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# Risk factors and prognosis of patients with recurrent hepatocellular carcinoma who undergo liver re-resections

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ABSTRACT

*Background:* Management of recurrent hepatocellular cancer (HCC) after liver resection is challenging, with unsatisfactory long-term patient outcomes. Liver re-resection, in theory, is a good treatment option. We therefore studied prognosis and risk factors of patients who undergo re-hepatectomy.
*Methods:* We retrospectively analyzed 103 patients who underwent re-hepatectomy.
*Results:* The re-resection postoperative complication rate was 31.1% (32/103). Patients with gross vascular invasion (GVI), cirrhosis, or hepatitis B (HBV) infections not treated with antiviral therapy had higher morbidity than patients without these diseases (per chi-square tests). In bivariate regression analysis, cirrhosis (odds ratio [OR]: 10.308, $P = 0.031$) and HBV not treated with antiviral therapy (OR: 3.982, $P = 0.011$) were associated with immediate postoperative morbidity. Median overall survival (OS) after re-resection was 65.0 months (range: 2.1–119.3 months); cumulative OS rates were 1-year: 92.1%, 2-year: 78.2%, and 5-year: 54.4%. Independent risk factors for worse survival were serum AFP level > 20 ng/mL at first resection, portal hypertension (PH) and GVI at recurrence. In the non-PH group, microvascular invasion (micro-VI), GVI and pTNM III–IV disease were associated with poor prognosis; patients with pTNM I–II disease had significantly less micro-VI and GVI than did patients with advanced disease.
*Conclusion:* Repeat hepatectomy has favorable long-term outcomes. Cirrhosis and HBV not treated with antiviral therapy were associated with immediate postoperative morbidity. Serum AFP > 20 ng/mL at first resection, PH, and GVI at recurrence are independent prognostic factors. For patients without PH, TNM staging can predict prognosis.


## Introduction

Hepatocellular cancer (HCC) is a common malignancy, with > 1,000,000 new diagnoses and 500,000 deaths per year worldwide [1]. Owing to its high recurrence rate, long-term outcomes are still unsatisfactory[2,3]. Current therapeutic options for recurrent HCC include salvage liver transplantation, liver re-resection, radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), radiotherapy, and systemic treatments (such as chemotherapy, targeted therapy [sorafenib], and immune therapy). Among these strategies, resection, transplantation and RFA are potentially curative[4–6].

Currently, RFA is considered to be an effective therapy only for small recurrent HCC tumors (<3.0 cm)[7,8]. Although liver transplantation can be curative, it is not widely used owing to the lack of donors[9–12]. Liver re-resection is reportedly safe [13,14], but prognostic factors that affect overall survival (OS) of patients with recurrent HCC are unclear. We therefore focused on prognoses and risk factors of patients after liver re-resection, on the basis of a single-center experience from Northern China.

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## Patients and methods

Between January 1997 and July 2015, 1106 patients who were diagnosed with HCC underwent curative hepatectomies (i.e., in which all cancerous cells were removed) at the Department of Surgery, Affiliated Hospital of Qingdao University, Qingdao. After their initial resections, patients were followed-up with monthly laboratory testing, and ultrasonography, contrast-enhanced CT and/or MRI every 3 months. 64 patients were lost to follow-up, HCC recurrence was detected in 709 patients, of whom 103 patients received second curative hepatic resections. The present study was approved by the Affiliated Hospital of Qingdao University Ethics Committee (approval number: QDFY WZ 03415), and informed consent was signed by each patient or his or her relatives.

Tumor recurrence was defined as a new lesion that was detected either by biopsy, or by follow-up imaging that showed characteristic features of HCC. Immediate postoperative morbidity was defined as events that extend hospital stays beyond 30 days after surgery. Surgery-related deaths were defined as deaths within 2 months after surgery. Portal hypertension (PH) was defined as a hepatic vein pressure gradient > 10 mm Hg, and was also clinically diagnosed by the presence of esophageal varices, or by splenomegaly with a platelet count < 100,000/μL [15].

