Clinical Original Article

Title: Safety and efficacy of preoperative chemotherapy followed by esophagectomy compared with upfront surgery for resectable esophageal squamous cell carcinoma

Takanori Kurogochi[1], M.D., Michitaka Honda[1, 2], M.D., Ph.D., Kotaro Yamashita[1], M.D., Masaru Hayami[1], M.D., Ph.D., Akihiko Okamura[1], M.D., Ph.D., Yu Imamura[1], M.D., Ph.D., F.A.C.S., Shinji Mine[1], M.D., Masayuki Watanabe[1], M.D., Ph.D., F.A.C.S.

[1]Department of Gastroenterological Surgery, The Cancer Institute Hospital of Japanese Foundation for Cancer Research

[2]Department of Minimally Invasive Surgical and Medical Oncology, Fukushima Medical University

Correspondence to: Masayuki Watanabe, M.D., Ph.D., F.A.C.S.
Department of Gastroenterological Surgery, The Cancer Institute Hospital of Japanese Foundation for Cancer Research. 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan.
TEL: +81-3-3520-0111
FAX: +81-3-3520-0141
e-mail: masayuki.watanabe@jfcr.or.jp

Key words: neoadjuvant chemotherapy, esophageal cancer, complications, daily clinical practice

Abstract

Purpose: Neoadjuvant chemotherapy (NAC) followed by esophagectomy has become a standard treatment for esophageal squamous cancer (ESCC) in Japan. We used propensity-matching analysis to clarify the safety and efficacy of NAC in daily clinical practice.

Methods: We reviewed the medical records of 335 patients with clinical Stage II/III ESCC diagnosed between 2007 and 2012, including 191 who received preoperative NAC (NAC group) and 144 treated by upfront surgery (US group). After propensity score matching, there were 118 patients in each group. We compared the postoperative complications and longterm outcomes between the groups.

Results: Seven patients in the NAC group underwent replacement therapy. Complications occurred in 76 (68.5%) and 76 (64.4%) patients in NAC and US groups, respectively ($p = 0.51$), and severe complications occurred in 17 (22.4%) and 30 (39.5%) patients, respectively ($p = 0.057$). One (0.8%) and three patients (2.5%) from the US group died within 30 days and 90 days after surgery, respectively, but none of the patients from the NAC group died within the same period. The 5-year survival rate was 54.9% in the NAC group and 41.2% in the US group ($p = 0.024$).

Conclusions: NAC is a safe and effective treatment to improve prognosis in the clinical

setting.

Introduction

The oncological benefits of neoadjuvant chemotherapy (NAC) on esophageal squamous cell carcinoma (ESCC) reported by the JCOG9907 trial had a significant impact on Japanese clinical practices [1]. Currently, the Japanese guideline for the treatment of ESCC recommends a combination chemotherapy of 5-fluorouracil (5-FU) and cisplatin, followed by esophagectomy, for patients with clinical stage II/III ESCC [2]. However, a recommendation based on the results of just one clinical trial needs to be considered carefully in relation with its applicability to all patients in the clinical setting.

Clinical trials tend to enroll patients in generally good physical condition with few comorbidities. However, many ESCC patients are elderly [3] [4] and most have smoking and/or drinking habits [5-7], so tend to have comorbidities, including respiratory or cardiovascular disorders, and may not tolerate intensive treatment. The clinical trial may not have included such patients. In clinical practice, it is assumed that adequate dose intensity cannot be achieved because of the side effects. There are reports of a gap between clinical trials and clinical practice [8] [9], raising concerns that the effectiveness of NAC has been overvalued in the Japanese clinical guidelines from the perspective of external validity of the clinical trial.

Esophagectomy is still associated with high risk of the development of many postoperative respiratory or circulatory complications, and it is feared that NAC might compromise a patient's tolerance for this invasive surgery or increase the risk of postoperative complications[10] [11]. There are some reports that preoperative chemotherapy or chemoradiotherapy followed by surgery did not increase the risk of postoperative morbidity or mortality compared with surgery alone [12-14]. However, many of these studies are from Western countries, where adenocarcinoma is the predominant subtype and operative procedures are different from those in Japan. Therefore, it is meaningful to clarify the relationship between NAC and postoperative complications in daily clinical practice in Japan.

The current study presents two hypotheses. The first is that NAC for patients with resectable ESCC increases the risk of postoperative complications, and the second is that the prognostic efficacy of NAC, as reported in clinical trials, is overestimated when compared with the reality of clinical practice. Through this study, we hope to provide information that is relevant to real clinical practice and that can help select suitable strategies for patients with ESCC.

