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Laparoscopic liver resection for living donation: Where do we stand?

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with left lateral sectionectomy, which is performed for adult to child living donation. In this setting, the laparoscopic technique is now well standardized, is associated with decreased donor blood loss and hospital stays and provides graft of similar quality compared to the open approach. On the other hand laparoscopic major right or left hepatectomies for adult-adult LDLT currently lack standardization and various techniques such as the full laparoscopic approach, the hand assisted approach and the hybrid approach have been reported. Hence, even-though several reports highlight the feasibility of these procedures, the true benefits of laparoscopy over laparotomy remain to be fully assessed. This could be achieved through standardization of the procedures and creation of international registries especially in Eastern countries where LDLT keeps on flourishing.

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Key words: Liver transplantation; Laparoscopy; Living donation; Postoperative course

Abstract

In Western countries, living donor liver transplantation (LDLT) may represent a valuable alternative to deceased donor liver transplantation. Yet, after an initial peak of enthusiasm, reports of high rates of complications and of fatalities have led to a certain degree of reluctance towards this procedure especially in Western countries. As for living donor kidney transplantation, the laparoscopic approach could improve patient's tolerance in order to rehabilitate this strategy and reverse the current trend. In this setting however, initial concerns regarding patient's safety and graft integrity, need for acquiring surgical expertise in both laparoscopic liver surgery and living donor transplantation and lack of evidence supporting the benefits of laparoscopy have delayed the development of this approach. Similarly to what is performed in classical resectional liver surgery, initial experiences of laparoscopy have therefore begun

Core tip: Initial concerns regarding patient's safety and graft integrity, need for acquiring surgical expertise in both laparoscopic liver surgery and living donor transplantation (LDLT) and lack of evidence supporting the benefits of laparoscopy have delayed the development of this approach in LDLT. Preliminary experiences of laparoscopic liver resection for LDLT have begun with laparoscopic left lateral sectionectomy for adult-child LDLT, where the procedure is now well standardized and provides satisfactory results. On the other hand, lack of standardization and multiplicity of the techniques currently limit the evaluation of this approach in the setting of major liver resection for adult-adult LDLT.

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INTRODUCTION

Liver transplantation (LT) is the mainstay treatment for patients with end-stage liver disease or early hepatocellular carcinoma occurring on cirrhosis with survival rates reaching up to 80% and 70% at 1 and 5 years respectively^[1]. Yet, the long-lasting imbalance between graft availability and an increasing number of patients on the waiting list required development of several other strategies. Living donor liver transplantation (LDLT) has emerged as a valuable alternative to deceased donor LT^[2]. In Eastern countries, where the hesitancy to donate organs after death corroborates with strong cultural and religious beliefs, rates of deceased organ donation of 0.05-6.0 per million^[3] are among the lowest observed and have led to successful development of LDLT. In Western countries, after an initial peak of enthusiasm during the late 90's, reports of fatal complications published in both scientific journals^[4,5] and in the public press have led to a marked decrease in the number of procedures. Hence, LDLT now barely account for 4%-5% of the total number of LTs in Europe and in the United States^[6,7]. This proportion contrasts with that of living kidney transplant, which has reached almost 40% in the last 10 years in the United States^[8,9]. While this large difference is certainly mainly the consequence of the higher risks of complications and death in live liver donors, one should nevertheless bear in mind that the use of the laparoscopic approach in living donor nephrectomy has led to an overall increase in donation rates^[10]. In living donor nephrectomy, several meta-analyses and randomized controlled trials have established that laparoscopy was associated with decreased morbidity rates and postoperative pain, shorter in-hospital stay, lower cost, better quality of life and faster return to work^[9,10].

In classical resectional liver surgery (*i.e.*, for malignant or benign disease), initial concerns regarding both safety and feasibility of the laparoscopic approach, especially for major hepatectomies have led to delay its development and it's only recently that this strategy has gained acceptance. Hence, the laparoscopy is now considered as the approach of choice for several procedures such as left lateral sectionectomy (LLS)^[11,12]. Yet, its use in the setting of living donation still raises several concerns about not only donor safety but also graft integrity^[13]. The objective of this comprehensive review is therefore to discuss on the past and present limits of the laparoscopic approach for living donation in order to provide relevant insights regarding its current place. To such end, a MEDLINE search was performed for relevant English full-text articles using a combination of the following key words "LDLT" with "laparoscopy" and/or "laparoscopy assisted hepatectomy" and/or "laparoscopic hepatectomy" and/or "LLS" and/or "left hepatectomy" and/or

"right hepatectomy" and/or "right posterior sectionectomy". The reference lists of the selected papers were also searched in order to obtain additional relevant articles.