### Treatments

Contraindications for liver re-resection include ECOG score > 1, BCLC stage C or D disease, Child–Pugh grade B or C, and insufficient residual liver volume[16]. We used the Child–Pugh score to evaluate liver function status. In the current study, each patient had a Child–Pugh grade A liver function status. The operative procedure and the volume of hepatectomy were dependent on tumor number, size and location, liver reserve function, ratio of residual liver volume to standard liver volume (measured by three-dimensional computed tomography)[17] and the retention rate of indocyanine green at 15 min (ICGR15)[18] used in the previous 5 years. In anatomical resections, we divided the tumor and the tumor-containing portal vein along the demarcation line that appears after occluding the corresponding extrahepatic Glisson's pedicle. In non-anatomical resections, we divided the tumor and tumor-containing portal vein along 1.0 cm away from the tumor's edge. Because the presence of liver cirrhosis and severe adhesion with surrounding tissues or organs during re-resection, and perioperative blood transfusion was associated with poor prognosis of patients after operation, we strictly abided by the principle of surgical contraindications and tried to keep surgical time as brief as possible to ensure low incidences of liver failure, and intraoperative or postoperative bleeding in patients after operation. In the present study, 11 patients underwent anatomical resections, and 92 patients underwent non-anatomical resections (Table 1).

**Table 1**
Extent of liver re-resection in 103 patients with recurrent hepatocellular carcinoma.

| Operative procedure | Number of patients (n = 103) |
|---|---|
| Anatomic resection | |
| right liver | 1 |
| left liver | 2 |
| Caudate | 1 |
| Combined segmentectomy | 5 |
| Segmentectomy | 3 |
| Non-anatomic resection | |
| More than 1 Subsegmentectomy | 38 |
| 1 Subsegmentectomy | 53 |

### Statistical analysis

To analyze factors associated with immediate postoperative mortality, we used the chi-square test; all variables found to be significant in the chi-square test were entered into binary logistic regression analysis. Cumulative survival rates were computed by the Kaplan–Meier method and compared by the log-rank test. All variables found to be significant in univariate analyses were entered into multivariate analyses (Cox proportional hazards model). $P < 0.05$ was considered significant.

## Results

### Clinicopathologic characteristics associated with HCC recurrence

Clinicopathologic factors associated with HCC recurrence and initial intraoperative and pathological factors of the 103 patients (90 men and 13 women; median age: 57 years; range: 30–77 years) are summarized in Table 2.

### Morbidity and mortality of the patients who underwent repeat liver resection

No patients in this group died during re-hepatectomy. Because only 1 patient died of liver failure 2 months after surgery, postoperative mortality in this cohort was 0.97%, which was not statistically different from the mortality rate (n = 0) for all patients who underwent first curative hepatectomies at our hospital during the study period (P > 0.05). The postoperative complication rate was 31.1% (32/103). Postoperative complications were seen in 32 patients including pulmonary infection (n = 1), postoperative bleeding (n = 2), liver failure (n = 1), and ascites (n = 28). Hepatic

