Preoperative peripheral blood neutrophil count predicts long-term outcomes following hepatic resection for colorectal liver metastases

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Received February 1, 2016; Accepted January 26, 2017

DOI: 10.3892/ol.2017.5873

Abstract. Preoperative systemic inflammatory response is associated with a poor long-term prognosis following resection surgery for malignant tumors. Several markers of systemic inflammation have been reported to be associated with the outcome; however, they have not currently been fully investigated. Therefore, the association between preoperative peripheral blood neutrophil count and oncological outcome following hepatic resection for colorectal liver metastasis (CRLM) was retrospectively investigated. The present study comprised 89 patients who had undergone hepatic resection for CRLM between January 2000 and March 2010. The association between preoperative peripheral blood neutrophil count and disease-free survival, in addition to overall survival, was investigated. In multivariate analysis, the presence of neoadjuvant chemotherapy (P=0.015), bilobar distribution (P=0.015) and neutrophil count ≥3,500/μl (P=0.025) were independent and significant predictors of poor disease-free survival, while significant predictors of poor overall survival consisted of >4 lymph node metastases (P=0.001), neo-adjuvant chemotherapy (P=0.003), bilobar distribution (P=0.039) and neutrophil count ≥3,500/μl (P=0.040). Additionally, tumor diameter (P=0.021) and monocyte count (P<0.0001) were observed to be significantly greater in the elevated neutrophil count group. In conclusion, preoperative peripheral blood neutrophil count may be an independent and significant indicator of poor long-term outcomes in patients with CRLM following hepatic resection.

Introduction

Colorectal cancer is a common type of malignancy and approximately 25% of individuals will have liver metastases at the time of the initial diagnosis. Furthermore, 40-50% of patients develop colorectal liver metastasis (CRLM) within three years of resection of the primary tumor (1). Hepatic resection is the most effective and potentially curative therapy for CRLM, with a reported five-year survival rate of 30-50% (2-4); the recent development of chemotherapeutic agents has further improved the outcome of patients with CRLM (5,6). Therefore, assessment of prognostic predictors is important for the management of patients with CRLM.

Previously, several studies have indicated that systemic inflammatory response predicts cancer-specific survival in patients with cancer. The Glasgow prognostic score (GPS), which is calculated by the combination of serum C-reactive protein (CRP) and albumin concentrations, and the elevated preoperative neutrophil-to-lymphocyte ratio (NLR), have been revealed to predict cancer-specific survival (7-12). The previous study reported negative impact of GPS on post-operative complications following hepatic resection (13,14), and the association between perioperative immunological response and prognosis subsequent to hepatic resection for HCC (15,16) and CRLM (17). In the present study, the association between preoperative peripheral blood neutrophil count and disease-free, as well as overall survival, following elective hepatic resection for patients with CRLM was retrospectively investigated.

Materials and methods

Between January 2000 and December 2010, 96 patients with CRLM underwent hepatic resection at the Department of Surgery, Jikei University Hospital (Tokyo, Japan). Of these, seven patients were excluded, one patient for mortality due to a cardiovascular event, two patients due to lack of data and four patients who were lost to follow up, leaving the remaining 89 patients for this study. All patients underwent macroscopic curative resection for liver, lung and lymph node metastases. Liver resection was carried out prior to any other therapy treatments in order to avoid the possibility of liver failure. Neoadjuvant chemotherapy was administered when liver metastases were identified as unresectable or borderline resectable. Pre-operative chemotherapy was discontinued >6 weeks prior to hepatic resection in order to reduce liver

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Key words: colorectal liver metastases, neutrophil, systemic inflammatory response, prognosis, hepatic resection

injury and bone marrow suppression by chemotherapy. Generally, the extent of hepatic resection was determined based on the retention rate of indocyanine green at 15 min (ICG_{R15}) prior to surgery and hepatic reserve, as previously described by Miyagawa *et al* (18). A percutaneous transhepatic portal embolization was performed for patients with an estimated residual hepatic volume of <30%. Nomenclature of segments and types of operations follow the Brisbane 2000 terminology (19). The type of resection was classified into two groups: Major resection (resection of ≥3 couinaud sub segments) and minor resection (resection <3 sub segments, or partial resection). The present study was approved by the Ethics Committee of The Jikei University School of Medicine (Tokyo, Japan).

