

Results of en bloc resection for hepatocellular carcinoma extending to adjacent organs

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Background: To curatively resect hepatocellular carcinoma (HCC) with adjacent organ extension, the combined resection of these organs is inevitable. We analyzed the safety and effectiveness of en bloc resection for HCC extending to adjacent organs.

Methods: From December 2002 to May 2006, we compared the surgical outcomes of patients with HCC extending to adjacent organs with those of closely matched, randomly selected patients with HCC without adjacent organ extension.

Results: We included 42 patients whose HCC extended to adjacent organs and 126 patients whose HCC did not extend to adjacent organs. There was no significant difference in survival, operative morbidity or mortality between the groups. In patients with HCC extending to adjacent organs, histopathological examination of the specimen revealed true tumour invasion in 13 and adhesion in 29 patients. Those with tumour invasion were more likely to have a high incidence of capsule infiltration, microvascular invasion and early intrahepatic recurrence (≤ 1 yr after hepatectomy). The 5-year overall survival of patients with tumour invasion was 11.5%, whereas that of patients with tumour adhesion was 38.1% ($p = 0.033$).

Conclusion: En bloc resection is a safe and effective therapy for HCC extending to adjacent organs. Tumour invasion to adjacent organs exhibits a more aggressive clinical behaviour and is associated with worse survival than tumour adhesion.

Contexte : La résection curative d'un carcinome hépatocellulaire ayant envahi des organes adjacents entraîne inévitablement la résection de ces organes. Nous avons analysé l'innocuité et l'efficacité d'une résection radicale dans les cas de carcinome hépatocellulaire s'étant propagé aux organes adjacents.

Méthodes : Pour la période allant de décembre 2002 à mai 2006, nous avons comparé les résultats de la chirurgie chez des patients atteints d'un carcinome hépatocellulaire ayant envahi des organes adjacents aux résultats obtenus chez des patients sélectionnés au hasard mais étroitement jumelés, atteints d'un carcinome hépatocellulaire sans propagation aux organes adjacents.

Résultats : Nous avons inclus 42 patients dont le carcinome hépatocellulaire s'était propagé aux organes adjacents et 126 patients dont le carcinome hépatocellulaire n'avait pas envahi les organes adjacents. On n'a noté aucune différence significative quant à la survie, la morbidité opératoire ou la mortalité entre les groupes. Chez les patients atteints d'un carcinome hépatocellulaire propagé aux organes adjacents, l'examen histopathologique du spécimen a révélé un réel envahissement tumoral chez 13 patients et des adhésions chez 29 patients. Les patients atteints d'un envahissement tumoral étaient plus susceptibles de présenter une forte incidence d'infiltration capsulaire, d'envahissement microvasculaire et de récurrence intrahépatique précoce (≤ 1 an après l'hépatectomie). La survie globale à 5 ans des patients présentant un envahissement tumoral était de 11,5 %, tandis que celle des patients qui présentaient une adhésion tumorale était de 38,1 % ($p = 0,033$).

Conclusion : La résection radicale est une approche sécuritaire et efficace pour le carcinome hépatocellulaire propagé aux organes adjacents. Ce type d'envahissement se comporte sur le plan clinique de façon plus agressive et est associé à une survie moins bonne que dans le cas d'une adhésion tumorale.

Hepatocellular carcinoma (HCC) accounts for 80%–90% of primary liver cancers. It is a major health problem worldwide, with an estimated incidence ranging from 500 000 to 1 million new cases annually. It is the fifth most common cancer in the world, and the third most common cause of cancer-related death.^{1,2} Surgical resection with complete

extirpation of the tumour provides the best chance of a cure for patients with HCC.³ With advances in surgical techniques and perioperative care, results of hepatic resection for HCC have greatly improved, permitting more extensive resection for large HCC.

Large, peripherally located HCC sometimes extend to the adjacent organs.⁴ To curatively resect HCC extending to adjacent organs, the combined resection of these organs is inevitable. Although combined resection of the organs is frequently performed during hepatectomy for HCC,⁵⁻⁷ only a few authors have reported their surgical experience.^{4,5,8-11} In the present study, we analyzed the safety and effectiveness of en bloc resection for HCC extending to adjacent organs.

