의학석사 학위논문

간암 절제술을 시행한 환자에서 수술 후 감시 프로토콜을 확립하기 위한 시간적 및 형태학적 재발 패턴에 관한 연구

An investigation of chronological and morphological recurrence patterns to determine postoperative surveillance protocol in patients undergoing surgical resection for hepatocellular carcinoma

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이 논문을 의학석사 학위 논문으로 제출함

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Abstract

Backgrounds and Aims: In spite of the noticeably common recurrence after resection of HCC, little evidence exists to directly inform reasonable frequency of postoperative surveillance for recurrence. We aimed to present the pattern of annual recurrence rates through 10 years in patients with HCC who were typically good candidates for hepatectomy, and identify prognostic determinants and outcomes according to period of recurrence.

Method: This study included 1,659 patients with Child-Pugh A liver function who had solitary HCCs detected under surveillance and underwent curative resection for the tumors, followed by screening for recurrence every 3-6 months at Asan Medical Center between 2007 and 2015. Chronologic recurrence rates in yearly intervals after resection were calculated. Risk factors, tumor characters, and prognostic relevance of the early and late periods of recurrences were also examined.

Results: During a median follow-up of 5.8 years, HCCs recurred in 801 (48.3%) surgical patients. An estimated recurrence rate per year peaked during the first year (19.7%/year), then steeply decreased until year 4 (6.2%/year) and thereafter, reached a plateau until the end of study at an average yearly rate of 5.5% at year 5 to 10. Multivariate Cox regression analyses of time-to-recurrence according to the relapse period by a cutoff time point of postoperative 4 years revealed that male gender, tumor size, serum AFP, and invasive pathologic findings; and male gender and cirrhosis were independent predictors of disease recurrence within and after 4 years after resection, respectively (All *Ps*<0.05). The greater proportions of multiple and metastatic recurrences were observed in the early 4-year phase (26.0% vs. 13.9%; and 9.9% vs. 3.8%; *P*<0.05 for both). The 5-year overall survival rate after initial recurrence was significantly lower in patients with disease recurred in the early period (58.1% vs. 85.1%, *P*<0.001).

Conclusions: Our study provides chronologic and morphologic patterns of recurrent HCC after curative surgical resection. This knowledge may help implement optimal

surveillance protocol specific for postoperative period in such patients.

Keywords: Hepatocellular carcinoma; recurrence pattern; surveillance

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Introduction

Hepatic resection is one of the potentially curative therapies in patients with hepatocellular carcinoma (HCC) with preserved hepatic function. However, given that HCC recurrences after surgery occur cumulatively up to 70% at five years, regular surveillance in the postoperative phase is a crucial approach for early detection of treatable recurrence followed by long-term survival (1, 2).

The timing of recurrence has generally been associated with biological factors indicative of tumor aggressiveness with a more negative effect of early episode on prognosis (3-7). Early recurrence appears to arise mainly from intrahepatic metastasis, whereas late recurrence is more likely to be a representation of a metachronous lesion related to underlying liver disease (8-11). Genetic or molecular studies of the clonal origin of recurrent HCCs more distinctively differentiate tumor characteristics between disease recurrences at early and late intervals from resection (12, 13).

Previous post-surgical investigations reported the second-peaked incidence of recurrence occurring around 4 years after HCC resection, which was thought to be mainly attributable to second primary tumors from the more carcinogenic background liver (8, 9). Most updated global guidelines only introduce the 1st to 2nd year recommendation for follow-up after resection at 3-4 month intervals, albeit not based on evidence but on practice (2, 14). However, there is no formal consensus on regular post-resection surveillance for recurrent HCC in chronological order.

In these circumstances, we examined the pattern of recurrence rate per year over time in a large set of HCC patients with an ideal surgical indication selected from a preconstructed hospital registry; and explored clinicopathological factors related to early and late recurrence of resected HCC. On the basis of findings driven from these analyses, we finally intended to propose a risk-based surveillance strategy for patients standardly undergoing hepatectomy for HCC.

Methods

Study population

From 2007 to 2015, all 2,554 consecutive patients older than 19 years who curatively underwent primary hepatic resection for HCC by radiologic examination at Asan Medical Center were screened and considered for inclusion of clinical study analyses. All included patients had been under regular surveillance prior to HCC diagnosis. Curative resection was individually confirmed by post-surgical pathology, which was principally defined as a local radical procedure (R0) with tumor-negative resection margins without gross vascular invasion or directly invaded adjacent organ. In order to include nearly ideal candidates for surgical resection in our analysis, the following exclusion criteria were used (2, 15): patients were excluded if they had 1) Child-Pugh class B or C liver function (n=32); 2) any preoperative adjuvant or bridging therapy (n=17); 3) any postoperative HCC treatment (n=58); 4) concomitant other cancers (n=36), 5) multiple HCC nodules on preoperative images (n=118), 6) Barcelona clinic liver cancer (BCLC) stage B, C, or D (n=591), and 7) Not R0 resection confirmed by post-operative pathology (n=43). Consequently, a total of 1,659 patients with single HCCs of any size and well-preserved liver function were eligible for the study **(Figure 1)**. There were no patients with receipt of adjuvant chemotherapy after surgery; or severe renal or cerebro-cardiovascular disorders or uncontrolled metabolic disease, which might have led to death unrelated to the underlying liver disease. Ethical approval for our research protocol involving the study of human subjects and tumor transcriptomes was obtained from the Asan Medical Center Institutional Review Board (IRB No., 2019-0694).

Staging work-ups and follow-up after surgery

The evaluation and management processes employed by our surgical team pre- and post-hepatectomy were as previously described (16). Briefly, pre-operative procedures included multiphase liver computed tomography (CT) and/or magnetic

resonance imaging (MRI) and chest CT and bone scans for staging of intra- and extra-hepatic tumor extension, in addition to measurement of detailed laboratory tests and serum alpha-fetoprotein (AFP) levels. After surgery, all patients were routinely followed up with liver protocol dynamic CT/MRI scans covering most of the chest, as well as blood tests including AFP assay. These assessments were continuously performed at an interval of 3-6 months until a recurrent lesion appeared, or a patient became lost to follow-up. Apart from pathologic diagnosis, intrahepatic recurrence found in the follow-up of a patient was diagnosed for a new nodule with typical imaging hallmarks of HCC, or a newly detected or growing nodule with positive ancillary imaging features favoring HCC. During surveillance after resection, extrahepatic recurrence was identified by CT or MRI studies in cases with symptoms attributable to metastatic lesions or abnormal elevation of serum AFP without evidence of intrahepatic recurrence (17-19).

Clinical endpoints and variables

The primary endpoints of this study were annual recurrence rate and time to first recurrence (TTR) after surgery. The secondary endpoint was overall survival after initial recurrence of HCC. In order to examine risk factors of recurrence, we used demographic (age of diagnosis, gender, exposure of alcohol and smoking, and comorbid illnesses such as hypertension and diabetes), clinic-laboratory (etiology of liver disease, Child-Pugh score, serial AFP level, and other various blood tests), and histologic factors (size of tumor, multiplicity of lesions not diagnosable on a radiograph, satellite lesions defined as tumor cells occurring within 2 cm of the primary tumor, microscopic lympho-vascular invasion, and Edmondson-Steiner differentiation grade of tumor) (20).

