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ORIGINAL ARTICLE

Anterior approach for right hepatectomy with hanging maneuver for hepatocellular carcinoma: a multi-institutional propensity score-matching study

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Abstract

Background This multi-institutional study aimed to assess the benefits of anterior approach for right hepatectomy with hanging maneuver (ARH-HM) for hepatocellular carcinoma (HCC) compared with conventional right hepatectomy (CRH).

Methods From January 2000 to December 2012, 306 patients with HCC ≥5 cm were divided into two groups: ARH-HM (n = 104) and CRH (n = 202).

Results After one-to-one propensity score-matched analysis, 72 ARH-HM and 72 CRH patients presented comparable background factors. Patients in the ARH-HM group demonstrated significantly less intraoperative blood loss (480 vs. 1,242 g, $P < 0.001$) and a lower frequency of red cell concentrate transfusion (21.1% vs. 50.7%, $P < 0.001$) compared with patients in the CRH group. The 5-year overall survival rate was significantly better in the ARH-HM group compared with the CRH group (50.2% vs. 31.4%, $P = 0.021$). Limited to patients with HCC ≥10 cm, recurrence-free and overall survival of the ARH-HM group was significantly greater than those of the CRH group.

Conclusion In comparison with CRH, ARH-HM for large HCC can provide better overall survival rates with a decrease in intraoperative blood loss and transfusion rates. Survival impact was evident especially in patients with HCC ≥10 cm.

Keywords Anterior approach · Hepatectomy · Hepatocellular carcinoma · Liver hanging maneuver · Propensity score

Introduction

Conventional right hepatectomy (CRH), which is complete mobilization of the right liver followed by parenchymal transection, has been used as the standard procedure. However, it is sometimes difficult and dangerous for CRH to resect huge liver tumors in the right liver, particularly with extrahepatic organ invasion. CRH can result in excessive blood loss, tumor rupture and liver ischemia due to prolonged rotation of the liver remnant. Anterior approach for right hepatectomy (ARH), initial liver transection without liver mobilization, was firstly demonstrated by Ken Takasaki to be an alternative for CRH [1–4]. Lately it has been recognized that ARH has some advantages over CRH, including patients with less intraoperative blood loss, fewer requirements for transfusion and better disease-free or overall survival (OS) following hepatectomy [5–10]. Conversely, one randomized control trial (RCT) failed to prove that ARH improves the amount of intraoperative blood loss and morbidity rate [11].

Liver hanging maneuver (HM) is a very useful tool in right-side hepatic resections [12–14]. Even in a huge tumor, HM allows transection of liver parenchyma without primary liver mobilization and can provide avoidance of iatrogenic rupture of the tumor capsule or spillage of cancer cells into the intrahepatic vessels. We have previously reported that HM is a safe procedure, which can decrease the amount of intraoperative blood loss and administration rates of blood product in right-side hepatectomy [14]. For large liver tumors compressing the inferior vena cava (IVC), ARH without HM risks massive bleeding during hepatectomy [15]. Two studies focusing on ARH in combination with HM have demonstrated a decreased blood transfusion requirement and a lower recurrence rate [16, 17].

Anterior approach for right hepatectomy has been selected for patients with larger liver tumors or those invading adjacent organs; therefore, some selection biases may exist with respect to patients' selection of an anterior or conventional approach. We conducted a propensity score-matching (PSM) analysis, which has been shown to decrease selection bias in retrospective studies and allow comparison between different approaches [18, 19]. Non-randomized studies with appropriate PSM can provide treatment effects similar to RCT [20].

Therefore, we conducted a multi-center PSM study to evaluate the operative, oncological and prognostic benefits of ARH using HM for patients with large hepatocellular carcinoma (HCC).

Methods

This clinical study was conducted by the "Project Committee of the Multi-Institutional Study by the Kyushu Study Group of Liver Surgery." Between January 2000 and December 2012, 544 consecutive HCC patients undergoing right or extended right hemihepatectomy were enrolled from 15 institutions. First, HCC ≥5 cm in diameter were selected. Second, patients with distant metastasis were omitted to calculate the correct postoperative recurrence. Third, patients undergoing "ARH without HM" or "ARH with HM following liver mobilization" were excluded. Finally, 306 patients were selected, 202 CRH and 104 "ARH with HM (ARH-HM) before liver mobilization." The flowchart of patient selection is listed in Figure 1. The diagnosis of HCC depended on a histological examination of the resected specimens in all patients. Using a uniform and shared database, we retrospectively collected clinicopathological data and outcome of the patients. Written informed consent was obtained from all patients, and the Institutional Review Board of Kumamoto University approved this study (approval number: 799). We examined 22 perioperative items (Table 1). Liver damage grade, clinical stage, tumor differentiation (well, moderate or poor) and vessel invasion were categorized according to the criteria of the Liver Cancer Study Group of Japan [21]. Staging for fibrosis (F0–F4) and grading for activity (A0–A3) in the background liver were assessed by the Inuyama classification [22]. Hepatectomy with no other prior treatments for HCC, except for portal vein embolization (PVE), was defined as "initial therapy."

Operative method for hepatectomy

The procedure for hepatectomy (conventional or anterior) and application of HM was selected depending on individual institutional strategies [12–14]. "Conventional approach" included hepatic resection following complete mobilization of the right liver, whereas "anterior approach" included prior dissection of in- and outflow vessels and transection of hepatic parenchyma [1–4].

Propensity score analysis

Propensity score analysis was used to build a matched group of patients for comparison of perioperative and survival outcomes between the ARH-HM and CRH groups [18, 19]. We included the following 20 clinical variables in Table 1 for propensity score generation. Clinical stage and liver damage grade were excluded because they included confounding factors. Logistic regression was applied to create a continuous propensity score ranging from 0 to 1. Matched ARH-HM and CRH groups were generated by one-to-one greedy data matching by Mahalanobis distance nearest-neighbor matching without replacement on the logit of the propensity score using calipers of a width equal to 0.2 times the standard deviation of the logit of the propensity score.

