Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial

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Summary

Background Indications for liver transplantation for hepatocellular carcinoma are evolving and so-called expanded criteria remain debated. Locoregional therapies are able to downstage hepatocellular carcinoma from beyond to within the Milan criteria. We aimed to investigate the efficacy of liver transplantation after successful hepatocellular carcinoma downstaging.

Methods We did an open-label, multicentre, randomised, controlled trial designed in two phases, 2b and 3, at nine Italian tertiary care and transplantation centres. Patients aged 18–65 years with hepatocellular carcinoma beyond the Milan criteria, absence of macrovascular invasion or extrahepatic spread, 5-year estimated post-transplantation survival of at least 50%, and good liver function (Child-Pugh A-B7) were recruited and underwent tumour downstaging with locoregional, surgical, or systemic therapies according to multidisciplinary decision. After an observation period of 3 months, during which sorafenib was allowed, patients with partial or complete responses according to modified Response Evaluation Criteria in Solid Tumors were randomly assigned (1:1) by an interactive web-response system to liver transplantation or non-transplantation therapies (control group). A block randomisation (block size of 2), stratified by centre and compliance to sorafenib treatment, was applied. Liver transplantation was done with whole or split organs procured from brain-dead donors. The control group received sequences of locoregional and systemic treatment at the time of demonstrated tumour progression. The primary outcomes were 5-year tumour event-free survival for phase 2b and overall survival for phase 3. Analyses were by intention to treat. Organ allocation policy changed during the course of the study and restricted patient accrual to 4 years. This trial is registered with ClinicalTrials.gov, NCT01387503.

Findings Between March 1, 2011, and March 31, 2015, 74 patients were enrolled. Median duration of downstaging was 6 months (IQR 4–11). 29 patients dropped out before randomisation and 45 were randomly assigned: 23 to the transplantation group versus 22 to the control group. At data cutoff on July 31, 2019, median follow-up was 71 months (IQR 60–85). 5-year tumour event-free survival was 76·8% (95% CI 60·8–96·9) in the transplantation group versus 18·3% (7·1–47·0) in the control group (hazard ratio [HR] 0·20, 95% CI 0·07–0·57; p=0·003). 5-year overall survival was 77·5% (95% CI 61·9–97·1) in the transplantation group versus 31·2% (16·6–58·5) in the control group (HR 0·32, 95% CI 0·11–0·92; p=0·035). The most common registered grade 3–4 serious adverse events were hepatitis C virus recurrence (three [13%] of 23 patients) and acute transplant rejection (two [9%]) in the transplantation group, and post-embolisation syndrome (two [9%] of 22 patients) in the control group. Treatment-related deaths occurred in four patients: two (8%) of 23 patients in the transplantation group (myocardial infarction and multi-organ failure) versus two (9%) of 22 patients in the control group (liver decompensation).

Interpretation Although results must be interpreted with caution owing to the early closing of the trial, after effective and sustained downstaging of eligible hepatocellular carcinomas beyond the Milan criteria, liver transplantation improved tumour event-free survival and overall survival compared with non-transplantation therapies. Post-downstaging tumour response could contribute to the expansion of hepatocellular carcinoma transplantation criteria.

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Introduction

Hepatocellular carcinoma is one of the leading causes of cancer-related death.[1,2] The incidence of hepatocellular carcinoma is increasing and is the main event leading to death in patients with cirrhosis.[1] Several treatment modalities are available for patients with hepatocellular carcinoma[2] and among them liver transplantation offers the best long-term outcomes when adequate patient

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Research in context

Evidence before this study

We searched PubMed for clinical studies published between Jan 1, 2000, and Sept 30, 2019, using the terms "hepatocellular carcinoma", "transplantation", "selection criteria", "tumor downstaging", "neoadjuvant therapy", "drop-out", "survival", or "recurrence-free survival". Of 25 identified publications, seven reported dropouts and 23 were retrospective, without an intention-to-treat analysis. In most studies, the endpoint of locoregional treatments (mainly transarterial chemoembolisation and ablation) was conversion of hepatocellular carcinoma presenting beyond the Milan criteria to within the criteria. Downstaging within the Milan criteria allows consideration for liver transplantation in most contexts, although with no consensus on patient priority. In all studies, tumour response, transplant-list dropout, and post-transplant recurrence were related to tumour burden at transplantation. Systematic reviews and guidelines recognise moderate evidence in favour of hepatocellular carcinoma downstaging and recommend it in subgroups of patients. Substantial heterogeneity exists between downstaging schedules and eligibility criteria. Two prospective cohorts established predetermined criteria for downstaging and added serum α-fetoprotein below 400 ng/mL and 1000 ng/mL, respectively, to conversion to within the Milan criteria. Limitations in graft allocation policies have so far prevented prospective randomised studies in this area.

Added value of this study

This is, to our knowledge, the first prospective randomised multicentre trial to show that, after successful downstaging of hepatocellular carcinoma beyond the Milan criteria and in the absence of extrahepatic spread or macrovascular invasion, liver transplantation results in improved overall survival and tumour-free survival compared with that achieved with continuation of non-transplantation therapies. In this study, we confirm the high success rate of hepatocellular carcinoma downstaging through locoregional therapies and the tendency for tumour regrowth after radiological response: a condition that might be limited by keeping the time to transplantation as short as possible. This study provides evidence to suggest that intermediate-advanced hepatocellular carcinomas can be selected for the curative option of liver transplantation on the basis of response to locoregional therapies.

