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Surgical resection for stage IV gastric cancer: Real-world insights with a focus on elderly patients (OGSG2301)

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ABSTRACT

Background: The introduction of molecular-targeted drugs and immune checkpoint inhibitors has improved survival in patients with stage IV gastric cancer (GC). However, the role of surgical resection for stage IV GC remains unclear, particularly in elderly patients.

Methods: This study retrospectively analyzed 376 patients with stage IV GC treated with chemotherapy across 36 institutions in 2022. We focused on differences between the elderly (≥75 years, n = 126) and non-elderly (<75 years, n = 250) groups. The surgical resection rate was the main outcome of interest; outcomes included adverse events, objective response rates (ORRs), postoperative complications, and overall survival (OS).

Results: Although the elderly group demonstrated a significantly higher adverse events (grade 3 or higher) than the non-elderly group (39.7% vs 26.8%, p = 0.013), ORRs were comparable between groups. Surgical resection rates were 12.7% and 20.4% in the elderly and non-elderly groups, respectively (p = 0.086). The elderly group exhibited more frequent postoperative complications but without significant differences (31.2% vs. 17.6%, p = 0.295). The incidence of postoperative pneumonia was higher in the elderly group (25.0% vs 2.0%). No mortality across all surgical cases was observed. Among resected cases, the 2-year OS rate was 87.5% in the elderly group and 82.2% in the non-elderly group (p = 0.741). Regarding unresected cases, the 2-year OS rates were 21.5% vs 28.4%, respectively (p = 0.112).

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Conclusions: Surgical resection after systemic chemotherapy was considered an acceptable option for selected elderly patients with stage IV GC, despite the increased risk of postoperative pneumonia.

1. Introduction

Gastric cancer (GC) represents one of the most common malignancies and the fourth leading cause of cancer-related death worldwide [1]. Although surgery remains the mainstay of treatment, systemic chemotherapy is the gold standard treatment for stage IV GC. Surgical resection following chemotherapy has recently gained traction as an optional treatment for stage IV GC.

Molecular-targeted drugs and/or immune checkpoint inhibitors (ICIs), in combination with cytotoxic chemotherapy, have been adopted as standard treatment for stage IV GC [2–5]. The addition of molecular-targeted drugs and/or ICI improves response rates by approximately 10% compared with chemotherapy alone [2–5]. As an association between post-chemotherapy R0 resection and favorable survival outcomes is well recognized [6,7], it is anticipated that improved response rates achieved with the addition of molecular-targeted drug and/or ICI may contribute to an increased likelihood of surgical resection in selected patients.

On the other hand, the Japanese population is rapidly aging, a trend that can also be observed in several countries. Elderly patients are generally less likely to continue chemotherapy for an extended period. This, in turn, suggests that surgical resection could occasionally be even more beneficial for elderly patients. However, no study has specially examined surgical resection in elderly patients, particularly in the era of molecular-targeted and ICI-based treatments. Therefore, investigating the current status regarding surgical resection in elderly patients with stage IV GC is crucial.

In this context, we planned a multi-institutional observational study for stage IV GC. This study mainly aimed to compare treatment courses and outcomes between elderly and non-elderly patients, as well as between resected and unresected cases. Finally, 36 institutions in the Osaka Gastrointestinal Chemotherapy Study Group (OGSG) agreed to participate in this study, and we have completed data collection for all patients with stage IV GC as real-world evidence.

2. Methods

We included patients who met the following criteria:

(1) Histologically confirmed gastric adenocarcinoma (including all common histological subtypes) [8].
(2) A diagnosis of stage IV GC
(3) Initiation of chemotherapy between January 1 and December 31, 2022

Thirty-six institutions in the OGSG agreed to participate in this study. Accordingly, data from 376 patients were collected. Clinicopathological data were collected using a web-based electronic medical record system (REDCAP). The Human Ethics Review Committee of Osaka Metropolitan University approved this retrospective study (approval number: 2024-45). Informed consent was waived, and an opt-out procedure was implemented.

The parameters collected in this study were listed in the supplementary method file.

2.1. Definitions

Macroscopic type, cStage, and pathological response were determined according to the Japanese Gastric Cancer Association classification (third English edition) [9]. Lymph node (LN) dissection was defined according to the Japanese GC Treatment Guideline (sixth edition). We defined elderly patients as those aged ≥75 years, in accordance with the age threshold used in the Japanese national health-care insurance system. Postoperative complications were graded on the basis of the Clavien–Dindo classification [10]. Adverse events of chemotherapy were assessed according to the Common Terminology Criteria for Adverse Events (v. 5.0).

Stage IV disease was stratified according to the classification proposed by Yoshida et al. (Supplementary method file) [11].

2.2. Statistical analysis

We compared the outcomes between the elderly (≥75 years old) and non-elderly groups (<75 years old), specifically focusing on the characteristics of the elderly population.

