginning of treatment to death from any cause or to the final follow-up.

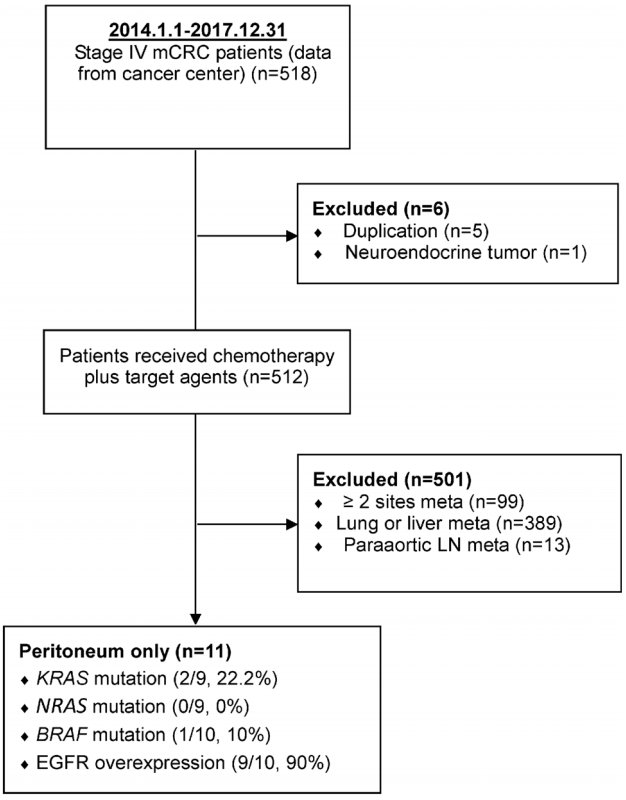

Fig. 1. CONSORT flowchart showing the 518 patients with stage IV mCRC, whose data were collected from a cancer center (2014.1.1-2017.12.31).

Results

Patient series, tumor characteristics, and mutation status

Eleven patients with peritoneal metastases-only mCRC were included in the analysis. Of these, 8 were identified through a CT scan, 1 patient through positron emission tomography, and 2 patients through operation. Table 1 provides a summary of their demographic and clinicopathological characteristics. The median age was 65 years (range, 37-71 years); 9 (81.8%) of the patients were men and 2 (18.2%) were women. The primary tumor was located in the right (4 patients) or left colon (7 patients). Ten patients underwent primary tumor resection, and all patients received systemic therapy plus target therapy in the first-line setting.

Genotyping of *KRAS*, *NRAS*, and *BRAF* analysis revealed *KRAS* mutation in 2 patients (22%, codon 12 mutation in 1 patient, *KRAS* codon 13 mutation in 1 patient), and *BRAF* codon V600E mutation in 1 patient (10%). Nine patients had epidermal growth factor receptor overexpression. No microsatellite instability-high was noted in these patients.

The demographic characteristics and treatment evaluation of each patient are presented in Table 2. According to the European Society for Medical Oncology guidelines, FOLFIRI (folinic acid + fluoro-

Table 1. Patients' characteristics at diagnosis and gene mutation profiles (N = 11)

Characteristic	Peritoneal meta only (n = 11)	Liver meta only (n = 124)	Lung meta only (n = 42)
Median age (years)	65 (37-71)	62 (26-90)	66 (41-86)
Gender (M:F)	9:2	76:48	19:23
Location of primary tumor			
Right colon	4	30	13
Left colon	7	94	29
PCI score (1~19:20~39)	10:1		
KRAS mutation	2/9, 22.2%	32/29, 36.0%	10/29, 34.5%
NRAS mutation	0/9, 0%	5/64, 7.8%	2/24, 8.3%
BRAF mutation	1/10, 10.0%	7/83, 8.4%	1/31, 3.2%
EGFR overexpression	9/10, 90.0%	58/67, 86.6%	12/15, 80%
MSI-H	0/4, 0%		
PFS (months)	10.6	14.4	16.3
OS (months)	13.8	28.6	35.9

CT, computed tomography; PET, positron emission tomography; OP, operation; PCI score, peritoneal cancer index score; EGFR, epidermal growth factor receptor; MSI-H, microsatellite instability-high; PFS, progression-free survival; OS, overall survival.