Materials and Methods

Patients

This was a retrospective cohort study. We extracted subject data registered between January, 2007 and December, 2012 in the esophageal carcinoma database of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. The inclusion criteria were as follows: histologically confirmed ESCC of clinical Stage II or III in accordance with the TNM Classification (AJCC/UICC 7th edition)[15], or clinical Stage IV when patients had only supraclavicular lymph node metastasis. Because the supraclavicular lymph nodes are classified as regional lymph nodes in the Japanese classification and treatment guideline, these patients were treated as for clinical Stage II/III. There were a total of 335 patients, including 191 who received NAC (NAC group) and 144 who were treated by upfront surgery (US group). The study was approved by the Institutional Review Board of our institute (No. 2016-1077).

Surgical Procedures

All surgery was performed by three experienced surgeons and the procedures did not change during the study period. Briefly, the procedure consisted of thoracolaparotomy, esophageal subtotal resection, and three-field lymph node

dissection. The patient was placed in the left lateral decubitus position and thoracotomy was performed via the fourth intercostal space, followed by combined resection of the thoracic duct, and en-bloc lymph node dissection around the recurrent nerve, the tracheobronchial region, and the lower mediastinum. In the abdomen, lymph node dissection around the celiac artery was performed, as well as supraclavicular lymph node dissection if metastasis was suspected before treatment or if the tumor was located in the upper or middle thoracic esophagus. In terms of reconstruction, after the gastric tube was created and elevated through the retrosternal or posterior mediastinal route, anastomosis was performed in the neck. In some patients with early-stage tumors, the thoracoscopic approach was selected.

Anesthesia and respiratory management

Patients were managed intraoperatively under general anesthesia induced with a combination of intravenous propofol and inhaled drugs, and epidural analgesia was used during the operation as well as in the postoperative period. The tracheal tube was removed just after the completion of surgery in the operating room in almost all patients in the two groups. Mechanical ventilation was used only for patients with delayed emergence from

general anesthesia or for those with impaired pulmonary gas exchange. Bronchial lavage using a bronchofiberscope was performed for patients with impaired expectoration.

Neoadjuvant Chemotherapy

The preoperative chemotherapy regimen consisted of two courses of 5-FU and cisplatin combination therapy. Specifically, cisplatin (80 mg/m2) was administered on day 1 and 5-FU (800 mg/m2) was administered on days 1–5, with one course lasting for 28 days. Two courses were planned. When Grade 3 or above adverse events were observed, the dose was reduced by up to 25%, and when adverse events such as serious myelosuppression, renal dysfunction, or impaired liver function were observed, treatment was stopped midway through the course and surgery was performed without the second course. When imaging during the course revealed clear exacerbation of the primary lesion or target lesion, the second course was omitted and surgery or alternative treatment was performed. Surgery was carried out after a period of 3–4 weeks following the completion of NAC.

Adjuvant chemotherapy

None of the NAC group patients received adjuvant chemotherapy. We recommended two courses of adjuvant FP therapy consisting of the same regimen as

NAC, for US group patients with pathological nodal metastasis, if they could tolerate it.

Pathological Response to Chemotherapy

The degree of histopathological tumor regression in the surgical specimen was classified into four categories. Theextent of viable residual carcinoma at the primary site was assessed semiquantitatively, based on the estimated percentage of viable residual carcinoma in relation with the macroscopically identifiable tumor bed that was evaluated histopathologically[16] . The percentage of viable residual tumor cells within the entire cancerous tissue was assessed as follows: Grade 3, no viable residual tumor cells (pathological complete response); Grade 2, less than one-third residual tumor cells; Grade 1b, more than one-third, but less than 2/3 residual tumor cells; and Grade 1a, more than 2/3 residual tumor cells.

Outcomes

The main outcomes were the incidence of postoperative complications, and the overall and disease-free survival times. Complications were graded according to the Clavien–Dindo classification [17] and the incidence of Grade III or higher complications were evaluated. Secondary outcomes were NAC dose intensity and the incidence of Grade 3 or more preoperative adverse events according to the Common

Terminology Criteria for Adverse Events Ver. 4.0. The survival time was defined as the duration from the start of chemotherapy until the events for patients who received NAC, and as the duration from the day on which surgery was carried out until the events for those who underwent US.

Data Collection and Staging

Patient information such as age, sex, BMI, comorbidities, tumor location, and clinical stage was extracted from the CIH esophageal carcinoma database. Depth of invasion was assessed comprehensively based on the findings of upper gastrointestinal endoscopy, CT scan, and barium-meal study. Lymph node metastasis was assessed based on the axial image from a CT scan: lymph nodes 10 mm or larger were diagnosed as metastasis. Lymph nodes were also regarded as metastasis-positive if FDG uptake was detected by a PET scan.

Adjusting of confounding factors and propensity score matching

To compare the outcomes of the NAC and US groups, some confounding factors needed adjustment to secure validity of the comparison. In the present study, we adjusted the confounding factors using propensity score matching (PSM). The

propensity score was calculated using a logistic model [18], and the covariates associated with decision-making, in relation with NAC or US, were inserted in the model according to clinical importance. As a result, clinical TNM factors, age, sex, body mass index, comorbidities (diabetes mellitus, chronic kidney disease, pulmonary distress, hepatic disorders, heart disease, and cerebrovascular disorders), and tumor location were selected. The PSM was carried out using the optimal method with a caliper score of 0.20 and 1:1 paired.

