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Significance of Glisson's capsule invasion in patients with colorectal liver metastases undergoing resection

Junko Hiroyoshi [a], Junichi Arita [a], Wataru Gonoi [b], Nobuhisa Akamatsu [a], Junichi Kaneko [a], Kiyoshi Hasegawa [a, *]

[a] Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[b] Department of Radiology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

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ABSTRACT

Background: Significance of Glisson's capsule invasion in colorectal liver metastases (CLM) patients undergoing resection has been little investigated.
Methods: CLM patients (244) with curative resection (2011–2016) were divided into two groups: patients with (Group 1; n = 49 [20%]) and without (Group 2; n = 195 [80%]) histologically-proven Glisson invasion. Eight (16%) Group 1 patients were identified by pre- or intra-operative findings. We compared characteristics between Groups 1 and 2 and determined independent prognosticators.
Results: Group 1 was more commonly associated with right-sided primary, CLM>5 cm, and R1 resections. Independent factors on reduced OS in entire cohort were pre-surgical chemotherapy [hazard ratio (HR): 2.68, P = 0.001], CLM>5 cm (HR: 4.39, P = 0.002), moderate or poor differentiation (HR: 2.38, P = 0.004), and R1 resection (HR: 1.92, P = 0.035).
Conclusions: CLM Glisson invasion was significantly associated with R1 resection. Advancements in determining Glisson invasion pre- or intra-operatively might produce benefits for CLM patients undergoing resection by reducing R1 resection.

Introduction

Colorectal liver metastases (CLM) occur in 30%–50% of colorectal cancer (CRC) patients and are associated with approximately 66% of CRC deaths.[1,2] Hepatectomy offers the best chance for long-term survival in CLM patients[3]; despite advancements in perioperative chemotherapy[4] and our increased understanding of tumor biology,[5] more than 50% of patients develop recurrences within 2 years of CLM resection, among which >50% are associated with intrahepatic recurrence.[6] These recurrences can be fatal due to liver insufficiency.[7] Even in the era of multidisciplinary treatment and genetic typing, R1 resection has been shown to be an independent predictor of intrahepatic recurrence following CLM resection.[6]

While CLMs commonly form nodular lesions in the liver parenchyma,[8] some researchers have reported CLM with Glisson's capsule invasion in a substantial percentage of patients.[9] In the context of parenchymal-preserving surgery for CLM to improve salvageability,[10] cases accompanied with Glisson invasion might be associate with a higher frequency of intrahepatic recurrence after resection due to R1 resection or narrower margins at initial resection.[11]

The actual frequency of Glisson invasion and its oncologic and clinical impacts in CLM have not been fully investigated; thus, the aims of this study were to (1) estimate the prevalence of Glisson invasion in a surgical cohort of CLM patients and (2) evaluate the clinical significance of Glisson invasion in CLM patients undergoing resection.

Materials and methods

Study design and population

This retrospective study was performed at a single tertiary hospital in Tokyo, Japan. The study protocol conformed to the ethical guidelines of the University of Tokyo Hospital as reflected in *a priori* approval by the institutional review board (Referee No. 2158-(7)), and because of its retrospective nature, informed

* Corresponding author. Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan.
E-mail address: kihase-tky@umin.ac.jp (K. Hasegawa).

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consent was not required. All procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Between January 2011 and December 2016, we enrolled 244 consecutive CLM patients who underwent hepatectomy with curative intent as initial treatment at the University of Tokyo Hospital; all medical, radiological, and pathological records were reviewed. To clarify the clinical impact of Glisson invasion in CLM patients who underwent resection, we divided the cohort (n = 244) into two groups: (1) patients with histologically proven Glisson invasion (Group 1; n = 49 [20%]), and patients without Glisson invasion (Group 2; n = 195 [80%]). Group 1 included both patterns of intra-Glisson growth, microscopic presence of a transition from the normal biliary epithelium to an abnormal epithelium, and a tumor plug within a dilated Glisson.[12] In patients with multiple tumors, Group 1 was assigned when at least one lesion was histologically associated with Glisson invasion.