WHY HAS THE DEVELOPMENT OF LAPAROSCOPY BEEN DELAYED IN THE SETTING OF LIVING LIVER DONATION?

Long and necessary learning curve

The most controversial topic in liver surgery is clearly the performance of laparoscopic living donor hepatectomy. In laparoscopic liver resection for LDLT, both expertise in LDLT as well as in laparoscopic liver surgery are required. On one hand, LDLT only represents a small proportion of all LT annually performed, especially in Western countries^[6,7], which clearly limits the possibility of fast development. On the other hand, mastering both liver surgery and laparoscopic techniques should be achieved before attempting laparoscopic liver resections. In this setting, several reports have emphasized that a minimum of 15-60 procedures depending on the extent of the resection was required before optimal results could be obtained^[14,15]. As experience with advanced technological support in minimally invasive surgery increased, laparoscopic liver resections have therefore trended from minor wedge resections and LLS for peripherally located lesions towards major resections^[15,16]. Altogether, it is not surprising that the development of laparoscopic liver resection for LDLT has been delayed until initial reports highlighting the safety and feasibility of laparoscopic liver surgery were released.

Interestingly, when it came to performing laparoscopic LLS for living donation, a learning curve of approximately 20 procedures was also observed before achieving optimal blood loss, warm ischemia times^[17], postoperative course and hospital stay^[18]. This finding supports that even the most experienced surgeons in both laparoscopic liver surgery and LT will have to face some kind of difficulties at the beginning of their experience.

Initial concerns regarding patient safety and graft integrity using the laparoscopic approach

Donor safety is clearly the main issue of this strategy. Mortality after living donation ranges from 0.05%-0.1% for left lateral section donation to 0.2% for right liver donation^[19]. Also, a consistently reported rate of complication of approximately 40%^[20,21] including major ones such as biliary fistula, infections or pulmonary complications^[22,23] in case of open right liver donation may discourage these healthy donors. These risks, superimposed with elevated rates of psychological difficulties^[21] following donation affect both medical teams and general opinion. In Western countries, where deceased LT is widely available, this has led to a certain degree of reluctance among medical teams and a decrease in living donation is currently observed. In this setting, laparoscopic liver donation could not suffer worse results than the open ap-

proach and should at the best reduce these risks in order to rehabilitate this strategy and reverse the current trend.

Several concerns regarding patients safety have long-limited the development of the laparoscopic approach in patients undergoing classical liver resectional surgery. In particular, an important initial reluctance was the risk and management of hemorrhage under laparoscopy. However, with technical refinements and growing expertise during the past two decades, several reports have emphasized decreased blood loss and transfusion rates in patients undergoing laparoscopic liver resection compared to patients operated under laparotomy^[24,26]. Possible explanations for this finding include the 30-degree reverse Trendelenburg position reducing hepatic back-flow, more effective hemostasis on the cut surface due to laparoscopic magnification and possibly the effects of pneumoperitoneum, which could both decrease cut surface bleeding^[27] and therefore leave enough time for laparoscopic haemostasis or conversion when required. Another important issue, which has now been sorted out, was the theoretical increased risk of gas embolism as a consequence of the pneumoperitoneum itself. In this setting, one should nevertheless bear in mind that this pneumoperitoneum is made of CO₂, which solubility is greater than that of nitrogen^[13] and that several experimental studies have clearly established that CO₂ was not associated significant hemodynamic instability^[13].

In donors undergoing open hepatectomy graft retrieval is generally achieved using large midline or subcostal laparotomies. In case of full laparoscopic approach, the graft has to be placed in a plastic bag and extraction is usually performed using smaller incisions such as suprapubic incisions. In this setting, several authors have raised some concerns regarding the risk of physical graft integrity and prolonged warm ischemia time (WIT)^[28]. First, it has now been established that liver function tests and graft functional recovery were identical in patients operated under laparotomy or laparoscopy. Second, our group has shown that even-though longer WIT were observed in laparoscopically retrieved grafts, this did not impact graft related postoperative complications or survival^[29]. Altogether, there is currently no argument supporting that the laparoscopic approach itself could jeopardize the quality of the graft.

