The effect and tolerability of second-line chemotherapy are associated with disease control of nivolumab chemotherapy in patients with gastric cancer

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Abstract

Background: Immune-related adverse events (irAEs) are associated with the efficacy of nivolumab. However, whether the tolerability of second-line chemotherapy is associated with the efficacy of nivolumab monotherapy (third-line chemotherapy) remains unclear. Our study aimed to investigate whether the results of second-line treatment were associated with the efficacy of nivolumab in patients with gastric cancer.

Methods: This was a retrospective cohort study. We enrolled Japanese patients aged ≥ 20 years with gastric cancer who were treated with nivolumab as a third-line chemotherapy at Fujita Health University Hospital from October 2017 to September 2021.

Patients with the evaluations of complete response, partial response, and stable disease after third-line chemotherapy were included in the disease control (DC) group, while others were included in the progressive disease (PD) group.

Results: A total of 126 patients were enrolled. The population of patients aged over 65 years in the DC group was significantly higher than that in the PD group (p = 0.017). The neutrophil-lymphocyte ratio in the PD group was higher than that in the DC group (p = 0.081). The number of patients continuing second-line chemotherapy for >7 months was significantly higher in the DC than in the PD group (p = 0.021). Age over 65 years (odds ratio [OR] =2.67, p = 0.040), duration of second-line chemotherapy over 7 months (OR = 3.10, p = 0.031), and the occurrence of irAEs (OR = 3.60, p = 0.006) were detected as the factors associated with disease control after nivolumab chemotherapy.

Conclusions: The effect and the tolerability of second-line chemotherapy, and age over 65 years are the factors of DC after nivolumab chemotherapy. The control of tumour inflammatory status might be important for improvements in treatment outcomes.

Background

The anti-programmed cell death protein 1 (PD-1) antibody activates the anti-tumour cytotoxic activity of T cells. Anti-PD-1 antibodies are currently used for the treatment of various types of cancer. Nivolumab was previously the standard treatment of third-line chemotherapy for advanced and recurrent gastric cancers. The latest treatment guideline indicates nivolumab plus combined chemotherapy as a new first-line treatment option for gastric or gastro-oesophageal junction cancers [1, 2]. Regarding the adverse events (AEs) of nivolumab combination chemotherapy, the results of the ATTRACTION-4 trial suggested that their frequency was no different from the placebo group [1]. In addition, the frequency of severe treatment-related AEs did not increase, and no new safety signals were identified in the CheckMate 649 study [2]. Together, these results indicate the potential of nivolumab as first-line chemotherapy.

Nivolumab has been used for cancer chemotherapy for over 7years, and immune-related adverse events (irAEs) are associated with the efficacy of the anti-PD-1 antibody treatment [3–7]. In addition, a durable

response with nivolumab was suggested in the ATTRACTION2 and CheckMate 032 trials [8]. Although the factors associated with the efficacy of nivolumab have been described, the objective response rate of nivolumab remains around 15% in the Japanese population [9], and, the factors associated with treatment outcomes are unclear. Although performance status, peritoneal metastasis, and mismatch repair deficiency are associated with the efficacy of nivolumab [10], it was not clear whether tolerability of first or second-line chemotherapy were associated with its efficacy.

S-1 plus oxaliplatin (SOX) has been recognised as first-line chemotherapy for gastric cancer, and SOX shows better tolerability than cisplatin plus S-1 (CS) [11, 12]. However, the frequency of peripheral neuropathy (PN) in patients receiving SOX was higher than in those who received CS [11]. The rate of severe PN was 4.5%, which was a cause for the discontinuation of SOX. Hence, the reason for the change in first-line treatment is not a progressive disease but intolerance.

Furthermore, a previous report suggested that the severity of PN and tolerability of second-line chemotherapy were affected by first-line chemotherapy with oxaliplatin [13]. However, whether the tolerability of second-line chemotherapy is associated with the efficacy of nivolumab (third-line chemotherapy) remains unclear. Understanding the efficacy of nivolumab as second-line treatment would provide information on its potential usefulness as first-line treatment. Here, we investigated whether the outcomes of second-line treatment was associated with the efficacy of nivolumab in patients with gastric cancer.

