*Annals of Surgical Oncology* (© 2007)
DOI: 10.1245/s10434-007-9518-1

# Long Term Outcome and Prognostic Factors for Large Hepatocellular Carcinoma (10 cm or more) after Surgical Resection

Durgatosh Pandey, MS, DNB, M.Ch,[1] Kang-Hoe Lee, MRCP,[2] Chun-Tao Wai, MRCP,[3] Gajanan Wagholikar, MS, M.Ch,[1] and Kai-Chah Tan, FRCS[1]

[1]Hepatobiliary Surgery and Liver Transplantation, Asian Centre for Liver Diseases and Transplantation, Singapore, Singapore
[2]Respiratory Medicine & Critical Care, Asian Centre for Liver Diseases and Transplantation, Singapore, Singapore
[3]Hepatology, Asian Centre for Liver Diseases and Transplantation, Singapore, Singapore

**Background:** Surgical resection is the standard treatment for hepatocellular carcinoma (HCC). However, the role of surgery in treatment of large tumors (10 cm or more) is controversial. We have analyzed, in a single centre, the long-term outcome associated with surgical resection in patients with such large tumors.

**Methods:** We retrospectively investigated 166 patients who had undergone surgical resection between July 1995 and December 2006 because of large (10 cm or more) HCC. Survival analysis was done using the Kaplan-Meier method. Prognostic factors were evaluated using univariate and multivariate analyses.

**Results:** Of the 166 patients evaluated, 80% were associated with viral hepatitis and 48.2% had cirrhosis. The majority of patients underwent a major hepatectomy (48.2% had four or more segments resected and 9% had additional organ resection). The postoperative mortality was 3%. The median survival in our study was 20 months, with an actuarial 5-year and 10-year overall survival of 28.6% and 25.6%, respectively. Of these patients, 60% had additional treatment in the form of transarterial chemoembolization, radiofrequency ablation or both. On multivariate analysis, vascular invasion ($P < 0.001$), cirrhosis ($P = 0.028$), and satellite lesions/multicentricity ($P = 0.006$) were significant prognostic factors influencing survival. The patients who had none of these three risk factors had 5-year and 10-year overall survivals of 57.7% each, compared with 22.5% and 19.3%, respectively, for those with at least one risk factor ($P < 0.001$).

**Conclusions:** Surgical resection for those with large HCC can be safely performed with a reasonable long-term survival. For tumors with poor prognostic factors, there is a pressing need for effective adjuvant therapy.

Hepatocellular carcinoma (HCC) is one of the most common cancers in Southeast and East Asia[1] because of high endemicity of hepatitis B and the recent alarming emergence of hepatitis C-related liver disease. Surgical resection remains the mainstay of treatment for HCC and is the only chance of cure. Large HCC poses a difficult challenge because of the technical complexity of surgical resection and fear of postoperative hepatic decompensation, especially when associated with cirrhosis. Liver transplantation is not an accepted modality for treatment for large HCC because of issues of organ allocation and the high rates of tumor recurrence.[2,3] The alternative

Received May 6, 2007; accepted June 11, 2007
Address correspondence and reprint requests to: Durgatosh Pandey, MS, DNB, M.Ch; E-mail: durgatosh@yahoo.co.in

therapeutic modalities, such as transarterial chemoembolization (TACE) and radiofrequency ablation (RFA), are limited by a lack of complete tumor eradication and are clearly not appropriate for such large tumors.[4–7]

Several studies have presented a gloomy picture of high postoperative morbidity and mortality coupled with dismal long-term survival following resection of large HCC.[8–11] This has reinforced the nihilistic approach to such patients among several surgeons and institutions. As such, these patients are usually left untreated without any hope. Nevertheless, we have followed an aggressive policy of surgical resection in patients with large HCC as we feel that it provides significant local control with good quality of life and a potential for cure in an otherwise hopeless situation. We have even extended the indications of surgery to patients with small contralateral lesions.

