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Different Patterns of Care and Survival Outcomes in Transplant-Centre Managed Patients with Early-Stage HCC: Real-World Data from an Australian Multi-Centre Cohort Study

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Simple Summary: Little is known about the differences in liver cancer care between liver cancer referral centres, with and without an integrated liver transplant program. Even after adjusting for other important factors, such as tumour stage and patient characteristics, we found that liver transplant centres systematically used different local cancer treatments compared to non-transplant centres. Patients managed at liver transplant centres showed improved overall survival, which was evident even after considering the increased rates of transplantation.

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Abstract: The management of early-stage hepatocellular carcinoma (HCC) is complex, with multiple treatment strategies available. There is a paucity of literature regarding variations in the patterns of care and outcomes between transplant and non-transplant centres. We conducted this real-world multi-centre cohort study in two liver cancer referral centres with an integrated liver transplant program and an additional eight non-transplant HCC referral centres across Australia to identify variation in patterns of care and key survival outcomes. Patients with stage Barcelona Clinic Liver Cancer (BCLC) 0/A HCC, first diagnosed between 1 January 2016 and 31 December 2020, who were managed at a participating site, were included in the study. Patients were excluded if they had a history of prior HCC or if they received upfront liver transplantation. A total of 887 patients were included in the study, with 433 patients managed at a liver cancer centre with a transplant program (LTC) and 454 patients managed at a non-transplant centre (NTC). Management at an LTC did not significantly predict allocation to resection (adjusted OR 0.75, 95% CI 0.50 to 1.11, $p = 0.148$). However, in those not receiving resection, LTC and NTC patients were systematically managed differently, with LTC patients five times less likely to receive upfront ablation than NTC patients (adjusted OR 0.19, 95% CI 0.13 to 0.28, $p < 0.001$), even after adjusting for tumour burden, as well as for age, gender, liver disease aetiology, liver disease severity, and medical comorbidities. LTCs exhibited significantly higher proportions of patients undergoing TACE for every tumour burden category, including those with a single tumour measuring 2 cm or less ($p < 0.001$). Using multivariable Cox proportional hazards analysis, management at a transplant centre was associated with reduced all-cause mortality (adjusted HR 0.71, 95% CI 0.51 to 0.98, $p = 0.036$), and competing-risk regression analysis, considering liver transplant as a competing event, demonstrated a similar reduction in risk (adjusted HR 0.70, 95% CI 0.50 to 0.99, $p = 0.041$), suggesting that the reduced risk of death is not fully explained by higher rates of transplantation. Our study highlights systematic differences in HCC care between large volume liver transplant centres and other sites, which has not previously been well-described. Further work is needed to better define the reasons for differences in treatment allocation and to aim to minimise unwarranted treatment variation to maximise patient outcomes across Australia.

Keywords: hepatocellular carcinoma; early; transplant centre; patterns of care; survival

1. Introduction

Hepatocellular carcinoma (HCC) is the third most common global cause of cancer-related deaths [1], with an estimated 830,000 deaths in 2020 [2]. Continuing to increase in incidence in most parts of the world [3,4], HCC is projected to account for 60% of all deaths due to chronic liver disease by 2030 [5]. HCC is staged using the BCLC algorithm [6], in which tumour burden, liver function, and cancer-related performance status are considered together. The goal of HCC surveillance is to identify HCC in the very early (BCLC 0) and early (BCLC A) stage, when HCC curative treatment modalities such as resection, ablation, and transplantation can be delivered [7]. However, multiple studies have shown poor adherence to standardised management guidelines, with up to 40% of patients with BCLC 0/A stage disease failing to receive upfront curative therapy [8–11]. Even in those who do receive upfront curative therapy, real-world outcomes leave much to be desired, with 5-year recurrence rates described as between 30–60%, depending on treatment choice, liver disease severity, and tumour burden [12–14].

Optimising care of BCLC 0/A stage HCC is therefore a clear priority to maximise patient outcomes. Little is known regarding variation in care between liver transplant centres (LTCs) and non-transplant centres (NTCs). In Australia, LTCs manage a greater volume of HCC patients than do NTCs. Additionally, at LTCs, the multidisciplinary meeting (MDM) involves transplant physicians and surgeons, unlike the MDMs at NTCs. Physicians, surgeons, and interventional radiologists working at an LTC are also exposed to a larger number of patients with more advanced liver disease. We therefore hypothesised that aside from increased rates of transplantation, there may be other differences in patterns

of care between LTCs and NTCs, even when considering only BCLC 0/A patients and adjusting for clinical covariates. We performed this real-world multi-centre retrospective study to test this hypothesis and additionally, to investigate whether there was any variation in survival outcomes between the two cohorts after adjusting for key clinical variables.

2. Materials and Methods

2.1. Participants

Our study involved participants with BCLC stage 0/A HCC, with a first diagnosis of HCC between 1 January 2016 and 31 December 2020, at two Australian LTCs and an additional eight NTCs across Victoria and New South Wales. Patients were eligible for the study if they met the following inclusion criteria: adult aged > 18 years of age; diagnosis of HCC documented between 1 January 2016 and 31 December 2020 on the basis of imaging fulfilling LI-RADS 5 criteria or histology confirming HCC; and confirmed BCLC 0 or A disease, with complete documentation of single lesion of any size or up to three lesions, with no lesions > 3 cm, Child–Pugh (CP) class A or B, an ECOG cancer-related performance status of 0, and the absence of extrahepatic disease or macrovascular invasion. Exclusion criteria were: receipt of upfront liver transplantation; prior diagnosis or past history of HCC; diagnosis of other solid organ malignancy, other than non-melanotic skin cancer; and insufficient data to determine stage of HCC, treatment, or follow-up.

Waiver of consent was sought, with all patient data entered in a deidentified form. Ethics for the study were approved by Monash University and the Human Research Ethics Committee (HREC), located at each respective site.

2.2. Study Design

This was a multi-centre retrospective cohort study. Data was collected retrospectively from the patient's medical records, from the date of initial diagnosis of HCC to the end of follow-up (either death or last medical record entry available at time of data extraction). The minimum dataset is outlined in full in Appendix A (Table A1). Data included key clinical variables, tumour characteristics, and biochemistry at time of diagnosis, as well as initial treatment and subsequent assessments of treatment response, and sequential treatments with subsequent treatment response. Modified RECIST criteria (mRECIST) were used at all sites to describe treatment response after initial treatment and at subsequent follow-up. Treatments were characterised as resection, ablation (including microwave ablation, radiofrequency ablation, and percutaneous ethanol injection), transarterial chemoembolisation (TACE, including the conventional treatment or with drug-eluting beads), or other (bland hepatic artery embolization, selective internal radiation therapy, stereotactic body radiation therapy, systemic therapy). For survival analysis, the date of diagnosis was considered as the index date. All data was de-identified and entered into a centralised database, using a REDCap electronic data capture system hosted at Monash University.

2.3. Statistical Analysis

Subjects were considered as an 'LTC' or 'NTC' patient, depending on their initial managing centre. NTC patients who went on to be referred to LTC and underwent subsequent treatment or transplantation during follow-up were still considered as NTC patients for the purposes of our study. Data were analysed using SPSS 29.0 (SPSS, Inc., Chicago, IL, USA) and STATA 18 (StataCorp. 2023, College Station, TX, USA) software. Categorical variables were described using a frequency table, and a Chi-square test was used to test statistical significance between the two groups. Non-parametric continuous variables were summarised using the median and interquartile range, and Mann−Whitney U test was used as the test of statistical significance. Parametric continuous variables were reported with mean and standard deviation, and the independent samples *t*-test was used to test for statistical significance in comparing the two groups. Binary logistic regression was used to assess the factors predicting treatment allocation to resection and to ablation. We did not perform such analysis on treatment allocation to transplantation

during follow-up; as multiple variables predicting transplant suitability were not captured (in particular, recency of alcohol intake, patients' wishes, presence of social support, and medical/psychological comorbidities not captured in the CCI), reverse causality could not be excluded as the leading cause for the difference in treatment allocation, and there were overall small numbers of transplanted patients, limiting statistical power. Multivariable Cox proportional hazards analysis was used to assess for predictors of all-cause death, with calculation of adjusted hazard ratios with 95% confidence intervals estimated for each inputted clinical variable and cumulative hazard function curves plotted. Variables were selected based on their clinical significance, with all variables included in the final model, including those that were statistically insignificant. To reduce the risk of competing-risk bias due to liver transplantation, which is known to significantly reduce risk of death, we performed competing-risks regression analysis, with liver transplantation as a competing risk for all-cause death. Adjusted hazard ratios, with 95% confidence intervals for each of the variables, as well as cumulative incidence function curves, were produced using the STATA 18 statistical software. In all tests of statistical significance performed, two-tailed $p < 0.05$ was deemed a statistically significant difference.

3. Results

3.1. Patients

Across all sites, 887 patients were eligible for inclusion, with 433 patients from the two LTCs and 454 patients from the remaining eight NTCs. Patient characteristics, in the distinct LTC and NTC populations, are presented in Table 1. Both LTC and NTC patients exhibited a similar male preponderance. LTC patients were significantly younger than NTC patients (mean age 63.6 vs. 65.5, $p = 0.011$). There were slight differences in liver disease aetiology, with NTC patients more likely to have HBV and alcohol as a cause of their liver disease. Medical comorbidities, measured using the Charlson Comorbidity Index (CCI), were similar between the two cohorts. Median platelet count was significantly lower in the LTC cohort compared to the NTC cohort (117 vs. 137, $p < 0.001$) suggesting greater prevalence and severity of portal hypertension on average in the LTC group. Similarly, LTC patients were more likely to exhibit more severe liver disease, with a greater proportion of Child−Pugh (CP) B patients ($p = 0.033$). Tumour burden was significantly different ($p = 0.024$) between the two groups, with LTC patients more likely to have both multinodular disease and large single tumours and NTC patients more likely to have small solitary tumours. A greater proportion of NTC patients underwent resection as the initial treatment, likely reflecting the higher numbers of patients without clinically significant portal hypertension. A significantly greater subset of LTC patients underwent initial TACE compared to those from the NTC (256 vs. 111, $p < 0.001$), but patients who did receive initial TACE were more likely to undergo ablation as a second follow-up treatment at LTCs compared to at NTCs (41.4% vs. 25.2%, $p = 0.016$), suggesting a differing treatment strategy. No patients who received initial TACE went on to receive resection later.

