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Real-life data on the impact of successful downstaging in patients with hepatocellular carcinoma: A Dutch Multicenter Study

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ABSTRACT

Patients with Barcelona Clinic Liver Cancer intermediate stage hepatocellular carcinoma (HCC) theoretically are an excellent group to consider downstaging using locoregional therapy (LRT) since they do not have extrahepatic spread or vascular invasion. Once successful, this can change the treatment strategy from palliative to curative intention. Although downstaging therapy is suggested in guidelines, it is still not widely accepted. Moreover, studies on downstaging are mainly performed in high-incidence HCC countries. Therefore, our aim was to gain insight in therapeutic strategies in patients with intermediate stage HCC and their impact on intention-to-treat survival in a real-life setting in a low-incidence HCC country.

We retrospectively analyzed data from the national Dutch HCC registry. From this database, consisting of 1409 patients with a diagnosis of HCC between 2005-2013 in 5 Dutch tertiary referral centers, we identified 165 patients with intermediate stage HCC. Out of these patients, 63 (38%) were not offered LRT, whereas 102 (62%) did receive LRT. Subsequently, 50 (49%) of the 102 patients who received LRT were successfully downstaged. Eleven patients (22% of successfully downstaged patients) eventually underwent liver transplantation. Cox regression analysis showed that a lower MELD score, an AFP value <100 ng/ml, successful downstaging and liver transplantation (all $\leq p = 0.01$) were positively associated to overall survival.

In conclusion, our results demonstrate that LRT is not routinely offered to intermediate stage HCC patients in the Netherlands. Nevertheless, we showed that patients with intermediate stage HCC who are successfully downstaged have a survival benefit compared to those who were not.

Introduction

The incidence of hepatocellular carcinoma (HCC) has risen significantly in the past years and HCC is becoming a rapidly growing problem worldwide [1]. Of all newly diagnosed HCC patients in developed countries, only 30-40% is diagnosed at an early stage when curative treatment still can be applied [2]. Hence, the majority of the newly diagnosed HCC patients is diagnosed at an advanced stage and are no longer candidates for treatment with curative intent [1,3].

The Barcelona Clinic Liver Cancer (BCLC) classification is a widely accepted staging system for HCC and links tumor stage with treatment

; MELD, Model for end-stage liver disease.

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Abbreviations

HCC	Hepatocellular Carcinoma
BCLC	Barcelona Clinic Liver Cancer
LT	Liver Transplantation
LRT	Locoregional therapy
AFP	Alpha-Phetoprotein
TACE	Transarterial Chemoembolization
TARE	Transarterial Radioembolization
SD	Successfully Downstaged
NSD	Not-successfully Downstaged

strategy. According to the modified BCLC treatment algorithm, liver transplantation (LT) is the preferred treatment in patients who fulfill Milan criteria (a single tumor $\leq$5 cm or $\leq$3 tumors $\leq$3 cm without extrahepatic spread or macrovascular invasion) if surgical resection is deemed unfeasible and transplantation is not contraindicated because of high age or comorbidity [1,4]. In patients who initially do not meet Milan criteria, downstaging using locoregional therapy (LRT) can be considered. Downstaging is defined as a reduction in size and/or number of tumors in response to LRT, leading to stage migration from BCLC intermediate stage to BCLC early stage HCC. It is considered successful if patients fulfill Milan criteria after LRT for at least 3 months [5]. Once the tumors in the liver are successfully downstaged, LT can be considered in selected patients without contraindications for LT [1].

Since patients with intermediate stage HCC do not have macroscopic extrahepatic spread or vascular invasion, they theoretically are an excellent group to consider downstaging [1]. Successful downstaging with subsequent LT could potentially cure these patients from cancer as well as the underling liver disease. This is supported in several studies which show a comparable overall 5-years survival after LT between downstaged patients and patients who met Milan criteria at time of diagnosis [6-12]. However, downstaging with the intention to offer liver transplantation is controversial and still not common practice in every center due to the scarcity of organs and limited available scientific evidence [13]. Moreover, much research on downstaging is performed in the United States of America, where the incidence of HCC is relatively high compared to other countries [14]. Those results can not immediately be translated to lower HCC incidence countries, like the Netherlands, and therefore there is a need to study the effectiveness of downstaging in low HCC incidence countries.

