*Original papers*

# Relationship between Period of Survival and Clinicopathological Characteristics in Patients with Hepatocellular Carcinoma who Underwent Hepatectomy

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*Running title:* Period of survival in liver carcinoma

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**Abstract**

***Backgrounds/Aims:*** Cancer death in the early period after hepatectomy remains problematic in patients with hepatocellular carcinoma (HCC). We examined the relationship between clinicopathological parameters and survival periods in 234 HCC patients who underwent hepatectomy.

***Methodology:*** Patients were divided into four groups: Group 1, survival >5 years; Group 2, survival for 2-5 years; Group 3, cancer death at 2-5 years; and Group 4, cancer death in <2 years.

***Results:*** Numbers of patients in each subgroup were: Group 1, n=87 (37%); Group 2, n=44 (19%); Group 3, n=46 (20%); and Group 4, n=57 (24%). Child-Pugh B status, blood loss >1500 ml, multiple tumors, tumor size >5 cm, not meeting Milan criteria**,** irregular macroscopic findings, invasion of Glissonian pedicle, invasion of hepatic vein, higher modified Japan Integrated Staging score (3-5), long-term ascites after hepatectomy and postoperative tumor recurrence within 12 months were frequent in Group 4 ($p$<0.05). Multivariate analysis revealed AFP level ≥1000 ng/ml (hazard ratio (HR), 2.6) and early tumor relapse (HR, 8.1) as independently related parameters ($p$<0.05).

***Conclusions***: Careful follow-up for early tumor relapse may be important for improving postoperative outcomes in HCC patients with high preoperative AFP levels.

**Key words** Hepatocellular carcinoma; Hepatectomy ·Survival; AFP; Postoperative early recurrence

**Abbreviations:**

hepatocellular carcinoma (HCC); liver transplantation (LT); computed tomography (CT) or magnetic resonance imaging (MRI); alpha-fetoprotein (AFP) and protein induced by Vitamin K antagonist or agonist II (PIVKA-II); Japan Integrated Staging (JIS)

## INTRODUCTION

Liver resection has become accepted as the most curative non-transplant treatment modality for patients with hepatocellular carcinoma (HCC) among various treatments including ablation therapy or chemoembolization.(1,2) Previous studies have reported improved survival after hepatectomy, but tumor relapse after hepatectomy remains common.(3) Some patients have shown tumor relapse soon after hepatectomy and may experience reduced survival rates.(4) Overall 5-year survival rate among HCC patients who have undergone hepatectomy is relatively favorable, at 27-52% according to recent reports.(5-7) Survival beyond 5 years can thus be achieved in many patients who undergo hepatectomy at this stage unless liver transplantation (LT) is performed. The current goal for this treatment is survival for ≥5 years with or without tumor relapse. In HCC patients with long survival, some patients have already received treatment for tumor relapse after hepatectomy.

Although previous studies have reported predictors of or features related to postoperative survival in HCC patients,(8,9) definite consensus has yet to be reached, and various predictive scoring systems for survival remain controversial.(10, 11) Regarding predictors, clinicopathologic parameters and tumor markers have been nominated as prognostic factors.(12) This study aimed to clarify factors including preoperative parameters, surgical history and period until post-operative tumor relapse related to overall post-operative survival after hepatectomy. The present series compared length of survival with these parameters in a >2-year follow-up of 234 Japanese HCC patients who had undergone hepatic resection. Our goal was to clarify the characteristics of shorter and longer survival in patients with HCC following hepatectomy at a Japanese single cancer unit.

## METHODOLOGY

### Patients and Methods

This retrospective study collected data from 234 HCC patients who underwent surgery in the Division of Surgical Oncology at the Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS), Japan, and associated cancer institutes between January 1994 and August 2007. Patients with tumor residues after hepatectomy and with operative death were excluded from the study.

Candidacy for surgery was typically limited to patients with Child-Pugh A status and some with Child-Pugh B status. All patients were medically fit for major laparotomy, showed no signs of preoperative dissemination or distant metastases and displayed tumors confined anatomically within the liver. Each patient underwent routine preoperative imaging studies, including whole-abdomen computed tomography (CT) or magnetic resonance imaging (MRI). Ultrasonography was used in each patient during surgery to find additional tumors and determine resection lines. Patients were followed-up at our outpatient clinic, and clinical course was determined by the attending physicians. Follow-up included measurement of serum alpha-fetoprotein (AFP) and protein induced by Vitamin K antagonist or agonist II (PIVKA-II)(12) every 3 months and abdominal CT every 3-6 months. When recurrence was detected, patients received re-operation, local ablation therapy or chemoembolization therapy. No defined protocols of adjuvant chemotherapy were applied before or after hepatectomy for prevention of tumor recurrence.