**Table 2**
Clinicopathologic characteristics of patients with recurrent HCC.

| Factors | n | % |
|---|---|---|
| Intraoperative and pathological factors of initial resection | | |
| PH(absent/present) | 91/12 | 89.3/11.7 |
| No. of segments resected (≦2/>2) | 94/9 | 91.3/8.7 |
| Resection margin (≦1/>1 mm) | 18/85 | 17.5/82.5 |
| Blood transfusion (Yes/No)[a] | 22/81 | 21.4/78.6 |
| Diameter of tumor (cm) (≦5/>5) | 79/24 | 76.7/23.3 |
| Multiple tumors (Yes/No) | 14/89 | 13.6/86.4 |
| GVI(Yes/No) | 2/101 | 1.9/98.1 |
| micro-VI(Yes/No) | 13/90 | 12.6/87.4 |
| Differentiation (I/II-IV) | 16/87 | 15.5/84.5 |
| Serum AFP level (≦20/>20 ng/mL) | 46/57 | 44.7/55.3 |
| The clinicopathologic factors of the second resection | | |
| Sex (M/F) | 90/13 | 87.4/12.6 |
| Age (≦60/>60 years) | 72/31 | 69.9/30.1 |
| Alcoholism (Yes/No) | 39/64 | 37.9/62.1 |
| Diabetes (Yes/No) | 6/97 | 5.8/94.2 |
| HBsAg (negative/positive) | 10/93 | 9.7/91.3 |
| Liver cirrhosis (Yes/No) | 87/16 | 84.5/15.5 |
| PH(absent/present) | 86/17 | 83.5/16.5 |
| Antiviral treatment (Yes/No) | 56/27 | 54.4/45.6 |
| Time to recurrence (≦1/>1 year) ** | 10/93 | 9.7/90.3 |
| Serum AFP level (≦20/>20 ng/mL) | 56/47 | 54.4/45.6 |
| Multiple tumors (Yes/No) | 23/80 | 22.3/77.7 |
| pTNM stage (I-II/III-IV) | 90/13 | 87.4/12.6 |
| GVI (Yes/No) | 5/98 | 4.9/95.1 |
| Differentiation (I/II-IV) | 8/95 | 7.8/92.2 |
| micro-VI (Yes/No) | 31/72 | 30.1/69.9 |
| No. of segments resected (≦2/>2) | 94/9 | 91.3/8.7 |

[a] Intra-or postoperative blood transfusion; ** from initial curative liver resection; PH: portal hypertension; GVI: gross vascular invasion; micro-VI: microvascular invasion.

decompensation was seen in 28.2% of the patients. Immediate postoperative morbidity was more common after these patients' second hepatectomies (n = 32) than their first hepatectomies (n = 120, P < 0.05). Chi-square test found patients with gross vascular invasion (GVI) or liver cirrhosis or with hepatitis B (HBV) infections that did not receive antiviral therapy had higher morbidity than patients without these diseases. In logistic regression analysis, liver cirrhosis (odds ratio [OR]: 10.308, P = 0.031) and HBV not treated with antiviral therapy (OR: 3.982, P = 0.003) were associated with immediate postoperative morbidity (Table 3).

*Univariate and multivariate analyses of risk factors for post-recurrence survival*

Median OS after liver re-resection was 65.0 months (range: 2.0–119.3 months). Cumulative OS rates were 1-year: 92.1%, 2-year: 78.2%, and 5-year: 54.4%.

Univariate analyses to identify factors significantly associated with post-recurrence survival found poor prognostic factors were serum alfa-fetoprotein (AFP) level > 20 ng/mL at the first resection, PH, GVI and advanced disease (pTNM stage III–IV) at recurrence (Table 4; Fig. 1). In multivariate analysis, serum AFP level >20 ng/mL at the first resection, PH, and GVI at recurrence were independent risk factors for poor survival after recurrence (Table 4).

In the non-PH group, microvascular invasion (micro-VI), GVI and advanced disease (pTNM III–IV) were associated with poor prognosis (Fig. 2). Patients with advanced disease had significantly more microVI and GVI than did those with early-stage disease (pTNM I–II).

## Discussion

We collected clinicopathologic data of patients who underwent liver re-resections, over a span of 19 years at a single center to provide guidance for clinical practice.

