

Supplementary Online Content

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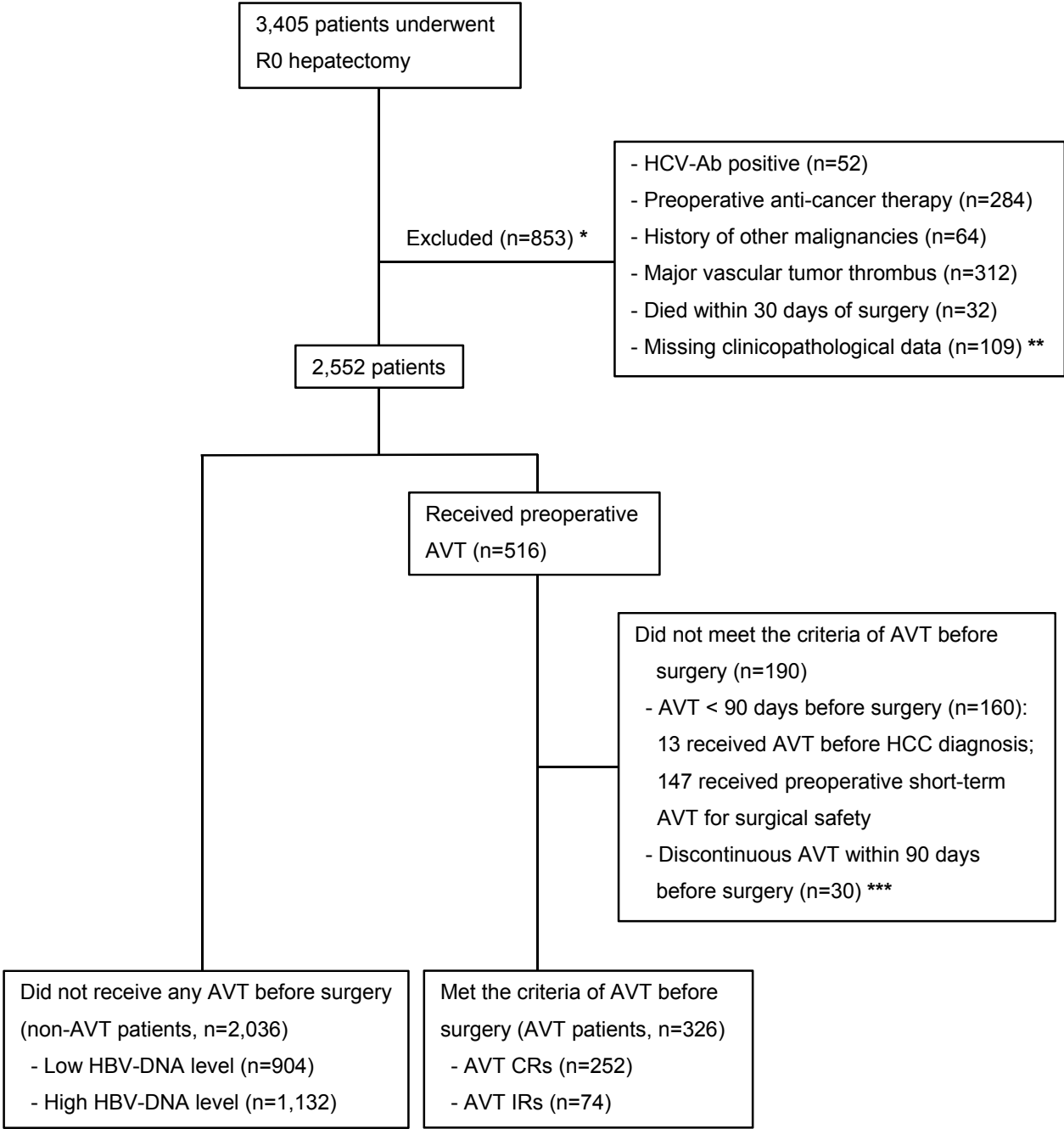
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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Flowchart of the study



