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Neoadjuvant chemotherapy strategies for optimizing safety and efficacy in elderly patients with locally advanced gastric cancer

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Abstract

Background The completion rate of adjuvant chemotherapy for gastric cancer (GC) is suboptimal, particularly in elderly patients. While neoadjuvant chemotherapy (NAC) for locally advanced GC has shown promise, data on elderly patients remain limited. Given the considerable physical burden of NAC, optimizing its administration is crucial. This study evaluates the safety and efficacy of a modified approach for elderly patients.

Methods A retrospective analysis was conducted on 38 patients with cStage II/III GC who received NAC between November 2015 and December 2023. Additionally, 25 patients aged ≥ 75 years with cStage III who underwent upfront surgery during the same period were analyzed.

Results The NAC group was divided into non-elderly (< 75 years, $n = 27$) and elderly (≥ 75 years, $n = 11$) groups. The elderly group had poorer ECOG-PS ($p = 0.016$). While all non-elderly patients completed ≤ 3 cycles, more elderly patients underwent 4 cycles ($p = 0.0047$). However, per-cycles of S-1 ($p = 0.0003$) and oxaliplatin ($p = 0.0018$) were lower in the elderly group. Importantly, adverse events and treatment efficacy were comparable between groups. Among patients aged ≥ 75 years, the upfront surgery group had poorer ECOG-PS ($p = 0.017$) and underwent more frequent distal gastrectomy ($p = 0.014$).

Conclusions NAC can be safely administered to elderly patients by increasing cycles while reducing per-cycle dosage. It may also serve as a viable alternative to upfront surgery.

Keywords Gastric cancer, Neoadjuvant chemotherapy, Elderly, Adverse events

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Introduction

Gastric cancer (GC) was the fifth most common malignancy and fourth leading cause of cancer-related deaths worldwide in 2020 [1]. The prognosis of patients with locally advanced GC remains poor, necessitating the development of effective treatment strategies. Standard approaches for locally advanced GC vary between East Asia and Europe [2]. In Europe, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial demonstrated the survival benefit of peri-operative chemotherapy [3]. Subsequent clinical trials have refined treatment strategies, with FLOT regimen (fluorouracil plus leucovorin, oxaliplatin and docetaxel) now offering superior overall survival compared to previous standard regimens [4]. In East Asia, the ACTS-GC [5], CLASSIC [6] and JACCRO GC-07 [7] trials demonstrated the benefits of postoperative chemotherapy. More recently, the PROGIDY study [8], similar to European trials, validated the efficacy of the three-drug regimen DOS regimen (docetaxel plus oxaliplatin, and S-1) as a neoadjuvant chemotherapy (NAC) approach.

In Japan, multiple clinical trials have investigated pre-operative chemotherapy. JCOG0405 [9] and JCOG1002 [10] targeted GC with extended lymph node metastasis, while JCOG0501 [11] focused on type 4 or large type 3 GC. However, none achieved satisfactory outcomes. Ongoing trials, including JCOG1509 [12] for clinical stage III GC and JCOG1704 [13] for GC with extended lymph node metastasis, are expected to provide valuable insights. Additionally, the JCOG2204 trial [14], comparing DOS and FLOT as NAC regimens, suggests that NAC is likely to become a standard treatment in Japan.

As Japan's elderly proportion continues to grow, developing appropriate treatment strategies for elderly GC patients is increasingly important. Aging is associated with a higher prevalence of comorbidities and physical frailty, though some elderly individuals remain as fit as younger patients. While postoperative mortality following gastrectomy tends to rise with age [15], treatment decision should not be based solely on chronological age. Instead, individualized therapeutic strategies tailored to each patient's condition are essential [16].

Here, given the potential for NAC to become a standard treatment for locally advanced GC in Japan, we conducted a retrospective analysis to explore treatment strategies that balance efficacy and safety. This study also examines the feasibility of administering NAC without complications in the growing population of elderly patients with GC.

