Requiem for a champion? Living donor liver transplantation

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Since its widespread application in the late 90s, adult-to-adult LDLT has been the focus of many debates in Western countries. While the number of LDLT procedures peaked in 2001 in Europe and the USA, there has been, thereafter, a significant decrease of cases in the USA and no further increase in Europe (Fig. 1). For example, the number of patients undergoing LDLT dropped from 518 in 2001 to 318 in 2005 and to a projected figure of 168 in 2009, representing a 67% decrease, which currently represents only 3% of all adult liver transplantations performed in the USA.

The recent history of LDLT at the University of Pittsburgh has been the subject of considerable external scrutiny in the public press [1] and professional liver transplantation community. The manuscript by Marsh et al. [2] comprehensively describes the outcomes of right lobe LDLT donors and recipients at Pittsburgh since 2003, when the volumes of LDLT dramatically increased with the arrival of a new surgical team. While there are other single-center, retrospective studies from mature liver programs reporting complications, most of which were published 8–10 years ago, this manuscript is novel in at least three aspects compared to previous reports. First, it comes from Dr. Thomas E. Starzl, and every transplant physician would like to know his opinion on the procedure, because he has been uncharacteristically quiet with his written, public expression regarding LDLT during its expansive application in the past 20 years. Second, it is the most careful and timely analysis on this topic currently available and third it is a call for caution as complications may occur, even more frequently, after the learning curve is completed. Therefore, this publication from Pittsburgh, at this particular time, from this particular author with a strong statement about the safety and general application of LDLT is worthy of careful consideration.

The main message of this study is the high incidence of complications, particularly severe biliary complications, in recipients from LDLT, although one year patient/graft survival was, respectively, 91% and 84%. Those results for morbidity are somewhat alarming considering the elective nature of the procedure and the relatively low MELD scores (MELD < 13 in most recipients) indicating a low risk of dying on the waiting list. Unexpectedly, the results even worsened during the last 2 years of the studied period, highlighting a potential risk for “relaxed vigilance once the procedure becomes routine”. While there was no donor death, a significant incidence of severe negative events was noted in the early postoperative period, mostly occurring in overweight living donors.

Acknowledging the unique relevance of this study, there are some criticisms, which must be discussed. The purpose of the study (as stated in the Introduction) is to clarify controversies surrounding LDLT simply by retrospectively reviewing 121 cases at their center over a 4-year period. Such a single-center study is not optimally configured to make this determination. Other series revealed a variety of results with usually lesser rates of postoperative negative events (Table 1). Noteworthy

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Abbreviations: LDLT, living donor liver transplantation; MELD, model of end-stage liver disease.
is the lower incidence of complications in the Asian series despite higher risk in recipients (MELD often > 22). This better outcome is likely related to the use of thin donors and possibly better donor–recipient match. The results from a study recently published by the adult-to-adult living donor liver transplant study group (A2ALL) indicates a significant survival advantage from the selection of LDLT compared to remaining on the transplant list [3]. The A2ALL study is the largest analysis about recipient risk and benefit from the time of donor evaluation.

On the donor side, the statement in the Methods that there ‘are insurance-driven policies mandating prompt return of the donor to their primary care provider’ is unusual in other areas in the US or elsewhere. Donors, can be, should be and, in fact, are seen or contacted at many centers for post-operative follow-up. We may suspect that in Pittsburgh the absence of such a protocol may likely lead to under-reporting of donor complications. Thus, the incidence of complications on the donor side might even be higher.

Despite those criticisms inherent in the study design, the conclusions drawn by the authors are critically important. For the first time, authors report an increasing incidence of complications in spite of increasing experience with better outcome (Table 1). This observation challenges the concept of the learning curve, as their incidence of complications increased with the number of cases performed, which is in contrast to every available report.

While this study does not offer the largest series of patients treated with this procedure, it is a most objective assessment of morbidity by the treatment based five-tier Clavien system [4,5]. Logically, two questions arise consequently:

- Are the results representative of the “real” world or are they more related to institutional problems of a single center?
- Is the data from other centers misleading because of less reported morbidity due to different and not comparable classification systems?

