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Neutrophil-Lymphocyte Ratio as a Prognostic Factor in Incurable Stage IV Colorectal Cancer

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Abstract

Objectives: Our aim is investigating the predictive potential of these available and convenient laboratory dates in stage IV colorectal cancer (CRC) patients. **Methods:** We identified the cases of 114 consecutive patients who underwent the surgery at our Hospital between January 2006 and December 2012 by using the multivariate analysis, the Cox proportional-hazard regression model. **Results:** Multivariate analysis for the predictors of survival showed metastatic lesion resection [hazard ratio (HR) = 3.2, 95% confidence interval (CI) 1.6 - 6.6; p = 0.007] and only primary lesion resection (HR = 1.9, 95% CI 1.1 - 4.0; p = 0.045) remained independently significant prognostic factors. Therefore, we divided in 3 groups, 1) metastatic lesion resection group with primary lesion resection (n = 52 in the Met/Prim lesion group), 2) primary lesion resection without metastatic lesion resection (n = 38 in the Primary lesion group) and 3) palliative operation (n = 24 in the Palliative group). Age was the only independent risk factor in the Met/Prim lesion group. In the Primary lesion group, Neutrophil lymphocyte ratio (NLR) > 5, elevated Alanine aminotransferase and patients without chemotherapy were correlated with poor survival. In the Palliative group, NLR > 5 and patients who could not be treated with chemotherapy remained independent predictors of worse survival. **Conclusions:** NLR is not only simple and convenient for classification of patients, but also one of the important predictors of mortality for stage IV incurable CRC patients.

Keywords

Colorectal Cancer, Neutrophil-Lymphocyte Ratio, Surgery, Prognosis, Metastasis

1. Introduction

The number of colorectal cancer (CRC) patients has been increasing rapidly

worldwide in recent decades, and the survival rates of CRC patients have increased in the past few years, possibly as a result of progress in diagnostic faculty and improved chemotherapy. Nonetheless, approximately 20% - 25% of CRC patients have metastatic disease at the time of first presentation. Of these patients, only less than 20% of the distant metastasis can undergo curative resection [1]. Several promising candidate markers have been reported to have potential usefulness in the prediction of radiation and chemotherapy responses among CRC patients, including metabolic enzymes (thymidine phosphorylase, thymidylate synthase), angiogenesis (vascular endothelial growth factor), apoptosis (bax, p 53, nuclear factor-kappa B, and survivin), inflammation (cyclooxygenase-2, interleukin [IL]-6, IL-10, C-reactive protein concentration [CRP]), proliferation (proliferating cell nuclear antigen), and cell adhesion or collagenase (CD44, CD133, matrix metalloproteinase [MMP] 2, and MMP9) [2] [3] [4] [5]. Genetic biomarkers such as microsatellite instability, CpG island methylator phenotype, and chromosomal instability have also been reported to be valid indicators of poor prognosis in CRC [6].

Consequently, there is a dire need to identify available, inexpensive and robust biomarkers that can clinically determine cancer prognosis. Simple laboratory markers including plasma CRP, albumin and absolute white blood cells or its fractions (neutrophils, lymphocytes) have been investigated as prognostic and predictive markers in CRC patients [7]. CRP and albumin have been used to provide a Glasgow Prognostic Score (GPS) in patients with advanced cancer based on a combination of hypoalbuminemia and an elevated CRP [8] [9], and neutrophils and lymphocytes have been used to obtain the neutrophil-to-lymphocyte ratio (NLR) [10] [11] [12] [13] [14]. In this study, we extended the prognostic analysis to CRC patients with metastasis who underwent surgery in order to select the predictive factors from these available and inexpensive laboratory data.

2. Patients and Methods

Patients with clinically confirmed stage IV CRC diagnosed at Juntendo University Hospital between January 2006 and December 2012 were eligible to be in this study. This patient series included those who underwent primary tumor resection, a bypass or a proctostomy and those who underwent the simultaneous resection of metastases with curative intent. In the cases of lung metastasis, metachronous resection was performed. Patients who had non-elective surgery, pre-operative radiotherapy and chemotherapy and showed clinical evidence of infection or other inflammatory conditions were excluded from the study.

After surgical resection, all specimens were histopathologically reviewed, and the pathological classification and stage were determined according to the classification established by the American Joint Committee on Cancer (AJCC) TNM staging system [15]. The presence or absence of liver metastasis, lung metastasis, and peritoneal metastasis was determined. The other clinicopathological para-

meters studied for prognostic value were tumor location, histologic differentiation, vessel involvement, and lymphatic invasion.

