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Intrahepatic recurrence of single nodular hepatocellular carcinoma after surgical resection: an analysis by segmental distribution

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Abstract

Background: Intrahepatic recurrence is the major cause of management failure after surgical resection of hepatocellular carcinoma (HCC). In the present study, we analysed intrahepatic recurrence by HCC distribution using Couinaud's liver segments.

Methods: Recurrence proximity levels were defined with respect to primary tumour locations from Level LR (locoregional) to Level IV. Initial and recurrent tumours were compared with segmental distribution of their locations, and recurrence proximity levels were compared with initial tumour locations and disease-free survival.

Results: Eighty-five (58.2%) of 146 patients with single nodular HCC experienced intrahepatic recurrence after surgical resection with a mean disease-free survival of 20.8 ± 21.1 months. Segmental distributions of initial and recurrent tumour locations were not significantly different ($P > 0.05$), and both were similar to the normal segmental volume distribution except segments S5, S6 and S8. Recurrences in proximity levels LR to IV were 11.1%, 34.9%, 25.4%, 21.4%, and 7.1%, respectively, and this distribution agreed well with theoretical proximity level distribution ($P > 0.05$). Disease-free survivals for different recurrence levels were not different ($P = 0.530$).

Conclusion: Intrahepatic recurrences after surgical resection of single nodular HCC occurred evenly in the remnant liver, and the timing was independent of the proximity between initial and recurrent tumours. Prevention was found to be proportional to the amount of liver segments removed. Surgical plans should take this into consideration.

Introduction

Although surgical resection is considered as the first-line therapy for the management of single nodular hepatocellular carcinoma (HCC), intrahepatic recurrences are common and constitute the major cause of management failure even after curative surgery.[1–4] Two underlying modes of intrahepatic recurrence have been suggested, that is, *de novo* or multicentric occurrence and intrahepatic metastasis. Multicentric occurrence is by definition a newly formed tumour, and tends to be associated with a few nodules, recur late, host-factor related, and thus, metachronous in nature.[5–7] On the other hand, intrahepatic metastasis involves tumour dissemination through pre-existing intrahepatic channels, such as the portal or hepatic veins, and tends to be multiple, recur early, tumour biology-related, and synchronous in origin.[8,9] Understanding the mode of intrahepatic recurrence of HCC after surgical resection is clinically important for determining further management guidelines as well as for prognostic reasons.[10,11] However, mode of HCC recurrence cannot be predicted at first presentation because either mode is possible and occult tumour foci may be present even in cases of seemingly single nodular HCC.[12,13]

A few studies have addressed the spatial and chronological relationships between the initial and recurrent tumour locations, but their definition of locations were rather ambiguous.[8,14,15] We aimed to analyse intrahepatic recurrence of single nodular HCC after surgical resection by locations using Couinaud's liver segment as coordinates. We examined the probability of HCC occurrence in all eight liver segments for initial and recurrent tumours, irrespective of modes of intrahepatic recurrence. By newly defining recurrence proximity levels to describe the vicinities of initial and recurrent tumours, we analysed spatial likelihoods of HCC recurrence in liver segments with respect to initial tumour locations. Disease-free survivals (DFSs) were compared for different recurrence proximity levels to determine whether recurrences in nearby or distant

segments differ chronologically. In addition, the effect of surgical resection extent on the rate of recurrence in remnant liver was investigated.

Methods

Study population and data collection

From November 2002 to October 2015, a total of 153 consecutive patients with pathologically proven single nodular HCC underwent surgical resection as the first-line therapy in our institution. Medical records were reviewed retrospectively, and clinical and histopathologic data obtained at index operations were collected. Follow-up was performed by computed tomography and/or magnetic resonance imaging every 3 to 6 months post-operatively, or when tumour markers (alpha-fetoprotein and protein induced by vitamin K absence) were elevated. Follow-up continued until death, loss to follow-up, detection of intrahepatic or extrahepatic recurrence by imaging, or June 2017. Seven patients (4.6%) were excluded due to the detection of another malignancy during follow-up (n = 3, 2.0%), the detection of extrahepatic recurrence prior to intrahepatic recurrence (n = 2, 1.3%) or adjuvant chemotherapy (n = 2, 1.3%). The demographic data and clinical characteristics of 146 enrolled patients are presented in Table 1. This study involved the collection of existing data and patients could not be identified by any means. Accordingly, the Institutional Review Board of our institution waived the requirement for patient consent.