Background characteristics were presented as medians and ranges, whereas operative variables (operative time and blood loss) were expressed as medians and interquartile ranges. Categorical variables were presented as frequencies and proportions. Binary outcomes were evaluated using odds ratios (ORs) and 95% confidence intervals (CIs) and compared using Fisher's exact test.

The surgical resection rate following chemotherapy among patients with stage IV GC was the main outcome of interest. All surgical resections included in this study were performed with curative intent. This rate was further evaluated according to Yoshida's classification, response status, dose reduction, ICI treatment (HER2 negative cases), and Trastuzumab treatment (HER2 positive cases). Moreover, we evaluated the presence or absence of timing for surgery solely by imaging diagnosis regardless of the patient's condition or age. Central monitoring was not performed, and operability was assessed by the attending physician or surgeon at the time of follow-up CT evaluation, without reference to predefined objective criteria. Multivariate logistic regression analyses were performed to adjust for potential confounding factors (age, sex, PS, albumin, histological type, macroscopic type, dose reduction, and Yoshida's classification) related to the surgical rate. A forced entry model using all factors was first constructed as a primary analysis, and a second model was developed using backward stepwise variable selection based on Akaike information criterion (AIC) as a supplementary exploratory analysis.

Dose reduction, adverse events, objective response rates (ORRs), R0 resection rate, postoperative complications, and overall survival (OS) were other evaluated outcomes.

OS was defined as the period from the date of chemotherapy initiation to the date of death due to any cause. The estimated survival curve for OS was calculated using the Kaplan–Meier method, and the 95% CI was calculated using Greenwood's formula. The log-rank test was employed for comparing survival curves between the elderly and non-elderly groups in both resected and unresected cases. Furthermore, survival analyses were conducted to compare the elderly and non-elderly groups, stratified by the following factors: Yoshida's classification category 1 or categories 2–4, response status, dose reduction, ICI treatment (HER2 negative cases), and Trastuzumab treatment (HER2 positive cases). Multivariate analysis using Cox hazard model was performed for adjusting potential confounding factors (PS and histological type) regarding survival.

All statistical analyses were performed using R version 4.4.0 (The R Foundation for Statistical Computing, Vienna, Austria). *P*-values of <0.05 were considered statistically significant, and all tests were two-sided.

3. Results

3.1. Patients' characteristics

The baseline patients' characteristics are presented in Table 1. Among the 376 patients, the number of elderly patients (≥75y.o.) and non-elderly patients (<75y.o.) was 126 and 250, respectively.

3.2. Chemotherapy related data

The regimens used for first-line chemotherapy are shown in Supplementary Table 1. Overall, the most frequently employed regimen was S-1 + oxaliplatin + nivolumab (SOX + Nivo), which was performed in 47.6% and 57.6% of the patients in the elderly and no-elderly groups, respectively. Among HER2-negative cases, Nivo was used in 69.2% (74/107) and 81.8% (171/209) of those in the elderly and non-elderly groups, respectively, showing a statistically significant difference ($p = 0.015$). Conversely, among HER2-positive cases, trastuzumab was used in 89.5% (17/19) and 82.9% (34/41) of those in the elderly and non-elderly groups, respectively, revealing no significant difference ($p = 0.71$). The percentage of adverse events (grade 3 or higher) was significantly higher in the elderly group (39.7%, 50/126) than that in the non-elderly group (26.8%, 67/250) ($p = 0.013$). The details of adverse events are shown in Supplementary Table 2. The elderly group (54.8%, 69/126) exhibited a significantly more frequent dose reduction at treatment initiation than the non-elderly group (27.6%, 69/250) ($p < 0.001$). The chemotherapy regimens and treatment responses following second-line therapy are summarized in Supplementary Table 3A and 3B The ORRs and disease control rates were not significantly different between groups (Supplementary Table 4).

3.3. Surgical resection rate

Patients were judged as operable by imaging diagnosis in 17.5% (22/126) and 24.8% (62/250) of the elderly and non-elderly groups, respectively (Table 2).

Overall, the surgical resection rate of the patients in the elderly group was 12.7% (16/126, 95% CI, 7.4%–19.8%), whereas that in the non-elderly group was 20.4% (51/250, 95% CI, 15.6%–25.9%). Although a trend toward a higher surgical resection rate was observed in the non-elderly group, the difference was not statistically significant (OR, 0.568 [95% CI, 0.288–1.071], $p = 0.086$).

In the analysis based on Yoshida's classification, patients with category 1, which is deemed initially resectable stage IV disease, demonstrated the highest resection rate in both groups: 40.0% (8/20) and 45.9% (17/37) in the elderly and non-elderly groups, respectively. The surgical resection rate of the elderly group was significantly lower than that of the non-elderly group in category 3, which is considered peritoneal dissemination disease (3.0% [1/33] vs. 18.9% [14/74], $p = 0.034$; Table 2).

