Observational Study

Medicine®

OPEN

Outcomes of anterior approach major hepatectomy with diaphragmatic resection for single huge right lobe HCC with diaphragmatic invasion

Jinli Zheng, MD, Shu Shen, MD, Li Jiang, MD, PhD*, Lunan Yan, MD, PhD,
Jiayin Yang, MD, PhD, Bo Li, MD, PhD, Tianfu Wen, MD, PhD, WenTao Wang, MD, PhD,
Mingqing Xu, MD, PhD

Abstract

The outcomes following anterior approach (AA) hepatectomy in huge hepatocellular carcinoma (HCC) patients with diaphragmatic invasion (DI) remain unclear. This study compared the outcomes of single huge right HCC patients with and without DI after AA hepatectomy. A total of 203 consecutive patients with single huge right lobe HCC who underwent AA major hepatectomy were included. They were divided into group PDI (n=53) and group ADI (n=150) according to the presence or the absence of DI. Their short- and long-term outcomes were compared, and a subgroup analysis was performed. There were no significant differences regarding postoperative complications and 90-day mortality between the 2 groups. The overall survival (OS) and recurrence-free survival (RFS) rates were similar between the 2 groups. The subgroup analysis also showed that patients with tumor resection en bloc with part of the diaphragm had similar OS and RFS rates as those who underwent diaphragmatic resection after hepatectomy. Tumor diameter ≥ 15 cm, serum AFP level ≥ 400 ng/mL, and tumor grade of G4 and microvascular invasion are independent predictors of poor prognosis. For the single huge right lobe HCC patients with DI, AA major hepatectomy combined with diaphragmatic resection could offer similar OS and RFS as those without diaphragmatic invasion.

Abbreviations: AA = anterior approach, ADI = absence of the diaphragmatic invasion, AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DI = diaphragmatic invasion, HBV DNA = hepatitis B virus deoxyribonucleic, HCC = hepatocellular carcinoma, OS = overall survival, PDI = presence of the diaphragmatic invasion, PHT = portal hypertension, PT = prothrombin time, RFS = recurrence-free survival, TB = total bilirubin, TBD = tumor resection before diaphragmatic resection, TED = tumor resection en bloc with part of the diaphragm.

Keywords: anterior approach, diaphragmatic invasion, hepatocellular carcinoma, resection, single huge tumor

1. Introduction

In China, the incidence and mortality of hepatocellular carcinoma (HCC) account for more than 50% of all HCC patients in the world.[1] Because early symptoms are not obvious, huge HCC, with a tumor diameter of ≥ 10 cm, can account for a considerable proportion of HCC patients at the time of initial diagnosis. Although patients with huge HCCs are thought to be difficult to treat and the prognosis is relatively poor, hepatectomy is regarded as the only potentially curative therapy for huge HCC patient with good liver functional reserve because these tumors are not amenable for other treatments such as liver transplantation, transcatheter arterial chemoembolization, and radiofrequency ablation.[2] According to the American Joint Committee on Cancer (AJCC) staging system, the solitary HCC without major vascular invasion is classified as T1 regardless of tumor size and surgical resection is recommended.[3,4] In the most recent reviews concerning the Barcelona Clinic Liver Cancer (BCLC) staging system,[5,6] patients with single tumor > 5 cm in diameter are classified as having stage A disease and are considered as suitable candidates for hepatectomy.

A peripherally located large HCC arising from the liver is clinically prone to involve the diaphragm, especially by the large tumor located in segment VII or VIII. Direct diaphragmatic involvement, according to autopsy studies, is found in 10% to 13% of HCC patients.[7] For patients with obvious invasion to diaphragm, tumor resection en bloc with part of the diaphragm is recommended.[8] However, for the cases with unobvious adherence to the diaphragm, the HCC tumor is also removed firstly and the suspected involved diaphragm is then resected. In conventional major right hepatectomy, complete mobilization of the right liver is performed before parenchymal transaction. However, it may lead to excessive bleeding from the right liver

Editor: Kelvin Ng.

ZJ and SS contributed equally to this study and are co-first authors; they coordinated and wrote the article.

Grant support: This study was supported by grants from the National Sciences and Technology Major Project of China (2012ZX10002-016) and (2012ZX10002-017) and the National Natural Science Foundation of China (81400636).

The authors have no conflicts of interest to disclose.

Department of Liver Surgery, Liver Transplantation Center, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China.

* Correspondence: Li Jiang, Department of Liver Surgery, Liver Transplantation Center, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China (e-mail: jiangli029@163.com).

Medicine (2018) 97:36(e12194)

Received: 9 October 2017 / Accepted: 9 August 2018

http://dx.doi.org/10.1097/MD.0000000000012194

attachment, iatrogenic tumor rupture, prolonged ischemia of the liver remnant from rotation of the hepatoduodenal ligament, and hematogenous tumor cell dissemination. To avoid these problems, the anterior approach, in which liver mobilization is performed at the end of parenchymal transaction, is recommended, especially for patients with right huge HCC.[9,10]

However, there are very few studies, to the best of our knowledge, investigating whether diaphragmatic invasion can result in poor outcomes in patients with single huge right lobe HCC who underwent the anterior approach major hepatectomy. To clarify this issue, we exclusively compared the short- and long-term outcomes of single huge right HCC patients with and without the diaphragmatic invasion after anterior approach hepatectomy. In addition, the influence of the different methods for diaphragm resection on outcomes following anterior approach hepatectomy in huge HCC patients with diaphragmatic invasion is still unclear. Therefore, we performed a subgroup analysis to compare postoperative outcomes in patients with diaphragmatic invasion using tumor resection en bloc with part of the diaphragm or diaphragmatic resection after tumor remove.

