Original Article

Prevalence, patterns, risk factors and outcomes of peritoneal metastases after laparoscopic hepatectomy for hepatocellular carcinoma: a multicenter study from China

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Background: We aim to investigate the prevalence, patterns, risk factors, and outcomes of peritoneal metastases (PM) after curative laparoscopic hepatectomy (LH) for hepatocellular carcinoma (HCC).

Methods: A multicenter cohort of 2,138 HCC patients who underwent curative LH from August 2010 to December 2016 from seven hospitals in China was retrospectively analyzed. The incidence of PM following LH was evaluated and compared with that in open hepatectomy (OH) after 1:1 propensity score matching (PSM).

Results: PM prevalence was 5.1% (15/295) in the early period [2010–2013], 2.6% (47/1,843) in the later period [2014–2016], and 2.9% (62/2,138) in all LH patients, which was similar to 4.0% (59/1,490) in the OH patients. The recurrence patterns, timing, and treatment did not significantly vary between the LH and OH patients (P>0.05). Multivariate logistic regression revealed that tumor diameter >5 cm, non-anatomical resection, presence of microvascular invasion, and lesions <2 cm from major blood vessels were independent risk factors of PM after LH. Of the 62 cases with PM, 26 (41.9%) had PM only, 34 (54.9%) had intrahepatic recurrence (IHR) and PM, and 2 (3.2%) had synchronous extraperitoneal metastases (EPM). Patients with resectable PM had a 5-year overall survival (OS) of 65.0% compared to 9.0% for unresectable PM (P=0.001).

Conclusions: The prevalence, patterns and independent risk factors of PM were identified for HCC patients after LH. LH was not associated with increased incidence of PM in HCC patients for experienced surgeons. Surgical re-excision of PM was associated with prolonged survival.

Keywords: Prevalence; hepatocellular carcinoma (HCC); peritoneal metastases (PM); laparoscopic hepatectomy (LH); open hepatectomy (OH)

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Introduction

Peritoneal metastases (PM) are recognized at laparoscopy or autopsy at a prevalence of 3% to 16% (1,2). PM are indicators of a dismal prognosis for patients with hepatocellular carcinoma (HCC) (3). Systemic chemotherapy is first-line treatment for PM in HCC (4), achieving a median survival of 2.1–12.5 months which is much lower than that for patients without PM (5). Several studies have reported that hyperthermic intraperitoneal chemotherapy (HIPEC) and aggressive peritoneal metastasectomy can prolong median overall survival (OS) to 46.7 months in patients with relapsed HCC (6-9). However, only 36.1% of these patients are eligible for curative re-excision (6,10), and the prognosis is strongly influenced by the extent of peritoneal lesions. Unfortunately, the detection methods and serum biomarkers employed for evaluation of PM recurrence fail to recognize them early and robust predictive markers for PM are lacking. Hence, early prediction of PM status in HCC is crucial to devise more individualized management to prolong survival.

Laparoscopic hepatectomy (LH) has been applied to treat HCC. The number of HCC patients undergoing LH has grown considerably (11). Studies have demonstrated that laparoscopic procedures carry an inspiring long-term prognosis compared with that using open hepatectomy (OH) (12-14). However, there are persistent doubts regarding the risk of PM because viable tumor cells may contaminate laparoscopic wounds via direct transfer from laparoscopic instruments or by aerosolization of malignant cells liberated into the peritoneal cavity during pneumoperitoneum (15). To date, only limited studies on PM following LH have been reported. However, due to the small number of patients and single-center data recruitment, the authors did not draw a convincing conclusion as to whether LH augmented the PM risk (16). Some researchers have argued that tumor diameter >5 cm, microvascular invasion (MVI), and positive margins are potential risk factors for PM during open surgery (6,17). Nevertheless, the prevalence, risk factors and molecular mechanism underlying PM after LH have not been elucidated. Furthermore, recognition of small peritoneal nodules at an early stage of HCC is difficult because of the unsatisfactory discrimination abilities of imaging devices. Therefore, the prevalence and risk factors for PM after LH merits further study so as to take preventive measures during resection as well as to plan the postoperative follow-up program.

Using a large, multicenter cohort, we investigated the prevalence, patterns, risk factors, treatment, and long-term outcomes associated with PM in HCC after LH. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-506/rc).

Highlight box

Key findings

- Peritoneal metastases (PM) prevalence after curative laparoscopic hepatectomy (LH) is 2.9% in this multi-center retrospective observational study.
- Laparoscopic surgery would not augment PM risk if undertaken by experienced surgeons.

What is known and what is new?

- The prevalence, patterns and independent risk factors of PM were identified for hepatocellular carcinoma (HCC) patients after LH.
- Aggressive surgery for recurrent PM might benefit long-term prognosis for HCC.

What is the implication, and what should change now?

- Increased caution is required for surgeons during the initial learning phase when performing LH for HCC.

Methods

Patient characteristics

Using a multicenter dataset, 2,138 consecutive patients who underwent curative LH for HCC between August 2010 to December 2016 in seven Chinese hospitals were identified. "Curative LH" was defined as complete removal of all lesions with a clear margin (R0 resection). The inclusion criteria were: (I) curative liver resection; (II) primary HCC diagnosed pathologically with absence of distant metastases; (III) no macroscopic vascular invasion or tumor rupture; (IV) no previous treatment for HCC; (V) precise follow-up information and data on prognostic variables. This research was carried out in accordance with the Declaration

of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Review Board of Tongji Hospital (Wuhan, China) (TJ-IRB20210935). Written informed consent for clinical research of the data generated during therapy was obtained from all enrolled patients.

Preoperative assessment and surgical procedures

Preoperative assessment was conducted 1–2 days before surgery. The resectability of liver lesions was defined according to complete imaging survey and preoperative liver function. Child-Pugh grade C was identified as an absolute contraindication to surgery. The type of hepatectomy was decided mainly by integrated consideration of the tumor, liver status, and the retention rate of indocyanine green, as described previously (18). Perioperative management was (in general) standardized and consistent at all participating centers.

Definition and management of PM

Follow-up details were obtained from outpatient review, medical records, and telephone interviews. In general, routine workup incorporated detection of liver function and tumor markers, ultrasonography, enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) once every 3 months in the first year, and every 4–6 months thereafter. Positron emission tomography (PET; using ^{18}F-FDG), and PET-CT were undertaken if necessary. Recognition of recurrent PM was based on positive findings of imaging examination and incorporation of data for enhanced CT and/or MRI (19,20). Further imaging examinations for recurrence screening were done if relevant laboratory abnormalities and symptoms were identified.

