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Clinical Trial Results

Safety and Efficacy of Apatinib Monotherapy for Unresectable, Metastatic Esophageal Cancer: A Single-Arm, Open-Label, Phase II Study

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT03285906
- **Sponsors:** Chinese Society of Gynecological Oncology and Chinese Anti-Cancer Association (CACA) Hengrui Cancer Research Fund (AHEAD-HBE001)
- **Principal Investigators:** Yu Zhen Tao, Zhanyu Pan
- **IRB Approved:** Yes

Lessons Learned

- Patient compliance with the oral dosage treatment was good, with no need for hospitalization.
- Patients with tracheal and esophageal fistulas can take crushed apatinib by nutrient tube, with the same bioavailability and efficacy.
- Apatinib may be an effective and safe second- or further-line treatment for advanced esophageal cancer.

Abstract

Background. Apatinib is an inhibitor of vascular endothelial growth factor receptor-2 (VEGFR2), which is thought to play a role in esophageal cancer progression. Our goal was to evaluate the efficacy and safety of apatinib in patients with unresectable esophageal cancer and to examine whether VEGFR2 expression influenced the clinical response.

Methods. This single-arm, open-label, investigator-initiated phase II study enrolled patients with advanced squamous cell carcinoma (SCC) or adenocarcinoma of the esophagus or esophagogastric junction who were admitted to Tianjin Medical University Cancer Institute and Hospital between August 2017 and January 2019. Apatinib monotherapy (500 mg/day) was given orally or via an enteral tube until disease progression, unacceptable toxicity, withdrawal, or death. Patients were followed until treatment was discontinued or death. The main endpoints were tumor response, progression-free survival (PFS), overall survival (OS), and adverse events (AEs).

Results. Among 32 patients screened for inclusion, 30 were included in the safety and survival analyses (i.e., received apatinib), and 26 were included in the efficacy analysis (at least one imaging follow-up). Median follow-up time and exposure to apatinib were 5.34 months and 72 days, respectively. Among 26 patients included in the efficacy analysis, 2 had a partial response (PR; 7.7%) and 14 had stable disease (SD; 53.8%). The overall response rate (ORR) was 7.7%, and the disease control rate (DCR) was 61.5%. Median PFS and OS were 4.63 months (95% confidence interval,

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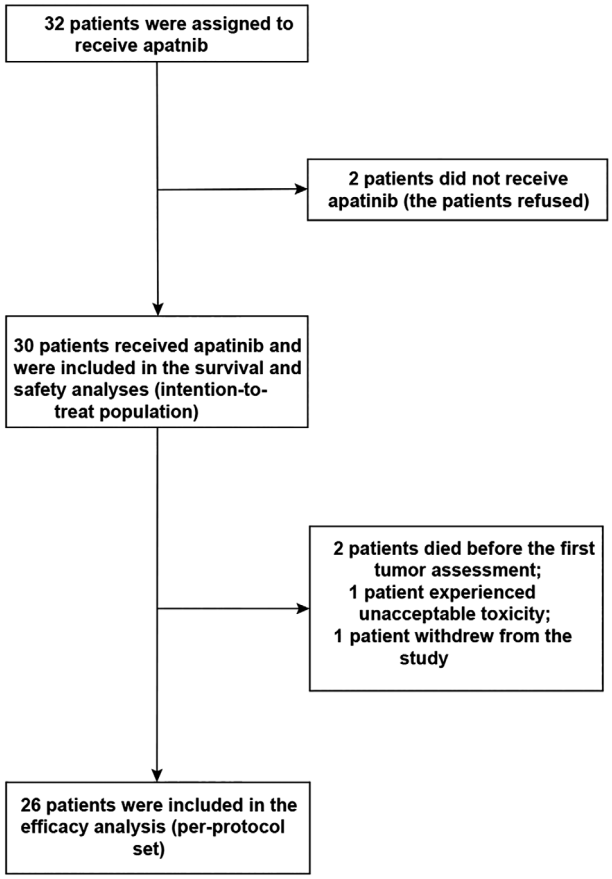

Figure 1. Patient disposition.