Implications of all the available evidence

An absence of trials has, until now, impeded a conclusive approach to neoadjuvant, pretransplantation hepatocellular carcinoma downstaging, specifically when competitive allocation of donated organs to patients with or without liver cancer are considered. This study shows that downstaging and post-downstaging tumour response should be included in proposed expanded hepatocellular carcinoma transplantation criteria. Additionally, our findings are likely to influence priority assignment to patients with hepatocellular carcinoma showing partial or complete tumour response to locoregional therapies. The utility and benefit of liver transplantation in hepatocellular carcinoma could be increased by more effective downstaging protocols, including pharmacological therapeutics combined with conventional locoregional treatments.

selection is provided.[2] The size of the tumour, number of tumour nodules, and α-fetoprotein (AFP) concentration are the main drivers for patient selection. Starting from the Milan criteria (single tumour <5 cm, or up to three tumours <3 cm),[2] patient eligibility for liver transplantation has evolved and the concept of expanded criteria has been proposed in many variants, although without consensus, because no prospective studies have been done with expanded limits that were determined a priori.

One attractive strategy in this context is the use of locoregional treatments to bring patients whose tumour burden is outside pre-established limits to within the Milan criteria. In prospective, uncontrolled studies, tumour downstaging was beneficial, with post-transplantation outcome not significantly different from that of historical patients whose tumours met the Milan criteria at presentation.[3–6] At present, no trial has investigated tumour downstaging as a tool to expand the conventional criteria for liver transplantation in hepatocellular carcinoma and to optimise the scarce resource of donated organs for both cancer and non-cancer indications.

Additionally, after the implementation of treatments against hepatitis C virus (HCV), a universal drop in the number of transplants for HCV-related cirrhosis occurred,[7,8] with a potential relative increase in graft availability for other indications. In this context, less restriction for hepatocellular carcinoma transplant candidates might be justified for those patients whose tumours have been successfully downstaged, with the aim of reducing the risk of both pre-transplantation progression and post-transplantation recurrence.[9]

To assess whether or not liver transplantation provides a survival benefit to patients with cirrhosis with hepatocellular carcinoma beyond the Milan criteria who had a demonstrated and sustained tumour response after neoadjuvant locoregional treatments, we did a randomised controlled trial to test the difference in outcomes after liver transplantation versus continuation of conventional anticancer therapies.

Methods

Study design and participants

The Expansion of Conventional Criteria for Liver Transplantation in Hepatocellular Carcinoma Through Downstaging (XXL) trial was an investigator-led, open-label, multicentre, randomised, controlled trial comparing

liver transplantation (intervention group) versus non-transplantation best available tumour treatment (control group) in patients who had successful downstaging of hepatocellular carcinoma. The trial was designed in two phases: in phase 2b (exploratory phase), we aimed to assess the benefit of transplantation in delaying tumour recurrence after successful tumour downstaging, and in phase 3 (confirmatory phase), we aimed to investigate whether the above benefit translates into prolonged overall survival.

Patients aged 18–65 years presenting with a hepatocellular carcinoma beyond the Milan criteria at nine Italian tertiary care and transplantation centres with availability of all types of therapies for hepatocellular carcinoma were eligible for inclusion. This study was approved by the institutional review board of each participating site and done in accordance with Good Clinical Practice and the Declaration of Helsinki. Ethics approval was granted by the internal ethical and scientific review committee (Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy) on Jan 13, 2010. The trial was registered with ClinicalTrials.gov on July 4, 2011, after the first patient was recruited, due to administrative issues. Eight of 74 patients were recruited between March 1, 2011, and July 4, 2011. All patients were recruited after ethics and protocol approval. All patients provided written, informed consent to the protocol and to each administered treatment.

At enrolment, the main tumour-related eligibility criteria were hepatocellular carcinoma, proven on biopsy or confirmed by the presence of radiological hallmarks, according to the American Association for the Study of Liver Diseases[5] or European Association for the Study of the Liver guidelines,[10] with a 5-year estimated post-transplantation survival of at least 50% at first presentation, according to the Metroticket Calculator.[11] Patients could only be deemed not eligible for curative treatments after multidisciplinary discussion. Only patients with liver function meeting Child-Pugh class A-B7 (to avoid non-cancer contraindication to locoregional treatment) and with Eastern Cooperative Oncology Group performance status 0–1 were included. Patients with recurrent hepatocellular carcinoma could be enrolled if the first occurring and treated hepatocellular carcinoma met the Milan criteria. General contraindications to transplantation, other previous or concurrent malignant diseases, and HIV infection were exclusion criteria.

The main tumour-related exclusion criteria were presence of extrahepatic spread on CT scan or MRI, presence of hepatic hilum lymph nodes with short axis greater than 2 cm, portal vein tumour thrombosis or invasion, and life expectancy of less than 3 months owing to hepatocellular carcinoma or less than 6 months owing to any other disease. A full list of inclusion and exclusion criteria is provided in the appendix (p 3).

Pre-randomisation procedures

During the downstaging phase, tumour downstaging was allowed through unrestricted use of approved therapies for hepatocellular carcinoma, alone or in combination, including surgical resection, radiofrequency or microwave ablation, transarterial chemoembolisation (TACE), and ^{90}Y-selective internal radiotherapy (SIRT). Choice of therapy and schedule of treatment cycles were centre based, according to local expertise. Each treatment cycle included a series of single or combined sessions of locoregional treatments[12] that were considered concluded after multidisciplinary discussion in case of (1) complete radiological tumour response, (2) best achievable response, or (3) technical infeasibility to proceed. Response to treatments was evaluated at 30-day intervals by CT scan or MRI, laboratory tests, and measurement of AFP. Treatments could be repeated or combined up to a maximum of 18 months.

At the end of the downstaging phase, tumour response was assessed by CT scan or MRI according to the modified Response Evaluation Criteria in Solid Tumors criteria. In case of stable disease or tumour progression, or if downstaging continued beyond 18 months, patients were excluded from the study and treated according to the centre's policy (ie, downstaging failures). Downstaging was considered successful if a patient had a partial response (ie, reduction of vital, tumour contrast-enhanced areas of ≥50% or decrease in the sum of diameters of viable target lesions of ≥30%) or complete response; these patients entered a non-intervention period of no less than 3 months (observation phase).

