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Clinical Impact of FOLFOXIRI Aiming for Conversion Surgery in Unresectable Multiple Colorectal Liver Metastasis

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Abstract. *Background/Aim: We evaluated the clinical impact of FOLFOXIRI regimen aiming for conversion surgery in patients with unresectable multiple colorectal liver metastasis (CRLM). Patients and Methods: A total of 42 patients with unresectable multiple CRLM who received chemotherapy with molecular agents were included in the analysis. The clinical results of FOLFOXIRI with other regimens were compared. Results: The total conversion rate of 42 unresectable CRLM was 48.1%, and conversion cases had a better prognosis. Clinicopathological characteristics of conversion cases were more frequent in FOLFOXIRI induction, liver limited disease and maximum diameter × number (MDN) over 70. FOLFOXIRI achieved a higher conversion rate compared to other regimens (72.2% vs. 37.5%, p=0.0334), and significantly reduced the medication period until conversion surgery (median 5.8 courses) with a higher tumour necrotic rate. Consequently, the overall survival of conversion cases with FOLFOXIRI was better than that with other regimens (p=0.0055). Conclusion: FOLFOXIRI plus molecular agents might provide a higher probability of conversion surgery with a prognostic benefit.*

Colorectal liver metastasis (CRLM) is the most frequent metastasis occurring in 15-25% of patients with colorectal cancer at first diagnosis (1, 2), and in up to 50% of patients with resection of primary cancer during the first 3 years (3-5). The only potential curative treatment for CRLM is surgical resection (6), which is also recommended as an upfront surgery for technically easy CRLM in the European Society for medical Oncology (ESMO) consensus guidelines (7, 8). Furthermore, these guidelines also encourage peri- and pre-operative chemotherapy, such as the FOLFOX regimen, according to oncological criteria. However, for initially unresectable CRLM, the best systemic chemo-regimen aiming for conversion surgery and definitive induction criteria have not been yet established.

Recent advancements in systemic chemotherapy, including molecular target agents, have been used to treat unresectable CRLM and several reports have demonstrated that patients who received radical (R0) resection gained prognostic benefit, even in initially unresectable CRLM (6, 9, 10). Under such situations, a powerful triple chemo-regimen, FOLFOXIRI with or without a molecular agent, is recommended for metastatic colorectal cancer, especially for patients with unresectable CRLM (11-15). In a randomised trial, Loupakis *et al.* have reported that FOLFOXIRI plus an anti-VEGF agent improved the prognosis of patients with metastatic colorectal cancer compared to FOLFIRI plus an anti-VEGF agent, with an acceptable incidence of adverse effects (16). Similarly, Gruenberger *et al.* have demonstrated that FOLFOXIRI plus an anti-VEGF agent was associated with a higher response and R0 resection rates of 49%, as well as prolonged progression-free survival compared with mFOLFOX-6 plus an anti-VEGF agent in initially unresectable CRLM (17). To date, two meta-analysis clinical studies of FOLFOXIRI have been reported. They found that FOLFOXIRI provided a higher conversion rate and subsequently prolonged patient survival compared with other double chemo-regimens based on oxaliplatin or irinotecan (18, 19). Regarding which patients might derive clinical benefit from FOLFOXIRI, Tomasello *et al.* have suggested that liver limited disease (LLD) and a higher number of chemo-cycles enhanced the conversion probability in unresectable CRLM (19).

However, there are currently no definitive induction criteria for FOLFOXIRI to achieve conversion surgery in patients with unresectable CRLM. These criteria should include tumour size, multiplicity, and the presence of remote organ metastasis, and guidance related to the optical medication

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period to ascertain whether conversion surgery is possible. In the current retrospective study, the clinical results of FOLFOXIRI for initially unresectable multiple CRLM were assessed based on our experience, and considered its advantages and disadvantages for conversion surgery.

Patients and Methods

Patients. Two hundred and seventy-three patients with CRLM from 1994 to 2017 in Tokushima University Hospital consisted of 156 initially resectable cases and 117 unresectable cases. Among the unresectable cases, 42 patients with unresectable multiple CRLM who received current chemotherapy, such as FOLFOX (n=14), XEROX (n=1), OPTIMOX (n=2), FOLFILI (n=7), and FOLFOXIRI (n=18), were included in this study. Molecular target agents including an anti-VEGF agent (bevacizumab) or anti-EGFR agent (cetuximab/panitumumab) were added to the group of unresectable cases.

First, we assessed the clinicopathological characteristics of all conversion cases, and then the patients were divided into two groups: a FOLFOXIRI group and other regimens group. The clinical benefit of FOLFOXIRI was analysed. This study was authorised in advance by the institutional review board of the University of Tokushima Graduate School (approval no.: 3215), and all patients provided written informed consent.

