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Prognostic factors of hepatectomy in initially unresectable colorectal liver metastasis: Indication for conversion therapy

HIROYA IIDA[1,2], MASAKI KAIBORI[2], HIROSHI WADA[3], FUMITOSHI HIROKAWA[4], TAKUYA NAKAI[5], MASAHIKO KINOSHITA[6], MICHIHIRO HAYASHI[4], HIDETOSHI EGUCHI[3] and SHOJI KUBO[6]

[1]Department of Surgery, Shiga University of Medical Science, Otsu, Shiga 520-2192; [2]Department of Surgery, Kansai Medical University, Hirakata, Osaka 573-1191; [3]Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Osaka 565-0871; [4]Department of General and Gastroenterological Surgery, Osaka Medical College, Takatsuki, Osaka 569-0801; [5]Department of Surgery, Faculty of Medicine, Kinki University, Osaka-Sayama, Osaka 589-0014; [6]Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, Abeno, Osaka 545-0051, Japan

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Abstract. The aim of the present study was to retrospectively identify prognostic factors for long-term cumulative survival following liver resection in patients with primarily unresectable colorectal cancer who had previously received conversion therapy. A multicentre study was designed to ascertain the appropriate indication for conversion therapy. The study included 34 patients who underwent conversion therapy at 5 university hospitals. Patients' background, operative factors, recurrence rate and survival rate were evaluated, and factors influencing therapy outcomes were identified. The median duration of preoperative chemotherapy was 3 months and the response rate was 39.8%. Upon resection, the median tumour size was 47 mm and the median number of tumours was 4. The recurrence-free and cumulative survival rates 5 years after liver resection were 13.7 and 39.3%, respectively. Postoperative complications developed in 12 patients. A response rate >40% was indicated with regards to the assessed prognostic factors for long-term cumulative survival following liver resection and an absence of postoperative complications was noted. It was revealed that conversion therapy should be considered prior to liver resection, particularly for patients with response rates exceeding 40%. Absence of postoperative complications is also an independent predictor of long-term cumulative survival after liver resection. In light of these findings, it was consisted that an optimal response rate >40% could be used as an indicator for surgical resection in conversion therapy. In addition, meticulous intra- and postoperative managements are important for decreasing postoperative complications and improving long-term cumulative survival.

Correspondence to: Dr Hiroya Iida, Department of Surgery, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan
E-mail: hiroya@belle.shiga-med.ac.jp

Abbreviations: BMI, body mass index; WBC, white blood cell; AST, aspartate aminotransferase; ALT, Alanine transaminase; ALP, alkaline phosphatase; ICGR 15, indocyanine green retention rate at 15 min; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; RECIST, response evaluation criteria in solid tumor (version 1.1); PR, partial response; SD, stable disease

Key words: liver metastasis, conversion therapy, hepatectomy

Introduction

One million individuals per year are diagnosed with colorectal cancer worldwide, and the prevalence is increasing with the aging of the world population. Generally, 35-45% of the colorectal cancer patients are associated with liver metastasis. Although the 5-year survival rate of resectable liver metastasis is reported to be 25-45% (1), many patients experience intra-hepatic recurrence postoperatively.

Recently, Nordlinger *et al* reported that patients who underwent perioperative chemotherapy for liver metastasis had a significantly higher progression-free survival rate than patients who did not receive chemotherapy (2,3). Therefore, perioperative chemotherapy is now recommended for resectable liver metastasis.

On the other hand, there is no other way than chemotherapy for initially unresectable liver metastasis because of huge and multiple tumours or invasion to the main vessels. Although traditional chemotherapy only suppressed tumour growth in previous, new powerful chemotherapy or molecular targeted drugs had been developed and led to tumour shrinkage and disappearance in recent years. Therefore, liver metastasis which was initially unresectable may become resectable by chemotherapy, that a procedure known as conversion therapy.

The usefulness of conversion therapy has been recently reported by a number of studies (4-14). The prognostic factors of resectable liver metastasis are generally the maximum tumor size, the number of tumors, the tumor markers, the stage

of primary tumor, the interval after primary tumor resection and the resection margin. However, the surgical indication and limitations of conversion therapy before hepatectomy have not yet been established due to difference of initially unresectable criteria, choice of chemotherapy and administration period in each institution.

In this multicentre, retrospective study, the prognostic factors for favourable outcomes after conversion therapy were identified to further define the indications for conversion therapy.

Patients and methods

Patient selection. The study included 34 patients who underwent conversion therapy before liver resection, at the 5 university hospitals of the Osaka Hepatic Surgery Study Group (Osaka, Japan) between January 2006 and August 2014. All patients were initially diagnosed with resectable colorectal cancer and unresectable liver metastasis; the patients did not have other distant metastases, such as lung and bone metastasis.