Abbreviations: HCV-Ab, hepatitis C virus antibody; AVT, antiviral treatment; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; CRs, complete responders; IRs, incomplete responders.
 *: only the main reason for exclusion is presented.
 **: included incomplete clinicopathological data (n=59) and lost to follow-up (n=50).
 ***: due to side effects (n=11) and miscellaneous reasons (n=19).

eTable 1. Information on AVT medication

Medication	AVT patients (n=326)	Patients failed to meet preoperative AVT criteria (n=190)
Lamivudine	102 (31.3%)	11 (5.8%)
Lamivudine + Adefovir	28 (8.6%)	7 (3.7%)
Lamivudine + Entecavir	18 (5.5%)	9 (4.7%)
Adefovir	84 (25.8%)	72 (37.9%)
Entecavir	47 (14.4%)	56 (29.5%)
Telbivudine	20 (6.1%)	21 (11.1%)
Interferon alpha (conventional or pegylated)	11 (3.4%)	4 (2.1%)
Interferon alpha + nucleos(t)ide analogues	6 (1.8%)	2 (1.1%)
Other combinations	10 (3.1%)	8 (4.2%)

Abbreviation: AVT, antiviral treatment.

Drugs and dosage: lamivudine (GlaxoSmithKline) 100 mg per day; adefovir (GlaxoSmithKline) 10 mg per day; entecavir (Sino-American Squibb) 0.5 mg per day; telbivudine (Novartis) 600 mg per day; interferon alpha: conventional (3SBio Inc or Hualida Biotech) 5 MIU thrice weekly; pegylated (Roche) 180 µg once weekly.

eTable 2. Logistic regression analysis of MVI presence in non-AVT patients (n = 2036)

Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age, years (continuous)	0.985	0.977-0.994	.001			
Sex, male vs. female	1.160	0.913-1.475	.23			
Diabetes mellitus, yes vs. no	0.909	0.677-1.221	.53			
HBeAg, positive vs. negative	1.012	0.841-1.219	.90			
HBeAb, positive vs. negative	0.850	0.699-1.033	.10			
HBV-DNA level, IU/mL, ≥ vs. <2,000	1.345	1.128-1.603	.001	1.399	1.151-1.701	.001
ALT, U/L, > vs. ≤44	0.857	0.718-1.024	.09			
AST, U/L, > vs. ≤40	1.324	1.111-1.579	.002			
GGT, U/L, > vs. ≤64	1.198	1.007-1.426	.04			
TBIL, μmol/L, > vs. ≤17	0.953	0.780-1.164	.64			
ALB, g/L, < vs. ≥35	0.732	0.471-1.137	.17			
PT, seconds, > vs. ≤13	0.995	0.786-1.261	.97			
PLT, 10 ⁹ /L, < vs. ≥100	0.851	0.681-1.063	.16			
GLU, mmol/L, > vs. ≤7	0.789	0.551-1.130	.20			
Creatinine, μmol/L, > vs. ≤104	0.561	0.237-1.329	.19			
WBC, 10 ⁹ /L, < vs. ≥4	0.899	0.725-1.113	.33			
Hemoglobin, g/L (continuous)	1.000	0.995-1.006	.87			
AFP, μg/L, > vs. ≤400	2.392	1.987-2.879	<.001	1.622	1.319-1.995	<.001
Blood loss, mL, > vs. ≤800	1.416	0.963-2.083	.08			
Transfusion, yes vs. no	1.406	1.072-1.845	.01			
Surgical margin, cm, < vs. ≥1	1.087	0.883-1.339	.43			
Tumor diameter, cm (continuous)	1.083	1.057-1.109	<.001	1.040	1.011-1.069	.007
Tumor number, multiple vs. solitary	1.298	0.985-1.709	.06			
Tumor encapsulation, incomplete vs. complete	1.650	1.472-1.850	<.001	2.441	2.006-2.970	<.001
Satellite nodules, presence vs. absence	2.773	2.150-3.576	<.001	1.949	1.473-2.579	<.001
Edmondson-Steiner grade, III/IV vs. I/II	4.252	3.463-5.221	<.001	3.107	2.476-3.897	<.001
Cirrhosis, yes vs. no	1.347	1.131-1.603	.001	1.852	1.507-2.275	<.001

