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Original Article

# HELPER study: A phase II trial of continuous infusion of endostar combined with concurrent etoposide plus cisplatin and radiotherapy for treatment of unresectable stage III non-small-cell lung cancer ☆

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ABSTRACT

*Purpose:* The prognosis of unresectable stage III non-small cell lung cancer (NSCLC) was poor even after concurrent chemoradiotherapy. There remains a great need to develop novel therapeutic agents in combination with CCRT to improve outcomes. This prospective study sought to evaluate the efficacy and toxicities of the addition of endostar, an anti-angiogenesis agent, to concurrent etoposide, cisplatin (EP) and radiotherapy for treatment of patients with NSCLC.

*Patients and methods:* Patients with untreated pathologically confirmed inoperable stage III NSCLC were eligible. Radiation at doses of 60–66 Gy, four cycles of endostar (7.5 mg/m$^2$/24 h × 120 h, 14 days/cycle), and two cycles of EP (etoposide 50 mg/m$^2$ on days 1–5 and cisplatin 50 mg/m$^2$ on days 1 and 8, 28 days/-cycle) were delivered. The primary endpoint was progression-free survival (PFS). The secondary endpoints were response rate and overall survival (OS), locoregional relapse-free survival (LRFS) distant metastasis-free survival (DMFS) and adverse events (AE).

*Results:* From November 2012 to June 2015, 73 patients were enrolled, and 67 patients were evaluable. The median age was 59 years. Sixty-six percent of the patients had squamous cell carcinoma. Grade ≥3 AEs occurred in 58.2% of the patients. The most common Grade ≥3 AE was leucopenia (44.8%). The response rate was 76.1%. The median times of PFS and OS were 13.3 months and 34.7 months, respectively. The 2-year PFS, OS, LRFS and DMFS rates were 34.8%, 59.9%, 54.7% and 68.5%, respectively.

*Conclusions:* For patients with unresectable stage III NSCLC, continuous intravenous endostar in combination with concurrent EP and radiotherapy did not prolong median PFS, although it got preferable OS, promising 2-year PFS with tolerable toxicities.



Accounting for 85% of lung cancers, non-small cell lung cancer (NSCLC) is the most common subtype [1,2]. At the time of the first diagnosis, approximately 30% of NSCLC is stage III disease [3]. For patients with this diagnosis, clinical studies have supported the use of chemoradiotherapy (CCRT) as the standard treatment. However, prognosis following this treatment is generally poor, with 5-year survival of 15–20% [4–7]. Several studies have shown that the prognosis could be improved by neither induction chemotherapy nor consolidation chemotherapy in addition to CCRT [8–11]. Therefore, there remains a great need to develop treatments involving novel therapeutic agents in combination with CCRT to improve outcome for stage III NSCLC.

Tumor angiogenesis plays a significant role in tumor growth and response to therapies. Accordingly, anti-tumor angiogenesis is one of the most important areas of studies. An anti-tumor

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angiogenesis agent, recombinant human endostatin (rhE, Endostar), a C-terminal fragment naturally derived from type XVIII collagen, can specifically inhibit the activity of vascular endothelial growth factor to block angiogenesis as well as induce cancer cell apoptosis [12]. Endostar has been shown to be efficient and safe in the treatment of NSCLC and was approved by Chinese Food and Drug Administration [13]. A meta-analysis demonstrated that the addition of endostar to chemotherapy increased the response rate in patients with advanced NSCLC [14]. Preclinical models have shown that endostar may transiently normalize the tumor vasculature and oxygen delivery, thereby providing a window of opportunity to enhance the sensitivity to radiation treatment [15]. Another trial indicated better survival and local control with no severe adverse reactions resulting from the use of endostar in combination with radiotherapy in NSCLC [16].

Hence, we sought to determine if the addition of endostar to CCRT would improve outcomes in patients with NSCLC. We previously reported a phase II study combining endostar with concurrent docetaxel, cisplatin, and radiotherapy, resulting in promising survival for stage III NSCLC patients [17]. However, other studies indicated that the etoposide and cisplatin (EP) regimen is considered more suitable in CCRT with an acceptable toxicity [18]. Consequently, we designed this phase II study (HELPER) to investigate the efficacy and toxicities of endostar and concurrent EP and radiotherapy. In addition, previous studies from other centers indicated that hypoxia was more pronounced on the first day after endostar administration, but lower levels of hypoxia was more obvious on the fifth day than on the first day and stronger on the tenth day than on the fifth day [14–16]. On the basis of these previous studies, we chose to use continuous intravenous endostar over 120 h every other week.

## Patients and methods

### *Ethics and registration*

The institutional ethics committee of the four participating institutions gave trial protocol approval, and written informed consent was obtained from eligible patients before the pre-study assessments. The study was registered on the website of ClinicalTrials.gov, and the URL is https://www.clinicaltrials.gov/ct2/show/NCT01733589 and the Identifier is NCT01733589.