"PM recurrence" was defined as intra-abdominal local recurrence with tumor growth in the peritoneum, microscopic tumor growth in the peritoneum or ascites containing cancer cells (21). We classified patients into those without PM ("No-PM") and those with PM. Further analysis of resectable PM and unresectable PM was carried out. Appropriate management strategies for relapsed disease were determined based on recurrence patterns and performance status. The criteria for patients receiving aggressive surgery were as follows: having resectable PM and without compromising essential anatomic structures such as major vasculature, manageable or resectable intrahepatic recurrences (IHRs), good Eastern Cooperative Oncology Group (ECOG) performance (0–1), Child's A liver disease, and adequate heart and renal function (6,10). In general, complete peritoneal metastasectomy [cytoreductive surgery (CRS)] plus HIPEC or concurrent liver resection was considered to be potentially curative resection. Palliative therapy incorporated repeat resection of peritoneal lesions as much as possible and/or local therapy in synchronous liver lesions.

Statistical analyses

Categorical variables are expressed as numbers and percentages. Continuous covariates are presented as the median and interquartile range (IQR). Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test (two-tailed χ^2 test). Comparisons between continuous variables were conducted using the Mann-Whitney U-test. Subsequently, X-tile (Yale University, New Haven, CT, USA) was used to identify the optimal cutoff of alpha-fetoprotein (AFP), diameter, and the Peritoneal Cancer Index (PCI). Age, sex, tumor size, tumor number and Barcelona Clinic Liver Cancer (BCLC) stage were taken as covariates, and 1:1 matching between the LH and OH groups was conducted within a caliper value of 0.02. Univariable and multivariable logistic regression analyses were undertaken to identify the potential risk factors of PM. OS was calculated using the Kaplan-Meier method. Subgroup analyses were done in patients who developed PM in HCC. The difficulty of LH was graded by the classification by Kawaguchi *et al.* (22). Univariate and multivariate Cox regression analyses were used to evaluate the predictors associated with long-term survival in patients with PM. R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses. $P<0.05$ (two-sided) was considered significant.

Results

Clinicopathological characteristics at the initial resection

Recruitment pathway of eligible HCC patients and work flow is presented in *Figure 1*. *Table 1* presents the clinicopathological characteristics of the enrolled LH patients. Of the 2,138 patients who were enrolled in the LH group, 1,826 (85.4%) were male and the median age of patients with primary HCC was 52.1 (IQR, 39.1–68.8) years. We found that 1,909 patients (89.3%) had chronic infection

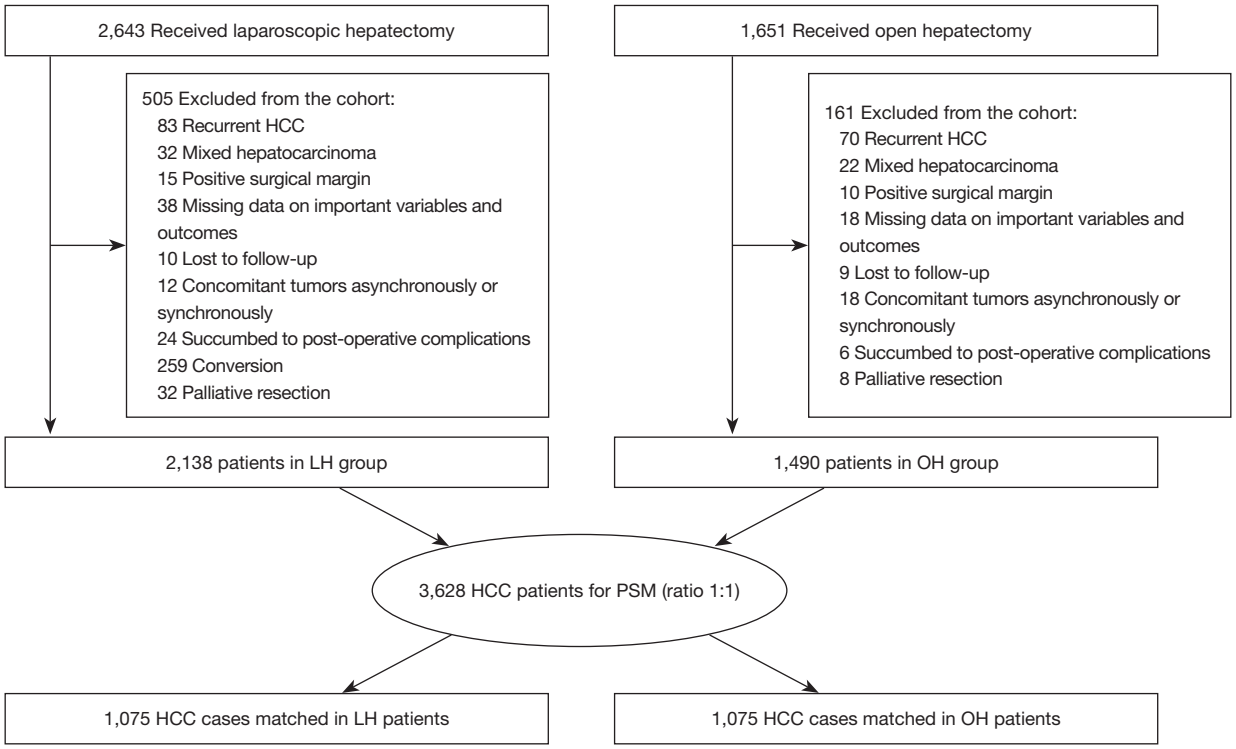

Figure 1 Flow diagram of the research strategy. HCC, hepatocellular carcinoma; LH, laparoscopic hepatectomy; OH, open hepatectomy; PSM, propensity score matching.

with the hepatitis-B virus and 672 (31.4%) patients had a high AFP level (≥400 ng/mL). Most individuals had an early-stage tumor (BCLC stage 0–A: n=1,997, 93.4%) and well-compensated liver function (Child-Pugh class A: n=2,049, 95.8%). Median tumor diameter was 4.2 (IQR, 2.5–5.0) cm and 239 (11.2%) patients had multiple lesions. A lesion <2 cm from a major blood vessel was noted for 30.1% patients (n=644). At the time of surgery, all patients underwent curative LH with a R0 resection. Postoperative pathology revealed a group of patients with satellite foci (n=338, 15.8%) and intratumor necrosis (n=216, 10.1%). Most masses were well-to-moderately differentiated (n=1,179, 55.1%); a subset of HCC lesions had MVI (n=663, 31.0%). There were 1,490 HCC patients enrolled in the OH group, while 1,075 cases were divided into the OH patients and analyzed subsequently after 1:1 propensity score matching (PSM). The baseline and clinicopathologic characteristics before and after PSM were presented in *Table 2*. The distributions of propensity scores before and after matching were summarized in Figure S1.