METHODS

We compared surgical outcomes of patients with HCC who underwent hepatic resection with curative intent between December 2002 and May 2006 at the Department of Special Treatment and Liver transplantation in Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China. We compared the outcomes of patients who had en bloc resection of the organs adjacent to the liver (group A) with those of randomly selected patients whose HCC did not extend to adjacent organs (group B). The groups were matched for age, sex, Child–Pugh class, hepatitis B surface antigen (HBsAg) status, tumour size and location. We obtained written informed consent from each patient before the procedure, and our study protocol was approved by the ethics committee of our hospital.

Routine preoperative imaging studies included chest radiography, abdominal ultrasonography and abdominal computed tomography (CT). Evaluation of liver function included serum biochemistry and prothrombin time. Patient selection for hepatic resection was based on their good general condition, favourable Child–Pugh class (grade A plus selected grade B), adequate liver remnant and the possibility of complete resection with curative intent.

Surgery was performed through a bilateral subcostal incision or “Mercedes-Benz incision.” Thoracic extension in the seventh intercostal space was used liberally in patients with large right lobe tumours to obtain adequate exposure. After an exploratory laparotomy, the liver was then assessed with intraoperative ultrasonography to assess the extent of local disease and to detect any extrahepatic metastases or peritoneal seedings. Resection began with a Pringle manoeuvre with clamp/unclamp cycles of 15/5 minutes. Transection of the liver parenchyma was performed along the demarcation line using a clamp-crushing method. Patients with HCC extending to adjacent organs received complete en bloc resection. Attempts were made to obtain a tumour-free margin during parenchymal transaction. Nomenclature for the extent of hepatic resection follows the Brisbane 2000 Guidelines for Liver Anatomy and

Resection.¹² Major resection was defined as a resection of 3 or more segments, whereas minor resection was defined as a resection of 2 or fewer segments according to the Couinaud classification of liver anatomy.

Each resected specimen was examined grossly and microscopically to determine tumour size, capsule formation, vessel invasion, satellite nodules, histological differentiation, chronic hepatitis, liver cirrhosis and hepatectomy margin status. When the HCC cells infiltrated the normal tissue of adjacent organs, it was defined as a histological invasion of HCC, whereas if they did not, it was defined as a histological adhesion.⁸

Operative morbidity and mortality were defined as complications or deaths, respectively, that occurred within 30 days after the operation or during the same hospital admission.

After discharge, patients attended monthly follow-up visits, and they underwent α -fetoprotein analysis and ultrasonography or CT at least every 3 months at our outpatient clinic, especially during the first 2 years after surgery. Intrahepatic recurrence was categorized as early (≤ 1 yr after hepatectomy) and late (> 1 yr after hepatectomy) recurrence.¹³

Statistical analysis

We compared categorical and continuous variables using χ^2 and Student *t* tests, respectively. The survival rate was determined using the Kaplan–Meier method. All statistical analyses were performed using SPSS version 11.0 for Windows (SPSS Inc.). We considered results to be significant at $p < 0.05$.

RESULTS

During the study period 407 patients with HCC underwent hepatic resection with curative intent at our centre. Of these patients, 42 (10.3%) underwent hepatic resections with en bloc combined resection of the organs adjacent to the liver (group A). Only 12 (28.5%) of these 42 patients were preoperatively suspected as extension of adjacent organs from HCC by radiological studies. The adjacent organs resected included the diaphragm ($n = 26$), right adrenal gland ($n = 13$), colon ($n = 3$), stomach ($n = 2$) and greater omentum ($n = 3$). Four patients had more than one combination of the above resections. For comparison, we randomly selected 126 closely matched (3:1) patients from among the remaining HCC patients (group B). Table 1 compares the clinicopathological features, operative procedures and perioperative outcomes between groups A and B; there was no statistical difference between the groups.

The overall cumulative survival results of group A (1-yr 81.0%, 3-yr 47.5%, 5-yr 33.2%; median survival 32 mo) was lower than that of group B (1-yr 88.1%, 3-yr 60.2%, 5-yr 40.0%; median survival 42 mo), but these results did not reach statistical significance ($p = 0.16$; Fig. 1A). In

group A, the median survival for patients with cancer involving the diaphragm, adrenal gland and gastrointestinal tract was 32, 38 and 54 months, respectively.

In group A, histopathological examination of the specimen revealed true tumour invasion in 13 patients and tumour adhesion in 29 patients. When the pathological features were compared between the patients with tumour invasion of or adhesion to adjacent organs, the patients with tumour invasion were more likely to have capsule infiltration ($p = 0.032$) and microvascular invasion ($p = 0.035$; Table 2).

