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Embryonic Origin of Primary Colon Cancer Predicts Pathologic Response and Survival in Patients Undergoing Resection for Colon Cancer Liver Metastases

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Abstract

Background—To determine the prognostic value of embryonic origin in patients undergoing resection after chemotherapy for colon cancer liver metastases (CCLM).

Methods—We identified 725 patients with primary colon cancer and known *RAS* mutation status who underwent hepatic resection after preoperative chemotherapy for CCLM (1990-2015). Survival after resection of CCLM from midgut origin (n=238) and hindgut origin (n=487) was analyzed. Predictors of pathologic response and survival were determined. Prognostic value of embryonic origin was validated with a separate cohort of 252 patients with primary colon cancer who underwent resection of CCLM without preoperative chemotherapy.

Results—Recurrence-free survival (RFS) and overall survival (OS) after hepatic resection were worse in patients with midgut origin tumors (RFS rate at 3 years: 15% vs. 27%, $P<0.001$; OS rate at 3 years: 46% vs. 68%, $P<0.001$). Independent factors associated with minor pathologic response were midgut embryonic origin (odds ratio [OR] 1.55, $P=0.010$), absence of bevacizumab (OR 1.42, $P=0.034$), and mutant *RAS* (OR 1.41, $P=0.043$). Independent factors associated with worse OS were midgut embryonic origin (hazard ratio [HR] 2.04, $P<0.001$), carcinoembryonic antigen value ≥5 ng/mL at hepatic resection (HR 1.46, $P=0.0021$), synchronous CCLM (HR 1.45, $P=0.012$), and mutant *RAS* (HR 1.43, $P=0.0040$). In the validation cohort, patients with CCLM of midgut origin had a worse 3-year OS rate (55% vs. 78%, $P=0.003$).

Conclusion—Compared to CCLM from hindgut origin, CCLM from midgut origin are associated with worse pathologic response to chemotherapy and worse survival after resection. This effect appears to be independent of *RAS* mutation status.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the third most common cause of death due to cancer in the United States.[1] Colorectal liver metastases occur in 30% of patients with CRC and account for two-thirds of deaths from CRC.[2] Hepatectomy offers the best chance for long-term survival in patients with colorectal liver metastases.[3]

As a result of genetic and molecular evaluation, CRC is no longer regarded as a single entity. Three distinct pathways of CRC development have been described: the chromosomal instability, germline mutation, and serrated/methylator pathways.[4] Furthermore, and of particular interest in the current study, midgut origin and hindgut origin CRCs have been demonstrated to follow different pathways of carcinogenesis.[5-8] Whereas midgut origin tumors are more likely to be diploid and exhibit mucinous histology, high microsatellite instability, high CpG island methylation, and *BRAF* mutations,[6, 7] hindgut origin tumors are more likely to be aneuploid and exhibit chromosomal instability.[6, 8]

Previous attempts to evaluate the effect of embryonic origin on survival in patients with CRC have yielded conflicting results because of high heterogeneity between studies with respect to patients' clinical characteristics (tumor stage, presence/absence and type of chemotherapy, etc) and limited information on molecular features (*RAS* mutation status, etc).[9, 10] Recently, Loupakis et al, in an analysis of three independent studies, demonstrated that midgut origin was independently associated with poor survival after treatment of unresectable metastatic CRC.[11] Additionally, a previous German multicenter study including 17,641 CRC patients with Union Internationale Contre le Cancer stage I to III identified midgut origin as an independent predictor of worse survival after resection with curative intent.[12] However, the effect of embryonic origin on survival in patients with colorectal liver metastases undergoing preoperative chemotherapy followed by resection of colorectal liver metastases has never been reported. In patients with resectable colorectal liver metastases, pathologic response to preoperative chemotherapy and *RAS* mutation status are established major predictors of survival.[12-14]

The aim of the current study was twofold: (1) to determine the prognostic value of embryonic origin in patients undergoing resection after chemotherapy for colon cancer liver metastases (CCLM) and (2) to investigate the correlations among embryonic origin, pathologic response to preoperative chemotherapy, and *RAS* mutation status in such patients.

