

1 Evaluation of resectability after neoadjuvant chemotherapy for primary non-resectable
2 colorectal liver metastases: a multicenter study

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31 bevacizumab; conversion; neoadjuvant chemotherapy

32

1 **ABSTRACT**

2 **Background/Aim:** The Kyushu Study Group of Clinical Cancer (KSCC) previously
3 reported the safety and efficacy of neoadjuvant chemotherapy with mFOLFOX6 +
4 bevacizumab for H2/H3 liver metastases of colorectal cancer. The aim of the current study
5 was to evaluate the resectability of these metastases before and after chemotherapy as
6 determined by independent liver surgeons. **Methods:** Between May 2008 and April 2010,
7 40 patients were registered in a multicenter phase 2 trial of neoadjuvant chemotherapy
8 (KSCC 0802). In Study 1, 5 independent liver surgeons from 5 different KSCC centers
9 evaluated the resectability of liver metastases of colorectal cancer based on imaging
10 studies performed before and after chemotherapy. Each surgeon was blinded to the other
11 surgeons' evaluations. In addition, no information about the patients' characteristics was
12 provided. In Study 2, 3 surgeons evaluated the resectability of these lesions based on
13 imaging studies with discussion with each other, with the surgeons being provided with
14 information on the patients' characteristics. **Results:** In Study 1, 13 patients (36.1%)
15 were evaluated to be resectable at baseline, whereas 17 patients (47.2%) were evaluated
16 to be resectable after chemotherapy. In Study 2, 4 patients (11.1%) were evaluated to be
17 resectable at baseline, compared to 23 patients (63.9%) after chemotherapy.
18 **Conclusion:** Neoadjuvant chemotherapy with mFOLFOX6 + bevacizumab was
19 confirmed to increase the resectability of non-resectable liver metastases of colorectal
20 cancer according to the independent assessments of surgeons.

21

1 INTRODUCTION

2 Tumor resection is the most effective method for achieving long-term survival in
3 patients with advanced liver-limited colorectal metastases (CRLMs). When complete
4 resection was performed successfully for patients with liver-limited CRLMs, a 5-year
5 survival rate of 40–50% could be achieved¹⁻⁴. Since the introduction of effective
6 chemotherapy, many primarily unresectable CRLMs can be considered resectable after
7 chemotherapy^{5,6}. However, “resectability” always depends on the judgment of individual
8 surgeons and/or institutional policies. An objective point of view is essential to treat the
9 patients appropriately.

10 The Kyushu Study Group of Clinical Cancer (KSCC) previously reported the safety
11 and efficacy of neoadjuvant chemotherapy with mFOLFOX6 + bevacizumab for
12 advanced liver metastases of colorectal cancer⁷. In this study, “advanced liver metastasis”
13 was defined by the H-factor categories of H2 and H3 according to the guidelines of the
14 Japanese Society for Cancer of the Colon and Rectum^{8,9}. Generally, H2/H3 lesions are
15 considered non-resectable or marginal cases for curative tumor resection. However, it
16 may be important to clarify the process of how each expert liver surgeon evaluates the
17 resectability for such cases based on imaging studies. The aim of the current study was to
18 evaluate the resectability of these metastases before and after chemotherapy according to
19 the judgment of independent liver surgeons via imaging studies.

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21

1 MATERIALS AND METHODS

2 Between May 2008 and April 2010, 40 patients were registered in a multicenter
3 randomized phase 2 trial of neoadjuvant chemotherapy with mFOLFOX6 + bevacizumab
4 for H2/H3 liver metastases of colorectal cancer (KSCC 0802)⁷. The patient and tumor
5 characteristics are listed in Table 1. Of these 40 cases, imaging results after chemotherapy
6 were not evaluable in 4 cases due to the poor quality of the imaging studies, and thus, 72
7 imaging results (scans for 36 patients obtained both before and after chemotherapy) of
8 contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI)
9 were included in this study. For these patients, 2 different studies were planned to evaluate
10 the resectability of liver-limited H2/H3 CRLMs.

