ORIGINAL PAPER

Nagoya J. Med. Sci. **84**. 388–401, 2022
doi:10.18999/nagjms.84.2.388

Tolerability of neoadjuvant chemotherapy for esophageal cancer in elderly patients over 76 years of age

Takafumi Suzuki, Yusuke Ishibashi, Hironori Tsujimoto, Hidekazu Sugasawa, Kotaro Wakamatsu, Keita Kouzu, Yujiro Itazaki, Takao Sugihara, Manabu Harada, Nozomi Ito, Yoji Kishi and Hideki Ueno

Department of Surgery, National Defense Medical College, Tokorozawa, Japan

ABSTRACT

Although the Japan Clinical Oncology Group trial demonstrated that neoadjuvant chemotherapy (NAC) with 5-fluorouracil plus cis-diamminedichloroplatinum had significant survival benefits, it excluded elderly patients aged ≥ 76 years. Therefore, our study aimed to evaluate the tolerability of NAC in elderly patients with esophageal cancer. Classified 174 patients with clinical stage II/III esophageal cancer who underwent esophagectomy from 2010 to 2020 into the E (aged ≥ 76 years; 55 patients) and Y (aged < 76; 119 patients) groups, and retrospectively investigated for clinicopathological findings, tolerability of NAC, relative dose intensity (RDI) and short- and long-term result. Patients who received NAC were fewer in the E group than in the Y group (51% vs 77%, $p = 0.001$). The E group had relatively lower completion rate of NAC (71% vs 85%, $p = 0.116$) and significantly lower mean RDI of 5-fluorouracil and cis-diamminedichloroplatinum than the Y group (73% vs 89%, $p < 0.001$). However, histological and radiological were comparable between both groups. Severe adverse events (grade ≥ 3) were relatively frequent (E, 42.9%; Y, 27.5%, $p = 0.091$), especially, neutropenia was significantly more frequent in the E group (25.0% vs 7.7%, $p = 0.022$). There were no differences in the incidence of postoperative complications between with and without NAC in both E and Y groups. Elderly patients with esophageal cancer might be more susceptible to toxicity of NAC. Hence, adequate case selection and careful of dose reduction are needed for elderly with esophageal cancer.

Keywords: esophageal cancer, neoadjuvant chemotherapy, elderly patients

Abbreviations:
NAC: neoadjuvant chemotherapy
RDI: relative dose intensity
5-FU: 5-fluorouracil
CDDP: cis-diamminedichloroplatinum
CCr: creatine clearance
eGFR: estimated glomerular filtration rate
L3: third lumbar vertebra
PMI: psoas muscle index
CTCAE: Common Terminology Criteria for Adverse Events
RECIST: Response Evaluation Criteria in Solid Tumors
CR: completer response

Received: July 21, 2021; accepted: September 1, 2021
Corresponding Author: Hironori Tsujimoto, MD, PhD
Department of Surgery, National Defense Medical College, 3-2 Namiki, Tokorozawa 359-8513, Japan
Tel: +81-4-2995-1637, Fax: +81-4-2996-5205, E-mail: tsujihi@ndmc.ac.jp

PR: partial response
PD: progressive disease
SD: stable disease
OS: overall survival
RFS: relapse-free survival

INTRODUCTION

In 2018, esophageal cancer had been the ninth most common type of malignancy and sixth leading cause of cancer-related deaths.[1] Since the Japan Clinical Oncology Group (JCOG) 9907 study showed that neoadjuvant chemotherapy (NAC) had a significant survival advantage over postoperative chemotherapy for locally advanced esophageal cancer,[2] NAC with 5-fluorouracil (5-FU) plus cis-diamminedichloroplatinum (CDDP) (FP therapy) followed by surgery has been regarded as the standard treatment for patients with resectable stage II/III esophageal cancer in Japan. The aging population and longer life expectancy in Japan have caused an increase in number of elderly patients with esophageal cancer. Indeed, according to the Japan Esophageal Society's registration, 9.1% of patients with esophageal cancer were over 80 years old.[3] However, considering that the JCOG9907 study excluded elderly patients over 76 years of age, physicians often hesitate to provide NAC for elderly patients because of the lack of evidence and poor physical capacity. Although Booka et al reported that NAC was not effective and should not be administered in elder adults, it is still controversial whether NAC is beneficial for elderly esophageal cancer patients.[4] In addition, few studies investigated the effect of NAC for the elderly esophageal cancer patients in terms of tolerability. Therefore, there is a pressing need to verify the tolerability and response of NAC in patients with esophageal cancer over 76 years of age, which is the aim of the current study.

METHODS

Study design

This study was approved by the Institutional Review Board of the National Defense Medical College, Tokorozawa, Japan. A total of 174 patients who underwent esophagectomy for clinical stage II or III esophageal cancer at our hospital from 2010 to 2020 were included in this study and subsequently classified into the E (aged ≥ 76 years; 55 patients) and Y (aged < 76 years; 119 patients) groups.

