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REVIEW

# Indications, limitations and maneuvers to enable extended hepatectomy: Current trends

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## Abstract

The liver is a solid organ with a wide variety of primary benign or malignant tumors as well as metastatic lesions. Surgical resection of these tumors remains the only curative modality. Several limitations, however, do not allow the performance of these operations. This review evaluates the indications and limitations regarding these extended hepatic resections, as well as describing all the manipulations that increase the candidates for such operations. A thorough review of the literature was performed in order to define indications for extended hepatectomy, as well as to present all methods that contribute to increasing the volume of the future remnant liver. The role of portal vein ligation, portal vein embolization, two-stage hepatectomy, and *in situ* liver transection are evaluated in the setting of indications and results. Extended hepatectomies are a necessity due to oncological reasons. All methods developed in order to increase the volume of the remnant liver are safe and efficient. *in situ* liver transection is a novel and revolutionary two-step procedure for extended hepatic resections. Further clinical studies are required to estimate long-term results and the oncological basis of this technique.



**Key words:** Extended hepatectomy; Portal vein ligation; Remnant liver volume

**Core tip:** All methods developed in order to increase the volume of the remnant liver are safe and efficient. *in situ* liver transection is a novel and revolutionary two-step procedure for extended hepatic resections. Further clinical studies are required to estimate long-term results and the oncological basis of this technique.

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## INTRODUCTION

Complete resection of liver lesions remains the only potential curative treatment modality for primary or metastatic liver disease. Major liver resections are required both for malignant [hepatocellular carcinoma (HCC), cholangiocarcionoma, and other rare types of malignant tumors] as well as benign primary liver tumors (giant haemangiomas, and adenomas) in order to achieve optimal therapeutic results. A multicenter analysis of 1115 patients with HCC, 539 of whom underwent major resections, concludes that expansion of surgical indications in order to perform major hepatectomies is justified[1]. In recent years, there has been a major effort in managing colorectal liver metastases by performing extended hepatectomies.

Major liver resections are associated with an increased risk of postoperative morbidity and mortality, mainly related to postoperative liver failure. The risk for postoperative liver failure depends on the quality and quantity of the liver parenchyma spared by resection, which is called remnant liver volume (RLV)[2]. The quantity of RLV depends on the quality of liver tissue. In the case of a healthy liver, we can expand the resection up to a RLV of 25% or equal to 0.5% of the patient's body weight. Impaired liver function due to liver disease such as cirrhosis requires a larger RLV. This is a serious issue in cases of preoperative chemotherapy treatment, because chemotherapeutical agents have liver cytotoxic properties, or in cases of colorectal liver metastases where the range of extended hepatectomy is restricted in comparison to normal liver tissue[3].

Progress in surgical techniques and imaging technology, as well as the achievements of basic science in every day clinical practice, has resulted in major and extended hepatic resections with acceptable mortality and morbidity rates, in order to achieve curative treatment for both benign and malignant liver disease. This review discusses liver manipulation techniques that are used to perform extended hepatectomies in a safe manner.

## INDICATIONS AND LIMITATIONS

Several studies have reported the beneficial effects of surgery for patients with HCC, even with large or multinodular tumors. Advances in the surgical management of HCC have expanded the indications for curative hepatectomy, including more extensive liver resections[4-6]. As described above, a multicenter analysis of 1115 patients with HCC revealed similar 90-d postoperative mortality rates for patients undergoing right hepatectomy and extended hepatectomy, whereas 5-year overall survival did not differ significantly between these groups[1]. Furthermore, another observational multicenter survey that retrospectively investigated the trend in large-volume hepatobiliary centers for treatment of HCC showed that surgery is the most favorable treatment modality in eastern and western countries, even for multinodular, large tumors with macrovascular invasion. The multivariate analysis, however, identified tumor size and macrovascular invasion as independent negative prognostic factors for overall survival[7].

