Benefit of downsizing hepatocellular carcinoma in a liver transplant population

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SUMMARY

Background

Long-term results after downstaging hepatocellular carcinoma (HCC) prior to liver transplantation (LT) remain unknown.

Aims

To investigate dropouts and post-transplant outcome among patients with downstaged HCC by transarterial chemo-lipiodolization (TACL).

Methods

Between 2000 and 2007, 386 patients with HCC initially exceeding Milan criteria underwent TACL for tumour downstaging and were consecutively enrolled.

Results

Overall, 160 (41.5%) patients achieved successful downstaging of HCC to within Milan criteria. During the follow-up, 82 eventually dropped off the waiting list for LT, with estimated dropout rates at 1, 2 and 5 years of 46.7%, 70.2%, and 87.2%, respectively. The overall post-transplant survival rates at 1, 2 and 5 years were 89.2%, 70.3% and 54.6% and the corresponding rates for recurrence-free survival were 74.7%, 71.8% and 66.3% respectively. Multivariate analysis indentified alpha-fetoprotein (AFP) levels $\geq 100$ ng/mL at LT $(P = 0.003)$, maximum tumour size $\geq 7$ cm $(P = 0.002)$ and the lack of complete necrosis by TACL $(P = 0.048)$ as independent predictors of HCC recurrence after LT. Patients with none of these risk factors had an excellent post-transplant outcome, with an 87.5% probability of recurrence-free survival up to 6 years.

Conclusions

These long-term results may contribute to the database for optimizing management of LT candidates with downstaged HCC. Based on our data, patients with a maximum tumour size <7 cm who achieve complete necrosis together with AFP levels <100 ng/mL at LT may be the best candidates for LT following downstaging using TACL.
INTRODUCTION

Liver transplantation (LT) in the treatment of hepatocellular carcinoma (HCC) is an ideal option that eliminates both cancer and the premalignant cirrhotic liver. Early series of LT have yielded disappointing results, in terms of a high incidence of HCC recurrence and an unacceptable survival rate, primarily because of selection of candidates with advanced disease.\(^1\), \(^2\) In 1996, a landmark study by Mazzaferro et al. reported an excellent post-transplant outcome.\(^3\) With the selection criteria they developed (Milan criteria: a single lesion \(\leq 5\) cm, up to three lesions with all \(\leq 3\) cm), the 4-year survival rate post-transplant was 75%, similar to the rates for patients with nonmalignant diseases. Additional experiences from other institutions showed a 5-year survival rate of 75% or greater for patients fulfilling these criteria.\(^4\), \(^5\) Currently, the Milan criteria have become widely accepted for selection of LT candidates and are incorporated into the pre-transplant evaluation process for patients with HCC in many transplant centres.\(^6\)

However, the Milan criteria have been challenged in recent years by many as being too restrictive. Emerging data from increasing experience with LT have demonstrated that the selection criteria can be expanded without compromising long-term outcomes\(^7\) and some patients with advanced HCC can also be cured by LT following effective neoadjuvant therapy.\(^8\), \(^9\) In this context, downstaging of advanced HCCs that initially do not meet the Milan criteria but which following pre-LT treatment fulfil the criteria raises a particular interest. Although the effect of tumour downstaging in LT recipients has formerly been tested by several groups,\(^9\)–\(^12\) it is difficult to reach valid conclusions with regard to its role in post-LT outcomes because these studies used different treatment options and adopted inconsistent definitions of tumour downstaging, with a small number of patients.

In theory, achieving successful downstaging by a therapy may reflect more favourable tumour biology associated with low recurrence potential. However, not all patients in this category had acceptable post-LT outcomes,\(^11\), \(^12\) indicating that there are additional parameters other than tumour dimensions that have to be taken into account before undergoing LT. Tumour grading\(^13\), \(^14\) or microvascular invasion\(^14\), \(^15\) which has been recently described as risk factors for recurrence, is indeed of limited use in this setting, as the accurate estimation of these variables can only be determined by examination of the explanted liver. Therefore, there is a crucial need for a better understanding of the disease course after downstaging as well as identification of pre-transplant prognostic variables so that we can decide to either undergo LT or choose other options for patients achieving successful downstaging of HCC. Unfortunately, there is a general lack of knowledge about long-term clinical course and pre-transplant prognostic parameters for patients with downstaged tumours awaiting LT.

