Evaluation of a delayed liver transplantation strategy for patients with HCC receiving bridging therapy: the DELTA-HCC study.

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Research Article
Liver transplantation

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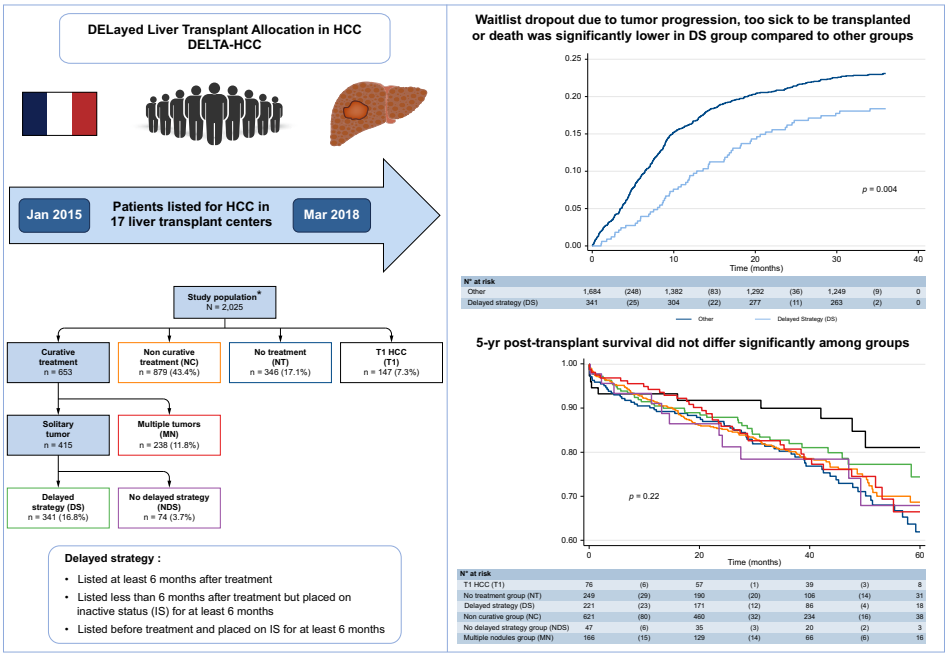
Graphical abstract



Highlights

- Patients with single curatively treated HCC account for 20% of LT candidates.
- In these patients, LT can be safely delayed without hampering pre/post-LT outcomes.
- This strategy has the potential to redirect spared organs to patients in urgent need.
- The DELTA-HCC study supports extension of a delayed strategy to other LT programs.

Impacts and implications

To maximize utility and prevent premature liver transplantation (LT), a delayed LT strategy was adopted in France in 2015. It involves postponing LT until recurrence in patients listed for any single HCC curatively treated by surgical resection or thermal ablation. The DELTA-HCC study was conducted to evaluate this nationwide strategy. It shows in a European LT program that delayed strategy does not negatively impact pre- nor post-LT patient outcomes and is relevant to up to 20% of LT candidates; thus, it could potentially enable the redistribution of organs to patients in more urgent need of LT. Such a delayed strategy can reasonably be pursued and extended to other LT programs. Of note, an unexpectedly high risk of dropout in T1 patients, seemingly related to MELD-based offering rules which underserve these patients, calls for further scrutinization and revision of allocation rules in this subgroup.

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Evaluation of a delayed liver transplantation strategy for patients with HCC receiving bridging therapy: the DELTA-HCC study

Catherine Lamarque[1,*], Lauriane Segaux[2], Philippe Bachellier[3], Benjamin Buchard[4], Faiza Chermak[5], Filomena Conti[6], Thomas Decaens[7], Sébastien Dharancy[8], Vincent Di Martino[9], Jérôme Dumortier[10], Claire Francoz-Caudron[11], Jean Gugenheim[12], Jean Hardwigsen[13], Fabrice Muscari[14], Sylvie Radenne[15], Ephrem Salamé[16], Thomas Uguen[17], José Ursic-Bedoya[18], Corinne Antoine[19], Aurélie Deshayes[19], Christian Jacquelinet[19], Pierre-André Natella[20], Vincent Leroy[1], Daniel Cherqui[21], Nadia Oubaya[2,20], Christophe Duvoux[1]

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Background & Aims: To maximize utility and prevent premature liver transplantation (LT), a delayed LT strategy (DS) was adopted in France in 2015 in patients listed for any single HCC treated with resection or thermal ablation during the waiting phase. The DS involves postponing LT until recurrence. The purpose of this study was to evaluate the DS to make sure that it did not hamper pre- and post-LT outcomes.
Methods: Patients listed for HCC in France between 2015 and 2018 were studied. After data extraction from the national LT database, 2,025 patients were identified and classified according to six groups: single tumor entering DS, single tumor not entering DS, multiple tumors, no curative treatment, untreatable HCC or T1 tumors. Kaplan-Meier estimates of the 18-month risk of dropout for death, too sick to be transplanted or tumor progression before LT, 5-year post-LT HCC recurrence and post-LT survival rates were compared.
Results: Median waiting-time in the DS group was 910 days. Pre-LT dropout probability was significantly lower in the DS group compared to other groups (13% *vs*. 19%, $p = 0.0043$) and significantly higher in the T1 group (25.4%, $p = 0.05$). Post-LT HCC recurrence rate in the multiple nodules group was significantly higher (19.6%, $p = 0.019$), while 5-year post-LT survival did not differ among groups and was 74% in the DS group ($p = 0.22$).
Conclusion: The DELTA-HCC study shows that DS does not negatively impact either pre- nor post-LT patient outcomes, and has the potential to allow for redistribution of organs to patients in more urgent need of LT. It can reasonably be proposed and pursued. The unexpectedly high risk of dropout in T1 patients seems related to the MELD-based offering rules underserving this subgroup.

Introduction

According to BCLC 2022,[1] liver transplantation (LT) is recommended as the first-line option for BCLC stage A hepatocellular carcinoma (HCC) or stage B HCC meeting extended liver transplant criteria,[2,3] when unsuitable for resection. Therefore, in order to prevent premature LT and spare liver grafts, LT is not considered, at first, for patients with early single tumors or even multiple tumors who can benefit from curative treatments such as liver resection or thermal ablation (TA). This approach to liver graft allocation for patients with HCC was also theorized by Mazzaferro in 2016[4] and by the ILTS Transplant Oncology Consensus working group.[5] In line with this concept, Mehta *et al.* showed that in patients listed for a single tumor <3 cm diameter, with AFP <20 ng/ml and complete response to pre-LT therapy, the 1- and 2-year probability of dropout was 1.3% and 1.6%, respectively.[6] These results strongly suggested that in patients with very early/early HCC responding to treatment, LT may be reasonably delayed to allow for LT in patients with more advanced tumors or decompensated cirrhosis (with medium-high model for end-stage liver disease [MELD] scores). Indeed, due to extra MELD point allocation systems, patients listed with early HCCs compete with advanced cirrhosis and HCC bridged to LT with loco-regional therapies, resulting in a potential excess in pre-LT mortality among patients with advanced liver diseases.[2,7–9]

Despite these considerations, a substantial number of patients with HCC amenable to curative treatments are still listed and transplanted in routine practice. Yet, it is still unclear how

Keywords: hepatocellular carcinoma; liver transplantation; delayed strategy; liver resection; thermal-ablation; organ allocation.
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postponing LT in patients with early HCC treated with curative approaches may impact their pre- and post-LT outcomes, an issue which was never evaluated prospectively.

