

## Is Primary Resection and Salvage Transplantation for Hepatocellular Carcinoma a Reasonable Strategy?

*Editor's note: The following letter by Prof. René Adam and Prof. Daniel Azoulay is in response to a letter by Professors R. T. P. Poon and S. T. Fan, published in the **Annals of Surgery** in November 2004, which commented on two previously published articles respectively by Professors Adam and Azoulay and by Professor Jaques Belghiti et al.*

### Reply:

We thank R. T. P. Poon and S. T. Fan for their comments and their deep review of our article<sup>1</sup> and that of Belghiti et al.<sup>2</sup> Their pertinent analysis is particularly useful since the 2 studies apparently showed discordant results which could impact clinical practice.

The "apparent discordance" relies on items that can be compared and others that cannot. The first point to elucidate is the definition of "salvage transplantation," which was obviously different between our study and that of Belghiti et al.<sup>2</sup> We restricted our analysis of secondary liver transplantation (LT) to patients who had tumor recurrence after liver resection, while in the study of Belghiti et al.,<sup>2</sup> 7 of the 18 secondary transplanted patients did not have recurrence but were transplanted either for deterioration of liver function (4 patients) or "de principe" (3 patients) for positive margins or satellite nodules on the liver resection specimen.<sup>2</sup> Accordingly, the selection of patients was different.

Operative mortality is the second discordance to clarify. In our study, it was high (4/17 - 23.5%) and obviously increased compared with the other study (1/18 - 5.6%). Noteworthy, the operative mortality of our very selected group of

patients also was significantly higher than our 4% operative mortality for LT of nonresected HCC, one of the lowest rates reported in the literature. We attributed this higher risk to the increased difficulty to transplant previously resected patients owing to postoperative adhesions, portal hypertension and impaired liver function. As pointed out by Poon and Fan,<sup>4</sup> 2 patients died of cardiac arrhythmia, a pathology apparently unrelated to hepatic disease. These 2 patients had no pre-existing cardiac disease and were evaluated by anesthesiologists in the same way as that of all the patients of our series. We also hypothesized that high intraoperative bleeding (mean: 16.7 blood units) could have been implicated in the poorer outcome of secondarily transplanted patients. By comparison, Belghiti et al reported a mean transfusion requirement of only 2 units but still, the operative management of patients was different. All our patients were resected via a transabdominal approach while a third of patients of the other study were resected through a laparoscopic or a transdiaphragmatic approach,<sup>2</sup> both operative approaches that could have minimized postoperative adhesions. In addition, 4 patients of our series underwent another intraabdominal operation before LT (2 repeat liver resections, 1 portacaval shunt, 1 esophageal and gastric devascularization) compared with none in the other study. Therefore, patient selection, type of liver resection and timing of LT were different in the 2 studies, explaining probably their difference in operative mortality for secondary LT.

Of much greater concern is the third issue concerning the "intention-to-treat" consideration of both strategies of primary resection versus primary LT. Indeed, the main problem is not to evaluate the outcome of "privileged" patients who are given transplantations after resection, but rather to determine the outcome of the overall group of patients treated by primary resection while being initially potential candidates for LT. The viability of the strategy of "salvage" LT

mainly relies on the absence of a drop-out from LT, of resected patients who develop recurrence. This was not the case in our study. While 77% of 98 patients had tumor recurrence after resection, only 17% could ultimately be transplanted, leaving 60% of patients who would have needed a transplant. Accordingly, the salvage transplantation strategy that we initially supported<sup>3</sup> does not give the resected patient all the chances to be transplanted that theoretical models easily attribute. Such analysis was not performed by Belghiti et al.,<sup>2</sup> and therefore no comparison could be made with our results.

In defending the concept of salvage transplantation, Poon and Fan<sup>4</sup> argued our results of a worse posttransplant survival of secondary transplanted patients (41% at 5 years) compared with that of primary transplanted ones (61%)<sup>1</sup> by suggesting that the longer time interval from diagnosis of HCC to LT for secondary transplanted patients (23.6 months) compared with that of only 9.2 months in primary LT would probably make the difference in global survival from the diagnosis of HCC to LT in the 2 groups, not significant. However, they forgot to mention that probably due to this increased time interval, tumor recurrence was significantly increased (54% versus 18%) and that disease-free survival which should be the real end-point of any cancer treatment was divided by a factor of 2 (29% versus 58% at 5 years).<sup>1</sup> In addition, the first objective of the study was to compare the respective outcome of primary and secondary LT. For this purpose, comparing survival from the time of each of these procedures was methodologically much more adequate.

