

Review article: liver transplantation for HCC. Treatment options on the waiting list

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SUMMARY

The most widely adopted criteria to admit and maintain patients with HCC and cirrhosis in the waiting list for liver transplantation are the Milano criteria, consisting in the presence of a single tumour ≤ 5 cm in diameter or up to three tumours, none exceeding 3 cm in diameter. Since the average time to transplantation has become longer than 10–12 months in most European and American Centers, the exclusion from the list during the waiting period due to increase of the neoplasm over the established criteria is not uncommon at present. It is mandatory, therefore, to seek an effective therapeutic strategy for patients with HCC waiting for transplantation. Surgical resection and eventual subsequent salvage transplantation seems a cost-effective strategy in resectable HCC. In unresectable neoplasms both transarterial chemoembolization and percutaneous ablation techniques are currently used

and one or the other are chosen according to individual applicability, limitations and specific risks. However, although positive trends were reported, no definitive evidence has been produced so far about their efficacy in increasing patient's survival and decreasing tumour recurrence rates after transplantation. Adult-to-adult living donor liver transplantation is one possible way to shorten the waiting list, but this strategy involves important ethical implications. At present it appears justified to take it into consideration only if the waiting time for cadaveric OLT is expected to exceed 7 months. A more general and definitive attempt to overcome problems related to long waiting times for patients with HCC and relatively preserved hepatic function has been introduced in the USA very recently and consists in prioritizing patients with HCC. However, the overall efficacy of this approach will be established only in some years.

INTRODUCTION

The development of hepatocellular carcinoma (HCC) is one of the most frequent and, from a prognostic point of view, one of the most dreaded complications in the natural history of chronic liver diseases.

Orthotopic liver transplantation (OLT) is the only treatment option available to radically remove both the tumour and the main risk factor for recurrence, i.e. the

cirrhotic liver. Nonetheless, the admittance of patients with HCC to the waiting lists for OLT is restricted, due to the limited resources and the risk of tumoural recurrence in the transplanted liver. Indeed, this risk increases with the size and number of neoplastic lesions in the explanted liver. Hence, various criteria, to be respected at the time of surgery, have been established in order to reduce recurrence and provide a survival rate comparable to that of patients transplanted for cirrhosis without HCC. The most widely adopted are the Milano criteria¹ consisting in the presence of a single tumour ≤ 5 cm in diameter or up to three tumours, none exceeding 3 cm in diameter.

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Tumour progression is usually only a matter of time and consequently OLT may become precluded sooner or later, due to the overcome of the criteria for transplantation. In agreement with studies on doubling time of tumour nodules and natural history of untreated HCC² it was suggested that around 25–45% of the patients will develop tumour-related contraindications to OLT during the first 12 months of waiting.³ In particular, intention-to treat analysis shows a cumulative probability of exclusion from the waiting list of 7.3% at 6, 25.3% at 12 and 43.6% at 24 months.³ The presence of multifocal tumour or a single tumour > 3 cm at initial presentation or a previous history of liver resection for HCC are predictors for dropout.³ Referring to these problems, the excellent outcome of patients receiving a transplant for HCC (5 years survival up to 75%), should be reconsidered taking into account also those candidates who are ultimately excluded whilst still on the waiting list. With this approach, a cost-effectiveness analysis⁴ showed that no benefit in survival is reached in patients with untreated HCC if the waiting period exceeds 6–10 months.

Cirrhotic patients with HCC on the waiting list for liver transplantation represent approximately 10% of the total number of patients at the Bologna Transplant Center. This figure corresponds to that of most centers in Europe. Currently, they undergo the same criteria of priority of cirrhotic patients without HCC (former UNOS criteria), and this leads to a long waiting time for those with mild liver insufficiency, who otherwise would be good candidates for transplantation. To our knowledge the same strategy is adopted in most European Transplant Centers at present.

