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ORIGINAL SCIENTIFIC REPORT

Prognostic Impact of the Neutrophil-to-Lymphocyte Ratio in Borderline Resectable Pancreatic Ductal Adenocarcinoma Treated with Neoadjuvant Chemoradiotherapy Followed by Surgical Resection

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Abstract

Background Increasing evidence suggests that cancer-associated inflammation, as indicated by markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and modified Glasgow Prognostic Score (mGPS), predicts poor outcomes in pancreatic cancer. In this study, the associations between systemic inflammation markers and survival were examined in borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC) patients who underwent neoadjuvant chemoradiotherapy (NACRT) followed by surgical resection.

Methods From April 2009 to December 2017, 119 patients diagnosed with BR-PDAC and receiving NACRT followed by radical surgery were included in this retrospective study. The associations between the pre- and post-NACRT NLR, PLR, mGPS, and clinicopathological characteristics, as well as their predictive values for survival outcomes, were analyzed. This study was approved by an institutional review board at Yokohama City University (B180600049).

Results On multivariate analysis with a Cox's proportional hazards regression model, post-NACRT NLR ≥ 3 ($p = 0.040$; hazard ratio, 2.24; 95% CI 1.28–3.91) and lymph node metastasis ($p = 0.002$; hazard ratio, 2.33; 95% CI 1.36–3.99) were significantly associated with shorter overall survival. The median survival time was 22.0 months for patients with post-NACRT NLR ≥ 3 and 45.0 months for patients with post-NACRT NLR < 3 ($p = 0.028$).

Conclusions The NLR following NACRT might predict survival in BR-PDAC patients. Patients with an elevated post-NACRT NLR or positive lymph node metastasis may be candidates for stronger adjuvant therapies.

Introduction

Pancreatic cancer is currently the fourth leading cause of cancer-related deaths, and 5-year overall survival of patients with pancreatic cancer has remained as low as 8% [1]. Pancreatic deaths are increasing and expected to become the second leading cause of cancer-related deaths by 2030 [2]. Most patients with PDAC are diagnosed in advanced stages, resulting in a poor prognosis. Gemcitabine has been a treatment choice for metastatic or recurrent pancreatic cancer. Several chemotherapeutic agents have been added to this regimen, including capecitabine, erlotinib, and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) [3–5]. A phase III trial has also shown improved survival with a median survival time of 11.1 months using a FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) regimen in metastatic pancreatic cancer compared to gemcitabine alone, in which the median survival time was 6.8 months [6]. Thus, it appears that neoadjuvant treatment for patients with borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC) may result in a similar or better prognosis than with

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upfront surgical treatment for resectable pancreatic ductal adenocarcinoma, suggesting the usefulness of neoadjuvant treatment [7, 8]. Although the prognosis in patients with PDAC improves marginally with such new regimens, it remains unsatisfactory.

Prognostic markers help formulate therapeutic strategies in the field of oncology. Reliable markers can be used to select patients who may not benefit from surgery and determine adequate chemotherapeutic regimens. Recently, several systemic inflammation markers correlated with prognosis have been found in many cancers [9–11]. Several studies have suggested that systemic inflammation plays a crucial role in carcinogenesis and cancer progression as well [12]. Markers such as the white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), and modified Glasgow Prognostic Score (mGPS) can be easily determined from routine blood tests [13]. Each of these factors has been studied in detail as a prognostic factor for PDAC patients. Moreover, these inflammation markers were reported to have predictive or prognostic significance in advanced rectal cancer treated with neoadjuvant chemoradiotherapy (NACRT) [14–17]. However, the associations between systemic inflammation markers and survival following NACRT for BR-PDAC have not yet been clarified. The aim of this study was to investigate the relationships between survival and systemic inflammation markers in pre- and post-NACRT in BR-PDAC patients.