In the present study, we conducted a retrospective multicenter cohort analysis of unselected consecutive cirrhotic patients diagnosed with intermediate stage HCC. The aim of the study was to gain insight in therapeutic strategies in multidisciplinary teams in Dutch tertiary referral centers, to determine the success rate of downstaging using LRT and to investigate the impact on intention to treat survival, by analyzing real-life data in a low-incidence HCC country.

Patients and methods

Patients

Case finding was performed using the database of the 'Dutch Hepatocellular & Cholangiocarcinoma Group'. This database consists of 1409 consecutive patients with an HCC diagnosis in the period of 2005-2013 in 5 Dutch academic centers (Amsterdam University Medical Centers, location Academic Medical Center and location VU Medical Center, Erasmus Medical Center, Leiden University Medical Center and University Medical Center Utrecht) and has formed the basis of previously published studies [15,16]. Diagnosis of HCC was based on AASLD 2005 and 2011 guideline criteria based on imaging or histology [15]. The inclusion criteria for this study were consecutive adult patients diagnosed with cirrhosis and who fulfilled the condition of BLCL intermediate stage HCC. Exclusion criteria were no proven cirrhosis (by clinical, laboratory, radiologic, and/or histologic findings), diagnosis after LT or any prior treatment for HCC. Treatment decisions in all patients were left to the treating multidisciplinary teams.

Data collection

Electronical medical records of all patients were retrospectively reviewed to collect additional data (AGCB). Information was collected on etiology of underlying liver disease, comorbidities, complications of cirrhosis, Child Pugh-score, Model for end-stage liver disease (MELD) score and alpha-fetoprotein (AFP) concentration at diagnosis. Furthermore, tumor characteristics (number of lesions $>$ 1 cm, diameter of largest lesion), portal vein thrombosis, type and number of consecutively applied LRT (i.e. thermal ablation, transarterial chemoembolization [TACE], transarterial radioembolization [TARE], stereotactic radiotherapy, resection or multimodal therapy), LT and survival data were collected.

For the determination of etiology of underlying liver disease, anamnestic-, laboratory-, radiologic-, and histologic findings were used. If, based on these parameters, no conclusion on etiology of underlying liver disease could be made, it was considered to be cryptogenic.

Imaging data

To assess whether a patient fulfilled Milan criteria after LRT, the reports of CT- and/or MRI-scans after LRT were reviewed. If the report was not of sufficient detail, the CT- or MRI-scan was reassessed by the researcher (AGCB) and a senior radiologist (MCB). Tumor response after LRT was evaluated according to the modified response evaluation criteria for solid tumors (mRECIST) by using contrast enhanced CT- or MRI-scan [17]. Presence of enhancement in the arterial phase followed by washout in the portal venous and/or late venous phase was considered as viable tumor.

Based on the radiologic response to LRT, patients were classified into 2 groups: successfully downstaged (SD) and not-successfully downstaged (NSD). Successful downstaging was defined as fulfilling Milan criteria for $\geq$3 months.

Statistical analysis

Data were analyzed according to an intention-to-treat principle. Data in tables are shown as mean $\pm$ standard deviation when normally distributed and when not normally distributed as median with interquartile range.

Factors associated with receiving LRT were estimated with a multivariate logistic regression analysis. Factors associated with overall survival were estimated with a multivariate Cox model with transplantation and successful downstaging as time-dependent covariates. The following baseline risk factors were used: age, sex, MELD score, AFP concentration, number of lesions and diameter of largest tumor at diagnosis. AFP concentration was dichotomized with a cut-off value of 100 ng/ml, which was chosen, based on the results of the studies of Bova et al. [18] and Duvoux et al. [19].