Patient characteristics were classified into two groups for the Log-rank test and the Cox proportional hazards regression model as follows: Age <65 or ≥65 years, number of regional lymph node metastases <4 or ≥4, size of largest tumor <50 or ≥50 mm, duration of operation <300 or ≥300 min and intraoperative blood loss <1,000 or ≥1,000 g, according to previous studies (10-14). Using the mean or median of preoperative white blood cell subsets counts, they were classified as follows: Neutrophil <3,500 or ≥3,500/μl, lymphocyte <1,500 or ≥1,500/μl, monocyte counts <500 or ≥500/μl.

Firstly, the association between clinical variables and disease-free or overall survival following hepatic resection by univariate and multivariate analysis was investigated. The following 13 variables were evaluated: Age, gender, number of regional lymph node metastases of primary colorectal cancer, synchronous or metachronous CRLM, status of neoadjuvant chemotherapy, tumor distribution, diameter of the largest tumor, type of resection, duration of operation, intraoperative blood loss and the neutrophil, lymphocyte, and monocyte count.

Subsequently, the correlation between neutrophil count and the patient characteristics was analyzed using the following 12 factors: Age, gender, number of regional lymph node metastases of primary colorectal cancer, synchronous or metachronous CRLM, status of neoadjuvant chemotherapy, tumor distribution, diameter of the largest tumor, type of resection, duration of operation, intraoperative blood loss and the lymphocyte and monocyte count.

Recurrence of colorectal cancer was defined as newly detected local, hepatic, lung or extrahepatic tumors by ultrasonography, computed tomography, or magnetic resonance imaging, with or without an increase in serum carcinoembryonic antigen or carbohydrate antigen 19-9 (CA 19-9). For recurrent liver metastasis, repeated hepatic resection, local ablation therapy or systemic chemotherapy was performed based primarily on the number, size and location of the recurrent liver tumors, in addition to hepatic functional reserve, including ICG_{R15}, and remnant liver volume. For lung metastasis, limited partial lung resection or systemic chemotherapy was performed. For local recurrence, tumor resection, radiotherapy or systemic chemotherapy was performed. With regards to chemotherapy, 5-fluorouracil (5-Fu)-based chemotherapy was selected as adjuvant and/or neoadjuvant chemotherapy prior to 2003. Following 2004, the patients received infusional 5-Fu/l-leucovorin with oxaliplatin and/or infusional 5-Fu/l-leucovorin with irinotecan.

Statistical analysis. Data are expressed as the mean ± standard deviation (SD). Analysis of disease-free and overall survival was performed using the Log-rank test. Univariate analysis was performed using the Mann-Whitney U-test and χ^2 test. Multivariate analysis was performed using the Cox proportional regression model, incorporating all variables with P<0.05 in the univariate analysis. These analyses were conducted using IBM® SPSS statistics version 20.0 (IBM SPSS, Armonk, NY, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. Patient characteristics are presented in Table I as the mean ± SD, range or ratio. Preoperative neutrophil counts were 3,466.3±1,206.6/μl (mean ± SD). Certain patients received neoadjuvant chemotherapy for liver resection (7/89).

Univariate and multivariate analysis of disease-free survival following hepatic resection and clinical variables. Table II presents the association between the clinical variables and disease-free survival following hepatic resection. In univariate analysis, disease-free survival was significantly poorer in patients with >4 lymph node metastases (P=0.018), presence of neoadjuvant chemotherapy (P=0.026), bilobar distribution (P=0.002) and neutrophil count ≥3,500/μl (P=0.021; Fig. 1A). In multivariate analysis, the presence of neoadjuvant chemotherapy (P=0.015), bilobar distribution (P=0.015) and neutrophil count ≥3,500/μl (P=0.025), were independent and significant predictors of disease-free survival.