Among patients classified as Yoshida's classification categories 2–4, which are considered initially unresectable disease and therefore represent the conventional population eligible for conversion surgery, the conversion surgery rate was 13.2% (42/318). The elderly group exhibited a significantly lower conversion surgery rate than the non-elderly group (7.5% [8/106] vs. 15.9% [34/213], $p = 0.036$).

Finally, multivariate analysis was conducted to adjust for confounding factors, including Yoshida's classification, related to resection rates (Table 3). Forced entry model revealed albumin level and Yoshida's classification as significant factors. The analysis using backward stepwise regression showed that PS, albumin level, and Yoshida's classification were significant factors associated with surgical resection. In both multivariate analyses, age was not identified as a significant factor.

Table 1
Comparison of pretreatment characteristics between the elderly and non-elderly groups.

	Elderly (n = 126)	Non-elderly (n = 250)
Baseline characteristics		
Sex		
Male	94 (74.6%)	163 (65.2%)
Female	32 (25.4%)	87 (34.8%)
Age (years)	79 (75–90)	67 (26–74)
Body mass index (kg/m^2)	20.8 (15.0–31.1)	21.3 (11.6–33.0)
PS		
0	54 (42.9%)	143 (57.2%)
1	61 (48.4%)	88 (35.2%)
2	9 (7.1%)	16 (6.4%)
3	2 (1.6%)	3 (1.2%)
Cardiovascular disease		
Present	19 (15.1%)	25 (10.0%)
Absent	107 (84.9%)	225 (90.0%)
Cerebrovascular disease		
Present	14 (11.1%)	10 (4.0%)
Absent	112 (88.9%)	240 (96.0%)
Diabetes mellitus		
Present	30 (23.8%)	30 (12.0%)
Absent	96 (76.2%)	220 (88.0%)
Pulmonary disease		
Present	13 (10.3%)	14 (5.6%)
Absent	113 (89.7%)	236 (94.4%)
Renal dysfunction		
Present	15 (11.9%)	14 (5.6%)
Absent	111 (88.1%)	236 (94.4%)
Tumor-related characteristics		
Tumor Location		
L	46 (36.5)	71 (28.4)
M	46 (36.5)	102 (40.8)
U	27 (21.4%)	53 (21.2%)
EGJ	7 (5.6%)	24 (9.6%)
Esophageal invasion		
Absent	111 (88.1%)	214 (85.6%)
Present	15 (11.9%)	35 (14.0%)
Unknown	0 (0.0%)	1 (0.4%)
Duodenal invasion		
Absent	111 (88.1%)	228 (91.2%)
Present	12 (9.5%)	18 (7.2%)
Unknown	3 (2.4%)	4 (1.6%)
Invasion to a greater curvature		
Absent	93 (73.8)	189 (75.6)
Present	33 (26.2)	55 (22.0)
Unknown	0 (0.0%)	6 (2.4%)
HER2 status		
0	58 (46.0)	131 (52.4%)
1	29 (23.0)	60 (24.0%)
2 (ISH−)	11 (8.7%)	13 (5.2%)
2 (ISH+)	6 (4.8%)	19 (7.6%)
3	13 (10.3%)	22 (8.8%)
Unknown	9 (7.1%)	5 (2.0%)
PD-L1 CPS		
<1	6 (4.8%)	31 (12.4%)
1–5	25 (19.8%)	62 (24.8%)
≥5	33 (26.2%)	67 (26.8%)
unknown	62 (49.2%)	90 (36.0%)
Macroscopic type		
1- IIa	0 (0.0%)	1 (0.4%)
1- IIc	5 (4.0%)	2 (0.8)
1- III	1 (0.8%)	0 (0.0%)
1	4 (3.2%)	4 (1.6%)
2	38 (30.2%)	52 (20.8%)
3	53 (42.1%)	116 (46.4%)
4	24 (19.0%)	73 (29.2%)
5	1 (0.8%)	2 (0.8%)
Histological type		
tub	69 (54.8%)	99 (39.6%)
por	47 (37.3%)	119 (47.6%)
sig	6 (4.8%)	26 (10.4%)
muc	1 (0.8%)	1 (0.4%)
Others	3 (2.4%)	5 (2.0%)
cT		
1	2 (0.8%)	2 (0.8%)

(continued on next page)

Table 1 (*continued*)