In France, a decree issued in 2014 by the French Organ Sharing Organization, Agence de la Biomedicine (ABM), recommended to move patients with any single HCC with a complete tumor response after liver resection or TA to inactive status until tumor recurrence.[10] These measures, gradually implemented from 2015, made it possible to delay LT for patients with HCC not in urgent need, while allocating preserved liver grafts to patients with severe decompensated cirrhosis or more advanced HCC.[11]

Thanks to the national ABM-driven database, Cristal, which is updated every 3 months pre-LT, and prospectively tracks dropout and death pre-LT as well as post-LT outcomes, the French allocation system coordinated by the ABM offers the unique opportunity to evaluate this strategy and to make sure that it is not detrimental to patients.

The aim of the Delayed Liver Transplant Allocation in HCC (DELTA-HCC) study was therefore to evaluate the delayed LT strategy (DS) proposed by ABM in patients with HCC, with a single tumor amenable to liver resection or TA. The main objectives were first to assess the proportion of patients with HCC entering the strategy, then among these patients, to assess the incidence of dropout before LT as well as the incidence of HCC recurrence after LT, and finally to compare these figures to those observed in patients with HCC not entering the delayed strategy, in order to verify the equity of the system.

Patients and methods

The French graft allocation system

The ABM allocation system for HCC

In brief, the ABM allocation system, notably for patients with HCC, is based on progressive attribution of extra MELD points to patients listed for HCC, irrespective of response to bridging therapies and tumor staging, except for T1 patients whose priority is driven by MELD only.[8] Of note, since 2013, the indication for LT in patients with HCC in France has relied on an AFP score ≤2.

The ABM Cristal national liver transplantation database

This study was based on the analysis of the prospective data Registry of ABM, named Cristal. Participating LT centers all adhered to the ongoing ABM data sharing agreement. For patients with HCC, the ABM Cristal Registry is prospectively completed by LT centers' data managers who upload the following mandatory variables quarterly to a centralized IT platform:

- Before listing (at diagnosis): size and number of HCC tumors, AFP;
- Before LT (at listing, then quarterly): age, sex, etiology of the underlying liver disease, AFP, MELD, Child-Pugh score, size and number of HCC tumors, AFP score, type of bridging treatment, time on the waitlist, time on inactive status, outcome on the waitlist;
- After LT: type of graft, outcome after LT including HCC recurrence and survival.

Collected data are periodically audited by ABM for quality and consistency.

For the purpose of this study, an agreement with ABM for data extraction was submitted in 2018 and granted in 2019. In addition, a specific data collection authorization was requested from the CNIL (French National Commission for Computer Science and Freedom) and obtained in February 2021. The 18-month time interval between the two above-mentioned authorizations was due to the COVID-19 pandemic which substantially increased the response time of CNIL.

Patients

Definition of the population of interest and control groups

Data on patients listed for HCC between January 2015 and March 2018 in the 17 French LT centers were considered for statistical analysis. Inclusion criteria were: Adult patients (>18 years-old) listed for HCC as a primary diagnosis between January 2015 and March 2018. Exclusion criteria were: past history of LT and listing for combined transplantation.

For each participating center, ABM extracted the pre-defined variables as described above. The pseudonymized data were then merged in a common database and transferred to the Clinical Research Unit of Henri Mondor-Paris Est University Hospital for curation, processing, and statistical analysis.

In 2014, the ABM officially defined patients entering the delayed strategy (DS) as: Patients with single HCC nodule >T1, listed with a composite AFP score ≤2,[2] undergoing liver resection or TA (curative intent) before or after being listed for LT, with no intrahepatic recurrence within 6 months after treatment.

Therefore, starting in 2014, the ABM encouraged centers to place LT candidates entering DS on the inactive list if treated by resection or TA before or after listing and, in case of recurrence, to offer extra MELD points, permitting LT within 6 months after recurrence. Starting in 2018, the ABM subsequently recommended delaying listing of patients eligible for DS until HCC recurrence. This principle was proposed to avoid accumulation of patients with HCC on the national waitlist. By design, the present study focuses on the first period of this strategy.

The population entering DS was identified in the ABM database using the following entry criteria (all had HCC): patients with a single nodule who underwent liver resection or TA and were listed for LT at least 6 months after treatment; patients with a single nodule who underwent, before listing, liver resection or TA, listed for LT less than 6 months after treatment and placed on the inactive list for at least 6 months after listing; patients with a single nodule who underwent liver resection or TA after being listed and were placed on the inactive list for at least 6 months.

Five control groups were defined to describe waitlist strategies in patients with other HCC profiles, and to objectively compare outcomes on the waitlist and after LT in the DS group with those not fulfilling the DS criteria:

- Patients with T1 HCC (T1): according to UNOS classification,[12] patients with solitary tumor <2 cm. These patients have access to liver transplantation based on MELD score only with no compensatory extra MELD points. It was therefore deemed important to assess these patients on the waitlist.
- Non-curative group (NC): patients >T1, receiving non-curative bridging therapies. This group was individualized as a reference group to assess the risk of waitlist dropout.
- No treatment group (NT): patients >T1, receiving no treatment. This group was individualized to assess the risk of

waitlist dropout for patients who are ineligible for bridging therapy, mainly because of advanced liver dysfunction.
- No delayed strategy group (NDS): patients eligible for the delayed strategy but not entering it. This group was individualized to assess the adherence of LT centers to the delayed strategy.
- Multiple nodules group (MN): patients >T1, with multiple HCC nodules, receiving a curative treatment. This group was individualized to assess whether patients treated curatively outside the eligibility criteria of ABM could benefit from a delayed access strategy.

Patients were removed from the waitlist according to five criteria:
- Too sick to be transplanted: patients removed from the list for deterioration of the underlying disease, co-morbidities, or occurrence of a comorbidity contraindicating liver transplantation (*e.g. de novo* cancer).
- Tumor progression beyond AFP score >2, as assessed by quarterly imaging and AFP monitoring while on the waitlist: after a multidisciplinary meeting, the decision to delist was taken in case of intrahepatic tumor progression, including vascular invasion, beyond AFP score 2 or extrahepatic spread.
- Death: whatever the cause.
- Patient decision: patient could change his mind about the LT project and so could ask to be removed from the list after a discussion and agreement with the LT team.
- Tumor regression: after a certain time spent on the waitlist, if a patient did not suffer any HCC recurrence after treatment, and after discussion with the LT team, they could be removed from the waiting list.

Methods

Primary endpoint

To assess the relevance of DS, the primary endpoint was defined as a composite criterion combining, in each group, the proportion of patients removed from the list for tumor progression, being too sick to be transplanted or death.

Secondary endpoints

The secondary endpoints were: Proportion of waitlist dropout for tumor progression; Proportion of waitlist dropout for death; proportion of waitlist dropout for too sick to be transplanted; proportion of patients removed from the list for personal decision or tumor regression; post-LT survival rate; post-LT HCC recurrence rate.

Statistical analyses

A descriptive analysis of patients listed for LT was performed first, using n (%) for qualitative variables and median (IQR) for quantitative variables.

Population listing characteristics were compared using Chi-square or Fisher's exact tests (depending on application conditions) for qualitative variables and Student's *t* or Mann-Whitney *U* tests for quantitative variables. SIDAK corrections for multiple tests were made.

The primary outcome (proportion of patients in each population not accessing LT due to HCC progression, being too sick to be transplanted, or death while on the waiting list) was estimated using a percentage. A comparison was made between the DS group and the different study groups following the same analysis strategy as before.