2. Patients and methods

This study was approved by the West China Hospital Ethics Committee, and in accordance with the ethical guidelines of the Declaration of Helsinki.

2.1. Diagnostic criteria and definitions

The HCC diagnosis and diaphragmatic invasion were confirmed by a histopathological examination of the surgical samples.

A single HCC tumor of ≥ 10 cm in diameter is defined as huge HCC.[11,12]

Clinically relevant portal hypertension (PHT) is defined as the presence of esophageal varices and/or a platelet count of less than 100,000/μL in association with splenomegaly.[13]

2.2. Cohort selection

Figure 1 shows inclusion and exclusion criteria for the cohort. A total of 281 consecutive patients with single huge right lobe HCC (not including those with recurrent HCC) underwent hepatectomy from January 2009 to December 2013 in our center. Of these, 21 patients who did not undergo anterior approach hepatectomy were excluded. Next, we excluded 27 patients who had macrovascular invasion. In addition, 3 patients died during the perioperative period were also excluded. After excluding 27 patients who were lost to follow-up or had incomplete medical records, 203 patients with single huge right lobe HCC who underwent the anterior approach major hepatectomy were finally enrolled in this study. They were then divided into 2 groups according to the presence or absence of the diaphragmatic invasion: the group PDI (n=53), which consisted of patients with diaphragmatic invasion and the group ADI (n=150), which consisted of patients without diaphragmatic invasion. They were monitored until March 2016 or their death, and their medical records were retrospectively reviewed.

2.3. Preoperative management and indications for heaptectomy

Briefly, before hepatectomy, all patients underwent routine laboratory tests, including blood routine test, measurement of

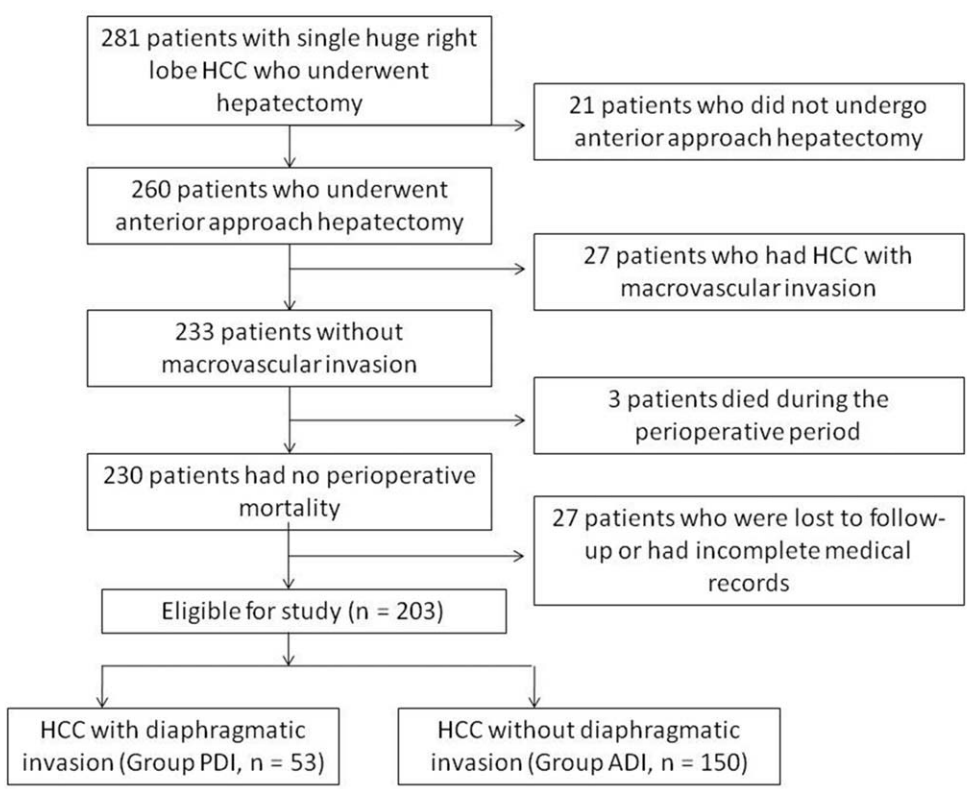

Figure 1. Flow chart of study participants.

serum alpha-fetoprotein (AFP) level, and liver function test. All the patients enrolled had the initial HCC for hepatic resection (HR). The indications of HR for single huge HCC were the presence of an appropriate residual liver volume evaluated by computed tomography or magnetic resonance imaging. For HCC patients without cirrhosis, we considered 40% remnant liver volume after hepatectomy to be adequate. However, for cases with intermediate or advanced cirrhosis, the remnant volume should be more than 50%. We also required well-preserved liver function as another necessary condition for hepatectomy. If the patient had intermediate or advanced cirrhosis with Child–Pugh B or C liver function, the major hepatectomy was not performed. All the patients had Child–Pugh A liver function.

2.4. Surgical technique

Surgery was performed via the right subcostal or reversed T-shaped incision. After finish abdominal exploration, intraoperative ultrasonography was used to assess the extent of tumor and its relationship with the main vascular structures and mark the demarcation line of parenchymal transaction. Hepatic hilus dissection was carried out to isolate and divide the right hepatic artery and the right portal vein. Hepatic parenchymal transaction was performed from the anterior liver surface posteriorly toward the inferior vena cava along the demarcation line using cavitron ultrasonic surgical aspirator without previous mobilization of the right liver. If adequate control of hemorrhage was not achieved by hemihepatic vascular occlusion, the Pringle maneuver was used to control the inflow system. All the small vessels were then individually ligated and divided, and the right or middle hepatic vein was isolated and divided intraparenchymally. When the right lobe was completely mobilized from the inferior vena cava, the right coronary and triangular ligaments were divided to allow for specimen removal (Fig. 2).