Delayed evidence supporting the benefits of the laparoscopic approach in liver surgery

Today, laparoscopic minor liver resections are considered to be safe and reproducible techniques and even superior to the open approach. In this setting, laparoscopic LLS is now considered the gold standard for malignant or benign lesions^[11,12]. Apart from obvious cosmetic benefits the reported advantages of laparoscopy over laparotomy are multiple. These include decreased surgical site infections^[30] and postoperative ascites^[25,26], shorter hospital stay^[30,31], and improved cost effectiveness^[32]. Still, these benefits mainly arose from the results of retrospective case-control series or meta-analyses of retrospective

studies. Hence, even-though laparoscopic surgery has certainly gained global acceptance over the last 20 years, current medical literature clearly lacks strong evidence when it comes to the specific subset of liver surgery. Among the several explanations that may account for this major drawback, ethical concerns clearly limited the feasibility of randomized controlled trials comparing open and laparoscopic approaches.

INITIAL EXPERIENCE WITH LAPAROSCOPIC LIVER RESECTION FOR LIVING DONATION: THE MODEL OF LAPAROSCOPIC LLS FOR ADULT-CHILD LDLT

As for liver resection for malignant or benign lesions, laparoscopic approaches to living donation were initially described for removing an adult left lateral segment graft for transplantation into a child. First described simultaneously in Brazil and Australia in 1989^[33,34], open LLS for adult-child LDLT is now a well-standardized procedure and has been shown to provide the best patient survival rates^[35,36]. In this setting, the rationale of performing this procedure through laparoscopy was to provide the healthy donors with the advantages of this modern minimal invasive approach and, at the same time, to assure maximal safety of the procedure and the procurement of grafts of optimal quality. Hence, since the first report of full laparoscopic LLS for adult-child LDLT in 2002^[37], this approach has progressively gained increased acceptance.

Table 1 summarizes the results of the three most important series focusing on laparoscopic LLS for adult-child LDLT^[18,29,38]. Of these, the first two series were small case control studies, which mainly aimed at reporting both safety and feasibility of this approach. From the donor point of view, the laparoscopic approach was associated with decreased blood loss^[29,38], improved postoperative course with decreased postoperative complication rates^[29], shorter postoperative recovery and hospital stays^[38] compared to the open approach. From the recipient point of view, even though the laparoscopic approach was associated with longer WIT^[29] compared to the open approach, recipients displayed similar postoperative liver function tests and identical rates of biliary complications, graft loss leading to retransplantation and overall postoperative mortality^[29,38]. Interestingly, our recent bicentric report of 70 LLS for adult-child LDLT highlighted an 8% rate of hepatic artery thrombosis (HAT)^[18]. This rate, which may seem higher compared to values reported in the literature, may account for several explanations. First, at the beginning of this experience, living donation was dedicated to emergency situations, including acute necrosis in biliary atresia recipients or retransplantation for acute liver graft failure, which are well known to be at higher risk of complications. In that sense, the same series reported a 0% HAT rate in the center where LLS for adult-child LDLT

Table 1 Summary of the studies reporting the results of full laparoscopic left lateral sectionectomy for adult-child living donor liver transplantation

Ref.	Study type	<i>n</i>	Major complication	Blood loss (mL)	Transfusion	Hospital stay (d)	Warm ischemia time (mn)	Recipient HAT	Retransplantation
Soubrane <i>et al</i> ^[29] , 2006	Case control	30	6.0%	19 ± 44	0%	7.5 ± 2.3	10 (6-12)	12.5%	6%
Kim <i>et al</i> ^[38] , 2011	Case control	22	0.0%	396 ± 72	-	6.9 ± 0.3	6 ± 2	0.0%	0%
Scatton <i>et al</i> ^[18] , 2014	Case series	70	1.4%	82 ± 79	0% ¹	6 (3-18)	9 ± 4.1	8.0%	9%

¹For allogenic transfusion, 6 (8.6%) donors underwent autogenic transfusion. HAT: Hepatic artery thrombosis.

was performed electively. Second, no anticoagulants were given to the donor at the time of vessels division suggesting that a systematic protocol for anticoagulation before retrieval should probably be introduced.