Abbreviations: MVI, microvascular invasion; AVT, antiviral treatment; OR, odds ratio; CI, confidence interval; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; HBV-DNA, hepatitis B virus deoxyribonucleic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; PLT, platelet count; GLU, glucose; WBC, white blood cell; AFP, alpha fetoprotein.

eTable 3. Incidence of MVI between AVT and non-AVT patients according to tumor size (n = 2362)

Tumor size	Non-AVT (%)	AVT (%)	P value
≤3 cm*	229/537 (42.6)	46/131 (35.1)	.12
≤5 cm	492/1133 (43.4)	77/225 (34.2)	.01
≤10 cm	820/1775 (46.2)	116/309 (37.5)	.005
>10 cm	169/261 (64.8)	10/17 (58.8)	.62

Abbreviations: MVI, microvascular invasion; AVT, antiviral treatment.

*: among all the patients who had tumor <3 cm (n=668), the incidence of MVI between the patients who received preoperative AVT ≥1 year (n=98) versus the patients who did not receive any preoperative AVT or received preoperative AVT <1 year (n=570) was 31.6% vs. 42.8% (P=.04).

eTable 4. Clinicopathological characteristics between CRs to AVT and non-AVT patients with a low viral level (n = 1156)

Variable	Number (%)/median (IQR)		
	Non-AVT with a low viral level (n=904)	AVT CRs (n=252)	P value
Age, years	50.0 (43.0–57.5)	50.0 (41.6-57.3)	.81
Sex, male	755 (83.5)	214 (84.9)	.59
Diabetes mellitus, yes	103 (11.4)	34 (13.5)	.36
HBeAg, positive	180 (19.9)	37 (14.7)	.06
HBeAb, positive	740 (81.9)	195 (77.4)	.11
HBV-DNA level, detectable (≥200 IU/mL)	70 (7.7)	21 (8.3)	.76
ALT, U/L, >44	286 (31.6)	73 (29.0)	.42
AST, U/L, >40	319 (35.3)	69 (27.4)	.02
GGT, U/L, >64	424 (46.9)	103 (40.9)	.09
TBIL, μmol/L, >17	228 (25.2)	66 (26.2)	.76
ALB, g/L, <35	26 (2.9)	6 (2.4)	.67
PT, seconds, >13	114 (12.6)	58 (23.0)	<.001
PLT, ×10 ⁹ /L, <100	149 (16.5)	74 (29.4)	<.001
GLU, mmol/L, >7	70 (7.7)	17 (6.7)	.60
Creatinine, μmol/L, >104	16 (1.8)	4 (1.6)	.84
WBC, ×10 ⁹ /L, <4	168 (18.6)	66 (26.2)	.008
Hemoglobin, g/L	143.0 (133.0-153.0)	144.0 (131.3-154.0)	.77
AFP, μg/L, >400	323 (35.7)	67 (26.6)	.007
Blood loss, mL, >800	56 (6.2)	7 (2.8)	.04
Transfusion, yes	108 (11.9)	18 (7.1)	.03
Adjuvant TACE, yes	292 (32.3)	86 (34.1)	.59
Postoperative AVT, yes	148 (16.4)	193 (76.6)	<.001
Surgical margin, cm, <1	675 (74.7)	189 (75.0)	.92
Tumor diameter, cm	4.6 (3.0-7.6)	3.7 (2.4-5.3)	<.001
Tumor number, multiple	92 (10.2)	25 (9.9)	.91
Tumor encapsulation, incomplete	490 (54.2)	110 (43.7)	.003
Microvascular invasion, presence	402 (44.5)	88 (34.9)	.007
Satellite nodules, presence	134 (14.8)	40 (15.9)	.68
Edmondson-Steiner grade, III/IV	616 (68.1)	155 (61.5)	.048
Cirrhosis, yes	415 (45.9)	164 (65.1)	<.001

