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Neutrophil–lymphocyte Ratio and Histological Response Correlate With Prognosis of Gastric Cancer Undergoing Neoadjuvant Chemotherapy

NAOKI URAKAWA, SHINGO KANAJI, TAKASHI KATO, RYUICHIRO SAWADA, HITOSHI HARADA, HIRONOBU GOTO, HIROSHI HASEGAWA, KIMIHIRO YAMASHITA, TAKERU MATSUDA, TARO OSHIKIRI and YOSHIHIRO KAKEJI

Division of Gastrointestinal Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

Abstract. *Background/Aim: Neoadjuvant chemotherapy (NAC) for advanced gastric cancer (GC) and esophagogastric junction cancer (EGC) is expected to effectively control the tumor; however, histological tumor response and immune function markers as prognostic factors for NAC remain unknown. This study assessed the prognostic significance of histological response and immune function markers in patients undergoing NAC for GC and EGC. Patients and Methods: Forty-two patients who underwent NAC followed by surgical resection for operable advanced GC or EGC from January 2007 to December 2019 were divided into two groups based on histological response. Overall survival (OS), tumor response, and immune function markers, such as the neutrophil/lymphocyte ratio (NLR), were the outcomes analyzed. Results: The 5-year OS for Grade 2b-3 (n=10, responder group) according to the Japanese Gastric Cancer Classification was 72.0% with a favorable prognosis, compared with 33.3% for Grade 0-1a (n=18), and 46.8% for Grade 1b-2a (n=14) in the non-responder group. There was no significant difference in the background between the two groups regarding clinical status or immune function markers. In a multivariate analysis of immune function markers, the NLR value before NAC was significantly associated with prognosis (p=0.048). Patients with an NLR value <3.4 had a favorable OS (p=0.03). Conclusion: Histological response scores for Grade 2b or higher may help predict a favorable prognosis for patients undergoing NAC for advanced GC and EGC. The outcomes may be further improved by considering NLR values.*

Correspondence to: Shingo Kanaji, MD, Ph.D., 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, 650-0017, Japan. Tel: +81 783825925, Fax: +81 783825939, e-mail: kanashin@med.kobe-u.ac.jp

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Neoadjuvant chemotherapy (NAC) for advanced gastric cancer (GC) and esophagogastric junction cancer (EGC) have recently become an effective standard of treatment, particularly in the Western countries (1). In Asia, the standard treatment for curatively resectable GC and EGC is primarily postoperative adjuvant chemotherapy; however, many adverse effects occur including postoperative malnutrition and weight loss. Several clinical trials on NAC have been conducted in Asia in recent years (2-5). Because advanced GC and EGC may have disseminated or distant metastases that are difficult to evaluate preoperatively, NAC is considered to have potential as it may control micrometastases systemically in the early stages of the disease (6).

Histological tumor response is a parameter for evaluating response to chemotherapy. Although there are some reports of histological tumor response as a useful prognostic predictor for NAC, definitive criteria remain unclear as various evaluation methods and criteria have been used in different studies (7) (8). Another issue with NAC is the need to determine whether the patient's general condition is sufficient to tolerate chemotherapy and surgery during the initial visit. Recently, it was reported that various nutritional markers measured in patient blood samples reflect their general condition (9, 10); however, it remains controversial which markers are useful, and whether they have prognostic utility in GC and EGC patients undergoing chemotherapy.

The purpose of this study was to determine the correlation of the histological response of the primary tumor with outcome in advanced GC and EGC patients treated with NAC and to assess whether the results may be used to

predict prognosis. In addition, we examined the association between immune function markers, which reflect the patient's general condition, and prognosis, to improve outcome associated with NAC treatment and to identify additional prognostic factors.

Patients and Methods

Patients. This study included 42 patients who underwent NAC followed by surgical resection for GC or EGC at Kobe University Hospital from January 2007 to December 2019. The inclusion criteria for preoperative chemotherapy in these patients were as follows: macroscopically resectable adenocarcinoma, depth of clinical T3 or higher, bulky lymph node metastasis, or para-aortic lymph node metastasis. Exclusion criteria included esophageal invasion of more than 4 cm, metastasis to other organs at initial diagnosis, palliative resection, D0 grade lymphadenectomy, or previous history of chemotherapy for any other cancer or synchronous cancer. GC and EGC were diagnosed by esophagogastroscopy biopsy with total-body CT scanning. To evaluate clinical lymph node metastasis, an 8 mm or greater size was considered positive. Histological and clinicopathological evaluations, including histological tumor response, were performed based on the 15th Japanese Classification of Gastric Carcinoma by the Japanese Gastric Cancer Association (11). All patients were followed up using total-body CT and blood collection. This study was approved by the Ethics Committee of Kobe University (No. B220029).

