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Laparoscopic liver resection: Wedge resections to living donor hepatectomy, are we heading in the right direction?

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this review into two sections as we believe they merit separate attention on technical and ethical grounds. The first part deals with laparoscopic liver resection (LLR) in patients who present with benign or malignant liver pathology, wherein we have discussed its overall outcomes; its feasibility based on type of pathology and type of resection and included a small section on application of LLR in special scenarios like cirrhosis. The second part deals with the laparoscopic living donor hepatectomy (LDH) experience to date, including its potential impact on transplantation in general. Donor safety, graft outcomes after LDH and criterion to select ideal donors for LLR are discussed. Within each section we have provided practical points to improve safety in LLR and attempted to reach reasonable recommendations on the utilization of LLR for units that wish to develop such a service.

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Key words: Liver; Laparoscopic; Transplantation; Resection; Living donor; Minimally invasive; Technique; Hepatocellular; Hepatectomy; Cirrhosis

Abstract

Despite inception over 15 years ago and over 3000 completed procedures, laparoscopic liver resection has remained mainly in the domain of selected centers and enthusiasts. Requirement of extensive open liver resection (OLR) experience, in-depth understanding of anatomy and considerable laparoscopic technical expertise may have delayed wide application. However healthy scepticism of its actual benefits and presence of a potential publication bias; concern about its safety and technical learning curve, are probably equally responsible. Given that a large proportion of our work, at least in transplantation is still OLR, we have attempted to provide an entirely unbiased, mature opinion of its pros and cons in the current invited review. We have divided

Core tip: Given that a liver resection is ideally suited for a laparoscopic approach (no anastomosis, very large incision in open approach) there is increasing interest in the technique worldwide. However actual experience is limited to a few centres, and guidelines remain inadequate. This article summarises the current available evidence on the significant aspects of the technique individually, to guide clinicians considering developing such a practice.

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INTRODUCTION

Since the first non-anatomical laparoscopic liver resection (LLR) in the early 1990s, and the first anatomic LLR in 1996^[1], there have been over 3000 cases performed laparoscopically clearly demonstrating its feasibility. However nearly 80% of these have been selected (*i.e.*, benign lesions, sited in the anterior aspect of the liver) or relatively minor resections (single or bisegment) with larger resections being confined to a handful of enthusiasts worldwide so far. The combined requirements of long experience with open liver resection (OLR); an in-depth understanding of liver anatomy; considerable technical laparoscopic expertise and a healthy scepticism regards its actual benefits are probably equally responsible for this slow uptake.

A potential danger with assessment of a new technique is the influence of institutional and publication biases, in that negative reports have not made it to press, as noted during the Louisville meeting^[2]. Moreover all or most of these procedures are performed in centres with an ardent interest in minimally invasive liver resection (MILR) and it is difficult not to let some “subjectiveness” into reports. On the other hand there is a learning curve with all procedures and overemphasis on individual mishaps could delay application of a good innovation as with experience complication rates decrease, akin to common bile duct injury in laparoscopic cholecystectomy. Given that our work, especially in liver transplantation is mostly open liver surgery, we have attempted to be entirely unbiased in the current invited review. We have divided this review into two sections as we believe they merit separate attention on both ethical and technical grounds. The first part deals with MILR for liver pathology (benign and malignant) in patients wherein we have discussed this approach on its overall outcomes, outcomes based on type of resection, its feasibility based on type of pathology and finally MILR in special scenarios like cirrhosis. At the end of each section we have tried to provide a reasonable conclusion. The second part deals with the laparoscopic living donor hepatectomy (LDH) experience including its impact on transplantation in general. As discussed previously, we agree MILR has the potential to convert previously unfit or unwilling donors into donation, but equally, negative outcomes could result in a significant impact on programmes such as ours, where over 85% of patients depend on such donation, for transplantation.

MILR IN PATIENTS, FOR LIVER DISEASE

Laparoscopic liver resection: outcomes, feasibility, benefits and morbidity

Outcomes: Needless to say, success of a technique is

often decided by its overall outcome and the most decisive basic outcome measure is mortality. In the world review of LLR by Nguyen *et al*^[3] in 2009, 9 patients of 2804 died showing an overall mortality of 0.3%. Mortality rate in LLR is consistently low in most original series and remains between 1 and 1.8%^[4,5]. In fact in some studies, mortality figures are superior in the LLR compared to OLR^[6]. A meta-analysis of laparoscopic and open hepatic resection done by Mirnezami *et al*^[7] analyzed the short and long-term outcomes of 1678 patients. Thirty-day mortality occurred in 0.6% of patients undergoing LLR (4 out of 717) compared with 1% of patients undergoing OLR (10 out of 961). Even in LLR for malignancy, there was no significant difference in survival or disease recurrence when compared to OLR whether it was an anatomical or a non-anatomical resection^[8]. On the contrary, no study to date has shown LLR to be associated with greater mortality, when compared to the open approach^[9]. On study of the mortality that has occurred, none were intra-operative and the most common cause for post-operative mortality remained liver failure, as with OLR^[3]. However mortality was related to “haemorrhage” from major blood vessels in some series^[5,10]. Median blood loss is significantly more for right-sided LLR than for the left sided liver surgery but whether it contributes to mortality is still unclear^[11]. Of course, mortality rates are significantly higher (0.3% *vs* 5.8%) in the cirrhotic versus non-cirrhotic resection group, but this would be true for OLR too^[4,12].