The patients' background characteristics are summarized in Table 1. Group 1 was more frequently associated with right-sided primary lesions with larger CLM. Among Group 1 patients, eight (16%) had macroscopic Glisson invasion, as defined by cases with suspected Glisson invasion by pre- and/or intra-operative diagnostic images and histological confirmation. Diagnostic imaging findings in these patients included intrahepatic biliary dilatation connecting with the primary tumor on preoperative computed tomography and/or magnetic resonance imaging (n = 8), and the presence of a thickened Glisson tract on intraoperative ultrasonography (n = 7). There were no significant differences in the frequencies of extrahepatic metastases or preoperative chemotherapy between Groups 1 and 2. A subgroup comparison of background characteristics among Group 1 between patients with macroscopic Glisson invasion and those without (named the microscopic subgroup) is described in Supplementary Table 1 and showed no significant differences. Representative case showing macroscopic Glisson invasion is shown in Supplementary Figure 1.

Treatment strategy

Upfront resections were performed for patients with initially resectable CLM[11] until around 2012. After 2012, this study included patients with technically unresectable CLM at initial presentation who were converted to resectable CLM after systemic chemotherapy, and patients who were assigned to a randomized controlled study of resectable CLM regarding the effect of perioperative chemotherapy (UMIN000007787, http://www.umin.ac.jp/ctr/index.htm).

The indications for hepatectomy were as follows: (1) all CLM could be removed with adequate margins and an acceptable volume of hepatic remnant, (2) both the primary CRC and extrahepatic metastases, if any, were resected or controllable, and (3) patients were fit for surgical resection.[11] Surgical indications were decided by mutual consent among members of a multidisciplinary team. The standard procedure for treating CLM was parenchymal-sparing hepatectomy.[10] Anatomical resection, namely complete resection of the territory supplied by the respective Glisson pedicle, was suboptimally selected based on pre- and intra-operative findings to ensure safer surgical margins. Frozen section diagnosis was used to secure the optimal surgical margin by additional resection.

Table 1
CLM Patients' clinical characteristics.

	Total		Group 1 (CLM with Glisson invasion)		Group 2 (CLM without Glisson invasion)		*P*[a]
	n = 244		n = 49		n = 195		
Age (years)	65	(29–87)	66	(29–83)	65	(34–87)	0.262[b]
Male, n (%)	147	(60)	29	(59)	118	(61)	0.865
Body mass index, kg/m^2	21.6	(14.6–30.7)	21.7	(14.6–30.2)	21.5	(15.7–30.7)	0.763[b]
Primary disease							
Right side, n (%)	41	(17)	13	(27)	28	(14)	**0.042**
T3/T4, n (%)	224	(92)	42	(84)	182	(93)	0.285
Node positive, n (%)	167	(68)	32	(64)	135	(69)	0.916
Histological differentiation							
Well, n (%)	91	(37)	22	(45)	69	(35)	0.095
Moderate, n (%)	138	(57)	21	(43)	117	(60)	
Poor, n (%)	8	(3)	4	(8)	4	(2)	
CEA, ng/dl	10.8	(0.8–710)	14.1	(1.8–591)	10.1	(0.8–710)	0.349[b]
CA19-9, U/ml	21	(1–4825)	26	(1–4825)	20	(1–4346)	0.103[b]
Fong's clinical risk score[23]	2	(0–4)	2	(0–4)	2	(0–4)	0.499
KRAS mutant, n (%)	74	(38)	16	(33)	58	(30)	0.284
Liver metastasis							
Number of nodules	2	(1–28)	2	(1–19)	2	(1–28)	0.852[b]
Maximum tumor size, cm	2.6	(0.4–15)	3.0	(0.8–12)	2.5	(0.4–15)	**0.015**[b]
Concurrent with extrahepatic metastasis, n (%)	46	(19)	6	(12)	40	(21)	0.186
Lung metastasis, n (%)	28	(11)	3	(6)	25	(13)	0.189
Nodal metastasis, n (%)	12	(5)	2	(4)	10	(5)	0.762
Dissemination, n (%)	11	(5)	1	(2)	10	(5)	0.352
Adrenal metastasis, n (%)	2	(1)	1	(2)	1	(1)	0.289
Others, n (%)	5	(2)	0	(0)	5	(3)	0.257
Pre-hepatic resection chemotherapy, n (%)	92	(38)	19	(39)	73	(37)	0.863
Oxaliplatin-based, n (%)	80	(33)	16	(33)	64	(33)	0.690
Irinotecan-based, n (%)	24	(10)	6	(12)	18	(9)	0.541
Bevacizumab, n (%)	50	(20)	11	(22)	39	(20)	0.728
Anti-EGFR agents, n (%)	42	(17)	9	(18)	33	(17)	0.866
≥7 cycles, n (%)	52	(21)	9	(18)	43	(22)	0.366
≥2 regimens, n (%)	31	(13)	8	(16)	23	(12)	0.384

