World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i39.11003

World J Gastroenterol 2015 October 21; 21(39): 11003-11015
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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TOPIC HIGHLIGHT

2015 Advances in Liver Transplantation

Current status and perspectives in split liver transplantation

Andrea Lauterio, Stefano Di Sandro, Giacomo Concone, Riccardo De Carlis, Alessandro Giacomoni, Luciano De Carlis

Andrea Lauterio, Stefano Di Sandro, Giacomo Concone, Riccardo De Carlis, Alessandro Giacomoni, Luciano De Carlis, Transplant Center, Department of General Surgery and Abdominal Transplantation, Niguarda Cà Granda Hospital, Piazza Ospedale Maggiore 3, 20162 Milan, Italy

Stefano Di Sandro, Giacomo Concone, Riccardo De Carlis, Department of General Surgery, University of Pavia Medical School, 27100 Pavia, Italy

Author contributions: Lauterio A drafted the article critically for important intellectual content; Di Sandro S, Concone G, De Carlis R and Giacomoni A gave substantial contributions to concept and design of the article, acquisition of data, and interpretation of data; Lauterio A and De Carlis L gave the final approval of the version to be published.

Conflict-of-interest statement: The authors listed have NO financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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Correspondence to: Andrea Lauterio, MD, FEBS, Transplant Center, Department of General Surgery and Abdominal Transplantation, Niguarda Cà Granda Hospital, Piazza Ospedale Maggiore 3, 20162 Milan, Italy. andrea.lauterio@ospedaleniguarda.it
Telephone: +39-02-64442252
Fax: +39-2-64442893

Received: April 28, 2015
Peer-review started: May 6, 2015
First decision: June 2, 2015
Revised: June 27, 2015
Accepted: August 30, 2015
Article in press: August 30, 2015
Published online: October 21, 2015

Abstract

Growing experience with the liver splitting technique and favorable results equivalent to those of whole liver transplant have led to wider application of split liver transplantation (SLT) for adult and pediatric recipients in the last decade. Conversely, SLT for two adult recipients remains a challenging surgical procedure and outcomes have yet to improve. Differences in organ shortages together with religious and ethical issues related to cadaveric organ donation have had an impact on the worldwide distribution of SLT. Despite technical refinements and a better understanding of the complex liver anatomy, SLT remains a technically and logistically demanding surgical procedure. This article reviews the surgical and clinical advances in this field of liver transplantation focusing on the role of SLT and the issues that may lead a further expansion of this complex surgical procedure.

Key words: Liver transplantation; Split liver; Segmental liver; Organ shortage; Graft sharing; Waiting list; *In situ*; *Ex vivo*; Allocation policy

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Core tip: The transplantation community has made numerous efforts to expand the donor pool. While conventional split liver transplantation in which a child received the left lateral segment and an adult the right liver has proved an effective approach to increase organ availability, current outcomes after split liver transplantation for two adult recipients are conflicting. Ongoing surgical refinements and innovations have been reported and dedicated organ allocation policies proposed to encourage the more widespread application of this challenging procedure in the future.

Lauterio A, Di Sandro S, Concone G, De Carlis R, Giacomoni A, De Carlis L. Current status and perspectives in split liver transplantation. *World J Gastroenterol* 2015; 21(39): 11003-11015

Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i39/11003.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i39.11003

INTRODUCTION

More than a quarter of century since the first cases were performed, split liver transplantation (SLT) remains one of the few surgical options to expand the donor pool in view of the ongoing shortage of organs and the increasing waiting list mortality rates.

Reduced-size liver transplantation has already been introduced to address the shortage of small donors, and surgical reduction of donor livers to treat small children has been performed successfully in several centers[1-3]. This option improved the allocation of livers without any increase in the organ supply discarding the removed part of the liver. The year 1988 saw the clinical application of the split liver procedure and the first attempts to expand the donor pool.

In February 1988, Pichlmayr's team in Hannover demonstrated that one donor liver could be transplanted in two recipients by splitting the liver along the umbilical scissure in such a way that the left part (segments Ⅱ and Ⅲ) could be transplanted into a child, and the right part (segments Ⅰ, Ⅳ, Ⅴ to Ⅷ) into an adult[4]. In the following months, other authors reported their initial experiences with this innovative surgical technique splitting the liver by an *ex vivo* dissection of the vascular structures and parenchymal transection. Bismuth and colleagues[5] from the Paul Brousse Hospital, reported an emergency orthotopic liver transplantation in two adult recipients with fulminant hepatic failure. Using one liver divided along the main scissure, they shared the right hemiliver (segments Ⅴ-Ⅷ) and left hemiliver (segments Ⅱ-Ⅳ) while the caudate lobe was resected. Both recipients recovered from coma and regained normal liver function, however both died within two months after transplant from causes not specifically related to the operative technique.

Emond *et al*[6] from the Chicago group reported their preliminary experience with SLT describing a different splitting procedure with technical details related to recipient and donor size. Outcomes demonstrated the feasibility of the procedure highlighting the advantages of SLT in the pediatric population and advocating its role in adult recipients. In the same year, the team at Saint-Luc University Hospital in Brussels, Belgium described the surgical technique applied in the first two cases of SLT at their Institution[7]. Later, many single-center series of *ex situ* SLT were reported from Europe and the United States reflecting efforts to encourage wider application of this surgical technique in clinical practice[8-15]. These initial experiences included a high proportion of high-risk patients in both the adult and pediatric recipient cohorts especially in the main American series.

