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Ex-situ hepatectomy: Indications, Techniques and Results

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ORIGINAL

Abstract

Background: Ex-situ hepatectomy is a novel approach, used in treating complicated liver tumours, which are otherwise unresectable via conventional methods including organ perfusion, liver transplant, hemodynamic management, vascular reconstruction or even extended hepatic resection.

Aim of the study: We conducted a literature review of studies reporting Ex vivo liver resection and autotransplantation (EVLRAT) to investigate the outcomes of this method.

Methods: We have retrospectively evaluated PUBMED databases. Studies were evaluated from 2000 to 2020. Only very few studies analyzed an “Ex vivo liver resection”.

Results: Studies demonstrated Ex vivo liver resection and autotransplantation (EVLRAT)is a feasible but very complex technique. It can apply to a few patients with unresectable hepatic tumours fit for surgery. Conclusion: At present, the future use of Ex situ hepatectomy is a technique used in patients with conventionally unresectable liver tumours to achieve a radical (R0) resection in difficult cases.

Keywords : Ex-situ hepatectomy, Liver Resection, Liver Transplantation, Ex vivo liver resection and autotransplantation (EVLRAT)

Introduction

Patients who suffer from liver malignancies such as liver and intrahepatic bile duct cancers as well as hepatic metastases, often have a median survival time of less than a year without receiving the appropriate medical attention. The main approaches which have been used in addressing the commonly occurring tumours are Liver resection, liver transplantation as well as the use of chemotherapy (1) .

The vast majority of such disorders can be treated with resection, which ensures long-term survival. Regrettably, not all patients are candidates for resection using traditional methods such as parenchyma sparing or right/left hepatectomy or Two-Stage Hepatectomy(TSH) or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS procedure). Nonetheless, some tumours prove difficult to treat through conventional tumour treatment techniques. The traditional techniques limit liver tumour treatment due to wanting intraoperative, limitation of the various indication standards as well as other complicated aspects. Selected cases of conventionally unresectable liver tumours might be treated with alternative innovative options in hepatobiliary and transplantation surgery performed in recent decades. Ex Situ hepatectomy was developed in light of the above challenges, to increase the success of the operation of otherwise difficult liver tumour surgeries. The core indicators for undertaking Ex-situ hepatectomy are liver tumours that are unresectable or are not amenable to resection through conventional surgical techniques, which would otherwise pose a danger given the proximity of venous confluence or the interference of

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the hepatic veins. Ex vivo liver resection and autotransplantation (EVLRAT) is a procedure that involves a total hepatectomy, extracorporeal liver resection, and autologous transplantation of the remnant hepatic parenchyma (2). Nonetheless, the high morbidity as well as the mortality rates limit the application of the above technique, despite numerous efforts, forwarded towards improving the above approach. As such, several surgeons have advanced significant skills, required for the technique, such as venovenous bypass, reimplantation as well as revascularization (3). The above procedures are regarded as some of the most complicated and high-risk approaches to surgeries conducted on humans. We conducted a literature review of studies reporting EVLRAT to investigate the outcomes of this method.

Methods

We searched (last updated on October 2021) PubMed, Embase, Scopus, and Web of Science databases for eligible studies. Peer-reviewed each query, dates of searches, their results, and other relevant details are reported. Studies were evaluated from 2000 to 2020. Only very few studies analyzed an “Ex vivo liver resection”. Two independent research DC and SL performed the review. The search terms were identified with the medical subject heading (MeSH).

2.1 Inclusion criteria

Research inclusion criteria were ”Ex vivo liver resection ”,” Ex situ liver resection”, “extracorporeal liver resection”, “liver autotransplantation”. The outcomes were complete were indications, operative time, blood loss, morbidity, and mortality.

2.2 Exclusion criteria

Unpublished data, book chapters, or conference abstracts and non-English manuscripts were excluded. No dates of coverage restrictions were applied After rejecting review articles and repetitive reports, the relevant literature included 9 manuscripts.

Results

(4) analyzed fifty-three studies with a total of 244 patients through a Meta-analysis. The study revealed R0 resection rate was achieved in 93% of cases with major surgical complications of 25%, 30-day mortality of 10%, the 90-day mortality rate was 12% for malignant tumours versus 8% in benign tumours and 1-year survival of 79%.In particular postoperative 1-year survival was 65% for malignant tumours and 90% for benign tumours. (5) describe EVLRAT in 43 patients suffering from Hepato Carcinoma and Cholangiocarcinoma (HCC/CCC). They demonstrated some notes: duration operative time 8 hours, blood loss about 1500 cc, anhepatic time high of 250 minutes, the mortality rate of 20% 9/43 patients.