MATERIAL AND METHODS

Study Population

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this study protocol (PA16-0162). A prospectively maintained hepatobiliary database of the Department of Surgical Oncology was reviewed to identify patients who underwent curative resection for colorectal liver metastases between November 1990 and February 2015. A total of 2195 patients were identified (Figure 1). Of those patients, we identified patients with known *RAS* mutation status who underwent preoperative

chemotherapy and curative resection. The following exclusion criteria were applied: (1) concomitant radiofrequency ablation, (2) primary rectal cancer, (3) primary transverse colon cancer, (4) absence of preoperative chemotherapy, (5) absence of pathologic description of response to preoperative chemotherapy, (6) use of anti-epidermal growth factor receptor (EGFR) agents before or after surgery, and (7) undetermined *RAS* mutation status. We excluded patients who had primary rectal cancer because rectal cancer is clinically and molecularly distinct from colon cancer and because rectal cancer treatment (such as preoperative chemoradiation) is different from colon cancer treatment.[15] We excluded patients who had primary transverse colon cancer because we could not affirm retrospectively whether such patients had midgut origin or hindgut origin tumors given that the division point between midgut and hindgut is the point separating the first two-thirds from the final third of the transverse colon. The final study set included 725 patients (Figure 1). For our validation set, from the original 2195 patients who underwent curative resection for colorectal liver metastases, we selected the 252 patients who did not receive concomitant radiofrequency ablation, did not have primary rectal or primary transverse colon cancer, and did not receive preoperative chemotherapy (Figure 1).

The following data were extracted from electronic patient medical records: sex, age, body mass index, primary tumor characteristics (embryonic origin, depth of invasion, and lymph node metastases), preoperative chemotherapy characteristics (number of cycles and regimen), preoperative carcinoembryonic antigen (CEA) level, perioperative outcomes (blood loss, red blood cell transfusion, operative time, and surgical procedure [major resection was defined as liver resection including three or more liver segments]), and CCLM characteristics (timing of diagnosis, tumor size, tumor number, differentiation, margin status [R0, defined as no tumor cells at the margin, or R1, defined as tumor cells <1 mm from the margin], pathologic response to preoperative chemotherapy [major response, defined as cancer cells accounting for 0% to 49% of residual cells, or minor response, defined as cancer cells accounting for ≥ 50% of residual cells], and *RAS* mutation status).[16]

Perioperative Management

During preoperative chemotherapy, restaging was performed, and CCLM were deemed resectable when a hepatectomy could achieve a negative margin while preserving more than 20-30% of the total estimated liver volume, sparing two continuous hepatic segments, and maintaining vascular inflow and outflow and biliary drainage.[17] Second-line chemotherapy was considered for patients with progression of disease or suboptimal tumor response after first-line chemotherapy.[18] Decisions regarding the treatment sequence (classic, combined, or reverse) for patients having synchronous CCLM with an intact primary were made at multidisciplinary consultation including hepatobiliary surgeons, colorectal surgeons and medical oncologists. It was primarily based on the extent of the primary tumor and CCLM.[20] In patients with an anticipated insufficient future liver remnant, preoperative portal vein embolization and staged hepatectomy were proposed. Postoperative chemotherapy was administered to complete a total of 12 cycles, including those given preoperatively.[19] Patients were followed after resection with history, physical examination, laboratory evaluation, and axial imaging every 3-4 months for the first 2 years, and every 4-6 months for the subsequent 3 years.

Somatic Gene Mutation Profiling

The mutational status was assessed using DNA from biopsy or resected specimens of primary tumors or metastases. *RAS* mutation status was determined as previously described: routine polymerase chain reaction-based primer extension assay was performed to screen for mutations in *KRAS* codons 12 and 13 in all patients and for mutations in *KRAS* codons 61 and 146 and *NRAS* codons 12, 13, and 61 in the majority of patients.[20] Single mutations in the various codons of *KRAS* and *NRAS* were analyzed together and reported as *RAS* mutations.

