ORIGINAL ARTICLE

Factors related to patient propensity to receive adjuvant chemotherapy and outcomes in stage III gastric cancer cases after D2 surgery

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Summary *Background:* Radical gastrectomy and extended lymph node (D2) dissection followed by adjuvant chemotherapy is the optimal treatment for patients with stage III gastric cancer in Asian population. The clinical factors associated with patient propensity to receive adjuvant chemotherapy and outcomes were analyzed.
Methods: In total, 509 patients with stage III gastric cancer who had undergone D2 surgery between 2007 and 2017 at a single medical center in Taiwan were analyzed. The patients' preoperative clinical characteristics relevant to adjuvant chemotherapy adherence were analyzed using multivariate regression. Significant variables were analyzed using recursive partitioning analysis (RPA) for identifying specific patient groups with the lowest and highest probabilities of adjuvant chemotherapy adherence.
Results: After surgery, 361 (70.9%) patients in the cohort had received adjuvant chemotherapy. All patients were categorized into five probability groups with adherence to adjuvant chemotherapy according to age, Eastern Cooperative Oncology Group (ECOG) performance status grade, and American Society of Anesthesiologists (ASA) class, which were discovered to be independent factors in the RPA-based probability prediction. In general, adjuvant

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chemotherapy improved survival across broad categories of stage III gastric cancer patients (overall survival hazard ratio: 0.53—0.75 and disease-free survival hazard ratio: 0.47—0.76).
Conclusions: Our study identified that age, ECOG grade, and ASA class were independent clinical factors associated with patient propensity to receive adjuvant chemotherapy in stage III gastric cancer. Knowledge of the clinical factors of patients may help clinicians identify and encourage specific patients to receive the adjuvant chemotherapy.

1. Introduction

Gastric cancer is the fourth most diagnosed cancer and the third leading cause of cancer-related deaths worldwide.[1,2] In Taiwan, gastric cancer is the ninth most common cancer and seventh leading cause of cancer-related death annually.[3] Radical surgery with extended lymph node (D2) dissection is the gold standard of curative treatment for patients with localized gastric cancer in Asian countries.[4] However, approximately 40% of patients with stage III gastric cancer experience tumor recurrence within 5 years after D2 dissection alone.[5,6] As a result, postoperative adjuvant chemotherapy is commonly recommended for patients with stage III disease based on the results of two large-scale meta-analyses conducted in 2009 and 2010.[7,8] Both studies concluded that adjuvant chemotherapy, regardless of the regimen of chemotherapy, results in significantly higher overall survival (OS) than observational treatment, with hazard ratios [HRs] in the range 0.78—0.82. Subsequently, two pivotal phase III studies demonstrated the clinical value of adjuvant chemotherapy in the treatment of gastric cancer. The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC study) phase III study in Japan first discovered significantly better outcomes of adjuvant chemotherapy in patients with stage II and III gastric cancer who had undergone D2 dissection.[9] The CLASSIC study from Korea, China, and Taiwan in 2012 also demonstrated that combination treatment with capecitabine and oxaliplatin in patients with stage II and III gastric cancer after D2 resection prolonged OS.[10] Nevertheless, radical surgery with extended lymph node D2 dissection followed by adjuvant chemotherapy has become the standard treatment for stage II and III gastric cancer in Taiwan,[11] and it has been included in the clinical guideline of the National Comprehensive Cancer Network for treating gastric cancer.[12]

Because of suboptimal survival outcome was observed in patients with stage III gastric cancer who did not receive adjuvant chemotherapy,[13] identification of the clinical characteristics of these patients may facilitate the identification of patient groups that might have the lowest likelihood to receive adjuvant chemotherapy. Furthermore, after identification, appropriate counseling can be provided to these patient groups before and after radical cancer surgery. Therefore, this study analyzed the clinical factors associated with patient propensity to receive adjuvant chemotherapy in patients with stage III gastric cancer after D2 surgery.

2. Material and methods

2.1. Patients and treatment

The records of 509 consecutive patients with stage III gastric cancer who had undergone radical gastrectomy and D2 lymph node dissection surgery between 2007 and 2014 at Linkou Chang Gung Memorial Hospital were analyzed retrospectively. The diagnoses of stage III disease were defined according to the 7th Edition American Joint Committee on Cancer (AJCC) staging system after pathological examination.[14] Patients were excluded from the study if they had recurrent tumors, metastatic tumors, or macroscopic residual tumors; had previously received chemotherapy or radiotherapy; died in hospital; or were completely bedridden after cancer surgery. The decision of whether the patients should undergo a total or subtotal gastrectomy was taken by the surgeon based on tumor location, tumor histology, and resection margin. All patients were advised to receive adjuvant chemotherapy within 6 weeks after radical surgery. However, the final decision of whether to undergo chemotherapy was taken by the doctor—patients discussion. Because no consensus regarding the standard regimen of chemotherapy was available during the study period, fluorouracil-based regimens were primarily used for adjuvant chemotherapy. The regimens were intravenous 5-fluorouracil (5-FU),[15] uracil-tegafur (UFT),[16] oral TS-1,[9] or oxaliplatin plus capecitabine (XELOX)[10] and were determined by the physician. Intravenous 5-FU or XELOX was administered for 6 months, whereas UFT or TS-1 was administered for up to 1 year. The patients were categorized into chemotherapy or nonchemotherapy arms based on whether they received adjuvant chemotherapy for ≥ 2 weeks or observational treatment following radical surgery. Patient characteristics were analyzed to identify the variables associated with adherence to adjuvant chemotherapy. This study was approved by the institutional review board in compliance with the Declaration of Helsinki (1996).