In this study, we retrospectively analyzed the long-term outcome for the patients with large HCC (10 cm or more) following surgical resection at a single centre. We also evaluated the prognostic factors that may influence the outcome in such patients. We hope that this data will provide new hope to these patients who would otherwise be abandoned in terms of therapeutic options.

## MATERIALS AND METHODS

Between July 1995 and December 2006, 166 patients with large HCC (10 cm or more in greatest dimension) underwent surgical resection at the Asian Centre for Liver Diseases and Transplantation, Singapore. The clinical and histopathological data were retrieved and analyzed.

Preoperative evaluation of the liver function included serum levels of bilirubin, transaminases, alkaline phosphatase, gamma glutamyl transferase, albumin and prothrombin time, in addition to a thorough clinical examination for ascites and encephalopathy. Patients with Child-Pugh class A were considered suitable for resection of such a magnitude. A triphasic CT scan of the abdomen and X-ray of the chest were performed in all cases to evaluate the extent of the primary tumor. Additional studies, such as hepatic angiogram, magnetic resonance imaging and indocyanin green retention test, were performed at the discretion of the attending surgeon. The tumor was considered resectable if: there was no extrahepatic metastasis; there was no thrombus in the main portal vein or inferior vena cava; the entire tumor (including the main tumor, satellites and multicentric tumors) could be encompassed in the proposed resection; and the liver remnant volume was considered adequate. There were a few patients with small contralateral lesions that were treated with resection or RFA during the same procedure or with TACE either before the surgery or after the postoperative recovery.

A standard operative technique for hepatectomy was followed for these tumors. The abdomen was entered with a Mercedez incision and a thorough laparotomy was performed. Depending on the part of liver to be resected, mobilization was performed. In a few patients in whom initial mobilization was considered hazardous, an anterior approach was used.[12] Selective clamping of the portal and hepatic artery branches was done where feasible; if not, intermittent Pringle maneuver was performed. Parenchymal transection was performed using CUSA under low central venous pressure (CVP) anaesthesia.[13] The extent of hepatic resection was classified according to the Brisbane 2000 Guidelines for Liver Anatomy and Resection.[14] Resection of one lobe of liver (hemihepatectomy) or more (extended resection) were considered as major hepatectomies.

A standard histopathological assessment was performed for the tumor and the background liver. Tumor size was based on the documentation of the gross examination in the pathology report. Microscopic margin was considered positive if viable tumor cells were present at the margin. The tumors were histologically graded according to Edmondson's scale,[15] and grouped as well differentiated (grade I), moderately differentiated (grade II), or poorly differentiated (grade III-IV). The background liver was staged on a 4-point scale based on fibrosis and vascular alterations; cirrhosis was defined histologically as stage 4 on the scale.[16,17]

Postoperative mortality was defined as all deaths within 30 days of surgery or during the same hospital stay after liver resection.

Patients were followed up postoperatively every 3 months for the first 2 years, every 6 months for the next 3 years, and yearly thereafter. Conventional liver function tests and serum AFP levels were carried out at each visit in addition to clinical examination and ultrasonography of the abdomen. CT scan and hepatic angiogram were done selectively for recurrences suspected on ultrasonography or because of rising levels of serum AFP. Recurrences were treated by TACE, RFA, systemic chemotherapy, or best supportive care.

The protocols, as described above, were approved by the institutional review committee and were in

accordance with the relevant guidelines of the Ministry of Health, Singapore.

### Statistical Analysis

Statistical analysis was performed using the SPSS statistical software (version 14.0, SPSS, Chicago, Illinois, USA). Survival analysis was done using the method of Kaplan-Meier.[18] The postoperative mortality was included when calculating the overall survival. Univariate analysis was performed using the log-rank test for categorical variables and the Wald test for continuous variables. A stepwise multivariate analysis was performed using a Cox proportional hazard model[19] on all variables that were significantly associated with survival on univariate analysis. Differences were considered significant for a two-tailed $P$ value of less than 0.05.

