

Supplementary materials

Supplementary Table 1 Treatment modalities at index presentation

	All (n = 104)	Synchronous (n = 59)	Sequential (n = 45)	P value
No treatment	2 (1.9)	2 (3.4)	0	0.21
Percutaneous ablation*	38 (36.5)	12 (20.3)	26 (57.8)	0.001
PEI	1 (1.0)	0	1 (2.2)	0.25
Resection	13 (12.5)	5 (8.5)	8 (17.8)	0.16
TACE[^]	23 (22.0)	19 (32.2)	4 (8.9)	0.005
Transplantation	2 (1.9)	2 (3.4)	0	0.21
Two modalities	24	18 (30.5)	6 (13.3)	0.04
Three or more modalities	1	1 (1.7)	0	0.38

Data are expressed as frequency (percentage).

*Inclusive of both radiofrequency ablation and microwave ablation.

[^]Inclusive of both conventional TACE and TACE with drug-eluting beads.

PEI: percutaneous ethanol injection; TACE: transarterial chemoembolisation

**Supplementary Table 2 Treatment modality of second lesion in the sequential group
(*n* = 45)**

	<i>n</i> (%)
No treatment	4 (8.9)
Percutaneous ablation*	14 (31.1)
PEI	0
Resection	2 (4.4)
TACE^	13 (28.9)
Transplantation	3 (6.67)
Two modalities	9 (20)
Three or more modalities	0

*Inclusive of both radiofrequency ablation and microwave ablation.

^Inclusive of both conventional TACE and TACE with drug-eluting beads.

PEI: percutaneous ethanol injection; TACE: transarterial chemoembolisation

Supplementary Table 3 Comparison of non-transplanted and transplanted patients

	Non-transplanted (n = 79)	Transplanted (n = 25)	P value
Age ^a	64 (6.5)	62	0.30
Gender ^b			0.69
Male	67 (84.8)	22 (88.0)	
Female	12 (15.2)	3 (12.0)	
Aetiology ^b			0.39
Alcohol	9 (11.4)	3 (12.0)	
HCV	29 (36.7)	13 (52.0)	
HBV	12 (15.2)	3 (12.0)	
NASH	4 (5.1)	1 (4.0)	
Alcohol & HCV	17 (21.5)	1 (4.0)	
Other*	8 (10.1)	4 (16.0)	
Cirrhosis status ^b			0.28
Non-cirrhotic	9 (11.4)	1 (4.0)	
Cirrhotic	70 (88.6)	24 (96.0)	
CTP score ^a	6 (2)	8 (4)	0.001
CTP class ^b			0.09
A	57 (72.2)	9 (36.0)	
B	18 (22.8)	7 (28.0)	
C	4 (5.1)	9 (36.0)	
MELD ^a	8 (5)	13 (6)	0.001
AFP (ug/L) ^a	9.8 (41.1)	7.8 (17.25)	0.46
Total tumour diameter (cm) ^a	3.6 (1.5)	3.1 (2.2)	0.50
Diameter of largest lesion (cm) ^a	2.2 (0.7)	2.0 (1.35)	0.50

Lesion group			0.08
Synchronous^a	41 (51.9)	18 (72.0)	
Sequential^a	38 (48.1)	7 (28.0)	
Death^a	32 (40.5)	4 (16.0)	0.02

Patient characteristics. Data are expressed as ^amedian (interquartile range) and ^bfrequency (percentage). AFP: alpha-feto protein, CTP: Child-Turcotte-Pugh, HBV: hepatitis B virus, HCV: hepatitis C virus, MELD: Model for End-Stage Liver Disease score, NASH: non-alcoholic steatohepatitis. *Other refers to aetiologies not listed here and is inclusive of: mixed aetiologies, autoimmune hepatitis, hereditary haemochromatosis, alpha-1-antitrypsin deficiency and cryptogenic liver disease

