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Comparing Paclitaxel Plus Fluorouracil Versus Cisplatin Plus Fluorouracil in Chemoradiotherapy for Locally Advanced Esophageal Squamous Cell Cancer: A Randomized, Multicenter, Phase III Clinical Trial

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abstract

PURPOSE This trial aimed to assess the efficacy and safety of the paclitaxel plus fluorouracil regimen versus the cisplatin plus fluorouracil regimen in definitive concurrent chemoradiotherapy (dCRT) in patients with locally advanced esophageal squamous cell carcinoma (ESCC).

PATIENTS AND METHODS Patients with locally advanced ESCC were enrolled and randomly assigned to either the paclitaxel plus fluorouracil group or the cisplatin plus fluorouracil group. The patients in the paclitaxel plus fluorouracil group were treated with paclitaxel and fluorouracil one cycle per week in dCRT for five cycles followed by paclitaxel and fluorouracil one cycle per month in consolidation chemotherapy for two cycles. The patients in the cisplatin/5-fluorouracil group were treated with cisplatin and fluorouracil one cycle per month in dCRT for two cycles followed by two cycles in consolidation chemotherapy. The radiotherapy dose was 61.2 Gy delivered in 34 fractions. The primary end point was 3-year overall survival (OS).

RESULTS Four hundred thirty-six patients with ESCC in six centers were recruited at a 1:1 ratio between April 2012 and July 2015. The median follow-up of the surviving patients was 48.7 months (interquartile range, 42.6-60.9). The 3-year OS was 55.4% in the paclitaxel plus fluorouracil group and 51.8% in the cisplatin plus fluorouracil group (hazard ratio, 0.905 [95% CI, 0.698 to 1.172]; $P = .448$). The 3-year progression-free survival was also not significantly different between the paclitaxel plus fluorouracil group and the cisplatin plus fluorouracil group (43.7% *v* 45.5%, respectively; hazard ratio, 0.973 [95% CI, 0.762 to 1.243]; $P = .828$). Compared with the cisplatin plus fluorouracil group, the paclitaxel plus fluorouracil group had significantly lower incidences of acute grade 3 or higher anemia, thrombocytopenia, anorexia, nausea, vomiting, and fatigue ($P < .05$), but higher incidences of acute grade 3 or higher leukopenia, radiation dermatitis, and radiation pneumonitis ($P < .05$).

CONCLUSION The paclitaxel plus fluorouracil regimen did not significantly prolong the OS compared with the standard cisplatin plus fluorouracil regimen in dCRT in patients with locally advanced ESCC.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In China in 2015, esophageal cancer was the third most common cancer, with an estimated 477,900 new cases, and the fourth most common cause of cancer deaths, with an estimated 375,000 deaths.[1] Ninety percent of these cases were squamous cell carcinoma.[2] On the basis of the results of Radiation Therapy Oncology Group (RTOG) 8501, definitive radiotherapy concurrent with cisplatin plus fluorouracil is a standard modality for patients with inoperable, locally advanced esophageal cancer.[3] However, the treatment toxicity and the survival outcomes of definitive concurrent chemoradiotherapy (dCRT) with cisplatin plus fluorouracil regimen were not satisfactory, with 42% grade 3 acute toxicities, 25% grade 3 late toxicities, and 26% 5-year overall survival (OS).[3]

Paclitaxel showed a considerable efficiency in metastatic esophageal cancer in clinical studies and was a radiation sensitizer in preclinical studies.[4-6] Paclitaxel-based chemoradiotherapy regimens had been investigated in phase I and II studies for neoadjuvant concurrent chemoradiotherapy and dCRT in patients with esophageal cancer, and they showed promising results.[5,7-9] Although there were differences

between these studies in terms of the paclitaxel dose and combination, the pathologic complete response rates were 19% to 53%, which were higher than those of the standard cisplatin plus fluorouracil regimen.[10-12] These inspiring results have led to a prevalence in the use of paclitaxel-based regimens for dCRT in patients with esophageal cancer, without the evidence of phase III randomized clinical trials.

Schnirer et al[13] from the MD Anderson Cancer Center first combined paclitaxel and fluorouracil in concurrent chemoradiotherapy for esophageal cancer, and they showed well-tolerated results. A small-sample-size trial, RTOG 0113, subsequently compared two paclitaxel-based regimens with the cisplatin plus fluorouracil regimen from the RTOG 9405 trial in dCRT for patients with localized esophageal cancer, and showed that the paclitaxel plus fluorouracil regimen had an increasing trend compared with the cisplatin plus fluorouracil regimen (1-year OS, 76% *v* 69%, $P = .104$), although the difference was not statistically significant.[14,15] Subsequently, several single-arm phase II trials of the paclitaxel plus fluorouracil regimen used for patients with locally advanced and advanced esophageal cancer showed promising efficacy, with 3-year OS rates of 35.8% to 42.0%.[16,17] High-quality data from prospective randomized controlled phase III trials are necessary to provide robust evidence for the efficacy of the paclitaxel-based regimen used in dCRT.

Considering these factors, we initiated ESO-Shanghai 1, a multicenter, randomized, open-label phase III study, in 2012 to investigate whether the paclitaxel plus fluorouracil regimen was superior in terms of 3-year OS to the standard cisplatin plus fluorouracil regimen in dCRT for patients with locally advanced esophageal squamous cell carcinoma (ESCC). The paclitaxel plus fluorouracil regimen used in this trial referred to the RTOG 0113 trial, with modifications because of the high toxicities in that trial.[15]

PATIENTS AND METHODS

Study Design

In the ESO-Shanghai 1 trial, we recruited patients in seven trial centers located in China (Appendix Table A1, online only) who met the following key eligibility criteria (for full inclusion and exclusion criteria, refer to Appendix Table A2, online only): histologically proven squamous cell esophageal carcinoma, stage IIA to IVa (American Joint Committee on Cancer, 6th edition), previously untreated; 18 to 75 years of age; Eastern Cooperative Oncology Group performance status of 2 or below; no severely abnormal hematopoietic, cardiac, pulmonary, renal, or hepatic function; and adequate hematologic function. The synopsis of the protocol for the study has been published elsewhere.[18] The protocol was approved by the Ethics Committee of the Fudan University Shanghai Cancer Center (1203108-4). All participants provided written informed consent.