Materials And Methods

Study design and data source

Japanese patients aged > 20 years with gastric cancer who were treated with nivolumab as third-line chemotherapy at Fujita Health University Hospital from October 2017 to September 2021 were enrolled in this retrospective cohort study. The follow-up period ended in October 2021. All patient data were collected from the medical records of Fujita Health University Hospital. Patients without baseline data and response evaluation were excluded. The objective response to treatment was divided into four categories according to response evaluation criteria in solid tumours v1.1 [14]. Patients with the evaluations of complete response, partial response, and stable disease after third-line chemotherapy represented the disease control (DC) group, while other patients were included in the progressive disease (PD) group (Figure 1).

We defined the AEs according to the evaluation in the ATTRACTION-2 trial [9]. Briefly, endocrine, gastrointestinal, hepatic, pulmonary, renal, and skin AEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The number of ascites was categorised into four grades according to the modified assessment in the PHOENIX-GC trial [15] and was assessed by computed tomography and categorised as low (ascites within the pelvic cavity), moderate (ascites beyond the pelvic

cavity) or high (the use of intraperitoneal drainage).The 8th edition of the tumour-node-metastasis (TNM) classification [16].

Outcome measure

To determine the factors associated with the efficacy of nivolumab, we performed univariate and multivariate analyses. Factors with clinical importance and those showing a statistically significant difference in the univariate analyses, were included in the multivariable model. These were age ≥65 years, the occurrence of irAEs, and duration of second-line chemotherapy ≥ 7.0 months. To assess whether these factors were associated with overall survival (OS) after the initiation of nivolumab chemotherapy, time-to-event curves were plotted using the Kaplan Meier method. In addition, we evaluated the predictive ability of these factors using receiver operating characteristic (ROC) curves.

Statistical analyses

Normally and non-normally distributed data were presented using the mean and standard deviation, and medians and ranges, respectively. The Student's *t*-test and the Mann–Whitney U test were used to compare normally and non-normally distributed data, respectively. We conducted chi-square and Fisher's exact tests to analyse nominal scales. Logistic regression analysis was used to determine the factors associated with the efficacy of nivolumab, and ORs and 95% confidence intervals (CIs) were reported. The Hosmer-Lemeshow statistical test was used for calculating the fitness of the logistic regression models. The log-rank test was used for the comparison of time-to-event curves. A two-sided *p*-value <0.05 was considered statistically significant. SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Ethics approval

This study was approved by the ethics board of the Fujita Health University Hospital (ethics committee approval number: HM21-485 approval date 22/March/2022), and conducted in accordance with appropriate guidelines. An opt-out approach, was used for informed consent, which was approved by ethics board.

Results

Baseline characteristics

In total 126 patients were enrolled. One patient without baseline data and nine patients without the evaluation of objective response until the end of the follow-up period were excluded (Figure 1). The baseline characteristics of patients are shown in Table 1. The median age of patients was 68 years, and 79 % were male. The median duration of second-line chemotherapy was 3.5 months. The age of patients in the DC group was higher than that in the PD group (p = 0.080), and the proportion of patients aged over 65 years was significantly higher in the DC compared to that in the PD group (p = 0.017). The neutrophil-

lymphocyte ratio (NLR) in the PD group was higher than that in the DC group (p = 0.081). The number of patients who continued second-line chemotherapy over the 3.5 months of this study did not fifer between the two groups (p = 0.395). However, the number of patients who continued second-line chemotherapy over 7 months was significantly higher in the DC group than that in the PD group (p = 0.021). The frequency of AEs in second-line chemotherapy and the proportion of patients with high ascites volume did not differ between the two groups.

