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Analysis of Recurrence Pattern after Partial Hepatectomies for Hepatocellular Carcinoma

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Aims

- The long-term outcome of HCC after resection were improved in these years and patients with recurrence should be treated with different strategies based on the regional recurrence or distant metastasis.
- Recurrence could be adjacent sector, multiple intrahepatic or distant metastasis, but the clinical relevance between the recurrence pattern and perioperative events were rarely studied. The aim of this study is to analysis the impact of recurrence pattern on HCC patient outcome.

Methods

- Of 764 HCC patients enrolled Linkou and Tucheng hospital from 2012 to 2021 March, 10(1.3%) developed hospital mortality. The demographic data was compatible with our previous studies; male 76.7% , diabetes 26.5%, HBV 59.3%, HCV 26.7%, Most were Child A patients.
- Overall 49.7% developed recurrence and 31.5% with cancer-specific mortality in the long-term follow-up.
- Recurrent patterns were classified as section margin and adjacent segment, multiple intrahepatic and distant mets. Cox regression and log rank tests were performed for disease-free and overall survival.

Demographic data of 746 HCC patients, comparison of recurrence pattern

Margin and adjacent sector 244 (32.4%)

Multiple intrahepatic 51 (6.8%)

Distant metastasis 80 (10.6%)

Variables	All (n=754)	No (n=379)	TYPE I (n=244)	TYPE II (n=51)	TYPE III (n=80)	p
Age	61.9 ± 11.0	62.1 ± 11.1	62.1 ± 10.7	60.3 ± 11.1	61.7 ± 11.9	0.730
Gender (male)	578 (76.7)	274 (72.3)	198 (81.1)	40 (78.4)	66 (82.5)	0.039*
Comorbidity(yes)	444 (58.4)	210 (55.4)	155 (63.56)	33 (64.7)	42 (52.5)	0.111
HBV positive	447 (59.3)	218 (57.5)	148 (60.7)	33 (64.7)	48 (60.0)	0.725
HCV positive	201 (26.7)	100 (26.4)	73 (29.9)	9 (17.6)	19 (23.8)	0.283
ICG R15	10.2 ± 8.0	9.7 ± 7.5	11.6 ± 10.4	9.6 ± 7.1	10.8 ± 9.7	0.073
Major hepatectomy	228 (30.2)	94 (24.8)	67 (27.5)	24 (47.1)	43 (53.8)	<0.001***
Complication (yes)	50 (6.7)	22 (5.8)	16 (6.6)	5 (9.8)	7 (8.8)	0.618
ALP (IU/L)	85.6 ± 46.7	82.3 ± 47.0	88.8 ± 50.4	98.4 ± 47.8	82.8 ± 28.3	0.074
AST(IU/L)	42.8 ± 26.7	39.5 ± 23.2	44.4 ± 27.1	49.2 ± 29.9	49.6 ± 35.7	0.002**
ALT(IU/L)	42.9 ± 36.8	40.8 ± 34.1	45.2 ± 41.5	46.7 ± 31.6	43.4 ± 36.9	0.428
BIL (mg/dl)	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.2	0.8 ± 0.4	0.027*
ALB(g/dl)	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	4.1 ± 0.4	4.2 ± 0.4	0.069
AFP (ng/ml)	3329.0 ± 25085.4	1468.7 ± 12505.9	1969.7 ± 8287.0	4848.3 ± 20970.3	15319.6 ± 67755.4	<0.001***
AFP (>1000ng/ml)	82 (10.9)	30 (7.9)	31 (12.7)	6 (11.8)	18 (18.8)	0.195

