Research Article

Clinical Significance of Eligibility Criteria Determined by the SPIRITS Trial in Patients with Advanced Gastric Cancer

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Short Title: Clinical Significance of Eligibility Criteria in Patients with Gastric Cancer

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Abstract

Introduction: This study aimed to assess the clinical significance of eligibility criteria determined by phase III clinical trials in the clinical practice of patients with advanced gastric cancer who underwent chemotherapy.

Methods: Patients with stage IV gastric cancer who received chemotherapy between February 2002 and December 2021 were retrospectively enrolled and divided into two groups (the eligible vs. ineligible group) based on eligibility criteria determined by the SPIRITS (S-1 vs. S-1 plus cisplatin) trial.

Results: Among the 207 patients, 103 (49.8%) and 104 (50.2%) patients were classified into eligible and ineligible groups, respectively. Eligibility criteria were significantly correlated with age, the first-line regimen of chemotherapy, the presence or absence of conversion surgery, and tumor response to the first-line chemotherapy (all $p < 0.01$). The eligible group had a significantly higher induction of post-progression chemotherapy after first- and second-line chemotherapy than did the ineligible group (all $p < 0.01$). The ineligible group had significantly poorer prognoses than the eligible group ($p < 0.0001$). Multivariate analysis showed that peritoneal dissemination, tumor response, conversion surgery, and eligibility criteria were independent prognostic factors (all $p < 0.05$).

Conclusion: Eligibility criteria determined by the SPIRITS trial may have clinical utility for predicting tumor response, the induction of conversion surgery, and prognosis in patients with advanced gastric cancer who underwent chemotherapy.

Introduction

The Japanese Gastric Cancer Treatment Guidelines recommend systemic chemotherapy as the initial treatment in patients with unresectable advanced or recurrent gastric cancer [1]. To date, randomized controlled trials (RCT) have certified the clinical utility of chemotherapy, including recommended regimens. Notably, the primary endpoint of S-1 Plus cisplatin versus S-1 In RCT In the Treatment for Stomach cancer (SPIRITS) trial showed that the median overall survival (OS) was significantly longer in patients who received S-1 plus cisplatin than in those who received S-1 alone (13.0 months vs. 11.0 months) [2]. Therefore, S-1 plus cisplatin is the currently recommended regimen for the first-line chemotherapy in patients with human epidermal growth factor receptor 2 (HER2)-negative unresectable advanced or recurrent gastric cancer [1].

According to the Japanese Gastric Cancer Treatment Guidelines, systemic chemotherapy is indicated for patients with performance status (PS) of 0–2, preserved major organ function, and no serious comorbidities [1]. Moreover, RCT including the SPIRITS trial commonly establish eligibility criteria for suitable patients who undergo chemotherapy [2–5]. An advanced age (≥ 75 years), PS of 3, hematopoietic disorder, non-preserved liver and renal function, and serious comorbidities were ineligibility criteria in the SPIRITS trial [2]. Consequently, clinicopathological factors of patients between RCT and clinical practice are likely to differ in the management of unresectable advanced gastric cancer. Furthermore, a discrepancy in clinicopathological factors may influence the therapeutic strategy and prognosis. However, very few studies have been conducted to assess these key issues in patients with advanced gastric cancer.

From the viewpoint of eligibility criteria determined by the SPIRITS trial, we investigated clinicopathological factors in the clinical practice of patients with advanced gastric cancer who

underwent chemotherapy. The present study aimed to assess the clinical impact of eligibility criteria by examining tumor response to chemotherapy, post-progression chemotherapy, the presence or absence of conversion surgery, and prognosis between the eligible and ineligible groups.

Materials and methods

Patients

Data from 207 patients with stage IV gastric cancer who underwent chemotherapy at Kagoshima University Hospital (Kagoshima, Japan) between February 2002 and December 2021 were retrospectively reviewed. Patients with synchronous or metachronous cancer in other organs and disease recurrence were excluded from this study. All patients underwent blood examinations, esophagogastroduodenoscopy, endoscopic ultrasonography, and computed tomography before chemotherapy. Patients were categorized and staged based on the TNM (tumor-node-metastasis) classification for gastric carcinoma [6]. This retrospective study was approved by the Ethics Committee of Kagoshima University and conducted in accordance with the Declaration of Helsinki (approval number: 200043). The informed consent requirement was waived due to the retrospective, observational design, and opt-out opportunity was provided on the institutional website.

Eligibility criteria determined by the SPIRITS trial

The SPIRITS trial excluded patients aged ≥ 75 years, with a PS of 3, ascites requiring drainage, hematopoietic disorder (absolute granulocyte count < lower limits of normal or > 12,000/mm^3, platelet count < 100,000/mm^3, and hemoglobin < 8.0 g/dL), non-preserved liver and renal functions (serum aspartate transaminase or alanine aminotransferase levels > 100

U/L, serum alkaline phosphatase level > two times upper limits of normal [ULN], serum bilirubin level > 1.5 mg/dL, serum creatinine level > ULN, and creatinine clearance < 50 mL/min), serious comorbidities, brain metastasis, and psychiatric disorder [2]. Therefore, according to these eight ineligibility criteria determined by the SPIRITS trial, patients were divided into eligible and ineligible groups. Patients with at least one of eight ineligibility criteria were considered ineligible in the present study.

