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Characterization of Conversion Chemotherapy for Secondary Surgical Resection in Colorectal Cancer Patients with Lung Metastases

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Metastatic colorectal cancer · Lung metastases · Conversion · Chemotherapy

Abstract
Objective: Clinical trials demonstrated that 6–37% of the patients with colorectal liver-limited metastases underwent surgical resection after first-line chemotherapy. However, limited information is available on the conversion of colorectal cancer patients with lung metastases to resection by systemic chemotherapy. ***Methods:*** We retrospectively investigated 156 patients with unresectable colorectal cancer who received oxaliplatin- or irinotecan-based first-line systemic chemotherapy with or without antibodies in our department between January 2007 and December 2015. The conversion rate to surgery and chemotherapeutic regimens and periods were analyzed with respect to the target organ. ***Results:*** In addition to 4 patients who achieved complete response, 73 exhibited tumor shrinkage of any extent. Twenty patients underwent secondary surgery, all of whom received targeting antibodies. In 75 patients with liver metastases, 18 (24%) were converted to resection after chemotherapy for a median of 110 days. In contrast, 4 (7%) out of 56 patients with lung metastases underwent resection after chemotherapy for a median of 449 days. Conversion was an independent prognostic factor in patients with lung metastases. ***Conclusion:*** The conversion rate to resection was lower for colorectal cancer patients with lung metastasis by systemic chemotherapy, which required a longer duration than for those with liver metastases.

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Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide, having the second highest mortality rate [1]. Twenty percent of CRC patients have metastatic disease at presentation, and another 30% of those diagnosed with CRC will develop metastatic disease metachronously [2, 3]. Systemic chemotherapy constitutes the main treatment option for these patients, except for those with resectable disease. Considerable advances in effective cytotoxic drugs together with molecular targeting agents have improved the survival of patients with initially unresectable CRC (mCRC) in recent years [4, 5] and have even allowed metastases to be resectable ("conversion") in a subpopulation of patients [6, 7].

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The lungs are the second most common site of metastasis from CRC [8, 9], and the excision of metastatic lesions is beneficial for selected CRC patients with lung metastases [10, 11]. However, conversion to pulmonary metastasectomy in CRC patients with initially unresectable lung metastases has rarely been described. Previous studies have mainly investigated conversion to resection in mCRC patients focused on liver-limited metastasis, with reported conversion rates being 6–37% [6, 7].

This study aimed to characterize conversion to resection in mCRC patients with various organ metastases, particularly lung involvement.

Methods

Patients and Data Retrieval

One hundred and fifty-six patients histologically diagnosed with mCRC who started receiving a 5-fluorouracil- (5-FU), oxaliplatin-, or irinotecan-based cytotoxic drug combination (as described below) with or without targeted antibodies as first-line chemotherapy in our department between January 2007 and December 2015 were retrospectively analyzed. We included patients who had received preoperative chemoradiation therapy for rectal cancer. Patients who developed recurrence during adjuvant chemotherapy and those who received neoadjuvant chemotherapy for resectable disease were excluded. Data regarding age, sex, the Eastern Cooperative Oncology Group (ECOG) performance status, serum tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 just before the initiation of chemotherapy, and the histological grade and location of the primary tumor were collected for all eligible patients. The *KRAS* status in exon 2 was analyzed in cases after 2010. The upper normal limits of serum CEA and CA 19-9 are 5 ng/mL and 37 U/mL, respectively, in our hospital.

The study protocol was approved by the local Ethics Committees of the University of Tokyo (reference number: 3252-(3)) and thus meets the standards of the Declaration of Helsinki in its revised version of 1975 and its amendments of 1983, 1989, and 1996. Written informed consent was obtained from all patients.

