

Perioperative Non-tumorous Factors Associated with Survival in HCC Patients Who Underwent Hepatectomy

ATSUSHI NANASHIMA, TAKAFUMI ABO, KEIKO HAMASAKI, KOUKI WAKATA,
TETSURO TOMINAGA, SHIGEKAZU HIDAKA, HIROAKI TAKESHITA and TAKESHI NAGAYASU

*Division of Surgical Oncology and Department of Surgery,
Nagasaki University Hospital, Sakamoto, Nagasaki, Japan*

Abstract. *Aim: To clarify perioperative factors associated with poor survival following hepatectomy. Patients and Methods: Clinical parameters and stress score, including surgical stress score (SSS) and comprehensive risk score (CRS) were examined from 183 hepatocellular carcinoma patients who underwent hepatectomy. Results: Factors associated with tumor relapse were increased blood loss/weight, uncontrolled ascites and grade B liver damage ($p<0.05$). Ascites was identified as an independent risk factor by multivariate logistic regression analysis. Increased blood loss/weight, transfusion, high SSS, high CRS, ascites, and grade B liver damage were associated with poor disease-free survival ($p<0.05$). Increased blood loss/weight, transfusion, ascites, and grade B liver damage were associated with poor overall survival ($p<0.05$), and ascites, transfusion, male sex and grade B liver damage were identified as independent risk factors. Conclusion: Reducing blood loss and avoiding transfusion appear important for improving prognosis. Maintenance of liver function is necessary in cases showing poor liver function and uncontrolled ascites.*

Liver resection is currently considered the best curative treatment modality for patients with hepatocellular carcinoma (HCC). The safety of hepatectomy for HCC patients with background liver diseases has improved markedly, with reduced mortality rates based on adequate preoperative evaluation of the extent of hepatectomy, precise evaluation of functional liver reserve and advances in

perioperative management (1-5). Patient prognosis after hepatectomy in HCC is influenced by the stage or biological characteristics of the tumor and hepatic function (6-8). Some reports have shown that patient demographics such as age, sex and viral status are associated with postoperative survival (6, 9-11). Others have shown that data from surgical records such as increased blood loss or postoperative complications are also associated with patient survival in HCC (6, 9, 12, 13). Perioperative parameters other than tumor-related factors or liver function may thus influence patient prognosis. However, no definite consensus has been reached to date. Our previous reports concerning tumor characteristics and staging in HCC patients have shown that blood loss and viral status might be associated with patient survival (14-16), although we have not focused on relationships between perioperative parameters and patient survival. Comprehensive analysis of such relationships may provide useful insights into the treatment of HCC patients who undergo hepatectomy. We hypothesize that clarifying the relationship between perioperative parameters and survival in HCC patients will provide information to improve patient survival by further management in the perioperative period. We therefore analyzed clinicopathological features, surgical data, postoperative complications and survival after hepatectomy in 183 patients with HCC.

Patients and Methods

Patients. This retrospective study collected data from 183 HCC patients, representing all patients who underwent hepatectomy for HCC in the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS), Japan, and associated cancer institutions, between January 1994 and August 2009, to obtain a minimum follow-up period of one year. Patients with residual tumor after hepatectomy or who died of surgery-related causes were excluded from the study. Surgery was typically indicated for 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 anatomically confined

Correspondence to: Atsushi Nanashima, MD, Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 8528501, Japan. Tel: +81 958197304, Fax: +81 958197306, e-mail: a-nanasm@net.nagasaki-u.ac.jp

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within the liver. Each patient underwent routine preoperative imaging, 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 (17). Patients were followed up at our outpatient clinic, and the 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) (18) every 3 months and abdominal CT every 3-6 months. When recurrence was detected, patients underwent re-operation, local ablation therapy or chemoembolization therapy. No defined protocol of adjuvant chemotherapy was applied before or after hepatectomy for prevention of tumor recurrence. The liver volume to be resected was estimated according to the indocyanine green retention rate at 15 min (ICGR15) using the formula of Takasaki *et al.* (19). The expected liver volume for resection, excluding the tumor, was measured by CT volumetry (20). Transection of the hepatic parenchyma was routinely performed using the Kelly-clamp crushing technique and an ultrasonic dissector was used only around the large Glissonian pedicle (21). 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 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 declare no conflicts of interest.