### Eligibility criteria

Inclusion criteria included: untreated pathologically confirmed inoperable stage III NSCLC according to the 7th edition of the American Joint Committee on Cancer staging system, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, 18–70 years of age, Eastern Cooperative Oncology Group performance status score (ECOG PS) of 0 to 1, neutrophil $\geq$1500/μL, hemoglobin $\geq$10 mg/dL, platelet $\geq$100,000/μL, serum creatinine $\leq$1.25 times of upper limit of normal (ULN), calculated creatinine clearance $\geq$60 ml/min, aspartate transaminase and alanine aminotransferase $\leq$2.5 × ULN, forced expiratory ventilation in 1 s $\geq$0.8 L, normal coagulation function.

Exclusion criteria included history of other malignant diseases, uncontrolled hypertension, any contraindications to chemoradiotherapy, pregnancy, breastfeeding or preexisting bleeding diatheses or coagulopathy.

### Pretreatment evaluation

Before participating in this study, all patients received a baseline evaluation that included medical history, physical examination and laboratory tests. The following tests were performed within one month before entry into the study: electrocardiograph (ECG), pulmonary function test, bronchoscopy, cervical lymph node ultrasonography, chest and abdominal CT, brain magnetic resonance imaging (MRI), radionuclide bone scan, and the adjunctive use of chest MRI or FDG positron emission tomography (FDG-PET) when available. CT scans were used for all subsequent evaluations to evaluate tumor measurements.

### Treatment

Intravenous endostar, thoracic radiotherapy, and chemotherapy were delivered concurrently. The treatment procedure is shown in Fig. 1.

### Recombinant human endostatin (Endostar)

Continuous intravenous infusion of endostar (Simcere Pharmaceutical, Nanjing, China) was made over 120 h before the beginning of radiotherapy, and then repeated every two weeks. The dose was 7.5 mg/m2/24 h × 120 h, 14 days/cycle. ECG monitoring was performed during the first delivery of endostar.

### Chemotherapy

Chemotherapy regimens consisted of 50 mg/m$^2$/d of cisplatin (DDP) on days 1, 8, 29, and 36 plus 50 mg/m$^2$/d of etoposide on days 1–5 and days 29–33. A protocol-mandated hydration and antiemetic regimen was used for all the patients.

### Radiotherapy (RT)

Intensity modulated radiation therapy was used for all patients. Gross tumor volume (GTV) included the primary tumor as well as any involved regional lymph node, determined by the thoracic CT (or FDG PET if possible). Contours of the primary tumor were evaluated using pulmonary window (width 1000, level -650) CT settings and nodal GTV using the mediastinal window (width 350, level 40). Clinical target volume (CTV) included GTV plus a 6–8 mm margin, ipsilateral hilum and involved lymph node regions. A total dose of 60–66 Gy was delivered in 30–33 fractions, 2 Gy per fraction, 5 fractions per week. The maximum dose to the cord was limited to 45 Gy. The lung volume receiving >20 Gy (V20) was limited to $\leq$35%. Radiotherapy quality assurance was performed by central review for all patients.

### Toxicity evaluation and treatment modifications

Toxicities were evaluated during the treatment and at each follow-up, according to National Cancer Institute Common Toxicity Criteria of Adverse Events (NCI-CTC AE) Version 3.0.

Radiotherapy interruption was permitted for patients with any grade $\geq$4 toxicities or grade $\geq$3 pulmonary toxicity and radiotherapy did not recommence until the toxicity had resolved to grade $\leq$2. Interruptions in radiotherapy lasting longer than 2 weeks resulted in removal of the patient from protocol treatment.

Chemotherapy was reduced to 75% of the original dosage if patients experienced any continuous grade $\geq$2 hematological toxicities or uncontrolled grade $\geq$3 nonhematological toxicities. If the neutrophil remained <500/μL or if the platelet remained <50,000/μL, chemotherapy was delayed. Resumption of chemotherapy was allowed once toxicities had resolved to grade $\leq$2.

Modification of the endostar dose was made at the discretion of the treating physicians. Attention was paid to blood pressure and bleeding at the time of endostar delivery. If abnormal blood