2.2. Data collection and follow-up

The administrative and clinical data of the patients included preoperative clinical features, such as age, sex, Eastern Cooperative Oncology Group performance (ECOG) grade, American Society of Anesthesiologists (ASA) class; history of previous cancer, preexisting comorbidities, stump cancer, family history of gastric cancer, body mass

index (BMI), carcinoembryonic antigen level, Cancer Antigen 19-9 level, operative method, and hospitalization from outpatient department or emergency room, as well as pathological findings including microscopic surgical margin, tumor grade, and tumor (T) and nodal (N) classification according to the 7th Edition AJCC staging system. Data were recorded by the primary care clinicians using an electronic patient record form at the time of cancer diagnosis, after cancer surgery, and after final pathological examination, if available. The comorbidities of the patients were recorded using the modified Charlson Comorbidity Index (CCI)[17] excluding patient age and diagnosis of cancer. The OS and DFS were calculated from the time of surgery to the time of death and tumor recurrence, respectively. The institutional cancer center registry or the National Register of Death Database in Taiwan provided the dates of surgery and tumor recurrence or date of death of each patient. All the included patients were followed up until their date of death or June 30, 2016.

2.3. Statistical analysis

Basic demographic data are summarized as n (%) for categorical variables and a median with a range or 95% confidence interval (CI) for continuous variables. The distribution of clinical variables is tabulated as n (%) and compared between groups using the Pearson chi-square test. Possible clinical factors associated with receiving adjuvant chemotherapy were examined using univariate and multivariate logistic regression. Variables with values of $p < 0.10$ in the univariate analysis were selected for analysis by using a multivariate model. Significant variables identified in the multivariate model were further analyzed using recursive partitioning analysis (RPA), which is a decision tree method for identifying specific groups of patients with higher probability of a specific outcome[18] and thus can be used to identify the appropriate patient classification for adjuvant chemotherapy adherence after cancer surgery. Survival time was analyzed using the Kaplan—Meier method. Log-rank tests were used to determine the significance of differences between the survival curves. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA), and a value of $p < 0.05$ was considered statistically significant.

3. Results

The patients' baseline demographic data are presented in Table 1. Of the 509 patients, 361 (70.9%) and 148 (29.1%) were categorized into the chemotherapy and nonchemotherapy groups, respectively. The patients in the nonchemotherapy group were generally older, exhibited a higher incidence of comorbidities, a higher percentage of admission from the emergency room, higher ECOG grades, and higher ASA classes than the chemotherapy patients. The other clinical and pathological variables did not differ significantly between the two patient groups. The significant differences between the chemotherapy and nonchemotherapy arms in demographic characteristics are summarized in Supplementary Figure.

Fig. 1 depicts the survival curve of patients in the overall cohort as well as those for the chemotherapy and nonchemotherapy arms. The median OS and DFS were 32.3 months (95% CI: 28.7—35.9) and 26.7 months (95% CI: 21.4—31.9), respectively, in the overall patient cohort; 35.6 months (95% CI: 29.9—41.3) and 32.4 months (95% CI: 22.4—42.6) for the chemotherapy patients; and 26.6 months (95% CI: 19.3—27.8) and 18.2 months (95% CI: 13.1—23.3) for the nonchemotherapy patients. The HR was 0.58 (95% CI: 0.46—0.74, $p < 0.001$) for OS and 0.64 (95% CI: 0.49—0.82, $p < 0.001$) for DFS when the chemotherapy and nonchemotherapy arms were compared.