11 *Study 1:*

12 Five independent liver surgeons from 5 different KSCC centers evaluated the
13 resectability of the patients based on imaging studies (contrast-enhanced CT or MRI)
14 before and after chemotherapy, referring to the CELIM study by Folprecht et al.¹⁰. Five
15 surgeons were partitioned off and forbidden from talking to each other while voting.
16 Patients were graded as follows: 1, resectable; 2, borderline resectable; 3, chemotherapy
17 preferred (resection is difficult, but the lesion may become resectable if chemotherapy is
18 administered); 4, non-resectable; and 5, unevaluable. All 5 liver surgeons worked at
19 centers that were registered as grade A by the Japanese Society of Hepato-Biliary-
20 Pancreatic Surgery, and each surgeon performed more than 50 hepatectomies per year.

21 The actual evaluation was performed as follows. The 72 imaging scans were presented
22 on a screen in random order, and each scan was assessed by all reviewers at the same time.
23 Only minimal information, such as the tumor location, was provided when the scans were
24 presented, and the timing of imaging (baseline vs. after chemotherapy), scans of other

1 sites, patient information, and treatment information were not provided. As mentioned
2 before, each reviewer was blinded to the other reviewers' voting, and they were not
3 permitted to discuss their decisions with each other. Patients were considered "resectable"
4 if 3 or more reviewers provided a grade of 1 or 2. Resectability was evaluated as the
5 incidence of "resectable" grades.

6 **Study 2:**

7 Three surgeons worked at three different centers evaluated the resectability of patients based
8 on imaging studies with discussion with each other, and patient characteristics were fully
9 described. The grading of resectability followed that described in Study 1.

10 The actual evaluation was performed as follows. The 72 scans (baseline and after
11 chemotherapy) were displayed in order based on the enrollment number on a computer
12 screen to all reviewers at the same time. All information requested by the reviewers, such
13 as the timing of imaging and treatment information, was provided when the scans were
14 presented. The reviewers evaluated the resectability of the lesions based on imaging
15 studies with discussion with each other, and the reviewers were provided the patient
16 characteristics.

17

18 **Statistics**

19 The rate of resectability before and after chemotherapy were statistically tested with
20 McNemar's test. The agreement of the ratings among reviewers was evaluated by Kappa
21 statistics. All statistical analyses were performed with the Stata version 11 software
22 program (Stata, College Station, TX, USA). Two sided *P*-values of 0.05 or less were
23 considered statistically significant.

24

1 RESULTS

2 *Study 1*

3 *The rate of resectability*

4 Before chemotherapy, 13 patients (36.1%) were evaluated to be “resectable,” whereas
5 after chemotherapy, 17 patients (47.2%) were evaluated to be “resectable”. Although
6 there was no significant difference ($p=0.21$), the rate of resectability increased after
7 chemotherapy. Of the above-mentioned 13 patients determined to have “resectable”
8 lesions before chemotherapy, 3 patients were evaluated as “unresectable” after
9 chemotherapy, of whom 1 actually underwent a hepatectomy. In total, the actual number
10 of resections performed after chemotherapy was 15 (41.7%). Of 17 patients evaluated to
11 be “resectable” after chemotherapy, 7 patients (41.1%) were evaluated to be “unresectable”
12 before chemotherapy, and 5 of these 7 patients actually underwent a hepatectomy. Finally,
13 hepatectomy was performed for 11 (64.7%) of 17 patients evaluated to be “resectable”
14 after chemotherapy. On the contrary, of 19 patients evaluated to be “unresectable” after
15 chemotherapy, hepatectomy was performed for 4 patients (21.1%) (Figure 1). The actual
16 distribution of hepatectomies according to the patients’ responsiveness to chemotherapy
17 is summarized in Table 2.