Routine laboratory measurements prior to surgery were analyzed in this study. Routine laboratory measurements including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (T.Bil), white blood cell count (WBC), neutrophil count, lymphocyte count, CRP, albumin, total protein (T.P) and the levels of tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were obtained before surgery.

The GPS was determined as described [16]. Briefly, patients with both an elevated CRP level (>1 mg/dl) and hypoalbuminemia (<3.5 g/dl) were allocated a score of 2. Patients in whom only one of these biochemical abnormalities was present were allocated a score of 1. Patients in whom neither of these abnormalities was present were allocated a score of 0. An NLR value was calculated from the absolute neutrophil count divided by the absolute lymphocyte count. In consideration of the proportions of the subgroups, an NLR value of 5.0 was used as a cut-offpoint, according to several previous studies [17]. Cut-off points of other laboratory data were caclulated by the receiver operating characteristic (ROC) curve.

In cases of resectable stage IV CRC, the current therapeutic options for chemotherapy are FOLFOX (5-FU, leucovorin [LV] and oxaliplatin), CapeOX (capecitabine and oxaliplatin) or FOLFIRI (5-FU, LV and irinotecan). When these therapies are not tolerated, oral tegaful-uracil/LV or capecitabine can be administrated.

In the present cases of incurable cancer, these options plus bevacizumab or cetuximab/panitumumab were selected according to the presence/absence of K-ras mutation. Only the cases of the patients who had been administered at least three consecutive cycles of one of these regimens were considered as chemotherapy cases.

This retrospective study was approved by our hospital's Institutional Review Board, and the requirement for patient consent was waived.

3. Statistical Analyses

We compared these general laboratory data with the patient categories in a contingency table analysis, based on the chi-square distribution. Cut-off points were derived by ROC. The survival curves were made using the Kaplan-Meier method and the comparison of the survival curves was done with the log-rank test. For the multivariate analysis, the Cox proportional-hazard regression model was used with the hazard ratio (HR). Data were analyzed using JMP 10 software (SAS, Cary, NC, USA).

4. Results

Table 1 summarizes the clinical characteristics of the 114 patients who underwent

Table 1. Univariate and multivariate analyses of prognostic predictors in 114 stage IV colorectal cancer (CRC) patients.

Variable	No. of patients		Univariate P	Multivariate P	HR	95% CI
Age	<70 years ≥70 years	n = 74 n = 40	<0.01	0.11	1.6	0.9 - 3.0
Gender	M F	n = 64 n = 50	0.44			
WBC (/μl)	<6500 ≥6500	n = 58 n = 56	0.02			
Neutrophil (/μl)	<5000 ≥5000	n = 73 n = 41	0.02			
Lymphcyte (/μl)	<1200 ≥1200	n = 41 n = 73	0.07			
NLR	<5 ≥5	n = 87 n = 27	<0.01	0.43	1.3	0.7 - 2.6
AST (IU/l)	<20 ≥20	n = 43 n = 71	0.10			
ALT (IU/l)	<30 ≥30	n = 84 n = 30	0.03	0.30	1.4	0.7 - 2.6
T.Bil (mg/dl)	<0.8 ≥0.8	n = 93 n = 19	0.73			
T.P (g/dl)	<6.0 ≥6.0	n = 17 n = 97	0.05			
Alb (g/dl)	<3.5 ≥3.5	n = 30 n = 84	<0.01			
CEA (ng/ml)	<5.0 ≥5.0	n = 15 n = 99	0.04	0.18	2.0	0.7 - 7.3
CA19-9 (U/ml)	<60 ≥60	n = 61 n = 53	0.33			
CRP (mg/dl)	<1 ≥1	n = 65 n = 49	<0.01			
GPS	<1 ≥1	n = 56 n = 58	<0.01	0.82	1.1	0.6 - 1.9
Tumor location	Colon Rectum	n = 90 n = 24	0.15			
Primary lesion resection	Yes No	n = 90 n = 24	<0.01	0.04	2.0	1.1 - 4.0
Metastatic lesion resection	Yes No	n = 52 n = 62	<0.01	<0.01	3.2	1.6 - 6.6
Hepatic metastasis	Yes No	n = 11 n = 103	<0.01	0.55	1.2	0.6 - 2.5
Lung metastasis	Yes No	n = 18 n = 96	0.56			
Peritoneal metastasis	Yes No	n = 15 n = 99	0.65			

surgery for stageⅣCRC. The median follow-up period was 14 months (range 0 - 69). The results of the univariate and multivariate analyses for the predictors of survival are listed in Table 1. The univariate analysis showed that age ($p < 0.01$), WBC ($p = 0.02$), elevated NLR ($p < 0.01$), elevated ALT ($p = 0.03$), hypoalbuminemia ($p < 0.01$), elevated CEA ($p = 0.04$), elevated CRP ($p < 0.01$), elevated GPS score ($p < 0.01$), primary lesion resection ($p < 0.01$), metastatic lesion resection ($p < 0.01$), and liver metastasis ($p = 0.03$) were significantly associated with a poorer survival rate (Table 1).

