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

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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 ≥ 400ng/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 acid, HCC = hepatocellular carcinoma, OS = overall survival, PDI = presence of the diaphragmatic invasion, PH = 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 the 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...
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 removed.

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 \( \geq 10 \text{cm} \) 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/\( \mu \text{L} \) 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 hepatectomy

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

![Figure 1. Flow chart of study participants.](image-url)
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 cmH2O 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; 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. 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 >1000mL 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 Edmondson–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 on en bloc with part of the diaphragm (subgroup TEG, n=32) or tumor resection before diaphragmatic resection (subgroup TEB, n=21). There was no significant difference in the OS between the subgroup TEG and TEB (1-, 3-, and 5-year OS rates of 68.8%, 43.8%, and 30.1%, respectively, in the subgroup TEG versus 76.2%, 33.3%, and 23.8% in the subgroup TEB, respectively, P=.600, Fig. 4A).

Table 1

| 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 (5–26.9) | 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 (5–513) | .189   |
| AST level, mean±SD (range), IU/L | 106±176 (19–567) | 73.4±647 (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 (8.6–17.1) | .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.
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 \(\geq 15\) cm, serum AFP level of \(\geq 400\) 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 \(\geq 15\) cm, serum AFP level of \(\geq 400\) ng/mL, tumor grade of G4, and microvascular invasion were found to be independent predictive factors for poor postoperative survival (Table 4).

Table 2

| 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 \(\pm\) SD (range), hour | 5.4 \(\pm\) 1.2 (3.9–10) | 5.0 \(\pm\) 0.9 (3.9–8.1) | .008 |
| Tumor resection en bloc with diaphragmatic resection, n (%) | 32 (60.4%) |                  |             |
| Resection margins, mean \(\pm\) SD (range), cm | 1.4 \(\pm\) 0.7 (0.2–3) | 1.5 \(\pm\) 0.7 (0.1–3) | .401 |
| Duration of postoperative hospital stay, mean \(\pm\) SD (range), day | 11.3 \(\pm\) 8.7 (6–109) | 10.8 \(\pm\) 9.2 (5–98) | .326 |

Complications
- Grade I: 14 (26.4%) vs. 33 (22.0%), \(P = .512\)
- Grade II: 7 (13.2%) vs. 19 (12.7%), \(P = .919\)
- Grade IIIa: 4 (7.5%) vs. 10 (6.7%), \(P = .762\)
- Grade IIIb: 3 (5.7%) vs. 6 (4.0%), \(P = .699\)
- Grade IVa: 3 (5.7%) vs. 9 (6.0%), \(P = 1.000\)
- Grade IVb: 1 (1.9%) vs. 3 (2.0%), \(P = 1.000\)
- Grade V: 0 (0%) vs. 0 (0%), \(P = .919\)
- 90-day mortality: 1 (1.9%) vs. 4 (2.7%), \(P = 1.000\)
- Microvascular invasion: 27 (50.9%) vs. 77 (51.3%), \(P = .961\)
- Tumor grade
  - G1–G2: 10 (18.9%) vs. 48 (32.0%), \(P = .069\)
  - G3: 21 (39.6%) vs. 59 (39.3%), \(P = .970\)
  - G4: 22 (41.5%) vs. 43 (28.7%), \(P = .085\)

\(ADI = \) absence of diaphragmatic invasion, \(PDI = \) presence of diaphragmatic invasion.

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.
4. Discussion

Although recent studies indicated that the tumor size of solitary HCC without major vascular invasion does 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. 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]
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.\[10\] 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.\[18,19\] 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 \(\geq 15\) cm, serum AFP level \(\geq 400\) 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 Milan 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 results of surgery for huge HCC were comparable to those who underwent diaphragmatic resection after hepatectomy.

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