18

19 *The voting patterns of the surgeons*

20 There was considerable inter-individual variation in the decision-making process, with
21 25–39% of lesions considered “resectable” and 2–15% of lesions considered
22 “unresectable” by the different surgeons (Figure 2). Kappa statistics for inter-surgeons
23 agreement was 0.372. In addition, the agreement among the surgeons displayed minor
24 variation, as the rate of agreement among the surgeons ranged from 54.2 to 68.1%,

1 whereas the rate of disagreement ranged from 16.7 to 29.2% (Figure 3).

2 **Study 2:**

3 The resectability of the lesions was determined again by 3 liver surgeons who were
4 provided complete patient data in an effort to conduct a central judgment under conditions
5 that resemble the local decision-making process. Four lesions (11.1%) were judged
6 “resectable” before chemotherapy, compared to 23 lesions (63.9%) after chemotherapy
7 (Table 3).

8

9 **DISCUSSION**

10 Although most physicians recognize that tumor resection is the most reliable method
11 for achieving long-term survival in patients with CRLMs, patients might not always
12 receive appropriate treatment because the decision concerning resectability depends on
13 the each individual surgeon’s judgment. Several reports described extremely aggressive
14 approaches for achieving R0 resection for advanced CRLM, including extracorporeal
15 liver resection or hepatic vein reconstruction^{8, 11}. However, these types of surgery are not
16 available in all centers, and thus, it is important to evaluate the assessment of resectability
17 from a multicenter perspective. According to this study, although there were considerable
18 inter-individual variations in the decision-making process, the proportion of tumors
19 considered resectable by liver surgeons from 5 major centers exceeded the actual rate of
20 resection. Additionally, although H2/H3 lesions are generally regarded to be unresectable
21 before chemotherapy, 36.1% of the lesions were deemed resectable. Accordingly, when
22 physicians find liver-limited CRLMs, they should consult skilled liver surgeons
23 concerning the resectability of the lesions prior to decision-making regarding treatment.

24 In principle, the evaluation procedure in this study referenced the CELIM study from
25 Germany and Austria, which demonstrated the efficacy of neoadjuvant chemotherapy for

1 unresectable CRLM using cetuximab¹⁰. Although the proportion of “resectable”
2 metastases at baseline was not different between the CELIM study (32%) and this study
3 (36%), the proportion of “resectable” metastases after chemotherapy was higher in the
4 CELIM study (60%) than in this study (47%). The reason for this discrepancy is not clear,
5 but it might be related to the method for determination of resectability. In the CELIM
6 study, resectability was categorized as “resectable,” “chemotherapy preferred,” or
7 “unresectable,” whereas in this study, 5 different categories were used. The variation in
8 agreement among the different reviewers appeared to be larger in this study than in the
9 CELIM study, possibly because of the same reason. In addition, the difference in tumor
10 control between cetuximab and bevacizumab might affect the rate of resectability. The
11 rate of radical resection (27.8%) in this study is comparable to that in other studies using
12 bevacizumab^{12, 13}; however, the rate of resection after chemotherapy did not significantly
13 increase in this study, contrary to the findings in the CELIM study. Accordingly, the
14 evaluation procedure of resectability in the CELIM study might not be suitable when
15 bevacizumab is used, as observed in this study.

16 Generally, the resectability of liver tumors is determined on the basis of both the tumor
17 location/number and liver function. In this study, we evaluated resectability based on
18 imaging studies only without considering liver function. Unlike hepatocellular carcinoma,
19 which generally develops in diseased liver states such as hepatitis B or C, most CRLMs
20 occur in normal livers, but after chemotherapy, drug-induced liver dysfunction is of great
21 concern concerning the utilization of aggressive hepatectomy^{14, 15}. Accordingly, in
22 clinical settings, we must consider liver function to avoid liver failure after hepatectomy,
23 especially after chemotherapy. However, the aim of this study was to provide an absolute
24 objective evaluation based on imaging studies only to avoid subjective evaluation based

1 on other clinical factors. Even with experts from high-volume centers, there were
2 considerable discrepancies among the surgeons, but we believe the result of this study is
3 a good reference for physicians who participate in the treatment of colorectal cancer.