Chemotherapy Regimen, Radiological Evaluation, and Decision of Conversion

FOLFOX (oxaliplatin 85 mg/m^2 and folinic acid 200 mg/m^2, followed by 5-FU, as a 400-mg/m^2 intravenous bolus and then a 2,400-mg/m^2 infusion over 46 h) was administered every 2 weeks [12]. CapeOX (oxaliplatin 130 mg/m^2 over 2 h on day 1 plus oral capecitabine 1,000 mg/m^2 twice daily on days 1–14) was administered every 3 weeks [13]. SOX (oxaliplatin 130 mg/m^2 over 2 h on day 1 plus oral S-1 40 mg/m^2 twice daily on days 1–14) was administered every 3 weeks [14]. FOLFIRI (150 mg/m^2 irinotecan, the dose approved in Japan, and 200 mg/m^2 folinic acid, followed by 5-FU, as a 400-mg/m^2 intravenous bolus then a 2,400-mg/m^2 infusion over 46 h) was administered every 2 weeks [15]. The choice of cytotoxic drugs and addition of targeted agents such as antiepidermal growth factor receptor (EGF-R) (cetuximab and panitumumab) and antivascular endothelial growth factor (VEGF) (bevacizumab) antibodies depended on the doctors' discretion; however, anti-EGF-R antibodies were exclusively used for CRC with wild-type *KRAS*. Dose reductions and the cessation of chemotherapy were considered based on the patient's preference and general condition.

CT scans were performed before chemotherapy, and every 2–3 months thereafter during the treatment in order to evaluate tumor responses. When serum tumor markers were elevated in an accelerated manner, or new symptoms suggesting that disease progression appeared, we performed additional imaging studies including CT scans and other modalities such as magnetic resonance imaging and positron emission tomography. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was applied to grade the best response in each case [16].

Resectability before chemotherapy was discussed at a multidisciplinary conference attended by surgeons, radiologists, medical oncologists, and pathologists. The decision to continue the ongoing therapy or to undergo secondary surgery (conversion) was also made at the multidisciplinary conference.

Long-Term Prognosis

Progression-free survival (PFS) was defined as the time between the initiation of first-line chemotherapy for mCRC and the date of diagnosis of disease progression by RECIST, and overall survival (OS) as the time between the initiation of first-line chemotherapy and death due to any reason. Surviving patients were censored at the last time point of patient contact either directly or indirectly.

Statistical Analysis

Comparisons of parameters between groups were performed using the Wilcoxon rank sum and Fisher exact tests. Predictive factors for disease progress and overall mortality were estimated by univariate and multivariate analyses using the Cox proportional-hazard model, where continuous variables were dichotomized by their median or mean values. Data were analyzed using JMP version 12.2.0 software (SAS Institute Inc., Cary, NC, USA), with p values <0.05 being considered significant.

Results

Patient Profiles

The clinical and pathological features of the study population are shown in Table 1. Rectal cancer was predominant (53%). Most patients (86%) had CRC of a differentiated histology. Approximately three-fourths of the patients had elevated CEA levels, whereas CA 19-9 levels were elevated in 47% of the patients before chemotherapy. The *KRAS* status was checked in 99 patients (63%); 41 carried mutations in exon 2. Multiple organs were involved in two-thirds of the patients. The most frequently metastasized organ was the liver (48%), followed by the lung (36%) and distant lymph nodes (35%). In 37% of the patients, the primary tumor was not resected before first-line chemotherapy.

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Table 1. Profiles of unresectable CRC patients who received systemic chemotherapy ($N = 156$)

Mean age (range), years	64 (30–84)
Gender	
Male	93 (60)
Female	63 (40)
ECOG PS	
0	149 (95)
1	6 (4)
2	1 (1)
Histological type[a]	
Differentiated adenocarcinoma	133 (86)
Others	23 (14)
Primary tumor location	
Colon	74 (47)
Rectum	82 (53)
Serum CEA	
Normal	38 (24)
Elevated	114 (73)
Not evaluated	4 (3)
Serum CA 19-9	
Normal	78 (50)
Elevated	74 (47)
Not evaluated	4 (3)
KRAS exon 2	
Wild type	58 (37)
Mutant	41 (26)
Not evaluated	57 (37)
Number of target organs	
1	53 (34)
2	62 (40)
≥3	41 (26)
Target organs[b]	
Primary tumor	58 (37)
Lung	56 (36)
Liver	75 (48)
Distant lymph nodes	55 (35)
Peritoneum	41 (26)
Local recurrence	12 (8)
Bone	12 (8)
Brain	9 (6)
Others	10 (6)

Values are presented as n (%) unless otherwise indicated. ECOG, Eastern Cooperative Oncology Group; PS, performance status; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; *KRAS*, Kirsten rat sarcoma gene. [a] Histology of major component was shown. [b] Multiple organs could be involved.