Clinicopathological features were assessed according to the tumor node metastasis criteria based on the eighth edition of the Union for International Cancer Control classification system for tumor staging.[5] In addition, the clinicopathological findings, NAC tolerance, and NAC response rates (histopathological and radiological responses) were retrospectively investigated and compared between both groups. Creatine clearance (CCr) was estimated using the Cockcroft–Gault equation, while renal function was evaluated using the estimated glomerular filtration rate (eGFR). A cross-sectional CT image of the third lumbar vertebra (L3) in the inferior direction was selected for estimating muscle mass as described previously.[6] The psoas muscle index (PMI) (cm^2/m^2) indicated L3 muscle cross-sectional areas computed from each image normalized for height. Relative dose intensity (RDI) was defined as the percentage of the actual dose the patient received to the scheduled dose over a given time period, while ARDI was defined as average

RDI of 5-FU and CDDP. Furthermore, we analyzed the long-term prognosis for the 119 patients who received NAC between 2010 and 2017.

Neoadjuvant chemotherapy

Physical and laboratory examinations were performed to evaluate NAC tolerability prior to its administration. Contraindications for NAC included a performance status of 3 and 4, insufficient organ function, and patient refusal.[2] Basically, two courses of chemotherapy composed of 5-FU and CDDP was scheduled every 3 weeks. CDDP dose of 80 mg/m^2 was infused on day 1, while 800 mg/m^2 of 5-FU was continuously infused from days 1 to 5. Physical and laboratory examinations were routinely performed throughout NAC. When continuation of NAC was determined to be difficult due to adverse effects, either dose reduction or termination of the second course was performed. 5-FU and CDDP dosages were reduced as needed according to the guidelines of Japanese Society of Nephrology.[7] We classified the adverse events of NAC according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Evaluation of pathological and radiological responses

Pathological response to NAC was evaluated based on the Japanese Classification of Esophageal Cancer.[8,9] The classification scheme was as follows: Grade 0, no tumor response; grade 1a, necrotic or fibrotic changes in less than one third of the tumor; grade 1b, necrotic or fibrotic changes in one third to two thirds of the tumor; grade 2, necrotic or fibrotic changes in more than two thirds of the tumor; and grade 3, no viable tumor cells.

To radiologically evaluate responses based on the reduction in the area of the targeted lesions according to Response Evaluation Criteria in Solid Tumors (RECIST), computed tomography using 5-mm slices was performed before and 4 weeks after NAC.[10] The classification scheme was as follows: complete response (CR), the disappearance of all target lesions and secondary changes associated with the tumor; partial response (PR), at least a 30% decrease in the sum of the greatest dimensions of the target lesions, taking the baseline sum of greatest dimensions as reference; progressive disease (PD), at least a 20% increase in the sum of greatest dimensions of target lesions, taking the smallest sum of greatest dimensions recorded since treatment initiation as reference; and stable disease (SD), neither PR nor PD.

Statistical analyses

Data are expressed as mean ± standard deviations. Statistical comparison was performed using the Wilcoxon test and chi-square tests, as appropriate. Recurrence-free and overall survival curves were generated using the Kaplan–Meier method, after which differences were compared using the log-rank test. Overall survival (OS) and relapse free survival (RFS) curves were calculated by the Kaplan–Meier method (log-rank test). All statistical analyses were performed using JMP 14 (SAS Institute Inc., Cary, NC, USA), with a p value of < 0.05 indicating statistical significance.

RESULTS

Demographic and clinicopathological data of patients

Demographic and clinicopathological data of the study cohort are summarized in Table 1. Significantly fewer patients in the E group received NAC compared to the Y group (50.9% vs 76.5%, $p = 0.001$). Accordingly, no significant differences in sex, tumor location, tumor depth, lymph node metastasis, pathological stage, tumor type, and degree of differentiation were observed between the two groups. Although no difference in body mass index was noted between the

two groups, the E group had a significantly lower psoas muscle index than the Y group ($p < 0.001$). The E group had significantly lower eGFR and CCr than the Y group. In the E group, the patients without NAC treatment were older than those with NAC treatment ($p < 0.001$); in both groups, former had a significantly worse CCr than latter ($p < 0.01$, respectively).

Table 1 Demographic and clinicopathological data of patients

	E group					Y group				
	NAC (+)		NAC (–)			NAC (+)		NAC (–)		
Variable	n = 28 (%)		n = 27 (%)		*P*-value	n = 91 (%)		n = 28 (%)		*P*-value
Age										
(mean ± SD)	78.2 ± 2.1		82.2 ± 4.4		< 0.001	66.4 ± 7.1		68.3 ± 6.9		0.324
Sex										
Male	19	67.9	26	96.3	0.006	74	81.3	25	89.3	0.206
Female	9	32.1	1	3.7		17	18.7	3	10.7	
Tumor location										
Upper	3	10.7	7	25.9		11	12.1	3	10.7	
Middle	14	50.0	6	22.2	0.076	44	48.4	9	32.1	0.245
Lower	11	39.3	14	51.9		36	39.6	16	57.1	
Depth of tumor										
pT1/T2	8	28.6	8	29.6	0.931	26	28.6	11	39.3	0.284
pT3/T4	20	71.4	19	70.4		65	71.4	17	60.7	
Lymph node metastasis										
pN0	11	39.3	10	37.0	0.864	24	26.4	6	21.4	0.598
pN1/N2/N3	17	60.7	17	63.0		67	73.6	22	78.6	
Pathological stage										
I/II	13	46.4	11	40.7	0.671	32	35.2	10	35.7	0.958
III/IV	15	53.6	16	59.3		59	64.8	18	64.3	
Tumor type										
Squamous	25	89.3	24	88.9	0.962	87	95.6	22	78.6	0.005
Others	3	10.7	3	11.1		4	4.4	6	21.4	
Degree of differentiation										
Well/Mod	26	92.9	26	96.3	0.575	80	87.9	22	78.6	0.313
Poor	2	7.1	1	3.7		10	11.0	5	17.9	
BMI										
(mean ± SD)	21.3 ± 2.9		20.8 ± 3.3		0.637	20.3 ± 3.6		20.7 ± 3.5		0.662
PMI										
(mean ± SD)	5.6 ± 8.9		3.9 ± 1.6		0.333	6.0 ± 2.6		5.9 ± 3.1		0.924
eGFR										
(mean ± SD)	67.9 ± 11.9		60.8 ± 16.0		0.069	81.8 ± 17.6		67.0 ± 22.4		< 0.001
Creatinine clearance										
(mean ± SD)	62.5 ± 14.2		47.0 ± 14.0		< 0.001	77.9 ± 18.6		65.4 ± 24.8		0.005