Assessment of tumor response to chemotherapy

Tumor response was determined every two or three chemotherapy cycles and assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST) [7]. This study classified tumor response into the following four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Statistical analysis

The relationship between eligibility criteria and clinicopathological factors, including tumor response and post-progression chemotherapy, was assessed using the chi-square test, Fisher's exact test, or Wilcoxon rank-sum test. OS was defined as the period from first-line chemotherapy initiation to death or last follow-up. Kaplan–Meier survival curves were generated, and prognostic differences were evaluated using the log-rank test. Prognostic factors were assessed using univariate and multivariate analyses (Cox proportional hazards regression modeling). All data were analyzed using JMP14 (SAS Institute Inc., Cary, NC, USA). A *p*-value of < 0.05 was considered statistically significant.

Results

Clinicopathological characteristics of patients

The present study enrolled 207 patients (132 men and 75 women; median age, 68.0 years, ranging from 30 to 91 years). Among the patients, 1, 3, 21, and 182 had clinical T1, T2, T3, and T4 tumors, respectively. Furthermore, 33, 38, 56, and 80 patients had a clinical nodal status of N0, N1, N2, and N3, respectively. All patients were clinically diagnosed with stage IV due to distant metastasis, including liver (*n* = 47), lung (*n* = 4), and distant lymph node (*n* = 71) metastases, and peritoneal dissemination (*n* = 125). Moreover, 152 and 55 patients had one and more than two distant metastatic sites, respectively. Among the patients enrolled herein, 8, 73, and 126 received S-1 alone, taxane-based, and platinum-based chemotherapy as a first-line treatment, respectively. Additionally, 45 patients received the first-line chemotherapy, including trastuzumab. Herein, 63 (30.0%) patients underwent conversion surgery after chemotherapy. Proximal gastrectomy, distal gastrectomy, total gastrectomy, and esophagectomy were performed in 5 (7.9%), 18 (28.6%), 38 (60.3%), and 2 (3.2%) patients, respectively. Five patients with liver metastasis underwent gastrectomy and partial hepatectomy in conversion surgery. R0 resection rate was 87.3% (55/63).

Classification based on eligibility criteria determined by the SPIRITS trial

Among the 207 patients, 60 (29.0%), 25 (12.1%), 15 (7.2%), 22 (10.6%), 47 (22.7%), 20 (9.7%), 2 (1.0%), and 1 (0.5%) had ≥ 75 years, PS of 3, ascites requiring drainage, hematopoietic disorder, non-preserved liver or renal function, serious comorbidities, brain metastasis, and psychiatric disorder, respectively. Therefore, 103 (49.8%) and 104 (50.2%) patients were divided into eligible and ineligible groups, respectively.

Relationship between eligibility criteria and clinicopathological factors

The median age of the eligible and ineligible groups was 61 and 76 years, respectively (Table 1). The ineligible group had a significantly higher age than the eligible group ($p < 0.0001$). Moreover, no one in the eligible group received S-1 alone. However, eight (7.7%) patients received S-1 alone in the ineligible group. Eligibility criteria were significantly correlated with the first-line regimen of chemotherapy ($p = 0.0068$; Table 1). Conversion surgery was undergone in 45 (43.7%) and 18 (17.3%) patients of eligible and ineligible groups, respectively. Accordingly, eligibility criteria were significantly associated with the presence or absence of conversion surgery ($p < 0.0001$; Table 1). No significant relationships between eligibility criteria and other clinicopathological factors, such as sex, tumor location, macroscopic type, depth of tumor invasion, lymph node metastasis, number of distant metastatic sites, histological type, and trastuzumab-based chemotherapy were shown (all $p > 0.05$; Table 1).

Among the 207 patients, 116 patients had target lesions for RECIST. Regarding tumor response, 4 (7.0%), 30 (52.6%), 12 (21.1%), and 11 (19.3%) patients had CR, PR, SD, and PD, respectively, in the eligible group (Table 1). In contrast, 21 (35.6%), eight (13.6%), 30 (50.9%) patients in the ineligible group had PR, SD, and PD, respectively. No one in the ineligible group had tumor response with CR. These results showed a strong association between eligibility criteria and tumor response to the first-line chemotherapy ($p = 0.0017$; Table 1).

Relationship between eligibility criteria and post-progression chemotherapy

A total of 88 (85.4%) and 62 (59.6%) patients received post-progression chemotherapy after first-line chemotherapy in the eligible and ineligible groups, respectively (Fig. 1). Furthermore, 56 (54.4%) and 36 (34.6%) patients received post-progression chemotherapy after second-line chemotherapy in the eligible and ineligible groups, respectively (Fig. 1).