The details of irAEs are summarised in Table 2. The frequency of irAEs in the DC group was significantly higher than that in the PD group (p = 0.003). The number of endocrine irAEs was highest in the DC group, whereas hepatic irAEs were most common in the PD group.

Factors associated with disease control after nivolumab chemotherapy

The univariate analysis revealed that age over 65 years (OR = 2.906, [95% CI: 1.183–7.140],

p = 0.017), duration of second-line chemotherapy over 7 months (OR= 2.978, [95% CI: 1.151–7.705] p= 0.021), and the occurrence of irAEs (OR = 3.477, [95% CI: 1.475–8.200], p = 0.003) were associated with disease control after nivolumab chemotherapy (Table 3). The multivariate analysis supported the results of univariate analysis, thus age over 65 years (OR = 2.666, [95% CI: 1.045–6.802], p = 0.040), duration of second-line chemotherapy over 7 months (OR = 3.100, [95% CI: 1.108–8.678], p = 0.031), and the occurrence of irAEs (OR = 3.600, [95% CI: 1.448–8.950], p = 0.006) were detected as the factors associated with disease control after nivolumab chemotherapy (Hosmer–Lemeshow test, p = 0.618) (Table 3).

To determine whether the above factors were predictors of DC, the predictive ability was evaluated by using receiver operating characteristic curve analysis. Age over 65 years showed a trend of good prediction ability (sensitivity, 0.795; specificity, 0.429; area under the curve [AUC], 0.612 [95% CI, 0.506-0.717], p = 0.050) (Figure 2a). Duration of second-line chemotherapy over 7 months did not show a significant prediction ability (sensitivity, 0.308; specificity, 0.870; AUC, 0.589 [95% CI, 0.475-0.702], p = 0.119) (Figure 2b). The occurrence of irAEs showed goodprediction ability (sensitivity, 0.436; specificity, 0.818; AUC, 0.627 [95% CI, 0.515–0.739], p = 0.026) (Figure 2c).

Overall survival time after nivolumab chemotherapy

We compared OS times between the DC and PD groups after nivolumab chemotherapy (Figure 3). In patients aged over 65 years, the median OS times (95% CI) of DC and PD groups were 27.0 (N/A) and 6.00 (4.13–7.87) months, respectively (log-rank test; $p < 0.001$) (Figure 3a). Among patients receiving second-line chemotherapy for over 7 months, the median OS times (95% CI) of DC and PD groups were 27.0 (5.34–48.7) and 8.00 (5.14–10.9) months, respectively (log-rank test; p = 0.014) (Figure 3b). Among patients experiencing irAEs, the median OS times (95% CI) were 27.0 (12.6–41.4) and 6.00 (3.01–8.99) months in the DC and PD groups, respectively (log-rank test; $p < 0.001$) (Figure 3c).

Discussion

Here, age over 65 years, duration time of second-line chemotherapy over 7 months, and irAEs were factors associated with DC after nivolumab chemotherapy, and OS time was prolonged in patients with these factors. The immune system of older patients is different which impacts the activity of immune checkpoint inhibitors (ICIs) [17, 18]. Although the CD4 T cells are less susceptible to age-dependent phenotypic and functional changes, the loss of CD28 with ageing in CD8 T cells is more frequent than that in CD4 T cells [19, 20]. Meanwhile, the increased expression of PD-1 on T cells might enhance primary responses of anti-PD-1 and anti PD-L1 antibodies [21]. It remains unclear how these factors affect the efficacy and adverse effects of ICIs. However, a previous meta-analysis revealed that ageing was not associated with differences in benefits from ICI chemotherapy [22]. Most studies in this analysis included patients with lung cancer and melanoma, while only three described patients with gastro-oesophageal junction cancer. In addition, nivolumab showed superior effects in patients over 65 years than in younger patients in the ATTRACTION-2 study, which was supported by our results. Further research is needed to evaluate the changes in the immune system with age and to validate these results.