Table 1. Patient characteristics across liver transplant and non-transplant centres.

	LTC ***n* = 433**	**NTC** ***n* = 454**	***p*-Value**
Age *	63.6 ± 10.0	65.5 ± 11.7	0.011
Sex			
Male	351 (81.1%)	362 (79.7%)	0.247
Female	82 (18.9%)	92 (20.3%)	

Table 1. *Cont.*

	LTC n = 433	NTC n = 454	p-Value
Aetiology			
Alcohol	62 (14.3%)	72 (15.9%)	
HBV	53 (12.2%)	57 (12.6%)	
HCV	74 (17.1%)	66 (14.5%)	
MASLD	49 (11.3%)	63 (13.9%)	0.047
Other	28 (6.5%)	26 (5.7%)	
metALD	26 (6.0%)	29 (6.4%)	
HBV/HCV	13 (3.0%)	19 (4.2%)	
HCV + SLD	119 (27.5%)	95 (20.9%)	
HBV + SLD	9 (2.1%)	27 (5.9%)	
Smoking			
Yes	102 (76.4%)	151 (66.7%)	0.001
No	331 (23.6%)	303 (33.3%)	
Charlson Comorbidity Index **	5 (3 to 6)	4 (3 to 6)	0.155
Cirrhosis			
Yes	369 (85.2%)	372 (81.9%)	0.188
No	64 (14.8%)	82 (18.1%)	
Platelets **	117 (80 to 164)	137 (92 to 204)	<0.001
Child–Pugh Score			
5	243 (56.1%)	248 (54.6%)	
6	100 (23.1%)	132 (29.1%)	0.033
7	44 (10.2%)	48 (10.6%)	
8	25 (5.8%)	17 (3.7%)	
9	21 (4.8%)	9 (2.0%)	
Tumour Burden Category			
Single $\leq$ 2 cm	121 (27.9%)	141 (31.1%)	
Single > 2 cm, $\leq$3 cm	95 (21.9%)	129 (28.4%)	0.024
Single > 3 cm, $\leq$5 cm	69 (15.9%)	72 (15.9%)	
Single > 5 cm	46 (10.6%)	35 (7.7%)	
Multinodular, all $\leq$ 3 cm	102 (23.6%)	77 (17.0%)	
Initial Treatment Allocation			
Resection	79 (18.2%)	120 (26.4%)	
Ablation	74 (17.1%)	185 (40.7%)	<0.001
TACE	256 (59.1%)	111 (24.4%)	
Other	24 (5.5%)	38 (8.4%)	
Follow-up ablation after TACE			
After first TACE	80 (31.3%)	18 (16.2%)	
After second TACE	12 (4.7%)	6 (5.4%)	0.016
After third or subsequent TACE	14 (5.5%)	4 (3.6%)	
No ablation during follow-up	150 (58.6%)	83 (74.8%)	

* mean ± standard deviation; ** median (25th percentile to 75th percentile). LTC, liver transplant centre; NTC, non-transplant centre; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; metALD, metabolic and alcohol related liver disease; SLD, steatotic liver disease; TACE, transarterial chemoembolisation.

3.2. Transplantation

Of the 887 patients included in our study, a total of 42 patients (4.7%) underwent transplantation during follow-up. Seven patients who were initially managed at an NTC were referred to a transplant centre and underwent transplantation during the period of observation in our study. The characteristics of patients who underwent transplant during follow-up are outlined in Table 2. The vast majority of patients who received transplantation did so after a recurrence after a documented complete response (CR), rather than as a salvage curative treatment (38 vs. 4). Patients originally from an NTC who

underwent transplantation during follow-up were more likely to have a lower initial CCI on average, as well as to receive a non-TACE initial treatment. Otherwise, NTC and LTC patients who underwent transplantation were similar with respect to age, sex, liver disease aetiology, CPS, and initial tumour burden. The time from initial diagnosis to receipt of transplant was similar between the two groups (median 504 days vs. 729 days, $p = 0.446$).

Table 2. Patient characteristics of those who underwent liver transplantation during follow-up.

	LTC n = 35	**NTC n = 7**	***p*-Value**
Age *	59.8 ± 5.1	53.7 ± 7.0	0.062
Sex			
Male	32 (91.4%)	5 (71.4%)	0.136
Female	3 (8.6%)	2 (28.6%)	
Aetiology			
Alcohol	4 (11.4%)	0	
HBV	4 (11.4%)	3 (42.9%)	
HCV	3 (8.6%)	1 (14.3%)	
MASLD	4 (11.4%)	0	0.170
Other	1 (2.9%)	1 (14.3%)	
metALD	4 (11.4%)	0	
HBV/HCV	1 (2.9%)	1 (14.3%)	
HCV + SLD	14 (40.0%)	1 (14.3%)	
Charlson Comorbidity Index **	5 (4 to 6)	3 (2 to 4)	0.028
Initial Child–Pugh Score			
5	16 (45.7%)	3 (42.9%)	
6	5 (14.3%)	2 (28.6%)	0.299
7	3 (8.6%)	2 (28.6%)	
8	4 (11.4%)	0	
9	7 (20.0%)	0	
Initial Tumour Burden Category			
Single ≤ 2 cm	8 (22.9%)	1 (14.3%)	
Single > 2 cm, ≤3 cm	9 (25.7%)	2 (28.6%)	0.696
Single > 3 cm, ≤5 cm	4 (11.4%)	0	
Single > 5 cm	2 (5.7%)	0	
Multinodular, all ≤ 3 cm	12 (34.3%)	4 (57.1%)	
Initial Treatment			
Resection	3 (8.6%)	1 (14.3%)	
Ablation	5 (14.3%)	4 (57.1%)	0.003
TACE	27 (77.1%)	1 (14.3%)	
Other	0	1 (14.3%)	
Indication for Transplant			
Salvage	3 (8.6%)	1 (14.3%)	0.562
Recurrence	32 (91.4%)	6 (85.7%)	
Time from initial diagnosis to transplant (days) **	504 (349 to 1019)	729 (546 to 743)	0.446

* mean ± standard deviation; ** median (25th percentile to 75th percentile). LTC, liver transplant centre; NTC, non-transplant centre; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; metALD, metabolic and alcohol related liver disease; SLD, steatotic liver disease; TACE, transarterial chemoembolization.

3.3. Resection

Of the 887 patients included in our study, a total of 199 patients (22.4%) underwent surgical resection as the initial treatment. The patient characteristics of those who received resection in the LTC and NTC cohorts are outlined in Table 3. There was no evidence of a systematic difference in any clinical characteristics, suggesting similar patient selection across all sites. In particular, LTC and NTC patients who underwent resection had similar

platelet counts (median 161 vs. 194, $p = 0.068$), similar CCI (median 3 vs. 3, $p = 0.372$), and nearly all had Child–Pugh A5 or A6 liver disease (96.2% vs. 97.5%, $p = 0.893$).

Table 3. Patient characteristics of those who received surgical resection.

	LTC n = 79	NTC n = 120	*p*-Value
Age *	64.0 ± 8.5	62.7 ± 10.3	0.346
Sex			
Male	62 (78.5%)	95 (79.2%)	0.908
Female	17 (21.5%)	25 (20.8%)	
Aetiology			
Alcohol	10 (12.7%)	8 (6.7%)	
HBV	21 (26.6%)	30 (25.0%)	
HCV	18 (22.8%)	18 (15.0%)	
MASLD	8 (10.1%)	15 (12.5%)	0.178
Other	5 (6.3%)	8 (6.7%)	
metALD	3 (3.8%)	3 (2.5%)	
HBV/HCV	2 (2.5%)	3 (2.5%)	
HCV + SLD	12 (15.2%)	25 20.8(%)	
HBV + SLD	0	10 (8.3%)	
Smoking			
Yes	18 (22.8%)	41 (34.2%)	0.085
No	61 (77.2%)	79 (65.8%)	
Charlson Comorbidity Index **	3 (2 to 4)	3 (2 to 4)	0.372
Cirrhosis			
Yes	43 (54.4%)	72 (60.0%)	0.436
No	36 (45.6%)	48 (40.0%)	
Platelets **	161 (131 to 216)	194 (142 to 242.5)	0.068
Child–Pugh Score			
5	66 (83.5%)	98 (81.7%)	
6	10 (12.7%)	19 (15.8%)	0.893
7	2 (2.5%)	2 (1.7%)	
8	1 (1.3%)	1 (0.8%)	
Tumour Burden Category			
Single ≤ 2 cm	19 (24.1%)	32 (26.7%)	
Single > 2 cm, ≤3 cm	22 (27.8%)	35 (29.2%)	0.331
Single > 3 cm, ≤5 cm	17 (21.5%)	34 (29.3%)	
Single > 5 cm	16 (20.3%)	12 (28.3%)	
Multinodular, all ≤ 3 cm	5 (6.3%)	7 (6.8%)	

* mean ± standard deviation; ** median (25th percentile to 75th percentile). LTC, liver transplant centre; NTC, non-transplant centre; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; metALD, metabolic and alcohol related liver disease; SLD, steatotic liver disease; TACE, transarterial chemoembolization.