Statistical Analyses

Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the $\chi 2$ test. For the evaluation of predictors of pathologic response, univariable and multivariable analyses were performed by logistic regression analysis. Recurrence-free survival (RFS) was measured from the date of hepatic resection until the date of radiographic detection of recurrence or last follow-up. Recurrence was defined as reappearance of a lesion with typical findings on standard imaging modalities (enhanced computed tomography, magnetic resonance imaging, and positron emission tomography, or a combination thereof). Overall survival (OS) was measured from the date of hepatic resection until the date of death or last follow-up. Survival curves were generated using the Kaplan-Meier method, and differences between curves were evaluated with the log-rank test. Univariable and multivariable analyses to identify predictors of survival were performed by using Cox proportional hazards regression models. Variables with $P<0.1$ in univariable analysis were entered into each multivariable analysis. $P<0.05$ was considered statistically significant in all analyses. Statistical analyses were performed with IBM SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics and Survival According to Embryonic Origin in Study Set

Of the 725 patients in the study set, 238 (33%) had primary tumors derived from midgut, and 487 (67%) had primary tumors derived from hindgut (Figure 1). Table 1 lists clinicopathologic and operative data for the midgut and hindgut groups. The rate of major pathologic response after preoperative chemotherapy in CCLM was higher for the hindgut group (71% vs. 62%, $P=0.012$). There were no significant differences between the two groups with respect to extent of primary tumor, type of preoperative chemotherapy or number of cycles, or proportion with *RAS* mutation (midgut 39%, hindgut 35%, $P=0.324$).

Predictors of Pathologic Response in Study Set

Minor pathologic response was observed in 229 patients (32%). Table 2 lists the results of univariable and multivariable analysis of the predictors of minor pathologic response. Independent predictors of minor pathologic response were midgut origin, absence of bevacizumab, and mutant *RAS*. The minor pathologic response rate in the patients with all three independent predictors was 53% (25/47), while the minor pathologic response rate in the patients with none of these three independent predictors was 23% (43/185) ($P=0.0001$).

Predictors of Survival in Study Set

After a median follow-up time of 27 months (range, 1-143), RFS and OS after hepatic resection were significantly worse in patients with midgut origin primary tumors (RFS rate at 3 years: 15% vs. 27%, $P<0.0001$; OS rate at 3 years: 46% vs. 68%, $P<0.0001$) (Figure 2A and 2B).

On multivariable analysis of factors associated with RFS after hepatic resection, independent predictors of worse RFS were midgut origin, CEA level ≥5 ng/mL at hepatic resection, multiple liver tumors, and *RAS* mutation (Table 3). On multivariable analysis of factors associated with OS after hepatic resection, independent predictors of worse OS were midgut origin, CEA level ≥5 ng/mL at hepatic resection, synchronous CCLM, and *RAS* mutation (Table 3).

In the subgroup of patients with wild-type *RAS* (n=463), RFS and OS were significantly worse in patients with midgut origin primary tumors. In the subgroup of patients with *RAS* mutation (n=262), RFS and OS were also significantly worse in patients with midgut origin primary tumors (Figure 2C and 2D).

Compared to the patients with *RAS* mutation and midgut origin primary tumors (n=92) the patients with wild-type *RAS* and hindgut origin primary tumors (n=317) had better RFS rates at 3 years (30% vs. 11%, $P<0.0001$) and 5 years (26% vs. 11%, $P<0.0001$) and better OS rates at 3 years (72% vs. 35%, $P<0.0001$) and 5 years (56% vs. 16%, $P<0.0001$) (Figure 2C and 2D).