Feasibility: Feasibility is the next outcome measure that requires study, and intra-operative conversion to an open approach is a surrogate marker for feasibility. Of course, feasibility also depends on type of resection and site of lesion, but this will be discussed elsewhere. Conversion rates are variable but most large series quote figures around 2%-4%^[4,5]. Conversion from laparoscopy to open laparotomy and from laparoscopy to hand-assisted approach occur in 4.1% and 0.7% of reported cases according to Nguyen’s world review^[3]. In the series reported by Kazaryan *et al*^[5], overall conversion rate was 3.4%. Conversions to laparotomy were because of intra-abdominal adhesions (2 cases) and haemorrhage (3 cases). Repeated resections after open liver resection are associated with a significantly higher rate of conversion to laparotomy but in most series, the conversion is due to intra-operative bleeding^[11]. In a recent series by Troisi *et al*^[13] the conversion rate was higher at 6.4%, and on univariate analysis, they identified “major” hepatectomy and resections involving posterior-superior segments as prognostic factors for conversion whereas multivariate analysis identified the latter as an independent risk factor. The Mirnezami *et al*^[7] meta-analysis found the conversion-to-open rate for all laparoscopic procedures was 7% (50 out of 717). However, it is important to stress that conversion from a pure laparoscopic method to hand assisted or laparotomy should and must not be considered a complication. The Louisville consensus conference summarised the opti-

mal approach well, by stating that all efforts should be made to control bleeding laparoscopically and conversion should be done in a staged manner starting from a hand assisted technique and finally laparotomy, as a significant blood loss can occur during conversion^[2]. They noted that patient safety and lack of progress were the primary indications worldwide for conversion, which is how it should be.

Benefits: Given above literature findings, LLR is feasible and safe in comparison with OLR. But does the technique actually deliver on the two most quoted reasons for its perusal- enhanced recovery and maintenance of abdominal wall integrity? Indeed, the most significant benefit of LLRs besides others is “lengths of hospital stay”, an easily measured but debatable surrogate for enhanced recovery. Most studies have consistently demonstrated a significantly lower hospital stay as compared to the open approach. Buell *et al* reported a mean hospital stay of 2.9 d as compared to 5.4 d in the open group^[4]. Kazaryan *et al*^[5] 2010 further elaborated that the length of hospital stay does not depend on LLRs done for either benign or malignant lesions, or anatomical and non-anatomical resections. For all kinds of resections their mean hospital stay was 3 d. Zhou *et al*^[14] pooled analysis of the 6 studies of LLRs for colorectal liver metastasis (CRLM) showed that hospital stay was shorter in the laparoscopic group (WMD: -3.54, 95%CI: -5.12-1.96; $P < 0.001$) in spite of significant heterogeneity in their patient cohort. The overall shorter hospital stay in LLRs is not merely ‘faster discharges’ but a by-product of an earlier return of bowel activity and lesser requirement of analgesia^[14,15]. The Louisville position is consistent with such studies and further states that the benefits of shorter hospital stay extend to both major and minor LLRs but added that these results may be dependent on the level of experience of surgeons in both advanced laparoscopy and liver surgery^[2]. Moreover given that financial considerations dictate some of our clinical decisions, cost-effectiveness of LLR has been looked into. Most mature series agree that LLR is indeed cost-effective, with minor increase in cost of consumables in theatre being offset by immense decrease in the cost of hospital stay, regardless of type of resection^[6,16]. This opinion was endorsed by the consensus conference^[2].

Morbidity: Despite comparable mortality, overwhelming morbidity clearly needs to be ruled out. However complications in LLRs are comparable in most reports and significantly lower than the open approach in many. Post-operative morbidity of LLR varies between 10% and 15% and is significantly lower than open liver resection (about 25%)^[17-19]. Several studies including Rowe *et al*^[6] in their study found that LLRs had significantly decreased intra-operative blood loss (287 mL *vs* 473 mL, $P = 0.03$) and post-operative complications (6% *vs* 42%, $P = 0.03$)^[7]. In the series by Buell, the overall complications in LLR were about 16% *vs* 22% in the open group^[4]. In fact, pa-

tients appear to be more likely to have complications or morbidity in the open resection group than in the laparoscopic group for both the simpler antero-lateral and more complex postero-superior resection subgroups^[20]. Furthermore we know that complication rates generally tend to decrease, as experience and exposure in LLRs increase^[21]. Predictably LLR is also associated with a higher complication rate when resections involve posterior/superior segment of liver, and tumors > 5 cm are resected^[21,22]. Most complications due to LLR appear to belong to Clavien grade 1 and 3 subgroups when they do occur^[13].

Intra-operative bleeding during LLR is a traumatic experience for most surgeons. A combination of large calibre, thin walled, high flow hepatic and portal veins, with variable anatomy, hidden within liver parenchyma makes parenchymal transection dangerous in inexperienced hands and is one of the reasons why LLR has not been taken up with the same enthusiasm as other laparoscopic procedures. But with the right technique and experience, perhaps surprisingly, several reports confirm that blood loss is significantly lower in LLR when compared to open^[14-16,23-25]. Mirnezami *et al*^[7] meta-analysis showed a median blood loss of 320 mL for LLR (range 122-620 mL) and 483 mL for OLR (range 214-895 mL). This is potentially due to higher magnification of structures viewed through high definition cameras, use of vessel sealing energy devices /endoscopic staplers, control of resection by laparoscopic ultrasonography and the automatic, conscious efforts by laparoscopic surgeons to clip/control even small vessels before their division at laparoscopic transection^[20,26]. We have found laparoscopic curved vascular clamps and energy devices like the Liga-Sure® Covidian Surgical solutions essential components in the operating set.