Statistics

The descriptive statistics were evaluated for all outcomes. When necessary, continuous variables were compared using Student's t test and categorical variables were compared using Fisher's exact test. All statistical tests were two-sided, and p values of 0.05 or less were considered significant. The Kaplan–Meier method, log-rank test, and Cox's proportional hazard model were used for survival time analysis. All analyses were performed using JMP version 11 (SAS Institute Inc, Cary, North Carolina).

Results

Patient characteristics and PSM

Table 1 summarizes the clinical characteristics of the patients in this study. Before PSM, the US group included more elderly patients, fewer with upper esophageal tumors, and fewer with T3 tumors than the NAC group. The Charlson comorbidity index, a tool for numerical conversion of comorbidities, tended to be higher in the US group than in the NAC group. After PSM, 118 patients were selected from each group. In the US group, 41 (60.3%) of the pN positive patients received postoperative chemotherapy, but adjuvant chemotherapy could not be given to the remaining 27 patients, either because of their poor general condition or their refusal. In the NAC group, 111 patients (94.1%) underwent radical resection, while 7 (5.9%) were treated with replacement therapy. Three patients were treated with chemoradiotherapy, two were treated with radiotherapy, one was treated with second line chemotherapy, and one underwent bypass surgery for an esophagotracheal fistula.

Surgical procedures and outcomes

Table 2 shows the surgical procedures and postoperative outcomes. There was no difference in surgical procedures between the groups. Although the operative time

was significantly longer in the NAC group than in the US group, the blood loss was comparable in the two groups. R0 resection was achieved in 105 (94.6%) and 109 (92.4%) patients in NAC and US groups, respectively (p = 0.50). Postoperative complications developed in 76 (68.5%) and 76 (64.4%) patients in the NAC and US groups, respectively (p = 0.51). The incidences of severe complications of Clavien–Dindo classification grade IIIa or higher were 22.4% (n = 17) in the NAC group and 39.5% (n = 30) in the US group (p = 0.057). Although the incidence of anastomotic leak was significantly lower in the NAC group (p = 0.017), other complications, including SSI, were comparable between the groups. One (0.8%) and three (2.5%) patients from the US group died within 30 days and 90 days after surgery, respectively, but there were no deaths in the NAC group in the same period. One patient died of an incarcerated diaphragmatic hernia on postoperative day (POD) 10, one died of acute respiratory distress syndrome (ARDS) on POD 34, and the other 2 died of leakage on PODs 74 and 90, respectively.

Survival

The median observation period was 3.41 years in the US group and 3.34 years in the NAC group. The median survival in the NAC and US groups was 45 months

(95% CI 36.3–44.9 months) and 31.2 months (95% CI 35.8–47.1 months), respectively, and the 5-year survival rates were 54.9% and 41.2%, respectively (p = 0.024) (Fig. 1a). The disease-free survival rate was also significantly better in the NAC group than in the US group (p = 0.016; Fig. 1b). Figure 2 compares the overall survival between the groups, stratified by clinical stage. The overall survival of cStage II patients was significantly better in the NAC group than in the US group (p = 0.0046). In contrast, the overall survival of cStage III patients was comparable between the groups (p = 0.90). During the follow-up, recurrence was found in 51 and 41 patients from the US and NAC groups, respectively. Lymph node, distant, and locoregional recurrences were observed in 19, 21, and 10 patients in the US group, respectively, and in 18, 17, and 1 in the NAC group, respectively. Although there was no significant difference in the recurrence patterns between the groups, there tended to be less locoregional recurrence in the NAC group than in the US group.

Pathological findings

Table 3 shows the pathological findings. One patient who died during the operation was not able to be evaluated. In the NAC group, there were 40 patients (36.0%) with pT0–1 disease and 73 (65.8%) with pN0–1 disease. The pT grade tended

to be lower and the pN grade was significantly lower in the NAC group than in the US group (pT grade, p = 0.081; pN grade, p = 0.045), suggesting a down-staging effect by NAC. In terms of the pathological response to chemotherapy, 77 (65.3%), 15 (12.7%), 14 (11.9%), and 5 (4.2%) had Grade 1a, 1b, 2, and 3 responses, respectively.

Results of NAC

Table 4 summarizes the results of completed planned NAC. Most patients (n = 78) received cumulative doses of 8000 mg/m2 5-FU and 160 mg/m2 cisplatin. Overall, 82 patients (69.5%) completed two courses of treatment and 36 patients (30.5%) completed one course. The dose intensity of cisplatin and 5-fluorouracil was 81.7% and 82.0%, respectively. The reasons for withdrawal after the first course of NAC included disease progression in 12 patients and adverse events in 20 patients (as renal dysfunction in 7, myelosuppression in 2, impaired liver function in 1, allergy to chemotherapeutic agents in 1, and unknown toxicities in 9). No treatment-related deaths were caused by chemotherapy. Among the 36 patients who could not complete two courses of chemotherapy, 31 underwent esophagectomy, as R0 resection in 25.

