ORIGINAL ARTICLE

Downstaging prior to liver transplantation for hepatocellular carcinoma: advisable but at the price of an increased risk of cancer recurrence – a retrospective study

Christian Toso[1,2], Glenda Meeberg[3], Axel Andres[1,2], Carolina Shore[1,2], Colleen Saunders[3], David L. Bigam[3], Andrew Mark James Shapiro[3], Philippe Compagnon[1,2], Thierry Berney[1,2], Pietro Majno[1,2] & Norman Kneteman[3]

1 Divisions of Transplant and Abdominal Surgery, Department of Surgery, University of Geneva Hospitals, Geneva, Switzerland
2 Hepato-Pancreato-Biliary Center, University of Geneva Hospitals, Geneva, Switzerland
3 Division of Transplantation, Department of Surgery, University of Alberta, Edmonton, AB, Canada

Correspondence
Christian Toso, Department of Surgery, University of Geneva Hospitals, Rue Gabrielle-Perret-Gentil, 1211 Geneva, Switzerland.
Tel.: 41-22-3723311;
fax: 41-22-3727755;
e-mail: christian.toso@hcuge.ch
and
Norman Kneteman, University of Alberta, 2D4.44 Mackenzie Centre, Edmonton, AB, Canada, T6G 2B7.
Tel.: 780-407-6168;
fax: 780-407-7374;
e-mail: kneteman@ualberta.ca

SUMMARY

The use of downstaging prior to liver transplantation for hepatocellular carcinoma (HCC) still needs refinement. This study included patients with HCC listed for transplantation according to the Total Tumour Volume (TTV) ≤115 cm^3 and alpha fetoprotein (AFP) ≤400 ng/ml criteria, with and without previous downstaging. Overall, 455 patients were listed, and 286 transplanted. Post-transplant follow-up was 38.5 ± 1.7 months. Patients downstaged to TTV115/AFP400 ($n = 29$) demonstrated similar disease-free survivals (DFS, 74% vs. 80% at 5 years, $P = 0.949$), but a trend to more recurrences (14% vs. 5.8%, $P = 0.10$) than those always within TTV115/AFP400 ($n = 257$). Similarly, patients downstaged to Milan criteria ($n = 80$) demonstrated similar DFS (76% vs. 86% at 5 years, $P = 0.258$), but more recurrences (11% vs. 1.7%, $P = 0.001$) than those always within Milan ($n = 177$). Among patients downstaged to Milan, those originally beyond TTV115/AFP400 ($n = 27$) had similar outcomes as those originally beyond Milan, but within TTV115/AFP400 ($n = 53$). However, the likelihood of being within Milan at transplant was lower for patients with more advanced original HCCs ($P < 0.0001$). Overall, despite an expected increase in post-transplant HCC recurrence, similar survivals can be achieved with and without downstaging, using the TTV115/AFP400 transplantation criteria, and including patients with advanced original HCCs. Downstaging should continue to be performed.

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Introduction

Liver transplantation is the best treatment for patients with hepatocellular carcinoma (HCC). Candidate selection has been historically based on the Milan criteria (one HCC ≤5 cm, or ≤3 HCC each ≤3 cm) [1], but recent transplant experience also includes patients with more advanced HCC, based on combined morphological and biological variables [2–5]. Such selection tools include the total tumour volume/alpha fetoprotein

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(TTV115/AFP400), the AFP and the Metroticket 2.0 models. Although differing in their designs, the new criteria converge on an upper size limit of 6 cm, for a single nodule, AFP ≤100–400 ng/ml [2,4,5]. They include approximately 20% more patients compared to Milan criteria, while preserving post-transplant outcomes [6].

In parallel, several studies have suggested that patients with marginally more advanced HCC can also benefit from transplantation after downstaging by interventional radiological and/or surgical treatments [7]. These observations were based on retrospective and prospective assessments, utilising Milan and/or AFP as main references [8–12]. They demonstrated post-transplant survivals that were similar in patients successfully downstaged, and in patients continuously within transplant criteria.

Still, a number of questions remain unanswered. First, most studies on downstaging focused on survival, affected by nontumoural mortality, and not on recurrences, a more precise parameter in investigating tumour treatments and biology [9,13–15]. Second, most investigations included patients only marginally outside Milan criteria prior to downstaging. To illustrate: Ravaioli *et al.* restricted their prospective assessment to patients with one HCC ≤8 cm, two HCCs ≤5 cm or three to six HCCs ≤4 cm with a total diameter ≤12 cm and Yao *et al.* did so with patients with one HCC ≤8 cm, two or three HCCs ≤5 cm or four or five HCCs ≤3 cm, with a total diameter ≤8 cm [8,9]. One should therefore determine whether patients with more advanced HCC, commonly encountered in specialized HCC centres, can also be considered for downstaging. In addition, most studies took Milan criteria as the downstaging goal to qualify patients for transplantation, and it is unclear whether expanded criteria can also be used. Finally, a fixed 3-month stability period between successful downstaging and transplantation has been recommended, but the relevance of this "no-transplant" window should be tested.