The volume of liver to be resected was estimated according to the indocyanine green retention rate at 15 min (ICGR15) using the formula of Takasaki *et al*. (13) The expected liver volume for resection, excluding the tumor, was measured by CT volumetry.(14) Transection of hepatic parenchyma was routinely performed using a Kelly-clamp crushing technique and an ultrasonic dissector was used only around the large Glissonian pedicle. Radical hepatectomy was performed to remove the hepatic tumor without leaving any residual tumor. All study protocols were approved by the Ethics Review Board of our department at NUGSBS. Mortality and morbidity data were collected from the NUGSBS database and provided by collaborating hospitals. No financial support was received for this study, and the authors have no conflicts of interests to declare.

We recorded the following clinical parameters: patient demographics; preoperative AFP and PIVKA-II levels (normal: <20ng/mL and <40mAU/ml, respectively); number of tumors; tumor size; preoperative liver function parameters; viral hepatitis status; pre-treatment for hepatectomy such as chemoembolization or ablation therapy, margin of surgical resection; tumor relapse within 12 months; macroscopic tumor morphology(15); histological vascular involvement of portal or hepatic vein(15); histological differentiation; presence of cirrhosis in non-cancerous liver; Milan criteria(16); and modified Japan Integrated Staging (JIS) score.(17, 18) Some histological findings were guided by the General Rules for the Clinical and Pathological Study of Primary Liver Cancer.(15) Based on our preliminary reports, postoperative survival in HCC patients with surgical margin <5 mm differed significantly from that in patients with surgical margin ≥5 mm, (19) so surgical margins of 5 mm were used as a cut-off level in the present study.

With respect to post-hepatectomy patient survival, subjects were divided into four subgroups as follows: Group 1, survival for >5 years; Group 2, survival for 2-5 years irrespective of tumor relapse; Group 3, cancer death within 2-5 years; and Group 4, cancer death at <2 years.

Continuous data are expressed as mean ± standard deviation (SD). Data of different groups were compared using one-way analysis of variance, followed by Student's *t*-test or Dunnet's multiple comparison test. In univariate analysis, categorical data were analyzed using the chi-square test or Fisher's exact test. In multivariate analysis, logistic multivariate regression analysis was applied. Two-tailed values of $p<0.05$ were considered significant. Statistical analyses were performed using SAS software (Statistical Analysis System, Cary, NC, USA).

**RESULTS**

The study group included 186 men (80%) and 48 women. Median age of the 234 patients at the time of surgery was 65 years (range, 23-83 years), and 82 patients (35%) were >70 years old. According to the Child-Pugh classification, 212 patients were classified as A (91%) and 22 as B (9%). Partial resection was performed in 98 patients (42%), segmental or sectional resection in 78 (33%), and hemihepatectomy or extended hemihepatectomy in 58 (25%).

Median and minimum follow-up periods for survivors were 64 and 24 months, respectively. By the time of the last follow-up, 108 patients (46%) had died and median time from hepatectomy to death was 37 months (range, 5-144 months). Numbers of patients in each subgroup were: Group 1, n=87 (37%); Group 2, n=44 (19%); Group 3, n=46 (20%); and Group 4, n=57 (24%).

Of 171 patients (73%) who showed tumor recurrence after hepatectomy (liver, n=167; bone, n=4; lung, n=7; adrenal gland, n=2; lymph node, n=3; and tumor thrombi in major vessel, n=2). Second resection was performed in 7 patients, ablation therapy in 38, chemoembolization in 110, and radiotherapy in 3, while 13 patients received no therapy for tumor relapse. Actuarial overall survival was 89% at 1 year after hepatectomy, 68% at 3 years, 50% at 5 years, 35% at 8 years and 31% at 10 years; median survival period was 80 months. The disease-free survival rate was 65% at 1 year after hepatectomy, 41% at 3 years, and 28% at 5 years, 14% at 8 years and 11% at 10 years; median survival period was 47 months.