Diagnosis of unresectable liver metastasis. We diagnosed 'unresectable liver metastasis' based on remnant liver volume and tumour location. Inability to preserve at least one major Glisson's branch (left or right) and one major hepatic vein (left, middle, or right), or <30% of the liver volume being free of macroscopic residual tumour deemed the liver metastasis unresectable. The unresectable nature of the metastasis was diagnosed by surgeons at each institute and retrospectively re-confirmed by the investigators of this study.

Contents of chemotherapy. In 26 of the 34 patients, chemotherapy was performed after resection of the colorectal mass. The remaining patients received chemotherapy before simultaneous surgical resection of colorectal and liver tumours. Oxaliplatin-based chemotherapy or combination of oxaliplatin-based chemotherapy and molecular-targeted drugs were administered in all but 4 patients before operation for liver metastasis. The 4 patients received 5-fluorouracil arterial infusion chemotherapy. The selected combination of chemotherapeutic drugs were decided by each institution.

The contents of the oxaliplatin-based chemotherapy were as follows: 11 patients received FOLFOX or XELOX; 9 patients, bevacizumab + FOLFOX or XELOX; 6 patients, panitumumab + FOLFOX or XELOX; and 1 patient, cetuximab + FOLFOX. FOLFOX consisted of leucovorin (200 mg/m^2) and oxaliplatin (85 mg/m^2), both administered as a 2-h infusion, followed by a bolus infusion of 5-fluorouracil (400 mg/m^2) and a 46-h continuous infusion of 5-fluorouracil (2,400 mg/m^2). This schedule was repeated every 2 weeks. XELOX consisted of oxaliplatin (130 mg/m^2) administered as a 2-h infusion on day 1 and every 3 weeks thereafter. Oral capecitabine (2,000 mg/m^2/day) was prescribed for 14 days, discontinued for 7 days, and this schedule was repeated every 3 weeks.

The irinotecan-based chemotherapy with molecular-targeted drugs was administered to 3 patients as follows: 2 patients received cetuximab + FOLFIRI and 1 patient received bevacizumab + FOLFIRI. FOLFIRI consisted of leucovorin (200 mg/m^2) administered as a 2-h infusion and irinotecan (150 mg/m^2) administered as a 1.5-h infusion, followed by a bolus infusion of 5-fluorouracil (400 mg/m^2) and a 46-h continuous infusion of 5-fluorouracil (2,400 mg/m^2). This schedule was repeated every 2 weeks.

The content of the preoperative chemotherapy was changed in 5 patients (14.7%) due to adverse events. At first, 2 patients received FOLFOX, another 2 received bevacizumab + FOLFOX, and another patient received panitumumab + FOLFOX. The regimen was changed to FOLFIRI, panitumumab + FOLFIRI, and bevacizumab + FOLFIRI, respectively. In another 5 patients (14.7%), the dose of the drug had to be reduced because of adverse events.

After liver resection, chemotherapy was performed for 26 patients. Twenty of these received oxaliplatin-based chemotherapy with or without molecular-targeted drugs. Four patients were prescribed irinotecan-based chemotherapy with molecular-targeted drugs, while the remaining 2 patients received arterial infusion chemotherapy. The dose of each drug was slightly different according to the policy of each institution and its side effects.

Data evaluation. We retrospectively evaluated patients' background data before hepatic resection, tumour factors, operative factors, and postoperative complications. Degree of lymph node metastasis was classified according to the TNM classification. Response to chemotherapy was defined according to the classification from Response Evaluation Criteria In Solid Tumors (RECIST) (15). The best response rate was defined as the highest reduction rate in the sum of the longest diameter of at least one target lesion during preoperative chemotherapy. Postoperative complications were classified based on the Clavien-Dindo classification (16,17).

Statistical analysis. The cumulative survival rates, as well as the factors that affect long-term survival after liver resection were calculated using univariate and multivariate analysis. Patient age, body mass index, and maximum tumour size are expressed as mean ± standard deviation. Other laboratory tests are expressed as median (interquartile range (IQR)). Univariate analysis was performed using the Kaplan-Meier method. When prognostic factors with continuous variables were used, patients were divided into 2 groups based on the median values. For the multivariate analysis, Cox proportional hazard model was used and factors with $P<0.05$ in the univariate analysis were included. P-values<0.05 were considered to indicate a statistically significant difference. All statistical analyses were performed with R (The R Foundation for Statistical Computing, version 3.3.1; https://cran.r-project.org/bin/macosx/).