**Table 3**
Risk factors linked to immediate postoperative morbidity in patients who undergo liver re-resections.

| Variables | Postoperative morbidity | | Chi-square | Binary logistic regression | |
|---|---|---|---|---|---|
| | No | Yes | P | HR (95%CI) | P |
| Sex | 60 | 30 | 0.336 | | |
| Meal | 11 | 2 | | | |
| Femeal | | | | | |
| Age (year) | 51 | 21 | 0.525 | | |
| ≦60 | 20 | 11 | | | |
| >60 years | | | | | |
| Alcoholism | 26 | 12 | 0.932 | | |
| Yes | 45 | 20 | | | |
| No | | | | | |
| Diabetes | 5 | 1 | 0.663 | | |
| Yes | 66 | 31 | | | |
| No | | | | | |
| HBsAg negative | 8 | 2 | 0.720 | | |
| positive | 63 | 30 | | | |
| Liver cirrhosis | 56 | 31 | 0.019 | 10.308 (1.233–86.199) | 0.031 |
| Yes | 15 | 1 | | | |
| No | | | | | |
| PH absent present | 58 | 28 | 0.462 | | |
| | 13 | 4 | | | |
| Antiviral treatment | 34 | 22 | 0.038 | 3.982 (1.373–11.546) | 0.011 |
| Yes | 27 | 6 | | | |
| No | | | | | |
| Time to recurrence[a] | 6 | 4 | 0.497 | | |
| ≦1 | 65 | 28 | | | |
| >1 year | | | | | |
| Serum AFP level | 36 | 20 | 0.266 | | |
| ≦20 | 35 | 12 | | | |
| >20 ng/mL | | | | | |
| Multiple tumors | 17 | 6 | 0.558 | | |
| Yes | 54 | 26 | | | |
| No | | | | | |
| pTNM stage | 64 | 26 | 0.217 | | |
| I-II | 7 | 6 | | | |
| III-IV | | | | | |
| GVI | 1 | 4 | 0.031 | | |
| Yes | 70 | 28 | | | |
| No | | | | | |
| Differentiation | 5 | 3 | 0.701 | | |
| I | 66 | 29 | | | |
| II-IV | | | | | |
| micro-VI | 21 | 10 | 0.864 | | |
| Yes | 50 | 22 | | | |
| No | | | | | |
| No. of segments resected | 61 | 33 | 0.719 | | |
| ≦2 | 5 | 4 | | | |
| >2 | | | | | |

[a] From initial curative liver resection; GVI: gross vascular invasion; micro-VI: microvascular invasion; PH: portal hypertension.

**Table 4**
Univariate and multivariate analysis risk factors for post-recurrence survival.

| Variables | Median OS | Univariate | Multivariate | |
|---|---|---|---|---|
| | (months) | P | HR (95%CI) | P |
| Clinicopathologic characteristics at recurrence | | | | |
| Sex (M/F) | 65.8/24.0 | 0.079 | | |
| Age (≦60/>60 years) | 65.0/65.6 | 0.949 | | |
| Alcoholism (Yes/No) | 46.6/70.9 | 0.326 | | |
| Diabetes (Yes/No) | 65.6/65.0 | 0.782 | | |
| HBsAg (negative/positive) | 46.8/65.6 | 0.277 | | |
| Liver cirrhosis (Yes/No) | 64.8/84.0 | 0.892 | | |
| PH(absent/present) | 65.8/38.3 | 0.029 | 3.072 (1.390–6.792) | 0.006 |
| Antiviral treatment (Yes/No) | 84.0/60.7 | 0.081 | | |
| Time to recurrence[a] (≦1/>1 year) | 37.4/65.6 | 0.238 | | |
| Serum AFP level (≦20/>20 ng/mL) | 65.6/46.8 | 0.243 | | |
| Multiple tumors (Yes/No) | 38.3/65.6 | 0.102 | | |
| pTNM stage (I-II/III-IV) | 65.6/28.2 | 0.004 | | |
| GVI (Yes/No) | 65.6/15.5 | 0.004 | 7.075 (2.257–22.182) | 0.001 |
| Differentiation (I/II-IV) | 60.0/63.3 | 0.577 | | |
| micro-VI (Yes/No) | 39.3/68.6 | 0.075 | | |
| No. of segments resected (≦2/>2) | 65.0/24.6 | 0.059 | | |
| Surgery and tumor factors at first resection | | | | |
| PH(absent/present) | 65.8/49.7 | 0.135 | | |
| No. of segments resected (≦2/>2) | 65.6/39.4 | 0.985 | | |
| Resection margin (≦1/>1 mm) | 96.0/61.3 | 0.469 | | |
| Blood transfusion (Yes/No)[a] | 39.4/65.8 | 0.269 | | |
| Diameter of tumor (≦5/>5 cm) | 65.0/65.8 | 0.516 | | |
| Multiple tumors (Yes/No) | 46.8/65.0 | 0.984 | | |
| GVI(Yes/No) | 37.4/65.6 | 0.250 | | |
| micro-VI (Yes/No) | 84.0/63.4 | 0.654 | | |
| Differentiation (I/II-IV) | 84.0/62.2 | 0.165 | | |
| Serum AFP level (≦20/> 20 ng/mL) | 68.6/39.3 | 0.021 | 3.182 (1.503–6.740) | 0.003 |

