J Hepatobiliary Pancreat Surg (2007) 14:447–454
DOI 10.1007/s00534-006-1193-2

Journal of HBP Surgery

Recent advances in the treatment of hilar cholangiocarcinoma: portal vein embolization

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Abstract
The clinical application of portal vein embolization (PVE) has contributed to improving the postoperative outcome of hilar cholangiocarcinoma. The enlarged nonembolized lobe after PVE protects the patient from postoperative hepatic failure, due to the increased functional reserve, and shortens the hospital stay. Although numerous reports have shown beneficial effects of PVE on postoperative outcome after extended hepatectomy, no randomized controlled study has been performed so far. It is urgent to establish a "gold standard" of PVE, because the indications, approach to the portal vein, types of embolic materials, and methods used to evaluate the function of the future liver remnant are variable among institutions. The indications and procedures of PVE for hilar cholangiocarcinoma may be different from those for hepatocellular carcinoma or colorectal metastasis, because, in many patients with hilar cholangiocarcinoma, biliary cancer is associated with biliary obstruction and cholangitis. This review article summarizes the contribution of PVE to the outcome of postoperative management in patients with hilar cholangiocarcinoma needing extended hepatectomy. We also describe our PVE procedure, which has been established from our experience of more than 240 cases of biliary cancer. Furthermore, the drawbacks of PVE, which may reduce the pool of candidates for surgery, are also discussed.

Key words Extended hepatectomy · Volumetry · Indocyanine green clearance · Future liver remnant · Embolic materials

Introduction

In patients with hilar cholangiocarcinoma, radical surgery is superior to any other therapeutic modalities in regard to survival rate and quality of life.[1] To improve survival rates for hilar cholangiocarcinoma, curative resection after aggressive preoperative management is an important surgical approach.[2] Minimal resection of the involved segment, such as en-bloc caudate lobectomy, anterior segmentectomy with caudate lobectomy, and central bisegmentectomy have been selected on the basis of the extent of cancer invasion to minimize the risk of postoperative hepatic failure.[3,4] However, in many patients with hilar cholangiocarcinoma, partial hepatectomy is insufficient and extended hepatectomy is required to obtain a safe surgical margin. The greater the volume of liver resected, the greater is the risk that patients will develop postoperative hepatic failure due to an insufficient remnant liver volume. This controversial issue has been overcome since the development of portal vein embolization (PVE) by Makuuchi et al.[5,6] in the 1980s. Preoperative enlargement of the nonembolized lobe by PVE contributes to protecting the patient from postoperative hepatic failure, by increasing the functional reserve.[7] Portal vein embolization is especially useful for marginal candidates for hepatic resection with a small liver remnant size.[8]

In general, PVE can benefit patients requiring a future liver remnant volume of less than 25%–35% of the original volume.[2,7,8] But the indication is still controversial, especially for patients with chronic liver disease. There is only one prospective, but not randomized, study that has analyzed the postoperative outcome of PVE.[9] The results showed that the hypertrophy of the functional liver remnant induced by PVE had no beneficial effect on the postoperative course in patients whose liver did not show chronic disease. In contrast, in patients with chronic liver disease, the hypertrophy of the functional liver remnant induced by PVE significantly decreased the rate of postoperative complications.[9] Does this mean that PVE is beneficial only for the liver with chronic liver disease? We cannot reach a conclusion from a single study, and we need more clinical evidence from a well-controlled prospective study.

Offprint requests to: Y. Yokoyama
Received: September 15, 2006 / Accepted: October 16, 2006

Furthermore, controversies remain with regard to the procedure for approaching the portal vein, the types of embolic materials, the necessity for segment IV embolization, and the methods used to evaluate the function of the future liver remnant. To establish a "gold standard" for PVE, a randomized controlled study including multiple institutions should be performed. Although PVE is generally considered to be a safe procedure, there are reports that have revealed the drawbacks of PVE. These should also be elucidated by the accumulation of data from multiple institutions.

This review article summarizes the contribution of PVE to the outcome of postoperative management in patients with hilar cholangiocarcinoma needing extended hepatectomy. The drawbacks of PVE, which may reduce the pool of candidates for surgery, will also be explored.