Prevalence, patterns, and distribution of PM after LH and OH

During a median follow-up of 67.0 months, a total of 1,158 (54.2%, LH group) and 752 (50.5%, OH group) patients had HCC recurrence, with median DFS times of 11 months (IQR, 6–17) and 11 months (IQR, 5–16), respectively. There was no significant difference between the two groups regarding the recurrence patterns, DFS values or treatments, except of LH having a higher risk of IHR compared with OH (70.6% *vs.* 69.1%, P=0.013), which was balanced after PSM (Table S1); 2.9% (62/2,138) of HCC patients developed PM after LH in our multicenter cohort, which was lower than 4.0% (59/1,490) in the OH patients (P=0.041). Nevertheless, after PSM, the PM of 3.3% in the LH group was close to the 3.5% in the OH group (P=0.906) (*Table 3*). Almost all of the PM occurred within 2 years after surgery (*Figure 2A*). Among PM patients in the LH group, 26 (41.9%) had PM alone, 34 (54.9%) had PM coupled with IHR and 2 (3.2%) had PM with extraperitoneal metastases

Table 1 Clinicopathological characteristics of enrolled HCC patients after curative LH

Variables	Value (n=2,138)
Age (years)	52.1 [39.1–68.8]
Gender (male)	1,826 (85.4)
BMI (kg/m^2)	
<18.5	190 (8.9)
18.5–24.9	1,584 (74.1)
≥25.0	364 (17.0)
Diabetes (yes)	210 (9.8)
HBV infection (yes)	1,909 (89.3)
HCV infection (yes)	66 (3.1)
AFP (≥400 ng/mL)	672 (31.4)
NLR	2.3 [1.4–2.6]
Platelet (×10^3/μL)	147.9 [104.0–190.0]
BCLC stage	
0	426 (19.9)
A	1,571 (73.5)
B	141 (6.6)
Child-Pugh grade (A)	2,049 (95.8)
Tumor diameter, cm	4.2 [2.5–5.0]
Tumor number (multiple)	239 (11.2)
Lesions <2 cm from major blood vessel[a] (yes)	644 (30.1)
Liver cirrhosis (yes)	1,342 (62.7)
Portal hypertension (yes)	694 (32.5)
Surgical difficulty[b]	
Low	1,067 (49.9)
Intermediate	398 (18.6)
High	673 (31.5)
Resection margin ≤1 cm	588 (27.5)
Blood loss (mL)	200 [80–430]
Type of hepatectomy (non-anatomical)	1,496 (70.0)
Extent of hepatectomy (major)	297 (13.9)
Satellite nodules (yes)	338 (15.8)
Intratumor necrosis (yes)	216 (10.1)
MVI (yes)	663 (31.0)
Tumor differentiation (poor)	959 (44.9)

Data are presented as median [interquartile range] or n (%). [a], major hepatic vein and inferior vena cava; [b], difficulty scoring system for laparoscopic liver resection proposed by Kawaguchi *et al*. HCC, hepatocellular carcinoma; LH, laparoscopic hepatectomy; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; NLR, neutrophil to lymphocyte ratio; BCLC stage, Barcelona Clinic Liver Cancer stage; MVI, microvascular invasion.

(EPM). The most common site of PM was the omentum (n=29, 46.7%). About one-quarter of patients had a single lesion (n=15, 24.2%). The median number of PM was 2.0 (IQR, 1.0–3.0) and median total diameter of PM was 5.6 (IQR, 2.7–8.0) cm. The patterns, and distribution of PM had no significant difference between the two groups neither before nor after PSM (P>0.05). Interestingly, in the LH group, the PM prevalence during the early period [2010–2013] was significantly higher than that during the later period [2014–2016] (5.1% *vs.* 2.6%, P=0.016), although the LH during the later period seemed to more difficult than the early period, e.g., larger tumors, more likely located in the posterosuperior segment of the liver, closer to major blood vessels than tumors, more anatomical resection and higher surgical difficulty during the later period (*Table 3*, Table S2). While, the PM incidence after OH was similar between the two periods (3.9% *vs.* 4.0%, P=0.148).

Risk factors for PM after LH

Univariate analyses using logistic regression demonstrated that the BCLC stage, tumor diameter, tumor number, intratumor necrosis, type of hepatectomy, lesion <2 cm from a major blood vessel, MVI, and tumor differentiation were significant factors that increased the likelihood of PM after curative LH (P<0.05 for all). Tumor diameter >5 cm [odds ratio, 2.383, 95% confidence interval (CI): 2.077–4.659], non-anatomical hepatectomy (odds ratio, 3.486, 95% CI: 1.004–6.189), lesion <2 cm from a major blood vessel (odds ratio, 3.959, 95% CI: 1.730–9.062) and MVI (odds ratio, 1.863, 95% CI: 1.215–5.196) remained independent risk factors of PM for HCC patients after curative LH by multivariate analysis (*Table 4*).

Table 2 Demographics, clinicopathologic, and treatment characteristics of patients before and after PSM

Variables	Before PSM			After PSM		
	LH (n=2,138)	OH (n=1,490)	P value	LH (n=1,075)	OH (n=1,075)	P value
Age (years)	52.1 [39.1–68.8]	52.4 [39.3–68.9]	0.075	52.2 [39.3–67.8]	52.7 [39.6–68.5]	0.556
Gender (male)	1,826 (85.4)	1,268 (85.1)	0.856	900 (83.7)	892 (83.0)	0.527
BMI (kg/m^2)			0.213			0.102
<18.5	190 (8.9)	148 (9.9)		99 (9.2)	103 (9.6)	
18.5–24.9	1,584 (74.1)	1,086 (72.9)		791 (73.6)	795 (73.9)	
≥25.0	364 (17.0)	256 (17.2)		185 (17.2)	177 (16.5)	
Diabetes (yes)	210 (9.8)	136 (9.1)	0.302	103 (9.6)	102 (9.5)	0.221
HBV infection (yes)	1,909 (89.3)	1,325 (88.9)	0.151	947 (88.1)	952 (88.6)	0.321
HCV infection (yes)	66 (3.1)	43 (2.9)	0.081	25 (2.3)	30 (2.8)	0.375
AFP (≥400 ng/mL)	672 (31.4)	486 (32.6)	0.137	361 (33.6)	353 (32.8)	0.210
NLR	2.3 [1.4–2.6]	2.2 [1.3–2.5]	0.412	2.2 [1.5–2.7)	2.2 [1.4–2.65]	0.301
Platelet (×10^3/μL)	147.9 [104.0–190.0]	148.1 [103.6–191.2]	0.321	147.2 [103.5–191.2]	148.3 [104.6–190.5]	0.710
Child-Pugh grade (A)	2,049 (95.8)	1,411 (94.7)	0.564	1,022 (95.1)	1,019 (94.8)	0.687
BCLC stage			0.015			0.375
0	426 (19.9)	282 (18.9)		226 (21.0)	215 (20.0)	
A	1571 (73.5)	1,107 (74.3)		777 (72.3)	788 (73.3)	
B	141 (6.6)	101 (6.8)		72 (6.7)	72 (6.7)	
Tumor diameter, cm	4.2 [2.5–5.0]	4.10 [2.1–5.5]		4.0 [2.5–5.0]	4.0 [2.5–5.0]	0.653
Tumor number (multiple)	239 (11.2)	162 (10.9)		113 (10.5)	112 (10.4)	0.0923
Lesions <2 cm from major blood vessel (yes)[a]	644 (30.1)	465 (31.2)	0.042	323 (30.0)	329 (30.6)	0.071
Liver cirrhosis (yes)	1,342 (62.7)	1,050 (70.5)	0.021	769 (71.5)	765 (71.2)	0.068
Portal hypertension (yes)	694 (32.5)	580 (38.9)	0.024	354 (32.9)	347 (32.3)	0.072
Resection margin ≤1 cm	588 (27.5)	337 (22.6)	0.216	259 (24.1)	268 (24.9)	0.196
Blood loss (mL)	200 [80–430]	210 [130–450]	0.012	200 [110–460]	200 [110–450]	0.056
Extent of hepatectomy (major)	297 (13.9)	246 (16.5)	0.008	156 (14.5)	159 (14.8)	0.092
Satellite nodules (yes)	338 (15.8)	224 (15.0)	0.191	161 (15.0)	167 (15.5)	0.635
Intratumor necrosis (yes)	216 (10.1)	185 (12.4)	0.035	118 (11.0)	112 (10.4)	0.321
MVI (yes)	663 (31.0)	456 (30.6)	0.073	323 (30.0)	325 (30.2)	0.231
Tumor differentiation (poor)	959 (44.9)	672 (45.1)	0.091	474 (44.1)	483 (44.9)	0.065