A competing risk model from three months after diagnosis (landmark time, the 3 months interval for definition of successful downstaging) with death without being successfully downstaged as a competing event, was used to estimate the cumulative incidence of successful downstaging [20]. To identify factors associated with successful downstaging, a cause-specific multivariate Cox proportional hazards model, censoring patients who died without being successfully downstaged, was employed, using the same fixed factors as mentioned above.

A p-value < 0.05 was considered to be statistically significant. Statistical analyses were performed using IBM SPSS statistics for windows (version 25.0; IBM Corp., Armonk, New York, USA). All statistical

analyses concerning the competing risks model were performed in the R-software environment with the mstate library [21,22].

Results

Of all 1409 patients from the database, 165 fulfilled the inclusion criteria and were included in this study. Baseline characteristics of those patients are summarized in Table 1.

Mean age in the population was 65.0 ± 9.1 years and 82% were male. In the majority of patients, alcoholic liver disease or viral hepatitis was the underlying liver disease.

98 patients had an AFP concentration ≤100 ng/ml, 65 patients had an AFP concentration >100 ng/ml and in 2 patients no AFP concentration was available at time of diagnosis.

The total number of lesions >1 cm at diagnosis ranged from 2 to ≥10. Ten patients (6%) were diagnosed with diffusely infiltrating HCC. A detailed overview of the distribution of number of lesions is shown in Table 1. Eight patients had multifocal HCC with classical radiologic features and absence of macrovascular invasion and extrahepatic metastases, but the exact number of tumors could not reliably be determined. The diameter of the largest lesion at diagnosis in the population ranged from 1.5 cm to 20 cm with a median of 4.9 cm (inter quartile range [IQR] 3.6-6.4).

Therapy

Out of the 165 included patients, 102 patients (62%) received LRT (Fig. 1).

Fifty-nine (36%) patients reached Milan criteria after LRT, with 50 patients (30%) fulfilling Milan criteria for ≥3 months. These 50 patients were subsequently assigned to the SD group. According to the intention-to-treat principle, 112 (68%) were assigned to the NSD group, with 63 (38%) patients who did not receive any LRT at all (characteristics of this group are shown in the supporting table S1), 40 patients (24%) who still did not meet Milan criteria after LRT and 9 (6%) who exceeded Milan criteria again within 3 months after LRT. Three patients (2%) were lost-to-follow up and could therefore not be assigned to any of the groups.

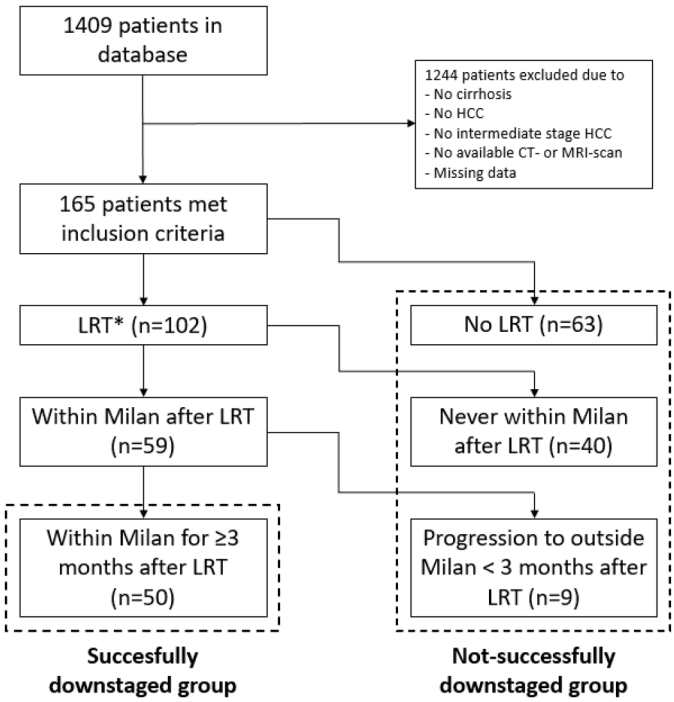

Fig. 1. Flowchart of the classification process into the successful and not successful downstaged group. Successful downstaging is defined as fulfilling Milan criteria for ≥3 months. Abbreviations: LRT, Locoregional Therapy; SD, successful downstaged; NSD, not-successful downstaged * 3 patients were lost-to-follow up after receiving locoregional therapies

Table 1
Baseline characteristics of the 165 patients diagnosed with intermediate stage HCC included in this study.