Neoadjuvant chemotherapy. Most patients in this study were registered in clinical studies involving NAC. We applied to the Ethics Committee of Kobe University Hospital when enrolling in each clinical trial. For each drug dose, we followed the indications of the respective clinical trials. NAC regimens included either cisplatin-based chemotherapy consisting mainly of S-1 + CDDP (total of 2 courses) or oxaliplatin-based chemotherapy consisting mainly of S-1 + Oxaliplatin or Cape + Oxaliplatin (total of 3 courses). Chemotherapy-related toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (version 5.0). Chemotherapy was delayed or discontinued based on the following parameters: WBC count ≤1,000/mm^3; neutrophil count ≤500/mm^3; platelet count ≤50,000/mm^3; or grade ≥3 nonhematological adverse events.

Surgery and adjuvant chemotherapy. The standard surgical procedure for GC was gastrectomy with D2 grade lymphadenectomy, whereas that for EGC was proximal or total gastrectomy plus lower esophagectomy and lower mediastinal lymphadenectomy via a transhiatal approach. Surgical complications were evaluated by the Clavien–Dindo classification (version 5.0). Postoperative adjuvant chemotherapy was performed in patients with a histological response of Grade 2a or lower. Adjuvant chemotherapy with S-1 or Docetaxel plus S-1 was started within 42 days following surgery; however, it was not administered to elderly patients or those who experienced adverse effects from preoperative chemotherapy.

Pathological assessment of tumor regression. The histological response of the primary tumor to NAC was evaluated by two or more pathologists in the area where the tumor was thought to have been located during the pretreatment assessment and in the areas in which the tumor cells were likely to remain. The extent of the tumor response to NAC was categorized based on the number of viable carcinoma cells within the tumor based on the Japanese Classification of Gastric Carcinoma (JCGC) as follows: Grade 3: complete response (no viable tumor cells remain), Grade 2b, moderate effect (viable tumor cells remain in less than 1/10 of the tumor area), Grade 2a, very moderate effect (viable tumor cells remain in less than 1/3 but more than 1/10 of the tumor area), Grade 1b: slight effect (Viable tumor cells remain in more than 1/3 but less than 2/3 of the tumor area), Grade 1a: very slight effect (Viable tumor cells occupy more than 2/3 of the tumor area), and Grade 0: no effect (no evidence of effect). We classified patients into two groups: responders (Grade 2b-3) and non-responders (Grade 0-2a) (11).

Blood analysis for the determination of inflammatory and nutritional markers. Blood samples were collected at the time of the initial medical examination. Each marker was defined as follows: CRP/albumin ratio (CAR); lymphocyte/monocyte ratio (LMR); neutrophil/lymphocyte ratio (NLR); prognostic nutritional index (PNI) (10×Alb + 0.05×Lymphocyte); platelet/lymphocyte ratio (PLR).

Statistical analyses. The associations between clinicopathological factors were estimated using a χ^2 test. Relapse-free survival and overall survival (OS) curves were constructed using the Kaplan–Meier method and compared by the log-rank test. Parameters significantly associated with disease-free survival rates in univariate analyses were further analyzed by multivariate analysis using the Cox proportional hazard regression model. Statistical analyses were performed using JMP ver. 14 software (SAS, Cary, NC, USA). A p-value of <0.05 was considered statistically significant.

Results

Pathological tumor response to neoadjuvant chemotherapy. The clinical characteristics of the patients and pathological findings are shown in Table I. The mean patient age was 69 and 32 (76%) were male. The tumor location was primarily in the stomach for 35 patients (83%), and more than half (59%) of the patients presented with macroscopic type 3/4. The number of cT4 cases was 22 (53%). Six cases with para-aortic lymph node metastasis were considered M1, but no patients had any other distant metastases.