For the **trial protocol** see http://www.hcc-olt-metroticket.org/XXL_TRIAL_protocol.pdf

During the observation phase, according to possible benefit of sorafenib in the neoadjuvant setting,[13] a non-mandatory treatment of the downstaged hepatocellular carcinomas was allowed with oral sorafenib 200–400 mg twice daily according to patient tolerance. Sorafenib withdrawal for toxicity or patient refusal was not considered an exclusion criterion.

For the **Metroticket Calculator** see www.hcc-olt-metroticket.org

By definition, patients in the observation phase had received the best possible treatment and therefore were not eligible for any further intervention. At the end of the observation phase, patients who had a sustained tumour response on CT scan or MRI (ie, patients not showing tumour progression) were considered eligible for random allocation. Patients who had tumour progression during the observation phase were excluded from the study and treated as necessary (ie, pre-randomisation dropouts).

During all the study phases, for patients with AFP at least 400 ng/mL at the time of enrolment, radiological tumour response was confirmed only in case of a parallel percentage decrease in AFP concentration. Moreover, in patients with AFP below 400 ng/mL at the time of recruitment, an increase in AFP concentration above that threshold at the end of the downstaging phase or observation phase was regarded as tumour progression independently of radiological assessment.

See **Online** for appendix

Randomisation and masking

Eligible patients (ie, those with a sustained response after the observation phase) were randomly assigned (1:1) to transplantation (intervention group) or the best alternative non-transplantation strategy at the time of progression (control group). A block randomisation, stratified by centre (appendix p 2) and compliance to sorafenib treatment (yes or no), was applied, separating compliance to sorafenib treatment during the observation phase into two groups depending on whether 50% or less or more than 50% of the standard dose (800 mg/day) had been administered. To guarantee an appropriate balance between the two groups in each stratum, permuted blocks of size two were applied.

The randomisation list was generated by OPIS (Desio, Italy) using a SAS (version 9.4) program. Random allocation was managed centrally by a validated interactive web-response system linked to the electronic case report form. According to the study protocol, the investigator sent the coordinating centre an automatic request for randomisation through the electronic case report form. Only in case of approval did the interactive web-response system allow assignment of a randomisation number and allocation to a treatment group. Investigators and patients were not masked to treatment allocation.

Post-randomisation procedures

Patients enlisted for liver transplantation did not receive specific prioritisation, even though centres were allowed to consider the waitlist duration of the patients in the study as starting at the time of downstaging inception. In the XXL trial, organ donation (liver) from brain-dead donors were used according to centre policy. Liver transplantation was done using conventional or split (adult–paediatric) techniques. The immunosuppression strategy was centre specific and included combinations of calcineurin inhibitors, mycophenolate mofetil, and steroids. A steroid-free immunosuppression regimen was recommended from the second month after transplantation onwards, although it was not mandatory; mTOR inhibitors were allowed in patients with suboptimal renal function.

Patients allocated to the non-transplantation strategy continued follow-up until progression; in such instance, locoregional, surgical, or systemic therapies were applied for tumour control, after a multidisciplinary decision. According to the pattern of recurrence and to the residual liver function, liver resection, ablation, TACE, and SIRT were applied in various combinations. In case of tumour progression beyond eligibility to locoregional therapy and in the case of extrahepatic spread, systemic treatment with sorafenib was administered. Blood tests, AFP, and abdominal and thoracic CT scan or MRI were done every 3 months in both groups to assess tumour-related events: progression in the control group and recurrence in the transplantation group.

Only adverse events of grade 3 or worse were recorded and graded according to the National Cancer Institute Common Toxicity Criteria (version 4.0) at monthly intervals and at any patient's referral. Adverse events were defined as serious when requiring prolonged (>3 days) hospital admission. According to clinical presentation, type of treatment, and recommended definitions, local investigators registered and rated serious adverse events as treatment-related or not.

Outcomes

In phase 2b, the primary outcome was 5-year tumour event-free survival. Time to tumour event was calculated as the interval between the randomisation date and the date of tumour recurrence or the date of tumour progression otherwise, with censoring at the date of death or last contact for event-free patients. In phase 3 of the study, the primary endpoint was 5-year overall survival. Overall survival was calculated as the interval between the randomisation date and that of death from any cause, with censoring at the date of last follow-up for patients remaining alive. Secondary endpoints were transplantation versus non-transplantation cost–benefit analysis, analysis of the efficacy of downstaging and systemic therapies during the observation phase, evaluation of pre-transplantation and post-transplantation radiology–pathology correlation, and validation of the Metroticket prognostication model. The secondary endpoints were not assessed because of the small sample size caused by early study closure.

Statistical analysis

Phase 2b was designed to require observation of 52 tumoural events, with accrual of 65 patients per group over 1·5–2 years and a minimum follow-up of 6 months. Such a calculation was done incorporating a futility stopping rule at 50% significance level, around 10% patient loss, a median baseline time to tumoural event of 12 months, and 90% power to detect a 30% relative hazard reduction (hazard ratio [HR] 0·70). A one-sided log-rank test ($p<0·5$) in favour of the experimental group at the end of phase 2b would have implied continuation of patient accrual to achieve the overall sample size required for phase 3; such a criterion may be regarded as a stopping rule based on futility. Phase 3 was designed to detect a 25% survival increase in the experimental group, from an anticipated 20% at 5 years in the control group (based on published literature and pilot data). Such a difference corresponds to a HR of 0·50. We estimated that 87 deaths, requiring the accrual of 130 patients per group over 3 years and a minimum follow up of 6 months, would yield 90% power to detect the target difference at a 2·5% significance level (one-sided log-rank test).