Regarding metastatic tumour status, the maximum diameter × number (MDN) was defined as the product of maximum tumour diameter and number of liver metastases according to our previous report (20). H-stage and grade classification were defined according to the Japanese Classification of Colorectal Carcinoma, 9th Edition (21). Liver metastasis was classified as H1–3, with H1 defined as four or fewer tumours with a maximum diameter <5 cm; H3 as more than five tumours of >5 cm in size; and H2 as anything in between. The liver metastasis grade was defined by H classification, lymph node (LN) metastasis and distant metastasis, with H1 and three or less regional LN metastases classified as grade A; H2 with more than three regional LN metastases or H1 with four or more LN metastases classified as grade B, and all other conditions classified as grade C.

To determine the tumour necrotic rate, the percentage necrotic area on resected tumour tissue was calculated by haematoxylin-eosin staining in five random fields at low power.

Modified FOLFOXIRI treatment. Our modified FOLFOXIRI was a 2-week course of treatment that included a triple combination of agents consisting of oxaliplatin, irinotecan and 5-fluorouracil, with a reduced dosage of each chemo-agent. Treatment also consisted of intravenous therapy with a molecular agent: bevacizumab 5 mg/kg over 1 h, cetuximab 400 mg/m^2 over 2 h, or panitumumab 6 mg/kg over 1 h, followed by irinotecan 150 mg/m^2 in 250 ml of normal saline over 1 h, followed by oxaliplatin 85 mg/m^2 in 250 ml of 5% dextrose and folinate 200 mg/m^2 concomitantly in 250 ml of 5% dextrose over 2 h through a Y-connector, on day 1. This was followed by fluorouracil 2400 mg/m^2 as a continuous infusion for 48 h starting on day 1.

Tumour markers and chest-abdominal CTs were examined at every two courses of FOLFOXIRI, and the possibility of conversion surgery was considered by at least three board-certified expert surgeons of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. Surgical indications were as follows: 1) R0 resection of CRLM, 2) no limitation of tumour size and number, 3) over 35% of future remnant liver volume, and 4) resectable extrahepatic disease. Chemotherapy was terminated for unacceptable toxicity, or upon patient request. After tumour relapse, patients could receive second-line chemotherapy including radiotherapy at the physician's discretion.

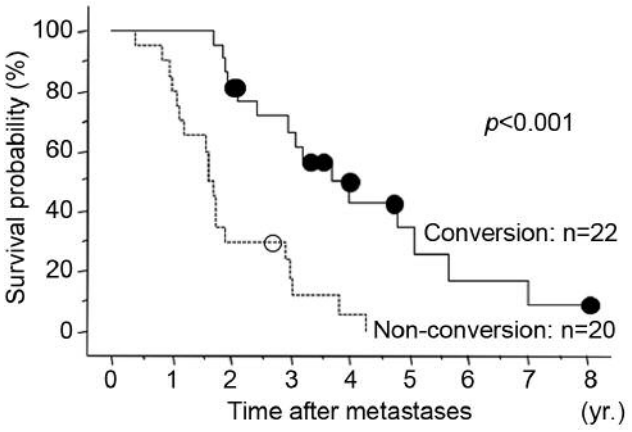

Figure 1. *Overall survival curves of patients with unresectable multiple CRLM according to the induction of conversion surgery.*

Statistical analysis. Statistical analyses were performed using JMP 11.2.0. software (SAS, Campus Drive, Cary, NC, USA). Data are presented as the median±standard deviation (SD). Statistical significance was defined as $p<0.05$. The significance of the relationships between each group and clinicopathological variables was analysed using the Mann–Whitney *U*-test and Fisher's exact test. Survival curves were calculated using the Kaplan–Meier method, and the differences were compared using the log-rank test. To identify independent factors that influenced overall survival, variables identified as $p<0.10$ by univariate analysis were included in the multivariate analysis using the Cox proportional hazards model.

Results

Clinicopathological characteristics of conversion cases. In all 42 patients with unresectable multiple CRLM, oxaliplatin- or irinotecan-based chemotherapies were applied, and FOLFOXIRI was administered to 18 patients. Consequently, the total conversion rate was 48.1%, and conversion cases had a better prognosis compared with non-conversion cases, with a 3-year survival rate of 67.7% (Figure 1). Regarding the clinicopathological characteristics of conversion cases, MDN under 70 and liver limited disease (LLD) were identified as significant tumour characteristics. The induction of FOLFOXIRI significantly enhanced the likelihood of conversion surgery (Table I). In our series, there were no significant differences in the primary tumour location and lymph node (LN) metastasis.