	Elderly (n = 126)	Non-elderly (n = 250)
2	8 (6.3%)	4 (1.6%)
3	22 (17.5%)	47 (18.8%)
4	83 (65.9%)	174 (69.6%)
x	2 (1.6%)	6 (2.4%)
cN		
0	23 (18.3%)	33 (13.2%)
1	26 (20.6%)	52 (20.8%)
2	34 (27.0%)	72 (28.8%)
3	41 (32.5%)	84 (33.6%)
x	2 (1.6%)	9 (3.6%)
Yoshida's classification		
1	20 (15.9%)	37 (14.8%)
2	35 (27.8%)	70 (28.0%)
3	33 (26.2%)	74 (29.6%)
4	38 (30.2%)	69 (27.6%)
Liver metastasis		
Absent	82 (65.1%)	193 (77.2%)
Present	44 (34.9%)	57 (22.8%)
Peritoneal metastasis		
Absent	71 (56.3%)	119 (47.6%)
Present	55 (43.7%)	131 (52.4%)
Distant lymph node metastasis		
Absent	79 (62.7%)	153 (61.2%)
Present	47 (37.3%)	97 (38.8%)
Pretreatment blood tests		
Lymphocyte (cells/μL)	1360 (18.8–6415)	1370 (12.0–5905)
ALB (g/dL)	3.3 (1.7–4.5)	3.6 (1.8–5.1)
CRP (mg/dL)	0.52 (0.015–26.0)	0.51 (0.01–24.1)
CEA (ng/mL)	5.8 (0.50–5863)	4.0 (0.40–27,967)
CA19-9 (U/mL)	27.0 (1.2–50,407)	18.0 (0.40–257,663)

Values are presented as numbers (percentages) or medians (ranges).
Abbreviations: *PS*, performance status; *L*, lower third; *M*, middle third; *U*, upper third; *EGJ*, esophagogastric junction; *ISH*, in situ hybridization; *CPS*, combined positive score; *tub*, tubular adenocarcinoma; *por*, poorly differentiated adenocarcinoma; *sig*, signet ring cell carcinoma; *muc*, mucinous adenocarcinoma; *ALB*, albumin; *CRP*, C-reactive protein; *CEA*, carcinoembryonic antigen; *CA19-9*, carbohydrate antigen 19-9.

Table 2
Differences in resectability and resection rate between the elderly and non-elderly groupsStructured

	Elderly	Non-elderly	P-value
Percentage of patients judged as operable based on imaging diagnosis[a]	22/126 (17.5%)	62/250 (24.8%)	0.12
Total number of patients receiving surgical resection	16/126 (12.7%) [7.4%–19.8%]	51/250 (20.4%) [15.6%–25.9%]	0.086
Surgical resection rate depending on Yoshida's classification			
Category 1	8/20 (40.0%) [19.1%–63.9%]	17/37 (45.9%) [29.5%–63.1%]	0.782
Category 2	5/35 (14.3%) [4.8%–30.3%]	16/70 (22.9%) [13.7%–34.4%]	0.438
Category 3	1/33 (3.0%) [0.1%–15.8%]	14/74 (18.9%) [10.7%–29.7%]	0.034
Category 4	2/38 (5.3%) [0.6%–17.7%]	4/69 (5.8%) [1.6%–14.2%]	1.00

Values in parentheses indicate percentages, and values in brackets represent 95% confidence intervals (95% CI).Structured.

[a] Surgeon's judgment by imaging data. Among these patients, six in the elderly group and 11 in the non-elderly group did not undergo surgical resection. In the elderly group, the reasons were patient refusal (n = 2), physician's decision (n = 2), immune-related adverse events (n = 1), and reduced cardiac function (n = 1). In the non-elderly group, the reasons were patient refusal (n = 4), physician's decision (n = 3), other reasons (n = 3), and interstitial pneumonia (n = 1).Structured.

Table 3
Multivariate analysis using logistic regression model regarding surgical resection rate.

variables	Multivariate analysis (Forced entry model)		Backward stepwise regression based on AIC	
	OR [95% CI]	*P*-value	OR [95% CI]	*P*-value
Age (Elderly/Non-elderly)	0.619 [0.306-1.201]	0.167	-	
Sex (M/F)	1.327 [0.708–2.572]	0.387	-	
PS (0/1-3)	1.739 [0.956-3.231]	0.073	1.825 [1.009-3.375]	0.049
Alb (≥3.5/<3.5)	2.140 [1.167-4.034]	0.015	2.283 [1.260-4.255]	0.007
Histological type (intestinal/diffuse)	1.165 [0.639-2.115]	0.614	-	
Macroscopic type (0-2/3-5)	1.129 [0.587-2.121]	0.710	-	
Dose reduction (With/Without)	0.637 [0.350-1.173]	0.142	0.593 [0.329-1.082]	0.084
Yoshida classification (Category 1/2-4)	4.940 [2.557-9.584]	<0.001	4.926 [2.591-9.380]	<0.001

Abbreviations: *OR*, odds ratio; AIC, Akaike information criterion, PS; *PS*, performance status; *Alb*, albumin.

3.4. Characteristics of surgical resection cases

Next, we compared the characteristics of surgical resection cases between the elderly and non-elderly groups (Supplementary Table 5).

The median duration from chemotherapy initiation to surgical resection was 151.5 and 179 days in the elderly and non-elderly groups, respectively.

Regarding the operative procedures, total gastrectomy was performed in 25.0% and 45.1% of the patients in the elderly and non-elderly groups, respectively. The R0 resection rate was comparable between both groups (elderly, 87.5% vs. nonelderly, 86.3%).