Table 4 presents a multivariable binary logistic regression assessing treatment allocation to resection vs. non-resection treatment in all 887 patients. Importantly, management at an LTC treatment site had no significant association with treatment allocation to resection (adjusted OR 0.748, 95% CI 0.502 to 1.114, $p = 0.153$). As expected, the presence of cirrhosis predicted against treatment allocation to resection (adjusted OR 0.346, 95% CI 0.210 to 0.570, $p < 0.001$). Correspondingly, higher platelet counts predicted treatment allocation to resection (adjusted OR 1.004, 95% CI 1.001 to 1.007, $p = 0.003$). Higher CPS and CCI both predicted against treatment allocation to resection (adjusted OR 0.504, 95% CI 0.370 to 0.685, $p < 0.001$; and adjusted OR 0.728, 95% CI 0.638 to 0.831, $p < 0.001$ respectively).

Table 4. Multivariable binary logistic regression-predictors of allocation to surgical resection vs. non-surgical treatment.

	Adjusted OR	95% CI	*p*-Value
Centre Type			
NTC	Reference	–	–
LTC	0.75	0.50 to 1.11	0.153
Age	1.00	0.98 to 1.02	0.922
Sex			
Male	Reference	–	–
Female	1.22	0.75 to 1.99	0.432
Diabetes			
No	Reference	–	–
Yes	0.69	0.41 to 1.17	0.170
Smoking			
No	Reference	–	–
Yes	1.30	0.82 to 2.06	0.262
HBV			
No	Reference	–	–
Yes	1.14	0.72 to 1.81	0.571
Alcohol			
No	Reference	–	–
Yes	0.87	0.55 to 1.36	0.535
Charlson Comorbidity Index	0.73	0.64 to 0.83	<0.001
Cirrhosis			
No	Reference	–	–
Yes	0.35	0.21 to 0.57	<0.001
Platelets	1.00	1.00 to 1.01	0.003
Child–Pugh Score	0.50	0.37 to 0.69	<0.001
Tumour Burden Category			
Single $\leq$ 2 cm	Reference	–	–
Single > 2 cm, $\leq$3 cm	1.35	0.82 to 2.22	0.233
Single > 3 cm, $\leq$5 cm	2.03	1.16 to 3.55	0.013
Single > 5 cm	0.94	0.47 to 1.88	0.855
Multinodular, all $\leq$ 3 cm	0.35	0.17 to 0.73	0.004

LTC, liver transplant centre; NTC, non-transplant centre; HBV, hepatitis B virus.

3.4. Locoregional Treatment

Of the remaining 689 patients in our study who did not receive surgical resection as the initial treatment, we found significant differences in treatment strategy between LTCs and NTCs. Table 5 presents the initial treatment choice between LTCs and NTCs for varying tumour burdens. Significant differences in treatment allocation were seen in all tumour burden categories. In patients with a single tumour measuring 2 cm or less, the majority of patients at the NTC underwent upfront ablation (77%), whereas most LTC patients underwent TACE as their first treatment (60%). Similarly, in those with a single tumour measuring 3 cm or less and larger than 2 cm, NTC patients mainly received ablation (56%), while LTC patients mainly received TACE (63%). For those with a single tumour larger than 3 cm, no LTC patients received upfront ablation, with most receiving TACE, whereas NTC continued to offer attempts at upfront ablation in small numbers in these patients. In those with a multinodular tumour within the BCLC A criteria (all nodules 3 cm or less), NTC offered upfront ablation to a sizeable minority of patients (46%), whereas LTC only proceeded to ablation first in 10% of patients.

Table 5. Choice of initial treatment by tumour burden category in those not undergoing resection.

	LTC n = 354	**NTC n = 334**	***p*-Value**
Single ≤ 2 cm			
Ablation	41 (40.2%)	84 (77.1%)	<0.001
TACE	61 (59.8%)	16 (14.7%)	
Other	0	9 (8.3%)	
Single > 2 cm, ≤3 cm			
Ablation	23 (31.5%)	53 (56.4%)	<0.001
TACE	46 (63.0%)	24 (25.5%)	
Other	4 (5.5%)	17 (18.1%)	
Single > 3 cm, ≤5 cm			
Ablation	0	13 (34.2%)	<0.001
TACE	49 (94.2%)	23 (60.5%)	
Other	3 (5.8%)	2 (52.6%)	
Single > 5 cm			
Ablation	0	3 (13.0%)	0.091
TACE	16 (53.3%)	13 (56.5%)	
Other	14 (46.7%)	7 (30.4%)	
Multinodular, all ≤ 3 cm			
Ablation	10 (9.7%)	32 (45.7%)	<0.001
TACE	84 (86.6%)	35 (50.0%)	
Other	3 (3.1%)	3 (4.3%)	

LTC, liver transplant centre; NTC, non-transplant centre; TACE, transarterial chemoembolisation.

Multivariable binary logistic regression, assessing only the population who did not receive resection (n = 689), was performed to examine the predictors of initial treatment allocation to ablation vs. non-ablation. The results are presented in Table 6. After adjusting for key covariates, management at LTC was associated with approximately a five-fold reduced chance of undergoing ablation as the initial treatment (adjusted OR 0.19, 95% CI 0.13 to 0.28, $p < 0.001$). Increased CPS was also associated with a reduced chance of allocation to ablation (adjusted OR 0.82, 95% CI 0.69 to 0.99, $p = 0.037$). As expected, compared to the presence of a single tumour 2 cm or less, larger tumour sizes or the presence of multinodular tumours were associated with a reduced chance of allocation to ablation. Age, sex, liver disease aetiology, CCI, and platelet count did not predict for or against treatment allocation to ablation.

Table 6. Multivariable binary logistic regression-predictors of allocation to upfront ablation vs. other treatment in those not undergoing resection.

	Adjusted OR	**95% CI**	***p*-Value**
Centre Type			
NTC	Reference	–	–
LTC	0.19	0.13 to 0.28	<0.001
Age	1.00	0.98 to 1.02	0.799
Sex			
Male	Reference	–	–
Female	1.07	0.67 to 1.70	0.789
Diabetes			
No	Reference	–	–
Yes	1.05	0.68 to 1.61	0.835
Smoking			
No	Reference	–	–
Yes	1.29	0.84 to 1.96	0.242

Table 6. *Cont.*

	Adjusted OR	95% CI	*p*-Value
HBV			
No	Reference	–	–
Yes	0.97	0.58 to 1.63	0.904
Alcohol			
No	Reference	–	–
Yes	0.96	0.64 to 1.45	0.854
Charlson Comorbidity Index	1.02	0.91 to 1.14	0.740
Cirrhosis			
No	Reference	–	–
Yes	1.94	0.92 to 4.08	0.082
Platelets	1.00	1.00 to 1.00	0.800
Child–Pugh Score	0.82	0.69 to 0.99	0.037
Tumour Burden Category			
Single ≤ 2 cm	Reference	–	–
Single > 2 cm, ≤3 cm	0.50	0.32 to 0.79	0.003
Single > 3 cm, ≤5 cm	0.10	0.05 to 0.21	<0.001
Single > 5 cm	0.04	0.01 to 0.13	<0.001
Multinodular, all ≤ 3 cm	0.22	0.14 to 0.36	<0.001

LTC, liver transplant centre; NTC, non-transplant centre; HBV, hepatitis B virus.

3.5. All-Cause Mortality

Median follow-up time from initial diagnosis to death or censorship was 3.39 years in the LTC group and 3.83 years in the NTC group ($p = 0.31$). a multivariable Cox proportional hazards analysis was performed on the entire cohort, and multivariable-adjusted hazard function curves are presented in Figure 1. Management at LTCs was associated with a reduced risk of mortality over the course of follow-up (adjusted HR 0.71, 95% CI 0.51 to 0.98, $p = 0.036$) despite adjusting for age, sex, smoking, diabetes, HBV, alcohol, cirrhosis status, CCI, platelet count, CPS and tumour burden category. Female sex was associated with reduced risk of death (adjusted HR 0.63, 95% CI 0.40 to 0.99, $p = 0.044$), while an increased risk of death was associated with CCI (adjusted HR 1.17, 95% CI 1.08 to 1.28, $p < 0.001$), CPS (adjusted HR 1.44, 95% CI 1.26 to 1.64, $p < 0.001$) and single tumour >5 cm (adjusted HR 2.22, 95% CI 1.20 to 4.09, $p = 0.011$). Age, smoking, diabetes, HBV, alcohol, cirrhosis status, platelet count, and multinodular tumour did not significantly affect all-cause mortality in the multivariable adjusted model. The model is presented in detail in Supplementary Table S1.

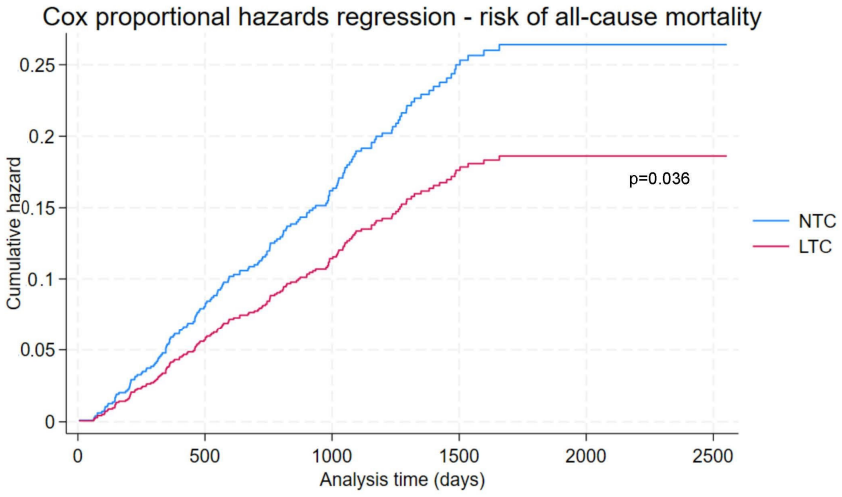

Figure 1. All-cause mortality hazard function after multivariable adjustment.