[a] From initial curative liver resection; * *intra-or postoperative blood transfusion; GVI: gross vascular invasion; micro-VI: microvascular invasion; PH: portal hypertension.

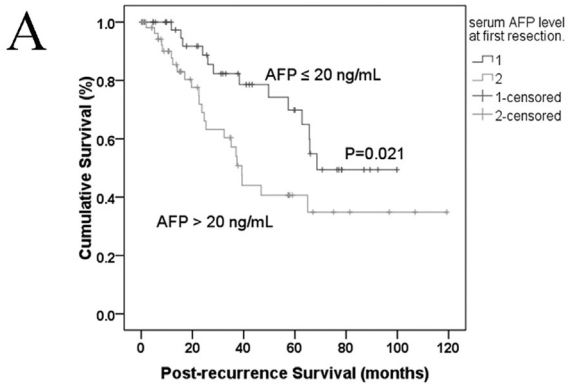
Repeated hepatectomy has been shown to offer a considerable survival benefit, with a cumulative 5-year survival rate of 52% (range: 41%–69%) after the second hepatectomy[19–21], which accords with the cumulative 5-year OS rate for the second liver resection of 54.4% in the current study. Although the rate of repeat hepatectomy is low, OS rates did not significantly differ between patients who underwent repeat hepatectomy and those who underwent initial hepatectomy[22]. Improvements in surgical techniques and perioperative management have led to decreased mortality and morbidity from re-hepatectomy for recurrent HCC. In the present study, we found that liver cirrhosis and HBV not treated with antiviral therapy were associated with postoperative complications. This result was not surprising. The previous study[23] confirmed that continued HBV replication and its accompanying inflammatory response are the leading causes of cirrhosis. Long-term anti-HBV treatment can even lead to regression of cirrhosis [24–26]. Patients with compensated cirrhosis, remain asymptomatic. Post-hepatectomy liver dysfunction and cirrhosis itself may lead to decompensated cirrhosis, which can cause ascites or variceal bleeding[27].

Reported predictors of poor prognosis after second hepatectomies include diameter of recurrent tumor > 5 cm, poorly differentiated cells (grade II–IV), and recurrent serum AFP level > 20 ng/mL[28–30]. In the present study, we found that initial serum AFP level > 20 ng/mL, gross blood vessel invasion at recurrence, and PH at recurrence were independent risk factors for poor survival.