Patient Characteristics and Survival in Validation Set

Among the 252 patients in the validation set, 89 (35%) had midgut origin and 163 (65%) had hindgut origin primary tumors (Figure 1). Supplementary table 1 lists clinicopathologic and operative data for the midgut and hindgut groups. There were no significant differences between the two groups in terms of basic demographics, perioperative outcomes, extent of primary tumor and CCLM, and presence of post-hepatic resection chemotherapy.

After a median follow-up time of 41 months (range, 1-206), RFS and OS after hepatic resection were significantly worse in patients with midgut origin primary tumors (RFS rate at 3 years: 32% vs. 41%, $P=0.027$; OS rate at 3 years: 55% vs. 78%, $P=0.0003$) (Figure 2E and 2F).

On multivariable analysis of factors associated with RFS after hepatic resection, independent predictors of worse RFS were midgut origin and largest CCLM lesion at least 3 cm (Table 3). On multivariable analysis of factors associated with OS after hepatic resection, the only independent predictor of worse outcome was midgut origin (Table 3). Subgroup analysis of survival stratified by *RAS* mutation status and embryonic origin in the validation cohort was not performed since the number of patients with available *RAS* mutation status was small (hindgut origin and wild-type *RAS*, n=16; hindgut origin and mutant *RAS*, n=26; midgut origin and wild-type *RAS*, n=6; midgut origin and mutant *RAS*, n=11).

DISCUSSION

In this study, we found that pathologic response to preoperative chemotherapy and survival after resection of CCLM were predominantly predicted by two biologic features: primary tumor embryonic origin and *RAS* mutation status.

Compared with patients with primary tumors of midgut origin, patients with primary tumors of hindgut origin had a better OS rate at 5 years (52% vs. 32%, $P<0.0001$), a better RFS rate at 5 years (24% vs. 14%, $P<0.0001$), and a better rate of major pathologic response (71% vs. 62%, $P=0.012$). In a separate validation cohort of patients who did not receive preoperative chemotherapy before CCLM resection, hindgut origin was also associated with a better OS rate at 5 years (62% vs. 38%, $P=0.0003$) and RFS rate at 5 years (37% vs. 26%, $P=0.027$). Previous reports have shown the prognostic effects of embryonic origin in patients with both primary CRC and unresectable metastatic CRC, but to the best of our knowledge, this is the first report to show the impact of embryonic origin on survival after resection of CCLM.[9, 11]

We also analyzed the impact of the interaction between embryonic origin of primary colon cancer and *RAS* mutation status on pathologic response to preoperative chemotherapy and survival after resection of CCLM. We previously reported that *RAS*-mutant colorectal liver metastases were associated with worse survival and inferior pathologic response to chemotherapy in patients with resectable colorectal liver metastases.[13, 14] In the current study, we found that the impact of *RAS* mutation status on response to chemotherapy and survival after resection of CCLM was independent of embryonic origin. Patients with the combination of wild-type *RAS* and hindgut primary tumor origin had markedly better survival than patients with the combination of *RAS* mutation and midgut primary tumor origin (RFS at 5 years: 26% vs. 11%, $P<0.0001$; OS at 5 years: 56% vs. 16%, $P<0.0001$).

Our findings suggest that in the era of effective chemotherapy, *RAS* mutation status and primary tumor embryonic origin have greater prognostic importance than the clinicopathologic and surgery-related factors that have traditionally been reported to be associated with outcome (lymph node metastases of primary tumor, size of liver tumors, R0/R1 resection, etc).[19, 21]

Previous studies of unresectable colorectal liver metastases suggested that the radiological response to chemotherapy differed according to embryonic origin.[22] The current study, which was based on resected CCLM, confirmed that the pathologic response to preoperative chemotherapy, which had previously been demonstrated to be associated with survival,[12] also differed according to embryonic origin.