Materials and methods

Patients.

Patients were categorized into two groups: the “elderly group” (≥ 75 years) and the “non-elderly group” (< 75

years). We analyzed patients treated at the Department of Gastroenterological Surgery at Okayama University Hospital between November 2015 and December 2023. During this period, NAC in our department consisted of a two-drug regimen with oxaliplatin. Furthermore, we also compared patients ≥ 75 years with cStage III GC who underwent upfront surgery (Upfront group) with those who received NAC (NAC group) during the same period.

Medical records of all patients were obtained from the hospital database. Patient factors (age, sex, eastern cooperative oncology group performance status [ECOG-PS], blood test results, pre/post-treatment Stage and computed tomography [CT]/positron emission tomography [PET]-CT image), NAC factors (regimen, cycles, relative dose intensity [RDI] and adverse events [AEs]), surgical factors (procedure, lymph node dissection, and Clarien-Dindo [CD] grade), postoperative factors (histopathological data, and follow-up data) were examined retrospectively.

Procedure.

This study focused on patients diagnosed with Stage II/III GC according to the Japanese Classification of Gastric Carcinoma (English edition, ver.3) who underwent NAC. The standard NAC regimen was SOX (S-1 + oxaliplatin) for three preoperative cycles. SOX treatment consisted of intravenous oxaliplatin on day 1, combined with oral S-1 twice daily on days 1–14, repeated every three weeks for three cycles. If significant disease progression or unacceptable adverse effects (assessed according to CTCAE version 5.0) occurred, surgery was performed even if fewer than three cycles were completed, provided it was deemed feasible. Both S-1 and L-OHP were generally initiated at the standard dose, but in elderly patients, dose reductions were made even for minor AEs of Grade 2 or lower, and for S-1, additional adjustments were made from the start according to renal function. Conversely, additional cycles up to a total of four were permitted based on the patient's condition and treatment response. The criteria for selecting four cycles included patients who had required dose reductions due to AEs during treatment, showed a favorable response after three cycles, and demonstrated sufficient tolerability to AEs. Standard surgical procedures included distal or total gastrectomy with D2 lymph node dissection, with modifications made as necessary. Postoperative management options included adjuvant chemotherapy with S-1 or DS (docetaxel + S-1) treatment or observation, based on the final pathological diagnosis and patient preference.

Statistical analysis

All statistical analyses were performed using JMP version 14.2 software (SAS Institute, Cary, NC, USA). Pearson's chi-squared test was used for categorical variables, and the Mann-Whitney *U* test was applied to continuous

Table 1 Clinicopathological features of the patients undergoing NACECOG-PS: Eastern cooperative oncology group-performance status

	Non-elderly group	Elderly group	p value
n	27	11	
Sex, n (%)			0.97
Male	17 (63.0)	7 (63.6)	
Female	10 (37.0)	4 (36.4)	
Age, years			0.0001
Median	66	78	
IQR	59–71	76–81	
ECOG-PS, n (%)			0.016
0	26 (96.3)	8 (72.7)	
1	0	3 (27.3)	
2	1 (3.7)	0	
cStage, n (%)			0.35
II	2 (7.4)	0	
III	25 (92.6)	11 (100)	

ECOG-PS: Eastern cooperative oncology group-performance status

Table 2 Neoadjuvant chemotherapy protocol

	Non-elderly group	Elderly group	p value
Cycles, n (%)			0.0047
1–3	27 (100)	8 (72.7)	
4	0	3 (27.3)	
RDI/cycle			0.0003
S-1			
Median	100	87.5	
IQR	100–100	80–100	
Oxaliplatin			0.0018
Median	100	94.2	
IQR	100–100	85–100	
RDI/total dose			0.55
S-1			
Median	100	86.7	
IQR	66.7–100	53.3–111.1	
Oxaliplatin			0.8
Median	100	100	
IQR	66.7–100	50–113.3	

variables. The Kaplan-Meier method was used to estimate relapse-free survival (RFS) and overall survival (OS), with survival rates compared using the log-rank test. A p-value of $p < 0.05$ was considered statistically significant.