Ageing promotes frailty and sarcopenia, which decrease the tolerability and the dose intensity of chemotherapy. Therefore, the benefits of nivolumab chemotherapy in older patients remain unclear [23]. For example, a study showed that patients with lung cancer aged over 65 years did not benefit from nivolumab chemotherapy [24, 25]. However, no studies compared patients aged over and under 65 years with gastric cancer. In our study, the proportion of patients aged over 65 years did not differ between the PD and DC groups, suggesting that patients aged over 65 years partially received benefits from nivolumab chemotherapy. The patients who received nivolumab chemotherapy as third-line therapy were enrolled in the present study, ; therefore, the tolerability of second-line chemotherapy could not be ignored. Kim et al. [26] reported that ramucirumab combination chemotherapy resulted in better prognoses than non-combination therapy when used as second-line therapy. Although the impact of second-line chemotherapy on third-line nivolumab chemotherapy has been unclear, our results suggest that the effects and tolerability are associated with the effect of nivolumab. The frequencies of weight loss and malnutrition are higher in patients with gastric cancer than those in patients with other cancers. In addition, moderate or severe malnutrition is associated with adverse drug events [27] induced by chemotherapy and poor outcomes [28]. These results support the usefulness of nivolumab before the declining tolerability.

In the current study, the volume of ascites was not detected as the predictor of the effect of nivolumab. Although a previous report suggested that ascites burden was associated with a high response rate of nivolumab [29], the total number of patients was low(n = 55). Here, the volume of ascites was not associated with the effect of nivolumab. However, both studies had a limited sample size, and whether the amount of ascites would be a predictor of the effect of nivolumab could not be assessed. Further multicentres studies should investigate this hypothesis.

The changing tumour microenvironment (TME) is associated with both the activation of T-cells and the silencing of regulatory T cells [30]; therefore, the changing TME induced by second-line chemotherapy might enhance the effects of nivolumab chemotherapy. Although we did not assess the biomarker of TME, baseline NLR (bNLR) was higher in the PD group than that in the DC group. Since NLR is a marker of systemic inflammatory response that reflects the tumour inflammatory status in patients with gastric cancer [31], our results support the importance of controlling tumour inflammatory status prior to nivolumab chemotherapy.

In this study, the occurrences of irAEs were associated with improvements in treatment outcomes, which was in agreement with previous reports [3–6]. Since irAEs occurred after the initiation of chemotherapy, it was not a predictor of treatment outcome. In addition, age and the duration of the second-line chemotherapy did not show good predictive abilities. Our study did not detect the significant predictor for treatment outcome but suggested that the patients with the tolerability of second-line chemotherapy and old patients received the clinical benefit from nivolumab chemotherapy.

This study had some limitations. First, it was retrospective, and the number of patients was small. Therefore we could not validate the association between the volume of ascites and treatment outcome. Second, we did not evaluate the biomarkers of TME in this study, which may be potent predictors of treatment outcomes.

Conclusions

The effect and the tolerability of second-line chemotherapy, and age over 65 years were associated with DC after nivolumab chemotherapy. The control of tumour inflammatory status might be important for improvements in treatment outcomes.

Abbreviations

AEs
adverse events
AUC
area under the curve
bNLR
baseline neutrophil-lymphocyte ratio
CIs
confidence intervals
CS
cisplatin plus S-1
CR
complete response
DC

disease control
HRs
hazard ratio
ICI
immune checkpoint inhibitors
irAEs
immune-related adverse events
OR
odds ratio
OS
overall survival
NLR
neutrophil lymphocyte ratio
PD
progressive disease
PD-1
programmed cell death protein 1
PN
peripheral neuropathy
PR
partial response
SOX
S-1 plus oxaliplatin
TME
tumour microenvironment
TNM
tumour-node-metastasis

Declarations

Ethics approval and consent to participate

The institutional review boards and Medical ethics committee at the Fujita Health University reviewed and approved the study (HM21-485), and this study was conducted according to the appropriate guidelines. The need for Informed Consent was waived by the institutional review boards and Medical ethics committee at the Fujita Health University due to the retrospective nature of the study.