The univariate and multivariate analyses of the clinical variables for predicting receipt of adjuvant chemotherapy after cancer surgery are presented in Table 2. The univariate analysis showed that the chemotherapy patients had a higher probability of being <70 years old (84.0% vs. 54.8%; odds ratio [OR]: 4.35; 95% CI: 2.86—6.67; $p < 0.001$), having a lower ECOG grade (ECOG scale 0 vs. ECOG grade 2—3: 81.6% vs. 53.8%; OR: 3.79; 95% CI: 2.19—6.56; $p < 0.001$; ECOG grade 1 vs. ECOG grade 2—3: 73.9% vs. 53.8%; OR: 2.43; 95% CI: 1.55—3.82; $p < 0.001$), being assigned ASA class 2 (82.0% vs. 60.6%; OR: 2.94; 95% CI: 1.96—4.55; $p < 0.001$), exhibiting lower CCIs (CCI 0 vs. CCI > 2: 73.8% vs. 48.3%; OR: 3.87; 95% CI: 1.76—8.54; $p = 0.001$; CCI 1 vs. CCI > 2: 68.6% vs. 48.3%; OR: 2.35; 95% CI: 1.06—5.21; $p = 0.036$), and being admitted via an outpatient department (74.1% vs. 61%; OR: 1.82; 95% CI: 1.19—2.78; $p = 0.005$) than did the nonchemotherapy patients. CCI and admission mode differences were nonsignificant, whereas age, ECOG grade, and ASA class were independent factors for predicting adherence to adjuvant chemotherapy in patients with stage III gastric cancer in the multivariate analysis.

The result of the RPA model is illustrated in Fig. 2. Patients were categorized into five groups ranging from the lowest (40.3%) to the highest (85.4%) probability of undergoing adjuvant chemotherapy based on the decision tree method. Patients who were aged >70 years, were assigned ASA class 3 or 4, and exhibited ECOG grades of 2—3 had the lowest probability of adjuvant chemotherapy adherence (defined as the reference group). The highest probability of adhering to adjuvant chemotherapy was observed among patients aged <70 years and with an ECOG grade of 0—1. Significant differences were observed between the reference group and other groups according to RPA, with ORs ranging from 1.75 to 8.86 (Supplementary Table).

Fig. 3 presents the HRs of OS and DFS comparing the chemotherapy and nonchemotherapy patients based on the probability groups derived from RPA. The differences in survival outcome did not differ significantly within the groups because of the small sample size and inhomogeneous distribution of patient numbers stratified by classification mode; however, the chemotherapy arm exhibited had better survival outcomes, with HRs in the range 0.53—0.75 for OS and 0.47—0.76 for DFS, than the nonchemotherapy arm, as determined in the subgroup analysis of five classification modes according to the results of RPA.

4. Discussion

Our study revealed that adjuvant chemotherapy was received by only 71% of the patients with stage III gastric cancer. Our results found that old age, high ECOG grade,

**Table 1** Basic demographic data of the patients.

Variable	Category	Overall, n = 509 (%)	Adjuvant chemotherapy arm, n = 361 (%)	No adjuvant chemotherapy arm, n = 148 (%)	p value
Sex	Male	328 (64.4)	238 (65.9)	90 (60.8)	0.72
	Female	181 (35.6)	123 (34.1)	58 (39.2)	
Age, year	Median, range	67 (18–97)	62.4 (18–95)	72.7 (30–97)	<0.001
BMI, Kg/m2	<18.5	62 (12.2)	42 (11.6)	20 (13.5)	0.81
	18.5–25	331 (65.0)	235 (65.1)	96 (64.9)	
	>25	116 (22.8)	84 (23.3)	32 (21.6)	
Stump cancer	Yes	25 (4.9)	19 (5.3)	6 (4.1)	0.57
Family history of gastric cancer	Yes	25 (4.9)	20 (5.5)	5 (3.4)	0.31
CCI	0	240 (47.2)	188 (52.1)	52 (35.1)	<0.001
	1	169 (33.2)	116 (32.1)	53 (35.8)	
	2	71 (13.9)	43 (11.9)	28 (18.9)	
	3	17 (3.3)	10 (2.8)	7 (4.7)	
	4	6 (1.2)	0 (0)	6 (4.1)	
	>4	6 (1.2)	4 (1.2)	2 (1.4)	
Admission mode	OPD	386 (75.8)	286 (79.2)	100 (67.6)	0.005
	ER	123 (24.2)	75 (20.8)	48 (32.4)	
AJCC stage	3A	126 (24.8)	94 (26.0)	32 (21.6)	0.57
	3B	171 (33.6)	119 (33.0)	52 (35.1)	
	3C	212 (41.7)	148 (41.0)	64 (43.2)	
T-classification	T2	17 (3.3)	11 (3.0)	6 (4.1)	0.57
	T3	167 (32.8)	123 (34.1)	44 (29.7)	
	T4	325 (63.9)	227 (62.9)	98 (66.2)	
N-classification	0	7 (1.4)	5 (1.4)	2 (1.4)	0.49
	1	51 (10.0)	38 (10.5)	13 (8.8)	
	2	136 (26.7)	99 (27.4)	37 (25.0)	
	3a	185 (36.3)	135 (37.4)	50 (33.8)	
	3b	130 (25.5)	84 (23.3)	46 (31.1)	
Tumor grade	Well	10 (2.0)	6 (1.7)	4 (2.7)	0.57
	Moderate	141 (27.7)	97 (26.9)	44 (29.7)	
	Poorly	358 (70.3)	258 (71.5)	100 (67.7)	
Gastrectomy method	TG	187 (36.7)	131 (36.3)	56 (37.8)	0.74
	STG	322 (63.3)	230 (63.7)	92 (62.2)	
CEA, ng/dL	≤5	424 (83.3)	304 (84.2)	120 (81.1)	0.39
	>5	85 (16.7)	57 (15.8)	28 (18.9)	
CA19-9, ng/dL	≤37	428 (84.1)	308 (85.3)	120 (81.1)	0.24
	>37	81 (15.9)	53 (14.7)	28 (18.9)	
ECOG scale	0	141 (27.7)	115 (31.9)	26 (17.6)	<0.001
	1	238 (46.8)	176 (48.8)	62 (41.9)	
	2	102 (20.0)	60 (16.6)	42 (28.4)	
	3	28 (5.5)	10 (2.8)	18 (12.2)	
ASA class	2	245 (48.1)	201 (55.7)	44 (29.7)	<0.001
	3	258 (50.7)	159 (44.0)	99 (66.9)	
	4	6 (1.2)	1 (0.3)	5 (3.4)	
Surgical margin	Positive	67 (13.2)	43 (11.9)	24 (16.2)	0.19
	Negative	442 (86.8)	318 (88.1)	124 (83.8)	

