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Conversion to Complete Resection with mFOLFOX6 with Bevacizumab or Cetuximab Based on K-RAS Status for Unresectable Colorectal Liver Metastasis (BECK study): Long-Term Results of Survival

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Abstract

Purpose: To investigate the long-term outcome and entire treatment course of patients with technically unresectable CRLM who underwent conversion hepatectomy and to examine factors associated with conversion to hepatectomy.

Methods: Recurrence and survival data with long-term follow-up were analyzed in the cohort of a multi-institutional phase II trial for technically unresectable colorectal liver metastases (the BECK study).

Results: A total of 22/12 patients with K-*RAS* wild-type/mutant tumors were treated with mFOLFOX6+cetuximab/bevacizumab. The conversion R0/1 hepatectomy rate was significantly higher in left-sided primary tumors than in right-sided tumors (75.0% vs. 30.0%, p=0.022). The median follow-up was 72.6 months. The 5-year OS rate in the entire cohort was 48.1%. In patients who underwent R0/1 hepatectomy (n=21), the 5-year RFS rate and OS rate were 19.1% and 66.3%, respectively. At the final follow-up, 7 patients had no evidence of disease, 5 were alive with disease, and 20 had died from their original cancer. All 16 patients who achieved 5-year survival underwent conversion hepatectomy, and 11 of them underwent further resection for other recurrences (median: 2, range: 1–4).

Conclusions: Conversion hepatectomy achieved a similar long-term survival to the results of previous studies in initially resectable patients, although many of them experienced several post-hepatectomy recurrences. Left-sided primary was found to be the predictor for conversion hepatectomy.

Abbreviations: CRLM, colorectal liver metastases; OS, overall survival; PVE, portal vein embolization; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; RFS, recurrence-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CT, computed tomography; MRI, magnetic resonance imaging; HR, hazard ratio

Clinical trial registration: This study was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) UMIN000004310.

Introduction

Hepatectomy is a potentially curative treatment for colorectal liver metastases (CRLM) with a 5-year overall survival (OS) of up to 58%.(1-3) However, only 25% of patients with CRLM were reported to be candidates for curative hepatic resection in the 1990s.(4) Recent advances in systemic chemotherapy and multidisciplinary treatment strategies such as portal vein embolization (PVE), a liver-first approach, and 2-stage hepatectomy have contributed to converting unresectable CRLM to resectable CRLM, which is called conversion therapy.(5-7) A previous study in the 2000s reported that 12.5% of patients with initially unresectable CRLM underwent conversion hepatectomy after systemic chemotherapy with cytotoxic anticancer agents, leading to a 5-year OS similar to that of patients with initially resectable CRLM who underwent hepatectomy.(8)

Conversion therapy has been widely adopted for initially unresectable CRLM patients, and the conversion rate with cytotoxic anticancer drugs (5-FU, oxaliplatin, and irinotecan) has been reported to be 10–60%.(9) Combination therapy of cytotoxic drugs with molecular targeted agents such as anti-vascular endothelial growth factor (VEGF) and anti-epidermal growth factor receptor (EGFR) antibodies provided additional efficacy with a 39–81% response rate.(9) However, there is little evidence from prospective clinical studies regarding whether such high response rates to molecular targeted agents contributed to the high conversion rate, high R0 resection rate, and better survival. In addition, long-term survival data from prospective studies with a sufficiently long follow-up period have not been reported, and definitions of unresectable disease vary extensively among the previous studies and have not been generalized. Although recent

studies have reported lower survival efficacy of anti-EGFR therapy for right-sided primary tumors,(10-12) the association between primary tumor sidedness and conversion from unresectable to resectable remains unclear.

To obtain actual data on the response rate, conversion rate, R0 resection rate, and survival data in patients with initially technically unresectable CRLM who were treated with cytotoxic drugs and molecular targeted agents, we conducted a prospective multi-institutional phase II trial (the BECK study).(13) The type of molecular targeted drug was selected based on *K-RAS* status, including 22 patients (64.7%) with wild-type *K-RAS* treated with mFOLFOX6 plus cetuximab and 12 patients (35.3%) with *K-RAS* mutant tumors treated with mFOLFOX6 plus bevacizumab. Since the tumor response to preoperative chemotherapy was reported to be correlated with the resection rate,(14) the hypothesis of this trial was that the anti-EGFR antibody, which is associated with a high response rate, increases the conversion rate in *K-RAS* wild-type patients who were candidates for anti-EGFR agents. Because a similar R0 resection rate in response to anti-VEGF agents was reported in patients with initially unresectable CRLM,(15) the use of an anti-VEGF antibody was also expected to increase the conversion rate in patients with *K-RAS* mutations who are not candidates for treatment with an anti-EGFR antibody. We previously reported the results of this trial with a 64.7% response rate, 70.6% conversion rate, and 50.0% R0 resection rate, which were similar to previous studies.(13)

The final aim of this analysis of the BECK study was to investigate recurrence-free survival (RFS) and OS with long-term follow-up of patients with initially technically

unresectable CRLM who received systemic chemotherapy with molecular targeted agents, expecting conversion to resection. In addition, we aimed to indicate the treatment course (recurrence, treatment for recurrence, and survival) of the patients who underwent conversion hepatectomy in the current trial. We also investigated the association between primary tumor sidedness and completion of conversion therapy.

Methods

Study design

"The efficacy of mFOLFOX6 with BEvacizumab or Cetuximab based on *K-RAS* status for unresectable hepatic metastasis of colorectal cancer (BECK) study" was a multicenter prospective phase II trial. This study was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) UMIN000004310 and approved by the ethics committees of Kyoto University Hospital (approval number: C438) and other participating facilities. The primary endpoint was the curative hepatectomy rate. All patients were planned to be followed-up for 5 years after the registration of the final case.