The present study included patients with advanced HCC into the downstaging process with no limit for size nor AFP at entry, and allowed activation for transplantation once the expanded TTV/AFP criteria were reached (TTV ≤115 cm^3 and AFP ≤400 ng/ml). The aims were: (i) to validate the potential of downstaging and transplanting patients, even if beyond TTV115/AFP400, (ii) to explore the limits of expanded criteria to be used for patient selection after downstaging and (iii) provide an estimate of the most appropriate time interval between downstaging and transplantation.

Patients and methods

Study design

The study was based on a retrospective assessment of a prospectively maintained web-based database. It included patients from the University of Alberta, Edmonton, Canada (patients entered from January 2004) and the University of Geneva, Geneva, Switzerland (patients entered from October 2009).

Two categories of patients could qualify for transplantation, be listed, and enter the database: those with TTV continuously ≤115 cm^3 and AFP continuously ≤400 ng/ml, and those with originally more advanced HCC (with no size, number, nor AFP limit) successfully downstaged and stable within TTV115/AFP400 for more than 3 months. Of note, patients entered into the database when they fulfilled TTV115/AFP400 according to mRECIST criteria (modified Response Evaluation Criteria in Solid Tumours) with no macro-vascular invasion or extra-hepatic metastasis. As such, the patients not reaching TTV115/AFP400 after downstaging were not included in the analysis. After listing, patients presenting with a progression beyond TTV115/AFP400 were put on hold while waiting for the outcome of re-downstaging, or delisted if re-downstaging was not possible or could not be achieved. The study was reviewed and approved by the ethical board of each institution.

Patient management

All patients newly diagnosed with HCC were discussed in a multi-disciplinary meeting at our or at partner institutions. Patients potentially qualifying for transplant, but with an HCC outside TTV115/AFP400, were systematically entered into a downstaging process. Downstaging was most frequently performed by transarterial chemo-embolisation (TACE), radio-frequency ablation (RFA), selective internal radiation therapy (SIRT) and surgical resection. The choice between treatment modalities was performed in multi-disciplinary rounds, and was based on HCC and patient characteristics and cirrhosis stage. A new computer tomography (CT) or magnetic resonance imaging (MRI) assessment was performed 1 month after TACE, the day after RFA (to confirm appropriate ablation) and 3 months after SIRT. With an expected waiting time of 10–12 months at both institutions (based on the allocation of exception MELD points), continuation of locoregional treatments was performed even in patients within TTV115/AFP400. Such bridging treatment was conducted until

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disappearance of all radiologically detectable HCCs or until transplantation. Standard wait-list monitoring was performed by AFP, and CT or MRI every 3 months, and bone scan every 6 months.

Transplantation was performed from deceased donors in most patients with replacement of the vena cava, and selective use of venovenous bypass [16]. Standard immunosuppression included sirolimus (trough levels 8–12 μg/ml) and tacrolimus (trough levels 5–7 μg/ml) starting from 1 month after transplantation or time of discharge from hospital [17]. Post-transplant monitoring was performed by AFP, and CT or MRI every 6 months for the first 2 years and yearly thereafter.

Collected variables and definitions

Data were collected prospectively, and the analysis was performed retrospectively. All HCC-targeting treatments performed prior to or after listing were recorded, including type, date and whether treatment was performed in view of bridging versus downstaging (to TTV115/AFP400). AFP, and HCC sizes and number were documented at the time of listing, at the time of the last assessment prior to transplant or delisting, and at the time of the highest values, which could have been prior to or after listing.

Hepatocellular carcinoma diagnosis was performed by histology or by radiology based on international clinical practice guidelines [18]. Total tumour volume was calculated based on the largest diameter of each HCC, and using the formula $(4/3)\pi r^3$ [4].

Analysis

Patients continuously within TTV115/AFP400 were compared to those originally beyond TTV115/AFP400 but successfully downstaged to TTV115/AFP400. In addition, patients continuously within Milan criteria were compared to those originally beyond Milan but successfully downstaged to Milan (keeping in mind that the aim of our wait-list management was to fully treat all HCCs, thus reaching Milan criteria in all patients). In addition, patients with an AFP continuously ≤400 ng/ml were compared to those originally >400 ng/ml but successfully downstaged to ≤400 ng/ml.