In the present study, we used a validation set of patients who had never received preoperative chemotherapy. Even in this validation set, the 5-year OS rate was better in the patients with hindgut origin tumors than in the patients with midgut origin tumors (62% vs. 38%), suggesting that the effect of embryonic origin on prognosis was independent of the effect of preoperative chemotherapy. In previous reports on studies of unresectable colorectal liver metastases and primary CRC, multiple reasons have been proposed for the worse prognosis of patients with midgut origin tumors, including the high rate of *BRAF* mutations, CpG island methylation, and *ERCC1* expression, all of which were regarded as predictors of

worse sensitivity to chemotherapy.[7, 11, 23-25] However, because colorectal liver metastases with mutant *BRAF* are rarely resected given their extremely rapid growth and aggressive behavior, *BRAF* mutations are not likely to be a main reason for prognostic differences between resectable colorectal liver metastases with midgut and hindgut origin.[20] Furthermore, CpG island methylation is also not likely to be a main reason for such differences because a previous study demonstrated that the proportion of tumors with CpG island methylation was lower in resected colorectal liver metastases (up to 10%) than in primary CRC (15-35%).[26] Further investigations regarding reasons for the differences of oncologic outcomes between midgut and hindgut origin in resectable colorectal liver metastases patients are needed using colorectal liver metastases specimens.

This study has several limitations. It is a retrospective study, but the data were prospectively collected. Additionally, the characteristics of the patients with midgut origin and hindgut origin primary tumors were equivalent in terms of extent of primary tumor and extent of CCLM. Second, the study did not include patients with transverse colon and rectal cancer, because the embryonic origin could not be determined with certainty in the patients with primary transverse colon cancer, and rectal cancers originate from hindgut are evaluated and treated separately in practice from colon cancers.[15] Third, *RAS* mutational status was determined either on resected CCLM or on the primary tumor and the two tumor sites might differ in mutational status. However, a growing body of evidence suggests a high rate of concordance (> 90%) in somatic gene mutational status between primary tumor and related metastases.[27] Finally, the current study excluded a small number of patients treated with anti-EGFR agents, as such treatment could have affected the comparison between patients with wild-type *RAS* and *RAS* mutation. The present patients with hindgut and midgut origin received similar preoperative chemotherapy regimens.