All specimens collected from radical resection of GC were evaluated with standard pathological analyses and tumor reactivity. Seven patients (17%) achieved a pathological complete response (CR) with NAC. We observed no recurrence and one death unrelated to cancer in patients with a pathological CR. The results of each histological response for NAC were as follows: Grade 1a: 18 patients, Grade 1b: 9 patients, Grade 2a: 5 patients, Grade 2b: 3 patients, and Grade 3: 7 patients. The percentage of patients with a histological efficacy rating of Grade 1b or higher was 57.1%. OS by histological response is shown in Figure 1. The median postoperative follow-up period was 3.7 years. The 5-year OS was 72.0% for Grade 2b-3 compared with 33.3% for Grade 0-1a, and 46.8% for Grade 1b-2a, indicating a favorable prognosis. Based on these results, we defined Grade 2b-3 as

Table I. *Patient characteristics and pathological findings*.

Variable	Total (n=42)	Histological response		*p*-Value
		Non-responder (n=32)	Responder (n=10)	
Sex (male/female)	32/10	23/9	9/1	0.40
Age (years)	69 (44-81)	68 (44-81)	71 (54-80)	0.68
Location (Stomach/EGJ)	35/7	28/4	7/3	0.33
Histologic type				
Differentiated	19 (45%)	12 (37%)	7 (70%)	0.14
Undifferentiated	23 (55%)	20 (63%)	3 (30%)	
Macroscopic type				
1	5(12%)	2 (5%)	3 (30%)	0.11
2	12 (29%)	8 (25%)	4 (40%)	
3	20 (47%)	18 (57%)	2 (20%)	
4	5 (12%)	4 (13%)	1 (10%)	
Clinical T status (%)				
T3	20 (47%)	14 (44%)	6 (60%)	0.63
T4a	18 (43%)	15 (47%)	3 (30%)	
T4b	4 (10%)	3 (9%)	1 (10%)	
Clinical N status (%)				
N0	6 (14%)	4 (13%)	2 (20%)	0.63
N1	14 (33%)	10 (31%)	4 (40%)	
N2	18 (43%)	14 (43%)	4 (40%)	
N3	4 (10%)	4 (13%)	0 (0%)	
Clinical M status (%)				
M0	36 (83%)	26 (81%)	10 (100%)	0.31
M1	6 (17%)	6 (19%)	0 (0%)	
CEA (ng/ml)	10 (0.7-28)	10 (0.7-140)	9.0 (1.1-47)	0.68
CA19-9 (U/ml)	37 (0.9-559)	42 (0.9-559)	22 (1-51)	0.66
Inflammatory and nutritional markers				
CAR	0.33 (0.9-3.34)	0.4 (0.01-3.34)	0.1 (0.01-0.35)	0.77
LMR	4.6 (0.9-559)	4.7 (0.81-12)	4.3 (2.7-6.6)	0.68
NLR	3.3 (1.0-9.2)	3.3 (1.0-9.2)	3.1 (1.3-5.2)	0.67
PLR	194 (60-476)	197 (49-476)	182 (60-388)	0.83
PNI	47 (33-60)	46 (33-60)	48 (33-57)	0.23
ypT status (%)				
T0	7 (17%)	0 (0%)	7 (70%)	<0.01*
T1	3 (7%)	1 (3%)	2 (20%)	
T2	2 (5%)	2 (6%)	0 (0%)	
T3	17 (40%)	16 (50%)	1 (10%)	
T4	13 (31%)	13 (41%)	0 (0%)	
ypN status (%)				
N0	13(31%)	6 (19%)	7 (70%)	0.03*
N1	8(19%)	6 (19%)	2 (20%)	
N2	10(24%)	9 (28%)	1 (10%)	
N3	11(26%)	11 (42%)	0 (0%)	
ypM status (%)				
M0	38 (90%)	28 (88%)	10 (100%)	0.56
M1	4 (10%)	4 (12%)	0 (0%)	
Postoperative chemotherapy	29 (73%)	25 (81%)	4 (40%)	0.03*

CAR: CRP/Albumin ratio; LMR: lymphocyte/monocyte ratio; NLR: neutrophil/lymphocyte ratio; PNI: prognostic nutritional index; PLR: platelet/lymphocyte ratio; EGJ: esophagogastric junction. *$p<0.05$.

the responder group and Grade 0-2a as the non-responder group. There was no significant difference in the background of responders and non-responders with respect to age, sex, histological type, clinical status, tumor markers, and inflammatory and nutritional markers before NAC.