Data are presented as median [interquartile range] or n (%). [a], major hepatic vein and inferior vena cava. PSM, propensity score matching; LH, laparoscopic hepatectomy; OH, open hepatectomy; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; NLR, neutrophil to lymphocyte ratio; BCLC, Barcelona Clinic Liver Cancer; MVI, microvascular invasion.

Table 3 PM status of patients after LH and OH before and after PSM

Variables	Before PSM			After PSM		
	LH	OH	P value	LH	OH	P value
PM incidence	62/2,138 (2.9)	59/1,490 (4.0)	0.041	36/1,075 (3.3)	38/1,075 (3.5)	0.906
Early period [2010–2013]	15/295 (5.1)	39/990 (3.9)	0.042	7/150 (4.7)	25/675 (3.7)	0.083
Later period [2014–2016]	47/1,843 (2.6)	20/500 (4.0)	0.098	29/925 (3.1)	13/400 (3.3)	0.094
Recurrent patterns						
PM only	26 (41.9)	23 (39.0)	0.262	16 (44.4)	17 (44.7)	0.725
PM coupled with IHR	34 (54.9)	33 (55.9)	0.523	19 (52.8)	20 (52.6)	0.109
PM with synchronous extraperitoneal metastasis	2 (3.2)	3 (5.1)	0.303	1 (2.8)	1 (2.7)	0.117
Distribution						
Location of peritoneal lesions						
Omentum	29 (46.7)	27 (45.7)	0.414	16 (44.5)	17 (44.7)	0.535
Posterior peritoneum	14 (22.6)	13 (22.0)	0.865	8 (22.2)	8 (21.1)	0.107
Anterior peritoneum/abdominal wall	12 (19.5)	13 (22.0)	0.657	7 (19.4)	8 (21.1)	0.802
Combination	7 (11.3)	6 (10.2)	0.582	5 (13.8)	5 (13.1)	0.904
Posterior peritoneum with omental nodules	4 (6.5)	3 (5.1)	0.694	3 (8.3)	3 (7.8)	0.186
Posterior peritoneum with abdominal wall	3 (4.8)	3 (5.1)	0.532	2 (5.5)	2 (5.3)	0.232
No. of lesions						
Single peritoneal lesion	15 (24.2)	15 (25.4)	0.412	9 (25.0)	10 (26.3)	0.613
Multiple peritoneal lesions	47 (75.8)	44 (74.6)	0.517	27 (75.0)	28 (73.7)	0.501
Median No. of lesions	2.0 [1.0–3.0]	2.3 [1.1–3.9]	0.044	2.2 [1.0–3.6]	2.2 [1.0–3.6]	0.122
Total diameter of peritoneal lesion, cm	5.6 [2.7–8.0]	5.5 [2.4–8.2]	0.856	5.6 [2.7–8.5]	5.6 [2.5–8.1]	0.182
DFS (mon)	8 [2–20]	7 [2–19]	0.636	7 [2–19]	7 [2–19]	0.165

Data are presented as median [interquartile range] or n (%). PM, peritoneal metastasis; LH, laparoscopic hepatectomy; OH, open hepatectomy; PSM, propensity score matching; IHR, intrahepatic recurrence; DFS, disease-free survival.

Treatments and outcomes of PM after LH

Of the 62 patients who developed PM in LH group, 24 patients (38.7%) underwent potentially curative treatments, which incorporated curative repeat resection of peritoneal lesions (n=16) or curative surgery for PM and IHR (n=8); 15 patients (24.2%) underwent palliative resection of peritoneal lesions; another 23 patients (37.1%) who had advanced tumor staging and/or poor liver function had nonoperative management (unresectable) (Table S3). Together, 39 (62.9%) patients underwent CRS. All PM patients who underwent re-excision experienced HIPEC therapy after surgery. The complications for CRS/HIPEC were graded according to the National Cancer Institute CTCAE v5.0. Grade 2 or 3 adverse events were observed in 4 patients as shown in Table S4. There were no grade 4 adverse events or perioperative fatalities in this study. With a median follow-up of 39 months in PM patients, 36 deaths from PM were observed; two cases with PM and synchronous EPM had OS of 13 months (bone metastases) and 6 months (lung metastases), respectively. No-PM patients had a significantly better long-term outcome than PM patients, and 5-year OS was 72.0% and 55.0%, respectively (P<0.001) (*Figure 2B*). However, 5-year OS for resectable PM (curative/palliative) patients was significantly