For the HCC tumor with obvious invasion to diaphragm, we performed tumor resection en bloc with part of the diaphragm. On the other hand, for the cases with unobvious adherence to the diaphragm, the HCC tumor was removed firstly and the suspected involved diaphragm was then resected. The diaphragm was repaired with nonabsorbable sutures (2-0 prolene) after resection. All the patients in our study received primary closure of defect of their diaphragm, and no one used biological or artificial patch. A 3.5F feeding tube was inserted into the pleural cavity through a diaphragmatic hole, and the anesthesiologist was asked to expand the lungs up to 30 cmH_2O with positive ventilation. The feeding tube was withdrawn as the suture was tightened.

2.5. Postoperative evaluation

All postoperative complications were graded according to the Dindo–Clavien classification;[14] a major complication was defined as any complication of grade III or higher. The follow-up exam was routinely performed in the outpatient clinic. AFP and hepatitis B virus deoxyribonucleic (HBV DNA) measurements and abdominal ultrasonography were performed every 3 months. Patients with positive HBV DNA received one nucleos(t)ide analog daily, such as lamivudine, entecavir and adefovir dipivoxil, and the same nucleos(t)ide analog was administered after surgery.[15] If the HBV-DNA was negative, it should be monitored closely for the reactivation. Besides, there was no HCV patient in our study. A contrast-enhanced computed tomography scan was performed every 6 months. When intrahepatic recurrence was difficult to ascertain, magnetic resonance imaging or contrast-enhanced ultrasonography were performed. The tumor recurrence was mainly based on radiographic evidence and/or the AFP level. The patients who showed tumor recurrence were treated with the following alternatives: re-resection, radio frequency ablation, salvage liver

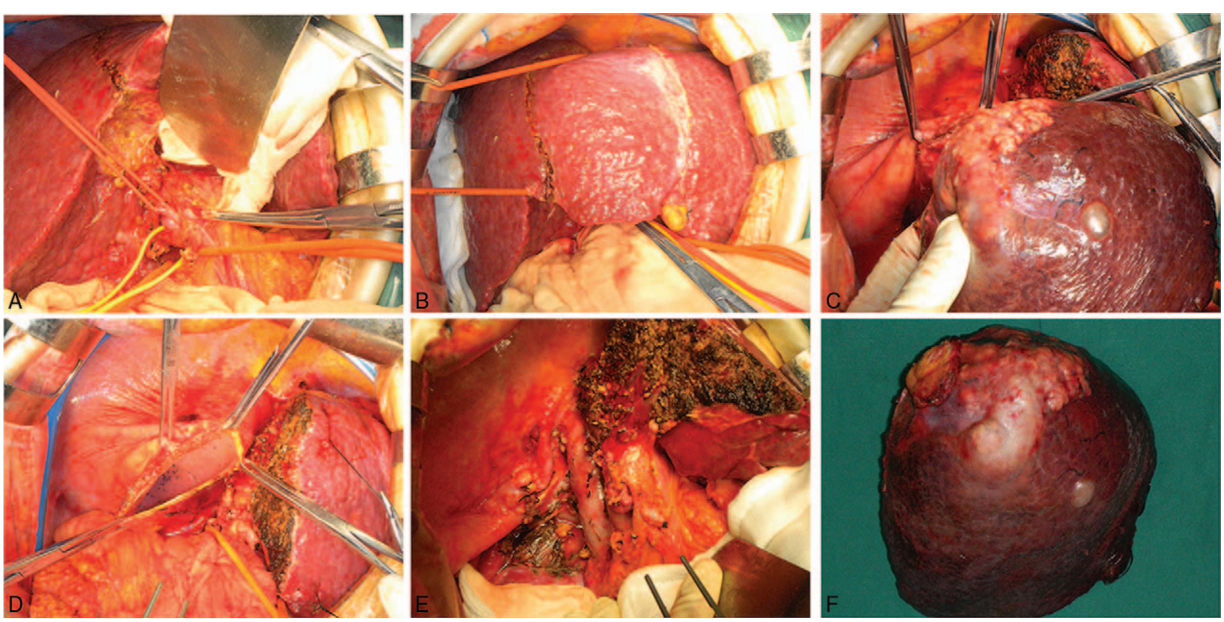

Figure 2. Anterior approach right hemihepatectomy en bloc with part of the diaphragm. (A) Isolation of the right hepatic artery and the right portal vein. (B) The hanging maneuver is performed. (C) En bloc resection of the involved diaphragm after parenchymal transaction. (D) Remnant right diaphragm after resection. (E) Remnant liver and repaired right diaphragm. (F) Specimen including the tumor and involved diaphragm.

transplantation, transcatheter arterial chemoembolization, sorafenib, radiotherapy, and chemotherapy.

2.6. Statistical analysis

The statistical software SPSS 21.0 (SPSS Inc) was used to analyze relevant data. Categorical data were presented as number (percent) and compared using Pearson Chi-square or Fisher's exact test. Continuous variables were expressed as the mean ± SD and analyzed using the *t*-test. Overall survival (OS) and recurrence-free survival (RFS) rates were estimated by the Kaplan–Meier method, and differences between the 2 groups were determined by log-rank test. The Cox proportional hazards model was used to test potential predictor of survival after surgery. The statistically significant variables ($P < .10$) identified by univariate analysis were then included in the multivariate analysis with proportional hazard regression. A 2-tailed $P < .05$ was considered statistically significant.