Clinicopathological parameters, surgical data, tumor staging, and subgroups of postoperative survival. We recorded the following clinical parameters: patient demographics including co-morbidities, performance status (PS), American Society of Anesthesiologists (ASA) score and preoperative risk score (PRS); surgical stress score (SSS); comprehensive risk score (CRS) (22); liver damage grade according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan as a comprehensive classification of preoperative liver function (23); surgical data: viral hepatitis status, extent of incision for laparotomy, extent of hepatectomy, blood loss, transfusion, operative time; postoperative complications (hepatectomy-associated complications and systemic complications); tumor recurrence; and disease-free and overall survival times after hepatectomy. Histological findings were guided by the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (23).

Equations for PRS, SSS and CRS were based on the equations of Haga *et al.* for estimation of physiologic ability and surgical stress (E-PASS) scores (22) as follows:

$$\text{PRS} = -0.0686 + 0.00345 X_1 + 0.323 X_2 + 0.205 X_3 + 0.153 X_4 + 0.148 X_5 + 0.0666 X_6$$

where X₁ is age, X₂ is presence (1) or absence (0) of severe heart disease; X₃ is presence (1) or absence (0) of severe pulmonary disease; X₄ is presence (1) or absence (0) of diabetes mellitus; X₅ is performance status index (0-4); and X₆ is the ASA physiological status classification (1-5).

$$\text{SSS} = -0.342 + 0.0139(X_1) + 0.0392(X_2) + 0.352(X_3)$$

where X is blood loss/body weight (g/kg); X₂ is operation time (h); X₃ is extent of skin incision (0, minor incision for laparoscopic or thoracoscopic surgery; 1, either laparotomy or thoracotomy alone; and 2, both laparotomy and thoracotomy).

$$\text{CRS} = -0.328 + 0.936(\text{PRS}) + 0.976(\text{SSS})$$

Statistical analysis. Continuous data are expressed as the mean±standard deviation (SD). Data of different groups were compared using one-way analysis of variance, followed by Student's *t*-test or Dunnett's multiple comparison test. In univariate analysis, categorical data were analyzed using the chi-square test or Fisher's exact test. Median values were identified as cutoff values for continuous data. Multivariate logistic regression analysis was examined to analyze associations with tumor recurrence. Disease-free and overall survival rates were calculated according to Kaplan-Meier methods, and differences between groups were tested for significance using the log-rank test. Multivariate Cox's proportional hazard test was used to analyze parameters independently associated with survival. Two-tailed values of *p*<0.05 were considered significant. Statistical analyses were performed using SPSS software (SPSS, Chicago, IL USA).

Results

The study group included 148 males (81%) and 35 females with mean and median ages of 65.0±9.6 years (range, 28-82 years) and 65 years, respectively. According to liver damage grade, 144 patients were classified as having grade A (78%) and 39 as having grade B disease. Partial resection was performed in 56 patients (31%), segmentectomy in 23 (13%), sectionectomy in 48 (26%), hemihepatectomy in 36 (20%) and extended hepatectomy in 20 (11%). Tumors were resected completely without residual tumor in all patients. Postoperative tumor recurrence was observed in 126 patients (69%), occurring in the liver in 119 patients, lung in 8, bone in 4, lymph nodes in 3, adrenal gland in 2, bile duct in 1 and inferior vena cava in 1. Treatment for tumor recurrence was performed in 91 patients, including chemoembolization in 50, transarterial anticancer drug infusion in 7, thermal ablation in 15, hepatectomy in 7, systemic chemotherapy in 3 and radiation in 2. Median and minimum follow-up periods were 47 and 12 months, respectively. Eighty-three patients (45%) had died of cancer-related causes by the time of the last follow-up and the mean duration from hepatectomy to death was 35 months (range, 12-144 months). The 3- and 5-year disease-free survival rates were 41% and 30%, respectively, and median survival was 46 months. The 3-, 5- and 10-year overall survival rates were 66%, 50% and 29%, respectively, and median survival was 79 months.