We further explored whether the original HCC stage had an impact on post-transplant outcome after successful downstaging. Among patients successfully downstaged to Milan, we compared those originally beyond Milan but within TTV115/AFP400, versus those beyond TTV115/AFP400. Outcomes of patients waiting ≤3 months vs. >3 months from successful downstaging to transplantation were also compared.

Disease-free survival (DFS) was the main outcome variable and was calculated from the time of transplantation to death or HCC recurrence. Results were provided as mean ± standard deviation or median ± interquartile range according to normality. Groups were assessed using Kaplan–Meier curves, and compared using the log-rank test. Further assessments included the Student's *t* test, Mann–Whitney test, Chi-squared test or Fisher test when appropriate. Significance was set at 0.05, and the SPSS 18.0 (SPSS, Chicago, IL, USA) software was used for analysis.

Results

Patient and transplant characteristics

From February 2004 to October 2017, 455 patients were listed for transplantation with a known HCC (no incidental HCC). Of them, 124 were delisted, and 286 transplanted (100 from Geneva and 186 from Edmonton) according to the TTV115/AFP400 criteria after a mean waiting time of 10.7 months (10.6 ± 0.8 and 10.7 ± 0.7 months in Edmonton and Geneva). Among the transplanted patients, the female/male ratio was 0.2, with a mean age of 57.6 ± 8.4 years and a MELD score of 13.3 ± 6.6 at transplantation. The most frequent causes of liver disease were hepatitis C virus (HCV), hepatitis B virus (HBV), previous alcohol abuse, and nonalcoholic steatohepatitis (NASH, Table 1).

The overall survival was 95.0 ± 1.4%, 88.9 ± 2.1% and 82.6 ± 2.9% and disease-free survival 93.8 ± 1.5%, 84.7 ± 2.4% and 78.9 ± 3.1% at 1, 3 and 5 years, after a mean post-transplant follow-up of 38.5 ± 1.7 months (median 33 ± 48 months). Nineteen patients (6.6%) experienced an HCC recurrence (16 in Edmonton, and three in Geneva, $P = 0.06$). Four recurrences occurred within the first 12 months after transplantation, 6 between 12 and 24 months, 4 between 24 and 36 months and the remaining thereafter (Fig. S1). Patients with recurrence were treated by combined means, including sorafenib ($n = 8$), radiation therapy ($n = 8$), resection ($n = 4$), TACE ($n = 2$), RFA ($n = 1$) and best supportive care ($n = 4$).

Downstaging based on TTV115/AFP400

Among the transplanted patients, 257 (89.8%) underwent a locoregional HCC treatment prior to transplantation. The most frequently used treatments were TACE

Table 1. Patient and transplant characteristics based on total tumour volume/alpha fetoprotein.

	Always within TTV/AFP	Downstaged to TTV/AFP	*P*
Patients (number)	257	29	
Age at transplant (years ±SD)	57.3 ± 8.4	59.5 ± 8.7	0.2
Gender (ratio)	Female: 43/male: 214	Female: 4/male: 25	0.91
Cause of liver disease (%)*			
HCV	154 (60)	14 (48)	0.23
HBV	37 (14)	11 (38)	0.001
Alcohol	96 (37)	10 (34)	0.76
NASH	24 (9)	1 (3)	0.29
Other	32 (12)	7 (7)	0.53
MELD at transplant (±SD)	13.6 ± 6.7	10.5 ± 4.7	0.02
Characteristics of most advanced HCC			
Number of HCC (±SD)	2 ± 2	1.9 ± 1.6	0.65
Total tumour volume (cm^3 ±SD)	11.2 ± 19.5	115 ± 181	0.006
Serum alpha fetoprotein level (ng/ml ±SD)	15.6 ± 37	531 ± 1157	0.001
Bridging/downstaging HCC management (%)†			
Trans-arterial chemo-embolisation (TACE)	243 (95)	43 (148)	0.08
Radio-frequency ablation (RFA)	177 (69)	27 (93)	0.29
Alcohol ablation	77 (30)	16 (55)	0.07
Resection	20 (8)	15 (52)	<0.001
Selective internal radiation therapy (SIRT)	25 (10)	9 (31)	0.005
Other‡	10 (4)	2 (7)	0.47
No HCC treatment prior to transplant	29 (11)	0	0.06
Last pre-transplant HCC characteristics			
Number of HCC (±SD)	1.5 ± 1.3	1.3 ± 0.7	0.37
Total tumour volume (cm^3 ±SD)	0.7 ± 6.4	0 ± 3.6	0.06
Serum alpha fetoprotein level (ng/ml ±SD)	7 ± 14	6 ± 72	0.5
Explant HCC characteristics			
Number of HCC (±SD)	1 ± 1	1 ± 2.5	0.42
Total tumour volume (cm^3 ±SD)	3.2 ± 14	0.4 ± 6.8	0.04

HBV, hepatitis B virus infection; HCC, hepatocellular carcinoma; HCV, hepatitis C virus infection; MELD, Model for End-Stage Liver Disease; TACE, trans-arterial chemo-embolisation.