3. Results

3.1. Preoperative characteristics of the whole cohort

Baseline demographic and preoperative data for all 203 patients are summarized in Table 1. Patients in the group PDI had larger tumor size than those in the group ADI ($P = .021$). There were no significant differences in age, sex, serum levels of total bilirubin (TB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, prothrombin time (PT) and platelet count, and the percentage of serum hepatitis B surface antigen positivity, HBV DNA of > 1000 IU/mL, AFP level of > 400 ng/mL and the patients with clinical PHT between the group PDI and ADI (all $P > .05$).

3.2. Short-term outcomes of the whole cohort

There were more patients with intraoperative blood loss of >1000 mL in the group PDI, as shown in Table 2, than that in the group ADI (13.2% vs 4.0%, $P = .043$). Similarly, more patients in the group PDI needed intraoperative blood transfusion than those in the group ADI (18.9% vs 8.7%, $P = .044$). Moreover, the mean duration of operation for patients in the group PDI was longer than those in the group ADI (5.4 ± 1.2 hours vs 5.0 ± 0.9 hours, $P = .008$). There were no significant differences in the duration of postoperative hospital stay and 90-day mortality rate between the group PDI and ADI (all $P > .05$).

Most postoperative complications were grade I and II and there were no significant differences between group PDI and ADI regarding the grades of postoperative complications. The degree of pathological differentiation of HCC was identified using Edmonson–Steiner classification.[16] Most tumors were grade G3 or G4 and there were no significant differences between the group PDI and ADI regarding the tumor grades. In addition, there was no statistical difference in microvascular invasion between the 2 groups.

3.3. Long-term outcomes of the whole cohort

During a mean follow-up period of 33.7 ± 23.1 months (range 0.7–84.9 months), 39 (73.6%) patients in the group PDI and 109 (72.7%) patients in the group ADI died, respectively. The OS rates in the group PDI were not significantly different from that in the group ADI: 1-, 3-, and 5-year OS rates were 71.7%, 39.6%, and 27.6%, respectively, for patients in the group PDI versus 76.0%, 46.0%, and 31.4%, respectively, for those in the group ADI ($P = .528$, Fig. 3A). During the follow-up period, 48 (90.6%) patients in the group PDI and 125 (83.3%) patients in the group ADI occurred tumor recurrence, respectively. Similarly, the RFS rates did also not differ between the 2 groups: 1-, 3-, and 5-year RFS rates were 53.9%, 28.1%, and 6.7%, respectively, for patients in the group PDI versus 60.1%, 33.8%, and 15.8%, respectively, for those in the group ADI ($P = .114$, Fig. 3B).

3.4. Subgroup analysis by the methods for diaphragmatic resection in the group PDI

To know the influence of the methods for diaphragmatic resection on postoperative survival, patients in the group PDI were divided into 2 subgroups, with tumor resection en bloc with part of the diaphragm (subgroup TED, n = 32) or tumor resection before diaphragmatic resection (subgroup TBD, n = 21). There was no significant difference in the OS between the subgroup TED and TBD (1-, 3-, and 5-year OS rates of 68.8%, 43.8%, and 30.1%, respectively, in the subgroup TED versus 76.2%, 33.3%, and 23.8% in the subgroup TBD, respectively, $P = .600$; Fig. 4A).

Table 1

Preoperative clinicopathologic data of the whole cohort.

Variable	Group PDI (n = 53)	Group ADI (n = 150)	*P* value
Age, mean ± SD (range), years	48.3 ± 12.1 (25–72)	47.8 ± 12.6 (19–76)	.828
Male, n (%)	46 (86.8%)	118 (78.7%)	.197
Tumor size, mean ± SD (range), cm	13.3 ± 2.9 (10–20)	12.2 ± 3.0 (10–25)	.021
HBsAg positivity, n (%)	47 (88.7%)	139 (92.7%)	.391
HBV DNA ≥ 1000 IU/mL, n (%)	17 (32.1%)	54 (36.0%)	.607
Serum AFP ≥ 400 ng/mL, n (%)	26 (49.1%)	89 (59.3%)	.194
Total bilirubin level, mean ± SD (range), μmol/L	14.7 ± 6.2 (5–28.9)	14.7 ± 6.3 (3.3–37.6)	.964
ALT level, mean ± SD (range), IU/L	77.9 ± 63.0 (8–894)	59.1 ± 67.5 (9–513)	.189
AST level, mean ± SD (range), IU/L	106 ± 176 (19–567)	73.4 ± 64.7 (19–548)	.192
Albumin level, mean ± SD (range), g/L	39 ± 7.9 (21–69.9)	39 ± 5.5 (23.6–49.1)	.972
Prothrombin time, mean ± SD (range), seconds	11.8 ± 1.4 (9.6–18.2)	11.8 + 1.2 (8.8–17.1)	.832
Platelet count, mean ± SD (range), 10^9/L	202.4 ± 77.6 (36.7–421)	195.1 ± 92.6 (18.6–488)	.611
PHT, n (%)	5 (9.4%)	25 (16.7%)	.202

ADI = absence of diaphragmatic invasion, AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, HBsAg = hepatitis B surface antigen, HBV DNA = hepatitis B virus deoxyribonucleic acid, PDI = presence of diaphragmatic invasion, PHT = portal hypertension.

Table 2

Short-term outcomes of the whole cohort.