Discussion

One of the major objectives of this study was to evaluate the external validity of evidence from a randomized control trial of using NAC to treat ESCC in the clinical setting. The present study revealed three important findings. First, the incidence of all postoperative complications was not higher in the NAC group than in the US group and there was no mortality. Second, there were more elderly patients, with comorbidities such as renal, pulmonary, and cardiovascular diseases, enrolled in this study than in the clinical trial. Therefore, 36% of the patients in the present study could not complete the planned FP regimen dosage. Finally, despite the low dose intensity, the long-term outcome of the patients in the present study was comparable to that of those in the clinical trial.

In our original hypothesis, there was a specific concern that the administration of cytotoxic anti-cancer agents might increase the risk of postoperative complications in patients with severe comorbidities. Furthermore, it was reported that the incidence of infectious complications may be correlated to a rise in tumor recurrence and poorer prognosis [19][20]. However, no significant differences were observed in the incidence of infectious postoperative complications between the groups in the present study.

Compared with the results of the previous clinical trials [1], postoperative pneumonia was more common in both groups, without a significant difference between them.

The operative time was significantly longer in the NAC group than in the US group, even in the PSM cohort, although the operative procedures and surgeons were the same for each group. Chemotherapy frequently causes fibrosis around the tumor and it may make surgical dissection difficult. Moreover, the percentage of patients who underwent three-field lymph node dissection, which takes longer than two-field lymph node dissection, was higher in the NAC group than in the US group, although the difference was not significant. We speculate that these factors influenced the difference in the operative time.

Meanwhile, the incidence of severe complications of Clavien–Dindo grade IIIa or more tended to be higher in the US group than in the NAC group. The incidence of anastomotic leakage was also significantly higher in the US group than in the NAC group. One possible reason for this is that the time spent in preparation for surgery was much longer in the NAC group. Many ESCC patients have a history of tobacco smoking and excessive alcohol consumption, both of which are known to increase the risk of postoperative complications after esophagectomy. We reported previously that longer periods of abstinence from smoking appear to be more effective for reducing the

incidence of postoperative severe complications in esophagectomized patients [21]. The longer preoperative abstinence period in our NAC group might have contributed to the decrease in postoperative mortality. At the same time, nutritional deficiency is one of the major causes of anastomotic leakage. The NAC group patients had enough time before surgery for their nutritional status to be improved with intervention. For patients with impaired oral intake as a result of esophageal stenosis, a naso-gastric tube was inserted and total enteral feeding was given during NAC. Although we do not have enough data to evaluate the efficacy, all these patients completed preoperative chemotherapy and underwent successful esophagectomy. Preoperative inflammation from advanced cancer can also cause postoperative complications. Effective preoperative chemotherapy can improve the tumor-derived inflammation.

The mean dose intensity of NAC was only 70% in the present study; however, the respective overall survival times were 3.75 and 2.6 years in the NAC and US groups, which were approximately equivalent to the results from JCOG 9907 [1]. These results suggest that neoadjuvant chemotherapy might have oncological benefits for patents with resectable ESCC in routine clinical practice. There was no difference in the recurrence pattern between the groups, although there was less locoregional recurrence in the NAC group. Because more than half of the patients in this study had T3 tumors,

NAC might contribute to assuring a lateral surgical margin. However, the fact that NAC failed to decrease distant metastasis indicates that FP may not have enough power to control distant metastasis. Although a significant survival benefit of NAC was observed in cStage II patients, NAC failed to improve the survival of patients with cStage III tumors. This result is consistent with that observed in the JCOG9907 study. A more powerful preoperative treatment regimen, such as triplet chemotherapy or chemoradiotherapy, may be needed to improve the survival of cStage III patients.

All consecutive patients with Stage II or III ESCC diagnosed within this study period were enrolled. As a result, half or more of the subjects were elderly or had moderate-to-severe comorbidities that would exclude them from clinical trials. In the clinical trial “JCOG 9907”, it was reported that only 11% of all patients with clinical stage II/III esophageal cancer treated in participating institutions were included [1]. Therefore, it was necessary to examine the generalizability to apply evidence from the clinical trial to our daily practice. Our results, which reflect outcomes in general hospitals, are more practically valuable and useful.