The statistical analyses planned for assessment of the post-randomisation phase data are reported in the study protocol. However, the study stopped early before reaching the prefixed number of events; thus, the statistical power was no longer achievable. We describe herein the statistical methods related to the results shown in the present report.

We used conventional descriptive statistics to describe continuous and categorical variables. Time to tumoural event and overall survival curves were estimated by the Kaplan-Meier method and compared using a log-rank test, with stratification by centre and compliance to sorafenib. HRs and 95% CIs were estimated using Cox proportional hazards regression models with stratification by centre and compliance to sorafenib; p values calculated by the two-sided Wald test are also shown. The Cox model proportional hazards assumption was checked using scaled Schoenfeld residuals.

Survival benefit was assessed in a post-hoc analysis and was estimated as the difference between restricted mean survival time in the treatment and control groups at 5 years by resorting the method based on pseudo values calculation and generalised estimating equation modelling.[14] An additional post-hoc analysis exploring the possible modifying effect of response status after downstaging on the benefit of transplantation was done by fitting a generalised estimating equation multivariable model including treatment group, response, and their interaction as covariates. A significant interaction would indicate a different post-transplantation gain in survival according to response status after downstaging.

Other post-hoc analyses were evaluation of tumour response according to duration of downstaging (Wilcoxon-Mann-Whitney *U* test), evaluation of survival according to duration of downstaging (estimated by the Kaplan-Meier method and compared by the log-rank test), progression rate after downstaging according to compliance to sorafenib treatment (Fisher's exact test), and differences in transplantation waiting time according to partial versus complete tumour response (Fisher's exact test). As in the Metroticket Calculator formulation, tumour burden was measured on digital imaging as the sum of tumour nodules and the size of the largest tumours as a whole.[11]

Statistical analyses were done according to the intention-to-treat population (ie, including all patients as randomly assigned) and were done in SAS (version 9.4) and R (version 3.4.1). Statistical test results were considered significant when the corresponding p values were below the 5% threshold.

This study is registered with ClinicalTrials.gov, number NCT01387503.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

After patient enrolment was started, a national programme for expansion of the donor pool, including donation after cardiac death and revision of transplantation priorities for hepatocellular carcinoma,[15] was implemented progressively. These major changes, not considered in the study design, forced the trial monitoring committee to recommend study closure on March 31, 2015. Between March 1, 2011, and March 31, 2015, 74 patients had been enrolled in the study. Baseline characteristics of these 74 patients are shown in the appendix (p 4). Owing to the study closure, the required number of tumoural events or deaths was not met. The trial monitoring committee suggested to test the results after 4 additional years of follow-up to have a minimum follow-up of 5 years for each patient recruited.

Of the 74 enrolled patients, seven were excluded and 13 had progressive disease before randomisation, leaving 54 who were successfully downstaged (24 partial responders and 30 complete responders; 73% response rate; figure 1). Median duration of tumour downstaging was 6 months (IQR 4–11). During the subsequent observation phase preceding randomisation, 30 (56%) of 54 patients received sorafenib, whereas 24 (44%) did not receive treatment on the basis of investigator judgment or had the drug withdrawn owing to intolerance or worsened