3.6. All-Cause Mortality with Liver Transplant as Competing Risk

Competing-risks regression analysis was performed on the entire cohort. Multivariable-adjusted incidence function curves are presented in Figure 2. After including liver transplant as a competing event, there was evidence of a similarly significant reduction in risk in LTC patients (adjusted HR 0.71., 95% CI 0.50 to 0.99, $p = 0.041$) with adjustment for age, sex, smoking, diabetes, HBV, alcohol, cirrhosis status, CCI, platelet count, CPS, and tumour burden category. Female sex was associated with reduced risk of transplant or death (adjusted HR 0.63, 95% CI 0.40 to 0.98, $p = 0.042$). Predictors of transplant or death included CCI (adjusted HR 1.17, 95% CI 1.07 to 1.29, $p = 0.001$), CPS (adjusted HR 1.43, 95% CI 1.25 to 1.64, $p < 0.001$) and a single tumour >5 cm (adjusted HR 2.17, 95% CI 1.17 to 4.01, $p = 0.014$). The results of the competing-risks regression analysis are presented in detail in Supplementary Table S2. Notably, other tumour burden categories, age, smoking, diabetes, HBV, alcohol, cirrhosis status, platelet count were non-significant predictors.

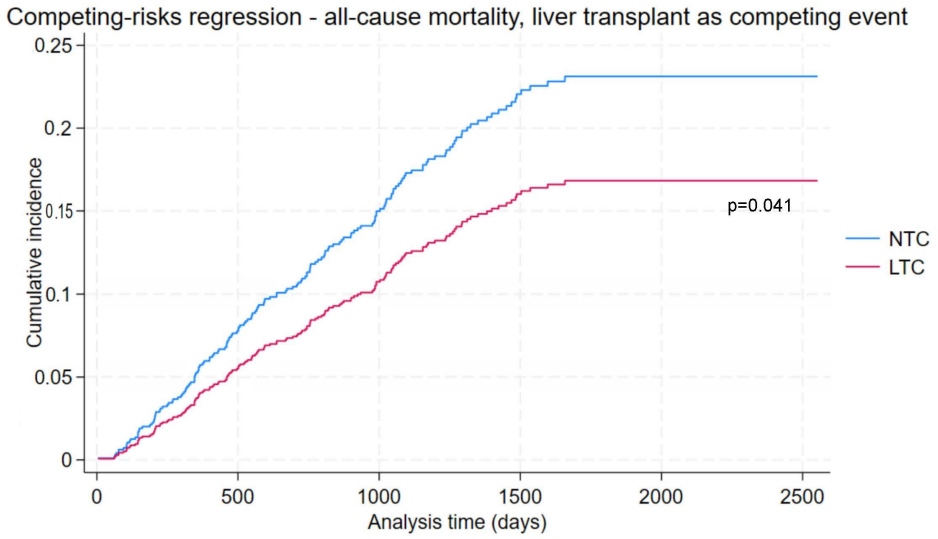

Figure 2. Competing-risks regression with cumulative incidence function of all-cause mortality, with liver transplant as a competing risk.

4. Discussion

HCC management is complex and highly individualised, with treatment decisions made based not just on BCLC stage alone but also using specific anatomical considerations, non-liver medical comorbidities, patient views and values, and centre-specific experience and resources. Variation in care across centres has been well described [15,16], but there is no published data, to our knowledge, regarding specifically differences between LTCs and NTCs and no published work describing variations in Australia. Our study is the first to show, in an Australian context, that there are systematic differences in the treatment approach between LTCs and NTCs, even after adjusting for the differences in patient characteristics between the two cohorts. Furthermore, our study demonstrated that patients receiving treatment for BCLC 0/A HCC at an LTC exhibit reduced all-cause mortality, primarily driven by the survival benefit associated with transplantation.

As expected, we found significant and systematic differences in the population between those managed at LTCs and NTCs. Patients managed at LTCs in Australia are comprised of a combination of those for whom the LTC is their closest hospital and others who were referred from further away for tertiary management of liver disease or HCC. We expect that those referred for tertiary management to a LTC rather than NTC are the reasons for the systematic differences, with referrers more likely to refer transplant-suitable patients to LTCs, even when there is no indication for transplant at the time of initial referral. The first of the observed differences was in liver disease aetiology, with LTC patients less likely to exhibit alcohol as a cause for their underlying liver disease. This may be due to patients

with ongoing active drinking being more likely to be referred for HCC treatment at an NTC rather than an LTC. LTC patients were also less likely to show HBV as a cause for their liver disease. Firstly, we suspect that this is due to non-cirrhotic CHB patients being managed more frequently at an NTC, for both unique Australian geographic reasons, in which many of the NTCs in our study serve communities with higher proportions of Southeast Asian migrants, as well as for clinical reasons, where low-risk resection patients are less likely to be referred to an LTC. Secondly, we found that the LTCs possessed a younger patient cohort compared to the NTCs, with a greater variation in age seen in the NTC population. This is due to a greater number of elderly patients observed in the NTC population, where these patients are also less likely to be referred to LTC due to their advanced age. Thirdly, liver disease was clearly more severe in the LTC cohort, with the lower median platelet count reflecting more significant portal hypertension and higher Child–Pugh scores, indicating more diminished hepatic reserve. We suspect that this reflects the diversion of patients with more advanced liver disease to the LTC from the NTC, as well as the higher proportion of non-cirrhotic CHB patients in the NTC. Lastly, LTC patients exhibited higher risk tumour burden categories, with greater numbers of large single tumours or multinodular tumours. Again, we expect that this is due to these patients being more likely to be referred to an LTC for management.

While a smaller proportion of LTC compared to NTC patients underwent resection (18.2% vs. 26.4%), after adjusting for the clinical predictors of treatment allocation to resection, patients were just as likely to undergo resection at LTCs as those managed at NTCs. There was a numerical signal that patients undergoing resection at an LTC had a lower median platelet count than did NTC patients, suggesting that LTCs may be offering resection to higher-risk patients, but this result was not statistically significant (median platelet 161 vs. 194, $p = 0.068$). There were otherwise no significant differences between the two groups, suggesting similar patient selection for resection irrespective of management at an LTC or an NTC. As resection is the most efficacious curative first line treatment, aside from transplantation, and access to resection has been defined as an HCC quality indicator [17,18], our results reassure us that access to resection is not centre-dependent in our study population.

After adjusting for all key clinical variables, management at an LTC was independently associated with a 5-fold reduced chance of upfront ablation. We found that in patients not deemed suitable for resection, LTCs instead favoured initial TACE across all tumour burden categories. Almost one-third of LTC patients who received TACE as their initial therapy at an LTC underwent ablation as a second therapy, with an additional 10% undergoing ablation as a third or subsequent treatment. The BCLC treatment algorithm recommends upfront ablation as the locoregional curative treatment choice for BCLC 0/A patients [19], and none of the major international or Australian guidelines recommend TACE as initial therapy in BCLC 0 or A disease [6,20–22]. However, a growing body of literature published over the last six years has described the beneficial effect of TACE prior to ablation [23–25], with improved outcomes postulated to be due to elimination of viable micrometastases adjacent to the tumour, as well as disruption of hepatic arterial flow, leading to a reduced heat sink effect at the time of ablation, increasing the size of the ablation zone, making it more likely for the treatment to be complete and efficacious. Furthermore, the intra-tumoural deposition of lipiodol with TACE can improve tumour visualisation at the time of ablation, increasing the likelihood of optimal ablation needle placement [23–25]. Further work is needed to determine whether a treatment approach with upfront ablation or initial TACE followed by ablation significantly affects outcomes, particularly if there is a delay between initial TACE and subsequent ablation therapy, as was the case for the majority of patients in our study. Beyond the benefits of TACE prior to ablation, the treatment choice of initial TACE vs. upfront ablation may also be biased by transplant eligibility (such as more aggressive pursuit of cure in those not eligible for transplantation or more judicious treatment with an emphasis on safety in those considered transplant candidates), although this is purely speculative and requires prospective evaluation.

In our study we did find that across all patients, there was superior overall survival in the LTC cohort. Patients managed at LTCs were 29% less likely to die over the course of follow-up, after adjusting for clinical factors at presentation. Even after considering liver transplant as a competing risk, with the same multivariable adjustment, LTC patients had a similar 30% reduced risk of death. The reason for the reduced risk of death is not certain with the difference in treatment strategy observed between LTCs and NTCs in non-resection treatments potentially being a key contributing factor. Notably, confounding from invisible patient factors as previously discussed above are another explanation, as these are likely systematically different between LTCs and NTCs and affect not just access to transplantation but also access to other cancer treatments as well as influence the risk of hepatic decompensation. Furthermore, survival analysis may be affected by guarantee-time bias, which we have been unable to mitigate due to the lack of granularity in the data regarding movement of patients between managing centres. Prospective assessment of similar patients managed at LTCs and NTCs is needed to further investigate our findings.

