Resection, transplantation, either, or both? Other pieces of the puzzle

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The study by Margarit et al. in this issue of *Liver Transplantation* provides additional information to manage patients with hepatocellular carcinoma who are candidates for both partial liver resection and liver transplantation (LT). For such patients, who are rare, it is necessary to focus on the advantages and drawbacks of these two treatments on how outcomes of LT are determined. Milestones in the debate on partial resection versus LT in such patients can be summarized as follows.

LT for hepatocellular carcinoma was initiated in patients in whom partial resection was not possible because of liver failure or because of an advanced stage of the tumor; perioperative mortality was high, and recurrences of tumor were frequent. In parallel, the problem of tumor recurrence after partial resection in the cancer-prone cirrhotic liver became apparent. In the early 1990s, a very low perioperative mortality enabled the group from Paul Brousse to assess the incidence of tumor recurrence after partial resection and LT. Patients transplanted with early tumors (one or two nodules of <3 cm diameter) and in whom partial resection was contraindicated because of poor liver function or non-solitary tumors had disease-free survival that was substantially longer than that in patients with solitary tumors of similar size who had undergone partial resection (83% vs. 18% at 3 years). Criteria for undertaking LT in patients with hepatocellular carcinoma were developed further and validated in a prospective study from Milan that was published in 1996; a disease-free survival of 83% at 4 years was achieved. Such good results led to questioning the role of partial resection: if intrahepatic recurrences were so frequent, was this only a palliative rather than a curative treatment? With the growing demand for LT, however, time on the waiting list became a key determinant. In theoretical models first: a decision analysis study suggested that partial resection was cost-effective over transplantation when the time waiting for an organ exceeded 9 months. Subsequently, in a cohort of real patients, the Barcelona Clinic Liver Cancer study group showed that the results of LT were adversely affected by increasing waiting times (2-year intention-to-treat survival falling from 84% for 62 days of waiting time to 54% for 162 days of waiting time). In addition, this group emphasized that survival, rather than disease-free survival, was the most important end point and that, using intention-to-treat analysis (i.e., including dropouts due to contraindications to LT or death while on the waiting list), appropriately selected patients who had undergone partial resection survived longer than those who had been placed on the waiting list for LT.

Is it always necessary, however, to consider the two treatments as opposing alternatives, or could a more flexible strategy be adopted, in which LT is used as a rescue procedure for recurrences after primary partial resection? In a preliminary study, in which the results of LT after a previous partial resection for single nodules of <5 cm in diameter in Child’s A patients were pooled, data on survival and recurrences were similar to those after primary LT. Subsequently, a Markov model predicted that, for a 60-year-old patient with a solitary hepatocellular carcinoma of <5 cm in diameter, the outcome of the rescue strategy would be similar to that for primary LT (7.8 vs. 8.8 yr gain in life expectancy) in a scenario where the waiting time would be 12 months: the dropout rate would be 4% per month, the incidence of tumor recurrence after partial resection would be 20% per year, and in 60% of the patients with recurrences after resection, salvage LT would still be feasible. Decision analysis, despite being unwieldy, had three advantages. The first was that it enabled the main determinants of the question to be set, as summarized above. The second was to show that these determinants, although difficult to estimate for entire cohorts, are more readily assessed in individual cases (e.g., waiting time, mortality of partial resection, and probability of tumor recurrence or of dropout from the waiting list) so

**Abbreviation:** LT, liver transplantation.

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1177
that deciding the most appropriate treatment for a given patient is relatively straightforward. The third was to show the outcome of treatment strategies in terms of years of life gained and of grafts used (23% for salvage and 52% for primary LT; relevant data are summarized in Fig. 1). This study did not analyze the intrinsic value of the graft used as it is highly variable, from almost none (e.g., a marginal graft that nobody would otherwise want) to very high (e.g., a perfect organ that could serve for a split-liver transplantation) but again, this can be easily appreciated in real clinical situations.