4 Because of the discrepancy in the rate of resectability between the CELIM study and
5 this study, we performed Study 2, in which the surgeons fully discussed the cases with
6 each other and they were sufficiently apprised of the characteristics of the patients.
7 Interestingly, the proportion of lesions deemed “resectable” after chemotherapy was
8 significantly higher than that in Study 1. The result illustrated that even though the
9 findings of imaging studies were the same, physicians are more likely to judge lesions to
10 be “resectable” when they know the scans were obtained after chemotherapy, possibly
11 because they generally expect that chemotherapy will be administered for marginal cases.
12 Also, the results of study 2 indicate the importance of a thorough discussion between
13 multiple liver surgeons to determine the appropriate treatment for CRLMs.

14 Compared to other studies such as the CELIM study, it might be difficult to determine
15 the resectability of metastases because the morphologic response after bevacizumab
16 treatment is different from that associated with other agents such as cetuximab or
17 panitumumab. The morphologic response is generally recognized as a significant factor
18 that affects patient survival¹⁶, and thus, it is important to elucidate the difference in
19 morphologic response between these agents.

20 In conclusion, this is the first report to provide an objective evaluation of resectability
21 for CRLMs in a multicenter study using bevacizumab based only on imaging studies.
22 This study might provide a good reference for physicians to select appropriate treatments
23 for CRLMs.

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1 **FIGURE LEGENDS**

2 Figure 1

3 The judgment of resectability before and after chemotherapy in Study 1. The X-axis
4 indicates the individual patients, while the Y-axis represents the reviewers' votes. The
5 dashed line indicates the border between "resectable" and "unresectable."

6

7 Figure 2

8 The voting patterns of the reviewers in study 1. The numbers in the graph indicated the
9 actual numbers for each category.

10

11 Figure 3

12 The agreement in voting among the reviewers. If a reviewer issued a grade of 1
13 (resectable) or 2 (borderline resectable) and the others issued a grade of 3 (chemotherapy
14 preferred) or 4 (unresectable), this was considered "disagreement."