Prognostic factor of conversion cases. In 22 conversion cases, univariate analysis revealed that the induction of FOLFOXIRI was a significant prognostic factor. When the induction of FOLFOXIRI was entered in a proportional

Table I. *Clinicopathological characteristics of patients with conversion surgery.*

Factor		Conversion (n=22)	Non-conversion (n=20)	*p*-Value
Primary site				
Location 1	Colon/Rectum	13/9	8/12	0.3543
Location 2	Right sided/Left sided	4/18	4/16	0.9999
Diff.	tub/poor	21/0*	13/1*	0.4000
Lymphatic invasion	–/+	12/9*	5/7*	0.4813
Vessel invasion	–/+	2/19*	1/11*	0.9999
LN metastasis	–/+	6/16	7/12*	0.7374
Metastatic site				
Meta. Period	Synchro/Metachro	21/1	17/3	0.3327
Tumour number	<5/>5	5/17	0/20	0.0492
Tumour size (cm)	<5/>5	6/16	7/13	0.7410
H	1.2/3	11/11	8/12	0.5512
Grade	A.B/C	7/15	4/16	0.4913
MDN	<70/>70	18/4	6/14	0.0015
Liver limited disease	–/+	5/17	16/4	0.0005
Chemo-regimen	FOLFOXIRI/Others	13/9	5/15	0.0334
Molecular agent	anti VEGF/anti EGFR	17/5	16/4	0.9999

*Missing values.

hazard model along with MDN under 70 and combination treatment with an anti-VEGF agent, only the induction of FOLFOXIRI was a good independent prognostic factor (hazard ratio=0.1010, p=0.0016) (Table II). In addition, MDN under 70 tended towards a good independent prognostic factor (hazard ratio=0.2470, p=0.0635).

Clinical benefit of FOLFOXIRI. In all 42 patients with unresectable multiple CRLM, no significant difference of clinicopathological features was observed between FOLFOXIRI and other regimen groups. Regarding patient backgrounds, FOLFOXIRI achieved a higher conversion rate of 72.2% compared with other regimens (Table III). Regarding tumour shrinkage of conversion cases, there was no difference between the two groups, with median rates of 42.3% for FOLFOXIRI and 45.3% for other regimens (Table IV). However, the preoperative medication period of conversion cases with FOLFOXIRI was significantly shorter (median 5.8 courses) before conversion surgery (Table IV). In addition, this regimen had a higher tumour necrotic rate compared with other regimens (Table IV). Consequently, conversion cases with FOLFOXIRI had a significantly better prognosis compared with those of other regimens, and the 3-year survival rates after metastasis were 83.1% and 44.4%, respectively (Figure 2).

Cautions for the induction of FOLFOXIRI. FOLFOXIRI achieved a better prognosis compared with other regimens in conversion cases; conversely, in non-conversion cases, FOLFOXIRI led to an extremely poor prognosis compared with other regimens (Figure 2). In our series of 18 patients with FOLFOXIRI, MDN under 70 and LLD were demonstrated to be requirements for conversion surgery (Table V).

Prevention of FOLFOXIRI-related hepatic injury. The development of chemotherapy-induced hepatic injuries is increasingly being recognised, including sinusoidal obstructive syndrome (SOS), steatosis, steatohepatitis, and biliary sclerosis. Therefore, we assessed hepatic injury in surgical specimens from conversion cases with FOLFOXIRI. Table VI summarises data from 13 conversion cases with FOLFOXIRI. Anti-VEGF antibody combination was administered to 11 patients. As a result, significantly severe steatohepatitis, evaluated by Kleiner's score, was not observed. Regarding SOS status established by Rubbia-Brandt *et al*., nine courses of anti-EGFR antibody caused grade 3 sinusoidal injury (Figure 3A). However, combination with the anti-VEGF agent did not induce severe sinusoidal injury, even after eight courses of FOLFOXIRI (Figure 3B).

Discussion

In our series of unresectable multiple CRLM receiving current chemotherapies, oxaliplatin and/or irinotecan-based chemo-regimens, the clinical benefit was identified and caution was suggested regarding the induction of FOLFOXIRI. Conversion surgery for unresectable CRLM provided a better prognosis as previously reported, and the potential requirements of candidates for conversion surgery were MDN under 70, LLD and the induction of FOLFOXIRI. Treatment with FOLFOXIRI achieved a higher conversion rate, and allowed early conversion with massive tumour necrosis. However, it should be noted patients for induction with this powerful regimen were strictly selected, because treatment failure for conversion surgery with FOLFOXIRI may lead to a poor patient outcome.