Post-operative bile leakage was observed in around 1%-2.7% and most of them were managed by percutaneous drainage with or without bile duct stenting^[3,16,27]. Once again, better visibility from the on-screen magnification presumably accounts for this low rate of bile leaks. As with other surgery, morbidity associated with LLR can be due to general complications like chest and urinary tract infections, deep vein thrombosis, paralytic ileus, or pyrexia's of unknown aetiology. But due to the faster mobilisation and improved respiratory function, in reality, incidences appear to be low. Awareness must exist of unusual procedure related complications like iatrogenic port insertion injury, rupture of the splenic capsule whilst performing a Pringle manoeuvre *etc.*, Gas (CO₂) embolism (GE) is a rare complication found during LLR and risk of GE is higher if dissection involves a major hepatic vein, long transaction plane, or a longer operative time. It is likely that a combination of low central venous pressure (CVP; which creates a greater suction effect), and high intra-abdominal gas pressure (IAP; which clearly encourages entry of gas into an open “sucking” vein) is responsible for GE. Hence a low IAP and use of an “abdominal lift” system has been used to minimize the

Table 1 Comparison of mortality, morbidity and conversion rates in some of the larger laparoscopic liver resection publications

Ref.	Year	Cases (n)	Malignant lesions (%)	Major hepatectomies (%)	Mortality (%)	Morbidity (%)	Conversion (%)
Descottes <i>et al</i> ^[92]	2003	87	0	3 (3.4)	-	4 (4.6)	9 (10)
Mala <i>et al</i> ^[93]	2005	53	89	-	-	8 (16)	3 (5.6)
Kaneko <i>et al</i> ^[51]	2005	52	NR	NR	-	5 (10)	1 (2)
Vibert <i>et al</i> ^[27]	2006	89	73	38 (43)	1 (1.1)	31 (34.8)	12 (13)
Cai <i>et al</i> ^[94]	2006	62	32	2 (3.2)	-	2 (3.2)	2 (3.2)
Koffron <i>et al</i> ^[16]	2007	273	37	96 (35)	-	NR	-
Chen <i>et al</i> ^[95]	2008	116	100	4 (3.4)	-	7 (6)	6 (5.2)
Buell <i>et al</i> ^[4]	2008	253	42	62 (42.5)	4 (1.6)	41 (16)	6 (2.4)
Bryant <i>et al</i> ^[32]	2009	166	60	31 (18.7)	-	25 (15.1)	16 (9.6)
Dagher <i>et al</i> ^[23]	2009	22	22	22	0	14	9
Yoon <i>et al</i> ^[39]	2010	69	-	21 (20)	-	5	5
Martin <i>et al</i> ^[25]	2010	90	90	90	0	23	4
Abu Hilal <i>et al</i> ^[24]	2011	36	-	36	0	14	11

risk^[28]. On the other hand, there are experimental studies in animals that showed GE occurred irrespective of the CVP-IAP gradient, suggesting other mechanisms might contribute to GE occurrences^[29]. Further studies are required to clearly identify the role of CVP and IAP, but it is important to note that CO₂ embolism is not as dangerous as air embolism, given its higher/faster solubility (in blood)^[30]. However patients who based on ECHO/capnography have clearly experienced CO₂ embolism, have gone on to have no harmful sequelae^[31,32].

Conclusion: In conclusion therefore, when compared with open liver resection, LLR can provide comparable mortality, shorter hospital stay, improved morbidity and better cosmesis, cost effectively (Table 1). Clearly, feasibility of most resections is now proven with very low conversion rates. Enhanced recovery with short hospital stays are real and not merely faster discharges. Decreased bile leak rates and consistently lower blood loss in many large series are significant advantages. LLR must be carried out under as low IAP as possible, with modern energy devices to complete transection, particularly laparoscopic CUSA® (Cavitron ultrasonic surgical aspirator, Valleylab, United States) and laparoscopic ultrasound.

Laparoscopic liver resection: type of resection

Historically anterolateral segments (segments 2, 3, 5, 6), were considered more amenable for LLR, and initial attempts at LLR were limited to non-anatomical resections of such segments. In most of the early reports, lesions in posterior-superior segments were even considered a relative contra-indication for LLR^[33,34]. But innovative techniques and increasing experience has led to a gradual progression towards left sectionectomies, right and left hepatectomies and finally posterior segment resections. Indeed almost all types of liver resections are currently being performed routinely, with investigators claiming equivalent or superior results with the laparoscopic as compared to the open approach, although most major hepatectomies still utilize a hand assisted or hybrid technique than pure laparoscopy^[4,23,24]. It has even been shown by several operators that even segment one (cau-

date), can be resected in isolation or as part of another major hepatectomy^[4,35]. Nevertheless, despite passage of over 15 years since the first LLR, the 2009 world review of LLR shows that an overwhelming majority of resections are still either segmentectomies (45%) or anatomic left lateral sectionectomies (20%) with anatomical hemihepatectomies constituting a lesser proportion of LLR [right (9%) and left (7%)]^[3]. We analyzed more than a 1000 LLRs in five recent, major case series^[4,5,16,32,36]. Of these patients, a vast majority (nearly 80%) of resections were again segmentectomies, left lateral sectionectomies or non-anatomical resections. In our opinion, this persistent trend accentuates the point that in most major hepatectomies, surgeons still prefer OLR, an approach that might be related to the fact that the type of resection correlates directly with morbidity and operating times^[13,34].

