



Impact of Glissonean Pedicle Approach for Centrally Located Hepatocellular Carcinoma in Mongolia

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Approaches to surgical resection of centrally located HCC remain controversial. Traditionally, hemi- or extended hepatectomy is suggested. However, it carries a high risk of postoperative complications in patients with cirrhosis. An alternative approach is Glissonean pedicle transection method. This study was conducted to assess the surgical and survival outcomes associated with central liver resection using the Glissonean pedicle transection. Sixty-nine patients with centrally located HCC were studied retrospectively. They were divided into conventional approach group with hemi- or extended hepatectomy, and Glissonean approach group with multisegmental central liver resection using the Glissonean pedicle transection. Glissonean pedicle transection method has comparable or superior surgical and survival outcomes to conventional hemi- or extended hepatectomy with regard to intraoperative bleeding, complications, hospital stay, and postoperative mortality and survival outcomes in patients with centrally located HCC. The 1-, 3-, and 5-year overall survival rates of the conventional approach group were 74%, 64%, and 55% respectively. For the Glissonean approach group, the 1 and 3-year overall survival rates were 86% and 61%, respectively. Glissonean pedicle transection method is a safe and effective surgical procedure in patients with centrally located HCC.

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Hepatocellular carcinoma (HCC) is the first leading cause of cancer-related mortality in both men and women in Mongolia, and its incidence is among the highest worldwide.¹ Surgical resection remains the first-line therapeutic strategy for HCC despite recent advancements in treatment modalities.^{2–4} However, underlying liver diseases significantly limit the number of HCC patients eligible for surgical resection. This is especially problematic, where the prevalence of chronic hepatitis B and C is over 10% in the general population, and 86.8% of HCC patients have cirrhosis.⁵ Therefore, refining surgical techniques to preserve as much liver parenchyma as possible could potentially improve treatment prospects for cirrhotic HCC patients, particularly in cases when the tumor is centrally located.

Traditionally, hemi- or extended hepatectomy is suggested for the treatment of centrally located HCC.⁶ However, such a major hepatic resection sacrifices a large volume of noncancerous liver parenchyma, which carries a high risk of postoperative liver failure in patients with cirrhotic background.^{6–8} Preservation of functioning liver parenchyma to a maximum extent possible is crucial to avoid postoperative liver failure in cirrhotic patients. Therefore, Glissonean pedicle transection method is increasingly considered as an effective alternative to hemi- or extended hepatectomies in such cases.^{9–16} Nonetheless, multisegmental central liver resection has not been widely used since its introduction for gallbladder cancer in 1972.^{17,18} Conventional central liver resection method is technically demanding, and may require prolonged surgical time in order to dissect and confirm each branch of hepatic artery, portal vein, and bile duct to the anterior section.^{19,20} This often results in increased risk of bleeding, bile leakage or parenchymal necrosis, and therefore, central liver resection particularly in cirrhotic patients remains controversial.^{21,22} The answer to the dilemma could lie with the Glissonean pedicle transection method, which was introduced in the mid-1980s owing to a better understanding of the surgical anatomy of the liver.^{20,23} When using this resection method, Glissonean pedicle supplying the target area is ligated and divided at the hepatic hilum prior to resection without exposing the vessels individually.²³ This simplifies hepatic resection, shortens operation time

and reduces intraoperative bleeding.^{23–25} Our previous experience with using this method for hemihepatectomy has resulted in considerable reduction of blood loss during resection, a major determinant of patient outcome.

This approach has allowed the ability to adapt the size of resection to the extent of the tumor and to preserve the maximum amount of liver parenchyma, which is crucial for the prevention of postoperative liver failure especially in patients with cirrhotic background. However, it remains unclear whether central liver resection using the Glissonean pedicle transection improves long-term survival. Therefore, the current retrospective study of patients with centrally located HCC, who underwent either hemi- or extended hepatectomy or multisegmental central liver resection, was conducted to assess the perioperative and long-term outcomes associated with central liver resection using the Glissonean pedicle transection.