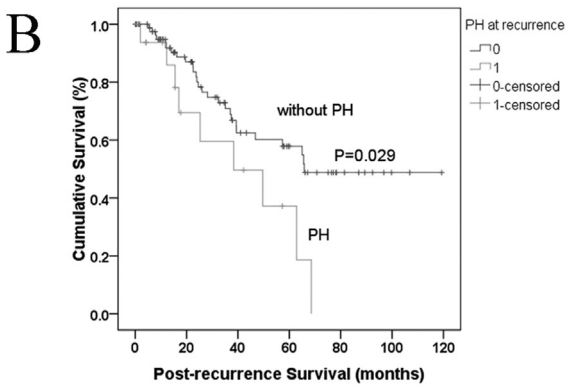
AFP promotes tumor metastasis and progression, and is an important prognostic factor for poor post-recurrence survival[31]. Higher levels of serum AFP may reflect tumor burden. Hu et al. concluded that higher serum AFP level (>1000 ng/mL) was associated with poor prognosis[32]. Liu et al. also found that AFP level (>400 ng/mL) was an independent risk factors for poor OS[33]. This is similar to our finding that serum AFP > 20 ng/mL at the time of first resection is associated with poor prognosis ($P = 0.003$). We therefore believe rigorous follow-up is needed for patients with higher serum AFP level (>20 ng/mL) at first resection, for early detection of recurrence. However, because the various studies of serum AFP level as a predictor of early occurrence used different AFP cut-off values, outpatient follow-up after initial hepatectomy for patients with low AFP levels (especially for AFP-negative HCC patients) should be assessed in conjunction with imaging data.

Tumor invasion of the portal vein system is an important cause of intrahepatic metastasis and HCC recurrence[34–36], and is associated with worse prognosis than that of multicenter recurrences[37]. Hsieh et al. [38] reported that the 3-year survival rate was 92.8% in patients without GVI, compared with 62.1% in patients with GVI ($P < 0.01$). We obtained a similar result: GVI independently affected survival ($P = 0.001$). Compared with patients who had portal vein invasion, those without portal vein invasion had significantly better 1-, 2-, and 5-year survival rates (94.8%, 80.1% and 57.9% vs 93.8%, 69.4%, and 37.2%, respectively; $P = 0.029$).

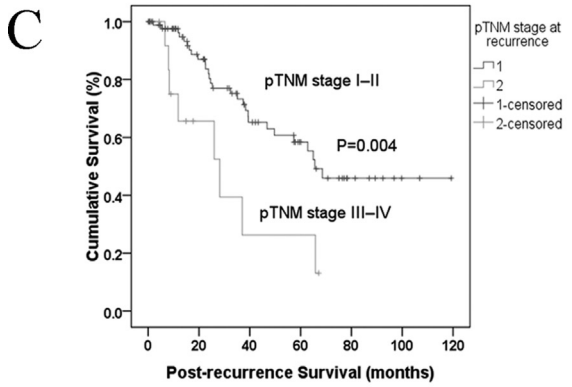
The effect of PH on postoperative clinical outcomes has not been confirmed, and conflicting results have been reported. Jang et al. [39] reported that among patients with Child–Pugh A or B liver function, clinical results for patients with PH were similar to those of patients without PH, and liver resection of recurrent HCC could be conducted safely, owing to improvements in clinical techniques. However, Ohkubo et al. [40] studied 892 patients who underwent liver resections and found that PH unfavorably affected postoperative survival (median survival—patients without PH: 8.6 years, patients with PH: 5.6 years, $P < 0.001$). In our study, PH is an independent risk factor for poor prognosis after repeated hepatectomy ($P = 0.006$).



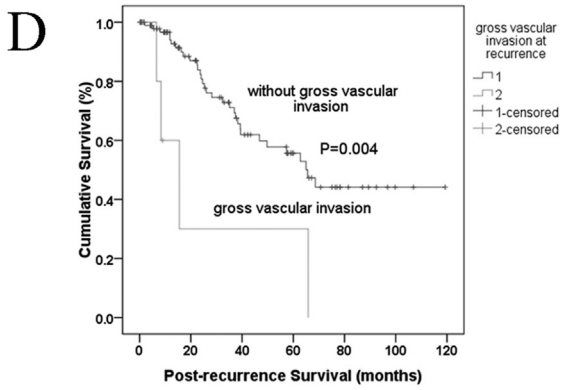

| Patients at risk | 0 months | 20 months | 40 months | 60 months |
|---|---|---|---|---|
| AFP≤20 ng/ml | 46 | 43 | 39 | 37 |
| AFP>20 ng/ml | 57 | 47 | 36 | 35 |




