Ex situ Liver Resection for Unresectable Tumors

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Key Words

Ex situ liver resection • Unresectable tumors • Key techniques

Abstract

Primary and secondary liver tumors are among the most common tumors in humans. Two surgical approaches may be used to address these tumors: liver transplantation and liver resection. However, some tumors cannot be treated by conventional techniques or liver transplantation due to poor intraoperative exposure, limitations of indication standards, and/or other complex factors. To overcome these problems, ex situ liver resection has been introduced and used successfully in many cases. This technique is based primarily on liver transplantation and perfusion with preservation solution under hypothermic conditions. The major indications for ex situ liver resection are liver tumors that are unresectable or in which resection using conventional surgical techniques is very dangerous due to the close proximity to or involvement of the venous confluence and/or the main hepatic veins. However, high mortality and morbidity rates limit the use of this technique despite the efforts of many surgeons to improve their skills. Patient selection is of utmost importance to achieve a good outcome. Emphasis on basic research (e.g.

on reperfusion injury) and the development of key techniques should improve the safety of the procedure and reduce mortality in the future.

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Introduction

Some primary and secondary liver tumors cannot be resected using a conventional approach due to their location or the involvement of the inferior vena cava (IVC) and/or main vessels of the liver. In such situations, ex situ surgery, first reported by Pichlmayr et al. [1] in 1990, may be an alternative. Many medical centers have reported the successful use of this technique in the past 20 years, but such operations remain uncommon due to their technical complexity and the high rates of perioperative morbidity and mortality. However, as an important extension of surgical treatment alternatives, ex situ resection has advantages over conventional approaches or cadaveric liver transplantation. Many surgeons have made great efforts to improve their proficiency in the skills required for this technique, including veno-venous bypass, revascularization, and reimplantation. The successful use of these procedures can improve outcomes and simplify ex

situ resection as demonstrated by several case reports [2, 3]. The aim of this study was to systematically review surgeons' experience and the development of key techniques in ex situ liver resection.

Surgical Treatment of Liver Malignancies

Primary liver malignancies, such as hepatocellular carcinoma (HCC) and cholangiocarcinoma, and metastatic liver tumors from other organs are among the most common tumors in humans. Patients with liver malignancies have a median survival time of <12 months without treatment [4]. The main treatment for such tumors involves chemotherapy and surgery [5]. Two surgical approaches may be used to address these malignancies: liver transplantation and liver resection. The benefits of liver transplantation include the simple surgical concept and the maturity of the technique. However, its application may be limited by several factors, including donor shortages and indication standards, in patients with liver malignancies. Furthermore, the high rate of recurrence resulting from postoperative immunosuppression also influences treatment outcomes. Thus, liver resection is currently considered the first option for the treatment of liver malignancies [5]. The detailed study of liver anatomy and physiology has led to the development of new clinical applications and has ensured the security of surgical resection, including the control of liver blood flow and techniques for liver parenchyma resection, which have become conventional in liver resection procedures. The main factor influencing outcomes is the success of complete (R_0) resection; the median 5-year survival rate after liver resection is 30–50% when R_0 is achieved, but only 7% in cases of $R_{1/2}$ resection [6].

However, many liver tumors cannot be resected using conventional techniques due to their enormous size or complex location. Large tumors allow insufficient space for operation; for centrally located tumors with invasion of the venous outflow tract and/or the retrohepatic vena cava, the adoption of a conventional curative approach is often impossible or very dangerous. These types of tumor are usually termed unresectable. In fact, they would be resectable if they were more accessible or if there were adequate time to address the complex situation while performing R_0 resection and reconstructing the main liver vasculature. However, the liver can safely tolerate total vascular occlusion for only about 60–90 min [7], which precludes the performance of a complex liver tumor resection using conventional methods. Lengthy periods of

total vascular occlusion will lead to severe hepatic ischemia, hemodynamic disturbances, and potential renal injury [8], which may be fatal. The success or failure of the operation thus depends on the resolution of intraoperative exposure and the reduction of liver damage.