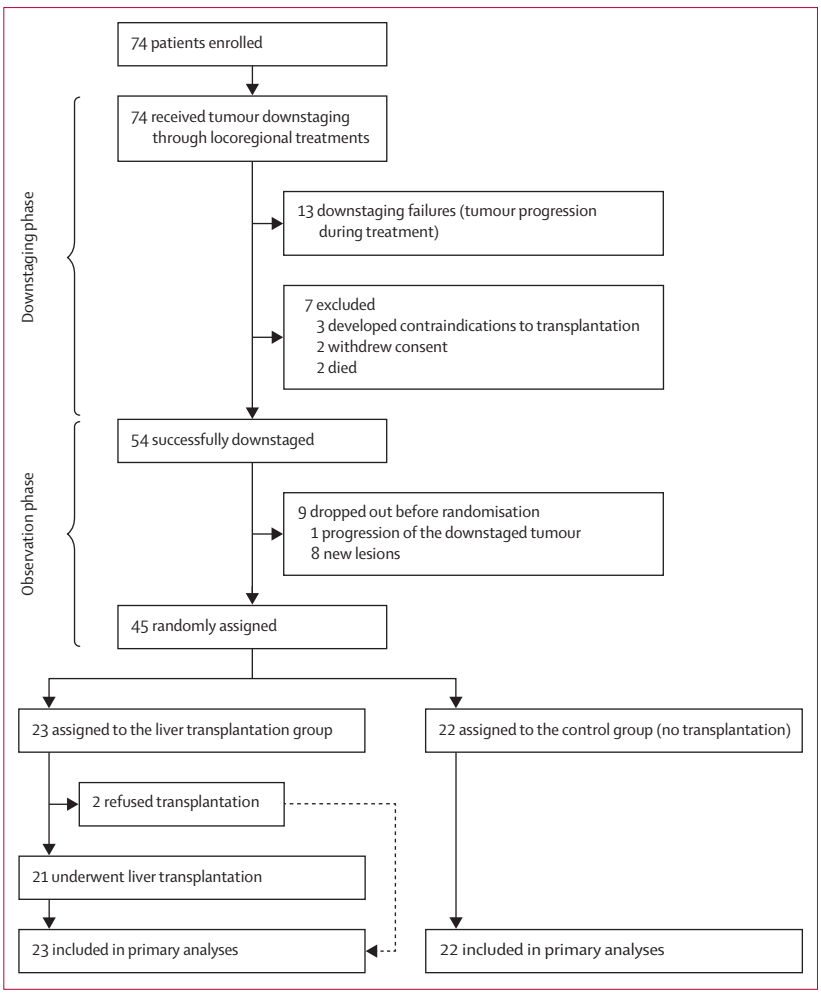

Figure 1: **Trial profile**

	Transplantation group (n=23)	Control group (n=22)
Age, years	54·8 (51·7–58·8)	59·1 (51·2–62·0)
Sex		
Male	22 (96%)	21 (95%)
Female	1 (4%)	1 (5%)
Body-mass index, kg/m²	26·7 (25·2–28·1)	25·5 (22·9–26·5)
Cause of liver disease		
Hepatitis C virus	11 (48%)	17 (77%)
Hepatitis B virus	5 (22%)	2 (9%)
Alcohol or metabolic	6 (26%)	2 (9%)
Other	1 (4%)	1 (5%)
Disease presentation		
First diagnosis	22 (96%)	17 (77%)
Recurrent hepatocellular carcinoma	1 (4%)	5 (23%)
Downstaging procedures		
TACE only	12 (52%)	10 (45%)
RFA, SIRT, or surgery only	5 (22%)	3 (14%)
RFA	2 (9%)	2 (9%)
SIRT	1 (4%)	0 (0%)
Surgery*	2 (9%)	1 (5%)
Combinations of treatments	6 (26%)	9 (41%)
At least one of:		
TACE	17 (74%)	18 (82%)
RFA	8 (35%)	9 (41%)
SIRT	1 (4%)	1 (5%)
Surgical resection	4 (17%)	3 (14%)
Number of treatment sessions		
1	10 (43%)	8 (36%)
2	8 (35%)	5 (23%)
3	4 (17%)	3 (14%)
>3	1 (4%)	6 (27%)
MELD score	8 (7–10)	7 (7–9)
Child-Pugh class		
A	21 (91%)	19 (86%)
B	2 (9%)	3 (14%)
Number of nodules	3·0 (2·0–4·0)	3·5 (2·0–4·0)
Largest tumour diameter (mm)	50·0 (40·0–55·5)	40·0 (24·3–54·5)
Sum of the diameters of viable tumour (mm)†	79·0 (70·5–95·5)	71·0 (60·8–93·5)
Tumour burden‡	7·5 (7·0–8·6)	7·0 (6·2–8·1)
α-fetoprotein (ng/mL)	12·4 (7·4–82·1)	8·5 (4·5–63·8)
Met Milan criteria		
Yes	0 (0%)	0 (0%)
No	23 (100%)	22 (100%)
Met Up-to-7 criteria		
Yes	7 (30%)	12 (55%)
No	16 (70%)	10 (45%)
Met UCSF criteria		
Yes	12 (52%)	13 (59%)
No	11 (48%)	9 (41%)
French model		
Low risk (≤2 points)	10 (43%)	11 (50%)
High risk (>2points)	13 (57%)	11 (50%)

(Table 1 continues on next page)

liver function. Median duration of the observation period was 3 months (IQR 2·8–3·2). During the observation period, tumour progression occurred in nine (17%) additional patients; these patients were excluded from the study, leaving 45 with sustained response to tumour downstaging who were randomly assigned to transplantation (n=23) or non-transplantation (n=22). Overall, 29 of the 74 enrolled patients were not randomised (failure rate of 39%). Tumour progression was the reason for downstaging failure in 22 (76%) of 29 patients, whereas seven developed other non-cancer conditions. Liver function and tumour characteristics at randomisation of these 45 patients are shown in the appendix (p 5). Serious adverse events observed during downstaging are reported in the appendix (p 6).

Baseline characteristics at enrolment of the patients who were subsequently randomised are shown in table 1. One patient in the control group exceeded the planned age limit, at 66 years old. He was accepted as eligible as his birthday was only 8 days before the date of enrolment. At randomisation, two (9%) of 23 patients in the transplantation group versus none of 22 patients in the control group had hepatocellular carcinoma beyond the Milan criteria, whereas all cases met University of California San Francisco (UCSF), Up-to-7, French model, and Hazard Associated with Liver Transplantation-hepatocellular carcinoma (HALT-HCC) low-risk score requirements (appendix p 5).

At data cutoff on July 31, 2019, median follow-up for the randomised population was 71 months (IQR 60–85). No patient randomly assigned to transplantation had recurrence or progression of hepatocellular carcinoma while on the waiting list. Median time from randomisation to transplantation was 3 months (IQR 2–5), leading to a total time to transplantation (ie, from first referral of a hepatocellular carcinoma beyond Milan criteria to transplantation after successful downstaging) of 12 months (IQR 10–14). Two of the 23 patients randomly assigned to transplantation refused the operation. After being treated with chemoembolisation, one patient had disease progression at 5 months and died at 17 months, the other patient had disease progression at 12 months and died at 20 months. These two patients were censored at the time of death in the intervention group according to the intention-to-treat principle.

All 21 patients who had liver transplantation received a graft from a brain-dead donor. Median donor age was 69 years (IQR 65–75); whole liver grafts were used in 19 liver transplantations (90%) whereas two patients (10%) received split livers. The median product of donor age and preoperative recipient Model for End-Stage Liver Disease score was 594 (IQR 494–723) and macrosteatosis of at least 10% was present in eight (38%) of 21 donated livers.

As direct antiviral agents against HCV were introduced in 2014, only two (9%) of 23 patients in the transplantation group and two (9%) of 22 in the control group received antiviral treatment. No irreversible deterioration of

hepatic function due to recurrent HCV was observed in either group; only one other patient survived re-transplantation at 22 months because of late graft malfunction due to biliary complications and recurrent viral hepatitis.