NAC: neoadjuvant chemotherapy
SD: standard deviation

BMI: body mass index
PMI: psoas muscle index
eGFR: estimated glomerular filtration rate
CCr: creatinine clearance

Reasons for not receiving neoadjuvant chemotherapy

Reasons for not receiving NAC are detailed in Table 2. In all patients, renal dysfunction was the most common reason for not receiving NAC (33.3%), followed by patient refusal. Meanwhile, the most common reason for not receiving NAC in the E and Y groups was renal dysfunction (48.1%) and patient refusal (28.6%), respectively.

Table 2 Reasons for not receiving NAC

	Total		E group		Y group		
Variable	n = 55	(%)	n = 27	(%)	n = 28	(%)	*P*-value
Renal dysfunction	18	33.3	13	48.1	5	17.9	
Patient's refusal	10	18.5	2	7.4	8	28.6	
History of other cancer	7	13.0	2	7.4	5	17.9	0.059
Histological type	4	7.4	2	7.4	2	7.1	
Others	16	29.6	8	29.6	8	28.6	

NAC: neoadjuvant chemotherapy

Tolerability of neoadjuvant chemotherapy

A total of 97 patients (81.5%) completed the scheduled two courses of NAC (Table 3). The completion rate of the two scheduled courses of NAC was not different between the two groups (E, 71.4%; Y, 84.6%; $p = 0.116$). Dose reduction frequency was higher in the E group than in the Y group during the first course (42.9% vs 3.3%) but was similar between such groups during the second course (E, 35.7%; Y, 33.0%). Consequently, only 21.4% of the E group completed full-dose NAC, while 63.7% of the Y group did not need any dose reduction ($p < 0.001$). The E group had significantly lower RDIs for both 5-FU (E group: 74.5 ± 23.6 vs Y group: 89.5 ± 18.3, $p < 0.001$) and CDDP (E group: 71.8 ± 23.6 vs Y group: 89.0 ± 18.5, $p < 0.001$), as well as ARDIs for 5-FU and CDDP (E group: 73.1 ± 23.1 vs Y group: 89.4 ± 18.2, $p < 0.001$), compared to the Y group.

Table 3 Tolerability of NAC

	Total		E group		Y group		
Variable	n = 119	(%)	n = 28	(%)	n = 91	(%)	*P*-value
Number of NAC course							
Two	97	81.5	20	71.4	77	84.6	0.116
One	22	18.5	8	28.6	14	15.4	

Dose reduction							
None	64	53.8	6	21.4	58	63.7	
From two course	40	33.6	10	35.7	30	33.0	< 0.001
From first course	15	12.6	12	42.9	3	3.3	
RDI of 5-FU (mean ± SD)	85.9 ± 20.6		74.5 ± 23.6		89.5 ± 18.3		< 0.001
RDI of CDDP (mean ± SD)	85.0 ± 21.1		71.8 ± 23.6		89.0 ± 18.5		< 0.001
ARDI of 5-FU and CDDP (mean ± SD)	85.5 ± 20.6		73.1 ± 23.1		89.4 ± 18.2		< 0.001

NAC: neoadjuvant chemotherapy
SD: standard deviation
RDI: relative dose intensity
ARDI: average relative dose intensity
5-FU: 5-fluorouracil
CDDP: cis-diamminedichloroplatinum

Response of neoadjuvant chemotherapy

Table 4 summarizes the histological and radiological responses. No difference was found in the ratio of grade 2 or 3, indicating that NAC was effective (E, 7.2%; Y, 4.4%). The ratio of clinical response, which included PR and CR, also showed no difference between the groups (E, 25.0%; Y, 28.6%).