In 1990, Pichlmayr et al. [1] reported a new method of ex situ (bench procedure) liver resection to resolve these issues. In this method, the whole liver is removed and perfused with a cold preservation solution. Hepatic resection is then performed on the back table and the remnant liver is reimplanted orthotopically. Veno-venous bypass, hypothermic perfusion, hepatic resection, vascular reconstruction, and remnant liver reimplantation are the key techniques in this procedure [9]. The advantages of ex situ over conventional resection include less blood loss, optimal access to all sites, and prolonged time for dissection and vascular reconstruction; it also avoids the problem of donor shortages for liver transplantation. Since the introduction of this technique, several groups have applied similar approaches to liver resection [10–12]. Hannoun et al. [13] and Sauvanet et al. [14] refined the technical details of the procedure and developed the ante situm technique of liver resection to increase its safety. The ante situm technique is similar to the ex situ procedure, but retains the important structure of the liver hilum and involves the division of only the three hepatic veins or a segment of the IVC before the liver is perfused with cold preservation solution through the portal vein. The advantage of the ante situm over the ex situ approach is that it does not require biliary and hepatic arterial anastomoses, thereby reducing ischemia time and potential anastomotic complications. It does not, however, provide the good exposure that is obtained with the complete ex vivo approach. An ex situ procedure is necessary in some cases, such as tumor invasion of the hilar vessels requiring the division of the entire hilar structure. Although reported cases employing the ex situ technique are rare, good results have been achieved. Oldhafer et al. [15] reported a median survival time of 21 months in a series of 6 patients who underwent ex vivo resection for colorectal metastases; 1 patient who underwent ex situ resection for HCC was alive and disease free at 7 years after surgery. Moreover, the ex situ technique has been curative in some patients with unresectable tumors [16, 17]. The technical experience required for ex situ or ante situm resection is derived from liver transplantation, and some problems of these techniques, such as long operation time and remnant liver protection, will be resolved with developments in modern liver transplantation. However, ex situ resection is an exceptional and unique liver resection proce-

ture that requires the investigation of technical details and potential indications, which can provide guidance for surgeons and increase the safety of its use.

Technical Aspects of ex situ Resection

Veno-venous bypass, hypothermic perfusion, hepatic resection, vascular reconstruction, and remnant liver reimplantation are the key techniques used in ex situ liver resection. Due to the longer operation time in this procedure, it is essential to maintain the stability of blood dynamics and avoid venous congestion; an effective veno-venous bypass should thus be used. The same technique is applied as in liver transplantation, with bypass from the portal and left femoral veins to the left axillary or jugular vein using heparin-coated shunts and a roller pump [18]. Yang et al. [2] reported an alternate technique to avoid adjuvant incisions and other shortcomings or shortages of conventional veno-venous bypass, in which the IVC was replaced with an artificial blood vessel, and a temporary veno-venous bypass was then performed after liver removal by anatomizing the portal vein and the supra- and infrahepatic venae cavae, respectively. In some cases without IVC involvement, a veno-venous bypass may not be necessary. Hemming et al. [3] reported another method involving a temporary veno-venous bypass and portacaval shunt, in which the IVC was preserved. Based on this reported experience, we recently performed an ex situ resection without a veno-venous bypass. We only ligatured the hepatocaval confluence while preserving the entire IVC in situ, then used a temporary portacaval shunt to decompress the portal bed during the anhepatic phase of the procedure. This technique is not appropriate in all cases; an effective veno-venous bypass is generally necessary.

Hypothermic perfusion is initiated through the portal vein after the hepatic artery and the supra- and infrahepatic venae cavae have been clamped. University of Wisconsin (4 °C) and histidine-tryptophan-ketoglutarate solutions are the best choices, although some European centers prefer to use histidine-tryptophan-ketoglutarate solutions exclusively due to its low viscosity, which allows very rapid and homogeneous perfusion of the liver, and its low potassium content, which reduces the risk of cardiac complications after reperfusion [9]. Local surface cooling should be performed by placing the liver in cold preservation solution and covering it with ice-cold towels.

An experienced surgeon can resect any liver portion without difficulty in an extracorporeal liver with a bloodless surgical field. All possibly infiltrated vessels and bile

ducts should be resected, and the stumps of these sites should be ligatured or sutured carefully to minimize postoperative complications. A Cavitron Ultrasonic Surgical Aspirator (Model 200T; Valleylab, Boulder, Colo., USA) can help identify and ligature the intrahepatic duct precisely, especially in critical areas. In this way, the ex situ resection technique facilitates R₀ resection.