Table 1 shows the relationships in the 4 subgroups of patient overall survival to patient demographics, tumor markers, and surgical records. Child-Pugh B status was significantly more common in Group 4 (18%) than in the other groups (4%, 9% and 11% in Groups 1-3, respectively), while prevalence of Child-Pugh B status did not differ between Groups 2 and 3. A short surgical margin tended to be more common in Group 4 (46%), but this difference was not significant (Group 1, 28%; Group 2, 36%; Group 3, 41%). Blood loss >1500 ml was significantly more frequent in Group 4 (42%) in comparison with other groups (Group 1, 22%; Group 2, 14%; Group 3, 15%). Table 2 shows the relationship of survival to tumor-related factors and postoperative complications or tumor recurrence within 12 months. Multiple tumors (44% vs. 9%, 27% and 28% in Groups 1-3, respectively), tumor size >5 cm (51% vs. 23%, 21% and 20%), not meeting Milan criteria (56% vs. 23%, 30% and 33%), irregular macroscopic findings (80% vs. 48%, 66% and 61%), invasion of the Glissonian pedicle (46% vs. 22%, 21% and 22%), invasion of the hepatic vein (46% vs. 13%, 9% and 15%), modified JIS score of 3-5 (26% vs. 9%, 20% and 11%), long-term ascites after hepatectomy (42% vs. 12%, 9% and 24%) and postoperative tumor recurrence within 12 months (81% vs. 14%, 21% and 41%) were all significantly more frequent in Group 4 than in Group 1. Postoperative tumor recurrence within 12 months tended to be more frequent in Group 3 compared with Group 2 ($p=0.056$). However, prevalence of other parameters did not differ significantly between Groups 1-3.

Parameters significantly predictive of tumor recurrence within 12 months ($p<0.05$) were blood loss ≥1500 ml (53% vs. 31% for blood loss <1500 ml), multiple tumors (55% vs. 31% for single tumor), tumor size ≥5 cm (56% vs. 30% for tumors <5 cm), not meeting Milan criteria (51% vs. 29% for meeting Milan criteria), confluent nodular type (52% vs. 28% for simple nodular and simple nodular with extra-growth), invasion of Glisson's pedicle (52% vs. 27% for negative invasion), hepatic vein invasion (57% vs. 33% for negative invasion), JIS score ≥3 (52% vs. 24% for score 0-2), and long-term ascites (63% vs. 31% for no long-term ascites). Patients with early tumor relapse showed higher levels of AFP (5109±18,760 vs. 845±3040 ng/ml) and PIVKA-II level (941±2372 vs. 484±2216 ng/ml) than patients without early relapse ($p<0.01$).

Univariate analysis revealed that increased AFP level, Child-Pugh B status, increased blood loss, not meeting Milan criteria, irregular macroscopic findings, invasion of the Glissonian pedicle or hepatic vein, higher modified JIS score, long-term ascites and early tumor relapse after hepatectomy were parameters significantly more associated Group 4 than other groups, particularly Group 1. Logistic multivariate regression analysis (Table 3) revealed AFP level ≥1000 ng/ml and tumor relapse within 12 months after hepatectomy as independently significant parameters for cancer death within 2 years.

**DISCUSSION**

Patient survival in HCC following tumor recurrence after hepatectomy has improved over time, with transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and repeat hepatectomy contributing to improved prognosis.(1,2,20-22) Even so, 2-year survival is poor in patients with tumor recurrence soon after hepatectomy. With this in mind, we examined characteristics for patients grouped according to survival period with and without tumor relapse in the present series. Recurrence of HCC within 2 years after hepatectomy was thought to be an intrahepatic metastasis and the late recurrence was thought to be multicentric carcinogenesis.(23) On the other hand, survival over 5 year after the first operation is usually defined as the point of curative result and, therefore, many physicians analyzed 5 year survivals.(24) We considered that the postoperative recurrence at the 2 and 5 years after operation might indicate different mechanism of tumor characteristics and, therefore, period of postoperative time was subdivided into the four groups in the present study. The present study was limited to a small series with data obtained from a single cancer unit for a district area in Japan. Furthermore, imaging and treatment modalities for tumor recurrence have changed dramatically during the past 2 decades, which might have influenced patient outcomes.(25) In our series, however, introduction of multi-detector CT and enhanced MRI, and changes in local treatment from alcohol injection to RFA for detection or treatment of tumor recurrence after hepatectomy do not appear to have contributed significantly to patient outcomes. The most powerful imaging modality is still intraoperative ultrasonography[5] and TACE was still applied in the majority of HCC patients with tumor recurrence in our series (data not shown). Advances in chemotherapy such as Sorafenib, a molecular inhibitor of several tyrosine protein kinases, have recently been introduced,(26) but preoperative or adjuvant chemotherapy using Sorafenib is not yet routinely performed. In our series, anatomical resection has been a standard option to preserve curability of hepatectomy,(19) but the limited resections proposed by Kanematsu et al.(27) were actually applied in patients with poor liver function. Our results thus include such a compounded factor of patient populations. The superiority of anatomical resection and limited resection of the liver remains controversial.(5,27,28)

