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Liberal Application of Portal Vein Embolization for Right Hepatectomy Against Hepatocellular Carcinoma: Strategy to Achieve Zero Mortality for a Damaged Liver

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Abstract. *Background/Aim: Right hepatectomy and extended right hepatectomy (Rt-Hr) are identified as risk factors for the development of post-hepatectomy liver failure (PHLF). Although portal vein embolization (PVE) has made it possible to safely perform extended hepatectomy, to ensure safety, in our department, PVE is performed prior to Rt-Hr for hepatocellular carcinoma (HCC) regardless of the resection rate. This study aimed to retrospectively investigate the clinical course of PVE prior to Rt-Hr for HCC cases resected in our department and the appropriateness of our policy by clarifying complications and deaths. Patients and Methods: The target period was from 2005 to 2020. Among the HCC cases resected at our hospital, those in which PVE was performed prior to Rt-Hr were included in this study. For PHLF, the definition of the International Study Group of Liver Surgery was used. The Clavien-Dindo classification was used for postoperative complications. Perioperative mortality was defined as the overall mortality within 30 days following surgery and surgery-related deaths within 90 days following surgery. Results: A total of 79 cases were included. Rt-Hr was possible in all cases after PVE and there were no cases in which serious complications occurred after PVE. PHLF was found in 14 cases (17.7%)/5 cases (6.4%)/0 cases (0%) of Grade A/B/C, respectively. Regarding postoperative complications, there were no Grade IV, and Grade IIIa/IIIb were found in 13 cases (16.5%). There were no perioperative deaths. Conclusion: Our department's policy of performing PVE prior to all Rt-Hr was considered to be a safe and reasonable treatment strategy.*

Treatment for primary liver cancer, metastatic liver cancer, and cholangiocarcinoma in the hepatic hilum varies; however, for anatomically resectable lesions, hepatectomy is selected as the first-line treatment strategy, provided that the hepatic reserve capacity is maintained. Although an extended hepatectomy may be required to increase the radical curability of the cancer, it is of utmost importance to anticipate liver failure that may develop after major hepatectomy and select the appropriate procedure. Prior to predicted major hepatectomy, the capacity of the remaining liver can be increased by systematically embolizing the portal vein passing through the region to be resected. This procedure is called portal vein embolization (PVE), the performance of which allows extended hepatectomy to be safely performed (1). Although the indication criteria for PVE varies from institution to institution, it is often performed when the estimated future remnant liver is below 25-30% of the normal liver, 40% in chronic liver disease patients, and 60% in liver cirrhosis patients (2).

Hepatocellular carcinoma (HCC) is thought to develop in the background of a variety of factors such as viral liver disorders including hepatitis C virus and hepatitis B virus, alcoholic liver disorders, and non-alcoholic fatty liver diseases (3). HCC often comes with liver damage (liver fibrosis) in the tumor bed and even if the appearance of the hepatic reserve is preserved, it is highly likely that diffuse liver fibrosis exists, along with the possibility of developing unexpected liver failure (3).

Various risk factors have been reported to be related to post-hepatectomy liver failure (PHLF). Regarding the operative procedures, more than four subsegmentectomies, including right hepatectomy, have been reported as independent risk factors for PHLF (4, 5). In PHLF, defined

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according to the International Study Group of Liver Surgery (ISGLS) (6), the frequency of Grade B/C PHLF after right hepatectomy is reported to be approximately 15-40% (7, 8), while operative morbidity after right hepatectomy is reported to be 2.3%-29.2% (2, 9, 10). In addition, according to the data from the National Clinical Database aggregated in Japan in 2014, the surgery-related mortality within 3 months following surgery was reported to be 5.5% for right hepatectomy and 9.5% for extended right hepatectomy (11).