In conclusion, beyond *RAS* mutation status, emerging data highlight the potential relevance of embryonic origin in predicting pathological response to preoperative chemotherapy and survival after resection in the era of effective chemotherapy and individualized management of resectable CCLM. In research practice, this knowledge has implications for future study design, interpretation of data, and analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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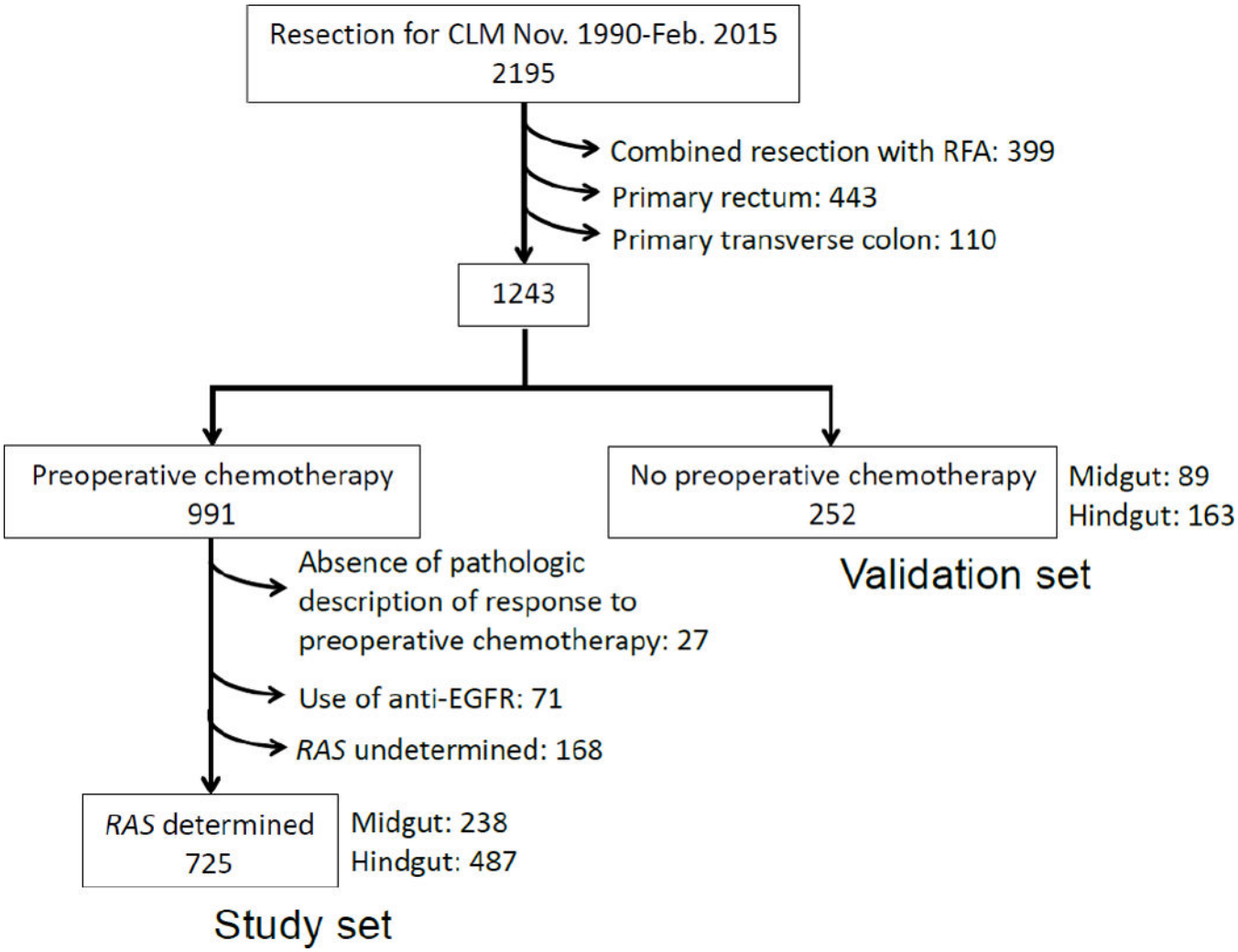

Fig. 1.
Patient selection.