Statistical analyses

For the overall cohort, clinical parameters were compared using the Mann–Whitney *U*-test for ordinal data and Fisher's exact test for categorical data. For the PSM cohort, exact McNemar's test was used for 2×2 categorical data, stratified conditional logistic regression analysis for $m \times 2$ categorical data and the Wilcoxon signed-rank test for continuous data. The Kaplan–Meier method was used to calculate recurrence-free survival (RFS) and OS rates. Median RFS and OS were shown as median values (95% confidence interval; CI). *P*-values were calculated using the log-rank test for the overall and five stratified log-rank tests and five stratified generalized Wilcoxon tests were used for

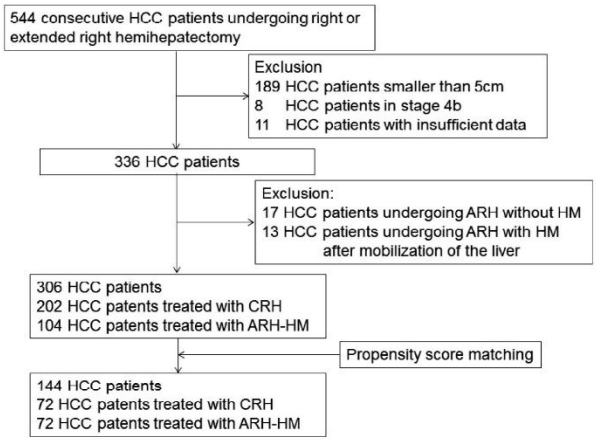

Fig. 1 Flowchart demonstrating inclusion of the study

the PSM cohort. A *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed using the Stata Statistical Software: Release 14.1 (StataCorp LP, College Station, TX, USA) and NCSS 10 Statistical Software (2015) (NCSS, LLC, Kaysville, UT, USA).

Results

Perioperative characteristics of patients in the overall cohort and PSM cohort are shown in Table 1. In the two groups, the following four factors were found to be positively related in univariate analysis ($P < 0.1$): application of PVE, initial therapy, resection rate before hepatectomy and tumor histology. After one-to-one case PSM, 72 ARH-HM and 72 CRH patients were selected for further analysis. All baseline characteristics of the PSM cohort were identical between the two groups. Comparison of continuous background factors is shown (Table S1). Standardized differences before and after PSM are demonstrated (Fig. S1). The imbalance was defined as an absolute value >10%; however, all values were well-balanced after PSM. Receiver operating characteristic (ROC) curves were used to estimate the accuracy of PSM. The area under the curve of the propensity score was 0.71.

Intraoperative and postoperative course

In the PSM cohort, the median operation time was short but not significant in the ARH-HM group than in the CRH group (390 vs. 420 min; $P = 0.089$). The median intraoperative blood loss (480 vs. 1,242 g; $P < 0.001$) and blood transfusion rate (21.1% vs. 50.7%; $P < 0.001$) were significantly lower in the ARH-HM group than in the CRH group (Table 2). The morbidity equal to or greater than Clavien–Dindo classification IIIA [23] was almost identical (33.3% in the ARH-HM group and 29.2% in the CRH group; $P = 0.719$). No specific postoperative complications were observed. In the ARH-HM and CRH groups, the 30-day mortality rate and the 90-day mortality rate was comparable. In patients with 5 cm ≤ HCC < 10 cm and HCC ≥10 cm in the PSM cohort, median intraoperative blood loss and blood transfusion rate was significantly less, respectively (Table S2).

Patients' recurrence and prognosis

In the overall cohort, the median observation periods in the ARH-HM and CRH group were 27.9 (22.7–34.3) months vs. 26.6 (21.1–33.2) months. RFS was comparable between the two groups, and OS of the ARH-HM group was significantly greater than that of the CRH group (Fig. 2a,b). In the PSM cohort, the median observation periods in the ARH-HM and CRH groups were 27.2 (21.5–34.0) months vs. 18.1 (13.6–30.1) months. RFS was comparable between the two groups; however, OS of the ARH-HM group was significantly greater than that of the CRH group (Fig. 2c,d). Based on the results of 10 random PSM analyses for OS, *P*-values were significant for seven of the 10 in the stratified log-rank test and all 10 in the generalized Wilcoxon test; median *P*-values (ranges) were 0.035 (0.003–0.096) and 0.012 (0.001–0.0498) respectively (Table S3).

Table 1 Perioperative clinical characteristics of HCC patients who underwent ARH-HM and CRH in the overall cohort and PSM cohort

	Overall cohort (n = 306)			PSM cohort (n = 144)		
	ARH-HM (n = 104)	CRH (n = 202)	P	ARH-HM (n = 72)	CRH (n = 72)	P
Categorical data						
Gender						
Female	23	39	0.553	11	13	0.824
Male	81	163		61	59	
Age						
≤69	53	115	0.334	40	30	0.11
>69	51	87		32	42	
HBs-Ag						
(−)	63	135	0.313	41	49	0.243
(+)	41	67		31	23	
HCV-Ab						
(−)	67	135	0.703	49	48	>0.999
(+)	37	67		23	24	
ICG R15						
≤12	47	94	0.709	35	28	0.487
>12	51	92		32	39	
Liver damage						
A	89	172	>0.999	58	62	0.534
B	14	29		13	10	
C	0	1		0	0	
Child-Pugh classification						
A	97	192	0.6	66	70	0.289
B	7	10		6	2	
Tumor number						
≤1	66	143	0.296	44	46	0.875
>1	36	59		28	26	
Maximum tumor size (mm)						
≤89	51	106	0.546	31	31	>0.999
>89	53	94		41	41	
Distant metastasis						
(−)	103	201	>0.999	72	72	>0.999
(+)	1	1		0	0	
PVE						
(−)	65	157	**0.007**	49	51	0.625
(+)	39	45		23	21	
Clinical stage						
1	0	1	0.834	0	1	0.763
2	36	66		20	21	
3	40	72		31	23	
4A	28	63		21	27	
AFP (ng/ml)						
≤92	47	99	0.47	31	34	0.728
>92	57	100		41	38	
AFP-L3 (%)						
≤11	42	50	0.459	29	27	0.455
>11	47	43		36	19	