At last follow-up, 31 patients in group A experienced recurrence in the remnant liver. Although the incidence of intrahepatic recurrence was not different between patients with tumour invasion of adjacent organs and patients with tumour adhesion (76.9% v. 72.4%, $p = 0.76$), the incidence of early recurrence after resection was significantly higher in patients with tumour invasion of adjacent organs than in patients with tumour adhesion (80.0% v. 38.1%, $p = 0.029$).

Table 1. Clinicopathological features, operative procedures and perioperative outcomes of patients with hepatocellular carcinoma with (group A) and without adjacent organ extension (group B)

Variable	Group; no. (%)*		p value
	Group A, n = 42	Group B, n = 126	
Age, mean (SD) yr	48.9 (10.6)	48.4 (11.4)	0.89
Sex, male:female	33:9	99:27	> 0.99
HBV-positive	40 (97.6)	120 (95.2)	> 0.99
Child–Pugh class, A:B	40:2	120:6	> 0.99
Serum AFP > 100 µg/L	24 (57.1)	72 (57.1)	> 0.99
Tumour size, cm			
Mean (SD)	8.5 (3.7)	8.3 (1.4)	0.67
> 5 cm	34 (80.9)	102 (80.9)	> 0.99
Tumour location			> 0.99
Right lobe	33 (78.6)	99 (78.6)	
Left lobe	7 (16.7)	21 (16.7)	
Both lobes	2 (4.7)	6 (4.7)	
Satellite nodules	15 (35.7)	37 (29.4)	0.44
Cirrhotic liver	23 (54.7)	68 (53.9)	0.93
Absence of capsule formation	22 (52.3)	52 (41.2)	0.21
Capsule infiltration, positive:negative	13:7	43:31	0.56
Macrovascular invasion	8 (19.0)	17 (13.4)	0.38
Microvascular invasion	34 (80.9)	87 (69.0)	0.14
Edmonson–Steiner grade, G1-G2:G3-G4	2:40	16:110	0.15
Extent of hepatectomy			0.62
Major resection	31 (73.8)	88 (69.8)	
Minor resection	11 (26.2)	38 (30.2)	
Clamping time, min	20.4 (9.1)	19.3 (7.8)	0.32
Blood loss, mL	975.6 (762.8)	816.9 (1126.4)	0.38
Perioperative blood transfusion	18 (42.9)	37 (29.4)	0.11
Postoperative complication	19 (45.2)	46 (36.5)	0.31
Mortality	0	0	
Postoperative hospital stay, d	13.5 (5.0)	12.6 (3.2)	0.34

AFP = α -fetoprotein; HBV = hepatitis B virus; SD = standard deviation.
*Unless otherwise indicated.

The overall survival of patients with tumour invasion of adjacent organs (1-yr 69.2%, 3-yr 30.8%, 5-yr 11.5%; median survival 17 mo) was significantly worse than that of patients with histological adhesion to adjacent organs (1-yr 86.2%, 3-yr 55.0%, 5-yr 38.1%; median survival 41 mo, $p = 0.033$; Fig. 1B).

DISCUSSION

Hepatocellular carcinoma is a highly malignant tumour, responsible for 500 000 deaths globally every year.