Based on the experience gained with living donor liver transplantation (LDLT), further expansion of this complex surgical procedure was pioneered by the Hamburg group in 1996 and by the UCLA group in 1997. They first reported a detailed description of the liver splitting procedure in a heart-beating deceased donor - the so-called "*in situ*" split liver technique - instead of the *ex vivo* procedure, using the technique described for left lateral live donor liver procurement[16,17]. Both teams claimed the *in situ* procedure provides superior results, mainly related to shorter cold ischemic time (CIT) avoiding prolonged bench surgery, and long-distance graft sharing between pediatric and adult liver transplant centers.

The first Asian SLT program started in Taiwan in 1997 after SLT had been performed in the other major liver transplant centers in the region with expertise in LDLT[18].

Splitting one liver between two adult recipients was the other goal to achieve to optimize the use of cadaver donors. After the initial attempts to transplant two adult recipients with one liver reported by the Bismuth group, other authors adopted this challenging surgical technique[5]. Two new surgical splitting techniques to transplant two adult recipients were proposed by Colledan *et al*[19] in 1999 and by the Hôpital Beaujon group in 2000 with detailed descriptions of the two surgical techniques[20]. Other small series subsequently demonstrated the feasibility of the procedure, reporting technical refinements and long-term outcomes after SLT for two adults.

The last decade has seen widespread application of SLT for adult and pediatric recipients as a result of the increasing experience of splitting techniques, and numbers are expected to increase in the near future. A similar evolution is to be expected in SLT for two adults especially in high-volume experienced hepatopancreatobiliary and transplant centers.

This article reviews the current status of SLT focusing on surgical technique, outcomes, and other clinical and logistical aspects regarding organ allocation policy and graft sharing.

TERMINOLOGY AND DEFINITIONS

There are two main types of SLT. The universally accepted definition of "conventional" split liver divides the liver to achieve a right extended graft (REG) (Couinaud segments Ⅰ, Ⅳ-Ⅷ) and a left lateral graft (LLG) (Couinaud segments Ⅱ and Ⅲ) for one adult and one pediatric recipient (A/P SLT). The split liver technique for two adult recipients (A/A SLT) divides the liver along Cantlie's line resulting in one right graft (RG) (Couinaud segments Ⅴ-Ⅷ) and one left graft (LG) (Couinaud segments Ⅰ-Ⅳ). Since it was first introduced, different definitions have been proposed for this surgical option including true-right/left split and

full right/full left SLT[21-24].

In addition, two surgical techniques can be applied to split a liver. The "*ex vivo*" procedure splits the liver after a standard multi-organ procurement and the parenchyma and vessels are dissected on a back table with the graft in an ice bath. Conversely, when hilar dissection and parenchymal transection are performed in a heart-beating deceased donor before procurement in a manner similar to LDLT, the technique is named "*in situ*" split.

SNAPSHOT OF SLT WORLDWIDE

Liver splitting is technically challenging and may increase morbidity and mortality. Despite the promising results reported in the last few years, SLT for two adult recipients has remained relatively uncommon, and no more than two hundred transplants have been performed worldwide. Conversely, conventional SLT has long been an established practice but its worldwide expansion differs widely.

European centers have been more active than those in other regions, and alternative procedures to whole liver transplantation (WLT) have been increasingly used in recent years: despite differences across countries in the rate of SLT, about 6% of all LT used split liver grafts[25]. Indeed, a 2006 report by the North Italian Transplant program (NITp) set a more than 20% split rate in a five-year period[26]. By contrast, SLT comprised only about 1% of all LT in the United States, and only 288 SLT were performed in adults between 2002 and 2009 despite estimates that approximately 20% of all deceased donors meet UNOS guidelines for split livers[27]. The reasons for such disparity are probably related to two main challenges in SLT such as graft allocation and recipient selection.

LT in Latin America is currently performed in 13 countries, and is growing heterogeneously despite a limited pool of available organs. Transplant programs from the largest countries of the region have continuously involved LT for almost two decades including LDLT, and reduced, partial, split, dual graft, and domino liver transplantation[28]. According to the 2013 report from the International Registry in Organ Donation, 35 of the 323 LT performed in Argentina were SLT accounting for about 10%[29].

Different reports from the Arab World have described a recent evolution in LT to pediatric transplantation and split liver techniques, and four split liver procedures were recently performed in Saudi Arabia[30,31].

Efforts to explore this surgical technique have been made in Africa and 14 cases of SLT in pediatric recipients were recently reported from a South African transplant center[32].

Split liver grafts continue to make a significant contribution to the total number of LT performed in Oceania, providing 223 (6%) of 3728 grafts by the end of 2013 in adult recipients[33].

Despite extensive experience in LDLT and liver resection, the extreme scarcity of cadaveric liver donors in Asia adversely affects the expansion of SLT. Nevertheless, the Taiwan group demonstrated the feasibility of SLT for two adult recipients in the MELD era performing 21 split liver procedures[18,34-36].

ANATOMICAL CONSIDERATIONS

«La race humaine veut des idées simples. Or, le réel est compliqué» - C. Couinaud.

The high incidence of surgical complications could not only be related to inherent technical failures but probably to an incomplete understanding of the segmental surgical anatomy of the liver, namely bile duct anatomy, the intrahepatic venous drainage, and the vascularization of segment Ⅳ. Some peculiar features of liver anatomy require a thorough understanding to perform split liver procedures.