Chemotherapy Regimens

Table 2 depicts the regimens used as first-line chemotherapy. Most patients (93%) received an oxaliplatin-based cytotoxic drug combination as backbone chemotherapy. Targeted biologics were administered to 58% of the patients; cetuximab or panitumumab was given to 38 (24%) patients, whereas bevacizumab was administered to 53 (34%) patients.

Table 2. Chemotherapy regimens used in the patients ($N = 156$)

Cytotoxic drug combination	
FOLFOX	125 (80)
CapeOX	21 (13)
SOX	1 (1)
FOLFIRI	9 (6)
Antibody	
None	65 (42)
Cetuximab	28 (18)
Panitumumab	10 (6)
Bevacizumab	53 (34)

Values are presented as n (%).

Table 3. Conversion rate to resection and chemotherapy period according to chemotherapeutic drugs

Regimens or biologics	Patients of conversion to resection, *n* (%)	Median chemotherapy period, days
Overall ($n = 156$)	20 (13)	110
FOLFOX ($n = 125$)	18 (14)	110
CapeOX ($n = 21$)	1 (5)	252
SOX ($n = 1$)	0 (0)	n.a.
FOLFIRI ($n = 9$)	1 (11)	63
No antibody ($n = 65$)	0 (0)	n.a.
Cetuximab ($n = 28$)	10 (36)	74
Panitumumab ($n = 10$)	2 (20)	131
Bevacizumab ($n = 53$)	8 (15)	198

n.a., not available.

Overview of Responses and Conversion

As the best response, complete response was achieved by 4 patients, none of whom underwent secondary surgery. Besides these patients, tumor volumes were reduced in 73 patients. Twenty patients underwent surgical resection after a median of 3.7 months (range 1.5–30.4) of systemic chemotherapy.

Table 3 summarizes the conversion rate to resection according to the chemotherapeutic regimen. Although patients who achieved complete response were considered to be oncologically equivalent to successful conversion, they were not counted in calculations from this

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Table 4. Conversion rate to resection and chemotherapy period according to target organs

Target organ	Patients of conversion to resection, *n* (%)	Median chemotherapy period, days
Primary tumor (*n* = 58)	12 (21)	86
Lung (*n* = 56)	4 (7)	449
Liver (*n* = 75)	18 (24)	110
Lymph node (*n* = 55)	4 (7)	231
Peritoneum (*n* = 41)	2 (5)	346
Local recurrence (*n* = 12)	0 (0)	n.a.
Bone (*n* = 12)	0 (0)	n.a.
Brain (*n* = 9)	0 (0)	n.a.
Others (*n* = 10)	1 (10)	646

n.a., not available.

analysis on. Moreover, there was only 1 female patient with local recurrence from rectal cancer who underwent surgical resection after additional chemotherapy and radiation therapy following the failure of first-line chemotherapy; she was also not tabulated as a case of conversion in this and subsequent results. Eighteen patients (14%) underwent resection after FOLFOX-based chemotherapy that continued for a median of 3.7 months. Regarding other regimens, 1 patient receiving CapeOX (5%) and 1 receiving FOLFIRI (11%) underwent secondary surgery.

No patient underwent surgical resection without the usage of antibodies. Conversion rates to resection were slightly higher in patients treated with anti-EGF-R antibodies than in those who received anti-VEGF antibodies (32 vs. 15%, $p = 0.11$). Moreover, in cases of conversion, chemotherapy periods were shorter in patients treated with anti-EGF-R antibodies than in those who received anti-VEGF antibodies (3.7 months vs. 6.6 months, $p = 0.02$).

Conversion to Resection according to Target Organs

Table 4 shows conversion rates to resection and chemotherapy periods with respect to the target organs. Cases may have overlapped among the several target organs. Liver and primary tumors were more likely to be resected (24 and 21%, respectively), whereas 4 CRC patients with lung metastases (7%) underwent resection after chemotherapy. Four patients with lung metastases underwent a total of 6 pulmonary metastasectomies; hyperglycemia was observed in 1 patient with type I diabetes, whereas no other significant postoperative complications were noted. The median period of chemotherapy before pulmonary metastasectomy (15.0 months) was longer than those for hepatectomy (3.7 months) and primary tumor resection (2.9 months).