The multivariate analysis revealed that the CRC patients' survival was dependenton the surgical treatment: primary lesion resection and metastatic lesion resection were significant predictors of better survival. Metastatic lesion resection (HR = 3.2, 95% confidence interval [CI] 1.6 - 6.6; $p < 0.01$) and primary lesion resection (HR = 1.9, 95% CI 1.1 - 4.0; $p = 0.04$) remained independent significant prognostic factors.

We therefore divided the 114 patients into three groups: 1) the metastatic lesion resection group with primary lesion resection (Met/Prim lesion group, n = 52), 2) the primary lesion resection without metastatic lesion resection (Primary lesion group, n = 38) and 3) the palliative operation group (Palliative group, n = 24).

We next examined the correlation between overall survival and clinicopathological findings, including GPS, NLR and other general laboratory measurements in the Met/Prim lesion group. The results of the univariate and multivariate analyses of postoperative mortality are shown in Table 2. Based on the univariate analysis, age ($p = 0.04$), liver metastasis ($p < 0.01$), and the absence of adjuvant chemotherapy ($p = 0.01$) were significant prognostic factors for poor overall survival. The multivariate analysis revealed that age ($p = 0.03$) was the only independent risk factor for predicting poor prognosis (Table 2).

In the Primary lesion group, *i.e.*, the patients who underwent primary resection without metastatic lesion resection, NLR > 5 ($p = 0.01$), elevated ALT ($p < 0.01$) and patients without chemotherapy ($p = 0.01$) had significantly poorer overall survival in the univariate analysis, and the multivariate analysis revealed that all three of these factors were independent risk factors for predicting poor prognosis, as shown in Table 3 (NLR > 5: HR 2.8, 95% CI 1.1 - 6.6, $p = 0.03$; elevated ALT: HR 5.0, 95% CI 1.9 - 13, $p < 0.01$; and patients without chemotherapy: HR 3.5, 95% CI 1.5 - 8.1, $p < 0.01$) (Table 3).

Lastly, we investigated the laboratory markers in the Palliative group, *i.e.*, the patients who underwent a palliative operation such as a by pass or proctostomy. The univariate analysis revealed that neutrophil count ($p = 0.04$), NLR > 5 ($p = 0.01$) and non-use of chemotherapy treatment ($p < 0.01$) were significant risk factors for predicting poor prognosis. The multivariate analysis (Table 4) showed that NLR > 5 (HR 7.3, 95% CI 2.1 - 32, $p = 0.01$) and the non-use of chemotherapy (HR 7.9, 95% CI 2.5 - 27.0, $p < 0.01$) remained independent predictors of worse survival.

Table 2. Univariate and multivariate analyses of prognostic predictors in the CRC patients who underwent curative resection.