Results

Patient characteristics. A total of 34 patients were enrolled in this study. The background data of the patients before liver resection, and the findings of the metastatic liver tumour(s) and operative factors are shown in Table I. The median patient age was 62 years and this study included a higher number of men than women. The median serum concentrations of carcinoembryonic antigen and carbohydrate antigen 19-9 were 8.2 ng/ml and 26.7 U/ml, respectively. The primary cancer originated from the colon in 20 patients and rectum in 14. The primary lesions were moderately differentiated

Table I. Characteristics, tumor and operative factors of conversion therapy patients.

Factor	Number (n=34)
Age (year)	60.4±11.8
Male:Female	21:13
BMI (kg/m^2)	22.4±3.5
WBC (/μl)	5,600 (4,925, 6,635)
Platelet count (10^4/μl)	20.4 (18.9,22.2)
Albumin (g/dl)	4.00 (3.7,4.2)
AST (IU/l)	25 (25,25)
ALT (IU/l)	24 (23,25)
Bilirubin (mg/dl)	0.5 (0.5,0.6)
ALP (IU/l)	266 (253,336)
Creatinine (mg/dl)	0.60 (0.59,0.72)
Prothrombin activity (%)	104 (98,114)
ICGR 15 (%)	7.5 (6.8,12.2)
CA19-9 (U/ml)	27 (8,73)
CEA (ng/ml)	8.2 (4.3,31.7)
Maximum tumor size (mm)	49.3±23.7
Tumor number	4 (3,10)
Primary cancer (rectum:colon)	14:20
Depth of tumor invasion more than subserosal invasion	19
Tumor differentiation (Moderate:well)	24:10
Lymph node metastasis (N0:N1:N2)	9:18:7
Duration of preoperative chemotherapy (month)	3 (3,7.8)
Duration of postoperative chemotherapy (month)	3 (1,3)
Response of chemotherapy by RECIST (PR:SD)	28:6
Best response rate (%)	39.8 (30.0,53.8)
Anatomical hepatic resection	26
Blood loss (ml)	959 (526,1895)
Blood transfusion	15
Positive of surgical margin pathologically	7
Postoperative complication	12

Age, BMI and maximum tumor size were expressed as mean ± standard deviation. Other laboratory tests were expressed as median (25 percentile, 75 percentile). BMI, body mass index; WBC, white blood cell; AST, Aspartate Aminotransferase; ALT, Alanine transaminase; ALP, Alkaline Phosphatase; ICGR 15, indocyanine green retention rate at 15 min; CA19-9, carbohydrate antigen 19-9; CEA, Carcinoembryonic antigen; RECIST, response evaluation criteria in solid tumor (version 1.1); PR, partial response; SD, stable disease.

adenocarcinoma in 24 patients and well-differentiated adenocarcinoma in 10 patients. Lymph node metastasis was found in 25 patients. The median duration of chemotherapy before liver resection was 3 months. According to the RECIST classification, the response to chemotherapy was classified as partial response in 28 patients and stable disease in 6 patients. The best response rate ranged from 30-54% (median, 40%). The median size of the metastatic tumour was 47 mm and the median tumour number was 4. Although macroscopic residual tumours were not observed after hepatic resection, the surgical margin was positive for cancer cells in 7 patients.

The adverse events were classified based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Grade ≥2 adverse events of preoperative chemotherapy included allergy in 2 patients (5.9%), fatigue in 7 (20.6%), hand-foot syndrome in 2 patients (5.9%), nausea in 4 (11.8%), neuropathy in 11 patients (32.4%), and anorexia in 8 (23.5%).

Operation methods used were anterior segmentectomy (n=1, 2.9%), anterior segmentectomy+partial hepatectomy (n=3, 8.8%), centra bisegmentectomy (n=1, 2.9%), lateral segmentectomy (n=1, 2.9%), lateral segmentectomy+partial hepatectomy (n=8, 23.5%), left lobectomy (n=1, 2.9%), left lobectomy+partial hepatectomy (n=1, 2.9%), posterior segmentectomy (n=2, 5.9%), posterior segmentectomy+partial hepatectomy (n=2, 5.9%), right lobectomy (n=1, 2.9%), right lobectomy+partial hepatectomy (n=4, 11.8%), and partial hepatectomy (n=9, 26.5%).

Pathological findings revealed sinusoidal obstruction syndrome (SOS) in 19 patients (57.6%). There was no significant difference in postoperative complications between SOS positive and negative patients (n=6 in both groups, 31.6 vs. 42.9%, P=0.716). The 5-year cumulative survival rate in either group was 38.1% (P=0.176).