Table I shows the relationship between tumor recurrence after hepatectomy and clinicopathological and surgical features, and postoperative outcomes. Among patient demographics, general status and liver function, viral hepatitis caused by hepatitis B or C and grade B liver damage were significantly associated with tumor recurrence (*p*<0.01). From the surgical records, blood loss by weight was significantly associated with tumor recurrence (*p*<0.05). Of the postoperative parameters, prevalence of postoperative complications tended to be associated with tumor recurrence, but no significant relationship was found (*p*=0.06). Uncontrolled ascites (massive ascites continuing for more than one week despite use of

Table I. Relationship between relationship between tumor relapse and demographics, clinicopathological features, surgical characteristics and postoperative outcomes.

	Tumor recurrence		P-value
	- (n=57)	+ (n=126)	
Gender (male/female)	45/12	103/23	0.81
Age (years; <50/50-69/≥70)	2/28/27	7/78/41	0.29
Body weight (kg; <60/≥60)	29/28	52/74	0.41
Co-morbidity (no/yes)	26/31	59/67	0.45
Diabetes mellitus (no/yes)	41/16	93/33	0.93
Background liver (viral/alcoholic/other)	38/1/18	114/2/10	<0.001
Performance status (0/1)	50/7	116/10	0.52
ASA (1/2/3)	22/27/8	58/58/10	0.37
Liver damage grade* (A/B)	51/6	92/34	0.025
Hepatectomy (partial/segmentectomy/ sectionectomy/hemihepatectomy/extensive)	19/10/ 13/12/3	37/13/ 35/24/17	0.32
Blood loss per weight (ml/kg; <15/≥15)	33/24	50/76	0.033
Transfusion (no/yes)	21/36	62/64	0.16
Operative time (min; <350/≥350)	30/27	62/64	0.79
Incision (laparotomy/thoracotomy)	39/18	80/46	0.63
Postoperative complication (no/yes)	36/21	59/67	0.06
Uncontrolled ascites (no/yes) [#]	51/6	91/35	0.016
Bile leakage (no/yes)	52/5	121/5	0.33
Hepatic failure (no/yes)	54/3	120/6	1.0
Systemic complications (no/yes)	52/5	120/6	0.34
PRS (<0.31/≥0.31)	24/33	66/60	0.26
SSS (<0.63/≥0.63)	34/23	58/68	0.12
CRS (<0.61/≥0.61)	32/25	59/67	0.31

ASA, American Society of Anesthesiologists (ASA) score; PRS, preoperative risk score; SSS, surgical stress score; CRS, comprehensive risk score (22). *Based on the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (23), [#]Massive ascites continuing more than one week under use of diuretics.

diuretics) was significantly associated with tumor recurrence ($p<0.05$). Multivariate analysis (Table II) showed that viral hepatitis status and blood loss by weight were independently associated with tumor recurrence ($p<0.05$).

Table III shows the relationship between postoperative disease-free and overall survivals after hepatectomy, clinicopathological and surgical features, and postoperative outcomes. Regarding disease-free survival, among the patient demographics, general status and liver function, viral hepatitis and grade B liver damage were significantly associated with poor disease-free survival ($p<0.05$). From the surgical records, blood loss by weight was significantly associated with poor disease-free survival ($p<0.01$). In terms of postoperative parameters, prevalence of postoperative complication tended to be associated with poor disease-free survival, but not significantly ($p=0.054$), whereas uncontrolled ascites was significantly associated with poor disease-free survival ($p<0.01$). Higher SSS and CRS were significantly associated with poor disease-free survival

Table II. Multivariate logistic regression analysis of postoperative tumor recurrence.

