<table>
<thead>
<tr>
<th>Title</th>
<th>Evaluation of resectability after neoadjuvant chemotherapy for primary non-resectable colorectal liver metastases: A multicenter study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Takatsuki, Mitsuhisa; Tokunaga, Shoji; Uchida, Shinji; Sakoda, Masahiko; Shirabe, Ken; Beppu, Toru; Emi, Yasunori; Oki, Eiji; Ueno, Shinichi; Eguchi, Susumu; Akagi, Yoshito; Ogata, Yutaka; Baba, Hideo; Natsugoe, Shoji; Maehara, Yoshihiko</td>
</tr>
<tr>
<td>Citation</td>
<td>European Journal of Surgical Oncology, 42(2), pp.184-189; 2016</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2016-02</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/10069/36968">http://hdl.handle.net/10069/36968</a></td>
</tr>
<tr>
<td>Right</td>
<td>© 2015. This manuscript version is made available under the CC-BY-NC-ND 4.0 license <a href="http://creativecommons.org/licenses/by-nc-nd/4.0/">http://creativecommons.org/licenses/by-nc-nd/4.0/</a></td>
</tr>
</tbody>
</table>
Evaluation of resectability after neoadjuvant chemotherapy for primary non-resectable colorectal liver metastases: a multicenter study

Mitsuhisa Takatsuki*1), Shoji Tokunaga2), Shinji Uchida3), Masahiko Sakoda4), Ken Shirabe5), Toru Beppu6), Yasunori Emi7), Eiji Ok8), Shinichi Ueno9), Susumu Eguchi1), Yoshito Akagi9), Yutaka Ogata3), Hideo Baba10), Shoji Natsugoe4), Yoshihiko Maehara5), Kyushu Study Group of Clinical Cancer (KSCC)

1)Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 2)Medical Information Center, Kyushu University Hospital, 3) Department of Surgery, Kurume University Medical Center, 4) Department of Digestive Surgery, Breast and Thyroid Surgery, Kagoshima University Graduate School of Medical and Dental Sciences, 5) Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 6)Department of Multidisciplinary Treatment for Gastroenterological Cancer, Kumamoto University Hospital, 7) Department of Surgery, Saiseikai Fukuoka General Hospital, 8) Clinical Oncology, Kagoshima University Graduate School of Medical and Dental Sciences, 9) Department of Surgery, Kurume University School of Medicine, 10) Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University

*Corresponding author:
Telephone:81-95-819-7316
Fax: 81-95-819-7319
E-mail:takatsuki@nagasaki-mc.com
Short title: Evaluation of liver metastasis by liver surgeon
Key words: liver metastasis; colorectal cancer; liver resection; mFOLFOX6; bevacizumab; conversion; neoadjuvant chemotherapy
ABSTRACT

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

Tumor resection is the most effective method for achieving long-term survival in patients with advanced liver-limited colorectal metastases (CRLMs). When complete resection was performed successfully for patients with liver-limited CRLMs, a 5-year survival rate of 40–50% could be achieved\textsuperscript{1-4}. Since the introduction of effective chemotherapy, many primarily unresectable CRLMs can be considered resectable after chemotherapy\textsuperscript{5,6}. However, “resectability” always depends on the judgment of individual surgeons and/or institutional policies. An objective point of view is essential to treat the patients appropriately.

The Kyushu Study Group of Clinical Cancer (KSCC) previously reported the safety and efficacy of neoadjuvant chemotherapy with mFOLFOX6 + bevacizumab for advanced liver metastases of colorectal cancer\textsuperscript{7}. In this study, “advanced liver metastasis” was defined by the H-factor categories of H2 and H3 according to the guidelines of the Japanese Society for Cancer of the Colon and Rectum\textsuperscript{8,9}. Generally, H2/H3 lesions are considered non-resectable or marginal cases for curative tumor resection. However, it may be important to clarify the process of how each expert liver surgeon evaluates the resectability for such cases based on imaging studies. The aim of the current study was to evaluate the resectability of these metastases before and after chemotherapy according to the judgment of independent liver surgeons via imaging studies.
MATERIALS AND METHODS

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

Study 1:

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

The actual evaluation was performed as follows. The 72 imaging scans were presented on a screen in random order, and each scan was assessed by all reviewers at the same time. Only minimal information, such as the tumor location, was provided when the scans were presented, and the timing of imaging (baseline vs. after chemotherapy), scans of other
sites, patient information, and treatment information were not provided. As mentioned before, each reviewer was blinded to the other reviewers’ voting, and they were not permitted to discuss their decisions with each other. Patients were considered “resectable” if 3 or more reviewers provided a grade of 1 or 2. Resectability was evaluated as the incidence of “resectable” grades.

**Study 2:**

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

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

**Statistics**

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

Study 1

The rate of resectability

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

The voting patterns of the surgeons

There was considerable inter-individual variation in the decision-making process, with 25–39% of lesions considered “resectable” and 2–15% of lesions considered “unresectable” by the different surgeons (Figure 2). Kappa statistics for inter-surgeons agreement was 0.372. In addition, the agreement among the surgeons displayed minor variation, as the rate of agreement among the surgeons ranged from 54.2 to 68.1%,
whereas the rate of disagreement ranged from 16.7 to 29.2% (Figure 3).