Consent for publication

Not Applicable. This manuscript does not contain any individual person's data in any form.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article (and its additional file).

Competing interests

The authors have no Conflict of interest to declare.

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The authors received no specific funding for this work.

Authors' contributions

HM made substantial contribution to designed the study, TM performed the statistical analysis and the verification of data accuracy, MS made data extraction, database creation, statistical analysis, K S, MS, MN, TT, SS, TH and KS have contributed to the acquisition of data and revision of the manuscript.

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Tables

Table 1. Baseline characteristics

Characteristics	All patients (n = 116)	PD (n = 77)	DC (n = 39)	*P*-value
Age (years) median (range)	68 (36–85)	66 (37–82)	69 (36–85)	0.080[a]
≥ 65, n (%)	75 (65)	44 (57)	31 (80)	0.017[b]
≥ 75, n (%)	21 (18)	13 (17)	8 (21)	0.620[c]
Male sex, n (%)	92 (79)	61 (79)	31 (80)	0.973[b]
Amount of ascites				
-High, n (%)	16 (14)	10 (13)	6 (15)	0.859[b]
-Moderate, n (%)	14 (12)	10 (13)	4 (10)	
-Low, n (%)	49 (42)	34(44)	15 (39)	
-None, n (%)	37 (32)	23 (30)	14 (36)	
Serum albumin (g/dL) mean±SD	3.4 ± 0.44	3.4 ± 0.50	3.3 ± 0.41	0.257[d]
Number of white blood cell (10^3/μL)	5.2 (2.2–12)	5.3 (2.2–12)	5.1 (2.8–11)	0.423[a]
Number of neutrophil (10^3/μL)	2.9 (0.8–9.2)	3.3 (0.8–9.2)	2.7 (1.1–7.9)	0.135[a]
Number of lymphocyte (10^3/μL)	1.4 (0.4–3.0)	1.4 (0.4–2.6)	1.4 (0.8–3.0)	0.379[a]
NLR	2.2 (0.6–13)	2.3(0.6–13)	2.2 (0.6–8.0)	0.081[a]
≥ 3.0, n (%)	39 (34)	30 (39)	9 (23)	0.100[c]
Second-line chemotherapy regimen				
-Ramucirumab, n (%)	105 (91)	71 (92)	34 (87)	0.383[b]
-Others, n (%)	11 (9.5)	6 (7.8)	5 (13)	
Response to second-line chemotherapy				
-CR or PR, n (%)	6 (5.2)	5 (6.5)	1 (2.6)	0.662[c]
-PD, n (%)	51 (44.0)	36 (46.8)	15 (39)	0.395[b]
-Duration of second-line chemotherapy (months)	3.5 (0.2–19)	3.3 (0.2–14)	4.9 (0.2–19)	0.225[a]
≥3.5, n (%)	59 (51)	37 (48)	22 (56)	0.395[b]
≥7.0, n (%)	22 (19)	10 (13)	12 (31)	

				0.021[b]
Second line chemotherapy AEs, n (%)	108 (93)	72 (94)	36 (92)	0.810[b]

PD: Progressive Disease, DC: disease control, SD: Stable Disease, NLR: Neutrophil-lymphocyte ratio, CR: Complete Response, PR: Partial Response, AE: Adverse event, [a]Mann–Whitney U test, [b]Chi-square test, [c]Fisher's exact test, [d]Student's t-test

Table 2. Immune-related adverse events (irAEs) during nivolumab chemotherapy

Characteristic	PD (n = 77)	DC (n = 39)	*P*-value
irAEs, n (%)	14 (18.2)	17 (43.6)	0.003
-Endocrine, n	2(2.5)	8(10.4)	
-Gastrointestinal, n	1(1.3)	3(3.9)	
-Hepatic, n	5(6.5)	3(3.9)	
-Pulmonary, n	2(2.5)	2(2.5)	
-Renal, n	1(1.3)	0	
-Skin, n	4(5.2)	4(5.2)	
-Others, n	0	1(1.3)	