## RESULTS

During the study interval, July 1995 to December 2006, 166 patients underwent surgical resection for large HCC (10 cm or more in greatest dimension). The clinicopathological features of the patients are shown in Table 1.

**TABLE 1.** *Clinicopathological features*

| | |
|---|---|
| Age (years) | |
| Median | 55 |
| Range | 12–83 |
| Gender | |
| Male | 143 (86.1%) |
| Female | 23 (13.9%) |
| Viral hepatitis | |
| Hepatitis B | 130 (78.3%) |
| Hepatitis C | 2 (1.2%) |
| Both hepatitis B and C | 1 (0.6%) |
| None | 33 (19.9%) |
| Alcohol abuse | 6 (3.6%) |
| Serum AFP | |
| Median | 147.5 ng/ml |
| Range | 2–364,653 ng/ml |
| Tumor size | |
| Median | 13 cm |
| Range | 10–24 cm |
| Surgery | |
| Wedge resection | 6 (3.6%) |
| Less than four segments | 64 (38.6%) |
| Four or more segments | 81 (48.8%) |
| Liver plus additional resection | 15 (9%) |
| Additional treatment | 101 (60.8%) |
| TACE | 94 |
| RFA | 3 |
| Both | 4 |
| Satellite lesions/ multicentricity | |
| Yes | 71 (42.8%) |
| No | 95 (57.2%) |
| Vascular invasion | |
| Yes | 102 (61.4%) |
| No | 64 (38.6%) |
| Tumor differentiation | |
| Well differentiated | 12 (7.2%) |
| Moderately differentiated | 107 (64.5%) |
| Poorly differentiated | 47 (28.3%) |
| Margin | |
| Negative | 155 (93.4%) |
| Positive | 11 (6.6%) |
| Cirrhosis | |
| Yes | 80 (48.2%) |
| No | 86 (51.8%) |
| Capsular invasion | 26 (15.7%) |

### Survival

The median survival of the patients who underwent resection for large HCC was 20 months, with overall actuarial 5-year and 10-year survival values of 28.6% and 25.9%, respectively (Fig. 1). There have been 23 actual 5-year survivors and 4 actual 10-year survivors.

The postoperative mortality was 3% (5 of 166). Of the 5 postoperative deaths, 2 occurred due to liver failure following resection, 1 to sepsis, 1 to myocardial infarction, and 1 because of very early recurrence. In addition to the postoperative mortality, there have been 96 documented deaths so far in this group of patients. Of these, 87 deaths were related to tumor recurrence and, in 9 cases, the cause of death was unknown.

### Prognostic Factors

Univariate analysis of prognostic factors for overall survival following resection in patients with large HCC identified viral hepatitis, satellite lesions/multicentricity, tumor size, cirrhosis, vascular invasion, and tumor differentiation as statistically significant factors determining poor prognosis (Table 2). Age, gender, type of surgery performed (major or minor hepatectomy), serum AFP, capsular invasion, and resection margin (positive or negative) were not statistically significant. It is difficult to draw a definite conclusion regarding the importance of margin because of the small number of patients (11) with a positive margin.

On multivariate analysis (Table 2), the statistically significant factors predicting adverse outcome were satellite lesions/multicentricity ($P = 0.006$), cirrhosis ($P = 0.034$), and vascular invasion ($P < 0.001$). The impact of these significant factors is depicted in Fig. 2 (satellite lesions), Fig. 3 (cirrhosis), and Fig. 4 (vascular invasion).