Postoperative complications. Post-hepatectomy complications developed in 12 patients. Bile leakage developed in 3 patients, organ/space infection in 3, superficial wound infection in 2, pneumonia in 2, and refractory ascites or pleural effusion in 2 patients. Based on the Clavien-Dindo classification, those complications were classified as over grade II, classifying them as major complications.

Prognostic factors for long-term survival. The prognostic factors affecting long-term cumulative survival after liver resection were analysed (Table II). Based on the univariate analysis, a small tumour number (<4 nodules), a best response rate >40%, and absence of postoperative complications were favourable prognostic factors. The multivariate analysis revealed a best response rate >40% and absence of postoperative complications as independent favourable prognostic factors for long-term cumulative survival.

Survival. The recurrence-free survival curve and cumulative survival curve were assessed. The 5-year recurrence-free survival rate was 14.1% and median survival was 7 months. The 5-year cumulative survival rate was 39.2% and median survival was 31 months (Fig. 1).

Discussion

Recently, chemotherapy for colorectal cancer has been improved by the addition of new regimens and agents, including molecular-targeting agents (18-23). In addition, arterial infu-

Table II. Univariate and multivariate analysis for prognosis factors after hepatic resection of conversion therapy patients.

Factor	n	Median survival (month)	P-value	HR (95% CI)	P-value
Age (year)					
<62	17	27	0.35		
≥62	17	46			
Sex					
Female	13	24.5	0.51		
Male	21	46			
BMI (kg/m^2)					
<22.5	17	29	0.68		
≥22.5	17	31			
WBC (/μl)					
<5,600	17	46	0.22		
≧5,600	17	29			
Platelet count (10^4/μl)					
<20	17	29	0.95		
≥20	17	31			
Albumin (g/dl)					
<4.0	17	46	0.67		
≥4.0	17	31			
AST (IU/l)					
<25	17	NA	0.38		
≥25	17	29			
ALT (IU/l)					
<25	17	46	0.35		
≥25	17	24.5			
Bilirubin (mg/dl)					
<0.5	17	NA	0.24		
≥0.5	17	29			
ALP (IU/l)					
<266	17	31	0.31		
≥266	17	18			
Creatinine (mg/dl)					
<0.6	17	29	0.95		
≥0.6	17	46			
Prothrombin activity (%)					
<104	17	NA	0.15		
≥104	17	24.5			
ICGR 15 (%)					
<8	17	NA	0.43		
≥8	17	29			
CEA (ng/ml)					
<8	17	31	0.85		
≥8	17	NA			
CA19-9 (U/ml)					
<26	17	NA	0.11		
≥26	17	27			
Maximum tumor size (cm)					
<47	17	31	0.68		
≥47	17	29			

Table II. Continued.

Factor	n	Median survival (month)	P-value	HR (95% CI)	P-value
Tumor number					
<4	18	NA	0.03	1.51 (0.48-4.74)	0.47
≥4	16	24.5			
Primary cancer site					
Colon	20	46	0.95		
Rectum	14	31			
Depth of tumor invasion					
<ss	15	NA	0.37		
≥ss	19	29			
Tumor differentiation					
Well	10	28	0.24		
Moderate	24	46			
Lymph node metastasis					
N2	7	46	0.22		
N0 or N1	27	29			
Lymph node metastasis					
N1 or N2	25	46	0.08		
N0	9	18			
Duration of preoperative chemotherapy (month)					
<3	18	31	0.97		
≥3	16	46			
Best response rate (%)					
≤40	17	24.5	0.03	3.09 (1.06-9.02)	0.03
>40	17	NA			
Hepatic resection					
Partial	8	46	0.81		
Anatomical	26	27			
Blood loss (ml)					
<950	17	31	0.56		
≥950	17	NA			
Transfusion					
Absence	19	31	0.71		
Presence	15	NA			
Pathological surgical margin					
Negative	27	46	0.09		
Positive	7	16			
Postoperative complication					
Absence	22	24.5	0.02	4.94 (1.11-21.9)	0.03
Presence	12	NA			
Early tumor shrinkage					
≤10% per month	19	31	0.78		
>10% per month	15	NA			

BMI, body mass index; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; ICGR 15, indocyanine green retention rate at 15 min; CA19-9, carbohydrate antigen 19-9; CEA, Carcinoembryonic antigen; NA, not applicable; HR, hazard ratio; CI, confidence interval.

sion chemotherapy has been applied with good results (24). Such improvements in chemotherapy have enabled the conversion to tumour resectability in patients with primarily unresectable colorectal liver metastasis (25). Several studies have reported that the prognosis of patients who received conversion chemotherapy and consequently underwent liver