Results

Patient characteristics of patients for whom NAC was performed

The clinicopathological characteristics of the 38 patients are summarized in Table 1. The study included 24 men and 14 women, with a median age of 70 years (interquartile range [IQR]: 62–76). ECOG-PS assessment revealed the following distribution: in the non-elderly group, 26 (96.3%) were class 0, none were class 1, and 1 patient

(3.7%) was class 1; in the elderly group, 8 (72.7%) patients were class 0, 3 (27.3%) were class 1, and none were class 2. The elderly group had significantly worse ECOG-PS ($p = 0.016$). Regarding clinical stage, 2 patients (7.4%) in the non-elderly group and none in the elderly group were classified as cStage II, while 25 patients (92.6%) in the non-elderly group and all 11 patients in the elderly group were classified as cStage III.

Neoadjuvant chemotherapy

The details of NAC procedures are summarized in Table 2. All non-elderly patients completed all three cycles, whereas only 8 patients (72.7%) in the elderly group did so, showing a significant difference ($p = 0.0047$). The median relative dose intensities (RDI) per cycle were 100% (IQR: 100–100) for both S-1 and oxaliplatin in the non-elderly group, compared to 87.5% (80–100) for S-1 and 94.2% (85–100) for oxaliplatin in the elderly group. The non-elderly group received significantly higher dose of S-1 ($p = 0.0003$) and oxaliplatin ($p = 0.0018$) per cycle. However, the median RDI over the entire treatment course was 100% (IQR: 66.7–100) for both S-1 and oxaliplatin in the non-elderly group, while in the elderly group, it was 86.7% (IQR: 53.3–111.1) for S-1 and 100% (IQR: 50–113.3) for oxaliplatin, with no significant differences between the groups.

AEs during NAC are shown in Table 3. Grade ≥ 3 treatment emergent AEs occurred in 8 patients (21.1%), including 6 patients (22.2%) in the non-elderly group and 2 patients (18.3%) in the elderly group, with no significant differences. These AEs included anorexia, diarrhea, neutropenia, elevated AST/ALT, and fatigue, but no significant differences were observed between groups.

Surgical and postoperative outcomes

The details of surgical procedures are summarized in Table 4. Among cases deemed unresectable, only 1 patient (3.6%) in the non-elderly group and 2 patients (18.2%) in the elderly group had progressive disease (PD) during NAC, with no significant differences between groups. The reasons for unresectability included tumor lysis syndrome due to rapid enlargement of metastatic lymph nodes in the non-elderly group, and the emergence of para-aortic lymph node metastasis and peritoneal dissemination in the elderly group. Among patients who underwent surgery, pathological therapeutic effects included cases with indeterminate Grade 2 responses, but the proportion of cases achieving $\geq$ Grade 1b or $\geq$ Grade 2 responses did not differ significantly between groups. No significant differences were observed in lymph node dissection, postoperative complications (Clavien-Dindo grade ≥ 3), pathological stage; however, the completion rates of adjuvant chemotherapy tended to be higher in the non-elderly group. Similarly, adherence

