Original article

Outcome of patients with huge hepatocellular carcinoma after primary resection and treatment of recurrent lesions

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Background: Tumour recurrence is common after hepatic resection of hepatocellular carcinomas (HCCs) greater than 10 cm in diameter. This study evaluated the outcome of patients with huge HCC after primary resection and treatment of recurrent lesions.

Methods: A retrospective review was undertaken of clinical data for 100 patients with huge HCC who underwent liver resection.

Results: Mean(s.d.) tumour diameter was 13·3(3·0) cm; 80 per cent were single lesions. Systematic and non-systematic resections were performed in 80 and 20 per cent of patients respectively, with R0 resection achieved in 86 per cent. Overall 1-, 3- and 5-year disease-free survival rates were 43, 26 and 20 per cent respectively. Risk factors for HCC recurrence were resection margin less than 1 cm and macrovascular invasion. Extensive tumour necrosis of 90 per cent or more after preoperative transarterial chemoembolization was not a prognostic factor. Some 85 per cent of patients with recurrence received various treatments, and these patients had a longer post-recurrence survival than those who were not treated. Overall 1-, 3- and 5-year survival rates were 66, 44 and 31 per cent respectively.

Conclusion: In patients with huge HCC, hepatic resection combined with active treatment for recurrence resulted in longer-term survival. Frequent protocol-based follow-up appears to be beneficial for the early detection and timely treatment of recurrence.

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Introduction

Hepatocellular carcinoma (HCC) is one of the commonest malignancies worldwide. The mainstay of treatment has been hepatic resection, although patients with smaller lesions are frequently treated non-surgically. A considerable proportion of patients present with advanced large lesions at the time of initial diagnosis. In patients with a HCC greater than 10 cm in diameter – so-called huge HCC – transarterial chemoembolization (TACE) resulted in a 5-year survival rate of less than 10 per cent[1], whereas hepatic resection has a 5-year survival rate of 16·7–33 per cent[2–8], which has not been surpassed by other treatment modalities. At present, hepatic resection is regarded as the treatment of choice for huge HCC, provided the patient's hepatic functional reserve is acceptable for resection.

Tumour recurrence is common after resection of huge HCC, and overall patient survival is usually based on the final outcome following primary liver resection and additional treatment for recurrence. Unlike other primary liver malignancies, recurrent lesions following HCC resection can be treated with various modalities, such as repeat resection, TACE and radio frequency ablation (RFA). Overall survival may be improved when local recurrences are detected and treated at an early stage. Most reports of the treatment of huge HCC have not clarified the prognostic effect of treatments for recurrence. To evaluate the overall outcome of huge HCC after primary resection and recurrence treatment, the clinical data for 100 patients with HCC greater than 10 cm in diameter were reviewed retrospectively.

Patients and methods

Of 738 patients with HCC who underwent hepatic resection at the Asan Medical Centre in Seoul between

January 1997 and December 2003, 104 (14·1 per cent) had HCC larger than 10 cm in the longest diameter. Four patients who had unusual pathological findings mixed with cholangiocarcinoma components were excluded from the study. The medical records of the remaining 100 patients were reviewed retrospectively, and the patients were followed up until April 2006.

Clinicopathological findings are summarized in *Table 1*. As the shape of many of the lesions was not spheroid and the longest diameter did not reflect the exact size of the mass, tumour volume was estimated by using the formula for ellipsoid masses. Preoperative portal vein embolization was performed in selected patients undergoing right lobectomy[9]. When conventional mobilization of the tumour-bearing right lobe did not appear to be possible, the liver was transected by an anterior approach[10]. Hepatic resection was classified as systematic and non-systematic hepatectomy. All patients were managed in the intensive care unit until liver function had recovered.

Because a single huge HCC is classified differently in the staging systems of the American Joint Committee on Cancer (AJCC) (sixth edition)[11] and the modified pathological tumour node metastasis (pTNM) classification proposed by the American Liver Tumor Study Group[12], both systems were used concurrently in this study.

Follow-up of all surviving patients included estimation of serum α-fetoprotein levels, dynamic liver computed tomography (CT), liver ultrasonography and chest radiography every 1–2 months, especially during the first 2 years. For suspected recurrence, all available diagnostic modalities including hepatic angiography, magnetic resonance imaging, high-resolution chest CT and positron emission tomography were performed. Any recurrences were treated as vigorously as possible. All patients with recurrence attended routinely for follow-up every month until the disease-free interval exceeded 2 years.