Materials and Methods

Patient selection

Patients with centrally located HCC from 2003 to 2012 were reviewed retrospectively. Centrally-located HCC cases were identified in 69 (8.4%) of 820 patients and divided into 2 groups: Conventional approach group (n = 24) and Glissonean approach (started from 2008) group (n = 45). According to institutional criteria used at National Cancer Center, hemi- or extended hepatectomy is performed in patients with no portal hypertension. In this study all patients in the conventional approach group did not have esophageal varices, and therefore, were considered eligible for hemi- or extended hepatectomy. In contrast, 60% of the patients in the Glissonean approach group had esophageal varices.

Analysis of prognostic factors

Preoperative, intraoperative and postoperative data were collected and analyzed to compare surgical outcomes and to identify factors affecting overall survival of patients who underwent liver resection using Glissonean (started from 2008) versus conventional approach.

The preoperative data included patient age, gender, liver function tests (serum albumin, total

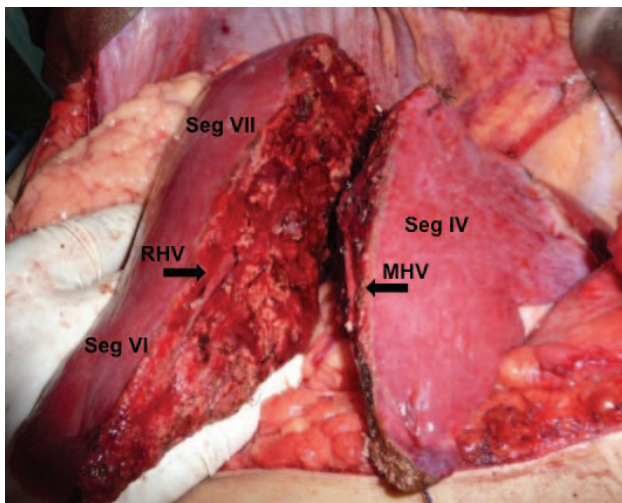


Fig. 1 Fig. 1 shows the liver after anterior sectionectomy.

bilirubin, creatinine, alkaline phosphatase and transaminase levels, prothrombin time and platelet count), hepatic risk factors (hepatitis B and C, cirrhosis and Child-Pugh's classification score), MELD (Model for End-Stage liver disease) score and tumor factors (alpha-fetoprotein level, tumor size, number of tumor nodules, venous invasion and TNM staging).

The intraoperative variables were method of hepatic resection (hemi- or extended hepatectomy versus Glissonean pedicle transection), operation time, duration of Pringle maneuver, estimated blood loss, and volume of intraoperative blood transfusion.

The postoperative variables included liver function tests on days 1, 3 and 5 following the resection, length of hospital stay, postoperative complications and postoperative mortality (defined as complications or death occurring within 30 days after surgery).

No follow-up data was available including recurrence reports, except for death status as of June 30, 2012 obtained from the Civil Registration Department and Hospital database.

Surgical technique

In the conventional approach group hemi- or extended hepatectomy was performed using surgical technique described elsewhere.^{20,23,26} In the Glissonean approach group right anterior sectionectomy (segments 5 and 8) and central hepatectomy (segments 4, 5, and 8) were performed according to the techniques described (Fig. 1).²³ Parenchymal

transection selective Pringle maneuver is used intermittently on left and right posterior pedicles. The inflow of left lobe were blocked for 15 minutes for parenchymal transection on the left side and followed by reperfusion for 15 minutes. During inflow of left lobe, the right posterior segment was blocked for parenchymal transection on the right side.

