Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial

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Background: The optimal chemotherapy regimen administered currently with radiation in patients with stage III non-small cell lung cancer (NSCLC) remains unclear. A multicenter phase III trial was conducted to compare the efficacy of concurrent thoracic radiation therapy with either etoposide/cisplatin (EP) or carboplatin/paclitaxel (PC) in patients with stage III NSCLC.

Patients and methods: Patients were randomly received 60–66 Gy of thoracic radiation therapy concurrent with either etoposide 50 mg/m² on days 1–5 and cisplatin 50 mg/m² on days 1 and 8 every 4 weeks for two cycles (EP arm), or paclitaxel 45 mg/m² and carboplatin (AUC 2) on day 1 weekly (PC arm). The primary end point was overall survival (OS). The study was designed with 80% power to detect a 17% superiority in 3-year OS with a type I error rate of 0.05.

Results: A total of 200 patients were randomized and 191 patients were treated (95 in the EP arm and 96 in the PC arm). With a median follow-up time of 73 months, the 3-year OS was significantly higher in the EP arm than that of the PC arm. The estimated difference was 15.0% (95% CI 2.0%–28.0%) and P value of 0.024. Median survival times were 23.3 months in the EP arm and 20.7 months in the PC arm (log-rank test P = 0.095, HR 0.76, 95%CI 0.55–1.05). The incidence of Grade ≥2 radiation pneumonitis was higher in the PC arm (33.3% versus 18.9%, P = 0.036), while the incidence of Grade ≥3 esophagitis was higher in the EP arm (20.0% versus 6.3%, P = 0.009).

Conclusion: EP might be superior to weekly PC in terms of OS in the setting of concurrent chemoradiation for unresectable stage III NSCLC.

Trial registration ID: NCT01494558.

Key words: non-small cell lung cancer, locally advanced, chemoradiotherapy, cisplatin and etoposide, carboplatin and paclitaxel
Introduction

Approximately 30% of patients with non–small cell lung cancer (NSCLC) have locally advanced diseases (LA-NSCLC) [1]. Although the concurrent chemotherapy and radiation (CRT) is considered the standard care [2], the optimal chemotherapy regimen remains unclear. The two most commonly used concurrent regimens are etoposide-cisplatin (EP) and weekly carboplatin-paclitaxel (PC) regimens. As an “older” form of chemotherapy, the EP regimen is generally considered suitable for the concurrent phase because it can be delivered at full dose together with thoracic radiotherapy (TRT) with an acceptable toxicity profile. Third-generation regimens, such as PC, have recently been shown to be more efficacious than the older generation agents in advanced NSCLC. However, no head-to-head phase III evidence has been reported to directly compare the clinical results.

We previously reported a randomized phase II study evaluating the activity and safety of weekly PC compared with EP with concurrent TRT in LA-NSCLC [3]. In that trial, a significantly better overall survival (OS) was found in the EP arm than in the PC arm (P = 0.04). Therefore, a decision was made to proceed to the phase III trial, the results of which are presented here.

Patients and methods

This was a prospective, randomized, open-label, multicenter phase III study. Patients were stratified by institution and stage before randomization. The trial protocol was approved by the ethics review boards of the participating institutions. All patients provided signed informed consent prior to enrollment.

Patient eligibility

Patients were required to have histologically/cytologically confirmed stage III NSCLC. Detailed inclusion and exclusion criteria were shown in supplementary Table S1, available at Annals of Oncology online.

Treatment

The treatment protocol is shown in Figure 1B. Patients in the EP arm received etoposide 50 mg/m² on days 1–5 and cisplatin 50 mg/m² on days 1, 8, every 4 weeks for two cycles; patients in the PC arm received 45 mg/m² paclitaxel and carboplatin (AUC 2) on day 1 once a week.

All of the patients underwent three-dimensional conformal radiotherapy (3D-CRT) or simplified intensity-modulated radiotherapy (sIMRT) [4]. The gross tumor volume included the primary disease as well as any involved regional lymph nodes, which were defined as those with a short-axis diameter of at least 1 cm on the CT scan or with high fluorodeoxyglucose (FDG) uptake on the positron emission tomography (PET)-CT scan. The clinical tumor volume included primary tumor plus a 0.6–0.8 cm margin, ipsilateral hilum, and mediastinal nodal stations involved. A dose of 60–66 Gy (2 Gy per fraction) started on the first day of chemotherapy. The mean dose to the lungs (MLD) should optimally be ≤17 Gy and not exceed 20 Gy; the lung volumes, minus GTV receiving more than 20 Gy (V20) and 30 Gy (V30), were limited to <30% and <20%, respectively.