Statistical analysis

All numerical data are reported as mean(s.d.) and as median (range). Survival curves were estimated using the Kaplan–Meier method and compared with the log rank test and Gehan's Wilcoxon test. Cox proportional hazard regression was used for multivariable analysis. $P < 0{\cdot}050$ was considered statistically significant.

Results

Patient demographics and tumour characteristics

Clinicopathological features and surgical treatments of the 100 patients are summarized in *Table 1*. Macrovascular invasion of the portal vein and hepatic vein was detected in 18 and eight patients respectively.

Table 1 Clinicopathological features and surgical treatments of 100 patients who underwent hepatic resection for hepatocellular carcinomas greater than 10 cm in diameter

Age (years)*	47(12) (24–79)
Sex	
M	77
F	23
Indocyanine green retention at 15 min (%)*	8·9(5·6) (0·9–30·4)
Preoperative portal vein embolization	6
Maximal tumour diameter (cm)	
Mean(s.d.)	13·3(3·0)
Median (range)	12·5 (10–21)
Tumour volume (ml)	
Mean(s.d.)	618(400)
Median (range)	495 (200–1800)
< 500	51
500–999	30
≥ 1000	19
Lymph node metastasis	
No	96
Yes	4
Sixth AJCC stage	
I	42
II	11
IIIA	35
IIIB	8
IIIC	4
IV	0
Modified pTNM stage	
I and II	0
III	62
IVA1	12
IVA2	22
IVB	4
Liver resection	
Systematic resection	80
Right lobectomy	50
Left lobectomy	17
Left lateral segmentectomy	8
Anterior segmentectomy	4
Posterior segmentectomy	1
Non-systematic resection	
Partial hepatectomy	20
Combined organ resection	10
Diaphragm excision	3
Gastrectomy	3
Right adrenalectomy	2
Left nephrectomy	1
Segmental colon resection	1

Values are numbers of patients unless indicated otherwise; *values are mean(s.d.) (range). Ellipsoid tumour volume = $(4\pi/3) \times$ (x-axis radius × y-axis radius × z-axis radius). AJCC, American Joint Committee on Cancer; pTNM, pathological tumour node metastasis.

As various preoperative treatments were performed (mainly TACE, in 57 patients), a wide range of tumour necrosis was observed in the 100 patients: total necrosis in one patient, 95 per cent necrosis in four, 90 per cent

necrosis in 12, 50–90 per cent necrosis in 19, necrosis of less than 50 per cent in 13 and no overt necrosis in 51. Microvascular invasion was present in one of the 17 patients with necrosis of 90 per cent or more, compared with 13 of the 19 patients with 50–90 per cent necrosis and 33 (65 per cent) of the 51 with no overt necrosis.

Ninety-eight of the 100 patients recovered from hepatectomy and two died from liver failure after surgery.

Treatment of recurrent hepatocellular carcinoma

Of the 98 surviving patients, 74 (76 per cent) developed HCC recurrence during a mean(s.d.) follow-up of 31(27) (range 3–104) months. Forty-nine (66 per cent) of these 74 patients presented initially with isolated intrahepatic recurrence and 25 (34 per cent) with extrahepatic, or concurrent intrahepatic and extrahepatic, recurrence. Initial recurrence sites and treatment for recurrence are summarized in *Table 2*; 63 (85 per cent) of the 74 patients received treatment.

Patient survival and risk factor analysis

Overall and disease-free survival curves are shown in *Fig. 1*. The overall cumulative 1-, 3- and 5-year survival rates were 66, 44 and 31 per cent respectively. Disease-free survival rates were 43, 26 and 20 per cent at 1, 3 and 5 years respectively, after excluding the two perioperative deaths, giving a recurrence rate at 1 year of 57 per cent. Survival after detection of recurrence was prolonged following specific treatments compared with that when no treatment was given (median survival 13 *versus* 3 months respectively;

Table 2 Initial treatments for recurrent hepatocellular carcinoma after resection

Recurrence site	Treatment	No. of patients
Liver	TACE	48
	Radio frequency ablation	1
Lung	Lung resection	4
	Radiotherapy	3
	Chemotherapy	2
	None	4
Peritoneum	Small bowel resection*	1
	None	2
Bone	Radiotherapy	1
	Chemotherapy	1
Adrenal gland	Adrenalectomy	1
Brain	None	1
Multiple sites	Chemotherapy and radiotherapy	1
	None	4

*As a result of intestinal obstruction. TACE, transarterial chemoembolization.