Chemotherapy and surgical findings are shown in Table II. The NAC regimens included 39% for cisplatin plus S-1 and 32% for oxaliplatin plus S-1. Radical surgery was performed in all 42 patients following NAC. No mortality associated with chemotherapy or surgery was observed.

Table II. *Chemotherapy regimen and surgical findings.*

Variable	Total (n=42)	Histological response		
		Non-responder (n=32)	Responder (n=10)	*p*-Value
NAC regimen				
Cisplatin-base	29 (69%)	23 (72%)	6 (60%)	0.48
Oxaliplatin-base	13 (31%)	9 (28%)	4 (40%)	
Completion rate (%)	88%	91%	84%	0.28
Adverse events (Grade ≥3)	13 (31%)	9 (28%)	4 (40%)	1.00
Diarrhea	4 (11%)	5 (16%)	1 (10%)	
Neutropenia	3 (8%)	3 (9%)	0 (0%)	
Thrombocytopenia	2 (6%)	2 (6%)	0 (0%)	
Anemia	2 (6%)	1 (3%)	1 (10%)	
Other	3 (8%)	1 (3%)	2 (20%)	
Surgical transition (%)	42 (100%)	32 (100%)	10 (100%)	1.00
Gastrectomy				
Distal	12 (29%)	9 (28%)	3 (30%)	0.67
Proximal	8 (19%)	5 (16%)	3 (30%)	
Total	22 (52%)	18 (56%)	4 (40%)	
Esophagectomy				
Lower	9 (21%)	6 (19%)	3 (30%)	0.51
None	33 (79%)	26 (81%)	7 (70%)	
Number of resected lymph nodes	44(10-128)	47.5 (10-128)	36 (21-84)	0.43
Complications (CD Grade ≥2)	13 (31%)	9 (28%)	4 (40%)	1.0
Pneumonia	6 (14%)	4 (13%)	2 (20%)	
Pancreatic fistula	3 (7%)	2 (6%)	1 (10%)	
Surgical site infection	2 (5%)	1 (3%)	1 (10%)	
Anastomotic leakage	2 (5%)	1 (3%)	1 (10%)	
Bleeding	1 (2%)	1 (3%)	0 (0%)	

NAC: Neoadjuvant chemotherapy; CD: Clavien–Dindo classification.

Table III. *Univariate and multivariate analyses of inflammatory and nutritional markers for overall survival.*

		Univariate analysis		Multivariate analysis	
		HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
CAR	≥0.01/<0.01	0.94 (0.37-2.39)	0.889		
LMR	≥7.2/<7.2	0.55 (0.201-1.47)	0.233	0.39 (0.13-1.24)	0.121
NLR	<3.4/≥3.4	0.37 (0.162-0.864)	0.021*	0.26 (0.07-0.99)	0.048*
PLR	≥188/<188	0.62 (0.27-1.41)	0.251	1.31 (0.33-5.18)	0.699
PNI	≥47/<47	0.58 (0.26-1.34)	0.206	1.17 (0.46-2.99)	0.73

CAR: CRP/albumin ratio; LMR: lymphocyte/monocyte ratio; NLR: neutrophil/lymphocyte ratio; PNI: prognostic nutritional index; PLR: platelet/lymphocyte ratio. *$p<0.05$.

Comparison of inflammatory and nutritional markers in peripheral blood tests. Patients were divided into groups with either high or low values of PNI, NLR, PLR, LMR, and CAR based on the cutoff values determined using Receiver Operating Characteristic analysis. The cutoff values of PNI, NLR, PLR, LMR, and CAR for survival were 47, 3.4, 188, 7.2, and 0.01, respectively. NLR was significantly associated with OS in the multivariate analyses, but other markers were not ($p=0.048$, Table III). The lower NLR group had a better prognosis for OS ($p=0.03$, Figure 2A). The OS curves of patients based on pathological tumor response and NLR are presented in Figure 2B. Although there was no statistically significant difference in the non-responder's group, there was a trend toward poorer prognosis with NLR of 3.4 or higher