Therefore, eligibility criteria were significantly correlated with post-progression chemotherapy after first- and second-line chemotherapy ($p < 0.0001$ and $p = 0.0052$, respectively; Fig. 1).

Relationship between eligibility criteria and prognosis

Eligible and ineligible groups had a median survival time (MST) of 718 and 315 days, respectively (Fig. 2a). Consequently, the ineligible group had a significantly poorer prognosis than the eligible group ($p < 0.0001$; Fig. 2a).

To assess the relationship between numbers of ineligibility criteria determined by the SPIRITS trial and prognosis, we classified patients into three groups based on numbers of ineligibility criteria (0 vs. 1 vs. ≥ 2). Patients with the ineligible numbers of 0 ($n = 103$), 1 ($n = 46$), and ≥ 2 ($n = 58$) had MSTs of 718, 390, and 287 days, respectively (Fig. 2b). There were significant prognostic differences among each group, except for patients with an ineligible number of 1 vs. ≥ 2 ($p < 0.05$; Fig. 2b).

Moreover, patients were categorized into the following four groups based on eligibility criteria and the presence or absence of conversion surgery: eligible surgery, eligible non-surgery, ineligible surgery, and ineligible non-surgery. Patients who were classified into the eligible surgery ($n = 45$), eligible non-surgery ($n = 58$), ineligible surgery ($n = 18$), and ineligible non-surgery ($n = 86$) had MSTs of 1235, 482, 1763, and 262 days, respectively; Fig. 3). We found significant prognostic differences among each group, except for groups with the eligible vs. ineligible surgery ($p < 0.0001$; Fig. 3).

Univariate analyses indicated that age (< 68 vs. ≥ 68 years), peritoneal dissemination, histological type, first-line regimen of chemotherapy, tumor response, conversion surgery, and eligibility criteria were significantly correlated with survival ($p = 0.0473$, $p = 0.0002$, $p =$

0.0014, $p < 0.0001$, $p < 0.0001$, $p < 0.0001$, and $p < 0.0001$, respectively; Table 2). Multivariate analysis revealed that peritoneal dissemination, tumor response, conversion surgery, and eligibility criteria were independent prognostic factors ($p = 0.0370$, $p = 0.0009$, $p < 0.0001$, and $p = 0.0148$, respectively; Table 2).

Further univariate and multivariate analyses were performed to assess the prognostic impact of each ineligible parameter. Univariate analyses indicated that age, PS, ascites requiring drainage, non-preserved liver or renal function, and serious comorbidities were significantly correlated with survival ($p = 0.0037$, $p < 0.0001$, $p = 0.0382$, $p = 0.0055$, and $p = 0.0040$, respectively; Table 3). Multivariate analysis showed that performance status was selected as an independent prognostic factor ($p < 0.0001$; Table 3).

Discussion

The prognosis of patients with unresectable advanced or recurrent gastric cancer has been improved by advancements in chemotherapy [8, 9]. However, we have occasionally experienced patients with poor chemotherapy adherence in the clinical practice. Therefore, we had a hypothesis that the background of patients between clinical practice and RCT would be strikingly different and its impact involved chemotherapy adherence. To our best knowledge, this is the first study to assess the clinical significance of eligibility criteria determined by RCT in patients with advanced gastric cancer.

Initially, we investigated ineligibility criteria determined by the SPIRITS trial in patients who underwent chemotherapy. Surprisingly, 104 (50.2%) patients were categorized into the ineligible group who had at least one of the eight ineligibility criteria determined by the SPIRITS trial in the present study. This result strongly suggests that there are differences in the background of patients between RCT and clinical practice. Of note, the proportion of

patients with ≥ 75 years was 29.0%. Elderly patients often have poor PS, hematopoietic disorders, non-preserved liver or renal functions, and serious comorbidities. Interestingly, Hayashi et al. [10] reported that there was no prognostic difference of the OS among patients with ≥ 75 and < 75 years who underwent chemotherapy (312 vs. 348 days) in a multicenter retrospective cohort study for inoperable advanced gastric cancer. Furthermore, multivariate analysis demonstrated that good PS, combination chemotherapy, and male sex were favorable independent prognostic factors [10]. Accordingly, it is clinically important to successfully manage elderly patients in the therapeutic strategy of advanced gastric cancer.

Although all patients of our eligible group received taxane- or platinum-based combination therapy, eight (7.7%) in the ineligible group received S-1 alone. Moreover, the ineligible group had a significantly poorer tumor response to chemotherapy than the eligible group. The SPIRITS trial showed that the objective response rate of patients who received S-1 plus cisplatin and S-1 alone was 54% and 31%, respectively, with the difference therein being statistically significant (p = 0.002) [2]. These findings indicated a close relationship between eligibility criteria and tumor response, suggesting a possibility of the first-line regimen of chemotherapy as its cause. Recent studies have demonstrated that tumor shrinkage caused by chemotherapy contributes to improve symptom palliation and quality of life [11–13]. As such, medical support for undergoing not only S-1, but also combination chemotherapy, is of critical importance in the therapeutic strategy of the clinical practice.