Poon et al<sup>4</sup> also pointed out one of the most important findings of our report: the low transplantability rate of recurrent tumors after resection (23%) contrasting with that of 80% expected from their theoretical considerations drawn from a very detailed analysis of recurrence in their resected patients.<sup>4</sup> Of our 75 patients who had recurrence after

liver resection, 23 were excluded from LT because of extrahepatic recurrence (31%). Of the 52 intrahepatic recurrences, 20 (27%) had multinodular recurrence (>3 nodules), a situation out of the Milan criteria, and 17 (23%) were transplanted. Among the 15 remaining patients for whom Poon and Fan<sup>4</sup> asked for more details, all had uninodular recurrence. Four died: one less than 3 months after recurrence and 3 after local treatment<sup>2</sup> or repeat resection.<sup>1</sup> Of the 11 patients still alive, 2 have been transplanted from the time of publication of our article, 4 have been treated by alternative treatments (cryotherapy,<sup>1</sup> radiofrequency,<sup>2</sup> arterial chemoembolization,<sup>1</sup> and 4 are followed by another center. We have therefore incremented the proportion of secondary transplanted patients from 23 to 25%. The fact that patients still alive are not considered for transplantation probably reflects that when not decided at once, LT could be secondarily considered with some reserve both by the patient and by the medical team.

The discrepancy between theoretical and real transplantability of resected patients is not specific to our experience. Secondary transplantation of resected patients, even in groups supporting primary resection, is actually very low: 4 of 77 (5%) in Barcelona,<sup>5</sup> 4 of 585 in Bologna (0.7%) (personal communication) and 20 of 163 (12%) in Clichy,<sup>6</sup> all proportions very close to that reported in our study. Also, the Hong Kong team mentioned only 2 salvage transplantations among the 53 patients with transplantable recurrence (3.8%) that they documented in their paper.<sup>4</sup> We are pleased to know from their letter that this experience has been incremented to 16 patients. But even if applied to the initial 53 patients, the proportion of effective LT would be 30%. While they estimated transplantability of recurrence to 79%, what is the explanation of the gap between theory and practice? Probably the same as that of our own experience and that of others. Knowing that recurrence averages 80% at 5 years after

resection, to consider a transplantability of around 80% as suggested by Poon,<sup>4</sup> would lead to an estimation of 64% secondary transplantation in previously resected patients. While LT is available from more than 15 years in many specialized units performing liver resection, the rates ranged from 1 to 12% and we are very far from the projected proportions.

Concerning the patients who developed extrahepatic recurrence, we agree with Poon and Fan that biologic aggressiveness of the tumor could have been increased compared with patients who only developed liver recurrence. However, the objective of the study was to take into account all the patients primarily resected and transplantable at the time of resection. To our knowledge, the current criteria of LT are not refined in such a way that some patients could be excluded while considered “transplantable” in view of the conventional criteria.

Another argument was about the intention-to-treat nature of our study. We agree that it would have been more adequate to include all patients initially listed for either resection or transplantation. Because of the retrospective pattern of the study, all patients listed for resection and finally nonresected were not available. Therefore, our intention-to-treat analysis began at the onset of each treatment. As our drop-out for patients listed for LT was 8%, lower than that reported by the Barcelona group<sup>5</sup> and probably similar to that of patients drop out from resection in the same period, it is very unlikely that the inclusion of all listed patients would have changed the message of our article.

With regard to living related transplantation that we suggested as a possibility to extend the number of primary transplantation, we are also concerned by the risk that this may represent for the donor and we agree that this possibility is far from always possible. However, our objective is for any patient to offer him what we consider the best option for his long-term outcome. In line with this, we do not know what is ethically more justified: to accept a donor risk for a

good outcome in a primarily transplanted patient or to accept the same donor risk for salvage LT with a less optimal outcome? In addition, ethics should also be applied to recipients and the fact that a significant proportion of patients could be discarded from LT by the choice of primary resection, is also debatable.

The same type of argument comes from the impact of organ shortage on the treatment strategy. We think really that the debate should first focus on objective results of the outcome of each strategy. Afterward, any unit could of course adapt its choice according to practical possibilities. As Poon and Fan, we have no doubt that other groups will help us to elucidate what is the best strategy. Our paper opens one way but the truth is still pending. It may differ from one group to another in relation to organ availability and to patient selection for “salvage” LT. Once again we thank Drs. Poon and Fan for their very pertinent analysis.

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