Five (22%) of 23 patients in the transplantation group and 16 (73%) of 22 patients in the control group died. Tumour progression was the main cause of death in both groups, occurring in three (60%) of five patients in the transplantation group and 14 (88%) of 16 patients in the control group. Five (22%) of 23 patients in the liver transplantation group had hepatocellular carcinoma recurrence. 18 (82%) of 22 controls had hepatocellular carcinoma progression and were treated according to liver function and pattern of recurrence. Of these progressions in control patients, ten (56%) occurred within 12 months of randomisation. In these patients, TACE was used in ten (56%) of 18 patients, sorafenib in seven (39%) patients, SIRT in four (22%) patients, resection in two (11%) patients, radiofrequency or microwave ablation in two (11%) patients, and a combination of treatments in six (33%) patients. Of the four patients in the control group whose disease did not recur after downstaging treatment, two died from other causes at 11 months and 24 months, whereas two achieved a prolonged complete response after successful tumour ablation and liver resection.

Figure 2 shows the Kaplan-Meier curves of time to tumour event and overall survival according to treatment group. Median time to tumour event was not reached in patients in the transplantation group compared with 13 months (95% CI 12–27) in the control group. 5-year tumour event-free survival was 76·8% (95% CI 60·8–96·9) in the transplantation group versus 18·3% (7·1–47·0) in the control group (HR 0·20, 95% CI 0·07–0·57; p=0·003). Median survival was not reached in the transplantation group compared with 30·5 months (95% CI 18·5–41·5) in the control group. 5-year overall survival was 77·5% (95% CI 61·9–97·1) in the transplantation group versus 31·2% (16·6–58·5) in the control group (HR 0·32, 95% CI 0·11–0·92; p=0·035). The Cox model proportional hazards assumption was checked and verified by relying on statistical tests on the basis of scaled Schoenfeld residuals for the Cox models for both time to tumoural event (p=0·97) and overall survival (p=0·24; appendix p 7).

The secondary endpoints in this study were not assessed because of the small sample size due to early study closure.

The most common registered grade 3–4 serious adverse events were HCV recurrence (three [13%] of 23 patients) and acute transplant rejection (two [9%]) in the transplantation group, and post-embolisation syndrome (two [9%] of 22 patients) in the control group (table 2). All reported adverse events were treatment related (ie, consequent to the transplantation or non-transplantation procedures).

In the transplantation group, two deaths were treatment related and occurred within 30 days from transplantation

	Transplantation group (n=23)	Control group (n=22)
(Continued from previous page)		
HALT-HCC score		
<17	23 (100%)	22 (100%)
≥17	0 (0%)	0 (0%)

Data are median (IQR) or number (%). TACE=transarterial chemoembolisation. RFA=radiofrequency or microwave ablation. SIRT=^{90}Y-selective internal radiotherapy. MELD=Model for End-Stage Liver Disease. UCSF=University of California, San Francisco. HALT-HCC=Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma. *Surgical resection was allowed in the downstaging protocol, if done laparoscopically, to transform partial tumour responses to locoregional therapies into complete removal of the targeted nodule. †Tumours are considered fully viable at baseline, whereas viability is measured on contrast enhancement hallmarks after downstaging. ‡Calculated as the sum of the number of nodules and the size (in cm) of the largest nodule.

Table 1: **Characteristics at baseline of the intention-to-treat population**

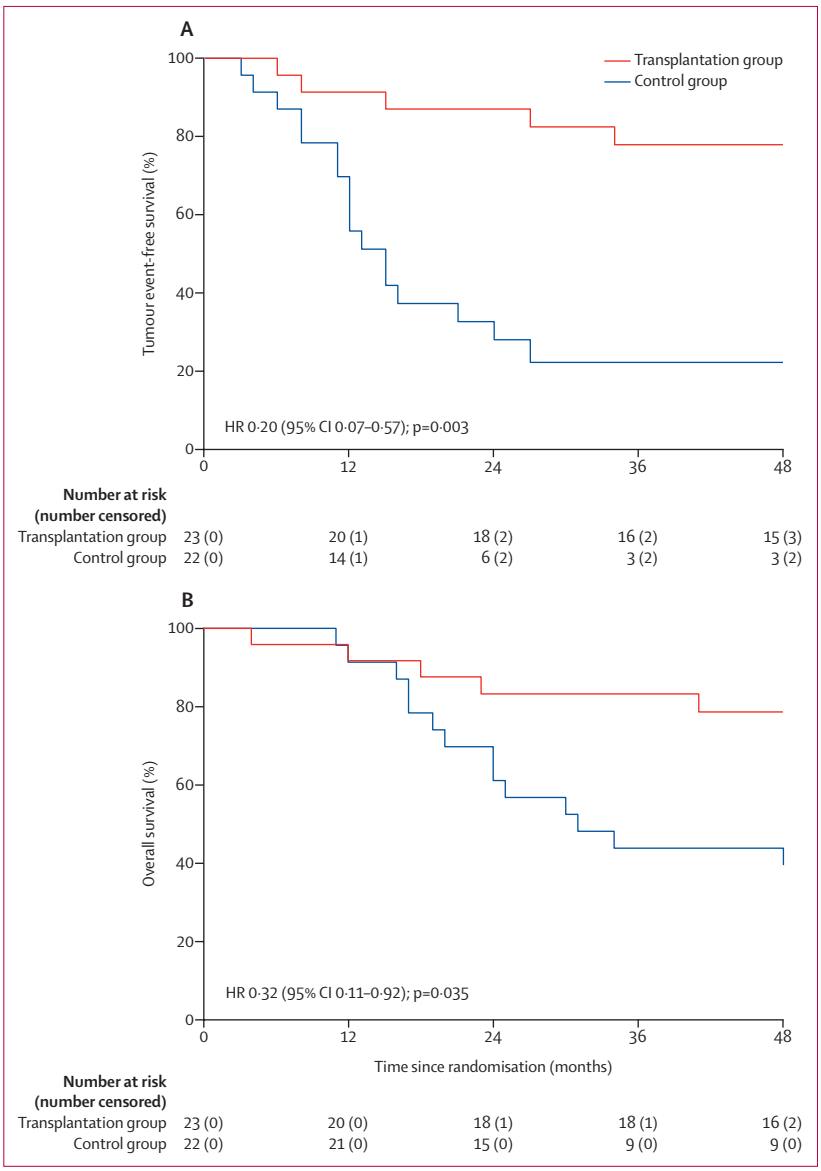

Figure 2: **Observed time to tumour event (A) and overall survival (B)**
HR=hazard ratio.