Table 3 Adverse events associated with NAC

	Non-elderly group	Elderly group	p value
Procedure, n (%)			0.31
DG	13 (48.2)	4 (36.4)	
TG	13 (48.2)	5 (45.4)	
Unresectable	1 (3.6)	2 (18.2)	
Lymph node dissection, n (%)			0.085
1+	0	1 (11.1)	
≥ 2	26 (100)	8 (88.9)	
Clavien-Dindo Grade, n (%)			0.9
2 ≥	23 (88.5)	8 (88.9)	
≥ 3	3 (11.5)	1 (11.1)	
pStage, n (%)			0.38
0	0	1 (11.1)	
IA	7 (26.9)	1 (11.1)	
IB	2 (7.7)	0	
IIA	3 (11.5)	1 (11.1)	
IIB	4 (15.4)	0	
IIIA	3 (11.5)	2 (22.2)	
IIIB	4 (15.4)	3 (33.4)	
IIIC	2 (7.7)	0	
X	1 (3.9)	1 (11.1)	
Pathological therapeutic effect, n (%)			0.62
1a	8 (30.8)	2 (22.2)	
1b	2 (7.7)	1 (11.1)	
2a	2 (7.7)	1 (11.1)	
2b	6 (23.1)	1 (11.1)	
2 (detail unknown)	7 (26.9)	2 (22.2)	
3	1 (3.8)	2 (22.2)	
Adjuvant chemotherapy, n (%)			0.10
Completed	14 (53.9)	2 (22.2)	
Discontinued or not initiated	12 (46.1)	7 (77.8)	
Regimen selection in accordance with guideline for Stage II (excluded T3N0) or III			0.055
Adherence (including drug intensification [S1 to DS])	6 (42.9)	0	
S1Non-adherence (including drug de-escalation [DS to S1] or omission)	8 (57.1)	6 (100)	

to guideline-recommended adjuvant chemotherapy, which prescribes S1 therapy for Stage II and DS therapy for Stage III except for T3N0, was also more common in the non-elderly group.

After a median follow-up of 56.1 months (IQR: 21–63.9) in the non-elderly group and 41.2 months (IQR: 13–63.9) in the elderly group, no significant differences were observed in RFS ($p=0.66$) or OS ($p=0.26$) between groups. Two-year RFS rates were 84.4% in the non-elderly group and 88.9% in the elderly group (Fig. 1). Tumor marker levels, including CEA and CA19-9, showed no significant differences between groups

Table 4 Surgical characteristics and postoperative outcomes

	Non-elderly group	Elderly group	p value
All adverse events, n (%)			
Any	18 (66.7)	8 (72.7)	0.72
≥ G3	6 (22.2)	2 (18.2)	0.78
Nausea, n (%)			
Any	2 (7.4)	0	0.35
≥ G3	0	0	
Vomiting, n (%)			
Any	1 (3.7)	0	0.52
≥ G3	0	0	
Anorexia, n (%)			
Any	8 (29.6)	3 (27.3)	0.88
≥ G3	4 (14.8)	2 (18.2)	0.80
Diarrhea, n (%)			
Any	3 (11.1)	2 (18.2)	0.56
≥ G3	1 (3.7)	1 (9.1)	0.50
Neuropathy, n (%)			
Any	1 (3.7)	0	0.52
≥ G3	0	0	
Neutropenia, n (%)			
Any	4 (14.8)	0	0.18
≥ G3	1 (3.7)	0	0.52
Thrombocytopenia, n (%)			
Any	3 (11.1)	1 (9.1)	0.85
≥ G3	0	0	
AST or ALT increased, n (%)			
Any	1 (3.7)	0	0.52
≥ G3	1 (3.7)	0	0.52
Fatigue, n (%)			
Any	2 (7.4)	1 (9.1)	0.86
≥ G3	1 (3.7)	0	0.52

TG: total gastrectomy, DG: Distal gastrectomy

before treatment or preoperatively (Fig. 2A). Additionally, based on RECIST criteria, a ≥ 50% reduction in target lesion size was observed in 7 of 14 cases (50.0%) in the non-elderly group and 2 of 9 cases (22.2%) in the elderly group; however, this difference was not statistically significant (Fig. 2B).