Variables	All (n=754)	No (n=379)	TYPE I (n=244)	TYPE II (n=51)	TYPE III (n=80)	p
Cirrhosis	355 (47.1)	153 (40.4)	139 (57.0)	23 (45.1)	40 (50.0)	0.001**
Satellite lesion						<0.001**
No	668 (88.6)	357 (94.2)	208 (85.2)	39 (76.5)	64 (80.0)	
Single	53 (7.0)	14 (3.7)	19 (7.8)	10 (19.6)	10 (12.5)	
Multiple	33 (4.4)	8 (2.1)	17 (7.0)	2 (3.9)	6 (7.5)	
Vascular inv.						<0.001**
No	481 (63.8)	279 (73.6)	149 (61.1)	24 (47.1)	29 (36.3)	
Microscopic	233 (30.9)	91 (24.0)	78 (32.0)	24 (47.1)	40 (50.0)	
Gross	40 (5.3)	9 (2.4)	17 (7.0)	3 (5.9)	11 (13.8)	
Margin <0.5cm	408 (54.1)	195 (51.5)	143 (58.6)	28 (54.9)	42 (52.5)	0.367
Size>5cm	212 (28.1)	79(20.8)	59 (24.2)	26 (51.0)	48 (60.0)	<0.001**
Tumor size (cm)	4.5 ± 3.2	3.9 ± 2.8	4.4 ± 3.1	5.9 ± 3.6	6.9 ± 3.9	<0.001**
Rupture	48 (6.4)	15 (4.0)	12 (4.9)	8 (15.7)	13 (16.3)	0.074
Grade III, IV	308 (41.0)	138 (36.4)	104 (43.2)	19 (37.3)	47 (58.8)	0.002
AJCC 8 staging						<0.001
I	403 (53.5)	249 (65.7)	115 (47.1)	18 (35.3)	21 (26.3)	
II	227 (30.1)	100 (26.4)	85 (34.8)	15 (29.4)	27 (33.8)	
III	124 (16.4)	30 (7.9)	44 (18.0)	18 (35.3)	32 (40.0)	

The analysis of recurrence patten

No recurrence 379 (50.3%)

I: Margin and adjacent sector 244 (32.4%)

II: Multiple intrahepatic 51 (6.8%)

III: Distant metastasis 80 (10.6%)

DFS 35.2 ± 30.0 (m)

