Efficacy and outcome analysis: Combination of Endostar and chemotherapy as a neoadjuvant treatment of stage IIIA/IIIB squamous cell lung cancer

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Abstract. Patients with stage IIIA/IIIB squamous non-small cell lung cancer (SqCLC) are particularly challenging to treat with a poor 5-year survival rate and new treatment strategies are needed. In the present study, a retrospective, single-center study was conducted to explore the efficacy and safety of Endostar combined with chemotherapy as the neoadjuvant treatment in patients with stage IIIA/IIIB SqCLC. A total of 27 patients with locally advanced SqCLC treated with Endostar combined with chemotherapy as neoadjuvant therapy from January 1, 2017 to December 31, 2019 at the Zhejiang Cancer Hospital (Hangzhou, China) were included. Short-term efficacy, rate of surgical resection, long-term outcome and adverse events were analyzed. After treatment with Endostar combined with chemotherapy, 37% of the patients underwent surgery and the radical resection rate was 90%. The objective response rate was 63% for the total population and 80% for patients who received surgery. Of note, 100% of the patients achieved disease control after treatment with Endostar combined with chemotherapy. In patients who underwent surgical resection, postoperative pathology showed that 100% of the patients achieved pathological downstaging. Furthermore, 1 (10%) patient showed a pathological complete response after surgery. The median progression-free survival was 13.5 months and overall survival was 27.9 months for the total cohort. The most common adverse events (AEs) were anemia (69.4% of patients), followed by hypertension (29.6% of patients). Most of the AEs were grade 1-2 and only 4 patients (14.8%) developed grade 3-4 AEs. Endostar combined with chemotherapy was well-tolerated and showed promising efficacy in patients with stage IIIA/IIIB SqCLC. Further prospective studies are warranted to explore its value as a neoadjuvant therapy.

Introduction

Non-small cell lung cancer (NSCLC) accounts for 80-85% of lung cancers and >15% of patients with NSCLC are diagnosed with locally advanced stage IIIA/IIIB disease (1). The second most prevalent histological subtype of NSCLC is squamous non-small cell lung cancer (SqCLC), characterized by poor prognosis and lack of specific target agents (2). Patients with stage IIIA/IIIB SqCLC are particularly challenging to treat and the 5-year survival rate is only 36-15% (3).

For patients with operable and potentially resectable NSCLC, neoadjuvant therapy is a viable treatment option. For patients with stage IIIA/IIIB NSCLC, neoadjuvant therapy may downstage the cancers and make them more operable, potentially enhancing the rate of complete resection (4). In the era of chemotherapy, meta-analyses of randomized trials of neoadjuvant chemotherapy showed a significant survival advantage over surgery alone with a 5% increase in the 5-year overall survival (OS) rate (5).

In stage IV NSCLC, immune checkpoint inhibitors (ICIs) have been the new standard of care as first-line therapy, including anti-programmed cell death 1 (PD-1) and PD-1 ligand 1 antibodies alone, or combined with chemotherapy, in accordance with the survival advantages over chemotherapy alone (6). Recently, clinical trials exploring neoadjuvant immunotherapy in resectable NSCLC have shown promising results, with the major pathologic response ranging from 21 to 45% (7,8). However, new therapeutic approaches are required for individuals with driver gene mutations and those who

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have contraindications to immunotherapy, as ICIs are not appropriate for everyone.

Angiogenesis is one of the most important features in cancers and is associated with more aggressive disease (9). Malignant cells secrete angiogenic cytokines to induce endothelial cell migration and angiogenesis to accelerate the growth of new vessels (10). Antiangiogenic therapy aims to disrupt those processes by normalizing the abnormal vasculature in tumors and improving delivery of drugs, enhancing its anti-tumor effect. Bevacizumab and recombinant human endostatin (Endostar) combined with cytotoxic drugs have been approved in advanced NSCLC by the Chinese National Medical Products Administration (NMPA). Recombinant human endostatin with chemotherapy had a better therapeutic effect than chemotherapy alone in advanced SqCLC, according to a meta-analysis. In addition, combination therapy did not increase the incidence of adverse reactions (11).