We also compared the 27 patients who had none of the three risk factors (satellite lesions/multicentricity,

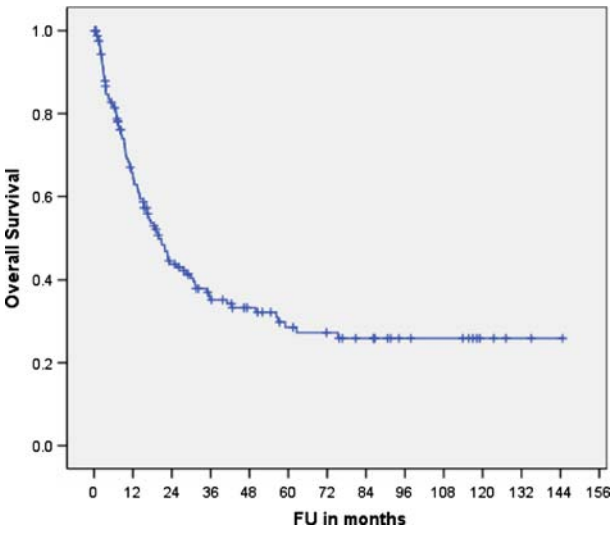


**FIG. 1.** Kaplan-Meier curve showing overall survival of the patients with large hepatocellular carcinoma (HCC) after surgical resection.

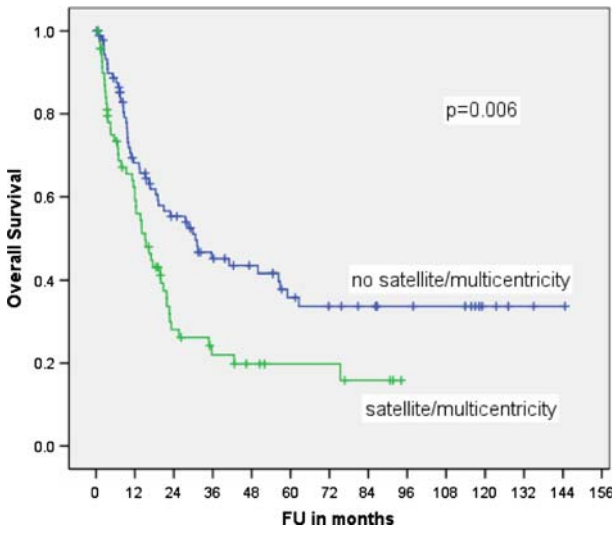


**FIG. 2.** Influence of satellite lesions/multicentricity on overall survival.

**TABLE 2.** *Prognostic factors for overall survival*

| Variables | *P* value (univariate analysis) | *P* value (multivariate analysis) |
|---|---|---|
| Age | 0.632 | |
| Gender | 0.089 | |
| Viral hepatitis | 0.041 | |
| Serum AFP | 0.241 | |
| Capsular invasion | 0.243 | |
| Type of surgery | 0.524 | |
| Additional treatment (TACE/RFA) | 0.482 | |
| Satellite lesions | 0.049 | 0.006 |
| Tumor size | 0.042 | |
| Cirrhosis | 0.004 | 0.028 |
| Vascular invasion | < 0.001 | < 0.001 |
| Tumor differentiation | 0.036 | |
| Resection margin | 0.068 | |