Table 1 *Continued*

	Overall cohort (n = 306)			PSM cohort (n = 144)		
	ARH-HM (n = 104)	CRH (n = 202)	P	ARH-HM (n = 72)	CRH (n = 72)	P
PIVKAII (mAU/ml)						
≤3,610	52	98	0.903	32	32	>0.999
>3,610	52	93		40	38	
Pre-hepatectomy %RLV						
≤51	62	58	**<0.001**	45	47	0.5
>51	30	85		27	25	
Initial therapy						
Yes	77	167	0.091	54	54	>0.999
No	26	33		18	18	
Extent of hepatectomy						
R-hepatectomy	78	154	0.888	52	52	>0.999
Ex R-hepatectomy	26	48		20	20	
Microscopic vessel invasion						
No	36	59	0.362	18	20	0.856
Yes	68	143		54	52	
Tumor histology						
Well-moderate	59	154	**0.005**	48	50	0.5
Poor	36	42		24	22	
Fibrosis stage						
F0-F2	72	128	0.333	53	45	0.23
F3/F4	24	58		18	24	
Activity grade						
A0/A1	59	112	>0.999	46	39	0.815
A2/A3	27	52		20	19	

Bold values signify $P < 0.05$. Clinical parameters were compared with Wilcoxon rank-sum (Mann–Whitney) test for ordinal, and Fisher's exact test for categorical data for overall cohort, exact McNemar's test for 2 × 2 categorical data, stratified conditional logistic regression, analysis for m × 2 categorical data for PSM cohort. Median (range)

%RLV percentage of resected liver volume, *AFP* alpha-fetoprotein, *AFP-L3* lens culinaris agglutinin-reactive fraction of AFP, *ARH-HM* anterior approach for right hepatectomy with hanging maneuver, *CRH* conventional right hepatectomy, *Ex* extended, *HBs-Ag* hepatitis B surface antigen, *HCC* hepatocellular carcinoma, *HCV-Ab* anti-hepatitis C antibody, *ICG R15* 15-min indocyanine retention rate, *PIVKA-II* protein induced by vitamin K absence or antagonists-II, *PSM* propensity score-matching, *PVE* portal vein embolization

Table 2 Perioperative data in HCC patients who underwent ARH-HM and CRH in the overall cohort and propensity score-matched cohort

	Overall patients (n = 306)			Propensity-matched patients (n = 144)		
	ARH-HM (n = 104)	CRH (n = 202)	P-value	ARH-HM (n = 72)	CRH (n = 72)	P-value
Operation time (min) median (range)	393 (225–995)	385 (195–1,120)	0.318	390 (229–995)	420 (240–1,120)	0.089
Blood loss (g), median (range)	502 (23–11,720)	1,166 (30–13,000)	**<0.001**	480 (100–5,470)	1,242 (230–7,755)	**<0.001**
RCC administration (%)	23 (22.6)	94 (47.5)	**<0.001**	15 (21.1)	36 (50.7)	**<0.001**
Morbidity (%)	31 (29.8)	58 (29.2)	0.895	24 (33.3)	21 (29.2)	0.719
Mortality (%)						
Within 1 month	2 (1.9)	5 (2.5)	>0.999	2 (2.8)	1 (1.4)	>0.999
Within 3 months	3 (2.9)	8 (4.0)	0.754	3 (4.2)	1 (1.4)	0.620

Bold values signify $P < 0.05$. Clinical parameters were compared with Wilcoxon rank-sum (Mann–Whitney) test for ordinal, and Fisher's exact test for categorical data for overall cohort, exact McNemar's test for categorical data, and Wilcoxon signed rank test for continuous data for PSM cohort

ARH-HM anterior approach for right hepatectomy with hanging maneuver, *CRH* conventional right hepatectomy, *FFP* fresh frozen plasma, *HCC* hepatocellular carcinoma, *RCC* red cell concentrate