Variable	Group PDI (n=53)	Group ADI (n=150)	*P* value
Intraoperative blood loss, mL			
< 100	1 (1.9%)	6 (4.0%)	.679
100–500	22 (41.5%)	60 (40.0%)	.847
501–1000	23 (43.4%)	78 (52.0%)	.282
> 1000	7 (13.2%)	6 (4.0%)	.043
Intraoperative blood transfusion	10 (18.9%)	13 (8.7%)	.044
Operative time, mean±SD (range), hour	5.4±1.2 (3.8–10)	5.0±0.9 (3.9–8.1)	.008
Tumor resection en bloc with diaphragmatic resection, n (%)	32 (60.4%)	—	—
Resection margins, mean±SD (range), cm	1.4±0.7 (0.2–3)	1.5±0.7 (0.1–3)	.401
Duration of postoperative hospital stay, mean±SD (range), day	11.3±8.7 (6–109)	10.8±9.2 (5–98)	.326
Complications			
Grade I	14 (26.4%)	33 (22.0%)	.512
Grade II	7 (13.2%)	19 (12.7%)	.919
Grade IIIa	4 (7.5%)	10 (6.7%)	.762
Grade IIIb	3 (5.7%)	6 (4.0%)	.699
Grade IVa	3 (5.7%)	9 (6.0%)	1.000
Grade IVb	1 (1.9%)	3 (2.0%)	1.000
Grade V	0	0	—
90-day mortality	1 (1.9%)	4 (2.7%)	1.000
Microvascular invasion	27 (50.9%)	77 (51.3%)	.961
Tumor grade			
G1–G2	10 (18.9%)	48 (32.0%)	.069
G3	21 (39.6%)	59 (39.3%)	.970
G4	22 (41.5%)	43 (28.7%)	.085

ADI=absence of diaphragmatic invasion, PDI=presence of diaphragmatic invasion.

Similarly, for patients in the subgroup TED, the 1-, 3-, and 5-year RFS rates were similar to that in patients in the subgroup TBD (56.3%, 28.1%, and 10.0% versus 50.1%, 23.4%, and 0, respectively, $P=.388$; Fig. 4B).

3.5. Risk factor analysis for postoperative survival

In univariate analysis, significant risk factors for postoperative survival were the age of < 60 years, tumor size of ≥15 cm, serum AFP level of ≥400 ng/mL, intraoperative blood loss of >1000 mL, intraoperative transfusion, resection margin of >1 cm, tumor grade of G4 and microvascular invasion (all $P<.10$, Table 3). However, in multivariate analysis, the variables including the tumor size of ≥15 cm, serum AFP level of ≥400 ng/mL, tumor grade of G4, and microvascular invasion were found to be independent predictive factors for poor postoperative survival (Table 4).

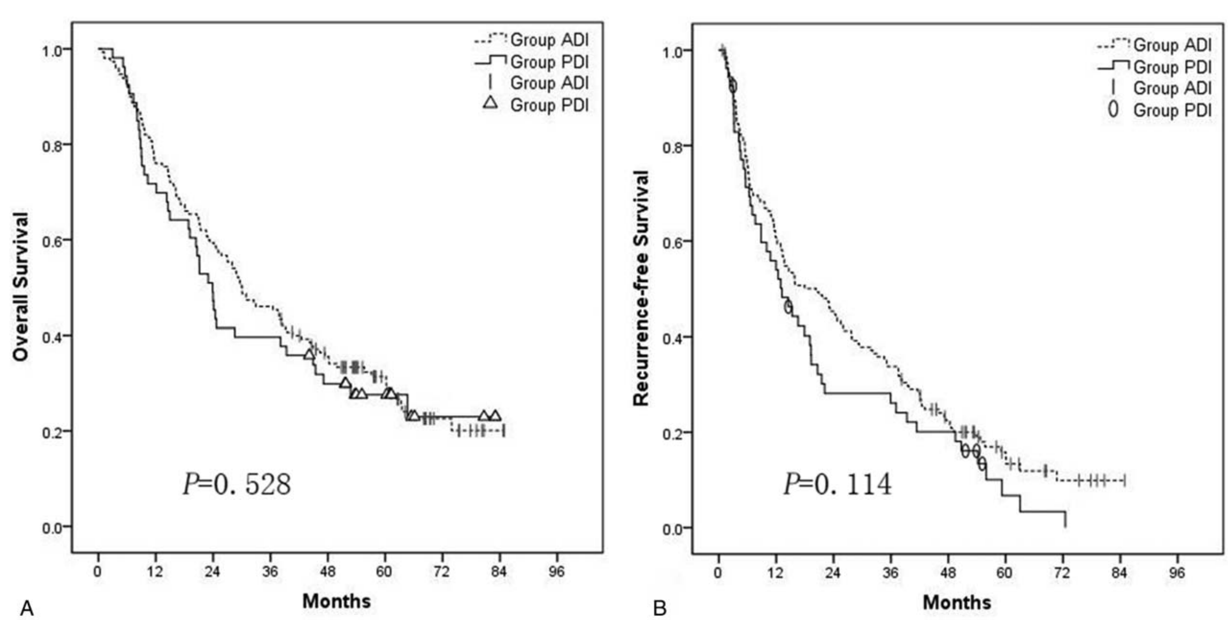

Figure 3. The OS (A) and RFS (B) for the single huge right lobe HCC patients with and without diaphragmatic invasion after surgery. ADI=absence of diaphragmatic invasion, HCC=hepatocellular carcinoma, OS=overall survival, PDI=presence of diaphragmatic invasion, RFS=recurrence-free survival.