Prior to vascular reconstruction, protection of the normal tube is essential due to the short vasculature in the remnant liver; careful operation and meticulous surgical design are thus extremely important. For vascular reconstruction, the adjacent main vessel can be repaired and shaped together with the adjacent main vessels to form a single integrated tube. However, a long venous segment must be resected in many cases due to tumor invasion, especially in the IVC, which increases the difficulty of vascular reconstruction using the intrinsic vasculature. Thus, an alloplastic material (e.g., polytetrafluoroethylene graft) or an autogenous vein graft [12, 19] is required in these cases, although the risk of postoperative graft thrombosis must be considered. Following vascular reconstruction, the main bile duct must also be repaired and shaped.

When all of these steps are completed, perfusion should be repeated to reveal any leakage in the remaining liver, and all potential sources of bleeding should be carefully sutured. The final step in an ex situ resection is the autotransplantation of the remnant liver; the guidelines for this procedure are the same as for cadaveric liver grafting, but, in contrast to allotransplantation, long vessels and patches are unavailable. A meticulous technique is thus of the utmost importance.

Indications for ex situ Liver Resection

The major indications for ex situ liver resection are liver tumors that are unresectable or in which resection using conventional surgical techniques is very dangerous due to the close proximity to or involvement of the venous confluence and/or the main hepatic veins. Ex situ resection can be applied to all types of liver tumor, including primary or secondary tumors and some huge benign tumors. In addition to intrahepatic tumors, extrahepatic tumors affecting the hepatic venae cavae or veins might also be candidates for ex situ resection; such tumors include renal carcinomas, extra-adrenal pheochromocytomas [20] and leiomyosarcomas of the vena cava [21]. Severe liver trauma, especially with injury of the IVC and/or hepatic vein, may be another indication for this approach. Boggi et al. [22] applied the ex situ technique to

Table 1. Published reports of ex situ liver resection and liver autotransplantation

Report	Year	Cases, n	Tumor type	In-hospital mortality, n
Yanaga et al. [23]	1993	2	colorectal metastases	0
Yagyu et al. [24]	1994	1	hepatocellular carcinoma	0
Hamazaki et al. [25]	1994	1	colorectal metastasis	1
Forni and Meriggi [26]	1995	3	colorectal metastases	1
Shimahara et al. [27]	1998	2	hepatocellular carcinoma	1
Oldhafer et al. [15]	2000	22	colorectal metastases (n = 9), leiomyosarcoma (n = 3), hepatocellular carcinoma (n = 2), cholangiocellular carcinoma (n = 2), Klatskin tumors (n = 4), focal nodular hyperplasia (n = 2)	6
Lodge et al. [12]	2000	4	colorectal metastases	1
Lechaux et al. [28]	2002	1	hepatocellular carcinoma	
Chui et al. [11]	2003	1	hilar cholangiocarcinoma	0
Gruttadauria et al. [16]	2005	2	colorectal metastases	0
Fusai et al. [21]	2006	1	extra-adrenal pheochromocytoma	0
Boggi et al. [22]	2006	1	liver trauma	1
Hemming and Cattral [29]; Hemming et al. [3, 30]	1999, 2006	3	colorectal metastases	0
Ikegami et al. [17]	2008	1	hemangiomas	0
Sugimachi et al. [31]	2010	1	hepatocellular carcinoma	0
Reports from China [2, 32, 33]	2005–2011	5	hepatocellular carcinoma (n = 2), hemangioma (n = 1), cholangiocellular carcinoma (n = 1), hamartoma (n = 1)	0

repair the vasculature and achieve liver autotransplantation in a patient with severe liver trauma; although that patient died of respiratory failure, ex situ resection is an efficient measure in such an emergency situation. Chui et al. [11] performed an advanced hilar cholangiocarcinoma resection with an ex situ hepatic resection. In their opinion, ex situ liver resection and partial liver autotransplantation offered a realistic approach to securing clear resection margins while protecting the liver from warm ischemic damage. In theory, ex situ hepatic resection is thus the best treatment option for lesions affecting the main vessels of the liver that cannot be resected using conventional surgical techniques.