For the following criteria – removal from the waitlist (for tumor progression, underlying liver disease progression, or death), HCC recurrence after LT, and post-LT survival – data were summarized in the different populations using Kaplan-Meier survival curves (for post-LT survival) or cumulative incidence. For the first two criteria, competing risks analyses were performed. For removal from the waitlist for tumor progression-underlying liver disease progression-death, removals for other reasons were considered as competing events. For HCC recurrence after LT, death was considered a competing event. A global log-rank test was also performed for post-LT overall survival and a Gray's test for the first two criteria.

The proportion of patients removed from the waiting list for tumor progression or death or too sick to be transplanted or personal decision or tumor regression, and the proportion of patients receiving a LT were summarized in the different groups using median (IQR) or n (%). Tests were performed for comparison as described above. The two-sided *p* value was set at 5%.

All analyses were carried out with stata v17.0 software (StataCorp, College Station, TX, USA) in the Public Health Department of Henri Mondor University Hospital. The results of the study were reported according to STROBE recommendations for observational studies.

Results

Study population

Fig. 1 shows the flow chart of the study population. A total of 2,148 patients listed for HCC over the study period were first identified in the ABM database. After applying exclusion criteria, the final study population consisted of 2,025 patients including 1,766 men (87.2%) and 259 women (12.8%) with a median age of 61 years.

During the study, 341 patients (16.8%) were enrolled in the DS group, 879 (43.4%) in the NC group, 346 (17.1%) in the NT group, 74 (3.7%) in the NDS group, 238 (11.8%) in the MN group and 147 (7.3%) in the T1 group.

The key characteristics of the 2,025 patients are described in Table 1.

The median size of the largest tumor at diagnosis was 2.5 cm (IQR 2–3.5) and the median number of tumors was 2.[1,2] The AFP score at listing was 0 in 66.27% and 4.47% had an AFP score >2. The median MELD at LT was 10.[7–15] HCCs occurred on alcohol-related cirrhosis in 60.94% of cases.

Regarding HCC bridging therapies, 1,614 patients (79.70%) were treated pre-LT, either curatively or non-curatively, and 411 (20.30%) did not receive any treatment while waiting. Of those who were treated, 1,388 patients (86.1%) were treated before listing. Bridging therapies comprised trans-arterial chemoembolization (TACE) (52.23%), TA (26%), liver resection (17.9%), radiotherapy (2%), radioembolization (1.1%) and systemic treatment (0.7%). The median time from listing to LT was 283 days (114.5–435.5) and the median time between treatment and LT was 527 days (313–856). Finally, 1,380 (68.2%) patients were transplanted and the overall dropout rate for tumor progression or too sick to be transplanted or death was 23.3%.

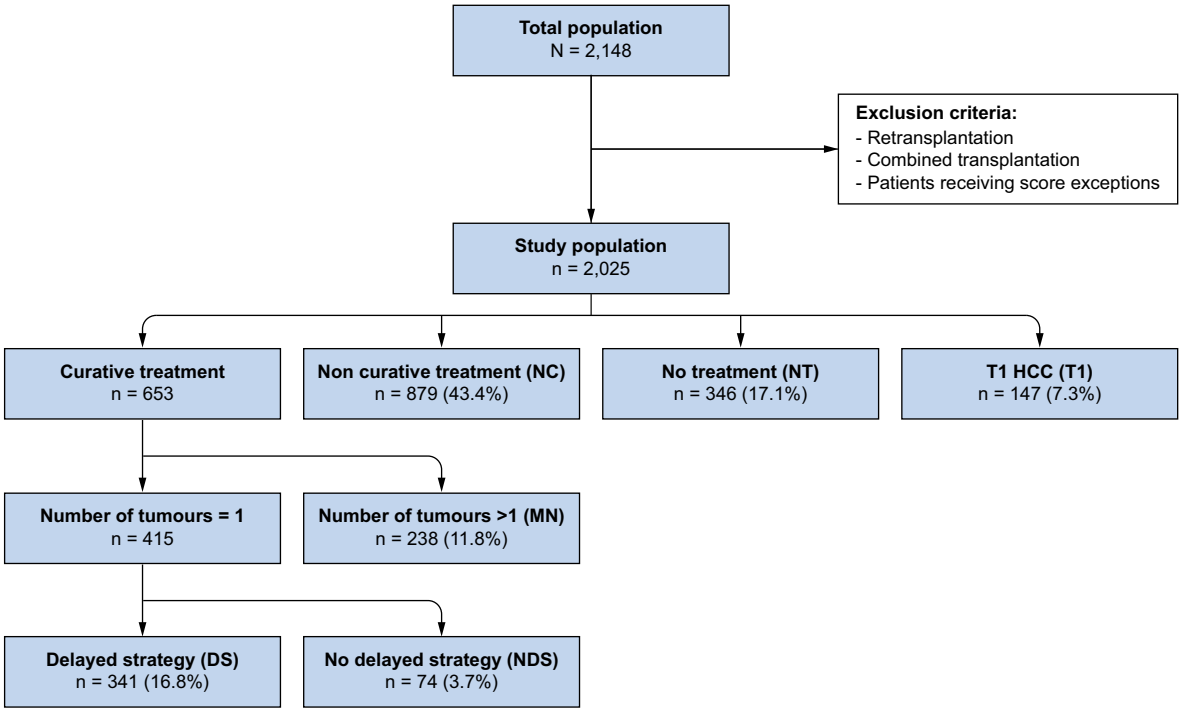


Fig. 1. Flow chart of the study population.

Table 1. Study population characteristics.

Age (years), median (IQR)	61.1 (55.9;64.9)
Sex, F/M, (%)	259/1,766 (12.8/87.2)
Underlying liver disease (%) N = 2,460*	
Alcohol/Virus	1,234 (60.9)/714 (35.3)
NASH/Others	211 (10.4)/301 (14.9)
Alpha feto-protein, at diagnosis, (ng/ml), median (IQR), N = 1,664	8 (4.2;22.3)
Size of largest tumor, at diagnosis, (cm), median (IQR), N = 1,952	2.5 (2.0;3.5)
Number of tumor, at diagnosis, median (IQR), N = 1,983	2 (1.0;2.0)
Child-Pugh A/B/C N=1,932 (%)	1,089/547/296 (56.4/28.3/15.3)
MELD, at transplant, median (IQR)	10 (7;15)
AFP score at listing, (%), N= 1,589	
0/1/2	1,053 (66.3)/298 (18.7)/167 (10.5)
>2	71 (4.5)
Type of treatment, (%), N = 1,614	
TACE	843 (52.2)
Thermal-ablation	420 (26)
Liver resection	289 (17.9)
Radiotherapy	32 (2)
Radioembolization	18 (1.1)
Systemic treatment	12 (0.7)
Time between treatment and transplant, (days), median (IQR), N = 1,131**	527 (313;856)
Time between listing and transplant, (days), median (IQR), N = 1,380	283 (114.5;435.5)
Outcome, (%)	
Liver Transplantation	1,380 (68.2)
Dropout on waitlist	472 (23.3)
Too sick to be transplanted	58 (2.9)
Tumor progression	243 (12)
Death	171 (8.4)
Tumor regression	46 (2.3)
Patient decision	53 (2.6)
Active on the waiting list	74 (3.6)

*Several etiologies could be present in the same patient, explaining why the number of causal etiologies is greater than the number of patients included.
**Does not consider patients not receiving any treatment and dropout patients.

Patient characteristics by study groups

Characteristics of the six subgroups are compared in Table 2.

Liver function and tumor characteristics

At diagnosis, the size of the largest tumor was significantly higher in the NC group (3.0 cm [IQR 2.1–4.0]) compared to the other groups and especially the DS group (2.5 cm [IQR 2.0–3.5] $p = 0.0005$). The highest rate of patients with Child-Pugh A cirrhosis was observed in the DS group (76.7%). In the NDS group, Child-Pugh A cirrhosis accounted for 55.9% of patients. In the T1 group, one-third of patients had Child-Pugh C cirrhosis (35.7%).

