Feasibility assessment of global standard chemoradiotherapy followed by surgery in patients with esophageal cancer

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Abstract. The present study aimed to assess the feasibility of global standard chemoradiotherapy (CRT) followed by surgery in patients with esophageal cancer. A prospective study was conducted at Nagoya University Hospital (Nagoya, Japan) to evaluate global standard CRT followed by surgery in patients with esophageal cancer. The CRT regimen consisted of 75 mg/m^2 cisplatin on day 1 and 1,000 mg/m^2 fluorouracil daily on days 1-4 given twice 4 weeks apart together with concurrent esophageal irradiation starting on day 1 (group A). For comparison, 17 patients with esophageal cancer who had received the same chemotherapy regimen but with lower drug doses were retrospectively reviewed: 70 mg/m^2 cisplatin on day 1 and 700 mg/m^2 fluorouracil daily on days 1-4 given twice 4 weeks apart together with concurrent esophageal irradiation starting on day 1 (group B). Grade 3 or worse adverse events were observed in 9 of the 12 patients (75%) in group A and in 5 of the 17 patients (29%) in group B. The patients in group A were more likely to experience grade 3 or worse neutropenia (50%) than those in group B (6%). No febrile neutropenia or treatment-related deaths occurred in either group. A total of 11 patients (92%) in group A and 16 patients (94%) in group B subsequently underwent an esophagectomy, and 9 (82%) and 14 (88%) of these patients, respectively, achieved microscopically margin-negative resection (R0 resection). In conclusion, global standard CRT was more likely to cause severe but manageable adverse events. There was no apparent difference in the R0 resection rate or postoperative complications between the two treatments. This clinical trial was registered at the Japan Registry of Clinical Trials (trial registration number: jRCT1041180004) on September 11, 2018.

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Introduction

Preoperative chemoradiotherapy (CRT) followed by surgery is a global standard treatment for resectable esophageal cancer (1). The most commonly used chemotherapy regimen consists of 75 mg/m^2 cisplatin on day 1 and 1,000 mg/m^2 fluorouracil daily on days 1 through 4, given twice 4 weeks apart. In Japan, unlike in most parts of advanced countries (2-4), chemotherapy regimens with lower drug doses have long been used outside clinical studies, such as 70 to 80 mg/m^2 cisplatin on day 1 plus 700 to 800 mg/m^2 fluorouracil on days 1 through 4 or 5 (5-9). In particular, chemotherapy regimens consisting of 70 mg/m^2 cisplatin on day 1 plus 700 mg/m^2 fluorouracil on days 1 through 4 are often used in Japan for unresectable locally advanced esophageal cancer (10). Following the evidence-based standardization of cancer treatment, some institutions in Japan have recently begun using global standard regimens in routine clinical practice (11,12). However, there is little information about the extent to which these differences in drug doses could alter clinical outcomes, especially feasibility. Therefore, by comparing past cases treated with the low-dose regimen to more current global standard-regimen cases, we assessed the feasibility of the global standard regimen, utilizing results from a prospective study of global standard CRT followed by surgery in Japanese patients with esophageal cancer.

Patients and methods

Prospective study (Group A). We conducted a prospective study in which patients with resectable esophageal cancer received global standard CRT followed by surgery in a university hospital in Japan. The study was designed and

conducted in line with the Helsinki Declaration and the Ethical Guidelines for Clinical Research (Ministry of Health, Labor and Welfare, Japan). It was approved by the Institutional Review Board (approval no. 2018-0453) and registered at the Japan Registry of Clinical Trials (jRCT1041180004). All participants provided written informed consent before study enrollment.

The main eligibility criteria included i) histologically confirmed esophageal squamous cell carcinoma or adenocarcinoma or adenosquamous carcinoma or basaloid cell carcinoma; ii) Stage I B, Stage II, Stage III (T4 included), or Stage IV (only supraclavicular lymph node metastasis included); iii) Eastern Cooperative Oncology Group performance status (PS) 0-1; iv) preserved organ functions; v) age 20-75 years; vi) with or without measurable lesion; and vii) no prior treatment for esophageal cancer.