Methods

Neoadjuvant chemoradiotherapy

NACRT was administered to BR-PDAC patients diagnosed by cytology or biopsy as a clinical trial since April 2009. Resectability was determined using computed tomography (CT) and positron emission tomography–CT according to National Comprehensive Cancer Network guidelines, and post-NACRT evaluation was performed using the same method [18]. Patients with BR-PDAC who received pancreatectomy from April 2009 to December 2017 were included in the present study. Patients who were diagnosed with metastatic pancreatic cancer at the time of surgery, including liver metastasis, peritoneal dissemination, or para-aortic lymph node metastasis, were excluded. From April 2009 to December 2015, the NACRT regimen consisted of two courses of gemcitabine (Eli Lilly and Co., Indianapolis, IN; 1000 mg/m^2 administered intravenously on days 8 and 15) plus tegafur/gimeracil/oteracil (S-1; Taiho Pharmaceutical Co., Ltd., Tokyo, Japan; 60 mg/m^2 administered orally on days 1–14). Following two courses of gemcitabine + S-1 chemotherapy, patients received 30 Gy radiation therapy combined with S-1 for 14 days. From January 2016 to December 2017, the NACRT regimen consisted of nab-paclitaxel 125 mg/m^2 (Abraxane; Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) followed by gemcitabine 1000 mg/m^2 administered on days 1, 8, and 15, every 28 days for two cycles, followed by 30 Gy radiation therapy combined with S-1 for 14 days.

Parameters measured

Laboratory data including WBC, neutrophil, lymphocyte, and platelet counts, CRP, albumin, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), DUPAN-2, and SPan-1 levels were obtained at the start of the first cycle of NACRT and after completion of NACRT. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The cutoff value of NLR was set to 3 in accordance with a previous report [19]. PLR was calculated as the platelet count divided by the absolute lymphocyte count. The PLR was categorized into two groups according to a cutoff value of 150 [20]. The mGPS was calculated as follows: Patients with an elevated level of both CRP (0.5 mg/dL) and hypoalbuminemia (albumin <3.5 mg/dL) were allocated a score of 2 and patients showing 1 or none of these abnormalities were allocated a score of 1 or 0, respectively [21]. Clinical responses to NACRT were assessed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) [22]. To evaluate the treatment response, CT, positron emission tomography–CT, and blood tests were performed 4 weeks after completion of NACRT. The optimal maximum standard uptake value (SUVmax) cutoff values to predict the tumor PR rate after NACRT were 5.6 for pre-NACRT and 4.5 for post-NACRT [23]. Tumors were classified according to the seventh edition of the tumor–node–metastasis (TNM) classification of the International Union Against Cancer [24].

Ethics approval and consent to participate

The study protocol was approved by an institutional review board at Yokohama City University (B180600049); written informed consent was obtained from all patients prior to their enrollment in the study. Clinicopathological data were collected retrospectively.

Statistical analysis

Overall survival (OS) was assessed as the outcome variable. OS was defined as the period from the start of chemotherapy to death from any cause. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Multivariate survival

analyses were performed by Cox proportional hazards regression. Significant parameters on univariate analyses were entered into multivariate analyses for OS. WBC and platelet counts and the CRP level were categorized by their upper normal limits, while sodium and albumin levels were categorized by their lower normal limits. A p value less than 0.05 was considered significant. All statistical analyses were performed using SPSS version 25.0 for Windows (IBM Co., Armonk, NY).

Results

A total of 119 patients who were diagnosed with BR-PDAC treated with NACRT followed by surgical resection were evaluated. The patients' baseline characteristics are given in Table 1. Their median age was 68 years. There were 66 male (55.5%) and 53 female (44.5%) patients. A total of 102 patients (85.7%) were treated with NACRT using gemcitabine + S-1 followed by radiation + S-1 therapy, whereas 17 patients (14.3%) were treated with gemcitabine + nab-paclitaxel followed by radiation + S-1. Partial response was shown in 22 patients (18.5%), with stable disease in the remaining 97 patients (81.5%). Ninety-two patients (77.3%) underwent pancreaticoduodenectomy, 25 patients (21.0%) underwent distal pancreatectomy or distal pancreatectomy with en bloc celiac axis resection, and two patients (1.7%) underwent total pancreatectomy. Ninety-six patients (80.7%) received adjuvant treatment including S-1 ($n = 68$), gemcitabine ($n = 5$), and gemcitabine + S-1 ($n = 23$).

A comparison of laboratory data before and after NACRT is given in Table 2. The NLR was significantly increased from 2.35 to 3.71 after NACRT ($p < 0.001$). The PLR was also significantly increased from 150 to 197 ($p < 0.001$). WBC and platelet counts, SUVmax, and the albumin level were significantly decreased after NACRT. The tumor markers CA19-9, DUPAN-2, and SPan-1 were significantly decreased. There was no significant change in mGPS between pre- and post-NACRT.