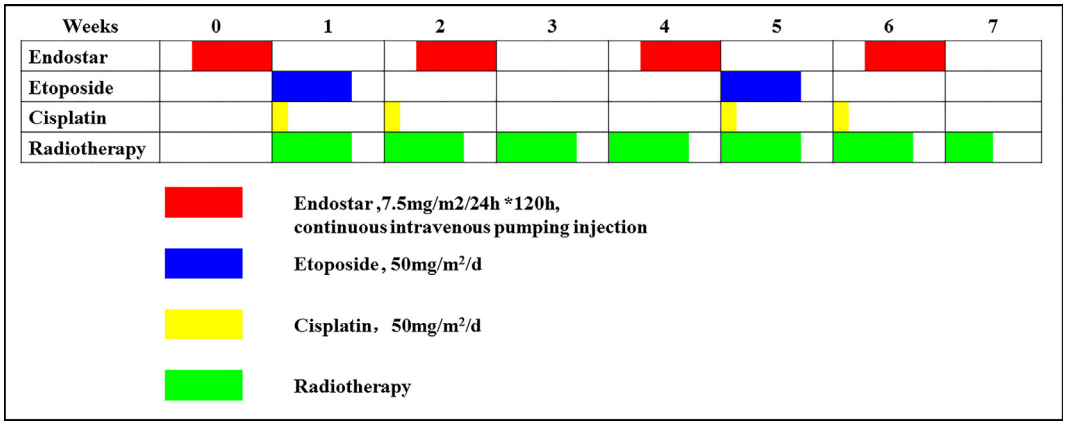


**Fig. 1.** Treatment procedure.

coagulation, platelet count <50,000/μL, or any hemorrhage toxicities were observed, endostar would be delayed.

If one or more treatment agents were discontinued, further treatment with the remaining therapies was allowed. If positive results for an allergic reaction were recorded, the related regimens were canceled.

### Follow-up evaluations

During the treatment, patients' symptoms, physical examinations, blood pressure and blood counts were re-assessed weekly. Electrolytes, glucose, calcium, albumin, transaminases, alkaline phosphatases, total bilirubin, and creatinine were re-assessed before the delivery of chemotherapy and endostar. ECG, chest and abdominal CTs, and cervical lymph node ultrasonography were assessed at the end of treatment, 1 month after treatment, and every 3 months for 2 years and thereafter every 6 months for 3 years. Imaging examinations were obtained when recurrence was suspected. Response was assessed by a senior radiologist and a radiation oncologist in enrolling site initially and then confirmed by a certain people for 1 month after treatment according to RECIST 1.0.

### Statistical design and analysis

The primary endpoints were progression-free survival (PFS). Previous studies had indicated a median PFS of about 12 months following CCRT [19]. We conjectured that our study would improve median PFS to 18 months. Using a 20% bilateral *Z* test (alpha = 0.05, beta = 0.2), 65 patients would need to be evaluated. Based on the assumption that 10% of the patients would be lost at follow-up, 72 patients were needed. The secondary endpoints were response, overall survival (OS), local regional relapse-free survival (LRFS), distant metastasis-free survival (DMFS) and toxicities. Survival time was calculated from the time of the diagnosis. PFS was calculated as the time to documented clinical progression or to the patient's death. OS was calculated as the time to death. LRFS was calculated as the time to local progression, which defined the primary tumor and regional lymph node recurrence (both in-field and out-of-field recurrence). DMFS was calculated as the time to distant metastasis. Survival was calculated with the use of Kaplan–Meier method. Univariate analysis including the following variables: sex, age, Eastern Cooperative Oncology Group performance status (ECOG PS) score, smoking, stage and histology, was performed using the log-rank test. A *P* value of <0.05 was considered statistically significant. All statistical analyses were conducted using the SPSS statistical software package version 20.0 (SPSS Inc., Chicago, IL).

## Results

From November 2012 to June 2015, 73 patients were enrolled and six patients were ineligible. Of these six patients, three had distant metastasis before treatment and three refused treatment after consenting to therapy. Sixty-seven patients were evaluable. The demographics and characteristics of the 67 patients are listed in Table 1.

A full course of the planned therapy was completed in 58 patients (86.6%). Radiation dose was reduced in three patients. The median volume of GTV and PTV were 95.3 ml (16.7–373.8 ml) and 440.2 ml (222.8–904.0 ml), respectively. The median mean lung dose was 15.6 Gy (8.6–19.6 Gy). The median relative volume of total lung received more than 20 Gy was 26.8% (18–34.5%). All but three of the 67 patients (95.5%) completed two cycles of chemotherapy. Chemotherapy dose reduction was recorded in six patients for hematological toxicities. Cycle reduction in endostar were recorded in 5 patients for patient refusal to continue on protocol. Patients refused to continue their medication of endostar by reasons of Grade 3–4 leukopenia (3 patients) and Grade 3 esophagitis (2 patients), although all the above toxicities were improved after intervention. Details of the treatment administration are listed in Supplement Table S1.

The adverse events (AEs) are outlined in Table 2. Overall, 39 patients (58.2%) had grade ≥3 AEs, including 14 patients (20.9%) with grade ≥3 nonhematologic AEs and 33 patients (49.3%) with grade ≥3 hematologic AEs. The most common AE was leucopenia (95.5%). No treatment-related cardiovascular events were observed. Hemoptysis was observed in 16.4% patients and for all it occurred before treatment, and no new cases were observed following treatment. Grade 5 AEs were observed in two patients (one with massive hemoptysis and one with suspected radiation induced pneumonitis).