In our department, PVE has been performed prior to right hepatectomy for HCC, to prevent PHLF regardless of the resection rate, since the background liver may be damaged. It is not clear at this time whether our empirical therapeutic approach suppresses PHLF and the intercurrence of post-hepatectomy complications and perioperative deaths compared to the reported frequency of cases of PHLF following right hepatectomy. In this study, we retrospectively investigated the success rate of PVE prior to right hepatectomy for HCC, which is our treatment strategy, the frequency of perioperative complications and PHLF, and the perioperative mortality rate. We also discuss the appropriateness of PVE prior right hepatectomy for damaged livers.

Patients and Methods

The subjects of this study were patients who underwent PVE prior to right hepatectomy (including extended right hepatectomy) in the 15-year and 7-month period from January 2005 to August 2020. A diagnosis of HCC was made using a combination of contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), and tumor markers. Albumin, total bilirubin, prothrombin time, platelet value, and indocyanine green retention rate at 15 min (ICG-R15) value, were measured as a hepatic reserve capacity test prior to PVE, and liver stiffness was also measured via transient elastography in cases from 2007 onwards. Cases with poor performance statuses and cases in which hepatectomy was considered inappropriate due to co-morbidities were not indicated for hepatectomy, so hepatic arterial infusion chemotherapy, transcatheter arterial chemoembolization, and molecular targeted drug treatment were performed. Localization of the tumor was limited to the right hepatic lobe. Cases in which resection was possible without remnants from right hepatectomy and extended right hepatectomy were subjected PVE prior to right hepatectomy. Right hepatectomy with middle hepatic vein + Segment 1 was selected for cases in which HCC was close to the middle hepatic vein or present in the right caudate lobe. Contrast enhanced CT was taken before PVE surgery and volumetry was performed by a surgeon using the Fujifilm three-dimensional image analysis system volume analyzer, SYNAPSE VINCENT® (Fujifilm Medical, Tokyo, Japan). The resection rate was measured by setting the scheduled resection line required for R0 resection in individual cases. After PVE, contrast enhanced CT was taken 7 to 10 days later and volumetry was performed again. The overall liver volume, predicted liver resection volume, predicted residual liver volume, and predicted liver resection rate were measured using contrast enhanced CT before and after PVE. The increase in future remnant liver volume was determined from the difference in the predicted liver residual capacity before and after PVE.

The conducted PVE was transileocolic portal embolization (TIPE). Iopamidol was used as the contrast agent to embolize the anterior branch of the portal vein following embolization of the posterior branch of the portal vein. Absolute ethanol was used as the embolic material and the amount of absolute ethanol used was the amount at which the entire tertiary branch of the portal vein was uniformly imaged. The portal vein pressure (PVP) was measured by placing the tip of the catheter in the portal vein trunk before and after the PVE. The difference in PVP before and after PVE was measured.

Hepatectomy was planned two weeks after PVE. If the hepatic resection rate was less than 60%, hepatectomy was performed. For patients with a resection rate of less than 60% before PVE, hepatectomy was performed approximately 2 weeks after PVE, regardless of the resection rate after PVE. For patients whose CT volumetry indicated a hepatic resection rate of 60% or more after PVE, a contrast enhanced CT was taken every week until the resection rate reached less than 60% by extending the waiting period. Once the resection rate had improved to less than 60%, hepatectomy was performed. The waiting period was set to a maximum of 4 weeks and for cases in which the resection rate did not improve to less than 60% during the above period, hepatectomy was performed at the resection rate at week 4. During the right hepatectomy, extrahepatic hilar dissection approach was performed and the right portal vein was disconnected after confirming that there was no thrombus on the resection line (12). PHLF after hepatectomy was classified as Grade A/B/C according to ISGLS (4). Clinically relevant liver failure was defined as PHLF Grade B/C as it often led to severe morbidity or mortality (13), the incidence of which was investigated retrospectively from the medical records. Postoperative complications were classified by the Clavien-Dindo classification and the incidence of Grade III/IV/V complications was investigated from the medical records (14). Perioperative death was defined as the total deaths within 30 days following surgery and surgery-related deaths within 90 days following surgery (11). Continuous variables were expressed as median (range). A statistical analysis was performed using the JMP version 13.0 software program (SAS Institute, Cary, NC, USA). This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies, and the ethics committee of our institution approved this research.