Univariate and multivariate analysis of overall survival following hepatic resection and clinical variables. Table III presents the association between the clinical variables and overall survival following hepatic resection. In univariate analysis, overall survival was significantly poorer in patients with >4 lymph node metastases (P<0.001), the presence of neoadjuvant chemotherapy (P=0.003), bilobar distribution (P=0.0007) and neutrophil count ≥3,500/μl (P=0.029; Fig. 1B). In multivariate analysis, >4 lymph node metastases (P=0.001), presence of neoadjuvant chemotherapy (P=0.003), bilobar distribution (P=0.039) and neutrophil count ≥3,500/μl (P=0.040), were independent and significant predictors of overall survival.

Univariate analysis of clinical variables in association with the neutrophil count. Table IV presents the association between clinical variables and the neutrophil count. In univariate analysis, tumor diameter (P=0.021) and monocyte count (P<0.001) were significantly greater in the group of patients with an elevated neutrophil count. Synchronous CRLM (P=0.088) and intraoperative blood loss (P=0.065) tended to be greater in patients with elevated neutrophil count group; however, this was not statistically significant.

Discussion

Systemic inflammation has been reported to correlate with poorer cancer-specific survival in numerous types of

Table I. Patient characteristics.

Factor	Mean ± SD or ratio	Range
Age (years)	64.0±9.8	39-85
Gender (male:female)	62:27	
No. of lymph node metastases (<4:≥4)	67:22	
Timing of tumor (synchronous:metachronous)	41:48	
Neoadjuvant chemotherapy (yes:no)	7:82	
Tumor distribution (unilobar:bilobar)	22:67	
Tumor size (mm)	43.4±31.8	10-200
Type of resection (major:minor)	33:56	
Duration of operation (min)	349.8±144.9	85-867
Intraoperative blood loss (g)	1,132.8±1,088.6	25-5,485
Neutrophil count (μl)	3,466.3±1,206.6	1,300-8,000
Lymphocyte count (μl)	1,514.6±443.0	700-2,700
Monocyte count (μl)	294.4±113.2	0-600

SD, standard deviation.

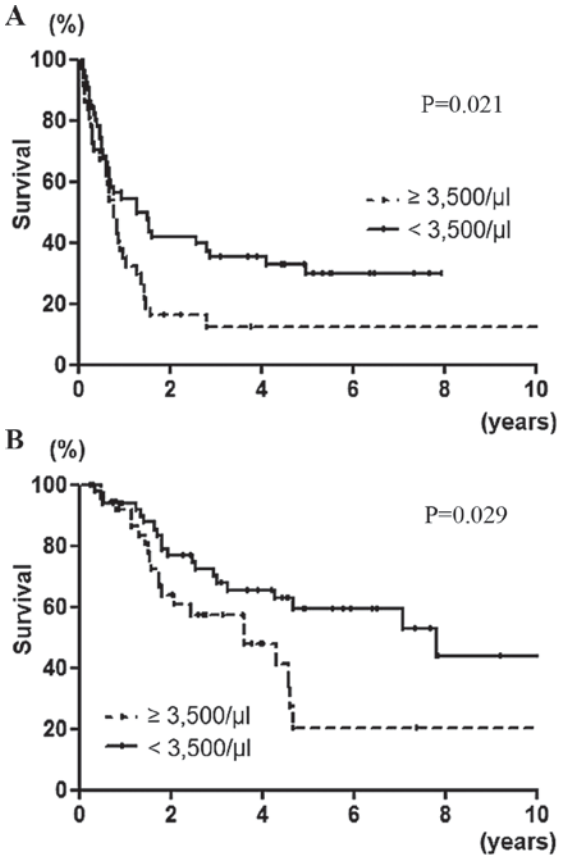

Figure 1. Kaplan-Meier curves of (A) disease-free and (B) overall survival following hepatic resection for CRLM. Elevated neutrophil count (≥3,500/μl) was significantly associated with the lowest disease-free survival (P=0.021) and overall survival rate (P=0.029). CRLM, colorectal liver metastasis.