There are several limitations to the present study, primarily because these data were from a retrospective cohort in a single institution. First, the year of operation, which may influence both the short- and long-term outcomes, significantly differed

between the groups, although rigorous propensity score analysis and matching were performed to adjust the confounding factors. Because the standard treatment strategy for adjuvant or neoadjuvant treatment changed during the study period, the PSM analysis is still the best way to evaluate the efficacy and safety of NAC in routine clinical practice. Second, thoracoscopic surgery, which may also influence the outcome, was performed only in the NAC group, although a relatively small number of patients underwent this procedure. Because the aim of this study was to evaluate the safety and efficacy of NAC in clinical practice, we calculated the propensity score using the preoperative variables. Although the difference in the proportion of thoracoscopic surgery was a potential bias, to remove the patients who underwent thoracoscopic surgery could be another bias to evaluate the main outcomes. When we reanalyzed both the short- and long-term outcomes after removing data on the ten patients who underwent thoracoscopic esophagectomy, the results were similar to those in Table 2 and Fig. 1 (data not shown). Third, some minor changes were made regarding perioperative management, such as perioperative nutritional intervention and the use of corticosteroids. Patients in the late study period were given preoperative immune-enhancing nutrition and/or preoperative corticosteroid. Therefore, some of patients in NAC group received either or both, whereas none of those in the US group received either. Although a meta-analysis

revealed that perioperative enteral immunonutrition decreases morbidity and hospital stay after major gastrointestinal surgery [22], there is not enough evidence to recommend routine immunonutrition for all patients undergoing esophagectomy [23]. Meanwhile, Engelman et al. reported that preoperative steroids reduce perioperative complications such as postoperative organ dysfunction, respiratory complications, sepsis, hepatic disorders, and cardiovascular disorders without causing adverse events [24]. The difference in the perioperative management might influence the decreased incidence of severe complications in the NAC group, although we do not think that it had a great influence on the fact that NAC did not increase postoperative complication.

In conclusion, we believe that the administration of NAC did not increase postoperative complications in consecutive patients with resectable ECSS in clinical practice. Thus, NAC is a safe and effective treatment to improve the prognosis of ESCC patients in the clinical setting.

Conflict of Interest

We have no conflicts of interest to disclose.

References

1. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu 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). Ann Surg Oncol 2012;19:68-74.
2. Kuwano H, Nishimura Y, Oyama T, Kato H, Kitagawa Y, Kusano M, et al. Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus April 2012 edited by the Japan Esophageal Society. Esophagus 2015;12:1-30.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
4. Coupland VH, Allum W, Blazeby JM, Mendall MA, Hardwick RH, Linklater KM, et al. Incidence and survival of oesophageal and gastric cancer in England between 1998 and 2007, a population-based study. BMC cancer. 2012;12:11.
5. Pandeya N, Olsen CM, Whiteman DC. Sex differences in the proportion of esophageal squamous cell carcinoma cases attributable to tobacco smoking and alcohol consumption. Cancer Epidemiol 2013;37:579-84.
6. Vioque J, Barber X, Bolumar F, Porta M, Santibanez M, de la Hera MG, et al. Esophageal cancer risk by type of alcohol drinking and smoking: a case-control study in Spain. BMC cancer. 2008;8:221.
7. Lee CH, Wu DC, Lee JM, Wu IC, Goan YG, Kao EL, et al. Carcinogenetic impact of alcohol intake on squamous cell carcinoma risk of the oesophagus in relation to tobacco smoking. Eur J Cancer 2007;43(7):1188-99.
8. Robert NJ, Goertz HP, Chopra P, Jiao X, Yoo B, Patt D, et al. HER2-Positive Metastatic Breast Cancer Patients Receiving Pertuzumab in a Community Oncology Practice Setting: Treatment Patterns and Outcomes. Drugs Real World Outcomes. 2017;4:1-7.
9. Salas-Vega S, Iliopoulos O, Mossialos E. Assessment of Overall Survival, Quality of Life, and Safety Benefits Associated With New Cancer Medicines. JAMA Oncol 2017;3:382-90.
10. Klevebro F, Lindblad M, Johansson J, Lundell L, Nilsson M. Outcome of neoadjuvant therapies for cancer of the oesophagus or gastro-oesophageal junction based on a national data registry. Br J Surg 2016;103(13):1864-73.

11. Mariette C, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol 2014;32:2416-22.
12. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002;359:1727-33.
13. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
14. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29(13):1715-21.
15. Sobin LH MKG, Wittekind C. TNM Classification of Malignant Tumours, 7th Edition. Hoboken New Jersey Wiley-Blackwell. 2011.
16. Japanese Classification of Esophageal Cancer, 11th Edition: part I. Esophagus 2017;14:1-36.
17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
18. Rubin PRRDB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41-5.
19. Kataoka K, Nakamura K, Mizusawa J, Fukuda H, Igaki H, Ozawa S, et al. Variations in survival and perioperative complications between hospitals based on data from two phase III clinical trials for oesophageal cancer. Br J Surg 2015; 102: 1088-1096.
20. Kataoka K, Takeuchi H, Mizusawa J, Igaki H, Ogawa S, Abe T, et al. Prognostic impact of postoperative morbidity after esophagectomy for esophageal cancer: exploratory analysis of JCOG9907. Ann Surg 2017; 265: 1152-1157.
21. Yoshida N, Baba Y, Hiyoshi Y, Shigaki H, Kurashige J, Sakamoto Y, et al. Duration of smoking cessation and postoperative morbidity after esophagectomy for esophageal cancer : How long should patients stop smoking before surgery? World J Surg 2016; 40: 142-147.
22. Cerantola Y, Hubner M, Grass F, Demartines N, Schäfer M. Immunonutrition in gastrointestinal surgery. Br J Surg 2011; 98: 37-48.