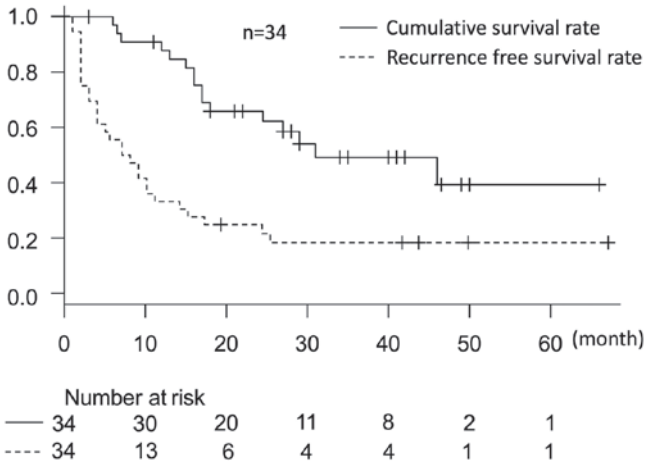

Figure 1. Recurrence-free survival and cumulative survival curves of conversion patients after hepatic resection.

resection, was better than that of unresectable patients. The 5-year survival rate for patients with unresectable tumour was 0% (26), while it significantly increased after conversion chemotherapy (30-60%) (10,27). However, the tumour recurrence rate in these patients was reportedly still high because of the original multiple liver metastases (9,28). Therefore, the indication for conversion therapy and the prevention of recurrence are currently important challenges.

In this study, a small tumour number (<4 nodules), best response rate >40%, and absence of postoperative complications were favourable prognostic factors in the univariate analysis. Importantly, best response rate >40% and absence of postoperative complications were independent favourable factors in the multivariate analysis. Previous studies have shown that the response rate of chemotherapy leads to a good prognosis (6,29). In addition, a main tumour size <3 cm, tumour number <3 (5), early response to chemotherapy (8), and low Ki-67 levels (30) have been reported as favourable prognostic factors. On the other hand, tumour progression during preoperative chemotherapy has been reported as a negative prognostic factor (1) and a negative predictor for outcomes in two-stage hepatectomy (4). This suggests that the response rate to chemotherapy may be affected by tumour biology and aggressiveness. Therefore, the response to chemotherapy is considered as an important prognostic factor. The indication for liver resection should be carefully reviewed when the best response rate is ≤40%.

The incidence of postoperative complications is reportedly high in converting patients (20-60%) (13,31,32), and have been attributed to liver disorder caused by chemotherapy, as well as the difficulty of liver resection because of the tumour location, such as near the main Glisson's capsule or hepatic vein. Recently, a significant relationship between postoperative complications and poor prognosis has been reported (33-36). Chronic inflammation and prolonged exposure to several cytokines that promote cancer growth, may be responsible for such poor prognosis. The current study demonstrated that the absence of postoperative complications is an independent favourable prognostic factor. Therefore, hepatic resection should be performed with care to avoid postoperative complications. Patients who experience postoperative complications might be unable to undergo postoperative chemotherapy. Therefore, the relationship between presence or absence of postoperative complications and the rate of postoperative chemotherapy was examined. In this study, 12 patients experienced postoperative complications, of whom 8 patients (66.7%) received postoperative chemotherapy. On the other hand, 18 (81.8%) of the 22 patients who had a normal postoperative course received postoperative chemotherapy (P=0.41).

In this study, it was difficult to obtain a definitive conclusion because of the small number of patients and inconsistency in the criteria of unresectability, despite assessing the data collected from multiple high-volume centres. Studies comprising larger patient number are necessary to confirm the results of this study.

In conclusion, a best response rate >40% to conversion therapy and absence of postoperative complications were identified as favourable prognostic factors of liver resection. Based on our results, the best response rate was the only factor that could be determined prior to surgery. Therefore, we believe that it could be used as a surgical indication in conversion therapy. However, the presence of major postoperative complications (Grade 2 and higher) represents the importance of careful intra- and postoperative management to reduce posthepatectomy complications and improve longer-term cumulative survival.

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Availability of data and materials

All datasets generated in this study are available from the corresponding author upon reasonable request.

Authors' contributions

HI contributed to the conception, design, acquisition, analysis and interpretation of data, and drafting of the manuscript. MKa, HW, FH, TN, MKi, MH, HE and SK took part in the acquisition and analysis of data. All the authors have read and approved the final version of this manuscript.

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the Institutional (Receipt no. 2017055) and National Research Committee, as well as the Declaration of Helsinki (1964) and its later amendments or

comparable ethical standards. Written informed consent was obtained from all patients included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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