The second most common malignancy among primary liver tumors after HCC is cholangiocarcinoma (CCC), with the highest incidence in Northeast Thailand, while in Europe and the United States it remains a rare tumor[8-10]. CCC is classified into three types according to its location: intrahepatic, perihilar and distal. Surgical excision of the tumor with clear surgical margins remains the gold standard, whereas major hepatectomies are required for the intrahepatic or perihilar location of the tumor, although 5-year survival remains poor[11]. An article reviewing the pertinent literature concludes that adequate extended surgical resection with adjuvant chemotherapy provides the best survival rate, while elevated serum carcinoembryonic antigen with lymph node metastases associated with advanced disease are negative prognostic factors[12]. Furthermore, due to the infiltrative tendency of CCC, the achievement of negative margins, although significant for survival, remains a challenging technical issue that requires extended resections. Jonas *et al*[13] have recommend extended resections to increase the rate of curative resections. In their series, 60% of patients underwent extended liver resections and R0 resections were possible in 71% of the total study group[14].

In addition to HCC and CCC, which are the two major representatives of primary liver malignancies, a variety of other malignant liver tumors need extended hepatectomy as a curative treatment strategy. This group of malignancies includes liver sarcomas, fibrolamellar tumors, histiocytomas, hepatoblastomas and other rare tumors that have been described as case series or case reports in the literature[15-18]. Hepatic epithelioid hemangioendothelioma is an entity that originates from the vascular endothelium and has intermediate characteristics between hemangioma and hemangiosarcoma. Due to its large size and often diffuse presentation the optimal therapeutic approach includes extended liver resections or liver transplantation[19,20]. Furthermore, except for these malignant or marginal tumors, regarding their malignant behavior, tumors, other benign liver tumors such hemangiomas, hepatic adenomas or focal nodular hyperplasia may present with a large size. In this cases extended hepatectomies are performed in order to confirm a questionable diagnosis or to provide relief from symptoms in the case of large or bleeding adenomas or giant hemangiomas (Kasabach-Meritt syndrome)[21-25].

In recent years, the presence of liver metastases was not a contraindication for surgery. On the contrary, resection of the primary tumor and metastatic liver lesions is the optimal therapeutic approach. The first example is the resectability of colorectal liver metastases, which has reached a rate of > 40% with the introduction of new chemotherapeutic agents and drug combinations. The diffuse nature of the metastases or their large size require extended liver resections in order to achieve no residual disease, which in combination with adjuvant treatment results in 5-year survival rate of 35%-50% for selected cases[26-28]. Other candidates for extended hepatectomies due to metastastic disease are patients with liver metastases originating from gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs). A meta-analysis provides evidence supporting the hypothesis that liver resection increases overall survival in patients with GEP-NETs[29]. The studies included in this meta-analysis compared surgical resection with embolization or other nonsurgical treatments. Liver transplantation, however, was compared only in one study and therefore this alternative could not be included in the meta-analysis. Liver resection for metastatic disease has also increased the survival rates of some other malignancies in selected cases, for example, eye melanoma and breast cancer[30,31].

As described above, the role of extended hepatectomy is crucial in a variety of primary or metastatic liver tumors, for therapeutic as well as diagnostic reasons. Extended hepatectomy is a challenging procedure, associated with a high rate of complications. More than four segments of the liver are resected and the remaining liver parenchyma accounts for only 20%-30% of the total liver volume. The estimated mortality rate after extended hepatectomy in high-volume centers is thought to be 6%-8%[32,33]. Several clinical and experimental studies have been performed in order to evaluate the minimum RLV needed for safe hepatectomy. In patients with normal liver function, an estimated RLV > 25%-40% has been proposed as adequate for major hepatectomy[34-36]. Several high-volume centers, however, have extended the criteria for major hepatic resections up to an RLV of 20% of total liver volume[37].

On the contrary, chronic underlying liver disease such as hepatitis B and C, alcoholic liver disease or further disorders leading to liver parenchyma damage ranging from fibrosis to cirrhosis, limit the possibility of extended hepatectomy and reduce the number of patients that benefit from these operations. Improvements in surgical technique and perioperative care have reduced the complications and mortality rate, but at the same time, careful patient selection is needed in order to achieve optimal results[38,39].