Changes in the NLR before and after NACRT for each case are shown in Fig. 1. Of the 79 patients who had pre-NACRT NLR <3, 39 (49.4%) still had NLR <3 after NACRT, while 40 (50.6%) had NLR ≥3 after NACRT. There were no correlations between the NLR and adverse events including blood test abnormalities, nausea, vomiting, diarrhea, canker sores, and rashes. Considering the change in the NLR after NACRT, the post-NACRT NLR ≥3 group showed an average increase of 2.97 after NACRT, while the post-NACRT NLR <3 group showed a decrease of 0.13 ($p < 0.0001$). Analyses of OS with respect to clinical parameters and inflammatory markers are summarized in Table 3. The median OS was 30.0 months [95% confidence interval (CI) 17.3–42.6 months]. On univariate analysis, post-NACRT NLR ≥3 ($p = 0.028$), male ($p = 0.034$), absence of adjuvant chemotherapy ($p = 0.035$), pre-NACRT CEA ≥5 ng/mL ($p = 0.009$), pre-NACRT DUPAN-2 ≥150 U/mL ($p = 0.049$), post-NACRT DUPAN-2 ≥150 U/mL ($p = 0.024$), and lymph node metastasis ($p < 0.001$) were significantly associated

Table 1 Patients' characteristics

Factor	
Age (year)	68 (8.9)
Sex, *n* (%)	
Male	66 (55.5%)
Female	53 (44.5%)
NACRT regimen, *n* (%)	
GS + RT	102 (85.7%)
GnP + RT	17 (14.3%)
Tumor response, RECIST, *n* (%)	
SD	97 (81.5%)
PR	22 (18.5%)
Surgical procedure, *n* (%)	
PD/TP	92 (77.3%)/2 (1.7%)
DP or DP-CAR	25 (21.0%)
Portal vein or arterial resection, *n* (%)	
Y	82 (68.9%)
N	37 (31.1%)
Operative time (min)	662 (160)
Blood loss volume (mL)	818 (987)
Pathologic tumor stage, *n* (%)	
T1/T2	11 (9.3%)/6 (5.0%)
T3/T4	100 (84.0%)/2 (1.7%)
Pathologic nodal status	
Negative	54 (45.4%)
Positive	65 (54.6%)
Pathologic TNM stage	
IA/IB	10 (8.4%)/4 (3.4%)
IIA/IIB	49 (41.2%)/54 (45.4%)
III/IV	2 (1.7%)/0
Adjuvant chemotherapy regimen, *n* (%)	
Gem + S-1	23 (19.3%)
Gem	5 (4.2%)
S-1	68 (57.1%)
Absent	22 (18.4%)

Continuous variables are shown as medians (SD)

NACRT neoadjuvant chemoradiotherapy, *GS* gemcitabine + S-1, *RT* radiation therapy, *GnP* gemcitabine + nab-paclitaxel, *RECIST* Response Evaluation Criteria in Solid Tumors, *SD* stable disease, *PR* partial response, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *DP-CAR* distal pancreatectomy with en bloc celiac axis resection, *TP* total pancreatectomy, *Y* yes, *N* no

Table 2 Changes in inflammatory and tumor markers and SUVmax from pre-NACRT to post-NACRT

Factor	Pre-NACRT	Post-NACRT	*p* value
White blood cells (/μL)	5700 (2806)	4700 (1526)	<0.001
Platelets ($\times 10^4$/μL)	22.8 (7.65)	16.0 (7.08)	0.001
Neutrophils (/μL)	3599 (2192)	2974 (1278)	<0.001
Lymphocytes (/μL)	1444 (621)	805 (457)	<0.001
CRP (mg/dL)	0.13 (0.77)	0.11 (1.61)	0.841
Albumin (g/dL)	4.1 (0.49)	3.8 (0.54)	<0.001
CEA (ng/mL)	3.3 (9.9)	3.5 (7.7)	0.140
CA19-9 (U/mL)	96 (3562)	30 (906)	<0.001
DUPAN-2 (U/mL)	190 (1624)	65 (1005)	<0.001
SPan-1 (U/mL)	49 (1023)	21 (318)	<0.001
mGPS score			0.057
Score 0	86 (72.3%)	71 (59.7%)	
Score 1	30 (25.2%)	36 (30.2%)	
Score 2	3 (2.5%)	12 (10.1%)	
NLR	2.35 (1.59)	3.71 (3.20)	<0.001
PLR	150.4 (68.5)	197.9 (124.6)	<0.001
SUVmax	5.4 (3.5)	4.0 (2.0)	<0.001

Continuous variables are shown as medians (SD)