Table II. *Prognostic factors of patients with conversion surgery.*

Factor		Univariate		Multivariate		
		3-yr survival (%)	*p*-Value	Hazard ratio	95%CI	*p*-Value
Primary site						
Location 1	Colon/Rectum	59.3/55.6	0.7904			
Location 2	Right sided/Left sided	75.0/52.5	0.4601			
Lymphatic invasion	–/+	47.6/76.2	0.5927			
Vessel invasion	–/+	50.0/61.4	0.5210			
LN metastasis	–/+	44.4/61.4	0.5893			
Metastatic site						
Meta. Period	Synchro/Metachro	54.9/100	0.9522			
Tumour number	<5/≥5	60.0/55.6	0.3828			
Tumour size (cm)	<5/≥5	50.0/56.2	0.5804			
H	1.2/3	46.8/63.6	0.7299			
Grade	A.B/C	53.6/58.7	0.4181			
MDN	≤70/>70	64.1/25.0	0.0639	0.2470	0.057-1.082	0.0635
Liver limited disease	–/+	63.3/40.0	0.4723			
Chemo-regimen	FOLFOXIRI/Others	83.1/22.2	0.0002	0.1010	0.024-0.421	0.0016
Molecular agent	anti VEGF/anti EGFR	63.7/30.0	0.0675	0.4593	0.111-1.901	0.2831

*Missing values.

Table III. *Clinicopathological features according to chemo-regimen.*

Factor		FOLFOXIRI (n=18)	Others (n=24)	*p*-Value
Primary site				
Location 1	Colon/Rectum	10/8	11/13	0.7557
Location 2	Right sided/Left sided	5/13	3/21	0.2562
Diff.	tub/poor	14/0*	20/1*	0.9999
Lymphatic invasion	–/+	6/8*	11/8*	0.4905
Vessel invasion	–/+	0/14*	3/16*	0.2443
LN metastasis	–/+	3/15	10/13*	0.0955
Metastatic site				
Meta. Period	Synchro/Metachro	18/0	20/4	0.1223
Tumour number	<5/>5	2/16	3/21	0.9999
Tumour size (cm)	<5/>5	5/13	8/16	0.7482
H	1.2/3	8/10	11/13	0.9999
Grade	A.B/C	4/14	7/17	0.7306
MDN	<70/>70	13/5	11/13	0.1201
Liver limited disease	–/+	7/11	14/10	0.3499
Molecular agent	anti VEGF/anti EGFR	16/2	17/7	0.2578
Conversion	yes/no	13/5	9/13	0.0334

*Missing values.

To date, many clinical trials have reported that hepatic resection contribute to prolonged patient survival and there is surgical cure for initially resectable CRLM; therefore, surgery for CRLM has become the standard treatment (6-10). However, conversion surgery should be considered even for initially unresectable CRLM. Folprech *et al*. have reported a strong correlation between the tumour reduction rate and the resection rate of unresectable CRLM, with or without patient selection bias (22). Therefore, the first choice of initial

Table IV. *Advantages of the FOLFOXIRI regimen in patients with conversion surgery.*

	FOLFOXIRI (n=13)	Others (n=9)	*p*-Value
Tumour shrinkage	42.299±11.023	45.315±11.600	0.7134
Medication period (course)	5.846±1.676	14.778±9.947	0.0253
Medication period (day)	164.385±32.699	316.667±202.991	0.1511
Tumour necrotic rate (%)	84.462±15.098	61.111±23.688	0.0056

Table V. *Clinicopathological features of patients with conversion surgery in the FOLFOXIRI group.*

Factor		Conversion (n=13)	Non-conversion (n=5)	*p*-Value
Primary site				
Location 1	Colon/Rectum	8/5	2/3	0.6078
Location 2	Right sided/Left sided	3/10	2/3	0.5827
Diff.	tub/poor	13/0*	1/0*	0.9999
Lymphatic invasion	–/+	6/7	0/1*	0.9999
Vessel invasion	–/+	0/12*	0/1*	0.9999
LN metastasis	–/+	3/10	0/5	0.5221
Metastatic site				
Meta. Period	Synchro/Metachro	13/0	5/0	0.9999
Tumour number	<5/>5	2/11	0/5	0.9999
Tumour size (cm)	<5/>5	4/9	1/4	0.9999
H	1.2/3	6/7	2/3	0.9999
Grade	A.B/C	4/9	0/5	0.2778
MDN	<70/>70	12/1	1/4	0.0077
Liver limited disease	–/+	3/10	4/1	0.0474
Molecular agent	anti VEGF/anti EGFR	11/2	5/0	0.9999

*Missing values.

chemo-regimen to obtain sufficient tumour shrinkage is the most important issue to achieve conversion surgery.