Factors affecting the volume change following portal vein embolization

Computed tomography (CT) is the most commonly used and probably the most reliable modality for evaluating the volume change after PVE. Usually, scans at 3- to 10-mm intervals, with enhancement by the intravenous infusion of contrast medium, are sufficient for evaluating the volume of each hepatic segment. Recent advances in multislice detector CT have provided more accurate volume analysis in each segment, by three-dimensional (3D)-CT volumetry.[10] Although 3D-CT volumetry appears to be more accurate than conventional 2D-CT volumetry, it still produces an error rate of approximately 10%. This error could be significant, because it is critical for the marginal candidates who will have a very small future liver remnant, i.e., 25%–35% of the original volume. A procedure that provides more accurate segmental volumetry with minimum error should be developed in the future.

In patients with hilar cholangiocarcinoma, the hypertrophy ratio of the nonembolized lobe after PVE, expressed as a percentage of the postembolization volume, is approximately 20%, and the atrophy ratio in the embolized lobe is almost equivalent to or slightly less than (<15%) the hypertrophy ratio. Generally, PVE produces compensatory hypertrophy in the nonembolized lobe within 14 days without serious complications. However, in patients with obstructive jaundice or cholangitis, the extent of hypertrophy is severely affected[11] and a longer interval between embolization and operation may be required to achieve a sufficient future liver remnant volume.[12] Even a segmental bile duct obstruction impairs the cellular function not only in the obstructed lobe but also in the nonobstructed lobe.[13] Moreover, when patients with bile duct carcinoma have intrahepatic segmental cholangitis, the morbidity and mortality rates for these patients after major hepatectomy are significantly worse than the rates in those without cholangitis.[14] Therefore, whenever possible, active drainage of the obstructed bile duct should be performed before PVE. At our institution, for patients with hilar cholangiocarcinoma, we would not perform PVE if the patients have cholangitis or if their serum total bilirubin level is more than 2 mg/dl.

When patients need biliary drainage, should we drain the biliary duct for both the embolized and nonembolized lobes? Or is drainage only for the nonembolized lobe, i.e., the future liver remnant, enough? There is an interesting report that showed a significantly higher hypertrophy ratio in the nonembolized lobe after PVE in patients with drainage only for the nonembolized lobe than in those with bilateral drainage.[15] The authors proposed that, whenever possible, biliary drainage should not be performed in the lobe that is to be subjected to hepatectomy. However, the mechanism underlying this observation remains unclear, and it seems that this suggestion should not be adhered to when the serum bilirubin level remains high with unilateral drainage.

Biliary drainage can be performed either internally or externally. Several studies have reported that internal drainage provides a better milieu for hepatic regeneration than external drainage.[16–18] Internal biliary drainage also contributes to the maintenance of intestinal integrity,[19] which may lead to a normal intestinal immune function and render the patient more tolerant to the severe insult produced by extended hepatectomy.[20] Because hilar cholangiocarcinoma requires preoperative biliary drainage in most patients, internal biliary drainage should be tried first before performing PVE. When only external drainage is possible, we replace the drained bile either by per os intake or by administration through a nasoduodenal tube.[19]

Other factors that are known to inhibit the capacity for hepatic regeneration include diabetes mellitus,[21] chronic alcohol consumption,[22] hepatitis,[23] and malnutrition.[24] These factors should be optimized, where possible, before PVE to maximize the extent of hypertrophy in the nonembolized lobe.

Indications for PVE in terms of future liver remnant volume

No clear indication for PVE has been provided so far in regard to the future liver remnant volume. Ladurner et al.[25] used PVE in patients in whom the estimated liver

remnant volume was 25% or less of the total liver volume. They limited the utilization of PVE only for patients with a small anticipated liver remnant, which is generally considered to be unresectable. Hemming et al.[7] also used the same indication (less than 25% of the future liver remnant volume). Other groups have used PVE for patients with estimated future liver remnant ratios of less than 30%[26] or less than 40%.[27] Because PVE apparently improves postoperative morbidity and mortality, should we limit the use of PVE only for marginal candidates? If PVE can be performed without any mortality and with minimum morbidity, we could extend the indication for those patients who are to undergo extended hepatectomy. At our institution, we have performed PVE in patients with hilar cholangiocarcinoma who are to undergo right hepatectomy or right or left trisectionectomy.[28]

The indication for PVE should be changed in order to take into account the status of the patient's condition. Elias et al.[26] proposed that the threshold for PVE should be raised if the patient had undergone multiple courses of chemotherapy. The indication should also be restricted in patients with chronic liver disease.[9,29]

Fortunately, the underlying liver in hilar cholangiocarcinoma is generally normal compared to the condition in hepatocellular carcinoma, in which, in many cases, there is associated irreversible hepatic fibrosis due to chronic viral infection. Fibrous change due to biliary obstruction, which is one of the most common symptoms of hilar cholangiocarcinoma, is mostly reversible if we perform biliary drainage appropriately. In this regard, preoperative biliary drainage is again important.