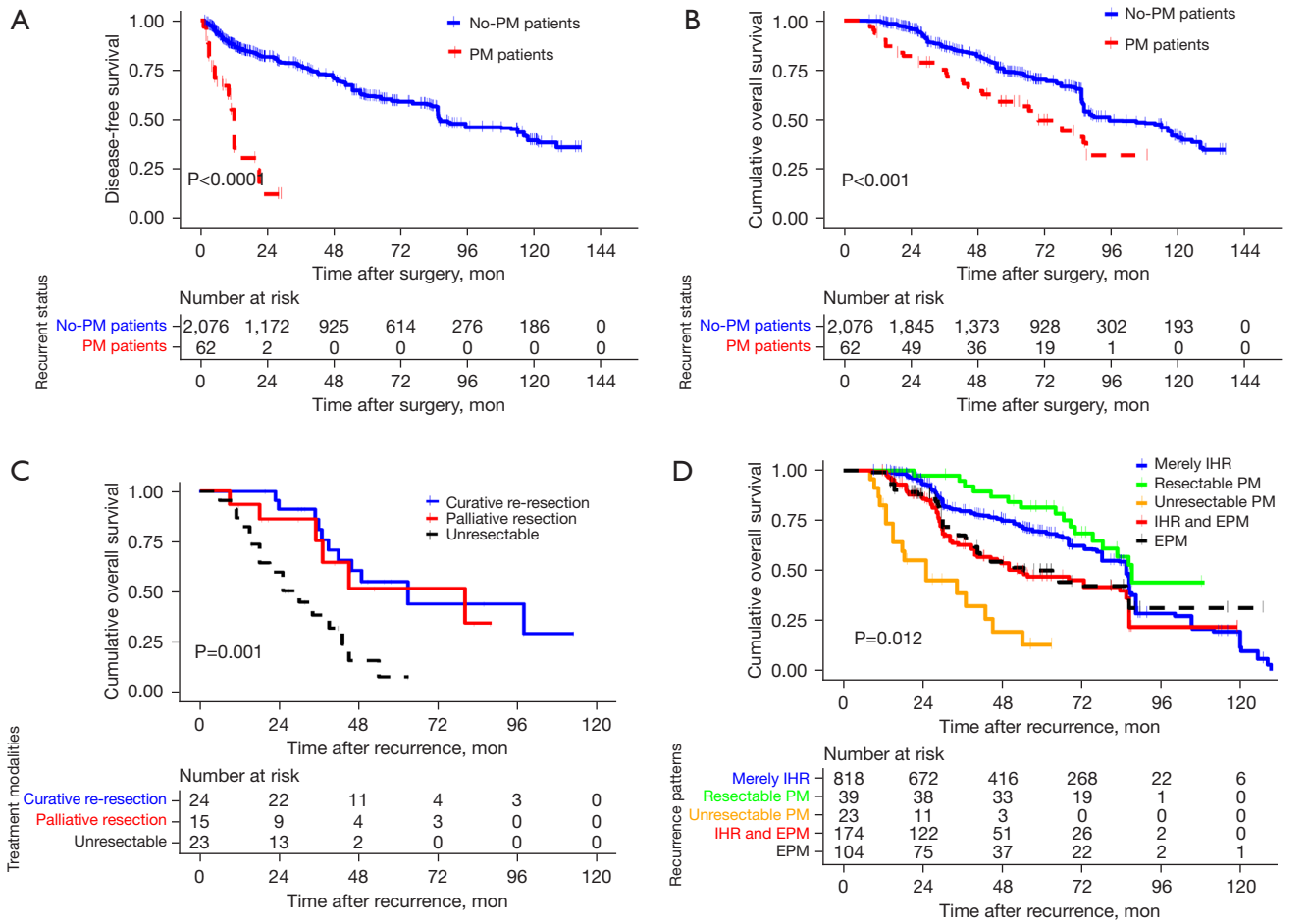

Figure 2 Kaplan-Meier analysis for patients after curative LH for HCC. (A) Disease-free survival for PM and no-PM patients after LH (P<0.0001). (B) Overall survival for PM and no-PM patients after LH (P<0.001). (C) Overall survival for PM patients with different treatment modalities (curative/palliative resection *vs.* unresectable, P=0.001). (D) Overall survival for resectable PM and other types of recurrence (resectable PM *vs.* IHR only, P=0.235; resectable PM *vs.* EPM only and IHR with EPM, P=0.012). PM, peritoneal metastases; IHR, intrahepatic recurrence; EPM, extraperitoneal peritoneal metastases; LH, laparoscopic hepatectomy; HCC, hepatocellular carcinoma.

longer (65.0%) compared with that of unresectable patients (9.0%) (P=0.001) (*Figure 2C*). *Figure 2D* illustrates OS for various groups of recurrences in comparison with resectable PM and unresectable PM. Patients with resectable PM had similar OS compared with that of patients with IHR alone (P=0.235) but it was significantly longer than that of patients with other types of EPM (P=0.012). It is worth mentioning that PM occurring within 1 year had a significant worse prognosis than late recurrence patients (≥1 year), as the Figure S2 depicted. Furthermore, we accessed the risk factors of prognosis for PM patients after LH. And we found PM coupled with IHR or PM with synchronous EPM (hazard ratio, 4.713, 95% CI: 1.278–9.639, P=0.032), PCI ≥8 (hazard ratio, 1.746, 95% CI: 1.017–3.250, P=0.021) and palliative/unresectable treatment mode (hazard ratio, 0.361, 95% CI: 0.151–0.602, P=0.035) were independent risk factors of the long-term outcomes for PM patients after LH. While time to recurrence ≥1 year was a favorable factor in univariate Cox regression analysis for PM patients, but not independent prognostic factor in multivariate Cox regression analyses (Table S5).

Discussion

Accumulating evidence suggests PM to be a significant

Table 4 Univariate and multivariate logistic regression analyses for risk factors of PM of HCC after LH (n=2,138)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value[a]	OR (95% CI)	P value
Sex (male *vs.* female)	1.162 (0.548–2.467)	0.695		
BMI (≥25.0 *vs.* <25.0 kg/m^2)	1.805 (0.807–4.037)	0.151		
Diabetes (yes *vs.* no)	1.374 (0.645–2.929)	0.410		
HBV infection (yes *vs.* no)	1.373 (0.416–4.527)	0.603		
AFP (≥400 *vs.* <400 ng/mL)	1.297 (0.768–2.189)	0.331		
BCLC stage (B *vs.* 0/A)	3.839 (2.290–6.433)	<0.001	1.015 (0.025–2.018)	0.978
Child-Pugh grade (B *vs.* A)	2.080 (0.813–5.325)	0.127		
Tumor diameter (>5 *vs*. ≤5 cm)	3.467 (2.068–5.737)	<0.001	2.383 (2.077–4.659)	0.003
Tumor number (solitary *vs.* multiple)	6.317 (3.741–10.668)	<0.001	1.127 (0.915–2.138)	0.075
Liver cirrhosis (yes *vs.* no)	1.115 (0.626–1.985)	0.526		
Portal hypertension (yes *vs.* no)	0.917 (0.530–1.568)	0.857		
Extent of hepatectomy (major *vs.* minor)	1.350 (0.695–2.621)	0.375		
Satellite nodules (yes *vs.* no)	1.583 (0.863–2.905)	0.138		
Intratumor necrosis (yes *vs.* no)	2.047 (1.050–3.993)	0.035	4.222 (0.964–9.120)	0.863
Type of hepatectomy (non-anatomical *vs.* anatomical)	4.847 (2.456–7.575)	0.016	3.486 (1.004–6.189)	0.029
Surgical difficulty (high *vs.* low/intermediate)	6.235 (2.632–13.536)	0.025	2.121 (0.969–3.698)	0.635
Lesions <2 cm from major blood vessel (yes *vs.* no)[b]	2.925 (1.758–4.866)	<0.001	3.959 (1.730–9.062)	0.002
MVI (yes *vs.* no)	3.583 (1.863–6.574)	0.008	1.863 (1.215–5.196)	0.032
Tumor differentiation (poor *vs.* well/moderate)	2.322 (1.197–4.192)	0.047	2.706 (1.815–4.033)	0.065