Among several effective chemo-regimens, FOLFOXIRI has been established as a powerful and effective chemo-regimen for metastatic colorectal cancer, which yielded an overall response rate of 72% and a conversion rate of 25% in a clinical phase II trial (11). Several investigators have attempted to prove the clinical benefit of FOLFOXIRI with or without a molecular agent in randomised and non-randomised trials (13-17). Most recently, two meta-analyses revealed the superiority of FOLFOXIRI compared with other double chemo-regimens in clinical settings. Leal *et al*. have used pooled data from four randomised controlled trials to show a significant benefit for the FOLFOXIRI arm regarding the overall response rate and progression-free survival (18). In addition, Tomasello *et al*. have clinically evaluated the pooled data of 889 unresectable CRLM patients receiving FOLFOXIRI plus an anti-VEGF agent, and reported an overall response rate of 69% and R0 resection rate of 28.1% (19). Of note, they emphasised that patients with LLD may obtain further clinical benefit from FOLFOXIRI plus an anti-VEGF agent with an R0 resection rate of 54.7%. Similarly, in our study, FOLFOXIRI plus a molecular agent contributed to a higher surgical conversion rate, but the rate of tumour shrinkage was similar to that of other double regimens. However, the advantages of FOLFOXIRI are that this regimen induces early tumour shrinkage with massive tumour necrosis after six courses compared with other double chemo-regimens.

To the best of our knowledge, the treatment outcome of FOLFOXIRI in non-conversion cases has not been clarified yet. In our series, these patients had an extremely poor prognosis, and died within 2 years after the diagnosis of

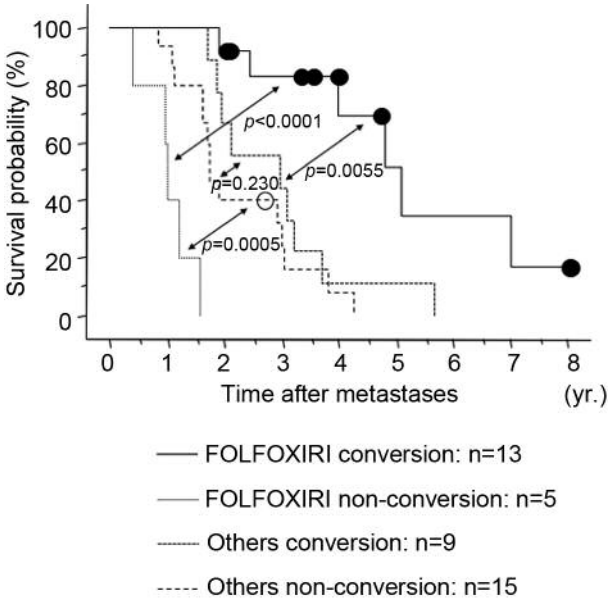

Figure 2. *Overall survival curves of patients with unresectable multiple CRLM according to the induction of conversion surgery, who received FOLFOXIRI or other regimens.*

CRLM. Considering this poor outcome, careful selection criteria should be established for the induction of FOLFOXIRI. A meta-regression analysis by Tomasello *et al*. has suggested that significant variables associated with conversion surgery include the rate of LLD and a higher median number of chemo-cycles (19). In addition, we presented evidence indicating that LLD and MDN under 70

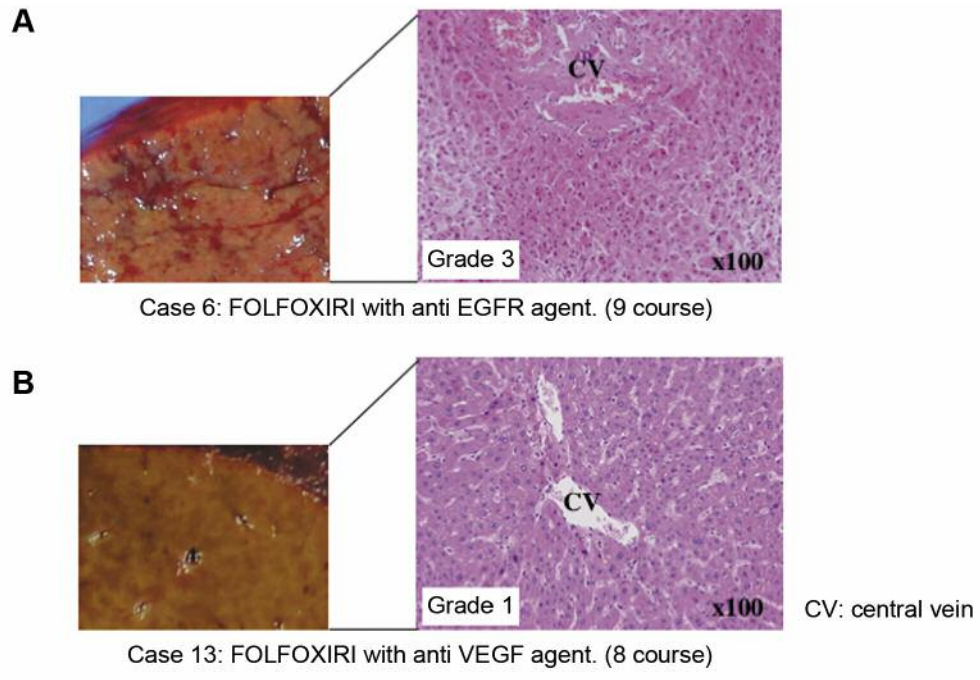

Figure 3. *Representative cases of sinusoidal obstructive syndrome according to molecular agent. A: Surgical specimen of non-tumour tissue after nine courses of FOLFOXIRI with an anti-EGFR agent. B: Surgical specimen of non-tumour tissue of eight courses of FOLFOXIRI with an anti-VEGF agent.*