Radiologic diagnosis and localization

Radiologic diagnoses of HCC recurrence and localization were performed using computed tomography or magnetic resonance imaging findings.[16–18] When a tumour was located across two or more Couinaud's segments, the location of the tumour centre was defined as the representative location.

Table 1 Demographic data and patient characteristics

Overall	n = 146
Age (years, mean ± SD)	55.3 ± 9.2
Sex	
Male	116 (79.5%)
Female	30 (20.5%)
Cause of liver cirrhosis	
Hepatitis B	112 (76.7%)
Others	34 (23.3%)
Tumour size (cm, mean ± SD)	3.6 ± 2.6
Operative method	
Anatomical	123 (84.2%)
Non-anatomical	23 (15.8%)
Resection margin length (cm, mean ± SD)	0.57 ± 0.65
Recurrence	
None	61 (41.8%)
Single	67 (45.9%)
Multiple	18 (12.3%)
Disease-free survival (months, mean ± SD)	34.9 ± 27.5

SD, standard deviation.

Recurrence proximity level matrix

Recurrence proximity levels were defined as Level LR (locoregional, same segment) to Level IV according to the vicinities of initial and recurrent tumour locations. Directly neighbouring segments are Level I – those that are diagonally placed are Level II, and so on. For example, when the initial tumour was located in segment 6 (S6) and recurrence was located in S5 or S7, recurrence was defined as Level I. If recurrence was in S4b or S8, then recurrence was Level II. S3 is next to S4b, and S4a is next to S4b and S8; these segments are Level III. Finally, S2 is adjacent to S3 and S4a, so the recurrence in S2 is Level IV. We assumed S1 is neighbouring S4a and S2. The recurrence level matrix is presented in Figure 1. Note that centrally located segments (S4a, S4b, S5 and S8) do not have Level IV recurrences. Also, theoretically possible recurrence levels are different for each initial tumour location. Overall, theoretical level distributions when recurrence occurred evenly in the remnant liver are as follows: Level LR, 9/81 (11.1%); Level I, 24/81 (29.6%); Level II, 26/81 (32.1%); Level III, 16/81 (19.8%); Level IV, 6/81 (7.4%). When two or more recurrences were detected in different segments, they were counted individually, and when they occurred in the same segment, they were counted as one.

Statistical analysis

Continuous variables are presented as means ± standard deviations (SD) and nominal variables as numbers (%). Pearson's chi-squared test or Fisher's exact test were used as appropriate to determine the differences of HCC occurrences. Predicted HCC occurrences based on normal segmental volume distribution and actual HCC occurrences were compared using chi-squared goodness-of-fit test. The DFSs of different recurrence proximity levels were calculated using the Kaplan–Meier method and differences were analysed using the log-rank test. The analyses were performed using IBM SPSS

Initial location / Recurrence	S1	S2	S3	S4a	S4b	S5	S6	S7	S8
S1	LR	I	II	I	II	III	IV	III	II
S2	I	LR	I	I	II	III	IV	III	II
S3	II	I	LR	II	I	II	III	IV	III
S4a	I	I	II	LR	I	II	III	II	I
S4b	II	II	I	I	LR	I	II	III	II
S5	III	III	II	II	I	LR	I	II	I
S6	IV	IV	III	III	II	I	LR	I	II
S7	III	III	IV	II	III	II	I	LR	I
S8	II	II	III	I	II	I	II	I	LR

Fig. 1. Proximity level matrix of Couinaud's liver segments for initial hepatocellular carcinoma and intrahepatic recurrence.

Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). *P*-values of <0.05 were considered statistically significant.