23. Mabvuure NT, Roman A, Khan OA. Enteral immunonutrition versus standard enteral nutrition for patients undergoing oesophagogastric resection for cancer. Int J Surg 2013; 11: 122-127.24.
24. Engelman E, Maeyens C. Effect of preoperative single-dose corticosteroid administration on postoperative morbidity following esophagectomy. J Gastrointest Surg 2010; 14(5):788-804.

Figure legends

Figure 1. Comparison of overall survival between the propensity score-matched upfront surgery (US) group and the neoadjuvant chemotherapy (NAC) group. a Overall survival was significantly better in the NAC group than in the US group (p = 0.023). b Disease-free survival was significantly better in the NAC group than in the US group (p = 0.016)

Figure 2. Comparison of overall survival between the groups stratified by clinical stage. **A** Overall survival was significantly better in the NAC group than in the US group for cStage II patients (p = 0.0046). **B** No significant difference in overall survival was observed between the groups for cStage III patients (p = 0.90)

Table 1. Patients' characteristics

	All patients (n=335)	Before Matching		*P*-value	After Matching		p-value
		US* (n=144)	NAC** (n=191)		US* (n=118)	NAC** (n=118)	
Age				0.0086			0.88
<70 years	252 (75.2)	98 (68.1)	154 (80.6)		90 (76.3)	89 (75.4)	
≧70 years	83 (24.8)	46 (31.9)	37 (19.4)		28 (23.7)	29 (24.6)	
Sex				0.25			0.46
Male	283 (84.2)	125 (86.8)	157 (82.2)		99 (83.9)	103 (87.3)	
Female	53 (15.9)	19 (13.2)	34 (17.8)		19 (16.1)	15 (12.7)	
Tumor location				0.017			0.84
Upper	49 (14.6)	30 (20.8)	19 (10.0)		16 (13.6)	13 (11.0)	
Middle	182 (54.3)	70 (48.6)	112 (58.6)		66 (55.9)	68 (57.6)	
Lower	104 (31.0)	44 (30.6)	60 (31.4)		36 (30.5)	37 (31.4)	
cT				0.017			0.92
1	43 (12.5)	22 (15.3)	21 (11.0)		17 (14.4)	19 (16.1)	
2	104 (31.0)	54 (37.5)	50 (26.2)		39 (33.1)	37 (31.4)	
3	188 (56.1)	68 (47.2)	120 (62.8)		62 (52.5)	62 (52.5)	
cN				0.88			0.98
0	84 (25.1)	37 (25.7)	47 (24.6)		29 (24.6)	32 (27.1)	
1	196 (58.5)	85 (59.0)	111 (58.1)		71 (60.2)	68 (57.6)	
2	51 (15.2)	21 (14.6)	30 (15.7)		17 (14.4)	17 (14.4)	

3	4 (1.2)	1 (0.7)	3 (1.6)		1 (0.9)	1 (0.9)	
cM				0.77			0.52
0	320 (95.5)	137 (95.1)	183 (95.8)		112 (94.9)	114 (96.6)	
1	15 (4.5)	7 (4.9)	8 (4.2)		6 (5.1)	4 (3.4)	
cStage				0.15			0.75
II	167 (49.9)	80 (55.6)	87 (45.5)		61 (51.7)	65 (55.1)	
III	153 (45.7)	57 (39.6)	96 (50.2)		51 (43.2)	49 (41.5)	
IV	15 (4.5)	7 (4.9)	8 (4.2)		6 (5.1)	4 (3.4)	
Body mass index				0.24			0.79
<18.5	60 (17.9)	20 (13.9)	40 (20.9)		18 (15.3)	21 (17.8)	
18.5< ≦25	229 (68.4)	104 (72.2)	125 (65.5)		83 (70.3)	84 (71.2)	
25<	46 (13.7)	20 (13.9)	26 (13.6)		17 (14.4)	13 (11.0)	
Medical comorbidity							
CCI[#]				0.088			0.76
0-5	255 (76.1)	103 (71.5)	152 (79.6)		91 (77.1)	89 (75.4)	
≥9	80 (23.9)	41 (28.5)	39 (20.4)		27 (22.9)	29 (24.6)	
Diabetes	34 (10.2)	17 (11.8)	17 (8.9)	0.39	11 (9.3)	11 (9.3)	-
CKD[##]	20 (6.0)	7 (4.9)	13 (6.8)	0.45	7 (5.9)	4 (3.4)	0.35
Pulmonary	81 (24.2)	40 (27.8)	41 (21.5)	0.18	31 (26.2)	33 (28.0)	0.77
Hepatic	21 (6.2)	9 (6.3)	12 (6.3)	0.99	6 (5.1)	8 (6.8)	0.58
Cardiovascular	45 (13.4)	25 (17.4)	20 (10.5)	0.069	17 (14.4)	16 (13.6)	0.85
Neurologic	20 (6.0)	11 (7.6)	9 (4.7)	0.26	7 (5.9)	4 (3.4)	0.35
Other cancer	50 (14.9)	26 (18.1)	24 (12.6)	0.16	19 (16.1)	21 (17.8)	0.73

(%); *US, Upfront surgery; **NAC, Neoadjuvant chemotherapy; #CCI, Charlson comorbidity index; ##CKD; Chronic kidney disease.