NACRT neoadjuvant chemoradiotherapy, *SUVmax* maximum standardized uptake value, *CRP* C-reactive protein, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *mGPS* modified Glasgow Prognostic Score, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio

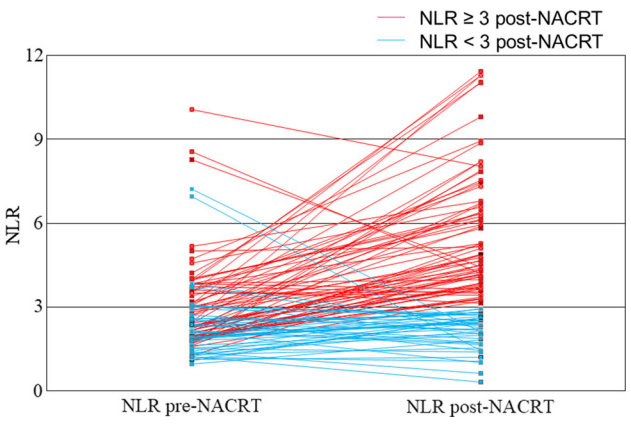

Fig. 1 Changes in the NLR before and after NACRT for each case

with shorter OS. On multivariate analysis, post-NACRT NLR ≥3 [$p = 0.040$; hazard ratio (HR) 2.24; 95% CI 1.28–3.91] and lymph node metastasis ($p = 0.002$; HR 2.33; 95% CI 1.36–3.99) were independent predictors of poor OS. The median survival time of patients with a post-NACRT NLR ≥3 was 22.0 months, whereas for patients with a post-NACRT NLR <3, it was 45.0 months ($p = 0.028$). Combining both post-NACRT NLR and pathological lymph node metastasis, patients were further categorized into four groups: group A, post-NACRT NLR <3 and pN (−); group B, post-NACRT NLR <3 and pN (+); group C, NLR ≥3 and pN (−); and group D, NLR ≥3 and pN (+). The median OS of group A was significantly longer than that that of group B (MST, 30 months, $p = 0.023$), group C (MST, 27 months, $p = 0.039$), and group D (MST, 15 months, $p < 0.001$) (Fig. 2).

Discussion

In the present study, post-NACRT NLR ≥3 and lymph node metastasis were found to be reliable predictive markers for shorter OS in patients with BR-PDAC.

Neutrophils are major effectors of acute inflammation but have also been shown to contribute to chronic inflammatory conditions and adaptive immune responses [25]. Lymphocytes are heterogeneous cell populations with different functional and phenotypical properties involved in adaptive immunity. On the other hand, in the tumor environment, these inflammatory cells have distinct functions. Neutrophils release various factors, such as interleukin-1, interleukin-8, tumor necrosis factor alpha, and reactive oxygen species, leading to DNA damage, genetic instability, and tumor growth [26, 27]. Neutrophils also lead to generation of vascular endothelial growth factor, an important contributor to tumor angiogenesis, growth, and metastasis [28]. Moreover, Fridlender et al. reported that there may exist subsets of tumor-associated neutrophils in cancer, termed N1 and N2, and that some of the pro- and anti-tumor effects may be linked to these different subtypes of neutrophils [29]. Lymphocytes play an important role in anti-tumor response through induction of cytotoxic cell death and inhibition of tumor cell proliferation and migration [12]. Thus, neutrophils and lymphocytes are strongly involved not only in inflammation, but also in the development and suppression of cancer.

Therefore, the NLR is thought to correlate with the development of cancer. Practically, an elevated NLR is associated with poor prognosis in cancers of the thyroid [11], lung [30], breast [9, 10], esophagus [31], stomach [32], prostate [33], and colon [34]. It has been reported that a high NLR is a prognostic factor for advanced pancreatic cancer or unresectable pancreatic cancer [35]. In addition, other studies showed that NLR ≥3.0 and NLR ≥5.0 were poor prognostic factors in patients with locally advanced rectal cancer who underwent radical resection after NACRT [14, 15]. The present study is the first to show the prognostic significance of the NLR for patients with BR-PDAC treated with NACRT. Chemotherapy regimens did not significantly affect change in NLR or survival. Previous

Table 3 Univariate and multivariate analyses to identify independent prognostic factors for OS