| Patients at risk | | | | |
|---|---|---|---|---|
| PH | 0 months | 20 months | 40 months | 60 months |
| Yes | 17 | 13 | 11 | 10 |
| No | 86 | 77 | 64 | 62 |




| Patients at risk | 0 months | 20 months | 40 months | 60 months |
|---|---|---|---|---|
| pTNM stage I–II | 90 | 81 | 69 | 66 |
| pTNM stage III–IV | 13 | 9 | 6 | 5 |




| Patients at risk | | | | |
|---|---|---|---|---|
| Gross vascular invasion | 0 months | 20 months | 40 months | 60 months |
| Yes | 5 | 2 | 2 | 2 |
| No | 98 | 88 | 73 | 70 |

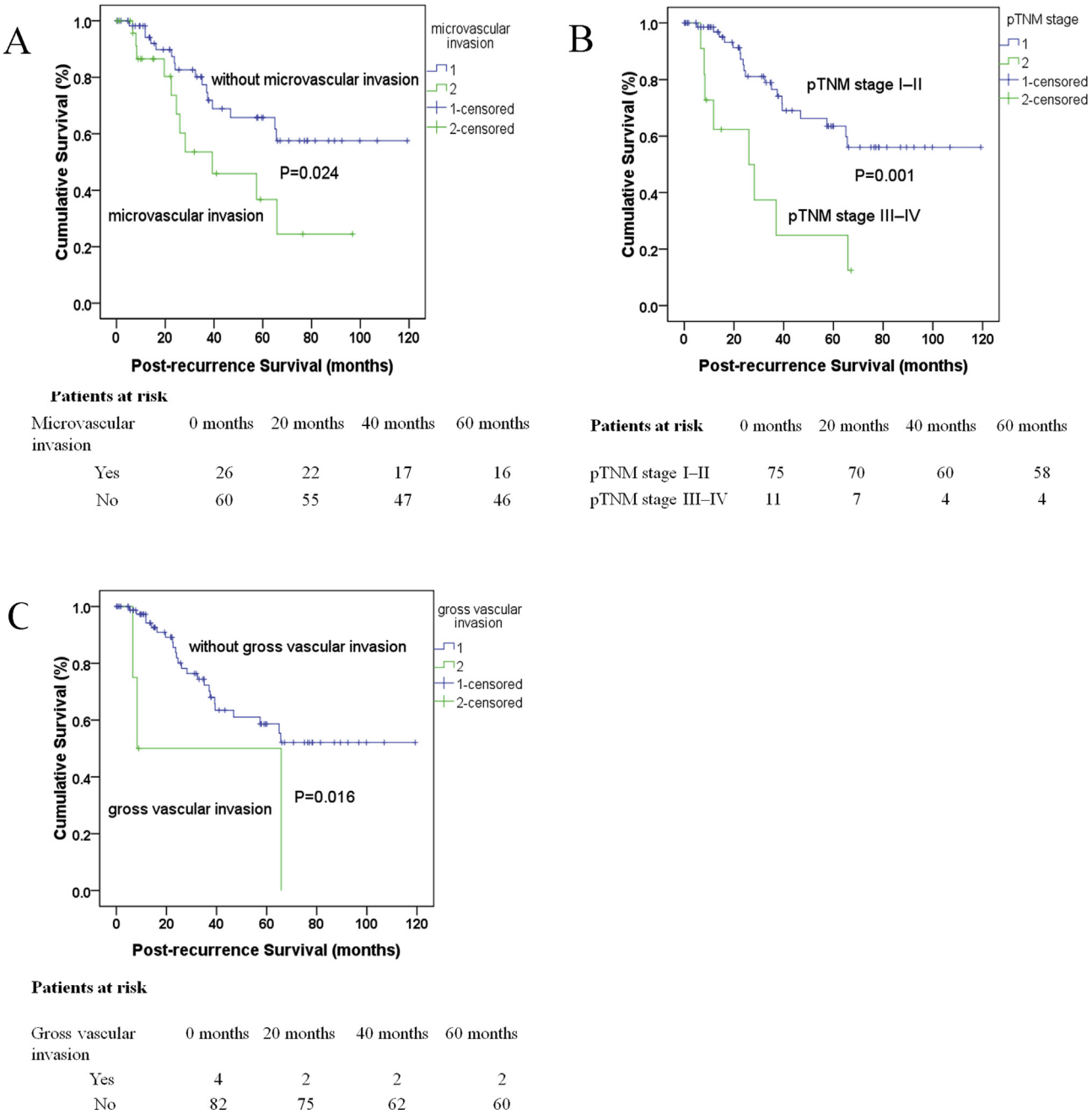
**Fig. 1.** Univariate analysis of risk factors related with post-recurrence survival. Portal hypertension at recurrence, serum AFP level >20 ng/mL at first resection, pTNM stage III–IV at recurrence and gross vascular invasion at recurrence were significantly associated with worse post-recurrence survival.