The patients first received global standard CRT consisting of 75 mg/m^2 cisplatin on day 1 plus 1,000 mg/m^2 fluorouracil daily on days 1 through 4, given twice 4 weeks apart (2 courses) together with concurrent irradiation for the esophagus starting on day 1 (1.8 Gy once daily in 23 fractions, a total of 41.4 Gy) and then underwent surgery. All AEs were evaluated according to the Common Terminology Criteria for Adverse Events v 4.0 (CTCAE). Treatment was continued until unacceptable AEs or disease progression occurred. The cisplatin doses for the first and the second courses were reduced based on the patient's creatine clearance calculated using the Cockcroft-Gault equation (13): if creatinine clearance was below 60 mL/min, the cisplatin dose was reduced to 80%; if below 50 ml/min, the dose was reduced to 50%. If creatinine clearance was below 40 ml/min, cisplatin was suspended. If the neutropenia and thrombocytopenia that occurred in the first course did not recover to grade 1 and 100,000/μl, respectively, by the beginning of the second course, the doses of both cisplatin and fluorouracil in the second course were reduced to 50%. If grade 4 neutropenia, grade 4 thrombocytopenia, or febrile neutropenia (FN) occurred in the first course, the doses of both cisplatin and fluorouracil in the second course were reduced to 80 and 75%, respectively. If grade 3 or worse stomatitis, esophagitis, or diarrhea occurred in the first course, the fluorouracil dose in the second course was reduced to 75%. Irradiation was suspended when patients had grade 4 neutropenia, grade 4 thrombocytopenia, or FN. The administration of antiemetics and the therapeutic use of granulocyte colony stimulating factor (G-CSF) and antimicrobials were allowed, but prophylactic administration of G-CSF was not allowed.

Initially, the primary endpoint was the objective response rate (RR), and a total of 21 patients were planned to be enrolled. The planning sample size was estimated based on a threshold RR of 40%, an expected RR of 75%, a 5% significance level (one-sided), and 90% power, given 10% of patient discontinuation or loss. However, because the study was closed when 12 patients were enrolled due to slow patient enrollment, the results of the study were analyzed primarily from the viewpoint of feasibility. Clinical response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. (14). Clinicopathologic parameters are expressed according to the 8th edition of TNM Classification of the Union for International Cancer Control (UICC) (15). Relapse-free survival (RFS) was defined as the time from the date of start of the preoperative treatment to the date of recurrence, and overall survival (OS) was defined as the time from the date of enrollment to the date of death from any cause or the last confirmation of survival. The severity of postoperative complications was assessed according to the Clavien-Dindo classification of surgical complications (16), of which grade 3 or worse complications were recorded. Grades of histopathological regression were assessed according to the criteria from the Japan Esophageal Society (17): Grade 0, no recognizable cytological or histological therapeutic effect; Grade 1a, two-thirds or more of the tumor tissue contains viable tumor cells; Grade 1b, one-third or more of the tumor tissue contains viable tumor cells; Grade 2, less than one-third of the tumor tissue contains viable tumor cells; and Grade 3, no viable tumor cells (pathological complete response).

Relative dose intensity (RDI) was calculated as the ratio of the total actual dose intensity (DI) to the total planned DI. RDI and DI were defined as follows: DI=total actual dose (mg/m^2)/total time to complete therapy (weeks); RDI (%)=(DI of actual therapy/DI of the planned regimen) x100.

Retrospective analysis (Group B). We retrospectively reviewed 17 patients under the age of 75 with the same disease between January 2018 and December 2021 who had received the same CRT as patients in the prospective study except for a chemotherapy regimen with lower drug doses (approval no. 2022-0191). The chemotherapy regimen was 70 mg/m^2 cisplatin on day 1 plus 700 mg/m^2 fluorouracil daily on days 1 through 4. Dose reduction or interruption was left to the discretion of the attending physicians. Prophylactic antiemetics, therapeutic G-CSF, and antibiotics were used according to the relevant clinical guidelines. Prophylactic G-CSF was not used.

All the patients in both groups received standard clinical care, including esophagectomy and chemotherapy in case of recurrence.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics version 28.0 (IBM Japan Ltd., Tokyo, Japan). The P-value for age between two groups was calculated using the Mann-Whitney U test, whereas those for other factors were calculated with Fisher's exact test. $P<0.05$ was considered to indicate statistical significance. Kaplan-Meier curves and the log-rank test were used to analyze and compare survival between the two groups.

Results

Prospective study (Group A). Between September 2018 and January 2022, 12 patients were enrolled in the study (Table I). All patients successfully completed two courses of chemotherapy without delay. Seven patients (58%) required dose reduction in the first (n=5) and second (n=7) courses due to grade 2 renal dysfunction, and another patient (8%) in the second course required dose reduction due to grade 2 neutropenia (Table SI). The overall mean RDIs of cisplatin and fluorouracil were 82% (range 40 to 100%) and 97% (range 75 to 100%), respectively. Three patients (25%) experienced interruption of irradiation due to grade 4 neutropenia, grade 1 hematemesis, and grade 3 lung infection.

Table I. Patient characteristics.