Table 4 Histological and radiological responses to NAC

		Total		E group		Y group	
Variables		n = 119	(%)	n = 28	(%)	n = 91	(%)
Histological response	Grade 0	2	1.7	1	3.6	1	1.1
	Grade 1a	106	89.1	22	78.6	84	92.3
	Grade 1b	5	4.2	3	10.7	2	2.2
	Grade 2	5	4.2	1	3.6	4	4.4
	Grade 3	1	0.8	1	3.6	0	0.0
Radiological response	PD	7	5.9	2	7.1	5	5.5
	SD	79	66.4	19	67.9	60	65.9
	PR	33	27.7	7	25.0	26	28.6
	CR	0	0.0	0	0.0	0	0.0

NAC: neoadjuvant chemotherapy
PD: progressive disease
SD: stable disease
PR: partial response
CR: complete response

Toxicity of neoadjuvant chemotherapy

Table 5 lists the adverse events during NAC. The most frequent severe adverse events (grade ≥ 3) were electrolyte disorder and neutropenia (11.8% individually). In the E group, severe adverse events were relatively frequent (E, 42.9%; Y, 27.5%, $p = 0.091$), but severe neutropenia was significantly frequent (E, 25.0%; Y, 7.7%; $p = 0.022$). Severe renal dysfunction during NAC was relatively frequent (E, 10.7%; Y, 2.2%; $p = 0.142$). Meanwhile, the severity of other complications, such as anorexia, electrolyte disorder, mucus membrane disorder, and hepatic disorder, showed no difference.

Table 5 Adverse events of NAC

	Percentage (%)							
	Grade 1		Grade 2		Grade 3		Grade 4	
Adverse event	E group	Y group	E group	Y group	E group	Y group	E group	Y group
Total	21.4	29.7	25.0	35.2	28.6	23.1	14.3	4.4
Renal dysfunction	7.1	5.5	25.0	20.9	10.7	2.2	0.0	0.0
Anorexia	14.3	16.5	25.0	26.4	10.7	5.5	0.0	0.0
Electrolyte disorder	7.1	3.3	10.7	4.4	0.0	9.9	10.7	2.2
Neutropenia	0.0	2.2	0.0	5.5	21.4	5.5	3.6	2.2
Mucous membrane disorder	7.1	7.7	7.1	6.6	0.0	3.3	0.0	0.0
Hepatic disfunction	3.6	4.4	3.6	3.3	0.0	1.1	0.0	0.0

	Percentage (%)						
	All grade		Grade < 3		Grade ≥ 3		
Adverse event	E group	Y group	E group	Y group	E group	Y group	*P*-value
Total	89.3	92.3	46.4	64.8	42.9	27.5	0.091
Renal dysfunction	42.9	28.6	32.1	26.4	10.7	2.2	0.142
Anorexia	50.0	48.4	39.3	42.9	10.7	5.5	0.341
Electrolyte disorder	28.6	19.8	17.9	7.7	10.7	12.1	0.265
Neutropenia	25.0	15.4	0.0	7.7	25.0	7.7	0.022
Mucous membrane disorder	14.3	17.6	14.3	14.3	0.0	3.3	0.348
Hepatic dysfunction	7.1	8.8	7.1	7.7	0.0	1.1	0.598

NAC: neoadjuvant chemotherapy

The reasons for dose reduction and discontinuation of NAC are summarized in Table 6. In both groups, the most frequent reason for NAC dose reduction and discontinuation was renal dysfunction (E, 63.6%; Y, 45.5%), followed by neutropenia and electrolyte disorder. Nevertheless, no difference was observed between the two groups.

Table 6 The reasons for dose reduction and discontinuation of NAC

	Total		E group		Y group		
	n = 55	(%)	n = 22	(%)	n = 33	(%)	*P*-value
Renal dysfunction	29	52.7	14	63.6	15	45.5	
Neutropenia	9	16.4	4	18.2	5	15.2	
Electrolyte disorder	7	12.7	3	13.6	4	12.1	
Anorexia	3	5.5	0	0.0	3	9.1	0.393
Mucous membrane disorder	3	5.5	0	0.0	3	9.1	
Hepatic dysfunction	1	1.8	1	4.5	0	0.0	
Others	3	5.5	0	0.0	3	9.1	

NAC: neoadjuvant chemotherapy

Short- and long-term results compared with and without neoadjuvant chemotherapy

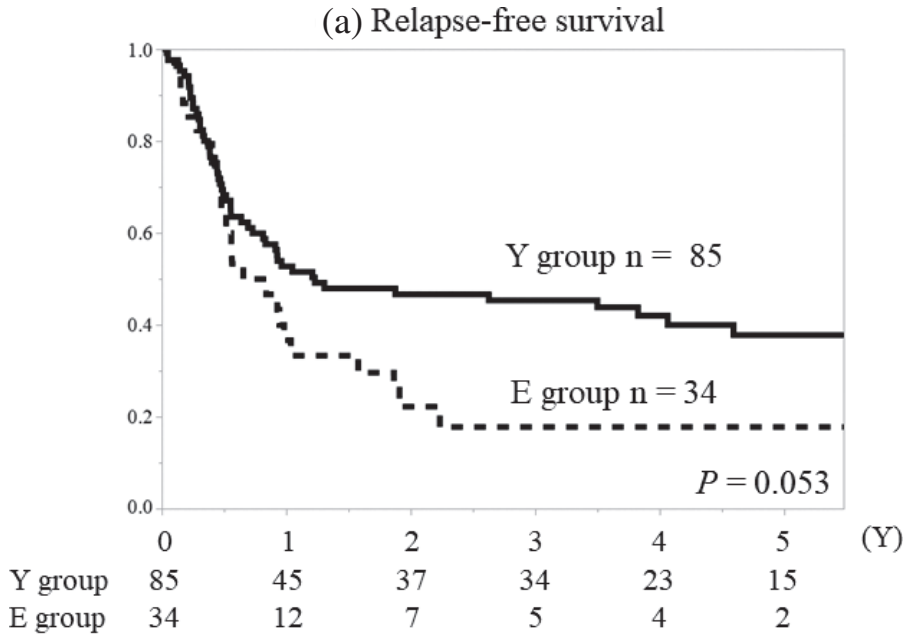
The surgical outcomes of patients who received NAC are detailed in Table 7. In both groups, there were no differences in operative time, estimated blood loss, incidence of postoperative complications, length of hospital stay, and the mortality between with and without NAC.