Altogether, with almost 100 procedures performed to date, both safety and reproducibility of laparoscopic LLS for adult-child LDLT have now been established. Even though some minor adjustments are still required, there is no doubt that this approach will become the standard of care in upcoming years.

LAPAROSCOPIC MAJOR LIVER RESECTION FOR ADULT-ADULT LIVING DONATION

Adult to adult (AA) LDLT was introduced almost a decade after LDLT for children^[39]. AA LDLT is mainly performed using two types of partial grafts *i.e.*, right hemiliver grafts and left hemiliver grafts, both with specific advantages and shortcomings. In this setting, the use of laparoscopy has raised several issues concerning both safety and feasibility but also usefulness. Hence, it's only very recently that the first reports of laparoscopic major hepatectomy for AA LDLT have been released.

Laparoscopic right hepatectomy for AA LDLT

Living donor right hepatectomy, which entails removal of about two thirds of the donor liver represents the main type of partial liver graft for AA LDLT. While right liver graft donation provides an adequate volume of transplanted functional liver parenchyma and therefore ensures recipients safety, it has raised much concern about donor safety. Indeed, less than 10 years ago, AA LDLT using right liver grafts was still associated with a 30% donor transfusion rate and a 40% postoperative complication rate^[20,21] including biliary tract complications and pulmonary complications in 3%-8%^[40] and 10%^[23] of the donors respectively. To rehabilitate this strategy and reverse the current trend of decreasing AA live donation rates, efforts in reducing these high complication rates were clearly required^[41]. In this context, several units have therefore advocated that the laparoscopic approach for AA LDLT living donation could be considered as an option to reduce donor morbidity. Indeed, increasing number of reports have emphasized that laparoscopic right hepatectomy for classical liver resection demonstrated better surgical outcomes than the open approach in terms

of reduced intraoperative blood loss and postoperative hospital stay^[42-45]. Various techniques of laparoscopic right hepatectomy have been reported^[46-50]. Currently, three main techniques of laparoscopic right hepatectomies have been described: (1) the pure "full" or "totally" laparoscopic approach where the whole procedure is performed through laparoscopy; (2) the hand assisted laparoscopic approach where a hand port is used to facilitate the operation; and (3) the laparoscopic assisted approach or "hybrid technique" where pedicular dissection and liver mobilization are performed under laparoscopy when parenchymal transection and specimen extraction are performed using a short (midline or subcostal) incision. Currently, there are no published data indicating the superiority of one technique over the others and the choice of the technique depends on the surgeons' expertise and preference as well as the indication for surgery. In our experience we believe that the hybrid method may be used as a valuable "salvage" alternative strategy, which offers the possibility for safe conversion in case of bleeding or large tumor with involvement of the hepatocaval confluence.

Some detractors of laparoscopic major hepatectomy for LDLT only consider this approach as a pure technical achievement^[28]. On the opposite, several HPB surgeons have focused on developing laparoscopic right hepatectomy using conceptual and standardized techniques^[29,51] with the aim to ensure donor safety through decreased intraoperative blood loss, improved postoperative course with decreased morbidity and faster rehabilitation^[46].

As shown in Table 2, 167 cases of laparoscopic right hepatectomy for AA LDLT have been reported between 2006 and 2014, mostly through case reports, case series or case match series with low statistical power^[51-62]. Of these, two procedures were performed using a full laparoscopic approach, one procedure was performed using a robot-assisted technique, while the 164 other cases were performed using hand assisted or hybrid techniques. In these reports, there was no evidence indicating that the laparoscopic approach for right hepatectomy living donation was superior to conventional open approach. However, it should be emphasized that (1) no death was reported; (2) the rate of severe complications (0% to 17%) was quite low; and (3) the lengths of hospital stay (3 to 12 d) were more than acceptable.