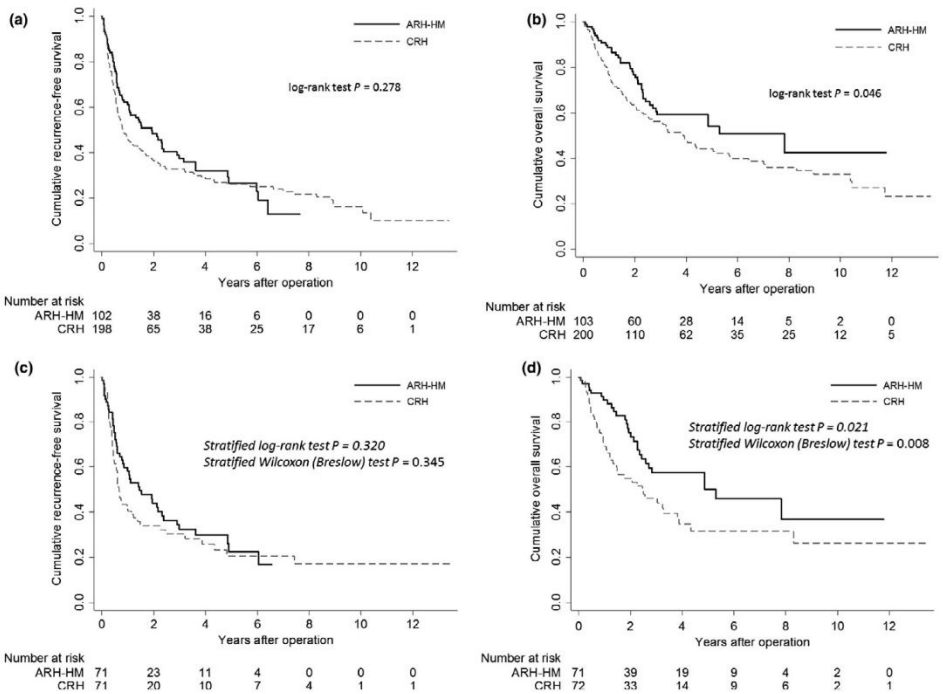

Fig. 2 Cumulative survival curves in the overall and propensity score-matching (PSM) cohorts. (**a**) Recurrence-free survival (RFS) in overall cohort. (**b**) Overall survival (OS) in overall cohort. (**c**) Recurrence-free survival in propensity score-matched cohort. (**d**) Overall survival in propensity score-matched cohort. In the overall cohort, median RFS and OS were 23.2 (12.6–34.9) vs. 9.6 (7.6–14.7) months and 93.9 (34.0–not available; N/A) vs. 46.7 (32.4–61.9) months, respectively. RFS and OS for 1, 3 and 5 years were 61.2%, 37.4% and 26.7%, respectively, vs. 45.7%, 32.8% and 26.1%, respectively, $P = 0.278$ and 88.7%, 59.3% and 54.1%, respectively, vs. 76.8%, 56.3% and 44.2%, respectively, $P = 0.046$ (**a, b**). In the PSM cohort, median RFS and OS were 17.4 (9.6–28.6) vs. 7.8 (5.6–14.7) months and 63.5 (29.2–N/A) vs. 29.5 (15.8–45.7) months, respectively. RFS and OS for 1, 3 and 5 years: 58.1%, 32.3% and 22.4%, respectively, vs. 40.4%, 30.5% and 20.6%, respectively, $P = 0.320$ and 1, 3 and 5 years: 89.5%, 57.3% and 50.2%, respectively, vs. 69.1%, 46.1% and 31.4%, respectively, $P = 0.021$ (**c, d**)

In the PSM cohort, RFS and OS were separately assessed according to the tumor size (Fig. S2). In 5 cm ≤ HCC < 10 cm patients, RFS and OS were comparable between the two groups. On the other hand, in patients with HCC ≥10 cm, RFS and OS of the ARH-HM group was significantly greater than that of the CRH group.

Table 3 Details of initial recurrence in propensity score-matched cohort

	ARH-HM (n = 72)	CRH (n = 72)	P-value
Recurrence +/− (%) (divided by total number of valid case)	41/30 (57.7)	44/28 (61.1)	0.735
Cumulative recurrence rate at 2 years (%, 95% CI)	51.8 (39.7–65.3)	62.8 (50.8–74.7)	0.231
Interval to initial recurrence median month (range)	9.3 (0.2–72.5)	5.6 (0.3–89.1)	0.157
Initial recurrence site			
Intrahepatic only	22	25	0.824
Including extrahepatic	17	17	

ARH-HM anterior approach for right hepatectomy with hanging maneuver, *CRH* conventional right hepatectomy

The pattern of recurrence was thoroughly investigated (Table 3). The incidence of recurrence was similar between the two groups. The 2-year recurrence rate was lower, but not significant, in the ARH-HM group than in the CRH group (51.8% vs. 62.8%, $P = 0.231$). Initial recurrence sites were not significantly different between the two groups; recurrences including extrahepatic were encountered 43.6% in the CRH group and 40.5% in the ARH-HM group ($P = 0.824$).

Discussion

Anterior approach for right hepatectomy was initially developed in Japan and later it spread all over the world [1–17]. Lately ARH has also been applied for laparoscopic hepatectomy [24, 25]. Liver resection for large HCC is associated with an increased operative blood loss and high operative morbidity and mortality, particularly in patients with underlying liver cirrhosis [8–10]. Additionally, a larger tumor size is a poor prognostic factor following liver resection for HCC [26]. To elucidate the effectiveness of ARH, the surgical outcome has been evaluated in patients undergoing hepatectomy for HCC >5 cm [7, 8, 16, 17]. Two prospective RCTs, one meta-analysis and one PSM study, have already reported the safety and efficacy of ARH compared with CRH; however, these studies included patients undergoing ARH with or without HM. The superiority of ARH compared to CRH for HCC is still being debated; furthermore, the clinical significance of additional HM in ARH remains unclear [8–11]. To minimize the differences in some baseline characteristics between the ARH-HM and CRH groups, PSM analysis was applied [18–20]. As a result, all perioperative background factors were equivalent in this study. After PSM, HCC patients in ARH-HM groups showed median values of 67 years old, 11.2% of ICG R15, one tumor and 10 cm in diameter. The results of this study are applicable for such selected patients.

Hanging maneuver has the following possible benefits: to decrease blood loss by lifting the liver, to maintain the correct dissection plane and to prevent intrahepatic dissemination of tumor cells. HM, even after mobilization, can provide the former two beneficial effects; however, from an oncological perspective, HM should be performed prior to liver mobilization [14]. Therefore, we initially excluded patients who received ARH without HM and ARH with HM after liver mobilization. We strongly believe that the combined use of HM and ARH for large HCC is a very important issue to prevent intraportal or intravenous seeding of tumor cells. Nowadays, specific circulating tumor cells can be detected both in primary tumor tissues and human blood [27]. CD44-positive circulating tumor cells expressing malignant mesenchymal phenotype remarkably increased after hepatectomy.

Our multi-center analysis in the PSM cohort clearly demonstrated that ARH-HM can provide significantly lesser intraoperative blood loss and lower transfusion rate than CRH. In fact, ARH-HM can decrease the blood loss by 762 g and the blood transfusion rate by 29.6%. Additionally these parameters were obviously smaller in ARH-HM patients despite of tumor size. Excessive blood loss and allogeneic blood transfusion are important predictors of postoperative complications and mortality as well as recurrence and long-term outcome following hepatic resection for HCC [28, 29]. Replacement of blood product can provide immune-suppressive state and can promote metastasis of HCC cells. Blood loss amount is one of the greatest factor to induce increased levels of inflammatory cytokines or growth factors after hepatic resection [30, 31]. It has been reported that ARH-HM can decrease blood loss and blood transfusion requirements, particularly in patients with HCC larger than 10 cm that were found to be adherent to the diaphragm and retroperitoneum [17].

In this study, we clearly demonstrated a significantly better OS than RFS in the ARH-HM group compared with the CRH group. Based on the results of 10 random PSM analyses (Table S2), *P*-values in OS estimation were seven times more significant in the log-rank test and 10 times in the stratified generalized Wilcoxon test. The former has equal weights to the contribution of each failure time; in contrast, the latter has heavier weights to earlier failure times [32]. RFS and OS were both significantly greater in ARH-HM group compared with the CRH group limited to patients with HCC ≥10 cm. In such patients, decrease of recurrence can improve OS in ARH-HM group. The postoperative recurrence in a metastatic manner instead of multicentric occurrence mainly occurs within 2 years [33]. In fact, the cumulative 2-year recurrence rate was lower in the ARH-HM group, but not significantly, than in the CRH group (51.8% vs. 62.8%, $P = 0.231$). Besides, recurrence sites were similar in the two groups. One previous RCT showed a similar result that the application of ARH was one of the independent factors to predict excellent OS (HR 0.416; $P = 0.007$) [8]. In that study, ARH was associated with significantly lower plasma albumin mRNA levels in the peripheral blood compared with CRH. Vascular invasion of the tumor in patients with large HCC is a frequent phenomenon; therefore, intraoperative vessel dissemination can be decreased by the use of ARH.