Statistical analysis

A chi-square test was used to examine the relationships between two categorical

variables, and a t-test to compare two mean values (± standard deviations [SDs]). To evaluate whether the variables selected in a univariate analysis were independent factors associated with TTR, a multivariate analysis was performed using the Cox's proportional hazard regression model, and the results were reported as the hazard ratios (HRs) with 95% confidence intervals (CIs).

The failure risk of recurrence over time was studied by using the life-table method to estimate the annual failure hazard rate. That is, the estimated recurrence rate means the conditional probability of manifesting disease failure in a year given that the patient is clinically free of any failure at the beginning of the year, estimating number of events occurring within one-year interval divided by the total years of follow-up during the interval accrued by patients at risk during the interval (21).

There was no death without recurrence during the entire observation time in all patients. The estimated hazard rates for events of interest were also calculated using the hazard function from right-censored data using kernel-based methods. A piecewise exponential model allowed to obtain smooth estimates of the baseline hazard function (22-24). Data analysis was performed using the SPSS statistical package ver. 21.0 (Chicago, IL, USA) and R statistical package ver. 3.5.2(R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristic profiles of the clinical set at the time of resection

Table 1 summarizes the demographic, clinical, and pathological characteristic of the study participants. There was a male predominance of 77.9% with a mean age at hepatectomy of 55.6 years. Of the 1,659 patients, 85.3% were positive for HBV, and 28.3% had serum AFP value of >200 ng/mL. On the basis of the pathologic indices of the surgical specimens, about half of the patients had liver cirrhosis (METAVIR score 4) (25); a median size of original tumors was 3.2 cm (range 0.8-26.0 cm); lesion multifocality, lympho-vascular and capsular invasion of the tumor, and presence of satellite nodules, were microscopically observed in 25 (1.5%), 308 (18.6%), and 52 (3.1%) patients, respectively; and the Edmondson-Steiner III or IV stage as the worst differentiation grade was designated in 69.4%.

Changes in recurrence rate and hazard over time after resection

During a median follow-up time of 5.8 years (range 0.1-12.1 years), HCCs recurred in 801 (48.3%) patients, and loss-to-follow-up censoring occurred in 824 (49.7%). **Fig. 2** depicts the chronologic recurrence rates in yearly intervals after hepatectomy in the entire clinical set of patients. An estimated recurrence rate per year peaked during the first postoperative year (19.7%/year), then gradually decreased until the fourth period of years (11.2%/year). Thereafter, it rapidly dropped and reached a plateau at the annual rate of below 6.5% (ranged from 4.3%/year to 6.3%/year; and averagely, 5.5%/year) until the end-of-study censoring. The number of loss-to-follow-up censoring per year was roughly comparable across a total of 10 postoperative yearly periods with a mean number of 82.4 (standard deviation [SD], ± 28.4). This trend persisted regardless of any pre- and post-resection variables, as shown in **Fig. 3**.

The smoothed hazard function curves for HCC recurrence by yearly interval showed that the overall recurrence was plotted with a nearly linear decreased hazard in years 0 to 10, as were the two divided events of interest, intra- and extra-hepatic

recurrences (**Fig.4**).

Contributing factors of period-specific recurrences

Postsurgical recurrence within and after 4 years was observed in 695 and 106 patients, respectively within the entire follow-up time. Factors contributing to cumulative recurrent events in the respective period were investigated in the 1,659 clinical series. Multivariate time-to-recurrence analyses revealed that male gender (Hazard ratio [HR] {95% confidence interval [CI]}, 1.285 {1.051-1.573}), size of tumor (1.476 {1.143-1.905} for 2-5cm; and 2.147 {1.625-2.838} for ≥5cm), serum AFP ≥200 ng/mL (1.330 {1.124-1.574}), microvascular invasion (1.317 {1.099-1.579}), satellite nodules (2.426 {1.727-3.410}, capsular invasion (1.516 {1.169-1.966}), and the Edmondson-Steiner III or IV (1.083 {0.912-1.286}; and only male gender (1.739 {1.058-2.859}) and cirrhotic liver (2.115 {1.410-3.172}) were independently related to recurrence within and beyond 4 years after resection, respectively (All *P*s<0.05) **(Table 2)**.

Patterns and outcomes of period-specific recurrences

Initial recurrences within or after 4 years of resection were largely presented with new nodules in the liver (86.2% vs. 95.3%, *P*=0.031; **Table 3**). The most common site of metastatic lesions was lung (63.0%), followed by bone (15.1%). Those extrahepatic patterns of recurrence were more frequently observed in a subset of patients who experienced the first recurrence <4 years after surgery (9.9% vs. 3.8%, *P*=0.045; **Table 3**). HCCs reoccurring in the former period had a greater proportion of multiple lesions in the liver (8.7% vs. 0%) and a greater mean value of serum AFP (617.8 ± 4013.5 ng/mL vs. 48.46 ± 20.15 ng/mL, *P*=0.025), resulting in significantly rarer application of potentially curative retreatments (17.1% vs. 26.4%, *P*=0.018; **Table 3**). In terms of the 5-year overall survival after initial recurrence, the later recurrence group had better prognosis (85.1% vs. 58.1%, *P*<0.001 by log-rank test; **sFig.1**).

Discussion

In this large-scale study of resected solitary HCCs, we found that the pattern of recurrence was that of a peak incidence equaling 19.7% during the first year of postoperative follow-up, followed by a steady decrease in the rate until year 4. In subsequent long years, the annual recurrence rate steeply decreased over the first 4 year after resection and then stabilized at an ongoing risk of recurrence of average yearly rate of 5.5 % at 5 to 10 years post-resection. This natural history after resection of HCC was supported by the similar pattern of annual hazard rates of recurrence through 10 years of follow-up.

We found that in addition to conventional risk factors such as men, high AFP level, and tumor size, microscopic features including satellite or non-satellite malignant nodules and lymphovascular invasion of tumors contributed to the first-period recurrences after resection, which has been replicated in previous works (7-11). In relation to HCC recurrences in the late postoperative period when was no longer affected by initial tumor characters, surrounding liver condition alone has been demonstrated to be a constant predictive factor in our and prior observations. (26). Interestingly, the late risk of development of new HCC lesions appeared to parallel the risk (1-7%) in patients with chronic liver disease undergoing secondary surveillance where semiannual tests are commonly recommended worldwide (27-29). These findings indicate that early-phase recurrences are likely attributed largely to growth of synchronous microtumors or dissemination of the resected primary tumor, while the later events are to metachronous de novo recurrence (12, 30).