The inclusion and exclusion criteria have been reported previously.(13) Briefly, the major inclusion criteria were as follows: 1) no history of treatment for liver metastasis, 2) unresectable liver-specific metastasis, 3) no detectable extrahepatic tumors (except for potentially resectable metastases), 4) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–1, and 5) age of 20–74 years. Technically unresectable CRLM was defined as 1) a future liver remnant predicted to be less than 30% of the total liver volume or 2) required extended liver resection larger than a trisegmentectomy or hepatectomy with vascular reconstruction.

The tumors were assessed as resectable when these factors were resolved by the response to chemotherapy. The resectability was decided by each institutional cancer board and retrospectively confirmed at the multi-institutional congress. The decision of the treatment strategy was made by a multidisciplinary cancer board comprising

medical oncologists, radiation oncologists, colorectal surgeons and hepato-biliary surgeons.

Finally, a total of 35 patients with technically unresectable CRLM were enrolled from 13 institutes between March 2011 and August 2013. A right-sided primary colorectal tumor was defined as a tumor located between the ileocecal junction and the transverse colon, and a left-sided tumor included all tumors located from the splenic flexure to the rectum.(16)

Chemotherapy regimens

All patients were assigned to receive mFOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2 d1 followed by 400 mg/m^2 bolus 5-FU and a 46-h 2,400 mg/m^2 5-FU infusion) with either bevacizumab or cetuximab based on their *K-RAS* mutation status. Bevacizumab (5 mg/kg) was administered every 2 weeks, and cetuximab (400 mg/m^2 only at first treatment, 250 mg/m^2) was administered every week. The planned treatment was for six cycles, and resectability was assessed every 3 cycles by contrast-enhanced computed tomography (CT) or plain-CT plus magnetic resonance imaging (MRI).

If the disease was still unresectable after 6 cycles, the chemotherapy regimen was switched from mFOLFOX6 to FOLFIRI (irinotecan 150 mg/m^2, leucovorin 200 mg/m^2 d1 followed by 400 mg/m^2 bolus 5-FU and a 46-h 2,400 mg/m^2 5-FU infusion) plus bevacizumab or cetuximab (Fig. 1).

Hepatectomy was performed between 6 and 10 weeks after the final administration of bevacizumab and between 4 and 8 weeks after the final administration of cetuximab.

Patients who underwent R0 hepatic resection received adjuvant chemotherapy with the same regimen as preoperative chemotherapy for 6 months or depending on the patients' postoperative condition.

Statistics

Data were analyzed using the Wilcoxon test, $\chi 2$ test, or Fisher's exact test where appropriate. Continuous variables were expressed as the median (range). RFS and OS were calculated after initial chemotherapy or after hepatectomy and estimated using the Kaplan–Meier method. The log-rank test was used to compare survival curves. A Cox regression model was used to identify factors associated with OS. All variables with $p<0.20$ in the univariate analysis were included in the multivariate analysis. All tests were 2-tailed, and $p<0.05$ was considered statistically significant. All statistical computations were performed using JMP pro 14.0 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics at baseline

Of a total of 35 enrolled patients, 1 patient was excluded from the analysis because of treatment delay due to colonic obstruction. As previously reported, there were no significant differences in age, sex, performance status, tumor location, histology, primary tumor resection, extrahepatic metastases, or the levels of CEA or CA19-9 between the *K-RAS* wild-type patients and *K-RAS* mutant patients. The number of tumors was higher in the *K-RAS* mutant patients than in the *K-RAS* wild-type patients (11 vs. 6.5, p=0.06). In contrast, the diameter of the largest tumor was larger in *K-RAS* wild-type patients than in *K-RAS* mutant patients (78.5 mm vs. 35.5 mm, p=0.10). Three of 10 right-sided primary tumors and 19 of 24 left-sided primary tumors exhibited wild-type *K-RAS*. Left-sided primary tumors were significantly associated with a higher rate of conversion to R0/R1 hepatectomy compared to right-sided primary tumors (75.0% vs. 30.0%, p=0.022) (Table 1).

Treatment

As previously reported, 22 patients (64.7%) with wild-type *K-RAS* tumors received mFOLFOX6 plus cetuximab, and 12 patients (35.3%) with *K-RAS* mutant tumors were treated with mFOLFOX6 plus bevacizumab. The overall response rate was 64.7% (22/34) (77.3% [17/22] in *K-RAS* wild-type patients vs. 41.7% [5/12] in *K-RAS* mutant patients, p=0.04). All 3 patients with right-sided primary tumors who received mFOLFOX6 plus cetuximab were defined as having a partial response. Of the 22

patients treated with mFOLFOX6 plus cetuximab, 16 (72.7%) underwent on-protocol hepatectomy, and 1 (4.5%) discontinued the protocol chemotherapy due to toxicity; this patient underwent off-protocol hepatectomy with a negative surgical margin. Of the 12 patients who received mFOLFOX6 plus bevacizumab, 4 (33.3%) underwent on-protocol hepatectomy, and 3 patients (25.0%) discontinued the protocol chemotherapy; these 3 patients underwent off-protocol hepatectomy with a negative resection margin (1 additional patient who underwent off-protocol hepatectomy was identified after the previous report). Finally, the overall conversion rate was 70.6% (24/34), and the R0 resection rate was 50.0% (17/34). No significant differences in the conversion rate (77.3% vs. 58.3%, p=0.271) or the R0 resection rate (50.0% vs. 50.0%, p=1.00) were observed between the *K-RAS* wild-type patients and the *K-RAS* mutant patients (Fig. 2).