BMI, body mass index; CCI, Charlson Comorbidity Index; OPD, outpatient department; ER, emergency room; AJCC, American Joint Committee on Cancer; TG, total gastrectomy; STG, subtotal gastrectomy; CEA, carcinoembryonic antigen; CA19-9, Cancer Antigen 19-9; ECOG, Eastern Cooperative Oncology Group; and ASA, American Society of Anesthesiologists.

and high ASA class were the independent clinical characteristics more predominantly observed among the non-chemotherapy patients compared with the chemotherapy patients. Finally, we discovered that adjuvant chemotherapy improved OS and DFS across broad categories—including those patients who were older (>70 years), had high ECOG grade, and were assigned a high ASA class—of stage III gastric cancer patients after D2 surgery.

Our previous study identified adjuvant chemotherapy as an independent prognostic factor that predicted OS and
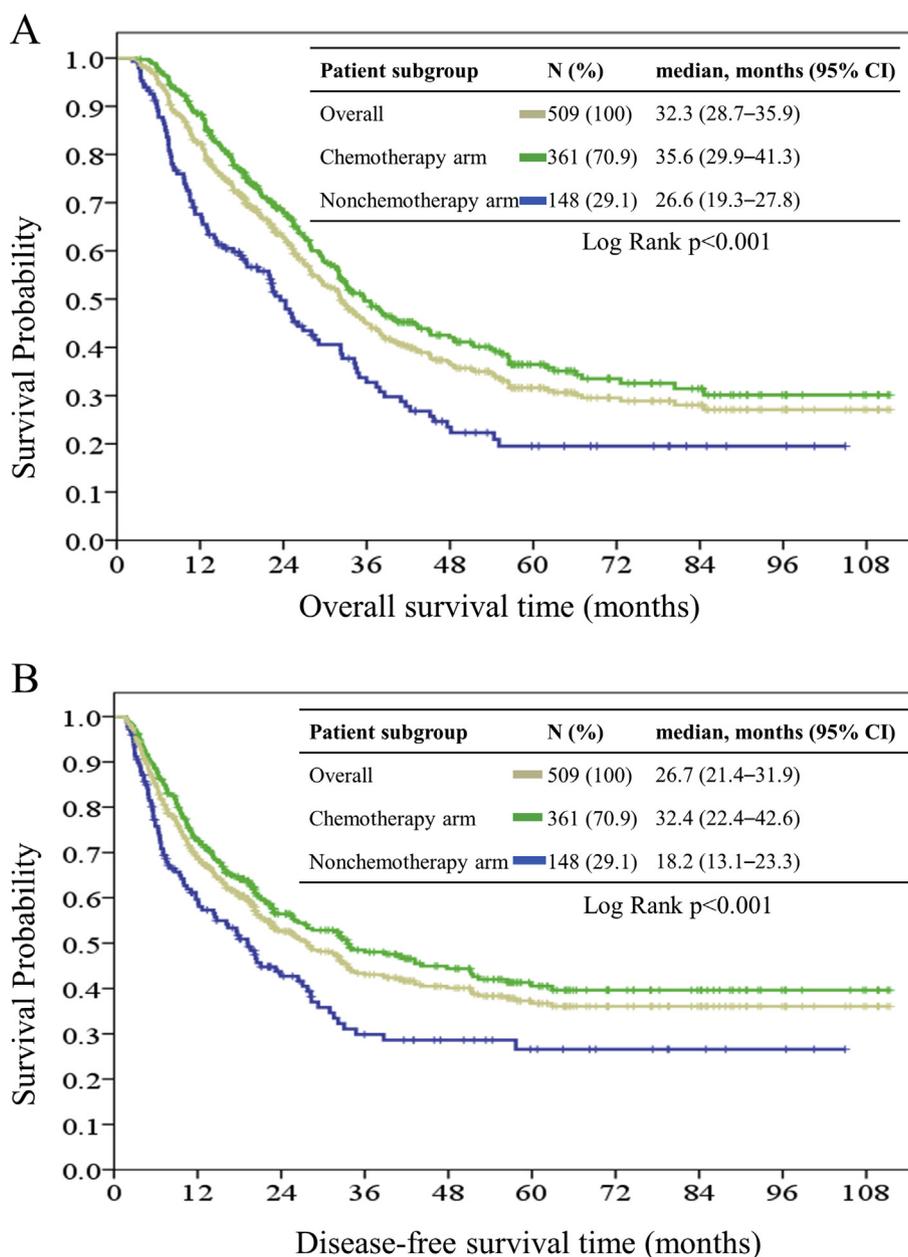
Figure 1 Kaplan—Meier OS curves (A) and DFS curves (B) for all the patients (overall), the chemotherapy patients, and the nonchemotherapy patients.