In the present results, overall and disease-free survival rates after hepatectomy were not markedly different from those in previous reports,5-7 and long-term survival >5 years was observed in 37%. The 5-year survival is a turning point to evaluate curability of treatments for HCC. (5-7) Conversely, recurrence within 1 or 2 years might fall within a period of intrahepatic metastasis associated with initial HCC,(29) and early death during the first 2 years after hepatectomy might thus indicate increased malignant behavior of the tumor. We hypothesized that the period of survival between 2 and 5 years after treatment would contend with the factors of intrahepatic metastasis and multi-centric carcinogenesis in the remnant liver. We compared various parameters among the four subgroups to clarify survival characteristics in the present study. Over the 5-year period after hepatectomy, many investigators have reported predictive factors associated with patient survival following hepatectomy.(8,9,12,30,31) Time of tumor recurrence after hepatectomy might be associated with overall survival. Kaibori et al. reported early tumor recurrence after hepatectomy as an important finding.(32) Kaido et al. reported a prognostic analysis of patients with subgroups of 5-year survivors and patients who died before 5 years.(33) In patient-related parameters, only prevalence of Child Pugh B status differed among these groups. In HCC, patient liver function is an important factor influencing survival according to other reports.(34) Patients with poor liver function underwent limited resection as described above. If limited resection offers limited curability for initial HCC in comparison with anatomical resections, early recurrence of metastasis would be plausible. In factors related to surgical records, increased blood loss or related red blood cell transfusion were associated with early patient death in the present study. In a recent report by Katz et al., blood transfusion or increased blood loss were also predictors of poor survival after hepatectomy in a large number of HCC patients who underwent hepatectomy.(35) The possibility remains that these factors influence host immunity, but detailed mechanisms by which tumor aggressiveness may be promoted remain unknown. A short surgical margin (<5 mm) tended to be more frequent in Group 4 compared with other groups, and was found to be a predictor of tumor relapse and poor prognosis, agreeing with the findings of the present study and previous reports.(19, 36) Recent reports have shown that surgical margins do not contribute to survival unless the tumor is exposed at the resected edge.(37)

Many tumor parameters were associated with early cancer death within 2 years in the present results, as identified in previous reports.(6-9,38) Preoperative AFP or PIVKA-II levels were candidate predictors of survival.(12, 39) but PIVKA-II level did not differ significantly among the four subgroups even though mean level was highest in Group 4. Among the tumor pathological factors, 6 parameters were selected as predictive factors in the present study. In addition, modified JIS score was examined in this analysis, as the best currently available system for combined staging of tumor and liver functional factors in Japan.(17,18) We found that high JIS score was significantly more frequent in Group 4. In addition, Milan criteria offer a useful system (≤3 cm and ≤3 lesions, or single HCC ≤5 cm) for predicting survival in HCC patients following LT was examined in the present analysis.(16) In HCC patients, LT is also an important treatment modality to dramatically improve patient outcomes, and timing and indications for LT during the course of conventional treatments and follow-up should thus be considered for HCC patients.(40) In Group 4, however, prevalence of not meeting Milan criteria (indicator of poor outcomes following LT) was more frequent, and HCC exceeding Milan criteria may thus indicate higher malignant behavior as well as LT.(16) As described above, early tumor recurrence was associated with early cancer death in our results, irrespective of the treatment modality. Time to tumor recurrence is thought to be related to malignant behaviors of HCC.(32) In the present study, other parameters related to shorter overall survival were also associated with early tumor recurrence. After all, rapid tumor spread or treatment resistance needs to be predicted in cases where tumor relapse is observed within 12 months after hepatectomy. The most curative treatments must be selected by considering patient condition and extent of tumor recurrence. In cases where the recurrent tumor meets the Milan criteria described above, LT should probably be considered as soon as possible in younger HCC patients.