Table 7 The short-term result compared with and without NAC

	E-group			Y-group		
	NAC (+)	NAC (–)		NAC (+)	NAC (–)	
Variable	n = 28 (%)	n = 27 (%)	*P*-value	n = 91 (%)	n = 28 (%)	*P*-value
Operative time (m)	450 ± 129	432 ± 72	0.531	465 ± 85	443 ± 62	0.215
Blood loss (g)	321 ± 660	313 ± 399	0.958	367 ± 650	358 ± 428	0.947
Overall complication	17 60.7	20 74.1	0.291	51 56.0	17 60.7	0.662
Pneumonia	12 42.9	8 29.6	0.308	29 31.9	8 28.6	0.742
Anastomotic leakage	3 10.7	7 25.9	0.144	21 23.1	4 14.3	0.318
Death						
In Hospital	3 10.7	0 0.0	0.080	5 5.5	3 10.7	0.335
In 30 days	1 3.6	0 0.0	0.322	4 4.4	1 3.6	0.849
Hospital stay (d)	42.8 ± 44.4	38.5 ± 22.7	0.653	33.3 ± 37.3	38.6 ± 40.6	0.528

NAC: neoadjuvant chemotherapy

Y group had relatively better RFS ($p = 0.053$) and OS ($p = 0.066$) than E group (Figure 1). No differences in both RFS and OS were observed between with and without NAC in E and Y groups (Figure 2).



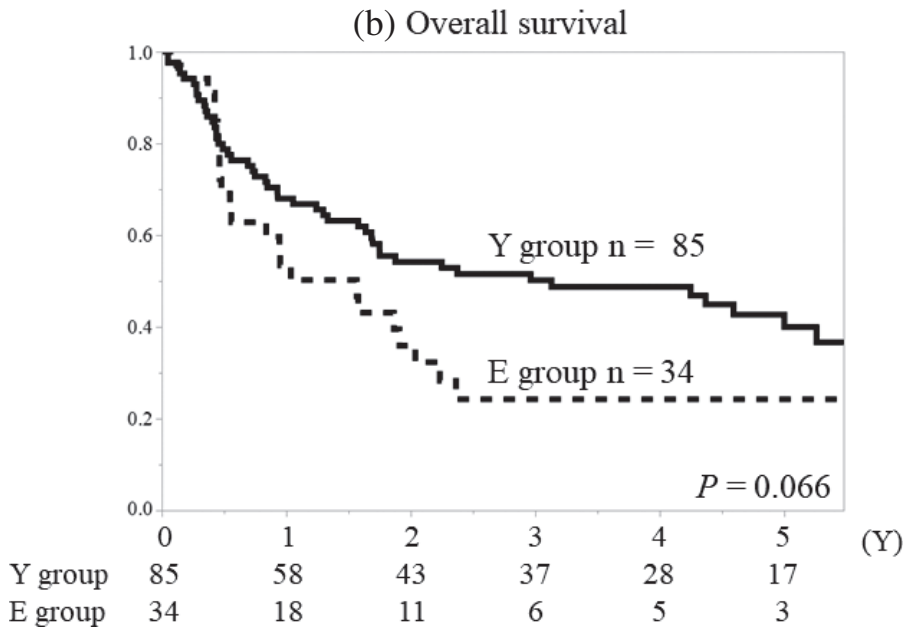
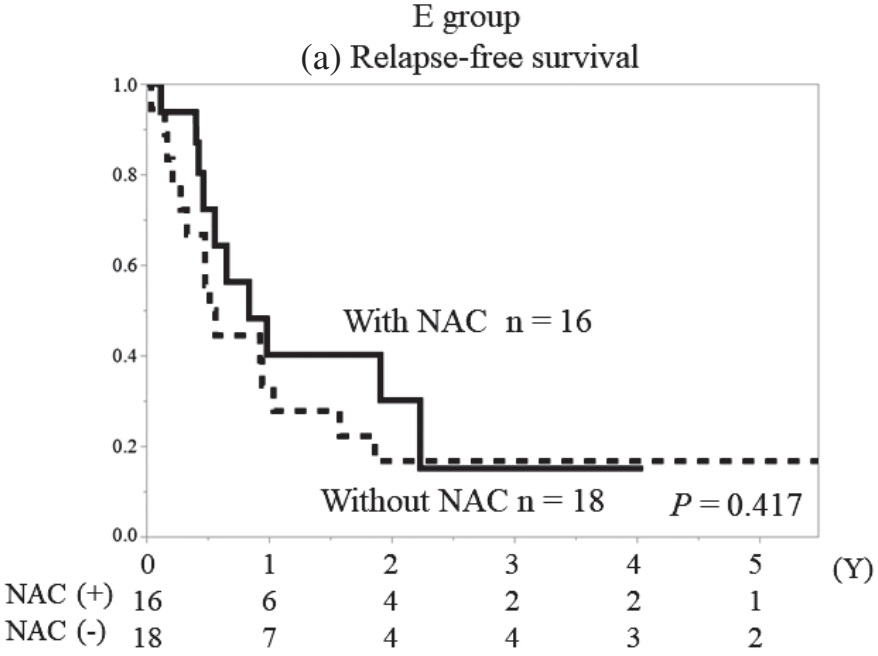
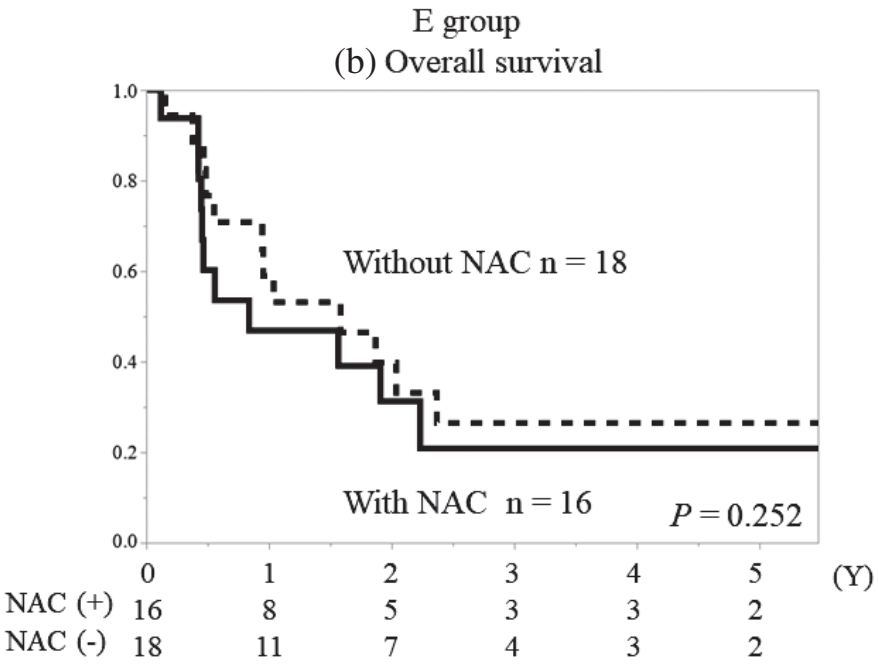