Variable	No of patients		Univariate P	Multivariate P	HR	95% CI
Age	<70	n = 37	0.04	0.03	3.4	1.2 - 10.2
	≥70	n = 15				
Gender	M	n = 34	0.12			
	F	n = 18				
WBC (/μl)	<6500	n = 33	0.12			
	≥6500	n = 19				
Neutrophil (/μl)	<5000	n = 41	0.38			
	≥5000	n = 11				
Lymphcyte (/μl)	<1200	n = 15	0.92			
	≥1200	n = 37				
NLR	<5	n = 48	0.63			
	≥5	n = 4				
AST (IU/l)	<20	n = 30	0.7			
	≥20	n = 22				
ALT (IU/l)	<30	n = 34	0.62			
	≥30	n = 18				
T.Bil (mg/dl)	<0.8	n = 43	0.38			
	≥0.8	n = 9				
T.P (g/dl)	<6.0	n = 6	0.49			
	≥6.0	n = 46				
Alb (g/dl)	<3.5	n = 9	0.78			
	≥3.5	n = 43				
CEA (ng/ml)	<5.0	n = 9	0.15			
	≥5.0	n = 43				
CA19-9 (U/ml)	<60	n = 29	0.89			
	≥60	n = 23				
CRP(mg/dl)	<1	n = 39	0.81			
	≥1	n = 13				
GPS	<1	n = 36	0.87			
	≥1	n = 16				
Tumor location	Colon	n = 43	0.76			
	Rectum	n = 9				
Pathology	Diff	n = 50	0.31			
	Non diff	n = 2				
Serosal invasion	Yes	n = 17	0.41			
	No	n = 35				
Vascular invasion	Yes	n = 38	0.51			
	No	n = 14				
Lymphatic invasion	Yes	n = 20	0.13			
	No	n = 32				
Lymph-node metastasis	Yes	n = 35	0.12			
	No	n = 17				
Hepatic metastasis	Yes	n = 4	<0.01	0.06	2.9	1.0 - 9.1
	No	n = 48				
Lung metastasis	Yes	n = 3	0.90			
	No	n = 49				
Peritoneal metastasis	Yes	n = 3	0.41			
	No	n = 49				
Chemotherapy	Yes	n = 43	0.01	0.09	3.0	0.1 - 1.1
	No	n = 9				

Table 3. Univariate and multivariate analyses of prognostic predictors in the patients who underwent only primary-lesion resection.

Variable	No of patients		Univariate P	Multivariate P	HR	95% CI
Age	<70	n = 17	0.45			
	≥70	n = 21				
Gender	M	n = 17	0.39			
	F	n = 21				
WBC (/μl)	<6500	n = 13	0.72			
	≥6500	n = 25				
Neutrophil (/μl)	<5000	n = 17	0.36			
	≥5000	n = 21				
Lymphcyte (/μl)	<1200	n = 15	0.82			
	≥1200	n = 23				
NLR	<5	n = 25	0.01	0.03	2.8	1.1 - 6.6
	≥5	n = 13				
AST (IU/l)	<20	n = 8	0.31			
	≥20	n = 30				
ALT (IU/l)	<30	n = 28	<0.01	<0.01	5.0	1.9 - 13.1
	≥30	n = 10				
T.Bil (mg/dl)	<0.8	n = 29	0.88			
	≥0.8	n = 9				
T.P (g/dl)	<6.0	n = 5	0.66			
	≥6.0	n = 33				
Alb (g/dl)	<3.5	n = 15	0.72			
	≥3.5	n = 23				
CEA (ng/ml)	<5.0	n = 3	0.06			
	≥5.0	n = 35				
CA19-9 (U/ml)	<60	n = 11	0.94			
	≥60	n = 27				
CRP (mg/dl)	<1	n = 18	0.52			
	≥1	n = 20				
GPS	<1	n = 14	0.73			
	≥1	n = 24				
Tumor location	Colon	n = 34	0.31			
	Rectum	n = 4				
Pathology	Diff	n = 32	0.19			
	Non Diff	n = 6				
Serosal invasion	Yes	n = 28	0.95			
	No	n = 10				
Vascular invasion	Yes	n = 32	0.38			
	No	n = 6				
Lymphatic invasion	Yes	n = 27	0.64			
	No	n = 11				
Lymph-node metastasis	Yes	n = 28	0.48			
	No	n = 10				
Hepatic metastasis	Yes	n = 4	0.59			
	No	n = 34				
Lung metastasis	Yes	n = 13	0.21			
	No	n = 25				
Peritoneal metastasis	Yes	n = 6	0.24			
	No	n = 32				
Chemotherapy	Yes	n = 26	0.01	<0.01	3.5	1.5 - 8.1
	No	n = 12				

Table 4. Univariate and multivariate analyses of prognostic predictors in the patients who underwent a palliative operation.