Multivariate analysis for cancer death within 2 years (Group 4) applying various predictive factors by univariate analysis revealed preoperative AFP level and early tumor relapse within 12 months after hepatectomy as independent risk factors in the present study. Measurement of AFP is easy and should offer a good indicator of poor survivals before and after treatment. Changes in tumor marker levels after hepatectomy might provide a useful parameter to evaluate curability of treatment. Our previous preliminary study showed that normalization of serum PIVKA-II levels at 1month after hepatectomy was associated with longer survival after hepatectomy in HCC patients with increased preoperative PIVKA-II level.(41) In cases with increased tumor markers that are not normalized after treatment, the possibility of early tumor recurrence must be carefully considered during the follow-up period. Early tumor recurrence showed the highest hazard ratio for early cancer death in the present results, suggesting that treatment strategies need to be made immediately in consultation with physiologists, surgeons, radiologists and transplant experts for HCC patients with early recurrence. However, these candidate parameters were not independent risk factors by Cox's proportional multivariate analysis in this series (data not shown). Cancer death beyond 2 or 5 years may thus be influenced by other factors.

Various other predictive parameters, such as tumor biological factors or findings from various imaging modalities, are needed to provide additional information relating to poor prognosis. As reported in our preliminary study, in the near future we plan to analyze other candidate predictive factors, such as microvessel counts.(42) Furthermore, new imaging technologies such as 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and diffusion-weighted MRI appear to enable definition of tumor grade, and thus could be useful as prognostic parameters in the next step.(43, 44) In the present series, FDG-PET was not applied to decide operative indications at all and we did not clarify the usefulness of MRI findings because of the small number cases in which such data were available at this stage.

In conclusion, we analyzed clinicopathologic and surgical features in HCC patients who had undergone hepatic resection, and compared these data in four subgroups with regard to survival period and tumor relapse. Child-Pugh B status, preoperatively increased AFP level, increased blood loss, tumor number and size, not meeting Milan criteria, high modified JIS score, irregular macroscopic findings, vascular involvement, long-term ascites after hepatectomy and shorter time to tumor recurrence after hepatectomy (<12 months) were factors significantly associated with cancer death within 2 years by univariate analysis. AFP level and early recurrence were factors independently associated with cancer death within 2 years by multivariate analysis. Careful follow-up and adequate and immediate decisions on treatment modality upon identification of tumor relapse are important for improving survival in the early period after surgery in HCC patients.

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**TABLE 1.** Relationship between Survival Period and Patient Demographics, Tumor Markers and Surgical Records

| | Group 1 (n=87) | Group 2 (n=44) | Group 3 (n=46) | Group 4 (n=57) | P value |
|---|---|---|---|---|---|
| Gender (Male / Female) | 67/20 | 34/10 | 38/8 | 47/10 | 0.79 |
| Age | 63 ± 10 | 66 ± 10 | 64 ± 9 | 65 ± 10 | |
| AFP (ng/ml)[a] | 634 ± 2471 | 1269 ± 3739 | 677 ± 1915 | 7350±22720[e] | |
| PIVKA-II (mAU/ml)[b] | 216 ± 1010 | 735 ± 3708 | 168 ± 495 | 1362 ± 2832 | |
| Child-Pugh (A / B) | 84/3 | 40/4 | 41/5 | 47/10 | 0.042 |
| Pre-treatment (Yes / no)[c] | 27/60 | 10/34 | 14/32 | 25/32 | 0.19 |
| Viral status (None / B / C / B&C) | 11/25/49/2 | 6/14/18/6 | 6/14/22/4 | 8/19/27/3 | 0.36 |
| Hepatectomy[d] (Major / minor) | 18/69 | 9/35 | 10/36 | 17/40 | 0.58 |
| Surgical margin (≥5 / <5 mm) | 63/24 | 28/16 | 27/19 | 31/26 | 0.10 |
| Blood loss (≥1500 / <1500ml) | 19/68 | 6/38 | 7/39 | 24/33 | 0.003 |
| Red cell transfusion (Yes / no) | 39/48 | 18/26 | 25/21 | 36/21 | 0.07 |

[a] AFP, alpha-feto protein; [b] PIVKA-II, protein induced by Vitamin K antagonist or agonist