Strengths of this study included the detailed assessment of post-progression chemotherapy after first- and second-line chemotherapy between the eligible and ineligible groups. Here, the eligible group had a higher proportion of patients receiving post-progression chemotherapy after first- or second-line chemotherapy than that of the ineligible group. The post-progression chemotherapy initiation rate after second-line

chemotherapy in ineligible group was 34.6%. Currently, the Japanese Gastric Cancer Treatment Guidelines recommends nivolumab, irinotecan monotherapy, or trifluridine/tipiracil for HER2-negative gastric cancer and trastuzumab deruxtecan for HER2-positive gastric cancer as the third-line chemotherapy [1]. Therefore, with the rapid development of attractive regimens for later-line chemotherapy, post-progression chemotherapy initiation rates after first- or second-line chemotherapy increase [9]. Several studies have reported that higher post-progression chemotherapy initiation rates after first- and second-line chemotherapy lead to longer OS and post-progression survival, proposing that post-progression chemotherapy might improve prognosis in patients with advanced gastric cancer [9, 14]. Therefore, there is a need to consider post-progression chemotherapy initiation at a suitable time.

The present study showed a significant prognostic difference between the eligible and ineligible groups. Furthermore, multivariate analysis identified eligibility criteria as well as tumor response as an independent prognostic factor. Interestingly, ineligible numbers were significantly correlated with prognosis. These findings suggest the clinical importance of medical support for improving PS, hematopoietic disorder, non-preserved liver and renal function, and disease control of serious comorbidities. In particular, PS was selected as the most important prognostic factor from these ineligible parameters. Nutritional supplements may be promising tools to achieve these goals in the clinical management of patients with advanced gastric cancer. Several reports have demonstrated that oral nutritional supplementation reduces body weight loss in patients with gastric cancer who undergo gastrectomy, while postoperative weight loss results in reduced survival via poor S-1 adherence [15, 16]. Toyomasu et al. [17] reported that oral nutritional supplements might have the clinical utility to prevent S-1 adjuvant chemotherapy-induced mucositis and to

maintain S-1 adherence in patients with stage II and III gastric cancer who underwent gastrectomy. Collectively, an aggressive intervention of nutritional supplements should be proposed to improve the prognosis in the clinical practice of patients with advanced gastric cancer. Moreover, we investigated relative dose intensity (RDI) of chemotherapy in the eligible and ineligible groups. In the eligible and ineligible groups, the RDI was 96.7% and 83.3%, respectively. Accordingly, the eligible group had a significantly higher RDI than the ineligible group ($p < 0.0001$, data not shown). Furthermore, the eligible group had a significantly higher post-progression chemotherapy initiation rate and longer overall survival than the ineligible group. These results may indicate that the difference of RDI between the eligible and ineligible groups has an impact on post-progression chemotherapy initiation rate and prognosis.

Conversion surgery has been highlighted as a promising tool for improving survival in responders with unresectable advanced gastric cancer after chemotherapy [18–20]. However, little evidence exists regarding the clinical significance of conversion surgery in gastric cancer. Moreover, the Japanese Gastric Cancer Treatment Guidelines weakly recommend conversion surgery in responders with tumors predicted to achieve R0 curative resection [1]. In this study, we assessed the prognostic impact of conversion surgery in the eligible and ineligible groups. In both of these, patients who underwent conversion surgery had a significantly better prognosis than those who underwent chemotherapy alone. Interestingly, there was no prognostic difference between the eligible and ineligible groups who underwent conversion surgery (1235 vs. 1763 days, respectively). Additionally, multivariate analysis identified that conversion surgery was an independent prognostic factor. These results suggest that conversion surgery has the clinical potential to improve prognosis, even in responders of the ineligible group after chemotherapy.

The present study had several limitations. First, this was a single-center retrospective study consisting of a small population (*n* = 207). Second, chemotherapy regimens for each line were clinically determined based on the Japanese Gastric Cancer Treatment Guidelines, although varying chemotherapy regimens had been administered based on clinical trial registration, patient condition, or physician discretion. These limitations might have resulted in bias, which could adversely affect our results. Therefore, further large studies are warranted to strengthen the conclusions presented herein.

In conclusion, our retrospective study suggested that eligibility criteria determined by the SPIRITS might have the clinical utility for predicting tumor response, the induction of conversion surgery, and prognosis in patients with advanced gastric cancer.