Statistical analysis

Surgical and survival outcomes of the Glissonean approach group were compared with those of the conventional approach group. Surgical outcome measures included length of hospital stay, postoperative complications, and postoperative death. Survival outcome measure included overall survival duration. Continuous variables were expressed as means with their standard deviations, and compared using either t-test or Wilcoxon rank sum test where appropriate. Categorical variables were expressed as proportions, and compared by chi-square or Fisher's exact test where appropriate. Cumulative overall survival was estimated by the Kaplan-Meier method and compared by the log-rank test. In order to identify independent predictors of overall survival multivariate analysis using Cox proportional hazard regression model was employed for variables found to be significant on univariate analysis. Results were considered statistically significant at $P < 0.05$. All statistical analyses were performed using STATA version 10.1 (Stata-Corp, Texas, USA).

Results

Preoperative data

Comparison of the preoperative data of 2 study groups is presented in Table 1. No significant differences were observed in age and gender distributions. The study groups were comparable in preoperative liver function tests. In terms of hepatic risk factors, 68.2% of patients in the conventional approach group and 70.5% of patients in the Glissonean approach group had liver cirrhosis, and the difference between the groups was not significant. Slightly less than half of patients in both groups had positive hepatitis B viral surface antigen (HBsAg) serology results. Significantly more patients in the Glissonean approach group had positive hepatitis C virus antibody (anti-HCV) serology results compared to the conventional approach group ($P = 0.043$).

Table 1 Preoperative characteristics of patients with centrally-located HCC who underwent conventional hemi- or extended hepatectomy versus multisegmental central liver resection using the Glissonean pedicle transection method

Variables	Conventional approach (n = 24)	Glissonean approach (n = 45)	P value
Age (year)	55.4 ± 9.2	59.8 ± 8.5	0.051
Gender (M:F)	12:12	23:22	0.930
HBsAg serology			
positive	8 (42.1%)	14 (43.8%)	0.909
Anti-HCV serology			
positive	7 (35.0%)	21 (63.6%)	0.043 ^a
Liver cirrhosis	15 (68.2%)	31 (70.5%)	0.850
Child Pugh class A	14 (93.3%)	30 (100%)	
Child Pugh class B	1 (6.7%)	0 (0%)	
Serum albumin (g/L)	40.5 ± 5.7	37.5 ± 7.1	0.059
Serum total bilirubin (μmol/L)	11.8 ± 4.9	15.7 ± 13.7	0.273
Serum creatinine (μmol/L)	62.7 ± 24.7	64.2 ± 16.8	0.830
Serum ALT (U/L)	63.5 ± 38.9	102.1 ± 80.7	0.089
Serum AST (U/L)	63.0 ± 49.6	80.4 ± 52.7	0.079
Serum alkaline phosphatase (U/L)	353.6 ± 381.9	141.3 ± 68.2	0.074
Prothrombin time (sec)	13.9 ± 3.8	12.6 ± 1.9	0.185
Platelet count (×10 ³ /uL)	172.8 ± 72.3	179.8 ± 43.9	0.691
Serum AFP (ng/mL)	210.9 ± 242.2	1,493.8 ± 6,667.5	0.093
MELD score	39 ± 5.8	37 ± 7.7	0.89
Tumor size (cm)	7.2 ± 2.1	5.9 ± 2.2	0.021 ^a
No. of tumors			0.736
Solitary	21 (87.5%)	37 (82.2%)	
Multiple	3 (12.5%)	8 (17.8%)	
Positive venous invasion	0 (0%)	1 (2.2%)	1.000
TNM stage			0.140
I	0 (0%)	0 (0%)	
II	2 (8.3%)	9 (20.0%)	
III	16 (66.7%)	32 (71.1%)	
IV	6 (25.0%)	4 (8.9%)	

Continuous data is expressed as mean ± standard deviation.

Categoric data is expressed as number (percent).

HBsAg, hepatitis B viral surface antigen; anti-HCV, hepatitis C virus antibody; AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

^a $P < 0.05$ denotes statistically significant difference.