Table 2. Surgical procedures and postoperative outcomes

		US* n=118	NAC** n=111	p-value
Operative approach	Open	114 (96.6)	101 (91.0)	0.072
	Minimally-invasive	4 (3.4)	10 (9.0)	
Operative time, min	Mean±SD	494±12	547±13	0.0039
Blood loss, g	Mean±SD	558±46	513±47	0.50
Lymphadenectomy	2 field	41 (34.7)	31 (27.9)	0.26
	3field	77 (65.3)	80 (72.1)	
Conduit	Stomach	109 (92.4)	101 (91.0)	0.43
	Jejunum	2 (1.7)	1 (0.9)	
	Colon	4 (3.4)	3 (2.7)	
	Not performed[#]	3 (2.5)	6 (5.4)	

Residual tumor	R0	109 (92.4)	105 (94.6)	0.50
	R1,2	9 (7.6)	6 (5.4)	
Complication	Total	76 (64.4)	76 (68.5)	0.52
	Grade IIIa or higher	30 (25.4)	17 (15.3)	0.057
	Events (Grade II or higher)			
	pneumonia	28 (23.7)	37 (33.3)	0.11
	leak	19 (16.1)	7 (6.3)	0.017
	vocal cord palsy	11 (9.3)	11 (9.9)	0.88
	surgical site infection	27 (22.9)	24 (21.6)	0.82
	arrythmia	6 (5.1)	9 (8.1)	0.19
Mortality	30-day	1 (0.8)	0	0.99
	90-day	3 (2.5)	0	0.25

(%); *US, Upfront surgery; **NAC, Neoadjuvant chemotherapy; #Not performed, including 2-stage reconstruction.

Table 2. Surgical procedures and postoperative outcomes

		US* n=118	NAC** n=111	p-value
Operative approach	Open	114 (96.6)	101 (91.0)	0.072
	Minimally-invasive	4 (3.4)	10 (9.0)	
Operative time, min	Mean±SD	494±12	547±13	0.0039
Blood loss, g	Mean±SD	558±46	513±47	0.50
Lymphadenectomy	2 field	41 (34.7)	31 (27.9)	0.26
	3field	77 (65.3)	80 (72.1)	
Conduit	Stomach	109 (92.4)	101 (91.0)	0.43
	Jejunum	2 (1.7)	1 (0.9)	
	Colon	4 (3.4)	3 (2.7)	
	Not performed[#]	3 (2.5)	6 (5.4)	
Residual tumor	R0	109 (92.4)	105 (94.6)	0.50
	R1,2	9 (7.6)	6 (5.4)	
Complication	Total	76 (64.4)	76 (68.5)	0.52
	Grade IIIa or higher	30 (25.4)	17 (15.3)	0.057
	Events (Grade II or higher)			
	pneumonia	28 (23.7)	37 (33.3)	0.11
	leak	19 (16.1)	7 (6.3)	0.017

	vocal cord palsy	11 (9.3)	11 (9.9)	0.88
	surgical site infection	27 (22.9)	24 (21.6)	0.82
	arrythmia	6 (5.1)	9 (8.1)	0.19
Mortality	30-day	1 (0.8)	0	0.99
	90-day	3 (2.5)	0	0.25

(%); *US, Upfront surgery; **NAC, Neoadjuvant chemotherapy; #Not performed, including 2-stage reconstruction.

Table 3. Pathological findings

Pathologic stage	US* n=117	NAC ** n=111	p-value
pT grade			0.081
0	0	5 (4.5)	
1	31 (26.5)	35 (31.5)	
2	17 (14.5)	18 (16.2)	
3	57 (48.7)	46 (41.4)	
4	12 (10.3)	7 (6.3)	
pN grade			0.045
0	26 (22.2)	43 (38.7)	
1	41 (35.0)	30 (27.0)	
2	33 (28.2)	22 (19.8)	
3	17 (14.5)	16 (14.4)	
pM grade			0.15
0	112 (95.7)	101 (91.0)	
1	5 (4.3)	10 (9.0)	

(%); *US, Upfront surgery; **NAC, Neoadjuvant chemotherapy.