Embolic materials

Gelfoam,[6] fibrin glue,[30] cyanoacrylate,[31] and absolute ethanol,[32] with or without an embolization coil,[33] have been used as embolic materials. There has been no randomized controlled study so far to compare the efficiency of these embolic materials. A report comparing Gelfoam and absolute ethanol showed that Gelfoam was not efficient in regenerating the nonembolized lobe, due to a high incidence of recanalization of the portal vein branch.[34] At our institution, we previously used fibrin glue as the embolic material, and we subsequently changed to a combination of ethanol and embolization coils. Although the rate of recanalization was slightly higher with fibrin glue embolization than with ethanol and coils (fibrin glue vs ethanol/coils; 8.3% vs 5.1%), there was no significant difference in either the hypertrophy ratio of the nonembolized lobe or the atrophy ratio of the embolized lobe[27] (Fig. 1).

It could be anticipated, however, that the liver tissue damage after infusing absolute ethanol is more severe than that caused by the other embolic materials, because ethanol easily perfuses to the sinusoidal levels and extensively damages the sinusoidal endothelial cells. Ethanol may drain into the terminal hepatic venules and subsequently enter the systemic circulation. It is difficult to predict the systemic effects of absolute ethanol when it enters the systemic circulation. Further study is necessary to elucidate the side effects caused by ethanol infusion and to determine the appropriate amount of ethanol that should be used.

Several new embolic materials have been developed in recent years. N-butyl cyanoacrylate (NBCA) mixed with iodized oil has been used as a new embolic agent.[35]

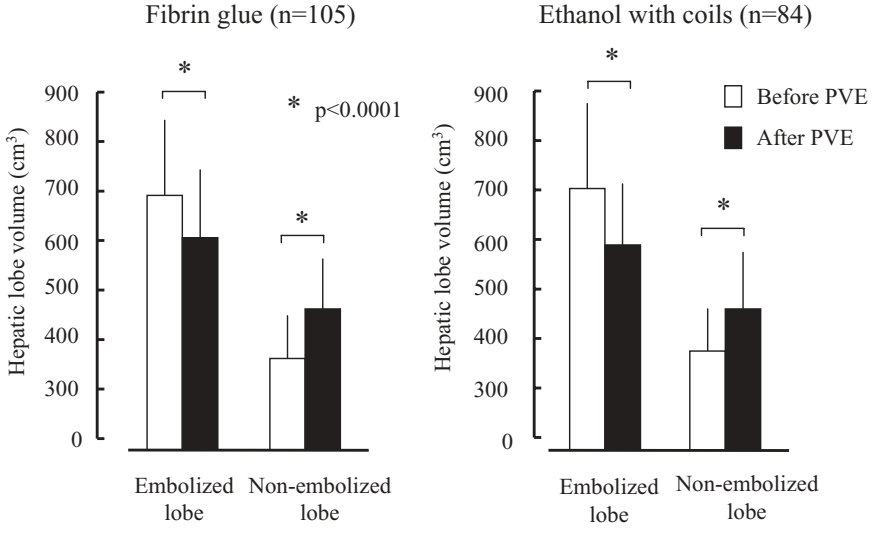

Fig. 1. Differences in liver volume before and after portal vein embolization (*PVE*); fibrin glue vs ethanol with coils

Polyvinyl alcohol (PVA) particles, nonspherical particles from 355 to 1000 μm in size, are widely used and have been shown to be useful in embolizing the portal vein branch in human patients.[36,37] More recently, small spherical embolizing particles (tris-acryl microspheres; 100–700 μm) have become commercially available.[38] A report showed that the extent of hypertrophy was significantly higher with small spherical embolizing particles than with larger, nonspherical particles (PVA).[38] The benefit of these microspheres is the wide selection of particle size, depending on the size of the portal vein branch to be embolized. One can use smaller particles to occlude distal branches, whereas larger particles can be used to occlude proximal branches. Histological findings have revealed more distal embolization in excised livers embolized with tris-acryl microspheres than in livers embolized with PVA particles. Small microspheres may not only occlude portal blood flow but may also reduce the arterial inflow by occluding arterioportal communications in the hepatic microcirculation.