Random Assignment

Eligible patients were randomly allocated at a 1:1 ratio to the cisplatin plus fluorouracil group or the paclitaxel plus fluorouracil group by a central randomization center (Fudan University Shanghai Cancer Center, Shanghai, China). Statistical analysis system 9.3 was used to generate a random permutation sequence and to produce patient random assignment numbers. Random assignment was stratified by the investigator centers, performed centrally by the statistician, and provided to the respective investigators via telephone.

Treatment

Both groups received the same radiotherapy with photons (6 MV) to a total dose of 61.2 Gy in 34 fractions (5 days per week at 1.8 Gy/d) according to the treatment guideline of radiotherapy for Chinese esophageal carcinoma.[19] The specific indications of chemotherapy in the cisplatin plus fluorouracil group were fluorouracil 1,800 mg/m^2 continuous intravenous 72 h on day 1 and cisplatin 25 mg/m^2/d on days 1 to 3 every 4 weeks for two cycles in concurrent chemotherapy and two cycles in consolidation chemotherapy. The specific indications of chemotherapy in the paclitaxel plus fluorouracil group were fluorouracil 300 mg/m^2 continuous intravenous 96 h (initiated on day 1 and terminated on day 4) and paclitaxel 50 mg/m^2/d on day 1 every week for five cycles in concurrent chemotherapy and fluorouracil 1,800 mg/m^2 continuous intravenous 72 h (initiated on day 1 and terminated on day 3) with paclitaxel 175 mg/m^2/d on day 1 every 4 weeks for two cycles in consolidation chemotherapy.

Outcomes

The primary end point of this trial was 3-year OS. We defined OS as the time between the start of the study treatment (day 1) and death from any cause or last follow-up for patients alive at the end of the study. The secondary end points included progression-free survival (PFS), defined as the time between day 1 and the first event of local failure, metastatic recurrence, progression, or death, and the number and grade of participants with adverse events (AE).

Statistical Analysis

We designed this trial to test the inferiority of 3-year OS in the paclitaxel plus fluorouracil group versus the cisplatin plus fluorouracil group. With a global alpha risk of 5% and 80% power, an accrual period of 48 months, a minimum follow-up of 36 months, and 6% patient loss, the inclusion of 436 patients (1:1 random assignment) would be necessary to demonstrate an improvement of 12% in OS at 3 years (from 30% in the cisplatin plus fluorouracil group to 42% in the paclitaxel plus fluorouracil group, on the basis of the results of the RTOG 8501 clinical trial and a phase II study).[3,16] The study would be terminated when 293 events occurred or when the follow-up times of the surviving

patients enrolled all surpassed 3 years. We did not plan to undertake interim analyses.

We used the Kaplan-Meier method to estimate the event time and to compare OS and PFS among the treatment arms with an unadjusted log-rank test on an intention- to-treat basis (including all patients who underwent random assignment). Cox regression was used to estimate the hazard ratios. Pearson's χ^2 or Fisher's exact tests were used to compare between the two groups the toxicities and treatment compliance in the patients who received at least one cycle of chemotherapy. A P value of $< .05$ was used as the significance threshold. Data were analyzed with SPSS version 19.0 (SPSS, Chicago, IL). Detailed correlations of the AE with the radiation dose volume histogram in radiotherapy treatment delivery will be presented in future articles.

RESULTS

Between April 2012 and July 2015, 436 patients with ESCC in six centers (Appendix Table A1) were randomly assigned (Fig 1). Both groups had acceptable completion rates, and the full treatment completion rates were similar between the paclitaxel plus fluorouracil group and the cisplatin plus fluorouracil group (138 of 217 [63.6%] *v* 152 of 219 [69.4%], respectively; $P = .199$). The baseline patient and tumor characteristics were well balanced between the two groups (Table 1). The median age was 62 years (interquartile range [IQR], 56-68 years) in the paclitaxel plus fluorouracil group and 62 years (IQR, 56-68 years) in the cisplatin plus fluorouracil group. We identified incorrect staging for supraclavicular lymph node metastasis in 42 patients (9.6%) after staging review. For this reason, 17 patients (7.8%) in the paclitaxel plus fluorouracil group and 25 patients (11.4%) in the cisplatin plus fluorouracil group who were staged IVa initially were upstaged to IVb. The median tumor lengths of the patients in the paclitaxel plus fluorouracil group and the cisplatin plus fluorouracil group were 6 cm (IQR, 4.5-7.5 cm) and 6 cm (IQR, 4.5-7.5 cm), respectively.

Details of the chemotherapy compliance in the randomly assigned patients are listed in Appendix Table A3 (online only). All patients in the cisplatin plus fluorouracil group completed at least 50% of concurrent chemotherapy, compared with 212 patients (97.7%) in the paclitaxel plus fluorouracil group ($P = .030$). Similar numbers of patients in the paclitaxel plus fluorouracil group (172 [79.3%]) and the cisplatin plus fluorouracil group (172 [78.5%]) completed at least one cycle of consolidation chemotherapy ($P = .853$). At least one delay was reported in 123 patients (56.7%) in the paclitaxel plus fluorouracil group, compared with 92 patients (42.0%) in the cisplatin plus fluorouracil group ($P = .002$). Chemotherapy delay and cessation were mainly caused by treatment-induced toxicities.