(6)analyzed 69 cases of EVLRAT for echinococcosis demonstrated similar operative time and blood loss but a better 30 day and 90-day mortality respectively of 7% and 11% and 1-year survival rate of 87% of patients, showing a better prognosis and utility of this technique for non-malignant liver tumours. Applying EVLRAT for alveolar Echinococcosis, (7) noted that the survival rate in the group of autotransplantation was greater than those who underwent allotransplantation. (8) applied the ex-situ technique repair in a patient with severe liver trauma in such an emergency. (9; 10; 11)used a temporary portacaval shunt avoiding an extracorporeal veno-venous bypass. (12) described the resection of a huge HCC of 18 cm involved IVC and RHC in a young patient. (13) described 22 cases of EVLRAT 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) with in-mortality rate of 6/22. (14) EVLRAT for 4 cases of colorectal metastases with1/4 in mortality while (15; 16) demonstrated no mortality after EVLRAT after hilar cholangiocarcinoma resections. (17) published a case of resection of hemangiomas with no mortality.

(18) in their literature review of 388 cases, demonstrated Ex vivo liver resection and autotransplantation (EVLRAT)is a feasible but very complex technique. It can apply in a few patients with unresectable hepatic tumour fit for surgery, benign tumour or malignant low-grade tumour with

long term survival with R0 resection about 60%-90% but outcomes are less satisfactory due to high complications rate of about 25% and low survival in 3 years. EVLRAT may offer a last resort when a conventional technique is not applicable.

Discussion

Ex-situ hepatectomy is a novel approach, used in treating complicated liver tumours, which are otherwise unresectable via conventional methods including organ perfusion, liver transplant, hemodynamic management, vascular reconstruction or even extended hepatic resection The Ex-situ hepatectomy technique denotes the entire removal of the liver, which is then perfused in a cold preservation solution, which allows the surgeon to remove tumours, which were otherwise unreachable when the liver is situated in the body. In so doing, the tumour is restricted ex-situ on the surgeon stable, while the remaining liver is implanted orthotopically. Notably, the works on Ex-situ hepatectomy techniques are credited to (19) , who proposed the surgical approach in the treatment of bilateral liver leiomyosarcoma.

The technique has been described in many patients with various types of liver tumours including hepatocellular carcinoma [HCC], cholangiocarcinoma [CCC], and colorectal cancer metastases [CRM]) as well as nonmalignant lesions including hepatic alveolar echinococcosis, focal nodular hyperplasia (FNH), and hemangioma. More to that, there are only a handful of successful Ex-situ hepatectomy cases which have been recorded on a global scale, given the complexity of the operation. Currently, there is no established report on the utilization of Ex situ hepatectomy as an alternative approach. The Ex-situ hepatectomy approach bears several advantages in comparison to the orthodox approaches, such as liver transplants. Some of the advantages include: reduced blood loss, optimal access to all sites of the liver, but some disadvantages include: a prolonged period for dissection as well as vascular reconstruction (20).

More to that, it reduces the redundancy associated with the shortage of liver donors, in the case of a transplant. On the other hand, (19) warns that the patients selected for the process have to meet a specified minimum criterion, given that the procedure cannot accommodate persons suffering from particular conditions. The selection of the patients, therefore, comes about as one of the most vital measures to achieving the success of the surgery. In developing the Ex-situ hepatectomy technique, various scholars such as (21) , have refined the technical details associated with the procedures and further developed the ante situm technique, regarding liver resection in a bid to increase the safety standards of the operation. Markedly, the ante situm technique is similar to the ex-situ procedures, but involves the training of the vital structure of the liver hilum and the division of three hepatic veins or a section of the IVC, before the liver is perfused with a cold preservative solution, via the portal vein. The ante situm approach is better than the Ex-situ hepatectomy in that it does not call for biliary as well as hepatic arterial anastomoses. The result is that it reduces the ischemia timeframe, as well as potential anastomotic complications which arise from the same (8). However, the approach does not provide the proper liver exposure as associated with the Ex-situ hepatectomy technique. In a longitudinal study conducted by (14) , the median survival time for six patients who underwent ex-situ resection was twenty-one months.

The study also indicated that one of the patients, who underwent an Ex-situ hepatectomy for HCC, lived disease-free for a period of seven years, following the date of the surgery. Additional studies, such as by (17)and (22), have found that Ex-situ hepatectomy operations have been curative to some patients, who were diagnosed with unresectable tumours. The technical experience required for Ex-situ hepatectomy is often gained from liver transplantation. However, some of the technical challenges associated with the procedure will be addressed in future developments of Ex situ hepatectomy. Furthermore, unlike other surgeries involving the liver, Ex-situ hepatectomy is delicate and requires a sufficient investigation of technical details as well as potential indicators, which may be used in guiding the surgeon, in terms of increasing the safety of the use of the model.