49.7 ± 30.6

24.8 ± 23.0

15.0 ± 14.1

10.9 ± 12.8

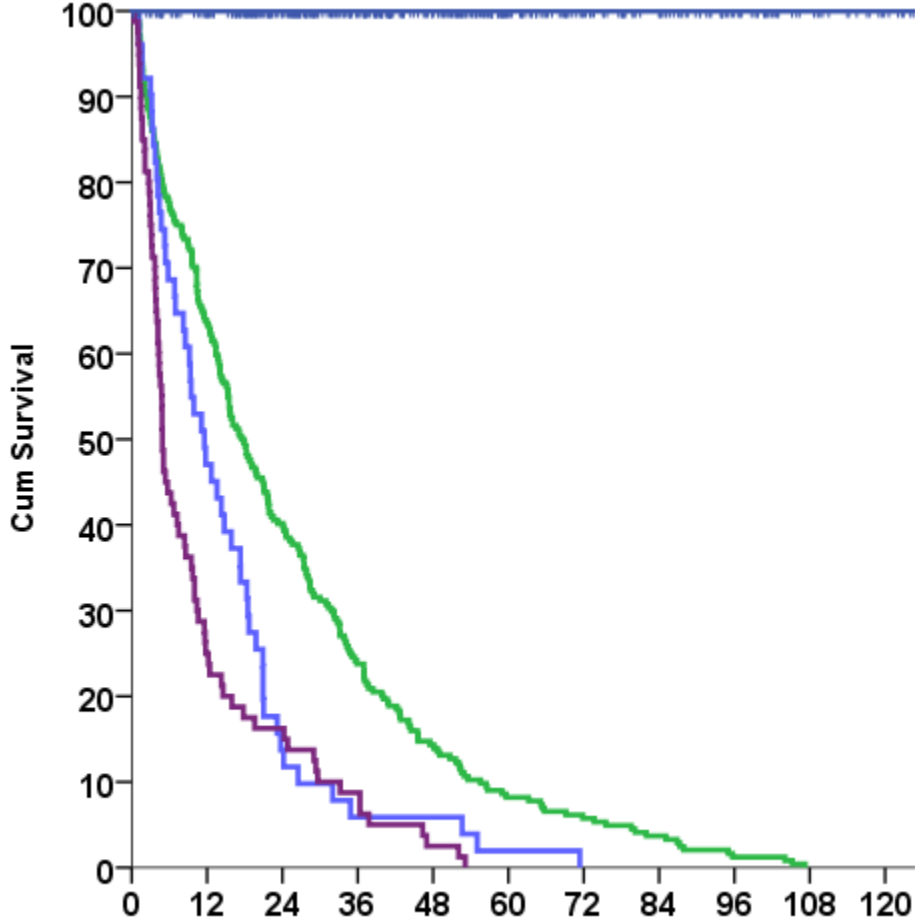
OS 51.2 ± 31.7 (m) p<0.001

51.1 ± 30.3

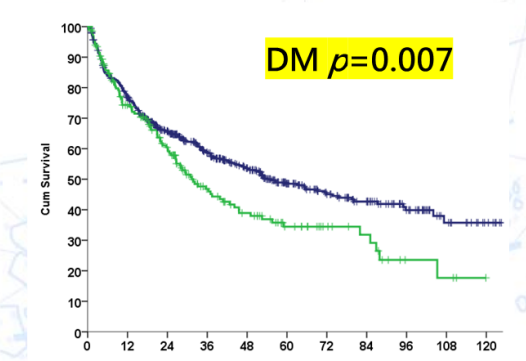
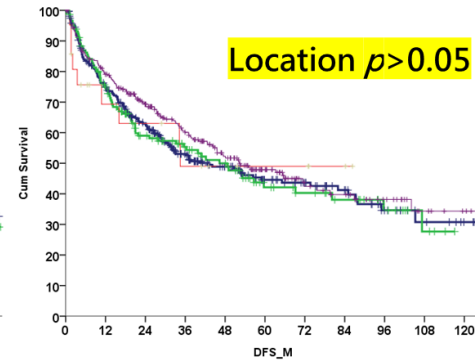
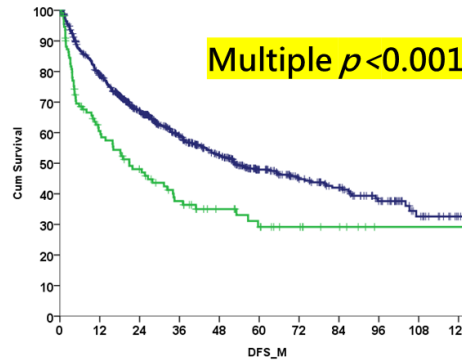
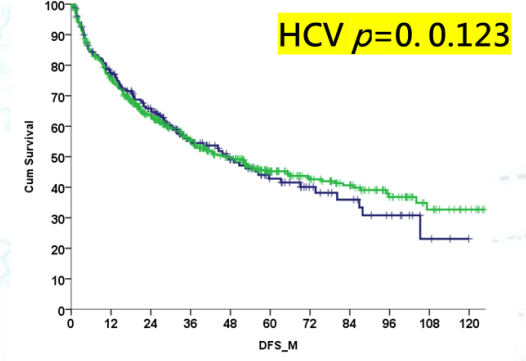
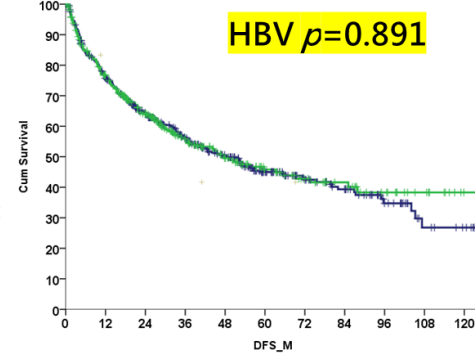
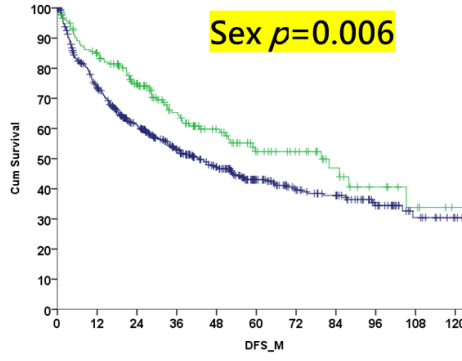
59.5 ± 32.9