**Study 2:**

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

**DISCUSSION**

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

In principle, the evaluation procedure in this study referenced the CELIM study from Germany and Austria, which demonstrated the efficacy of neoadjuvant chemotherapy for
unresectable CRLM using cetuximab. Although the proportion of “resectable”
metastases at baseline was not different between the CELIM study (32%) and this study
(36%), the proportion of “resectable” metastases after chemotherapy was higher in the
CELIM study (60%) than in this study (47%). The reason for this discrepancy is not clear,
but it might be related to the method for determination of resectability. In the CELIM
study, resectability was categorized as “resectable,” “chemotherapy preferred,” or
“unresectable,” whereas in this study, 5 different categories were used. The variation in
agreement among the different reviewers appeared to be larger in this study than in the
CELIM study, possibly because of the same reason. In addition, the difference in tumor
control between cetuximab and bevacizumab might affect the rate of resectability. The
rate of radical resection (27.8%) in this study is comparable to that in other studies using
bevacizumab; however, the rate of resection after chemotherapy did not significantly
increase in this study, contrary to the findings in the CELIM study. Accordingly, the
evaluation procedure of resectability in the CELIM study might not be suitable when
bevacizumab is used, as observed in this study.

Generally, the resectability of liver tumors is determined on the basis of both the tumor
location/number and liver function. In this study, we evaluated resectability based on
imaging studies only without considering liver function. Unlike hepatocellular carcinoma,
which generally develops in diseased liver states such as hepatitis B or C, most CRLMs
occur in normal livers, but after chemotherapy, drug-induced liver dysfunction is of great
concern concerning the utilization of aggressive hepatectomy. Accordingly, in
clinical settings, we must consider liver function to avoid liver failure after hepatectomy,
especially after chemotherapy. However, the aim of this study was to provide an absolute
objective evaluation based on imaging studies only to avoid subjective evaluation based
on other clinical factors. Even with experts from high-volume centers, there were
considerable discrepancies among the surgeons, but we believe the result of this study is
a good reference for physicians who participate in the treatment of colorectal cancer.

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

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

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


7. Beppu T, Emi Y, Tokunaga S, Oki E, Shirabe K, Ueno S et al. Liver resectability of advanced liver-limited colorectal liver metastases following mFOLFOX6 with


FIGURE LEGENDS

Figure 1
The judgment of resectability before and after chemotherapy in Study 1. The X-axis indicates the individual patients, while the Y-axis represents the reviewers’ votes. The dashed line indicates the border between “resectable” and “unresectable.”

Figure 2
The voting patterns of the reviewers in study 1. The numbers in the graph indicated the actual numbers for each category.

Figure 3
The agreement in voting among the reviewers. If a reviewer issued a grade of 1 (resectable) or 2 (borderline resectable) and the others issued a grade of 3 (chemotherapy preferred) or 4 (unresectable), this was considered “disagreement.”
<table>
<thead>
<tr>
<th></th>
<th>Reviewer 1</th>
<th>Reviewer 2</th>
<th>Reviewer 3</th>
<th>Reviewer 4</th>
<th>Reviewer 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewer 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reviewer 2</td>
<td>16 (22.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reviewer 3</td>
<td>19 (26.4%)</td>
<td>19 (26.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reviewer 4</td>
<td>13 (18.1%)</td>
<td>19 (26.4%)</td>
<td>12 (16.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reviewer 5</td>
<td>21 (29.2%)</td>
<td>15 (20.8%)</td>
<td>20 (27.8%)</td>
<td>20 (27.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Agreement | Disagreement
Table 1 The patient characteristics of KSCC0802

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>63</td>
<td>(37-74)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>29</td>
<td>72.5</td>
</tr>
<tr>
<td>female</td>
<td>11</td>
<td>27.5</td>
</tr>
<tr>
<td>Tumor size, median (range)</td>
<td>52.5</td>
<td>(10-135)</td>
</tr>
<tr>
<td>Tumor number, median</td>
<td>5</td>
<td>(1-20)</td>
</tr>
<tr>
<td>H-factor category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>H3</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Bilateral / unilateral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bilateral</td>
<td>28</td>
<td>70</td>
</tr>
<tr>
<td>unilateral</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>Synchronous /</td>
<td></td>
<td></td>
</tr>
<tr>
<td>synchronous</td>
<td>33</td>
<td>82.5</td>
</tr>
<tr>
<td>metachronous</td>
<td>7</td>
<td>17.5</td>
</tr>
</tbody>
</table>
Table 2. The result of evaluation from study 1 and concordance of actual liver resection cases

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Liver resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before chemotherapy</td>
<td>After chemotherapy</td>
</tr>
<tr>
<td>resectable → resectable</td>
<td>10</td>
</tr>
<tr>
<td>unresectable → resectable</td>
<td>7</td>
</tr>
<tr>
<td>resectable → unresectable</td>
<td>3</td>
</tr>
<tr>
<td>unresectable → unresectable</td>
<td>16</td>
</tr>
</tbody>
</table>
Table 3. Resectability before and after chemotherapy determined by Study 2

<table>
<thead>
<tr>
<th></th>
<th>Before chemotherapy</th>
<th></th>
<th>After chemotherapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Resectable*1</td>
<td>4</td>
<td>11.1</td>
<td>23</td>
<td>63.9</td>
</tr>
<tr>
<td>Unresectable*2</td>
<td>32</td>
<td>88.9</td>
<td>13</td>
<td>36.1</td>
</tr>
</tbody>
</table>

*1 Resectable include the grade 1 (resectable) and 2 (borderline resectable).
*2 Unresectable include the grade 3 (chemotherapy preferred) and 4 (non-resectable).