However, as an invasive procedure, ex situ hepatic resection is associated with high (about 30%) morbidity and mortality rates [9]; the main cause of perioperative mor-

talidity is liver failure. Although liver failure may be attributed to many causes, preexisting impaired liver function remains a main factor and ex situ resection should be avoided in such patients. In addition, the use of this technique is risky in patients with cholestatic liver malfunction; preoperative biliary drainage of the liver should be considered to improve liver function prior to resection [18], but the safe target bilirubin level remains undefined for these rare cases.

Review of the Literature

To understand the current clinical application and development of key techniques of ex situ hepatic resection worldwide, we reviewed the English- and Chinese-lan-

Table 2. Ex situ operation and follow-up data

Report	Number of removed liver segments	Total operating time, h	Anhepatic phase, min	Complications	Postoperative follow-up
Yanaga et al. [23]	all >2	mean 14.5	mean 232	none	tumor recurrence (n = 1)
Yagyū et al. [24]	6	16	328	bleeding	uneventful
Hamazaki et al. [25]	4	13	184	bleeding, liver failure	na
Forni and Meriggi [26]	3	14	243	bleeding	na
Shimahara et al. [27]	all >2	mean 10.4	mean 215	liver failure	uneventful
Oldhafer et al. [15]	17 >2; 5 ≤2	mean 13.5	mean 338	liver failure (n = 6), sepsis (n = 6)	allogenic liver transplantation (n = 4), tumor recurrence (n = 10)
Lodge et al. [12]	all >2	NA	mean 222.5	respiratory and renal failure (n = 1)	tumor recurrence (n = 1)
Lechaux et al. [28]	4	12	330	none	uneventful
Chui et al. [11]	6	15.5	330	large ascites	uneventful
Gruttadauria et al. [16]	all >2	mean 14	mean 240	biliary leakage (n = 1)	uneventful
Fusai et al. [21]	1	7	120	none	uneventful
Boggi et al. [22]	vascular repair only	NA	168	respiratory failure	NA
Hemming and Cattral [29]; Hemming et al. [3, 30]	all >2	NA	mean 225	none	uneventful
Ikegami et al. [17]	6	16	351	portal vein thrombosis	uneventful
Sugimachi et al. [31]	4	19.3	364	none	uneventful
Reports from China [2, 32, 33]	all >2	mean 12.5	mean 270	biliary leakage (n = 2), bleeding (n = 1), pleural effusions (n = 2)	uneventful

NA = Data not available.

guage literature published between January 1988 and December 2011 by searching the PubMed and China National Knowledge Infrastructure (CNKI) databases using the key words ‘extracorporeal hepatic resection’, ‘ex situ (or ex vivo) liver resection’, and ‘liver autotransplantation’. After rejecting review articles and repetitive reports, the relevant literature included 52 cases (mean patient age, 52.3 years), reported in 17 English publications and 3 Chinese publications, and 1 case from our center (table 1). The literature review did not identify any case-control study.

Few reports contained details of liver function status or comorbidities; however, 45 cases were malignancies, such as HCC, cholangiocellular carcinoma, leiomyosar-

coma and colorectal carcinoma. Large hemangiomas were predominant among 6 benign lesions, which also included focal nodular hyperplasia, hamartoma, and liver trauma. Colorectal metastasis was most common among 24 liver tumors.

Table 2 shows the operation details and follow-up data for the identified cases of ex situ operation. Between 1988 and 1998, Oldhafer et al. [15] performed 54 extracorporeal liver resections in 52 patients, of whom 22 underwent ex situ liver resection. This series is the largest reported to date. All patients in the study sample but 1 underwent liver segment resection, primarily of the fourth segment, followed by the first and eighth segments. All of these patients also underwent vascular reconstruction or repair