Statements

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Statement of Ethics

Study approval statement: This retrospective study was approved by the Ethics Committee of Kagoshima University in accordance with the Declaration of Helsinki (approval number: 200043). Consent to participate statement: Written informed consent was obtained from all patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Souichi Satake, Takaaki Arigami, Daisuke Matsushita, Keishi Okubo, Masataka Shimonosono, Ken Sasaki, Yusuke Tsuruda, Kan Tanabe, Shinichiro Mori, Shigehiro Yanagita, Yoshikazu Uenosono, Akihiro Nakajo, Hiroshi Kurahara, and Takao Ohtsuka contributed to the study design. Souichi Satake, Takaaki Arigami, Daisuke Matsushita, Keishi Okubo, Masataka Shimonosono, Ken Sasaki, and Yusuke Tsuruda were involved in data collection and data interpretation. Souichi Satake, Takaaki Arigami, Kan Tanabe, Shinichiro Mori, Shigehiro Yanagita, Yoshikazu Uenosono, Akihiro Nakajo, Hiroshi Kurahara, and Takao Ohtsuka contributed to the statistical analyses. Souichi Satake wrote the manuscript. All authors read

and approved the final manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Figure legends

Fig. 1. The proportion of patients who underwent post-progression chemotherapy after first- or second-line chemotherapy. **a** After first-line chemotherapy. **b** After second-line chemotherapy.

Fig. 2. Kaplan–Meier survival curves based on eligibility criteria. **a** Eligible group vs. ineligible group. **b** Ineligible number of 0 vs. 1 vs. ≥ 2.

Fig. 3. Kaplan–Meier survival curves based on eligibility criteria and the presence or absence of conversion surgery.

Table 1. Relationship between eligibility criteria and clinicopathological factors

Factor	Eligibility criteria, *n* (%)		
	Eligible group (*n* = 103)	Ineligible group (*n* = 104)	*p* value
Sex			0.7728
Male	67 (65.1)	65 62.5)	
Female	36 (35.0)	39 (37.5)	
Median age, years	61	76	<0.0001
Tumor location			1.0000
Whole/upper	62 (60.2)	62 (59.6)	
Middle/lower	41 (39.8)	42 (40.4)	
Macroscopic type			0.4565
Type non–4	68 (66.0)	74 (71.2)	
Type 4	35 (34.0)	30 (28.9)	
Depth of tumor invasion			1.0000
cT1–2	2 (1.9)	2 (1.9)	
cT3–4	101 (98.1)	102 (98.1)	
Lymph node metastasis			0.8842
cN0–1	36 (35.0)	35 (33.7)	
cN2–3	67 (65.1)	69 (66.4)	
Number of distant metastatic sites			0.8759
1	75 (72.8)	77 (74.0)	
$\geq$ 2	28 (27.2)	27 (26.0)	
Liver metastasis			0.5075

Absence	21 (20.4)	26 (25.0)	
Presence	82 (79.6)	78 (75.0)	
Lung metastasis			1.0000
Absence	2 (1.9)	2 (1.9)	
Presence	101 (98.1)	102 (98.1)	
Distant lymph node metastasis			0.1894
Absence	40 (38.8)	31 (29.8)	
Presence	63 (61.2)	73 (70.2)	
Peritoneal dissemination			0.7771
Absence	61 (59.2)	64 (61.5)	
Presence	42 (40.8)	40 (38.5)	
Histological type			0.3456
Differentiated	24 (23.3)	31 (29.8)	
Undifferentiated	79 (76.7)	73 (70.2)	
First-line regimen of chemotherapy			0.0068
S-1 alone	0 (0.0)	8 (7.7)	
Taxane-based or platinum-based	103 (100.0)	96 (92.3)	
Trastuzumab-based chemotherapy			0.6165
Absence	24 (23.3)	21 (20.2)	
Presence	79 (76.7)	83 (79.8)	
Conversion surgery			<0.0001
Absence	58 (56.3)	86 (82.7)	
Presence	45 (43.7)	18 (17.3)	

Tumor response			0.0017
Complete response	4 (7.0)	0 (0.0)	
Partial response	30 (52.6)	21 (35.6)	
Stable disease	12 (21.1)	8 (13.6)	
Progressive disease	11 (19.3)	30 (50.9)	

Table 2. Univariate and multivariate analyses of survival

Independent factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Sex			0.5453			
Male	1.000	Reference				
Female	1.102	0.805–1.508				
Age (median)			0.0473			0.7605
<68 years	1.000	Reference		1.000	Reference	
≥68 years	1.361	1.004–1.845		0.917	0.526–1.600	
Tumor location			0.8799			
Middle/lower	1.000	Reference				
Whole/upper	1.024	0.751–1.397				
Macroscopic type			0.1395			
Type non–4	1.000	Reference				
Type 4	1.272	0.924–1.751				
Depth of tumor invasion			0.1435			
cT1–2	1.000	Reference				
cT3–4	2.833	0.702–11.435				
Lymph node metastasis			0.4676			
cN0–1	1.000	Reference				
cN2–3	1.125	0.819–1.546				
Number of distant metastatic sites			0.1383			
1	1.000	Reference				