The elderly group showed a higher postoperative complication rate than the non-elderly group (any grade: 5/16 [31.2%] vs 9/51 [17.6%]); however, the difference was not statistically significant (OR = 2.095 [95% CI, 0.456–8.842], p = 0.295). The details of postoperative complications are presented in Supplementary Table 6. The incidence of pneumonia in the elderly and non-elderly groups was 25% (n = 4) and 2.0% (n = 1), respectively.

Adjuvant chemotherapy was less frequently administered in the elderly group (68.7%) than that in the non-elderly group (88.2%) (Supplementary Table 7).

3.5. Survival outcomes

The OS in resected and unresected cases was compared between the elderly and non-elderly groups (Fig. 1). The median follow-up time for the entire cohort was 13.5 months. Among resected cases, the 2-year OS rates were 87.5% (95% CI, 58.6%–96.7%) and 82.2% (95% CI, 67.1%–90.8%) in the elderly and non-elderly groups, respectively (hazard ratio [HR] = 0.772 [95% CI, 0.167–3.581], p = 0.741). Among unresected cases, the 2-year OS rates were 21.5% (95% CI, 13.1%–31.2%) and 28.4% (95% CI, 21.5%–35.7%) in the elderly and non-elderly groups, respectively (HR = 1.259 [95% CI, 0.947–1.675], p = 0.112).

We further compared the elderly group with the non-elderly group according to Yoshida's classification category 1 or categories 2–4 (Fig. 2). Among patients classified as Yoshida's classification category 1, the 2-year OS rates for resected cases were 100% in the elderly group and 64.9% (95% CI, 33.9%–84.1%) in the non-elderly group (HR = not available, p = 0.103). For unresected cases, the rates were 37.5% (95%

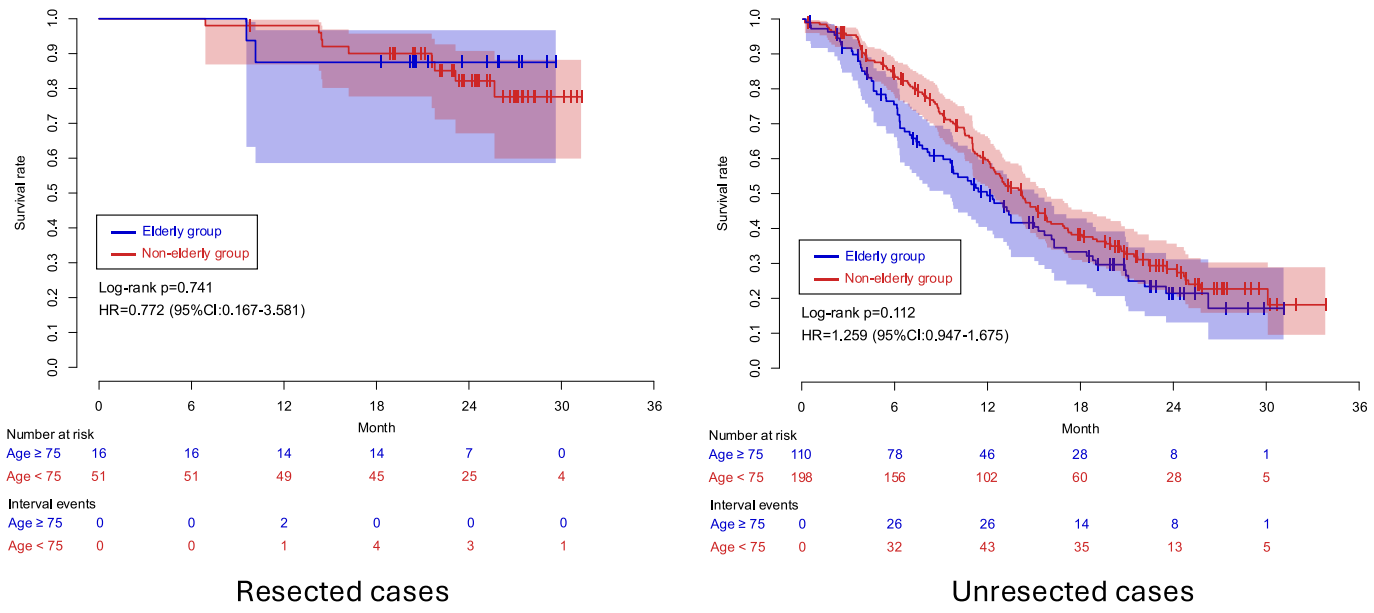


Fig. 1. Survival curves comparing the elderly and non-elderly groups among resected (left) and unresected cases (right).

CI, 11.7%–63.8%) and 53.4% (95% CI, 28.0%–73.4%) in the elderly and non-elderly groups, respectively (HR = 1.620 [95% CI, 0.586–4.479], p = 0.345).