Table 3. Data for 11 cases of death in association with the ex situ procedure

Number	Age, years/ sex	Liver lesion	Operation time, h	Anhepatic phase, min	Removed liver segments	Cause of death
1	63/M	metastasis from colonic carcinoma	13	184	I–V	bleeding
2	54/M	metastasis from colonic carcinoma	14	243	II–V	bleeding
3	47/M	hepatocellular carcinoma	NA	225	II–IV, V, VIII	liver failure
4	58/M	metastasis from colonic carcinoma	11	420	I/IV–VIII	liver failure, sepsis
5	48/F	Klatskin tumor	16	180	I–V	liver failure, sepsis
6	62/M	Klatskin tumor	18	540	hilar resection	liver failure, sepsis
7	62/M	Klatskin tumor	18	540	hilar resection	liver failure, sepsis
8	55/F	Klatskin tumor	13	240	IV–VIII	liver failure
9	52/M	metastasis from colonic carcinoma	12	300	I, IV	pneumonia
10	42/F	metastasis from colonic carcinoma	NA	240	II, IV–VIII	respiratory and renal failure
11	16/M	liver trauma	NA	168	vascular repair only	severe respiratory distress
NA = Data not available.						

using alloplastic material or autogenous vein grafts. The operating time often exceeded 10 h (range, 7–21 h), although some reports did not provide this information. The duration of the anhepatic period during ex situ liver surgery was also very long (up to 450 min). The in-hospital mortality rate was high (22.5%) due to various infrequent but severe complications.

Table 3 provides data for 11 patients who died after ex situ procedures. Liver failure ($n = 6$) was the main cause of in-hospital mortality, followed by pulmonary embolism, postoperative bleeding and respiratory failure. Oldhafer et al. [15] investigated the reasons for liver transplantation after ex situ liver surgery, and found that 4 patients experienced liver failure and 3 patients had postoperative bleeding.

Most existing reports have focused on the technical feasibility of ex situ surgery; although many have also provided follow-up data, the reporting and analysis of long-term results after ex situ surgery remain insufficient. Oldhafer et al. [15] reported the outcomes of 22 patients; those with liver metastasis from colonic carcinoma

had a median survival time of 21 months, and the 2 patients in the series with focal nodular hyperplasias remained alive at 5 and 9 years after ex situ liver resection. Hemming et al. [30] reported that 1 patient who underwent ex vivo resection for HCC was alive and disease free at 7 years after surgery.

Some case reports discussed the use of improved techniques. Hemming et al. [3] and our center preserved the entire IVC and built a temporary portacaval shunt in 1 patient each, which abrogated the need for veno-venous bypass. Yang et al. [2] and Mo et al. [33] replaced the IVC with a 20-mm synthetic interposition tube for IVC transfusion and used a temporary portacaval shunt, thereby avoiding an extracorporeal veno-venous bypass. In China, ex situ liver resection is rarely performed; Wen et al. [32] reported its first use in 4 patients with intrahepatic cholangiocarcinoma in 2006, none of whom died perioperatively.

Discussion

Surgical resection is the principal treatment for hepatic tumors, and resectioning techniques have improved markedly in recent decades with increased anatomical understanding and the development of methods to protect liver function. Unfortunately, some lesions cannot be treated using conventional techniques due to their complex location or large size. A common example is a tumor involving the suprahepatic IVC or the hepatocaval confluence. The main limiting factors of conventional techniques are the ischemia tolerance of the liver and the accessibility of the tumor. Furthermore, R_0 resection of some malignancies cannot be achieved within the limited time and blood-obscured operative field of conventional procedures, which influences survival outcomes. Liver transplantation may be an appropriate method, but is not possible in most patients due to donor shortages and indication criteria. Penn [34] has also shown that transplantation in general should not be considered in patients with metastatic liver disease, due to a 59% recurrence rate. Another group [35] has shown that patients with intrahepatic cholangiocarcinoma must also be excluded from liver transplantation. Within this context, ex situ liver resection allows the removal of otherwise unresectable tumors and provides a benefit to patients, although it has been performed infrequently. This approach can be used to treat all types of liver tumor, including some extrahepatic tumors [21] and emergency situations [22].