The present study aimed to explore the efficacy and safety of Endostar combined with chemotherapy as the neoadjuvant treatment in patients with stage IIIA/IIIB SqCLC.

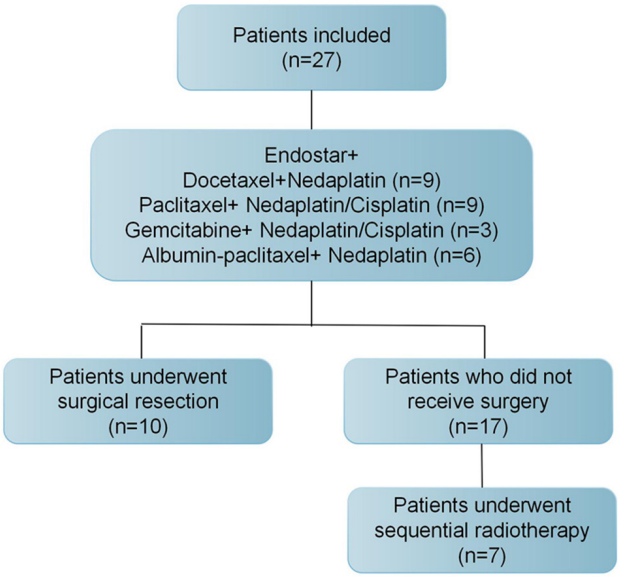

Figure 1. Flow chart of patients' treatment schedule.

Patients and methods

Subjects. This study was performed in line with the principles of the Declaration of Helsinki. All methods were performed in accordance with the relevant guidelines and regulations. Patients with locally advanced SqCLC (TNM stage: IIIA/IIIB) treated with Endostar combined with chemotherapy as neoadjuvant therapy from January 1, 2017 to December 31, 2019 at Zhejiang Cancer Hospital (Hangzhou, China) were included. Exclusion criteria in this study were as follows: i) Patients with other types of malignancy; ii) patients who were lost to follow-up. Patient data were collected, including age, gender, histological subtype, clinical TNM stage (8th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis staging system) (12), date of start of treatment, regimen of chemotherapy, cycles of chemotherapy, cycles of chemotherapy before surgery/radiotherapy, percentage of target lesions change, the best response [evaluated using computed tomography (CT) according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) (13)], surgical resection, date of surgery, pathological stage, radiotherapy, date of disease progression, date of death, adverse events.

Treatment schedule

Endostar. Endostar was administered at a dose of 7.5 mg/m^2 by intravenous (iv) infusion daily on day (D)1-D14; repeated every 3 weeks.

Chemotherapy. Participants received one of the platinum-based chemotherapies as follows: i) DP regimen: Docetaxel 60 mg/m^2 by iv infusion on D1; nedaplatin 100 mg/m^2 by iv infusion on D1; repeated every 3 weeks; ii) TP regimen: Paclitaxel 175 mg/m^2 or albumin paclitaxel 260 mg/m^2 by iv infusion on D1; nedaplatin 100 mg/m^2 or cisplatin 75 mg/m^2 by iv infusion on D1; repeated every 3 weeks; iii) GP regimen: Gemcitabine 1,000 mg/m^2 by iv infusion on D1; nedaplatin 100 mg/m^2 or cisplatin 75 mg/m^2 by iv infusion on D1; repeated every 3 weeks.

Follow-up procedures. Patients receiving Endostar and chemotherapy were evaluated for response every two treatment cycles during treatment and then every 2 months after treatment. The response evaluation of the tumor to therapy was based on computed tomography or magnetic resonance imaging scanning. The short-term efficacy was defined based on version 1.1 of the RECIST guidelines (13). The objective response rate (ORR) was defined as the percentage of patients who had a tumor response [complete response (CR) and/or partial response (PR)]. The long-term efficacy was evaluated according to progression-free survival (PFS) and OS. PFS was defined as the time from the initiation of treatment to radiological evidence of progressive disease (PD). OS was calculated from the initiation of treatment to mortality. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (14).