PD: Progressive Disease, DC: disease control

Table 3. Factors for disease control after nivolumab chemotherapy

Characteristics	Univariate analysis	*P*-value	Multivariate analysis	*P*-value
	OR (95% CI)		OR (95% CI)	
Age ≥ 65 years	2.906 (1.183–7.140)	0.017	2.666 (1.045–6.802)	0.040
Duration of second-line chemotherapy ≥ 7.0 months	2.978 (1.151–7.705)	0.021	3.100 (1.108–8.678)	0.031
irAEs	3.477 (1.475–8.200)	0.003	3.600 (1.448–8.950)	0.006

OR: Odds ratio, CI: Confidence interval, irAEs: Immune-related adverse events

Figures

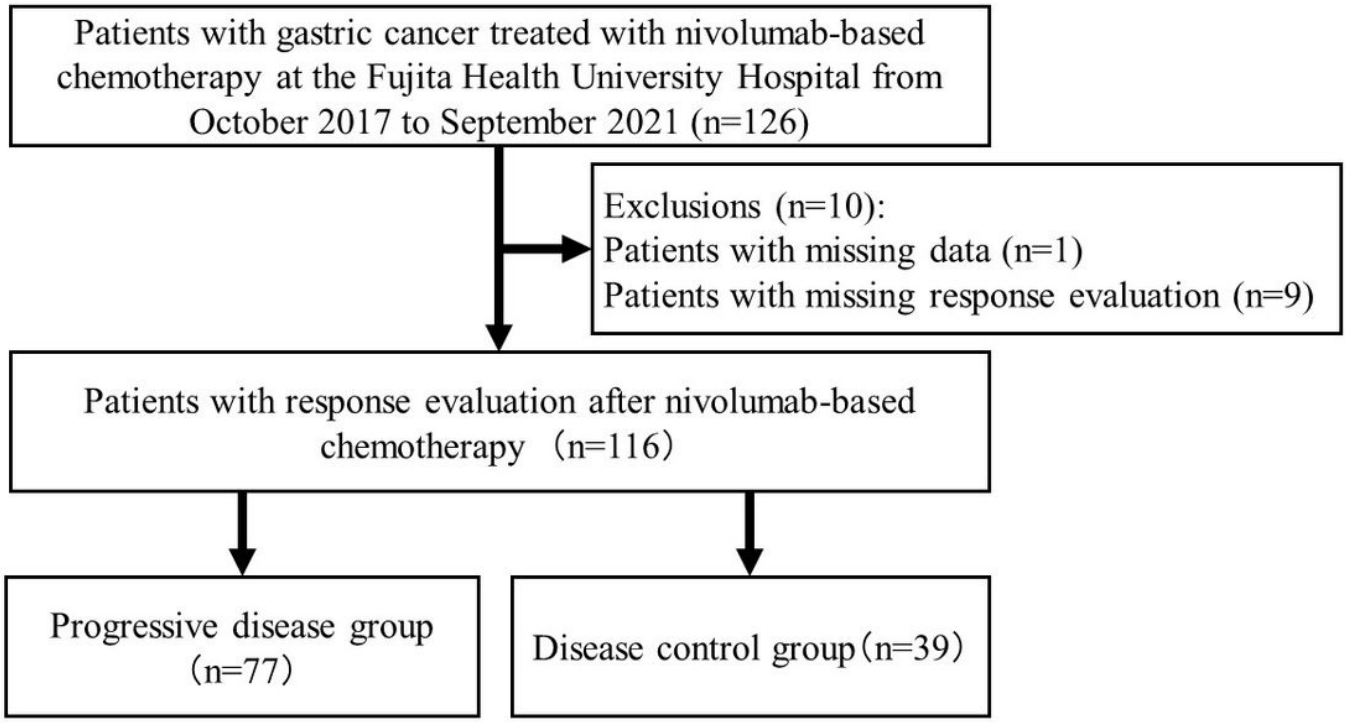

Figure 1

Patient recruitment