	Transplantation group (n=23)			Control group (n=22)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Myocardial infarction	0	0	1 (4%)	0	0	0
Liver failure	0	0	0	0	0	2 (9%)
Post-embolisation syndrome	0	0	0	2 (9%)	0	0
Multi-organ failure	0	0	1 (4%)	0	0	0
Hepatitis C virus recurrence	2 (9%)	1 (4%)	0	NA	NA	NA
Hepatic artery stenosis	0	1 (4%)	0	NA	NA	NA
Left hepatic vein thrombosis	1 (3%)	0	0	NA	NA	NA
Acute rejection	2 (9%)	0	0	NA	NA	NA

NA=not applicable.

Table 2: **Serious adverse events requiring hospitalisation (>3 days)**

(one at 10 days from myocardial infarction and one at 20 days from multi-organ failure), whereas the other three deaths were caused by hepatocellular carcinoma recurrence or progression (in a patient who refused liver transplantation). Of 16 deaths in the control group, 14 were caused by tumour progression and two by liver failure related to treatment and not to cancer progression.

In post-hoc analyses, the survival benefit from liver transplantation versus no transplantation at 5 years was 14·5 months (95% CI 3·6–25·3; p=0·009). In a multivariable model, median post-liver transplantation gain in survival was 26·5 months (95% CI 13·6 to 39·3) in patients presenting with partial response after downstaging and 9·9 months (–5·5 to 25·3) in those presenting with complete response ($p_{interaction}$=0·105). Median wait time to transplantation was 3 months (IQR 1·9–3·6) and did not differ between complete (3·3, 2·1–4·9) and partial responders (2·8, 1·9–2·9; p=0·28).

Tumour burden for trial eligibility was predetermined with the Metroticket Calculator as the adjunctive sum of maximum tumour size and number of nodules.[11] Effect of downstaging on tumour burden was measured post hoc at different timepoints and is summarised in table 1 and in the appendix (pp 5, 8). After sustained downstaging, tumour burden decreased from a median of 7·3 (IQR 6·7–8·4) at pre-downstaging baseline to 0 (0–3·3) at randomisation (n=45; p<0·0001). On explant pathology at the time of transplantation (n=23), compared with the randomisation timepoint, median tumour burden had increased to 4·8 (IQR 3·3–6·7; p=0·16).

Post-hoc analyses showed that the tumour burden was related to the duration of downstaging (appendix p 9), whereas duration of tumour downstaging was not associated with overall survival (appendix p 10). In another post-hoc analysis comparing progression in four (13%) of 30 sorafenib-tolerant patients versus five (21%) of 24 sorafenib-intolerant patients or patients who withdrew, tumour progression during the observation phase was not significantly related to the use of sorafenib after downstaging (p=0·49).

Discussion

To our knowledge, this is the first prospective, randomised, controlled trial to explore the benefit of liver transplantation in patients who achieved successful and sustained downstaging of hepatocellular carcinomas exceeding the Milan criteria. Although study recruitment was stopped early and the analyses were underpowered, the study shows significantly longer patient survival and fewer tumoural events in patients in the liver transplantation group compared with those in the non-transplantation therapy group. We also noted a significant survival benefit from liver transplantation versus no transplantation at 5 years. The secondary outcomes of the study were not assessable because of the small sample size due to early study closure.

These results provide additional evidence to previous observations showing comparable post-transplantation outcomes in patients with hepatocellular carcinoma beyond the Milan criteria who underwent downstaging to within the Milan criteria.[3,4,16–21] Additionally, the study shows that different schemes and combinations of neoadjuvant locoregional therapies aimed at reduction of intrahepatic tumour load might be proposed to patients with hepatocellular carcinoma beyond the Milan criteria, who can be transformed into transplant candidates according to the end-treatment tumour response. Hepatocellular carcinoma downstaging could become a selection tool for liver transplantation, enabling clinicians to switch the transplantation decision from tumour presentation to the end of multidisciplinary treatments.[22]

Although patients with hepatocellular carcinoma downstaged to Milan criteria are allowed liver transplants in many areas worldwide, the quality of evidence of this practice has been low in the absence of randomised trials.[10,23] The results presented in this study provide evidence to encourage universal adoption of liver transplantation as a standard of practice in case of hepatocellular carcinoma that has been downstaged successfully.

Randomised control trials testing transplant intervention are difficult to do and this study was no exception. Owing to concurrent national changes in graft allocation policy and hepatocellular carcinoma priorities, not predictable in the study design,[15] patient recruitment to the trial was restricted, forcing the study to be concluded ahead of time. A further limitation was that data were insufficient to allow a cost–benefit analysis of transplantation versus non-transplantation. Nevertheless, the multi-phase study design sheds light on optimisation of liver transplantation in hepatocellular carcinoma beyond conventional criteria.