Statistical analysis. Statistical analysis was performed using the software SPSS 23.0 (IBM Corp.). Continuous variables were expressed as the median (minimum and maximum), and qualitative data were expressed as frequencies and percentages. Survival analysis was conducted using the Kaplan-Meier method and subgroups were compared using the log-rank test. All P-values were two-sided and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient cohort and clinical characteristics. In total, 27 patients with locally advanced SqCLC (TNM stage: IIIA/IIIB) treated with Endostar combined with chemotherapy as neoadjuvant therapy from January 1, 2017 to December 31, 2019 were included. After efficacy assessment, 10 patients (10/27; 37%) underwent radical surgical resection. Of the 17 patients who did not receive surgery, 7 patients underwent sequential radiotherapy (Fig. 1).

Table I. Patients' clinical characteristics and treatment information.

Item	Value
Male sex	100 (100.0)
Age, years	64 (49-74)
Performance status	
1	24 (88.9)
2	3 (11.1)
Histology of squamous cell carcinoma	100 (100.0)
Differentiation	
G2	6 (22.3)
G2-3	4 (14.8)
G3	4 (14.8)
NA	13 (48.1)
Stage	
IIIA	13 (48.1)
IIIB	14 (51.9)
Smoking history	
Yes	26 (96.3)
No	1 (3.7)
ALK/ROS-1/c-MET protein expression	
Negative	5 (18.5)
NA	22 (81.5)
Regimen of chemotherapy	
Docetaxel + Nedaplatin	9 (33.3)
Paclitaxel + Nedaplatin/Cisplatin	9 (33.3)
Gemcitabine + Nedaplatin/Cisplatin	3 (11.1)
Albumin-paclitaxel + Nedaplatin	6 (22.3)
Cycles of chemotherapy and Endostar	3 (2-6)
Local treatment	
Surgical resection	10 (37.0)
Radiotherapy	7 (25.9)
None	10 (37.0)

Values are expressed as n (%) or the median (range). NA, not available; ALK, anaplastic lymphoma kinase; ROS-1, ROS proto-oncogene 1; c-Met, hepatocyte growth factor receptor.

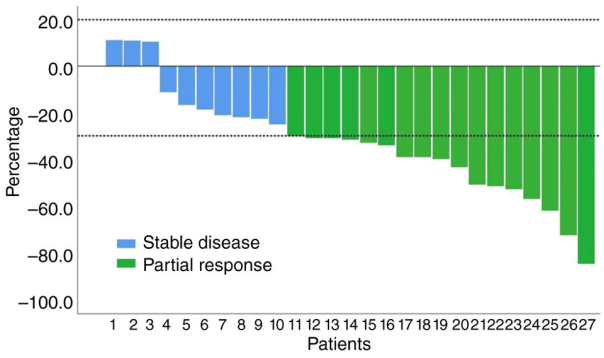

Figure 2. Waterfall plot of response to Endostar combined with chemotherapy as neoadjuvant therapy. Bars show data from individual patients. Negative values suggest tumor shrinkage and positive values suggest tumor growth. The dashed lines show the thresholds for partial response (shrinkage by 30%) or for progressive disease (growth by 20%) according to RECIST criteria.

Baseline characteristics, treatment details and efficacy of the 27 patients are presented in Table I. All of the 27 patients were male and the median age was 64 (49-74) years. A total of 24 (88.9%) patients exhibited a performance status of 1, while 3 patients (11.1%) displayed a performance status of 2. All 27 patients had squamous cell carcinoma on histopathology of their biopsy specimen. Among them, there were 6 (22.3%) cases of moderately differentiated carcinoma, 4 (14.8%) cases of moderate-low differentiated carcinoma, 4 (14.8%) cases of poorly differentiated carcinoma and 13 (48.1) cases of squamous carcinoma that could not be staged. A total of 13 (48.1%) patients were diagnosed with stage IIIA and 14 (51.9%) patients with stage IIIB. 26 (96.3%) patients reported a smoking history, while only 1 patient (3.7%) had no smoking history. None of the 27 patients exhibited any protein expression, including anaplastic lymphoma kinase, ROS proto-oncogene 1 and hepatocyte growth factor receptor (c-Met) protein expression, among others. The 27 patients received a median of 3 (range, 2-6) cycles of combination of Endostar and chemotherapy. Among them, 9 patients received Endostar plus docetaxel and nedaplatin, 9 received Endostar plus paclitaxel and nedaplatin/cisplatin, 3 received Endostar plus gemcitabine and nedaplatin/cisplatin and 6 received Endostar plus albumin-paclitaxel and nedaplatin.