Since the waiting time is increasing everywhere and has become longer than 10–12 months in most European and American centres, it is mandatory to seek an effective strategy to prioritize cirrhotic patients with HCC or to maintain these patients within the criteria for transplantation while waiting for OLT. To this end, several forms of adjuvant treatment have been tested. Each has its own advantages, but also implies limitations and specific risks, such as, for instance, severe hepatic decompensation or tumour seeding. Therefore, no definite efficient strategy has been established so far. Another possible approach to reduce the need for transplantations and hence shortening the waiting list could be surgical resection and eventual subsequent salvage transplantation, which has been proposed as cost-effective in resectable HCC.⁵

The recent introduction of adult-to-adult living donor liver transplantation is another possible way to shorten the waiting list, despite the shortage of cadaveric organs, but this solution is still restricted, due not only to limited diffusion, but also to ethical implications. A recent cost-effectiveness analysis suggested that this option should be taken into consideration only if the waiting time for cadaveric OLT is expected to exceed 7 months.⁴

Finally, an attempt to overcome problems related to long waiting times, prioritising patients with HCC, has been introduced in the USA very recently, at the beginning of March 2002. Since then, presence of HCC provides additional scores to the Model for end-stage liver disease (MELD),⁶ the currently used scale in USA to create priority in the waiting list of patients,⁷ leading to a shortening of the waiting time and increasing the number of patients undergoing transplantation for HCC, up to about 20% of the total number of liver transplantations (as announced at the Annual Meeting of the American Association for the Study of Liver Disease, Boston MA, USA 1–5 nov 2002).

TRANS-ARTERIAL CHEMOEMBOLIZATION

Trans-arterial chemoembolization (TACE) is probably the most used treatment for multifocal HCC in patients awaiting OLT. It consists in the injection of a chemotherapeutic agent (generally epirubicin), lipiodol and subsequently an embolizing agent in the hepatic artery. Embolization seems to be the main factor responsible for the therapeutic effect, but ischaemia of nontumoural portions of the liver may further impair hepatic function and cause decompensation. Therefore, embolization is contraindicated in those cases with an advanced Child–Turcotte–Pugh score or severe portal hypertension and when the embolization cannot be performed selectively in one or only very few hepatic segments.

At present, despite its large use, there is no general agreement concerning the effectiveness of TACE in reducing dropout from the waiting list or in improving survival and recurrence rate after OLT. A Cochrane meta-analysis⁸ of eight randomized controlled trials totalling 548 patients with operable HCC treated with different kinds of adjuvant chemo- and immunotherapy (both preoperative and post-operative, systemic and locoregional) did not prove the effectiveness of any of the protocols tested.

Albeit, several single reports of nonrandomized trials support the use of TACE whilst on the waiting list

for OLT. Majno *et al.*⁹ reported a higher recurrence-free survival in patients successfully treated with TACE when compared with a group of patients who did not respond to or received no treatment. Total necrosis was achieved in 27% of treated patients and partial response in 50%. However, a high rate of major complications (up to 33%) has been reported.⁹ In another trial, recurrence among treated patients was observed only in those not achieving tumour necrosis, which is usually the case in 25–40% of patients. Another two studies^{10, 11} reported good post-transplantation survival rates in patients treated with TACE (84% survival at 2 years, 79% at 5 years), comparable to those of patients transplanted for cirrhosis without HCC. However, a group of patients not submitted to treatment while in the waiting list was not included in these studies.⁹ A recent prospective trial suggests that TACE is effective in reducing HCC recurrence prior to and after OLT and resection¹² but also shows harmful adverse effects. Other Authors have suggested the combined use of TACE and percutaneous treatments to improve efficacy¹³ but definitive data on combined treatments are still awaited.

Finally, a recent work¹⁴ analysed whether TACE might favour subsequent arterial complications after surgery (through a theoretically possible sub-clinical damage of the vessels). In this study, arterial complications (including pseudoaneurysm, stenosis, anastomotic disruption and thrombosis) were non significantly more frequent in the group of 47 patients who had undergone TACE before OLT than in 1154 patients who had not undergone this procedure (13 vs. 6%, $P = \text{N.S.}$). Also arterial thrombosis was not different between the two groups (8 vs. 5%), confirming the absence of significant additional risk at surgery related to the treatment.