Supplementary Table 4 Univariate analysis of factors impacting overall survival

	<i>n</i> (%)	1-year survival (%)	3-year survival (%)	5-yr survival (%)	HR	95%CI	<i>P</i> value
Age (yr)							
< 70	86 (82.7)	94.0	71.0	68.9	-	-	-
≥ 70	18 (17.3)	88.9	46.7	37.3	2.19	1.08 - 4.45	0.03
Gender							
Male	89 (85.6)	95.4	68.5	64.3	-	-	-
Female	15 (14.4)	78.6	51.6	51.6	1.71	0.70 - 4.15	0.24
Aetiology							
Alcohol	12 (11.5)	100	54.7	54.7	-	-	-
HCV	42 (40.4)	95.1	66.6	62.7	0.79	0.29 - 2.20	0.56
HBV	15 (14.4)	86.7	65.0	65.0	0.86	0.25 - 2.96	0.81
NASH	5 (4.8)	80.0	80.0	40.0	1.44	0.34 - 6.05	0.62
Alcohol & HCV	18 (17.3)	94.1	51.6	51.6	1.38	0.43 - 4.38	0.59
Other*	12 (11.5)	90.9	90.9	90.9	0.35	0.07 - 1.80	0.21
Cirrhosis status							
Cirrhotic	94 (90.4)	93.4	66.7	62.6	-	-	-
Non-cirrhotic	10 (9.6)	90.0	54.0	54.0	0.92	0.28 - 3.01	0.89
CTP class							
A	66 (63.5)	98.4	62.7	59.4	-	-	-
B	25 (24)	84.0	66.7	60.6	1.23	0.58 - 2.59	0.60
C	13 (12.5)	92.3	76.9	76.9	0.73	0.25 - 2.14	0.57
MELD at diagnosis							
≤14	85 (81.7)	96.3	69.5	64.6	-	-	-
>14	19 (18.3)	78.9	50.8	50.8	1.87	0.89 - 3.90	0.10
AFP at diagnosis							
<10	58	92.8	69.0	61.5	-	-	-

≥10	46	93.4	62.9	62.9	1.17	0.61 - 2.25	0.64
Lesion group							
Synchronous	59 (56.7)	91.3	63.8	61.1	-	-	-
Sequential	45 (43.3)	95.3	69.5	64.6	0.75	0.38 - 1.49	0.41
Transplantation							
No	79 (76)	90.7	54.3	48.6	-	-	-
Yes	25 (24)	95.8	95.8	95.8	0.19	0.07 - 0.55	0.002

AFP: alpha-feto protein (ug/L), CTP: Child-Turcotte-Pugh, HBV: hepatitis B virus, HCV: hepatitis C virus, MELD: Model for End-Stage Liver Disease score, NASH: non-alcoholic steatohepatitis. *Other refers to aetiologies not listed here and is inclusive of: mixed aetiologies, autoimmune hepatitis, hereditary haemochromatosis, alpha-1-antitrypsin deficiency and cryptogenic liver disease

Supplementary Table 5 Multivariate analysis of factors impacting overall survival

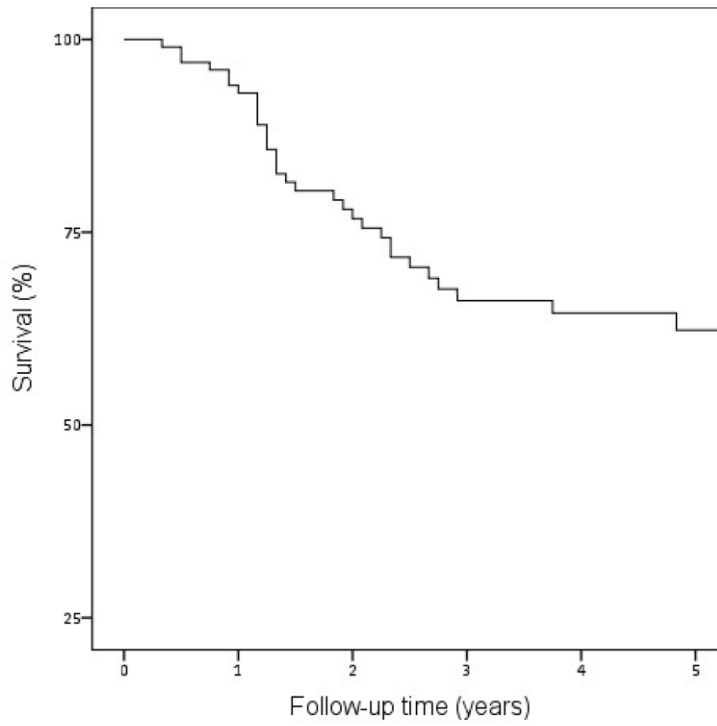
	<i>n</i> (%)	HR	95%CI	<i>P</i> value
Age				
Age ≤ 70	86 (82.7)	-	-	-
Age > 70	18 (17.3)	1.72	0.84 - 3.52	0.14
Liver transplantation				
Not transplanted	79 (76.0)	-	-	-
Transplanted	25 (24.0)	0.20	0.07 - 0.61	0.004

Supplementary Table 6 Univariate analysis of factors impacting transplant-free survival