Data are presented as median (range) unless otherwise indicated.
CLM, colorectal liver metastases; CEA, Carcinoembryonic antigen; CA19-9, Carbohydrate antigen 19-9; EGFR, epidermal growth factor receptor.
[a] χ^2 test unless otherwise indicated.
[b] Wilcoxon rank-sum test.

Table 2
Intraoperative and postoperative findings.

	Total		Group 1 (CLM with Glisson invasion)		Group 2 (CLM without Glisson invasion)		P[a]
	n = 244		n = 49		n = 195		
Operative findings							
Anatomical resection, n (%)	86	(35)	27	(55)	59	(30)	**0.001**
Operation time (min)	400	(113–970)	423	(137–868)	393	(113–970)	0.274[b]
Blood loss (ml)	500	(10–2750)	625	(30–1920)	490	(10–2750)	**0.043**[b]
Blood transfusion, n (%)	20	(8)	5	(10)	15	(8)	0.567
R1 resection, n (%)	50	(20)	15	(31)	35	(18)	**0.0496**
Parenchymal margin, n (%)	41	(17)	8	(16)	33	(17)	0.921
Glisson margin, n (%)	8	(3.3)	8	(16)	0		–
Detachment margin from hepatic vein, n (%)	1	(0.4)	0		1	(0.5)	0.615
Detachment margin from adjacent organ, n (%)	1	(0.4)	0		1	(0.5)	0.615
Histological differentiation of CLM							
Well, n (%)	69	(28)	18	(37)	51	(26)	0.182
Moderate, n (%)	109	(45)	19	(39)	90	(46)	
Poorly, n (%)	4	(2)	2	(4)	2	(1)	
Unknown, n (%)	62	(25)	10	(20)	52	(27)	
Major complications (Clavien–Dindo Grade 3a+)	26	(11)	3	(6)	23	(12)	0.250
90-day mortality, n (%)	5	(2)	1	(2)	4	(2)	0.996
Recurrences, n (%)	169	(69)	33	(67)	136	(70)	0.745
Liver, n (%)	105	(43)	29	(59)	76	(39)	**0.011**
Lung, n (%)	54	(22)	8	(16)	46	(24)	0.274
Lymph node, n (%)	21	(9)	4	(8)	17	(9)	0.902
Dissemination, n (%)	13	(5)	3	(6)	10	(5)	0.782
Colon, n (%)	7	(3)	1	(2)	6	(3)	0.698
Others, n (%)	8	(3)	0	(0)	8	(4)	0.149
Postoperative chemotherapy, n (%)	108	(44)	16	(33)	92	(47)	0.067

Data are presented as median (range) unless otherwise indicated.
CLM, colorectal liver metastases.
[a] χ^2 test unless otherwise indicated.
[b] Wilcoxon rank-sum test.