PERCUTANEOUS TREATMENTS

Over the last two decades, several percutaneous techniques have been developed. Among them, the two most utilized in Western Countries, at present, are the classic well experimented percutaneous ethanol injection (PEI), and the recently introduced radio-frequency (RF) thermal ablation.

Percutaneous treatments have the advantage over TACE of preserving hepatic function, but their efficacy in obtaining complete tumour necrosis is somewhat limited in HCC nodules > 3 cm in diameter. Furthermore, feasibility in patients with 2–3 nodules is

questionable. The main risk related to percutaneous techniques concerns tumoural seeding, namely the diffusion of neoplastic cells along the needle-track. A low rate of tumoural seeding has been reported after PEI (0.6%)¹⁵ but it has been sufficient to make the use of PEI in the pretransplantation setting debatable. Patients treated with PEI are not seen as favourable candidates to OLT in some transplant centers, although no clear evidence for this decision was ever produced. Radiofrequency thermal ablation has recently attracted a great interest as an efficient and safe procedure. The risk of seeding is theoretically lower using RF thermal ablation rather than PEI, because fewer sessions (1.2 vs. 4.8) are needed to achieve the tumoural necrosis¹⁶ and the needle can be kept hot when withdrawn, with the aim of 'sterilizing' the needle track. The high seeding rate of 12.4% recently reported by Llovet *et al.*¹⁷ in a group of 32 patients treated with RF thermal ablation, is probably related to the characteristics of the tumours treated: over 30% of the cases were superficial nodules. All cases of seeding occurred, in fact, in patients with subcapsular locations of the nodules, which were approached rather directly. If it is impossible to approach the lesion through non tumoural tissue of at least 1 cm in thickness, then this should be considered a contraindication to percutaneous treatments.

Few data are reported, so far, in the literature concerning the effectiveness of percutaneous treatments in patients with HCC waiting for OLT. Veltri *et al.*¹³ report good rates of complete tumour necrosis in patients treated with adjuvant PEI alone or in combination with TACE (respectively 80% and 100%). RF thermal ablation led to a complete necrosis rate of 75% in a group of 14 patients with HCC (mean diameter of 3.5 cm); no major complication nor tumoural seeding has been reported.¹⁸

Microwave coagulation therapy is another thermal ablation technique under evaluation in OLT candidates with HCC:¹⁹ in 8 patients who underwent OLT, complete necrosis, confirmed upon histologic examination of explanted livers, was achieved.

A cost-effectiveness analysis performed on a theoretical model²⁰ suggests that the use of a percutaneous technique for the treatment of HCC whilst on the waiting list confers a relevant survival advantage independently of the expected waiting time, while surgical resection give a significant advantage only if waiting time for OLT exceeds 1 years.

Both transarterial and percutaneous treatments may lead to a temporary downstaging of HCC. Thus, the

possibility of determining a tumour necrosis sufficient to return a patient with advanced HCC within the limits accepted for OLT has open new a field of investigation in the perspective of liver transplantation. Whether these individuals can be considered acceptable candidates to transplantation remains in fact to be demonstrated.

PARTIAL HEPATECTOMY

The role of liver transplantation in patients with compensated liver cirrhosis and small HCC remains controversial: due to organ shortage, partial hepatectomy is currently the most widespread approach. A cost-effectiveness analysis⁵ suggests that OLT offers a significant improvement in survival rate as well as an economic gain (from 1 to 4.7 years and from US\$ 44454 to US\$ 183840, respectively) when compared to partial hepatectomy. Nevertheless, if the waiting time for OLT is expected to exceed 6–10 months, the risk of complications and exclusion from the list outweighs the estimated gain. In this case, a possible approach consists in primary resection followed by OLT in the event of liver decompensation or tumour recurrence. A recent study by Poon *et al.*²¹ seems to support this strategy in the presence of unifocal HCC, while a poor survival rate was observed in patients resected for 2–3 small (< 3 cm) nodules on cirrhosis (5-years survival rate 48%; with 0% disease free rate). Another theoretical model²⁰ indicates that, in case of an expected waiting time for OLT over 12 months, partial hepatectomy performed in patient with HCC and compensated cirrhosis (Child–Pugh A class) produces an increase in the transplantation rate by 10% due to a reduction in dropout rate.