Fifty-one patients (76.1%) achieved objective response, including eight (11.9%) with CR and 43 (64.2%) with PR as their best outcome. Twelve patients (17.9%) had stable disease (SD) and 4 (6.0%) had progressive disease (PD).

The median follow-up time was 37.1 months (20.1–52.1 months). At the last follow-up, 32 patients (47.8%) had died. Forty-four patients (65.7%) developed disease progression. Locoregional recurrence was observed in 29 patients (43.3%), and distal metastasis was observed in 23 patients (34.3%), including 8 patients (11.9%) with both locoregional recurrence and distant metastasis. Among the patients with locoregional relapse, 27

**Table 1**
Patient demographics and characteristics ($N = 67$).

| | *n* (%) | | *n* (%) |
|---|---|---|---|
| Sex | | Age (years) | 59 (31–69) |
| Male | 56 (83.6) | Comorbidities | |
| Female | 11 (16.4) | Yes | 35 (52.2) |
| ECOG PS | | No | 32 (47.8) |
| 0 | 9 (13.4) | Diabetes | 6 (9.0) |
| 1 | 57 (85.1) | Hypertension | 17 (25.4) |
| 2 | 1 (1.5) | Coronary disease | 2 (3.0) |
| Tumor Location | | Arrhythmia | 3 (4.5) |
| Left | 32 (47.8) | T Stage | |
| Right | 35 (52.2) | T1 | 8 (11.9) |
| Pathology | | T2 | 17 (25.4) |
| Squamous carcinoma | 44 (65.7) | T3 | 21 (31.3) |
| Adenocarcinoma | 19 (28.4) | T4 | 21 (31.3) |
| Large cell carcinoma | 1 (1.5) | N Stage | |
| Not defined | 3 (4.5) | N0 | 1 (1.5) |
| Great vessel invasion | | N1 | 3 (4.5) |
| Yes | 9 (13.4) | N2 | 38 (56.7) |
| No | 58 (86.6) | N3 | 25 (37.3) |
| Smoking | | Stage | |
| Yes | 51 (76.1) | IIIA | 29 (43.3) |
| No | 16 (23.9) | IIIB | 38 (56.7) |

patients were with in-field recurrence and 3 patients with out-of-field local recurrence, including 1 patient with both. The median PFS, OS, LRFS and DMFS were 13.3 months, 34.7 months, 27.1 months and 41.7 months, respectively. The 1, 2, and 3-year PFS were 50.7%, 34.8%, and 28.2%, respectively. The corresponding OS were 82.1%, 59.9% and 47.7%; LRFS were 72.7%, 54.7% and 49.9%; and DMFS were 73.8%, 68.5% and 65.7% respectively. Survival curves are shown in Fig. 2a–d.

Univariate analysis indicated that sex, smoking, age, pathology type, or stage subgroups (IIIa/IIIb) were not associated with PFS, OS or LRFS. Sex, smoking, stage subgroups and histology were associated with DMFS in univariate analysis while none of them was an independent prognosticator in multivariate analysis (Table 3).

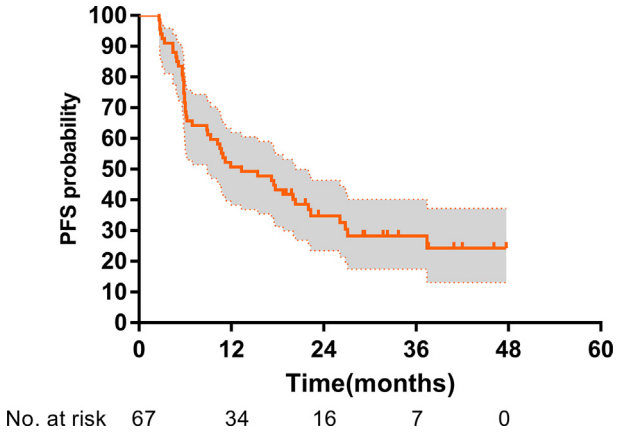


**Fig. 2a.** Progression free survival.

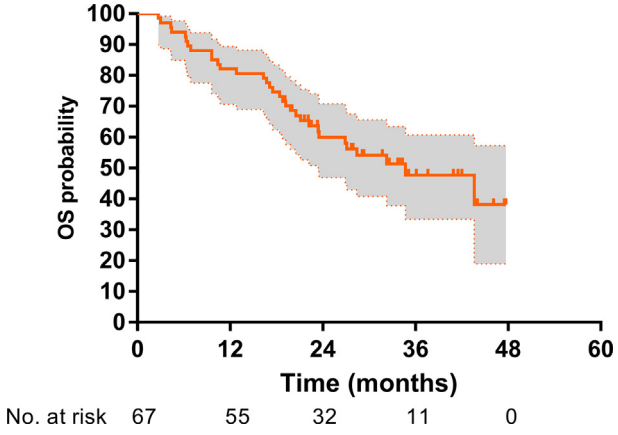


**Fig. 2b.** Locoregional relapse-free survival.

## Discussion

In our study, MPFS (13.3 months) was not improved as we conjectured (18 months). MPFS in our study was better than in the RTOG 9106 and PROCLAIM studies and was similar to Liang's study, all of which used CCRT alone [18,20,21]. Still, 2-year PFS in our study was superior to that in NPC 9501 and RTOG9106 [7,20]. The inconsistency of promising 2-year PFS but modest MPFS in the comparisons might on account of different data from different trials and limited number of patients in HELPER study. Additionally, several studies stated that PFS is only a surrogate for OS in studies with limited follow up time and OS should remain the gold standard endpoint [22,23].