[c] Local ablation therapy or chemoembolization before hepatectomy

[d] Major hepatectomy is hemihepatectomy or more extended hepatectomy

[e] p<0.039; Group 4 vs. Group 1

**TABLE 2.** Relationship between Survival Period and Tumor-related Findings or Period to Tumor Relapse

| | Group 1 (n=87) | Group 2 (n=44) | Group 3 (n=46) | Group 4 (n=57) | P value |
|---|---|---|---|---|---|
| Number of tumor | | | | | |
| Solitary/Multiple | 79/8 | 32/12 | 33/13 | 32/25 | <0.0001 |
| Tumor size | | | | | |
| <2cm / 2-5cm / ≥5cm | 27/40/20 | 11/24/9 | 9/26/9 | 3/25/29 | 0.0006 |
| Milan criteria [a] | | | | | |
| Met / non-met | 67/20 | 31/13 | 31/15 | 25/32 | 0.0006 |
| Macroscopic findings [b] | | | | | |
| SN/ SNEG / CM, IF | 45/17/25 | 15/14/15 | 18/13/15 | 12/16/29 | 0.0034 |
| Histological differentiation | | | | | |
| Well/moderately/poor | 18/65/4 | 8/33/3 | 6/36/4 | 8/38/11 | 0.12 |
| Glisson's pedicle invasion | | | | | |
| No/Yes | 68/19 | 35/9 | 36/10 | 31/26 | 0.032 |
| Hepatic vein invasion | | | | | |
| No/Yes | 76/11 | 40/4 | 39/7 | 31/26 | 0.008 |
| Presence of cirrhosis | | | | | |
| No/Yes | 47/40 | 23/21 | 25/21 | 30/27 | 0.99 |
| Modified JIS score [c] | | | | | |
| 0-1/2/3-5 | 59/20/8 | 25/10/9 | 22/19/5 | 26/16/15 | 0.039 |
| Ascites after hepatectomy (>2weeks) | | | | | |
| No/Yes | 77/10 | 40/4 | 35/11 | 33/24 | <0.0001 |
| Early recurrence within 12 months | | | | | |
| No/Yes | 75/12 | 35/9 | 27/19 | 11/46 | <0.0001 |
| Period of tumor relapse (months) | 45 ± 31 | 18 ± 12 | 19 ± 12 | 7 ± 6 [d] | |

Histological findings were based on the General Rules for the Clinical and Pathological Study of Primary Liver Cancer.[21]

[a] ≤3cm in tumor size and ≤3 lesions, or ≤5cm in tumor size and one lesions, without vascular involvement and distant metastasis[22]

[b] SN, simple nodular; SNEG, simple nodular with extranodular growth; CM, confluent multinodular; IF, infiltrative[21]

[c] Scoring system proposed by the Nanashima et al.[23] and Liver Cancer Study Group of Japan[24]

[d] Group 4 vs. other Groups

**TABLE 3.** Multivariate Logistic Regression Analysis of Cancer Deaths within 2 Years [a]

| | HR | 95%CI<br>Lowest-highest CI | P value |
|---|---|---|---|
| Alpha-feto protein level<br>≥1000ng/ml vs. <1000ng/ml | 2.6 | 1.0 – 6.5 | 0.048 |
| Child-Pugh classification<br>B vs. A | 1.8 | 0.4 – 7.9 | 0.47 |
| Blood loss<br>≥1500ml vs. <1500ml | 2.1 | 0.7 – 5.9 | 0.17 |
| Milan criteria<br>non-Met / Met | 1.5 | 0.6 - 3.8 | 0.39 |
| Macroscopic findings [b]<br>SN vs. SNEG, CM, IF | 1.6 | 0.6 - 4.3 | 0.31 |
| Glisson's pedicle invasion<br>Yes vs. No | 1.1 | 0.3 - 3.6 | 0.94 |
| Hepatic vein invasion<br>Yes vs. No | 2.2 | 0.6 – 7.9 | 0.23 |
| Modified JIS score [c]<br>3-5 vs. 0-2 | 1.1 | 0.3 – 4.1 | 0.88 |
| Ascites after hepatectomy (>2weeks)<br>Yes vs. No | 1.7 | 0.7 – 4.2 | 0.28 |
| Early recurrence within 12 months<br>Yes vs. No | 8.1 | 3.3-19.8 | <0.001 |

[a]HR, hazard ratio; CI, confidence interval.

[b] See Table 2