Given enormous differences between “minor” and “major” LLR in terms of expertise required, morbidity and intra-operative technique, we decided to review them separately after an arbitrary division into: (1) minor LLR which includes left lateral sectionectomy, segmentectomy, anterior bisegmentectomy and non-anatomical resections of anterolateral segments; and (2) major LLR which includes right and left hepatectomies, extended right and left liver resections. At this point it must be added that many authors consider a left hepatectomy (although a “hemihpatectomy”) to be imminently suited for LLR, without the increase in morbidity noted with right or postero-superior LLR^[37-39]. Moreover as most left liver specimens are < 450 g in weight, extraction through small incisions is feasible and an added attraction.

In a review of a recent series by Troisi *et al*^[13] major hepatectomy and resections involving posterior-superior segments were identified as prognostic factors for conversion on univariate analysis, whereas multivariate analysis identified the latter as an independent risk factor. Recently Yoon *et al*^[39] compared outcome after LLR of HCC situated in the anterolateral segment versus those in the postero-superior segment and found that the postero-superior patients had longer operative time ($P = 0.001$) longer hospital stay ($P = 0.039$), higher rate of open conversion ($P = 0.05$) and greater blood loss ($P = 0.068$), but with no

significant difference in post-operative complications or cancer recurrence. Other reports also reconfirm that major hepatectomies were associated with higher blood loss (mean 313 mL *vs* 128 mL; $P = 0.05$), longer hospital stay, recovery and operative time^[34]. Yet despite the above findings, even on comparison of major hepatectomies alone, surgical outcomes were better in LLR in terms of blood loss, complication rates, and length of hospital stay compared to OLR^[23-25,40]. However, it is important to note that some segmental or sectional resections such as a posterior sectionectomy performed laparoscopically can be more technically demanding than a hemi-hepatectomy, given that these are often performed without inflow control at the hilum, occur in an awkward plane and surprisingly, involves more extensive areas of parenchymal transection than an anatomical right hepatectomy.

Single incision liver resections [Laparoendoscopic single-site surgery (LESS)] are now being performed for smaller liver lesions with equivalent or superior results. Tan *et al*^[41] used in 7 patients successfully. Five left lateral sectionectomies, one segment 3, and one segment 5 resection were performed. Similar results were reported by Aikawa *et al*^[42] who performed 8 single site Lap liver resections. However discussion of this technique is beyond the scope of this report.

Conclusion: Therefore in our opinion, there is enough evidence to suggest that for certain resections such as segmentectomies, wedge resections, left lateral sectionectomies and even left hemi-hepatectomies when compared with open liver resection, LLR appears to provide comparable mortality, shorter hospital stay, improved morbidity including decreased blood loss and better cosmesis, cost effectively. It can be suggested that for these procedures a laparoscopic approach should be the standard of care at centres where surgeons are experienced in both liver surgery and advanced laparoscopy. However, it is yet to be conclusively established whether these benefits are extendible to major/postero-superior segment laparoscopic hepatectomies as data is still evolving and patient numbers small. It is essential to recognize requirement of considerable experience in at least 100 major OLR before attempting minor LLR and at least 50 minor LLR before major LLR (opinion).

Laparoscopic liver resection: type of pathology

LLR for benign liver disease: Removal of concern about 'tumour clearance' makes LLR attractive in benign liver lesions and indeed many surgical units started with LLR being limited to benign conditions. On an overview of the current literature, approximately 25% of LLR in benign disease were for cystic lesions, followed by 21% for haemangioma, 18% for focal nodular hyperplasia, 7% for adenomas and 5% for hepaticolithiasis. Understandably most of these patients treated for benign disease were younger (mean age 48 years) and female (M/F 1/8.5) compared to overall LLR cohorts^[32,43,44]. LLR for other benign lesions such as localized intra-hepatic duct

dilatation, and Caroli's disease limited to segment II and III have also been reported with comparable results, in term of operative time, blood loss and mean hospital stay^[45-47]. Although difficult to accurately estimate, one worries that introduction of a less invasive procedure might lead to more benign lesions are being managed surgically. At the risk of stating the obvious we wish to emphasize that "minimal invasive" is not equal to "non-invasive" and indication for surgery must not change^[48].

LLR in malignant liver disease: On review of reports published over the last 7 years, we found that approximately 58% of LLR were done for malignancy, most of which were for Hepatocellular carcinoma (HCC; 57%) or CRLM. Customary concerns when utilising laparoscopic surgery for malignancy, includes anticipated difficulties in intra-operative tumour localization with deep seated tumours, achievement of a safe tumour free margin and port site seeding. However in a meta-analysis of LLR for malignancy, Mirnezami *et al*^[7] did not find any significant difference in the size of the resection margin with LLR when compared with OLR (OR = -0.356; 95%CI:-1.061-0.349, $P = 0.318$) and similarly in the world review by Nguyen *et al*^[49] negative surgical margins were achieved in 82%-100% of reported series, which is clearly comparable to other OLR series. A single center series published in 2011, reported comparable mid-term survival between pure laparoscopic and open right hepatectomy for liver metastases^[3,24].