To secure homogeneity of the various downstaging protocols, two requirements were determined upfront. First, no predefined upper limit for implementing downstaging was set, with the exception of tumour macroscopic vascular invasion. The upper limit for downstaging eligibility was determined on prediction of outcome (ie, at least 50% survival at 5 years on the Metroticket Calculator[11]), and not on predetermined cutoff in size and

number of tumour nodules at presentation.[21] Second, when downstaging was concluded, an observation period of 3 months before enlisting allowed the selection of favourable tumour biology.[24] Such a precaution avoided early post-transplantation recurrences, as observed in patients beyond the Milan criteria who received a living donor[25] or being transplanted in regions with short waiting times.[26] For hepatocellular carcinoma beyond the Milan criteria, a total time-to-transplantation of about 1 year, from first referral to transplantation after successful downstaging, seems reachable even in areas with organ allocation systems that differ from the one used in this study.[15]

Similar to the UCSF experience,[6] our downstaging-aimed therapies achieved a response rate of 73%, with 41% complete responses, which confirms the antitumour activity of neoadjuvant protocols despite different schedules. Less than a fifth of the control patients (four patients [18%]) were spared transplantation because they did not have hepatocellular carcinoma recurrence after downstaging. The potential of complete tumour downstaging to eradicate hepatocellular carcinoma and avoid transplantation in a subset of patients emphasises the role of response to neoadjuvant treatment as a key determinant of the management of hepatocellular carcinoma.[3,22] Utility and benefit of liver transplantation with respect to non-transplantation therapies in curing hepatocellular carcinoma could be increased by more effective downstaging protocols combining modern drugs with conventional locoregional treatments.

Patient outcomes in the control group were similar to those expected after modern locoregional treatments for intermediate stage hepatocellular carcinoma (Barcelona Clinic Liver Cancer stage B). Therefore, the consistent advantage observed in the transplantation group was not due to suboptimal results obtained in the control group.

Post-transplantation survival in patients with partial tumour responses (26·5 months) was nearly triple that of patients who had complete responses (9·9 months). This finding supports the current tendency to assign priority to patients with hepatocellular carcinoma in the transplantation waitlist on the basis of tumour reassessment after neoadjuvant therapies rather that at presentation,[22,27,28] also considering the time-related tendency of hepatocellular carcinoma to progress even after complete radiological response. The presented results support the proposal of prioritising patients with partially responding hepatocellular carcinoma that still meets transplantation criteria, which is worth discussion within organ allocation agencies.

Predictability of tumour downstaging success in patients with hepatocellular carcinoma beyond the Milan criteria was beyond the scope of this study. This assessment would require specific protocols, particularly in the case of HCV-related liver disease. Although the future of liver transplantation for hepatocellular carcinoma will predictably be HCV free,[7,8] the aim of tumour downstaging in patients with well-compensated liver function will persist, regardless of the cause of cirrhosis. Patients with cirrhosis related to non-alcoholic steatohepatitis or non-alcoholic fatty liver disease present more frequently with hepatocellular carcinomas beyond the Milan criteria,[29] and thus are more likely to have tumours that can be successfully downstaged compared with those whose disease is virus related.

There is an association between tumour response to neoadjuvant therapies and biological behaviour in hepatocellular carcinoma.[30] Even though pathology features and morphology of patients with downstaged hepatocellular carcinoma might be similar to those in patients who are T2 at presentation (ie, within the Milan criteria), the results of this study suggest that downstaged hepatocellular carcinomas tend to exhibit an accelerated time-dependent risk of progression. The present study did not assess radiology–pathology correlations in downstaged hepatocellular carcinoma, nor did it investigate genetic and microenviromental conditions that might affect the probability of cancer progression. If the granularity of treatment response to downstaging could be captured in a more standardised manner, downstaging strategies could become the best tool for expanding hepatocellular carcinoma criteria according to the transplantation benefit principle.[22] This study confirms the growing role of AFP monitoring in improving patient selection for liver transplantation, and although we did not set an AFP threshold for hepatocellular carcinoma treatment a priori, no patient in this trial was randomly assigned above the level of 257 ng/mL.

Although presurgical treatment per se might not necessarily change the outcome of liver transplantation for hepatocellular carcinomas beyond the Milan criteria, most of the current cancer indications are represented by downstaged tumours. Thus, the results of this trial confirm that liver transplantation after effective and sustained downstaging of hepatocellular carcinomas beyond the Milan criteria led to improved tumour event-free and overall survival compared with other currently available non-transplantation therapies.

Further international trials, particularly including the Asian population, might confirm the presented results. The practice of neoadjuvant therapies in liver transplantation for hepatocellular carcinoma could become, as in other cancers, a standard that favours patient selection, waiting list management, and postoperative survival.

Contributors

VM was the chief investigator of the trial. DC, MB, RM, MDdB, and CS were involved in conception, study design, and data analysis. All authors contributed to the recruitment of patients, data collection, and interpretation of results. VM, CS, and RM were responsible for data analysis and interpretation. VM, SB, MB, and CS were responsible for the preparation and writing of the manuscript. All authors contributed to the manuscript and approved the final manuscript.

Declaration of interests

SB reports personal fees from Eisai, Biotest, Bayer Health Care, BTG-Boston Scientific, and Biocompatibles. MC has received advisory

board fees from Astellas and Novartis. LB reports personal fees from Biotest and Merck, and grants from Grifols. SF reports personal fees from Gilead, AbbVie, Novartis, Merck, Bayer, Intercept, and Kedrion. MI reports personal fees from Bayer, Gilead Sciences, Merck, BTG-Boston Scientific, AbbVie, Guerbet, and Eisai. All other authors declare no competing interests.

Data sharing

Individual de-identified participant data and the data dictionary that underlie the results reported in this Article will be made available after publication. Data will be available to researchers who provide methodologically sound proposals (all types of analyses including meta-analyses).

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