Altogether, currently published results seem to confirm previous assertions regarding the feasibility of the laparoscopic approach for right hepatectomy in the setting of AA LDLT. Whether potential physical and psy-

Table 2 Summary of the studies reporting the results of laparoscopic assisted, hand assisted, robot assisted or full laparoscopic right hepatectomy for living donor liver transplantation

Ref.	Study type	n	Major complication	Blood loss (mL)	Transfusion	Hospital stay (d)
Laparoscopic right hepatectomy using midline incision "Hybrid Method"						
Koffron <i>et al</i> ^[52] , 2006	Case series	4	0%	150	0%	3 ± 1
Kurosaki <i>et al</i> ^[53] , 2006	Case series	3	0% ¹	300 ± 190 ¹	0% ¹	11 ± 3 ¹
Baker <i>et al</i> ^[54] , 2009	Case control	33	0%	420 ± 220	0%	4.3
Nagai <i>et al</i> ^[55] , 2012	Case series	4	-	350 ± 174	-	6.3 ± 1.3
Soyama <i>et al</i> ^[56] , 2012	Case series	6	6% ¹	520 ± 290 ¹	0% ¹	-
Zhang <i>et al</i> ^[57] , 2014	Case control	25	0%	380 ± 110	0%	7 ± 1.4
Laparoscopic hand-assisted right hepatectomy using a transverse or subcostal incision						
Suh <i>et al</i> ^[58] , 2009	Case series	7	14%	-	-	10 ± 7
Choi <i>et al</i> ^[59] , 2012	Case control	20	-	870 ± 653	-	12.1 ± 2.8
Hwang <i>et al</i> ^[60] , 2012	Case control	20	0%	290 ± 67	0%	10.7 ± 2.6
Single port laparoscopic hand-assisted right hepatectomy using a transverse or subcostal incision						
Choi <i>et al</i> ^[59] , 2012	Case control	40	-	450 ± 316	-	11.8 ± 4.4
Hand assisted laparoscopic right-Lobe Hepatectomy						
Suh <i>et al</i> ^[58] , 2009	Case series	2	0%	-	-	12 ± 2
Robot-assisted right lobe donor hepatectomy						
Giulianotti <i>et al</i> ^[61] , 2012	Case report	1	0%	350	0	5
Totally Laparoscopic right-Lobe Hepatectomy						
Soubrane <i>et al</i> ^[62] , 2013	Case report	1	0%	100	0	7
Rotellar <i>et al</i> ^[62] , 2013	Case report	1	0%	100	0	4

¹Specific results of right hepatectomy were not detailed, and separated from left hepatectomy.

chological benefits of a smaller incision superimposed on at least similar postoperative results may change the landscape for living liver donors leading to an increased willingness to donate will nevertheless clearly require further investigations.

Laparoscopic left hepatectomy for AA LDLT

The rationale of left hemi-liver graft donation for AA LDLT would be to reduce the risk brought on the donor while providing the recipient with a sufficient amount of functional liver parenchyma at the same time. From the donor point of view, left hemi-liver grafts account for approximately 40% of the donors' total liver volume and this type of hepatectomy is generally associated with decreased rates of postoperative biliary and pulmonary complications^[23,63,64]. Yet, some authors advocate that the use of these smaller grafts essentially transfers the risk from the donor to the recipient^[65] in the form of small-for-size syndrome (SFSS). Indeed, a graft to recipient weight ratio (GRWR) under 0.8% or a graft volume standard liver volume (GV/SLV) less than 40% is considered as an increased risk factor for graft failure after LT in adult recipients. In this context, the first published series of adult LT using left liver grafts reported worse outcomes as compared to right liver grafts. Nowadays however, improvements in the preoperative planning with tailoring of the type of donor hepatectomy to the recipients' needs^[66] as well as refinements in surgical technique with optimal outflow reconstruction^[67,68] and both selective use of splenic artery occlusion^[69] or portocaval shunt creation^[70] allow patients and grafts survivals to reach those of right grafts for LDLT^[71-73]. Altogether, even if these considerations may appear to be beyond the scope of this review, they largely explain the delayed develop-

ment of AA LDLT using laparoscopically harvested left hemiliver-grafts, which was not correlated to technical difficulties but rather to inherent limitations related to this type of grafts.