2.11–7.16 months) and 6.57 months (4.90 months to not estimable), respectively. Fifteen patients (50.0%) experienced treatment-related AEs, most commonly hypertension (26.7%), diarrhea (20.0%), and hand-foot-skin reaction (10.0%). No patients had grade ≥4 treatment-related AEs.

Conclusion. Apatinib was effective as second- or further-line treatment for advanced esophageal cancer. ***The Oncologist*** 2020;25:e1464–e1472

Discussion

Apatinib is an anticancer agent with oral bioavailability that selectively targets VEGFR2 to exert antiangiogenic and antiproliferative effects. Few previous studies have explored the use of apatinib monotherapy in the setting of advanced cancer of the esophagus or gastroesophageal junction. This study assessed the efficacy and safety of apatinib as a single agent in patients with metastatic, unresectable cancer of the esophagus or esophagogastric junction for whom standard second-line therapy had failed or was not suitable and to examine whether the clinical response to apatinib was related to VEGFR2 expression.

This phase II trial enrolled 30 patients with advanced SCC or adenocarcinoma of the esophagus or esophagogastric junction (Fig. 1). Apatinib monotherapy (500 mg/day) was given orally or via an enteral tube until disease progression, unacceptable toxicity, withdrawal, or death. The main endpoints were tumor response, PFS, OS, and AEs.

Results showed that 7.7% of patients had a PR and 53.8% had SD after apatinib monotherapy, with an ORR of 7.7% and a DCR of 61.5%. Median PFS and OS were 4.63 months and 6.57 months, respectively. Although half the patients experienced treatment-related AEs, all were grade ≤3. Thus, the findings of this study are broadly consistent with those of previous clinical investigations, indicating that apatinib monotherapy (at a daily dose of 500 mg) may be an effective second- or further-line treatment for advanced esophageal cancer.

Treatment-related AEs were observed in 50% of patients, and these were most commonly hypertension (26.7%), diarrhea (20.0%), and hand-foot-skin reaction (10.0%). Most AEs were grade 1 in severity; only one patient experienced a grade 3 AE (hypertension), and no patients had grade ≥4 treatment-related AEs. The AEs observed in this study are comparable to those observed in previous research, indicating that apatinib has an acceptable toxicity profile when used as a single agent for the management of advanced esophageal cancer.

In conclusion, apatinib monotherapy appears to be an effective and safe second- or further-line treatment for patients with metastatic, unresectable cancer of the esophagus or esophagogastric junction.

Trial Information	
Disease	Esophageal cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	More than 2 prior regimens
Type of Study	Phase II, single arm
Primary Endpoint	Overall survival
Secondary Endpoint	Progression-free survival
Additional Details of Endpoints or Study Design	
The main inclusion criterion was histologically confirmed stage III/IV SCC/adenocarcinoma of the esophagus or SCC/adenocarcinoma of the gastroesophageal junction accompanied by high expression of VEGFR2. The inclusion criteria were (a) able to understand the nature of the study and provided informed written consent; (b) histologically confirmed stage III/IV SCC/adenocarcinoma of the esophagus or SCC/adenocarcinoma of the gastroesophageal junction accompanied by high expression of VEGFR2; (c) did not respond to or relapsed after treatment with platinum-containing or 5-fluorouracil-containing chemotherapy or unable to tolerate previous chemotherapy; (d) aged 18–80 years and with an expected survival time of at least 12 weeks; (e) Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2;	

(f) at least one measurable lesion according to RECIST version 1.1 [19], which had not been treated previously by radiotherapy; (g) bone marrow, hepatic, and renal functions measured by the Central Laboratory within 14 days after inclusion met the following criteria: white blood cell count ≥3.5 × 10^9/L (3,000/mm^3), hemoglobin ≥10 g/dL, absolute neutrophil count ≥1.0 × 10^9/L (1,500/mm^3), platelet count ≥100 × 10^9/L; v) total bilirubin ≤2 × upper limit of normal (ULN), alanine transaminase and aspartate transaminase ≤100 IU/L, serum creatinine ≤1.5 × ULN, and creatinine clearance ≥60 mL/minute according to the Cockroft-Gault equation (other methods such as the ethylenediaminetetraacetic acid method, inulin clearance method, or 24-hour urine analysis were used for patients with low body weight or when use of another equation yielded a substantially different result to the Cockroft-Gault equation); (g) for women of childbearing age, a serum pregnancy test performed within 7 days before treatment was negative (all participants were required to use adequate methods of barrier contraception throughout the treatment period and for 4 weeks after treatment); and (h) high adherence to therapy and able to be followed up.