39.1 ± 29.0

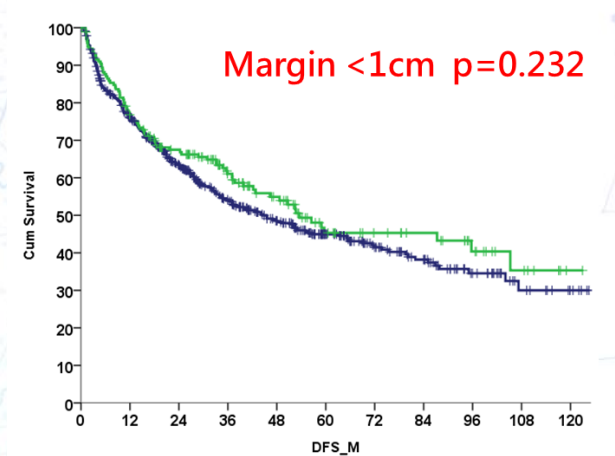
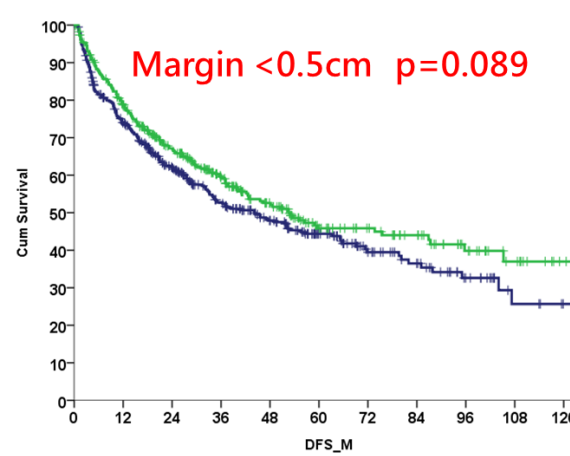
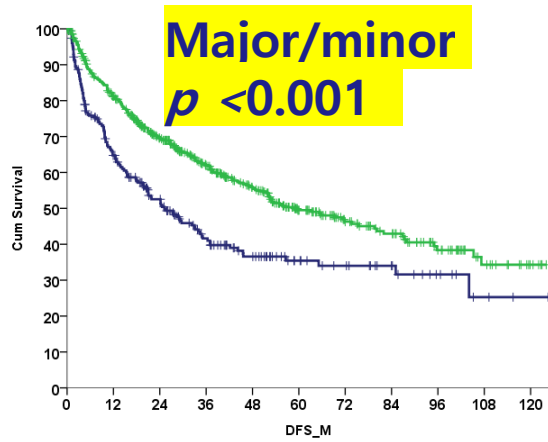
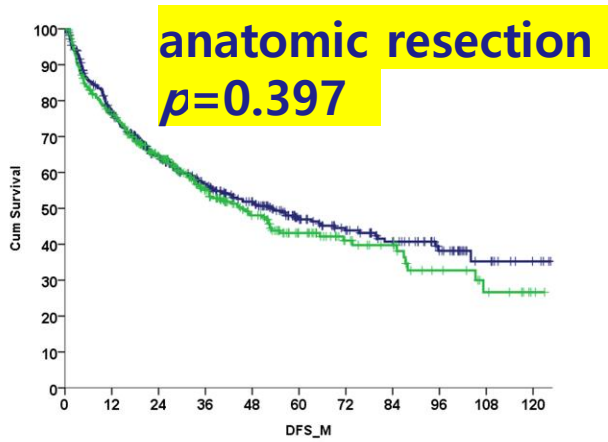
33.6 ± 26.6