Abbreviations: CRs, complete responders; AVT, antiviral treatment; IQR, interquartile range; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; HBV-DNA, hepatitis B virus deoxyribonucleic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; PLT, platelet count; GLU, glucose; WBC, white blood cell; AFP, alpha fetoprotein; TACE, transarterial chemoembolization.

eTable 5. Logistic regression analysis of MVI presence in CRs to AVT and non-AVT patients with a low viral level (n = 1156)

Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age, years (continuous)	0.993	0.982-1.004	.20			
Sex, male vs. female	1.061	0.772-1.458	.71			
Diabetes mellitus, yes vs. no	0.998	0.695-1.431	.99			
HBeAg, positive vs. negative	0.911	0.675-1.230	.54			
HBeAb, positive vs. negative	0.886	0.659-1.190	.42			
HBV-DNA level, detectable vs. undetectable	0.926	0.599-1.431	.73			
AVT, yes vs. no	0.670	0.501-0.896	.007	0.690	0.500-0.952	.02
ALT, U/L, > vs. ≤44	0.776	0.602-1.001	.051			
AST, U/L, > vs. ≤40	1.299	1.015-1.661	.04			
GGT, U/L, > vs. ≤64	1.147	0.908-1.450	.25			
TBIL, μmol/L, > vs. ≤17	1.026	0.785-1.341	.85			
ALB, g/L, < vs. ≥35	0.705	0.337-1.477	.36			
PT, seconds, > vs. ≤13	0.846	0.608-1.179	.32			
PLT, 10 ⁹ /L, < vs. ≥100	0.861	0.639-1.160	.33			
GLU, mmol/L, > vs. ≤7	0.862	0.551-1.349	.52			
Creatinine, μmol/L, > vs. ≤104	0.728	0.288-1.838	.50			
WBC, 10 ⁹ /L, < vs. ≥4	0.834	0.622-1.118	.23			
Hemoglobin, g/L (continuous)	1.001	0.994-1.008	.86			
AFP, μg/L, > vs. ≤400	2.939	2.285-3.781	<.001	2.173	1.652-2.857	<.001
Blood loss, mL, > vs. ≤800	1.877	1.123-3.135	.02			
Transfusion, yes vs. no	1.630	1.124-2.362	.01			
Surgical margin, cm, < vs. ≥1	0.924	0.707-1.208	.56			
Tumor diameter, cm (continuous)	1.080	1.046-1.115	<.001			
Tumor number, multiple vs. solitary	0.834	0.564-1.235	.37			
Tumor encapsulation, incomplete vs. complete	2.675	2.100-3.407	<.001	1.991	1.531-2.590	<.001
Satellite nodules, presence vs. absence	2.498	1.794-3.478	<.001	1.850	1.293-2.648	.001
Edmondson-Steiner grade, III/IV vs. I/II	3.905	2.954-5.164	<.001	2.815	2.079-3.812	<.001
Cirrhosis, yes vs. no	1.398	1.106-1.767	.005	1.902	1.460-2.478	<.001

Abbreviations: MVI, microvascular invasion; CRs, complete responders; AVT, antiviral treatment; OR, odds ratio; CI, confidence interval; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; HBV-DNA, hepatitis B virus deoxyribonucleic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; PLT, platelet count; GLU, glucose; WBC, white blood cell; AFP, alpha fetoprotein.

eTable 6. Cox regression analysis of OS and tumor recurrence in AVT and non-AVT patients (n = 2362)