disease-free survival (DFS) in 534 patients with stage III gastric cancer; however, adjuvant chemotherapy was applied only in 68.4% of the patients after D2 dissection.[13] The Taiwan Cancer Registry database also showed that only 71% of patients with stage III gastric cancer underwent adjuvant chemotherapy after cancer surgery in a nationwide survey conducted in 2015.[3] The patients aged >70 years had a relatively low probability of adhering to adjuvant chemotherapy in our study. Age was the first key factor for predicting whether patients had received adjuvant chemotherapy according to RPA. Old age is frequently associated with an increase in the prevalence of frailty, comorbidities, decline of physical performance, and organ reserves; therefore, aging is a well-known negative prognostic factor for patients after cancer surgery.[19,20] The age

of populations and cancer incidence are increasing globally; hence, more geriatric patients with gastric cancer should be referred for surgical management followed by adjuvant chemotherapy.[21] For example, the median age at diagnosis of gastric cancer was 69 years in the United States in 2014[2] and 70 years in Taiwan in 2015[3]; this indicates that half of the patients who undergo gastric cancer treatment are aged >70 years. Excessive concern regarding the ability of geriatric patients to tolerate antitumor treatment may increase the vulnerability of such patients to receiving suboptimal treatments and may compromise their survival outcomes.[22] An increasing number of studies are reporting that although elderly patients may exhibit a higher postoperative morbidity rate than their younger counterparts, mortality rates are comparable between the two age

Table 2 Univariate and multivariate analyses of the clinical variables associated with adherence to adjuvant chemotherapy among patients with stage III gastric cancer after D2 extended lymph node (D2) dissection.

Variable	Category	No. of patients receiving adjuvant chemotherapy/no. of total patients (%)	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Age, year	≥70	125/228 (54.8)	1		1	
	<70	236/281 (84.0)	4.35 (2.86−6.67)	<0.001	2.91 (1.85−4.56)	<0.001
ECOG scale	2−3	70/130 (53.8)	1		1	
	1	176/238 (73.9)	2.43 (1.55−3.82)	<0.001	1.68 (1.01−2.80)	0.049
	0	115/141 (81.6)	3.79 (2.19−6.56)	<0.001	2.18 (1.19−4.01)	0.012
ASA class	3−4	160/264 (60.6)	1		1	
	2	201/245 (82.0)	2.94 (1.96−4.55)	<0.001	1.64 (1.02−2.62)	0.041
CCI	>2	14/29 (48.3)	1		1	
	2	43/71 (60.6)	1.65 (0.69−3.93)	0.262	1.46 (0.62−3.45)	0.38
	1	116/169 (68.6)	2.35 (1.06−5.21)	0.036	1.51 (0.60−3.80)	0.38
	0	188/240 (78.3)	3.87 (1.76−8.54)	0.001	1.59 (0.64−3.84)	0.31
Admission mode	ER	75/123 (61.0)	1		1	
	OPD	286/386 (74.1)	1.82 (1.19−2.78)	0.005	1.34 (0.85−2.15)	0.20
Sex	Female	123/181 (68.0)	1			
	Male	238/328 (72.6)	1.25 (0.84−1.85)	0.27		
BMI, Kg/m2	>25	84/116 (72.4)	1			
	<18.5	42/62 (67.7)	1.17 (0.65−2.08)	0.61		
	18.5−25	235/331 (71.0)	1.25 (0.64−2.44)	0.51		
Stump cancer	No	342/484 (70.7)	1			
	Yes	19/25 (76.0)	1.32 (0.51−3.36)	0.57		
Family history of gastric cancer	No	341/484 (705)	1			
	Yes	20/25 (80.0)	1.67 (0.20−4.56)	0.31		
AJCC stage	3A	94/126 (74.6)	1			
	3B	119/171 (69.6)	0.78 (0.46−1.31)	0.34		
	3C	148/212 (69.8)	0.79 (0.48−1.29)	0.35		
T-classification	T2	11/17 (64.7)	1			
	T3	123/167 (73.7)	1.53 (0.53−4.37)	0.43		
	T4	227/325 (69.8)	1.26 (0.45−3.51)	0.65		
N-classification	0	5/7 (71.4)	1			
	1	38/51 (74.5)	1.17 (0.20−6.77)	0.86		
	2	99/136 (72.8)	1.07 (0.20−5.76)	0.94		
	3a	135/185 (73.0)	1.08 (0.20−5.75)	0.93		
	3b	84/130 (64.6)	0.73 (0.14−3.91)	0.71		
Tumor grade	Well	6/10 (0.60)	1			
	Moderate	97/141 (68.8)	1.47 (0.40−5.47)	0.57		
	Poorly	258/358 (72.1)	1.72 (0.48−6.22)	0.41		
Gastrectomy method	TG	131/187 (70.1)	1			
	STG	230/332 (71.4)	1.07 (0.72−1.59)	0.74		
CEA, ng/dL	≤5	304/424 (71.7)	1			
	>5	57/85 (67.1)	0.80 (0.49−1.32)	0.39		
CA19-9, ng/dL	≤37	308/428 (72.0)	1			
	>37	53/81 (65.4)	0.74 (0.45−1.22)	0.24		
Surgical margin	Negative	318/442 (71.9)	1			
	Positive	43/67 (64.2)	0.70 (0.41−1.20)	0.19		

ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists; CCI, Charlson comorbidity index; OPD, outpatient department; ER, emergency room; BMI, body mass index; AJCC, American Joint Committee on Cancer; TG, total gastrectomy; STG, subtotal gastrectomy; CEA, carcinoembryonic antigen; CA19-9, Cancer Antigen 19-9.

groups.[23] If the surgical treatment is selected appropriately, the long-term outcomes appear similar for old and young patients.[23,19]

In the ACTS-GC study, patients aged >70 years accounted for 24% (247 of 1034 patients) of all the study patients.[9]

Moreover, no upper age limit was specified for inclusion of a patient in the CLASSIC study.[10] The HRs were 0.78 (95% CI: 0.53−1.15) for OS and 0.71 (95% CI: 0.3−1.02) in the ACTS-GC study[9] and 0.70 (95% CI: 0.44−1.12) for OS and 0.51 (95% CI: 0.42−0.71) for DFS in the CLASSIC study[24]; these data
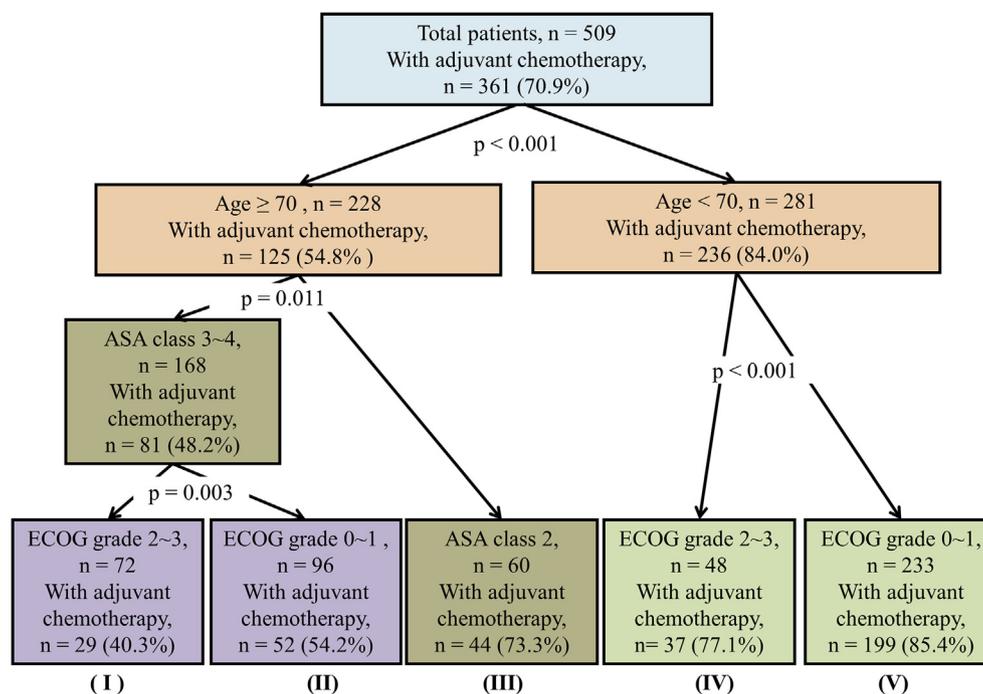
Figure 2 RPA of all patients (n = 509). The classification mode used for univariate logistic regression analysis in Supplementary Table is presented as numbers below the nodes of the decision tree.

indicate the relatively high treatment efficacy of adjuvant chemotherapy in subgroup analysis for patients aged >65 or >70 years. Therefore, old age is neither the only nor the most reliable clinical factor determining adherence to adjuvant chemotherapy in patients with gastric cancer. Adjuvant chemotherapy can be considered with care for elder patients with adequate functional reserve and physical performance after D2 lymph node dissection.