Recent meta-analysis [9], including HCC and metastatic liver cancer, demonstrated that ARH has the advantages of lower transfusion rate (odds ratio

(OR) = 0.37, 95% CI: 0.21–0.63), recurrence rate (OR = 0.57, 95% CI: 0.37–0.87) and mortality rate (OR = 0.29, 95% CI: 0.13–0.63) compared with CRH. Interestingly, the ARH group had significantly less intrahepatic recurrence than the CRH group ($P = 0.02$). The other study showing better OS instead of similar RFS after hepatectomy for HCC demonstrated more frequent multiple or extrahepatic recurrences in worse OS group [34]. Postoperative deterioration of liver function can restrict the treatment selection for recurrence and can worsen OS. The time course of liver function was unknown in this study; however, lower blood loss and fewer blood transfusions may provide some beneficial effects on liver functional reserve.

This study has some limitations. First, this is a multi-institutional study based on limited data from a shared database; therefore, we cannot discuss the individual information such as postoperative changes in laboratory data or treatments for recurrence in detail. Second, therapeutic strategy or operative procedures were different in each institution. Third, this study was a retrospective and non-RCT study. Although a well-designed PSM analysis was reported to be as accurate as RCT [19], minimal confounding factors could affect the results.

In conclusion, patients with large HCC in the ARH-HM group provided excellent long-term prognosis and had decreased blood loss and fewer transfusion requirements compared with those in the CRH group. Especially, the impact of ARH-HM on better RFS and OS was distinct in patients with HCC ≥10 cm. However, this study cannot resolve the question of whether HM is essential for ARH. Further well-designed, multi-center trials are needed to evaluate the outcome in HCC patients undergoing ARH with or without HM.

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Conflict of interest None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Standardized differences before and after PSM.

Figure S2. RFS and OS according to the tumor size in the PSM cohort. (**a**) Recurrence-free survival (RFS) in patients with 5 cm ≤ HCC < 10 cm. (**b**) Overall survival (OS) in patients with 5 cm ≤ HCC < 10 cm. (**c**) Recurrence-free survival in patients with HCC ≥10 cm. (**d**) Overall survival in patients with HCC ≥10 cm. In the PSM cohort, median RFS and OS were 25.9 (8.3–58.7) vs. 14.7 (7.2–89.1) months and 93.9 (29.2–N/A) vs. 45.7 (21.1–N/A) months, respectively. RFS and OS for 1, 3 and 5 years were 65.5%, 35.1% and 28.1%, respectively, vs. 54.7%, 45.2% and 32.3%, respectively, $P = 0.937$ and 87.2%, 65.2% and 57.1%, respectively, vs. 79.6%, 63.8% and 36.5%, respectively, $P = 0.342$ (**a, b**).

Median RFS and OS were 12.6 (6.6–35.8) vs. 5.5 (3.6–8.2) months and 58.4 (25.6–N/A) vs. 14.4 (8.4–30.1) months, respectively. RFS and OS for 1, 3 and 5 years were 51.2%, 29.8% and 16.6%, respectively, vs. 26.6%, 16.6% and 10.0%, respectively, $P = 0.049$ and 91.5%, 51.0% and 44.7%, respectively, vs. 58.5%, 27.3% and 23.4%, respectively, $P = 0.005$ (**c, d**).

Table S1. Comparison of continuous background factors in HCC patients for ARH-HM and CRH in the overall cohort and PSM cohort.

Table S2. Perioperative data in HCC patients who underwent ARH-HM and CRH in the PSM cohort according to the tumor size.

Table S3. *P*-values in 10 random PSM analyses.

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REVIEW ARTICLE

Perioperative management of hepatectomy in patients with interstitial pneumonia: a report of three cases and a literature review

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Abstract
Purpose Interstitial pneumonia (IP) is a progressive and irreversible fibrosis and can be fatal if acute exacerbation (AE) occurs. While a useful risk-scoring system has been established for lung surgery, no risk evaluation exists for AE of IP related to non-pulmonary surgery. The objective of this review is to describe the management for patients with IP.
Methods We experienced three hepatectomy cases with IP. The first was a 72-year-old male patient diagnosed with hepatocellular carcinoma. Preoperative computed tomography (CT) revealed IP with reticular shadow at the base of both lungs. After hepatectomy, his IP became acutely exacerbated and did not improve with steroid or sivelestat treatment. The second was a 74-year-old male patient diagnosed with hepatocellular carcinoma, and the third was a 75-year-old male patient with liver metastasis. In both these cases, CT revealed a reticular shadow in the lung fields, with increased serum KL-6 levels. We administered pirfenidone for perioperative management, during which time no respiratory complications occurred.
Results Perioperative management with pirfenidone for hepatectomy accompanied by IP was successful in our cases.
Conclusion We reviewed reports on the perioperative prevention, intraoperative risk factors, and treatment of postoperative AE of IP and summarized the perioperative management techniques for IP patients undergoing non-pulmonary surgery.

Keywords Pirfenidone · Interstitial pneumonia · Acute exacerbation · Abdominal surgery · Hepatectomy

Introduction

Although hepatectomy can be performed safely with various devices and maneuvers [1, 2], it still carries potential risk, especially in patients with preoperative complications. Interstitial pneumonia (IP) is a chronic and diffuse lung disease with progressive and irreversible fibrosis. When acute exacerbation (AE) of IP occurs, the mortality rate is in the range of 33.3–100% despite aggressive intensive-care management, mechanical ventilation, antibiotics, and steroid therapy [3, 4]. It is difficult to predict preoperatively whether or not AE of IP will occur, although a risk-scoring system for predicting AE of IP after pulmonary resection has been reported [5, 6].