In comparing the patients who received transplant during follow-up, patients at LTCs and NTCs exhibited overall similar characteristics, suggesting similar patient selection. Specifically, the two groups were similar with respect to age, sex, liver disease aetiology, Child–Pugh Score, and tumour burden category. The one area in which the two groups differed was in CCI, where LTC patients had a slightly higher CCI, which was statistically significant, raising the possibility that patients may be more likely to proceed to transplantation, with greater medical comorbidities, if their initial managing centre is an LTC. Importantly, the time to transplant from initial diagnosis was not significantly different between the two groups, suggesting that where LT was required, patients being referred from an NTC were not subjected to significant delays. It is important to note that as a retrospective study, reverse causality is an important consideration for the larger numbers of LTC patients who received transplantation. Important factors such as recency of alcohol intake, social situation, patient wishes, and other medical/psychological comorbidities not captured by the CCI may all have contributed to an individual patient's suitability for transplant, and these factors have not been captured in our data collection and therefore remain unadjusted for. It should also be noted that while some patients have been considered as LTC patients in our study, they may have actually received their initial diagnosis in the community, in the private health care sector, or at a small peripheral hospital and may have been selected for LTC over NTC referral due to their perceived transplant suitability, despite not requiring transplant at the time of initial referral. Indeed, between 65% and 75% of patients were referred to centres from outside their direct local hospital catchment, suggesting that selection bias in the preferential referral of transplant-suitable patients to an LTC in preference to an NTC played a significant role in producing distinct populations, with resultant differences in transplant suitability. Explicit data regarding referral origin, time at managing centre prior to HCC diagnosis, clear documentation regarding perceived transplant suitability, and transplant waitlisting were not available for analysis in our study. We are therefore unable to distinguish between LTC patients who were referred specifically for transplant and those who were referred solely for HCC management as the most-suitable HCC referral centre. Overall, we do not believe that our study provides reliable evidence to form conclusions regarding differential access to transplantation, but instead, it provides some early insights that can be further investigated prospectively. Equitable access to transplantation is a major goal in maximizing the quality of HCC care across the nation, and we will report our prospective results in due course.

Our study has several strengths. Firstly, we report real-world data giving insights into the day-to-day patterns of care and outcomes of Australian early-stage HCC patients across multiple centres. Secondly, we were able to adjust for the majority of important factors in considering both treatment allocation and survival outcomes, increasing confidence regarding the authenticity of the differences observed between LTCs and NTCs. Lastly, we have reported on a large population, allowing us the statistical power required to observe the significant differences in locoregional treatment strategy and overall survival.

As alluded to above, our study also has significant limitations. Firstly, because our study is retrospective in nature, it is susceptible to information bias, particularly in association with clinical factors and treatment allocation. Secondly, differences in the survival outcomes observed may be affected by selection bias, both direct and indirect, by confounding and in our competing-risks regression, by guarantee-time bias. The use of a multivariable model to mitigate this increases our confidence in the findings, but some factors, such as the anatomical location of the tumour or ongoing alcohol intake, have not been captured. Future studies would benefit from collecting explicit information regarding eligibility for liver transplantation to better evaluate reasons for differences in treatment selection between LTC and NTC.

5. Conclusions

Our study provides valuable evidence that there are indeed systematic differences in patterns of care in BCLC 0/A HCC between HCC referral centres, with and without an integrated liver transplant program, with the main difference involving difference in preference between upfront ablation and initial TACE in patients not suitable for resection. While patients managed at LTCs have improved overall survival, even after considering transplant as a competing-risk, it is not certain if the difference in treatment strategy is the direct cause for this result. Further work is needed to prospectively evaluate the differences in treatment strategy, access to transplantation, and long-term survival outcomes, both within and across centres, in order to identify opportunities for quality improvement.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers16111966/s1, Table S1: Cox proportional hazards analysis-factors predicting all-cause mortality; Table S2: Competing-risks regression factors predicting all-cause mortality, with liver transplant as a competing risk.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of Monash Health (HREC Reference Number: HREC/80727/MonH−2022−302788(v3), 23 February 2022).

Informed Consent Statement: Patient consent was waived for the following reasons: the study did not involve an intervention, and was low-risk in terms of data collection and participant burden, we did not anticipate any risk of harm associated with collecting de-identified data, a significant proportion of the population targeted for recruitment were likely to be unwell or deceased at the time of inclusion in the study, and there was sufficient protection of patient privacy as the data is de-identified.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Table A1. Minimum Dataset.

Ref	Data Item	Field Type and Values
Participant Details		
1.1.1	Record ID	Text
PARTICIPANT DETAILS		
1.2.1	Recruiting Hospital	Dropdown 2, Alfred Health | 6, Austin Health | 102, Eastern Health | 9, Monash Health | 221208, Prince of Wales Hospital | 1, Royal Melbourne Hospital | 220208, Royal Prince Alfred Hospital | 3, St Vincent's Hospital Melbourne | 106, Western Health | 109, John Hunter Hospital (Hunter New England)
1.2.2	Date of Birth	Date
1.2.3	Sex at Birth	Dropdown 1, Male | 2, Female | 3, Intersex or indeterminate | −99, Not stated/inadequately described
1.2.4	Postcode	Text
1.2.5	Country of Birth	Radio 1, Australia | 2, Country other than Australia
1.2.6	Country of birth	Text
1.2.7	Estimated first arrival year to Australia	Text
1.2.8	Ethnicity	Dropdown 1, Australian Indigenous | 2, African | 3, Caucasian (Australia, Europe, UK, Nth America etc.) | 4, North−East Asian (China, Japan, Sth/Nth Korea, Mongolia, Taiwan) | 5, Hispanic (Central, South American, North American) | 6, Middle Eastern/North African | 7, Polynesian/Pacific Islander | 8, Southern Asian (Indian, Pakistan, Bangladesh, Nepal, Afghanistan) | 9, South−East Asian (Vietnamese, Thai, Burmese, Khmer etc.) | 98, Other | −99, Unknown
1.2.9	Other ethnicity	Text
1.2.10	Aboriginal and Torres Strait Islander status	Dropdown 4, Neither Aboriginal nor Torres Strait Islander origin | 1, Aboriginal but not Torres Strait Islander | 2, Torres Strait Islander but not Aboriginal | 3, Both Aboriginal and Torres Strait Islander origin | −99, Not stated/inadequately described
FORM STATUS		
1.3.1	Complete?	Dropdown 0, Incomplete | 1, Unverified | 2, Complete
Health Status and End of Life Details		
HEALTH STATUS AND END OF LIFE		
2.1.1	Was patient alive at 31 December 2020?	Radio 1, Yes | 2, No | −99, Unknown
2.1.2	Date of death	Date
2.1.3	Cause of death	Radio 1, Directly related to HCC | 2, Related to underlying liver disease | 3, Related to combination HCC and underlying liver disease | 4, Non−Liver related | 5, Not ascertained but probably/definitely related to HCC | 6, Not ascertained but unlikely or not related to HCC | 7, Unable to be ascertained

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
2.1.4	If non-liver related, specify cause of death	Text
FORM STATUS		
2.2.1	Complete?	Dropdown 0, Incomplete | 1, Unverified | 2, Complete
Risk Factors		
RISK FACTORS		
3.1.1	Risk Factors	Checkbox 1, rf___1 Cirrhosis | 2, rf___2 Alcohol | 3, rf___3 NAFLD/MAFLD | 4, rf___4 Smoking history | 5, rf___5 Diabetes | 6, rf___6 HCV positive | 7, rf___7 HBV positive | 8, rf___8 Autoimmune hepatitis | 9, rf___9 PSC | 10, rf___10 PBC | 11, rf___11 Alpha 1 anti−trypsin deficiency | 12, rf___12 Wilsons disease | 13, rf___13 Family History | 14, rf___14 Other: {rf_other} | 15, rf___15 None of the above | −99, rf____99 Unknown − factors contributing to HCC unknown
3.1.2	Alcohol	Dropdown 1, Current heavy user | 4, Current non−heavy user | 2, Past heavy alcohol use | 3, Never consumed alcohol | −99, Unknown − consumption not reported
3.1.3	Family History Type	Dropdown 1, First degree relative | 2, Second degree relative
3.1.4	Other	Text
3.1.5	Smoking status	Radio 1, Current smoker | 2, Ex−smoker | 3, Never smoked | 4, Non−smoker (no further specification) | −99, Unknown/Not documented
3.1.6	Past HCC	Radio 1, Yes | 2, No
3.1.7	Date of past HCC	Date
3.1.8	Was the past HCC in the same location as the current one—i.e., is this a recurrence?	Dropdown 1, Yes | 2, No | −99, Unknown
FORM STATUS		
3.2.1	Complete?	Dropdown 0, Incomplete | 1, Unverified | 2, Complete
Diagnosis Details		
DIAGNOSIS DETAILS		
4.1.1	Date of HCC diagnosis	Date
4.1.2	Mode of HCC Diagnosis	Radio 1, Histopathology (includes biopsy, surgical resection) | 2, Imaging
4.1.3	Histology type	Dropdown 1, Biopsy | 2, Surgical Specimen
4.1.4	Imaging type	Radio 1, Multiphase CT | 2, MRI Liver | 3, CEUS | 4, Other: clinical: {dx_other}
4.1.5	Other mode of diagnosis	Text