*Some patients have multiple causes of liver disease.

†Number of procedures, multiple procedures have been performed in some patients.

‡Includes systemic chemotherapy, selective beam radiation therapy (SBRT), microwave ablation.

with 286 procedures and 1.9 ± 1.4 procedures per patient, RFA with 204 procedures and 1.5 ± 0.9 per patient, and alcohol ablation with 93 procedures and 3 ± 2.3 per patient (Table 1). Of note, alcohol ablation was mainly used in the earlier era.

Of these patients, 29 with HCC beyond TTV115/AFP400 successfully underwent HCC treatment as downstaging (Table 1). At the beginning of treatment, these patients had similar number, but had larger HCCs ($P = 0.006$) and higher AFP levels ($P = 0.001$) than patients always within criteria. Successfully downstaged patients used more HCC-directed treatments, and especially so for resection and SIRT (consistent to the larger size of their HCCs). At the time of transplantation, patients always within TTV115/AFP400 and patients downstaged to TTV115/AFP400 had similar numbers of HCCs, total tumour volume and AFP levels.

Patients successfully downstaged to TTV115/AFP400 ($n = 29$), and those always within TTV115/AFP400 ($n = 257$) had statistically similar DFS (74% vs. 80% at 5 years, $P = 0.95$, Fig. 1a). However, patients downstaged to TTV115/AFP400 tended to show a higher rate of post-transplant HCC recurrence than those always within TTV115/AFP400 (4/29, 14% vs. 15/257, 5.8%, $P = 0.10$). Of note, follow-up times were similar in patients with and without downstaging. Four patients were successfully downstaged from beyond TTV115/AFP400, and subsequently progressed back beyond TTV115/AFP400. Only one of them could be downstaged again and subsequently transplanted.