In cases of lung cancer associated with IP, the frequency of AE of IP after surgery has been reported to range from 7.4 to 25% [3, 7, 8]. Postoperative pulmonary complications are frequent and represent a major source of perioperative morbidity and mortality [9, 10]. However, as yet, there have been no reports on the risk evaluation of postoperative AE of IP with regard to abdominal surgery. The literature is limited to case reports of AE of IP after non-pulmonary surgery and the perioperative management of AE of IP patients receiving non-pulmonary resection [11, 12].

We herein report the successful perioperative management of hepatectomy using pirfenidone to prevent AE of IP.

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Case reports

We encountered three cases of hepatectomy complicated with IP. The first case was a 72-year-old male patient diagnosed with a liver tumor who had a history of esophageal carcinoma treated by chemotherapy and radiation therapy 3 years previously. Preoperative chest X-ray did not reveal anything remarkable (Fig. 1a). Preoperative computed tomography (CT) revealed IP with reticular shadow at the base of both lungs (Fig. 1b). Under the risk-scoring system for pulmonary resection developed by Sato et al. [5], the risk score for AE of IP in this patient was 7, and the predicted incidence of AE was 3.3%. We performed subsegmentectomy for hepatocellular carcinoma (HCC) in segment 8 of the liver. The operation time was 348 min, and the ventilation time was 387 min. Blood loss was 1183 g, and the intraoperative fluid balance was +1647 mL. Six days after surgery, he developed dyspnea, and his SpO_2 decreased. Chest X-ray revealed loss of permeability in both lung fields with reticular shadow (Fig. 1c). CT revealed retention of the hydrothorax on both sides and an enhanced IP image (Fig. 1d). We initiated treatment with methylprednisolone and sivelestat sodium. The patient's breathing gradually worsened, and he was intubated. Despite percutaneous cardiopulmonary support and enforced breathing management, he succumbed 29 days after surgery.

Our second case was a 74-year-old male patient with hepatitis C virus infection who was admitted to our hospital with elevated levels of tumor markers. The tumor, which was enhanced on CT, was 40 mm in diameter in the posterior segment of the right hepatic lobe and was diagnosed as HCC. Chest X-ray showed a diffuse reticular shadow in both lower lung fields (Fig. 2a). CT detected a diffuse reticular shadow, tractional bronchus expansion, and pleural thickening in the inferior lobe of both lungs (Fig. 2b). Ground-glass opacity was apparent in the inferior lobe of the left lung. He had no respiratory symptoms but was considered to be at risk for IP or respiratory complications after hepatectomy. The risk score for AE of IP was 7. We consulted a respiratory physician regarding the perioperative management of IP. Before the operation, pirfenidone was administered at a daily dose of 600 mg for the prevention of AE of IP. After 2 week pirfenidone therapy, the serum KL-6 levels decreased from 954 to 835 U/mL. CT revealed no change in the usual IP pattern after 2 weeks of therapy, suggesting that the IP was stable and without inflammatory reaction. The results of pulmonary function testing and an arterial blood gas analysis were within the normal range. We diagnosed the patient with HCC with IP and performed posterior segment hepatectomy and cholecystectomy under

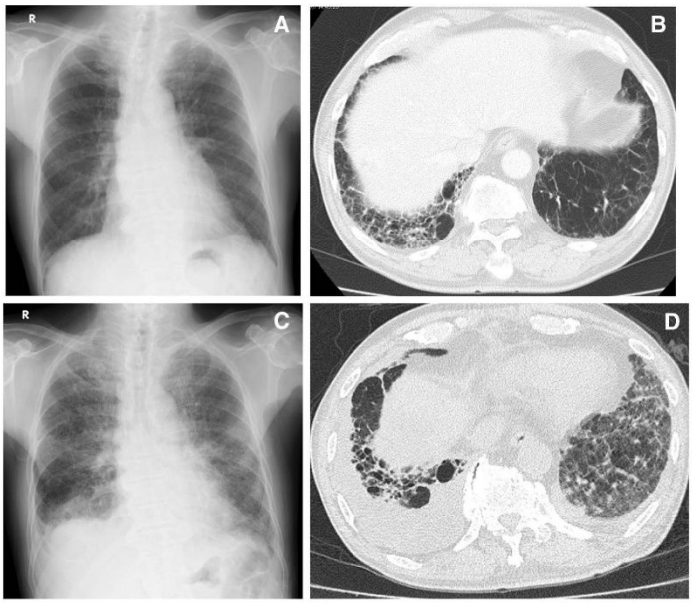

Fig. 1 Case 1. **a** Preoperative chest X-ray revealed nothing remarkable. **b** Preoperative computed tomography (CT) revealed IP with reticular shadow at the base of both lungs. **c** Chest X-ray revealed loss of permeability in both lung fields with reticular shadow. **d** CT revealed retention of hydrothorax on both sides and enhanced IP images

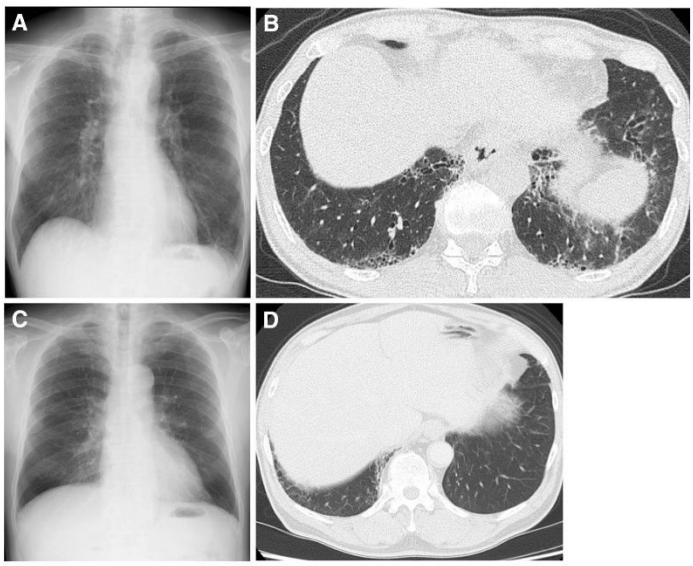

Fig. 2 **a** Case 2. Chest X-ray showed ground-glass opacity in both lower lung fields. **b** Chest CT before surgery revealed diffuse ground-glass opacities and interstitial changes in both lower lung fields. **c** Case 3. Preoperative chest X-ray revealed nothing remarkable. **d** CT detected diffuse reticular shadows in the inferior lobe of both lungs