However, ex situ liver resection is associated with a high rate of in-hospital mortality (22.5% in our analysis). The main causes of death are liver failure and sepsis. Ex situ resection is not a routine procedure; it should only be used in select patients with unresectable tumors, and is not appropriate for patients with preoperative impaired liver function and accompanying diseases. Thus, the preoperative assessment of patients is very important, and is similar to that for liver transplantation; any significant cardiac abnormality or even mild renal dysfunction would preclude the use of this technique. The functional reserve of the remnant liver is a major limitation of this procedure that influences surgical outcomes. A variety of methods are available for the evaluation of liver function, including laboratory examinations and imaging studies; patients with positive results should not undergo ex situ resection. Three-dimensional volumetric computed tomography reconstruction is an important preoperative evaluative method to precisely locate liver tumors, determine the invasion range and estimate the remnant liver volume [8]. Indocyanine green clearance (ICGR) is a

quantitative test of liver (and remnant liver) function that should be routine prior to liver resection (recommended index: $\text{ICGR}_{15} < 10\%$) [36], although the results are influenced by other factors, such as hepatic blood flow and jaundice. Child grade does not reflect the reserve liver function accurately. In our opinion, patients with any grade of cirrhosis or compromised liver parenchyma (steatosis/fibrosis) with an inadequate hepatocellular reserve should not be considered suitable for the ex situ procedure. In patients with cholestatic liver malfunction, preoperative biliary drainage of the liver should be considered to improve liver function prior to resection. The safe value of bilirubin is $< 10 \text{ mg/dl}$ [36]. However, no single test can assess liver reserve function accurately, and a combination of assessments must be used. A comprehensive evaluation should also include a general examination and the analysis of all test results.

Considering the high mortality and morbidity rates associated with ex situ procedures, the ante situm technique first described by Hannoun et al. [13] was developed to replace ex situ resection for otherwise unresectable liver tumors. This technique, which has resulted in a significant reduction of morbidity and mortality rates [37], involves the full mobilization of the vena cava from its dorsal attachments, but not from the liver. The biliary and hepatic arteries are not divided, but the procedure is similar in other ways to ex situ resection. It also offers optimal access to the posterior areas and theoretically reduces complications because biliary duct and arterial anastomoses are not required. However, ante situm resection does not provide the good exposure obtained with an ex situ approach. Our analysis of the literature indicated that biliary complications occurred in only a few cases. Therefore, the approach to reducing mortality and mobility should depend on basic research (e.g. on reperfusion injury) and meticulous patient selection. Ex situ liver resection must also be performed by a surgeon who is familiar with advanced techniques in liver resection and liver transplantation, which restricts the procedure to relatively few centers.

The major advantages of using the ex situ procedure in comparison with conventional techniques are the markedly prolonged ischemic tolerance for dissection and vascular reconstruction, and optimal access to tumors in all locations. Compared with liver transplantation, the major advantage is that there is no need for long-term postoperative immunosuppression, which is associated with complications that may include stimulating effects on tumor growth. However, tumor recurrence remains a problem after ex situ procedures. In the series

reported by Oldhafer et al. [15], 10 patients died due to tumor recurrence at 12–36 months postoperatively despite the achievement of R₀ resection; such recurrence has also been described in other reports. We believe that this problem is not related to the procedure, but rather to the need for comprehensive treatment of the liver malignancy. The ex situ procedure does not resolve all problems. However, in contrast to a palliative treatment with no curative prospect and a life expectancy of only a few months [38], this procedure offers potentially curative surgery and may improve the patient's quality of life. Some patients, especially those with benign tumors, have benefited greatly from the use of this procedure. Thus, after weighing the advantages and disadvantages, the ex situ procedure may be the most appropriate approach in certain patients. These reasons explain the rare use of ex situ resection to date. However, the procedure will be improved in the future along with the development of liver transplantation techniques such as perfusion technology, which has focused on protecting livers with impaired function and has achieved successful results [39, 40].

In conclusion, the ex situ liver resection technique is the most sophisticated and complex procedure for the treatment of liver tumors. It offers a curative opportunity and the potential for an improved quality of life in patients with tumors encroaching on the IVC or the main hepatic veins, which cannot be resected using conventional procedures. However, the potential risks of this procedure and the postoperative complications, which may lead to high mortality, must be clearly realized. Appropriate indication and patient selection are of utmost importance to achieve better outcomes. Finally, basic research (e.g. on reperfusion injury) and the development of techniques, such as veno-venous bypass, isolated liver perfusion and vascular reconstruction, should improve the safety of the procedure and reduce mortality in the future.

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