Subsequent studies analyzed the clinical relevance of the above findings, with somewhat conflicting results. The group from the Queen Mary Hospital in Hong Kong reported their experience of recurrences after resection and showed that the majority were detected at a stage that permitted salvage LT, a finding consistent with the Markov model.11 Adam et al.12 evaluated the experience of Paul Brousse with 20 patients after salvage transplantation and 195 patients who had undergone primary LT; they reported that the transplantability of patients with recurrences was low (25%), and only a small proportion of patients were candidates for salvage LT (20%). Furthermore, the results of secondary LT were worse than those of primary LT with respect to mortality (28% vs. 2.1%) and recurrences (54% vs. 18%). In contrast, the group from Beaujon reported their experience of 18 patients after salvage LT; survival was similar to that following primary LT in 70 patients (61% 5-year survival and recurrences in only 5% in both groups).13 In addition, the Beaujon team introduced the concept that the pathological analysis of the resection specimen could be used to estimate the risk of recurrence in a given patient and that patients in whom the histology of the specimen was unfavorable should undergo LT without waiting for a clinical recurrence. The Barcelona Clinic Liver Cancer study group added a subsequent piece to the picture.14 This group investigated prospectively a selective approach to salvage LT: 17 patients who had undergone partial resection were divided into two groups according to the histology of the tumor. Eight patients with vascular invasion or additional tumors were offered immediate LT. Patients with less aggressive tumors were observed and underwent LT when recurrences were detected. After a median follow-up of 55 months, the survival in the series was 82%; only six grafts were used for the 17 patients. This study could have been the final word to the question, illustrating excellent patient outcome and use of grafts.

The investigation by Margarit et al.1 in the present issue of Liver Transplantation contributes further depth
and a new piece to the puzzle. The selection criteria for partial resection and LT were clear and practical (e.g., the peripheral vs. central location of the lesion), and the management of patients was state of the art. The data are comprehensive and transparent. The study confirms that, currently, the results of salvage LT are similar to those of primary LT; these findings add to the experience of the Beaujon group, the Barcelona Clinic Liver Cancer study group, and our units (in a total of 19 patients with salvage transplantation in Milan and Geneva, there were two deaths from sepsis and only one recurrence in a long-term survivor). These recent series suggest that the poorer outcomes reported from Paul Brousse could be attributed to a different era of LT (the series was started in 1984) or to chance events in a small cohort. The new finding is that the discrepancy between the potential number of salvage procedures and those effectively undertaken is mainly due to factors independent of the pattern of tumor recurrence. Old age was a major determinant; but other factors, such as compliance, access to a waiting list, and the patient’s preference, may influence the rate of salvage procedures in specific settings. Further studies in which the reasons for not performing salvage LT are detailed according to the categories of Margarit et al.1 may well be enlightening.

The authors ask a new question: specifically, whether it is appropriate to undertake LT immediately in patients with unfavorable histology in a resected specimen. The approach of the Beaujon group and of the Barcelona Clinic Liver Cancer group immediate listing may not necessarily be the best one if the main concern is to avoid recurrences of tumor after transplantation. Who is right? The answer may again depend on the scenario. If grafts are abundant, early salvage LT may maximize the chances of long-term survival for the patient. If donor organs are scarce, as in Milan and Geneva, waiting provides time to assess whether extrahepatic metastases appear, and optimizes the use of a graft for the transplant program or the community. The positive side of waiting implies that, for some patients with large tumors (and possibly a favorable tumor histology), partial resection could be used as a first step, aiming at a later rescue on the transplant program. How long should the wait be in these cases? Only informed guesses are possible. Our tentative suggestion would be 6 months to 1 yr; this period is similar to that advocated in other expanded criteria protocols that aim to construct solid evidence by adhering to guidelines.15

On the basis of recent studies, we recommend that the majority of patients with hepatocellular carcinoma who meet modern criteria for partial hepatectomy on the cirrhotic liver should preferentially undergo resection rather than primary LT, with salvage LT as a reserve option. This recommendation would apply at least for the most common clinical scenarios of advanced age (60 years) and liver disease (hepatitis C), which are associated with relatively poor results after LT. We believe that there is no need for a prospective randomized trial to prove this statement. If the debate may continue when we limit our analysis to patient survival, a more comprehensive view that takes into account the best use of the grafts settles the question. In these cases, the increment in life expectancy associated with LT is minimal (especially if quality-adjusted life expectancy is considered), and it is obvious that the majority of grafts would be better used for other indications. A young patient, a different disease, a marginal donor organ, or a living-donor graft would create a different clinical scenario, which would lead to different conclusions. For example, for a 30-year-old patient with hepatitis B, LT would be the preferred option, and the graft should be associated with a gain of several years of life. Different clinical situations, including complicated ones, are accessible to a similar approach to determine the optimal therapeutic strategy.

Overall, we believe that the debate on resection, transplantation, and salvage transplantation, including the outstanding recent contributions by the groups in Barcelona, is an edifying example of a responsible approach to LT. It illustrates how we can build on each other’s experiences to optimize the treatment of our patients, taking into account what is best for them and what is the best use of the grafts that are trusted to us.

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