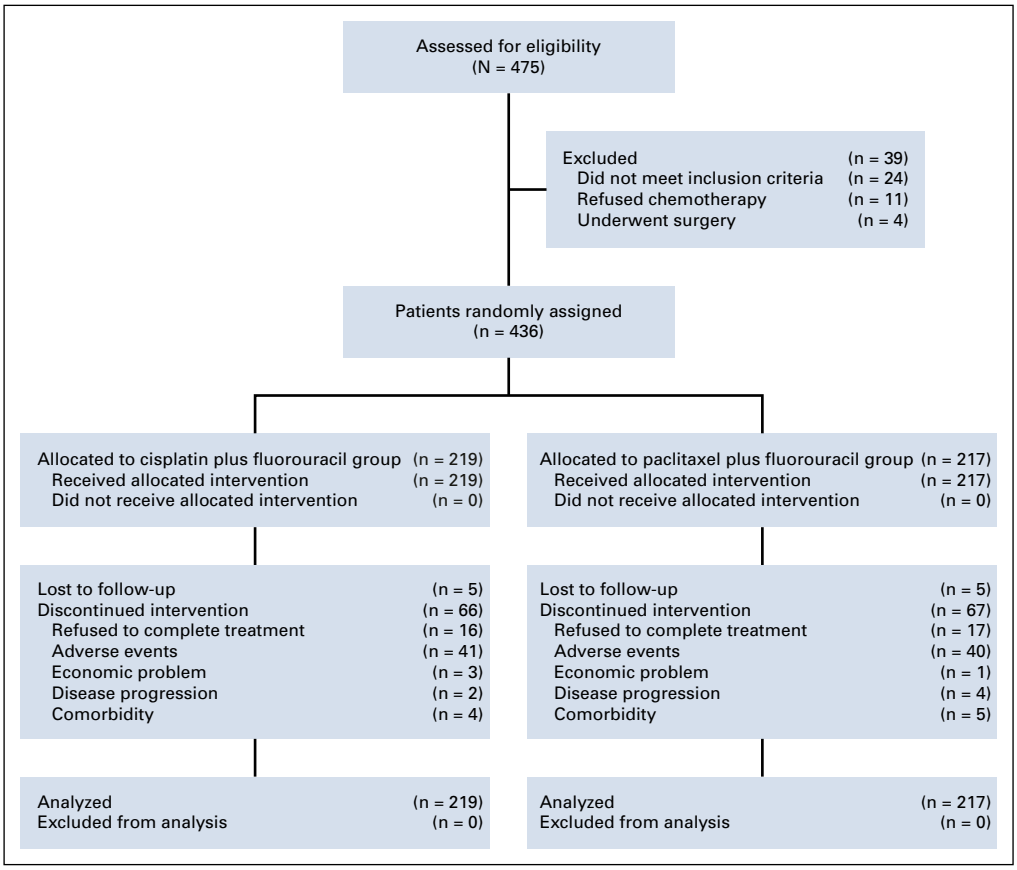

FIG 1. Trial profile. Four hundred seventy-five patients with esophageal squamous cell carcinoma were assessed for eligibility at registration in seven centers in China. Two hundred nineteen patients were assigned to the cisplatin plus fluorouracil group and 217 patients were assigned to the paclitaxel plus fluorouracil group as an intention-to-treat population.

TABLE 1. Characteristic Parameters of Enrolled Patients

Patient Characteristic	Group	
	Cisplatin Plus Fluorouracil (n = 219)	Paclitaxel Plus Fluorouracil (n = 217)
Sex		
Male	168 (76.7)	176 (81.1)
Female	51 (23.3)	41 (18.9)
Age, years		
≥ 70	41 (18.7)	37 (17.1)
< 70	178 (81.3)	180 (82.9)
Smoking history		
Never	77 (35.2)	83 (38.2)
Former or current	142 (64.8)	134 (61.8)
Drinking history		
Never	108 (49.3)	110 (50.7)
Former or current	111 (50.7)	107 (49.3)
Stage (AJCC, 6th edition)		
IIa	37 (16.9)	30 (13.8)
IIb	29 (13.2)	42 (19.4)
III	102 (46.6)	102 (47.0)
IVa	26 (11.9)	26 (12.0)
IVb*	25 (11.4)	17 (7.8)
Site		
Cervical	56 (25.6)	53 (24.4)
Upper	49 (22.4)	60 (27.6)
Middle	92 (42.0)	82 (37.8)
Lower	16 (7.3)	15 (6.9)
Multiple	6 (2.7)	7 (3.2)
Tumor length, cm		
≤ 7	163 (74.4)	156 (71.9)
> 7	56 (25.6)	61 (28.1)
ECOG performance status		
0	183 (83.6)	189 (87.1)
1	33 (15.1)	25 (11.5)
2	3 (1.4)	3 (1.4)
Reason for no surgery		
Inoperable	155 (70.8)	149 (68.7)
Comorbidities	21 (9.6)	18 (8.3)
Patient refusal	43 (19.6)	50 (23.0)

NOTE. Data are presented as No. (%)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group.

*Seventeen patients in the paclitaxel plus fluorouracil group and 25 patients in the cisplatin plus fluorouracil group had incorrect staging for supraclavicular lymph node metastasis, and the stage was changed from IVa to IVb after staging review.

Radiotherapy parameters and compliance for the two groups are detailed in Appendix Table A4 (online only). The tumor volume and dose volume histogram parameters of the lung and heart were well balanced between the two groups. Two hundred ten patients (96.8%) in the paclitaxel plus fluorouracil group and 213 patients (97.3%) in the cisplatin plus fluorouracil group completed at least 50 Gy radiotherapy. The main reason for the premature cessation of radiotherapy was treatment-induced toxicities. There was no significant difference between the two groups in the total delay of the radiotherapy delivery time.

At the analysis time of Aug 1, 2018, the median follow-up of the surviving patients was 48.7 months (IQR, 42.6-60.9 months) for intention to treat (48.7 months [IQR, 42.6-60.9 months] in the paclitaxel plus fluorouracil group and 54.7 months [IQR, 42.6-60.9 months] in the cisplatin plus fluorouracil group). Two hundred thirty deaths (52.8%) were recorded, including 110 deaths (50.7%) in the patients allocated to the paclitaxel plus fluorouracil group and 120 deaths (54.8%) in the patients allocated to the cisplatin plus fluorouracil group. There was no significant difference in 3-year OS (55.4% *v* 51.8%, respectively; hazard ratio, 0.905 [95% CI, 0.698 to 1.172]; $P = .448$) or median survival (47.6 months *v* 40.3 months, respectively) between the paclitaxel plus fluorouracil group and the cisplatin plus fluorouracil group, respectively (Fig 2). The 1, 2, and 5-year OS rates were 79.3%, 60.6%, and 44.3%, respectively, in the paclitaxel plus fluorouracil group and 76.2%, 61.5%, and 40.8%, respectively, in the cisplatin plus fluorouracil group. This pattern was consistent across the relevant predictive and prognostic factors (Fig 3).