In general, the left liver shows a more constant anatomy compared to the complex right lobe. Therefore, the more you stay on the left, the fewer the anatomical variations you will encounter. More than 50 years later, the anatomical studies performed by Couinaud remain of paramount importance in current practice[37]. Regardless of the type of split live procedure performed, biliary anatomy is one of the most demanding issues in SLT.

In 2000, Dr. Emond[38], one of the pioneers of SLT, published a comprehensive clinicopathological study investigating the liver anatomy applied to SLT. Anatomical data from *ex vivo* analysis of human liver casts were correlated to in vivo data from partial liver transplants performed in their initial experience. Four specific patterns of left biliary anatomy and three patterns of left hepatic venous drainage were identified and described. The study focused on the left biliary system, identifying a left bile duct plate at the junction of the ducts from segments Ⅱ and Ⅲ, and specific anatomical patterns were described. From the study' s anatomical considerations, when a conventional split liver procedure is performed, the dissection plane would have to be maintained one centimeter lateral to the umbilical fissure in segment Ⅳ to have a 90% chance of a single duct from segments Ⅱ and Ⅲ. Surgical considerations on this issue and the need for two different biliary anastomoses when transplanting a segment Ⅱ and Ⅲ graft have been reported by other authors[17,39].

Almost all centers experienced in LDLT have published benchmark studies investigating the consequences of venous anatomy for the split liver surgeon[40,41]. Different surgical techniques to assure optimal venous drainage will be mentioned in another chapter.

A precise knowledge of segment Ⅳ anatomy is of paramount importance when approaching split liver procedures regardless of the type of graft procured as adult recipients often suffer surgical complications

related to segment Ⅳ ischemia or impaired vascularization and biliary drainage. Many authors involved in this field of LT have called for special attention to be paid to the arterial supply to segment Ⅳ especially when the splitting line runs close to the falciform ligament removing and impairing all the portal branches to segment Ⅳ[27,42]. Another original article from the Korean experience describes in detail the anatomical variations of the origin of the segment Ⅳ hepatic artery and their surgical implications in SLT. As previously reported by Couinaud, Jin *et al*[43] highlighted some interesting aspects of hepatic embryology related to the complex segmental liver anatomy.

SPLIT PROCEDURE: TECHNICAL ASPECTS AND SURGICAL REFINEMENTS

Little has changed in the surgical technique adopted for conventional SLT since the first cases described, whereas different surgical refinements have been proposed to the technique first adopted in A/A SLT for both donor and recipient.

Although many authors advocated leaving the celiac trunk to the LLG in A/P SLT to give a surgical advantage to the pediatric population, certain anatomical situations in both donor and recipient should be discussed on a case-by-case basis and the surgical technique adapted accordingly[9,44,45].

As widely reported in adult LDLT, the venous outflow of the right graft and the addressing of the MHV remain controversial in SLT for two adult recipients. In recent years, many authors have reported their experience and proposed different algorithms based mainly on the dominance of one of the hepatic veins on imaging studies, graft-to-recipient weight ratio (GRWR) and remnant liver volume[46].

In March 2000, the group from Hôpital Beaujon, Paris Ⅶ University, Clichy, France described a modification of the *in situ* splitting technique consisting in a transection performed along the main portal scissure retaining the MHV with the left graft[20]. In the same year, Gundlach *et al*[47] first described how to split the vena cava (the so-called "split cava technique") to provide an optimal venous drainage of both hemiliver grafts and to overcome the decision on addressing the MHV and the vena cava to the left or to the right graft. In two different donor procedures they performed liver transection and bile duct division *in situ* while the vena cava was divided by a longitudinal transection of the front and back walls on the back table after division of the right hepatic artery and right portal vein. The resulting two grafts, each with a large venous patch including both the main suprahepatic vein plus all the additional smaller veins draining directly into the vena cava were transplanted using the piggy-back technique with a side-to-side cavo-colostomy[48]. Although this surgical refinement should solve the disadvantages of both options on where to leave the MHV, the split cava technique was not widely applied in subsequent years.

In 2001, Andorno *et al*[49] reported the long-term results obtained in the first series of eight adult patients undergoing A/A SLT. In their initial experience, no impairment in venous outflow of the right hemiliver was observed leaving the MHV with the left hemiliver provided that the entire right accessory inferior hepatic vein (IHV), with a diameter greater than 5 mm, was reconstructed. Similarly, Azoulay *et al*[50] described a split liver graft preparation where the MHV was kept on the left in continuity with the common trunk of the left and middle hepatic veins. This was also undertaken by Humar *et al*[51] and Zamir *et al*[52] while reporting the first cases performed.