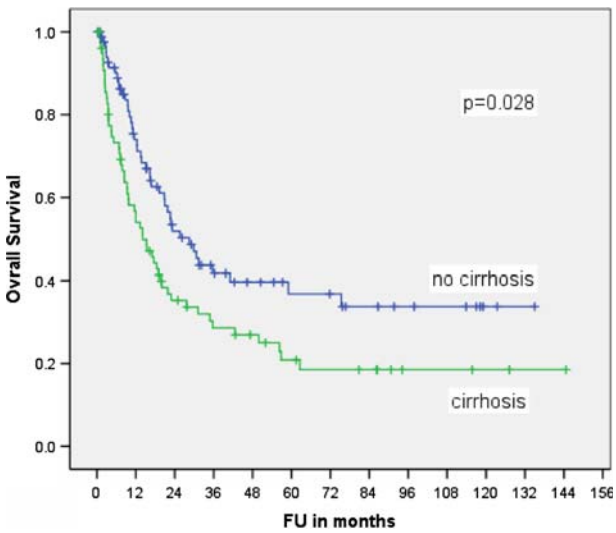


**FIG. 3.** Influence of cirrhosis on overall survival.

cirrhosis, and vascular invasion) with the others (139 patients) who had at least one. Those with no risk factors had overall actuarial 5-year and 10-year survivals of 57.7% each. In contrast, the patients with at least one risk factor had overall actuarial 5-year and 10-year survivals of 22.5% and 19.3%, respectively (Fig. 5). The difference in their survival was statistically significant ($P < 0.001$).

## DISCUSSION

The efficacy of surgical resection for large HCC has been a subject of considerable controversy and debate. With the improvements in surgical techniques and perioperative care, there has been a significant improvement in the postoperative outcome for patients following major hepatic resections in large volume centers.[20–22] This has encouraged some surgeons to reconsider surgical resection for large tumors.

In the present study, the 5-year and 10-year overall survival values were 28.6% and 25.9%. The Kaplan-Meier curve showing the survival shows a steep decline within 3 years. However, the curve effectively plateaus after 5 years. Consistent with the Asian experience, 80% of these patients had viral hepatitis and nearly half (48.2%) had histological evidence of cirrhosis in the background liver. Despite these ad-

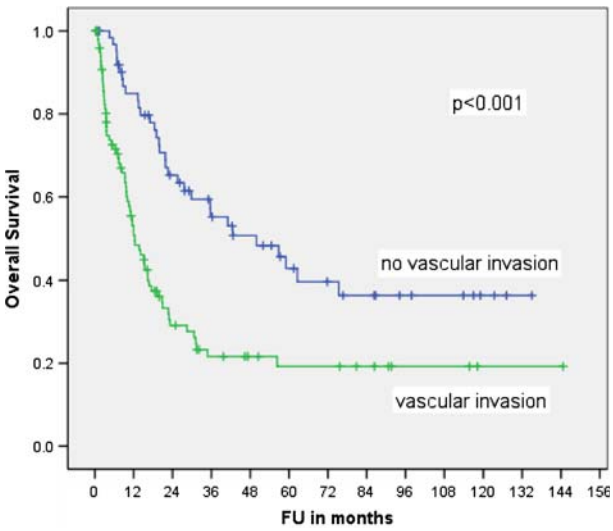


**FIG. 4.** Influence of vascular invasion on overall survival.

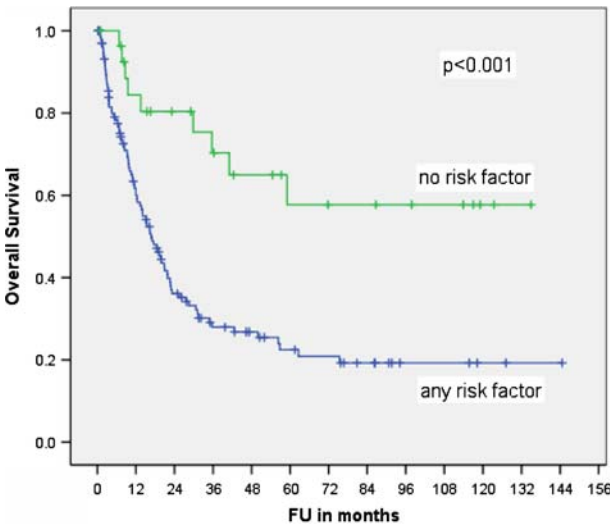


**FIG. 5.** Comparison of patients with no risk factors versus those with at least one risk factor.

verse factors, the postoperative mortality was 3%, which compares favorably with the results from other major studies on large HCC. The values reported in these other studies are depicted in Table 3.