Previous observational studies of resected HCCs described double-peaked incidence of recurrence bi-modally at one year and 4-5 years after surgery (8, 9). Contradictorily, the second peak of HCC recurrence was not detected in our series with longer follow-up periods and accurate censored data. Unlike our single HCC cohort, a number of participants with multiple tumors who are formally not considered indicative of surgical resection were included in prior Japanese (26.5%) and Canadian cohorts (15.6%), even together with a few cases with R1-resection (8, 9). Indeed, any trustworthy

clinical practice guidelines should state recommendations based on evidence from treatment candidates meeting standard criteria. Moreover, the Japanese investigation proved tumor multiplicity to be a factor related to late phase recurrence. In addition, HBV was infected in >85% of the present cohort, while only in <30% of the previous ones and instead, HCV was in over half of the patients. An Italian randomized controlled study with only 7% of HCV clearance showed that chemopreventive interferon after HCC resection could reduce the late-recurrence peak of the tumor by 50% with respect to controls (31). Most of HCV-infected patients from the two past studies, many of whom had been enrolled before early 2000 when effective anti-HCV agents were not available, might not be virologically cured, perhaps resulting in the failure to prevent the second-peak recurrence (8, 31). In contrast, HBV has been potently suppressed by nucleot(s)ide analogues in >70% of our HBV-infected patients (*data not shown*). These explanations may support the medical reliability of our recurrence profile.

At this time, there is no direct evidence to guide the optimal surveillance strategy after curative intent surgery for HCC. Current recommendations are merely to surveil the individuals more strictly for 1-2 years after HCC resection, which is based on expert opinion (2, 14). Recent evidence demonstrated that the regular recurrence surveillance improved survival of patients with resected HCC (11). Furthermore, given that the best chance at effective therapy for recurrent HCC is surely through early detection of the recurrence (32), high-intensity surveillance after surgery should be preferred, especially during the first few years when more multiple and deadly recurrence disease would be manifested as shown in our data. Based on our findings of the linear decline over time and the similarity to HCC-naive cirrhotics after 4 years of resection in terms of annual recurrence risk, we collectively suggest close follow-up, for instance, every 3-4 months for the first 4 years, more carefully in cases with a large tumor or bad microscopic predictors, and thereafter, routine surveillance every 6 months in patients undergoing curative hepatectomy for HCC. Importantly, HBV or HCV should be purified to minimize the late recurrence at best for the duration of the

patient's lifespan (8, 31, 33, 34).

Unfortunately, no data to properly inform the optimal modality of surveillance for recurrent HCC after resection also remain scarce (35). Our approach identified a considerable number of extrahepatic recurrences mostly in the lung during follow-up: these lesions were mainly developed in the first 4 year-period and resulted in poor outcome. Therefore, at least early-phase surveillance should fully or alternatively include chest CT or liver dynamic images covering the most part of lung to detect potential extrahepatic disease at an earlier phase.

As a limitation of our retrospective study, this study population mostly has HBV infection in the background liver unlike the Japanese or Western patients dominantly related to HCV disease that may have higher rates of poorly differentiated HCC, vascular invasion, and cirrhosis as well as higher recurrence rates (36). In addition, surgical patients with multiple HCCs who were not ideal candidates for resection by guidelines but sometimes encountered in real clinical practice were excluded from the analysis. The results of our study including the cutoff time point of 4 years for postoperative screening should be replicated in and extended to different clinical sets possibly to be generalized.

In conclusion, this study provides updated insight into chronologic and morphologic patterns of recurrence after HCC resection, in which anticipated annual risks of recurrence decrease and in turn recurrences with better biology increase as postsurgical time goes on. We therefore present reliable evidence to implement period-based surveillance protocol in surgically-treated patients with HCC. Further cost-effectiveness studies will allow clinicians or surgeons to determine reasonable frequency and intensity to screening recommendations for recurrent disease in such patients.

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Table 1. Baseline clinical and pathological characteristics of the study population

Variable	All patients (n=1,659)
Clinical factor	
Male gender	1,293 (77.9%)
Age (years)	55.5 ± 9.6
Body mass index (kg/m^2)	24.4 ± 2.9
Diabetes mellitus	279 (16.8%)
Essential hypertension	473 (28.5%)
Alcohol drinking	1,067 (64.3%)
Smoking habitus	943 (56.8%)
Hepatitis B virus infection	1,415 (85.3%)
Hepatitis C virus infection	85 (5.1%)
Serum AFP, ≥200 ng/mL	470 (28.3%)
Platelet count (X10^3/mm^3)	165 ± 58
Prothrombin time (INR)	1.04 ± 0.07
Serum Creatinine (mg/dl) -	0.9 ± 0.5
Serum albumin (g/dl)	4.0 ± 0.4
Serum bilirubin (mg/dl)	0.8 ± 0.3
Serum AST (IU/L)	49 ± 38
Serum ALT (IU/L)	43 ± 39
Pathological factor	
Tumor size, ≥2cm	1,407 (84.8%)
Multifocality	25 (1.5%)
Lymphovascular invasion	308 (18.6%)
Satellite nodules*	52 (3.1%)
Capsular invasion	115 (6.9%)
Edmond-Steiner grade, III or IV†	1,152 (69.4%)
Histopathologic cirrhosis‡	869 (52.4%)

Categorical variables are presented as number (percentage), and continuous variables as mean value ± standard deviation.

Abbreviations: AFP, alpha-fetoprotein; INR, international normalized ratio; AST, aspartate

transaminase; and ALT, alanine transaminase

*Defined as tumor cells occurring within 2 cm of the primary tumor

†By the worst Edmond-Steiner grade

‡By the METAVIR score of 4

Table 2. Multivariate Cox regression analyses for factors contributing to period-specific recurrences

	Model for all recurrences		Model for recurrences within 4 years of resection		Model for recurrences after 4 years of resection	
	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
Male gender	1.371 (1.141-1.648)	0.001	1.285 (1.051-1.573)	0.015	1.739 (1.058-2.859)	0.029
Age, >50 years	-		-		-	
Hepatitis B virus	0.804 (0.661-0.978)	0.029	-		-	
Tumor size						
<2 cm	1.0		1.0		-	
2 - 5 cm	1.565 (1.240-1.974)	<0.001	1.476 (1.143-1.905)	0.003	-	
≥5 cm	2.593 (1.999-3.365)	<0.001	2.147 (1.625-2.838)	<0.001	-	
AFP, ≥200 ng/mL	1.110 (0.949-1.299)	0.192	1.330 (1.124-1.574)	0.001	-	
Pathological multifocality	1.909 (1.192-3.059)	0.007	-		-	
Lymphovascular invasion	1.538 (1.295-1.826)	<0.001	1.317 (1.099-1.579)	0.003	-	
Satellite nodules	1.945 (1.399-2.704)	<0.001	2.426 (1.727-3.410)	<0.001	-	
Capsular invasion	1.307 (1.020-1.675)	0.035	1.516 (1.169-1.966)	0.002	-	
Edmond-Steiner grade, III or IV	1.080 (0.920-1.267)	0.345	1.083 (0.912-1.286)	0.364	-	
Histopathologic cirrhosis	1.573 (1.357-1.823)	<0.001	-		2.115 (1.410-3.172)	<0.001