In 2002, Yersiz *et al*[53,54] from Dumont-UCLA Transplant Center, University of California, Los Angeles described details of two different *in situ* split procedures for the creation of split grafts suitable for two adult recipients. To create a left graft including segments Ⅱ, Ⅲ, Ⅳ and a right graft including segments Ⅰ, Ⅴ-Ⅷ, they preserve the common portal vein and the common hepatic duct with the right graft, while the celiac axis is preserved with the left graft in order to maximize the arterial supply to segment Ⅳ. A common cuff including MHV and the left hepatic vein (LHV) is divided from the vena cava and retained with the left graft. The same group also described a different technique for the creation of a larger left graft including segment Ⅰ. The right hepatic vein (RHV) is identified and any accessory IHV larger than 5 mm in diameter is preserved. Before parenchymal transection, the left bile duct is sharply transected at the hilar plate. An isolated Pringle maneuver of the left hilar structures is performed to create a line of demarcation where the transection line runs along the main portal fissure. All the major venous branches draining segments Ⅴ and Ⅷ are preserved for later perfusion and revascularization. The parenchymal transaction is completed at the level of the inferior vena cava (IVC). After cold perfusion, the right portal vein, and the right hepatic artery (RHA) are divided just distal to the bifurcation, and the RHV is divided from the suprahepatic vena cava with a caval patch to complete the creation of a right segment Ⅴ through the Ⅷ graft.

Fan *et al*[34] reported the first case of an *ex vivo* A/A SLT performed at University of Hong Kong Medical Centre in 2003. Their technique consisted in a right lobe including the vena cava and the MHV with parenchymal transection to the left of the MHV. The patient transplanted with the left lobe suffered massive bleeding from the transection surface and congestion of segment Ⅳ and an arterial-portal regurgitation in segment Ⅳ, which finally became atrophied. In this case, the authors raised several concerns on the venous drainage of segment Ⅳ in the left lobe graft and segments Ⅴ and Ⅷ in the right lobe graft. This phenomenon seems to be similar to the remnant liver

of a living donor who had undergone an extended right lobectomy including the MHV[55]. However, the development of arterial regurgitation and venous collateral formation may be impaired in SLT due to the additional preservation-reperfusion injury.

In 2004, Humar *et al*[51,56] modified the splitting technique previously reported, and advocated several advantages in preserving the vena cava with the right graft. Indeed, by preserving the IVC with the right lobe, all short hepatic veins draining the right lobe are kept intact, and all the major hepatic tributaries to the MHV can be reconstructed on the back table improving the venous outflow, minimizing warm ischemic time thereby resulting in a less technically demanding and time-consuming procedure.

Conversely, in the same year Hwang *et al*[57] integrated their surgical knowledge from hundreds of adult LDLT into the first successful A/A SLT performed at the Asan Medical Center, Seoul, Korea transplanting a left lobe (segments Ⅰ to Ⅳ) with the vena cava, common bile duct, and celiac trunk. They advocate thorough planning of the splitting procedure with donor liver size assessment by CT scan before donor surgery as one of the essential steps as in LDLT, and hepatic venous anatomy evaluation especially in routing the MHV.

Again in 2004, Broering *et al*[58] from the Hamburg group published a review discussing the anatomical and technical aspects applied to SLT and summarizing their experience of both conventional SLT and A/A SLT. For conventional SLT, they reported different tips and tricks concerning the anatomic situation after dissection of the portal branches to segment Ⅳ, exposure of the left hilar plate behind the left portal vein, and dissection of the bile duct(s) from segments Ⅱ and Ⅲ. In A/A SLT, their practice is to retain the MHV with the left graft and the vena cava with the right graft as the division of the veins draining segment Ⅰ lead to uncertain viability of the caudate lobe that may require resection. Different strategies to provide optimal venous drainage of both hemiliver grafts were reported including the cava split and other venous reconstructions. Lastly, they discussed the merits of intraoperative cholangiography to identify anatomical bile duct variations, and to decide whether to leave the common bile duct to the left or right grafts. Individual donor arterial anatomy - especially the origin of the segment Ⅳ artery - should govern the sharing of the arterial trunk in both conventional and A/A SLT.

A retrospective study of our experience reported in 2008 pointed out some interesting surgical aspects related to our initial series of 16 *in situ* A/A SLT[59]. As for living donor liver surgery, the resection line was defined both by the parenchymal demarcation obtained after clamping the right hepatic artery and right portal vein, and by intraoperative ultrasound assessment of the MHV course leaving the MHV to the left graft[60].

As for LDLT, the inclusion of the MHV with one or the other graft remains controversial. In 2005, Broering *et al*[61] first described this challenging surgical option to optimize the outflow in both the full right and full left grafts in A/A SLT. They reported the first two livers split according to this new technique for *ex vivo* splitting. After dissection of the hilar structures and opening the vena cava in the midplane, the MHV was split in the middle from its orifice in the vena cava. After completion of the liver parenchyma transection, the two halves of the MHV were reconstructed using donor iliac vein patches.

In 2009, Chakravarty *et al*[62] remarked on the significance of caudate lobe outflow reconstruction in A/A SLT left lobe recipients as previously reported by others in LDLT[63]. They proposed the routine reconstruction of caudate lobe veins greater than 3 mm in diameter to preserve graft volume and function.

Recently, Lee *et al*[36] from the Taiwan group reported some important technical measures applied to A/A SLT when liver grafts were thick and the IVC might be compressed after graft implantation. In this circumstance, the left hemiliver graft (including the MHV) was turned over and implanted in the right liver fossa. A longitudinal incision was made on the IVC and the conference orifice of the middle and left hepatic veins of the graft was anastomosed directly to the IVC.