Liver function assessment is important to ensure safe surgical procedures in patients with hepatocellular disease. The liver influences a wide variety of functions, including protein synthesis and metabolic, immune and storage functions, no single parameter is sufficient to address adequately all of these functions. Therefore, there are scoring systems, functional tests, plasma parameters and imaging modalities used to evaluate liver function. The Child-Pugh scoring system is the gold standard for liver disease assessment. In another modification, the Child-Campbell system, a scoring system similar to that of Child-Pugh is used, where nutritional status is considered. The liver damage grading system recommended by the Liver Cancer Study Group of Japan is also useful. Another liver function score is the model for end-stage liver disease. The indocyanine green clearance test is widely accepted, but other assessments have not been used routinely for clinical evaluations (monoethylglycinexylidide test, galactose elimination capacity test and $^{13}$C-liver-function breath tests). The levels of plasma proteins, including albumin, prealbumin, retinol binding protein, apolipoprotein, coagulation factors and antithrombin Ⅲ, represent the liver productivity. Liver fibrotic markers such as the aspartate aminotransferase-to-platelet ratio index, collagens and hyaluronic acid also correlate with liver function. Finally, imaging modalities such as $^{99m}$Tc-galactosyl serum albumin scintigraphy, $^{99m}$Tc-mebrofenin hepatobiliary scintigraphy and transient elastography are also available, but future studies are needed to validate their clinical efficacy[40].

Child-Pugh stage C is considered as an absolute contraindication for liver resection. Yang *et al*[38] evaluated the mortality and morbidity in 305 patients with liver cirrhosis or fibrosis who underwent major hepatic resections. Overall morbidity rate was 37% and overall mortality rate was 2.8%. Low platelet count and increased intraoperative blood loss were recognized as independent factors related to high morbidity rates in patients with underlying liver disease who undergo hepatic resections. The authors conclude that careful preoperative evaluation in combination with reduced intraoperative blood loss could offer the opportunity of safe hepatic resection in a selective group of patients with underlying liver disease[38]. This conclusion is in accordance with other similar studies in the literature[41].

Limitations regarding major hepatectomies exist in the cases of preoperative chemotherapy, mainly for metastatic liver lesions such as colorectal liver metastases. Chemotherapeutic agents used in oncology have some severe effects on the liver. Histological lesions are known to occur on liver parenchyma after chemotherapy with the type of lesion being specific for the agent used. Sinusoidal obstructive syndrome is characterized by erythrocytic congestion and can be accompanied by perisinusoidal fibrosis and fibrotic venous occlusion. A further adverse effect of chemotherapy on the liver is associated with vascular lesions such as hemorrhagic centrilolular necrosis. Both these adverse effects are associated with impaired liver regeneration and bleeding complications during hepatectomy, so that the extent of liver resection as well as the time between the administration of chemotherapy and surgery must be carefully selected[42-44].

## PORTAL VEIN EMBOLIZATION

The most common method used in order to overcome the above-mentioned limitations and enlarge the RLV is portal vein embolization (PVE). In 1920, Rous and Larimore first reported occlusion of one portal branch[45]. Ligation of one branch of the portal vein in rabbits led to atrophy of the ipsilateral lobe and hypertrophy of the contralateral. In humans this phenomenon was first described in patients with hilar CCC, which induced portal vein occlusion by tumor invasion[46]. It was Makuuchi *et al*[47] who actually first performed this novel approach for routinely inducing atrophy and contralateral hypertrophy in patients with cholestatic liver disease, chronic hepatitis or cirrhosis. In order to increase the number of patients amenable to curative hepatic resection his team performed preoperative PVE in patients with hilar bile duct carcinomas before major hepatectomies. Since then several investigators have extended the indications of portal vein occlusion for patients with HCC or metastatic liver tumors[48,49].

A number of materials have been used in order to achieve maximal effect with gelatin sponge or *n*-butylcyanoacrylate being the most commonly used[50]. The hypertrophy response and the atrophy of the embolized lobe are estimated by mathematical types on the basis of computer tomography, while the majority of review articles have concluded that the mean growth of the estimated remnant liver is nearly 40% and the part of the liver planned to be resected is reduced by nearly 20%[51,52]. The most common complications of portal vein embolization (total complication rate of 0.4%) are cholangitis, abscess formation, and portal or porto-mesenteric thrombosis[53]. There is no consensus about the ideal waiting between PVE and resection, but the shorter the time between these procedures, the less the chance of spreading the disease in the case of metastatic lesions. The majority of patients undergo successful liver resection after embolization and only 3% have no progress in liver hypertrophy. One to twenty patients develop liver failure after hepatectomy. The basic cause of cancelling liver resection after PVE is the presence of peritoneal or distal metastases and not inadequate hypertrophy. Patients who received chemotherapy between PVE and hepatectomy seem to have increased atrophy and a similar hypertrophy response, except for those who receive platin agents. Fibrotic and cirrhotic livers have poor results compared to those without an underlying liver disease. Nevertheless, PVE is a useful method for gaining liver hypertrophy in cirrhotic patients, so that these patients may become candidates for major surgery[54-56].