Abbreviations: AFP, alpha-fetoprotein

Table 3. Comparison of recurrence patterns within and after 4 years of resection

Variable	Recurrences within 4 years of resection (n=695)	Recurrences after 4 years of resection (n=106)	*P* value
Intrahepatic recurrence	599 (86.2%)	101 (95.3%)	0.031
Solitary tumor	443 (74.0%)	87 (86.1%)	0.008
Maximum size (cm)*	1.67 ± 1.30	1.50 ± 0.80	0.127
Portal invasion	2 (0.3%)	0 (0%)	-
Extrahepatic recurrence	69 (9.9%)	4 (3.8%)	0.045
Involvement of single organ			
Lung	43 (56.5%)	3 (75%)	
Bone	11 (11.6%)	0	
Adrenal gland	5 (2.9%)	0	
Involvement of multiple organs	6 (8.7%)	0	
Treatment after recurrence			0.021
Curative options	119 (17.1%)	28 (26.4%)	
Non-curative options†	576 (82.9%)	78 (73.6%)	
Serum AFP at recurrence (ng/mL)	617.8 ± 4013.5	48.46 ± 20.15	0.025

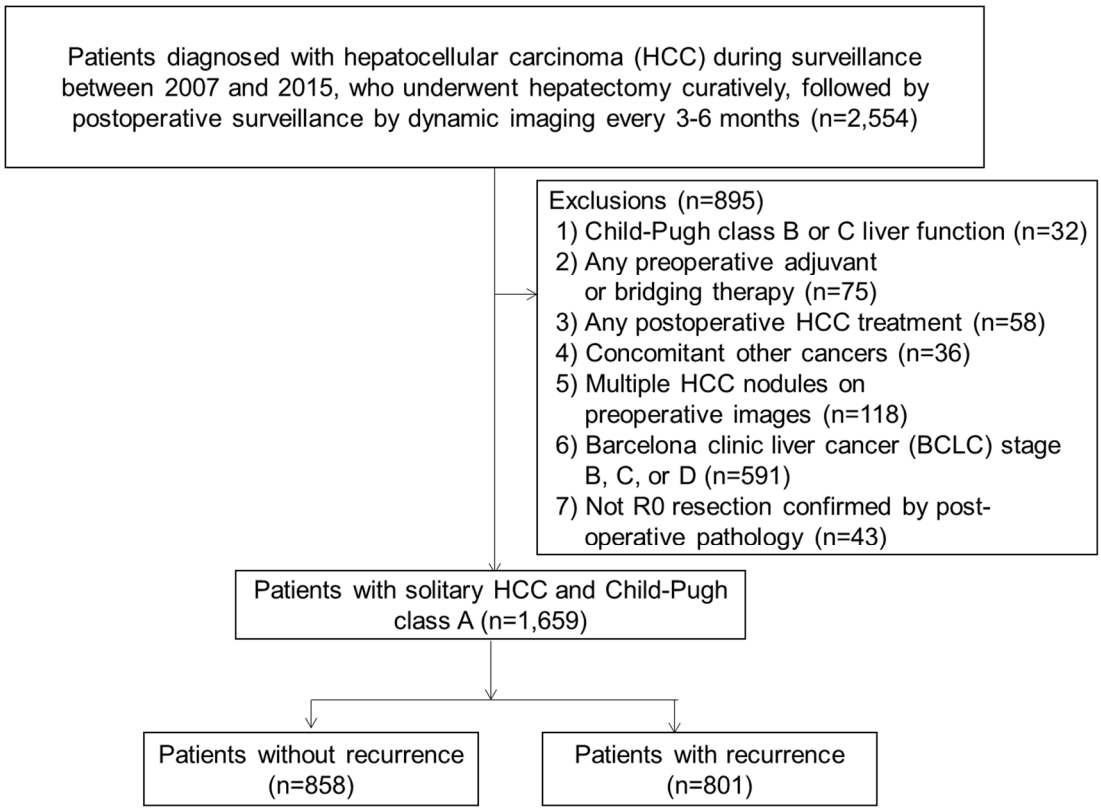
Categorical variables are presented as number (percentage), and continuous variables as mean value ± standard deviation.

Abbreviations: AFP, alpha-fetoprotein

*Among 635 tumors recurred within 4 years of resection, 2 non-measurable lesions occurring on resection margin; 1 presented as portal vein thrombosis; and 1 presented as an infiltrative type were excluded.

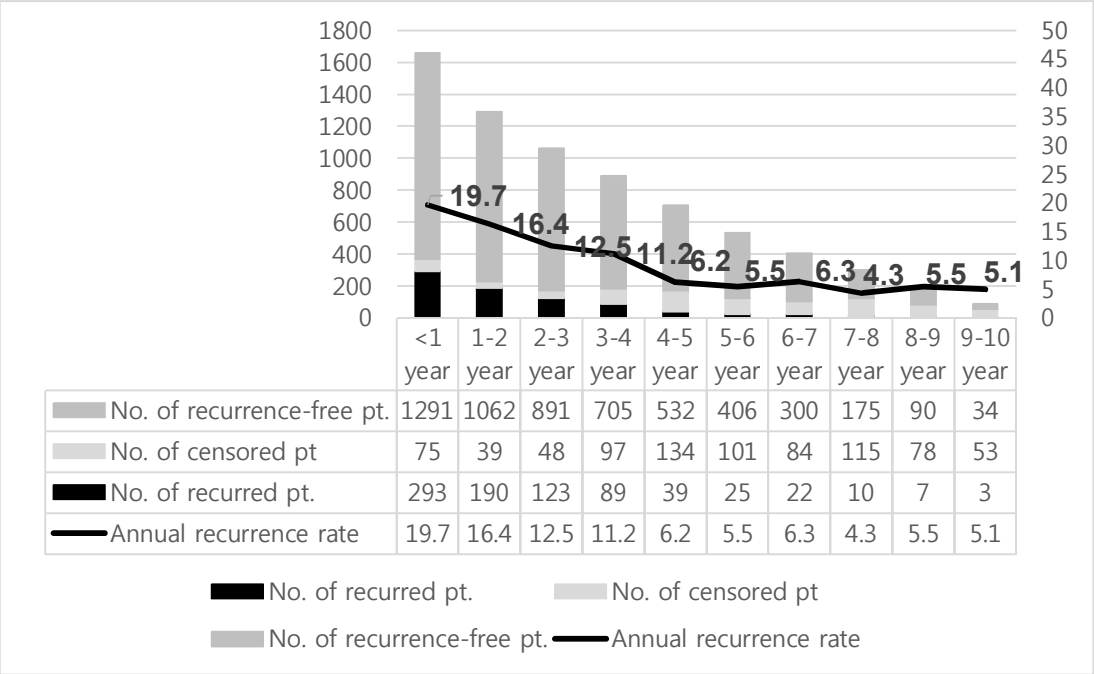
†We included 20 and 4 patients with loss to follow-up after recurrence who had initial recurrence within and after 4 years of resection, respectively into the ‘non-curative option’ category.