Characteristics	Group A (n=12)	Group B (n=17)	P-value
Median age, years (range)	69 (58-75)	68 (48-74)	0.444
Sex			0.403
Male	8 (67)	14 (82)	
Female	4 (33)	3 (18)	
Performance status			1.000
0	10 (83)	13 (76)	
1	2 (17)	4 (24)	
Creatinine clearance, ml/min			0.369
≥60	8 (67)	10 (59)	
50-60	4 (33)	3 (17)	
40-50	0	3 (17)	
<40	0	1 (6)	
Histopathology			0.414
Squamous cell carcinoma	11 (92)	17 (100)	
Adenocarcinoma	1 (8)	0	
Primary tumor location			0.588
Upper	6 (50)	6 (35)	
Middle	4 (33)	9 (53)	
Lower	2 (17)	2 (12)	
T stage			0.311
T2	1 (8)	0	
T3	11 (92)	15 (89)	
T4	0	2 (12)	
N stage			0.177
N0	0	4 (24)	
N1	6 (50)	5 (29)	
N2	5 (42)	8 (47)	
N3	1 (8)	0	
Clinical stage			0.098
II	0	3 (18)	
III	10 (83)	14 (82)	
IV	2 (17)	0	

Data are presented as n (%), unless otherwise specified. P<0.05 was considered to indicate statistical significance.

Table II. Adverse events.

Adverse events	Any grade	Grade≥3
Group A		
Leukopenia	11 (92)	7 (58)
Neutropenia	11 (92)	6 (50)
Anemia	12 (100)	2 (17)
Thrombocytopenia	8 (67)	1 (8)
Hypoalbuminemia	12 (100)	1 (8)
Hyponatremia	10 (83)	1 (8)
Hyperkalemia	5 (42)	0
Hypokalemia	4 (33)	1 (8)
Creatinine increased	5 (42)	0
Elevated aspartate aminotransferase	5 (42)	1 (8)
Anorexia	2 (17)	1 (8)
Nausea	4 (33)	0
Diarrhea	4 (33)	1 (8)
Lung infection	3 (25)	2 (17)
Hematemesis	1 (8)	0
Group B		
Leukopenia	10 (59)	1 (6)
Neutropenia	10 (59)	1 (6)
Anemia	17 (100)	2 (12)
Thrombocytopenia	7 (41)	0
Hypoalbuminemia	17 (100)	0
Hyponatremia	14 (82)	0
Hyperkalemia	11 (65)	0
Creatinine increased	9 (53)	0
Elevated aspartate aminotransferase	7 (41)	0
Elevated alanine aminotransferase	8 (47)	0
Anorexia	6 (35)	2 (12)
Nausea	8 (47)	0
Fatigue	10 (59)	0
Edema	2 (12)	1 (6)

Data are presented as n (%).

All the patients experienced hematological or nonhematological AEs during CRT (Table II). The most common AEs of any grade were anemia and hypoalbuminemia, which occurred in all patients. The most common grade 3 or worse AEs were leukopenia and neutropenia, with frequencies of 58 and 50%, respectively. Grade 3 or worse AEs were observed in nine patients (75%), of whom two and one suffered from grade 4 neutropenia and grade 4 hyponatremia, respectively. The one patient experiencing grade 4 neutropenia required the therapeutic use of G-CSF and antibiotics. In addition, two other patients required the application of therapeutic antibiotics. No one experienced FN or treatment-related death.

Eleven patients [91.7; 95% confidence interval (CI): 61.5-99.8%] subsequently underwent an esophagectomy, of which 9 (81.8; 95% CI: 48.2-97.7%) achieved microscopically margin-negative resection (R0 resection). The remaining patient underwent esophageal bypass surgery due to disease progression. The histopathological responses of the 11 patients who underwent esophagectomy were grade 1a in two, grade 1b in two, grade 2 in five, and grade 3 in two. Regarding postoperative complications, four patients experienced grade III or worse lung infection (Table III). The median follow-up period

Table III. Postoperative complications.

Postoperative complications	Number (%)
Group A (n=11)	
Pleural effusion	1 (9)
Lung infection	4 (36)
Mediastinal infection	1 (9)
Dyspnea	1 (9)
Dysphagia	1 (9)
Postoperative hemorrhage	1 (9)
Wound infection	1 (9)
Gastric fistula	1 (9)
Group B (n=16)	
Pleural effusion	2 (13)
Lung infection	5 (31)
Dyspnea	2 (13)
Pneumothorax	1 (6)
Atelectasis	1 (6)
Dysphagia	1 (6)
Anastomotic leakage	2 (13)
Wound infection	1 (6)

The total number of complications does not equal the number of patients because some patients had no complications.

was 24.1 months (range 12.7 to 35.5 months). Kaplan-Meier curves of RFS and OS are shown in Fig. S1A and B, respectively. Four patients (33%) experienced recurrence, and two patients (17%) died at 6 and 15 months after surgery.