Table VI. *Summary of FOLFOXIRI-related liver injury.*

Case	*Kras* status	Molecular target agent	Course	Steatohepatitis*	SOS status
1	---	Anti VEGF	7	1	Grade 0
2	---	Anti VEGF	6	0	Grade 0
3	---	Anti VEGF	5	1	Grade 1
4	---	Anti VEGF	2	0	Grade 1
5	Wild	Anti EGFR	6	1	Grade 1
6	Wild	Anti EGFR	9	1	Grade 3
7	Wild	Anti VEGF	5	0	Grade 1
8	Mutant (13)	Anti VEGF	6	1	Grade 1
9	Mutant (12)	Anti VEGF	6	2	Grade 1
10	Mutant (12)	Anti VEGF	5	1	Grade 0
11	Mutant (13)	Anti VEGF	6	0	Grade 0
12	Wild	Anti VEGF	5	1	Grade 1
13	Wild	Anti VEGF	8	0	Grade 1

*Kleiner's score.

of CRLM may be oncological selection criteria for the induction of FOLFOXIRI, although the number of patients evaluated was very small. Therefore, FOLFOXIRI, a powerful chemo-regimen, should be introduced in these selected patients.

Regarding the optimal preoperative medication period of FOLFOXIRI, one previous meta-analysis has suggested that approximately 12 chemo-cycles enhanced conversion probability. However, the potential disadvantage of associated liver injury should be considered during FOLFOXIRI treatment, considering that oxaliplatin induced sinusoidal obstructive syndrome (SOS) and irinotecan induced steatohepatitis (23, 24). Regarding the correlation between the number of chemo-cycles of oxaliplatin and SOS onset, Kishi *et al*. have shown that SOS was significantly increased by a long duration of treatment of over nine cycles, which did not enhance the improvement of pathologic response rates (25). Moreover, Nakano *et al*. have reported that at least six cycles

of oxaliplatin administration significantly correlated with SOS onset (26). In our conversion cases with FOLFOXIRI, severe steatohepatitis was not observed, although cases receiving nine courses with an anti-EGFR agent developed grade 3 SOS. However, there was no severe grade SOS in short-duration treatment cases, and combination with an anti-VEGF agent did not induce severe sinusoidal injury even after eight courses. Taken together, these data suggest that the optimal number of chemo-cycles with FOLFOXIRI may be between six and nine, and that the ideal molecular agent for combination with FOLFOXIRI is an anti-VEGF agent, which might inhibit SOS (27-30).

The limitations of our study were its retrospective design, the presence of patient selection bias, and the small number of patients. We did not consider the molecular profile of patients, including their RAS and BRAF status. However, to obtain sufficient tumour cytoreduction (shrinkage), this triple chemo-regimen with or without a molecular agent has been recommended regardless of the molecular profile (8, 9). We found that conversion surgery with FOLFOXIRI provided prognostic benefit compared to other double chemo-regimens in our experience, although definitive selection criteria should be established. In conclusion, FOLFOXIRI plus a molecular agent provided a higher probability of conversion surgery with a prognostic benefit in selected CRLM patients with LLD and MDN under 70.

Conflicts of Interest

The Authors disclose no conflicts of interest regarding this study.

Authors' Contributions

Yuji Morine designed the study, and wrote the initial draft of the manuscript. Mitsuo Shmada contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All Authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1 Fong Y, Kemeny N, Paty P, Blumgart M and Cohen AM: Treatment of colorectal cancer: hepatic metastasis. Semin Surg Oncol *12*: 219-252, 1996. PMID: 8829283. DOI: 10.1002/(SICI)1098-2388(199607/08)12:4<219::AID-SSU3>3.0.CO;2-8

2 Ruers T and Bleichrodt RP: Treatment of liver metastases, an update on the possibilities and results. Eur J Cancer *38*: 1023-1033, 2002. PMID: 11978527.