Variable	No of patients		Univariate P	Multivariate P	HR	95% CI
Age	70 ≥70	n = 20 n = 4	0.77			
Gender	M F	n = 13 n = 11	0.51			
WBC (/μl)	<6500 >6500	n = 12 n = 12	0.08			
Neutrophil (/μl)	<5000 >5000	n = 15 n = 9	0.04			
Lymphcyte (/μl)	<1200 >1200	n = 12 n = 12	0.99			
NLR	<5 >5	n = 14 n = 10	0.01	<0.01	7.3	2.1 - 32.2
AST (IU/l)	<20 ≥20	n = 15 n = 9	0.76			
ALT (IU/l)	<30 ≥30	n = 17 n = 7	0.91			
T.Bil (mg/dl)	<0.8 ≥0.8	n = 21 n = 3	0.20			
T.P (g/dl)	<6.0 ≥6.0	n = 9 n = 15	0.26			
Alb (g/dl)	<3.5 ≥3.5	n = 16 n = 8	0.10			
CEA (ng/ml)	<5.0 ≥5.0	n = 3 n = 21	0.17			
CA19-9 (U/ml)	<60 ≥60	n = 12 n = 12	0.96			
CRP (mg/dl)	<1 ≥1	n = 8 n = 16	0.50			
GPS	<1 ≥1	n = 6 n = 18	0.44			
Tumor location	Colon Rectum	n = 13 n = 11	0.88			
Hepatic metastasis	Yes No	n = 3 n = 21	0.95			
Lung metastasis	Yes No	n = 7 n = 17	0.14			
Peritoneal metastasis	Yes No	n = 6 n = 18	0.43			
Chemotherapy	Yes No	n = 16 n = 8	<0.01	<0.01	7.9	2.5 - 27.7

5. Discussion

Most of the surgeons have concluded that metastatic lesion resection is feasible and improves the survival of patients with resectable stage IV CRC [18]. However, there is controversy regarding whether a primary resection should be undertaken in incurable stage 4 CRC patients. A primary resection does ensure that the primary cancer is removed, preventing perforation and stenosis and improving the likelihood of survival, as we also found in the present study. Although a previous study showed that primary site resection has benefits for incurable metastatic CRC [19], the results of prospective randomized studies are awaited, such as the JCOG1007 trial comparing resection of the primary tumor plus chemotherapy with chemotherapy alone.

Our present findings may reflect a selection bias for primary resection or palliative operation because these depended on the patients' tolerance. Regarding chemotherapy, previous findings have indicated that for patients with resectable liver metastases, the overall survival afforded by the addition of perioperative FOLFOX4 chemotherapy was not significantly different from that provided by surgery alone [20]. Concomitantly, in the present retrospective study there was no significant difference in survival among the three groups of resectable stage IV CRC patients. In cases of incurable CRC, as a matter of course, the use of some chemotherapy improved the overall survival.

This study was designed to determine the prognostic importance of the NLR in incurable stage IV CRC patients. The finding that these inflammatory data are correlated with cancer progression is not novel. In 1863, Virchow noted leucocytes in neoplastic tissues and made a connection between inflammation and cancer. He also hypothesized that the origin of cancer was at sites of chronic inflammation [21]. Myelomonocystic cells such asneutrophils are an essential component of innate immunity. These cells act as a first line of resistance against pathogens (e.g., microbes, viruses and cancer) and they activate adaptive lymphocytes responses. It was shown that cancer abrogates the immune system's resistance, which eventually adapts to the microenvironment orchestrated by cancer [22] [23]. These disruptions of the inflammatory process lead to cancer progression and poor prognosis.

The results of the present investigation did not show a correlation between resectable stage IV CRC and the NLR, although previous studies indicated that the NLR is a significant prognostic factor for stage II CRC patients [13] [14]. It seems that high levels of these inflammatory factors, *i.e.*, the NLR, are notable in progressive cancers such as incurable stage IV CRC. Of note, it seems meaningful that the relative ratio of leukocytes is more informative about the prognosis of stage IV CRC patients compared to the GPS.

There have been many significant developments and discoveries in cancer genomics. However, these new predictors are expensive and not available at many hospitals. A useful biomarker must be not only accurate and reproducible but also easily accessible.

Our study has several limitations, including the small number of patients and its retrospective nature, as well as the need for a validation study including factors that are essential in a multivariate analysis. Further study is required to test the validity, reliability, reproducibility and clinical usefulness of our results for patients with stage IV CRC. In summary, to our knowledge, the adoption of the pretreatment measurement of the NLR is not only simple and convenient for the classification of patients, but also one of the important predictors of mortality for incurable stage IV CRC patients.

Author Contributions

Study concept and design (SM, KS); data acquisition (SM, KH, MK, MT, YK, MG, SK, HK, MO, YT); analysis and interpretation of data (SM); drafting of the manuscript (SM, KS, KS); critical revision of the manuscript (SM).

Ethical Approval

This study was performed in accordance with the ethical standards of the Committee on Human Experimentation of our institution (Institutional Review Board No. 12-106).

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Abbreviations

CI: Confidence Interval

GPS: Glasgow Prognostic Score

HR: Hazard Ratio

NLR: Neutrophil-Lymphocyte Ratio

ROC: Receiver Operating Characteristic