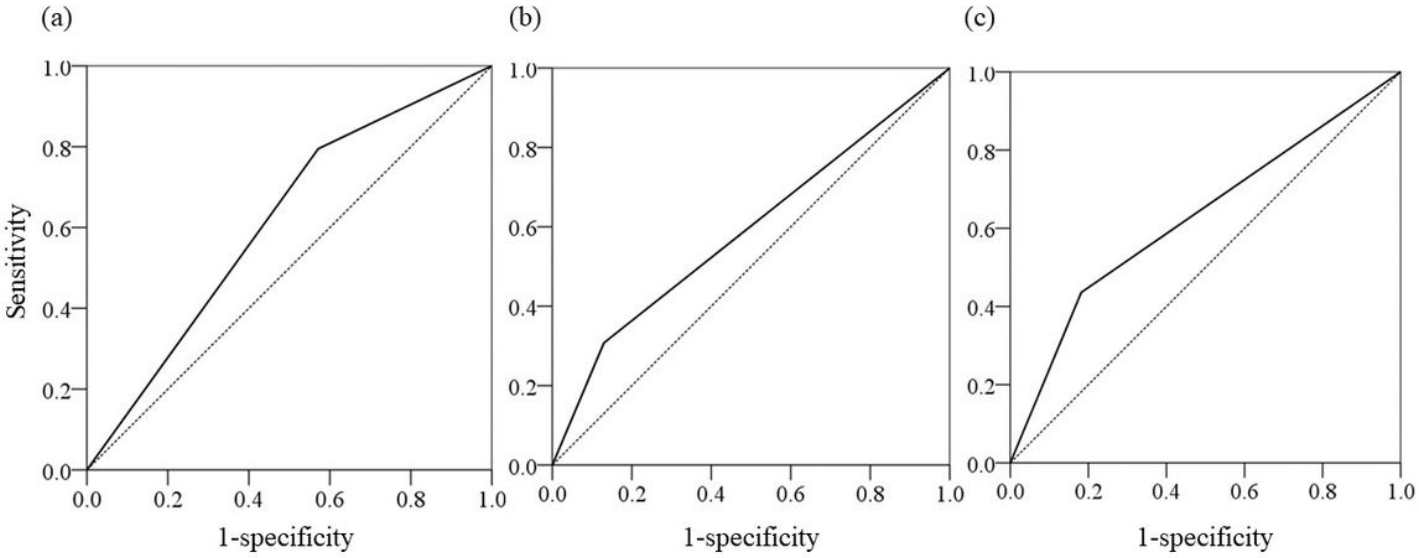

Figure 2

Receiver operating characteristic curves of the factors for disease control after nivolumab chemotherapy. **(a)** Age ≥ 65 years old: sensitivity = 0.795; specificity = 0.429; area under the curve [AUC] = 0.612, *p* = 0.050 (95% confidence interval [CI] 0.506–0.717), **(b)** Duration of second-line chemotherapy ≥ 7.0 months: sensitivity = 0.308; specificity =0.870; AUC=0.589, *p*= 0.119 (95% CI 0.475–0.702), **(c)** immune-related adverse events: sensitivity=0.308; specificity=0.818; AUC, 0.625, *p* = 0.026 (95% CI 0.515–0.739)