Heaton *et al*[64], another pioneer in this field of liver transplantation, proposed a technical strategy to expand graft availability by combining the established techniques of conventional SLT and use of the dual graft technique pioneered by Lee *et al*[65]. He suggests using two LLS grafts from two conventional split donor procedures performed simultaneously or by combining a LLG from a living donor and a conventional split liver graft from a deceased donor[64]. The advantages are significantly lower morbidity and mortality for the LLS living donor and a satisfactory liver volume for the adult recipient, improving outcome and reducing the risk of small-for-size syndrome. This strategy is technically demanding and requires surgical skills and significant infrastructure, logistical, and organizational changes but could lead to a potential increase in the number of adult transplants in the United Kingdom of 15%-20% per year.

A recently reported creative solution to the organ shortage is the option of performing sequential or domino liver transplantation with split livers from patients with familial amyloidotic polyneuropathy[66-68]. This uncommon surgical procedure had led to three transplants and represents the maximum example of organ sharing with a true domino effect: the combination of SLT using a cadaveric graft and sequential transplantation using a living whole liver donor.

Issues related to graft size are of paramount importance in partial liver transplantation and especially in A/A SLT. Generally speaking, an estimated GRWR of 0.8% or more is considered a reference in adult to adult LDLT[69]. According to recently published data on a large cohort of A/A SLT from Taiwan, it is

better to allocate split liver grafts to recipients with GRWR greater than 1%[36].

In the authors' experience, a comparison of clinical profiles between recipients of RL grafts and LL grafts showed that low GRWR was the only significant difference for the LL graft recipients and the small-for-size syndrome was common when transplanting LL graft. Although SLT often lacks the pre-operative imaging essential for a liver volume estimation due to logistic and administrative limitations, a precise estimation of liver mass remains crucial. The same authors reported a simply and accurate method to evaluate liver mass using bedside liver ultrasonography and standard liver volumes as an alternative to measuring hemiliver graft sizes.

In situ vs ex vivo SLT

The choice to split a liver *in situ* or *ex vivo* deserves special mention. The advantages of both these options have been widely discussed over the years since the introduction of the *in situ* procedure[16,17]. Data from a national survey published in 2004 demonstrated comparable results for the two different surgical methods in terms of morbidity and mortality except for a higher rate of post-operative bleeding after *ex vivo* SLT, confirming the feasibility of both splitting techniques[70]. A paper published in 2011 by Vagefi *et al*[22] described a large single-center experience with SLT performed from 1993 to 2010 comparing outcomes of *in situ vs ex vivo* split liver grafts emphasizing operative technique and surgical morbidity. They reported no significant differences in survival between adult recipients of grafts split *ex vivo vs in situ* or complication rates. More recently, the same authors retrospectively analyzed nine true right/left *ex vivo* split liver procedures performed during the same period and demonstrated that excellent long-term patient and graft survival can be obtained in A/A SLT with the *ex vivo* option[71]. From a surgical point of view, the *in situ* procedure abolishes *ex vivo* benching and prolonged ischemia times, allowing a better definition of the transection plane and providing two grafts with hemostasis accomplished. In addition, performing intraoperative ultrasound and vascular clamping during the parenchymal transection provides a better evaluation of venous drainage especially for A/A SLT while vascular and biliary evaluation during the *ex vivo* procedure is accomplished using angiography, cholangiography, or the instillation of dilute methylene blue[71].

Lee *et al*[36] recently described a modified *in situ* technique where the liver was split as much as possible during the donor operation but completed after perfusion with preservation solution. In the authors' practice, the bile ducts were divided before cold perfusion for a better understanding of the correct cut point while the parenchyma transection was completed quickly *in situ* with the liver surrounded by ice after procurement of thoracic organs in order to save time for other organ recovery teams.

However, the *in situ* procedure requires a longer operative time that should be expected in the setting of a multivisceral procurement especially in the presence of some degree of hemodynamic instability. The choice of the preferred technique should take into account the habits and experience of the surgical team, donor characteristics and logistic considerations, as well as the allocation policy applied in sharing the second graft. Indeed, it is the wider application of SLT, regardless of the technique preferred by the center, that will result in the largest number of split grafts benefitting the most recipients.

SPLITTABLE DONOR

Which donor livers are splittable? Clearly, the ideal donor suitable for splitting is young with no history of liver disease, normal liver enzymes, hemodynamically stable, and with a short hospital stay. Different criteria for donor splitting have been proposed in recent years and vary among countries and transplant centers[26,72-75]. A recently published report from a specific multicenter SLT program established in 1997 by the NITp listed the following donor eligibility criteria for the split procedure: age less than 60 years, intensive care unit stays shorter than five days, low inotropic support (dopamine $\leqslant$ 5 μg/kg per minute, dobutamine $\leqslant$ 10 μg/kg per minute, and no epinephrine or norepinephrine), and near-normal liver function tests[76].

While criteria for a conventional split liver procedure have been extended in recent years with adjustments to many parameters such as donor age and organ quality, donor requirements remain more pronounced if an A/A SLT procedure is planned[74]. Although donor parameters are critical for selecting livers for splitting procedures, defining absolute contraindications to splitting is difficult and donors should be evaluated on a case-by-case basis after *in situ* evaluation of the liver by an experienced surgeon.