Efficacy of NAC in cStage III GC patients aged ≥ 75 years

Next, we compared patients aged ≥ 75 years with cStage III GC between Upfront group and NAC group. The clinicopathological characteristics of both groups before and after PSM are summarized in Table 5. Gender distribution did not differ significantly. Although the Upfront group was slightly older, this difference was not statistically significant. However, the NAC group had significantly better ECOG-PS ($p=0.017$) and a higher proportion of patients underwent total gastrectomy ($p=0.014$). No significant differences were observed in lymph node dissection or postoperative complications. Kaplan-Meier curves generated using these data

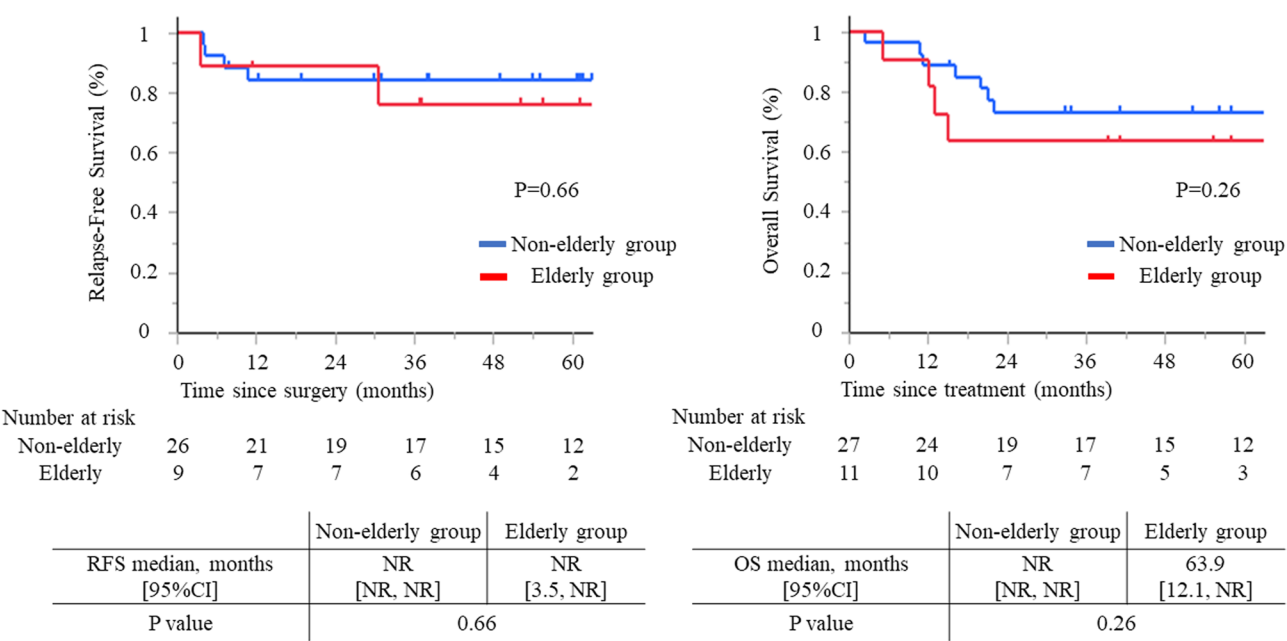


Fig. 1 Kaplan-Meier curves for non-elderly and elderly groups undergoing NAC. Upper half: Relapse-free survival. Bottom half: Overall survival RFS: relapse-free survival, OS: Overall survival, NR:

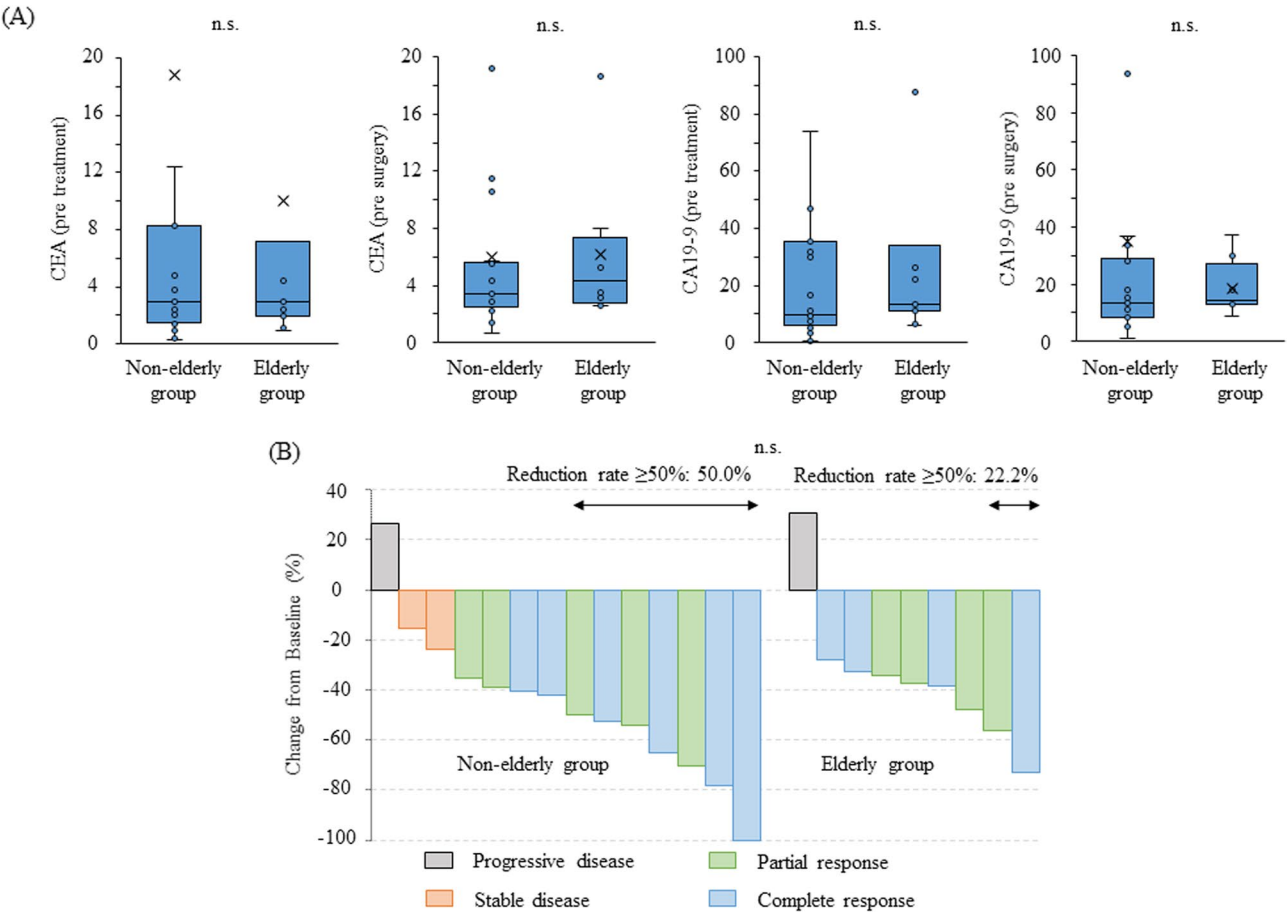


Fig. 2 Blood test and CT imaging findings. (A) Tumor markers (CEA and CA19-9) before treatment and preoperatively, comparing the two groups. (B) Treatment efficacy in cases with target lesions

Table 5 Clinicopathological features of elderly patients with upfront surgery or NAC treatment