Is it necessary to embolize segment IV?

Hilar cholangiocarcinoma frequently shows intraductal tumor spreading. Under such conditions, extensive hepatectomy such as right trisectionectomy is required. Portal vein embolization is apparently necessary for these patients because the expected volume of the future liver remnant is extremely small. Controversy still exists as to whether the left medial segment (segment IV) should be embolized when right trisectionectomy is performed. Because the portal branches to segments II, III, and IV usually originate from the umbilical portion, insufficient hypertrophy of segments II and III, and unexpected hypertrophy of segment IV is anticipated after right portal branch embolization alone. We have developed right plus segment IV embolization (right trisegment PVE) through an ipsilateral approach.[39,40] Right trisegment portal embolization was more useful than standard right PVE in preparation for right hepatic trisectionectomy, and had the potential to increase the safety of this high-risk surgery for patients with hilar cholangiocarcinoma. Madoff et al.[38] also reported the usefulness of segment IV embolization. In contrast to these reports, Capussotti et al.[41] reported that extension of embolization to segment IV portal branches should not be routinely used, because a similar volume increase of segments II-III could be simply achieved by right PVE. The answer is still unclear, because these studies include only small numbers of patients and no randomized controlled study has been performed so far.

What should we do when we cannot achieve sufficient hypertrophy with PVE?

A sufficient volume increase in the nonembolized lobe is not always achieved following PVE. If the volume increase is too small, hepatectomy should be abandoned, even in those patients with no factors suggestive of impaired liver regeneration. The mechanism of impaired hepatic regeneration in response to PVE in such patients is unclear. What kind of strategy should we choose for these patients as a next step? Hepatic arterial flow in the embolized lobe is significantly increased due to the hepatic arterial buffer response[42] and this increased flow contributes to maintaining the volume of the embolized lobe.[43] Therefore, one of the possible procedures that could be used to further enhance the effect of PVE is arterial embolization of the embolized lobe. We[44] and others[45] have reported the usefulness of sequential ipsilateral portal vein and hepatic artery embolization for those patients who did not show sufficient volume increase after PVE. However, this essentially means "in-situ hepatectomy" for the embolized lobe, and there is a high risk of development of a hepatic abscess. Therefore, the indication for this aggressive dual embolization should be strictly selective and we should always be ready to treat a subsequent liver abscess by an interventional approach.

Selective intrahepatic biliary ablation with absolute ethanol can induce atrophy of the infused lobe and hypertrophy of the noninfused lobe.[46] An experimental study using rats showed that selective infusion of absolute ethanol to 70% of total liver weight decreased the weight of the infused lobe to less than 50% of the entire liver weight 14 days after the treatment.[46] In contrast, the weight of the noninfused lobe increased to 1.6-fold of the original value. The infused ethanol soaked through Glisson's capsule and destroyed hepatocytes without damaging the portal veins and hepatic arteries. If the biliary duct in the embolized lobe is completely separated from other branches by cancer and there is no risk present to damage the bile duct of the future liver remnant, this procedure (i.e., selective intrahepatic biliary ablation with absolute ethanol) could be another option to achieve further volume change.

Extrahepatic hematopoietic progenitor cells are known to participate in liver proliferation after hepatic resection.[47–49] $CD133^+$ stem cells have been used therapeutically to support tissue and organ regeneration in the myocardium.[50] Using a similar technique, Am Esch et al.[51] recently reported the portal application of autologous CD133+ bone marrow cells to the liver, concomitant with PVE. After the completion of PVE, CD133+ cells were selectively applied to the

nonembolized portal branches of the liver. Despite the small number of patients involved in this preliminary study, the data provided were promising. The daily mean volume gain in the nonembolized lobe in the group after PVE plus bone marrow stem cell application was well superior to the group with only PVE. This procedure could be a future strategy for those patients whose volume increase is insufficient with PVE alone.