cancer (7-12,20). Previous studies have demonstrated that the host inflammatory response to cancer and/or the systemic effects exerted by cancer cells leads to the upregulation of the inflammatory process, predisposing the cancer to proliferation and metastasis by the inhibition of apoptosis, promotion of angiogenesis and repair of DNA damage (21,22). The presence of a systemic inflammatory response may be detected by the elevation of the CRP level and neutrophil count (7-12). Using these parameters, prognostic markers, including GPS and NLR, were reported to be associated with poor survival following hepatic resection for CRLM (9-11,23). In the present study disease-free and overall survival of patients with preoperative high neutrophil counts following elective hepatic resection for CRLM, was revealed to be significantly poorer by statistical analyses. The prognostic value of NLR in the present study cohort was also investigated; however, NLR was not a significant predictor of the overall survival (P=0.193, data not presented). This result indicates that neutrophil counts may themselves be an inflammatory and prognostic marker. Neal *et al* (24) demonstrated that the neutrophil count had a greater predictive value on long-term outcomes compared with NLR, when the multivariate Cox proportional regression model analyzed factors.

Inflammatory status represents a response process to detection of CRLM (25). In the present study, tumor size was larger in patients with higher neutrophil counts. These results indicate that tumor invasion or expansion elicits inflammation in the microenvironment. Neutrophils contribute to continuous angiogenic stimulation, including the release of endothelial growth factor (26). This condition may accelerate the growth of cancer cells or micro-metastases (27). Additionally, systemic inflammation also induces the suppression of antitumor immunity by recruitment of regulatory T cells and activation of cytokines (25). Preoperative systemic inflammation and an immunosuppressive state may increase the risk of postoperative infectious complications, which influence long-term outcomes in patients with CRLM (24,28).

In the present study, neoadjuvant chemotherapy demonstrated a negative impact on long-term outcomes following hepatic resection for CRLM. Neoadjuvant chemotherapy prior to hepatic resection in patients with resectable CRLM

Table II. Univariate and multivariate analysis of clinical variables in association with disease-free survival following hepatic resection.

		Univariate analysis		Multivariate analysis	
Factor	N	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age (years)			0.192		
≥65	46	1.382			
<65	43	(0.850-2.246)			
Gender			0.913		
Male	62	1.030			
Female	27	(0.606-1.751)			
No. of lymph node metastases			0.018[a]		0.079
≥4	22	2.107		1.656	
<4	67	(1.133-3.917)		(0.947- 2,895)	
Timing of tumor			0.200		
Synchronous	41	1.381			
Metachronous	48	(0.843-2.260)			
Neoadjuvant chemotherapy			0.026[a]		0.015[a]
Yes	7	4.170		3.155	
No	82	(1.182-14.71)		(1.249-7.966)	
Tumor distribution			0.002[a]		0.015[a]
Bilobar	22	2.770		1.961	
Unilobar	67	(1.458-5.265)		(1.143-3.366)	
Tumor size (mm)			0.402		
≥50	24	1.272			
<50	65	(0.724-2.234)			
Type of resection			0.818		
Major	33	1.061			
Minor	56	(0.639-1.762)			
Duration of operation (min)			0.397		
≥300	55	1.238			
<300	34	(0.756-2.028)			
Intraoperative blood loss (g)			0.875		
≥1,000	39	1.040			
<1,000	50	(0.639-1.691)			
Neutrophil count (μl)			0.021[a]		0.025[a]
≥3,500	37	1.827		1.838	
<3,500	52	(1.093-3.052)		(1.087-3.134)	
Lymphocyte count (μl)			0.805		
≥1,500	49	1.063			
<1,500	40	(0.653-1.730)			
Monocyte count (μl)			0.899		
≥300	57	1.143			
<300	32	(0.694-1.883)			

[a]P<0.05; CI, confidence interval.

may facilitate the resectability of liver lesions and treat occult metastasis; however, it may also lead to hepatic parenchymal injury, which may increase morbidity and mortality following surgery (29,30). There are conflicting opinions over the oncological benefit of this practice in patients who may already be suitable for a curative hepatic resection (31,32). Additionally, in the present study patients treated with neoadjuvant chemotherapy were limited and

Table III. Univariate and multivariate analysis of clinical variables in association with overall survival following hepatic resection.