In a scenario assuming intermediate values for the 4 main variables (12-months waiting list; tumour progression outside transplantation criteria: 4% per month; recurrence after tumour resection: 20% per year; recurrence eligible for transplantation: 60%) the life expectancy was 8.8 years for primary transplantation vs. 7.8 years for primary resection and salvage OLT in the study by Majno *et al.*²² with a calculated use of grafts at 5 years of 52% for a strategy of primary transplantation vs. 23% for a strategy of salvage transplantation.

CONCLUSION

In conclusion, no clearcut evidence supporting the effectiveness of adjuvant therapy for HCC in patients

awaiting OLT is available in the literature. However, candidates to OLT for HCC with preserved hepatic function and without ascites, who can undergo optimal oncologic treatment (either complete chemoembolization or percutaneous thermal ablation), are expected to show the highest likelihood of obtaining a large necrosis of the neoplasm and hence a very low rate of post-transplant tumoural recurrence. The impossibility of an adequate local treatment in the remaining patients whilst on the waiting list, strongly warrants a critical revision of the criteria of priority and an investigation of a different strategy for organs allocations in order to prioritize them and prevent exclusion from the waiting list.

For instance the treatment strategy for patients awaiting liver transplantation for HCC on cirrhosis at the Bologna Liver Transplantation Center is the following:

If the expected waiting time exceeds 4 months, the patient is evaluated for adjuvant therapy for HCC.

Patients with one single lesion either in Child-Turcotte-Pugh class B or in Child-Turcotte-Pugh class A with significant portal hypertension are evaluated for radiofrequency thermal ablation or, as second choice, for percutaneous ethanol injection.

Patients with 2 or 3 nodules and preserved hepatic function (Child-Turcotte-Pugh class A) undergo TACE.

Patients with subcapsular nodules are excluded from percutaneous treatments and evaluated for TACE.

A revision of the criteria for allocation of liver grafts is planned in our Center in the near future and will be based on a modified MELD score⁷ including correction to prioritize patients with HCC.

The historical case series for the treatment of patients with HCC waiting for OLT at the Bologna Liver Transplantation Center is reported in the Audit.

Case series of HCC in patients on the waiting list for OLT at the Bologna Liver Transplantation Center

At Bologna Liver Transplantation Center, 106 patients with HCC underwent OLT between November 1986 and August 2001; HCC was detected before OLT in 70 cases and was incidental in the remnant 36 cases. Ten cases of HCC recurrences were observed, only one of which among patients with incidental HCC (1/36 = 2.8%). Forty-one patients out of 70 with

diagnosis of HCC received a pretransplantation treatment for HCC (34 TACE, 3 PEI, 1 RF thermal ablation, 3 combined treatments); no significant difference in HCC recurrence was observed between treated and untreated patients (6 vs. 3 cases, corresponding to 14.6% vs. 10.1% HCC recurrence rates, respectively, $P = \text{N.S.}$). HCC recurrences were statistically more frequent in patients transplanted before the introduction of the Milano criteria (7 out of 30 patients transplanted before 1997 vs. 3 out of 76 patients transplanted between 1997 and 2001, $P = 0.002$). However, also the usual daily dosage of immunosuppressants was reduced in the same years and this fact might additionally contribute to explain the reduced rate of HCC recurrences.²³ To date, six of the nine patients with HCC on waiting list have undergone TACE (four patients) or RF thermal ablation (two patients) after admission to the waiting list.

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