In the DS group, AFP score was 0 in 77% of patients. The distribution of AFP scores was significantly different among groups compared to the DS patients, notably, the proportion of patients with an AFP score of 1 or 2 was larger in the NT and NC groups (p <0.0001).

In the DS group, the median MELD scores at listing and at LT were 8.5 [7.3–10.7] and 8.0 [6.0–12.0], respectively, which were significantly lower than in the other groups (p <0.001).

Pre-LT treatment

In the DS group, patients received either TA (52.5%) or liver resection (47.5%), with 84.6% of patients treated more than 6 months before listing. The median post-treatment AFP level in the DS group was significantly lower than the AFP level at diagnosis (5.00 ng/ml [3.10–10.00] *vs.* 7.95 ng/ml [4.3; 21.43], p <0.001), respectively. In the non-curative treatment group, 93.2% of patients received TACE. In the T1 group, 62.1% of patients had bridging therapies, including TA, TACE and liver resection in 50%, 29.3% and 18.3%, respectively.

Table 2. Characteristics of the study groups.

	Delayed access strategy	Non curative therapy	No treatment	No delayed access strategy	Multiple nodules	T1	
	n = 341	n = 879	n = 346	n = 74	n = 238	n = 147	*p* value
Underlying liver disease (%)							
Alcohol	152 (44.57)	554 (63.03)	260 (75.14)	40 (54.05)	141 (59.24)	87 (59.18)	<0.0001
Virus	152 (44.57)	304 (34.58)	76 (21.97)	27 (36.49)	104 (43.70)	51 (34.69)	<0.0001
NASH	39 (11.44)	102 (11.60)	24 (6.94)	9 (12.16)	19 (7.98)	18 (12.24)	0.132
Others	60 (17.60)	129 (14.68)	49 (14.16)	11 (14.86)	36 (15.13)	16 (10.88)	0.546
Alpha feto-protein, at diagnosis, (ng/ml), median (IQR)	7.95 (4.30;21.43)	9.30 (5.00;27.00)	5.71 (3.90;12.00)	7.00 (4.20;38.10)	9.20 (4.00;32.00)	7.00 (3.60;14.60)	1.00
Size of largest tumor, at diagnosis, (cm), median (IQR)	2.50 (2.00;3.50)	3.00 (2.10;4.00)	2.30 (1.80;3.00)	2.55 (2.10;3.50)	2.40 (1.90;3.20)	1.50 (1.20;1.70)	0.0005
Number of tumors, at diagnosis, median (IQR)	1.00 (1.00;1.00)	2.00 (1.00;3.00)	2.00 (1.00;2.00)	1.00 (1.00;1.00)	2.00 (2.00;3.00)	1.00 (1.00;1.00)	0.006
Alpha feto-protein, at listing, (ng/ml), median (IQR)	5.60 (3.18;10.45)	7.58 (4.60;18.90)	5.86 (4.00;12.90)	5.35 (3.55;13.76)	6.08 (3.54;12.00)	5.39 (3.00;12.05)	0.941
Size of largest tumor, at listing, (cm), median (IQR)	1.90 (1.30;2.60)	2.40 (1.80;3.30)	2.40 (1.90;3.20)	2.20 (1.50;2.90)	1.80 (1.30;2.40)	1.50 (1.15;1.80)	<0.0001
Number of tumors, at listing, median (IQR)	1.00 (1.00;2.00)	2.00 (1.00;3.00)	2.00 (1.00;2.00)	1.00 (1.00;1.00)	2.00 (1.00;2.00)	1.00 (1.00;1.00)	0.0002
MELD, at listing, median (IQR)	8.47 (7.29;10.72)	9.93 (7.94;12.99)	15.54 (11.87;20.01)	10.25 (7.69;13.07)	8.95 (7.47;11.86)	13.21 (8.93;17.93)	<0.0001
MELD, at transplant, median (IQR)	8.00 (6.00;12.00)	9.00 (7.00;14.00)	16.00 (11.00;24.00)	10.00 (6.00;14.00)	8.50 (6.00;12.00)	11.00 (6.00;21.00)	0.009
Child Pugh (%)							
A	250 (76.69%)	531 (62.91%)	51 (15.69%)	38 (55.88%)	164 (71.62%)	55 (39.29%)	<0.0001
B	68 (20.86%)	247 (29.27%)	128 (39.38%)	22 (32.35%)	47 (20.52%)	35 (25.00%)	
C	8 (2.45%)	66 (7.82%)	146 (44.92%)	8 (11.76%)	18 (7.86%)	50 (35.71%)	
AFP score at listing, (%)							
0	184 (76.99)	421 (58.47)	203 (62.46)	37 (86.05)	117 (73.58)	91 (88.35)	<0.0001
1	27 (11.30)	173 (24.03)	75 (23.08)	4 (9.30)	17 (10.69)	2 (1.94)	
2	22 (9.21)	89 (12.36)	30 (9.23)	2 (4.65)	18 (11.32)	6 (5.83)	
>2	6 (2.51)	37 (5.14)	17 (5.23)	0 (0.00)	7 (4.40)	4 (3.88)	
Number of patients treated, (%)	341 (100.00)	879 (100.00)		74 (100.00)	238 (100.00)	82 (62.12)	<0.0001
Number of patients receiving a treatment before listing (%)	318 (93.26%)	720 (81.91%)		54 (72.97%)	223 (93.70%)	73 (91.25%)	<0.0001
Number of patients treated before listing (%)							<0.0001
<6 months	49 (15.41%)	442 (61.39%)		54 (100.00%)	87 (39.01%)	22 (30.14%)	
≥6 months	269 (84.59%)	278 (38.61%)		0 (0.00%)	136 (60.99%)	51 (69.86%)	
Type of treatment (%)							
Thermal-ablation therapy	179 (52.49%)	0 (0.00%)		46 (62.16%)	154 (64.71%)	41 (50.00%)	<0.0001
Liver resection	162 (47.51%)	0 (0.00%)		28 (37.84%)	84 (35.29%)	15 (18.29%)	
Chemoembolisation	0 (0.00%)	819 (93.17%)		0 (0.00%)	0 (0.00%)	24 (29.27%)	
Systemic treatment	0 (0.00%)	12 (1.37%)		0 (0.00%)	0 (0.00%)	0 (0.00%)	
Radioembolisation	0 (0.00%)	17 (1.93%)		0 (0.00%)	0 (0.00%)	1 (1.22%)	
Radiotherapy	0 (0.00%)	31 (3.53%)		0 (0.00%)	0 (0.00%)	1 (1.22%)	
Time between listing and treatment (days), median (IQR)*	-431.00 (-925.00;-205.00)	-107.00 (-233.00;-24.00)		-58.50 (-129.00;5.00)	-231.50 (-579.00;-100.00)	-307.50 (-745.50;-60.50)	<0.0001
Time between listing and treatment if treatment received before listing (days)	502.50 (246.00;942.00)	143.00 (64.00;275.00)		88.50 (45.00;141.00)	245.00 (112.00;642.00)	387.00 (144.00;793.00)	<0.0001
Time between listing and treatment if treatment received after listing (days)	46.00 (29.00;154.00)	39.00 (19.00;99.00)		54.00 (13.00;94.00)	45.00 (11.00;71.00)	71.00 (3.00;135.00)	0.853
Time between treatment and transplantation (days), median (IQR)	910.00 (590.00;1494.00)	442.00 (273.00;633.00)		285.00 (157.00;488.00)	666.00 (396.00;1104.00)	716.50 (282.00;1039.00)	<0.0001