Fig. 1 Long-term survival rates in the E and Y groups
Fig. 1a: Y group had relatively better RFS than E group (p = 0.053).
Fig. 1b: Y group had relatively better OS than E group (p = 0.066).


E group
(a) Relapse-free survival
1.0
0.8
0.6
0.4
0.2
0.0
With NAC n = 16
Without NAC n = 18
P = 0.417
0 1 2 3 4 5 (Y)
NAC (+) 16 6 4 2 2 1
NAC (-) 18 7 4 4 3 2


E group
(b) Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
Without NAC n = 18
With NAC n = 16
P = 0.252
0 1 2 3 4 5 (Y)
NAC (+) 16 8 5 3 3 2
NAC (-) 18 11 7 4 3 2

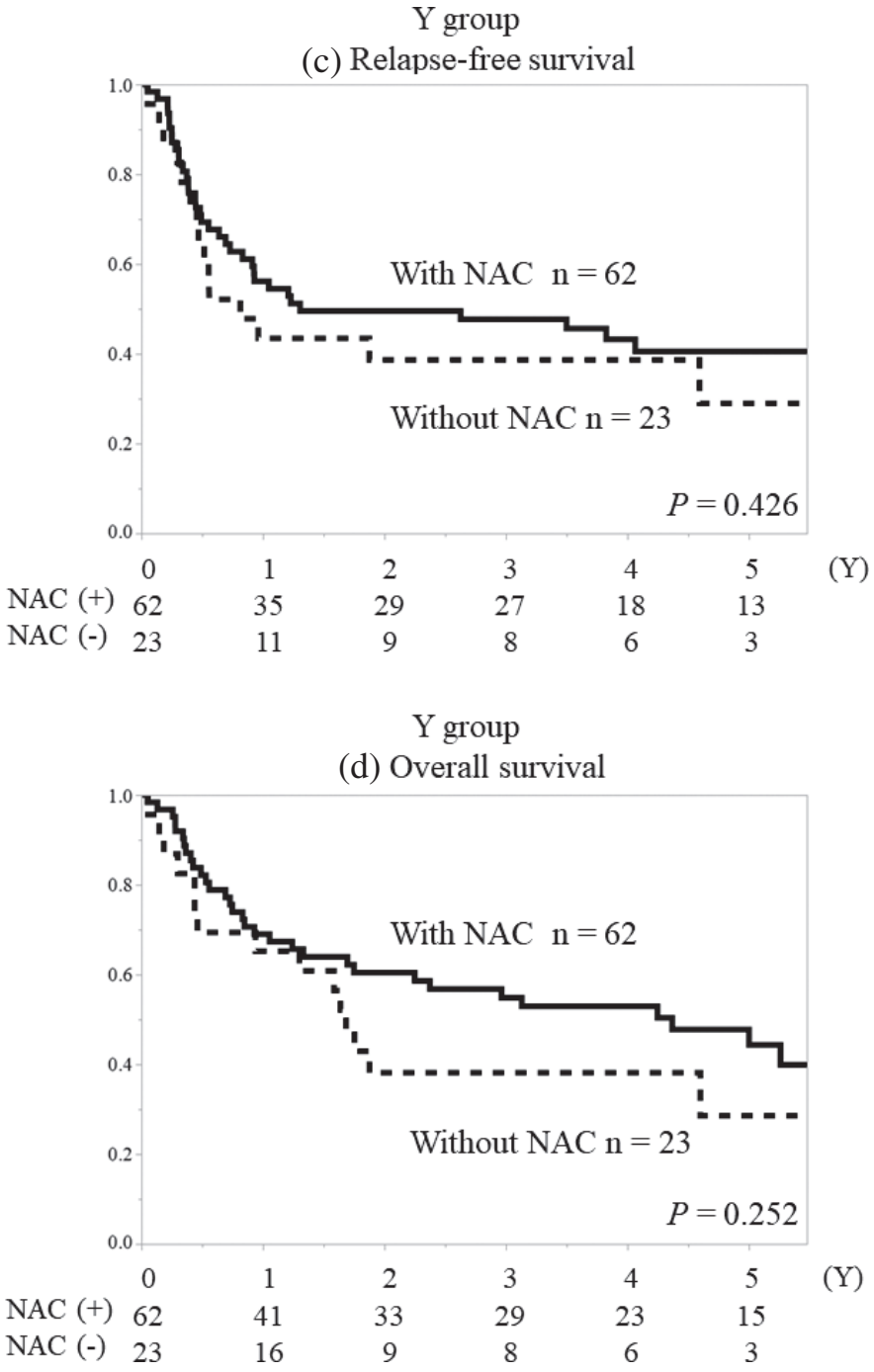


Fig. 2 Relapse-free and overall survival rates in patients with or without NAC in the E and Y groups
Fig. 2a: Relapse-free survival rates with or without NAC in the E group.
Fig. 2b: Overall survival with or without NAC in the E group.
Fig. 2c: Relapse-free survival rates with or without NAC in the Y group.
Fig. 2d: Overall survival with or without NAC in the Y group.
No differences in both RFS and OS were observed between with and without NAC in E and Y groups.

DISCUSSION

Despite the need for adequate case selection and dose reduction depending on renal function and performance status, the present study demonstrated that elderly patients with esophageal cancer aged ≥ 76 years could safely receive NAC.

Among the adverse events associated with NAC for esophageal cancer, Onodera et al reported that renal dysfunction was the most frequent reason for NAC discontinuation and dose reduction.[11] In the current study, 52.7% of NAC reduction and discontinuations were caused due to renal dysfunction, reaching 63.6% among patients aged ≥ 76 years. Furthermore, renal function before starting NAC was significantly lower and severe renal dysfunction during NAC was relatively frequent in the elderly patients. Thus, elderly patients may have potentially poorer renal function and greater susceptibility to toxicities associated with NAC. Alternatively, our result showed that more than 70% of elderly patients aged 76 years were able to complete scheduled NAC with appropriate dose reduction, suggesting that indications for NAC should not be determined based solely on age.