Survival

The median follow-up after initial chemotherapy was 72.6 months for the current analysis. The median, 3-year, and 5-year OS after initial chemotherapy in the entire cohort (n=34) were 59.6 months, 72.7% and 48.1%, respectively (Fig. 3a). The median OS was longer in the patients with wild-type *K-RAS* than in the patients with mutant *K-RAS* (74.3 months vs. 31.6 months, p=0.123) although this difference was not significant (Fig. 3b).

Among the patients who underwent R0/R1 hepatectomy (n=21), the median, 3-year, and 5-year OS after hepatectomy were 70.3 months, 85.7%, and 66.3%, respectively (Fig. 4a). Additionally, the median, 1-year, 3-year and 5-year RFS after hepatectomy

were 10.3 months, 47.6%, 23.8%, and 19.1%, respectively (Fig. 4a). There were no significant differences in OS (median: 78.7 months vs. 63.0 months, p=0.454, Fig. 4b) or RFS (median: 11.3 months vs. 8.5 months, p=0.733, Fig. 4c) between *K-RAS* wild-type patients and *K-RAS* mutant patients who underwent R0/R1 hepatectomy. In terms of pathological surgical margin, no significant differences in OS (median: 70.1 months vs. 57.1 months, p=0.973, Fig. A1a) or RFS (median: 11.6 months vs. 9.3 months, p=0.971, Fig. A1b) were observed between the patients who underwent R0 hepatectomy and the patients who underwent R1 hepatectomy.

OS after initial chemotherapy was significantly worse in the patients who did not undergo R0/1 hepatectomy (n=11) than in the patients who did undergo R0/1 hepatectomy (median, 3-year, and 5-year OS were 29.6 months, 50.0%, and 8.3%, respectively, p=0.0004).

Factors associated with overall survival

The univariate analysis showed that right-sided primary tumor (hazard ratio [HR]: 3.11, 95% CI: 1.18–7.98, p=0.023) and non-R0/R1 resection (HR: 4.39, 95% CI: 1.80–10.8, p=0.0014) were significant prognostic factors for poor OS after initial chemotherapy. In the multivariate analysis, non-R0/R1 resection (HR: 5.09, 95% CI: 1.78–15.3, p=0.0025) was an independent prognostic factor for poor OS. *K-RAS* mutation was also found to exhibit a trend towards being a significant factor for poor OS (HR: 2.59, 95% CI: 0.93–7.32, p=0.069) (Table 2).

Treatment course after recurrence

Thirteen of 19 patients (68.4%) with recurrence at any location after initial hepatectomy could undergo surgical resection. Of these 13 patients, 11 (84.6%) experienced a 2nd recurrence, and 8 patients (72.7%) underwent surgical resection for their 2nd recurrence. Seven of these 11 patients (63.6%) experienced a 3rd recurrence, and 4 patients (57.1%) underwent surgical resection for their 3rd recurrence. Finally, 3 of these 4 patients (75.0%) experienced a 4th recurrence, and 1 patient (33.3%) underwent surgical resection for their 4th recurrence, although this patient also experienced a 5th recurrence that was unresectable (Fig. 2).

Characteristics of 5-year survivors

Of the 33 patients, except for 1 patient who was lost to follow-up, 16 patients survived for 5 years after initial chemotherapy. At the final follow-up, 7 patients had no evidence of recurrent disease (including 1 patient who initially had R2 hepatectomy; right hepatectomy with ethanol injection therapy), 5 patients were alive with recurrent disease, 3 patients had died from the original cancer, and 1 patient had died from another type of cancer (Table 3). Of the patients who did not undergo initial hepatectomy, none survived for 5 years. One patient with wild-type *K-RAS* who received R1 hepatectomy (a pathological positive resection margin) experienced no recurrence after initial hepatectomy. Of the 16 patients, 11 patients (68.8%) underwent further resection(s) for recurrence (median: 2, range: 1–4). No patient or tumor characteristics were found to be associated with 5-year cancer-free survival in the univariate and multivariate analyses.

Discussion

The results of this prospective phase II trial for patients with initially technically unresectable CRLM, including 22 patients (64.7%) with wild-type *K-RAS* treated with mFOLFOX6 plus cetuximab and 12 patients (35.3%) with *K-RAS* mutant tumors treated with mFOLFOX6 plus bevacizumab, showed a median OS of 59.6 months after initial chemotherapy in the entire cohort (n=34) after 72.6 months of median follow-up. Of the patients who underwent conversion hepatectomy (n=21), a favorable median OS after hepatectomy of 70.3 months was observed, whereas the median RFS was short, at only 10.3 months. A primary tumor located on the left side of the colon (located from the splenic flexure to the rectum) was the only significant factor associated with conversion to R0/R1 hepatectomy.

In the era of molecular targeted agents, the 5-year OS after conversion hepatectomy reached 54%.(17-19) The 5-year OS of 66.3% in this study that included only patients with technically unresectable CRLM was better than any of the previous prospective studies for initially unresectable CRLM.(9, 18) In contrast, RFS after conversion hepatectomy was similar to that reported in previous studies, which ranged from 6 to 17 months.(9, 18) As previously reported, the amenability of patients for surgical resection of recurrent tumors is associated with better OS.(20) In the current study, 13 of 19 patients (68.4%) who had recurrence at any location after conversion hepatectomy could undergo surgical resection, which was a higher rate than that reported in previous studies, which ranged from 29% to 58%.(18, 20-22) Therefore, the high amenability of patients to surgical resection (aggressive multiple resections) for recurrences might have led to

the favorable OS in this study.