Among patients classified as Yoshida's classification categories 2–4, the 2-year OS rates for resected cases (conversion surgery cases) were 75.0% (95% CI, 31.5%–93.1%) and 90.4% (95% CI, 72.7%–96.8%) in the elderly and non-elderly groups, respectively (HR = 2.647 [95% CI, 0.481–14.58], p = 0.245). For unresected cases, the rates were 18.8% (95% CI, 10.3%–29.2%) and 25.1% (95% CI, 18.0%–32.8%) in the elderly and non-elderly groups, respectively (HR = 1.240 [95% CI, 0.920–1.670], p = 0.157).

Lastly, multivariate analysis was conducted to adjust for confounding factors related to survival outcomes (Table 4). Because of the limited number of events in resected cases, we decided to include PS and histological type as covariates. This analysis revealed that age was not a significant factor regarding survival in either resected or unresected Stage IV GC patients.

3.6. Additional stratified analyses

We performed stratified analyses of the resection rate and OS (Supplementary Table 8A–D, Supplementary Fig. 1A–D) according to response, dose reduction, ICI treatment, and trastuzumab treatment.

Surgical resection rates among patients with response were 25.0% in the elderly group and 29.1% in the non-elderly group, whereas the rate was significantly lower in the elderly group than in the non-elderly group among patients without response (7.0% vs 15.9%, p = 0.048). Although OS did not differ significantly between the two groups among patients with response, the elderly group showed significantly worse OS than the non-elderly group among patients without response (HR = 1.516 [95% CI: 1.105–2.080], p = 0.009, Supplementary Fig. 1A).

Dose reduction did not significantly affect the difference in resection rates between the two groups, although the resection rate was numerically lower in the elderly group among patients without dose reduction (11.5% vs 26.7%, p = 0.121). Among patients without dose reduction, the elderly group demonstrated significantly worse survival than the non-elderly group (HR = 1.823 [95% CI: 1.029–3.230], p = 0.037, Supplementary Fig. 1B).

ICI and trastuzumab treatment did not alter the difference in resection rates between groups. However, there was a trend toward a lower resection rate in the elderly group compared with the non-elderly group among patients who received ICI treatment (8.1% vs 15.8%, p = 0.152). Among patients who received ICI treatment, survival outcomes were comparable between the two groups, whereas the elderly group showed significantly worse survival than the non-elderly group among patients who did not receive ICI treatment (HR = 2.191 [95% CI: 1.239–3.874], p = 0.006, Supplementary Fig. 1C). Stratification by trastuzumab treatment did not affect survival outcomes between the two groups (Supplementary Fig. 1D).

4. Discussion

We here showed a trend toward a lower surgical resection rate in the elderly group. The overall surgical resection rate of the patients in the elderly group was 12.7%, whereas that in the non-elderly group was 20.4%. When analyzed based on Yoshida's classification, patients with category 1, which is deemed initially resectable stage IV disease, resection rates were 40.0% and 45.9% in the elderly and non-elderly groups, respectively. Among patients classified as Yoshida's classification categories 2–4, which are considered initially unresectable disease and eligible for conversion surgery, the elderly group exhibited a significantly lower conversion surgery rate than the non-elderly group (7.5% vs. 15.9%). Previous studies have reported conversion surgery rates of 8.8%–50.0% [12–16].

To date, two studies have investigated conversion surgery following chemotherapy combined with ICI, reporting rates of 11.5% (12 of 104 patients) [17] and 30.8% (42 of 136 patients) [18], respectively. These wide variations in surgical resection rates may be attributable to differences in patient backgrounds, including age, number of patients evaluated, and surgeons' decision-making criteria. Therefore, comparing resection rates using objective criteria is significant. Moreover, patient age should be considered when evaluating these rates.

In this regard, our study showed the following strengths: (1) minimal treatment period-related bias as all patients were treated within a single year, (2) currently the largest cohort of patients treated following ICI introduction, and (3) explicit consideration of age as an influencing factor. (4) the use of Yoshida's classification as an objective framework for evaluating unresectability. Our data therefore serve as a crucial reference for evaluating surgical resection for stage IV GC.

Both the surgical resection rate and proportion of patients judged operable based on imaging findings were lower in the elderly group.