Overall, at the analysis time of Aug 1, 2018, 178 patients (40.8%) were alive without disease progression, with 90 patients (41.5%) in the paclitaxel plus fluorouracil group and 88 patients (40.2%) in the cisplatin plus fluorouracil group. Median PFS was 21.0 months (95% CI, 8.7 to 33.3 months) in the paclitaxel plus fluorouracil group and 24.3 months (95% CI, 10.9 to 37.7 months) in the cisplatin plus fluorouracil group. No significant differences were identified in 3-year PFS (43.7% *v* 45.5%, respectively; hazard ratio, 0.973 [95% CI, 0.762 to 1.243]; $P = .828$) between the paclitaxel plus fluorouracil and the cisplatin plus fluorouracil group (Fig 2). Moreover, the differences between the two groups in terms of locoregional recurrence-free survival and metastasis-free survival were not significant (Appendix Fig A1, online only). The patterns of treatment failure in each group are listed in Appendix Table A5 (online only).

Because all randomly assigned patients received at least one cycle of chemotherapy, the safety population in this trial was equal to the intention-to-treat population. All grade 3 or higher AE and grade 1 to 2 AE that occurred in more than 10% of patients reported during treatment are listed in Table 2. There was no significant difference between the two groups in the incidence of acute grade 3 or higher AE

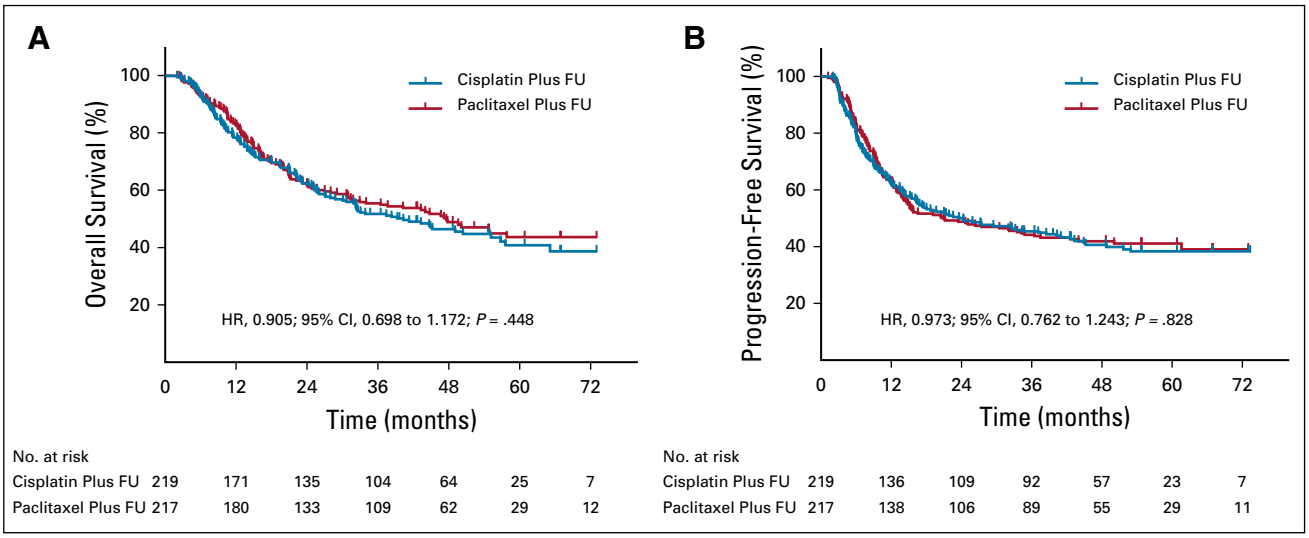

FIG 2. (A) Overall survival and (B) progression-free survival in enrolled patients. There was no significant difference between the paclitaxel plus fluorouracil group and the cisplatin plus fluorouracil group in terms of overall survival or progression-free survival. HR, hazard ratio.

(106 [48.8%] in the paclitaxel plus fluorouracil group *v* 113 [51.6%] in the cisplatin plus fluorouracil group, respectively, $P = .566$). The paclitaxel plus fluorouracil group had significantly lower incidences of acute grade 3 or higher anemia (six [2.8%] *v* 16 [7.3%], respectively; $P = .030$), thrombocytopenia (one [0.5%] *v* 33 [15.1%], respectively; $P = .000$), anorexia (three [1.4%] *v* 33 [15.1%], respectively; $P = .000$), nausea (three [1.4%] *v* 32 [14.6%], respectively; $P = .000$), vomiting (five [2.3%] *v* 41 [18.7%], respectively; $P = .000$), and fatigue (15 [6.9%] *v* 46 [21.0%], respectively; $P = .000$) and significantly higher incidences of acute grade 3 or higher leukopenia (68 [31.3%] *v* 40 [18.3%], respectively; $P = .002$), radiation dermatitis (11 [5.1%] *v* three [1.4%], respectively; $P = .032$), and radiation pneumonitis (19 [8.8%] *v* six [2.7%], respectively; $P = .007$) than the cisplatin plus fluorouracil group. Long-term AE are listed in Table 3. Late cardiac disorders and late radiation pneumonitis were similar between the two groups. Although the patients in the paclitaxel plus fluorouracil group had a significantly higher incidence of grade 1 or higher late esophagitis than did the patients in the cisplatin plus fluorouracil group (28 [12.9%] *v* 11 [5.0%], respectively; $P = .004$), there was no significant difference in the patients who had grade 2 or higher late esophagitis between the two groups.

DISCUSSION

For several decades, paclitaxel-based regimens have been widely used in concurrent chemoradiotherapy in patients with inoperable esophageal cancer in routine clinical practice and in trials worldwide, despite the lack of level 1 evidence.[7-9,20] To our knowledge, our trial is the first multicenter, randomized, phase III trial to compare the paclitaxel-based regimen with the cisplatin plus fluorouracil regimen in dCRT in patients with locally advanced ESCC. Our findings showed that dCRT with paclitaxel plus fluorouracil was not superior to cisplatin plus fluorouracil, whereas the AE profiles of the two regimens were different. On the basis of our results, we suggest that the cisplatin plus fluorouracil regimen remain the standard regimen in dCRT for patients with locally advanced ESCC.