Results

Segmental distributions of initial and recurrent HCCs

The distributions of initial HCC locations and recurrence locations by liver segment are presented in Figure 2. Percent HCC occurrence and percent volume of each Couinaud's segment is presented as the area of a square. Initial and recurrent tumours were most common in S6 (n = 60, 22.1%), and least common in S1 (n = 4, 1.5%). Couinaud's segmental distributions of initial and recurrent tumour locations were not significantly different ($P > 0.05$). Also, the distributions of occurrences were similar to the normal segment volume distribution reported by Mise *et al.*,[19] except that initial HCC locations were more frequent in S5 ($P = 0.011$) and S6 ($P = 0.000$) than were expected, and that recurrence locations were more frequent in S6 ($P = 0.000$). Both initial and recurrent HCCs occurred less frequently in S8 ($P = 0.001$ and 0.007, respectively), as compared to the expected occurrence.

Proximity level distribution of recurrences and relations with DFS

Proximity levels of HCC recurrence according to the segmental locations of initial tumours are presented in Table 2. Overall recurrences at Level LR to Level IV were 14 (11.1%), 44 (34.9%), 32 (25.4%), 27 (21.4%) and 9 (7.1%), respectively, and this distribution of recurrences did not differ from theoretical proximity level distribution ($P > 0.05$). DFSs at recurrence levels LR to IV were 20.4 ± 20.4, 20.6 ± 18.4, 15.7 ± 12.2, 17.8 ± 25.1 and 10.9 ± 9.7 months, respectively. DFSs for recurrence levels were not significantly different ($P = 0.530$, Fig. 3).

Discussion

Intrahepatic localization of HCC is hard to standardize three-dimensionally. Moreover, the unique anatomical configuration of the liver