general anesthesia combined with spinal-epidural anesthesia. During the operation, the fraction of inspired oxygen, tidal volume during surgery, and intraoperative fluid balance was minimized by the anesthesiologist. The operation time was 368 min, and the ventilation time was 441 min. Blood loss was 357 g, and the intraoperative fluid balance was +3093 mL. After surgery, the patient was extubated immediately and transferred to the intensive-care unit. Pirfenidone was administered as soon as oral intake was possible. Seven days after surgery, CT revealed no development of IP, and the KL-6 had decreased further to 528 U/mL. The perioperative respiratory function was unremarkable, without any pulmonary complications. The patient was discharged 13 days after surgery with continuing administration of pirfenidone.

The third case was a 75-year-old male patient who had undergone sigmoidectomy 2 years previously. Liver metastasis was detected on follow-up CT. Preoperative chest X-ray did not reveal any particular findings (Fig. 2c). CT detected a diffuse reticular shadow in the inferior lobe of both lungs (Fig. 2d). The KL-6 levels were elevated to 1059 U/mL and increased to 1559 U/mL after a single administration of pirfenidone. The AE of IP risk score was 9. After 3 months of pirfenidone therapy, the serum KL-6 levels had decreased to 784 U/mL. We then performed laparoscopic partial hepatectomy. The operation time was 313 min, and the ventilation time was 418 min. Blood loss was 15 g, and the intraoperative fluid balance was +1860 mL. Perioperative management with pirfenidone was continued as described for the second case. The patient was discharged 8 days after surgery with continuing administration of pirfenidone.

We explained the risk of AE of IP after surgery with the risk score and obtained informed consent from all three patients before surgery. Informed consent included explaining alternative therapies with curative effects, such as radiofrequency ablation or transcatheter arterial chemoembolization, and the risk of these therapies.

Discussion

In this study, the presented cases were classified in possible UIP with CT images based on the criteria of the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement for IPF [13]. The diagnosis of IPF required a surgical lung biopsy when identified in possible UIP pattern cases. We believed that we could reduce the risk of AE of IP by preoperative treatment with pirfenidone, as in respiratory surgery [14]. The risk factors of AE of IP after abdominal surgery have not yet been sufficiently studied. The first patient we encountered had received radiation therapy for esophageal cancer in the past. Radiation pneumonitis had not been noted on CT, and 3 years had passed since the radiation therapy when we treated the patient. We,

therefore, believe that the radiation therapy was unlikely to have been involved in the onset of AE of IP in this patient. When the first case underwent surgery, the risk of AE of IP in this patient was still unclear, and anesthesia management was carried out as usual. AE of IP is an infrequent complication after abdominal surgery but can be fatal in some cases. The indications for surgery need to be assessed in detail with focus on the pulmonary function and the risk of AE of IP after surgery.

The risk factors for AE of IP that have been reported include surgical procedures at pulmonary resection, male sex, history of exacerbation, preoperative steroid use, high levels of serum sialylated carbohydrate antigen KL-6, a typical IP appearance on CT, reduced percent predicted vital capacity, low body mass index, emergency surgery, lung surgery, and long anesthesia time [9, 15]. A risk-scoring system for predicting AE of IP after pulmonary surgery has also been suggested, which includes a history of AE, surgical procedures, UIP appearance, male sex, preoperative steroid use, high KL-6 levels, and a low vital capacity [5]. Our predicted risk of AE of IP after hepatectomy was 3.3% for cases 1 and 2 and 6.0% for case 3, primarily based on the patients being male and having the usual IP appearance on CT with or without a high level of KL-6. Table 1 describes several cases of AE of IP after non-pulmonary surgery [9, 11, 12], but the frequency is unknown. The occurrence of AE in non-pulmonary surgery raises the possibility that perioperative lung dynamics may be responsible for the high oxygen concentration, mechanical insult due to higher airway pressures, or higher tidal volumes [12]. AE of IP after non-pulmonary surgery can occur in any patient undergoing surgery with general anesthesia, as in case 1. We determined the indication of hepatecomy with due consideration of the risk of AE of IP based on the risk-score system; we then explained the risk to all three patients and obtained their informed consent before surgery. No method of assessing the risk of AE of IP in abdominal surgery patients has yet been developed. Nationwide surveillance and a system for evaluating the risk of AE of IP after non-pulmonary resection, especially abdominal surgery, are clearly needed.

KL-6, surfactant protein (SP)-A, SP-D, and monocyte chemoattractant protein-1 (MCP-1) are reported to be sensitive markers for interstitial lung disease (ILD). The half-life of SP-A was reported to be 4.5 min, and the half-life of KL-6 is longer than that of SP-A [16]. Ohnishi suggested that KL-6 is the best serum marker for IP with respect to its sensitivity, specificity, and diagnostic accuracy [17]. A preventive effect of perioperative pirfenidone treatment for postoperative AE of IP in patients with lung cancer was reported [14]. The KL-6 levels in the patients who received perioperative pirfenidone treatment decreased significantly during the preoperative period and further after surgery

Table 1 Acute exacerbation of interstitial pneumonia after non-pulmonary surgery

Author	Age (years)	Sex	VC (% pred)	DLCO (% pred)	FEV1.0 (% pred)	KL-6 (U/mL)	Predicted scoring	Diagnosis	Surgery	Time to AE (POD)	Treatment
Choi SM	69	M	90	74	–	–	>7	Prostate cancer	Robot-assisted laparoscopic radical prostatectomy	–	–
	66	F	–	–	–	–	>4	Hemo peritoneum	Intestinal anastomosis appendectomy	–	–
Kubota T	76	F	57	–	90	353	>1	Nuchal lipoma	Remove a lipoma	4	Sivelestat sodium methylprednisolone
Ghatol A	58	M	77	68.8	82.3	–	>8	Orthopedic disorder	Total knee replacement	7	–
	61	M	46.2	35.8	52.1	–	>13	Coronary disease	Coronary artery bypass graft surgery	2	–