Variable	OS						Tumor recurrence					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age, years (continuous)	1.002	0.995-1.009	.53				0.998	0.993-1.003	.41			
Sex, male vs. female	1.208	0.991-1.472	.06				1.171	1.016-1.349	.03			
Diabetes mellitus, yes vs. no	1.194	0.969-1.471	.10				0.913	0.771-1.081	.29			
HBeAg, positive vs. negative	1.266	1.097-1.460	.001	1.262	1.092-1.460	.002	1.301	1.169-1.448	<.001	1.309	1.174-1.459	<.001
HBeAb, positive vs. negative	0.853	0.735-0.989	.04				0.822	0.736-0.919	.001			
HBV-DNA level, IU/mL, ≥ vs. <2,000	1.261	1.100-1.446	.001				1.243	1.123-1.376	<.001			
AVT, yes vs. no	0.641	0.510-0.805	<.001	0.752	0.598-0.947	.02	0.677	0.577-0.796	<.001	0.764	0.649-0.899	.001
ALT, U/L, > vs. ≤44	1.294	1.128-1.483	<.001				1.287	1.161-1.426	<.001			
AST, U/L, > vs. ≤40	1.809	1.578-2.073	<.001	1.237	1.057-1.449	.008	1.561	1.410-1.729	<.001	1.129	1.004-1.268	.04
GGT, U/L, > vs. ≤64	1.689	1.471-1.939	<.001	1.174	1.003-1.373	.045	1.557	1.406-1.724	<.001	1.193	1.064-1.338	.002
TBIL, μmol/L, > vs. ≤17	1.131	0.970-1.320	.12				1.049	0.934-1.178	.42			
ALB, g/L, < vs. ≥35	1.515	1.126-2.040	.006	1.366	1.009-1.849	.04	1.337	1.051-1.699	.02			
PT, seconds, > vs. ≤13	1.169	0.983-1.390	.08				1.078	0.945-1.230	.26			
PLT, 10 ⁹ /L, < vs. ≥100	1.060	0.898-1.252	.49				1.041	0.920-1.178	.52			
GLU, mmol/L, > vs. ≤7	1.270	0.986-1.636	.06				1.018	0.830-1.248	.86			
Creatinine, μmol/L, > vs. ≤104	1.134	0.608-2.115	.69				0.750	0.443-1.269	.28			
WBC, 10 ⁹ /L, < vs. ≥4	0.882	0.744-1.046	.15				0.961	0.850-1.087	.53			
Hemoglobin, g/L (continuous)	0.995	0.991-0.999	.02				0.999	0.996-1.002	.53			
AFP, μg/L, > vs. ≤400	1.657	1.444-1.901	<.001	1.247	1.080-1.440	.003	1.428	1.286-1.585	<.001	1.159	1.039-1.292	.008
Blood loss, mL, > vs. ≤800	2.328	1.824-2.970	<.001				1.819	1.479-2.238	<.001			
Transfusion, yes vs. no	2.117	1.764-2.542	<.001	1.351	1.105-1.652	.003	1.693	1.458-1.966	<.001	1.199	1.020-1.411	.03
Adjuvant TACE, yes vs. no	1.095	0.951-1.261	.21				1.111	0.999-1.234	.052			

Postoperative AVT, yes vs. no	0.856	0.737-0.995	.04				0.897	0.803-1.001	.053			
Surgical margin, cm, < vs. ≥1	1.732	1.438-2.085	<.001	1.259	1.036-1.531	.02	1.594	1.399-1.816	<.001	1.270	1.107-1.458	.001
Tumor diameter, cm (continuous)	1.109	1.092-1.126	<.001	1.051	1.030-1.071	<.001	1.087	1.074-1.100	<.001	1.041	1.025-1.057	<.001
Tumor number, multiple vs. solitary	1.603	1.326-1.938	<.001	1.440	1.186-1.748	<.001	1.446	1.247-1.677	<.001	1.291	1.110-1.502	.001
Microvascular invasion, presence vs. absence	1.907	1.661-2.189	<.001	1.518	1.310-1.758	<.001	1.655	1.495-1.833	<.001	1.392	1.248-1.552	<.001
Tumor encapsulation, incomplete vs. complete	1.374	1.198-1.576	<.001				1.277	1.153-1.413	<.001			
Satellite nodules, presence vs. absence	1.910	1.618-2.254	<.001	1.321	1.111-1.571	.002	1.859	1.636-2.112	<.001	1.413	1.236-1.616	<.001
Edmondson-Steiner grade, III/IV vs. I/II	2.062	1.750-2.429	<.001	1.385	1.159-1.655	<.001	1.650	1.472-1.849	<.001	1.206	1.065-1.366	.003
Cirrhosis, yes vs. no	0.849	0.741-0.973	.02				0.946	0.855-1.047	.28			