Variable	All patients (n = 165)
Age (years)	65.0 ± 9.1
≤70	114 (69.1)
Gender, male	135 (81.8)
Etiology	
Alcoholic liver disease	65 (39.4)
Hepatitis B and/or C	55 (33.3)
Other causes[†]	23 (14.0)
Cryptogenic	22 (13.3)
Ascites (n=146)	35 (24.0)
Cardiovascular disease	34 (20.6)
Child-Pugh class (n=123)	
A	79 (64.2)
B	42 (34.2)
C	2 (1.6)
MELD score (n=126)	7 (7-11)
≤16	117 (92.9)
>16	9 (7.1)
AFP (ng/ml) (n=163)	
≤100	98 (60.1)
>100	65 (39.9)
No. of lesions (n=157)	
2	57 (36.3)
3	32 (20.4)
4	28 (17.8)
≥5	30 (19.1)
Diffuse	10 (6.4)
Diameter largest tumor (cm)	4.9 (3.6–6.4)
Portal vein thrombosis	5 (3.2)

Abbreviations: MELD, model for end-stage liver disease.
Note: Data are expressed as mean ± standard deviation, number (%) or median and interquartile range.
[†] Other causes of underlying liver disease were non-alcoholic fatty liver disease (n=11), haemochromatosis (n=7), primary biliary cholangitis/primary sclerosing cholangitis (n=2), auto immune hepatitis (n=1), alpha 1-antitrypsin deficiency (n=1) and Wilson's disease (n=1).

In Table 2, the types and numbers of consecutively received LRT(s) in all patients are shown.

Of note, 17 out of 63 patients who were not treated by LRT, received systemic therapy (i.e. sorafenib). Seventy-one patients (43%) received one session of LRT (i.e. TACE, TARE, ablation, resection or stereotactic radiation). Thirty-one patients (19%) received consecutive sessions of LRT. The number of treatment cycles per patient ranged from 1 to 11 with a median number of 2. After successful downstaging, 11 (22%) out of 50 patients underwent LT. In the NSD group 3 patients (3%) underwent LT, although they did not meet Milan criteria.

To assess possible factors associated with treatment decision for receiving LRT, a multivariate logistic regression analysis was performed (table S2). A lower age and a lower number of lesions were independently associated with receiving LRT (OR 0.95 and 95% CI 0.91-1.00, OR 0.62 and 95% CI 0.47-0.81, respectively). Moreover, hepatitis B and/or C as underlying liver disease was also independently associated with receiving LRT (alcoholic liver disease versus hepatitis B and/or C OR 0.32, 95% CI 0.11-0.89, all other etiologies versus hepatitis B and/or C OR 0.29, 95% CI 0.09-0.89).

Overall survival

Median follow-up time from time of diagnosis was 14.6 months (IQR 6.8-30.0 months). A multivariate Cox regression model was estimated to investigate the effect of the covariates on overall survival. The results of this analysis showed that a higher MELD score (Hazard ratio [HR] 1.07, 95% CI 1.02-1.12) and AFP concentration >100 ng/ml (HR 1.93, 95% CI

Table 2
Types and numbers of locoregional therapies consecutively offered to included patients.