Postoperative follow-up

Major complications were defined as those classified as Clavien–Dindo Grade 3a + that developed within 90 d of surgery.[13–15] Postoperative chemotherapy was administered to patients who were candidates for adjuvant chemotherapy based on their primary disease and to patients assigned to clinical trials (UMIN000007787 and UMIN000000013, http://www.umin.ac.jp/ctr/index.htm).[16] Patients were followed-up after surgery by obtaining histories and performing physical examinations, laboratory evaluations, and axial imaging every 3–4 months for the first 2 years and every 4–6 months for the subsequent 3 years. When recurrences were diagnosed, the treatment strategy was decided by multidisciplinary consensus. The indications for repeat hepatectomy for recurrent tumors was the same as those for initial resection.

Statistical analysis

Continuous variables are expressed as median (range) and were compared using the Wilcoxon rank-sum test. Categorical variables were compared with Pearson's chi-square test. Overall survival (OS) and recurrence-free survival (RFS) were defined as the duration between the date of initial treatment and the date of death, and the

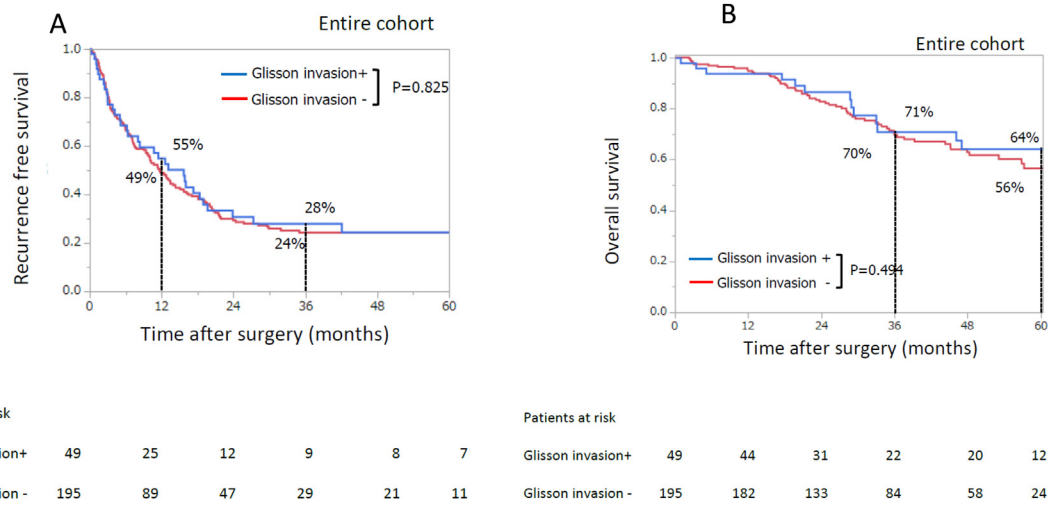

Fig. 1. Recurrence-free (A) and overall (B) survival rates were similar between Group 1 (with Glisson invasion) and Group 2 (without Glisson invasion) patients.

duration between the date of radical resection and the date of diagnosing the first recurrence, respectively. Survival curves were generated by the Kaplan–Meier method, and differences between curves were evaluated with the log-rank test. Univariable and multivariable analyses for RFS and OS were performed using the Cox proportional hazards model. Variables for which P was <0.2 in univariable analysis were entered into multivariable analysis. $P < 0.05$ was considered significant in all analyses. Statistical analyses were performed with JMP PRO software, v13.2.0 (SAS Institute Inc., Cary, NC, USA).

Results

Intraoperative and postoperative findings

Intraoperative findings are summarized in Table 2. The frequency of anatomical resection and the amount of estimated blood loss were both significantly higher in Group 1 compared with Group 2. Group 1 patients underwent R1 resection significantly more often, and the findings of frozen sections from four patients (8.2% [4/49]) showed that they required additional resection to

Table 3
Univariable and multivariable analysis of recurrence-free survival.