The mean tumor size was 5.9 ± 2.2 cm in the Glissonean group, which was significantly smaller than the mean tumor size of 7.2 ± 2.1 cm in the conventional approach group ($P = 0.021$). There was a trend towards higher serum alpha fetoprotein (AFP) level in the Glissonean approach group although not statistically significant. There were no statistically significant differences in MELD score, number of tumor nodules, venous invasion, or TNM staging between the study groups.

Table 2 Intraoperative data of patients with centrally-located HCC who underwent conventional hemi- or extended hepatectomy versus multisegmental central liver resection using the Glissonean pedicle transection method

Variables	Conventional approach (n = 24)	Glissonean approach (n = 45)	P value
Operation time (min)	223.5 ± 59.3	269.1 ± 93.9	0.022 ^a
Blood loss (mL)	522.2 ± 528.7	447.8 ± 377.6	0.953
Blood transfusion (mL)	334.0 ± 210.0	331.0 ± 200.9	0.917
Pringle maneuver (min)	29.3 ± 13.0	51.4 ± 25.0	0.028 ^a

Continuous data is expressed as mean ± standard deviation.

^a $P < 0.05$ denotes statistically significant difference.

Intraoperative data

The intraoperative data are summarized in Table 2. Mean operating time was 269 minutes (range, 150–690 minutes) in the Glissonean approach group, which was significantly longer than mean operating time of 224 minutes (range, 130–420 min) in the conventional approach group ($P = 0.022$). Similarly, the inflow control time (Pringle maneuver) was significantly longer in the Glissonean compared to the conventional approach group (51 versus 29 minutes, $P = 0.028$). The mean estimated blood loss during operation was 447.8 ± 377.6 mL in the Glissonean and 522.2 ± 528.7 mL in the conventional approach groups. However, the difference was not statistically significant.

Postoperative data

Operative outcomes in the study groups are presented in Table 3. There was a trend toward more favorable postoperative liver function tests in the conventional approach group, especially in serum ALT levels being significantly less on postoperative days 1, 3, and 5 compared to the Glissonean approach group ($P < 0.02$).

However, patients in the Glissonean approach group had significantly shorter hospital stay than patients in the conventional group ($P = 0.004$). The mean length of hospital stay was 14.9 ± 5.1 days in the Glissonean approach group, and 21.3 ± 9.6 days in the conventional approach group. Fifteen (33.3%) cases had surgical complications in the Glissonean approach group, including liver failure comprising ascites, gastrointestinal bleeding, encephalopathy, and hyperbilirubinemia ($n = 13$, 28.9%) and bile leakage ($n = 2$, 4.4%). In contrast, 13 of 24 (54.2%) patients in the conventional approach group developed complications, includ-

Table 3 Postoperative data of patients with centrally-located HCC who underwent conventional hemi- or extended hepatectomy versus multisegmental central liver resection using the Glissonean pedicle transection method