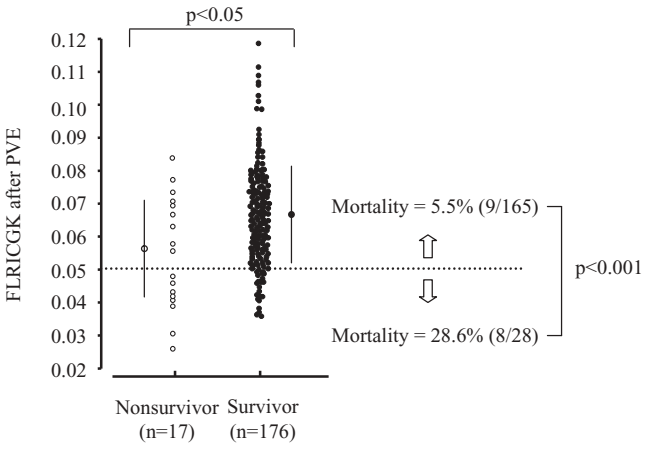

Fig. 2. Indocyanine green clearance rate (ICGK) of the future liver remnant (*FLR ICGK*) stratified by survivors and nonsurvivors. FLR ICGK = ICGK × % volume of the future liver remnant/100. From reference 28 with permission

Evaluation of future liver remnant function

The ultimate goal of liver resection in patients with hilar cholangiocarcinoma is to treat the patients with the minimum operative risk. To achieve this goal, specific preoperative assessment of the risk is mandatory. How can we accurately predict the future liver remnant function, which correlates to the postoperative morbidity and mortality? Methods for the assessment of future liver remnant function are discussed below.

Usefulness of the indocyanine green clearance rate (ICGK)

The indication for hepatectomy after PVE should not be determined simply by the volume of the future liver remnant. It is generally considered that 65% hepatectomy is safe for patients with normal liver function. For patients with chronic liver disease, hepatectomy should be restricted to less than 60%.[52] The indocyanine green retention rate at 15 min (ICGR15) or the clearance rate (ICGK) is probably the most useful method for assessing future liver remnant function and determining the extent of hepatectomy. Kubota et al.[27] have proposed that PVE should be indicated for the patients whose ICGR15 values are between 10% and 20%. Another report showed that a post-PVE ICGR15 value of less than 16% was a significant prognostic factor for postoperative morbidity after major hepatectomy.[53] Our data, in which we analyzed 240 consecutive cases of PVE performed for biliary cancers, showed that the patients with an ICGK of the future liver remnant (FLR ICGK) of less than 0.05 had a significantly higher postoperative mortality rate compared to the patients with an FLR ICGKvalue of more than 0.05[28] (Fig. 2). This is a simple and reliable method to evaluate the function of the future liver remnant.

Galactosyl human serum albumin scintigraphy

99 mTc Diethylenetriaminepentaacetic acid galactosyl human serum albumin (99mTc-GSA) liver dynamic single-photon emission tomography for the preoperative assessment of residual liver function before hepatectomy is another useful method to assess the future liver remnant function.[54] Scintigraphy with 99mTc-GSA causes specific binding to viable hepatocytes and serves as an index of liver function. The nonembolized lobe not only increases in volume but also shows increased 99mTc-GSA uptake for the first week after PVE.[15] Postoperative liver failure was observed more often in patients with a significantly smaller 99mTc-GSA uptake. The benefit of this test is the ability to differentiate the functions of the embolized lobe and the nonembolized lobe. Kubo et al.[55] reported that the average increase in the receptor index of the nonembolized lobe was around 30%, even though the average volume change was less than 10% of the total liver. In contrast, the average decrease in the receptor index of the embolized lobe was around 20%. Nishiguchi et al.[56] showed similar results when analyzing cholangiocarcinoma patients (37% increase in the nonembolized lobe; 23% decrease in the embolized lobe). These results indicate that the extent of functional increase in the future liver remnant surpasses the extent of volume increase. Interestingly, similar results were observed in the study of Uesaka et al.,[57] who compared biliary ICG excretion in the embolized lobe and the nonembolized lobe, using a separately inserted percutaneous transhepatic biliary drainage (PTBD) catheter. In their study, the biliary ICG excretion in the nonembolized lobe, as a percentage of the whole-liver excretion, showed a mean increase of 20.1%, whereas the percentage of nonembolized lobar volume to the total liver volume increased by only 8.3% after PVE. Therefore, the function of the future liver remnant should not be estimated simply from its volume.