We also compared the response rates and survival of patients from the HELPER study to historical studies of treatment of stage III NSCLC that used concurrent EP plus radiotherapy. The results

**Table 2**
Adverse events.

| AE | No. of Patients (%) | | | | | |
|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Total |
| RIP | 7(10.4) | 5(7.5) | 2(3.0) | 0 (0.0) | 1(1.5) | 15(22.4) |
| Esophagitis | 0(0.0) | 53(79.1) | 9(13.4) | 0 (0.0) | 0 (0.0) | 62(92.5) |
| Dermatitis | 45(67.2) | 6(9.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 51(76.1) |
| Hair Loss | 48(71.6) | 2(3.0) | 0(0.0) | 0 (0.0) | 0 (0.0) | 50(74.6) |
| Fatigue | 33(49.3) | 13(19.4) | 1(1.5) | 0 (0.0) | 0 (0.0) | 47(70.1) |
| Anorexia | 42(62.7) | 9(13.4) | 4(6.0) | 0 (0.0) | 0 (0.0) | 55(82.1) |
| Nausea | 31(46.3) | 6(9.0) | 4(6.0) | 0 (0.0) | 0 (0.0) | 41(61.2) |
| Vomiting | 20(29.9) | 6(9.0) | 2(3.0) | 0 (0.0) | 0 (0.0) | 28(41.8) |
| Renal Injury | 0(0.0) | 1(1.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1(1.5) |
| Hemoptysis | 8(11.9) | 2(3.0) | 0 (0.0) | 0 (0.0) | 1(1.5) | 11(16.4) |
| Leucopenia | 9(13.4) | 25(37.3) | 19(28.4) | 11(16.4) | 0 (0.0) | 64 (95.5) |
| Neutropenia | 12(17.9) | 23(34.3) | 18(26.9) | 8(11.9) | 0 (0.0) | 61(91.0) |
| Anemia | 20(29.9) | 21(31.3) | 8(11.9) | 2(3.0) | 0 (0.0) | 51(76.1) |
| TBC | 15(22.4) | 10(14.9) | 7(10.4) | 4(6.0) | 0 (0.0) | 36(53.7) |
| Febrile | 0 (0.0) | 0 (0.0) | 14(20.9) | 0 (0.0) | 0 (0.0) | 14(20.9) |

*Abbreviations*: AE = adverse event; RIP = radiation induced pneumonitis; TBC = thrombocytopenia.

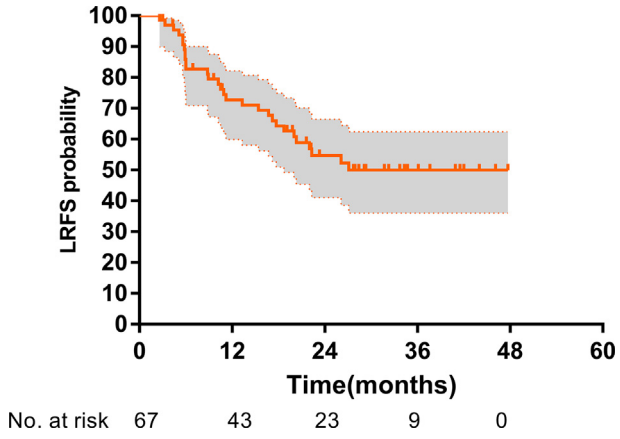


**Fig. 2c.** Locoregional relapse-free survival.

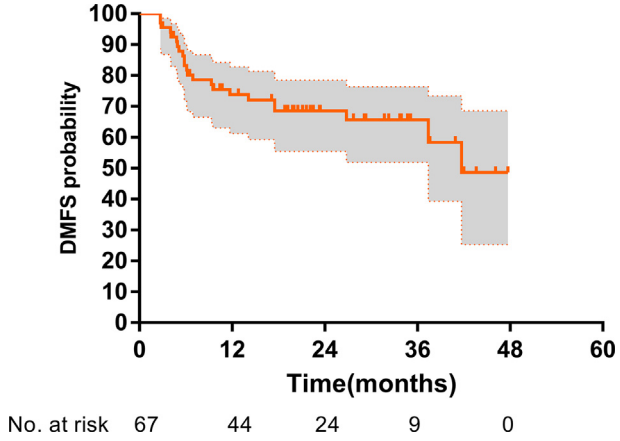


**Fig. 2d.** Distant metastasis-free survival.

are listed in Table 4. Generally, RR and CR rates in the HELPER study were similar to those of RTOG 9106 and Liang's study [18,20], and better than those reported in RTOG 9410, SWOG 9504, NPC95-01 and PROCLAIM [4,7,11,21]. However, we also noted that most of these studies were conducted in the 1990s and in the 2D RT era aside from PROCLAIM and Liang et al's study while IMRT was delivered in our study [18,21]. Modern techniques might bring substantial benefits in both prognosis and toxicities.