Variable	All patients (n = 165*)	Succesfully downstaged group† (n = 50)	Not-successfully downstaged group (n = 112)
No LRT	63 (38.2)	0 (0.0)	63 (56.3)
Single LRT treatment			
TACE	47 (28.5)	16 (32.0)	29 (25.9)
TARE	5 (3.0)	1 (2.0)	4 (3.6)
Thermal ablation	16 (9.7)	9 (18.0)	6 (5.4)
Resection	2 (1.2)	2 (4.0)	0 (0.0)
Stereotactic radiation	1 (0.6)	1 (2.0)	0 (0.0)
Multimodal LRT treatment			
Thermal ablation+TACE	15 (9.1)	8 (16.0)	7 (6.3)
Thermal ablation+Resection	7 (4.2)	5 (10.0)	2 (1.8)
TACE+TARE	3 (1.8)	2 (4.0)	1 (0.9)
Other	6 (3.6)	6 (12.0)	0 (0.0)
Number of treatments per patient			
1	35 (21.2)	16 (32.0)	18 (16.1)
2	40 (24.2)	22 (44.0)	17 (15.2)
3	16 (9.7)	9 (18.0)	6 (5.4)
4	6 (3.6)	2 (4.0)	4 (3.6)
≥5	5 (3.0)	1 (2.0)	4 (3.6)
Liver transplantation	15 (9.1)	11 (22.0)	3 (2.7)

Abbreviations: LRT, locoregional therapy; TACE, Transarterial chemoembolization; TARE, Transarterial radioembolization.
Note: Data are expressed as number and percentages.
* 3 patients were lost to follow-up.
† Description of the types and numbers of LRT received until successful downstaging was achieved

1.22-3.04) were associated with increased mortality (Table 3).

Successful downstaging of the tumors and undergoing LT were associated with lower risk of mortality (respectively HR 0.38, 95% CI 0.22-0.67 and HR 0.17, 95% CI 0.06-0.52).

Table 3
Multivariate cox regression model for overall survival.

Variable	HR (95% CI)	p-value
Age	0.998 (0.97-1.03)	0.915
Female sex (versus male)	1.03(0.58-1.84)	0.926
Cause of liver disease		
Hepatitis B and/or C (versus alcoholic liver disease)	0.95 (0.55-1.65)	0.861
Others (versus alcoholic liver disease)	0.94 (0.56-1.56)	0.805
MELD score	1.07 (1.02-1.12)	0.010
AFP >100 ng/ml	1.93 (1.22-3.04)	0.005
Number of lesions	1.09 (0.92-1.29)	0.331
Diameter largest tumor	1.04 (0.96-1.13)	0.342
Successful downstaging (versus not successfully downstaged)†	0.38 (0.22-0.69)	0.001
Liver transplantation (versus no LT)†	0.17 (0.06-0.52)	0.002

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; MELD, model for end-stage liver disease; LT, liver transplantation.
† Time from diagnosis to successful downstaging and time from diagnosis to liver transplantation as time dependent covariates.

Predictors for successful downstaging

In Fig. 2, the cumulative incidence of two competing events, successful downstaging and death without being successfully downstaged, is shown.

A cause-specific Cox regression model from 3 months after diagnosis was estimated to assess the association between factors and successful downstaging. Results are shown in Table 4.

A lower age at diagnosis (HR_{CS} 0.96, 95% CI 0.93-1.00), a lower number of lesions (HR_{CS} 0.55, 95% CI 0.41-0.74) and a smaller diameter of largest tumor (HR_{CS} 0.82, 95% CI 0.67-0.99) were independently associated with successful downstaging. Noteworthy, AFP concentration was not significantly associated with successful downstaging (HR_{CS} 0.83, 95% CI 0.44-1.55).

Discussion

In this Dutch, multicenter, retrospective study of consecutive patients with intermediate stage HCC in a low incidence country, we found that 62% of the patients in our cohort received LRT. Of all included patients, 30% was successfully downstaged according to the definition in the Zurich consensus meeting (fulfilling Milan criteria for ≥3 months after LRT) within 3 years after diagnosis. Considering only the patients who underwent any session of LRT, the success rate was 49%. Importantly, only 22% of the successfully downstaged patients eventually underwent liver transplantation. However, considering the low number of transplantations, our results show that successful downstaging of HCC by itself is independently associated with a lower risk of mortality.