To address these issues, we have conducted a long-term follow-up study of a large number of patients with HCC outside the Milan criteria who were downstaged to fit the criteria by transarterial chemotherapy. The clinical course, including dropouts from the waiting list, post-LT recurrence of HCC, and survival, were analysed in the current study. With particular analysis of pre-transplant parameters predicting post-LT recurrence, we have also identified the best candidates for LT after tumour downstaging.

PATIENTS AND METHODS

Patients

The study population consists of subjects who underwent transarterial chemo-lipiodolization (TACL) for downstaging of HCC. Treatment allocation for newly diagnosed HCC in our institution was as follows: briefly, patients eligible for surgical treatments were assigned to receive either LT if a donor organ was available or partial hepatectomy if the HCC was resectable. Otherwise, patients with decreased hepatic function were subjected to percutaneous ethanol injection therapy or radiofrequency ablation when appropriate. The remaining patients underwent TACL, if they met the following selection criteria: a serum bilirubin level <3 mg/dL, an albumin level >2.8 g/dL, and a prothrombin time >50%. Some exceptions to these criteria were made on a case-by-case basis.

Between June 2000 and December 2007, a total of 386 patients with HCC exceeding the Milan criteria, but with no evidence of metastatic lesions or vascular invasion underwent TACL according to the aforementioned treatment allocation. During the study period, patients who were successfully downstaged to within the Milan criteria after TACL were consecutively accepted into the waiting list and offered LT. With the extreme scarcity of deceased donor livers in Korea, the option of LT was often chosen as living donor liver
transplantation (LDLT) by family members when intra-
familial donations were available.

The diagnosis of HCC was made based on the con-
sistent findings of at least two separate imaging stud-
ies including computed tomography (CT), magnetic
resonance imaging (MRI) or angiography. Otherwise,
liver biopsy was performed for radiologically atypical
lesions. The study was approved by the Institutional
Review Board of the Catholic University of Korea and
treatment was performed only after the informed con-
sent was obtained from each patient. Clinical data of
all patients were collected consecutively and analysed
retrospectively.

Treatment and follow-up

The treatment regimen used for TACL was a combina-
tion of intraarterial epirubicin (50 mg/m²) and/or cis-
platin (60 mg/m²) in a mixture of lipiodol (5–10 mL),
without gelfoam embolization. The transarterial proce-
dure was repeated at one-to-two monthly intervals.
The drug dosage and treatment interval were modified
as previously described in one of our reports.16 The
transarterial chemotherapy was continued without any
limit on the number of cycles, until complete necrosis
of all intrahepatic tumour lesions was achieved. For
patients who achieved complete necrosis, an abdomi-
nal CT scan and α-fetoprotein (AFP) were monitored
every 2 to 3 months. While remaining on the waiting
list for LT, patients were removed from the waiting
list, in the case of a radiological suggestion of a
tumour progression above the Milan criteria or death,
which was defined as a dropout. Loco-regional treat-
ments were performed for tumour recurrence as
appropriate. Patients with tumour recurrence, but
within the Milan criteria, remained on the waiting list
for LT on anti-cancer therapy until the time of LT or
dropout.

Downstaging

Entry criteria for tumour downstaging included
patients with HCC initially beyond the Milan criteria,
but with no evidence of extrahepatic metastasis or
vascular invasion. There were no specific upper limits
in tumour size and number for inclusion. Successful
downstaging was defined as a reduction in tumour size
and number meeting the Milan criteria or complete
tumour necrosis indicating the lack of contrast
enhancement and disappearance of the viable tumour
on CT/MRI and angiography, irrespective of tumour
size or number.