Results

During the 15 years and 7 months from January 2005 to August 2020, 115 cases of HCC were eligible for hepatectomy after PVE. Of these, a total of 79 cases (67.7%) including 65 cases of right lobectomy (56.5%) and 14 cases of extended right lobectomy (12.2%) underwent PVE prior to hepatectomy and were included in this study (Table I).

The median age of the subjects was 71 years (range=33-84 years). The background of HCC carcinogenesis was 34 cases of hepatitis C virus infection-related hepatitis/cirrhosis (43%), 18 cases of hepatitis B virus infection-related hepatitis/cirrhosis (23%), and 27 cases of non-viral hepatitis/cirrhosis (34%). The blood biochemical test results before PVE were albumin 4.0 g/dl (range=3.1-4.9 g/dl), total bilirubin 0.7 mg/dl (range=0.3-1.6 mg/dl), prothrombin time 95% (range=70-140%), platelets $16.9\times10^2/\mu l$ ($7.3\text{-}34.0\times10^2/\mu l$), and ICG-R15 value 16.2%

Table I. *Scheduled types of hepatectomy followed by portal vein embolization against hepatocellular carcinoma.*

Scheduled types of hepatectomy	Number of patients (%)
Right trisegmentectomy	2 (1.7)
Left trisegmentectomy	4 (3.4)
Extended right hepatectomy	14 (12.2)
Right hepatectomy	65 (56.5)
Extended left hepatectomy	6 (5.2)
Left hepatectomy	3 (2.6)
Bilateral paramedian segmental resection	1 (0.9)
Central bi-segmentectomy	2 (1.7)
Anterior segmentectomy	2 (1.7)
Extended posterior segmentectomy	3 (2.6)
Posterior segmentectomy	11 (9.6)
Subsegmentectomy	1 (0.9)

Table II. *Baseline characteristics of patients with hepatocellular carcinoma who had planned right hepatectomy followed by portal vein embolization.*

Valuables	Median (range)
Age (years)	71 (33-84)
Sex (Male/Female)	65/14
HCV/HBV/Non-viral infection	34/18/27
Child-Pugh score 5/6/7	74/4/1
AST (IU/l)	30 (15-68)
ALT (IU/l)	26 (9-72)
Cholinesterase (U/l)	239 (75.0-399)
Albumin (g/dl)	4.0 (3.1-4.9)
Total bilirubin (mg/dl)	0.7 (0.3-1.6)
Prothrombin time (%)	95 (70-140)
Platelet count ($\times 10^4/\mu l$)	16.9 (7.3-34.0)
Hyaluronic acid (ng/ml)	72.5 (19-761)
ICG-R15 (%)	16.2 (3.0-32.0)
Liver stiffness (kPa)	9.2 (3.6-30.8)

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; HCV: Hepatitis C virus; HBV: hepatitis B virus; ICG-R15: indocyanine green retention rate at 15 min.

(range=3.0-32.0%). The liver stiffness measured by Fibroscan® had a median value of 9.2 kPa (range=3.6-30.8 kPa). The Child-Pugh score was B (7) for one case, while all other cases were A, with 74 cases being A (5) (Table II).