Since consolidation chemotherapy (CCT) after CRT is not a standard care and no strong data support the use of it, delivering CCT by medical oncologists as per local protocol was permitted. Either platinum-based doublet chemotherapy regimen or single agent chemotherapy regimen was acceptable.

Evaluation and follow-up

Pre-treatment evaluation included chest and abdominal CTs, brain MRI/CTs, bronchoscopies, and radionuclide bone scans. PET-CTs were recommended but not mandatory.

Figure 1. (A) Consort diagram and (B) treatment schema. EP, etoposide/cisplatin; PC, paclitaxel/carboplatin; DDT, Cisplatin; VP-16, etoposide; RT, radiation therapy.
The follow-up evaluations consisted of patient history, a physical examination, and a thoracic CT at intervals of 3 months for 2 years and then 6 to 12 months for 3 years, or earlier if clinically indicated. Other imaging examinations were obtained when recurrence was suspected.

The treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCICTC), version 3.0.

Statistical analyses

SWOG 9504, which combined CRT with the EP regimen, reported a 3-year OS rate of 35% [5]. Choy et al. reported a 3-year OS rate of 18% with a weekly PC regimen for CRT [6]. The power analysis and sample size estimation were completed using the log-rank test. With the proposed sample size of 93 subjects per arm, it provides 80% power to detect 17% superiority (35% versus 18%) in OS at three years from randomization with a two-sided type I error rate of 0.05.

The primary endpoint was overall survival (OS). The secondary end points were treatment-related toxicities, progression-free survival (PFS), and cancer specific survival (CSS). Survival rates were calculated from the day of randomization and estimated using the Kaplan–Meier method. The difference between two arms was estimated using the method described by Uno Hajime et al. [7] Hazard ratios (unadjusted and adjusted) were estimated using Cox proportional hazards models. In the multivariable Cox regression models (with robust standard errors), in addition to the chemotherapy regimen, protocol completeness or incompleteness, and the interaction between them, we included other covariates, such as ECOG, age, tumor stage, pathology, nodal stage, and consolidation chemotherapy. A competing risk survival analysis was performed for CSS with the non-cancer death (grade 5 toxicity was considered as cancer death) as a competing risk. Cumulative incidence of cancer death was estimated, and sub-distribution hazard regression was carried out using Fine and Gray’s method to answer the specific scientific questions while controlling potential confounding factors [8,9]. Toxicity rates and response rates were compared by Fisher’s exact test. A two-sided P < 0.05 was considered statistically significant. All the analyses were done using the SPSS software package (version 17.0, SPSS, Inc.) or R version 3.2.0 (https://www.R-project.org/), including packages “surv2sampleComp”, “survival”, “cmprsk”, “mstate”, and “rms”.

This trial was registered with CAMSCC Clinical Trials Registry, number 07-10/213, and ClinicalTrials.gov, number NCT01494558.

Results

Patient characteristics

Between August 2007 and August 2011, 200 patients were initially enrolled at nine institutions in China, with 100 patients in each arm. Nine patients (5 in the EP arm and 4 in the PC arm) did not receive the protocol treatment because of ineligibility in 5 patients (stage IV, n = 3 and SCLC, n = 2) and refusal in four patients. Therefore, a total of 191 patients (95 in the EP arm and 96 in the PC arm) were eventually treated and evaluable for efficacy. No patients were lost to follow-up.

The baseline characteristics were well balanced between the two arms (Table 1). Patients with ECOG 2 were more allocated in PC arm (41.7% versus 32.6%), although without statistical significance (P = 0.196).

Treatment delivery

As shown in Figure 1A, TRT was given in compliance with guidelines in 96.9% in both arms. Chemotherapy interruptions were more common in the PC arm than in the EP arm in the concurrent phases (37.5% versus 13.6%, P < 0.001). In the EP arm, 48 (50.5%) patients received consolidation treatment after CRT, as did 34 (35.4%) patients in the PC arm (P = 0.035). The most common consolidation regimen was PC, which was administered to 37 and 26 patients in the EP and PC arm, respectively.

Response and survival

The overall response rate was 73.7% in the EP arm and 64.5% in the PC arm (P = 0.21) (supplementary Table S2, available at Annals of Oncology online). The patterns of first failure were not statistically significantly different between the two arms (supplementary Table S3, available at Annals of Oncology online).