Table 4. Results of neoadjuvant chemotherapy

Chemotherapy cycles	2 cycles	82 (69.5)
	1 cycle	36 (30.5)
Dose intensity	Cisplatin	81.7 (35-100)
	5-fluorouracil	82.0 (50-100)
Reason for discontinuation	Progressive disease	12 (10.2)
	Renal dysfunction	7 (5.9)
	Myelosuppression	2 (1.7)
	Liver dysfunction	1 (0.8)
	Allergy	1 (0.8)
	Unknown toxicities	9 (7.6)
	Patients' refusal	4 (3.4)

(%)

Figure1

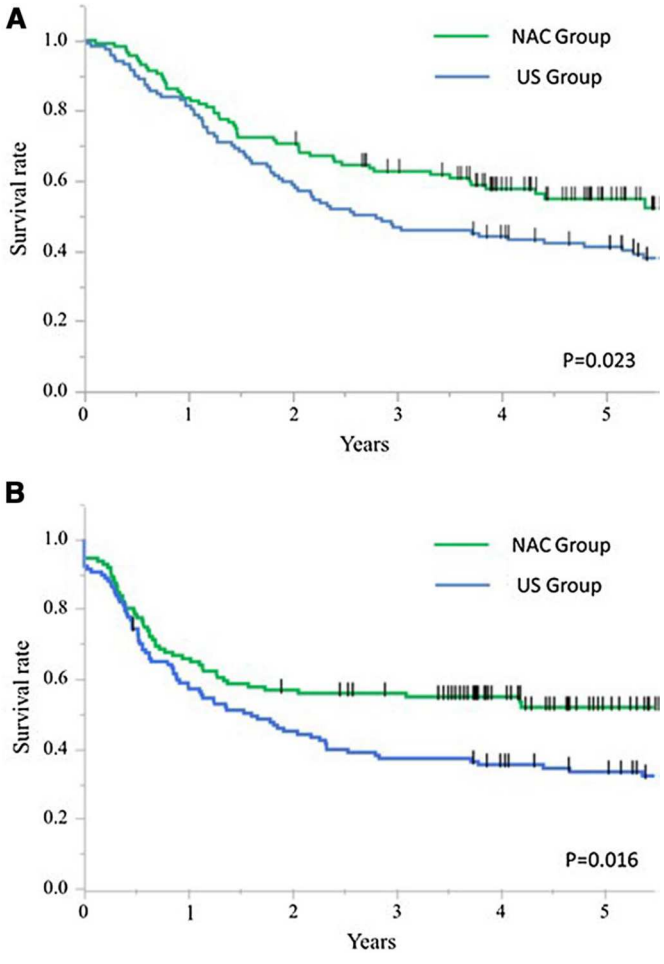
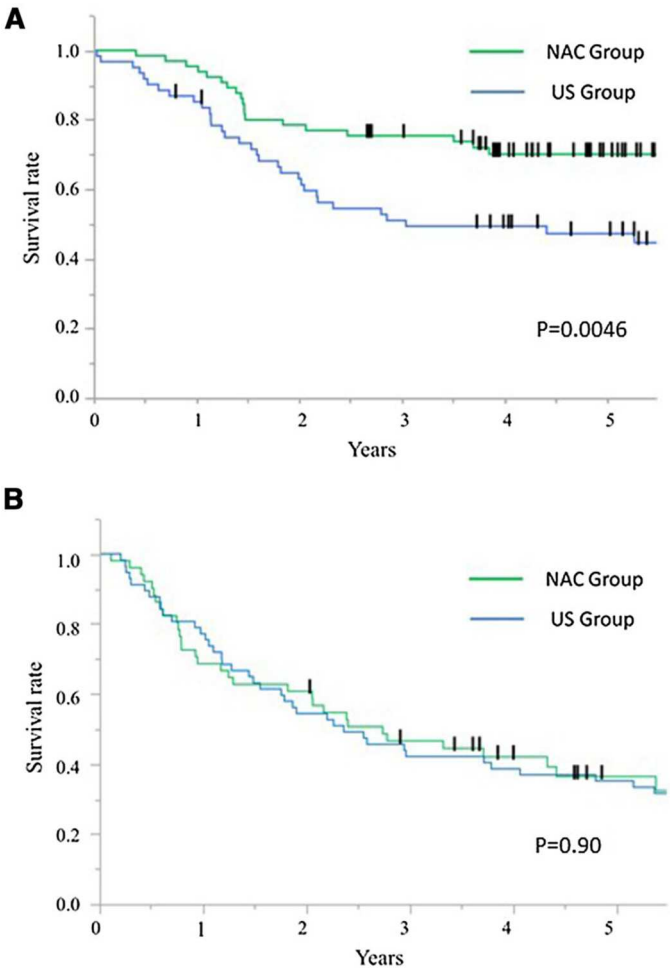


Figure2


A
NAC Group
US Group
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
P=0.0046
0
1
2
3
4
5
Years
B
NAC Group
US Group
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
P=0.90
0
1
2
3
4
5
Years