Efficacy of Endostar combined with chemotherapy. After treatment by Endostar combined with chemotherapy, 37% of the patients (10/27) underwent surgery and the radical resection rate was 90% (9/10). The ORR was 63% (17/27) for the total population and 80% (8/10) for patients who received surgery. Of note, 100% (27/27) of the patients achieved disease control after treatment with Endostar combined with chemotherapy (Fig. 2; Table II). In the patients who underwent surgical resection, postoperative pathology showed that 100% (10/10) achieved pathological downstaging. Among them, 90% (9/10) achieved downstaging of the T stage and 80% (8/10) achieved downstaging of the N stage. Furthermore, 1 (10%) patient achieved a pathological CR after surgery (Table III).

Survival analysis. The last follow-up date was December 26, 2021 and the median follow-up time was 38.0 months (range, 27.8-57.7 months). Until the last follow-up, 20 patients had disease progression; 17 patients died of lung cancer progression and none died of other diseases or unknown causes. The median PFS was 13.5 months (95% CI: 9.6-17.4 months) and the median OS was 27.9 months (95% CI: 18.8-37.0 months) for the total cohort. Figs. 3 and 4 show two representative examples.

In the subgroup analysis, the median PFS of patients who underwent surgical resection (not reached; NR) was significantly longer than that of patients who did not undergo surgery (11.0 months; 95%CI: 3.0-19.0 months; P=0.003). The median OS of patients underwent surgical resection (NR) was significantly longer than that of patients who did not undergo surgery (15.9 months; 95%CI: 0-32.6 months; P=0.004). Patients without surgery or radiotherapy had the

Table II. Response in the total population and patients who received surgery.

Response	The total population (n=27)	Patients who received surgery (n=10)
Radical resection rate	9 (33.3)	9 (90.0)
Pathological downstaging	10 (37.0)	10 (100.0)
Partial response	17 (63.0)	8 (80.0)
Stable disease	10 (37.0)	2 (20.0)
Objective response	17 (63.0)	8 (80.0)
Disease control	27 (100.0)	2 (20.0)

Values are expressed as n (%).

Table III. TNM stage and tumor size of patients who underwent surgical resection.

	Before treatment		After surgery			
Patient no.	TNM stage	Tumor size, cm	TNM stage	Tumor size, cm	Downgrade N	Downgrade T
1	cT2bN2M0, IIIA	4.3x3.7	ypT2aN2M0, IIIA	3.5x2.8	No	Yes
2	cT2aN2M0, IIIA	3.6	ypT1bN2M0, IIIA	2.0x1.8	No	Yes
3	cT3N2M0, IIIB	5.4x3.8	ypT1aN0M0, IA	0.8x0.7	Yes	Yes
4	cT3N2M0, IIIB	5.1x4.6	ypT0N0M0, pCR	No nodules	Yes	Yes
5	cT2aN2M0, IIIA	3.5x3.2	ypT1cN1M0, IIB	3 .0x3.0	Yes	Yes
6	cT3N2M0, IIIB	6.4x4.9	ypT1cN0M0, IA	2.9x3.0	Yes	Yes
7	cT3N1M0, IIIA	6.0x3.8	ypT1cN1M0, IIB	2.5x1.5	Yes	No
8	cT4N1M0, IIIA	NA	ypT1cN0M0, IA	2.1x1.2	Yes	Yes
9	cT4N2M0, IIIB	9.7x4.3	ypT1bN1M0, IIB	2.0x2.0	Yes	Yes
10	cT2aN2M0, IIIA	2.3x3.1	ypT1aN0M0, IA	No nodules	Yes	Yes

CR, complete response; NA, not available.

worst median PFS (7.4 months; 95%CI: 4.5-10.3 months; P=0.002) and OS (12.2 months; 95%CI: 8.5-15.9 months; P=0.009; Fig. 5).