The clinical efficacy of NAC for elderly patients still remains uncertain. Nonetheless, studies have reported radiological response rates to FP therapy of 19%–40%.[2,12-14] Notably, the current study obtained response rates of 25.0% and 28.6% in the E and Y groups, respectively, which was consistent with those published in previous reports. Interestingly, the present study found that the E group did not exhibit inferior response rates compared to the Y group, although ARDIs of 5-FU and CDDP were significantly lower in the E group than in the Y group. According to Khattak et al, elderly patients with advanced colon cancer are less likely to receive chemotherapy despite the potential of achieving oncological benefits.[15] In the current study, age did not influence the response of NAC for esophageal cancer.

Reports have shown that the response of cancer cells to chemotherapy was determined by two factors: drug concentration in the tumor environment and sensitivity of cancer cells to the drug.[14] Multiple studies involving various cancers have noted a close relationship between the efficacy and toxicity of chemotherapy, especially neutropenia.[14,16-20] Given that CDDP is eliminated through the kidneys, renal function has been found to affect the pharmacokinetics of CDDP.[21] Higher drug concentrations significantly correlate with the severity of adverse events.[16-20] Our study demonstrated that although elderly patients had more neutropenia, the NAC response was not inferior to younger patients despite the low RDI.

Thus, we hypothesized that impaired renal function in the E group could have reduced CDDP elimination, resulting in sustained drug concentrations within the tumor environment. Elderly patients might be more susceptible to both NAC response and toxicity. To verify this hypothesis, additional pharmacological examinations analyzing drug metabolism in patients with esophageal cancer with impaired renal function would be necessary in the future.

However, this study has several limitations. First, it has a single-center retrospective design with a relatively small sample size. Second, NAC dose reduction and discontinuation have no certain criteria. In this study, experienced surgeons decided to either reduce the dose or discontinue NAC when severe adverse events occurred. Thirdly, the selection bias of patients who received NAC might influence the result of this study. To elucidate the prognostic benefit of NAC in patients aged ≥ 76 years, further studies with larger number of patients should be mandatory in near future.