[a], variables with a P value <0.05 in univariate analysis were subjected to multivariate logistic regression analyses using forward stepwise variable selection; [b], major hepatic vein and inferior vena cava. PM, peritoneal metastasis; HCC, hepatocellular carcinoma; LH, laparoscopic hepatectomy; OR, odds ratio; CI, confidence interval; BMI, body mass index; HBV, hepatitis B virus; AFP, α-fetoprotein; BCLC stage, Barcelona Clinic Liver Cancer stage; MVI, microvascular invasion.

cause of mortality after curative LH for HCC. Although PM prevalence of 3–18% has been reported in HCC patients from autopsy evidence (23), such metastases may be overlooked due to the limited sensitivity of examination methods, which could severely limit the prognosis of HCC patients. Investigations on the prevalence, patterns, risk factors, treatment, and outcomes of PM after LH for HCC are lacking. Our study represents the first multi-center study on the postoperative PM following LH, providing convincing evidence that LH had no effect on increasing PM prevalence. Furthermore, aggressive surgery for recurrent PM may improve the prognosis of HCC patients.

Studies have demonstrated that laparoscopic surgery has comparable long-term outcomes compared with open surgery (24-26), and this is also confirmed by our present findings (Figure S3). However, concerns remain among many surgeons about PM risk, especially during the initial learning phase. Some researchers have considered that viable cancer cells might contaminate the abdominal cavity via direct transfer from laparoscopic instruments. Further, the pneumoperitoneum may promote seeding of cancer cells into the peritoneal cavity (27). Nevertheless, recent studies have found that laparoscopic surgery and open surgery have a comparable prevalence of local recurrence and peritoneal dissemination in cervical and rectal cancer (28-30). The PM prevalence for HCC patients after LH and OH in the present study were 2.9% and 4.0%, respectively. And the difference was not significant after PSM, as with the patterns, timing, and treatments of recurrence between the two approaches. The PM rates of 2.9% after LH in

the present study was comparable with that of 3.0% in a nationwide study from 1,222 cases underwent OH in Korea (6). Interestingly, the PM prevalence of 5.1% in the early period of the LH group was significantly higher than 2.6% in the later period of the LH group. Studies have demonstrated individual surgeons during the learning curve to be the dominant risk factors of poor outcomes (31,32). Similarly, the prevalence of local recurrence in laparoscopic surgery for rectal cancer was shown to decrease with increasing experience of surgeons, especially in those with advanced disease (33). Therefore, it is reasonable to suggest that LH had no effect on increasing the prevalence of PM in HCC patients for experienced surgeons. However, close supervision during surgery by highly experienced surgeons, selection of patients with a low risk of recurrence, and careful intraoperative manipulation should be advocated for inexperienced surgeons to reduce the risk of PM in HCC patients.

In this large multicenter retrospective study, tumor diameter >5 cm, non-anatomical hepatectomy, MVI, and a lesion <2 cm from a major blood vessel were identified as independent risk factors for PM. Larger tumor diameter (>5 cm) and MVI have been reported to be associated with PM (6,17). However, whether non-anatomical hepatectomy is associated with PM in HCC patients is not known. Kaibori and colleagues found non-anatomical resection to be associated significantly with extrahepatic recurrence (especially local dissemination) after hepatic resection (34). Studies have illustrated that non-anatomical resection does not remove small, subclinical metastases in the residual liver segment (35,36). Intrahepatic microscopic metastases disseminating via the portal-vein branches along the residual liver segment are the main reasons for tumor recurrence in HCC patients (incorporating intrahepatic and extrahepatic recurrence) (37,38). Moreover, a non-anatomical resection procedure would augment the risk of tumor cells becoming detached and spreading to the free peritoneal cavity, as depicted in gastric cancer (39,40). In addition, non-anatomical resection could contribute to extrahepatic recurrence via circulating tumor cells with epithelial-to-mesenchymal transition in the residual segment (41,42), which increases the risk of abdominal metastases significantly.

We found that tumor location <2 cm from a major blood vessel during LH was associated significantly with PM development. During LH, the proximity of a lesion to a major blood vessel will increase the difficulty of surgery, particularly for inexperienced surgeons. Moreover, greater intraoperative blood loss and an increased risk of tumor recurrence has been observed for a tumor <2 cm from a major blood vessel because massive intraoperative bleeding can increase the risk for intraoperative tumor spillage to the abdominal cavity and hematogenous spread (43), especially in patients who have non-anatomical resection (44). Presumably, a tumor close to a major blood vessel would carry a greater risk of extra-tumoral MVI and potential distant hematogenous metastases (45,46). Notably, high degree of surgical difficulty was associated with higher risk of PM in the univariate analysis, but this was not an independent predictor in the multivariable analysis. Generally, the higher difficulty score of LH usually accompanied by prolonged operation time and increased risk of bleeding, which is associated with worse outcomes (44).

The rationale of surgical treatment for PM remains controversial and standard treatment is not available (8). Treatment guidelines for PM in HCC in Japan and Western countries recommend systemic chemotherapy (4). In general, PM in HCC are rarely suitable for curative repeat surgical excision, and most patients have PM with synchronous IHR or distant metastases, which was also demonstrated in our cohort. Nevertheless, studies have suggested that surgical removal of peritoneal lesions as much as possible might improve the prognosis of selected patients. In Japan, one study which investigated the largest number of PM patients so far reported 5-year OS of 92 patients who underwent peritoneal metastasectomy plus HIPEC to be 36.0% (17). A multicenter international study demonstrated that aggressive surgical management of PM generated favorable long-term survival (47). In the present study, 5-year OS of PM patients was 55.0%, which is higher than that reported previously (6.0–49.4%) (6,8,47). This difference might be attributed to more aggressive intervention in our study: 62.9% (39/62) of PM patients underwent potentially curative or palliative treatments in our cohort, which reduced the tumor burden in PM patients significantly. Hence, we recommend removing as much PM as possible to improve the long-term prognosis of PM patients.

Our study benefited from a large cohort and a multicenter-study design. Nevertheless, it had four main limitations. First, owing to complex anatomy and the limitations of imaging, recognition of small recurrent lesions was challenging and evaluation of follow-up outcomes was influenced. Second, though there is a unified treatment plan in HCC patients, there would inevitably be differences between centers (e.g., surgical plan, surgeon's experience,

postoperative management), which might influence data reproducibility. Nevertheless, our results are reflective of real-world conditions and make them generalizable to some degree. Third, the retrospective, non-randomized nature of our study represents its biggest limitation because it entails a selection bias. Hence, further prospective multicenter studies are warranted to verify our conclusions. Fourth, comparative investigations in patients who did not undergo peritoneal metastasectomy were lacking, and inclusion of such work is planned in our future studies.