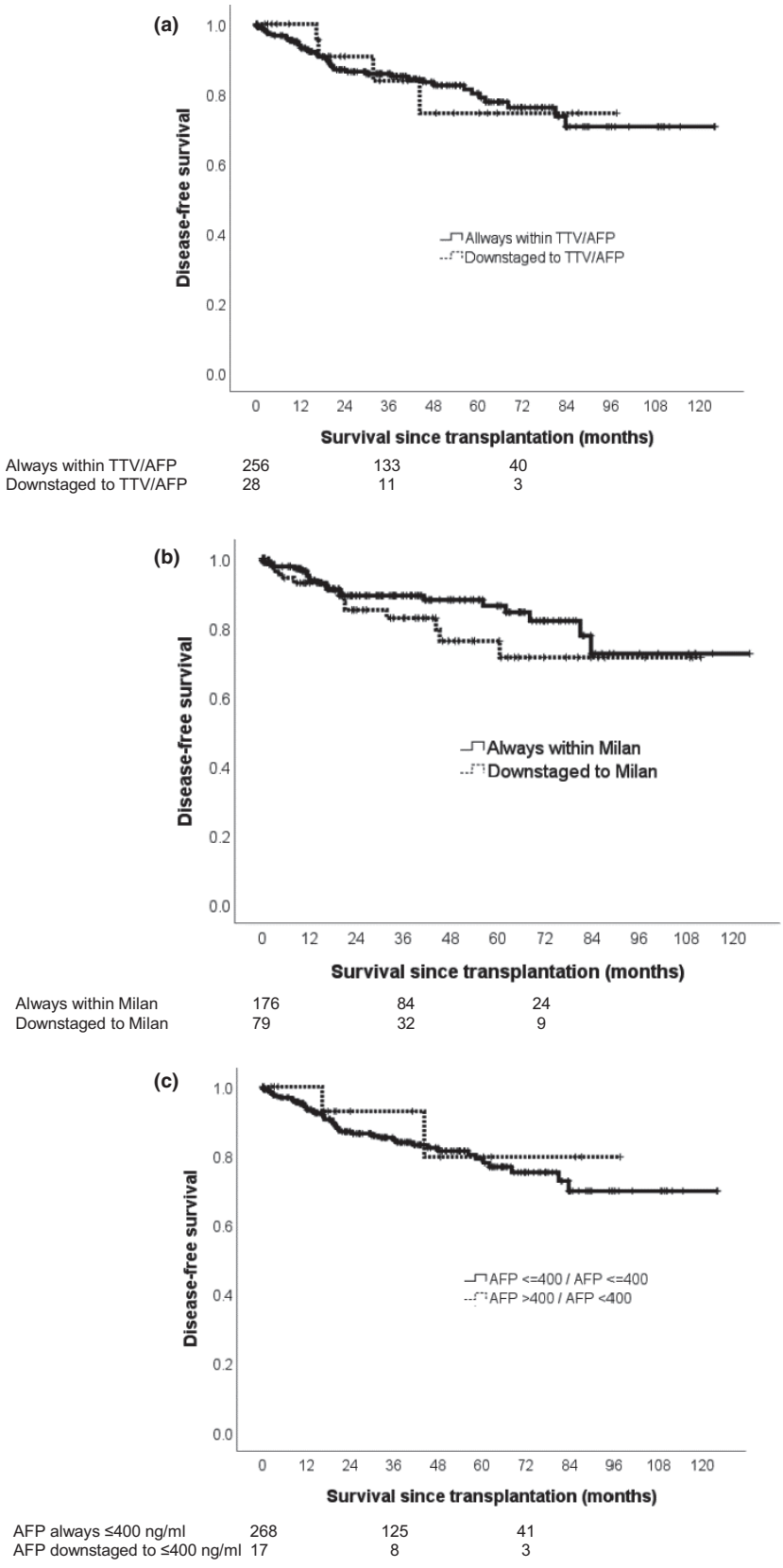

Figure 1 Disease-free survival (DFS) according to downstaging based on TTV115/AFP400 (74% vs. 80% at 5 years, $P = 0.95$, a). DFS based on Milan criteria (76% vs. 86% at 5 years, $P = 0.26$, b). DFS based on AFP ≤400 ng/ml (80% vs. 80% at 5 years, $P = 0.62$, c).

Downstaging based on Milan or AFP

Among the transplanted patients, 80 with HCC beyond Milan were downstaged (either from beyond TTV115/AFP400 or from beyond Milan, but within TTV115/AFP400) to within Milan criteria. These patients originally had more advanced HCCs with more numerous lesions, larger HCCs and higher AFP levels than patients always within Milan (Table 2). At the time of transplantation, patients downstaged to Milan and those always within Milan showed similar HCC features (Table 2).

Patients successfully downstaged to Milan ($n = 80$), and those always within Milan ($n = 177$) demonstrated similar DFS (76% vs. 86% at 5 years, $P = 0.258$, Fig. 1b). However, patients downstaged to Milan showed a higher rate of post-transplant HCC recurrence than those always within Milan (9/80, 11% vs. 3/177, 1.7%, $P = 0.001$).

Among the transplanted patients, 18 were downstaged from an AFP >400 ng/ml to an AFP ≤400 ng/ml. They showed similar DFS as those with an AFP continuously ≤400 ng/ml (80% vs. 80% at 5 years, $P = 0.62$, Fig. 1c). However, patients downstaged to AFP ≤400 ng/ml showed a trend to a higher rate of post-transplant HCC recurrence than those always within AFP ≤400 ng/ml (2/18, 11% vs. 18/268, 6.7%, $P = 0.48$). Of note, two patients with successfully treated macro-vascular HCC invasion were included in the cohort, and were transplanted 13.6 and 15 months after downstaging. One presented a post-transplant recurrence.

Table 2. Patient and transplant characteristics based on Milan criteria.

	Always within Milan	Downstaged to Milan	*P*
Patients (number)	177	80	
Age at transplant (years ±SD)	57.1 ± 6.9	58.6 ± 8.0	0.2
Gender (ratio)	Female: 32/male: 145	Female: 14/male: 66	0.91
Cause of liver disease (%)*			
HCV	106 (60)	43 (54)	0.36
HBV	28 (16)	17 (21)	0.29
Alcohol	63 (36)	28 (35)	0.93
NASH	15 (8)	8 (10)	0.69
Other	25 (14)	7 (9)	0.28
MELD at transplant (±SD)	13.9 ± 6.9	11.6 ± 6.0	0.01
Characteristics of most advanced HCC			
Number of HCC (±SD)	1.4 ± 0.7	3.1 ± 3.1	<0.001
Total tumour volume (cm^3 ±SD)	8.1 ± 11	34 ± 69	<0.001
Serum alpha fetoprotein level (ng/ml ±SD)	14 ± 37	20 ± 321	0.015
Bridging/downstaging HCC management (%)†			
Trans-arterial chemo-embolisation (TACE)	143 (81)	115 (144)	0.002
Radio-frequency ablation (RFA)	110 (62)	74 (93)	0.05
Alcohol ablation	62 (35)	31 (39)	0.7
Resection	13 (7)	21 (31)	<0.001
Selective internal radiation therapy (SIRT)	4 (2)	25 (31)	<0.001
Other‡	4 (2)	6 (8)	0.06
No HCC treatment prior to transplant	24 (14)	0	0.001
Last pre-transplant HCC characteristics			
Number of HCC (±SD)	1.2 ± 0.5	1.2 ± 0.5	0.77
Total tumour volume (cm^3 ±SD)	0.1 ± 4.7	0.1 ± 3.5	0.94
Serum alpha fetoprotein level (ng/ml ±SD)	6.9 ± 11	6.6 ± 11	0.97
Explant HCC characteristics			
Number of HCC (±SD)	1 ± 1	2 ± 4	0.73
Total tumour volume (cm^3 ±SD)	2.2 ± 14	3 ± 21	0.58

HBV, hepatitis B virus infection; HCC, hepatocellular carcinoma; HCV, hepatitis C virus infection; MELD, Model for End-Stage Liver Disease; TACE, trans-arterial chemo-embolisation.