In addition to age, our study also discovered that ECOG grade and ASA class were independent factors predicting probability of adherence to adjuvant chemotherapy. Both factors are commonly used to assess a patient's physical fitness in oncological practice.[25,26] One recent study compared the performance of ECOG grade and ASA class in predicting length of hospital stay after surgery for colon cancer; the predictive values of both the factors were similar. Most importantly, the predictive performance when both factors were used simultaneously was higher than that when either factor was used singly.[27] In our study, we showed that using the age, ECOG grade, and ASA class of the patients simultaneously, as in the model developed using RPA classification, enabled identification of the characteristics of patients with the highest probability (85.4%) of adherence to adjuvant chemotherapy after cancer surgery. Furthermore, the RPA model identified a small subset of patients (72 of 509 patients, 14.1%)—who were aged >70 years, were assigned ASA class 3–4, and had an ECOG grade of 2–3—that had the lowest probability (40.3%) of adherence to adjuvant chemotherapy. The frailest patients who had the lowest probability of adherence to adjuvant chemotherapy after cancer surgery in our study also experienced a survival benefit after receiving adjuvant chemotherapy compared with those who did not receive the therapy.

Two clinical factors did not differ significantly between the chemotherapy and nonchemotherapy patients; hence, the roles of these factors in predicting the probability of adherence to adjuvant chemotherapy warrants further discussion. First, the incidence of comorbidities indicates the presence of an additional medical illness and is often associated with a decline in functional reserves as well as an increase in frailty. Patients with comorbidities are more likely to exhibit poor adherence to adjuvant treatments in bladder,[28] lung,[29] and colorectal cancer[30] than are patients without comorbidities. Mayr et al compared the performance of CCI and ASA class in predicting postoperative 90-day mortality in patients with bladder cancer; ASA class exhibited a superior predictive ability to CCI.[31] In our study, patients without comorbidities had significantly higher probability of adherence to adjuvant chemotherapy than did those with high numbers of comorbidities in the univariate analysis. The difference was statistically nonsignificant in the multivariate analysis because the patients with higher comorbidities were more likely to be old, have a high ECOG grade, and have a high ASA class.[32] Second, our previous report demonstrated that total gastrectomy increased the probability of toxicity after adjuvant chemotherapy with TS-1.[33] Furthermore, total gastrectomy might affect the survival benefit by increasing the postoperative mortality risk and causing a larger reduction in functional reserve than that caused by subtotal gastrectomy.[34] The probability of adherence to adjuvant chemotherapy in patients who received total gastrectomy and in those who received subtotal gastrectomy was comparable (70.1% and 71.4%, respectively) in our study. This result suggested that the toxicity related to surgical extent or treatment is not the major concern while providing adjuvant chemotherapy in clinical practice.
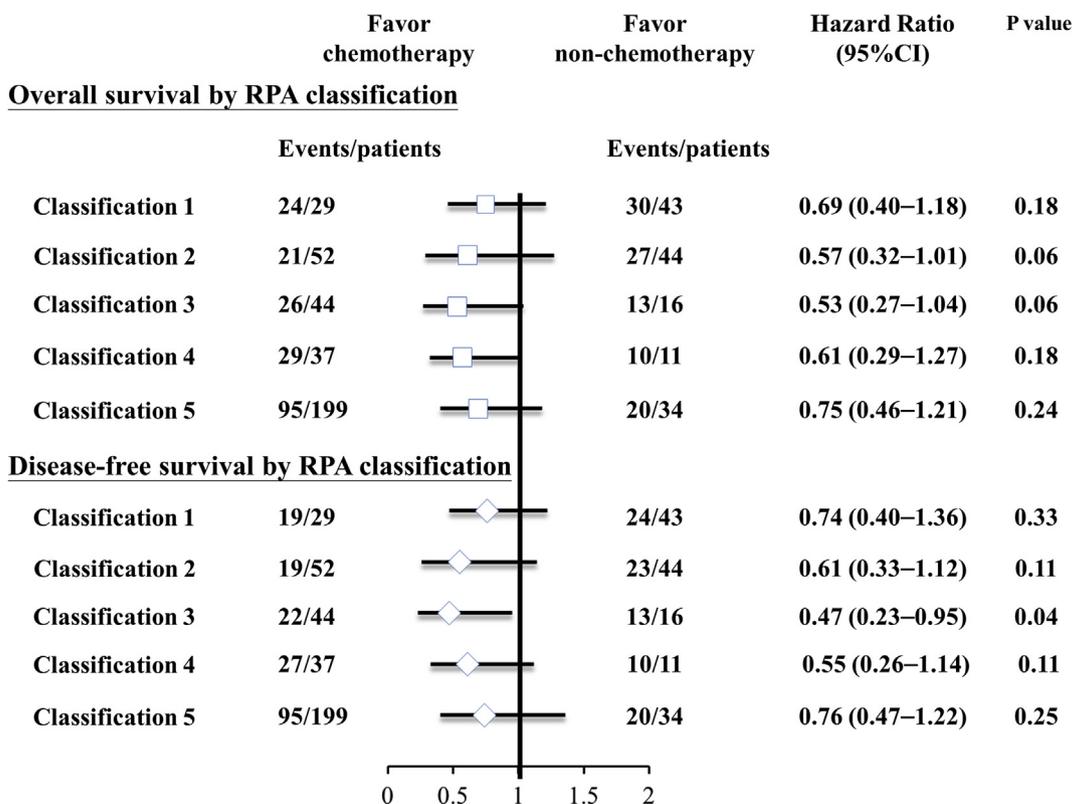
	Favor chemotherapy			Favor non-chemotherapy	Hazard Ratio (95%CI)	P value
Overall survival by RPA classification						
	Events/patients			Events/patients		
Classification 1	24/29			30/43	0.69 (0.40–1.18)	0.18
Classification 2	21/52			27/44	0.57 (0.32–1.01)	0.06
Classification 3	26/44			13/16	0.53 (0.27–1.04)	0.06
Classification 4	29/37			10/11	0.61 (0.29–1.27)	0.18
Classification 5	95/199			20/34	0.75 (0.46–1.21)	0.24
Disease-free survival by RPA classification						
Classification 1	19/29			24/43	0.74 (0.40–1.36)	0.33
Classification 2	19/52			23/44	0.61 (0.33–1.12)	0.11
Classification 3	22/44			13/16	0.47 (0.23–0.95)	0.04
Classification 4	27/37			10/11	0.55 (0.26–1.14)	0.11
Classification 5	95/199			20/34	0.76 (0.47–1.22)	0.25