One hundred forty-seven patients died (68 patients in the EP arm; 79 patients in the PC arm), and 44 patients were still alive with a median follow-up time of 73 months (range 41–88 months). The 3-year OS rate was 41.1% (95% CI 31.1%–50.7%) in the EP arm versus 26.0% (95% CI 17.8%–35.1%) in the PC arm. The difference between the two arms was estimated to be 15.0% with 95% CI 2.0%–28.0%, and statistically significant (P = 0.024). A similar trend was found for the patients who completed chemotherapy (42.7% versus 28.3%) and for the patient with good performance status (PS) (50.0% versus 38.2%).

Median survival times (MST) were 23.3 months in the EP arm and 20.7 months in the PC arm (log-rank test P = 0.095, HR 0.76, 95%CI 0.55–1.05; Figure 2A). The 2- and 5-year OS rates in the EP arm were 48.4% and 28.0%, and were 42.7% and 19.7% in the PC arm, respectively. A similar trend was found for the patients who completed concurrent chemotherapy (Figure 2B).

Because there were more patients in the PC arm who did not complete the planned chemotherapy than in the EP arm, we decided to investigate this effect on survival. As shown in Figure 2C, the patients in the EP arm who completed the chemotherapy tended to have better survival rates than those who did not, although we were limited by the relatively small number of patients who did not complete the therapy. In the PC arm, this difference is minimal (Figure 2D, P = 0.701). From multivariable analysis, for chemo-completed patients, the adjusted HR of EP to PC was 0.71 (95% CI 0.48–1.05), but it was 1.13 (95% CI 0.60–2.16) for the chemo-not-completed patients. For the PC arm, the HR of chemo-not-completed to chemo-completed was 0.97 (95% CI 0.63–1.50), but for the EP arm, it was 1.55 (95% CI 0.84–2.86). These results suggest that EP may be better for OS than PC when the chemotherapy is completed with the TRT, and completing the chemotherapy may be necessary for the EP to be beneficial.

We also investigated the effect of CCT due to more patients receiving CCT after CRT in the EP arm than in the PC arm. As shown in supplementary Figure S1A, available at Annals of Oncology online, the OS was similar for patients who received CCT as compared to those who did not (MST, 22.6 months versus 21.0 months; log-rank test P = 0.874). From the multivariable analysis, the adjusted HR was 1.19 (95% CI 0.86–1.66). There were no obvious survival advantages of CCT in either the
<table>
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<tr>
<th>Patient characteristic</th>
<th>EP arm (n = 95)</th>
<th>PC arm (n = 96)</th>
<th>P value</th>
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<td>Age (years)</td>
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<tr>
<td>&lt;65</td>
<td>74 (77.9%)</td>
<td>72 (75.0%)</td>
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<td>≥65</td>
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<td>59 32–70</td>
<td>57 39–70</td>
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<td>0–1</td>
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<td>56 (58.3%)</td>
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<td>59 (62.1%)</td>
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<td>AJCC stage</td>
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<td>IIIA</td>
<td>25 (26.3%)</td>
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<td>70 (73.7%)</td>
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<td>Tumor stage</td>
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<td>T1</td>
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<td>T2</td>
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<td>55 (57.3%)</td>
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<tr>
<td>T3</td>
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<td>26 (27.1%)</td>
<td></td>
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<tr>
<td>T4</td>
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<td>15 (15.6%)</td>
<td></td>
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<tr>
<td>Nodal stage</td>
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<td>N2</td>
<td>32 (33.7%)</td>
<td>37 (38.5%)</td>
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<td>N3</td>
<td>63 (66.3%)</td>
<td>59 (61.5%)</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>70 (73.7%)</td>
<td>73 (76.0%)</td>
<td>0.707</td>
</tr>
<tr>
<td>No</td>
<td>25 (26.3%)</td>
<td>23 (24.0%)</td>
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<tr>
<td>Radiotherapy (Gy)</td>
<td></td>
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<tr>
<td>≥60</td>
<td>79 (83.2%)</td>
<td>82 (85.4%)</td>
<td>0.668</td>
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<tr>
<td>&lt;60</td>
<td>16 (16.8%)</td>
<td>14 (14.6%)</td>
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<td>Total radiation duration (day)</td>
<td>42 (35–52)</td>
<td>42 (35–56)</td>
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</tr>
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<td>Chemotherapy</td>
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<td>EP = 2 cycles or PC ≥5 weeks</td>
<td>82 (86.3%)</td>
<td>60 (62.5%)</td>
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<tr>
<td>EP &lt; 2 cycles or PC &lt;5 weeks</td>
<td>13 (13.7%)</td>
<td>36 (37.5%)</td>
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<tr>
<td>Consolidation Chemotherapy</td>
<td>48 (50.5%)</td>
<td>34 (35.4%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Yes</td>
<td>47 (49.5%)</td>
<td>62 (64.6%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-RT pulmonary function</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FEV1 (L)</td>
<td>2.1 (1.2–4.4)</td>
<td>2 (1.2–3.1)</td>
<td>0.531</td>
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<tr>
<td>FEV1 (% predicted)</td>
<td>68% (40%–117%)</td>
<td>76% (42%–104%)</td>
<td>0.460</td>
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<tr>
<td>FVC (L)</td>
<td>2.6 (1.7–5.0)</td>
<td>2.6 (1.5–3.8)</td>
<td>0.664</td>
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<tr>
<td>FVC (% predicted)</td>
<td>74% (46%–110%)</td>
<td>79% (47%–127%)</td>
<td>0.619</td>
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<tr>
<td>DLCO (ml/min/mm Hg⁻¹)</td>
<td>6.1 (3.6–11.3)</td>
<td>6.2 (3.8–9.3)</td>
<td>0.840</td>
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<tr>
<td>DLCO (% predicted)</td>
<td>60% (41%–112%)</td>
<td>63% (37%–104%)</td>
<td>0.950</td>
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<td>GTV (cm³)</td>
<td>107.5 (20.6–383.3)</td>
<td>114.8 (8.6–485.4)</td>
<td>0.815</td>
</tr>
<tr>
<td>Mean lung dose (cGy)</td>
<td>1583 (900–2100)</td>
<td>1576 (969–2004)</td>
<td>0.642</td>
</tr>
<tr>
<td>V20 of both lungs (%)</td>
<td>27 (14–35)</td>
<td>26 (13–35)</td>
<td>0.418</td>
</tr>
</tbody>
</table>