Results from the HELPER study indicated a prolonged MST compared with results from historical studies which treated patients with concurrent EP and radiotherapy [7,10,11,20]. Two-year and 3-year OS were superior to the previous studies, as well. Before the HELPER study, our team carried out another multicenter trial to compare the efficacy of concurrent radiotherapy with EP or carboplatin/paclitaxel (PC) in patients with stage III NSCLC, whose enrollment criteria and participating institutions were similar to those of our study. Grade 3–4 leucopenia was almost equivalent between these two studies. The median survival time and 2-year OS of EP plus radiotherapy in that study were 23.3 months and 48.4%, respectively [18,19]. The comparison indicates that the addition of endostar resulted in better treatment responses, longer survival without increment of severe toxicities.

After these comparisons, one important finding in our study was the demonstration of the equal MPFS but significantly better OS. Besides available salvage therapeutic options for patients who progress nowadays, favorable OS may also attribute to favorable DMFS in HELPER study. Despite the longer median follow up time compared with PROCLAIM study (37.1 months vs. 22.5 months), distant failure in HELPER study was much lower (34.3% vs.76.1%) [21]. MDMFS and 3-year DMFS in our study were also longer than that in several retrospective studies using CCRT alone (41.7 months vs. 11.7–15 months; 68.5% vs.24%) [24,25]. However, longer MDMFS might also attribute to modern radiation technique, different pathology types and different PTV volumes beside the addition of new regimens. Meanwhile, two-year LRFS (54.7%) was lower than RTOG 9410 (71%), RTOG 0617 (62.4%),

**Table 3**
Univariate Analysis.

| Factors | MPFS (m) | 2y PFS % | MST (m) | 2y OS | MLRFS (m) | 2y LRFS % | MDMFS (m) | 2y DMFS % |
|---|---|---|---|---|---|---|---|---|
| Sex | | | | | | | | |
| Male | 15.4 | 36.6 | 32.3 | 57.4 | 26.1 | 52.6 | NA | 75.3 |
| Female | 6.9 | 24.2 | 36.7 | 72.7 | NA | 65.6 | 9.5 | 36.4 |
| *P* value | 0.491 | | 0.551 | | 0.291 | | 0.008 | |
| Age | | | | | | | | |
| <60 | 10.9 | 35.6 | 34.7 | 60.1 | NA | 55.8 | 41.7 | 65.3 |
| ≥60 | 17.2 | 34.0 | 32.3 | 59.8 | 26.1 | 53.7 | NA | 72.9 |
| *P* value | 0.908 | | 0.619 | | 0.938 | | 0.644 | |
| Smoking | | | | | | | | |
| Yes | 17.7 | 40.2 | 28.4 | 55.1 | 27.0 | 54.0 | NA | 76.7 |
| No | 8.8 | 16.7 | 34.7 | 75.0 | NA | 56.9 | 9.5 | 43.8 |
| *P* value | 0.089 | | 0.314 | | 0.555 | | 0.003 | |
| *ECOG PS* | | | | | | | | |
| 0 | 18.7 | 44.4 | NA | 77.8 | 18.7 | 50.0 | 37.4 | 87.5 |
| ≥1 | 11.2 | 33.0 | 28.4 | 56.8 | NA | 55.1 | NA | 65.9 |
| *P* value | 0.857 | | 0.273 | | 0.540 | | 0.673 | |
| Stage | | | | | | | | |
| IIIa | 22.3 | 47.0 | NA | 67.8 | 27.1 | 61.5 | NA | 81.4 |
| IIIb | 10.5 | 25.5 | 32.2 | 54.1 | 22.0 | 49.0 | 37.4 | 58.8 |
| *P* value | 0.121 | | 0.220 | | 0.623 | | 0.034 | |
| Histology | | | | | | | | |
| Squamous | 15.4 | 34.4 | 28.4 | 55.5 | 21.9 | 43.5 | NA | 81.1 |
| Adeno | 11.9 | 31.6 | NA | 72.9 | NA | 70.6 | 17.5 | 42.1 |
| *P* value | 0.674 | | 0.258 | | 0.052 | | 0.002 | |

*Abbreviations*: Adeno = Adenocarcinoma; DMFS = distant metastasis free survival; ECOG PS = Eastern Cooperative Oncology Group performance status score; LRFS = local-regional relapse-free survival; m = months; MDMFS = median distant metastasis-free survival time; MLRFS = median localregional relapse-free survival time; MPFS = median progression-free survival time; MST = median survival time; NA = not achieved; OS = overall survival; PFS = progression free survival.