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
4.1.6	Method or presentation of HCC Diagnosis	Radio 1, Screening/surveillance−please specify reason for doing so: {dx_screen_reason}|2, Incidental−please specify how so: {dx_incident_how}|3, Symptoms|4, Other: {dx_other_method}
4.1.7	Reason for screening/surveillance	Text
4.1.8	Incidental (how)	Text
4.1.9	Other (method or presentation)	Text
4.1.10	Tumour Size (largest lesion measured in cm)	Text
4.1.11	Site of the largest lesion(s)	Checkbox 1, dx_largelesion_location___1 Seg 1 (caudate lobe)|2, dx_largelesion_location___2 Seg 2|3, dx_largelesion_location___3 Seg 3|4, dx_largelesion_location___4 Seg 4a|5, dx_largelesion_location___5 Seg 4b|6, dx_largelesion_location___6 Seg 5|7, dx_largelesion_location___7 Seg 6|8, dx_largelesion_location___8 Seg 7|9, dx_largelesion_location___9 Seg 8|10, dx_largelesion_location___10 Diffuse type not easily determined|11, dx_largelesion_location___11 Right Lobe (segment not specified)|12, dx_largelesion_location___12 Left Lobe (segment not specified)|13, dx_largelesion_location___13 None of the above|−99, dx_largelesion_location____99 Not recorded
4.1.12	Number of HCC lesions	Text
4.1.13	Total lobes with lesion(s)	Dropdown 1, one lobe only|2, both lobes|−99, unknown site of lesion(s)
4.1.14	Child–Pugh Class	Dropdown 1, A (5−6)|2, B (7−9)|3, C (10−15)|−99 Unknown–unknown result
4.1.15	You have selected: [dx_childpugh_class] This equates to: [calc_childpugh_c2s]	Descriptive
4.1.16	Calculation—Class to Score	Text
4.1.17	Child–Pugh Score	Text
4.1.18	You have selected: [dx_childpugh_score] This equates to: [calc_childpugh_s2c]	Descriptive
4.1.19	Calculation—Score to Class	Text
4.1.20	BCLC staging score	Dropdown 0, 0−Very early (single < 2 cm)|1, A−Early (single, 3 nodules $\leq$ 3 cm)|2, B−Intermediate (multinodular)|3, C−Advanced (portal invasion)|4, D−End−stage|−99, Unknown−unknown result
4.1.21	Other comorbidities	Dropdown 1, Yes−see next field for details|2, No−no other known comorbidities

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
4.1.22	Charlson Comorbidity Index	Checkbox 1, dx_comorbidet___1 Prior myocardial infarction | 2, dx_comorbidet___2 Congestive heart failure | 3, dx_comorbidet___3 Peripheral vascular disease | 4, dx_comorbidet___4 Cerebrovascular disease or Transient ischemic attack (TIA) | 5, dx_comorbidet___5 Dementia | 6, dx_comorbidet___6 Chronic obstructive pulmonary disease | 7, dx_comorbidet___7 Rheumatologic disease or Connective tissue disease | 8, dx_comorbidet___8 Peptic ulcer disease | 9, dx_comorbidet___9 Mild liver disease | 10, dx_comorbidet___10 Moderate or severe liver disease (Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history, mild = chronic hepatitis (or cirrhosis without portal hypertension)) | 11, dx_comorbidet___11 Diabetes with chronic complications | 12, dx_comorbidet___12 Cerebrovascular (hemiplegia) event | 13, dx_comorbidet___13 Moderate−to−severe chronic renal/kidney disease (Severe = on dialysis, status post kidney transplant, uraemia, moderate = creatinine > 3 mg/dL (0.27 mmol/L)) | 14, dx_comorbidet___14 Cancer without metastases/localised solid tumour | 15, dx_comorbidet___15 Metastatic solid tumour | 16, dx_comorbidet___16 Leukaemia | 17, dx_comorbidet___17 Lymphoma | 18, dx_comorbidet___18 Acquired immuno−deficiency syndrome (AIDS) | 19, dx_comorbidet___19 Other: {dx_other_comorbidity} | 20, dx_comorbidet___20 Atrial fibrillation (AF)/Supraventricular tachycardia (SVT) | 21, dx_comorbidet___21 Uncomplicated diabetes | 22, dx_comorbidet___22 None of the above | −99, dx_comorbidet____99 Unknown
4.1.23	Other comorbidity	Text
4.1.24	Diabetes at time of diagnosis	Dropdown 0, No−did not have diabetes | 1, T1DM−had type 1 diabetes mellitus | 2, T2DM−had type 2 diabetes mellitus (NIDDM) | 3, T2IDM−had type 2 insulin−dependent diabetes mellitus (IDDM) | 4, Yes−unspecified−known to have diabetes but specific type missing | −99, Unknown−diabetes status unknown
4.1.25	Portal hypertension	Dropdown 1, Yes−had portal hypertension at diagnosis | 2, No−did not have portal hypertension at time of diagnosis | −99, Unknown
4.1.26	AFP measured	Text
4.1.27	AFP result—unit of measurement	Dropdown 1, μg/mL | 2, ng/ml or μg/L | 3, Other | −99, Unknown−units unknown
4.1.28	Platelets $\times 10^9$/L	Text
4.1.29	Albumin	Text
4.1.30	Other AFP Unit Measurement	Text

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
4.1.31	ECOG at time of diagnosis	Dropdown 0, 0 = Fully active, able to carry on all pre−disease performance without restriction | 1, 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work | 2, 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours | 3, 3 = Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours | 4, 4 = Completely disabled; cannot carry on any selfcare; totally confined to bed or chair | 5, 5− Dead | −99, ECOG not documented
4.1.32	Presence of ascites	Radio 1, Yes | 2, No | −99, Not recorded
4.1.33	Presence of hepatic encephalopathy	Radio 1, Yes | 2, No | −99, Not recorded
FORM STATUS		
4.2.1	Complete?	Dropdown 0, Incomplete | 1, Unverified | 2, Complete
Viral Status at Diagnosis		
HEPATITS B STATUS		
5.1.1	Hepatitis B virus (HBV)	Dropdown 1, Yes (either past or present)− had HBV at diagnosis | 0, No−(neither past nor present) | −99, Unknown−results unknown
5.1.2	Hepatitis B viral treatment after HCC diagnosis	Dropdown 1, Yes–on HBV treatment | 2, No–not on HBV treatment | −99, Unknown–treatment status unknown
HEPATITIS C STATUS		
5.2.1	Hepatitis C virus (HCV)	Dropdown 1, Current infection (i.e HCV RNA PCR positive) at diagnosis | 2, Past infection (i.e HCV RNA PCR negative AND HCV Ab positive) at diagnosis | 0, No current or past HCV−HCV at diagnosis | −99, Unknown−results unknown
5.2.2	Hepatitis C virus treatment history	Dropdown 1, Naïve−never treated | 2, Non−responder−treated but still RNA PCR positive | 3, Ongoing−on treatment at time of diagnosis | 4, Relapse−treated, end−of−treatment RNA PCR negative but subsequently RNA PCR positive | 5, SVR (sustained virological response)−treated, end−of−treatment RNA PCR negative and maintains RNA PCR negative | −99, Unknown−HCV treatment history
5.2.3	Date of past HCV cure	Date
COINFECTION		
5.3.1	Viral coinfection	Dropdown 1, Yes | 0, No
5.3.2	Viral coinfection type	Checkbox 1, dx_coinf_yes___1 HDV (only if hepatitis B sAg positive) | 2, dx_coinf_yes___2 HIV
FORM STATUS		
5.4.1	Complete?	Dropdown 0, Incomplete | 1, Unverified | 2, Complete

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
Treatment		
TREATMENT		
6.1.1	Modality of initial treatment	Dropdown 1, Resection | 2, Transplantation | 3, Locoregional | 4, Systemic
6.1.2	First HCC treatment type	Checkbox 1, rx_1type___1 Conventional Transarterial chemoembolization (cTACE) | 2, rx_1type___2 Drug Eluting Bead (DEB)−TACE | 3, rx_1type___3 Radiofrequency ablation (RFA) | 4, rx_1type___4 Irreversible electroporation | 5, rx_1type___5 Percutaneous Ethanol Injection (PEI) | 6, rx_1type___6 Hepatic Resection | 7, rx_1type___7 Microwave ablation | 8, rx_1type___8 Medication | 9, rx_1type___9 Stereotactic Body Ablation Radiotherapy | 10, rx_1type___10 Liver Transplant | 11, rx_1type___11 Selective Internal Radiation Therapy (SIRT) | 12, rx_1type___12 No Treatment | 13, rx_1type___13 Other {rx_1other}cc | 14, rx_1type___14 Distant hepatic recurrence | 15, rx_1type___15 None of the above
6.1.3	Medications	Checkbox 1, rx_medications___1 Sorafenib | 2, rx_medications___2 Lenvima (Lenvatinib) | 3, rx_medications___3 Atezolizumab | 4, rx_medications___4 Others: please specify: {rx_medications_other} | 5, rx_medications___5 Clinical trial medication: please specify: {rx_medications_clintrial}
6.1.4	Other medications	Text
6.1.5	Clinical trial medications	Text
6.1.6	Date of treatment 1	Date
6.1.7	Other	Text
6.1.8	Reason no treatment	Checkbox 1, rx_1notreat___1 Patient unable to tolerate treatment | 2, rx_1notreat___2 Patient moved before treatment | 3, rx_1notreat___3 Patient lost to follow-up | 4, rx_1notreat___4 Patient died before treatment
6.1.9	Curative intent	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.10	Treatment response at time interval 1	Dropdown 1, PD−progressive disease (An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started) | 2, SD−stable disease (Any cases that do not qualify for either partial response or progressive disease) | 3, PR−partial response (At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions) | 4, CR−complete response (Disappearance of any intratumoral arterial enhancement in all target lesions) | −99, Not recorded/not measurable
6.1.11	Date of response assessment to treatment 1	Date
6.1.12	Date complete response confirmed	Date