The current study indicated that there were no differences in OS or RFS between the patients who underwent R0 hepatectomy and the patients who underwent R1 hepatectomy although this might be due to the small sample size. However, after the preoperative treatment with recent effective chemotherapy, margin status might have small impact on recurrence and long-term survival.

Although the better OS of patients with left-sided tumors compared to right-sided tumors has been reported previously,(10) the current analysis found a left-sided primary tumor to be a predictor of R0/R1 conversion hepatectomy. In addition to a higher incidence of *RAS* (*K-RAS*) mutations, higher rates of other somatic gene mutations, such as *PIK3CA*, *SMAD4*, and *BRAF V600,* in right-sided colon cancer have been reported.(11, 16) These differences in mutations may lead to differences between left-sided and right-sided tumors in terms of their response to not only standard chemotherapy, but also anti-EGFR and anti-VEGF therapies (12); they could also be associated with the lower conversion rate in right-sided primary tumors observed in the current analysis. While recent studies have reported no benefit of anti-EGFR antibody on OS among patients with right-sided primary cancer in a palliative setting,(10, 12) the benefit on the response rate is uncertain. Previous studies showed a trend towards higher response rate to anti-EGFR agents with chemotherapy than to chemotherapy only among patients with right-sided primary cancer.(12) Since the response rate is correlated with the conversion rate,(9) anti-EGFR antibody might show efficacy in potentially resectable CRLM patients with right-sided primary tumors. Further investigations into the

association of the sidedness of colorectal cancer and conversion rates may be necessary to confirm the current results.

The advantage of the current study is that almost all the patients were followed-up until their death, even if the patients exhibited recurrences. To the best of our knowledge, no previous prospective studies on patients with initially unresectable CRLM have followed-up all recurrence(s) until the patient's death. Although the recurrence rate after initial hepatectomy or following resections was high, from 64% to 86%, which is similar to previous studies of 54–91%,(18, 20, 23-25) the resectability of each recurrence (72.7% for a 2nd recurrence, 57.1% for a 3rd recurrence and 33.3% for a 4th recurrence) was higher than that of previous studies.(18, 20-22) Since the amenability of patients for resection of a 2nd or later recurrence has also been reported to be associated with a better OS,(21, 22) the amenability of patients for multiple resections for several recurrences might also be associated with a better OS.

Since the *RAS* (*K-RAS*) mutation itself has been reported to be associated with poor OS after hepatectomy,(26) worse response to preoperative chemotherapy,(27) poor survival after repeat hepatectomy for intrahepatic recurrence,(28) and higher incidence of unsalvageable recurrence after hepatectomy,(20) the results regarding the better OS observed among *K-RAS* wild-type patients might be due to simply the *K-RAS* status itself. However, another possibility is a higher efficacy of the anti-EGFR agent compared to the anti-VEGF agent. A meta-analysis of 3 randomized studies in *K-RAS* wild-type patients with unresectable metastatic colorectal cancer (FIRE-3, PEAK, and CALGB 80405) showed a better response rate and OS for anti-EGFR therapy than for anti-VEGF therapy,

whereas the PFS was similar.(29) Therefore, the strategy of the current study using molecular targeted agent selection based on *K-RAS* (*RAS*) may be reasonable for patients with initially unresectable CRLM. To maximize the survival and conversion rate of patients with unresectable CRLM, FOLFOXIRI with anti-VEGF antibody may be an option for *RAS* wild-type patients.(30)

The limitations of this study include the relatively small sample size; however, the study was designed with the support of a statistician, and the cohort was derived from multiple institutions and was analyzed prospectively. Further investigation with a larger sample size may be needed before the current results can be applied in clinical practice. Another limitation is that selection of the molecular targeted agents was not based on all-*RAS* or *BRAF* but on K-*RAS* mutation status because the tests of all-*RAS* and *BRAF* mutation status were not standard at the time of the study design. The incidences of *N-RAS* and *BRAF* mutations among CRLM patients who undergo hepatectomy are reported to be low, at 3.6% and 2%,(31, 32) which might not affect the results of the current study.

In conclusion, the results of this study indicate that the treatment strategy for patients with initially technically unresectable CRLM achieved long-term survival results that were similar to those of previous studies conducted with initially resectable CRLM patients. While the recurrence rate after conversion hepatectomy was high, at 81%, surgical resection of a 2nd or additional recurrence provided a chance for a cure. These results offer encouragement to patients who may need to undergo several resections for multiple recurrences.

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Figure legends

Fig. 1 Trial profile

Fig. 2 Consort diagram of the treatment course.

Fig. 3 (a) Overall survival (OS) in overall patients after initial chemotherapy. (b) OS after initial chemotherapy according to *K-RAS* mutation status.

Fig. 4 (a) Overall survival (OS) and recurrence-free survival (RFS) after hepatectomy in patients who underwent R0/1 conversion hepatectomy. (b) OS after hepatectomy in patients who underwent R0/1 conversion hepatectomy according to *K-RAS* mutation status. (c) RFS after hepatectomy in patients who underwent R0/1 conversion hepatectomy according to *K-RAS* mutation status.