Variable	N	Recurrence-free survival (%)[a]				Multivariable P-value[c]
		1-year	3-year	Univariable P-value[b]	Hazard ratio (95% confidence interval)	
All patients	244	50	25			
Sex						
M	147	48	25	0.658	–	–
F	97	53	26			
Age, years						
≤70	74	54	24	0.877	–	–
>70	170	47	25			
Body mass index, kg/m^2[d]						
≤25	198	54	21	0.889	–	–
>25	45	49	26			
Primary location						
Right side	41	57	17	0.566	–	–
Left side	203	49	26			
Primary T category[d, e]						
≥T3	224	49	25	0.146	2.18 (1.02–5.67)	**0.045**
≤T2	17	69	33			
Primary nodal status[d, e]						
Positive	167	44	21	**0.005**	1.73 (1.14–2.71)	**0.001**
Negative	70	67	38			
CEA[e]						
>5 ng/ml	184	43	21	**0.003**	1.40 (0.91–2.24)	0.130
≤5 ng/ml	60	71	37			
CA19-9[e]						
>37 U/ml	80	41	14	**0.001**	1.94 (1.31–2.83)	**0.001**
≤37 U/ml	164	54	30			
KRAS[d]						
Mutant	74	43	17	0.552	–	–
Wild-type	122	46	23			
Pre-hepatic resection chemotherapy[e]						
Yes	92	35	13	**<0.001**	1.99 (1.33–2.96)	**0.001**
No	152	59	32			
Number of liver metastases[e]						
Multiple	159	44	17	**<0.001**	1.57 (1.04–2.41)	**0.032**
Solitary	85	61	41			
Maximum size of liver metastases[e]						
>5 cm	31	28	9	**0.001**	2.51 (1.30–4.49)	**0.008**
≤5 cm	213	53	27			
Concurrent with extrahepatic metastasis[e]						
Yes	50	25	12	**0.026**	1.43 (0.88–2.26)	0.146
No	194	57	28			
Surgical margin of CLM[e]						
R1	50	31	10	**<0.001**	1.65 (1.06–2.51)	**0.026**
R0	194	55	29			
CLM histological differentiation[d, e]						
Moderate or poor	113	46	22	0.167	1.40 (0.96–2.08)	0.080
Well	69	55	25			
CLM with Glisson invasion						
Yes	49	55	28	0.825	–	–
No	195	49	24			
Postoperative chemotherapy[e]						
No	136	46	26	0.182	1.21 (0.82–1.78)	0.334
Yes	108	55	25			

Threshold CEA and CA19-9 levels were decided according to the value that was the upper normal serum level in this institution.
CEA, Carcinoembryonic antigen; CA19-9, Carbohydrate antigen 19-9; CLM, colorectal liver metastases.
[a] Kaplan-Meier analysis.
[b] Log-rank test.
[c] Cox regression model.
[d] Some data were missing.
[e] Variables entered into the Cox regression model.

ensure optimal surgical margins. In terms of the specific type of positive margins in Group 1, the frequency of positive Glisson margins was same as that of R1 parenchymal margins (Table 2). Although there were only eight patients with macroscopic Glisson invasion, they were associated with a higher frequency of anatomical resection, longer operation times, and a higher frequency of R1 resection than patients with microscopic Glisson invasion (Supplementary Table 2). The frequencies of R1 resection in patients with macroscopic Glisson invasion, microscopic Glisson invasion, and without Glisson invasion were 63%, 24%, and 18%, respectively (Table 2 and Supplementary Table 2).

Long-term outcomes

While patients in Group 1 were more frequently associated with intrahepatic recurrence after curative resection, there was no significant difference in the total frequency of postoperative recurrence (Table 2). Among the 29 Group 1 patients with intrahepatic recurrence after curative resection, 13 underwent repeated hepatic resection, and 4 (31%) were found with Glisson invasion during the

Table 4
Univariable and multivariable analysis of overall survival.