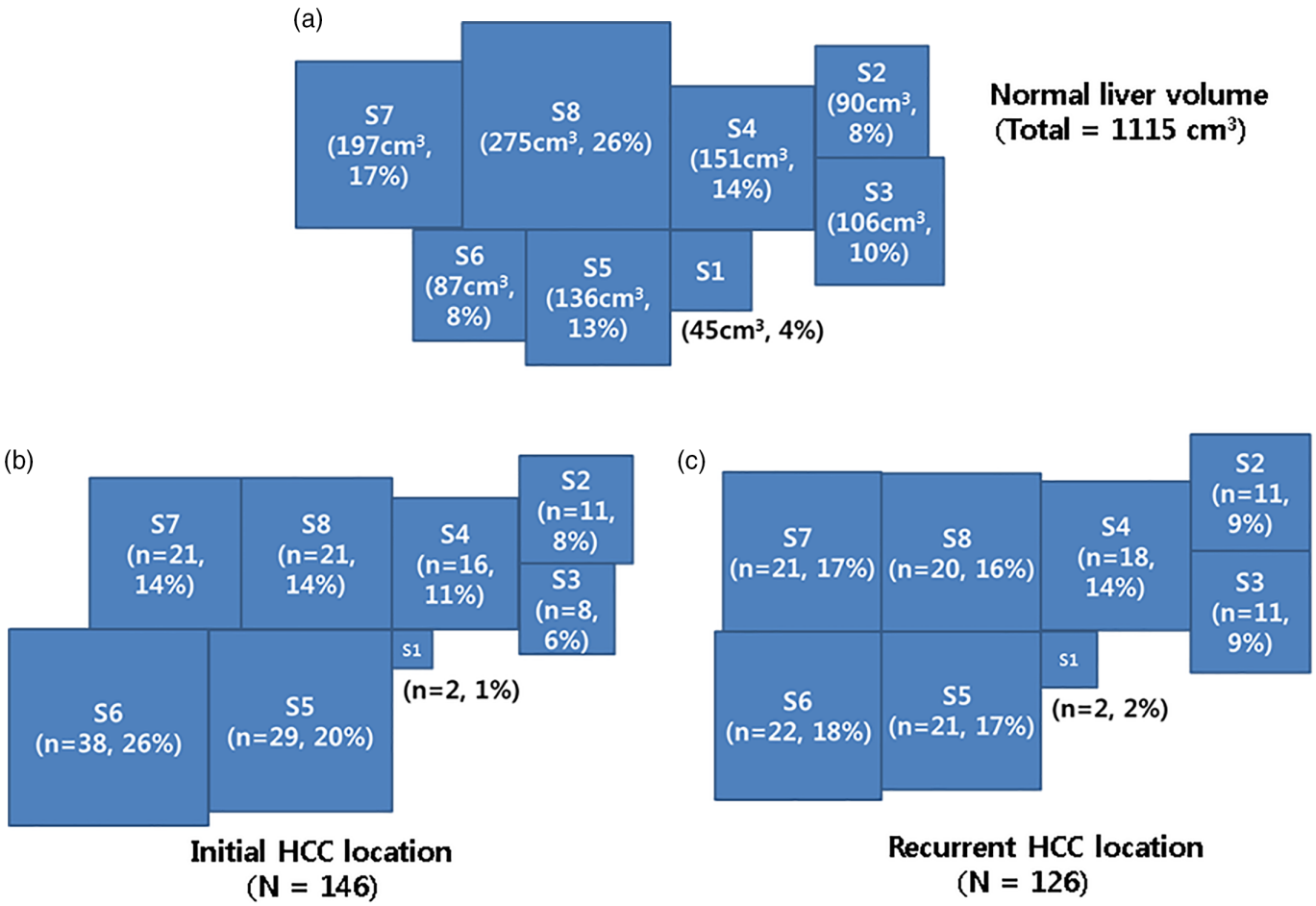

Fig. 2. (a) Segmental distribution of a normal liver segment volumes (total = 1115 cm^3),[19] (b) initial hepatocellular carcinoma (HCC) locations (n = 146) and (c) recurrent HCC locations (n = 126). The areas of the squares in the diagram represent the percentage volumes (a) or occurrences (b and c) occupied by individual Couinaud's segments.

Table 2 Proximity level distributions of intrahepatic recurrences after surgical resection of single nodular hepatocellular carcinoma

Initial location	Level LR	Level I	Level II	Level III	Level IV
S1 (*n* = 2, 1.6%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)
S2 (*n* = 13, 10.3%)	0 (0.0%)	1 (7.7%)	3 (23.1%)	7 (53.8%)	2 (15.4%)
S3 (*n* = 7, 5.6%)	1 (14.3%)	2 (28.6%)	1 (14.3%)	3 (42.9%)	0 (0.0%)
S4a (*n* = 6, 4.8%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	0 (0.0%)	0 (0.0%)
S4b (*n* = 6, 4.8%)	0 (0.0%)	1 (16.7%)	4 (66.7%)	1 (16.7%)	0 (0.0%)
S5 (*n* = 29, 23.0%)	4 (13.8%)	15 (51.7%)	7 (24.1%)	3 (10.3%)	0 (0.0%)
S6 (*n* = 29, 23.0%)	3 (10.3%)	12 (41.4%)	6 (20.7%)	4 (13.8%)	4 (13.8%)
S7 (*n* = 22, 17.5%)	3 (13.6%)	6 (27.3%)	4 (18.2%)	6 (27.3%)	3 (13.6%)
S8 (*n* = 12, 9.5%)	1 (8.3%)	5 (41.7%)	4 (33.3%)	2 (16.7%)	0 (0.0%)
Total (*n* = 126, 100.0%)	14 (11.1%)	44 (34.9%)	32 (25.4%)	27 (21.4%)	9 (7.1%)
Theoretical level distribution (total matrix no. = 81)	9 (11.1%)	24 (29.6%)	26 (32.1%)	16 (19.8%)	6 (7.4%)
P-value*	1.000	0.429	0.295	0.772	0.943

*Comparison between actual recurrence levels and theoretical level distribution (see Fig. 1).