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
6.1.13	If complete response, was there a recurrence?	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.14	Date of recurrence	Date
6.1.15	Type of recurrence: liver	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.16	Liver recurrence	Dropdown 1, Local | 2, Distant | 3, Vascular invasion | −99, Unknown
6.1.17	Extrahepatic	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.18	Where is the extrahepatic spread?	Text
6.1.19	Complications after initial treatment	Checkbox 1, rx_complications___1 Liver related morbidity | 2, rx_complications___2 Post procedural infections | 3, rx_complications___3 Post procedural bleeding | 4, rx_complications___4 Bile duct injury | 5, rx_complications___5 Respiratory events | 6, rx_complications___6 Local events | 7, rx_complications___7 Other {comp1_other}
6.1.20	Other complications	Text
6.1.21	Secondary therapies	Checkbox 1, rx_2type___1 Conventional Transarterial chemoembolization (cTACE) | 2, rx_2type___2 Drug Eluting Bead (DEB)−TACE | 3, rx_2type___3 Radiofrequency ablation (RFA) | 4, rx_2type___4 Irreversible electroporation | 5, rx_2type___5 Percutaneous Ethanol Injection (PEI) | 6, rx_2type___6 Hepatic Resection | 7, rx_2type___7 Microwave ablation | 8, rx_2type___8 Medication | 9, rx_2type___9 Stereotactic Body Ablation Radiotherapy | 10, rx_2type___10 Liver Transplant | 11, rx_2type___11 Selective Internal Radiation Therapy (SIRT) | 12, rx_2type___12 No Treatment | 13, rx_2type___13 Other {rx_2other} | 14, rx_2type___14 Distant hepatic recurrence | 15, rx_2type___15 None of the above
6.1.22	Medications	Checkbox 1, rx_medications_2___1 Sorafenib | 2, rx_medications_2___2 Lenvima (Lenvatinib) | 3, rx_medications_2___3 Atezolizumab | 4, rx_medications_2___4 Others: please specify: {rx_medications_other_2} | 5, rx_medications_2___5 Clinical trial medication: please specify: {rx_medications_clintrial_2}
6.1.23	Other medications	Text
6.1.24	Clinical trial medications	Text
6.1.25	Date of treatment 2	Date
6.1.26	Other	Text
6.1.27	Reason no treatment	Checkbox 1, rx_2notreat___1 Patient unable to tolerate treatment | 2, rx_2notreat___2 Patient moved before treatment | 3, rx_2notreat___3 Patient lost to follow-up | 4, rx_2notreat___4 Patient died before treatment

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
6.1.28	Treatment response at time interval 2	Dropdown 1, PD−progressive disease (An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started) | 2, SD−stable disease (Any cases that do not qualify for either partial response or progressive disease) | 3, PR−partial response (At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions) | 4, CR−complete response (Disappearance of any intratumoral arterial enhancement in all target lesions) | −99, Not recorded/not measurable
6.1.29	Date of response assessment to treatment 2	Date
6.1.30	Date complete response confirmed	Date
6.1.31	If complete response, was there a recurrence?	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.32	Date of recurrence	Date
6.1.33	Type of recurrence: liver	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.34	Liver recurrence	Dropdown 1, Local | 2, Distant | 3, Vascular invasion | −99, Unknown
6.1.35	Extrahepatic	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.36	Where is the extrahepatic spread?	Text
6.1.37	Complications after second treatment	Checkbox 1, rx_complications_2___1 Liver related morbidity | 2, rx_complications_2___2 Post procedural infections | 3, rx_complications_2___3 Post procedural bleeding | 4, rx_complications_2___4 Bile duct injury | 5, rx_complications_2___5 Respiratory events | 6, rx_complications_2___6 Local events | 7, rx_complications_2___7 Other {comp2_other}
6.1.38	Other complications	Text
6.1.39	Third therapies	Checkbox 1, rx_3type___1 Conventional Transarterial chemoembolization (cTACE) | 2, rx_3type___2 Drug Eluting Bead (DEB)−TACE | 3, rx_3type___3 Radiofrequency ablation (RFA) | 4, rx_3type___4 Irreversible electroporation | 5, rx_3type___5 Percutaneous Ethanol Injection (PEI) | 6, rx_3type___6 Hepatic Resection | 7, rx_3type___7 Microwave ablation | 8, rx_3type___8 Medication | 9, rx_3type___9 Stereotactic Body Ablation Radiotherapy | 10, rx_3type___10 Liver Transplant | 11, rx_3type___11 Selective Internal Radiation Therapy (SIRT) | 12, rx_3type___12 No Treatment | 13, rx_3type___13 Other {rx_3other} | 14, rx_3type___14 Distant hepatic recurrence | 15, rx_3type___15 None of the above

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
6.1.40	Medications	Checkbox 1, rx_medications_3___1 Sorafenib | 2, rx_medications_3___2 Lenvima (Lenvatinib) | 3, rx_medications_3___3 Atezolizumab | 4, rx_medications_3___4 Others: please specify: {rx_medications_other_3} | 5, rx_medications_3___5 Clinical trial medication: please specify: {rx_medications_clintrial_3}
6.1.41	Other medications	Text
6.1.42	Clinical trial medications	Text
6.1.43	Date of treatment 3	Date
6.1.44	Other	Text
6.1.45	Reason no treatment	Checkbox 1, rx_3notreat___1 Patient unable to tolerate treatment | 2, rx_3notreat___2 Patient moved before treatment | 3, rx_3notreat___3 Patient lost to follow-up | 4, rx_3notreat___4 Patient died before treatment
6.1.46	Treatment response at time interval 3	Dropdown 1, PD−progressive disease (an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started) | 2, SD—stable disease (any cases that do not qualify for either partial response or progressive disease) | 3, PR—partial response (at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions) | 4, CR—complete response (disappearance of any intratumoral arterial enhancement in all target lesions) | −99, not recorded/not measurable
6.1.47	Date of response assessment to treatment 3	Date
6.1.48	Date complete response confirmed	Date
6.1.49	If complete response, was there a recurrence?	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.50	Date of recurrence	Date
6.1.51	Type of recurrence: liver	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.52	Liver recurrence	Dropdown 1, Local | 2, Distant | 3, Vascular invasion | −99, Unknown
6.1.53	Extrahepatic	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.54	Where is the extrahepatic spread?	Text
6.1.55	Complications after third treatment	Checkbox 1, rx_complications_3___1 Liver related morbidity | 2, rx_complications_3___2 Post procedural infections | 3, rx_complications_3___3 Post procedural bleeding | 4, rx_complications_3___4 Bile duct injury | 5, rx_complications_3___5 Respiratory events | 6, rx_complications_3___6 Local events | 7, rx_complications_3___7 Other {comp3_other}

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
6.1.56	Other complications	Text
6.1.57	Did the patient receive additional treatments beyond those above?	yesno 1, Yes | 0, No
6.1.58	Fourth therapy(ies)	Checkbox 1, rx_4type___1 Conventional Transarterial chemoembolization (cTACE) | 2, rx_4type___2 Drug Eluting Bead (DEB)−TACE | 3, rx_4type___3 Radiofrequency ablation (RFA) | 4, rx_4type___4 Irreversible electroporation | 5, rx_4type___5 Percutaneous Ethanol Injection (PEI) | 6, rx_4type___6 Hepatic Resection | 7, rx_4type___7 Microwave ablation | 8, rx_4type___8 Medication | 9, rx_4type___9 Stereotactic Body Ablation Radiotherapy | 10, rx_4type___10 Liver Transplant | 11, rx_4type___11 Selective Internal Radiation Therapy (SIRT) | 12, rx_4type___12 No Treatment | 13, rx_4type___13 Other {rx_4other} | 14, rx_4type___14 Distant hepatic recurrence | 15, rx_4type___15 None of the above
6.1.59	Other	Text
6.1.60	Medications	Checkbox 1, rx_medications_4___1 Sorafenib | 2, rx_medications_4___2 Lenvima (Lenvatinib) | 3, rx_medications_4___3 Atezolizumab | 4, rx_medications_4___4 Others: please specify: {rx_medications_other_4} | 5, rx_medications_4___5 Clinical trial medication: please specify: {rx_medications_clintrial_4}
6.1.61	Other medications	Text
6.1.62	Clinical trial medications	Text
6.1.63	Date of treatment 4	Date
6.1.64	Reason no treatment	Checkbox 1, rx_4notreat___1 Patient unable to tolerate treatment | 2, rx_4notreat___2 Patient moved before treatment | 3, rx_4notreat___3 Patient lost to follow-up | 4, rx_4notreat___4 Patient died before treatment
6.1.65	Treatment response at time interval 4	Dropdown 1, PD−progressive disease (An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started) | 2, SD−stable disease (Any cases that do not qualify for either partial response or progressive disease) | 3, PR−partial response (At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions) | 4, CR−complete response (Disappearance of any intratumoral arterial enhancement in all target lesions) | −99, Not recorded/not measurable
6.1.66	Date of response assessment to treatment 4	Date
6.1.67	Date complete response confirmed	Date
6.1.68	If complete response, was there a recurrence?	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.69	Date of recurrence	Date