Conclusions

We identified in a multicenter study, for the first time, PM prevalence after curative LH to be 2.9%. We revealed that tumor diameter >5 cm, non-anatomical resection, presence of MVI, and a lesion <2 cm from a major blood vessel to be independent risk factors of PM after curative LH for HCC. Laparoscopic surgery would not augment PM risk if undertaken by experienced surgeons. Nevertheless, increased caution is required for surgeons lacking laparoscopic experience when treating PM. For peritoneal lesions, aggressive surgery may improve the prognosis of HCC patients significantly.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-506/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-506/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-506/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This research was carried out in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent for data use was obtained from all patients. The study protocol was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, within Huazhong University of Science and Technology (TJ-IRB20210935).

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Supplementary

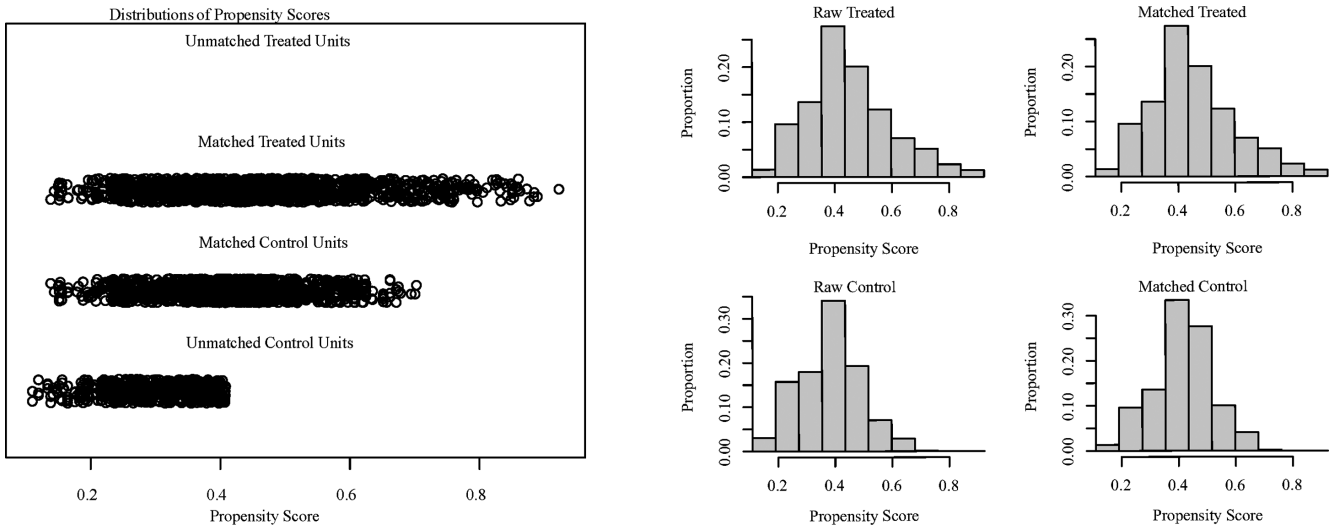

Figure S1 The distributions of propensity scores before and after matching.

Table S1 Recurrence patterns, timing, and treatments between LH and OH before and after PSM

	Before PSM			After PSM		
	LH (n=1,158)	OH (n=752)	P value	LH (n=576)	OH (n=529)	P value
Patterns, n (%)						
Resectable PM	39 (3.4%)	27 (3.6%)	0.108	26 (4.5%)	27 (5.1%)	0.312
IHR only	818 (70.6%)	520 (69.1%)	0.013	400 (69.4%)	365 (69.0%)	0.256
IHR and extra–abdominal metastasis	174 (15.0%)	109 (14.5%)	0.327	86 (15.0%)	79 (14.9%)	0.712
EPM only	104 (9.0%)	81 (10.8%)	0.097	54 (9.4%)	43 (8.2%)	0.352
Unresectable PM	23 (2.0%)	15 (2.0%)	0.573	10 (1.7%)	15 (2.8%)	0.335
DFS (mon)[a]	11 (6–17)	11 (5–16)	0.421	11 (6–16)	11 (6–16)	0.925
Treatment, n (%)						
Surgery	199 (17.2%)	136 (18.1%)		99 (17.2%)	93 (17.5%)	
RFA	152 (13.1%)	144 (19.1%)		92 (16.0)	86 (16.3%)	
TACE	426 (36.8%)	302 (40.2%)		213 (37.0%)	196 (37.1%)	
Radiotherapy	36 (3.1%)	15 (2.0%)		11 (1.9%)	10 (1.9%)	
Conservative treatment	345 (29.8%)	155 (20.6%)		161 (27.9%)	144 (27.2%)	

[a] median (IQR). LH, laparoscopic hepatectomy, OH, open hepatectomy; PSM, propensity score matching; DFS, disease-free survival; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

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Table S2 Characteristics and outcomes of patients in different periods of LH

Variables	Whole Cohort (n=2,138)		
	2010–2013, (n=295) (13.8%)	2014–2016, (n=1,843) (86.2%)	P value
PM incidence	15/295 (5.1%)	47/1,843 (2.6%)	0.016
Patients			
Age (<53/≥53 years)	141/154	907/936	0.651
Female/Male	40/255	273/1,570	0.572
BMI (<25/≥25) kg/m^2	251/44	1,524/319	0.065
Liver function			
Child-Pugh (A/B)	274/21	1,755/88	0.368
HBV positive (yes/no)	263/32	1,645/198	0.516
HCV positive (yes/no)	10/285	31/1,812	0.638
Tumor factors			
Number (solitary/multiple)	267/28	1,632/211	0.322
Tumor diameter (≤5 *vs*. >5 cm)	262/33	1,445/398	0.035
Location of the tumor (anterolateral/posterosuperior segment)	176/119	977/866	0.041
Lesions <2 cm from major blood vessel (yes/no)[a]	60/235	583/1,260	0.002
Surgical factors			
Hepatectomy (minor/major)	238/57	1,603/240	0.074
Surgical difficulty (low/intermediate/high)[b]	176/64/55	691/534/618	0.013
Anatomical resection of the liver (yes/no)	56/239	586/1,257	0.048
Peritoneal metastasis (yes/no)	15/280	47/1,796	0.016
Multiple recurrent peritoneal lesions (yes/no)	11/4	38/9	0.655

[a] Major hepatic vein and inferior vena cava; [b] Difficulty scoring system for laparoscopic liver resection proposed by Japanese Society of Hepato–Biliary–Pancreatic Surgery. LH, laparoscopic hepatectomy; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus.