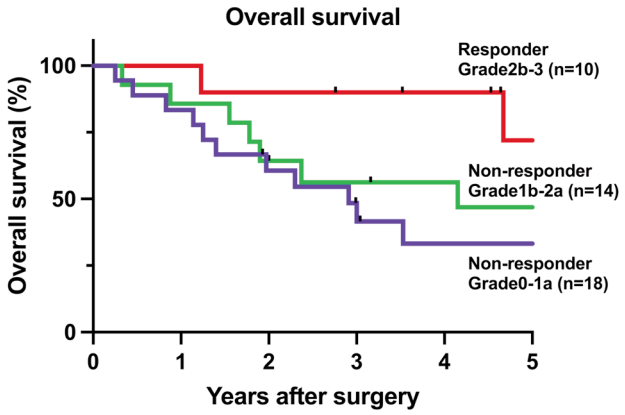

Figure 1. *Survival analysis of all 42 patients with gastric and esophagogastric cancer. Overall survival of patients with gastric adenocarcinoma and esophagogastric junction cancer according to pathological tumor response with Grade 0-1a, Grade 1b-2a (non-responder), and Grade 2b-3 (responder).*

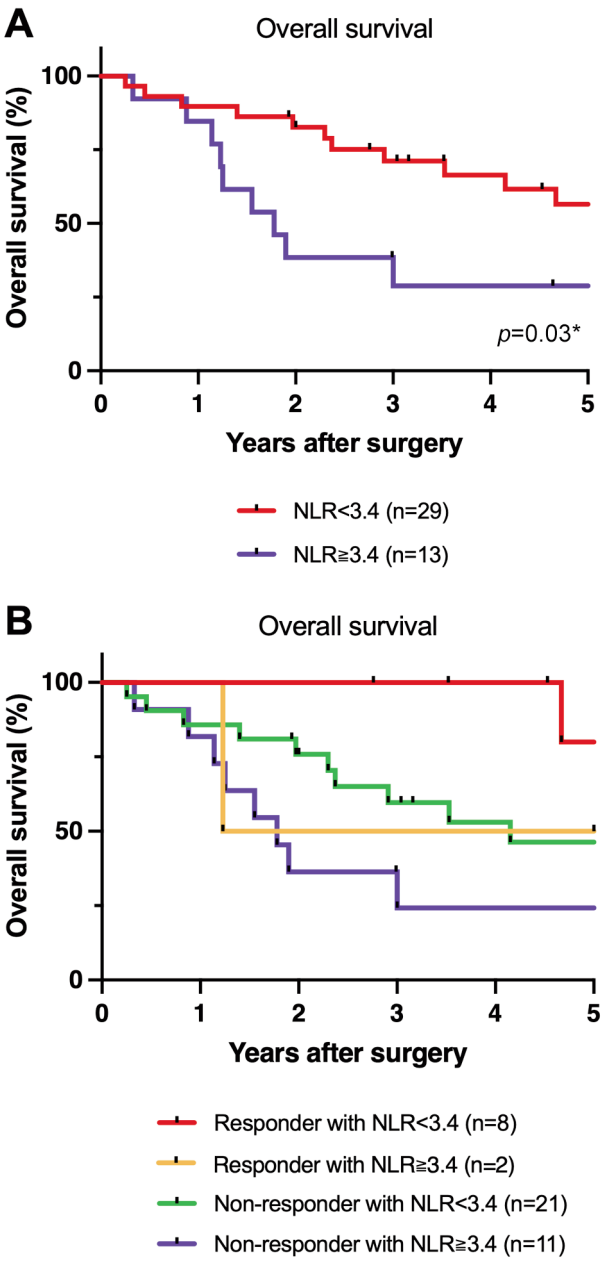

Figure 2. *Correlation between neutrophil/lymphocyte ratio and overall survival of patients with gastric and esophagogastric cancer. A) Overall survival of patients with gastric adenocarcinoma and esophagogastric junction cancer based on the neutrophil/lymphocyte ratio (NLR). B) Overall survival for patients with gastric adenocarcinoma and esophagogastric junction cancer according to pathological tumor response and NLR value.*

in OS (p=0.094). In the responder's group, patients with NLR of 3.4 or higher showed favorable outcomes (p=0.046).