The association of short-term efficacy and long-term survival in the total cohort was further analyzed. The results indicated that patients who achieved PR had better PFS [24 (95%CI: 5.2-42.8) vs. 6.4 (95%CI: 2.5-10.3) months; P<0.001] and OS [37.2 (95%CI: ∞-∞) vs. 13.4 (95%CI: 7.7-19.1) months; P=0.001] than patients who did not achieve a PR (Fig. 6).

AEs. Endostar combined with chemotherapy was well tolerated in the total cohort. The most common AEs were anemia, which occurred in 69.4% (19/27) of patients, followed by hypertension in 29.6% (8/27) of patients. Most of the AEs were grade 1-2 and only 4 (14.8%) patients showed grade 3-4 AEs (Table IV).

Discussion

Previously reported phase III clinical trials evaluating neoadjuvant chemotherapy in stage IIIA/IIIB NSCLC showed unsatisfactory and inconsistent results. Roth *et al* (15) explored the efficacy of cyclophosphamide+etoposide+cisplatin as neoadjuvant therapy in stage IIIA NSCLC and 60 patients were included with 37% of SqCLC cases. The ORR was 35% in the total cohort and the complete resection rate was 39% in patients receiving induction chemotherapy. The median OS was 64 and 11 months in patients receiving induction chemotherapy and surgery alone, respectively (15). In another study, mitomycin+ifosfamide+cisplatin were evaluated in stage IIIA NSCLC; 60 patients were included with 70% of SqCLC cases. The ORR was 60% and the complete resection rate was 85% for the total population. However, the median OS was only 22 months in patients receiving induction chemotherapy (16). Nagai *et al* (17) explored the efficacy of cisplatin+vindesine in stage IIIA NSCLC and 62 patients were included with 24% of SqCLC cases. The ORR was 28% in the total cohort and the complete-resection rate was 65% in patients receiving induction chemotherapy. The median OS was 17 months in patients receiving induction chemotherapy (17). Mattson *et al* (18) explored the efficacy of docetaxel in stage IIIA-IIIB NSCLC and 274 patients were included with 62% of SqCLC cases. The ORR was 28% in the total cohort and the complete resection rate was 77% in patients receiving induction chemotherapy. The median OS was 14.8 months in patients receiving induction chemotherapy (18).

Table IV. AEs during Endostar combined with chemotherapy.

AE	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3	CTCAE grade 4
Leukocytopenia	2 (7.4)	2 (7.4)	1 (3.7)	2 (7.4)
Anemia	17 (63.0)	2 (7.4)	0 (0.0)	0 (0.0)
Thrombocytopenia	3 (11.1)	3 (11.1)	1 (3.7)	0 (0.0)
Hypertension	8 (29.6)	0 (0.0)	0 (0.0)	0 (0.0)

Values are expressed as n (%). AE, adverse event; CTCAE, Common Terminology Criteria for AEs.

