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Commentary

From individual to population-based benefit of split liver transplantation

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In the last three decades, alternative surgical procedures for liver transplantation (LT), including split liver and living related donor, have helped increase the donor pool [1,2]. The split technique, allowing a cadaveric liver to be divided into 2 functional segments, has led to an increasing number of organs available for child and adult transplant populations [1,2]. From a historical point of view, the first split LT was made in 1988 in Germany and showed inferior patient and graft survival rates compared to conventional transplants; however, improvements in surgical techniques and improved size matching between recipients and their donor grafts has allowed physicians/surgeons to achieve results similar to those of the standard technique [3]. In its 2018 annual report, the European Liver Transplant Registry (ELTR) showed that, between 1988 and 2016, 32% of the alternative surgical procedures for LT were represented by the split liver technique [4].

In a recent issue of the journal, Graviilidis et al. [5] present a systematic review and cumulative meta-analysis of 14 high-quality selected studies published from 2002 to 2017, which compare the transplant outcome of right split liver graft (RSLG) versus whole liver transplantation (WLT) in 6791 patients, most of whom were transplanted in Europe (60%). The results of this meta-analysis ultimately established that recipients receiving an RSLG had a similar post-LT patient and graft survival rate compared to those transplanted with a WLT, as also suggested by clinical experience in Europe [4]. Interestingly, the authors also evaluated, by a subanalysis of the RSLG patient's cohort, the impact of the "splitting method" on surgery-related complications and they found comparable biliary and vascular complications in RSLG and WLT groups only when an "in situ method of splitting" was used. These findings are in line with previous observations reported by Wan et al [3] and strongly encourage a proper worldwide use of the "in situ" splitting technique over the "ex-situ" splitting LT procedure.

If we analyze the results of this meta-analysis, from an epidemiological point of view, some factors need to be better evaluated. The fact that split LT recipients had received significantly younger liver grafts compared to the WLT cohort was not unexpected since, in this setting, a donor age cut-off is often established (i.e. 50 years in Italy). More difficult to explain in such a study is the clinical significance of the lower scores of Model for End-Stage Liver Disease (MELD) observed in the RSLG recipients with respect to the WLT group. In fact, a similar prevalence of hepatocellular carcinoma (HCC) was observed in both cohorts of split and standard LT (HCC 17 vs 15%) and did not justify the low MELD scores, as reported in the study. Moreover, the overall low prevalence of HCC as an indication for any type of liver transplant presented in the LT population reported by Graviilidis et al. [5] need to be carefully examined in view of the recent epidemiological changes of the transplant waiting list worldwide [6].

Liver transplant selection and organ allocation policies for liver transplantation are currently managed by three main principles:

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utility, urgency and transplant benefit [7–9]. Moreover, these principles might be strongly influenced by the progressive reduction of patients listed for end-stage viral diseases and an increase of patients enlisted for HCC.

If we analyze the results of this study [5] from the perspective of individual utility, urgency or transplant benefit [7–9], controversial conclusions may be reached regarding the option to use RSLG. The utility principle selects patients for LT according to a high expectation of post-transplant survival [7–9]. Conversely, a system based on urgency (MELD–based) selects and prioritizes the sickest patients with a high wait-list mortality rate and the greatest need for LT. Transplant-related survival benefit is defined as the life expectancy with transplant minus the life expectancy without it. It can be conceptualized as the amount of life gained each time a transplant is performed. Ideally, transplant benefit is the best principle, since it combines both utility (post-LT life expectancy) and urgency (wait-list life expectancy). Patients with the highest survival benefit are those who have the highest expected post-LT survival and the lowest expected survival without transplantation (i.e. highest MELD score or HCC without other therapeutic options). Remarkably, the Gavriilidis et al. study [5] showed a similar graft and patient survival in the RSLG and WLT groups, suggesting a comparable utility of RSLG and WLT techniques at the individual level.

When we evaluate this study [5] from an urgency or transplant benefit perspective, at the individual level, we could argue that those patients with lower urgency (lower MELD score at LT) within the RSLG group received the transplant. Based on this consideration, we could assume that given a similar utility and a simultaneous lower urgency, also the individual transplant benefit (i.e. the difference between utility and urgency) of the RSLG group was significantly lower than the WLT group. Considering the results of RSLG through the lens of individual urgency and transplant benefit [7,11,12], therefore the study from Graviilidis et al. underlines how the split technique, a technically demanding surgical procedure, follows the principle of utility similarly to WLT at the expense of transplanting patients with lower urgency (i.e. lower MELD score at LT) [3,5]. This is a crucial point since the proportion of patients with HCC and their tumour characteristics might strongly influence individual urgency and transplant benefit [7–11]. In fact, urgency and transplant benefit of RSLG patients would increase significantly if patients with low MELD score had HCC.

Transplant benefit is theoretically the best available system not only at the individual level but also on a population basis [7–11]. In fact, a survival benefit–based system maximizes the overall survival (i.e. before and after transplantation) of all patients on the waiting list and, by extension, all patients in need of an LT [12]. While it may seem evident, it still needs to be stressed that the main benefit of the split liver technique is the chance of a simultaneous transplant of two recipients with a single donor graft.

If we consider the results of the Gavriilidis et al. study [5] from a population-benefit perspective, the interpretation of the results changes significantly. The opportunity to transplant two recipients with a single organ, in fact, gives a tremendous advantage to the split procedure, in terms of intention-to-treat gain of life expectancy to the whole waiting list population when compared to the WLT procedure [12]. From this perspective, we could also accept a small utility or urgency disadvantage in the adult recipient receiving the RSLG, since this disadvantage disappeared when considering the great gain of life expectancy obtained for the pediatric patient.

Finally, we can underline another potential use of segments 2–3 of a splitted liver graft in the future, dedicated to selected patients with unresectable colorectal liver metastases fitting for LT [13]. This is the so-called RAPID concept (Resection and Partial Liver Segment 2/3 Transplantation with Delayed Total Hepatectomy), which is under evaluation in a prospective pilot study in Oslo (clinicaltrials.gov NCT02215889). However, though the preliminary results are promising, it is too early to determine the future role of this approach in clinical practice.

In conclusion, the results of the study by Gavriilidis et al. strongly support the adoption, and possibly the diffusion, of the split liver technique, since this option does not decrease the utility of LT on an individual basis, especially when the “in situ” procedure is applied. On the other hand, the use of RSLG in HCC patients seems to be an appropriate solution to guarantee a high level of individual urgency and transplant benefit [7–11], and it allows for a maximization of the population benefit, simultaneously transplanting two recipients with a liver single graft. Prospective intention-to-treat studies are strongly recommended to test and confirm the individual and population benefit of this technique.

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