Advanced disease, micro-VI, and GVI unfavorably affected survival in the non-PH group. In fact, in the non-PH group, patients with GVI were considered to have pTNM stage III–IV disease. Those with advanced disease had more microvascular thrombosis than did those with early-stage disease ($P < 0.01$). Large blood vessel invasion can often be detected at preoperative examinations, whereas micro-VI cannot be detected before surgery and can only be found in pathological examination. Therefore, among patients without PH, those with early-stage disease are particularly suited to re-hepatectomy.

Limitations of this study include its retrospective design and single-center cohort, which may create selection bias. Our subanalyses found that microscopic venous invasion, GVI and advanced disease were unfavorable factors for OS in the non-PH group. All the patients are from China, which is a high-risk area for HBV. Prospective studies from different countries or different ethnic groups are needed to verify our results.

## Conclusion

Repeated hepatectomies have favorable long-term outcomes. Liver cirrhosis and HBV not treated with antiviral therapy were associated with immediate postoperative morbidity. Independent risk factors that affect post-recurrence survival are serum AFP > 20 ng/mL at first resection, PH, and GVI at recurrence. Preoperative TNM staging can predict prognosis of patients without PH.




**Patients at risk**

| Microvascular invasion | 0 months | 20 months | 40 months | 60 months |
|---|---|---|---|---|
| Yes | 26 | 22 | 17 | 16 |
| No | 60 | 55 | 47 | 46 |

| Patients at risk | 0 months | 20 months | 40 months | 60 months |
|---|---|---|---|---|
| pTNM stage I–II | 75 | 70 | 60 | 58 |
| pTNM stage III–IV | 11 | 7 | 4 | 4 |

**Patients at risk**

| Gross vascular invasion | 0 months | 20 months | 40 months | 60 months |
|---|---|---|---|---|
| Yes | 4 | 2 | 2 | 2 |
| No | 82 | 75 | 62 | 60 |

**Fig. 2.** Among patients without portal hypertension, microvascular invasion, gross vascular invasion and advanced disease (pTNM III–IV) were associated with poor prognosis.

## Abbreviations

HBV: hepatitis B virus; GVI: gross vascular invasion; HCC: hepatocellular carcinoma; micro-VI: microvascular invasion; AFP: alfa-fetoprotein; OS: overall survival; PH: portal hypertension; RFA: radiofrequency ablation; TACE transcatheter arterial chemoembolization.

## Conflict of interest

The authors declare no conflict of interest.

## Ethical approval

This study was approved by the Affiliated Hospital of Qingdao University Ethics Committee (approval number: QDFY WZ 03415).

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