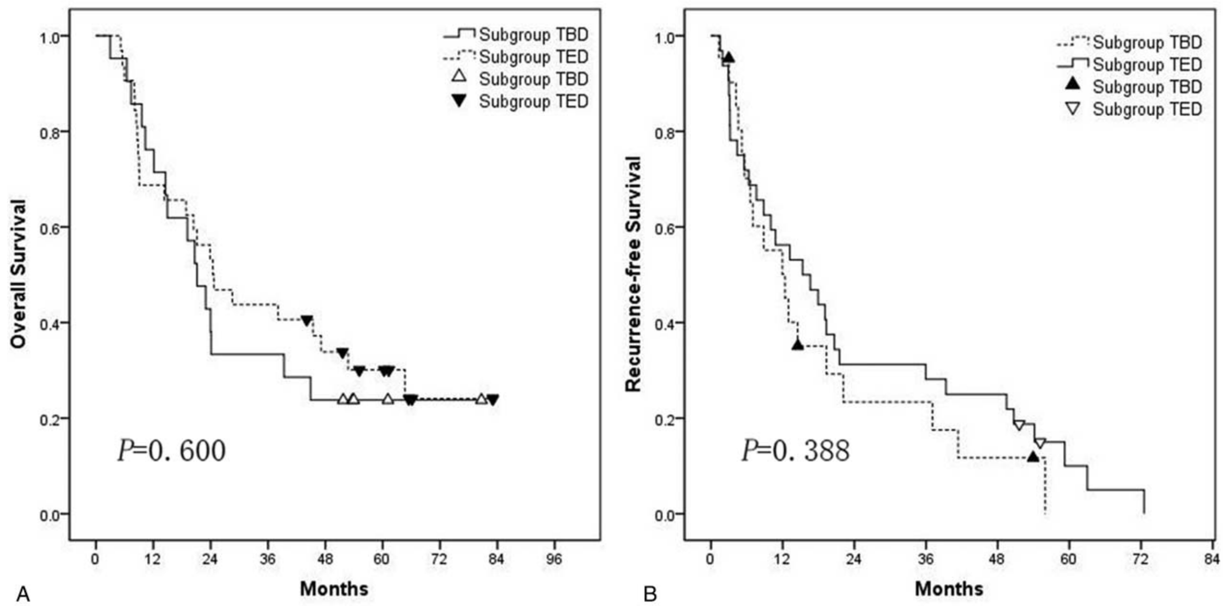

Figure 4. Subgroup survival analysis by the methods for diaphragmatic resection in the group PDI. (A) The OS for patients with tumor resection en bloc with part of the diaphragm and those with tumor resection before diaphragmatic resection; (B) The RFS for patients with tumor resection en bloc with part of the diaphragm and those with tumor resection before diaphragmatic resection. PDI=presence of the diaphragmatic invasion, RFS=recurrence-free survival, TED=tumor resection en bloc with part of the diaphragm, TBD=tumor resection before diaphragmatic resection.

4. Discussion

Although recent studies indicated that the tumor size of solitary HCC without major vascular invasion dose not impair the surgical outcome,[17,18] the influence of diaphragmatic invasion of single huge HCC on outcomes following surgical resection is still unclear. Therefore, we designed the present study to exclusively compare the short- and long-term outcomes of single huge right HCC patients with and without the diaphragmatic invasion after anterior approach hepatectomy. To focus on clinical outcomes relating to the diaphragmatic invasion of the right huge HCC, we restricted the method of hepatectomy to the anterior approach major hepatectomy. All cases with diaphragmatic invasion were confirmed by the histopathological examination. And all patients enrolled in this study had the initial HCC not the recurrent HCC. In addition, we also excluded patients who had macrovascular invasion, which could lead to poor prognosis. We believe that the inclusion and exclusion criteria in this study could result in a more accurate analysis for outcomes. As shown in Table 1, we found that huge HCC patients with or without diaphragmatic invasion did not show any significant differences in the baseline demographic and preoperative data except larger tumor size in the group PDI.

With the improvement of the surgical technique and perioperative care, the anterior approach major hepatectomy can be safely performed on huge HCC patients with or without diaphragmatic invasion. There was no significant difference between the 2 groups in regard to various grades of postoperative complications, and most postoperative complications were grade I and II (Table 2). However, our study revealed there was a possibility of increased intraoperative blood loss of $>$ 1000 mL, intraoperative transfusion and an increased duration of operation when the diaphragm was resected, which is similar to the results reported by Lin et al.[19]

Table 3

Univariate analysis of prognostic factors for survival.

Variable	N	χ^2	*P* value
Sex (M/F)	164/39	0.201	.654
Age (≥60/<60 years)	43/160	5.717	.017
Tumor size (≥15/<15 cm)	50/153	9.418	.002
Child–Pugh score=5 (Yes/No)	141/62	1.623	.203
HBsAg (+/−)	186/17	0.061	.805
HBV DNA (≥1000/<1000 IU/mL)	71/132	0.546	.308
AFP (≥400/<400 ng/mL)	115/88	9.212	.002
PHT (Yes/No)	30/173	0.072	.788
Intraoperative blood loss > 1000 mL (Yes/No)	13/190	3.486	.062
Intraoperative transfusion (Yes/No)	23/180	2.729	.099
Diaphragmatic invasion (Yes/No)	53/150	0.399	.528
Resection margin > 1 cm (Yes/No)	80/123	3.077	.079
Tumor grade=G4 (Yes/No)	65/138	8.417	.004
Microvascular invasion (Yes/No)	104/99	7.139	.008

AFP=alpha-fetoprotein, F=female, HBsAg=hepatitis B surface antigen, HBV DNA=hepatitis B virus deoxyribonucleic acid, M=male, N=number, PHT=portal hypertension.

Table 4

Multivariate analysis of prognostic factors for survival.

Variable	HR	95% CI	*P* value
Age ≥ 60 years	0.704	0.452–1.097	.121
Tumor size ≥ 15 cm	1.569	1.070–2.300	.021
AFP ≥400 ng/mL	1.642	1.166–2.311	.005
Intraoperative blood loss > 1000 mL	1.873	0.769–4.563	.167
Intraoperative transfusion (yes)	1.134	0.494–1.874	.911
Resection margin > 1 cm	0.857	0.603–1.218	.391
Tumor grade=G4	1.628	1.125–2.357	.010
Microvascular invasion (Yes)	1.648	1.174–2.312	.004

AFP=alpha-fetoprotein, CI=confidence interval, HR=hazard ratio.