In cases of multiple or metastatic liver lesions, the principle of PVE is surgically extended. In this case there are two operations performed. During the first operation, the lesions in the lobe with less disease are removed and the contralateral branch of the portal vein is ligated, while in the second operation the atrophic liver lobe is resected. This procedure is most commonly performed for colorectal liver metastases. There is a debate in the literature regarding the preferred method for portal vein occlusion. The majority of the studies conclude that PVE shows better results. Broering *et al*[3] have assessed the efficacy of right PVE *vs* portal vein ligation for induction of hypertrophy of the left lateral liver lobe before extended right hepatectomy. They have concluded that PVE results in a significantly more efficient increase in liver volume and shorter hospital stay[57]. On the other hand, Aussilhou *et al*[58] performed a retrospective comparison of the efficacy of PVE and portal vein ligation in the setting of gaining liver hypertrophy. The authors have concluded that both methods result in comparable results and that during the first laparotomy of a two-stage liver resection, portal vein ligation can be efficiently and safely performed.

## *IN SITU* LIVER TRANSECTION

Several methods and combinations in order to obtain sufficient volume of the future remnant liver and increase the number of patients amenable to profit by major hepatic resections have been described above. Nevertheless, insufficient hypertrophy of the future liver remnant or disease progression may cancel curative liver resection in a significant percentage of these patients[59]. In order to overcome this obstacle, a combination of portal vein ligation and *in situ* liver transection, in the setting of a two-stage hepatectomy, has been described. The initial idea for the use of *in situ* liver transection as a tool to increase the volume of the remnant liver arose when intraoperative frozen section analysis in a patient scheduled for right hepatectomy revealed infiltration of segment Ⅳ, creating an indication for extended right hepatectomy. This operation, however, led to postoperative liver failure due to an estimated small volume of the segments Ⅱ and Ⅲ, according to preoperative imaging. At this point, the decision was made to transect the liver on the right side of the falciform ligament. During this procedure all portal branches to the right liver as well as segments Ⅰ and Ⅳ were dissected and ligated, while the transected liver retained its arterial blood support. Completion of the surgery was performed a few days later by dividing the bile duct, the arterial supply and the right and middle hepatic veins[60-63].

This initial procedure was modified, so that de Santibanes and Clavien proposed the acronym Associating Liver Partition and Portal vein ligation for Staged hepatectomy to include all these surgical alternatives[64]. The feasibility and usefulness of this new strategy has still to be proven. Associating liver partition and portal vein ligation for a staged hepatectomy represents a revolutionary and promising new two-step technique in liver surgery. This technique is now used in several high-volume liver surgery centers worldwide, however, the results of larger studies are expected to resolve questions raised such as optimal selection of patients, impact of tumor biology and long-term survival. Furthermore, there is always room for surgical issues to be improved so that this technique takes its place in the treatment of patients with large or multinodular primary or metastatic liver tumors.

## CONCLUSION

The liver remains prone to the development of a wide variety of primary or metastatic tumors, large and diffuse or multinodular, while the optimal strategy with curative intent remains surgical resection. Extended hepatectomies for large liver tumors are a necessity for oncological reasons, according to several studies. These operations, however, cannot always be performed due to a small RLV that leads to postoperative liver failure. Several methods, such as PVE, portal vein ligation and two-stage hepatectomy, have been developed in order to increase the future RLV. Combination of these methods has been proposed, and a novel revolutionary two-step liver resection has been developed, where portal vein ligation and *in situ* liver transection are performed during first laparotomy, while the final operation is completed a few days later. Further studies are needed to estimate the long-term results.

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