Table 5 shows the conversion rate to resection and chemotherapy period in patients with metastasis confined to a single organ. Each category included both cases of primary CRC resected and unresected. Since each patient fell into only 1 category, the values of this table were statistically analyzed between categories. Nearly one half of liver-limited metastases (48%) were resected after a limited period of chemotherapy (median 2.8 months). In contrast, lung-limited metastases were resected in 1 patient (7%) after long-term chemotherapy (30.4 months). The only patient with peritoneal metastases who underwent conversion surgery had transverse colon cancer that invaded the second portion of the duodenum, which was deemed very difficult to resect at the initial presentation; a 1.5-month cetuximab-plus-FOLFOX regimen enabled the primary tumor and peritoneal metastases to be removed with oncologically safe surgical margins. No mCRC patients with metastases confined to another single organ underwent secondary surgery after chemotherapy. The conversion rate of lung-limited metastases or peritoneum-limited metastases was significantly lower than that of liver-limited metastases (both $p = 0.006$).

Table 6 summarizes conversion therapy focusing on the combination of metastasized organs. Overall, secondary surgery was performed after a median of at least 7 months of chemotherapy for multiple organ metastases. The most frequent combination for resection after chemotherapy was the liver and lymph nodes (19%). Ten percent of the unresectable CRC patients with lung and liver metastases underwent surgical resection. One female patient was counted in the "liver and peritoneum" and "lung and peritoneum" combinations. She had cecal cancer that metastasized to the liver, lung, peritoneum, and spleen, and received bevacizumab and FOLFOX therapy. Extensive tumor shrinkage enabled her to undergo staged resection of the primary tumor and all metastases, and she subsequently achieved a tumor-free status 23 months after the initiation of chemotherapy.

Prognostic Factors

Finally, we performed the univariate and multivariate analyses using the Cox proportional hazards model in order to identify clinicopathological predictors of disease progression and mortality. As shown in Table 7, conver-

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Table 5. Conversion rate to resection and chemotherapy period according to target in cases with single-organ-limited metastasis[a]

Target organ	Patients of conversion to resection, *n* (%)	*p* value[b]	Median chemotherapy period, days	*p* value[b]
Lung (*n* = 15)	1 (7)	0.006	912	0.14
Liver (*n* = 25)	12 (48)	–	84	–
Lymph node (*n* = 13)	0 (0)	0.003	n.a.	n.a.
Peritoneum (*n* = 16)	1 (6)	0.006	45	0.14
Others (*n* = 1)	0 (0)	1	n.a.	n.a.

n.a., not available. [a] Including patients with unresected primary tumor. [b] In comparison with liver metastasis.

Table 6. Conversion rate to resection and chemotherapy period according to specific combinations of metastasized organs[a]

Combination of target organs	Patients of conversion to resection, *n* (%)	Median chemotherapy period, days
Lung, liver (*n* = 29)	3 (10)	252
Lung, lymph node (*n* = 17)	1 (6)	252
Lung, peritoneum (*n* = 9)	1 (11)	646
Liver, lymph node (*n* = 21)	4 (19)	231
Liver, peritoneum (*n* = 13)	1 (8)	646
Lymph node, peritoneum (*n* = 11)	0 (0)	n.a.

n.a., not available. [a] Including patients with primary unresected tumor.

Table 7. Univariate and multivariate Cox proportional hazards modeling to predict progression-free survival in mCRC patients with lung metastases (*n* = 56)

Variables	Univariate	Multivariate		
	p value	*p* value	HR	95% CI
Usage of antibody				
No (vs. yes)	0.046	0.30	1.50	0.69–3.21
Conversion to resection				
No (vs. yes)	0.0003	0.0015	2.01×10^9	3.07–n.a.

HR, hazard ratio; CI, confidence interval; n.a., not available.

sion to resection was the only independent prognostic factor for PFS with a hazard ratio (HR) of 2.01×10^9 (p = 0.0015). Histology other than differentiated adenocarcinoma (HR 5.48, p = 0.013), local recurrence (HR 15.67, p = 0.010), and no conversion to resection (HR 9.48×10^8, p = 0.0052) were independently associated with significantly worse OS (Table 8).