Table 1 Characteristics of patients according to hepatectomy

	total n=34	R0/1 hepatectomy n=21	R2/no hepatectomy n=13	p
Age, y.o.	60 (36-74)	60 (36-69)	60 (51-74)	0.696
Sex, n (%)				
Male	16 (47.1)	8 (38.1)	8 (61.5)	0.291
Female	18 (52.9)	13 (61.9)	5 (38.5)	
Performance status, n (%)				
0	33 (97.1)	20 (95.2)	13 (100)	1.00
1	1 (2.9)	1 (4.8)	0 (0)	
Location of primary tumor, n (%)				
Colon	24 (70.6)	14 (66.7)	10 (76.9)	0.704
Rectum	10 (29.4)	7 (33.3)	3 (23.1)	
Sidedness of primary tumor, n (%)				
Right	10 (29.4)	3 (30.0)	7 (70.0)	0.022
Left	24 (70.6)	18 (75.0)	6 (25.0)	
Primary tumor resection at hepatectomy, n (%)				
Resected	21 (61.8)	10 (47.6)	11 (84.6)	0.067
Unresected	13 (38.2)	11 (52.4)	2 (15.4)	
K-*RAS* mutation status				
Wild-type	22 (64.7)	14 (66.7)	8 (61.5)	1.00
Mutant	12 (35.3)	7 (33.3)	5 (38.5)	
Extrahepatic metastases, n (%)				
No	26 (76.5)	14 (66.7)	12 (92.3)	0.116
Yes	8 (23.5)	7 (33.3)	1 (7.7)	
CEA, ng/ml	158 (1.2-29798)	158 (3.7-11761)	148 (1.2-29798)	0.986
CA19-9, U/ml	174 (0.4-21600)	126 (0.4-4852)	556 (9.2-21600)	0.123
Timing of liver metastases, n (%)				
Synchronous	33 (97.1)	20 (95.2)	13 (100)	1.00
Metachronous	1 (2.9)	1 (4.8)	0 (0)	
Number of metastases	7 (1-50)	7 (1-26)	9 (2-50)	0.522
Largest tumor diameter, mm	62 (11-134)	55 (16-134)	64 (11-126)	0.832
Reason for unresectable*, n				
Insufficient remnant liver volume	30	18	12	
Require revascularization	4	4	0	
Others	2	1	1	

*There are some overlapping

Table 2 Factors associated with overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age, y.o.						
≥60						
<60	1.34	0.56-3.21	0.506			
Sex, n (%)						
Male						
Female	1.25	0.51-3.13	0.622			
Location of primary tumor, n (%)						
Colon						
Rectum	0.82	0.29-2.06	0.687			
Sidedness of primary tumor, n (%)						
Left						
Right	3.11	1.18-7.98	0.023	1.37	0.43-4.12	0.587
Primary tumor resection at hepatectomy, n (%)						
Resected						
Unresected	0.58	0.21-1.42	0.219			
K-*RAS* mutation status						
Wild-type						
Mutant	1.96	0.79-4.66	0.139	2.59	0.93-7.32	0.069
Extrahepatic metastases, n (%)						
No						
Yes	0.87	0.28-2.21	0.776			
CEA, ng/ml						
<100						
≥100	1.11	0.47-2.72	0.819			
CA19-9, U/ml						
<100						
≥100	1.53	0.63-4.06	0.353			
Timing of liver metastases, n (%)						
Synchronous						
Metachronous	1.92	0.11-9.64	0.568			
Number of metastases						
≤5						
>5	0.69	0.28-1.76	0.417			
Largest tumor diameter, mm						
<50						
≥50	0.83	0.35-2.06	0.695			
R0/R1 hepatectomy						
Yes						
No	4.39	1.80-10.8	0.0014	5.09	1.78-15.3	0.0025

HR, hazard ratio

Table 3 Characteristics of 5-year survivors

Patient	OS after initial chemotherapy (months)	Status at final follow-up	K-*RAS* status	Hepatectomy	Surgical margin	Recurrence after initial hepatectomy	RFS after initial hepatectomy (months)	Recurrence site	Metasectomy for recurrence	Type of metasectomy	Recurrence	RFS (DFI) (days)
1	82.7	Dead	Wild	On-protocol	R0	Yes	14.0	Lung	Yes	Partial lung resection	Yes	43
								Liver	Yes	Left lateral segmentectomy	Yes	122
								Liver, lung, LN	No			
2	74.3	Dead	Wild	On-protocol	R0	Yes	44.4	Pleura	No			
3	87.3	NED	Wild	On-protocol	R2 (EIT)	Yes	14.0	Liver, local, local LN	Yes	Left lateral segmentectomy+HAR	Yes	414
								Liver	Yes	S2 segmentectomy	No	1471
4	85.4	NED	Mutant	Off-protocol	R0	No	74.7	-	-			
5	88.0	NED	Mutant	On-protocol	R0	Yes	12.8	liver	Yes	Partial hepatectomy	No	2003
6	83.6	NED	Wild	Off-protocol	R0	No	77.3	-	-			
7	69.2	Death by other cancer	Mutant	On-protocol	R0	No	61.8	-	-			
9	81.5	AWD	Wild	On-protocol	R1 (Macroscopically)	Yes	12.4	Liver	Yes	Partial hepatectomy	Yes	124
								Liver	No			
10	63.6	Dead	Wild	On-protocol	R0	Yes	1.3	Liver	Yes	Partial hepatectomy	Yes	592
								Liver	Yes	Partial hepatectomy	Yes	111
								Liver	No			
11	74.2	AWD	Wild	On-protocol	R0	Yes	3.5	Liver, Lung	Yes	Partial hepatectomy	Yes	200
								Liver	Yes	Partial hepatectomy	Yes	840
								Lung	Yes	Partial lung resection	Yes	372
								Lung	No			
12	72.6	NED	Wild	On-protocol	R1 (Microscopically)	No	67.8	-	-			
13	68.9	AWD	Mutant	Off-protocol	R0	Yes	8.5	Liver	Yes	Partial hepatectomy	Yes	188
								Lung	Yes	Partial lung resection	Yes	55
								Liver	No			
14	59.2	NED	Wild	On-protocol	R0	Yes	14.0	Peritoneum, Lung	Yes	Partial lung resection	No	523
15	64.2	NED	Wild	On-protocol	R0	Yes	20.0	Liver	Yes	Left hepatectomy	Yes	476