There have been a few other important studies in which large HCC has been defined as tumors larger than 5 cm in size. In a report from a multi-institutional database, 380 patients with large (>5 cm) or multinodular (>3 nodules) HCC underwent surgical resection with a postoperative mortality of 2.4% and a 5-year overall survival of 39%.[23] In another large study from China, 2,102 patients underwent surgery for HCC greater than 5 cm in size between 1990 and 2003. The authors separated the patients into groups representing two time intervals: before and after the end of 1996. The postoperative mortality in the earlier and later time intervals was 3.6% and 0.7%, respectively. The 5-year overall survival improved from 27.9% during the earlier time interval to 38.7% during the later interval.[24] Unfortunately, the authors of both of the above studies did not separately analyze the results of tumors greater than 10 cm and, hence, their data cannot be compared with the present study.

In the present study, 48.2% of the patients had cirrhosis. This is in contrast to most other studies in which the proportion of cirrhotic patients is lower. The cirrhotic background not only presents difficulty during the postoperative recovery, but is also fertile soil for future tumor recurrences. Indeed, the presence of cirrhosis was an independent prognostic factor influencing survival in our study. The report from Memorial Sloan Kettering Cancer Center[25] offers a perspective from the West, with only 10% of the patients having cirrhosis. Their 5-year survival of 33% is somewhat better than ours (28.6%), which can possibly be explained by their lower proportion of cirrhotic patients.

In our study, satellite lesions/multicentricity, cirrhosis and vascular invasion were independent variables predicting poorer overall survival. The size and differentiation of tumor and the margin of resection were not significant predictors of adverse outcome. Other studies have found resection margin to be a significant prognostic factor. The small number of patients with positive margin (11) in our study makes it difficult to draw a firm conclusion regarding the importance of margin.

We have not considered the presence of small contralateral lesions to be a contraindication for surgery. The presence of cirrhosis predisposes to multicentricity and this should not be considered as metastatic disease. In addition, small lesions in a cirrhotic liver are difficult to characterize on imaging.[26,27] These lesions were either resected or ablated by RFA during the same procedure or were treated by TACE either preoperatively or postoperatively. Indeed, TACE or RFA or both were used in 60.8% of our patients; the indications being multicentricity, satellite lesions, tumor rupture, or as a palliative modality in the patients who refused surgery initially. TACE and RFA are suited best for small lesions.[28,29] A combination of resection of large tumor and TACE/RFA for smaller lesions can provide a chance of cure, even in patients with bilobar tumors. However, we could not find any prognostic significance of additional treatment (TACE or RFA or both).

**TABLE 3.** *Results of studies on resection for large hepatocellular carcinoma*

| Author | Year of publication | Number of patients | Cirrhosis | Postoperative mortality | 5-Year overall survival |
|---|---|---|---|---|---|
| Lee NH et al.[32] | 1998 | 40 | - | 2% | 28% |
| Poon RTP et al.[33] | 2002 | 120 | 26.7% | 5% | 27.5% |
| Mok KT et al.[34] | 2003 | 56 | 50% | 2% | 24.5% |
| Zhou XD et al.[35] | 2003 | 621 | 59.9% | 4.5% | 26.2% |
| Chen XP et al.[36] | 2004 | 525 | - | 2.7% | 16.8% |
| Liau KH et al.[25] | 2005 | 82 | 10% | 2% | 33% |
| Nagano Y et al.[37] | 2005 | 26 | 19.2% | 3.8% | 29.3% |
| Pawlik TM et al.[38] | 2005 | 300 | 26% | 5% | 27% |
| Present study | | 166 | 48.2% | 3% | 28.6% |

Another study has emphasized the importance of intraoperative blood loss as an independent prognostic factor.[25] Although we have not analyzed this factor, it needs careful interpretation. Blood transfusion has been implicated as a poor prognostic factor in surgery for other cancers, such as colorectal cancer.[30,31] However, the extent of intraoperative blood loss and the need for transfusions may be indicative of adverse host and tumor factors and, thus, may influence survival only indirectly. This factor needs further exploration in large studies.