EP, etoposide/cisplatin; PC, paclitaxel/carboplatin; ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusion capacity of CO (ml · min⁻¹ · mm Hg⁻¹); GTV, gross tumor volume. *Median (range).
EP arm or PC arm (supplementary Figure S1B and C, available at Annals of Oncology online).

Predictive interactions were further analyzed according to baseline characteristics (supplementary Figure S2, available at Annals of Oncology online). Although the EP regimen generally tended to provide better OS than the PC arm for most subsets, no significant difference in treatment effect across subgroups was observed. In subgroups of younger patients (<65 years old), the EP regimen tended to provide a greater treatment benefit than PC for OS ($P=0.052$, HR 0.69, 95% CI 0.48–1.00).

The median PFS times were 14.0 (95% CI 11.0–18.0) and 12.0 (95% CI 9.0–13.0) months in the EP and PC arms, respectively (Figure 2E, log-rank test $P=0.111$). The multivariable analysis for PFS demonstrated that after adjusting for other covariates, if both EP and PC chemotherapies were completed, EP patients tended to have better PFS (HR 0.72, 95% CI 0.49–1.06). Considering the non-cancer related death (5 due to other causes) as a competing risk, competing risk survival for the CSS was performed. The 3-year cumulative incidence of cancer death was 57.9% (95% CI 48.2–67.9%) and 71.9% (95% CI 62.7–81.5%) for the EP and PC arms, respectively. As shown in supplementary Figure S3, available at Annals of Oncology online, cancer specific risk tended to be lower for EP patients than for PC patients when the chemotherapy was completed (adjusted sub-hazard ratio 0.81 from multivariable analysis), but it was not statistically significant (95% CI 0.55–1.20). In the EP arm, patients who did not complete the chemotherapy tended to have a higher risk, with a sub-hazard ratio of 1.68 with 95% CI 0.89–2.97. This result was consistent with the OS. For the patients in the PC arm, the effect of completeness of chemotherapy seemed less with a sub-hazard ratio of 1.15 (95% CI 0.75–1.78). In summary, the patients in the EP arm tended to have a better OS and PFS than patients in the PC arm if they completed their chemotherapy protocol. Completing the protocol is proved to be important for the benefit of EP chemotherapy on OS and CSS.