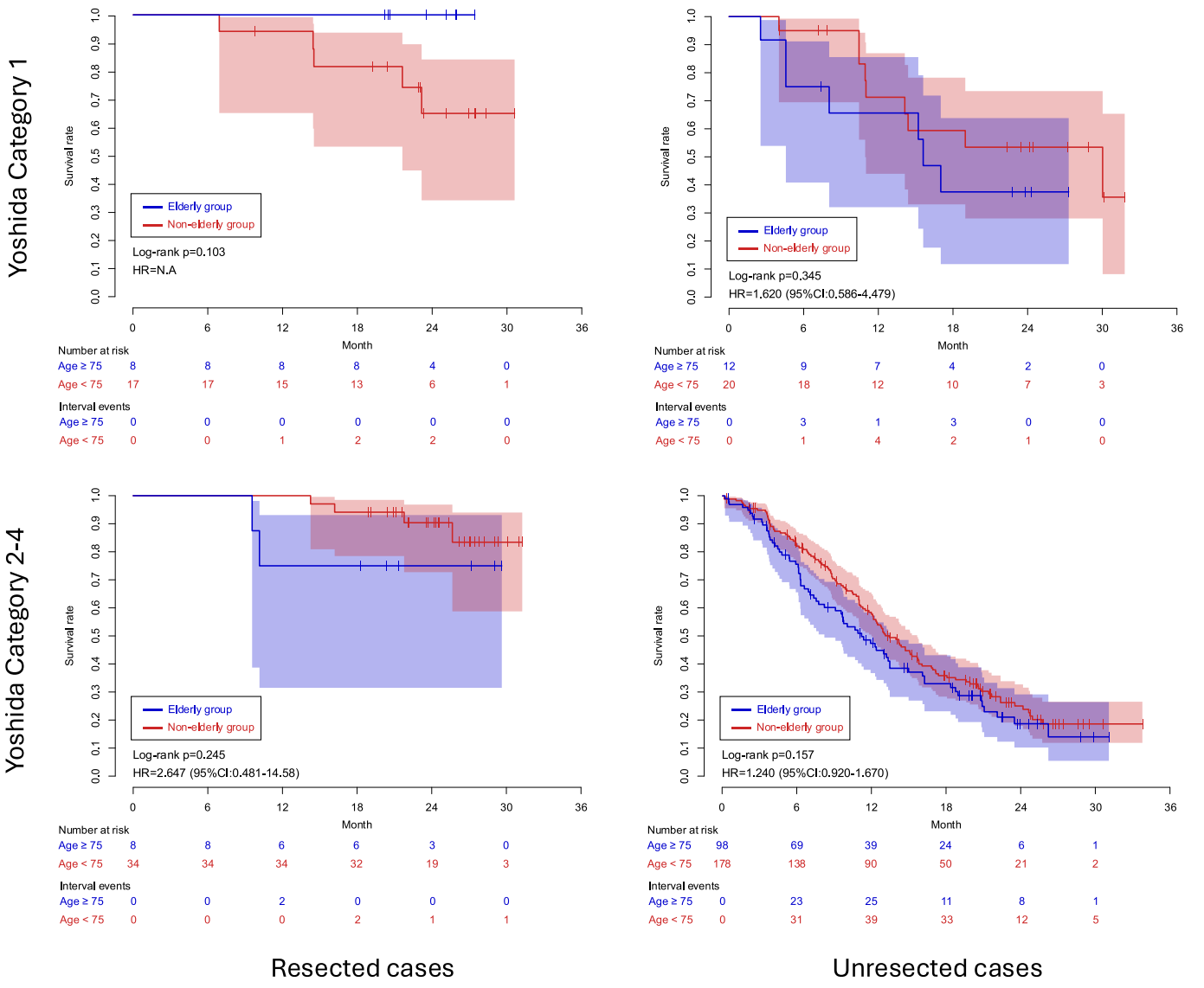


Fig. 2. Survival curves comparing the elderly and non-elderly groups according to Yoshida's classification categories: upper left, category 1 (resected); upper right, category 1 (unresected); lower left, categories 2–4 (resected); lower right, categories 2–4 (unresected).

Table 4
Multivariate analysis using Cox hazard model regarding survival

variables	Univariate analysis		Multivariate analysis[a]	
	HR [95% CI]	P-value	Adjusted HR [95% CI]	P-value
Resected cases	0.772 [0.167-3.581]	0.741	0.832 [0.171-4.051]	0.819
Unresected cases	1.259 [0.947-1.675]	0.112	1.186 [0.889-1.582]	0.245

The HR of the elderly group relative to the non-elderly group is presented.
Abbreviations: HR, hazard ratio; CI, confidence interval
[a] Adjusted by performance status and histological typeStructured

Although the underlying reasons remain uncertain, several factors, including more frequent dose reductions at treatment initiation, a higher adverse event incidence, and less frequent use of ICIs in elderly patients, may have contributed to the difference in the proportion of patients judged operable based on imaging findings. Regarding surgical resection, it is also likely that the criteria used for determining resectability varied between the two groups, as surgical resection was less frequently performed in elderly patients with ycT4, ycM1, or Yoshida's classification categories 2–4. Multivariate analysis (Table 3) indicated that PS, albumin level, and Yoshida category were significantly associated with resection rate, while age was not. This suggested baseline frailty reflected by poor PS and low albumin level may influence the decision to perform surgery, and that even elderly patients may be suitable candidates for surgical resection when they are fit.