Although one half of the patients enrolled were stage III or IV, the 3-year OS rates in both groups in our trial (55.4% in the paclitaxel plus fluorouracil group and 51.8% in the cisplatin plus fluorouracil group) were higher than in the RTOG 8501 and PRODIGE5/ACCORD17 trials (19.9% to 30.0%).[3,21] The full chemotherapy compliance rate in our trial was substantially higher (65% in the paclitaxel plus fluorouracil group and 69% in the cisplatin plus fluorouracil group) than in the RTOG 8501 trial (54% in combined therapy with cisplatin plus fluorouracil) and was similar to that of the PRODIGE5/ACCORD17 trial (71% in the FOLFOX group and 76% in the cisplatin plus fluorouracil group). Reasons likely included improvements in radiotherapy techniques, staging methods, and best supportive care. We used involved field irradiation with intensity modulated radiation therapy to decrease the toxicities of normal tissues, pragmatically reduced the dose of fluorouracil, and split the administration of cisplatin into 3 days on the basis of the experiences of our institute to reduce chemotherapy toxicities.[22,23] Furthermore, ethnic differences may have played an important role.[24,25]

Our findings showed that the AE profiles significantly differed between the two regimens. The incidences of severe acute GI toxicities and thrombocytopenia in the cisplatin plus fluorouracil group were approximately 10 times to 30 times those of the paclitaxel plus fluorouracil group, respectively (anorexia, 15.1% *v* 1.4%; nausea, 14.6% *v*

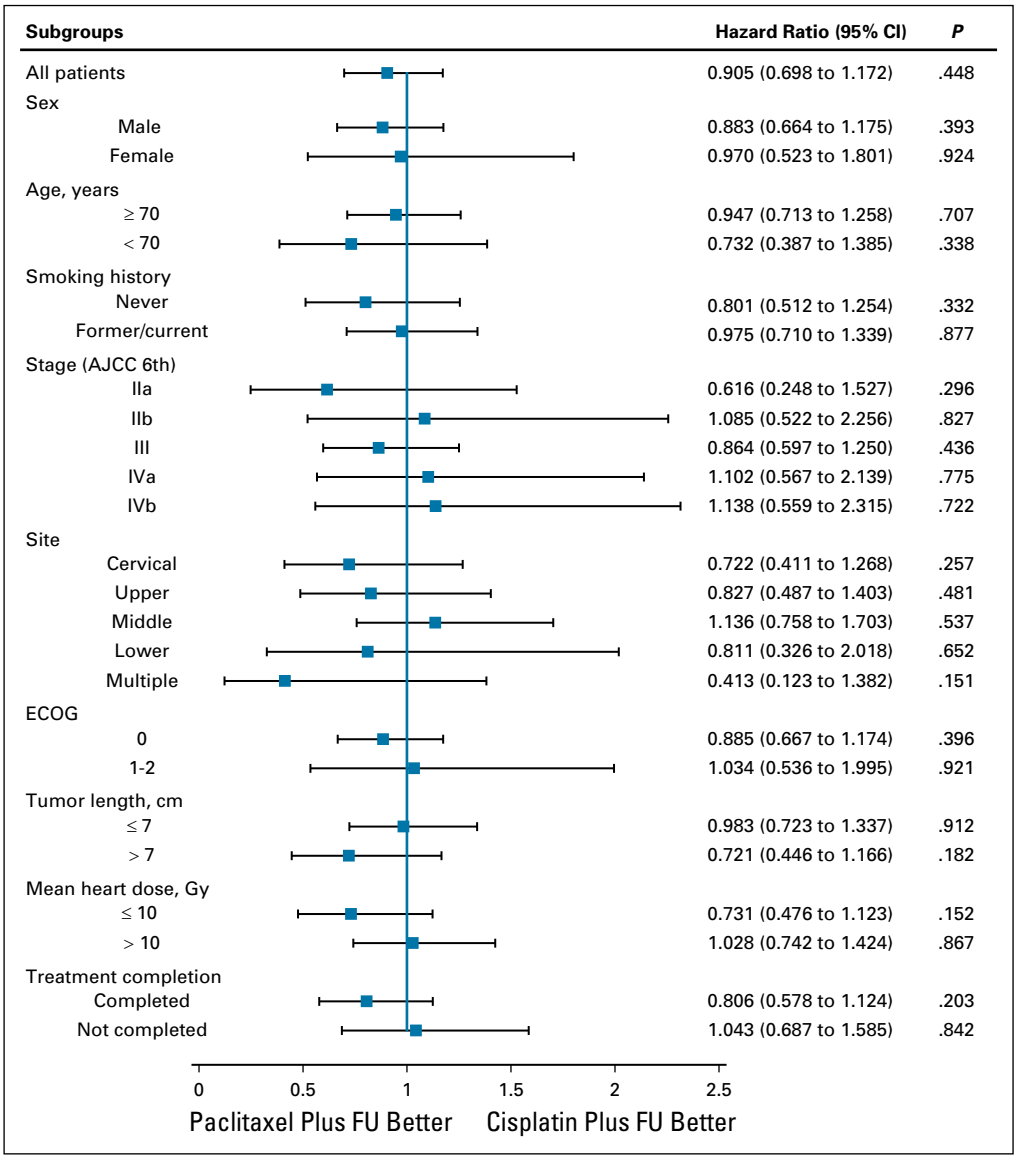

FIG 3. Subgroup analyses of overall survival. The effects of different regimens on overall survival according to the predictive and prognostic factors (sex, age, smoking history, stage, tumor site, Eastern Cooperative Oncology Group (ECOG), tumor length, mean heart dose, and treatment completion) were not significantly different between the two groups. AJCC, American Joint Committee on Cancer.

1.4%; vomiting, 18.7% *v* 2.3%; and thrombocytopenia, 15.1% *v* 0.5%). Moreover, severe anemia was also higher in the cisplatin plus fluorouracil group than in the paclitaxel plus fluorouracil group (7.3% *v* 2.8%, respectively). In contrast, although the paclitaxel plus fluorouracil group showed significantly higher incidences of severe acute leukopenia, radiation-induced dermatitis and radiation pneumonitis compared with the cisplatin plus fluorouracil group, the incidence of each severe nonhematologic AE in the paclitaxel plus fluorouracil group was under 9%.