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; HBV-DNA, hepatitis B virus deoxyribonucleic acid; AVT, antiviral treatment; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; PLT, platelet count; GLU, glucose; WBC, white blood cell; AFP, alpha fetoprotein; TACE, transarterial chemoembolization.

eTable 7. Tumor recurrence and OS between AVT and non-AVT among patients with MVI (n = 1115)

Groups		Early tumor recurrence				Overall tumor recurrence				OS			
		6-month (%)	1-year (%)	2-year (%)	P value	1-year (%)	3-year (%)	5-year (%)	P value	1-year (%)	3-year (%)	5-year (%)	P value
All	Non-AVT (n=989)	30.7	46.6	62.4	.003	46.6	70.5	77.2	.009	82.0	59.6	47.0	.02
	AVT (n=126)	20.7	33.9	49.3		34.1	59.8	70.0		91.1	68.3	59.2	
≤3 cm	Non-AVT (n=229)	16.2	30.4	46.1	.23	30.3	56.6	66.0	.21	91.6	77.7	65.9	.73
	AVT (n=46)	13.0	24.2	36.3		24.4	44.9	56.8		93.3	79.4	70.8	
≤5 cm	Non-AVT (n=492)	21.2	37.1	53.6	.045	37.1	61.8	69.6	.053	88.7	70.8	58.2	.34
	AVT (n=77)	14.3	27.7	41.2		28.0	50.5	59.8		92.0	73.8	65.9	
≤10 cm	Non-AVT (n=820)	26.3	43.0	59.4	.02	43.0	67.7	75.3	.04	84.7	63.4	51.1	.10
	AVT (n=116)	19.0	33.1	47.7		33.5	59.1	68.6		93.0	69.2	59.4	
>10 cm	Non-AVT (n=169)	52.1	63.9	76.9	.46	63.9	84.5	86.4	.48	69.1	41.2	26.8	.29
	AVT (n=10)	42.1	42.1	70.0		42.1	67.8	89.3		70.0	58.3	58.3	

Abbreviations: OS, overall survival; AVT, antiviral treatment; MVI, microvascular invasion.

eTable 8. Multivariate Cox regression analysis of tumor recurrence and OS between AVT and non-AVT among patients with MVI (n = 1115)

Variable	Early tumor recurrence			Overall tumor recurrence			OS		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
HBeAg , positive vs. negative	1.337	1.137-1.572	<.001	1.390	1.199-1.612	<.001	1.408	1.164-1.703	<.001
AVT , yes vs. no	0.717	0.548-0.938	.02	0.787	0.622-0.996	.046			
AST , U/L, > vs. ≤40				1.174	1.008-1.367	.04			
GGT , U/L, > vs. ≤64							1.262	1.033-1.542	.02
ALB , g/L, < vs. ≥35				1.441	1.015-2.046	.04			
AFP , µg/L, > vs. ≤400	1.422	1.217-1.662	<.001	1.327	1.151-1.530	<.001	1.376	1.143-1.656	.001
Transfusion , yes vs. no							1.296	1.002-1.675	.048
Surgical margin , cm, < vs. ≥1	1.508	1.211-1.877	<.001	1.390	1.147-1.683	.001	1.448	1.104-1.900	.008
Tumor diameter , cm (continuous)	1.050	1.030-1.070	<.001	1.039	1.020-1.059	<.001	1.051	1.026-1.076	<.001
Tumor number , multiple vs. solitary							1.498	1.170-1.920	.001
Satellite nodules , presence vs. absence	1.414	1.187-1.684	<.001	1.487	1.263-1.750	<.001	1.245	1.009-1.537	.04
Edmondson-Steiner grade , III/IV vs. I/II	1.335	1.055-1.688	.02	1.240	1.011-1.520	.04	1.687	1.243-2.290	.001

Abbreviations: OS, overall survival; AVT, antiviral treatment; MVI, microvascular invasion; HR, hazard ratio; CI, confidence interval; HBeAg, hepatitis B e antigen; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; ALB, albumin; AFP, alpha fetoprotein.