Variable	N	Overall survival (%)[a]				Multivariable P-value[c]
		3-year	5-year	Univariable P-value[b]	Hazard ratio (95% confidence interval)	
All patients	244	70	58			
Sex						
M	147	71	63	0.202	–	–
F	97	67	50			
Age, years						
≤70	74	67	64	0.671	–	–
>70	170	71	56			
Body mass index, kg/m^2[d]						
≤25	198	68	56	0.338	–	–
>25	45	77	70			
Primary location						
Right side	41	61	51	0.332	–	–
Left side	203	71	60			
Primary T category[d]						
≥T3	224	71	58	0.656	–	–
≤T2	17	66	66			
Primary nodal status[d e]						
Yes	167	68	57	0.135	1.24 (0.67–2.47)	0.511
No	70	78	65			
CEA						
>5 ng/ml	184	68	55	0.239	–	–
≤5 ng/ml	60	74	71			
CA19-9[e]						
>37 U/ml	80	59	51	0.056	1.32 (0.75–2.30)	0.337
≤37 U/ml	164	75	61			
KRAS[d]						
Mutant	74	52	52	0.903	–	–
Wild-type	122	54	54			
Pre-hepatic resection chemotherapy[e]						
Yes	92	58	36	**<0.001**	2.68 (1.48–4.89)	**0.001**
No	152	76	69			
Number of liver metastases[e]						
Multiple	159	66	53	0.055	1.02 (0.52–1.92)	0.953
Solitary	85	76	68			
Maximum size of liver metastases[e]						
>5 cm	31	55	41	**0.027**	4.39 (1.83–9.46)	**0.002**
≤5 cm	213	72	61			
Concurrent with extrahepatic metastasis[e]						
Yes	50	47	63	**0.002**	1.70 (0.85–3.22)	0.131
No	194	73	62			
Surgical margin of CLM[e]						
R1	50	55	37	**0.001**	1.92 (1.05–3.40)	**0.035**
R0	194	74	65			
CLM histological differentiation[e]						
Moderate or poor	113	60	49	**0.021**	2.38 (1.32–4.50)	**0.004**
Well	69	77	67			
CLM with Glisson invasion						
Yes	49	71	64	0.494	–	–
No	195	69	57			
Postoperative chemotherapy						
Yes	108	71	57	0.636	–	–
No	136	69	61			

Threshold CEA and CA19-9 levels were decided according to the value that was the upper normal serum level in this institution.
CEA, Carcinoembryonic antigen; CA19-9, Carbohydrate antigen 19-9; CLM, colorectal liver metastases.
[a] Kaplan-Meier analysis.
[b] Log-rank test.
[c] Cox regression model.
[d] Some data were missing.
[e] Variables entered into the Cox regression model.

Table 5
Studies of the frequency and prognosis of colorectal liver metastases patients with Glisson invasion undergoing radical resection.

Author	Year	Frequency		5-year overall survival	Significance on survival
		Macroscopic Glisson invasion	Microscopic Glisson invasion		
Yamamoto et al.[17]	1995	8/40 (20%)	16/40 (40%)	NA	NA
Okano et al.[9]	1999	18/149 (12%)	62/149 (42%)	80% (macroscopic) 48% (microscopic) 57% (no invasion)	Macroscopic invasion was an independent predictor of good prognosis
Povoski et al.[18]	2000	7/313 (2.2%)	8/313 (2.6%)	NA	NA
Kubo et al.[19]	2002	23/217 (11%)	89/217 (41%)	NA	NA
Sugiura et al.[11]	2006	6/103 (5.8%)	NA	NA	NA
Estrella et al.[12]	2013	9/170 (5.3%, prospective cohort) 22/1144 (1.9%, retrospective cohort)	18/170 (11%, prospective cohort) 41/1144 (3.6%, retrospective cohort)	33% (macroscopic) 57% (microscopic) 49% (no invasion)	Not significant
Present study	2018	8/244 (3.3%)	49/244 (20%)	64% (with Glisson invasion) 56% (without Glisson invasion)	Not significant

NA; not applicable.

second surgery.

During the median follow-up time of 33 months (range: 0.9–82 months) RFS and OS in Groups 1 and 2 were similar (Fig. 1). Among the subgroup of patients with Glisson invasion, the RFS in patients with macroscopic Glisson invasion (n = 8) was relatively poor compared with patients with microscopic Glisson invasion (n = 41), although this result was not statistically significant (Supplementary Figure 2A). OS was not significantly different between patients with macroscopic and microscopic Glisson invasion (Supplementary Figure 2B).