4.0.1 Technical aspects of Ex situ hepatectomy

The Ex-situ hepatectomy technique, hordes its distinct set of technicalities, which are brought about by the complexity of the procedure. For instance, the long period spent in the operation of the procedure dictates the necessity to be able to maintain the stability of blood dynamics, as well as avoid venous congestion which may occur due to the longer time spent at the operation table. The use of bypass from the portal, left femoral veins, to the left axillary of the jugular vein, through the use of heparin-coated shunts as well as the roller pump, is the most common technique to provide the stability of blood and to prevent venous congestions (23) . Additional techniques to avoid the adjuvant incision as well as other challenges associated with the conventional veno-venous bypass, the IVC was replaced with artificial blood vessel, as well as temporary veno-venous bypass, could be performed through liver removal via anatomization of the portal vein, as well as the supra-and intrahepatic vena cava. Nonetheless, some situations did not require the application of the veno-venous bypass, especially without the involvement of IVC (13; 24; 25; 26).

Table 1. Included Studies And The Outcomes

Authors	Studies	Type of study	Major surgical complications	30-day mortality	1-year survival	R0 resection	Anhepatic phase (min)	Operative time	Hospital stay
Zawistowski et al. 2020	Fifty-three studies	Meta-analysis	50.0% (malignant) 21.0% (not-malignat)	11.3% (malignant) 6.3% (not malignat)	65.0% (malignant) 89.7% (not malignat)	98.6%	314 [102-879] minutes	16.0 [6.4-31.0] hours	34 [7-128] day
Cheng F et al.2018	43 patients	Retrospective	6%-23%	9/43	NR	NR	250±45 minutes	8h	26.1± 10.3 days
Aji et al.2018	69 patients	Retrospective	10/69 patients	7.24% (5/69)	11.5% (8/69)	NR	360 (104–879)min	15.9 (8–24)h	34.5 (12–128) days
Oldhafer KJ. Et al.2000	22 patients	Retrospective	4/22 patients had liver failure	9/22 patients	6/15 patients	NR	5.6 +/- 1.1 h	17-19h	36.5 +/- 16 days
Coco et Leanza, 2021	388 patients	Review	25%	12%-20% malignant 7%-11% benign	65% for malignant tumors and 87%-90% for benign tumors	60%-90%	250 minutes	8h	NR

4.0.2 Risk of bias and limitations

The field of research on EVLRAT lacks evidence-based data or studies of reliable statistical significance of randomized controlled trials. Some limitations may result from the included studies' low level of evidence due to a lack of high-quality research in this field. It is the last resort therapy reserved for a small and selected group of patients who, after resection, maintain a preserved one liver function and normal Future Liver Remanent (FLR). The results for patients with malignant diseases appear to be lower than for benign diseases based on the results of studies showing a higher relapse rate and prevalence of mortality at 30 days, 90 days and in hospital.

Conclusion

Liver resection has become a safe operation, and its mortality rate is now almost zero. During the classic technique of right or left hepatectomy, studies demonstrated fewer complications rates compared to EVLRAT: Post-Hepatectomy Liver Failure (PHLF) is the most serious complication after liver resection. Renal failure is closely associated with PHLF. Studies stated that complications such as ascites, surgical site infections, coagulation disorders have a percentage inferior to ERAT. The incidence of BL is reported to be 4.0% to 17% and the overall morbidity rate of open liver surgery has been reported to range from 4.1% to 47.7%. In conclusion, EVLRAT is a complex procedure, applicable only in patients selected with unresectable liver tumours with normal conventional techniques. It can reveal itself as a potentially curative radical treatment.

It is, however, the last resort therapy reserved for a small and selected group of patients who, after resection, maintain a preserved one liver function and normal Future Liver Remnant (FLR). ERAT allows the complete reduction of heat ischemia and allows resection of the tumour (s) in a bloodless and total field without the pressure of time. Ex vivo liver resection and autotransplantation for end stage hepatic alveolar echinococcosis seem to demonstrate an overall mortality rate of 12% after a mean follow-up of 22 months. Although experience with the procedure evolves, some controversies are still present. The studies show the proven fact of excellent efficacy in patients suffering from echinococcosis. The results for patients with malignant diseases appear to be lower than for benign diseases based on the results of studies showing a higher relapse rate and prevalence of mortality at 30 days, 90 days and in hospital.

Conflicts Of Interest

All the aforementioned authors declare no competing commercial, personal, political, intellectual, or religious conflicts of interest in relation to the present work. No grant or other financial support has been received for the drawing up of the present paper.

Ethical Approval

All procedures were in accordance with the ethical standards of the Institutional and National Research Committee and with the Helsinki Declaration and its later amendments or comparable ethical standards.

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