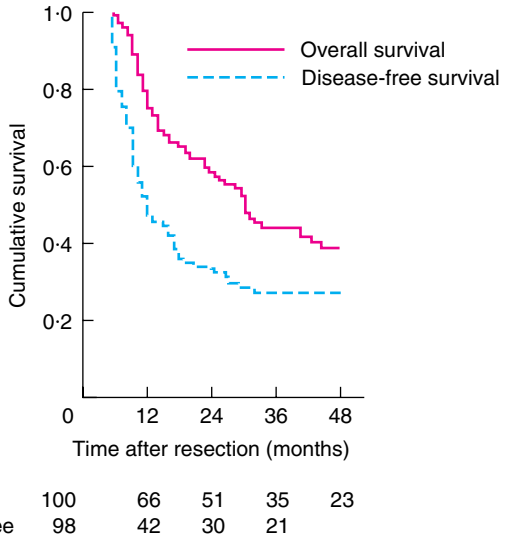

Fig. 1 Kaplan–Meier overall and disease-free survival curves for 100 patients who underwent resection of hepatocellular carcinomas greater than 10 cm in diameter

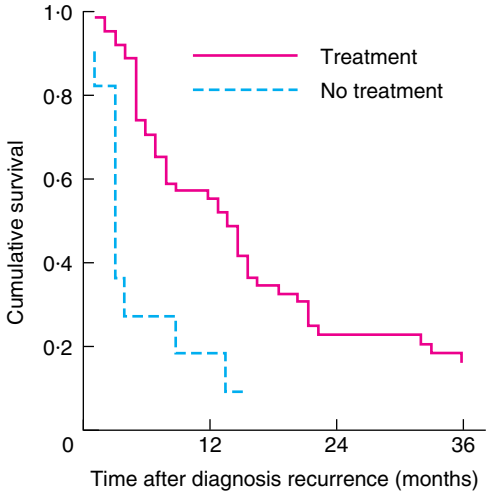

Fig. 2 Kaplan–Meier post-recurrence survival curves for patients who received, or did not receive, specific treatment for recurrence. $P = 0{\cdot}025$ (log rank test)

$P = 0{\cdot}025$) (*Fig. 2*). Tumour volume showed no consistent relationship with recurrence rates (*Fig. 3*), as patients with a tumour volume of 500–999 ml had a longer recurrence-free survival than those with a volume of less than 500 ml ($P < 0{\cdot}001$).

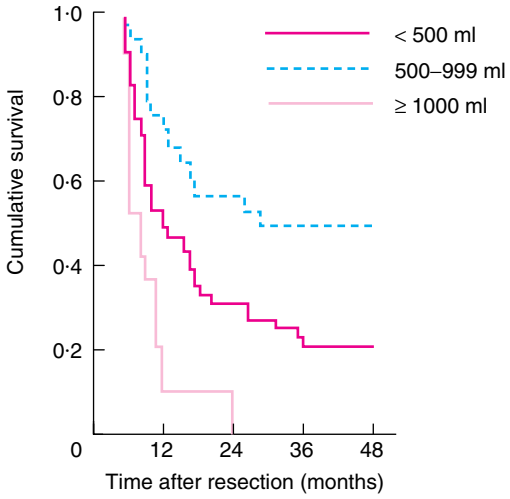

Fig. 3 Kaplan–Meier recurrence-free survival curves according to tumour volume. $P < 0{\cdot}001$ (log rank test)

In terms of stage classification, the AJCC staging system showed inconsistent outcomes between the stage I and II, because the survival outcome of stage II was better than that of stage I, whereas the modified pTNM system showed consistent correlations according to the tumour stage during analysis of HCC recurrence ($P = 0{\cdot}003$) and patient survival ($P < 0{\cdot}001$).