According to the BCLC treatment algorithm, the recommended treatment modality for intermediate stage HCC is TACE, provided that no contraindications are present [1]. However, as outlined in a review of Galle et al. [13], recent studies cautiously propose new therapeutic options for this patient group. The ultimate choice of treatment depends on multiple factors like guideline recommendations, treatment availability, local expertise, and suitability and preferences of the patient. Recent studies have shown that the management of intermediate stage HCC in the real world differs significantly from guideline recommendations and between centers [13,23]. These findings are in line with our results: we determined that only 29% of the patients in our cohort, when treated, received TACE as a single modality, all other patients received different types of LRT. One possible explanation might be the presence of heterogeneity of the intermediate stage population. There are differences in liver function as well as tumor burden between intermediate stage patients, which makes the ultimate choice of treatment complex. Moreover, the lack of strong scientific evidence and discrepancies between guidelines make it even more complicated [13].

Downstaging can be considered as a tool to identify patients with a favorable tumor biology and could therefore be used to select patients who are more likely to respond to treatment [1,6]. Our finding of successful downstaging, and thus successful stage migration from BCLC intermediate stage to BCLC early stage HCC, being independently associated with lower risk of mortality supports this view of successful downstaging being a surrogate for lower tumor aggressiveness. However, since only 49% of patients responded well to LRT, it is of urgent need to better define upfront what therapeutic strategy would be most beneficial to an individual patient. In order to do this, predictors for successful downstaging need to be identified. Until now, a few studies have been published on this topic and identified different predictors for successful downstaging, varying from tumor characteristics such as a non-infiltrative tumor and total tumor volume to different AFP concentrations [6,7,10,18]. However, the results of those studies vary greatly due to different methodologies (i.e. inclusion criteria, definitions of successful downstaging, variables used, statistical methods and type of LRT's) and relatively small populations. We identified lower age, lower numbers of tumors and smaller diameter of largest tumor as factors positively associated with successful downstaging using a