The diaphragm has been considered to be a barrier between the thoracic and abdominal cavities, and venous and lymphatic drainage from the diaphragm may, theoretically, lead to the tumors cells into the circulation if the diaphragm is involved by tumor, resulting in a poor outcome.[20,21] However, our study showed that there was no significant difference in the OS and RFS in single huge right lobe HCC patients with or without diaphragmatic invasion after anterior approach major hepatectomy (all $P > .05$, Fig. 3), which was consistent with other studies.[8,19] Notably, the influence of the different methods of diaphragm resection for single huge HCC with diaphragmatic invasion on outcomes following hepatectomy, to our knowledge, has not been reported to date. To answer this question, we further performed a subgroup analysis by the methods of diaphragm resection. The similar results, those patients with tumor resection en bloc with part of the diaphragm had similar OS and RFS rates as those who underwent diaphragmatic resection after hepatectomy, were found in this study (all $P > .05$, Fig. 4).

Our multivariate Cox modeling identified 4 independent risk factors of poor survival, including tumor diameter ≥ 15 cm, serum AFP level ≥ 400 ng/mL, tumor grade of G4 and microvascular invasion (Table 4). Of the 4 variables included in the model, the effects of microvascular invasion and Edmonson–Steiner grade on prognosis of HCC patients after surgery have been well described.[22,23] Among the prognostic factors for survival, tumor size is important and may form the basis of tumor staging systems. The cut-off value of tumor size at 2 and 5 cm was introduced as a criterion of the traditional TNM system. The Milian and UCSF criteria provided guidelines on liver transplantation for patients with single HCC according to the cut-off of 5 and 6.5 cm, respectively.[24,25] However, for tumor size >5 cm, the prognostic significance varied, with inconsistent conclusions. Some studies[26,27] identified the tumor size of > 5 cm as a poor prognostic factor for overall survival, but other several studies[28,29] suggested that the results of surgery for huge HCC were comparable to those of surgery for smaller tumors. Our result implies that the postoperative prognosis of patients with a single tumor diameter < 15 cm may be relatively better. However, its prognostic role remains to be further confirmed because the small sample of patients with tumor size ≥ 15 cm may limit the interpretation and application of the results. An increasing number of studies found that preoperative serum AFP level had an important role on patients outcomes after hepatectomy.[30–32] Moreover, several transplant centers have proposed that serum AFP level should be an additional useful variable to optimize the transplant criteria for HCC.[33,34] Our findings further support this point and indicated that patients with serum AFP level ≥ 400 ng/mL had significantly poorer prognosis than those with AFP level < 400 ng/mL. It is worth mentioning that some studies showed that the elderly patient possibly had a better OS and/or RFS than that of the younger patients,[35,36] however, our modeling did not finally identify the age of < 60 years as an independent predictor of poor long-term survival. Hence, the prognostic role of age remains to be confirmed.

This study is mainly limited by its retrospective nature and a single-center experience. However, this study, to the best of our knowledge, represents the first and largest cohort to exclusively compare the short- and long-term outcomes of single huge right HCC patients with and without the diaphragmatic invasion after anterior approach major hepatectomy, and to investigate the role of the different methods of diaphragm resection for single huge HCC with diaphragmatic invasion on outcomes following hepatectomy, and some results may be vital for guiding the surgeon in clinical practice. However, well-designed, long-term, randomized, controlled, prospective trials are still necessary to further confirm some points proposed in this study.

In conclusion, for the single huge right lobe HCC patients with diaphragmatic invasion, anterior approach major hepatectomy combined with diaphragmatic resection could offer similar OS and RFS as those without diaphragmatic invasion, the diaphragmatic invasion may not be considered as one risk factor for poor survival after surgery. Moreover, patients with tumor resection en bloc with part of the diaphragm had similar outcomes as those who underwent diaphragmatic resection after hepatectomy. Some factors were observed to be associated with postoperative poor survival, such as tumor diameter ≥ 15 cm, serum AFP level ≥ 400 ng/mL, tumor grade of G4 and microvascular invasion.

Acknowledgments

The authors thank Dr Wei Zhang for his contribution in statistical analysis.

Author contributions

Study conception and design: Li Jiang, Lunan Yan, Jiayin Yang
Acquisition of data: Mingqing Xu
Analysis and interpretation of data: Tianfu Wen, Bo Li, Wentao Wang
Drafting of manuscript: Jinli Zheng, Shu Shen
Critical revision: Li Jiang
Conceptualization: Li Jiang, Lunan Yan, Jiayin Yang.
Data curation: Bo Li, Tianfu Wen, Wentao Wang.
Formal analysis: Mingqing Xu.
Writing – original draft: Shu Shen.
Writing – review & editing: Jinli Zheng, Li Jiang.