								Liver	Yes	Partial hepatectomy	Yes	503
								Liver	Yes	Partial hepatectomy	No	87
16	63.2	AWD	Wild	On-protocol	R0	Yes	0.9	Lung	Yes	Partial lung resection	Yes	484
								Liver	Yes	S2 segmentectomy	Yes	294
								Lung	Yes	Partial lung resection	Yes	148
								Lung, LN	No			
17	61.1	AWD	Wild	On-protocol	R0	Yes	5.0	Liver	Yes	Partial hepatectomy	Yes	93
								Lung	Yes	Partial lung resection	Yes	121
								Lung	Yes	Partial lung resection	Yes	74
								Lung	Yes	Partial lung resection	Yes	91
								Lung	No			

RFS, recurrence-free survival; DFS, disease-free interval; OS, overall survival; NED, no evidence of disease; AWD, alive with disease; EIT, ethanol injection therapy; LN, lymph nodes; HAR, high anterior resection

Fig. 1

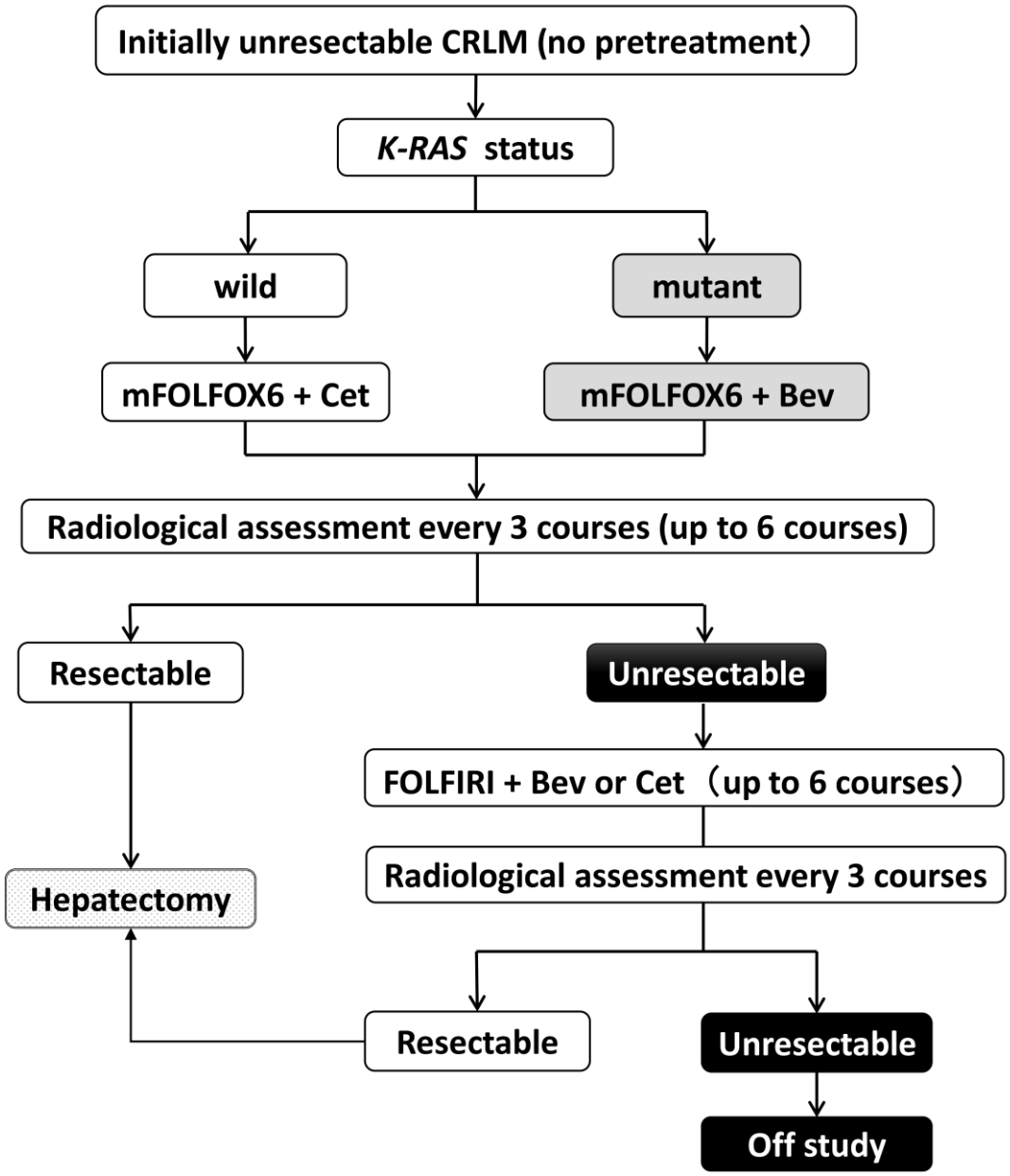

Fig. 2

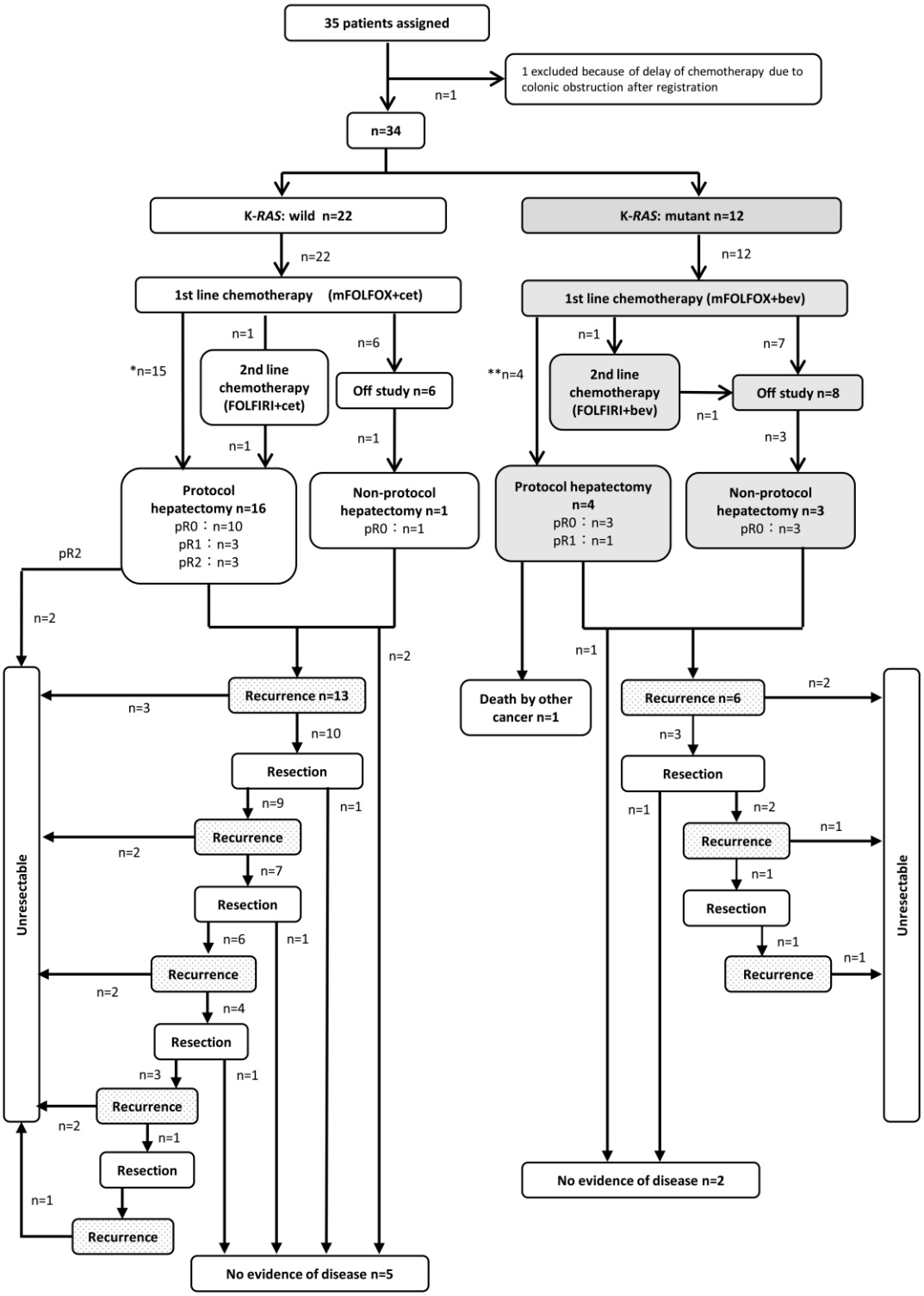

Fig. 3

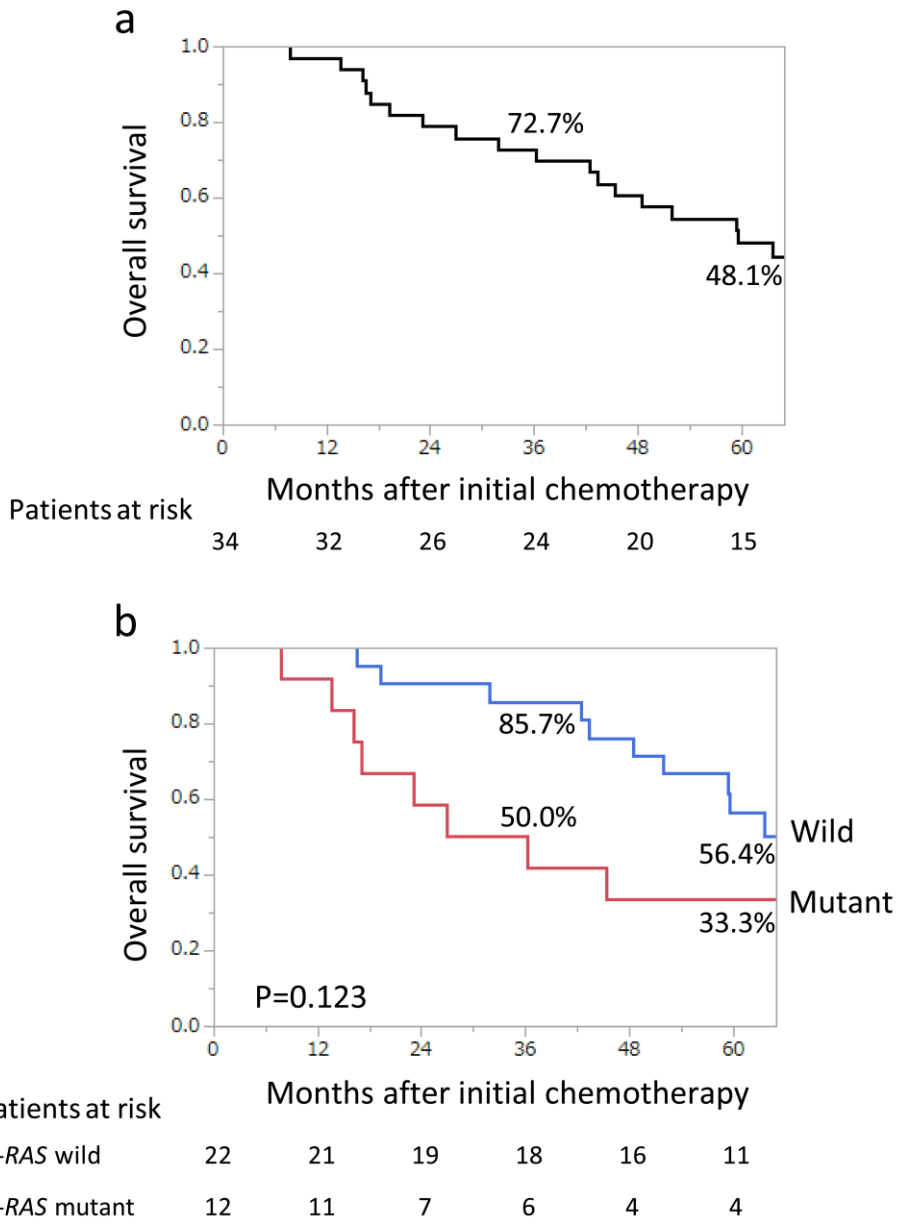

Fig. 4

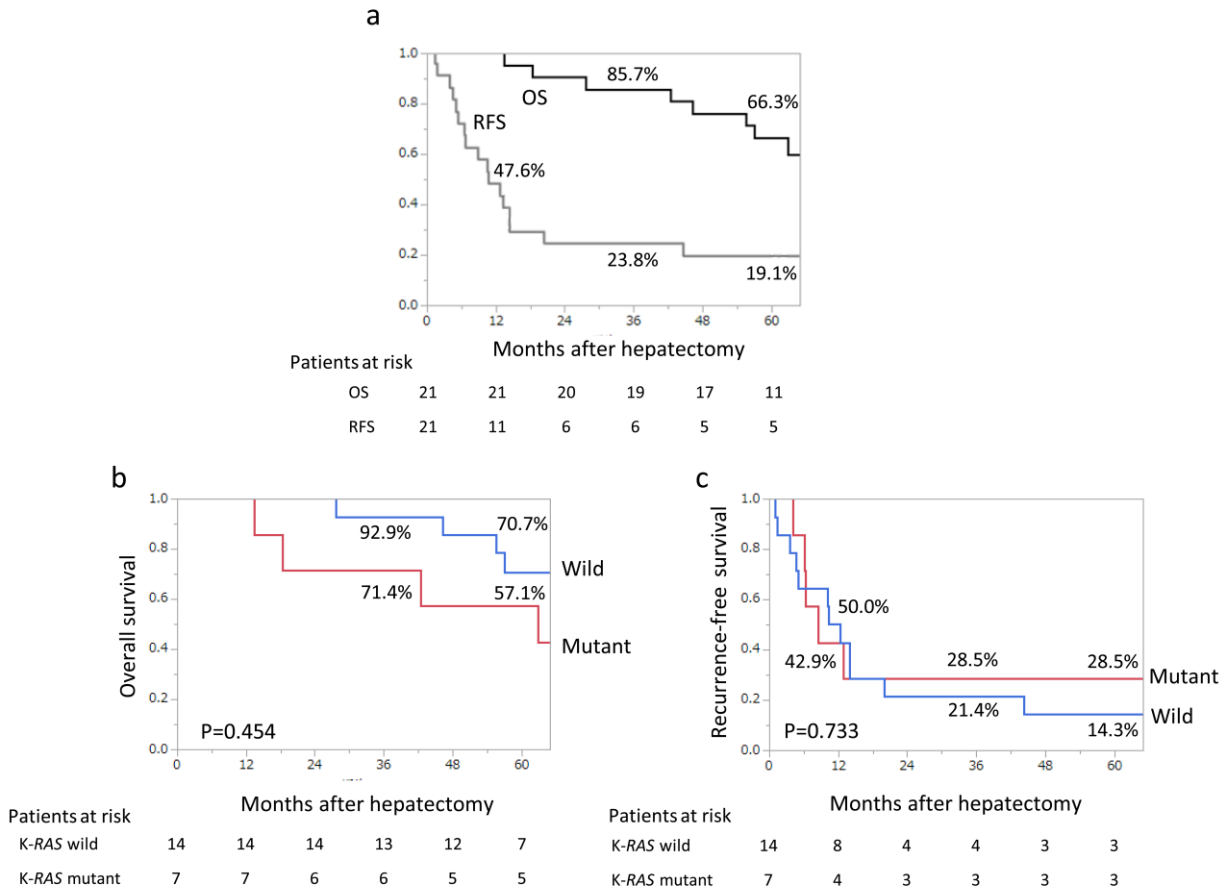

Fig. A1　Overall survival (a) and recurrence-free survival (b) after hepatectomy in patients who underwent R0/1 conversion hepatectomy according to pathological surgical margin.