Figure 1. Flowchart of patients included in the study



Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, Hepatocellular carcinoma

Figure 2. Number of recurrence events per year and estimated annual recurrence

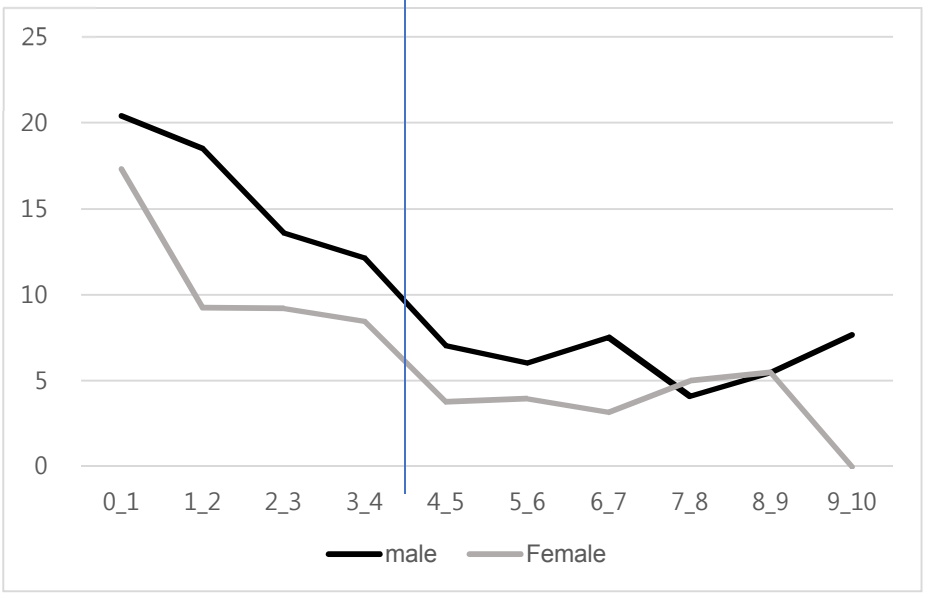


	<1 year	1-2 year	2-3 year	3-4 year	4-5 year	5-6 year	6-7 year	7-8 year	8-9 year	9-10 year
No. of recurrence-free pt.	1291	1062	891	705	532	406	300	175	90	34
No. of censored pt	75	39	48	97	134	101	84	115	78	53
No. of recurred pt.	293	190	123	89	39	25	22	10	7	3
Annual recurrence rate	19.7	16.4	12.5	11.2	6.2	5.5	6.3	4.3	5.5	5.1

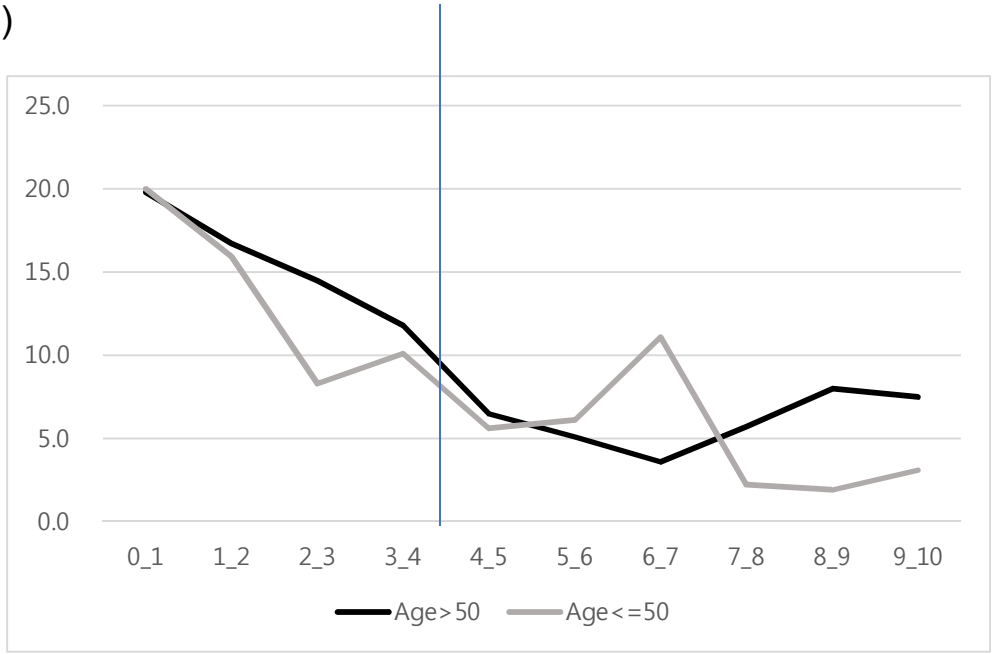
An estimated recurrence rate per year peaked during the first postoperative year (19.7%/year), then gradually decreased until the fourth period of years (11.2%/year). Thereafter, it rapidly dropped and reached a plateau at the annual rate of below 6.5% (ranged from 4.3%/year to 6.3%/year; and averagely, 5.5%/year) until the end of observation.

Figure 3. Pattern of annual recurrence rates by clinical variables

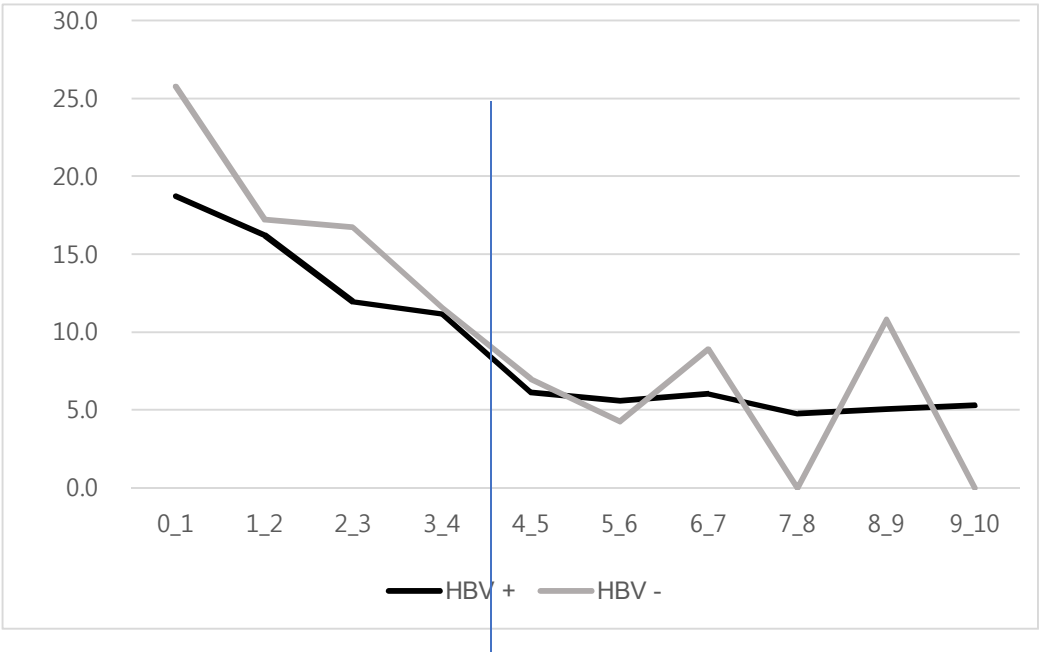
(A)



(B)