Table 2. Demographic and clinicopathological characteristics of 11 patients with peritoneal metastases only (N = 11)

Case No.	Sex	Age (years)	Performance status	Tumor location	Gene mutation	Regimen of therapy	PFS (months)	OS (months)	Survival (yes or no)
1	M	64	1	Sigmoid	*KRAS* codon 13 mutation	FOLFIRI + Bevacizumab	19.8	19.8	Yes
2	F	65	1	Sigmoid		FOLFIRI + Bevacizumab	11.7	11.7	Yes
3	M	55	0	Recto-sigmoid		FOLFIRI + Bevacizumab	19.6	19.6	Yes
4	M	65	0	Sigmoid		1st line FOLFIRI + Bevacizumab 2nd line FOLFOX6 3rd line FOLFIRI + Cetuximab	10.9	18.9	Yes
5	F	71	1	Ascending	*KRAS* codon 12 mutation	FOLFIRI + Bevacizumab	7.1	7.1	Yes
6	M	73	0	Ascending		FOLFIRI + Bevacizumab	3.7	5.1	No
7	M	51	0	Sigmoid		FOLFIRI + Bevacizumab	6.1	9.0	No
8	M	37	0	Sigmoid	*BRAF* codon V600E mutation	1st line FOLFIRI + Bevacizumab 2nd line FOLFOX6 + Bevacizumab	6.3	11.6	No
9	M	44	0	Ascending		FOLFIRI + Bevacizumab	18.0	18.0	No
10	M	66	1	Ascending		1st line FOLFIRI + Bevacizumab 2nd line FOLFOX6 3rd line FOLFIRI + Regorafenib 4th line FOLFIRI + Cetuximab	4.1	13.8	No
11	M	70	0	Sigmoid		FOLFIRI + Bevacizumab	10.6	14.5	No

Performance status evaluation with the ECOG (Eastern Cooperative Oncology Group) scale; PFS, progression-free survival; OS, overall survival; FOLFIRI, folinic acid + fluorouracil + irinotecan; FOLFOX, folinic acid + fluorouracil + oxaliplatin.

uracil + irinotecan) plus bevacizumab is the first-line treatment for patients with mCRC with *RAS* gene mutations. If the tumor is located in the left colon with a wild-type *RAS* gene, FOLFIRI plus cetuximab may be considered for the first-line treatment.[7] Among the 11 patients, 5 remained alive at the final follow-up visit conducted in April 2019.

Survival evaluation

The median PFS was 10.6 months (range, 3.7-19.8 months) (Fig. 2A), and the median OS was 13.8 months (range, 5.1-19.8 months) (Fig. 2B). Among the 11 patients, 5 remained alive at the final follow-up conducted in April 2019. During the same period between January 2014 and December 2017, the overall survival of lung metastases-only and liver metastases-only were 28.6 months and 35.9 months. Peritoneum metastases-only had a significantly worse overall survival when compared to lung metastases-only ($p = 0.006$), but did not exhibit a significant correlation compare to liver metastases-only ($p = 0.186$, Fig. 3). The possible explanation may be due to the limited peritoneum metastases-only patients.

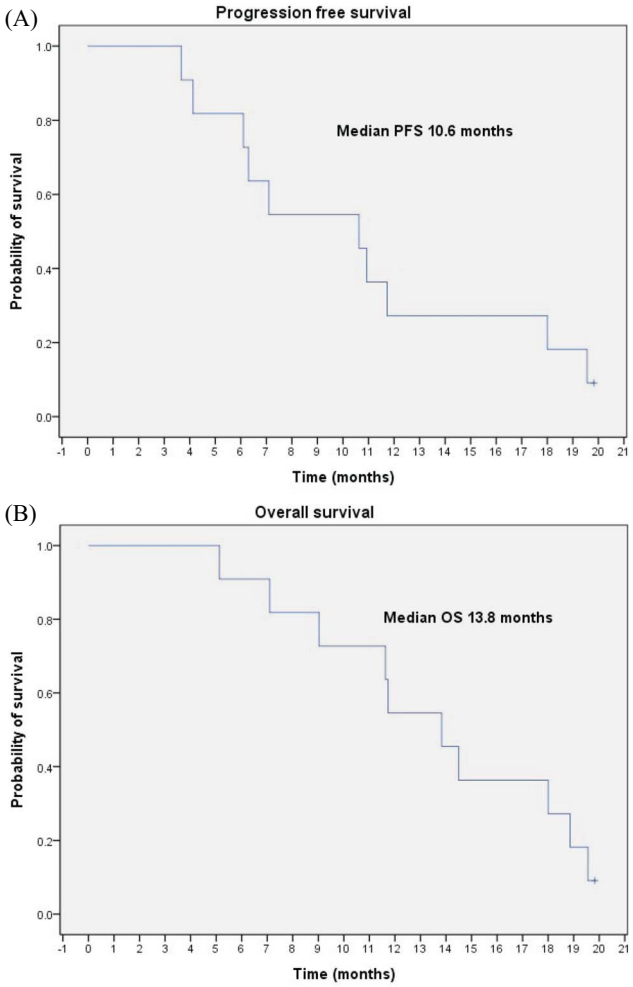

Fig. 2. Kaplan-Meier survival analysis. (A) Progression-free survival of all 11 patients (range, 3.7-19.8 months); (B) Overall survival of all 11 patients (range, 5.1-19.8 months).