15

Figure 1

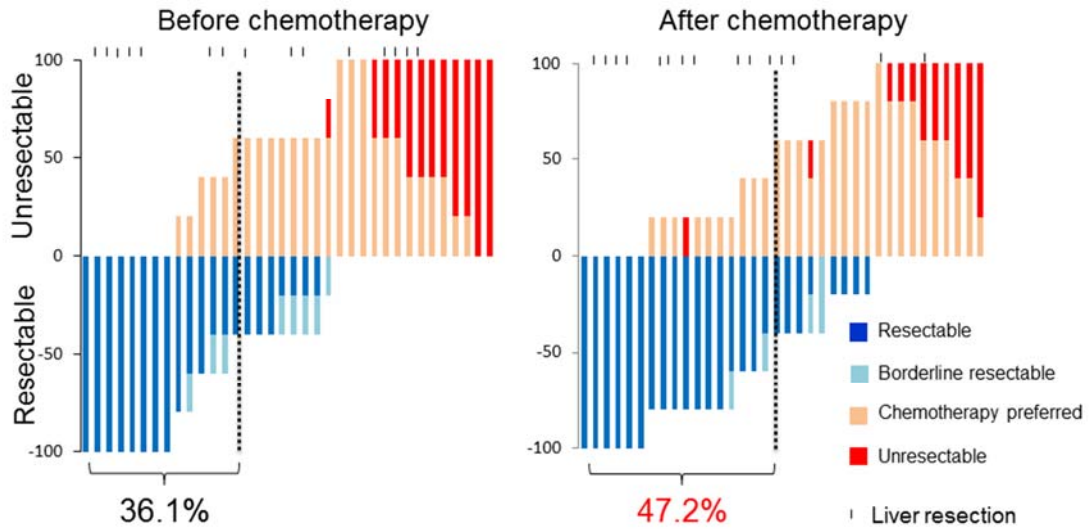


Figure 2

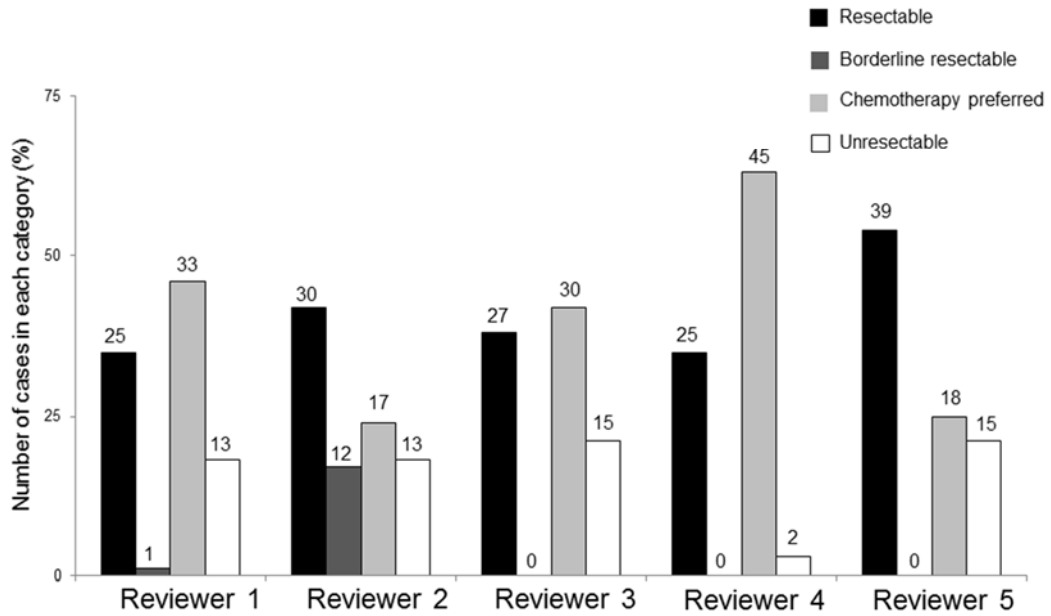


Figure 3

	Reviewer 1	Reviewer 2	Reviewer 3	Reviewer 4	Reviewer 5
Reviewer 1		41 (56.9%)	42 (58.3%)	49 (68.1%)	41 (56.9%)
Reviewer 2	16 (22.2%)		42 (58.3%)	40 (55.6%)	41 (56.9%)
Reviewer 3	19 (26.4%)	19 (26.4%)		47 (65.3%)	46 (63.9%)
Reviewer 4	13 (18.1%)	19 (26.4%)	12 (16.7%)		39 (54.2%)
Reviewer 5	21 (29.2%)	15 (20.8%)	20 (27.8%)	20 (27.8%)	

Agreement
 Disagreement

Table 1 The patient characteristics of KSCC0802

	n	%
Age, median (range)	63 (37-74)	
Sex		
male	29	72.5
female	11	27.5
Tumor size, median (range)	52.5 (10-135)	
Tumor number, median	5 (1-20)	
H-factor category		
H2	30	75
H3	10	25
Bilateral / unilateral		
bilateral	28	70
unilateral	12	30
Synchronous /		
synchronous	33	82.5
metachronous	7	17.5

Table 2. The result of evaluation from study 1 and concordance of actual liver resection cases

Evaluation			Liver resection		
Before chemotherapy		After chemotherapy	n	n	%
resectable	→	resectable	10	6	60
unresectable	→	resectable	7	5	71.4
resectable	→	unresectable	3	1	33.3
unresectable	→	unresectable	16	3	18.8

Table 3. Resectability before and after chemotherapy determined by Study 2

	Before chemotherapy		After chemotherapy	
	n	%	n	%
Resectable*1	4	11.1	23	63.9
Unresectable*2	32	88.9	13	36.1

*1Resectable include the grade 1 (resectable) and 2 (borderline resectable).

*2Unresectable include the grade 3 (chemotherapy preferred) and 4 (non-resectable).