Statistical analysis

Clinical outcomes of interest in this study were drop-
outs because of tumour progression or death after suc-
cessful downstaging by TACL and post-transplant
recurrence and survival in the downstaged patients.
The cumulative rate of the events was estimated using
the Kaplan–Meier method on an intention-to-treat
basis, and the difference was determined by the log-
rank test. To evaluate the independent factors for
post-LT recurrence of HCC, Cox hazard regression
analysis was used for multivariate analysis of variables
that were significant in the univariate analysis. Data
were expressed as the mean ± s.d. or median (range).
A P value <0.05 was considered statistically significant
in the analyses. The software for analysis was the Sta-
tistical Package for Social Science (SPSS Inc., Chicago,
IL, USA), version 11.5.

RESULTS

Baseline characteristics

Between 2000 and 2007, the 386 potential candidates
in our institution for LT underwent TACL for down-
staging of HCC. Of these, 160 (41.5%) patients
achieved finally successful downstaging of HCC to
within the Milan criteria. The baseline characteristics
of the 160 downstaged patients are summarized in
Table 1. A majority of the patients had virus-related
HCC [hepatitis B virus (105 patients, 65.6%), hepatitis
C virus (30 patients, 18.8%) and co-infection of the
viruses (2 patients, 1.3%)], and the other 23 (14.4%)
patients had non-viral diseases. The Child-Pugh classi-
fication was A in 129 (80.6%) patients, B in 25
(15.6%) patients and C in 6 (3.8%) patients. The maxi-
mum tumour diameter at baseline was <5 cm in 83
(51.9%) patients, 5–7 cm in 57 (35.6%) patients, and
≥7 cm in the remaining 20 (12.5%) patients, with a
mean of 4.95 ± 2.19 cm for all patients. Fifty-six
(35.0%) patients had a single lesion, and the remaining
104 (65.0%) patients had multiple tumour lesions
before downstaging.

With regard to tumour response at the time of suc-
cessful downstaging, 90 (56.3%) patients achieved
complete necrosis of all tumour lesions by TACL, while
the remaining 70 (43.7%) patients had marked tumour
regression to within the Milan criteria, but still had viable tumour lesions that were incompletely obliterated.

### Treatment after downstaging

Of the 160 patients with successful downstaging, eight patients received hepatectomy after downstaging and 37 patients ultimately underwent LT, including seven deceased donor LTs and 30 LDLTs. The median time interval from the initial downstaging to LT was 61 days (range: 27–194 days). Among the remaining 115 patients awaiting LT, 82 patients dropped off the list and 33 patients were still on the waiting list for LT until the last visit. Follow-ups after enrollment and downstaging for the entire population are depicted in Figure 1.

### Dropout from the waiting list after downstaging

During the follow-up, 82 patients were eventually dropped out from the list for LT. The major cause of dropout was tumour progression in 74 patients and the other causes in the remaining eight patients were medical delistings, including five cases of progressive worsening in hepatic function, two cases of sepsis and one case of interstitial pneumonitis.

The cumulative rates of overall dropout at 1, 2 and 5 years after downstaging among all 160 patients were 46.7%, 70.2% and 87.2% respectively (Figure 2). The dropout rates due to tumour progression at 1, 2 and 5 years were 42.6%, 64.5% and 84.7% respectively. The median time to overall dropouts from the initial downstaging was 13.5 months in our study population.

### Outcome after liver transplantation following downstaging

Of the 37 patients who underwent LT after downstaging, 23 (62.2%) were alive and the remaining 14 (37.8%) were dead at the last follow-up. Four patients had died of causes other than recurrence of HCC, which included persistent poor graft function (one patient), hepatic decompensation as a consequence of recurrent hepatitis B virus (one patient), development of pancreatic cancer (one patient) and perioperative mortality (one patient). During the median post-transplant follow-up of 29.3 months, eleven (29.7%) patients experienced a recurrence of HCC. One of the patients had a pulmonary metastasis 6 months after LT, but is still alive being free of HCC up to 45 months after thoracoscopic resection and the other 10 patients died of HCC recurrence. Overall, the cumulative post-transplant survival rates at 1, 2 and 5 years were 89.2%, 70.3% and 54.6% respectively. The cumulative recurrence-free survival rates at 1, 2 and 5 years were 74.7%, 71.8% and 66.3% respectively (Figure 3).