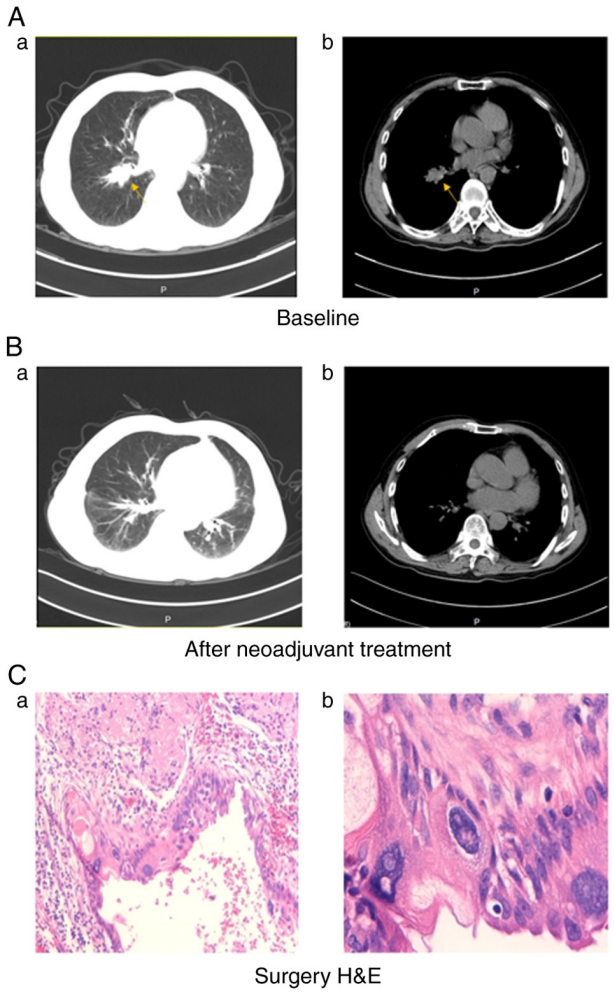

Figure 3. Chronological summary of imaging examination and pathological images of patient 1, a 63-year-old male, who underwent surgical resection. (A) At the baseline (March 2019), the CT scan showed a 3.1x2.3 cm right lung nodule (arrow). (a) Chest CT in a lung window; (b) chest CT in mediastinal window) (B) Two months later, after two cycles of neoadjuvant chemotherapy consisting of nab-paclitaxel+nedaplatin and Endostar (May 2019), the CT scan showed no nodules. (a) Chest CT in a lung window; (b) Chest CT in mediastinal window. (C) The pathological diagnosis was severe dysplasia of the squamous epithelium derived from residual tumors identified at lamina propria of bronchial margin (magnification, x100 in a and x400 in b).

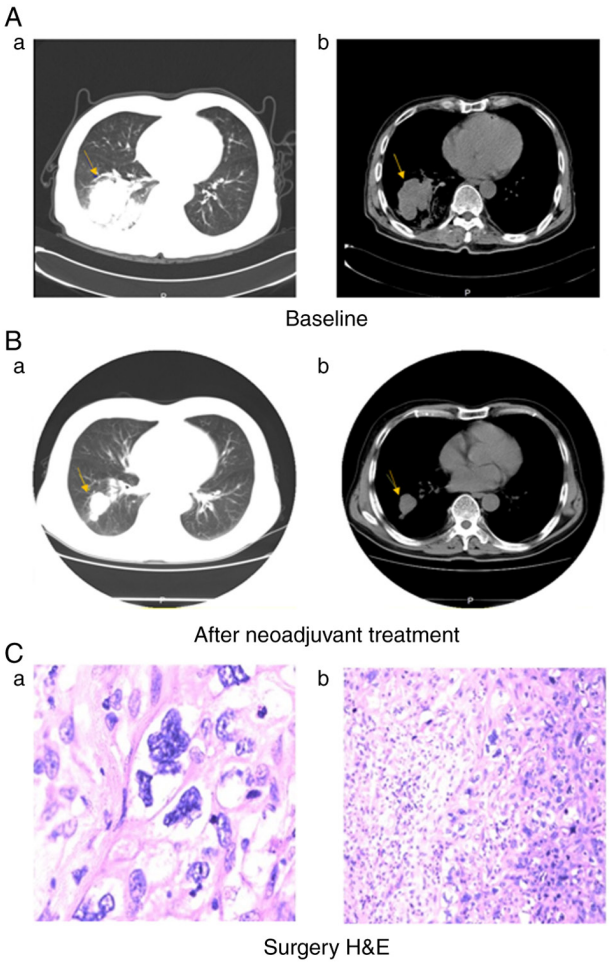

Figure 4. Chronological summary of imaging examination and pathological images of patient 2, a 72-year-old male, who underwent surgical resection. (A) At the baseline (February 2018), the CT scan showed a 6.4x4.8 cm right lung nodule (arrow). (a) Chest CT in a lung window; (b) chest CT in a mediastinal window. (B) Three months later, after three cycles of neoadjuvant chemotherapy consisting of cisplatin with docetaxel and Endostar (May 2018), the CT scan showed a 3.0x2.9 cm right lung nodule (arrow). (a) Chest CT in lung window; (b) Chest CT in mediastinal window. (C) The pathological diagnosis of the resected specimens was squamous cell carcinoma (magnification, x400 in a and x100 in b).