(C)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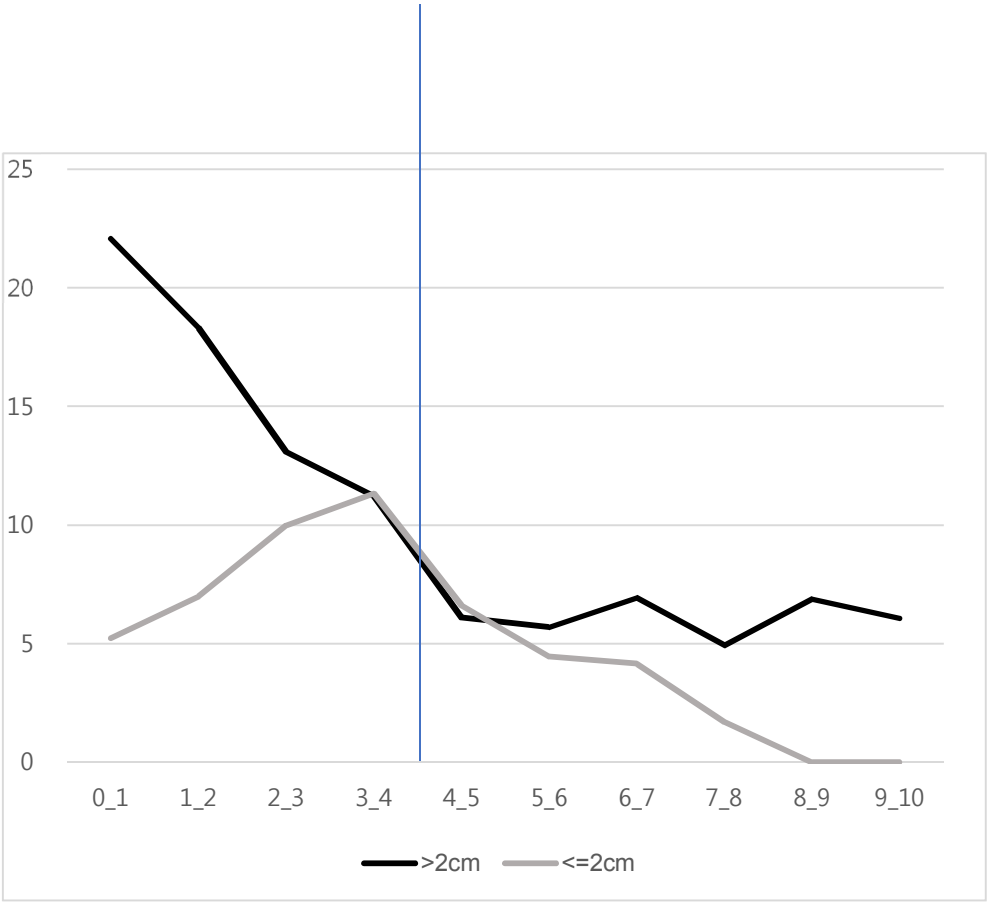
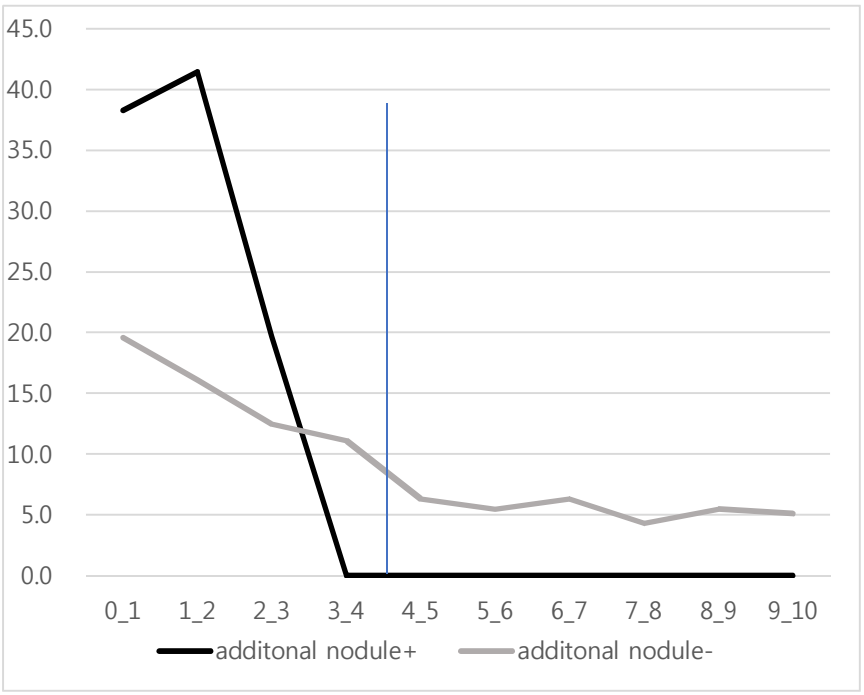
20.0
15.0
10.0
5.0
0.0
0_1
1_2
2_3
3_4
4_5
5_6
6_7
7_8
8_9
9_10
HBV +
HBV -

(D)


25
20
15
10
5
0
0_1
1_2
2_3
3_4
4_5
5_6
6_7
7_8
8_9
9_10
>2cm
<=2cm

(E)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30.0
25.0
20.0
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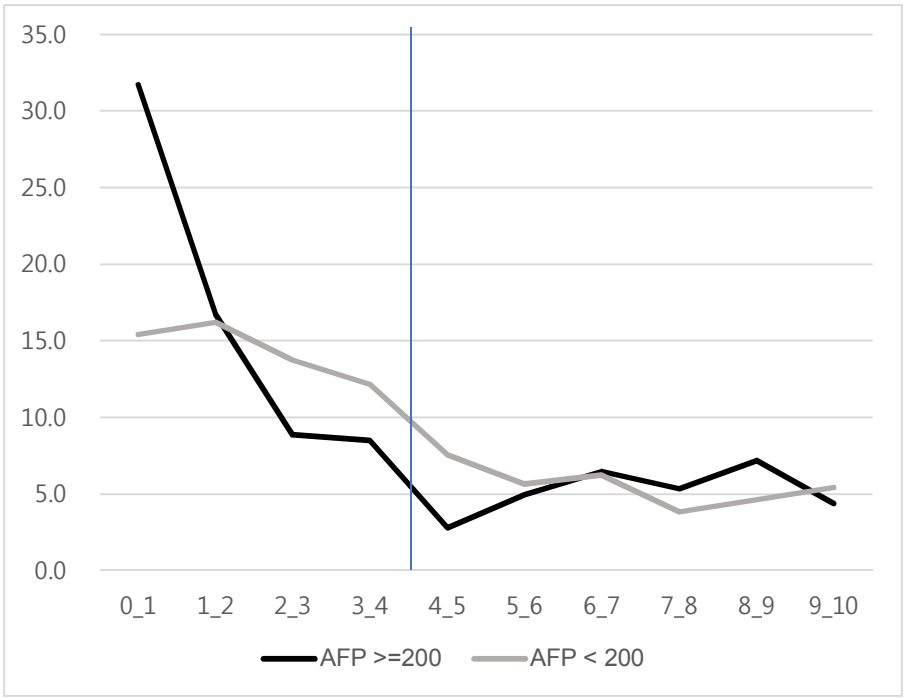
10.0
5.0
0.0
0_1
1_2
2_3
3_4
4_5
5_6
6_7
7_8
8_9
9_10
additonal nodule+
additonal nodule-