Remarkably, postoperative survival outcomes did not differ between the elderly and non-elderly groups in either Yoshida's classification category 1 or categories 2–4. In addition, this trend was observed in the multivariate analysis; however, the confidence interval was wide, indicating limited precision. Furthermore, survival data were immature, and the 2-year OS rate should be interpreted with caution. Moreover, there are two concerns when interpreting the outcomes of resected cases. First, patients who underwent surgical resection represented a highly selected population with favorable performance status, nutritional condition, response to chemotherapy, metastatic burden, and tumor biology. Second, survival analyses involving patients who underwent surgical resection may have been affected by guarantee-time bias, because these patients were required to survive and remain eligible for surgery after the initiation of chemotherapy. Therefore, the favorable

survival outcomes observed among resected patients should not be regarded as direct evidence of the therapeutic benefit of surgery.

The elderly group exhibited more frequent postoperative complications (31.2% vs. 17.6%, $p = 0.295$), while no mortality was observed in either group. Although postoperative complication rates were not statistically significant between groups. given the limited number of elderly patients who underwent surgical resection, this study is underpowered to establish equivalence or non-inferiority regarding postoperative morbidity, and definitive conclusions regarding postoperative safety cannot be drawn. Notably, the elderly group demonstrated a markedly higher incidence of pneumonia (25% vs. 2.0%). The presence of comorbidities might contribute to the higher incidence of postoperative pneumonia in the elderly group. Although advanced age is a well-recognized risk factor for postoperative pneumonia [19,20], particular caution is warranted when managing elderly patients with stage IV GC undergoing surgical resection. More specifically, preoperative rehabilitation has gained attention as a means of reducing postoperative pneumonia [21,22], and its implementation might be important for elderly patients scheduled to undergo gastrectomy following chemotherapy.

In the stratified analysis, elderly patients showed lower surgical resection rates and worse survival outcomes than non-elderly patients among those without dose reduction. However, this subgroup analysis was exploratory in nature and should be interpreted cautiously, given the potential influence of patient selection and other unmeasured confounders. Therefore, no causal inference regarding the benefit of dose reduction can be drawn from the present study. Interestingly, our findings are broadly consistent with previous studies suggesting that treatment intensity should be carefully tailored for elderly and/or vulnerable patients. The GO2 phase III trial demonstrated that reduced intensity chemotherapy provided a better patient experience without significantly compromising cancer control and should be considered for elderly and/or frail patients [23]. In addition, the WJOG8315G study showed the survival benefit of SOX over S-1 alone was not observed among patients with G8 score $\leq$11 [24]. These observations may support the need for individualized treatment strategies in elderly patients, although further studies are required to clarify the optimal treatment intensity. On the other hand, among patients with response, surgical resection rates and survival outcomes did not differ significantly between the two groups. This indicates that achieving a favorable response remains critical for treating elderly Stage IV GC patients.

This study has several limitations. First, its retrospective design entails inherent risks of selection bias and unmeasured confounding, although conducting a sufficiently powered prospective study—particularly involving elderly patients undergoing resection for stage IV GC—is not currently feasible. Second, operability assessment was not based on predefined objective criteria; therefore, inter-surgeon and inter-institutional variability may have influenced the assessment. In addition, because participating institutions may have different policies or thresholds regarding surgical resection, some degree of institutional clustering could have occurred. Third, formal geriatric assessment, such as G8 screening, comprehensive geriatric assessment, and frailty evaluation, was not performed. Consequently, differences in biological age and vulnerability among elderly patients may not have been fully captured. Future prospective studies should incorporate standardized geriatric assessment tools. In addition, the survival data remain immature because the cohort initiated chemotherapy in 2022 (median follow-up: 13.5 months), necessitating longer follow-up to clarify long-term outcomes. Continued data collection is planned to enable a more definitive survival analysis.

It is widely recognized that patients undergoing conversion surgery achieve significantly better survival outcomes. This finding was strongly supported by the CONVO-GC-01 study [7], which investigated a large-scale retrospective cohort. The current study adds a crucial perspective by demonstrating this trend specifically in elderly patients. Although our findings on postoperative safety are not definitive and survival data are immature, surgical resection may be feasible and considered an acceptable option in carefully selected elderly patients with stage IV GC. Therefore, we consider it important not to exclude elderly individuals with stage IV GC as potential candidates for surgical resection in clinical practice.

CRediT author statement

Yuichiro Miki: Conceptualization, Methodology, Writing-Original Draft, Project administration. Taroh Satoh: Investigation, Writing-Review&Editing, Supervision. Daisuke Sakai: Investigation. Toshihiko Matsumoto: Investigation, Jin Matsuyama: Investigation, Takuya Hamakawa: Investigation, Ryohei Kawabata: Investigation, Shunji Endo: Investigation, Toshifumi Yamaguchi: Investigation, Masaaki Motoori: Investigation, Naoki Urakawa: Investigation, Masato Nakamura: Investigation, Osamu Takayama: Investigation, Hiroaki Tanaka: Investigation, Kohei Akiyoshi: Investigation, Aya Sugimoto: Investigation, Shogen Boku: Investigation, Yukinori Kurokawa: Supervision, Toshio Shimokawa: Formal analysis, Writing-Review&Editing, Kiyoshi Maeda: Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2026.112202.

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