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (year)		0.750		
<70 (*n* = 54)	1.00			
≥70 (*n* = 65)	0.92 (0.57–1.49)			
Sex		0.034		0.536
Female (*n* = 53)	1.00		1.00	
Male (*n* = 66)	1.71 (1.04–2.83)		1.18 (0.69–2.00)	
NACRT regimen				
GnP + RT (*n* = 17)	1.00	0.410		
GS + RT (*n* = 102)	1.39 (0.63–3.09)			
Tumor response, RECIST		0.510		
PR (*n* = 15)	1.00			
SD (*n* = 104)	1.23 (0.65–2.31)			
Surgical procedure		0.893		
DP/DP-CAR (*n* = 25)	1.00			
PD/TP (*n* = 94)	1.03 (0.59–1.80)			
Portal vein or artery resection		0.617		
N (*n* = 37)	1.00			
Y (*n* = 82)	1.04 (0.62–1.74)			
Operative time		0.609		
<600 min (*n* = 34)	1.00			
≥600 min (*n* = 85)	1.13 (0.70–1.83)			
Blood loss		0.334		
<1000 mL (*n* = 75)	1.00			
≥1000 mL (*n* = 44)	1.28 (0.77–2.12)			
Tumor stage		0.360		
T1–2 (*n* = 17)	1.00			
T3–4 (*n* = 102)	1.41 (0.674–2.96)			
Nodal status		<0.001		0.002
Negative (*n* = 65)	1.00		1.00	
Positive (*n* = 54)	2.51 (1.52–4.13)		2.33 (1.36–3.99)	
Adjuvant chemotherapy		0.035		0.074
Y (*n* = 23)	1.00		1.00	
N (*n* = 96)	1.86 (1.04–3.33)		1.78 (0.94–3.35)	
Pre-CEA		0.009		0.074
<5 ng/mL (*n* = 81)	1.00		1.00	
≥5 ng/mL (*n* = 38)	1.90 (1.17–3.09)		1.60 (0.95–2.70)	
Pre-CA19-9		0.791		
<37 U/mL (*n* = 36)	1.00			
≥37 U/mL (*n* = 83)	0.93 (0.54–1.58)			
Pre-DUPAN-2		0.049		
<150 U/mL (*n* = 61)	1.00			
≥150 U/mL (*n* = 58)	1.69 (1.00–2.86)			
Pre-SPan-1		0.999		
<30 U/mL (*n* = 44)	1.00			
≥30 U/L (*n* = 75)	1.00 (0.59–1.68)			
Pre-mGPS		0.901		
Score 0 (*n* = 86)	1.00			

Table 3 continued

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Score 1–2 (*n* = 33)	1.03 (0.60–1.77)			
Pre-NLR		0.668		
<3 (*n* = 79)	1.00			
≥3 (*n* = 40)	1.11 (0.67–1.86)			
Pre-PLR		0.603		
<150 (*n* = 60)	1.00			
≥150 (*n* = 59)	0.88 (0.54–1.42)			
Pre-SUVmax		0.059		
<5.6 (*n* = 62)	1.00			
≥5.6 (*n* = 57)	1.55 (0.98–2.59)			
Post-CEA		0.096		
<5 ng/mL (*n* = 88)	1.00			
≥5 ng/mL (*n* = 31)	1.55 (0.92–2.60)			
Post-CA19-9		0.509		
<37 U/mL (*n* = 68)	1.00			
≥37 U/mL (*n* = 51)	1.17 (0.72–1.92)			
Post-DUPAN-2		0.024		0.426
<150 U/mL (*n* = 76)	1.00		1.00	
≥150 U/mL (*n* = 43)	1.76 (1.07–2.89)		1.24 (0.72–2.14)	
Post-SPan-1		0.300		
<30 U/mL (*n* = 79)	1.00			
≥30 U/mL (*n* = 40)	1.30 (0.78–2.16)			
Post-mGPS		0.481		
Score 0 (*n* = 71)	1.00			
Score 1–2 (*n* = 48)	1.19 (0.73–1.93)			
Post-NLR		0.028		0.040
<3 (*n* = 46)	1.00		1.00	
≥3 (*n* = 73)	1.76 (1.05–2.95)		2.24 (1.28–3.91)	
Post-PLR		0.532		
<150 (*n* = 33)	1.00			
≥150 (*n* = 86)	1.19 (0.68–2.10)			
Post-SUVmax		0.428		
<4.5 (*n* = 71)	1.00			
≥4.5 (*n* = 48)	1.21 (0.75–1.96)			