Contribution of PVE to improvement of postoperative outcome

Has PVE contributed to the improvement of postoperative outcome? As mentioned above, there is no randomized controlled clinical study of the effectiveness of PVE, and this issue is still debatable. However, many reports have shown the beneficial effects of PVE on the postoperative outcome of major hepatectomy.[28,58,59] At our institution, the incidence of postoperative hepatic failure following major hepatectomy decreased from 33.3% to 23.8% after we started the application of PVE. Concomitantly, the mortality rate after major hepatectomy for biliary cancer, including gallbladder cancer and cholangiocarcinoma, decreased from 21.9% to 9.5%. In the most recent period (2001 to the present), the mortality rate has been only 1.6%. Because the benefit of PVE is clear, and the risk for patients with a small future liver remnant is devastating, it is unethical to conduct a randomized control study.[60] From the evidence of a retrospective clinical study, there was no perioperative mortality and no statistically significant difference in the incidence of perioperative complications between those who did and those who did not undergo PVE.[8] These results suggest that at least PVE is not a harmful procedure. Nonetheless, we should not ignore the side effects of PVE, which may reduce the pool of candidates for surgery. These negative aspects are discussed below.

Potential problems with PVE

Generally, PVE is considered to be a safe procedure. There are minor side effects such as mild abdominal pain, low-grade fever,[9] and nausea and vomiting.[7] The levels of aspartate transaminase (AST), alanine transaminase (ALT), and total bilirubin may also increase after PVE, but the extent of the increase is moderate and values usually return to the preoperative levels within 1 week.[61] Although reports showing critical side effects of PVE are not many, we must be aware of the risks associated with the PVE procedure.

The incidence of unfavorable side effects caused by PVE varies among different reports.[28,62] Di Stefano and colleagues[62] retrospectively assessed adverse events after PVE in 188 patients, including those with cholangiocarcinoma, hepatocellular carcinoma, and colorectal metastasis. With N-butyl cyanoacrylate mixed with iodized oil as the main embolic agent, complications occurred in 24 (12.8%) of the 188 patients. The complications included thrombosis of the portal vein feeding the future remnant liver, migration of emboli in the portal vein feeding the future remnant liver, hemoperitoneum, hemobilia, subcapsular hematoma, and liver failure. Furthermore, in about 10% of the patients, liver resections were cancelled due to cancer progression, insufficient hypertrophy of the nonembolized liver, and complete portal thrombosis. Complications after PVE were also analyzed by Kodama et al.[63] Complications occurred in 7 of 47 procedures (14.9%); the complications included pneumothorax, subcapsular hematoma, arterial puncture, pseudoaneurysm, hemobilia, subcapsular hematoma, and portal vein thrombosis in the nonembolized branch, although no patient died of complications.

We have an experience with extensive portal and mesenteric embolization after PVE carried out in a patient with protein S deficiency.[64] Acute embolization of a major vessel may have triggered a coagulation cascade in this patient. Although the routine evaluation of a hypercoagulable state is not practical, this should be done at least for those patients in the high-risk group.[64] The approach to the embolized portal vein should be from the ipsilateral side if possible, to minimize damage in the nonembolized lobe.[30]

If the embolic material migrates to an unexpected portal branch and embolizes the future liver remnant, severe deterioration in hepatic function will occur. Also, we cannot expect sufficient liver volume increase in such a condition, and the patient may not be able to undergo subsequent hepatectomy.[41]

Tumor progression may be accelerated by circulating growth factors released in response to PVE.[65] In patients with highly advanced cancer, this may accelerate an advance of the clinical stage of the cancer and render the patients inoperable.

Our portal vein embolization procedure

Through our experience of more than 240 cases of PVE carried out for biliary cancer, with zero mortality and very low morbidity, we have developed our own "gold standard" for PVE. When the patients have obstructive jaundice, we aggressively drain the obstructed bile duct, either by PTBD or endoscopic nasal biliary drainage (ENBD) to relieve these symptoms. The externally drained bile is replaced either by oral intake or through a nasoduodenal tube as far as possible.[19] Portal vein embolization is applied for patients with a future liver remnant of less than 40%. The approach for PVE is basically from the ipsilateral side. Initially, we used fibrin glue as an embolic material; however, we changed to absolute ethanol and embolization coils (because the Prefectural Insurance System prohibited the use of fibrin glue because of its high price). Two to three weeks after PVE, CT volumetry and an ICG test are performed to re-evaluate the future liver remnant function. If the patients cannot meet the criterion of future liver

remnant function, transcatheter arterial embolization (TAE) or biliary ablation is considered to further enhance atrophy of the embolized lobe and hypertrophy of the nonembolized lobe.

Through the above-mentioned protocol, we have successfully improved the postoperative outcome of extended hepatectomy for hilar cholangiocarcinoma. Nonetheless, we have to further pursue better indication criteria, more suitable techniques, and the more accurate evaluation of future liver remnant function to improve the surgical outcome of hilar cholangiocarcinoma.

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