### Tumour necrosis

Tumour necrosis was examined in the liver explants of the 37 patients who underwent LT. Extensive tumour necrosis (>90%) was found in 21 patients. When compared with pre-transplant radiological findings, 17 (73.9%) of the 23 patients with radiological complete necrosis and 4 (28.6%) of the 14 with radiological viable tumour prior to LT had nearly complete necrosis (>90%) of all tumour lesions in the explanted livers.

### Predictors of post-transplant recurrence of downstaged HCC

The pre-transplant parameters listed in Table 2 were evaluated to determine if they could predict HCC

**Table 1. Baseline characteristics of 160 patients who achieved successful downstaging by transarterial chemotherapy**

| Characteristics | (n = 160) |
|-----------------|----------|
| Gender (male:female) | 128:32 |
| Age (years) | 58.8 ± 9.8 |
| Causes | |
| HBV/HCV/IBV+HCV/Non-viral | 105/30/2/23 |
| ALT (IU/L) | 50.2 ± 39.0 |
| Total bilirubin (mg/dL) | 1.35 ± 1.29 |
| Albumin (g/dL) | 3.56 ± 0.58 |
| Prothrombin time (INR) | 1.17 ± 0.28 |
| AFP level (ng/mL) | 43.1 (0.7–488 760) |
| Maximum tumour size (cm) | 4.95 ± 2.19 |
| <5/5–7/‡/78 | 83/57/20 |
| Tumour number | |
| Single/Multiple | 56/104 |
| 1–3/4–5/‡/6 | 121/26/13 |
| Child-Pugh class | A/B/C |
| 129/25/6 |

HBV, hepatitis B virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; AFP, α-fetoprotein.
recurrence after transplantation. Among these, AFP levels ≥100 ng/mL at LT ($P = 0.004$), maximum tumour size ≥7 cm ($P = 0.010$), the sum of tumour size ≥10 cm ($P = 0.001$) and failure to achieve complete necrosis by TACL ($P = 0.038$) were significantly associated with post-transplant recurrence after downstaging (Table 2). The Cox proportional hazard model was used to determine independent predictors of post-transplant recurrence. As a result, AFP levels ≥100 ng/mL at LT [odds ratio (OR) = 14.39; 95% confidence interval (CI): 2.48–83.55, $P = 0.003$], maximum tumour size ≥7 cm (OR = 19.42; 95%CI: 2.88–130.96, $P = 0.002$) and the lack of complete necrosis by TACL (OR = 3.83; 95%CI: 1.02–14.52, $P = 0.048$) were identified as three independent predictors of HCC recurrence after LT following downstaging using TACL (Table 3). In the subgroup analysis using these risk factors, patients with a maximum tumour size <7 cm who achieved complete necrosis and maintained a low AFP level <100 ng/mL at the time of transplantation had a significantly better post-transplant outcome than those who had at least one of these risk factors, with an 87.5% probability of recurrence-free survival up to 6 years ($P = 0.014$; log-rank test) (Figure 4).

Survival of the entire cohort

Among all 386 patients in whom tumour downstaging was attempted, 276 (71.5%) patients died during the median follow-up of 25.9 months. The Kaplan–Meier survival rates at 1, 2 and 5 years were 71.3%, 50.6% and 24.6% respectively (Figure 5). The median overall survival for all the patients was 24.8 months.

DISCUSSION

With recent advances of therapeutic options and surveillance for HCC, more patients with large HCC have become able to achieve successful downstaging of tumours to within the transplant criteria during therapy than in the past. The challenge now is to determine which factors, other than tumour size and
number that are not enough for decision-making, offer an effective prognostication to permit or deny transplantation for downstaged patients. Despite the favourable tumour biology that is expected in successfully downstaged patients, previously published data have yielded inconsistent results in relation to post-transplant outcomes,9–12 highlighting the need for a better understanding of long-term clinical course of downstaged HCC and identification of pre-transplant prognostic factors establishing the basis on which we choose LT for downstaged patients.