References

[1] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[2] Min YW, Lee JH, Gwak GY, et al. Long-term survival after surgical resection for huge hepatocellular carcinoma: comparison with transarterial chemoembolization after propensity score matching. J Gastroenterol Hepatol 2014;29:1043–8.
[3] Chan AC, Fan ST, Poon RT, et al. Evaluation of the seventh edition of the American Joint Committee on Cancer tumour-node-metastasis (TNM) staging system for patients undergoing curative resection of hepatocellular carcinoma: implications for the development of a refined staging system. HPB (Oxford) 2013;15:439–48.
[4] Minagawa M, Ikai I, Matsuyama Y, et al. Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. Ann Surg 2007;245:909–22.
[5] Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut 2014;63:844–55.
[6] Forner A, Gilabert M, Bruix J, et al. Treatment of intermediate-stage hepatocellular carcinoma. Nat Rev Clin Oncol 2014;11:525–35.
[7] Maruyama H, Yoshida H, Hirakata A, et al. Surgical treatment of a patient with diaphragmatic invasion by a ruptured hepatocellular carcinoma with biliary and portal venous tumor thrombi. J Nippon Med Sch 2012;79:147–52.
[8] Lau WY, Leung KL, Leung TW, et al. Resection of hepatocellular carcinoma with diaphragmatic invasion. Br J Surg 1995;82:264–6.
[9] Liu CL, Fan ST, Cheung ST, et al. Anterior approach versus conventional approach right hepatic resection for large hepatocellular carcinoma: a prospective randomized controlled study. Ann Surg 2006;244:194–203.
[10] Wang CC, Jawade K, Yap AQ, et al. Resection of large hepatocellular carcinoma using the combination of liver hanging maneuver and anterior approach. World J Surg 2010;34:1874–8.
[11] Goh BK, Kam JH, Lee SY, et al. Significance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and prognostic nutrition index as

preoperative predictors of early mortality after liver resection for huge (≥10 cm) hepatocellular carcinoma. J Surg Oncol 2016;113:621–7.
[12] Li Y, Xia Y, Li J, et al. Prognostic nomograms for pre- and postoperative predictions of long-term survival for patients who underwent liver resection for huge hepatocellular carcinoma. J Am Coll Surg 2015;221:962–74.
[13] Santambrogio R, Kluger MD, Costa M, et al. Hepatic resection for hepatocellular carcinoma in patients with Child-Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? HPB (Oxford) 2013;15:78–84.
[14] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
[15] Liver Cancer Study Group, Chinese Society of Hepatology, Chinese Medical AssociationRecommendation on antivirai therapy to hepatitis B/C virus related hepatocellular carcinoma. Zhong Hua Gan Zang Bing Za Zhi 2013;21:96–100.
[16] Shin E, Yu YD, Kim DS, et al. Adiponectin receptor expression predicts favorable prognosis in cases of hepatocellular carcinoma. Pathol Oncol Res 2014;20:667–75.
[17] Chang YJ, Chung KP, Chang YJ, et al. Long-term survival of patients undergoing liver resection for very large hepatocellular carcinomas. Br J Surg 2016;103:1513–20.
[18] Zhang H, Yuan SX, Dai SY, et al. Tumor size does not independently affect long-term survival after curative resection of solitary hepatocellular carcinoma without macroscopic vascular invasion. World J Surg 2014;38:947–57.
[19] Lin MC, Wu CC, Chen JT, et al. Surgical results of hepatic resection for hepatocellular carcinoma with gross diaphragmatic invasion. Hepatogastroenterology 2005;52:1497–501.
[20] Matsukuma S, Sato K. Peritoneal seeding of hepatocellular carcinoma: clinicopathological characteristics of 17 autopsy cases. Pathol Int 2011;61:356–62.
[21] Komatsu S, Murakami M, Fukumoto T, et al. Risk factors for survival and local recurrence after particle radiotherapy for single small hepatocellular carcinoma. Br J Surg 2011;98:558–64.
[22] Hirokawa F, Hayashi M, Asakuma M, et al. Risk factors and patterns of early recurrence after curative hepatectomy for hepatocellular carcinoma. Surg Oncol 2016;25:24–9.
[23] Colecchia A, Scaioli E, Montrone L, et al. Pre-operative liver biopsy in cirrhotic patients with early hepatocellular carcinoma represents a safe and accurate diagnostic tool for tumour grading assessment. J Hepatol 2011;54:300–5.
[24] Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.
[25] Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394–403.
[26] Arnaoutakis DJ, Mavros MN, Shen F, et al. Recurrence patterns and prognostic factors in patients with hepatocellular carcinoma in non-cirrhotic liver: a multi-institutional analysis. Ann Surg Oncol 2014;21:147–54.
[27] Liao W, Zhang J, Zhu Q, et al. Preoperative neutrophil-to-lymphocyte ratio as a new prognostic marker in hepatocellular carcinoma after curative resection. Transl Oncol 2014;7:248–55.
[28] Liau KH, Ruo L, Shia J, et al. Outcome of partial hepatectomy for large (> 10 cm) hepatocellular carcinoma. Cancer 2005;104:1948–55.
[29] Pawlik TM, Poon RT, Abdalla EK, et al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. Arch Surg 2005;140:450–7.
[30] Yang SL, Liu LP, Yang S, et al. Preoperative serum α-fetoprotein and prognosis after hepatectomy for hepatocellular carcinoma. Br J Surg 2016;103:716–24. [Epub ahead of print].
[31] Lv Y, Wang W, Jia WD, et al. High preoparative levels of serum periostin are associated with poor prognosis in patients with hepatocellular carcinoma after hepatectomy. Eur J Surg Oncol 2013;39:1129–35.
[32] He J, Shi J, Fu X, et al. The clinicopathologic and prognostic significance of gross classification on solitary hepatocellular carcinoma after hepatectomy. Medicine (Baltimore) 2015;94:e1331.
[33] Zheng SS, Xu X, Wu J, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation 2008;85:1726–32.
[34] Kim SH, Moon DB, Kim WJ, et al. Preoperative prognostic values of α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) in patients with hepatocellular carcinoma for living donor liver transplantation. Hepatobiliary Surg Nutr 2016;5:461–9.
[35] Huang J, Li BK, Chen GH, et al. Long-term outcomes and prognostic factors of elderly patients with hepatocellular carcinoma undergoing hepatectomy. J Gastrointest Surg 2009;13:1627–35.
[36] Cucchetti A, Sposito C, Pinna AD, et al. Effect of age on survival in patients undergoing resection of hepatocellular carcinoma. Br J Surg 2016;103:e93–9.