	HR	95% CI	P-value
Background liver status			
Alcoholic and other vs. viral hepatitis	3.87	1.61-9.12	0.002
Liver damage grade			
A vs. B	2.65	0.92-7.63	0.07
Blood loss per weight (ml/kg)			
<15 vs. ≥15	2.00	1.02-3.95	0.043
Uncontrolled ascites			
No vs. yes	1.79	0.69-4.76	0.24

HR, Hazard ratio; CI, confidence interval.

($p<0.05$). Regarding overall survival, in the patient demographics, general status and liver function, male sex, viral hepatitis caused by hepatitis B or C, performance status 1, and grade B liver damage were significantly associated with poor overall survival ($p<0.05$). From the surgical records, blood loss by weight was significantly associated with poor overall survival ($p<0.01$). Major hepatectomy and blood transfusion tended to be associated with poor overall survival, but not significantly ($p=0.06$ and 0.09 , respectively). In terms of postoperative parameters, uncontrolled ascites was significantly associated with overall survival ($p<0.01$).

In multivariate analysis (Table IV), viral hepatitis status and grade B liver damage were independently associated with poor disease-free survival ($p<0.05$). Male sex, grade B liver damage and increased blood loss by weight were independently associated with poor overall survival ($p<0.05$).

Discussion

Survival of patients who had undergone hepatectomy for HCC was shown to be mainly influenced by tumor-associated factors (6-8, 14-16). Co-existing factors, such as patient demographics, co-morbidity, preoperative liver function, surgical results and postoperative complications, have also been closely associated with tumor recurrence and patient survival (6, 9-13, 24-29). Although Poon *et al.* indicated that TNM classification was more related to survival than other co-existing factors (11), these factors may have strong influence in some patients. To clarify the influence of these factors and improve survival of HCC patients, we performed the present comprehensive analysis, as our preliminary study concerning HCC-related parameters also showed that some non-tumor factors were associated with tumor relapse and survival (14-16). With respect to patient demographics, HCC patients with viral hepatitis and lower liver function in the present study had a poorer prognosis than those with normal or fatty liver with preserved liver function. These factors were also independently associated with tumor relapse after hepatectomy. Previous

Table III. Relationship between demographics, clinicopathological features, surgical characteristics and postoperative outcomes and disease-free and overall survival after hepatectomy.

		Disease-free survival (%), 3-/5-year	P-value	Overall survival (%), 5-/10-year	P-value
Gender	Male	39/27	0.27	47/23	0.042
	Female	48/40		61/52	
Age (years)	<50	33/22	0.91	56/22	0.91
	50-69	39/31		52/26	
	≥70	45/33		66/35	
Body weight (kg)	<60	36/27	0.11	44/27	0.16
	≥60	50/36		58/40	
Co-morbidity	No	48/37	0.22	58/34	0.10
	Yes	37/26		31/20	
Diabetes mellitus	No	38/30	0.57	49/29	0.29
	Yes	48/31		53/30	
Background liver status	Viral	38/23	0.016	33/20	0.004
	Alcoholic/other	61/54		58/44	
Performance status	0	42/39	0.41	52/31	0.044
	1	29/20		19/5	
ASA	1	36/25	0.54	48/24	0.84
	2	46/33		47/39	
	3	41/20		57/19	
Liver damage grade	A	44/34	0.006	58/37	0.004
	B	25/11		32/21	
Hepatectomy	Minor*	44/30	0.15	46/34	0.06
	Major	34/31		29/22	
Blood loss by weight (ml/kg)	<15	51/43	0.002	61/32	0.009
	≥15	33/21		40/27	
Transfusion	No	33/24	0.06	66/34	0.09
	Yes	48/36		43/32	
Operative time (min)	<350	36/26	0.22	44/28	0.11
	≥350	46/34		56/32	
Incision	Laparotomy	46/35	0.23	55/27	0.65
	Thoracolaparotomy	33/22		65/43	
Postoperative complications	No	50/36	0.054	55/27	0.16
	Yes	32/22		44/34	
Uncontrolled ascites	No	49/33	0.007	55/30	0.012
	Yes	22/19		35/26	
Bile leakage	No	41/30	0.91	50/29	0.56
	Yes	42/29		69/31	
Hepatic failure	No	41/30	0.97	51/28	0.74
	Yes	44/33		56/33	
Systemic complications	No	41/30	0.71	50/29	0.75
	Yes	48/24		59/32	
PRS	<0.31	38/29	0.61	49/30	0.76
	≥0.31	45/31		66/50	
SSS	<0.63	50/41	0.015	58/29	0.15
	≥0.63	33/20		43/32	
CRS	<0.61	47/39	0.012	55/30	0.15
	≥0.61	35/22		45/30	