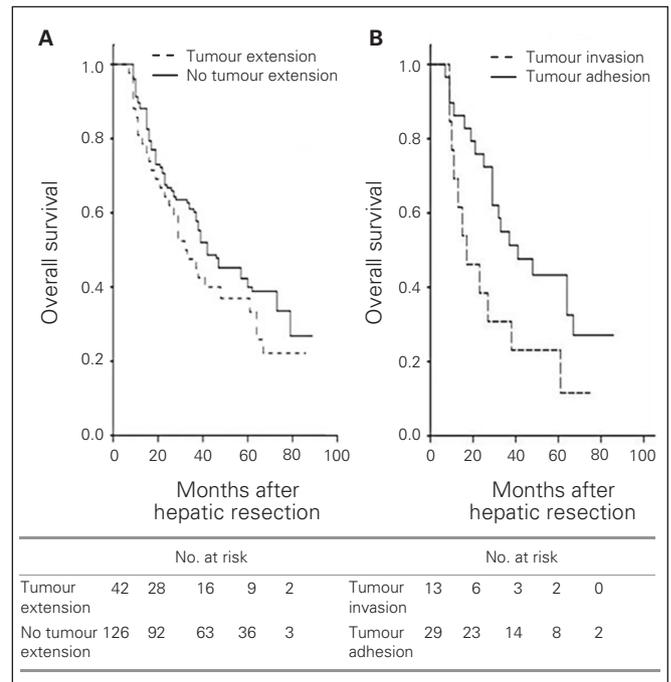


Fig. 1. (A) Overall survival of patients with hepatocellular carcinoma with (group A) and without (group B) extension to adjacent organs. **(B)** Overall survival of patients with tumour extension (group A) stratified according to tumour invasion of and adhesion to adjacent organs.

Table 2. Pathological features of group A patients stratified according to tumour invasion of and adhesion to adjacent organs

Variable	Tumour behaviour; no. (%)*		p value
	Invasion, n = 13	Adhesion, n = 29	
Tumour size, mean (SD) cm	8.2 (3.4)	8.7 (3.9)	0.80
Satellite nodules	6 (46.2)	9 (31.0)	0.34
Cirrhotic liver	7 (53.8)	16 (55.1)	0.94
Absence of capsule formation	7 (53.8)	15 (51.7)	0.90
Capsule infiltration, positive:negative	6:0	7:7	0.032
Macrovascular invasion	4 (30.8)	4 (13.8)	0.20
Microvascular invasion	13 (100)	21 (72.4)	0.035
Edmonson–Steiner grade, G1-G2:G3-G4	0:13	2:27	0.33

SD = standard deviation.
*Unless otherwise indicated.

Although it is characterized by a soft consistency and extensive growth, it can directly invade adjacent organs. Sometimes transcatheter arterial embolization and transarterial chemoembolization can induce exophytic growth of the HCC owing to an inflammatory reaction and change in the extrahepatic blood supply; as a result, HCC may invade adjacent organs.¹⁴ Rarely, intra-abdominal adhesions and scarring induced by the previous operation may cause HCC adhesion to and invasion of the gastrointestinal tract serosa.¹⁵

To date, 6 retrospective studies^{4,5,8-11} in the English literature report that a total of 147 patients with HCC extending to adjacent organs have undergone en bloc resection (Table 3). The mean age of these patients ranged from 46.2 (standard deviation [SD] 15.3) to 61.3 (SD 11.8) years. The male:female ratio in the pooled data was 6:1. Of these patients, 101 had liver cirrhosis on histopathological examination, and 161 had positive serology for hepatitis B virus. The most frequent location of HCC extension in other organs was the diaphragm, followed by the right adrenal gland, abdominal wall, colon, stomach and pancreas. We made similar observations in the present study.

Tumour extension to the adjacent organs does not necessarily indicate tumour invasion. According to published research, 7%–43% of HCC extending to the adjacent organs found during surgery had histologically proven evidence of tumour invasion.^{4,5,8,9} This figure was 30.9% in the present study. Intraoperatively, it is hard to differentiate whether local invasion has occurred or not. Tumour invasion can be intraoperatively diagnosed by frozen section. However, separating the tumour from the organs to which it adheres may cause tumour rupture, massive bleeding and tumour dissemination.⁵ Thus, we fully agree with other

authors^{4,5,8,9,15} that only en bloc resection should be performed in such patients.

Although en bloc resections of HCC extending to adjacent organs is technically challenging, postoperative mortality and morbidity were not significantly higher in group A than group B in the present study. Similarly, several previous studies compared perioperative outcomes between HCC patients with or without adjacent organ extension and did not find any statistically significant difference.^{4,5,8,9} These data suggest that en bloc resection of HCC extending to adjacent organs is safe.

The presence of histological tumour invasion of adjacent organs other than the gallbladder, which is stage IV disease according to the tumour-node-metastasis classification for primary liver cancer devised by the International Union Against Cancer, indicates poor prognosis.¹⁶ Poon and colleagues¹⁷ reported a median survival of 10.9 months after resection for such patients. A cumulative analysis of the 29 patients with HCC invading the gastrointestinal tract showed that the median survival of patients who received nonsurgical therapy, curative surgery and supportive therapy was 3.0, 9.7 and 1.2 months, respectively.¹⁵ In contrast, Jeng and colleagues⁵ found no significant difference in survival between patients with and without true adjacent organ invasion after surgery. It should be noted that the favourable results might partly be owing to a greater selection of patients with a solitary type tumour with no daughter nodule and no evidence of vascular invasion or intravascular tumour thrombi. Moreover, the duration of follow-up was only 18 months in the study by Jeng and colleagues. In one study⁴ involving 22 patients with HCC who underwent combined resection of the adjacent organs, there was no significant difference in long-term prognosis of the patients with respect to whether the adjacent organs were actually histologically invaded. However, these results could be biased by the small number of patients in the cohort.