There has been continued controversy over whether the paclitaxel-based regimen would enhance the risk of radiation pneumonitis when combined with radiotherapy. A systematic review and Veterans' Health Administration data in the United States showed that carboplatin plus paclitaxel compared with etoposide plus cisplatin did not increase the risk of radiation pneumonitis in dCRT for stage III non–small-cell lung cancer.[26,27] However, retrospective studies have indicated that paclitaxel-based dCRT did significantly increase the risk of radiation pneumonitis, with an odds ratio of 3.33.[28,29] Liang et al[30] recently published a phase III trial that compared etoposide plus cisplatin with carboplatin plus paclitaxel in dCRT for patients with stage III non–small-cell lung cancer. The results showed that the incidence of grade 2 or higher radiation pneumonitis was significantly higher in the carboplatin plus paclitaxel arm than in the etoposide plus cisplatin arm (33.3% *v* 18.9%, respectively; $P = .036$); however, the incidence of grade 4 or 5 radiation pneumonitis was not significantly different (5.2% *v* 4.2%, respectively). In our trial, we observed similar results, with a significantly higher incidence of grade 2 or 3 acute radiation pneumonitis and similar incidences of grade 4 or 5 acute radiation pneumonitis and late radiation pneumonitis. In view of the consistent results of the two phase III studies, both of which had well-balanced baselines of the lung parameters of dose-volume histogram, we suggest that

TABLE 2. Safety Results (Acute) of Patients in Each Group

	Cisplatin Plus Fluorouracil Group (n = 219)					Paclitaxel Plus Fluorouracil Group (n = 217)				
Adverse Event*	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hematologic										
Anemia	109 (49.8)	47 (21.5)	15 (6.8)	1 (0.5)	0	115 (53.0)	7 (3.2)	6 (2.8)	0	0
Leukopenia	49 (22.4)	107 (48.9)	37 (16.9)	3 (1.4)	—	57 (26.3)	66 (30.4)	57 (26.3)	11 (5.1)	—
Thrombocytopenia	61 (27.9)	53 (24.2)	24 (11.0)	9 (4.1)	—	31 (14.3)	11 (5.1)	1 (0.5)	0	—
Hypokalemia	0	8 (3.7)	0	0	0	0	4 (1.8)	3 (1.4)	0	0
Hyponatremia	14 (6.4)	—	2 (0.9)	0	0	8 (3.7)	—	4 (1.8)	0	0
GI										
Anorexia	51 (23.3)	60 (27.4)	33 (15.1)	0	0	49 (22.6)	26 (12.0)	3 (1.4)	0	0
Nausea	53 (24.2)	64 (29.2)	32 (14.6)	—	—	46 (21.2)	18 (8.3)	3 (1.4)	—	—
Vomiting	36 (16.4)	38 (17.4)	41 (18.7)	0	0	22 (10.1)	9 (4.1)	5 (2.3)	0	0
Constitutional symptoms										
Fatigue	44 (20.1)	36 (16.4)	46 (21.0)	—	—	53 (24.4)	25 (11.5)	15 (6.9)	—	—
Fever	12 (5.5)	3 (1.4)	1 (0.5)	0	0	49 (22.6)	5 (2.3)	2 (0.9)	0	0
Cardiac										
Cardiac disorders	50 (22.8)	0	0	0	2 (0.9)	46 (21.2)	0	0	0	0
Renal and hepatic										
Creatinine increased	61 (27.9)	6 (2.7)	0	0	0	14 (6.5)	0	0	0	0
ALT increased	14 (6.4)	1 (0.5)	1 (0.5)	0	0	17 (7.8)	0	0	0	0
Nutrition										
Hypoalbuminemia	27 (12.4)	8 (3.7)	0	0	0	36 (16.7)	8 (3.7)	0	0	0
Radiation induced										
Dermatitis	30 (13.7)	3 (1.4)	3 (1.4)	0	0	32 (14.7)	14 (6.5)	11 (5.1)	0	0
Esophagitis	121 (55.3)	37 (16.9)	7 (3.2)	1 (0.5%)	3 (1.4)†	113 (52.1)	71 (32.7)	11 (5.1)	2 (0.9)	2 (0.9)†
Pneumonitis	91 (41.6)	21 (9.6)	5 (2.3)	0	1 (0.5)	97 (44.7)	44 (20.3)	16 (7.4)	0	3 (1.4)
Mediastinal										
Hiccups	5 (2.3)	2 (0.9)	1 (0.5)	—	—	17 (7.8)	9 (4.1)	2 (0.9)	—	—
Hoarseness	18 (8.2)	1 (0.5)	0	—	—	38 (17.5)	4 (1.8)	0	—	—
Neurologic										
Insomnia	21 (9.6)	0	0	—	—	22 (10.1)	0	0	—	—
Headache	42 (19.2)	0	0	—	—	26 (12.0)	0	0	—	—
Arthralgia and myalgia	2 (0.9)	2 (0.9)	0	—	—	19 (8.8)	13 (6.0)	0	—	—
Peripheral neuropathy	36 (16.4)	6 (2.7)	0	0	0	42 (19.4)	13 (6.0)	1 (0.5)	0	0

NOTE. Data are presented as No. (%).

*The table 2 listed all grade 3 or higher acute AE and grade 1 to 2 acute AE occurred in > 10% of patients reported during treatment.

†Patients died as a result of esophageal hemorrhage without clear evidence of progression.

the paclitaxel-based regimen only increased the risk of grade 2 to 3 radiation pneumonitis and did not increase grade 4 to 5 acute radiation pneumonitis or any grade of late radiation pneumonitis when combined with thoracic radiotherapy.

Several limitations should be considered when interpreting our findings. First, we may have underestimated the efficacy of the standard cisplatin plus fluorouracil regimen. The 3-year OS of the cisplatin plus fluorouracil regimen was substantially higher in our trial than in the RTOG 8501 trial (51% *v* 30%, respectively).[3] Therefore, it may not be appropriate to use the historical data of the RTOG 8501 trial, which was conducted decades ago, to estimate the 3-year OS of the standard cisplatin plus fluorouracil group in our trial and calculate the sample size. We overestimated the expected change of the 3-year OS between the paclitaxel plus fluorouracil group and cisplatin plus fluorouracil group and did not design for a noninferiority comparison. Second, we did not assess the quality of life. We may find a difference in the quality of life between the two groups

TABLE 3. Safety Results (Late) of Patients in Each Group

	Cisplatin Plus Fluorouracil Group (n = 219)					Paclitaxel Plus Fluorouracil Group (n = 217)				
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cardiac	30 (13.7)	0	0	0	3 (1.4)	28 (12.9)	0	0	0	1 (0.5)
Esophagitis	2 (0.9)	7 (3.2)	0	0	2 (0.9)*	14 (6.5)	10 (4.6)	0	0	4 (1.8)*
Pneumonitis	58 (26.5)	1 (0.5)	0	0	1 (0.5)	67 (30.9)	2 (0.9)	3 (1.4)	0	1 (0.5)

NOTE. Data are presented as No. (%).