Discussion

In patients with mCRC, the optimal treatment for OS is the combination of contemporary systemic chemotherapy and resectable metastases.[3,8,9] The respective 5-year survival rates in resectable hepatic, pulmonary, and peritoneal metastases are nearly 60%, 40%, and 20%.[10-14]

pcCRC is associated with higher risks of death from all causes, a 20% reduction in PFS, and a 30% reduction in OS compared with for patients with mCRC.[15] The natural history of the disease has a poor median survival of approximately 6 months,[4,5] which varies between 13 and 34 months with new chemo-

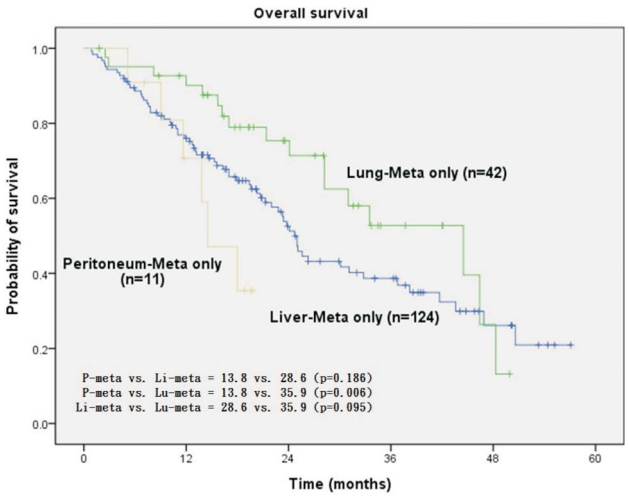

Fig. 3. Kaplan-Meier survival curve illustrating the overall survival difference between peritoneum metastases-only, liver metastases-only, and lung metastases-only. P-meta, peritoneum metastases-only, Li-meta, liver metastases-only; Lu-meta, lung metastases-only.

therapeutic and molecular targeting agents.[16-18] The median OS of our 11 patients was 13.8 months with current systemic chemotherapy regimens.

Because the plasma-peritoneal barrier decreases intraperitoneal drug penetration, systemic chemotherapy treatment for pcCRC has only limited efficacy for long-term survival. Cytoreductive surgical (CRS) techniques incorporated with intraperitoneal chemotherapy has been used as a logical treatment strategy to improve long-term survival.[19,20] A meta-analysis revealed that CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) provide survival benefits for selected patients with peritoneal carcinomatosis from colorectal cancer.[21] The summarizing analysis of these 76 studies showed that the median OS was approximately 29 months in the CRS plus HIPEC group. However, the patients were selected according to their good performance statuses and were able to receive surgical intervention, and the mean mortality and morbidity for the HIPEC program were 2.8% and 33.0%, respectively.

Our results demonstrate relatively similar findings to those from other systemic chemotherapy studies, but this is only an observational study with a small sample size. Future investigations could include larger sample sizes and increased follow-up duration for confirming the findings of this study.

Conclusions

Although chemotherapy regimens with new chemotherapeutic and molecular targeting agents improved the outcome in patients with mCRC, our research suggested that pcCRC might be associated with poor clinical outcomes among patients with mCRC. Further comparison studies and prospective randomized trials based on carcinomatosis status should be considered. With precision medicine, research on the molecular and genetic profile of CRCs may be helpful for patients with pcCRC.

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原　著

第四期大腸直腸癌純腹膜轉移的預後 — 單一機構治療經驗

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目的　轉移性的大腸直腸癌會依據轉移位置的不同，而有不同的預後。此研究呈現單一醫療機構純粹腹膜轉移之轉移性大腸直腸癌的預後。

方法　此研究收集 11 位接受全身性治療的純粹腹膜轉移大腸直腸癌患者，從 2014 年 1 月到 2017 年 12 月。追蹤時間是到 2019 年 4 月。本研究分析患者的資料，包含基因的變異、使用何種全身性治療藥物、以及臨床成果。

結果　患者年齡中位數為 65 歲 (範圍是 37 歲到 71 歲)。最初腫瘤的位置，其中 4 位患者在右半大腸，而剩餘 7 位患者在左半。10 位患者接受了原發位腫瘤切除手術，而所有的患者都接受了全身性的治療。在 11 位患者中，有一位是 *KRAS* codon 12 突變，一位是 *KRAS* codon 13 突變，一位是 *BRAF* codon V600E 突變，而其中有 9 位是表皮生長因子受體 (EGFR) 的過度表現。這 11 位患者的預後，無惡化存活時間中位數為 10.6 個月 (範圍為 3.7 到 19.8 個月)，總生存期的中位數為 13.8 個月 (範圍是 5.1 到 19.8 個月)。

結論　即使近年來新的化療及標靶藥物的出現，讓轉移性大腸直腸癌的預後有顯著進展，但在純粹腹膜轉移這類的病人上，預後還是不盡理想。希望未來能有更多的研究針對腹膜轉移這群患者。

關鍵詞　預後、轉移性大腸直腸癌、腹膜轉移。