The current study showed that approximately 42% of patients with HCC over Milan criteria who were eligible for a tumour downstaging scheme using TACL could be successfully downstaged and thereby placed on the waiting list for LT. However, a considerable proportion of those patients were ultimately dropped from the list because of tumour progression, with a 43% dropout rate up to 1 year. This appears to be higher, when compared with the reported dropout rates ranging from 21% to 25% of patients with HCC within the Milan criteria treated with transarterial therapy,17, 18 representing more aggressiveness of tumours in this group. Thus, this characteristic distinction in dropout times depending on initial tumour stages should be considered for prioritization of transplant recipients among patients with HCC awaiting LT.

Most importantly, our study elucidated pre-transplant predictors of recurrence after LT, including baseline tumour size, AFP levels and complete necrosis at transplantation. Of these, tumour size is already known as an indicator for other important prognostic factors, such as microvascular invasion and tumour grade.19, 20 In contrast, we found no effect of tumour number on post-transplant recurrence in the analysis. Although tumour number has also been reported to be a negative prognostic variable,21 thereby being incorporated into the currently available LT selection criteria for HCC,3, 7 it is likely that the impact of tumour number on post-transplant recurrence is not as significant as that of tumour size for patients with downstaged HCC.

### Table 2. Univariate analysis of risk factors for post-transplant recurrence of downstaged HCC

|                      | No Recurrence | P value |
|----------------------|---------------|---------|
| Gender               |               |         |
| Male                 | 31            | 32.3%   | 0.345   |
| Female               | 6             | 16.7%   |         |
| Age                  |               |         |
| £55 years            | 26            | 23.1%   | 0.247   |
| >55 years            | 11            | 45.5%   |         |
| Cause                |               |         |
| Viral                | 32            | 25.0%   | 0.218   |
| Non-viral            | 5             | 60.5%   |         |
| AFP level            |               |         |
| <100 ng/mL           | 21            | 19.0%   | 0.106   |
| ≥100 ng/mL           | 16            | 43.8%   |         |
| AFP level at LT      |               |         |
| <100 ng/mL           | 25            | 16.0%   | 0.004   |
| ≥100 ng/mL           | 12            | 58.3%   |         |
| Child-Pugh class     |               |         |
| A                    | 27            | 33.3%   | 0.436   |
| B or C               | 10            | 20.0%   |         |
| Maximum tumour size  |               |         |
| <7 cm                | 32            | 21.7%   | 0.010   |
| ≥7 cm                | 5             | 80.0%   |         |
| Sum of tumour size   |               |         |
| <10 cm               | 31            | 19.4%   | 0.001   |
| ≥10 cm               | 6             | 83.3%   |         |
| Tumour number        |               |         |
| ≤3                   | 24            | 25.0%   | 0.558   |
| ≥4                   | 13            | 38.5%   |         |
| Response at LT       |               |         |
| Complete necrosis    | 23            | 17.4%   | 0.038   |
| No complete necrosis | 14            | 50.0%   |         |

AFP, α-fetoprotein; LT, liver transplantation.
In this analysis, we employed broad entry criteria for downstaging process, in which only patients with vascular invasion or metastasis were excluded, but none of other tumour characteristics such as size or number was considered a contraindication for entry into the study. With regard to tumour size, we found that there is indeed little chance of tumour downstaging to within the transplant criteria for patients with large tumours. Only 16.5% (20/121) of our patients with a HCC >7 cm were eventually downstaged (data not shown); very few among them (9.9%, 12/121) achieved complete necrosis that was identified as one of the most important predictors of recurrence-free survival after LT in this study. In agreement with previous data, our results also support postulation that there is probably an upper limit of tumour size above which pre-transplant downstaging of tumour will provide no benefit after transplantation.