(*continued on next page*)

Table 2. (*continued*)

	Delayed access strategy	Non curative therapy	No treatment	No delayed access strategy	Multiple nodules	T1	
	n = 341	n = 879	n = 346	n = 74	n = 238	n = 147	*p* value
Time between listing and transplant, (days), median (IQR)	356.00 (216.00;520.00)	320.00 (171.00;461.00)	107.00 (48.00;238.00)	303.00 (149.00;414.00)	335.50 (128.00;477.00)	90.50 (31.50;266.50)	<0.0001
Cumulative IS duration							
<6 months	108 (37.50)	325 (50.31)	173 (74.57)	46 (100.00)	92 (51.11)	60 (57.69)	<0.0001
6 to 18 months	90 (31.25)	215 (33.28)	46 (19.83)	0 (0.00)	58 (32.22)	29 (27.89)	
>18 months	90 (31.25)	106 (16.41)	13 (5.6)	0 (0.00)	30 (16.66)	15 (14.43)	
Outcome (%)							
Too sick to be transplanted	14 (4.11)	22 (2.50)	10 (2.89)	1 (1.35)	9 (3.78)	2 (1.36)	<0.0001
Tumor progression	45 (13.20)	114 (12.97)	33 (9.54)	9 (12.16)	25 (10.50)	17 (11.56)	
Death	13 (3.81)	73 (8.30)	35 (10.12)	4 (5.41)	20 (8.40)	26 (17.69)	
Liver transplantation	221 (64.81)	621 (70.65)	249 (71.97)	47 (63.51)	166 (69.75)	76 (51.70)	
Patient decision	16 (4.69)	23 (2.62)	8 (2.31)	1 (1.35)	0 (0.00)	5 (3.40)	
Tumor regression	16 (4.69)	11 (1.25)	5 (1.45)	0 (0.00)	7 (2.94)	7 (4.76)	
Active on the wait-list	16 (4.69)	15 (1.71)	6 (1.73)	12 (16.22)	11 (4.62)	14 (9.52)	
Type of graft (%)							
Marginal quality grafts	31 (14.03)	117 (18.81)	49 (19.68)	9 (19.15)	29 (17.37)	25 (32.47)	0.095
Non marginal quality grafts	166 (75.11)	433 (69.61)	176 (70.68)	33 (70.21)	116 ((69.46))	38 (49.35)	
Others	24 (10.85)	72 (11.57)	24 (9.62)	5 (10.64)	22 (13.17)	14 (18.18)	

Levels of significance $p \leq 0.05$ (Chi^2 or fisher-exact tests for qualitative variables and Student or Mann-Whitney tests for quantitative variables).
*Negative interval of time because a majority of patients were treated before listing.

Temporal listing trends

The median time between listing and treatment significantly differed among groups: the longest -431 days (-925 to -205) was observed in the DS group, indicating that most patients in the DS group had been treated before listing while in the NC group, time between listing and treatment was only -107 days (-233 to -24) (p <0.0001). The median time between listing and transplantation also differed significantly between groups, ranging from 90.5 days (31.5–266.5) in the T1 to 356 days (216–520) in the DS group (p <0.0001). Overall, time between treatment and transplantation was significantly longer in the DS group (910 days [590–1,495]), reflecting the delayed strategy compared to other groups. Notably, time between treatment and LT was 285 days (157–488) in the NDS group and 442 days (273–633) in the NC group (p <0.0001).

The proportion of patients moved to inactive status in the DS group was significantly higher than for the other groups, with 62% of patients inactive for more than 6 months (p <0.0001).

Type of grafts

In the T1 group, a larger proportion of patients (32.47%) received an expanded criteria graft compared to DS and NC groups (14.03% and 18.81%, respectively, p = 0.003).

Outcomes on the waitlist

Probability of dropout

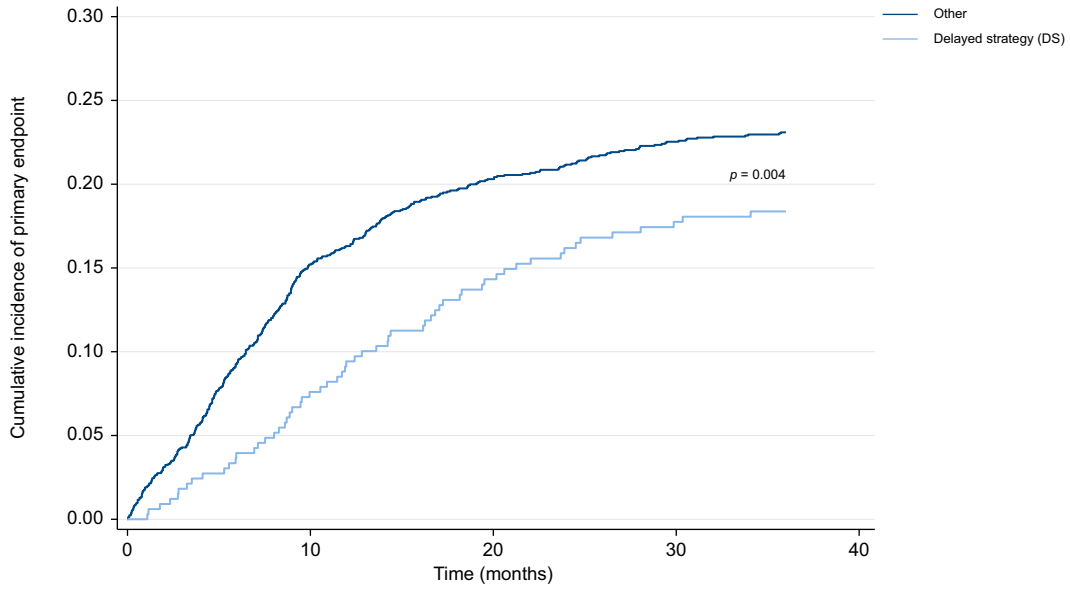
In the DS group, crude rates of dropout by cause of delisting were: 13.2% for tumor progression, 3.81% for death, and 4.11% for too sick to be transplanted (Table 2). Fig. 2 shows the risks of waitlist dropout according to time in DS *vs*. non-DS patients. The 18-month risks of dropout were 13.1% (9.9–17.2) and 19.6% (17.8–21.6) in DS and non-DS patients, respectively, and significantly lower in DS patients (p = 0.004). The difference was also significant at month 36 (p = 0.04). Fig. 3 shows the risk of waitlist dropout for tumor progression or too sick to be transplanted or death by subgroups of patients. The risk was statistically different among groups at month 18 (p = 0.05) and month 36 (p = 0.03). Of note, the 18-month risk of dropout was the lowest (13.1% [9.9–17.2]) in the DS group, and the highest (25.4% [18.9–33.7]) in the T1 group.

Identification of DS patients at very low risk of dropout

Data on response to treatment were available in 268 out of 341 DS patients. Based on tumor characteristics and response to treatment in the DS group, by competing risk analysis, the 18-month risk of dropout in patients with tumor size ≤3 cm, complete response to treatment (TA or liver resection) and AFP <20 ng/ml after treatment was significantly lower than for the rest of DS patients: 7.32% [3.73–14.10] *vs.* 18.37% [12.98–25.63], p = 0.02), respectively (Fig. 4). The 1-, 2- and 3-year risks of dropout in this very specific subgroup were 4.55% (1.92–10.58), 8.24% (4.37–15.24), 12.05% (7.18–19.86), respectively.

Probability of transplantation

Fig. S1 shows the probability of LT by subgroup. The 18- and 36-month probability of LT significantly differed among groups (p <0.001) at each time point. Notably, the 18-month probability of LT was the lowest in the DS and T1 groups, and the highest in the non-treated group of patients.