Variables	Conventional approach (n = 24)	Glissonean approach (n = 45)	P value
Serum bilirubin (μmol/L)			
Day 1	48.7 ± 70.9	34.4 ± 26.6	0.132
Day 3	39.7 ± 43.5	32.4 ± 15.4	0.500
Day 5	63.3 ± 71.7	25.7 ± 13.4	0.668
Serum albumin (g/L)			
Day 1	35.7 ± 6.8	29.0 ± 3.7	<0.001 ^a
Day 3	31.1 ± 3.7	27.8 ± 3.9	0.003 ^a
Day 5	29.2 ± 6.1	29.0 ± 4.6	0.997
Serum creatinine (μmol/L)			
Day 1	93.0 ± 52.7	83.2 ± 41.8	0.607
Day 3	96.7 ± 62.8	65.4 ± 28.1	0.049 ^a
Day 5	68.8 ± 27.1	55.8 ± 18.9	0.154
Serum ALT (U/L)			
Day 1	227.6 ± 142.6	393.3 ± 213.1	0.001 ^a
Day 3	183.5 ± 113.0	305.3 ± 186.5	0.016 ^a
Day 5	82.8 ± 40.7	134.4 ± 67.7	0.004 ^a
Serum AST (U/L)			
Day 1	293.8 ± 176.6	431.9 ± 213.1	0.015 ^a
Day 3	210.2 ± 135.1	288.2 ± 189.3	0.363
Day 5	83.1 ± 34.9	93.3 ± 52.8	0.851
Platelet count (x10 ³ /uL)			
Day 1	179.9 ± 53.0	154.9 ± 41.3	0.173
Day 3	145.7 ± 55.8	149.6 ± 41.3	0.785
Day 5	180.7 ± 62.4	168.7 ± 63.5	0.614
Hospital stay (days)	21.3 ± 9.6	14.9 ± 5.1	0.004 ^a
Surgical complications	13 (54.2%)	15 (33.3%)	0.093
Liver failure	12 (50.0%)	13 (28.9%)	0.082
Bile leakage	1 (4.2%)	2 (4.4%)	0.957
Postoperative deaths	3 (12.5%)	4 (8.9%)	0.636

Continuous data is expressed as mean ± standard deviation.

Categoric data is expressed as number (percent).

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

^a $P < 0.05$ denotes statistically significant difference.

ing liver failure (n = 12, 50.0%) and bile leakage (n = 1, 4.2%). Compared to the conventional approach group patients in the Glissonean approach group tended to have less surgical complications although not statistically significant ($P = 0.093$). There was no significant difference in postoperative mortality between the groups (8.9% versus 12.5%, $P = 0.636$).

Survival outcomes

The median follow-up of patients was 23 months in the conventional approach group and 14 months in the Glissonean approach group. In the latter group shorter follow-up is explained by the fact that

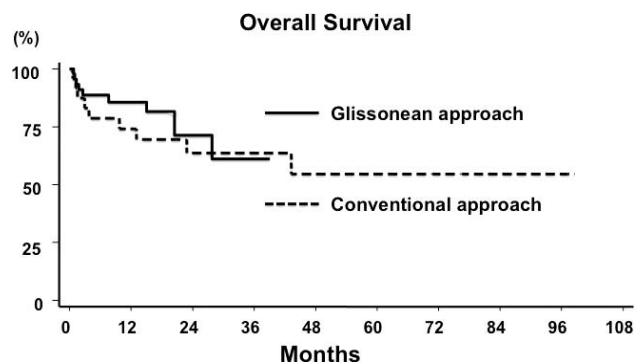


Fig. 2 Fig. 2 shows Cumulative overall survival of patients with centrally-located HCC who underwent conventional hemi- or extended hepatectomy versus multisegmental central liver resection using the Glissonean pedicle transection method. No significant difference ($P = 0.664$) observed between the study groups.

multisegmental central liver resection using the Glissonean pedicle transection was only introduced in 2008 in our center.

The overall cumulative survival was comparable between the study groups ($P = 0.664$) in Fig. 2. The 1-, 3-, and 5-year overall survival rates of the conventional approach group were 74%, 64%, and 55%, respectively. For the Glissonean approach group, the 1- and 3-year overall survival rates were 86% and 61%, respectively.

Statistical analysis was performed to identify independent factors associated with the overall survival of all patients in this study. Univariate analysis revealed that age, sex, tumor stage, tumor size, tumor nodule number, vascular invasion, Glissonean, and conventional approach were not found to be significant prognostic factors.