When splitting a liver for two adult recipients, other issues play an important role in the decision whether to split or not to split. The body weight and clinical status of the potential recipient, as well as the availability of an experienced surgeon, and a number of logistical considerations have to be evaluated. While an *in situ* conventional split procedure can be done in any hospital, and no specialized equipment is required, logistical aspects may play a crucial role in planning a split procedure to create grafts for two adult recipients where preoperative imaging evaluation of the liver anatomy and volume may advance donor-to-recipient match and graft allocation. An algorithm for the "real-time" matching of donors and recipients on the waiting lists was recently reported in a multicenter Italian study. The algorithm is based on the GRWR

and graft sharing considering a liver suitable for an A/ASLT procedure whenever no pediatric recipients are available[77].

OUTCOMES

The majority of published series have compared the outcomes of SLT and WLT. We report the outcomes after split liver transplantation from different series considering the different type of graft transplanted. In addition, some special aspects related to the surgical technique and other important issues such as allocation policy, donor and recipient selection, and logistical considerations published in the last ten years are also discussed.

The results of conventional SLT are equivalent to those of whole liver transplantation when performed by experienced groups, and SLT has become a standard procedure in pediatric liver transplant centers.

In 2006, a matched pair analysis by the Hamburg group compared long-term results after extended right SLT and WLT in adults, confirming no differences in patient and graft survival rates[45]. These findings were confirmed in a matched pair analysis by another experienced group from Bergamo[78] and in other single-center reports[79,80].

Results from another large-volume transplant center further confirmed equivalent long-term graft survival rates in both adults and children for segmental grafts with those in WLT. Hong *et al*[81] from the UCLA Transplant Center reported a single-center analysis of 2988 LT performed between August 1993 and May 2006 with a median follow-up of five years. Split-liver grafts included 109 left lateral and 72 extended right partial livers while 49 left lateral and 41 right grafts (segments Ⅴ-Ⅷ with MHV inclusion) from living donors were performed. The ten-year patient survival rates for WLT, SLT, and LDLT were 72%, 69%, and 83%, respectively (P = 0.11), while graft survival rates were 62%, 55%, and 65%, respectively (P = 0.088). Comparing outcomes between adults and children separately by graft types, the adult ten-year patient survival rate was significantly lower for split extended right liver graft compared with adult whole liver and living-donor right liver graft (57% *vs* 72% *vs* 75%, respectively, P = 0.03), while graft survival for adults was similar for all graft types. Conversely, in children, the ten-year patient and graft survival rates were similar for all graft types. Although ten-year graft survival rates after WLT, SLT, and LDLT were comparable in adults, the patient survival was lower for split grafts compared with whole grafts when used in retransplants and critically ill recipients. Interestingly, the authors proposed an alternative system to allow optimal use of split grafts in the current MELD system. In the algorithm proposed, when a donor meets the split criteria proposed by Toso *et al*[72] and the LLG is allocated, the REG instead is matched to an ideal recipient by the splitting transplant center rather than through the MELD system. According to the authors, an organ allocation system with such flexibility would encourage adult-to-child candidate pairing by the same transplantation center and allow preoperative surgical and logistic planning to minimize graft ischemia duration. This proposal aims to optimize graft-to-recipient matching that not only would substantially reduce the loss of lives on the transplant waiting list but also improve outcomes after liver transplantation.

In 2009, Cescon *et al*[21] from the University of Bologna group raised some important considerations regarding recipient selection (donor/recipient match) as a critical aspect of SLT in adult recipients especially in centers implementing a MELD-based allocation policy. They reported the outcomes of 22 *in situ* SLT performed in five years from 2003 comprising both A/A SLT and conventional SLT (2 RG, 3 LG, 11 ERG, ad 6 LLG) in adult recipients. A flexible donor procedure was proposed and the choice how to split was related to donor liver size, and to recipient size and clinical conditions on the basis of the harvesting surgeon's judgment. Recipients with higher MELD scores received right grafts, while smaller adults with no or mild portal hypertension were given left grafts. Overall patient and graft survival rates were 90% and 86% respectively. Patient survival was 84% in recipients of right grafts and 100% in recipients of left grafts. Graft survival was 84% and 89%, respectively. Vascular and biliary complications occurred in 14% and 4% of cases. The authors claimed that LLS should not be excluded a priori for a small adult, and SLT for two adult recipients can be successfully performed even using left lateral segments by assigning one graft according to the MELD score, with a more liberal allocation of the second graft.

In 2012, Zambelli *et al*[24] reported a retrospective analysis of an Italian multicenter experience including long-term results after A/A SLT and graft sharing between November 1998 and January 2005. Their data concerned 43 A/A SLT performed by five centers with more than 60% of grafts shared among centers. According to the Clavien[82] classification, 31 (72%) had complications above grade Ⅱ while three (6.9%) were retransplanted. Hospital mortality was 23% and sepsis was the main cause of death. Actuarial survival rates at one and ten years were 72.1%, 62.6% and 65.1%, 57.9%, respectively for patients and grafts, similar to those reported for adult LDLT by the European Registry over a similar period[83]. The authors emphasized the importance of their multicenter collaboration especially in graft sharing in order to overcome organizational limits and increase the application of this complex procedure.

Another approach to expand the donor pool has been the use of donation after circulatory death (DCD) donors, and these now represent approximately 20 per cent of the cadaveric liver transplant activity in the United Kingdom[84]. Interestingly, Mallik *et al*[85] retrospectively compared outcomes after 17 *ex vivo*

adult SLT (extended right grafts) from donors after brain death (DBD) and 32 WLT from "controlled" donors after DCD (Maastricht category Ⅲ donors) performed at the Cambridge Transplant Centre between January 2004 and December 2010[86]. No formal guidelines exist as to which segment the common hepatic artery and aortic patch are preserved and this is usually left for discussion between the adult and pediatric centers.