N° at risk									
Other	1,684	(248)	1,382	(83)	1,292	(36)	1,249	(9)	0
Delayed strategy (DS)	341	(25)	304	(22)	277	(11)	263	(2)	0

Fig. 2. Cumulative incidence of waitlist dropout due to tumor progression, too sick to be transplanted or death at 18 months, $p = 0.004$. Level of significance $p \leq 0.05$ (Competing risks analysis and Gray's test).

Therefore, over the study period, the 18-month probability of LT was 61.3% (59.1–63.4), and by subgroups, 51.5% (43.4–60.2), 53% (47.7–58.5), 61.3% (58.1–64.6), 61.9% (50.1–73.7), 62.1% (55.8–68.4), and 70% (65.1–74.8) in the T1, DS, NC, NDS, MN and NT groups, respectively.

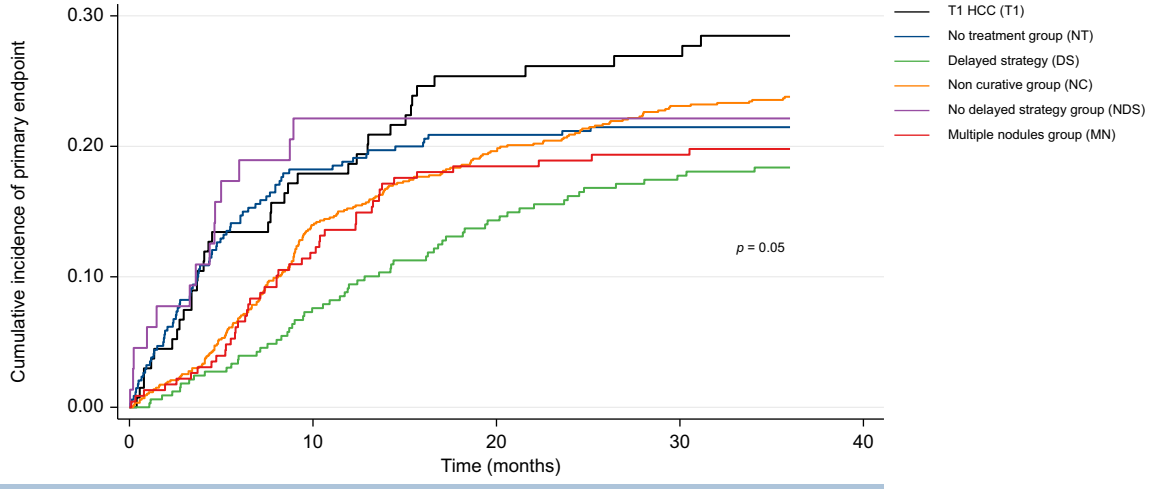
Pathology of explanted livers in the DS group

Details on explant pathology and HCC staging of the 221 patients undergoing LT in the DS group are shown in Tables S1 and S3.

Post-transplant survival and HCC recurrence

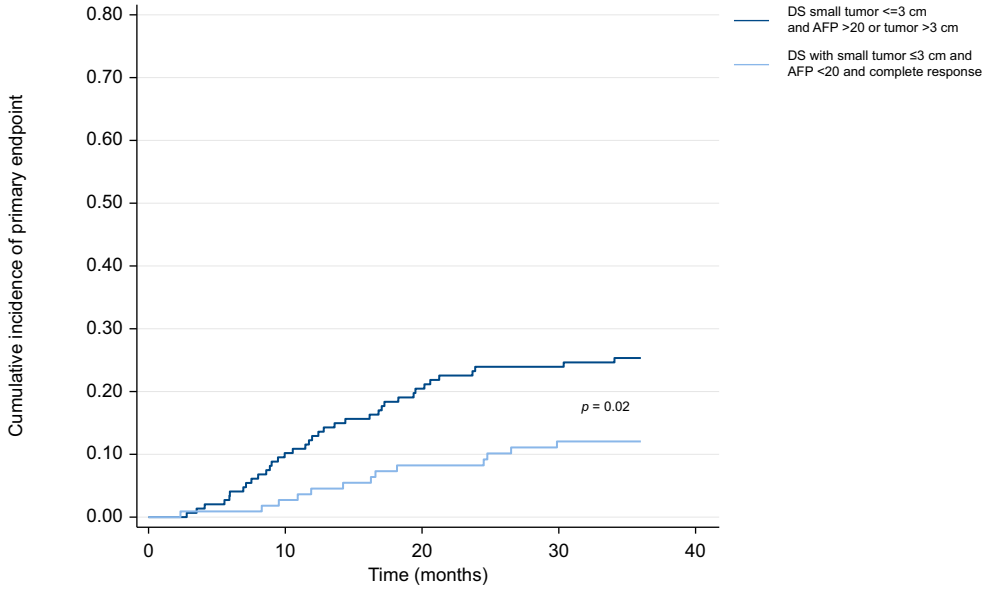
Post-transplant survival

The Kaplan-Meier post-LT survival rate at 5 years for all groups was 68% (64–72). It did not differ significantly among groups and was 74% (64–82) in the DS group, 62% (52–70) in the NT group, 69% (62–74) in the NC group, 68% (52–80) in the NDS group, 66% (54–76) in the MN group and 81% (66–90) in the T1 group ($p = 0.22$) (Fig. 5).



N° at risk									
T1 HCC (T1)	147	(24)	110	(10)	96	(2)	94	(2)	0
No treatment group (NT)	346	(62)	277	(9)	268	(2)	7	(0)	0
Delayed strategy (DS)	341	(25)	304	(22)	277	(11)	263	(2)	0
Non curative group (NC)	879	(121)	745	(49)	696	(30)	666	(6)	0
No delayed strategy group (NDS)	74	(14)	24	(0)	6	(0)	1	(0)	0
Multiple nodules group (MN)	238	(27)	201	(15)	184	(2)	182	(1)	0

Fig. 3. Cumulative incidence of waitlist dropout due to tumor progression, too sick to be transplanted or death by subgroups ($p = 0.05$ and 0.03) at 18 and 36 months, respectively. Level of significance $p \leq 0.05$ (Competing risks analysis and Gray's test). (This figure appears in color on the web.)



N° at risk									
DS small tumor ≤3 cm and AFP >20 or tumor >3 cm	152	(15)	132	(15)	114	(5)	109	(2)	0
DS with small tumor ≤3 cm and AFP <20 and complete response	116	(3)	107	(6)	97	(4)	13	(0)	0

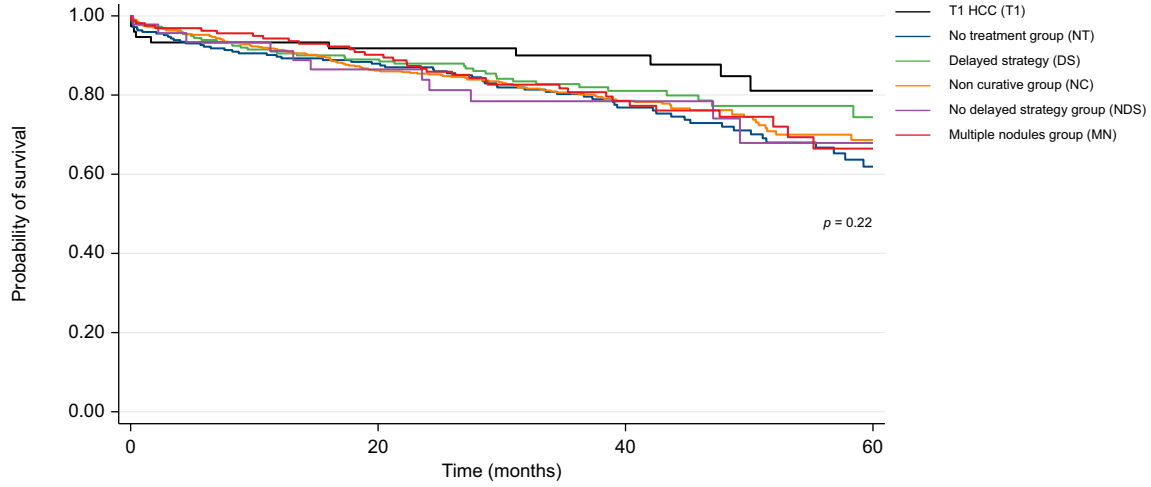
Fig. 4. Cumulative incidence of waitlist dropout due to tumor progression, too sick to be transplanted or death in DS group according to tumor size, AFP level and response to treatment at 18 months, *p* = 0.02 and 36 months, *p* = 0.01. Level of significance *p* ≤0.05 (Competing risks analysis and Gray's test). DS, delayed transplantation strategy.