(F)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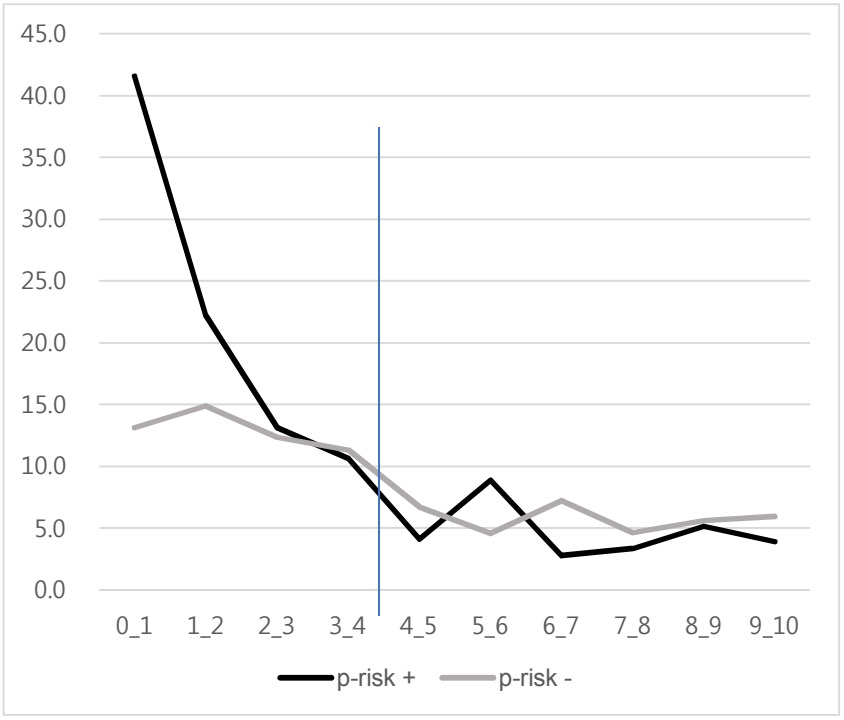
30.0
25.0
20.0
15.0
10.0
5.0
0.0
0_1
1_2
2_3
3_4
4_5
5_6
6_7
7_8
8_9
9_10
AFP >=200
AFP < 200

(G)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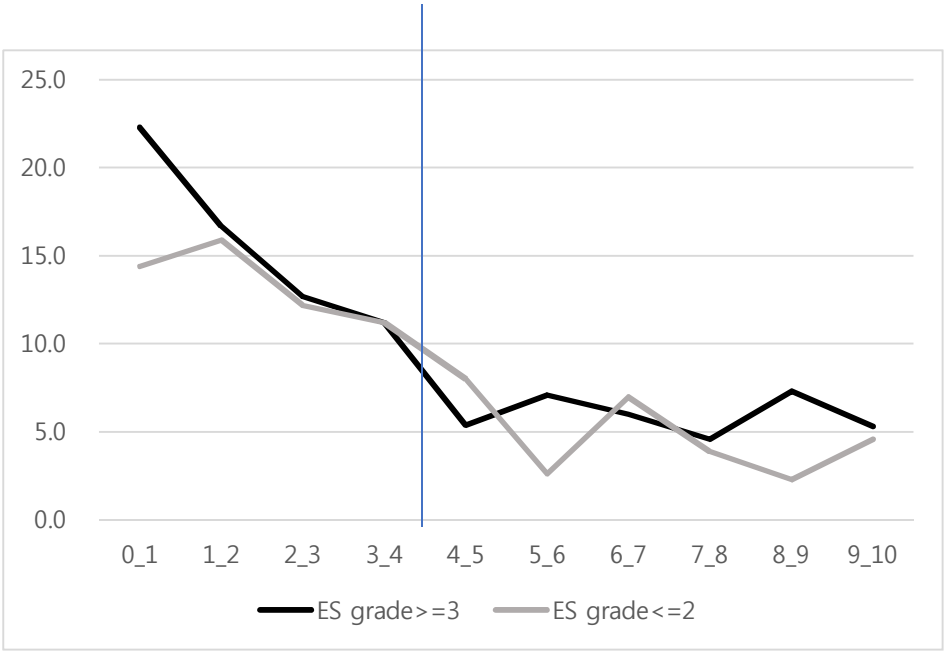
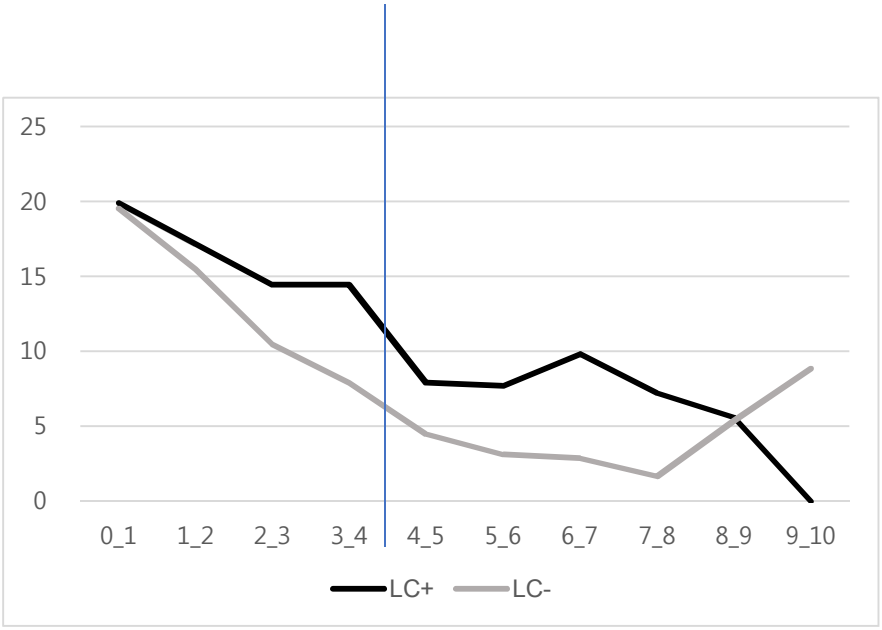
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
0_1
1_2
2_3
3_4
4_5
5_6
6_7
7_8
8_9
9_10
p-risk +
p-risk -

(H)

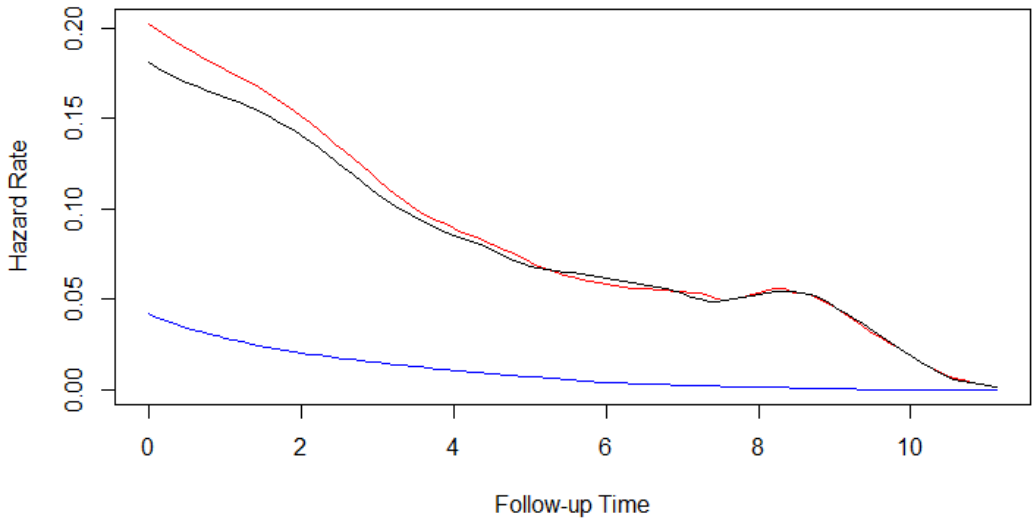

25.0
20.0
15.0
10.0
5.0
0.0
0_1
1_2
2_3
3_4
4_5
5_6
6_7
7_8
8_9
9_10
ES grade>=3
ES grade<=2