3 Steele GJ and Ravikumar TS: Resection of hepatic metastases from colorectal carcinoma: biologic perspectives. Ann Surg *210*: 127-138, 1989. PMID: 30231355. DOI: 10.1200/EDBK_200941

4 O'Reilly DA and Poston GJ: Colorectal liver metastases: current and future perspectives. Future Oncol 2: 525-531, 2006. PMID: 16922619. DOI: 10.2217/14796694.2.4.525

5 Haruki K, Shiba H, Fujiwara Y, Furukawa K, Wakiyama S, Ogawa M, Ogawa M, Ishida Y, Misawa T and Yanaga K: Perioperative change in peripheral blood monocyte count may predict prognosis in patients with colorectal liver metastasis after hepatic resection. J Surg Oncol *106*: 31-35, 2012. PMID: 22231029. DOI: 10.1002/jso.23033

6 Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, Hamaguchi T, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kawano H, Kinugasa Y, Kokudo N, Murofushi K, Nakajima T, Oka S, Sakai Y, Tsuji A, Uehara K, Ueno H, Yamazaki K, Yoshida M, Yoshino T, Boku N, Fujimori T, Itabashi M, Koinuma N, Morita T, Nishimura G, Sakata Y, Shimada Y, Takahashi K, Tanaka S, Tsuruta O, Yamaguchi T, Yamaguchi N, Tanaka T, Kotake K and Sugihara K; Japanese Society for Cancer of the Colon and Rectum: Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol *23*: 1-34, 2018. PMID: 28349281. DOI: 10.1007/s10147-017-1101-6

7 Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A and Arnold D: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol *27*: 1386-1422, 2016. PMID: 27380959. DOI: 10.1093/annonc/ mdw235

8 Yoshino T, Arnold D, Taniguchi H, Pentheroudakis G, Yamazaki K, Xu RH, Kim TW, Ismail F, Tan IB, Yeh KH, Grothey A, Zhang S, Ahn JB, Mastura MY, Chong D, Chen LT, Kopetz S, Eguchi-Nakajima T, Ebi H, Ohtsu A, Cervantes A, Muro K, Tabernero J, Minami H, Ciardiello F and Douillard JY: Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO–ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol *29*: 44-70, 2018. PMID: 29155929. DOI: 10.1093/ annonc/mdx738

9 Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghémard O, Levi F and Bismuth H: Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg *240*: 644-657, 2004. PMID: 15383792. DOI: 10.1097/01.sla.0000141198.92114.f6

10 Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN and Mahvi D: Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol *13*: 1271-1280, 2006. PMID: 16955381. DOI: 10.1245/s10434-006-9045-5

11 Masi, G. Allegrini, S. Cupini, Marcucci L, Cerri E, Brunetti I, Fontana E, Ricci S, Andreuccetti M and Falcone A: First-line treatment of metastatic colorectal cancer with irinotecan, oxaliplatin and 5-fluorouracil/leucovorin (FOLFOXIRI): results of a phase II study with a simplified biweekly schedule. Ann Oncol *15*: 1766-1772, 2004. PMID: 15550581. DOI: 10.1093/ annonc/mdh470

12 Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E,

Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G and Gruppo Oncologico Nord Ovest: Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The Gruppo Oncologico Nord Ovest. J Clin Oncol *25*: 1670-1676, 2007. PMID: 17470860. DOI: 10.1200/JCO.2006.09.0928

13 Masi G, Loupakis F, Salvatore L, Fornaro L, Cremolini C, Cupini S, Ciarlo A, Del Monte F, Cortesi E, Amoroso D, Granetto C, Fontanini G, Sensi E, Lupi C, Andreuccetti M and Falcone A: Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial. Lancet Oncol *11*: 845-852, 2010. PMID: 20702138. DOI: 10.1016/S1470-2045 (10)70175-3

14 Saridaki Z, Androulakis N, Vardakis N, Vamvakas L, Kabouraki E, Kalbakis K, Hatzidaki D, Voutsina A, Mavroudis D, Georgoulias V and Souglakos J: A triplet combination with irinotecan (CPT-11), oxaliplatin (LOHP), continuous infusion 5-fluorouracil and leucovorin (FOLFOXIRI) plus cetuximab as first-line treatment in KRAS wt, metastatic colorectal cancer: A pilot phase II trial. Br J Cancer *107*: 1932-1937, 2012. PMID: 23169296. DOI: 10.1038/bjc.2012.509

15 Folprecht G, Hamann S, Schütte K, Trarbach T, Stoehlmacher-Williams J and Ehninger G: Dose escalating study of cetuximab and 5-FU/folinic acid (FA)/oxaliplatin/irinotecan (FOLFOXIRI) in first line therapy of patients with metastatic colorectal cancer. BMC Cancer *14*: 521, 2014. PMID: 25038824. DOI: 10.1186/1471-2407-14-521