See Table I for abbreviations. *Minor consists of partial, segmental and sectional resections; Major consists of hemihepatectomy and more extended hepatectomy.

reports have shown that these factors were also related to postoperative hepatic complications, risk of tumor recurrence and poor survival (6, 12, 13, 26, 27-29). This result is unsurprising, as postoperative hepatic complications are usually caused by underlying liver dysfunction and postoperative

complications themselves may lead to poor survival (30, 31). Multicentric recurrence of HCC might be associated with the status of viral hepatitis or inflammatory activity of the liver (32, 33), so tumor recurrence in the present study may have involved carcinogenesis in the remnant liver. In our series,

Table IV. Multivariate Cox proportional hazard regression analysis of postoperative survival.

Disease-free survival	HR	95% CI	P-value
Background liver status			
Alcoholic and other vs. viral hepatitis	2.07	1.12-3.80	0.02
Liver damage grade			
A vs. B	1.69	1.10-2.63	0.02
Blood loss by weight (ml/kg)			
<15 vs. ≥15	1.45	0.96-2.17	0.075
Uncontrolled ascites			
No vs. yes	1.25	0.81-1.93	0.32
SSS			
<0.63 vs. ≥0.63	1.05	0.60-1.84	0.86
CRS			
<0.61 vs. ≥0.61	1.29	0.75-2.20	0.36
Overall survival	HR	95% CI	P-value
Gender			
Female vs. male	1.72	1.10-2.67	0.033
Performance status			
0 vs. 1	1.69	0.96-2.63	0.052
Background liver status			
Alcoholic and other vs. viral hepatitis	1.25	0.81-1.93	0.43
Liver damage grade			
A vs. B	1.65	1.06-2.28	0.036
Blood loss by weight (ml/kg)			
<15 vs. ≥15	2.07	1.12-3.82	0.010
Uncontrolled ascites			
No vs. yes	1.29	0.75-2.20	0.082

HR, Hazard ratio; CI, confidence interval.

distinguishing between tumor recurrence as intrahepatic metastasis or multicentric carcinogenesis was difficult. Such a liver background may lead to reduced survival after treatment. Serum albumin level or degree of intrahepatic fibrosis might also be a prognostic factor (11, 28). Recently, combined clinical staging of HCC consisting of tumor-related factors and liver functions have been proposed, as liver function is closely associated with patient survival (27, 34, 35). Clarification of these parameters is thus necessary to predict HCC patient survival after hepatectomy. Male patients had a poor prognosis after hepatectomy in the present study, and male sex was also an independent prognostic factor for poor survival in previous reports (6, 9, 11). Qin *et al.* suggested that differences in survival between the sexes were attributable to differences in receptors for sex hormones, such as androgen or estrogen (6), and estrogen receptor -positivity was associated with less malignant behavior of HCC (6, 36). Female patients with estrogen receptor-positive tumors may thus show better survival. Basically, male patients were more frequently observed in the HCC population and such a large group included a subgroup with more advanced stage disease. Patient survival thus tended to be lower in this large population. The

presence of diabetes mellitus, obesity and a younger age might also be prognostic factors associated with survival (6, 10, 24, 25, 31), but were not identified as significant prognostic factors in the present series. Metabolic parameters were carefully and well controlled in the perioperative period in the present series.