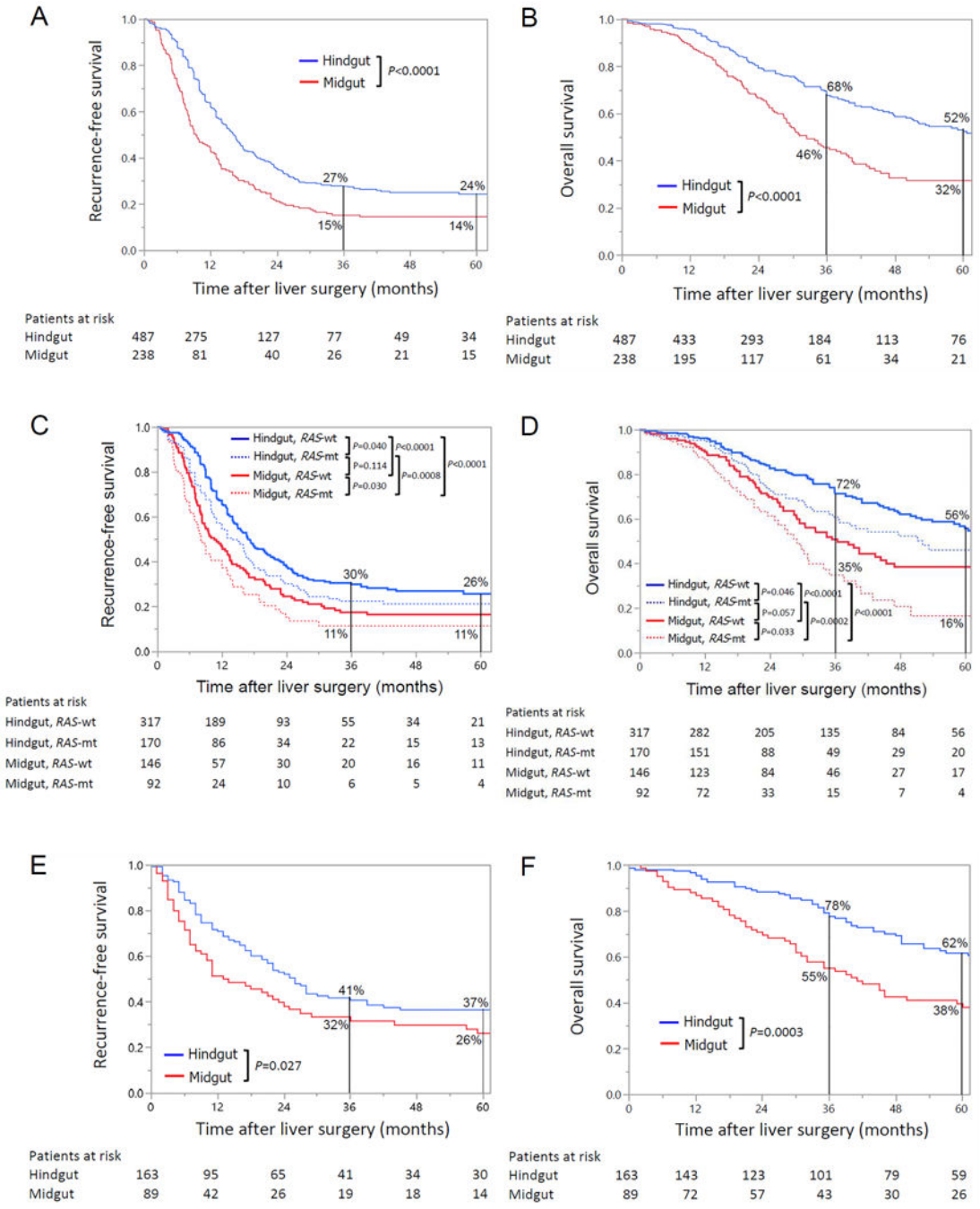

Fig. 2.

Recurrence-free survival (A) and overall survival (B) by embryonic origin of primary colon cancer in patients with colorectal liver metastases who underwent preoperative chemotherapy followed by curative resection. Recurrence-free survival (C) and overall survival (D) by *RAS* mutation status and embryonic origin of primary colon cancer in patients with colorectal liver metastases who underwent preoperative chemotherapy followed by curative resection. Recurrence-free survival (E) and overall survival (F) by

embryonic origin of primary colon cancer in patients with colorectal liver metastases who underwent curative resection without preoperative chemotherapy.