In conclusion, although patients aged ≥ 76 years had lower RDIs, the histological and radiological responses to NAC were comparable between elderly and younger patients. Elderly patients with esophageal cancer might be more susceptible to NAC toxicity than younger patients, but more than 70% of elderly patients aged >76 years were able to complete the scheduled NAC

with appropriate dose reduction. In addition, we could not find any differences in the incidence of postoperative complications associated with NAC in the elderly patients. Thus, even in the elderly patients, NAC was tolerable with appropriate dose reduction. Therefore, certain criteria for NAC introduction and dose reduction must be established, and the prognostic benefit of NAC in patients aged ≥ 76 years should be confirmed by conducting a randomized prospective study in the future.

ACKNOWLEDGMENTS

The authors would like to thank Enago (www. Enago.jp) for English language review.

CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

REFERENCES

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424. doi:10.3322/caac.21492.

2 Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). A*nn Surg Oncol*. 2012;19(1):68–74. doi:10.1245/s10434-011-2049-9.

3 Watanabe M, Tachimori Y, Oyama T, et al. Comprehensive registry of esophageal cancer in Japan, 2013. *Esophagus*. 2021;18(1):1–24. doi:10.1007/s10388-020-00785-y.

4 Booka E, Haneda R, Ishii K, Tsushima T, Yasui H, Tsubosa Y. The negative impact of preoperative chemotherapy on survival after esophagectomy for vulnerable elderly patients with esophageal cancer. *Ann Surg Oncol*. 2021;28(3):1786–1795. doi:10.1245/s10434-020-09072-7.

5 Brierley JD, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours*. John Wiley & Sons; 2017.

6 Nagata K, Tsujimoto H, Nagata H, et al. Impact of reduced skeletal muscle volume on clinical outcome after esophagectomy for esophageal cancer: a retrospective study. *Medicine (Baltimore)*. 2018;97(30):e11450. doi:10.1097/md.0000000000011450.

7 Japanese Society of Nephrology, Japan Society of Clinical Oncology, Japanese Society of Medical Oncology, The Japanese society of Nephrology and pharmacotherapy. Clinical practice guidelines for the management of kidney disease in cancer survivors [in Japanese]. *Jpn J Nephrol*. 2016;58(7):985–1050.

8 Matsubara H, Ando N, Fujita H, et al. Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus*. 2017;14(1):1–36. doi:10.1007/s10388-016-0551-7.

9 Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part II and III. *Esophagus*. 2017;14(1):37–65. doi:10.1007/s10388-016-0556-2.

10 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. doi:10.1016/j.ejca.2008.10.026.

11 Onodera K, Miyata G, Ichikawa H, Kamei T, Nakano T, Satomi S. Neoadjuvant chemotherapy for esophageal squamous cell carcinoma [in Japanese]. *Jpn J Gastroenterol Surg*. 2013;46(12):877–884. doi:10.5833/jjgs.2012.0254.

12 Ancona E, Ruol A, Santi S, et al. Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma. *Cancer*. 2001;91(11):2165–2174. doi:10.1002/1097-0142(20010601)91:11<2165::AID-CNCR1245>3.0.CO;2-H.

13 Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med*. 1998;339(27):1979–1984. doi:10.1056/nejm199812313392704.

14 Motoori M, Yano M, Yasuda T, et al. Chemotherapy-induced toxicities and treatment efficacy in advanced

esophageal cancer treated with neoadjuvant chemotherapy followed by surgery. *Esophagus*. 2011;8(2):81–87. doi:10.1007/s10388-011-0267-7.

15 Khattak MA, Townsend AR, Beeke C, et al. Impact of age on choice of chemotherapy and outcome in advanced colorectal cancer. *Eur J Cancer*. 2012;48(9):1293–1298. doi:10.1016/j.ejca.2011.09.029.

16 Di Paolo A, Lencioni M, Amatori F, et al. 5-fluorouracil pharmacokinetics predicts disease-free survival in patients administered adjuvant chemotherapy for colorectal cancer. *Clin Cancer Res*. 2008;14(9):2749–2755. doi:10.1158/1078-0432.Ccr-07-1529.

17 Gamelin EC, Danquechin-Dorval EM, Dumesnil YF, et al. Relationship between 5-fluorouracil (5-FU) dose intensity and therapeutic response in patients with advanced colorectal cancer receiving infusional therapy containing 5-FU. *Cancer*. 1996;77(3):441–451. doi:10.1002/(SICI)1097-0142(19960201)77:3<441::AID-CNCR4>3.0.CO;2-N.

18 Gusella M, Frigo AC, Bolzonella C, et al. Predictors of survival and toxicity in patients on adjuvant therapy with 5-fluorouracil for colorectal cancer. *Br J Cancer*. 2009;100(10):1549–1557. doi:10.1038/sj.bjc.6605052.

19 Santini J, Milano G, Thyss A, et al. 5-FU therapeutic monitoring with dose adjustment leads to an improved therapeutic index in head and neck cancer. *Br J Cancer*. 1989;59(2):287–290. doi:10.1038/bjc.1989.59.

20 Vokes EE, Mick R, Kies MS, et al. Pharmacodynamics of fluorouracil-based induction chemotherapy in advanced head and neck cancer. *J Clin Oncol*. 1996;14(5):1663–1671. doi:10.1200/jco.1996.14.5.1663.

21 Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. *Cancer Treat Rev*. 1995;21(1):33–64. doi:10.1016/0305-7372(95)90010-1.