Given the success of targeted therapy and immunotherapy for patients with stage III/IV lung cancer, there is increasing interest in exploring these agents as neoadjuvant therapy in earlier disease settings (19). The neoadjuvant targeted therapy tended to have a higher ORR than chemotherapy. However, whether tumor shrinkage of neoadjuvant-targeted therapy could translate into an improvement of OS remains to be determined. In the CTONG 1103 trial, the erlotinib group achieved a higher ORR compared with the group treated with gemcitabine plus cisplatin as neoadjuvant therapy (54.1 vs. 34.3%), but the

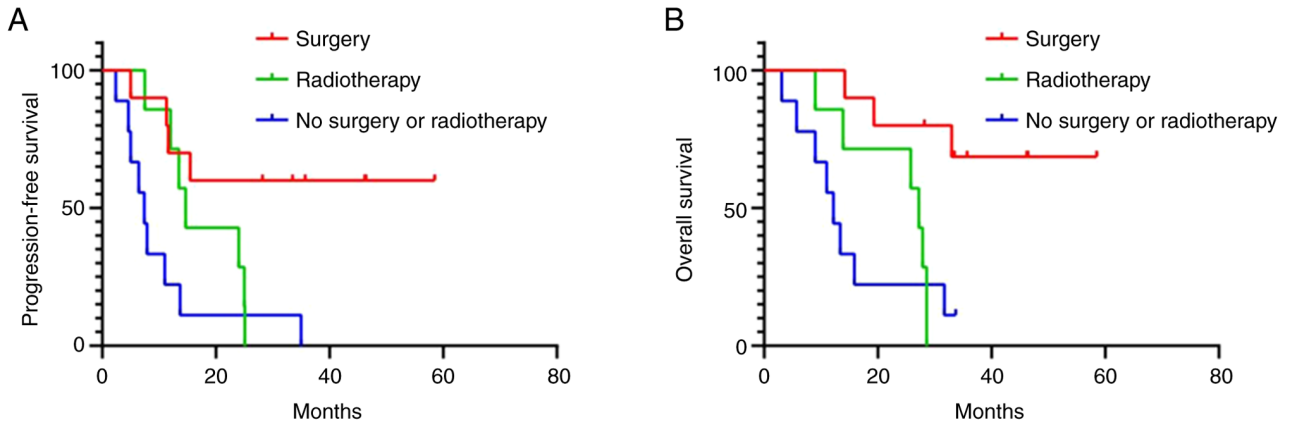

Figure 5. Survival analysis for patients receiving different subsequent therapies. (A) Comparison of PFS for patients receiving different subsequent therapies. The median total PFS for all the patients was 13.5 months, the median PFS of patients who underwent surgical resection (NR) was 11.0 months and the median PFS of patients without surgery or radiotherapy was 7.4 months. (B) Comparison of OS for patients receiving different subsequent therapies. The total median OS for all patients was 27.9 months, the median OS of patients who underwent surgical resection (NR) was 15.9 months and the median OS of patients without surgery or radiotherapy was 12.2 months. PFS, progression-free survival; OS, overall survival; NR, not reached.