HR hazard ratio, *CI* confidence interval, *OS* overall survival, *NACRT* neoadjuvant chemoradiotherapy, *GnP* gemcitabine + nab-paclitaxel, *GS* gemcitabine + S-1, *RT* radiation therapy, *RECIST* Response Evaluation Criteria in Solid Tumors, *PR* partial response, *SD* stable disease, *DP* distal pancreatectomy, *DP-CAR* distal pancreatectomy with en bloc celiac axis resection, *PD* pancreaticoduodenectomy, *TP* total pancreatectomy, *Y* yes, *N* no, *Pre-* pre-NACRT, *Post-* post-NACRT, *mGPS* modified Glasgow prognostic score, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *SUVmax* maximum standardized uptake value

studies reported that the RECIST criteria for evaluating pancreatic cancer treatment did not correlate with overall survival [36, 37]. Similarly, no correlation between treatment response defined by the RECIST criteria and survival outcomes was shown in the present study. Conroy et al. reported that in patients with resected pancreatic cancer, adjuvant therapy with a modified FOLFIRINOX regimen results in significantly longer survival than gemcitabine, but with higher incidence of adverse effects [38]. In consideration of the high toxicity, selection of patients is important, and post-NACRT NLR ≥3 or pN (+) might be a useful marker for selecting stronger adjuvant regimens.

In the present study, both neutrophils and lymphocytes were decreased during NACRT, but lymphocytes decreased to a high degree, resulting in an increased NLR during NACRT. Lymphocytes and lymphocyte stem cells

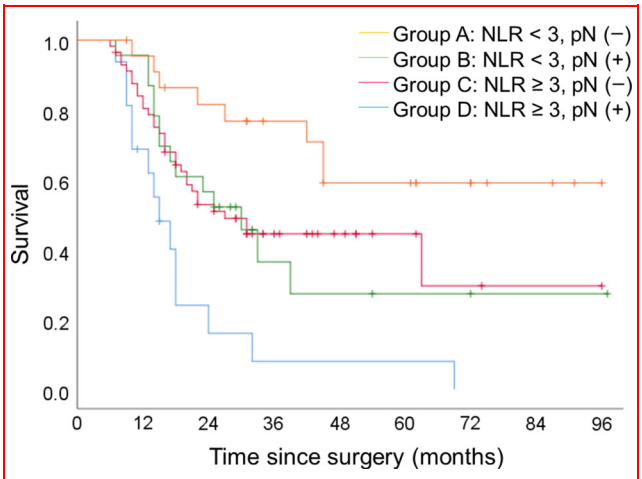

Fig. 2 Kaplan–Meier analysis of overall survival according to the post-NACRT NLR and pathological lymph node metastasis. Overall survival curves in patients with advanced pancreatic cancer according to the four risk groups (combining pre-NACRT NLR and pathological lymph node metastasis). Survival curves were estimated using the Kaplan–Meier method

have been reported to be highly sensitive to ionizing radiation in vitro [39–43]. Therefore, lymphocytes are considered to be decreased more, particularly with the strong effect of radiation. In addition, it seems that the NLR could also play a role in patient selection for NACRT. With NACRT, it was thought that patients would be divided into an NLR low group and an NLR high group. Indeed, there was no factor that could predict NLR ≥3 after NACRT.

Immunogenic cell death associated with chemotherapy or chemoradiotherapy can increase CD8+ and CD4+ tumor-infiltrating lymphocytes and contribute to the regulation of tumor growth and metastasis [44, 45]. We previously reported that the preoperative peripheral lymphocyte count correlated with CD8+ tumor-infiltrating lymphocytes and thus could be a marker for immunomodulation after NACRT [46]. In addition, regulatory T cells decreased after gemcitabine-based chemotherapy [47]. These facts suggest that immunomodulation induced by NACRT may be present in peripheral blood as well. Focusing on changes in the NLR after NACRT, the NACRT ≥3 group showed an increase, but the NACRT <3 group showed a decrease in the NLR. These changes might reflect an immunological response.

There are several potential limitations. The present study was a retrospective, single-center analysis, and the number of patients was relatively small. In addition, the NLR could be affected by infection, such as persistent cholangitis, drugs, or non-tumorous diseases such as rheumatoid disease, coronary artery disease, or metabolic syndrome [48–50]. Despite these possibilities, the fact that the NLR after NACRT was a useful predictor on multivariate analysis may be a great help in future medical treatment.

Conclusions

A high NLR (≥3.0) following NACRT was a useful predictor of worse OS in patients with BR-PDAC treated with surgical resection. Patients with an elevated post-NACRT NLR or positive lymph node metastasis may be candidates for stronger adjuvant therapies.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

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