The median total liver volume before PVE was 1,058 ml (range=629-2,005 ml). The median predicted hepatic resection volume before PVE was 638 ml (range=237-1,481 ml), the median predicted residual liver volume was 420 ml (range=266-930 ml), and the median predicted resection rate was 58.5% (range=23.9-73.9%). The median time from PVE to the first contrast enhanced CT was 9 days (range=3-17 days). The median total liver volume after PVE was 1,128 ml (range=623-2,047 ml). The median predicted hepatic resection volume after PVE was 550 ml (range=182-1,466 ml), the median predicted residual liver volume was 554 ml (range=358-1,222 ml), and the median predicted resection rate was 49.7% (range=17.6-71.6%). The median residual liver volume increase was 107 ml (range=–15-292 ml). Three cases (resection rate: 63.2%, 64.9%, 71.6%) still had hepatic resection rates ≥60% after the 4-week waiting period. The median pre-embolization PVP measured at PVE was 9.6 mmHg (range=5-20 mmHg), whereas the median post-PVE PVP was 13.5 mmHg (range=7-25 mmHg). The median rise in PVP before and after PVE was 4 mmHg (range=–2-13 mmHg) (Table III).

Table III. *Volumetry data of patients before and after portal vein embolization.*

Parameters	Median (range)
Before portal vein embolization	
Total liver volume (ml)	1058 (629-2,005)
Resection volume (ml)	638 (237-1,481)
Future liver remnant volume (ml)	420 (266-930)
Resection rate (%)	58.5 (23.9-73.9)
After portal vein embolization	
Total liver volume (ml)	1128 (623-2,047)
Resection volume (ml)	550 (182-1,466)
Future liver remnant volume (ml)	554 (358-1,222)
Resection rate (%)	49.7 (17.6-71.6)
Volume increase (before - after, ml)	107 (–15-292)
Portal vein pressure	
Before embolization (mmHg)	9.6 (5-20)
After embolization (mmHg)	13.5 (7-25)
Elevation of portal vein pressure (after - before, mmHg)	4 (–2-13)

Post-PVE complications were observed in 12 of 79 cases (15.2%). Since the portal vein thrombus after PVE was extended to the main trunk of the portal vein, five cases (6.3%) requiring heparin administration were identified. In the five cases with portal vein thrombus extensions, heparinization was performed for a week, and after confirming that the thrombus of the portal vein trunk had disappeared on contrast enhanced CT, hepatectomy was performed. Five cases (6.3%) were identified in which ascites were observed and diuretic administration was required. There were no cases of ascites retention that required drainage as well as refractory ascites. Two cases (2.5%) were found in which fever and high sustained inflammatory reactions were observed that were believed to be caused by liver infarction. There were no cases that became unresectable due to tumor progression or complications following PVE and the planned right hepatectomy/extended right hepatectomy was completed in all cases (resection success rate: 100%) (Table IV). The median time from PVE to hepatectomy was 16 days (range=6-32 days).

Liver failure after right hepatectomy included 4 cases (5.1%) with Grade B PHLF and 0 cases (0%) with Grade C, with an incidence of clinically relevant PHLF of 5.1%. All cases of PHLF under this investigation had no severe PHLF onset, 61 cases (77.2%) did not have PHLF, and 14 cases (17.7%) had Grade A PHLF (Table V). Clavien-Dindo classification of complications indicated grade IIIa or higher complications in 13 cases (16.5%). Twelve (15.2%) patients (Grade IIIa) underwent percutaneous drainage for ascites and bile fistulas. Grade IIIb complications included only one case (1.3%) in which open hemostasis was performed due to postoperative hemorrhage, with no complications requiring ICU management of Grade IVa or higher and no perioperative deaths of Grade V (Table VI). There were no deaths within 30 days and 90 days (mortality 0%). In the evaluation of liver fibrosis using the METAVIR score of the resected specimen, F0/F1/F2/F3/F4 were 5/26/20/16/12, respectively, with 16 cases (20.3%) of pre-cirrhosis (F3) and 12 cases (15.2%) of cirrhosis (F4).

Table IV. *Detail of postoperative complications after portal vein embolization.*

Complications	Number of patients (%)
Yes	12 (15.2)
Prolonged portal vein thrombosis requiring heparinization	5 (6.3)
Ascites requiring diuretics (non-refractory)	5 (6.3)
Febrile related to liver infarction/ Continuous elevation of inflammatory reaction	2 (2.5)
Unresectability related to exacerbation of hepatocellular carcinoma	0 (0)

Table V. *Incidence of postoperative liver failure after right hepatectomy.*

Grade of PHLF after right hepatectomy	Number of patients (%)
None	61 (77.2)
Grade A	14 (17.7)
Grade B	4 (5.1)
Grade C	0 (0)

PHLF: Post-hepatectomy liver failure.