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
6.1.70	Type of recurrence: liver	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.71	Liver recurrence	Dropdown 1, Local | 2, Distant | 3, Vascular invasion | −99, Unknown
6.1.72	Extrahepatic	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.73	Where is the extrahepatic spread?	Text
6.1.74	Complications after fourth treatment	Checkbox 1, rx_complications_4___1 Liver related morbidity | 2, rx_complications_4___2 Post procedural infections | 3, rx_complications_4___3 Post procedural bleeding | 4, rx_complications_4___4 Bile duct injury | 5, rx_complications_4___5 Respiratory events | 6, rx_complications_4___6 Local events | 7, rx_complications_4___7 Other {comp4_other}
6.1.75	Other complications	Text
6.1.76	Fifth therapy(ies)	Checkbox 1, rx_5type___1 Conventional Transarterial chemoembolization (cTACE) | 2, rx_5type___2 Drug Eluting Bead (DEB)−TACE | 3, rx_5type___3 Radiofrequency ablation (RFA) | 4, rx_5type___4 Irreversible electroporation | 5, rx_5type___5 Percutaneous Ethanol Injection (PEI) | 6, rx_5type___6 Hepatic Resection | 7, rx_5type___7 Microwave ablation | 8, rx_5type___8 Medication | 9, rx_5type___9 Stereotactic Body Ablation Radiotherapy | 10, rx_5type___10 Liver Transplant | 11, rx_5type___11 Selective Internal Radiation Therapy (SIRT) | 12, rx_5type___12 No Treatment | 13, rx_5type___13 Other {rx_5other} | 14, rx_5type___14 Distant hepatic recurrence | 15, rx_5type___15 None of the above
6.1.77	Other	Text
6.1.78	Medications	Checkbox 1, rx_medications_5___1 Sorafenib | 2, rx_medications_5___2 Lenvima (Lenvatinib) | 3, rx_medications_5___3 Atezolizumab | 4, rx_medications_5___4 Others: please specify: {rx_medications_other_5} | 5, rx_medications_5___5 Clinical trial medication: please specify: {rx_medications_clintrial_5}
6.1.79	Other medications	Text
6.1.80	Clinical trial medications	Text
6.1.81	Date of treatment 5	Date
6.1.82	Reason no treatment	Checkbox 1, rx_5notreat___1 Patient unable to tolerate treatment | 2, rx_5notreat___2 Patient moved before treatment | 3, rx_5notreat___3 Patient lost to follow-up | 4, rx_5notreat___4 Patient died before treatment

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
6.1.83	Treatment response at time interval 5	Dropdown 1, PD−progressive disease (An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started) | 2, SD−stable disease (Any cases that do not qualify for either partial response or progressive disease) | 3, PR−partial response (At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions) | 4, CR−complete response (Disappearance of any intratumoral arterial enhancement in all target lesions) | −99, Not recorded/not measurable
6.1.84	Date of response assessment to treatment 5	Date
6.1.85	Date complete response confirmed	Date
6.1.86	If complete response, was there a recurrence?	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.87	Date of recurrence	Date
6.1.88	Type of recurrence: liver	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.89	Liver recurrence	Dropdown 1, Local | 2, Distant | 3, Vascular invasion | −99, Unknown
6.1.90	Extrahepatic	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.91	Where is the extrahepatic spread?	Text
6.1.92	Complications after fifth treatment	Checkbox 1, rx_complications_5___1 Liver related morbidity | 2, rx_complications_5___2 Post procedural infections | 3, rx_complications_5___3 Post procedural bleeding | 4, rx_complications_5___4 Bile duct injury | 5, rx_complications_5___5 Respiratory events | 6, rx_complications_5___6 Local events | 7, rx_complications_5___7 Other {comp5_other}
6.1.93	Other complications	Text
6.1.94	Sixth therapy(ies)	Checkbox 1, rx_6type___1 Conventional Transarterial chemoembolization (cTACE) | 2, rx_6type___2 Drug Eluting Bead (DEB)−TACE | 3, rx_6type___3 Radiofrequency ablation (RFA) | 4, rx_6type___4 Irreversible electroporation | 5, rx_6type___5 Percutaneous Ethanol Injection (PEI) | 6, rx_6type___6 Hepatic Resection | 7, rx_6type___7 Microwave ablation | 8, rx_6type___8 Medication | 9, rx_6type___9 Stereotactic Body Ablation Radiotherapy | 10, rx_6type___10 Liver Transplant | 11, rx_6type___11 Selective Internal Radiation Therapy (SIRT) | 12, rx_6type___12 No Treatment | 13, rx_6type___13 Other {rx_6other} | 14, rx_6type___14 Distant hepatic recurrence | 15, rx_6type___15 None of the above

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
6.1.95	Other	Text
6.1.96	Medications	Checkbox 1, rx_medications_6___1 Sorafenib | 2, rx_medications_6___2 Lenvima (Lenvatinib) | 3, rx_medications_6___3 Atezolizumab | 4, rx_medications_6___4 Others: please specify: {rx_medications_other_6} | 5, rx_medications_6___5 Clinical trial medication: please specify: {rx_medications_clintrial_6}
6.1.97	Other medications	Text
6.1.98	Clinical trial medications	Text
6.1.99	Date of treatment 6	Date
6.1.100	Reason no treatment	Checkbox 1, rx_6notreat___1 Patient unable to tolerate treatment | 2, rx_6notreat___2 Patient moved before treatment | 3, rx_6notreat___3 Patient lost to follow-up | 4, rx_6notreat___4 Patient died before treatment
6.1.101	Treatment response at time interval 6	Dropdown 1, PD−progressive disease (An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started) | 2, SD−stable disease (Any cases that do not qualify for either partial response or progressive disease) | 3, PR−partial response (At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions) | 4, CR−complete response (Disappearance of any intratumoral arterial enhancement in all target lesions) | −99, Not recorded/not measurable
6.1.102	Date of response assessment to treatment 6	Date
6.1.103	Date complete response confirmed	Date
6.1.104	If complete response, was there a recurrence?	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.105	Date of recurrence	Date
6.1.106	Type of recurrence: liver	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.107	Liver recurrence	Dropdown 1, Local | 2, Distant | 3, Vascular invasion | −99, Unknown
6.1.108	Extrahepatic	Dropdown 1, Yes | 2, No | −99, Unknown
6.1.109	Where is the extrahepatic spread?	Text
6.1.110	Complications after sixth treatment	Checkbox 1, rx_complications_6___1 Liver related morbidity | 2, rx_complications_6___2 Post procedural infections | 3, rx_complications_6___3 Post procedural bleeding | 4, rx_complications_6___4 Bile duct injury | 5, rx_complications_6___5 Respiratory events | 6, rx_complications_6___6 Local events | 7, rx_complications_6___7 Other {comp5_other}
6.1.111	Other complications	Text

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
FORM STATUS		
6.2.1	Complete?	Dropdown 0, Incomplete | 1, Unverified | 2, Complete
Subsequent Treatments		
7.1.1	This is a repeating form. If the patient had multiple subsequent treatments beyond the previous six, please complete this and if needed, add a new repeating form or instance by either clicking the dropdown arrow next to "Current instance:" above and select "+Add new" OR at the bottom, press the blue drop down arrow and select "Save & Add New Instance".	Descriptive
SUBSEQUENT TREATMENT		
7.2.1	Subsequent Treatment	Checkbox 1, rx_sub___1 Conventional Transarterial chemoembolization (cTACE) | 2, rx_sub___2 Drug Eluting Bead (DEB)−TACE | 3, rx_sub___3 Radiofrequency ablation (RFA) | 4, rx_sub___4 Irreversible electroporation | 5, rx_sub___5 Percutaneous Ethanol Injection (PEI) | 6, rx_sub___6 Hepatic Resection | 7, rx_sub___7 Microwave ablation | 8, rx_sub___8 Medication | 9, rx_sub___9 Stereotactic Body Ablation Radiotherapy | 10, rx_sub___10 Liver Transplant | 11, rx_sub___11 Selective Internal Radiation Therapy (SIRT) | 12, rx_sub___12 No Treatment | 13, rx_sub___13 Other {rx_sub_other} | 14, rx_sub___14 Distant hepatic recurrence | 15, rx_sub___15 None of the above
7.2.2	Other	Text
7.2.3	Medications	Checkbox 1, rx_submed___1 Sorafenib | 2, rx_ submed ___2 Lenvima (Lenvatinib) | 3, rx_ submed ___3 Atezolizumab | 4, rx_ submed ___4 Others: please specify: {rx_ submed _other} | 5, rx_ submed ___5 Clinical trial medication: please specify: {rx_ submed _clintrial}
7.2.4	Other medications	Text
7.2.5	Clinical trial medications	Text
7.2.6	Date of subsequent treatment	Date
7.2.7	Reason no treatment	Checkbox 1, rx_sub_notreat___1 Patient unable to tolerate treatment | 2, rx_sub_notreat___2 Patient moved before treatmen | 3, rx_sub_notreat___3 Patient lost to follow-up | 4, rx_sub_notreat___4 Patient died before treatment

Table A1. *Cont.*

Ref	Data Item	Field Type and Values
7.2.8	Treatment response at time interval of subsequent treatment	Dropdown 1, PD−progressive disease (An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started) | 2, SD−stable disease (Any cases that do not qualify for either partial response or progressive disease) | 3, PR−partial response (At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions) | 4, CR−complete response (Disappearance of any intratumoral arterial enhancement in all target lesions) | −99, Not recorded/not measurable
7.2.9	Date of response assessment to subsequent treatment	Date
7.2.10	Date complete response confirmed after subsequent treatment	Date
7.2.11	If complete response, was there a recurrence?	Dropdown 1, Yes | 2, No | −99, Unknown
7.2.12	Date of recurrence	Date
7.2.13	Type of recurrence: liver	Dropdown 1, Yes | 2, No | −99, Unknown
7.2.14	Liver recurrence	Dropdown 1, Local | 2, Distant | 3, Vascular invasion | −99, Unknown
7.2.15	Extrahepatic	Dropdown 1, Yes | 2, No | −99, Unknown
7.2.16	Where is the extrahepatic spread?	Text
7.2.17	Complications after subsequent treatment	Checkbox 1, rx_sub_complications___1 Liver related morbidity | 2, rx_sub_complications___2 Post procedural infections | 3, rx_sub_complications___3 Post procedural bleeding | 4, rx_sub_complications___4 Bile duct injury | 5, rx_sub_complications___5 Respiratory events | 6, rx_sub_complications___6 Local events | 7, rx_sub_complications___7 Other {compsub_other} | 8, rx_sub_complications___8 Systemic treatment (chemotherapy)
7.2.18	Other complications	Text
FORM STATUS		
7.3.1	Complete?	Dropdown 0, Incomplete | 1, Unverified | 2, Complete

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