VC vital capacity, *DLCO* diffusion capacity for carbon monoxide, *FEV1.0* forced expiratory volume, *AE* acute exacerbation, *POD* postoperative day

Table 2 Studies related to the acute exacerbation of interstitial pneumonia

Classification by contents	Number of patients	Number of patients with AE (%)	Notable features
Predicted scoring system			
Simple risk-scoring system [10]	1022	100 (9.8)	Predict with seven preoperative factors
High-resolution computed tomography score system [4]	28	9 (32.1)	Predict with computed tomography images
Preservation of AE of IP			
Pirfenidone [14]	28	6 (21.4)	Pirfenidone prevented postoperative AE of IP in clinical study
Nintedanib [15]	–	–	Nintedanib prevented postoperative AE of IP in clinical study
Macrolides [16, 17]	–	–	Preventing effect of erythromycin in vivo
N-Acetylcysteine [18, 19]	–	–	*N*-Acetylcysteine had an inhibitory effect on IL-8 and MMP-9 release and progress of IP
Neutrophil elastase inhibitor [20]	–	–	Neutrophil elastase inhibitor decreased fibrosis in vivo
Sivelestat sodium hydrate with low-dose methylprednisolone [21]	31	0	Perioperative administration may be useful as prophylaxis for AE of IP
Perioperative management			
Mechanical ventilation during operation [22]	68	3 (4.4)	High oxygen concentration, airway pressures and tidal volume increase the risk
Intraoperative excessive fluid infusion [23]	52	7 (13.5)	The amount of intraoperative fluid was a risk factor for AE of IP
Treatment for AE of IP			
High-dose corticosteroids [24]	–	–	Corticosteroid therapy demonstrated clinical improvement
Cyclosporine A [25, 26]	–	–	The prognosis of the cyclosporine-treated patients was better
Cyclophosphamide [27]	–	–	Improved AE of IP with cyclophosphamide
Recombinant human soluble thrombomodulin [29]	22	–	The mortality rate was significantly lower in the thrombomodulin group
Nintedanib [31]	–	–	Improved AE of IP with nintedanib
Polymixin B-immobilized fiber column	–	–	Neutrophils and MMP-9 levels were significantly decreased
Hemoperfusion [32–34]	–	–	The PaO_2/fraction of the inspired oxygen ratio increased

[18]. KL-6 >1000 U/mL was included in the risk-score system, and the baseline serum KL-6 was an independent predictive factor for AE of IP in a multivariate analysis [19]. We believe that a reduction in the KL-6 levels reduces the risk of postoperative AE of IP. In this study, we used KL-6 as a marker of indication for surgery.

Only a few drugs have been established as successful in reducing the incidence of AE of IP. Pirfenidone was used as an oral antifibrotic therapy and reduced disease progression, as measured by the decline in the vital capacity or forced vital capacity, in patients with pulmonary fibrosis [20]. A significant difference was reported in the incidence of AE of IP between patients treated with pirfenidone and a placebo group [21], while in another study, there were no severe drug-related complications or IP-related events in the pirfenidone-treated group [22]. AE of IP was significantly less frequent in the pirfenidone-treated group than in the control group in a pulmonary resection study [18]. In the present study, pirfenidone was used perioperatively, and the authors propose that the absence of pulmonary complications was due to pirfenidone therapy. Other drugs have also been reported as useful for the prevention of AE of IP. Nintedanib is a potent tyrosine kinase inhibitor with distinct specificity, targeting growth factors involved in fibrotic changes in the lungs of patients with IP [23]. For perioperative administration to prevent AE, macrolides [24, 25], *N*-acetylcysteine [26, 27], and proteinase inhibitors [28] have been reported to be useful. Combination administration with sivelestat sodium hydrate and low-dose methylprednisolone may also be beneficial as prophylaxis for AE of IP [29].

The intraoperative administration of supplemental oxygen at a high concentration and mechanical ventilation-related lung injury has been suggested as likely major causes of AE of IP in pulmonary resection [30]. Intraoperative excessive fluid infusion has also been reported to be a risk factor for AE of IP [31]. Cooperation between surgeons and anesthesiologists to perform less-invasive surgery is of great importance in preventing AE of IP, and intraoperative management that minimizes the concentration of oxygen, tidal volume, and intravenous fluid administration is warranted.

There is little evidence that the currently accepted treatments are effective for AE of IP. Some studies have reported that immunosuppressive agents, such as high-dose corticosteroids [32], cyclosporine A [33, 34], and cyclophosphamide [35], were efficacious. By contrast, however, patients receiving methylprednisolone pulse therapy in combination with cyclophosphamide or cyclosporine A did not achieve significantly improved outcomes for AE of IP [36]. Recombinant human soluble thrombomodulin is associated with reductions in the mortality rate in patients with AE of IP [37]. Disorders of coagulation and fibrinolysis are major components of AE of IP, and anticoagulant therapy is reported to be beneficial [38]. It was reported that the administration of nintedanib in patients who developed AE of IP was effective [39]. Furthermore, recent reports have suggested that the use of polymyxin B-immobilized fiber-column hemoperfusion (PMX-DHP) may be effective in patients with AE of idiopathic pulmonary fibrosis [40–42]. One study reported that the serum levels of cytokines, including interleukin (IL)-9, IL-12, IL-17, and vascular endothelial growth factor, were significantly decreased immediately after PMX-DHP and contributed to the rapid improvement in oxygenation by suppressing vascular permeability in the lung [43].

For major surgery, such as hepatectomy with severe IP, the selection of appropriate therapy based on an accurate evaluation of the IP activity and the careful management of the perioperative respiratory state are required. Table 2 summarizes the reports on IP that all non-respiratory surgeons should review. When there is inflammation or progression of IP, we should avoid surgery and prioritize antifibrotic therapy. Pirfenidone may be useful for the management of abdominal surgery with IP, but further well-designed, prospective, multicenter studies are required to help us better understand the risks for AE of IP in relation to non-pulmonary surgery.

Compliance with ethical standards

Conflict of interest All authors have nothing to disclose.

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