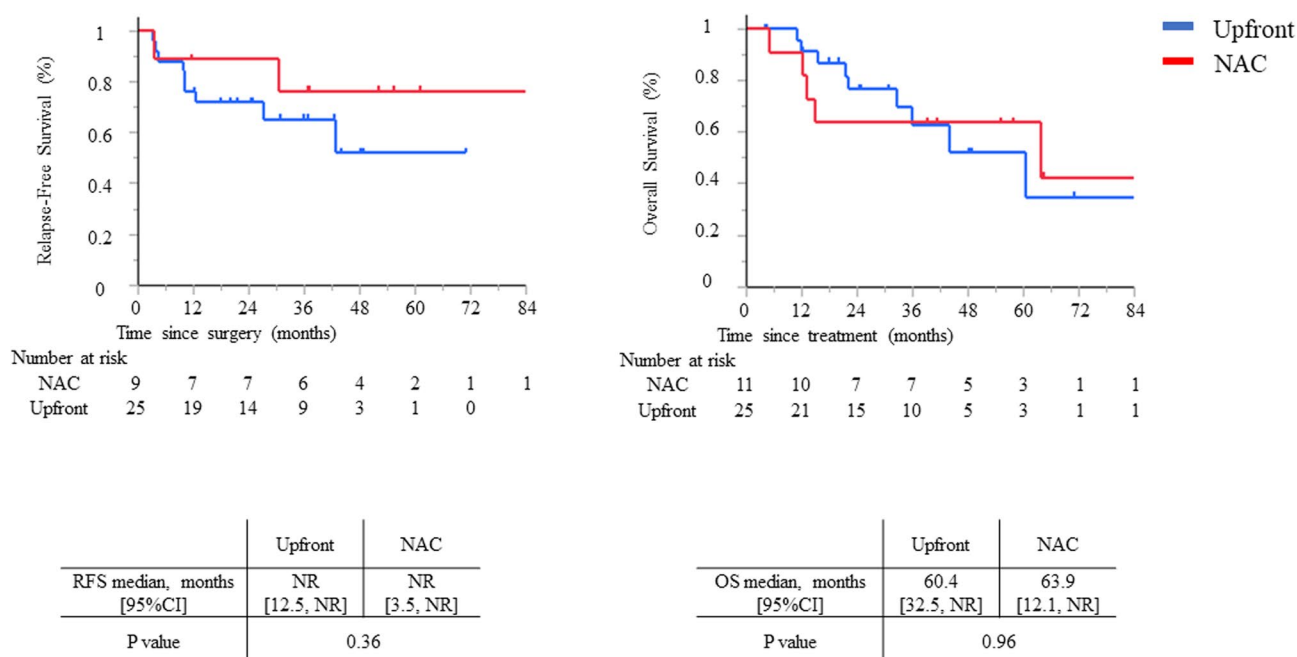
	Upfront	NAC	p value
n	25	11	
Sex, n (%)			0.45
Male	19 (76.0)	7 (63.6)	
Female	6 (24.0)	4 (36.4)	
Age, years			0.18
Median	81	78	
IQR	77–84	76–81	
ECOG-PS, n (%)			0.017
0	6 (24.0)	8 (72.7)	
1	14 (56.0)	3 (27.3)	
2	5 (20.0)	0	
Procedure, n (%)			0.014
DG	20 (80.0)	5 (45.4)	
TG	5 (20.0)	4 (36.4)	
Unresectable	0	2 (18.2)	
Lymph node dissection, n (%)			0.091
1+	0	1 (11.1)	
≥ 2	25 (100)	8 (88.9)	
Clavien-Dindo Grade, n (%)			0.78
< 3	23 (92.0)	8 (88.9)	
≥ 3	2 (8.0)	1 (11.1)	
Recurrence, n (%)	9 (36.0)	2 (22.2)	0.45
Alive, n (%)	16 (64.0)	6 (54.6)	0.59
Cause of death, n (%)			0.60
Gastric cancer	6 (66.7)	4 (80.0)	
Other	3 (33.3)	1 (20.0)	

ECOG-PS: Eastern cooperative oncology group-performance status

showed no significant differences in RFS ($p = 0.36$) or OS ($p = 0.96$) between the two groups (Fig. 3).