*Some patients have multiple causes of liver disease.

†Number of procedures, multiple procedures have been performed in some patients.

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Impact of original HCC stage on outcome after downstaging

We further explored the impact of the original HCC status on transplantation outcome after a successful downstaging. Among patients successfully downstaged to Milan, we compared those originally beyond TTV115/AFP400 ($n = 27$) versus those originally within TTV115/AFP400, but beyond Milan ($n = 53$). They showed similar DFS (76.2% vs. 75.8% at 5 years, $P = 0.44$, Fig. 2a), and similar rates of post-transplant HCC recurrence (6/53, 11.3% vs. 3/27, 10.7%, $P = 1$). However, when taking all listed patients into account, the likelihood of being within Milan at the last assessment was higher for patients originally within Milan, compared to those originally beyond Milan but within TTV115/AFP400, and those beyond TTV115/AFP400 (97.6% vs. 56.8% vs. 48.5%, $P < 0.0001$, Fig. 2b). Also, RFA was the only variable predicting the chance of being downstaged to Milan criteria at the last assessment prior to transplant or delisting (44/49 vs. 57/34, $P = 0.026$).

Impact of time between downstaging and transplant

Listing was possible as early as 3 months after a downstaging into TTV115/AFP400, meaning that some patients were transplanted less than 3 months after reaching Milan criteria. Based on this observation, we explored the time between downstaging to Milan and transplantation, comparing patients waiting 0–3 ($n = 11$), >3 months ($n = 46$). We did not observe a difference of DFS between groups ($P = 0.59$, Fig. 2c). However, patients with a time between downstaging to Milan and transplantation ≤3 months had a trend towards more post-transplant recurrences (3/11, 27%; 4/48, 8.3%; $P = 0.08$).

Impact of type of HCC treatment procedure

We compared patients treated by RFA or microwave ablation versus by TACE prior to transplantation. They showed similar DFS (78.9% vs. 77.2% at 5 years, $P = 0.74$), and similar rates of post-transplant HCC recurrence (4/73, 5.5% vs. 13/164, 7.9%, $P = 0.50$). The same was true only looking at patients with a successful downstaging ($P = 0.97$ and $P = 0.67$). Of note, patients with a complete necrosis on the explants demonstrated better post-transplant DFS (88.1% vs. 75.4% at 5 years, $P = 0.045$).

Discussion

Taken together, the present data supports the use of downstaging in patients with HCC outside transplant criteria. We confirm that good post-transplant survivals can be achieved, similar to those of patients always within transplant criteria [8–10].

The increased rate of post-transplant HCC recurrence in downstaged patients deserves further attention. With an overall low rate of recurrence (6.6% in the present study), and a low proportion of post-transplant deaths linked to HCC (17% in the present study), changes in cancer recurrence have a modest impact on survival. This observation highlights the need to assess recurrence as a specific research outcome in studies looking at downstaging.

More globally, the present report shows that any deviation from the restrictive Milan criteria is made at the price of an increased risk of cancer recurrence. Until now, single studies have not supported this point (potentially linked to a limited power), but aggregated data shows the higher rate of post-transplant recurrence in downstaged patients (20/178, 11%) compared to patients always within transplant criteria (37/554, 6.7%, $P = 0.045$) [8,11,12,15]. This observation should be taken in parallel to the heat maps of the Metroticket studies, where post-transplant outcome is seen as a continuum linked to tumour characteristics [5,19]. Beyond these observations, all observed post-transplant recurrence rates remained within an acceptable limit of 10%–15%, and we still support the use of downstaging in the interest of the patient to be treated, and without unfairly impacting those on the list. Transplantation after downstaging offers better survival than palliation.

Of note, we used 35 resections in 30 patients, who were subsequently listed because they have recurred after resection ($n = 26$), or because of signs of HCC aggressiveness (microvascular invasion, poorly differentiated) on the resected specimen ($n = 4$). One can debate whether such a resection strategy should be considered as downstaging. We would argue that 20 resections were performed in patients outside transplant criteria, and that resection should be seen as a way of downstaging. One important message there is that transplantation is a viable option even in patients with a history of resection of HCC outside transplant criteria.