Predictors of survival

Multivariable analysis of RFS in the entire cohort (n = 244) showed that the independent predictors of worse outcomes were advanced primary T category (≥T3), primary node positivity, higher CA19-9 (>37 U/ml), presence of pre-hepatic resection chemotherapy, multiple CLM, larger CLM (>5 cm), and R1 resection (Table 3). Multivariable analysis of OS in the entire cohort (n = 244) showed that the independent predictors of worse outcomes were presence of pre-hepatic resection chemotherapy, larger CLM (>5 cm), moderately or poorly differentiated CLM, and R1 resection (Table 4).

Discussion

Our results demonstrated that there was a substantial proportion (20%) of CLM patients with Glisson invasion among patients undergoing curative resection. Furthermore, the majority of cases (84%) were accompanied with microscopic Glisson invasion rather than macroscopic. While patients with Glisson invasion had a higher frequency of intrahepatic recurrence after resection, a significant prognostic impact of Glisson invasion was not identified.

According to previous studies, the frequencies of macroscopic and microscopic Glisson invasion among CLM patients undergoing radical resection are 2.2%–20% and 2.6%–42%, respectively (Table 5), which encompass our results.[9,11,12,17–19] Regarding the prognostic impact of Glisson invasion in CLM patients undergoing radical resection, one report indicated that the presence of macroscopic Glisson invasion was associated with better prognoses compared with the presence of microscopic or the absence of Glisson invasion,[9] while another report, similar to this study, failed to reach such conclusions.[12] This study found that CLM patients with macroscopic Glisson invasion who underwent resection might have poorer RFS.

We also determined that Glisson invasion in CLM patients undergoing resection was significantly associated with R1 resection, which was an independent predictor of worse RFS and OS after curative resection, despite the higher frequency of anatomical resection for these patients. The higher frequency of R1 resection in Group 1 might be attributable to the substantial frequency of positive Glisson margins in Group 1. On the basis of these results, pre- or intra-operative recognition of Glisson invasion during CLM surgery is important to avoid unnecessary R1 resection. While typical imaging findings of CLM Glisson invasion have not been clinically established, a recent case report demonstrated the usefulness of contrast-enhanced intraoperative ultrasound to visualize the extent of Glisson invasion, leading to accurate R0 resection.[20]

The frequency of right-sided primary disease was significantly higher in Group 1 compared with Group 2, which was in-line with the suggestion from previous studies that right-sided primary CRC is associated with an increased frequency of lymphovascular invasion.[21,22] Whereas, two studies have suggested that patients with macroscopic Glisson invasion were paradoxically associated with less aggressive features, such as a high frequency of well-differentiated histology, low frequency of primary vascular invasion, and a long disease-free interval between primary CRC and CLM.[9,19] An explanation of this discrepancy regarding predictors of Glisson invasion is difficult, and further studies are necessary to clarify the predictors of Glisson invasion.

This study had limitations, including its retrospective nature and small number of patients with Glisson invasion. As the majority (159/244, 65%) of this cohort showed multiple CLM, further analysis evaluating Glisson invasion, R0/R1 resection, and local tumor progression-free survival per lesion would be intriguing. Furthermore, this study lacked mutational information (*KRAS* was evaluated in 196/244 [80%] samples). Finally, due to our previous policy of upfront surgery, the cohort undergoing resection following preoperative chemotherapy could be limited to those with aggressive tumor biology, which might be associated with the negative prognostic impact of the presence of pre-hepatic resection chemotherapy. For the same reason, only 92/244 (38%) and 108/244 (44%) patients underwent pre- and post-operative chemotherapy, respectively.

Conclusions

While a considerable proportion of CLM patients undergoing resection had Glisson invasion, which could enhance the possibility of R1 resection, it was determined histologically in most patients. Pre- or intra-operative recognition of Glisson invasion could lead an avoidance of R1 resection, which might improve long-term post-surgical outcomes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.01.023.

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