(I)



The similar pattern of annual recurrence rate persisted regardless of (A) gender, (B) age, (C) hepatitis B virus infection, (D) size of tumor, (E) multifocality (F) serum alpha-fetoprotein level, and (G) three pathologic risk factors (microvascular invasion, satellite nodules and capsular invasion), (H) the Edmondson–Steiner grade, (I) Presence of cirrhosis.

Figure 4. Hazard function curves for recurrences by yearly interval



Red: Hazard function curve for overall recurrence, Black: Hazard function curve for intrahepatic recurrence, Blue: Hazard function curve for extrahepatic recurrence.

The smoothed hazard function curves for HCC recurrence by yearly interval showed that the overall recurrence was plotted with a nearly linear decreased hazard in years 0 to 10. This trend towards the annual hazard was maintained when intra- and extra-hepatic recurrences were divided.

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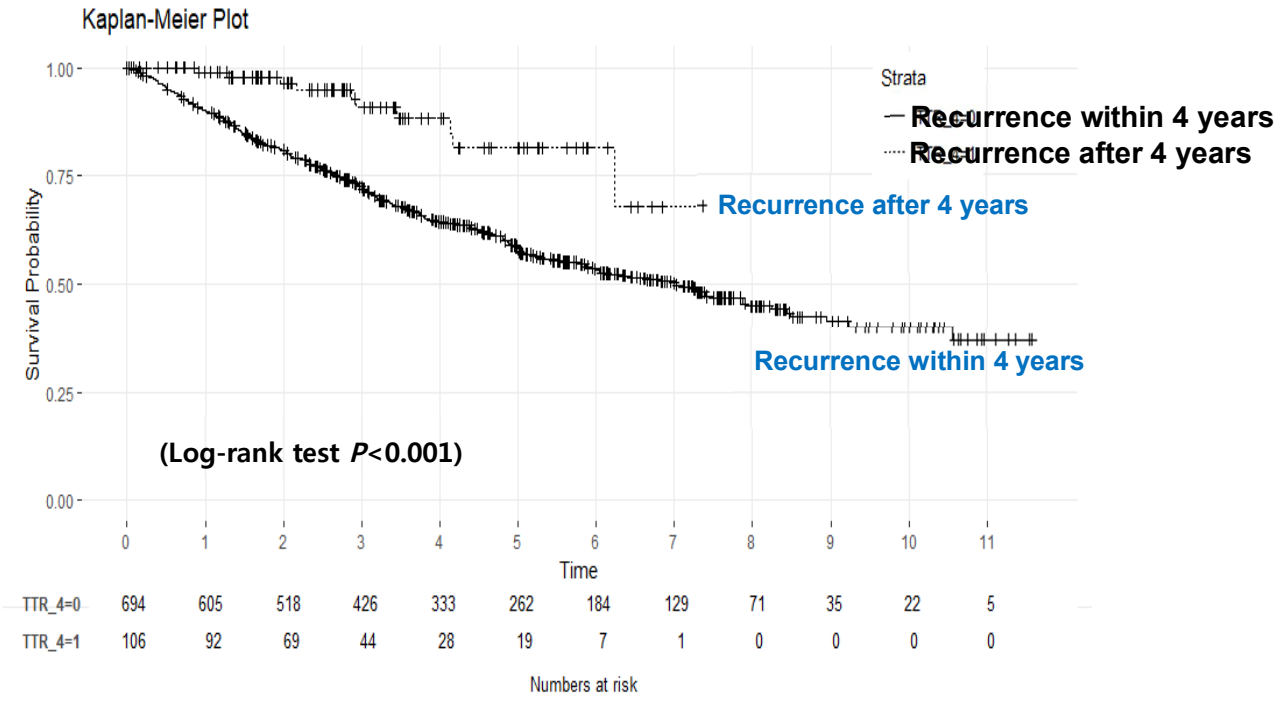
Supplement Figure 1. Comparison of post-recurrence overall survival between patients experiencing recurrences within and after 4 years of resection



OS survival

The 5-year overall survival rate after initial recurrence was significantly lower in patients experiencing recurrence within 4 years of resection, compared to those recurred after the period (58.1% vs. 85.1%, *P*<0.001 by log-rank test).

국문요약

간암 절제술 이후 재발이 흔하게 발생하나, 수술 후 적절한 감시기간과 그 빈도에 대해 명확히 연구는 없었다. 본 연구는 간 절제술에 적합한 간암 환자에서 10년 동안의 연간 재발률의 패턴 및 재발 기간에 따라 예후 결정 인자와 그 결과를 확인하는 것을 목표로 하였다. 2007년부터 2015년까지 본원에서 간 절제술을 받은 Child-Pugh A의 단일 간세포암 환자로 수술 후 3~6개월 마다 재발 발생 여부에 대해 감시 검사를 시행했던 1,659명을 대상으로 연구를 진행하였다. 환자들의 수술 후 연간 재발률 및 초기와 후기의 재발 위험 인자, 종양의 특성 및 예후와의 관련성 등을 조사하였다. 총 801명 (48.3%)의 환자에서 수술 후 재발이 발생하였고, 연간 추정 발생률은 첫 해(19.7%/year)에 정점을 찍었고, 이후 4년까지 급격히 감소한 후 수술 후 5년에서 10년까지는 연평균 5.5%의 비율로 정체를 보였다. 수술 후 4년을 기준으로 재발 기간에 따른 다변량 콕스 분석에 의하면 4년 이후 에는 남성 (Hazard ratio 1.739, P =0.029) 및 간경변증 (Hazard ratio 2.115, P<0.001)이 재발의 독립적인 예측 인자로 확인되었다. 그리고 수술 후 4년 이전의 초기에 재발한 군에서 다발성 및 간외 재발이 더 흔하게 나타났다 (26.0% vs. 13.9%; and 9.9% vs. 3.8%, P<0.05 for both). 또한 재발 이후 5년 생존률은 4년 이전의 재발군에서 4년 이후 재발군에 비하여 유의하게 낮았다(58.1% vs. 85.1%, P <0.001). 본 연구의 결과는 간 절제술을 받은 간암 환자에서 최선의 수술 후 감시 검사 프로토콜을 마련하기 위한 중요한 근거가 될 수 있다.