Our series shows that, in the ranges of TTV and AFP of our series, all HCC patient should be considered for downstaging, even those with advanced HCC

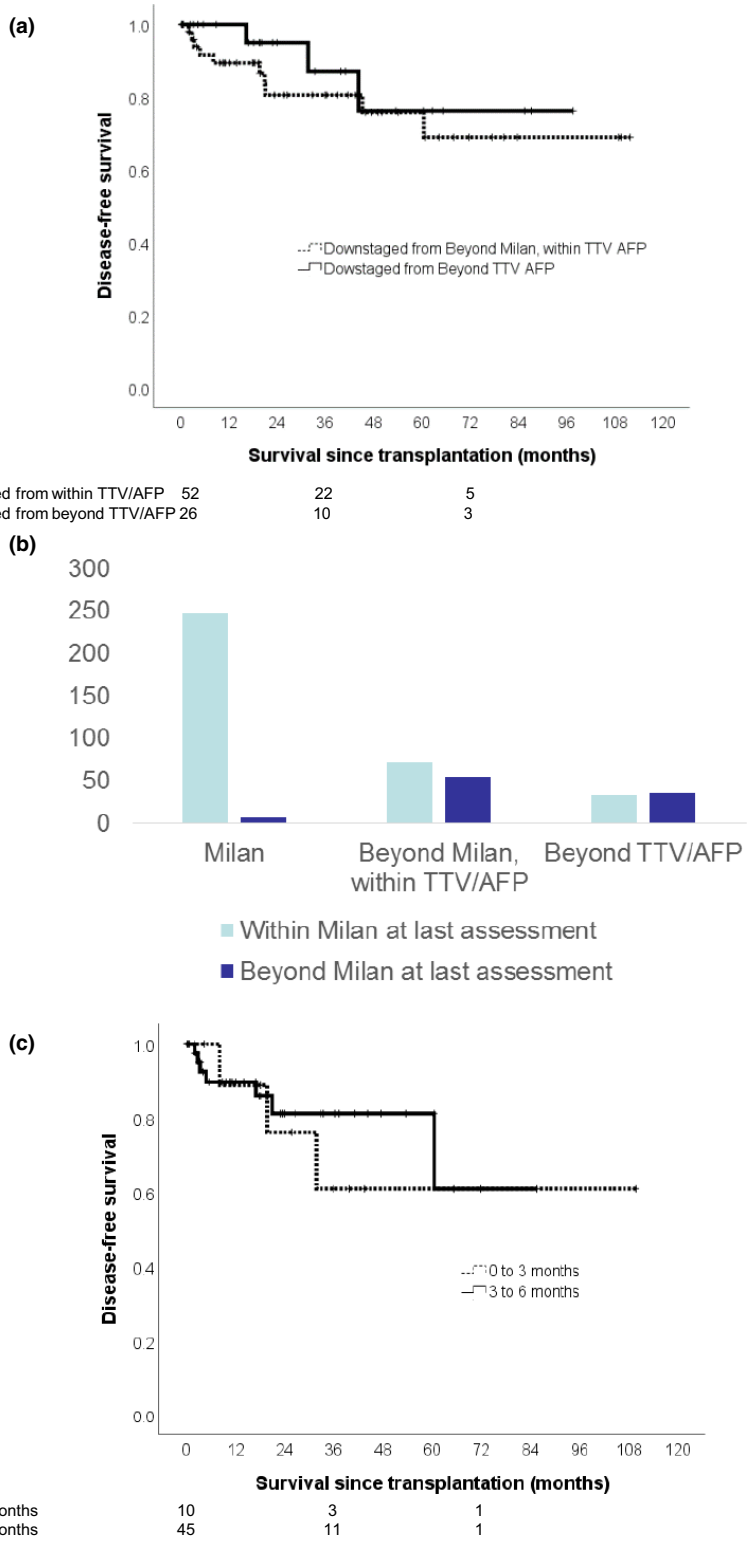

Figure 2 Disease-free survival among patients successfully downstaged to Milan and comparing those originally beyond Milan but within TTV115/AFP400 to those originally beyond TTV115/AFP400 (76.2% vs. 75.8% at 5 years, $P = 0.44$, a). Likelihood of being within versus beyond Milan at the last assessment for patients originally within Milan, beyond Milan but within TTV115/AFP400 versus beyond TTV115/AFP400 (97.6% vs. 56.8% vs. 48.5%, $P < 0.0001$, b). DFS for patients with a time between downstaging and transplant ≤3 months vs. >3 months (61% vs. 81% at 5 years, $P = 0.59$, c).