Host factors and recurrence-free survival



Operative factors with Disease-free survival



Margin	n
Involved	27 (3.6%)
$< 0.5\text{ cm}$	381 (54.5%)
0.5-1 cm	157 (22.1%)
1-2 cm	124 (16.4%)
$> 2\text{ cm}$	55 (7.3%)

Margin, RFS(yr)	n	1	3	5	10
$< 0.5\text{ cm}(\%)$	408	74.0	52.8	44.4	25.7
$\geq 0.5\text{ cm}$	346	78.8	59.5	45.9	37.0
$< 1\text{ cm}$	575	76.0	54.2	45.0	30.0
$\geq 1\text{ cm}$	179	76.8	61.8	45.3	35.3

No difference of disease-free survival between narrow and wide resection margin

The analysis of overall survival

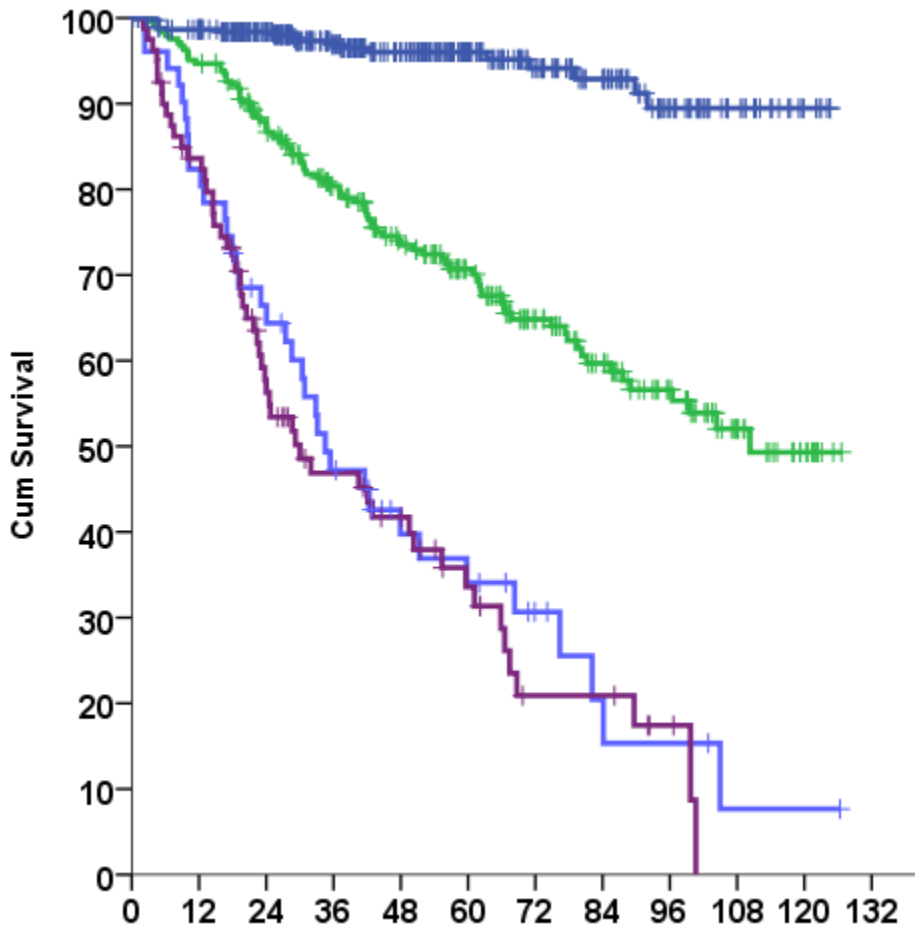
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I: Margin and adjacent sector 244 (32.4%)