HCC recurrence post LT

Considering death as a competitive risk, the overall incidence of post-LT tumor recurrence at 5 years was 10%. By subgroups, the probabilities of post-LT tumor recurrence at 5 years were 13.0% (6.4–24.5) in the DS group, 5.9% (3.1–11.0) in the NT group, 5.9% (1.9–17.2) in the T1 group, 8.0% (5.1–12.8) in the NC group, 9.7% (2.4–34.1) in the NDS group, and 19.6% (11.8–31.5) in the MN group (*p* = 0.02) (Fig. 6). Recurrence rates in DS *vs.* NDS, and DS *vs*. NC groups did not differ significantly (*p* = 0.89 for both comparisons).

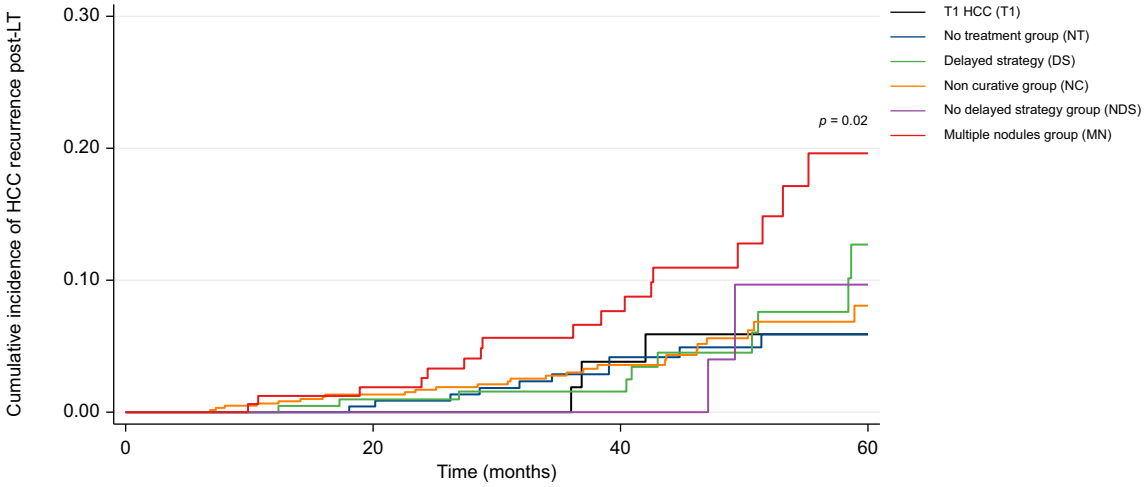
Discussion

The DELTA-HCC study enables, for the first time in Europe, a nationwide real-life evaluation of a strategy to delay LT in patients listed with a single HCC and bridged either by resection



N° at risk							
T1 HCC (T1)	76	(6)	57	(1)	39	(3)	8
No treatment group (NT)	249	(29)	190	(20)	106	(14)	31
Delayed strategy (DS)	221	(23)	171	(12)	86	(4)	18
Non curative group (NC)	621	(80)	460	(32)	234	(16)	38
No delayed strategy group (NDS)	47	(6)	35	(3)	20	(2)	3
Multiple nodules group (MN)	166	(15)	129	(14)	66	(6)	16

Fig. 5. Post-transplant survival at 5 years by subgroups (*p* = 0.22). Level of significance *p* ≤0.05 (Kaplan-Meier Estimates and Log-rank test). (This figure appears in color on the web.)



N° at risk							
T1 HCC (T1)	76	(0)	64	(2)	46	(1)	8
No treatment group (NT)	249	(1)	225	(7)	138	(2)	31
Delayed strategy (DS)	221	(2)	192	(1)	107	(7)	18
Non curative group (NC)	621	(8)	556	(10)	294	(8)	38
No delayed strategy group (NDS)	47	(0)	39	(0)	27	(2)	3
Multiple nodules group (MN)	166	(3)	147	(7)	84	(7)	16

Fig. 6. HCC recurrence post-LT by subgroups at 5 years ($p = 0.02$). Level of significance $p \leq 0.05$ (Competing risks analysis and Gray's test). (This figure appears in color on the web.)

or TA. Considering both the continuous increase of HCC burden on waitlists and persisting organ shortages, this strategy was proposed by the ABM HCC experts' group in 2014, and nationally implemented in 2015. Fundamentally, this strategy was intended to postpone LT in patients with HCC not in urgent need of LT, and to allocate grafts that would have been prematurely used in DS patients to patients with more advanced HCC or end-stage decompensated cirrhosis.

However, it remained essential to determine whether patients entering this strategy were not ultimately penalized in terms of risks of waitlist dropout or survival post-LT. Several important findings can be drawn from the DELTA-HCC study.

First, over the study period, 16.8% of patients listed for HCC entered the DS and another 3.7% (NDS) were identified as potential DS candidates. This shows that almost one out of five patients listed for HCC can enter this graft savings approach, subject to demonstration that it is not harmful to patients.

Second, overall, patients entering the DS had a statistically lower risk of waitlist dropout for death, tumor progression or too sick to be transplanted (primary endpoint) compared to other patients (13% *vs.* 19%, Fig. 2), notably when compared to patients treated with regional therapies (NC group). In addition, we found that risk of dropout was even lower in a subgroup of DS patients with tumors ≤3 cm, complete response to treatment, and AFP <20 ng/ml after treatment with 1-, 2- and 3-year risks of dropout of 4.55%, 8.24%, and 12.05%, respectively (Fig. 4). The net result was therefore a lower probability of LT over the study in the DS group compared to other groups (Fig. S1), and notably to the NC group (53% *vs*. 61.3%). This result confirms the potential of DS for graft saving.

Third, regarding post-LT outcomes in the DS group, the overall 5-year survival rate (74%) was not lower, and HCC recurrence probability (13%) was not higher than in control groups. Therefore, these results show that postponing LT in patients entering the DS did not negatively impact pre- nor post-LT outcomes and opened the door to a more appropriate use of grafts that would have been prematurely used otherwise. Although further evaluation was beyond the scope of the present study, the fact that nearly 10% of DS patients were removed from the list for tumor regression or personal decision could even suggest an individual benefit for these patients, owing to avoidance of the early risks of transplantation (death, postoperative morbidity) and later constraints of LT (side effects of immunosuppressive drugs).