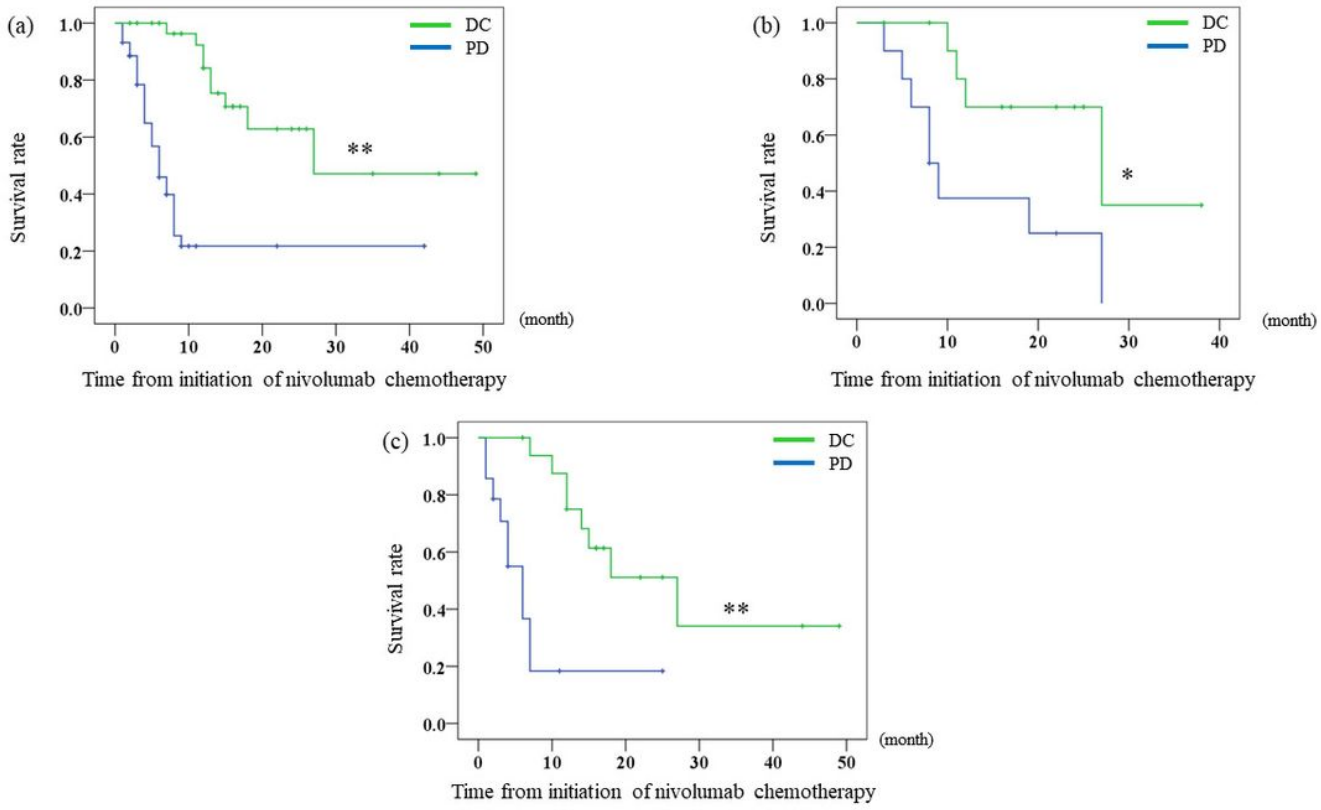

Figure 3

Kaplan–Meier survival curves for patients with gastric cancer treated with nivolumab chemotherapy in the disease control (DC) and progressive disease (PD) groups. **(a)** Kaplan–Meier survival curves for patients aged 65 years or older. The median overall survival (OS) times (95% confidence interval [CI]) of DC and PD groups were 27.0 (N.A) and 6.00 (4.13–7.87) months, respectively (log-rank test; $p < 0.001$). **(b)** Kaplan–Meier survival curves for patients with a duration of second-line chemotherapy over 7 months. The median OS times (95% CI) of DC and PD groups were 27.0 (5.34–48.7) and 8.00 (5.14–10.9) months, respectively (log-rank test; $p = 0.014$). **(c)** Kaplan–Meier survival curves for patients with immune-related adverse events. The median OS times (95% CI) of DC and PD groups were 27.0 (12.6–41.4) and 6.00 (3.01–8.99) months, respectively (log-rank test; $p < 0.001$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- datasetsuppl.xlsx