In classical resectional surgery, laparoscopy may indeed be considered a valuable approach with low intra-operative blood loss, overall complications, and mortality rates. This has led some authors to considering this approach as the future standard of care for this procedure^[74,75]. This widely contrasts with the small number of series reporting the results of laparoscopic assisted or full laparoscopic left hepatectomy in the setting of LDLT^[53,56,76-78] (Table 3). Still, preliminary studies of laparoscopic assisted left hemi-hepatectomies for AA LDLT with or without caudate lobe harvesting have emphasized that this approach was associated with low postoperative morbidity and provided shorter hospital stays than in the open approach. On the other hand, the very limited experience of 6 cases of totally laparoscopically harvested left hemi-liver grafts for LDLT arising from two expert centers^[77,78] currently does not allow drawing any solid conclusion regarding the safety of this approach.

FUTURE EXPECTATIONS

Need for standardization

With increasing reports highlighting the safety and feasibility of the laparoscopic approach for both traditional liver resectional surgery and live donor liver hepatectomy, several improvements such as laparoscopic right posterior sectionectomy or full robotic right and left hepatectomies are likely to be expected in upcoming years. However, these refinements may be considered as pure technical achievements and there is a more important need for

Table 3 Summary of the studies reporting the results of laparoscopic assisted or full laparoscopic left hepatectomy for living donor liver transplantation

Ref.	Study type	n	Major complication	Blood loss (mL)	Transfusion	Hospital stay (d)
Laparoscopic assisted left hemi-hepatectomy using midline incision "Hybrid Method"						
Kurosaki <i>et al</i> ^[53] , 2006	Case series	10	0% ¹	300 ± 190 ¹	0% ¹	11 ± 3 ¹
Soyama <i>et al</i> ^[56] , 2012	Case series	9	6% ¹	520 ± 290 ¹	0% ¹	-
Marubashi <i>et al</i> ^[76] , 2013	Case control	14	6.5% ²	353 ± 396 ²	0%	11.5 ± 3.6
Totally laparoscopic left hemi-hepatectomy						
Samstein <i>et al</i> ^[77] , 2013	Case series	2	0%	125	0%	4 ± 1
Troisi <i>et al</i> ^[78] , 2013	Case series	4	25% ³	50-80	0%	5 ± 1

¹Specific results of left hepatectomy were not detailed, and separated from right hepatectomy; ²Specific results of left hepatectomy were not detailed, and separated from left lateral sectionectomy; ³One out of four patient required roux-y hepaticojejunostomy for right posterior duct stenosis.

surgical units to achieve standardization of the existing procedures. Indeed, the technique of major liver resections is not standardized even through laparotomy and countless techniques including those focusing on vascular control strategy of resection with primary mobilization of the right liver or anterior approach without mobilization or parenchymal transection have been reported. In the setting of laparoscopic major liver resection, there is no doubt that standardization would both increase the reproducibility of the techniques and allow overcoming reluctances to promote the widespread development of this approach. The question on how the progression from surgical innovation to more standardized techniques can be achieved is still an open debate. As an example, our group has recently reported a conceptual technique of laparoscopic right hepatectomy based on facts and oncologic principles, the so-called "caudal approach"^[49]. Hopefully, this technique, which was developed in order to both decrease morbidity and improve reproducibility regardless of the indication for liver resection will also promote standardization.

Need for reports arising from Eastern countries

Apart from LLS for adult-child living donation, large sided series or studies comparing the results of full laparoscopic right and left major liver resection for living donation to similar open procedures are currently lacking and need to be conducted. Knowing that randomized controlled trials are unlikely to be undertaken, creating an international registry and comparing the results to open cohorts might allow us to evaluate the relevance and risks of the approach. Furthermore, the fact that all four reports focusing on full laparoscopic major hepatectomy for living donation arose from either European or American centers suggests an underdevelopment of this approach in Eastern countries. In France, as in many other Western countries, the number of major liver resection for liver donation is particularly low. This is at least partly due to the continuously decreasing overall number of LDLT. In this setting, there is a crucial need for reports of laparoscopic LDLT arising from Eastern expert centers, which annually perform hundreds of major hepatectomies for LDLT^[79-81].

CONCLUSION

Apart from laparoscopic LLS for adult-child LDLT, the current place of laparoscopy in living donor hepatectomy still lacks high level of evidence. Creation of international registries especially in Eastern countries should be undertaken in order to assess the relevance of this approach. Even-though preliminary reports tend to support both safety and potential benefits of laparoscopy in the setting of LDLT, future challenges should include standardization of the technique in order to achieve a certain degree of reproducibility and favor widespread development.

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