In terms of outcome, our study confirmed that the survival of patients with adjacent organ tumour invasion after surgery was worse than that of patients with tumour adhesion. Our comparison of tumour features in the 2 groups demonstrated that HCC with true invasion of adjacent organs was more aggressive biologically, with a high incidence of capsule infiltration and microvascular invasion. A study from Hong Kong showed that satellite lesions, microscopic venous invasion and absence of tumour capsule occurred in 22.2%, 74.1% and 74.1% of patients with HCC invasion of adjacent organs, respectively.¹⁷ These unfavourable factors may, at least in part, account for the poor prognosis in this subset of patients. Despite the poor prognosis of patients with adjacent organ invasion, given the lack of effective alternative therapies, our current practice is to perform hepatectomy with complete removal of invaded organs when a curative operation seems feasible.

The postoperative recurrence of HCC remains the

Table 3. Characteristics of reported cases of hepatocellular carcinoma with extension to adjacent organs

Characteristic	No.*
Sex, male:female	127:20
Age, mean (SD) range yr	46.2 (15.3) to 61.3 (11.8)
HBsAg positive	161
Tumour size, mean (SD) range cm	8.5 (3.9) to 12.4 (3.8)
Cirrhosis	101
Organs involved	
Diaphragm	132
Adrenal gland	6
Abdominal wall	6
Colon	5
Stomach	3
Pancreas	3
Kidney	1
Spleen	2
Inferior vena cava	1
Great omentum	1

HBsAg = hepatitis B surface antigen; SD = standard deviation.
*Unless otherwise indicated.

major cause of death and the main obstacle to long-term survival.¹⁸ We classified the timing of recurrences as early (≤ 1 yr) or late (> 1 yr) recurrences. Early recurrences appear to arise mainly from intrahepatic metastases, whereas late recurrences are more likely to be multicentric in origin. Despite similar treatments, the prognosis for patients with early recurrence was worse than that of patients with late recurrence.¹³ In the present study, patients with HCC invasion of adjacent organs most frequently experienced early recurrence after resection. Thus, an effective adjuvant therapy is needed to improve the prognosis after hepatic resection in this subset of patients. It has been suggested that postoperative transarterial chemoembolization¹⁹ or adoptive immunotherapy²⁰ may reduce the incidence of early recurrence after hepatectomy. Recently, sorafenib, an antiangiogenic and antiproliferative agent, has been shown to improve survival in patients with advanced HCC.²¹ So far, however, there is no clear evidence concerning the effect of sorafenib on tumour recurrence after hepatectomy for high-risk patients. Further investigation of this therapy is warranted.

Since accurate diagnosis and staging are of paramount importance in establishing a treatment strategy, preoperative means of assessing the probability of HCC extension to adjacent organs are needed. However, preoperative diagnosis by radiological investigation was confirmed in only 12 (28.5%) patients in the present study. In addition, there were no significant differences regarding the clinicopathological features between patients with or without adjacent organ extension. Future studies should attempt to find novel molecular markers to predict the presence of extension to adjacent organs in patients with HCC treated with resection.

CONCLUSION

We found that en bloc resection is a safe and effective therapy for HCC extending to adjacent organs. Tumour invasion of adjacent organs exhibits a more aggressive clinical behaviour and worse survival than tumour adhesion. Adjuvant therapy should be required for this subset of patients.

Competing interests: None declared.

Contributors: Y.-M. Zhou, F. Xu, T. Kan and J.-M. Yang designed the study. Y.-M. Zhou, C.-J. Sui, F. Xu, T. Kan and J.-M. Yang acquired the data, which Y.-M. Zhou, B. Li, F. Xu, T. Kan and J.-M. Yang analyzed. Y.-M. Zhou, C.-J. Sui, B. Li, T. Kan and J.-M. Yang wrote the article, which C.-J. Sui, B. Li, F. Xu, T. Kan and J.-M. Yang reviewed. All authors approved its publication.

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