		Univariate analysis		Multivariate analysis	
Factor	N	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age (years)			0.947		
≥65	46	1.021			
<65	43	(0.552-1.890)			
Gender			0.885		
Male	62	0.952			
Female	27	(0.488-1.856)			
No. of lymph node metastases			<0.001[a]		0.001[a]
≥4	22	4.311		3.023	
<4	67	(1.968-9.447)		(1.585-5.765)	
Timing of tumor			0.423		
Synchronous	41	1.287			
Metachronous	48	(0.694-2.389)			
Neoadjuvant chemotherapy			0.003[a]		0.003[a]
Yes	7	12.46		5.058	
No	82	(2.370-65.60)		(1.748-14.436)	
Tumor distribution			0.007[a]		0.039[a]
Bilobar	22	2.093		2.021	
Unilobar	67	(1.337-6.304)		(1.035-3.944)	
Tumor size (mm)			0.275		
≥50	24	1.510			
<50	65	(0.721-3.160)			
Type of resection			0.884		
Major	33	1.049			
Minor	56	(0.556-1.977)			
Duration of operation (min)			0.373		
≥300	55	1.335			
<300	34	(0.707-2.522)			
Intraoperative blood loss (g)			0.185		
≥1,000	39	1.527			
<1,000	50	(0.817-2.853)			
Neutrophil count (μl)			0.029[a]		0.040[a]
≥3,500	37	2.066		2.016	
<3,500	52	(1.078-3.960)		(1.031-3.941)	
Lymphocyte count (μl)			0.660		
≥1,500	49	1.149			
<1,500	40	(0.620-2.130)			
Monocyte count (μl)			0.822		
≥300	57	0.930			
<300	32	(0.492-1.757)			

[a]P<0.05; CI, confidence interval.

had a more aggressive disease, including bilobar distribution (P=0.038, data not presented), compared with patients without neo-adjuvant chemotherapy on initial presentation, as liver resection had priority over other therapies at Jikei University Hospital.

In summary, preoperative elevation of the peripheral neutrophil count is an independent risk factor for disease-free as well as overall survival. Prevention of systemic inflammatory response may improve perioperative outcomes and long-term survival following resection of malignant tumors. Several

Table IV. Univariate analysis of clinical variables in association with preoperative neutrophil counts.

	Neutrophil count		
Factor	<3,500/μl (n=52)	≥3,500/μl (n=37)	P-value
Age (years)	63.8±8.9	64.2±11.1	0.723
Gender (male:female)	34:18	28:9	0.298
No. of lymph node metastases (<4:≥4)	42:10	27:10	0.155
Timing of tumor (synchronous:metachronous)	20:32	21:16	0.088
Neoadjuvant chemotherapy (yes:no)	6:46	1:36	0.127
Tumor distribution (unilobar:bilobar)	40:12	27:10	0.670
Tumor size (mm)	35.4±19.4	54.5±41.6	0.021
Type of resection (major:minor)	20:32	13:24	0.749
Duration of operation (min)	341.3±142.7	361.8±149.0	0.524
Intraoperative blood loss (g)	939.1±962.3	1,405.0±1,206.1	0.065
Lymphocyte count (/μl)	1,526.9±422.0	1,497.3±476.4	0.789
Monocyte count (/μl)	251.9±101.9	354.1±101.6	<0.001[a]

[a]P<0.05.

therapeutic agents targeting the inflammatory response are undergoing clinical trials (33). Further investigation to clarify the association between the immunosuppressive mechanisms induced by systemic inflammation and tumor progression is important in order to improve the therapeutic outcome of oncological surgery. In conclusion, preoperative peripheral blood neutrophil count is an independent and significant indicator of long-term outcomes in patients with CRLM following hepatic resection.

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