Discussion

It has been reported that the incidence of liver failure after right hepatectomy is 20-40% (7, 8). The incidence of Grade B/C PHLF in our department was only 5.1%, with no Grade C cases. No PHLF or clinically irrelevant Grade A PHLF were approximately 95% of the total and the resection result of HCC with damaged liver as the background was extremely good. When planning right hepatectomy for HCC, PVE is performed in all cases prior to hepatectomy according to our treatment strategy. Therefore, it cannot be compared with cases in which right hepatectomy is performed without PVE. However, the frequency of PHLF in other facilities to date is reportedly 40.5% for right hepatectomy and 45.2% for extended right hepatectomy (7). Therefore, the incidence of PHLF in our department is considered to be extremely low. Grade IIIa/IIIb complications after right hepatectomy occurred in a total of 13 cases (12/1 cases, respectively) (16.5%), which was comparable to 2.3%-29.2% of operative morbidities reported to date (2, 9, 10). However, most of the complications involved the storage of ascites (9 cases) or bile leakage (3 cases) that required percutaneous drainage. There was only one case with Grade IIIb complications requiring treatment under general anesthesia, which was an open hemostasis due to postoperative bleeding, and there were no life-threatening Grade IV complications or Grade V (death). This could have been the result may be the result of our liberal application of PVE for damaged livers.

In our hospital, transiliocolic PVE (TIPE) is performed. The reason for our preference for TIPE over percutaneous transhepatic PVE (PTPE) is that PTPE is recommended for ipsilateral puncture rather than contralateral puncture (15, 16). However, in cases requiring right lobectomy, large tumors and tumors in proximity to the hepatic hilum, often make ipsilateral portal vein puncture difficult and require contralateral puncture. When performing a contralateral puncture, we prefer TIPE because the complication of PTPE can lead to hematoma and bile duct injuries in the liver, making the tumor to be unresectable. Post-PVE complications in this study were seen in 15.2% of cases. The occurrence of serious complications after PTPE has been reported to be 0.4-12.8% (15, 17). However, the complications in our cases were only minor, including ascites retention and unexpected inflammatory reactions. It is believed that the absence of hepatic puncture as well as hepatic artery, hepatic veins, and bile duct accidental puncture, which are PTPE-related complications, contributed to the reduction in the occurrence of complications. In all cases, it was safely implemented.

Our right hepatectomy cases were evaluated using contrast enhanced CT on median day 9 and right hepatectomy was performed on median day 16. When PTPE and TIPE are both included, the waiting period from PVE to hepatectomy was often reported to be 3 to 12 weeks (15, 16, 18, 19), with 6.3% of cases reported as having become unresectable due to tumor progression during the waiting period (20). In our cases, there were no cases in which the tumor became unresectable due to progression as hepatectomy was performed relatively early after PVE. Although the waiting period was short, with volumetry after PVE, the resection rate decreased from a median of 58.5% to a median of 49.7%, and in many cases, the increase in residual liver volume was sufficient. In