0   0.5   1   1.5   2

Figure 3   HRs of OS and DFS in the chemotherapy and nonchemotherapy patients based on RPA classification mode.

Based on a prospectively formulated electronic record, our study identified several independent clinical factors for predicting probability of adherence to adjuvant chemotherapy in patients with stage III gastric cancer after D2 dissection. We also observed better survival outcomes in chemotherapy than in nonchemotherapy patients regardless of the differences in the patients' clinical characteristics. We believe that these results may inform clinicians regarding the characteristics of patients who have a low probability of adherence to adjuvant chemotherapy in stage III gastric cancer. Clinicians can encourage these patients to receive the treatment. However, our study had several limitations. First, although this was a retrospective study, which analyzed data of 8 years of practice, the concept of providing adjuvant chemotherapy and adherence to it may have varied before the availability of the positive results from the two phase III studies (ACTS-GC and CLASSIC trial) that were conducted during our study period.[9,10] Second, several regimens of chemotherapy were included for analysis in our study because no consensus on the standard regimen of adjuvant chemotherapy in stage III gastric cancer is currently available. A physician's preference, availability of the regimen, patient's financial support, and postoperative fitness are all factors contributing to selection bias in the decision of whether to receive adjuvant chemotherapy. Third, all the clinical variables were recorded preoperatively; therefore, the ECOG grade and ASA class in our analysis did not represent the patients' postoperative conditions. Fourth, the decision of nonadherence to adjuvant chemotherapy was sometimes attributable to personal factors, and these factors varied among patients as well as according to the doctors' judgment. In this study, we could not analyze all the reasons underlying the decisions of patients who refused adjuvant chemotherapy. Finally, the differences in survival outcome were statistically nonsignificant, which may mainly be due to the few patients in the subgroup analysis using RPA. The benefit of adjuvant chemotherapy on survival outcome for geriatric patients with high ECOG grades and high ASA class remained uncertain. Therefore, conducting a prospective study for analyzing these issues would be preferable.

5. Conclusion

Our study identified that age, ECOG grade, and ASA class were independent clinical factors associated with patient propensity to receive adjuvant chemotherapy in stage III gastric cancer. We showed that adjuvant chemotherapy improved survival outcomes across broad categories—including those patients who were older (>70 years), had high ECOG grade, and were assigned a high ASA class—of stage III gastric cancer patients. Knowledge of the clinical factors of patients may help clinicians identify and encourage specific patients to receive the adjuvant chemotherapy.

Conflict of interest

The authors declare that no competing interests exist.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.08.001.

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