None of the 32 patients in the DCD cohort suffered early graft failure, compared with five of 17 in the ERL-DBD series. Reasons for graft failure were hepatic artery thrombosis (HAT) in three cases, progressive cholestasis, and a small-for-size syndrome. In the DCD group, ischemic cholangiopathy developed in six patients, resulting in graft failure within the first year in two, whereas the other recipients remained stable. The incidence of biliary anastomotic complications was similar in both groups. Kaplan-Meier survival analysis confirmed superior graft survival in the DCD liver group (93% at three years *vs* 71% in the ERL-DBD cohort, $P = 0.047$), comparable to that of the remaining 426 whole DBD liver transplants (93% at three years). Patient survival was similar in all groups. According to the authors, one of the reasons possibly related to the poorer outcome in the RL-DBD cohort was the unavoidable much longer CIT due to the splitting procedure and the time required to transport these graft to different centers. As reported elsewhere, we believe that scrupulous recipient selection and an aggressive approach to minimize CIT by considering *in situ* rather than *ex vivo* splitting may improve outcomes with SLT from DBD donors[87].

In 2013, Doyle *et al*[88] demonstrated equivalent outcomes between SLT and WLT reporting the results from a single center retrospective analysis investigating 53 recipients receiving SLT out of 1261 (4.2%) transplants performed from 1995 to 2012. Interestingly, they advocated the use of intraoperative cholangiography to identify a suitable biliary anatomy for splitting and described why they commonly leave the celiac axis with the left lateral segment graft. Twenty-three adults received split grafts: 18 (78%) were right trisegment grafts, four (17.4%) were right lobes, and one (4.3%) was a left lobe. The rates of patient and graft survival at one, five and ten years in adult recipients of split grafts were 95.5%, 89.5%, and 89.5%, respectively. Survival was similar to that of whole organ recipients ($P = 0.15$). Thirty children received split grafts. At one, five and ten years, pediatric split overall and graft survival rates were 96.7%, 80.0%, 80.0%, and 93.3%, 76.8, and 76.8%, respectively ($P = 0.81$). Complications included three retransplantations (10.0%), five bile leaks (16.7%), two cases of HAT (6.7%), two bowel perforations (6.7%), and two bleeds (6.7%). Once again, the authors concluded calling for collaborative networks to be established to maximize liver splitting and consolidate suitable organ allocation.

Very recently, Lee *et al*[36] from the Taiwan group examined the outcomes of A/A SLT in the MELD era, reporting comparable results with those of LDLT even in patients with high MELD scores. Forty-two patients who underwent *in situ* A/A SLT (21 RG and 21 LG) were compared to 282 adult patients who underwent LDLT performed in the period between 2003 and 2010. In a MELD-based allocation policy one of the grafts was allocated to the first priority patient in the waiting list with the highest MELD score while the other was allocated to a size-matched recipient. The MHV was preserved to the left lobe while the IVC was preserved to the right lobe. The large tributary veins (> 5 mm in diameter) of segments Ⅴ and Ⅷ were reconstructed with venous grafts and drained into the IVC. Among 42 A/A SLT recipients, 24 (57.1%) had MELD scores higher than 20. The median (interquartile) MELD score was significantly higher than that for the recipients with LDLT ($P < 0.001$). The complication rates for right or left hemiliver allograft transplantation did not differ ($P = 0.213$), nor did the overall survival rate ($P = 0.457$). The survival rates for SLT at one, five and ten years were comparable with those of LDLT ($P = 0.489$).

These findings were confirmed by the Hannover group after a case by case evaluation of their series of cases performed in the MELD era. In the authors large experience the survival of patients with MELD score greater than 30 at time of SLT were not worse as compared to recipient with a lower MELD[89].

Once again, Hashimoto *et al*[90] reported favorable outcomes after A/A SLT when a MELD system regulates organ allocation. In a 9-years review of their experience the Cleveland group report outcomes of 25 grafts (10 left lobes and 15 right lobes) transplanted in adult sized recipients between 2004 and 2012. Split graft recipients experienced biliary complications more frequently (32% *vs* 10.7%, $P = 0.01$); however, the 5-years graft survival for split grafts was comparable to WLT (80% *vs* 81.5%, $P = 0.43$).

Aseni *et al*[77] compared the outcomes of 64 recipients of A/A SLT prospectively selected using a computerized algorithm in the NITp over a 12-year period among seven collaborative centers with WLT performed in the same period. They described in detail the value of the algorithm developed for "real-time" matching of donors and recipients on the waiting lists on the basis of calculated GRWR and graft sharing considering a liver suitable for AASLT whenever no pediatric recipients are available. The retransplantation rate (9.2%) after A/ASLT was similar to the 10.2% in the WLT group and to the European and United States liver retransplantation figures. The one- and five-year patient and graft survival rates with A/ASLT were significantly lower than for the WLT control group. The five-year graft survival rate of 58.3% for A/A SLT seems closer to the 56% reported in other high-risk liver graft recipients using "marginal donors" or "cardiac death" donors[83]. According to the type of split liver graft, five-year survival rates for patients receiving full

left grafts or full right grafts were 67.2% and 59.3% for patients and 60.7% and 56.6% for grafts but the differences were not significant.