With respect to surgical results, the amount of blood loss and related transfusion were significant prognostic factors, as noted in previous reports (6, 9, 12, 13, 31). Some studies have reported associations of survival with the extent of hepatectomy or operative time (9, 12, 30, 31), which could be correlated with blood loss. However, in the present study, type of hepatectomy or operative time were not significantly associated with prognosis, processes in which blood loss might be limited by improved decision-making for surgical indications or by the development of operative procedures such as the hanging maneuver or use of vessel sealers (37-39). We applied the parameter of blood loss by weight because this parameter better reflected the relationship with patient survival than volume of blood loss in the present study. We suppose that body weight might affect tolerance to anemia. We attempted to avoid blood transfusions as much as possible in the present series providing vital signs were stable. Blood transfusion has been suggested to increase the risk of intrahepatic tumor recurrence by a few reports, although no clear mechanisms have been defined (9). One possibility is that blood transfusion leads to impaired immunological activity (40). Postoperative complications are closely associated with poor survival in patients with HCC undergoing surgical resections, as described above (30). Various complications may be involved, and hepatic complications in particular are likely to be related to poor patient outcomes such as ascites, abdominal infections and postoperative liver failure (37). In the present study and our preliminary analyses (14-16), uncontrolled ascites tended to confer a poor prognosis but this was not statistically significant. Postoperative uncontrolled ascites may be due to hepatic damage and reduction of potential hepatic functional reserve. In cases where hepatic immunity has been lost for a long time, we speculate that occult cancer cells easily spread or multicentric carcinogenesis occurs in damaged liver cells. At this stage, no effective adjuvant chemotherapy has been established for HCC (41), and no means are available to prevent tumor recurrence if such prognostic factors are found. Patients with impaired liver function are thus at the disadvantage of being at increased risk of tumor recurrence after stressful treatments.

Postoperative risk in patients has been evaluated using risk scores such as APACHE II and POSSUM (42, 43). There is general agreement that morbidity and mortality rates tend to be higher among high-risk HCC patients who undergo hepatectomy. Haga *et al.* recently proposed a new scoring system, the E-PASS score, to predict postoperative morbidity and mortality(22). E-PASS provides a more accurate

reflection of postoperative complications than POSSUM (44) and has been applied recently to evaluate patients after liver surgery (45). In the present study, PRS did not influence survival, while SSS and CRS as indicators of operative severity were significantly associated with poor disease-free survival in both this study and the report by Hashimoto *et al.* (46). This result is probably attributable to the longer operative time and large amount of blood loss. Hepatectomy in HCC patients with liver dysfunction itself led to a higher SSS or CRS in comparison with surgery of other parts of the digestive tract (45). The severity of hepatectomy thus appears to increase the risk of tumor recurrence. Attempts to reduce these scores may improve patient prognosis in HCC. With respect to overall survival, however, E-PASS scores were not associated with survival, and PS was more important as a systemic parameter.

In conclusion, we analyzed relationships between patient survival and non-tumor-related factors such as patient demographics, clinicopathological and surgical features and E-PASS scores in HCC patients who had undergone hepatic resection. Male patients had a poor prognosis in comparison with female patients. Viral hepatitis and preoperative hepatic dysfunction were significantly associated with tumor recurrence and reduced overall survival. Blood loss by weight and postoperative uncontrolled ascites were significantly associated with tumor recurrence and poor patient survival. Multivariate analysis identified viral hepatitis status, grade B liver damage, and increased blood loss as significant predictors of poor survival of HCC patients after hepatectomy. Improvement of adjuvant management for liver dysfunction or anticancer chemotherapy is needed to prolong patient survival.

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