Toxicities

Grade 2–5 toxicities of treatments are listed in supplementary Table S4, available at Annals of Oncology online. Both treatment regimens were well tolerated. The incidence of grade ≥3 esophagitis was significantly higher in the EP arm (20.0%) than in the PC arm (6.3%) ($P=0.009$, odds ratio [OR] 3.75, 95% CI 1.46–9.58). Grade ≥2 radiation pneumonitis (RP) were more frequent in the PC arm (33.3%) than in the EP arm (18.9%) ($P=0.036$, OR 0.47, 95% CI 0.24–0.90). No significant difference in grade ≥3 leukopenia was observed. Of the 9 (4.7%) acute treatment-related deaths, all were due to RP, and there was no noted evidence of differences between the arms in the rates of these grade 5 toxicities.

Discussion

The MSTs of both arms were slightly longer than anticipated based on historical data [10–16] but were shorter than those reported recently in PROCLAIM (25.0 months in the EP arm) and the RTOG 0617 trial (28.7 months in the PC arm) [17, 18]. This may be attributed to the extensive use of staging PET scans in the two trials, resulting in a stage migration. Another possible reason is that more patients in this study had stage IIIB disease (75%); In the PROCLAIM and RTOG 0617 studies, only 52.3% and 34.9% patients had stage IIIB disease, respectively.

Findings leading to the development of this phase III study, including our previous phase II trial, implied a survival benefit
from EP [10–16]. Although the survival benefit was not obvious in the early phase of this study, it became significant in the later phase (3-year OS 41.1% versus 26.0%). A similar trend was found among the sub-group patients who completed chemotherapy and subgroup analysis excluding ECOG 2 patients (3-year OS 50.0% versus 38.3%, \( P = 0.199 \)). The survival benefit of EP over PC might be due to two possible reasons. First, cisplatin is thought to be one of the active drugs in NSCLC and two meta-analyses showed that cisplatin-based chemotherapy is superior to carboplatin-based chemotherapy in first-line treatment of advanced NSCLC [19, 20]. Second, weekly PC with reduced dose intensity may decrease the efficacy [14].

Several phase III clinical trials have compared different regimens of consolidation chemotherapy or different RTT regimens using EP- or PC-based CRT in LA-NSCLC and suggested a favorable survival from the EP regimen despite confounding factors. Recently, Rafael et al. compared the outcomes of patients treated with either EP- or PC-based CRT within the Veterans Health Administration (VA) [21]. Matched analyses of 381 pairs of patients receiving either EP or PC failed to demonstrate a survival advantage for EP (HR 1.07, 95% CI 0.91–1.24). The reasons behind these contradictory results are as yet unclear, but it should be noted that, from the unadjusted analysis of all eligible patients, EP conferred a 2.7-month survival benefit in MST, as compared with PC (HR 0.88, 95% CI 0.79–0.99), which was similar to our study (a 2.6-month survival benefit in MST).

Different toxicity profiles between the EP and PC regimens were observed. The incidence of Grade ≥2 RP was significantly higher in the PC arm than in the EP arm. In our prior phase II study, the rate of Grade ≥2 RP was 25% in the EP arm and 48.5% in the PC arm (\( P = 0.09 \)). In a meta-analysis of 836 patients, Palma et al. [22] found that the PC regimen was an independent predictive factor of RP (OR of PC relative to EP = 3.33; \( P < 0.001 \)). The incidence of another dose-limiting toxicity, Grade 3 or 4 esophagitis, was significantly higher in the EP arm than in the PC arm (20.0% versus 6.3%, \( P = 0.009 \)).

In conclusion, we show evidence that a concurrent EP regimen might be better than a weekly PC regimen when completed in terms of survival, whether by univariate or multivariable survival analysis. Completing the EP chemotherapy seemed to be important for the benefit, but we were limited by the small number of patients who did not complete the chemotherapy. More patients in the PC arm could not complete the therapy than the EP arm in China, possibly due to more Grade ≥2 RP and more patients with poor PS of PC therapy, although subgroup analysis did not show any difference in the chemotherapy compliance between the two PS groups (\( P = 0.669 \), supplementary Table S5, available at *Annals of Oncology* online). Due to the small number of patients in some subgroups and other unknown characteristics of patients, our analysis results could be potentially biased. However, the results from the multivariable analysis were consistent with those from the univariate analysis.

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**Disclosure**

The authors have declared no conflicts of interest.

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