*Patients died as a result of esophageal hemorrhage without clear evidence of progression.

because the cisplatin plus fluorouracil regimen showed a significantly more frequent incidence of severe GI toxicities than did the paclitaxel plus fluorouracil regimen in our trial. Third, we did not compare different paclitaxel-based regimens or optimize the dosage of the paclitaxel plus fluorouracil regimen before this trial. Because of this, we are launching a comparison of paclitaxel plus cisplatin, paclitaxel plus carboplatin, and paclitaxel plus fluorouracil concurrent with radiotherapy for patients with ESCC (ESO-Shanghai 2) in China as a multicenter randomized phase III trial (ClinicalTrials.gov identifier: NCT02459457) to clarify the optimal paclitaxel-based regimen.

In conclusion, we failed to confirm that the paclitaxel plus fluorouracil regimen was superior in terms of OS to the standard cisplatin plus fluorouracil regimen in the dCRT for patients with ESCC. The cisplatin plus fluorouracil regimen remained the standard regimen in dCRT for patients with locally advanced ESCC. In addition, when we compared the different AE profiles between the two regimens, we found that the paclitaxel plus fluorouracil regimen had higher incidences of severe leukopenia, radiation dermatitis, and radiation pneumonitis and lower incidences of anemia, thrombocytopenia, GI toxicities, and fatigue.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Comparing Paclitaxel Plus Fluorouracil Versus Cisplatin Plus Fluorouracil in Chemoradiotherapy for Locally Advanced Esophageal Squamous Cell Cancer: A Randomized, Multicenter, Phase III Clinical Trial

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APPENDIX

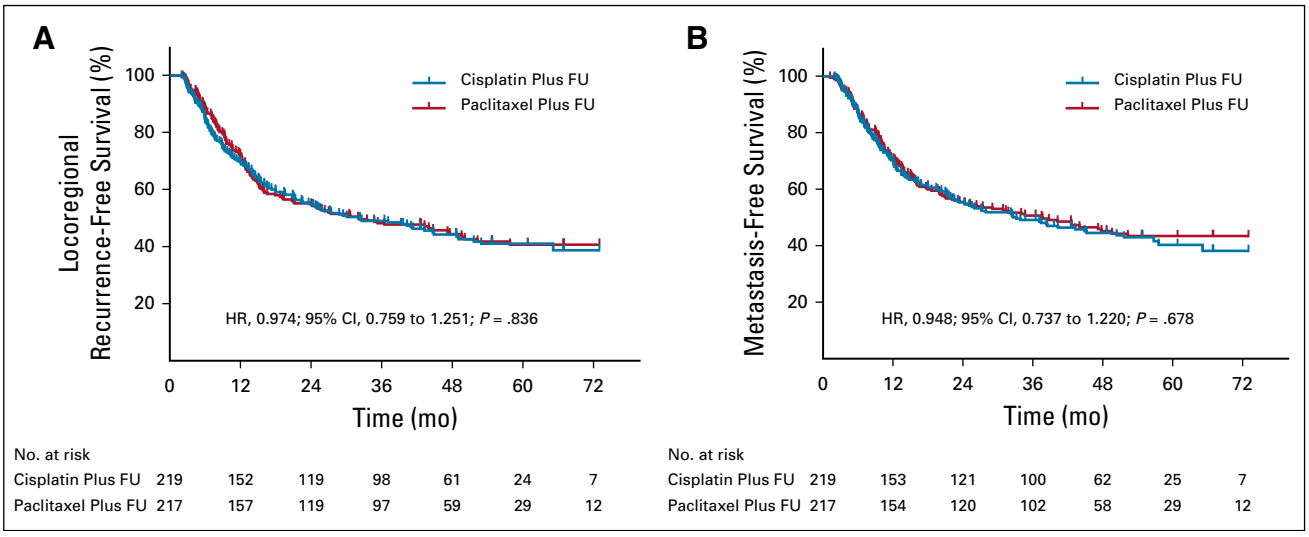

FIG A1. (A) Locoregional progression-free survival and (B) metastasis-free survival in enrolled patients. Differences between the paclitaxel plus fluorouracil group and the cisplatin plus fluorouracil group in terms of locoregional progression-free survival (locoregional progression included recurrences at the primary tumor and regional lymph node) and metastasis-free survival (metastases included any site beyond the primary tumor and regional lymph nodes) were not significant. FU, fluorouracil; HR, hazard ratio.

TABLE A1. Recruitment by Center

Center	Principal Investigator	No. Patients
Fudan University Shanghai Cancer Center	Kuaile Zhao	365
Fudan University Shanghai Cancer Center	Zhengfei Zhu	14
Fudan University Shanghai Cancer Center	Weixin Zhao	8
Fudan University Shanghai Cancer Center	Min Fan	3
Fudan University Shanghai Cancer Center	Ling Li	3
Jiangsu Cancer Hospital	Jinjun Ye	26
Affiliated Hospital of Jiangnan University	Jialiang Zhou	7
Zhenjiang First People's Hospital	Chaoyang Wu	5
The First Affiliated Hospital of Xiamen University	Qin Lin	3
Fudan University Shanghai Cancer Center Minhang Branch	Yi Xia	2
Fujian Provincial Cancer Hospital	Jiancheng Li	0

TABLE A2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Joined the study voluntarily and signed informed consent form	Complete esophageal obstruction, deep esophageal ulcer, esophageal perforation, or hematemesis
18-75 years of age; both sexes	History of radiotherapy or chemotherapy for esophageal cancer
Esophageal squamous cell carcinoma confirmed by pathology. No radiotherapy, chemotherapy, or other treatments before enrollment	History of surgery within 28 days before day 1
Local advanced esophageal squamous cell carcinoma (T2N0M0-TxNxM1a, AJCC, 6th edition)	History of prior malignancies (other than skin basal cell carcinoma or cervical carcinoma in situ with a disease-free survival of at least 3 years)
Use of an effective contraceptive for adults to prevent pregnancy	Participation in other interventional clinical trials within 30 days
No severely abnormal hematopoietic, cardiac, pulmonary, renal, or hepatic function; no immunodeficiency	Pregnant or breast-feeding women or fertile patients who refused to use contraceptives
WBC $\geq 3 \times 10^9$/L, hemoglobin ≥ 9 g/dL, neutrophils $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, ALAT and ASAT $< 2.5 \times$ ULN, TBIL $< 1.5 \times$ ULN, and creatinine $< 1.5 \times$ ULN	Drug addiction, alcoholism, or AIDS
ECOG 0-2	Uncontrolled seizures or psychiatric disorders
Life expectancy of > 3 months	Patients with metastatic disease (ie, M1b according to AJCC, 6th edition)
	Any other condition that in the investigator's opinion would not make the patient a good candidate for the clinical trial

Abbreviations: AJCC, American Joint Committee on Cancer; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; TBIL, total bilirubin; ULN, upper limit of normal.