≥2	1.306	0.918–1.857				
Liver metastasis			0.7413			
Absence	1.000	Reference				
Presence	0.940	0.652–1.356				
Lung metastasis			0.7965			
Absence	1.000	Reference				
Presence	0.860	0.274–2.699				
Distant lymph node metastasis			0.1121			
Absence	1.000	Reference				
Presence	0.765	0.549–1.065				
Peritoneal dissemination			0.0002			0.0370
Absence	1.000	Reference		1.000	Reference	
Presence	1.867	1.346–2.589		1.648	1.030–2.636	
Histological type			0.0014			0.5141
Differentiated	1.000	Reference		1.000	Reference	
Undifferentiated	1.851	1.269–2.700		1.190	0.706–2.007	
First-line regimen of chemotherapy			<0.0001			0.0538
S-1 alone	1.000	Reference		1.000	Reference	
Taxane-based or platinum-based	0.096	0.039–0.238		0.330	0.107–1.018	
Trastuzumab-based chemotherapy			0.1613			
Absence	1.000	Reference				
Presence	0.766	0.527–1.113				
Tumor response			<0.0001			0.0009

SD–PD	1.000	Reference		1.000	Reference	
CR–PR	0.292	0.190–0.450		0.464	0.294–0.731	
Conversion surgery			<0.0001			<0.0001
Absence	1.000	Reference		1.000	Reference	
Presence	0.165	0.110–0.247		0.094	0.042–0.211	
Eligibility criteria			<0.0001			0.0148
Eligible status	1.000	Reference		1.000	Reference	
Ineligible status	2.062	1.514–2.809		2.029	1.148–3.586	

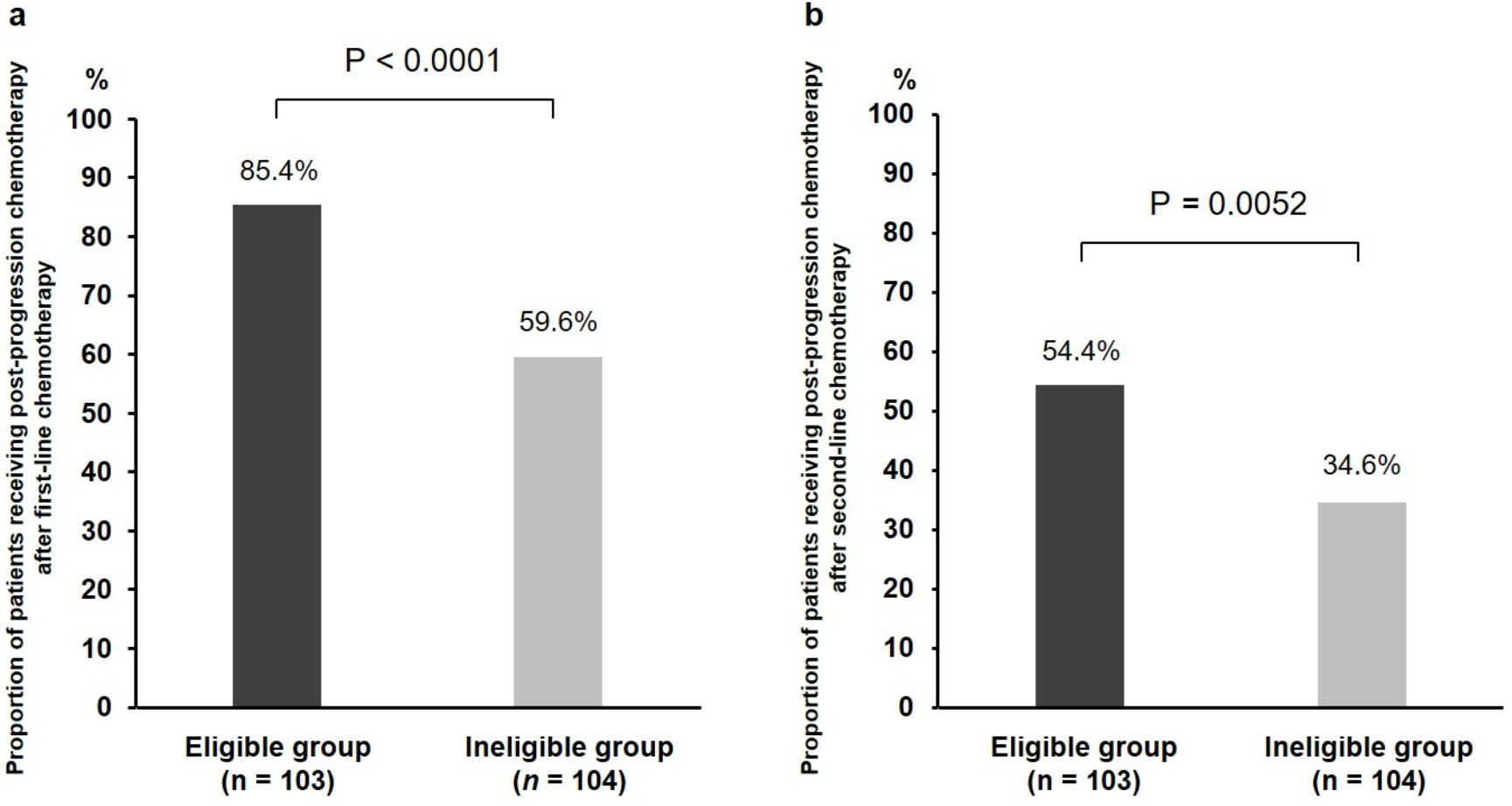
CI, confidence interval; CR, complete response; HR, hazard ratio; PD, progressive disease; PR, partial response; SD, stable disease.