While many available studies provided a focus on donor morbidity, the data in terms of recipient outcome are mostly incomplete ([6–14], Table 1). Rarely standardized grading systems are applied and only limited series report on complication development over time. In addition, most single centers have yielded a lower incidence of biliary and vascular complications than reported here despite the use of higher MELD recipients. From that point of view, the answer to the

<table>
<thead>
<tr>
<th>Author</th>
<th>Period</th>
<th>n</th>
<th>Survival</th>
<th>MELD</th>
<th>Biliary complications</th>
<th>Vascular complications</th>
<th>No serious complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsh et al. [2]</td>
<td>First half</td>
<td>60</td>
<td>95% (1y)</td>
<td>13</td>
<td>23 (38%)</td>
<td>6 (10%)</td>
<td>26 (43%)</td>
</tr>
<tr>
<td></td>
<td>Second half</td>
<td>61</td>
<td>87% (1y)</td>
<td>13</td>
<td>28 (46%)</td>
<td>12 (20%)</td>
<td>15 (25%)</td>
</tr>
<tr>
<td>Freise et al. [3]</td>
<td>LDLT &lt; 20</td>
<td>167</td>
<td>#c</td>
<td>15</td>
<td>84 (50%)</td>
<td>21 (13%)</td>
<td>#c</td>
</tr>
<tr>
<td></td>
<td>LDLT &gt; 20</td>
<td>217</td>
<td></td>
<td></td>
<td>77 (36%)*</td>
<td>15 (7%)</td>
<td></td>
</tr>
<tr>
<td>Chan et al. [6]</td>
<td>Era I*</td>
<td>50</td>
<td>86% (3y)</td>
<td>29</td>
<td></td>
<td></td>
<td>#c</td>
</tr>
<tr>
<td></td>
<td>Era II</td>
<td>184</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shah et al. [7]</td>
<td></td>
<td>128</td>
<td>#c</td>
<td>14</td>
<td>41 (32%)</td>
<td>#c</td>
<td>#c</td>
</tr>
<tr>
<td>Shah et al. [8]</td>
<td></td>
<td>153</td>
<td>91% (1y)</td>
<td>15</td>
<td>#c</td>
<td>#c</td>
<td>#c</td>
</tr>
<tr>
<td>Hwang et al. [9]</td>
<td></td>
<td>215</td>
<td>#c</td>
<td></td>
<td>48 (21%)</td>
<td>#c</td>
<td>#c</td>
</tr>
<tr>
<td>Kokudo et al. [10]</td>
<td></td>
<td>114</td>
<td>85% (3y)</td>
<td>17</td>
<td>31 (27%)</td>
<td>#c</td>
<td>#c</td>
</tr>
<tr>
<td>Icoz et al. [11]</td>
<td></td>
<td>50</td>
<td>78% (1y)</td>
<td>#c</td>
<td>15 (30%)</td>
<td>#c</td>
<td>#c</td>
</tr>
<tr>
<td>Fan et al. [12]</td>
<td></td>
<td>100</td>
<td>#c</td>
<td></td>
<td>26 (26%)</td>
<td>#c</td>
<td>51 (51%)</td>
</tr>
<tr>
<td>Marcos et al. [13]</td>
<td>A^b</td>
<td>20</td>
<td>80% (?)</td>
<td>#c</td>
<td>7 (35%)</td>
<td>0</td>
<td>#c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>95% (?)</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Testa et al. [14]</td>
<td>B</td>
<td>30</td>
<td>80% (1y)</td>
<td>#c</td>
<td>8 (27%)</td>
<td>#c</td>
<td>#c</td>
</tr>
</tbody>
</table>

* LDLT between May 1996 and May 2006, Era I: first 50 cases, Era II: remaining 184 cases.

a LDLT between June and December 1998, B: LDLT between January and October 1999.

Not reported.

* p < 0.05.
The above-mentioned questions will be decisive and will have a key impact on further policies to offer LDLT. The authors of this study provide new, objective and timely information which will be useful to better discuss LDLT. Of importance, they do not condemn right hemi-liver living donor liver transplantation, but make a call for appropriate monitoring of outcome, and a need for improvement to enable this approach to remain a viable option in some patients with cancer or end-stage liver diseases. The fact that complications increased over time within the same surgical team may serve as an alarming signal for all programs and help to ensure more accurate and continuous assessment of morbidity. Because the conclusions are those of the single most important liver transplant physician in the world, whose name is synonymous with the procedure, all LDLT physicians would be well-served by carefully reading the finale (the last four paragraphs) of this work as they continue their work in this important and ever-evolving field.

References