Widespread use of intra-operative ultrasound has more or less removed concerns about the lack of tactile feedback as an aid to tumour localisation^[28]. Concerns about a higher risk of peritoneal tumour seeding and subsequent recurrence due to positive pressure pneumoperitoneum and use of liver transection devices which could disseminate tumour cells in the spray created during device oscillation have been raised. We scrutinized studies reporting on comparative oncological outcome data for LLR and OLR. Data from these numerous studies many of which are reporting on mature cohorts with at least medium term follow-up, indicates an equivalent recurrence rate between LLR and OLR, indeed proving that above mentioned concerns are unfounded^[18,50-53]. Moreover in none of these reports do specifically either port site metastasis or tumour seeding mentioned as a major concern even with medium to long term follow-up after LLR for malignancy. Hence it can be concluded that LLR presents no greater risk for malignant liver tumours than classic OLR. A number of other authors also agree that the benefits of almost all laparoscopy techniques can be extended to malignant lesions without compromising oncological principles^[54]. Given that the bulk of LLR for malignancy are for two causes, we reviewed below, outcomes in LLR specifically for HCC and CRLM.

LLR for CRC metastasis: Liver resection is now considered standard treatment for CRLM. Kazaryan *et al*^[5] reported a 10-year Norwegian single-centre experience in

Table 2 Some of the major laparoscopic liver resection for colorectal cancer series

Ref.	Year	n	Operative time(min)	Mortality	Blood loss (mL)	Conversion (%)	Hospital stay (d)
Rau <i>et al</i> ^[96]	1998	17	183	0	457	6	7.8
Shimada <i>et al</i> ^[97]	2001	17	325	0	400	0	12
Mala <i>et al</i> ^[98]	2002	13	187	0	600	0	4
Kaneko <i>et al</i> ^[51]	2005	30	182	0	350	3	14.9

Table 3 Some of the major laparoscopic liver resection for hepatocellular cancer series

Ref.	Year	PTS (n)	Cirrhosis present (%)	Tumor size (cm)	Morbidity (%)	Mortality (%)	OS (1 yr/5 yr, %)	RFS (1 yr/5 yr, %)
Dagher <i>et al</i> ^[96]	2010	163	73.6	3.6	22	1.2	92.6/64.9	77.5/32.2
Aldrighetti <i>et al</i> ^[99]	2010	16	56.2	4 + 2.2	25	0	-	-
Nitta <i>et al</i> ^[100]	2010	15	80	4.5	11.6	0	-	-
Yoon <i>et al</i> ^[99]	2010	69	55	3.1	21.7	0	90.4 (3 yr)	60.4 (3 yr)
Cherqui <i>et al</i> ^[101]	2009	37	74	-	34	0	-/72	-/44
Bryant <i>et al</i> ^[32]	2009	64	28	3.5	15.1	0	70 (3 yr)/65 (5 yr)	46 (3 yr)/34 (5 yr)
Chen <i>et al</i> ^[95]	2008	116	100	2.1	6	0	90/61	-
Buell <i>et al</i> ^[4]	2008	36	56	4.6	16	1.6	90/80	23 (2 yr)
Kaneko <i>et al</i> ^[51]	2005	30	100	3	10	0	97/61	87/31
Teramoto <i>et al</i> ^[102]	2005	11	67	2	26	0	100/80	75/40

OS: Overall survival; RFS: Recurrence-free survival.

96 patients undergoing LLR for CRLM (median tumour size 3.0 cm), and described a R0 resection rate of 94%, and 5-year overall survival of 46%, comparable to large open resection series. As most CRLM would have received hepatotoxic pre-operative chemotherapy, a specific concern with LLR in CRLM was intra-operative bleeding (due to liver parenchymal fragility) and post-operative liver failure and compromised liver regeneration after a partial hepatectomy as shown by Stureson *et al*^[55]. Zhou *et al*^[14] pooled analysis of the 6 studies of LLRs for colorectal metastasis showed that hospital stay was shorter in the laparoscopic group ($P < 0.001$), once again with lower blood loss and no greater incidence of post-operative liver failure, despite significant heterogeneity in the analysis cohort. In fact recently synchronous resections of primary colorectal tumour and liver metastasis by laparoscopic approach has been reported^[56] (Table 2).

LLR for hepatocellular carcinoma: When resection for HCC is discussed, an important aspect is the state of the liver, as clearly, incidence of HCC is vastly increased among cirrhotics. However LLR in cirrhotics is discussed elsewhere and emphasis here is placed on analysis of studies comparing LLR to OLR for HCC in terms of survival. Most of them support the use of LLR with no significant differences in 5-year overall survival (61% *vs* 62%) or disease-free survival (31% *vs* 29%) between the LLR and OLR groups^[51]. Similarly Nguyen *et al*^[5] showed, 5-year overall (OS) and disease-free survival (DFS) rates after LLR for HCC to be 50%-75% and 31%-38.2%, respectively. One situation where LLR might be of advantage is when the possibility of salvage transplant after resection exists as post-operative adhesions are clearly reduced after a laparoscopic procedure when compared to open^[57]. In the presence of portal hy-

pertension, adhesiolysis is not just tiresome, but can cause significant haemorrhage and morbidity^[58] (Table 3).