Discussion

In the present study, we demonstrated that the conversion rate to resection after first-line chemotherapy was 7% in mCRC patients with lung metastases, irrespective of other organ involvement. In addition, distant lymph nodes and peritoneal dissemination were excised with cu-

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Table 8. Univariate and multivariate Cox proportional hazards modeling to predict overall survival in mCRC patients with lung metastases ($n = 56$)

Variables	Univariate	Multivariate		
	p value	*p* value	HR	95% CI
Histological type[a]				
Others (vs. diff.)	0.017	0.013	5.48	1.51–16.17
Local recurrence				
Yes (vs. no)	0.0023	0.010	15.67	2.21–73.61
Conversion to resection				
No (vs. yes)	0.0030	0.0052	9.48×10^8	2.19–n.a.

Diff., differentiated adenocarcinoma; HR, hazard ratio; CI, confidence interval; n.a., not available. [a] Histology of major component was analyzed.

rative intent after systemic chemotherapy with a similar percentage to lung metastases. To the best of our knowledge, this is the first study to describe conversion rates in mCRC patients by upfront chemotherapy with a special focus on the target organs.

We found that a longer chemotherapeutic period was required for successful conversion to pulmonary metastasectomy than conversion therapy in mCRC patients with liver metastases. Systemic chemotherapy aimed at conversion has been postulated to maximize response rates and resectability and also to eradicate or control micrometastases [17]. Therefore, in mCRC involving the lung that has less reparative capacity than the liver [18], more time will be required to judge responses and resectability after chemotherapy. We also surmised that the chemotherapy period was generally longer in mCRC patients disseminating to multiple target organs than in those with single-organ metastasis for the same reasons. On the other hand, adverse events such as sinusoidal dilatation in the liver and steatohepatitis are major concerns in the implementation of preoperative chemotherapy [17]. A previous study reported that 9 or more cycles of preoperative FOLFOX (plus bevacizumab) increased the risk of postoperative hepatic insufficiency in liver-limited mCRC patients without increasing the hepatic resection rate [19]. In accordance with this finding, the median period of chemotherapy until the second surgery was shorter than 4 months in mCRC patients with liver metastases in our study. Although we did not encounter surgery-related complications in patients with lung metastases, it has yet to be clarified whether a prolonged preoperative chemotherapy increases the risk of postoperative complications in surgical procedures other than hepatectomy.

In mCRC patients with lung metastasis, conversion to resection was a robust predictor for a better PFS and OS. The long-term survival of CRC patients who underwent surgical resection for initially unresectable liver metastases was previously reported to be similar to that of patients with initially resectable colorectal liver metastases [20–22]. Further studies using accumulated cases are needed in order to establish whether a similar long-term outcome is expected for patients with extrahepatic lesions such as lung metastases from CRC.

Since the lung and liver are frequently metastasized organs in mCRC, it is clinically important to address conversion to resection in metastatic disease of this combination. In our study, the conversion rate for lung and liver metastases (10%) was similar to that for lung-limited metastasis (7%). Therefore, these mCRC patients must not become discouraged in systemic chemotherapy simply because of multiple-organ involvement.

Our study is a single-institute experience and contains several limitations. Due to its retrospective nature, potential biases may have existed in the selection of chemotherapy regimens. The chemotherapeutic period was only compared among patients with successful conversion to surgery. We did not stratify patients by the number, size, or anatomical distribution of lesions within involved organs. Furthermore, our study cohort comprised several patients lacking information on the *KRAS* status and the extended *RAS* status, and other genetic changes such as *BRAF* mutations were not available in most patients.

In conclusion, we demonstrated that a smaller number of CRC patients with initially unresectable lung metastases underwent resection after a longer period of chemotherapy than those with liver metastases.

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Disclosure Statement

Dr. Watanabe has received fees for lectures and grants and endowments for research from Chugai Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., Bristol-Myers Squibb, and Merck Serono Japan. He has also received fees for writing manuscripts outside the submitted work from Takeda Pharmaceutical Co. Ltd. and Merck Serono Japan. For the remaining authors, there are no conflicts of interest to disclose.

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