The results of the DELTA-HCC study are in line with those of the ablate-resect-and-wait strategy which was initially proposed by the UCSF group.[6] In a first retrospective monocentric study, Mehta *et al.*[6] identified a subgroup of patients with favorable tumor characteristics, including a single tumor of 2-3 cm, with AFP <20 ng/ml, and complete response to treatment. In these patients, 1- and 2-year dropout rates were 1.3% and 1.6%, respectively, and supported the concept of postponing LT when these criteria were achieved. As stated above, figures in a similar range were also observed in the DELTA-HCC study in patients selected on the same criteria. Also, in a subsequent multicenter UNOS registry-based study[13] Mehta *et al.* observed a 24-month dropout rate of 12.4% in patients with a single tumor <3 cm, AFP <20 ng/ml, and MELD <15. Here again, a similar figure was observed in the whole DS population of the DELTA-HCC study.

Giving a lower priority to these patients was again recently suggested by the ILTS Transplant Oncology working group, with a moderate quality of evidence indicating that LT should be recommended as a second-line treatment in resectable patients with single <3 cm HCC in case of tumor recurrence or liver failure after resection or ablation.[5] The results of the DELTA-HCC study further support this strategy and provide, for the first time in a non-US program, real-life prospective data reinforcing its evidence level.

Two results, observed independently of the primary outcome of the study, are also essential to consider, namely a significantly higher risk of waitlist dropout (25.4% at 18 months) in patients listed for T1 HCC and a higher risk of HCC recurrence in patients treated by resection or TA for multiple tumors (19.6%)

Allocation in patients with T1 tumors is universally based on MELD score such that these patients do not benefit from extra MELD points for HCC.[8,12] The reason for that is to avoid futile LT in patients with very early HCC because of an expected insignificant survival benefit and to favor first-line curative treatments (*e.g.* resection or TA). However, the Delta-HCC study shows that in some instances this strategy can be harmful to patients. Careful analysis of T1 patient features in this study (Table 2) shows that listed T1 patients had relatively high MELD (median MELD score 13) and Child-Pugh (one patient out of three with Child-Pugh C cirrhosis) scores justifying listing, and that death was the main reason for waitlist dropout. It can be assumed that these T1 patients were listed because their tumors were not resectable nor ablatable, and that they were unfairly served by the ongoing allocation system by having no opportunity for MELD exception points. Such an observation calls for an urgent revision of allocation rules in T1 patients with medium MELD scores, keeping in mind the excellent (81%) 5-year survival rate in this population.

The higher incidence of post-LT recurrence in patients with multiple nodules treated with resection or TA suggests that these patients might have more aggressive tumors compared to patients treated with TACE or that the type of treatment chosen while waiting for LT could impact post-LT recurrence.[1,14] These two unexpected results underline the importance of periodical assessments and audits of allocation strategies, in order to consider corrective actions when required.

In conclusion, the DELTA-HCC study shows that, in line with EASL and BCLC recommendations,[1,15] which propose to consider LT in non-resectable HCCs, adopting a delayed strategy in patients listed for a single HCC amenable to curative bridging therapies does not negatively impact pre- nor post-LT outcomes. Such a strategy avoids a premature use of grafts in about 20% of patients listed for HCC and should be pursued.

On the contrary, the present results do not support an expansion of DS to patients with multiples nodules treated by resection or TA, as bridging therapies. Also, pre-LT outcome observed in patients listed for T1 HCC certainly calls for a revision of current allocation rules to minimize dropout in this subgroup. Pre-LT outcomes of T1 patients should also be scrutinized in other LT programs, considering that these patients certainly share specific features that justify listing, such as relatively high MELD scores. Their access to LT should therefore be facilitated in some instances.

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Abbreviations

ABM: Agence de la Biomédecine; AFP: alpha-fetoprotein; DELTA-HCC: Delayed Liver Transplant Allocation in HCC; DS: delayed transplantation strategy; LT: liver transplantation; MT: multiple tumors; NC: no curative treatment; NDS: no delayed transplantation strategy; NT: no treatment; TA: themal-ablation; TACE: transarterial chemoembolization.

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Conflict of interest

There is no conflict of interest to declare in relation with this study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

C. Lamarque wrote the original draft. C.Duvoux co-drafted the manuscript and critically reviewed it. C.Lamarque and C.Duvoux drafted the research protocol, designed the study, edited the manuscript. C.Lamarque, C.Duvoux, L.Segaux and N.Oubaya conceived and designed the analysis. C.Lamarque, C.Duvoux, L.Segaux, N.Oubaya and A.Deshayes performed the data curation. L.Segaux and N.Oubaya performed the statistical analysis. C.Lamarque, C.Duvoux, N.Oubaya, P-A Natella wrote the funding application. Special acknowlegements to D.Cherqui who reviewed the manuscript for critical feedback. All co-authors supervised collection of data and pathological reports, and approved the manuscript.

Data availability statement

The raw/processed data required to reproduce the above findings can only be shared with the French Liver Transplant centers as the data belong to the French Organ Sharing Organization, Agence de la Biomedicine (ABM) and therefore their data are not currently publicly available.

References

[1] Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022 Mar 1;76(3):681–693.

[2] Duvoux C, Roudot–Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of milan criteria. Gastroenterology 2012 Oct;143(4):986–994.e3.

[3] Mazzaferro V, Sposito C, Zhou J, et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. Gastroenterology 2018 Jan;154(1):128–139.

[4] Mazzaferro V. Squaring the circle of selection and allocation in liver transplantation for HCC: an adaptive approach: adaptive Approach to Liver transplantation for HCC. Hepatology 2016 May;63(5):1707–1717.

[5] Mehta N, Bhangui P, Yao FY, et al. Liver transplantation for hepatocellular carcinoma. Working group report from the ILTS transplant Oncology Consensus conference. Transplantation 2020 Jun;104(6):1136–1142.

[6] Mehta N, Dodge JL, Goel A, et al. Identification of liver transplant candidates with hepatocellular carcinoma and a very low dropout risk: implications for the current organ allocation policy. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc 2013 Dec;19(12):1343–1353.

[7] ABM_PG_Organes_Foie2021_MB.pdf [Internet]. [cited 2023 Feb 20]. Available from: https://rams.agence-biomedecine.fr/sites/default/files/pdf/2022-07/ABM_PG_Organes_Foie2021_MB.pdf.
[8] French-liver-allocation-policy-handbook.pdf [Internet]. [cited 2022 Jul 1]. Available from: https://www.agence-biomedecine.fr/IMG/pdf/french-liver-allocation-policy-handbook.pdf.
[9] Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003 Jan;124(1):91–96.
[10] AFEF. Nouvelles règles d'allocation de greffons pour le carcinome hépatocellulaire [Internet]. AFEF - Société Française d'Hépatologie; 2016 [cited 2023 Feb 20]. Available from: https://afef.asso.fr/nouvelles-regles-dallocation-de-greffons-pour-le-carcinome-hepatocellulaire/.
[11] Recommandations-AFEF-Indications-de-transplantation-hepatique.pdf [Internet]. [cited 2021 Nov 10]. Available from: https://afef.asso.fr/wp-content/uploads/2021/02/Recommandations-AFEF-Indications-de-transplantation-hepatique.pdf.
[12] optn_policies.pdf [Internet]. [cited 2023 Feb 27]. Available from: https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf.
[13] Mehta N, Dodge JL, Hirose R, et al. Predictors of low risk for dropout from the liver transplant waiting list for hepatocellular carcinoma in long wait time regions: implications for organ allocation. Am J Transplant 2019;19(8):2210–2218.
[14] Gelli M, Sebagh M, Porcher R, et al. Liver resection for early hepatocellular carcinoma: preoperative predictors of non transplantable recurrence and implications for treatment allocation. Ann Surg 2020 Nov;272(5):820–826.
[15] European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018 Jul;69(1):182–236.