Discussion

Treatment strategies for locally advanced GC are undergoing significant changes due to advancements in pharmacotherapy. NAC regimens, such as FLOT and DOS, have demonstrated efficacy, and clinical trials, including JCOG1509 [2], are currently underway in Japan. However, limited data exist regarding the efficacy and tolerability of these treatment in elderly patients. For instance, the median ages in FLOT4 [4] and PRODIGY [8] trials were 62 and 58 years old, respectively, indicating that these studies primarily included younger populations. In Japan, where the elderly population continues to grow, individual differences in physical condition become more pronounced with age, making it increasingly challenging to determine treatment suitability based solely on chronological age. There are few reports on the effectiveness of NAC in elderly patients. Some reports indicate that NAC in elderly patients does not significantly improve overall survival because many patients are unable to proceed to surgery [17] and is less frequently administered because of the high risk of treatment interruption [18]. Consistent with these reports, our results also was a tendency toward a higher rate of unresectability in elderly patients. Conversely, other studies suggest that NAC is associated with better prognosis. However, even in studies supporting a favorable prognosis [19, 20] or tumor shrinkage [21], there is little discussion on drug administration

**Fig. 3** Relapse-free survival and overall survival in the Upfront and NAC groups in elderly

methods or specific treatment modifications. Against this backdrop, our study focused on the appropriateness of NAC and dosing strategies for elderly patients.

In the elderly group, we adopted a strategy of increasing the total number of doses while reducing the dosage per administration to maintain the overall planned chemotherapy dose. As a result, there were no significant differences in the incidence of PD compared to the non-elderly group, and no cases of treatment failure due to reasons other than PD were observed. This outcome suggests that AEs were effectively managed within an acceptable range, even in patients considered to have lower tolerability based on age or ECOG-PS. Regarding treatment efficacy, the elderly group showed comparable results to the non-elderly group in terms of RFS and OS. However, the response rate of target lesions tended to be higher in the non-elderly group, likely due to differences in the dosage per administration. In the elderly group, the smaller shrinkage of target lesions was attributable to the lower dosage, but increasing the number of cycles was considered to provide sufficient efficacy against micro-metastases, which are thought to be the main cause of recurrence.

Although there was no significant difference between the Upfront and NAC groups in elderly patients, the NAC group appeared to showed a trend toward better RFS and OS. This may be partly due to the selection of patients with a relatively good physical condition for NAC. However, the NAC group also included a higher proportion of patients undergoing TG, which has a greater impact on postoperative outcomes. These findings suggest that chemotherapy eligibility should not be determined by age alone but should be based on a comprehensive assessment of overall health. This interpretation is further supported by the stronger trend observed after performing PSM. While the exclusion of patients who progressed to PD in the NAC group may have influenced these results, our findings suggest that NAC could be beneficial for elderly patients in good overall condition.

The present study may have some important implications for clinical practice but also several limitations. First, this study was not a randomized controlled trial, and instead retrospectively investigated a small cohort from a single institution. Second, since patients were older, some were not able to be contacted during follow-up. Despite these limitations, the results were considered acceptable for NAC in elderly GC patients.

In conclusion, administering NAC for locally advanced GC in elderly patients requires careful consideration of overall health status. Reducing the dose per cycle while increasing the total number of cycles could contribute to maintaining adequate drug exposure and minimizing adverse effects, potentially enhancing treatment safety. Moreover, the therapeutic efficacy was comparable to

that observed in younger patients receiving standard dosing. Among elderly patients who demonstrated sufficient tolerability to NAC, appropriate administration of NAC may potentially improve RFS and OS compared with upfront surgery.

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Authors' contributions

Y.K. and Shi.K. were involved in this study conception and design, and Y.K. wrote the manuscript. Shi.K., S.H., N.K., H.K., Sa.K., K.S., Shu.K. and T.F. reviewed and revised the manuscript. All authors have read and approved the final manuscript for publication.

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Data availability

The reader can access the research data by contacting the corresponding author.

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the institutional review board (IRB) of Okayama University Hospital (Approval no.2503-014). The study was performed in accordance with the Declaration of Helsinki. The informed consent was obtained from the patients or their families according to the IRB.

Consent for publication

No applicable.

Conflict of interest

No authors have any conflicts of interest for this article.

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