Discussion

In this study, GC and EGC patients who underwent NAC had a better prognosis in the responder group with a histological response score of Grade 2b or higher. One of the criteria for determining treatment response is the RECIST evaluation using CT, which is a widely accepted standard for evaluating the effects of chemotherapy. However, in patients who were administered NAC, evaluation using RECIST is difficult because the lesion is not apparent or often disappears with treatment, thus CT evaluation and histopathologic results often differ (12). The JCOG0507A study showed that the histological efficacy assessment correlated better with prognosis compared with RECIST in patients who underwent NAC for GC, and the histological assessment of the primary tumor was optimal for accurately evaluating response to NAC (7). Some studies using JGCA criteria found that patients with Grade 1b or higher, in which less than 2/3 of the viable cells remain, had an excellent prognosis (7, 12). Grade 2 is classified as 2a and 2b based on the latest JCGC criteria. The responder group was defined as Grades 2b and 3 in our study, whereas the assignment of Grades 1b and 2a is different from that of previous studies. Our results indicated that 14 patients had Grade 1b and 2a. Seven patients (50%) had a recurrence (3 with disseminated disease, 3 with metastasis in other organs, and 2 with lymph node metastasis), which indicated that the Grade 1b and 2a assignments were inadequate to control micrometastases with NAC. For the NAC cases involving advanced GC and EGC, JCGC histological grade is a good prognostic factor, especially for Grade 2b or higher, which may represent an excellent predictive criterion.

Our findings suggest that the combined evaluation of histological response with NLR value in NAC for GC and

EGC may result in a more detailed prognostic prediction. We determined whether there were other systemic indicators besides histopathological examination that may predict the prognosis of patients who underwent NAC for GC and EGC. NLR is an indicator of host inflammation and immune function. The association between immune function markers and prognosis has been reported in various cancers including PLR, CAR, and NLR (13-16). Neutrophils play an essential role in producing ligands that induce tumor cell proliferation and invasion as well as cytokines that promote angiogenesis (17). Therefore, an increase in neutrophils may promote tumor growth and metastasis. Studies that evaluated NLR in NAC cases have used post-NAC NLR values to determine the value of NLR changes before and after NAC as prognostic indicators (18-20). Li et al. reported that in NAC for locally advanced GC, preoperative NLR, hemoglobin, and LMR, in combination with age, sex, tumor site, and clinical stage, was predictive for survival (21). The NLR value after NAC and the change in NLR before and after NAC have been considered prognostic predictors; however, these values were not useful prognostic indicators in our study (data not shown). It is controversial as to whether indicators based on the number of neutrophils and lymphocytes after NAC reflect tumor growth potential because chemotherapy not only alters the tumor microenvironment within the primary tumor, but also reduces hematopoiesis by suppressing normal tissue bone marrow. It may be necessary to consider changing from a doublet to a triplet chemotherapy regimen combined with nutritional therapy if the NLR value before NAC is high. Furthermore, combined with the histological response, this may help to determine whether adjuvant chemotherapy should be administered in both the non-responder and responder groups.

We demonstrated that NAC is a safe and effective treatment for GC and EGC. Surgery after chemotherapy was performed safely with no significant postoperative complications. The rate of pathological CR in this study was 17%, which is comparable to that of the Flot4 trial (1). Most of the regimens in this study were doublets, such as SOX, CapeOX, and SP, and there may be sufficient efficacy with doublet regimens. In the future, NAC may become the standard treatment in Asian countries.

This study has several limitations. First, it was a retrospective study with a nonrandomized nature. In addition, because the study was conducted at a single institution, pathology was not evaluated by central review. In addition, the number of patients studied was small and the optimal value of the NLR cutoff may be flexible.

In conclusion, a histological response score of Grade 2b or higher in GC and EGC patients who underwent NAC is associated with a good prognosis and is a significant prognostic factor. Furthermore, a low NLR value is associated with a more favorable prognosis. The two indices of histological response and NLR value may predict the prognosis of patients who undergo NAC.

Conflicts of Interest

The Authors have no conflicts of interest to declare and received no grants, equipment, or funding for this study.

Authors' Contributions

Conception and design: Yoshihiro Kakeji, Shingo Kanaji, Naoki Urakawa; Acquisition of data: Naoki Urakawa, Takashi Kato, Hitoshi Harada, Ryuichiro Sawada, Hironobu Goto, Hiroshi Hasegawa, Kimihiro Yamashita, Takeru Matsuda, Taro Oshikiri; Analysis and interpretation of data: Naoki Urakawa, Shingo Kanaji; Writing, review, and revision of manuscript: Naoki Urakawa, Shingo Kanaji, Yoshihiro Kakeji.

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