16 Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, Cortesi E, Tomasello G, Ronzoni M, Spadi R, Zaniboni A, Tonini G, Buonadonna A, Amoroso D, Chiara S, Carlomagno C, Boni C, Allegrini G, Boni L and Falcone A: Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Eng J Med *371*: 1609-1618, 2014. PMID: 25337750. DOI: 10.1056/NEJMoa1403108

17 Gruenberger T, Bridgewater J, Chau I, García Alfonso P, Rivoire M, Mudan S, Lasserre S, Hermann F, Waterkamp D and Adam R: Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomized phase II trial. Ann Oncol *26*: 702-708, 2015. PMID: 25538173. DOI: 10.1093/ annonc/mdu580

18 Leal F, Ferreira FP and Sasse AD: FOLFOXIRI regimen for metastatic colorectal cancer: a systematic review and meta-analysis. Clin Colorectal Cancer *16*: 405-409, 2017. PMID: 28433602. DOI: 10.1016/j.clcc.2017.03.012

19 Tomasello G, Petrelli F, Ghidini M, Russo A, Passalacqua R and Barni S: FOLFOXIRI plus bevacizumab as conversion therapy for patients with initially unresectable metastatic colorectal cancer: A systematic review and pooled analysis. JAMA Oncol *3*: e170278, 2017. PMID: 28542671. DOI: 10.1001/jamaoncol. 2017.0278

20 Yoshimoto T, Morine Y, Imura S, Ikemoto T, Iwahashi S, Saito YU, Yamada S, Ishikawa D, Teraoku H, Yoshikawa M, Higashijima J, Takasu C and Shimada M: Maximum diameter and number of tumors as a new prognostic indicator of colorectal liver metastases. In Vivo *31*: 419-423, 2017. PMID: 28438872. DOI: 10.21873/invivo.11076

21 Japanese Society for Cancer of the Colon and Rectum Japanese classification of colorectal carcinoma. The 9th Edition. Kanehara & CO., LTD., Tokyo, 2018.

22 Folprecht G, Grothey A, Alberts S, Raab HR and Kohne CH: Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol *16*: 1311-1319, 2005. PMID: 15870084. DOI: 10.1093/annonc/mdi246

23 Schwarz RE, Berlin JD, Lenz HJ, Nordlinger B, Rubbia-Brandt L and Choti MA: Systemic cytotoxic and biological therapies of colorectal liver metastases: expert consensus statement. HBP (Oxford) *15*: 106-115, 2013. PMID: 23297721. DOI: 10.1111/j.1477-2574.2012.00558.x

24 Viganò L, Capussotti L, De Rosa G, De Saussure WO, Mentha G and Rubbia-Brandt L: Liver resection for colorectal metastases after chemotherapy: impact of chemotherapy-related liver injuries, pathological tumor response, and micrometastases on long-term survival. Ann Surg *258*: 731-740, 2013. PMID: 24045448. DOI: 10.1097/SLA.0b013e3182a6183e

25 Kishi Y, Zorzi D, Contreras CM, Maru DM, Kopetz S, Ribero D, Motta M, Ravarino N, Risio M, Curley SA, Abdalla EK, Capussotti L and Vauthey JN: Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol *17*: 2870-2876, 2010. PMID: 20567921. DOI: 10.1245/s10434-010-1166-1

26 Nakano H, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P, Bachellier P and Jaeck D: Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg *247*: 118-124, 2008. PMID: 18156931. DOI: 10.1097/SLA.0b013e31815774de

27 Ribero D, Wang H, Donadon M, Zorzi D, Thomas MB, Eng C, Chang DZ, Curley SA, Abdalla EK, Ellis LM and Vauthey JN: Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. Cancer *110*: 2761-2767, 2007. PMID: 17960603. DOI: 10.1002/cncr.23099

28 Klinger M, Eipeldauer S, Hacker S, Herberger B, Tamandl D, Dorfmeister M, Koelblinger C, Gruenberger B and Gruenberger T: Bevacizumab protects against sinusoidal obstruction syndrome and does not increase response rate in neoadjuvant XELOX/FOLFOX therapy of colorectal cancer liver metastases. Eur J Surg Oncol *35*: 515-520, 2009. PMID: 19200687. DOI: 10.1016/j.ejso.2008.12.013

29 Rubbia-Brandt L, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, Brezault C, Soubrane O, Abdalla EK, Vauthey JN, Mentha G and Terris B: Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology *56*: 430-439, 2010. PMID: 20459550. DOI: 10.1111/j.1365-2559.2010.03511.x

30 van der Pool AE, Marsman HA, Verheij J, Ten Kate FJ, Eggermont AM, Ijzermans JN and Verhoef C: Effect of bevacizumab added preoperatively to oxaliplatin on liver injury and complications after resection of colorectal liver metastases. J Surg Oncol *106*: 892-897, 2012. PMID: 22552819. DOI: 10.1002/jso.23142

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