The outcomes of univariable analysis of risk factors for HCC recurrence and patient survival are summarized in *Table 3*. In multivariable analysis, independent risk factors were macrovascular invasion (hazard ratio (HR) 4·46; $P = 0{\cdot}003$) and resection margin of less than 1 cm (HR 3·13; $P = 0{\cdot}001$) for HCC recurrence, and macrovascular invasion (HR 3·11; $P = 0{\cdot}004$) for patient survival.

Discussion

The size of HCC has traditionally been considered an important risk factor for patient survival, although since the introduction of the sixth AJCC tumour staging system[11] the size of a single HCC mass in the absence of vascular invasion is no longer regarded as a critical factor. Survival after resection of T1 tumours greater than 10 cm in size is not significantly less favourable than that following resection of small T1 lesions[13]. This feature of the sixth AJCC staging system implies that patients with HCC should not be excluded from surgical resection solely because of the huge size of the lesion. Such HCC lesions, however, are classified as pT3 according to the modified pTNM staging system, indicating a less favourable prognosis[12]. Based on the results of the present study, the modified pTNM staging system appears to be more appropriate for huge HCC lesions than the sixth AJCC system.

The large size of HCCs larger than 10 cm indicates that the lesion is already advanced, with a greater possibility of tumour spread, including the existence of satellite nodules or macrovascular invasion[14]. Such advanced tumours carry a higher risk of recurrence, even after radical resection, so that the advantage of hepatic resection becomes marginal[2]. The present finding of a 1-year recurrence rate of 57 per cent is comparable to values of 35–72 per cent reported from other institutions (*Table 4*)[2,3,6]. However, 85 per cent of patients in the present series underwent treatment for recurrence. Although a meta-analysis of the effect of recurrence treatment was not possible owing to the lack of data in literature, the overall 5-year survival rate of 31 per cent in this series appears to indicate an improved outcome in comparison with other reports of 16·7–33 per cent (*Table 4*)[2–8].

In this study, independent risk factors for HCC recurrence were a resection margin of less than 1 cm and macrovascular invasion, whereas macrovascular invasion alone was an independent risk factor for patient survival. Although macrovascular invasion has been well described as a risk factor for survival[2–8], the clinical significance of a narrow resection margin has varied[2,5]. In contrast, the results of the present study indicate that systematic hepatic resection is not associated with a prognostic advantage, suggesting that partial hepatectomy may be a reasonable alternative when a sufficient resection margin can be obtained[7]. As macrovascular invasion was shown to be the only significant risk factor for both HCC recurrence and patient survival, liver resection is not reasonably indicated for patients with huge HCC and evidence of macrovascular invasion on preoperative imaging studies at the same time[6].

Because of the high recurrence rate after resection of huge HCC, preventive treatment appears to be necessary even after curative resection. As no standard treatment has yet been shown to be effective for wide usage[15,16], thorough postoperative surveillance should be undertaken as early detection of recurrence is essential for the institution of appropriate treatment.

Two-thirds of initial HCC recurrences in the present series involved isolated intrahepatic recurrence, and the other third involved extrahepatic recurrence with or without intrahepatic recurrence. To treat intrahepatic recurrent HCC, TACE has been the modality used most commonly after hepatectomy[17], particularly in patients with multifocal recurrence within the remnant liver[1].

Table 3 Univariable analysis of risk factors related to tumour recurrence and survival in 100 patients who underwent liver resection for hepatocellular carcinomas greater than 10 cm in diameter

	No. of patients	1-year disease-free survival rate (%)	*P*†	3-year survival rate (%)	*P*†
Viral hepatitis B			0·839		0·477
Yes	83	43		46	
No	17	46		35	
Child–Pugh class			0·219		0·167
A	88	57		62	
B	12	36		25	
Serum α-fetoprotein (ng/ml)			0·023		0·314
< 1000	59	65		58	
≥ 1000	41	41		53	
Tumour differentiation			0·243		0·377
Well	23	57		49	
Moderate	55	39		46	
Poor	20	37		37	
Tumour number			0·639		0·214
Single	80	43		48	
Multiple*	20	44		24	
Tumour necrosis (%)			0·557		0·974
< 90	83	42		45	
≥ 90	17	50		41	
Microvascular invasion			0·001		0·033
No	53	52		54	
Yes	47	33		32	
Macrovascular invasion			0·001		< 0·001
No	78	47		51	
Yes	22	29		19	
Systematic resection			0·377		0·369
Yes	80	42		41	
No	20	45		51	
R0 resection			< 0·001		0·079
Yes	86	49		46	
No	14	7		33	
Width of resection margin (cm)			0·009		0·075
≥ 1	44	56		54	
< 1	56	33		36	

*Includes satellite nodules. †log rank test.

