Left split grafts in pediatric liver transplantation: an unexploited resource open to a multiple scenario evolution

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We read with particular interest the article by Angelico and colleagues entitled "Outcomes of left split graft transplantation in Europe: report from the European Liver Transplant Registry" (1), published recently in *Transplant International*. The manuscript, reporting the outcome of 1,500 pediatrics transplantation performed in different European transplant centers using left split grafts (LSG) from deceased donors, makes an updated continental point on one of the most complex activities in the liver transplant (LT) area. Importantly enough, the study represents the widest LSG transplantation series ever reported.

In 1990s split liver technique was widely introduced to shorten the pediatric waiting-list for LT and then mortality without decreasing the pool of organs available for adults. Since then this strategy has been diffusely adopted achieving satisfactory results as reported by Angelico *et al.*

Pediatric waiting list pressure, however, still represent a relevant issue. A 2015 United Network for Organ Sharing (UNOS) registry study on 582 pediatrics LTs reported overall excellent outcomes with 1 and 5 years patient survival around 89–95% (2) and 82.7% (3) respectively, but 30 children deaths on the waiting list and 23 drop out from the list for clinical deterioration due to paucity of resources (3). Mortality in waiting list ranged between 7% and 12% (4).

Although recent analyses suggested that graft and patient survival, for both adults and children, are comparable using whole LT (WLT) or partial organs [split LT (SLT) (5,6), in Europe split grafts transplantation representing only 6% (7,8) of total procedures.

This effect is related to an extremely heterogeneous penetration of split liver techniques in the different clinical programs around the world: UNOS registry in the period 2010–2015 reported a 28% of children receiving a LSG [*vs.* WLT 60% and living donor liver transplantation (LDLT) 12%] (2); from 2008 to 2014 in UK more than 65% of children received a partial graft (7) from cadaver; in Italy in 2017, 64%* of pediatric transplants were performed using a split graft. In Asiatic countries, on the contrary, pediatrics is mainly transplanted using a LDLT graft (9). In this sense, the technique is only a partially exploited resource to overcame donor scarcity. The reasons for such a variability are clearly numerous but inefficient allocation systems and logistic difficulties are among the most relevant.

Splitting a liver adds technical complexity at the procurement and increases the risk of post-transplant complications such as bile leak, strictures and vascular thrombosis (10) and an experienced hepatobiliary surgeon is always required. In situ splitting may hold this condition by better identification of anatomical variant, an easier control of hemostasis of the cut surface and a shorter cold ischemia time (CIT) as well. In the report by Angelico *et al.*, indeed, CIT (significantly longer in *ex situ* splitting) was significantly associated to a worst outcome at multivariate with a dramatic negative effect in smaller recipient suggesting that the *in-situ* approach might bring greater advantages.

* Unpublished data, courtesy of CNT (Centro Nazionale Trapianti).

Strict donor selection remains a key aspect for successful liver splitting; criteria are different around countries and in careful expansion. In the Eurotransplant area donors who meet the condition “<50 years and body weight >50 Kg” are considered potential split donors (11); Italian selection criteria for splitting a liver include age less than 50 years, intensive care unit (ICU) <5 days, low inotropic support and near-normal liver function test (12).

Data from the European Liver Transplant Registry (ELTR) confirm that in LSG from donors 40 years or greater the risk progressively increases suggesting that, in particular after 50 years, the choice to split has to be carefully balanced with the other cofactors of postoperative risk with particular reference to recipient age and severity of clinical conditions.

In the paper by Angelico *et al.* low recipient weight, donor age (<10 years and >50 years), prolonged CIT and urgency negatively impacted short and long-term outcomes. Similar findings were described also for adult recipients using split grafts: UNOS 1, Model for End-stage Liver Disease (MELD) >30, donor age >45 years, long CIT and low-volume center (12-14) have been found to influence survival as well. In addition, Angelico's analysis highlighted that for neonatal recipients a whole liver is rarely available and a partial graft is usually too big to be utilized: large-for-size graft syndrome and high risk of vascular and biliary complications are expected and need to be prevented. For this category of small-size recipients usually the only option is represented by hyper-reduced liver grafts or monosegmental grafts. In urgent clinical scenarios, size mismatch has even more relevant negative impact prompting more cautious analysis of pros and contras of a splitting technique adoption.

Beside lack of capillary adoption and challenges in donor selection, LSG is now facing the further challenge of the comparison with LDLT as far as very long-term results are concerned.

Scrupulous donor and recipient selection, appropriate graft-recipient matching, excellent anaesthesiologic management, dedicated resources and surgeon experience have enabled LDLT to dramatically progress in the last two decades.

Importantly enough, donor mortality in LDLT for pediatric recipient is extremely low and comparable to that expected after kidney donation, with relevant clinical and ethical implications.

In a single center experience Hong *et al.* (14) reported, for adult and pediatrics, no difference in 10 years graft and patient survival using WLT, SLT or LDLT. Similar finding was described for adults in a recent 5-year follow-up meta-analysis (15). US experience in the use of partial graft in adults, however, showed better graft and patient survival for LDLT than SLT (16). Recent long-term data focused on pediatrics LDLT from a Japanese Experience reported 20-year patient excellent survival around 80% (17).

There is a relevant number of direct and indirect evidences (18) suggesting that LDLT may intrinsically be associated to increased very long-term performances due to a better donor selection, shorter CIT, more controllable technical variables and the advantages of a programmable procedure if compared with cadaveric donation.

Jain *et al.* (19) reported lower fibrosis score in HCV-positive adults in a setting of LDLT compared with deceased donor-LT but literature data are contrasting (20) and with limited follow-up.

Studies reporting long-term histological follow up using partial grafts are though required.

If the data on LDLT superiority will be corroborated by further solid longitudinal studies, we might need to be prepared to the evolution to different scenarios for LSG.

Indeed, nevertheless split grafts from deceased donors will still hold tremendous potential for meeting the shortage of organs and reducing waiting list time and mortality in children, future direction may be represented by a relevant increase of the adoption of LDLT in pediatric programs. This strategy may allow to reserve optimal splittable grafts for two adult recipients (“full-right full-left SLT”). Limited case series are described but a wide evolution in two-adult SLT has to be expected especially in high volume transplant centers. This strategy might be corroborated by the fact that in the adult population the gap between offer and request of liver grafts will remain much more relevant than in the pediatric setting.

The Angelico's reports and other recent evidences anticipate a multiple scenario evolution for LSG and related techniques.

LSG will represent the main source of organs for those pediatric recipients without a living donor available. The penetration of the technique in the pediatric centers worldwide is expected to increase based on the good early- and long-term results published. For those pediatric recipients with a living donor available a LDLT will probably be the best choice due to the extremely favorable equipoise between donor risk and very long-term recipient results. The amount of potentially splittable organs "saved" by the expansion of LDLT adoption in children will be converted to split for two adults. If the RAPID technique (auxiliary partial orthotopic transplant of left lateral segments in patients with liver metastases from colon-rectal carcinoma) will confirm its validity a part of the organs with criteria for split will be diverted to that oncologic indication.

Overall, the good results published from the ELTR series prompt the introduction/implementation of allocation roles to mandate a SLT in all donors with favorable prognostic profile in Europe and to promote surgeon technical expertise and logistic support for transplant centers.

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