Discussion

Traditionally, centrally-located HCC required an extensive resection with hemi- or extended hepatectomy because of their proximity to major vessels and technically demanding controlled central liver resection methods.^{6,19,20} However, these conventional major hepatectomies sacrifice a large volume of noncancerous liver parenchyma, which aggravates the risk of postoperative liver failure and death especially in patients with cirrhosis.⁶⁻⁸ An alternative surgical treatment approach or central liver resection could potentially improve prospects for surgical treatment of centrally-located HCC in cirrhotic patients.^{17,21} Central liver resection extirpates 40% to 60% of

liver parenchyma compared to 60% to 85% in hemi- or extended hepatectomy. The rate of complications after central hepatectomy ranges from 17 to 26.3% and surgical mortality rate is between 0 and 6.25%.¹⁶ Several groups have used a novel technique, namely the Glissonean pedicle transection method, in multisegmental central liver resections.^{8,20,23,27,28} When using the Glissonean pedicle transection method the Glissonean pedicle, which is a single bundle consisting of a capsule enclosing 3 types of vessels (hepatic artery, portal vein, and bile duct), is ligated and divided at the hepatic hilum prior to resection without exposing the vessels individually.²³ This simplifies hepatic resection, shortens operation time and reduces intraoperative bleeding.^{23–25} Mean operating time in the Glissonean approach group in this study is comparable to that of conventional central liver resection reported in other studies.^{6,12,21,29} Similarly, the mean estimated blood loss during operation (447.8 ± 377.6 mL) is well within the range (300–7,500 mL) reported for other central hepatectomies.²¹ The mean length of hospital stay of patients in the Glissonean approach group was 15 days, which was comparable to the reported range (11–18 days) for central liver resections.^{16,21,30} There was a trend toward more favorable postoperative liver function tests, especially serum AST and ALT levels, in the conventional approach group in this study. The longer inflow control time (Pringle maneuver) could be responsible for higher serum AST and ALT levels in the Glissonean approach group. In the literature, the incidence of complications after central hepatectomy ranges from 17% to 26.3%.¹⁶ In our series, the overall complication and postoperative liver failure rates are fairly high at 33.3% and 28.9%, respectively. However, it should be noted that 70.5% of the patients in the current study had cirrhosis, which, on its own, carried a considerable risk of postoperative liver failure. In some studies, central hepatectomy has been identified as an independent risk factor for bile leakage because of the presence of 2 transection planes and exposure of the hepatic hilum.⁹ Biliary complications following central liver resections develop in 3–11% of cases according to other studies.^{11,12,16,21} Our results are comparable with those of the previous reports. Compared to the conventional approach group, patients in the Glissonean approach group tended to have less surgical complications although not statistically significant. Postoperative mortality after central hepatectomy ranges from

0% to 6.2% in earlier reports.^{7,16,21} Our results are fairly high (8.9%) compared to these earlier reports.

Previously reported cumulative overall 1-, 3-, and 5-year survival rate ranges for central liver resection are 53%–82%, 30%–50%, and 17%–30%, respectively.^{11,13,21,22} In our series, the 1- and 3-year overall survival rates in patients undergoing central liver resection using the Glissonean pedicle transection method were 86% and 61%, respectively. Our findings demonstrate that central liver resection using the Glissonean pedicle transection method achieved the same overall patient survival rates as conventional hemi- or extended hepatectomy for centrally-located HCC. The lack of significant correlation might possibly be the result of the more cirrhotic and HCV positive patients in the Glissonean approach group. The current study demonstrated that Glissonean pedicle transection method has comparable or superior results to conventional hemi- or extended hepatectomy with regard to intraoperative bleeding, complications, hospital stay, postoperative mortality and survival outcomes in patients with centrally located HCC. However, concern remains that central liver resection because of its design is more likely to be associated with smaller resection margins, thus, could potentially compromise oncologic safety. HCC tends to disseminate through the portal venous system, and therefore, intrahepatic recurrences are usually distant from the resection margin.³¹ For that reason, the removal of the entire territory of the feeding portal pedicle is more important than just a wider resection margin to prevent cancer recurrence.^{27,31,32}

In conclusion, multisegmental central liver resection using the Glissonean pedicle transection method is a safe and effective surgical procedure in patients with centrally-located HCC with cirrhotic background.

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