TABLE A3. Chemotherapy Compliance in Randomly Assigned Patients

Chemotherapy Compliance	Cisplatin Plus Fluorouracil Group (n = 219)	Paclitaxel Plus Fluorouracil Group (n = 217)	*P*
Concurrent chemotherapy cycles started			
One	20 (9.1)	1 (0.5)	
Two (completed two-cycle regimen)	199 (90.9)	4 (1.8)	
Three	NA	8 (3.7)	
Four	NA	22 (10.1)	
Five (completed five-cycle regimen)	NA	182 (83.9)	
Total completed concurrent chemotherapy	199 (90.9)	182 (83.9)	.028
Consolidation chemotherapy cycles started			
None	47 (21.5)	45 (20.7)	.983
One	19 (8.7)	19 (8.8)	
Two (completed two-cycle regimen)	153 (69.9)	153 (70.5)	
Chemotherapy compliance			
Completed	152 (69.4)	140 (64.5)	.278
Not completed	67 (30.6)	77 (35.5)	
Reasons for premature cessation of chemotherapy			
Refusal	16 (7.3)	22 (10.1)	.560
Economic problem	3 (1.4)	1 (0.5)	
Tumor progression	2 (0.9)	4 (1.8)	
Treatment-induced toxicities	42 (19.2)	43 (19.8)	
Comorbidity	4 (1.8)	7 (3.2)	
Delays to cycles			
No	127 (58.0)	94 (43.3)	.011
Within 1 week	57 (26.0)	65 (30.0)	
> 1 week but within 2 weeks	22 (10.0)	38 (17.5)	
> 2 weeks	13 (5.9)	20 (9.2)	

NOTE. Data are presented as No. (%).
Abbreviation: NA, not applicable.

TABLE A4. Radiotherapy Parameters and Compliance in Randomly Assigned Patients

Radiotherapy Parameter and Compliance	Cisplatin Plus Fluorouracil Group (n = 219)	Paclitaxel Plus Fluorouracil Group (n = 217)
Radiotherapy parameters		
Dose, Gy	59.9 ± 7.0	60.2 ± 4.4
Completed full dose of planning radiotherapy	207 (94.5)	201 (92.6)
Not completed, but total dose ≥ 50 Gy	6 (2.7)	9 (4.1)
Not completed, but total dose < 50 Gy	6 (2.7)	7 (3.2)
GTV, cm^3	48.2 ± 31.2	55.6 ± 46.3
≤ 40	109 (49.8)	101 (46.5)
> 40	110 (50.2)	116 (53.5)
PTV, cm^3	375.2 ± 196.6	369.3 ± 150.4
Lung V5, %*	51.5 ± 17.1	51.9 ± 17.8
Lung V20, %*	20.6 ± 6.0	19.8 ± 6.3
Mean lung dose, Gy*	11.3 ± 3.3	11.0 ± 3.4
Heart V30, %*	22.3 ± 20.6	23.5 ± 21.3
Mean heart dose, Gy*	15.2 ± 12.3	15.3 ± 12.3
≤ 10	91 (41.7)	91 (41.9)
> 10	127 (58.3)	126 (58.1)
Radiotherapy compliance		
Completed	207 (94.5)	201 (92.6)
Not completed	12 (5.5)	16 (7.4)
Reasons for premature cessation of radiotherapy		
Refusal	3 (1.4)	1 (0.5)
Economic problem	1 (0.5)	1 (0.5)
Tumor progression	0 (0.0)	2 (0.9)
Treatment-induced toxicities	7 (3.2)	10 (4.6)
Comorbidity	1 (0.5)	2 (0.9)
Deliver over the planned overall radiotherapy time		
No delay	190 (86.8)	182 (83.9)
Within 1 week	8 (3.7)	12 (5.5)
> 1 week but within 2 weeks	14 (6.4)	15 (6.9)
> 2 weeks	7 (3.2)	8 (3.7)

NOTE. Data are presented as mean ± SD with available data or No. (%).

Abbreviations: GTV, gross tumor volume; Heart V30, percentage of the heart receiving > 30 Gy; Lung V5, percentage of the lung (PTV excluded) receiving > 5 Gy; Lung V20, percentage of the lung (PTV excluded) receiving > 20 Gy; PTV, planning target volume.

*Dose volume histogram of normal tissue of one patient in the cisplatin plus fluorouracil group was missing.

TABLE A5. Pattern of Treatment Failure

Type of Event in the Intention-to-Treat Population	Cisplatin Plus Fluorouracil Group (n = 219)	Paclitaxel Plus Fluorouracil Group (n = 217)
Live without treatment failure	88 (40.2)	90 (41.5)
Failure	131 (59.8)	127 (58.5)
Locoregional only	50 (22.8)	42 (19.4)
Distant only	30 (13.7)	31 (14.3)
Locoregional and distant	25 (11.4)	30 (13.8)
Second primary tumor	10 (4.6)	11 (5.1)
Toxicity-induced death	12 (5.5)	11 (5.1)
Died as a result of other cause*	4 (1.8)	2 (0.9)

NOTE. Data are presented as No. (%).

*One patient in the paclitaxel plus fluorouracil group and two patients in the cisplatin plus fluorouracil group died as a result of pneumonia, two patients in the cisplatin plus fluorouracil group died as a result of cerebral infarction, and one patient in the paclitaxel plus fluorouracil group died as a result of an unknown cause.