Percutaneous RFA is another effective and safe method for treating recurrent HCC in the remnant liver[18]. Repeat liver resection is indicated for well controlled intrahepatic recurrence[17,19], although patient selection is intricate following major hepatectomy. Salvage liver transplantation can be a feasible treatment strategy for intrahepatic HCC recurrence. In the present series one patient underwent salvage living-donor liver transplantation 7 years after initial surgery; the underlying reason was progressive deterioration of hepatic function, not HCC recurrence[20]. Aggressive management with resection of isolated extrahepatic recurrence, especially solitary lung metastasis, has been reported to offer long-term survival[19,21]. In the present study 15 per cent of patients with recurrent HCC were not treated specifically for recurrence because of their poor general condition or rapid tumour spread to multiple organs. Treatment of local recurrences was shown to prolong patient survival in the present study; although the median post-recurrence survival interval was 13 months with treatment, 24 per cent of patients survived for more than 2 years after diagnosis of recurrence.

Preoperative treatments such as TACE were found occasionally to induce extensive tumour necrosis and to lower the rate of microvascular invasion. However, tumour necrosis of 90 per cent or more showed no relationship with tumour recurrence or patient survival. According to the sixth AJCC tumour staging system, the disappearance of microvascular invasion indicates downstaging of single tumours. Such downstaging did not improve patient survival. Thus, preoperative TACE does not appear to be effective for the treatment of huge HCC[1,22].

Table 4 Comparison of present results with published outcomes of surgical resection of hepatocellular carcinomas greater than 10 cm in diameter

Reference	Year	Country	No. of patients	1-year recurrence rate (%)	5-year survival rate (%)	Perioperative mortality rate (%)
Mok *et al.*[2]	2003	Taiwan	56	72	25	2
Yeh *et al.*[3]	2003	Taiwan	211	67·1	16·7	4·3*
Zhou *et al.*[4]	2003	China	621	NA	26·2	4·5
Chen *et al.*[5]	2004	China	525	NA	16·8	2·7
Nagano *et al.*[6]	2005	Japan	26	35	29	4
Liau *et al.*[7]	2005	USA	82	56†	33	2
Pawlik *et al.*[8]	2005	International	300	NA	26·9	5
Present study	2007	Korea	100	57	31	2

*Overall mortality rate including resection of smaller lesions; †2-year recurrence rate. NA, data not available.

In view of recurrence patterns during the first 5 years after resection of HCC, the following postoperative follow-up protocol is proposed for huge HCC: for patients with no recurrence, every month during the first year, every 2 months during the second year and every 3 months thereafter; and for patients with recurrence, every month until the disease-free survival interval exceeds 2 years.

In conclusion, hepatic resection combined with active treatment of recurrence resulted in longer-term survival of patients with HCC greater than 10 cm in diameter. Frequent protocol-based follow-up appears to be beneficial for the early detection and timely treatment of recurrences.