(Fig. 3). This statement is supported by the new observation of similar outcomes (survival and recurrence) in successfully downstaged patients originally just beyond Milan versus beyond TTV115/AFP400. Until now, this observation had only been made based on AFP, with patients successfully downstaged

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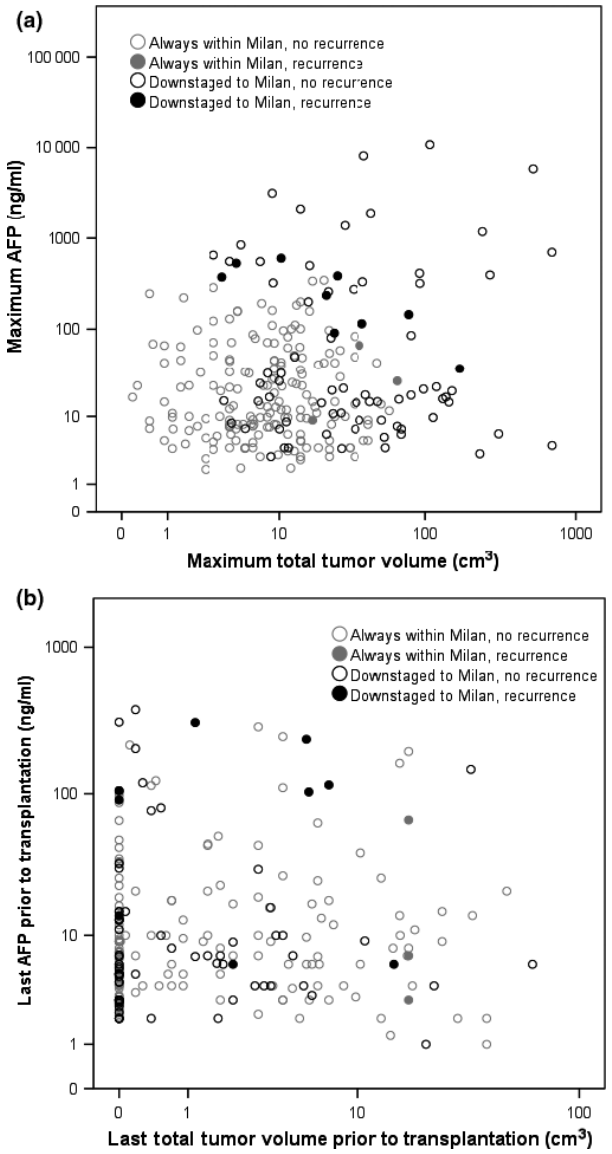

Figure 3 Maximum (a) and last pre-transplant (b) total tumour volume and alpha fetoprotein in patients downstaged to Milan criteria or always within Milan criteria, and with and without post-transplant hepatocellular carcinoma recurrence.

from AFP >1000 ng/ml to AFP <400 ng/ml demonstrating significantly better outcomes than those with lower original AFP values prior to downstaging [10]. This point is important, providing hope for all patients, although knowing that those with the most advanced HCCs have less chance of reaching transplant criteria with downstaging (shown in the present study and in [10,15]).

Based on the present data, one would suggest waiting at least 3 months after downstaging to TTV115/AFP400. In addition, one can intuitively assume that patients with the most advanced original HCCs should wait longer after a successful downstaging [11]. At our institutions, we allow listing after 3 months of stability after downstaging, keeping in mind that patients will still be surveyed during about 1 year on the waiting list. This said the optimal time between downstaging and transplantation remains to be confirmed with a larger number of patients.

The present study shows a number of limitations, especially considering its retrospective nature, and the relatively limited number of patients downstaged from beyond TTV115/AFP400. Also, it could have been improved by the assessment of all patients considered for downstaging (successful or not), better defining which patients should qualify for such a strategy. This was difficult because many patients are originally managed in collaborating hospitals often at some distance from the transplant center, and some of these patients are never referred for transplantation. However, the proposed data provides accurate information on patients undergoing transplantation.

Overall, the study supports the use of downstaging in all patients potentially qualifying for transplantation and with HCC beyond transplant criteria, and demonstrates the potential of using expanded criteria (TTV115/AFP400) to assess the success of downstaging. This strategy has been maintained at our two institutions. Similar post-transplant survivals can be achieved in downstaged patients compared with patients always within criteria, yet at the price of a modest but acceptable increase in the risk of HCC recurrence (<15% in all groups).

Authorship

CT, GM, AA, PM and NK: participated in research design. CT, GM, AA, CS, CS, DLB, AMJS, PC, TB, PM and NK: participated in data management and analysis. CT, GM, AA, DLB, AMJS, PC, TB, PM and NK: participated in writing of the paper.

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Conflicts of interest

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Distribution of recurrence according to time since transplantation.

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