Table VI. *Postoperative complications after right hepatectomy.*

Clavien-Dindo grade	Detail of complications and number of patients	Number of patients (%)
None	None	42 (53.1)
Grade I	Wound infection: n=3	
	Ascites or pleural fluid collection requiring diuretics: n=6	9 (12.6)
Grade II	Ileus: n=5, transfusion (Albumin): n=5	
	portal vein thrombosis: n=5	15 (17.7)
Grade IIIa	Ascites or pleural fluid collection requiring percutaneous drainage: n=9	
	bile leakage requiring percutaneous drainage: n=3	12 (15.2)
Grade IIIb	Postoperative bleeding requiring open surgery: n=1	1 (1.3)
Grade IVa	None	0 (0)
Grade IVb	None	0 (0)
Grade V	None	0 (0)

addition, although 3 cases had a waiting period of 4 weeks and were unable to achieve our targeted resection rate of less than 60%, it was reported that the increase in volume would plateau in approximately 3 weeks (21), so it was possible to complete the surgery without complications in the 3 cases mentioned above. Some have reported that elevated PVP after hepatectomy is associated with mortality and PHLF (22, 23); however there are also reports stating that elevated PVP after PVE decreases to pre-embolization level in 24 hours (24). In our cases, PVP during the hepatectomy is unknown because it was not measured. However, as mentioned above, modulation of the PVP was completed in a relatively short period of time, which may be the reason why we were able to successfully perform right hepatectomy without severe PHLF.

Although this study covered only HCC, due to co-morbid hepatic impairment, the background liver had various degrees of liver fibrosis. Among them, precirrhosis and cirrhosis were present in 38 cases (35.5%) and although the liver functional test was preserved as Child-Pugh A (5) in all but one case, it was found that there were many cases with a high risk of developing liver failure due to right lobectomy. For F3 and F4 cases, the risk of surgery itself is high and conservative surgery is also considered. Preoperative liver biopsy is also worth considering in order to decide surgical indication. However, a liver biopsy only takes a small portion of the liver and it has been reported that liver fibrosis is difficult to accurately diagnose by liver biopsy. If liver biopsy is performed, it is necessary to make multiple punctures on the residual liver. Avoiding placing a burden on the residual liver from a complications perspective is also one of the reasons why liver biopsy is not performed (25). In our cases, median resection rate before PVE was 58.5%, and in some cases, even without PVE, right hepatectomy could have been performed safely. However, the median PVP measured before embolization was higher than normal at 9.6 mmHg in many cases. Since performing PVE before right lobectomy would pseudo-create a right lobe resection state, this is also considered to be a test material for determining whether we can actually proceed to the next resection. In a multi-center study, Beppu *et al*. reported a better prognosis for right-sided hemihepatectomy associated with HCC, among cases in which surgery was performed with prior PVE, compared to cases in which upfront surgery was performed (9). HCC is known to cause transportal vein metastasis; however, it has been suggested that hepatectomy after PVE may prevent intraoperative kneading. Also, from an oncological point of view, performing PVE prior to right hepatectomy for HCC may be acceptable.

Franken *et al*. reported that the structured use of PVE may be considered for perihilar cholangiocarcinoma requiring extended hepatectomy with reconstruction in particular (26). In addition, Olthof *et al*. reported that by performing PVE before perihilar cholangiocarcinoma, not only liver failure, but also the risk of bile fistula, intraperitoneal abscess, and death is reduced (27). Levi Sandri *et al*. compared the surgical prognoses IN their facility around 2007; they reported that after 2008, they performed portal vein ligation or PVE in all cases of HCC, which significantly reduced the mortality (28). This liberal application of PVE is believed to be adaptable to damaged livers. In fact, considering that in this study, right hepatectomy was able to be completed in all cases without the occurrence of serious complications or serious liver failure, it is also possible to adapt this to HCC with a background of damaged liver.

Conclusion

In our department, we have a policy of performing PVE prior to right hepatectomy/extended right hepatectomy for cases of HCC. In this study, right hepatectomies with prior PVE were completed in all cases, and since there were no serious complications including death, this surgical procedure is therefore considered to be a safe and appropriate treatment strategy.

Conflicts of Interest

All Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Nobuhisa Shirahama and Yuichi Goto contributed equally to this article, and both should be considered first author. Nobuhisa Shirahama and Yuichi Goto designed the study, and wrote the initial draft of the manuscript. Nobuhisa Shirahama and Yuichi Goto and Toru Hisaka contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript.

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