	<i>n</i> (%)	1-year survival (%)	3-year survival (%)	5-yr survival (%)	HR	95%CI	<i>P</i> value
Age (yr)							
< 70	86 (82.7)	81.9	46.2	39.1	-	-	-
≥ 70	18 (17.3)	77.8	41.7	31.3	1.13	0.58 - 2.19	0.72
Gender							
Male	89 (85.6)	79.2	48.6	40.1	-	-	-
Female	15 (14.4)	64.3	23.4	23.4	1.63	0.79 - 3.34	0.18
Aetiology							
Alcohol	12 (11.5)	83.3	36.5	36.5	-	-	-
HCV	42 (40.4)	72.8	38.1	29.0	1.21	0.52 - 2.81	0.65
HBV	15 (14.4)	73.3	52.4	52.4	0.76	0.27 - 2.18	0.61
NASH	5 (4.8)	60.0	60.0	0	1.50	0.38 - 5.84	0.56
Alcohol & HCV	18 (17.3)	94.1	51.6	25.8	0.89	0.32 - 2.48	0.82
Other*	12 (11.5)	73.3	64.2	64.2	0.62	0.20 - 1.99	0.43
Cirrhosis status							
Non-cirrhotic	10 (9.6)	80.0	48.0	48.0	-	-	-
Cirrhotic	94 (90.4)	76.8	44.9	36.7	1.62	0.58 - 4.51	0.35
CTP class							
A	66 (63.5)	83.8	50.4	47.3	-	-	-
B	25 (24.0)	76.0	48.6	34.0	1.54	0.83 - 2.84	0.17
C	13 (12.5)	30.8	15.4	0	5.17	2.59 - 10.29	0.001
MELD at diagnosis							
≤14	85 (81.7)	84.0	53.1	45.9	-	-	-
>14	19 (18.3)	47.4	11.8	5.9	4.07	2.27 - 7.32	0.001
AFP at diagnosis							

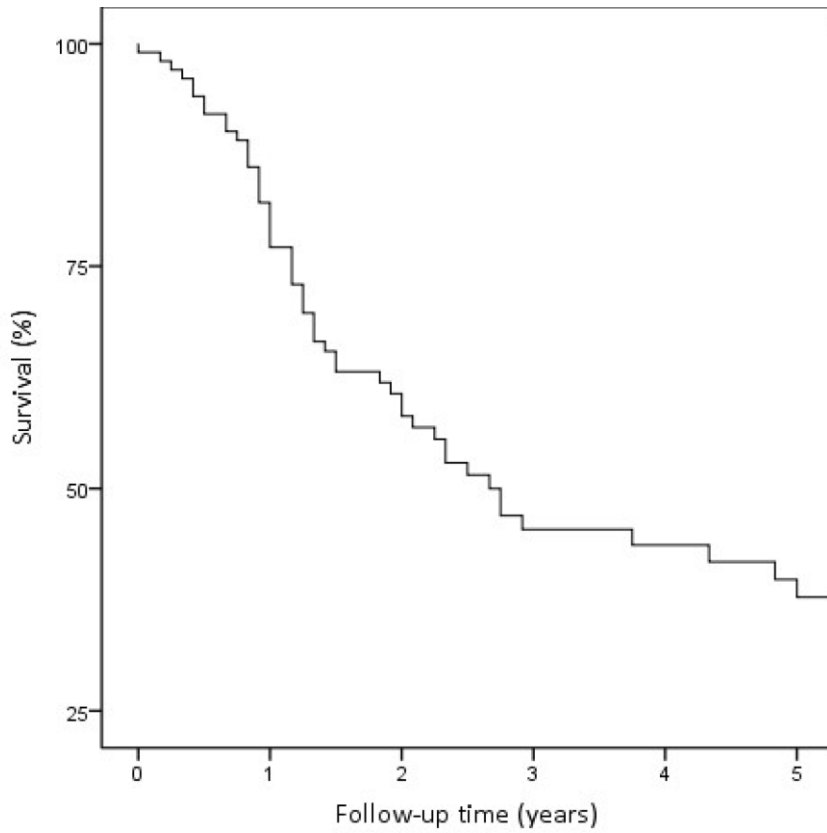
<10	58 (55.8)	81.9	46.8	37.0	-	-	-
≥10	46 (44.2)	78.0	44.2	39.3	1.18	0.70 - 2.01	0.53
Lesion group							
Synchronous	59 (56.7)	68.5	37.3	29.7	-	-	-
Sequential	45 (43.3)	93.2	56.6	48.5	0.53	0.31 - 0.92	0.02

AFP: alpha-feto protein (ug/L), CTP: Child-Turcotte-Pugh, HBV: hepatitis B virus, HCV: hepatitis C virus, MELD: Model for End-Stage Liver Disease score, NASH: non-alcoholic steatohepatitis. *Other refers to aetiologies not listed here and is inclusive of: mixed aetiologies, autoimmune hepatitis, hereditary haemochromatosis, alpha-1-antitrypsin deficiency and cryptogenic liver disease