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References

1 Poon RT, Ngan H, Lo CM, Liu CL, Fan ST, Wong J. Transarterial chemoembolization for inoperable hepatocellular carcinoma and postresection intrahepatic recurrence. *J Surg Oncol* 2000; **73**: 109–114.
2 Mok KT, Wang BW, Lo GH, Liang HL, Liu SI, Chou NH *et al.* Multimodality management of hepatocellular carcinoma larger than 10 cm. *J Am Coll Surg* 2003; **197**: 730–738.
3 Yeh CN, Lee WC, Chen MF. Hepatic resection and prognosis for patients with hepatocellular carcinoma larger than 10 cm: two decades of experience at Chang Gung Memorial Hospital. *Ann Surg Oncol* 2003; **10**: 1070–1076.
4 Zhou XD, Tang ZY, Ma ZC, Wu ZQ, Fan J, Qin LX *et al.* Surgery for large primary liver cancer more than 10 cm in diameter. *J Cancer Res Clin Oncol* 2003; **129**: 543–548.
5 Chen XP, Qiu FZ, Wu ZD, Zhang BX. Chinese experience with hepatectomy for huge hepatocellular carcinoma. *Br J Surg* 2004; **91**: 322–326.
6 Nagano Y, Tanaka K, Togo S, Matsuo K, Kunisaki C, Sugita M *et al.* Efficacy of hepatic resection for hepatocellular carcinomas larger than 10 cm. *World J Surg* 2005; **29**: 66–71.
7 Liau KH, Ruo L, Shia J, Padela A, Gonen M, Jarnagin WR *et al.* Outcome of partial hepatectomy for large (> 10 cm) hepatocellular carcinoma. *Cancer* 2005; **104**: 1948–1955.
8 Pawlik TM, Poon RT, Abdalla EK, Zorzi D, Ikai I, Curley SA *et al.* Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. *Arch Surg* 2005; **140**: 450–457.
9 Madoff DC, Abdalla EK, Vauthey JN. Portal vein embolization in preparation for major hepatic resection: evolution of a new standard of care. *J Vasc Interv Radiol* 2005; **16**: 779–790.
10 Jeng KS, Chen BF, Lin HJ. *En bloc* resection for extensive hepatocellular carcinoma: is it advisable? *World J Surg* 1994; **18**: 834–839.
11 Liver (including intrahepatic bile ducts). In *In AJCC Cancer Staging Handbook*, Green FL, Page DL, Flemming ID, Fritz AG, Balch CM, Haller DG, Morrow M (eds), Sixth edition. Springer: New York, 2002; 131–144.
12 American Liver Tumor Study Group. A randomized prospective multi-institutional trial of orthotopic liver transplantation or partial hepatic resection with or without adjuvant chemotherapy for hepatocellular carcinoma. Investigators booklet and protocol, Kargar N: Basel, Switzerland 1998.
13 Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N *et al.* Simplified staging for hepatocellular carcinoma. *J Clin Oncol* 2002; **20**: 1527–1536.
14 Pawlik TM, Delman KA, Vauthey JN, Nagorney DM, Ng IO, Ikai I *et al.* Tumor size predicts vascular invasion and histologic grade: implications for selection of surgical treatment for hepatocellular carcinoma. *Liver Transpl* 2005; **11**: 1086–1092.
15 Sun HC, Tang ZY. Preventive treatments for recurrence after curative resection of hepatocellular carcinoma – a literature review of randomized control trials. *World J Gastroenterol* 2003; **9**: 635–640.
16 Ren ZG, Lin ZY, Xia JL, Ye SL, Ma ZC, Ye QH *et al.* Postoperative adjuvant arterial chemoembolization improves

survival of hepatocellular carcinoma patients with risk factors for residual tumor: a retrospective control study. *World J Gastroenterol* 2004; **10**: 2791–2794.
17 Chen WT, Chau GY, Lui WY, Tsay SH, King KL, Loong CC *et al*. Recurrent hepatocellular carcinoma after hepatic resection: prognostic factors and long-term outcome. *Eur J Surg Oncol* 2004; **30**: 414–420.
18 Choi D, Lim HK, Kim MJ, Lee SH, Kim SH, Lee WJ *et al*. Recurrent hepatocellular carcinoma: percutaneous radiofrequency ablation after hepatectomy. *Radiology* 2004; **230**: 135–141.
19 Poon RT, Fan ST, O'Suilleabhain CB, Wong J. Aggressive management of patients with extrahepatic and intrahepatic recurrences of hepatocellular carcinoma by combined resection and locoregional therapy. *J Am Coll Surg* 2002; **195**: 311–318.
20 Belghiti J, Cortes A, Abdalla EK, Regimbeau JM, Prakash K, Durand F *et al*. Resection prior to liver transplantation for hepatocellular carcinoma. *Ann Surg* 2003; **238**: 885–892.
21 Zhou XD, Tang ZY, Yang BH, Lin ZY, Ma ZC, Ye SL *et al*. Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. *Cancer* 2001; **91**: 1479–1486.
22 Zhang Z, Liu Q, He J, Yang J, Yang G, Wu M. The effect of preoperative transcatheter hepatic arterial chemoembolization on disease-free survival after hepatectomy for hepatocellular carcinoma. *Cancer* 2000; **89**: 2606–2612.