LLR in patients with cirrhosis: Given the incidence of HCC in patients with cirrhosis, clearly a large proportion of patients who come for liver resection will be cirrhotic. Buell *et al*^[2] had by 2008 performed about 500 hand-assisted LLR, of which 31 were in the presence of cirrhosis. These resections included 18 segmentectomies, 6 bisegmentectomies, 4 left lateral segmentectomies, 2 left lobectomies, and 1 central hepatic resection. No right hemihepatectomies were attempted in cirrhotics^[4]. On review of more recent series that deal with HCC only, the percentage of cirrhotic resections would be expected to be higher, and in reality ranges between 45% and 100%^[49,59]. Hence the outcome of LLR in these selected patients is important to note. There are several reasons for LLR to be complicated by cirrhosis: (1) the stiff liver is difficult to manipulate; (2) presence of portal hypertension; (3) underlying clinical or sub-clinical coagulopathy which is often not easy to control accurately; (4) deep tumours or lesions might be hard to palpate when compared to normal pliable livers; (5) pneumoperitoneum with its impact on portal flow, might have a unpredictable influence on post-operative liver function; (6) a fibrotic liver is likely to increase overall bleeding as the stiff, deranged architecture does not allow vessels to collapse/constrict when injured as they might in normal tissue; and (7) last but not least, patients with chronic liver disease are less likely to tolerate complications when compared to patients with no liver disease and indeed need a greater future liver remnant. However a review of the literature however shows that LLR in cirrhotics is indeed safe and feasible^[12,60-63].

In fact these studies uncovers several important find-

Table 4 Some of the larger laparoscopic donor hepatectomy series wherein operative time, transfusion, blood loss, and hospital stay are discussed

Ref.	Method	n	Operative time (min)	Blood Loss (mL)	Transfusion	Conversion	Donor Morbidity	Hospital stay (d)
Soubrane <i>et al</i> ^[69]	Pure laparoscopy LLS	16	320 ± 67 vs 244 ± 55	18.7 ± 44.2 vs 199.2 ± 185.4	NIL	1/16	18.7% vs 35.7% (NS)	7.5 ± 2.3 vs 8.1 ± 3.0 (NS)
Kim <i>et al</i> ^[70]	Pure laparoscopy LLS	11	330 ± 68 vs 306 ± 29	396 ± 72 vs 464 ± 78	NIL	-	0/11 vs 1/11	6.9 ± 0.3 vs 9.8 ± 0.9
Koffron <i>et al</i> ^[66]	Lap assisted Right hepatectomy	20	-	-	-	-	-	-
Wakabayashi <i>et al</i> ^[63]	Lap assisted Right hepatectomy	7	-	-	-	-	-	-
Baker <i>et al</i> ^[78]	Lap assisted Right hepatectomy	33	265 ± 48 vs 316 ± 61	417 ± 217 vs 550 ± 305	-	-	21.3% vs 21.3%	4.3 vs 3.9
Eguchi <i>et al</i> ^[79]	Hybrid Lap Assisted (Both Lobes)	15 (6-RL, 9-LL)	456	NA	NA	-	6.60%	-
Marubashi <i>et al</i> ^[80]	Hybrid Lap Assisted (Left lobe)	31 (LLS-17, LL-14)	510 ± 90	353 ± 396	-	NIL	6.70%	10.3 ± 3.3
Choi <i>et al</i> ^[91]	Lap Assisted and Single Port Lap Assisted	60 20(LADH) 40(SPLADH)	278 ± 72.25(SPLADH) 383.55 ± 41.73(LADH)	450 ± 316.43 (SPLADH) 873 ± 653.01 (LADH)	0.25 ± 0.81 (SPLADH) 1.25 ± 2.05 (LADH)	4/60	12/60	-

ings that suggests that LLR is better than OLR in these patients in term of reduced post-operative ascites, electrolyte disturbances, operating time and blood loss apart from the other more routine benefits of laparoscopy^[60]. Clearly, outcomes are also related to severity of liver disease and hence we reviewed LLR series that dealt with Child's B/C patients. Morise *et al*^[63] in 2011 showed that even in this unwell cohort of patients (with ICG retention > 40% at 15 min), LLR outcomes were favourable, as did Hosokawa *et al*^[64].

Conclusion: Therefore in our opinion, in addition to benign liver disease, LLR is clearly safe in malignancy and achieves equivalent outcomes in terms of resection margins and tumour recurrence compared to OLR with similar benefits as detailed several times above. Incidences of port site or peritoneal recurrences appear insignificant. Despite the technical difficulties posed by cirrhosis for LLR, post-operative outcomes in cirrhotic patients after LLR appear to be better than after OLR, presumably due to less frequent liver decompensation which might be related to less venous collaterals being divided, and reduced inflammatory response after LLR. Hepatotoxic pre-operative chemotherapy did not seem to worsen outcomes in the CRLM cohort. Amongst HCC patients who have undergone resection, fewer adhesions (seen after LLR) in the eventuality of a salvage transplant seems attractive.

MILR IN HEALTHY LIVING DONORS, FOR IMPLANTATION

Open donor hepatectomy(ODH) in live donors substantially affects quality of life, with the patients often developing wound related issues and symptoms such as infection, pain, and deformity^[65,66]. A recent report of donor morbidities in Japan showed that the incidence of donor surgery-related morbidities was 8.4% in total, and the leading morbidity was bile leak (2.6%), followed by wound infection (1.2%)^[67]. As discussed in the sections above, over 150 publications have shown the safety and efficacy of LLR and collectively nearly 3000 LLR have been performed for benign and malignant tumors with a reported peri-operative mortality of 0.3% and morbidity of 10.5%^[2,3]. This combined expertise has led surgeons to consider applying these techniques to a living donor setting with the hope of 'improving the donor experience' and the first laparoscopic left lateral donor hepatectomy(DH) was reported by Cherqui *et al*^[68] in 2002, throwing open the most controversial topic in LLR. Given the limited worldwide experience in minimal assess (MA) donor hepatectomies (MADH) to date, we reviewed both hybrid/hand assisted laparoscopic DH (HALDH) techniques as well as the pure laparoscopic approach (LDH) (Table 4).