One of the most important findings emerging from our study is the clarification of value of a dynamic approach over a fixed approach based on tumour morphology to the decision-making in the selection of LT recipients after downstaging. Of the three predictors for post-LT recurrence in this analysis, AFP levels and complete necrosis were not baseline data, but only variables at the time of transplantation. All evaluated baseline data, except tumour size, had no significant effect on HCC recurrence post-transplant in our analysis. This suggests that post-transplant outcomes are affected not only by initial tumour burden, but also by other parameters indicative of biological behaviour or viability of tumours, further supporting the previous observations. It is speculated that AFP levels and complete necrosis at transplantation can serve as surrogate markers for tumour aggressiveness and residual viability, helping with the selection process for LT.

### Table 3. Multivariate analysis of risk factors for post-transplant recurrence of downstaged HCC

| Risk Factor                          | OR (95% CI)     | P value |
|--------------------------------------|-----------------|---------|
| **AFP level at LT**                  |                 |         |
| ≥100 ng/mL                           | 14.39 (2.48–83.55) | 0.003   |
| <100 ng/mL                           | 1               |         |
| **Maximum tumour size**              |                 |         |
| ≥7 cm                                | 19.42 (2.88–130.96) | 0.002   |
| <7 cm                                | 1               |         |
| **Sum of tumour size**               |                 |         |
| ≥10 cm                               | 1.50 (0.26–8.65) | 0.649   |
| <10 cm                               | 1               |         |
| **Complete necrosis at LT**          |                 |         |
| No                                   | 3.83 (1.02–14.52) | 0.048   |
| Yes                                  | 1               |         |

OR, odds ratio; CI, confidence interval; AFP, α-fetoprotein; LT, liver transplantation.

**Figure 4.** Comparison of Kaplan–Meier curves of recurrence-free survival after liver transplantation by status of pre-transplant prognostic factors. Group A showed a significantly better recurrence-free survival after transplantation than Group B (5-year rates of 87.5% vs. 54.6%, P = 0.014; log-rank test). Group A, patients with a maximum tumour size <7 cm who achieved complete necrosis and maintained a low AFP level <100 ng/mL before transplantation; Group B, patients who had a least one of these three risk factors before transplantation.

**Figure 5.** Kaplan–Meier survival curve for the entire cohort of 386 patients in whom tumour downstaging was attempted. The overall survival rates at 1, 2 and 5 years were 71.3%, 50.6% and 24.6% respectively, with a median time of 24.8 months.
after tumour downstaging. Thus, one should take into account evolutionary events regarding response to pre-transplant therapy as well as tumour size, when selecting LT recipients in this particular group.

This study has some limitations. Under the shortage of deceased donor grafts in Korea, a small number of patients among the entire study population could ultimately undergo LT, in most cases LDLT, while we included a large number of downstaged patients. Consequently, whether our study results are also applicable to external populations that receive DDLT within an acceptable waiting time remains unclear. Additionally, based on the current data, it is difficult to draw conclusions regarding the value of a certain observational period before LT to select candidates with aggressive tumour biology because most of the recipients in our study were transplanted soon after achieving downstaging. Finally, tumour downstaging would be maximized with the optimal combination of varying treatment modalities, although this study included patients treated with TACL exclusively. However, we believe that transarterial therapy might be the main option under minimal exclusion criteria for downstaging. Thus, the homogeneity of treatment in our study would rather allow a more reliable data analysis.

In conclusion, this large cohort study showed a long-term clinical course of patients with HCC successfully downstaged to meet the transplant criteria by TACL. Transplant time and selection of LT recipients from this particular group should be determined with a comprehensive understanding of such clinical features of downstaged HCCs. Although the overall long-term outcome of patients with downstaged HCC appears to fall somewhat short of that of patients initially meeting the Milan criteria, in terms of a relatively increased risk of dropout and recurrence after transplantation, it seems evident that meticulously selected patients can have a significant chance for long-term survival after LT. On the basis of our data, patients with a maximum tumour size <7 cm who achieve complete necrosis together with AFP levels <100 ng/mL during pre-transplant transarterial therapy may be the best candidates for LT following downstaging. Our information will be helpful in selecting suitable LT recipients with low recurrence potential in the setting of tumour downstaging. Future studies are needed to confirm these results.

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