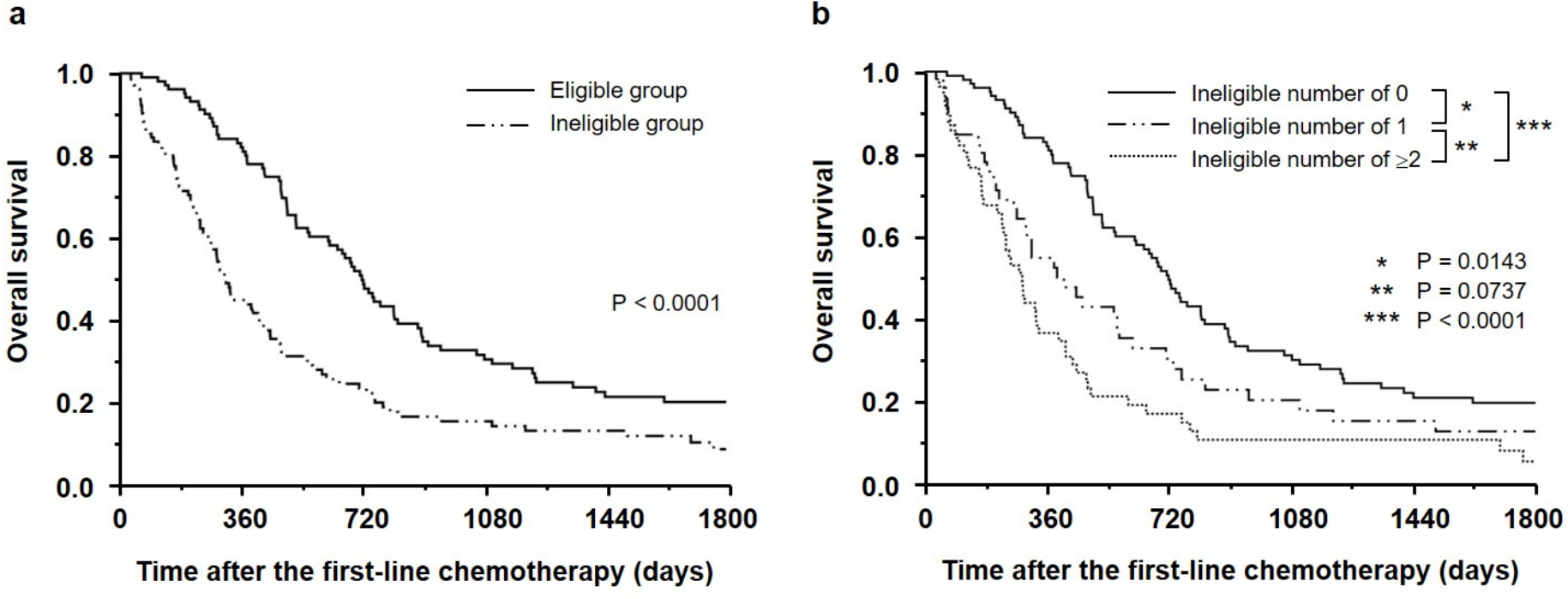
Table 3. Univariate and multivariate analyses of survival for ineligible parameters