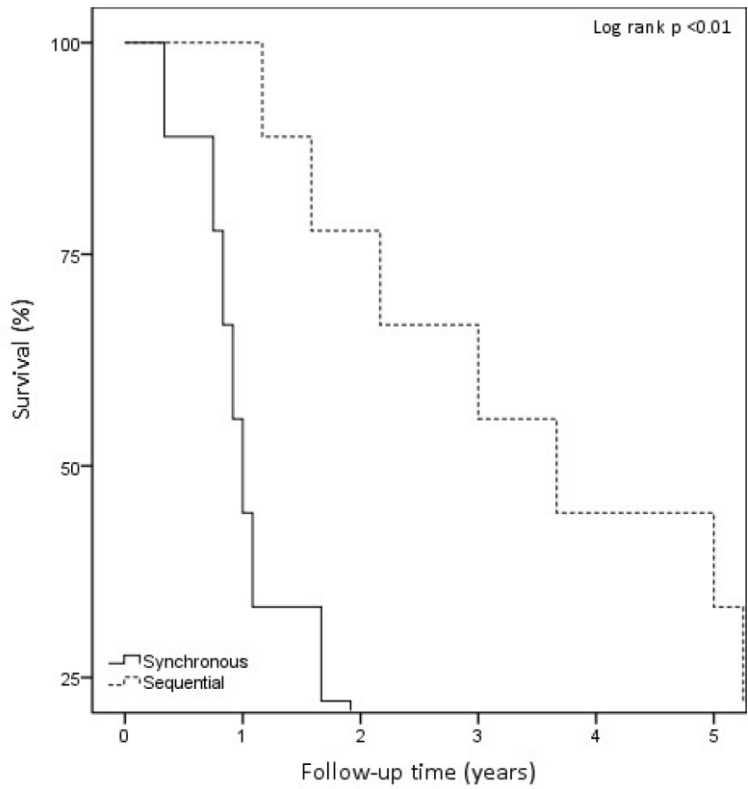
Time (years)	0	1	2	3	4	5
Number at risk (n)	104	93	63	44	37	27

Supplementary Figure 1 Kaplan Meier curve of overall survival curve for 104 patients with two hepatocellular carcinomas.



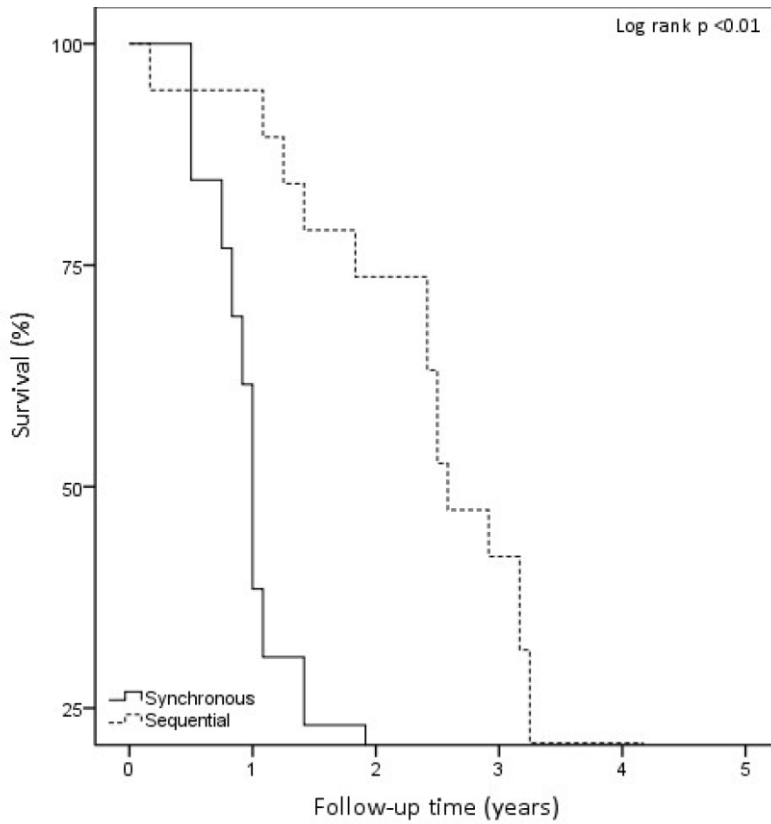
Time (years)	0	1	2	3	4	5
Number at risk (n)	104	77	46	29	24	19

Supplementary Figure 2 Kaplan-Meier curve of transplant-free survival for 104 patients with two hepatocellular carcinomas.



Time (years)	0	1	2	3	4	5
Number at risk						
Synchronous (n)	9	4	1	0	0	0
Sequential (n)	9	9	7	5	4	3

Supplementary Figure 3 Kaplan-Meier curve of progression-free survival (local recurrence) for synchronous compared to sequential groups.



Time (years)	0	1	2	3	4	5
Number at risk						
Synchronous (n)	13	5	2	0	0	0
Sequential (n)	19	18	14	8	4	2

Supplementary Figure 4 Kaplan-Meier curve of progression-free survival (new lesions) for synchronous compared to sequential groups.