Laparoscopic left lateral segmentectomy

Up until recently all the pure LDH were Laparoscopic left lateral segmentectomy (LapLLS), mainly by two groups, the French (Cherqui D, Sourbane O, *etc.*) and Korean (Lee SG, Kim KH, *etc.*) who between them performed about 25 LDH. With no mortality in either series, comparable morbidity and quicker recovery times, they separately concluded that this is a feasible and reproducible procedure in selected centres^[68-71]. First described in 1996, left lateral sectionectomy (LLS) is one of the most anatomic resections in liver surgery and hence benefits from the most standardized laparoscopic surgical approach^[1,37]. Understandably it is clearly associated with a lower rate of complications and mortality than other donor hepatectomies^[16,27,33,69,72-76]. The results are on par with the open procedure with acceptable outcomes. Several studies have shown its advantage over traditional open surgery in reducing the physical and emotional stress experienced by patients^[70,77,78].

Surgical technique for left lateral sectionectomy for donation: Usually performed with the patient in supine and 30° anti-Trendelenburg position, and the surgeon standing between the patient's legs (French position), utilising 4 ports [one 5 mm-irrigation and aspiration; one 10 mm-harmonic scalpel (Ultracision; Ethicon Endosurgery, Cincinnati OH, United States) or surgical aspirator CUSA Excel (Integra Life Science Ltd., IDA Business and Technology Park, Ireland); and two 12 mm - 30° optical device, linear stapler). Carbon dioxide pneumoperitoneum is kept at about 10 mmHg to reduce the risk of CO₂ gas embolism.

The left lobe of liver is mobilised, hilar dissection done and the left hepatic artery and the left portal vein dissected and looped. The portal venous branches to the caudate lobe are dissected, clipped and divided. The liver parenchyma is divided on the right side of the round and falciform ligaments with a harmonic scalpel and an Ultrasonic dissector without vascular clamping. As in open resections, the central venous pressure (CVP) is kept as low as possible, to decrease blood loss from the divided parenchyma. Unfortunately, due to 10-12 mmHg pressure pneumoperitoneum, CVP readings are not reliable during LLR and hence readings prior to insufflation and large visual fluctuations of the venacava with respiration movements serve as useful surrogate estimates of filling pressures. Bleeding during transection is controlled with bipolar electrocoagulation and clips. We divided pedicles to segment 4 during transection using a linear stapler (EndoGIA, Tyco, United States). When the dissection reached the hilar plate, the left biliary duct is cut with a curved sharp scissors in a straight line transversely, and the proximal end is closed with a running suture (PDS 5/0). Once the transaction is complete, a Gelport laparoscopic system (Applied Medical, Rancho Santa Margarita, CA, United States) is inserted to allow hand extraction of the graft through a Pfannestiel incision. Then before inflow occlusion 5000 U of heparin is given intravenously.

With double Hem-o-lock clips (Weck Surgicals, Teleflex, United States) on both the hepatic arteries (Endo TA, 30 mm; Autosuture, United States) and on the left portal vein, the EndoGIA (45 mm) was used to secure and cut the left hepatic vein. The graft is retrieved through the Pfannestiel incision and perfused with cold University of Wisconsin Solution in the standard manner. Once retrieved, the Pfannestiel incision is closed, pneumoperitoneum re-established and hemostasis secured. The cut surface is visualised for any bile leaks and if found, suture ligated before removing ports under vision. Many laparoscopic centres including ours do not place abdominal drains after left lateral resection.

Hand/hybrid assisted laparoscopic donor hepatectomy surgery: In addition to the LDH experience, between 2006 and 2013 there have been several reports on hand/hybrid assisted laparoscopic donor hepatectomy surgery (HALDH)^[16,71,78-83]. Hand assisted or Hybrid technique refers to the placement of an additional hand port through a 10-12 cm incision, through which the surgeon manipulates the liver for mobilization, parenchymal transection and control of bleeding. The devices commonly used are a Gelport (Applied Medical, Rancho Santa Margarita, CA) which is placed through a 6-8 cm incision. The incision can be sited at different locations based on the lobe being harvested (26-29). Right lobe HALDH is advocated by some groups in order to reduce donor morbidity and faster recovery.

Of the authors of 3 of the larger series Baker, Wakabayashi and Koffron have performed collectively, approximately, 60 right hepatectomies *via* HALDH. None have reported mortality, and overall morbidity was comparable to the open approach, with the added advantage of faster recovery and reduced blood loss^[16,78,83]. Although the purists feel hand ports remove the advantage of MILR surgery, these reports confirm better recovery, shorter stay even in this group of patients when compared to the open cohort^[71,80-82]. Moreover on analysing papers that combine data on both pure LDH and HALDH, there appears to be an advantage in utilising these procedure sequentially, to safely ease one through the laparoscopic learning curve, working towards a pure laparoscopic approach^[16]. On a contentious note, some authors feel that given the need for the graft to be removed without damage, pure LDH for a large right lobe can only have a limited benefit. According to Ha *et al*^[71], a 10-cm-long incision is needed to deliver a small-sized right liver graft of 500 g, and a 700 g graft requires an incision of up to 12 cm. Owing to this inevitable limit of the skin incision, they go as far as to say that a totally laparoscopic approach is not suitable when harvesting right liver grafts in contrast to small grafts which can be delivered through a transverse supra-pubic incision.