**Table 4**
Comparative toxicities, responses and survivals across clinical trials of CCRT (EP + RT).

| | No. of patients | Grade ≥3 esophagitis (%) | Grade ≥2 RIP (%) | Grades 3–4 leucopenia (%) | Grade 5 AEs (%) | RR, % | MST (months) | 2yOS (%) | 3yOS (%) | MPFS (months) | 2yPFS (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HELPER | 67 | 13.4 | 11.9 | 44.8 | 3.0 | 76.1 | 34.7 | 59.9 | 47.7 | 13.3 | 34.8 |
| RTOG9410* [4] | 187 | 45 | 2.1 | 67 | 4.3 | 65 | 15.6 | – | – | – | – |
| NPC9501 [7] | 100 | 32 | 5 | 48 | – | 32 | 16.3 | 39.3 | 24.8 | – | 29.5 |
| SWOG9504 [11] | 83 | 17 | 7 | 54 | 4 | 67 | 26 | 54 | 37 | – | – |
| RTOG9106 [20] | 76 | 53 | 25 | – | – | 70 | 18.9 | 35 | – | 8.3 | 21 |
| SWOG9019 [10] | 50 | 20 | 0 | – | – | – | 15 | 33 | 17 | – | – |
| PROCLAIM [21] | 272 | 18.8 | 2.6 | 25.4 | 0.4 | 33.0 | 25 | 52 | 37 | 9.8 | – |
| Liang [18] | 95 | 20.0 | 18.9 | 30.5 | 4.2 | 73.7 | 23.3 | 48.4 | 41.1 | 14 | – |

*Abbreviations*: AE = adverse events; CCRT = concurrent chemoradiotherapy; CR = complete response; EP = etoposide and cisplatin; MPFS = median progression free survival time; MST = median survival time; OS = overall survival; PFS = progression free survival; RIP = radiation induced pneumonitis; RR = response rate; RT = radiotherapy; y = year.
* Radiotherapy was delivered twice daily.

PROCLAIM (54.2%), better than RTOG 9106(29%, 15.4 months). After the comparison, it is still difficult to draw a definite conclusion of whether this treatment impact the LRFS because of high ratio of squamous carcinoma in our study, which is more likely to develop to local progression than other subtypes. Based on the result that the majority of locoregional recurrences were with infield recurrence, simultaneous integrated boost of GTV should be taken into consideration in the future.

Previous randomized studies showed that CCRT confers a long-term survival benefit compared with the sequential delivery of these therapies, but at the expense of increased toxicities for patients with locally advanced NSCLC [4,5,7]. Therefore, the safety of endostar combined with CCRT was of concern. In our study, grade 5 AEs were observed in two patients, a finding consistent with previous reports of CCRT alone [4,11]. Compared with CCRT using EP regimens in previous studies, the incidence of grade ≥2 radiation-induced pneumonitis was not increased. One suspected grade 5 pneumonitis in our study occurred in a 60-year-old male patient, who was treated with a full dose of chemoradiotherapy and two cycles of endostar. Severe cough, short of breath and fever were observed at the third month after treatment. The patient refused any further intervention and died 4.4 months after treatment.

The most common AEs were leucopenia and esophagitis, which are similar to those of CCRT studies [7,10,11,20,21]. However, if the comparison is restricted to the more modern studies, such as PROCLAIM and Liang's study, the Grade 3–4 leukopenia risk of the current study was a little higher. Grade ≥ 2 radiation induced pneumonitis was higher than that in PROCLAIM but lower than that in Liang's study. Generally, the addition of endostar to concurrent EP and radiotherapy proved to be well tolerated and did not result in serious AEs. Details of the comparison are presented in Table 4.

A recently published meta-analysis indicated that the use of angiogenesis inhibitors is associated with a significantly higher odds ratio of hypertension, arterial thromboembolism, cardiac dysfunction, and cardiac ischemia (OR1.35–5.59) [26]. Bevacizumab was the predominant treatment used in the meta-analysis, while endostar was not included. In our study, none of the previous toxicities were observed, although more than 25% of study patients were diagnosed with simultaneous cardiovascular disease. Hemoptysis was observed in 11 patients before treatment, and no new cases were observed following treatment. One patient diagnosed with T4 disease with severe thoracic aorta tumor invasion received a full course and dose of therapy and died of massive hemoptysis 1 month after treatment. We could not definitively determine if the hemoptysis was associated with therapeutic agents, or primary disease. The other 10 patients developed grade 1–2 hemoptysis which were successfully treated.