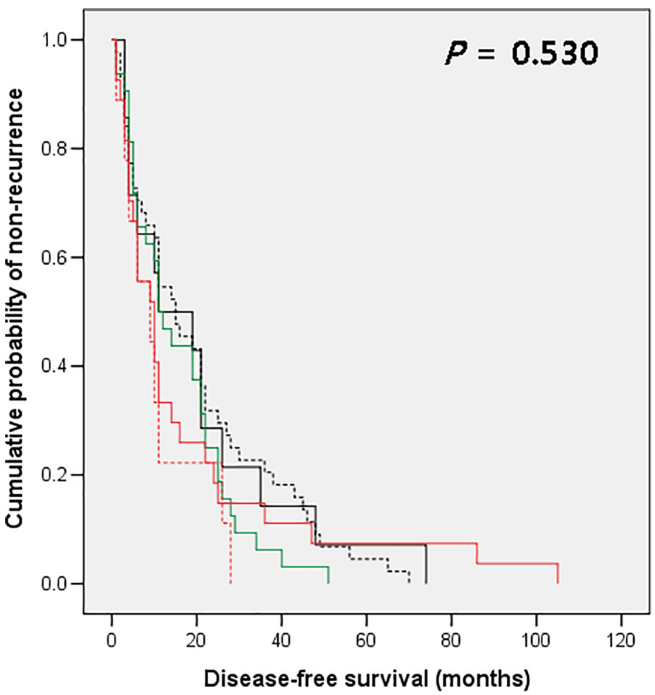

Fig. 3. Disease-free survivals of intrahepatic recurrence proximity levels after surgical resection of single nodular hepatocellular carcinoma. Recur level: (——) LR (*n* = 14); (- - - -) I (*n* = 44); (——) II (*n* = 32); (——) III (*n* = 27); (- - - -) IV (*n* = 9).

indicates the direct measurements of distances between two lesions within liver parenchyma do not reflect the lengths of intrahepatic channels, such as the portal or hepatic veins.[8] In the present study, we investigated the distribution of intrahepatic locations of HCC using Couinaud's segments. This study is unique in that recurrences were analysed according to the proximities between liver segments harbouring initial and recurrent tumours, and not by the absolute distance between them.

The present study showed that the segmental distributions of initial HCC and intrahepatic recurrence locations are not different statistically, and that both are similar to the normal segmental volume distribution. The discrepancies between observed occurrences and normal segmental volumes may have been due to our defining liver segments based on hepatic venous outflow rather than portal venous inflow. Altogether, these findings suggest that the initial and recurrent tumours were evenly distributed in liver. Arguably, it is possible that recurrence in nearby segments was underestimated in the present study (Level LR/I), because these segments could have been removed by surgical resection.[8] If recurrence in adjacent segments had been biased, Level LR or Level I recurrences would have been lower than expected. However, the observed recurrence proximity level distribution was similar to the theoretically possible level distribution, which indicated that the distribution had not been affected by surgical resection. The theoretical level distribution represents the expected level distribution if intrahepatic recurrence occurred evenly in remnant liver segments: the finding that 9 (7.1%) recurrences occurred at Level IV did not mean Level IV recurrences were not common, but rather that observed recurrences well matched the theoretically possible Level IV recurrences (6 of 81 possible proximity levels, 7.4%). The time-course of recurrence at each proximity level showed that DFSs were not significantly related to recurrence proximity.

Residual liver function is an important determinator of the extent of liver resection for HCC.[1–3] In the present study, prevention of intrahepatic recurrence was found to be proportional to the amount of liver parenchyma removed. For example, when subsegmentectomy or tumourectomy was performed for a single nodular HCC located in S6, which involves removing Level LR only, about 10% of recurrences were prevented, while after right hemihepatectomy which involves removing Level LR, Level I, and a half of Level II, an additional 51% of recurrences were prevented (Table 2). In surgical planning of single nodular HCC, preventive potential of removed liver segments should be balanced with the remnant liver function.[20,21]

Our study has several limitations. First, the relatively small cohort size reduced statistical power, and thus, the details of our results. We suggest a further study be undertaken using more refined criteria and a larger cohort. Second, the allocations of initial and recurrent tumours to specific Couinaud's segments were difficult in some cases, especially for large tumours, in which case we assumed originated from the apparent tumour centre. Third, we did not have a strict protocol regarding follow-up after HCC resection, and it is possible that DFS was overestimated by as much as 6 months in some cases. Also, DFS data might have been skewed by the limited sensitivities and specificities of imaging modalities

used to detect HCC recurrence. Nevertheless, we are inclined to believe these factors did not substantially alter our results.

In conclusion, we found that presenting locations and locations of intrahepatic recurrence from single nodular HCC after surgical resection were distributed evenly throughout liver segments. Also, DFSs were not different for recurrences in nearby or distant segments. Because it cannot be predicted when and where an HCC will recur within remnant liver before recurrence actually occurs, and because prevention of recurrence is proportional to the extent of liver segments removed, surgical resection should be planned accordingly at the initial presentation.

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Conflicts of interest

None declared.

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