II: Multiple intrahepatic 51 (6.8%)

III: Distant metastasis 80 (10.6%)

DFS	35.2 ± 30.0 (m)	OS	51.2 ± 31.7 (m)	p<0.001
	49.7 ± 30.6		51.1 ± 30.3	
	24.8 ± 23.0		59.5 ± 32.9	
	15.0 ± 14.1		39.1 ± 29.0	
	10.9 ± 12.8		33.6 ± 26.6	



- No difference of recurrence-free survival between narrow and wide resection margin.
- Distant recurrence is associated with early recurrence, whereas local recurrence detected later. (10.9 m vs. 15.0 vs. 24.8 m)

Table. Clinicopathologic data of 754 HCC patients in univariate and multivariate regression analysis for overall survival (OS)

- Diabetes, Surgical complication, AJCC staging and recurrence pattern were the independent prognostic factors for overall survival
- Recurrence should be addressed in surgical patients outcome

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (60 years) >60 vs. ≤60	1.101	0.826-1.462	0.507			
Sex (M/F) M vs. F	1.393	0.962-2.016	0.079			
Diabetes Yes vs. No	1.568	1.159-2.121	0.004**	1.657	1.214-2.263	0.001**
Comorbidity Yes vs. No	1.276	0.953-1.707	0.102			
ICG-R15 (10%) Higher vs. lower	1.060	0.737-1.524	0.754			
AST (68 U/L) Higher vs. lower	1.934	1.351-2.768	<0.001***	1.249	0.847-1.842	0.263
ALT (72 U/L) Higher vs. lower	1.319	0.884-1.970	0.175			
AFP (1000ng/ml) Higher vs. lower	1.755	1.201-2.565	0.004**	1.142	0.760-1.716	0.522
Major hepatectomy Yes vs. No	1.893	1.418-2.525	<0.001***	1.075	0.762-1.517	0.678
Anatomic resection Yes vs. No	1.072	0.807-1.424	0.630			
Close margin Yes vs. No	1.280	0.962-1.706	0.091			
Complication Yes vs. No	2.617	1.692-4.048	<0.001***	2.086	1.307-3.329	0.002**
Tumor size (cm) >5.0 vs. ≤5.0	2.758	2.076-3.665	<0.001***	1.271	0.865-1.866	0.222
Satellite lesions Multiple vs. single vs. no	1.766	1.478-2.236	<0.001***	0.997	0.757-1.313	0.982
Vascular invasion Thrombus vs. microscopic vs. no	1.818	1.478-2.236	<0.001***	0.913	0.669-1.245	0.565
Grading I/ II/ III, IV III, IV vs. I, II	1.411	1.064-1.872	0.017*	1.138	0.840-1.543	0.404
Tumor rupture Yes vs. No	2.322	1.502-3.589	<0.001	0.646	0.378-1.103	0.109
Cirrhosis Yes vs. No	1.478	1.110-1.968	0.007**	1.223	0.900-1.331	0.198
AJCC 8th Stage^a III vs. II vs. I	2.008	1.685-2.393	<0.001***	1.474	1.086-2.001	0.013**
Recurrence type III vs. II vs. I	2.144	1.919-2.395	<0.001***	1.955	1.733-2.205	<0.001***

Conclusion

- No difference of recurrence-free survival between narrow and wide resection margin.
- Distant recurrence is associated with early recurrence, whereas local recurrence detected later. (10.9 m vs. 24.4 m)
- Improved in overall survival but distant recurrence had poorer long-term outcome.
- Distant recurrence is associated with aggressive tumor biology.
- Local recurrence is associated with satellite lesions and cirrhosis.
- Recurrence pattern is associated with tumor biology (size , grading, AFP level, vascular invasion and satellite lesions) and very important in surgical patients long-term outcome.