Our study shows that major liver resection can be performed safely in cirrhotic patients with large liver tumors with a reasonably good oncologic outcome. Meticulous attention to surgical technique, minimizing blood loss, low CVP anesthesia, selective portal clamping, and attentive postoperative care all contribute to the safety of such a major surgical endeavor. Proper patient selection, attention to the principles of surgical oncology, and multimodal approach to treatment (surgery, TACE, RFA) are responsible for the good long-term outcome.

## CONCLUSION

Surgical resection can be performed safely in patients with large HCC. The long-term survival of such patients (28.6% at 5 years and 25.9% at 10 years) justifies this aggressive approach. There is a pressing need for effective adjuvant therapy in patients with tumor-related poor prognostic factors such as vascular invasion and satellite lesions. There is also a need for effective agents that can halt or reverse the process of cirrhosis in the background liver in order to reduce the formation of new tumors.

## ACKNOWLEDGEMENT

We gratefully acknowledge Ms. Pamela Jenkin's contribution in the data collection.

## REFERENCES

1. Parkin DM, Whelan SL, Ferlay J, et al. Cancer incidence in five continents, vol. VII. IARC Science Publications No. 143. Lyon, France: IARC 1997.
2. Yokoyama I, Todo S, Iwatsuki S, Starzl TE. Liver transplantation in the treatment of primary liver cancer. *Hepatogastroenterology* 1990; 37:188–93.
3. Margarit C, Charco R, Hidalgo E, Allende H, Castells L, Bilbao I. Liver transplantation for malignant diseases: selection and pattern of recurrence. *World J Surg* 2002; 26:257–63.
4. Poon RTP, Ngan H, Lo CM, Liu CL, Fan ST, Wong J. Transarterial chemoembolization for inoperable hepatocellular carcinoma and postresection intrahepatic recurrence. *J Surg Oncol* 2000; 73:109–14.
5. Aguayo A, Pat YZ. Nonsurgical treatment of hepatocellular carcinoma. *Semin Oncol* 2001; 28:503–13.
6. Curley SA, Izzo F, Ellis LM, Vauthey JN, Vallone P. Radiofrequency ablation of hepatocellular carcinoma in 110 patients with cirrhosis. *Ann Surg* 2000; 232:381–91.
7. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Ierace T, Solbiati L, Gazelle GS. Hepatocellular carcinoma: radiofrequency ablation of medium and large lesions. *Radiology* 2000; 214:761–8.
8. Nagasue N, Kohno H, Chang YC, et al. Liver resection for hepatocellular carcinoma. Results of 229 consecutive patients during 11 years. *Ann Surg* 1993; 217:375–84.
9. Furuta T, Sonoda T, Matsumata T, Kanematsu T, Sugimachi K. Hepatic resection for a hepatocellular carcinoma larger than 10 cm. *J Surg Oncol* 1992; 51:114–7.
10. Regimbeau JM, Farges O, Shen BY, Sauvanet A, Belghiti J. Is surgery for large hepatocellular carcinoma justified?. *J Hepatol* 1999; 31:1062–8.
11. Abdel-Wahab M, Sultan A, el-Ghawalby A, et al. Is resection for large hepatocellular carcinoma in cirrhotic patients beneficial? Study of 38 cases. *Hepatogastroenterology* 2001; 48:757–61.
12. Liu CL, Fan ST, Lo CM, Poon RTP, Wong J. Anterior approach for major right hepatic resection for major right hepatic resection for large hepatocellular carcinoma. *Ann Surg* 2000; 232:25–31.
13. Melendez JA, Arslan V, Fischer ME, Wuest D, Jarnagin WR, Fong Y, Blumgart LH. Perioperative outcomes of major hepatic resections under low central venous pressure anesthesia: blood transfusion, and the risk of postoperative renal dysfunction. *J Am Coll Surg* 1998; 187:620–5.
14. Terminology Committee of the International Hepato-Pancreato-Biliary Association. IHPBA Brisbane terminology of liver anatomy and resections. *HPB* 2000; 2:333–9.
15. Craig JR, Peters RL, Edmondson HA. Tumors of the liver and intrahepatic bile ducts. In: Atlas of Tumor Pathology. Armed Force Institute of Pathology (AFIP), Washington DC, 1988:48–169.
16. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995; 22:696–9.

17. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol* 1991; 13:372–4.
18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958; 53:457–81.
19. Cox DR. Regression models and life tables. *J R Stat Soc Ser B* 1972; 34:187–220.
20. Kawasaki S, Makuuchi M, Miyagawa S, et al. Results of hepatic resection for hepatocellular carcinoma. *World J Surg* 1995; 19:31–4.
21. Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J. Hepatectomy for hepatocellular carcinoma: towards zero hospital deaths. *Ann Surg* 1999; 229:322–30.
22. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1803 consecutive cases over the past decade. *Ann Surg* 2002; 236:397–406.
23. Ng KK, Vauthey JN, Pawlik TM, et al. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. *Ann Surg Oncol* 2005; 12:364–73.
24. Chen XP, Qiu FZ, Wu ZD, Zhang ZW, Huang ZY, Chen YF. Long-term outcome of resection of large hepatocellular carcinoma. *Br J Surg* 2006; 93:600–606.
25. Liau KH, Ruo L, Shia J, et al. Outcome of partial hepatectomy for large (> 10 cm) hepatocellular carcinoma. *Cancer* 2005; 104:1948–55.
26. Fung KT, Li FT, Raimondo ML, et al. Systematic review of radiological imaging of hepatocellular carcinoma in cirrhotic patients. *Br J Radiol* 2004; 77:633–40.
27. Varela M, Sanchez W, Bruix J, Gores GJ. Hepatocellular carcinoma in the setting of liver transplantation. *Liver Transpl* 2006; 12:1028–36.
28. Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology* 2006; 131:461–9.
29. Xu HX, Lu MD, Xie XY, et al. Prognostic factors for long-term outcome after percutaneous thermal ablation for hepatocellular carcinoma: a survival analysis of 137 consecutive patients. *Clin Radiol* 2005; 60:1018–25.
30. Bufalari A, Giustozzi G, Burattini MF, et al. Rectal cancer surgery in the elderly: a multivariate analysis of outcome risk factors. *J Surg Oncol* 2006; 93:173–80.
31. Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. *Cochrane Database Syst Rev* 2006; 1:CD00503.
32. Lee NH, Chau GY, Lui WY, King KL, Tsay SH, Wu CW. Surgical treatment and outcome in patients with a hepatocellular carcinoma greater than 10 cm in diameter. *Br J Surg* 1998; 85:1654–7.
33. Poon RTP, Fan ST, Wong J. Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. *J Am Coll Surg* 2002; 194:592–602.
34. Mok KT, Wang BW, Lo GH, et al. Multimodality management of hepatocellular carcinoma larger than 10 cm. *J Am Coll Surg* 2003; 197:730–8.
35. Zhou XD, Tang ZY, Ma ZC, Fan J, Qin LX, Zhang BH. Surgery for large primary liver cancer more than 10 cm in diameter. *J Cancer Res Clin Oncol* 2003; 129:543–8.
36. Chen XP, Qiu FZ, Wu ZD, Zhang BX. Chinese experience with hepatectomy for huge hepatocellular carcinoma. *Br J Surg* 2004; 91:322–6.
37. Nagano Y, Tanaka K, Togo S, et al. Efficacy of hepatic resection for hepatocellular carcinomas larger than 10 cm. *World J Surg* 2005; 29:66–71.
38. Pawlik TM, Poon RT, Abdalla EK, et al. International Cooperative Study Group in Hepatocellular Carcinoma. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. *Arch Surg* 2005; 140:450–8.