Retrospective analysis (Group B). There were no significant differences in the patients' background characteristics between the two groups (Table I). Among the 17 patients, two (12%) required a delay in starting the second course: one because of lung infection and another because of percutaneous coronary intervention for angina pectoris as a preexisting complication. Six patients (35%) required dose reduction or omission of cisplatin due to renal dysfunction (Table SII), including one who did not receive cisplatin at all. The overall mean RDIs of cisplatin and fluorouracil in global standard chemotherapy, i.e., 75 mg/m^2 cisplatin on day 1 plus 1,000 mg/m^2 fluorouracil daily on days 1 through 4, were 80% (range 0 to 93%) and 69% (range 58 to 70%), respectively. None of the patients experienced interruption of concurrent irradiation for the esophagus.

The most common AEs of any grade were anemia and hypoalbuminemia, which occurred in all patients (Table II). None of the patients experienced grade 4 AEs. The most common grade 3 AEs were anemia and anorexia, both occurring at a rate of 12%. Grade 3 AEs were observed in five patients (29%), one of whom suffered from grade 3 neutropenia but did not require the therapeutic use of G-CSF. None of the patients experienced FN or treatment-related death.

Sixteen patients (94.1%; 95% CI: 71.3-99.9) received an esophagectomy, which achieved R0 resection in 14 (87.5%; 95% CI: 61.7-98.4%). The other patient (the seventeenth) received esophageal bypass surgery due to lung metastasis. The histopathological responses of the 16 patients who underwent esophagectomy were Grade 1b in six patients, Grade 2 in six, and Grade 3 in four. The most common grade III or worse postoperative complications was lung infection in five patients (Table III). Five patients (29%) experienced recurrence, and five patients (29%) died; the median follow-up period was 18.8 months (range 17.3 to 20.3 months).

We compared RFS between groups A and B (Fig. S1A), as well as OS between groups A and B (Fig. S1B). With the small number of patients in each group, there was no significant difference in RFS or OS between the two groups.

Discussion

This study assessed the feasibility of global standard CRT followed by surgery in Japanese patients with esophageal cancer by comparing results from the prospective study with the global standard chemotherapy regimen (group A) to those from past cases treated with the low-dose regimen (group B). Apparently, the patients treated with the global standard regimen were more likely to experience grade 3 or worse AEs, particularly neutropenia, than those treated with the low-dose regimen. However, as expected, the AEs that occurred in the patients who received the global standard regimen were manageable, and there were no FN- or treatment-related deaths. On the other hand, there appeared to be no apparent difference in R0 resection rates and postoperative complications between the two treatments.

The overall mean RDIs of cisplatin and fluorouracil in group A were higher than those in group B. In particular, there was a large difference in the DI of fluorouracil (97% vs. 69%). Although there were no apparent differences in the R0 resection rate and possibly survival between the global standard and low-dose regimens, there was a tendency that OS was possibly better with a global standard regimen, and the difference may be obvious when larger numbers of patients are analyzed. Given the feasibility of the global standard regimen, it is reasonable to recommend preoperative CRT with global standard-dose chemotherapy in Japanese patients with esophageal cancer.

There were some limitations in the present analysis. First, because the number of patients in each group was too small to objectively conclude that a global standard dose of cisplatin and fluorouracil is feasible and could provide survival benefit, to verify the survival differences with different doses of cisplatin and fluorouracil, a randomized study with a larger patient sample is needed in the future. Second, the present study was not randomized and was controlled with a historic sample set. Nevertheless, because the patients in the two groups had similar backgrounds, they were considered to be comparable. Third, because dose reduction or interruption was based on the discretion of the attending physicians, it could bring favorable results for AEs in group B. Despite the limitations, the global standard CRT followed by surgery was suggested to be feasible and should be recommended in Japanese patients with esophageal cancer. However, further discussion or more data is needed to support the conclusion.

In conclusion, the global standard regimen was manageable, although potentially associated with more adverse events when compared to the low-dose regimen. The difference in R0 resection rates was not apparent, possibly due to the small number of patients in both groups. Differences in RFS and OS also need to be examined in a larger sample of patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

OM designed the study. KM, MiK, DS, SS, TO, JI, MaK, SI, YK and YA conducted the clinical trial and provided clinical data. OM and YA confirmed the authenticity of all the raw data. MN and MA performed the statistical analysis. YL and OM analyzed the data and wrote the manuscript. OM, YK and YA revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Nagoya University Hospital (approval nos. 2018-0453 and 2022-0191). All participants of the prospective study (jRCT1041180004) (Group A) provided written informed consent before enrollment in the study. Informed consent for the retrospective analysis (Group A and Group B) was obtained in the form of opt-out at the website.

Patient consent for publication

All participants of the prospective study (jRCT1041180004) (Group A) provided written informed consent for publication. Informed consent for publication for the retrospective analysis (Group A and Group B) was obtained in the form of opt-out at the website.

Competing interests

The authors declare that they have no competing interests.

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