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Table S3 Clinicopathological characteristics of the peritoneal metastasis patients after LH

Factors at initial hepatectomy	PM patients (n=62)
Age (years)[a]	52 (28–74)
Gender (male/female)	51/11
Virus hepatitis (positive/negative)	52/10
BMI (<18.5/18.5–24.9/≥25 kg/m^2)	13/29/20
Platelet count (×10^3/μL)[a]	151.6 (102.5–191.2)
Albumin (g/L)[a]	36.4 (32.6–41.2)
AFP (≥400/<400 ng/mL)	23/39
NLR[a]	2.5 (1.2–4.1)
Child–Pugh class (A/B)	33/29
Liver cirrhosis (yes/no)	46/16
Type of hepatectomy (anatomical/non-anatomical)	8/54
Width of surgical margin (≥5 mm/<5 mm)	62/0
Tumor number (solitary/multiple)	14/48
Main tumor diameter (cm)[a]	6 (4–7)
Lesions <2 cm from the major blood vessel (yes/no)	37/25
Cancer cell differentiation	
Well/Moderate	30 (48.4%)
Poor	32 (51.6%)
Microscopic vascular invasion (yes/no)	45/17
Factors at first recurrence of PM	
Time to recurrence (≥1 year/<1 year)	20/42
Child–Pugh class (A/B)	30/32
Tumor number (solitary/multiple)	20/42
NLR[a]	2.8 (1.7–4.1)
AFP (≥400/<400 ng/mL)	20/42
Main tumor diameter (cm)[a]	2.2 (1.6–4.1)
Treatment modalities for recurrence	
Curative resection	24 (38.7%)
Palliative resection	15 (24.2%)
Nonoperating management (Unresectable)	23 (37.1%)
PCI (≤8/>8)[b]	37/25
CC score (0/1)	41/21
At last follow–up	
Alive	26 (41.9%)
Died from HCC	36 (58.1%)
Median OS (mon)	39

[a] median (IQR); [b] The optimal cut off level of the PCI were 8, using the software X–tile. PM, peritoneal metastasis; BMI, body mass index; AFP, α–fetoprotein; NLR, Neutrophil to lymphocyte ratio; PCI, Peritoneal Cancer Index; CC score, Completeness of Cytoreduction score; OS, overall survival.

Table S4 Peri-operative complications for PM patients according to National Cancer Institute CTCAE v5.0.

Grade 2/3 adverse events	4
Type of serious complications[a]	
Infectious complications	1
Respiratory/Thoracic/Mediastinal complications	1
Gastrointestinal	2
Hepatobiliary	1
Post-operative death	0

[a] Details of complications, few patients could undergo more than one complication.

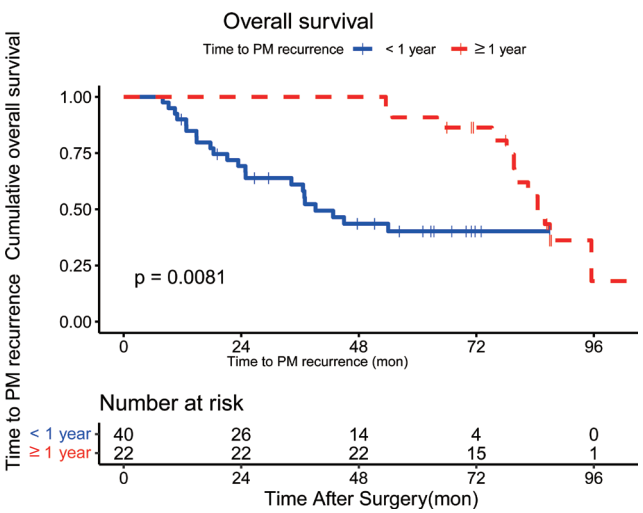

Figure S2 Peritoneal metastasis occurred within one year had a significant worse prognosis than late recurrence patients (≥1 year).

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Table S5 Univariate and multivariate Cox regression analyses for prognostic factors in patients with PM

Variables	Univariate analysis HR (95% CI)	P value	Multivariate analysis HR (95% CI)	P value
BMI (<18.5 *vs.* ≥18.5 Kg/m^2)	3.785 (1.153–8.423)	0.058		
AFP at detection of PM (≥400 *vs.* <400 ng/mL)	0.736 (0.363–1.490)	0.393		
Child grade (B *vs.* A)	2.443 (1.188–5.025)	0.045	1.013 (0.157–2.036)	0.071
Time to recurrence (≥ 1 year *vs.* <1 year)	0.213 (0.012–0.9231)	0.011	0.59 (0.232–1.231)	0.062
Recurrent tumor diameter (≥ 3.5 *vs.* <3.5 cm)	2.576 (1.226–5.415)	0.033	3.112 (2.210–3.221)	0.245
Recurrence patterns[a]	2.289 (1.074–4.880)	0.032	4.713 (1.278–9.639)	0.032
PCI (≥8 *vs.* <8)	2.367 (1.176–4.767)	0.016	1.746 (1.017–3.250)	0.021
Treatment model (curative *vs.* palliative/unresectable)	0.251 (0.113–0.557)	0.001	0.361 (0.151–0.602)	0.035
Numbers of recurrent lesions (multiple *vs.* single)	3.705 (1.297–7.582)	0.014	1.115 (0.352–3.242)	0.635
CC score (1 *vs.* 0)	2.267 (1.144–4.493)	0.019	0.567 (0.121–1.656)	0.265

[a] PM coupled with IHR/PM with synchronous extraperitoneal metastasis *vs.* PM only; IHR, Intrahepatic Recurrence. HR, hazard ratio; CI, confidence interval; BMI, body mass index; AFP, α–fetoprotein; PCI, Peritoneal Cancer Index; CC score, Completeness of Cytoreduction score.

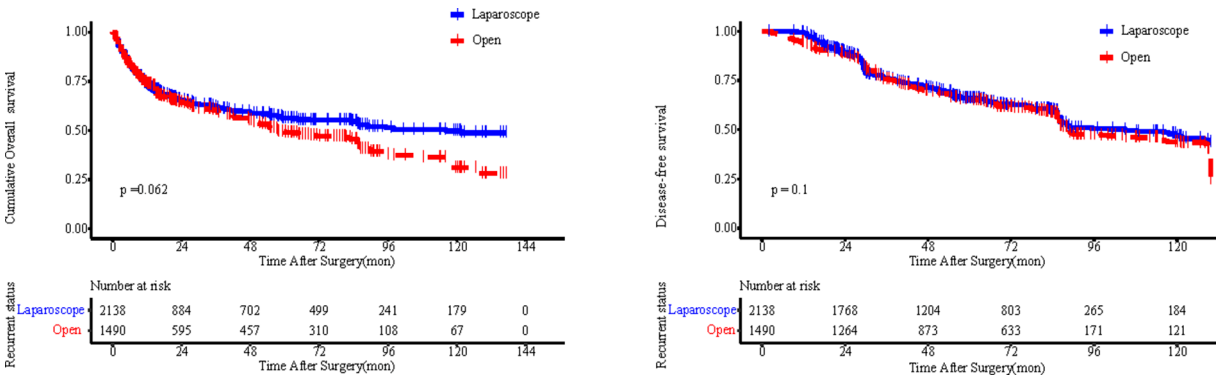

Figure S3 The overall survival and disease-free survival were comparable between the LH and OH patients. LH, laparoscopic hepatectomy; OH, open hepatectomy.

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