Nevertheless, we note in the current issue of the *American Journal of Transplantation*, three articles that describe pure LDH approach to left and right lobe grafts^[84-86]. These 3 groups separately, successfully com-

pleted 7 pure LDH (1 right DH) between them with one graft failure, due to an intra-hepatic abscess. Clearly the expertise required was carefully gained over several years as all of these centres have considerable experience in both LLR and liver transplantation. In our opinion clearly these landmark papers answer the first “Can we do it?” question. However when assessing MADH, the second question of “should we do it?” is more difficult to answer and two concerns take precedence, one graft outcomes (considering the “specimen” is expected to function normally after extraction and implantation) and perhaps more importantly, donor safety (considering that DH is peculiar in that healthy humans are exposed to the risk of death).

Graft outcomes: Based on a report by Thenappan *et al*^[87] in 2011, early graft function is at least as good if not better in grafts procured through the MADH approach. Thenappan *et al*^[87] compared 15 MA to 15 open donor hepatectomies with regards to peak bilirubin, AST and INR levels, up to 90 d after transplant and found no significant differences except a minor increase in INR on day 7 in the MA group versus the open group. In fact a trend towards a decrease in biliary and vascular complications was noted (NS), with a one year graft and patient survival of 100% in the MADH group. One could speculate that the closer, magnified vision possible with the laparoscope that enabled better intra-operative detection of bile leaks accounted for the decrease in biliary complication rate. The inevitable increase in warm ischemia time (WIT) was thought to be a potential issue with MADH. However Soubrane *et al*^[69] counter-intuitively showed no significant difference in WIT, but more significantly, no appreciable difference in graft function with the laparoscopic approach. However in this 2006 French paper, of the 16 recipients (All LLS) in the LLR group, there were 2 hepatic artery thrombosis (HAT) and one portal vein thrombosis compared to one each among the 14 open donor hepatectomies (overall rate of HAT in group-3 /30 patients, which is higher than most published reports). With small numbers and short follow-up it is difficult to draw conclusions from this data, and neither have the authors volunteered a possible explanation for this high thrombosis rate.

Donor safety: The second concern of donor safety is more difficult to address given the limited experience. A recent worldwide survey of ODH revealed that the donor mortality rate was 0.20% (23/11553), with 19 of these 23 deaths related to the actual procedure^[88]. In addition, potentially life-threatening near-miss events were reported, with an incidence of not less than 1.1%. Clearly whilst considering MADH, we must not underestimate such “near-miss” events that are unlikely during open hepatectomy, *e.g.*, trocar injury. Of the several original articles on MADH to date, none have reported mortality, and overall morbidity was said to be comparable to the open approach, with the added advantage of faster recovery and reduced blood loss^[16,69,70,78,83]. However in

the Marubashi *et al*^[89] study evaluating the efficacy of HALDH in 31 donors (17 left lateral donation and 14 left lobes), short term outcomes were compared with historical open hepatectomy groups when despite lack of mortality, there were two major morbidities in laparoscopic group, one a diaphragmatic injury and the other, an injury to the right hepatic vein requiring conversion for control. Nonetheless, all donors made early recovery, and assessment by SF36-v2 questionnaire revealed early recovery of all components. As seen with the advent of donor nephrectomy, given the results of more experienced centres, despite occasional mishaps, one might expect numbers to build as time passes, leading to such procedures becoming standard operations. But despite the results discussed above, concerns about technical management of sudden blood loss during liver transaction, length of graft vessels available for implantation (especially extra-hepatic length of the hepatic vein) appear potential issues to the uninitiated. It is reassuring that none of these reports have detected post-operative venous outflow issues during follow-up.

Special issues in MADH-donor selection, liver regeneration:

Given the peculiarities of LDH, it makes sense to have at least loose criteria to try and select the perfect candidates for the MADH approach apart from the type of resection. In our opinion, in addition to the safety criteria that is currently in use for the open approach (age between 18-45 years, medically fit *etc.*), graft steatosis less than 10% (to allow better toleration of portal flow disturbances), estimated graft weight less than 700 g, and conventional hepatic, portal and biliary anatomy, appear at least for the time being reasonable criteria. Avoidance of donors with IRHV and abnormal anatomy allows standardisation of the procedure and reduces operating time. In terms of donor body mass index (BMI) most programmes have a upper limit of 27 or 30 to qualify for donation surgery. However in contrast to the open approach, in those unusual donors in whom despite a high BMI (> 30), liver steatosis appears < 10%, the LDH route appears particularly suited. Interestingly, liver regeneration is a crucial aspect in returning living donors to their pre-morbid state. Although this phenomenon has not been completely studied or understood, there is some evidence that regeneration after MADH is better when compared to the open technique [86% *vs* 73% regeneration at 3 mo ($P = 0.03$)]^[78]. Many prior studies have established a diminished acute-phase stress response and improved immune system function after laparoscopic surgery including 1 study in an animal model of liver resection^[90]. Clearly this is a significant potential advantage that needs further study in a randomized manner.

CONCLUSION

In conclusion LDH is still a controversial indication for LLR and must be “self-restricted” to centres performing at

least 2 such procedures a month. Laparoscopic left lateral sectionectomy has been well validated and has been reproduced by many centres. Laparoscopic assisted or pure left lobe hepatectomy is attractive too in order to reduce the wound related morbidity and enable faster recovery. Pure laparoscopy for right lobe donation needs to be more carefully evaluated in larger series with post-operative outcome data showing its safety and clear benefits before it can be recommended (especially as the incision required to safely deliver a large graft, might negate the benefits).

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