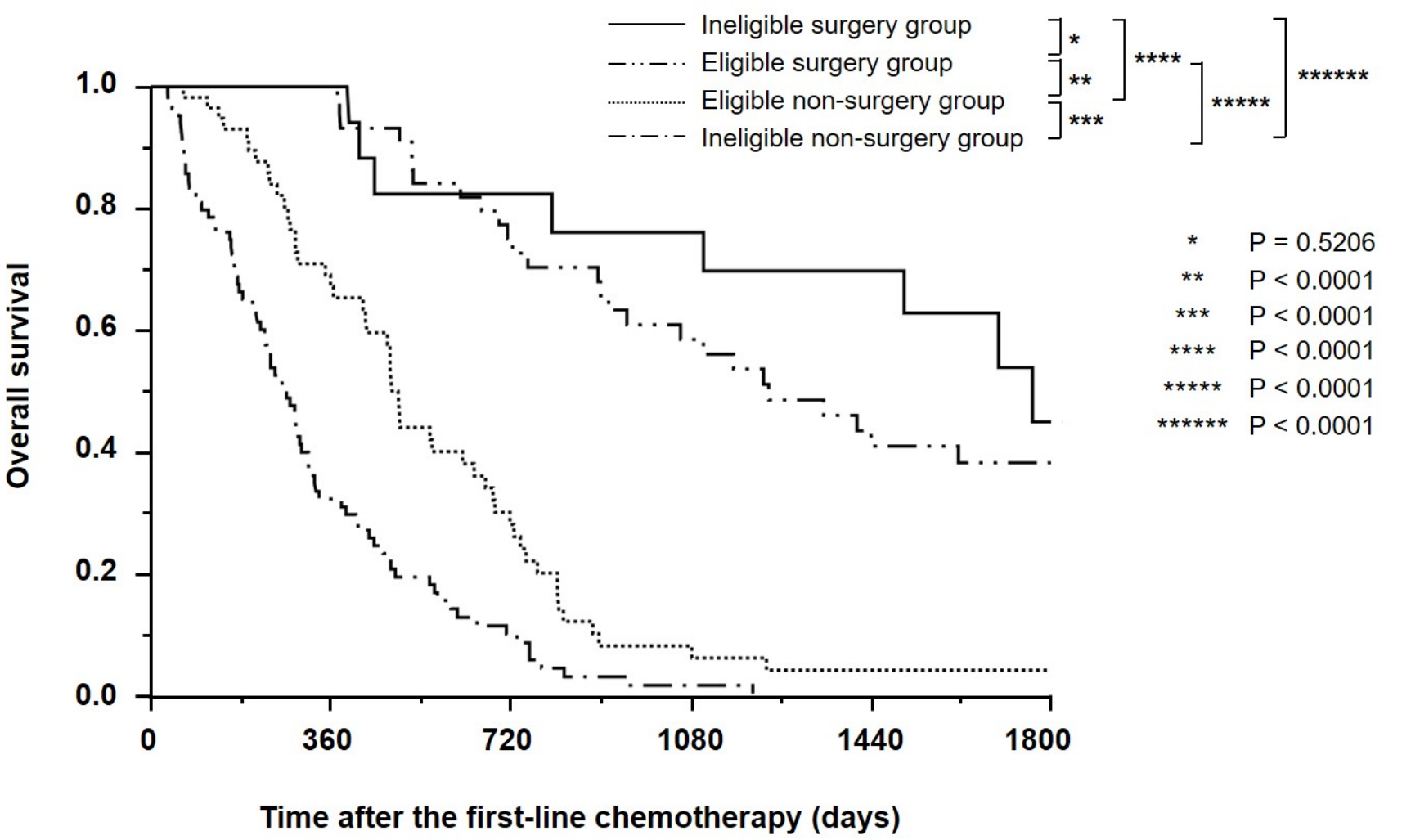
Independent factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age			0.0037			0.0916
<75 years	1.000	Reference		1.000	Reference	
≥75 years	1.639	1.174–2.289		1.404	0.947–2.083	
Performance status			<0.0001			<0.0001
0–2	1.000	Reference		1.000	Reference	
3	4.211	2.670–6.643		4.184	2.375–7.370	
Ascites requiring drainage			0.0382			0.6087
Absence	1.000	Reference		1.000	Reference	
Presence	1.789	1.032–3.100		0.832	0.411–1.683	
Hematopoietic disorder			0.1441			
Absence	1.000	Reference				
Presence	1.457	0.879–2.413				
Non-preserved liver or renal function			0.0055			0.3209
Absence	1.000	Reference		1.000	Reference	
Presence	1.658	1.160–2.370		1.231	0.817–1.856	
Serious comorbidities			0.0040			0.1954
Absence	1.000	Reference		1.000	Reference	
Presence	2.105	1.269–3.491		1.426	0.833–2.442	
Brain metastasis			0.1114			
Absence	1.000	Reference				

Presence	3.124	0.768–12.702	
Psychiatric disorder			0.1511
Absence	1.000	Reference	
Presence	4.275	0.588–31.064	

CI, confidence interval; HR, hazard ratio.


a
P < 0.0001
%
100
90
80
70
60
50
40
30
20
10
0
85.4%
59.6%
Proportion of patients receiving post-progression chemotherapy after first-line chemotherapy
Eligible group (n = 103)
Ineligible group (n = 104)
b
P = 0.0052
%
100
90
80
70
60
50
40
30
20
10
0
54.4%
34.6%
Proportion of patients receiving post-progression chemotherapy after second-line chemotherapy
Eligible group (n = 103)
Ineligible group (n = 104)


a
1.0
0.8
0.6
0.4
0.2
0.0
Overall survival
Eligible group
Ineligible group
P < 0.0001
0
360
720
1080
1440
1800
Time after the first-line chemotherapy (days)
b
1.0
0.8
0.6
0.4
0.2
0.0
Overall survival
Ineligible number of 0
Ineligible number of 1
Ineligible number of ≥2
*
**
***
* P = 0.0143
** P = 0.0737
*** P < 0.0001
0
360
720
1080
1440
1800
Time after the first-line chemotherapy (days)


Ineligible surgery group
Eligible surgery group
Eligible non-surgery group
Ineligible non-surgery group
*
**
***
****
*****
******
* P = 0.5206
** P < 0.0001
*** P < 0.0001
**** P < 0.0001
***** P < 0.0001
****** P < 0.0001
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
360
720
1080
1440
1800
Time after the first-line chemotherapy (days)