One- and five-year survival rates for the 64 AASLT were 73.2% and 63.3% for patients, and 63.3% and 58.7% for grafts. One- and five-year survival rates for the 1199 patients who received WLT in the same period were 87.2% and 83.1% for patients and 85.2% and 80.4% for grafts. Outcomes were significantly different, with better survival rates in the WLT group ($P = 0.0003$ for patients and $P < 0.0001$ for grafts).

Cauley *et al*[91] recently aimed to determine the current risk of graft failure in adult recipients after SLT. They analyzed data from UNOS concerning 889 split live grafts performed from 1995 to 2010. Similarly to previous analyses from the United States, the authors noted a significantly increased risk of graft failure in split grafts compared with whole grafts in the pre-MELD era from 1995 up to March 1, 2002 when the MELD score was first introduced. Conversely, the risk of graft failure was similar between SLT and WLT recipients in the most recent MELD era with a split-liver hazard ratio of 1.10 ($P = 0.28$) in the MELD era (2002-2010).

Queen Elizabeth Hospital group from Birmingham, United Kingdom, first systematically analyzed SLT outcomes from a technical reconstruction point of view comparing 171 adult right lobe SLT procedures and 1412 WLT procedures performed between January 2000 and June 2012[74]. They described different vascular and biliary reconstruction options in detail, analyzing specific surgical complications against reconstruction techniques. The overall incidence of vascular and biliary complications in the SLT group was greater that in the WLT group ($P = 0.009$ and $P = 0.001$, respectively) whereas no survival difference between the two groups was reported. Overall patient survival rates at one, three and five years were 83%, 80%, and 76% for SLT patients and 86%, 81%, and 77% for WLT patients (0.58). Graft survival was 79% *vs* 83%, 76% *vs* 78%, and 72% *vs* 74% at one, three and five years for SLT and WLT patients, respectively ($P = 0.45$). Their findings indicate that multiple hepatic arteries supplying a right lobe graft were probably related to a higher risk of early graft loss from HAT, although any option of arterial reconstruction using the RHA of the graft combined with a direct biliary anastomosis may result in an increased incidence of biliary complications.

Our experience

By the end of 2014, 1763 LT had been performed at our institution, the Niguarda Hospital Cà Granda, Milan, including 178 segmental liver grafts. We started to expand the donor pool using SLT in 1996. Seventy-one adult recipients underwent conventional A/P SLT and 19 A/A SLT, while since March 2001 (initiation of our LDLT program) 88 adult LDLT have been performed. Except for the first four cases of conventional A/P SLT, the splitting procedures were performed *in situ*. A detailed description of the surgical technique adopted at our center, the algorithm applied for donor selection, and the split-liver allocation policy have been described elsewhere together with a detailed analysis of morbidity[26,59,77]. Concerning A/A SLT, some technical adaptations have been implemented thanks to the growing experience in LDLT and liver surgery such as the use of different surgical devices for parenchymal transection, the addition of intraoperative ultrasound and the mandatory application of a radiological anatomical evaluation before donor surgery.

Patient and graft survival rates at one, five and ten years after conventional A/P SLT were 88.2%, 79.2%, and 68.8%, and 85%, 77.4%, and 69.3% respectively. According to the Clavien classification of surgical complications, 12.7% (9/71) of patients experienced grade 4a complications leading to retransplantation, 7% (5/71) grade 3b complications, and 2.8% (2/71) grade 3a complications.

Patient and graft survival rates at one, five and ten years after A/A SLT were 73.7%, 73.7%, and 67%, and 73.7%, 68%, and 68% respectively. Five patients (26.3%) experienced grade 5 complications (one anastomotic bile leak, one HAT, one hepatic vein thrombosis, and two sepsis) leading to death, one (5.26%) a grade 4a complication (HAT) leading to retransplantation, and four (21%) grade 3b complications with a complete recovery after surgical treatment. The outcomes of our single-center series compare favorably with the overall outcomes reported by others and recently published.

FUTURE PERSPECTIVES

Favorable results with SLT depend not only on the technical factors described over the years but also on scrupulous recipient and donor selection, and dedicated resources. The need to expand the donor pool has justified perseverance in improving the surgical technique after the initial experience with the conventional procedure that led to the current good results. Transplanting two adult patients with one cadaveric liver is the ultimate way of meeting the liver organ shortage without the risks associated with using a living donor. Although A/A SLT still carries a relatively high risk of surgical complications and failure, it is our hope that it will become an established routine in the future. Past failures will help us to understand and define the circumstances under which this type of transplant can be safely performed and how to avoid some of the more frequent complications unique to this procedure.

Close cooperation among centers with adequate experience in split liver techniques is mandatory and should be encouraged. SLT often lacks the preoperative imaging essential for a liver mass estimation and anatomical evaluation. Administrative

limitations must be overcome to accommodate these imaging requirements before donor surgery and organ allocation in order to advance the best graft-to-recipient match. Improving allocation policies by better patient and donor selection plays a crucial role in SLT, and "ad hoc" algorithms for donor-to-recipient matching should be developed and widely applied. Dedicated resources and incentives must be made available to implement programs and facilitate surgeon recruitment and training even though current data do not yet fully justify the investment. In the words of Professor Henry Bismuth, "the highest risk for a patient needing a new liver is the risk never to be transplanted".

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P- Reviewer: Diao TJ **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Liu XM

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ISSN 1007-9327

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