Table 1

Clinicopathologic characteristics by embryonic origin of primary colon cancer *

Characteristic	Total	Midgut	Hindgut	p value (midgut vs hindgut)*
n	725	238	487	
Sex, M: F	422: 303	132: 106	290: 197	0.295
Age, y, median (interquartile range)	58 (50-65)	56 (49-64)	58 (50-66)	0.137‡
Body mass index ≥25 kg/m^2	524 (72)	168 (71)	356 (73)	0.478
Primary tumor				
T1/T2: T3/T4	157: 568	54: 184	103: 384	0.637
Lymph node metastases present	490 (68)	155 (65)	335 (69)	0.323
Pre-hepatic resection chemotherapy				
≤6 cycles	426 (59)	147 (62)	279 (57)	0.250
Fluorouracil-based chemotherapy regimen				
Oxaliplatin	496 (68)	168 (71)	328 (67)	0.379
Irinotecan	225 (31)	66 (28)	159 (33)	0.179
Use of bevacizumab	398 (55)	132 (55)	266 (55)	0.831
Pre-hepatic resection CEA value, ng/mL, median (interquartile range)	2.5 (1.0-7.4)	2.7 (1.0-6.7)	2.5 (1.0-7.7)	0.999‡
Hepatic resection				
Estimated blood loss, g, median (interquartile range)	200 (100-400)	200 (100-390)	200 (100-400)	0.460‡
Red blood cell transfusion	50 (6·9)	10 (8·0)	31 (6·4)	0.420
Operative time, min, median (interquartile range)	210 (130-251)	210 (130-240)	210 (130-259)	0.331‡
Surgical procedure, major: minor	401: 324	132: 106	269: 218	0.954
Liver metastases				
Synchronous	537 (74)	181 (76)	356 (73)	0.395
Classic/Combined/Reverse	414/86/37	140/31/10	274/55/27	0.621
Maximum tumor size, mm, median (interquartile range)	22 (14-35)	21 (13-33)	22 (15-35)	0.737‡
Tumor number, solitary: multiple	278: 447	90: 148	188: 299	0.838
Residual cancer, R0: R1	673: 52	218: 20	455: 32	0.369
Well/moderately/poorly differentiated	71/545/109	25/174/39	46/371/70	0.666
Pathologic response				
Major (viable tumor 0-49%)	496 (68)	148 (62)	348 (71)	*0.012*
Minor (viable tumor 50-100%)	229 (32)	90 (38)	139 (29)	
RAS mutation status				
Wild-type	463 (64)	146 (61)	317 (65)	0.324
Mutant	262 (36)	92 (39)	170 (35)	
Post-hepatic resection chemotherapy	480 (66)	157 (66)	323 (66)	0.924

*Values in table are number of patients (percentage) unless indicated otherwise.

†$\chi 2$ test unless indicated otherwise.

‡Wilcoxon rank-sum test.

CEA, carcinoembryonic antigen.

Table 2

Univariable and multivariable analyses of minor pathologic response

	Minor pathologic response					
	n	**n (%)**	**Univariable p value**	**Odds ratio**	**95% confidence interval**	**Multivariable p value**
All patients	725	229 (32)				
Primary tumor embryonic origin						
Midgut	238	90 (38)	*0.012*	1.55	1.10-2.16	*0.010*
Hindgut	487	139 (29)				
Use of bevacizumab						
Absence	327	119 (36)	*0.012*	1.42	1.03-1.96	*0.034*
Presence	398	110 (28)				
RAS mutation status						
Mutant	262	98 (37)	*0.011*	1.41	1.01-1.95	*0.043*
Wild-type	463	131 (28)				

Table 3

Multivariable Cox regression models for RFS and OS in study set and validation set

	Study set (n=725)				Validation set (n=252)			
	RFS		OS		RFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Midgut origin	1.71 (1.41-2.07)	<*0.0001*	2.04 (1.60-2.59)	<*0.0001*	1.48 (1.05-2.08)	*0.026*	1.90 (1.29-2.77)	*0.0009*
CEA value at hepatic resection ≥5 ng/mL	1.40 (1.15-1.69)	*0.0006*	1.46 (1.15-1.86)	*0.0021*	NS		NS	
Multiple tumors	1.33 (1.10-1.61)	*0.0030*	1.26 (0.99-1.63)	0.066	NS		NS	
Synchronous	1.18 (0.95-1.48)	0.127	1.45 (1.08-1.96)	*0.012*	NS		1.19 (0.81-1.76)	0.373
Maximum size of tumor ≥3 cm	1.16 (0.96-1.40)	0.122	1.26 (0.99-1.60)	0.057	1.45 (1.04-2.03)	*0.030*	1.37 (0.94-2.01)	0.106
Mutant *RAS*	1.30 (1.08-1.57)	*0.0063*	1.43 (1.12-1.82)	*0.0040*	NA		NA	

RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; NA, not applicable; CEA, carcinoembryonic **antigen**; NS, not significant on univariable analysis.