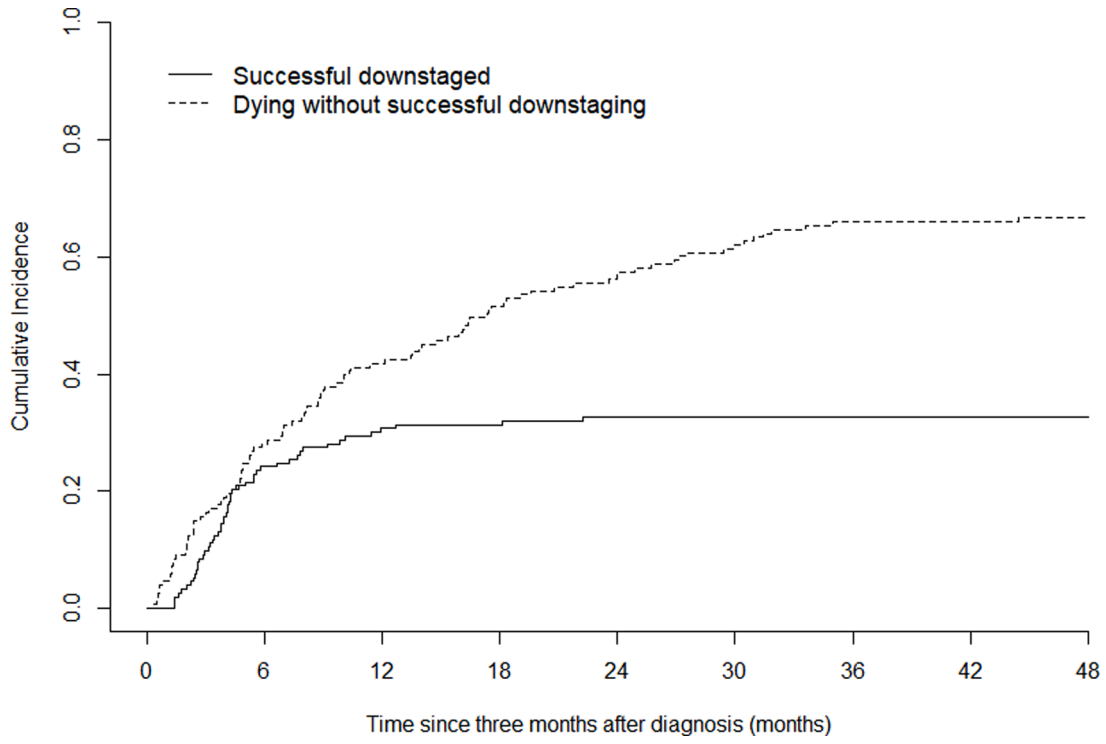

Fig. 2. Cumulative incidence of successful downstaging with death without being successfully downstaged as competing event from landmark time (3 months after diagnosis).

Table 4
Cause-specific hazard ratios (HR_{CS}) estimated with a Cox regression model for successful downstaging.

Variable	HR_{CS} (95% CI)	*p*-value
Age	0.96 (0.93-1.00)	0.048
Cause of liver disease		
Hepatitis B and/or C (versus alcohol liver disease)	2.07 (0.99-4.33)	0.054
Others (versus alcoholic liver disease)	1.15 (0.54-2.43)	0.722
AFP >100 ng/ml	0.83 (0.44-1.55)	0.555
Number of lesions	0.55 (0.41-0.74)	<0.001
Diameter largest tumor	0.82 (0.67-0.99)	0.039

Abbreviations: 95% CI, 95% confidence interval.
Note: Multivariate Cox proportional hazard model with death without being successfully downstaged as competing risk.

competing risk analysis, but for the same reasons as mentioned above, it is not possible to compare our findings with their results. We would therefore suggest to consider LRT aimed at stage migration in all patients with intermediate stage HCC who are suitable and motivated to undergo LRT, because successful downstaging, reflecting a more favorable tumor biology, is associated with a lower risk of mortality.

Our analysis on real-time data of therapeutic strategies in a low incidence country showed some unexpected results. Firstly, almost 40% of the patients did not receive any form of LRT. Secondly, only 22% of the successfully downstaged patients underwent LT. Unfortunately, due to the retrospective study design, we could not retrieve the motivation for treatment choices. Therefore, we could not determine what the reason was to not offer LRT at all, what the role of patients' preferences was in the treatment decisions and whether LRT was offered with the intention to perform liver transplant in the future. Our data suggest that a possible determinant for treatment decision could be the underlying liver disease, but due to the low numbers within the different etiology groups it is difficult to draw any definite conclusions regarding this topic. These are limitations of this study and we cannot exclude that some patients were being undertreated. Other limitations that need to be considered, due to the retrospective design, are potential selection bias and some missing values. Apart from Child Pugh score and MELD score, the number of missing values was low for most of the important variables. Moreover, in a substantial number of patients no cause of underlying liver disease was found. It should be noted that the etiology of underlying liver disease is difficult to determine when there is end-stage cirrhosis, and we therefore cannot exclude that some of these patients did develop cirrhosis due to causes such as NAFLD.

In conclusion, these results demonstrate that LRT is not routinely applied to intermediate stage HCC patients in the Netherlands. Moreover, even when successfully downstaged after LRT, LT is rarely performed. Despite that, we observed that patients with intermediate stage HCC have a lower risk of mortality after successful downstaging, independently of undergoing a liver transplant. There is an urgent need for additional biomarkers based on which favorable tumor biology can be identified and to improve knowledge to define upfront which tumor will positively respond to locoregional treatment. Therefore, prospective studies with larger patient populations, standardized downstaging protocols and studies exploring biomarkers for tumor biology are warranted. For now, we propose to always consider downstaging therapies in all patients with intermediate stage HCC who are suitable for LRT, since the fundamental principle behind downstaging is selecting patients with a more favorable tumor biology.

Declarations of interest

The authors have declared no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in

the online version, at doi:10.1016/j.ejim.2021.12.009.

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