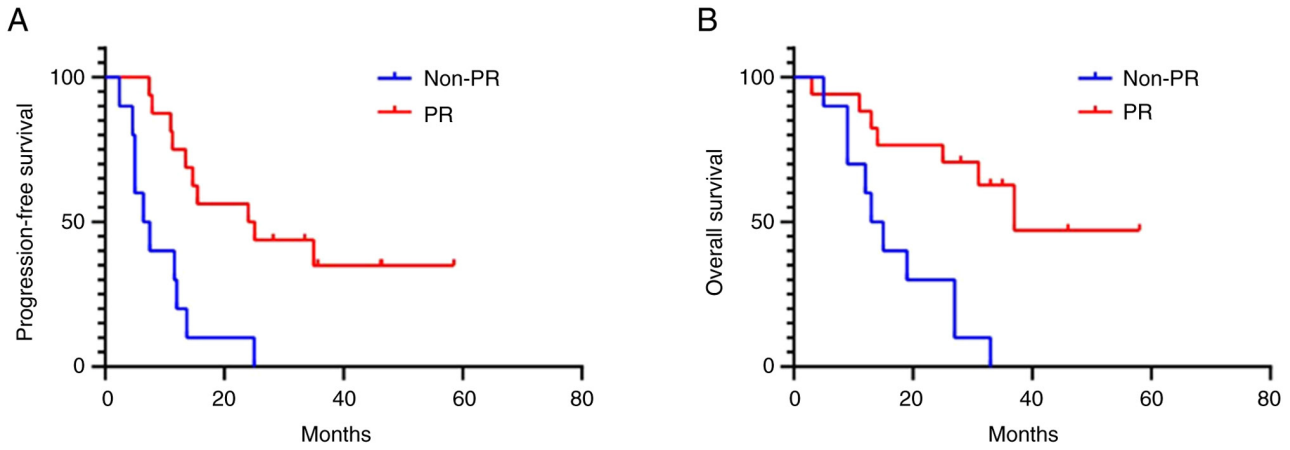

Figure 6. Survival analysis for patients with PR or Non-PR. (A) Comparison of PFS for patients with PR and those with Non-PR. The median PFS of patients with PR was 24.0 months and that of patients with Non-PR was 6.4 months. (B) Comparison of OS for patients with PR and those with Non-PR. The median OS of patients with PR was 37.2 months and that of patients with Non-PR was 13.4 months. PR, partial response; PFS, progression-free survival; OS, overall survival.

OS was not significantly different between the two groups (45.8 vs. 39.2 months) (20). In the past years, the advent of neoadjuvant immunotherapy has revolutionized the treatment landscape of NSCLC. Early findings from various ongoing clinical trials suggest that neoadjuvant ICIs alone or combined with chemotherapy may significantly reduce systemic recurrence. However, the median OS data are not yet mature. In addition, ICIs are not suitable for all patients, including those with immunological contraindications and those with driver gene alterations (21).

In the present study, the efficacy and safety of Endostar combined with chemotherapy as the neoadjuvant treatment in patients with stage IIIA/IIIB SqCLC were explored. The results were better than the previous results of neoadjuvant platinum-based two-drug chemotherapy (15-17). Endostar, as a novel recombinant human endostatin, was approved by the NMPA in 2005 to treat advanced NSCLC. Targeting the growth of vessels in tumors, Endostar was found to exert its antiangiogenic effects through the VEGF-triggered signaling pathway (22). In the HELPER study, the addition of Endostar to concurrent etoposide, cisplatin and radiotherapy in patients with unresectable stage III NSCLC achieved a median PFS and OS of 13.3 and 34.7 months, respectively (23). A meta-analysis of 15 clinical studies indicated that Endostar combined with vinorelbine plus cisplatin improved the ORR and one-year OS rate of advanced NSCLC (24). In the cohort of the present study, the most common AEs were anemia (69.4% of patients), followed by hypertension (29.6% of patients). Most of the AEs were grade 1-2 and only 14.8% of patients showed grade 3-4 AEs. In a clinical trial by Bao *et al* (25), the addition of Endostar to concurrent chemoradiotherapy did not increase toxicity. A meta-analysis also demonstrated that the combination of Endostar and platinum-based doublet chemotherapy (PBDC) was not associated with a higher incidence of leukopenia, thrombocytopenia and anemia compared with PBDC alone (26).

Of note, the present study had certain limitations. First, constrained by the retrospective and single-arm design, the results of the current study lacked comparison with patients

receiving chemotherapy alone, which weakened the reliability of the study. Therefore, prospective studies are needed to further validate the present results. Furthermore, the sample size of the present study was relatively small. Consequently, a multi-center study is needed to address the issue and provide a more robust result based on a larger sample size.

In conclusion, the combination of Endostar and chemotherapy demonstrated promising efficacy and was well tolerated among patients diagnosed with stage IIIA/IIIB SqCLC. Due to the limited cohort size, further prospective studies are necessary to investigate the potential efficacy of this neoadjuvant therapy.

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Availability of data and materials

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

Authors' contributions

WH and YJ designed the study. FC, SD, CG, YZ, YJ and WH contributed to the data collection and investigation. FC and SD wrote the original draft of the manuscript. CG and YZ confirm the authenticity of the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of Zhejiang Cancer Hospital (Zhejiang, China) approved the present study (approval no. IRB-2023-410).

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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