In the last decade, another antiangiogenic agent, bevacizumab, has been evaluated in phase I/II trials in combination with chemoradiotherapy, but has been found to induce high rates of pneumonitis (Grade 2: 4/6) and pulmonary hemorrhage (Grade 3:12.5%, Grade 5: 8.3%) especially in patients with squamous cell carcinoma [27–29]. In our study, the hemoptysis rate (Grade 3:0%, Grade 5:1.5%) is significantly lower than the former studies, even though the majority (65.7%) of patients in our study had squamous cell carcinoma histology. Hence, the advantage of endostar compared with bevacizumab is its lower rate of hemoptysis and pneumonia as well as its applicability to different histological pathologies. Another advantage is that the response rate of patients in the HELPER study was higher than SWOG S0533 (76.1% vs. 66.7%), which used CCRT and sequential bevacizumab [29].

Several studies have focused on the addition of an epidermal growth factor receptor inhibitor to CCRT [30,31]. Both RTOG 0324 and RTOG 0617 evaluated the combination of cetuximab with chemoradiotherapy. The MST and 2-year OS in our study was superior to RTOG 0324 and RTOG 0617 (34.7 months vs. 22.7–25 months, 59.9% vs. 49.3%-52.3%) [30,31]. Our study also got higher overall response rate (76.1% vs. 62%) than RTOG 0324, as well as higher 2-year PFS (34.8% vs. 24.2%) and 2-year DMFS (68.5% vs. 47.4%) than RTOG 0617.

Recently, several studies stated to evaluate the efficacy of immunotherapy. PACIFIC study showed a significant increment in PFS and no new safety signals with durvalumab in patients with stage III, unresectable NSCLC who had received chemoradiotherapy [32]. The MPFS and 2-year PFS in PACIFIC study was preferable to our study (16.8 months vs. 13.3 month, 44.2%vs. 34.8%), although OS was not reported. Compared with PACIFIC study, our study got prolonged MDMFS (41.7 months vs.23.2 months), partly due to the different distribution of pathological types (squamous in PACIFIC and our study: 47.1% vs. 65.7%). Meanwhile, some studies demonstrated that antiangiogenic agents have the potential for enhancing the results of immunotherapy by modulating the tumor microenvironment [33]. Accordingly, a new strategy combining the endostar with durvalumab might be investigated in the future.

To date, there are two published phase II trials in which patients with unresectable stage III NSCLC were treated with CCRT and endostar (Supplement Table S2) [17,34]. The major differences between the HELPER study and the two studies were the chemotherapy regimens and the drug delivery methods. In Bao's study, docetaxel and cisplatin were delivered and in Sun's study, PC was delivered [17,34]. The HELPER study resulted in similar response rates but with better survival compared to either of the previous studies just cited. All AEs, except for hematologic AEs, were equal or reduced in severity from the previous two studies. These results are consistent with our previous study which

compared EP with PC regimens in the administration of CCRT in NSCLC [18]. Moreover, the difference in stage IIIA vs IIIB distribution among patients in our study and these two cited studies is a confounder with respect to survival time comparisons (Stage IIIB: 57% vs. 83% and 74%,). However, four patients (21.1%) experienced grade 3 pulmonary injury in Sun's study [34], which delivered endostar as a consolidated therapy, leading to the early closure of the trial. Therefore, it remains unclear if consolidation with endostar after concurrent treatment is a safe and effective method.

The importance of our results is multifold. To our knowledge, this is the first study involving continuous intravenous endostar treatment plus concurrent EP chemoradiotherapy to treat unresectable locally advanced NSCLC. The actual enrolled number and evaluable number of patients met protocol requirements. The trial also met its feasibility endpoint regarding compliance because most of the enrolled patients were able to complete the intended therapy. Patients enrolled in the HELPER study also achieved favorable survival rates and favorable DMFS.

As a pilot study, our study has some limitations. First, although the statistical calculation was based on MPFS and the result demonstrated higher 2-year PFS, MPFS was not improved as we conjectured before. Secondly, the most effective endostar delivery method and the most feasible number of cycles are still uncertain despite the result that continuous intravenous pumping in our study got favorable survivals. Thirdly, consolidation chemotherapy with endostar was not evaluated in this study. Lastly, because this was a single arm study with a limited number of patients, the comparison between endostar plus CCRT and CCRT alone was not performed.

For treatment of patients with unresectable stage III NSCLC, the addition of continuous intravenous human recombinant endostatin to concomitant etoposide plus cisplatin and radiotherapy got preferable OS, promising 2-year PFS and favorable DMFS with tolerable toxicities, a finding consistent with our previous CCRT study. A randomized phase III study has been planned. According to the drawbacks of our study and the inspiring results in PACIFIC study, simultaneous integrated boost of GTV and consolidated durvalumab might be considered in the next study as well.

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## Disclosure

The authors have declared no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.10.032.

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