The exclusion criteria were (a) other targeted antiangiogenic agents, such as bevacizumab or endostar, had been used as the first-line therapy; (b) concurrent administration of other antitumor therapies, including hormone therapy (oral contraceptives and physiologic replacement of hormones was permitted), immunotherapy, and targeted therapy; (c) cerebral or meningeal metastases (excluding cerebral parenchymal metastases that had been controlled after local therapy and did not require hormone maintenance therapy); (d) history of interstitial lung disease, drug-induced interstitial diseases, or radiation pneumonitis requiring hormone therapy; (e) clinical evidence suggestive of active interstitial lung disease; (f) baseline computed tomography (CT) scanning suggested idiopathic pulmonary fibrosis; (g) uncontrollable, high-volume pleural effusion or pericardial effusion; (h) in the investigator's opinion, evidence suggesting severe or uncontrollable systemic disease (such as unstable or noncompensatable respiratory, cardiac, hepatic, or renal disease); (i) diagnosed with another malignant tumor within the last 5 years (except for completely cured cervical carcinoma in situ or basal cell carcinoma/squamous cell carcinoma of the skin); (j) clear history of psychologic or mental disorders, including epilepsy and dementia; (k) history of allograft transplantation; (l) major surgery or severe trauma within the 3 weeks before the first day of drug therapy; (m) severe allergy to any of the study drugs or vehicles; (n) also treated with phenytoin sodium, carbamazepine, rifampicin, barbital, or St John's Wort; (o) treated with an unapproved drug or another trial drug within 30 days before the first day of drug therapy; (p) pregnant or breastfeeding; (q) history of drug abuse or with medical, psychologic, or social conditions that might influence participation or outcome assessment; and (r) any condition that could endanger the safety of the patient or the adherence of the patient to the study protocol.

Patients were followed up until death or patient withdrawal or May 14, 2019 (whichever occurred first). Tumor response was assessed using enhanced CT or magnetic resonance imaging at baseline, 4 weeks after the initiation of apatinib therapy and then every 6–8 weeks. The tumor response was defined as complete response (CR), PR, SD, or progressive disease (PD) based on RECIST version 1.1 [19]. In addition, patients were followed up every month in the clinic or by telephone for the assessment of survival status, physical status (clinical examination), ECOG performance status, and use of any further anticancer treatment. The primary endpoint was OPR (defined as CR rate + RR rate). The secondary endpoints included DCR (defined as the percentage of patients with a complete response, partial response, or stable disease), PFS (defined as the time between enrollment of the patient and any recorded tumor progression or death from any cause), and OS (defined as the time between enrollment of the patient and death from any cause). Safety was assessed based on the occurrence of any AEs, which were classified and graded according to Common Terminology Criteria for Adverse Events version 4.0 [20].

Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1	
Generic/Working Name	New drug
Trade Name	Apatinib
Company Name	Hengrui company
Drug Type	Small molecule
Drug Class	VEGF
Dose	500 mg per flat dose
Route	p.o.
Schedule of Administration	Daily

Patient Characteristics

Number of Patients, Male	28
Number of Patients, Female	4
Stage	Histologically confirmed stage III/IV SCC/adenocarcinoma of the esophagus or SCC/adenocarcinoma of the gastroesophageal junction accompanied by high expression of VEGFR2
Age	Median (range): 60 (23–72) years

Primary Assessment Method	
Title	New assessment
Number of Patients Screened	32
Number of Patients Enrolled	30
Number of Patients Evaluable for Toxicity	30
Number of Patients Evaluated for Efficacy	26
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 2 (7.7%)
Response Assessment SD	*n* = 14 (53.8%)
Response Assessment PD	*n* = 8 (30.8%)
Response Assessment OTHER	*n* = 2 (7.7%)
(Median) Duration Assessments PFS	4.63 months
(Median) Duration Assessments OS	6.57 months
(Median) Duration Assessments Response Duration	4.76 months
(Median) Duration Assessments Duration of Treatment	12 months

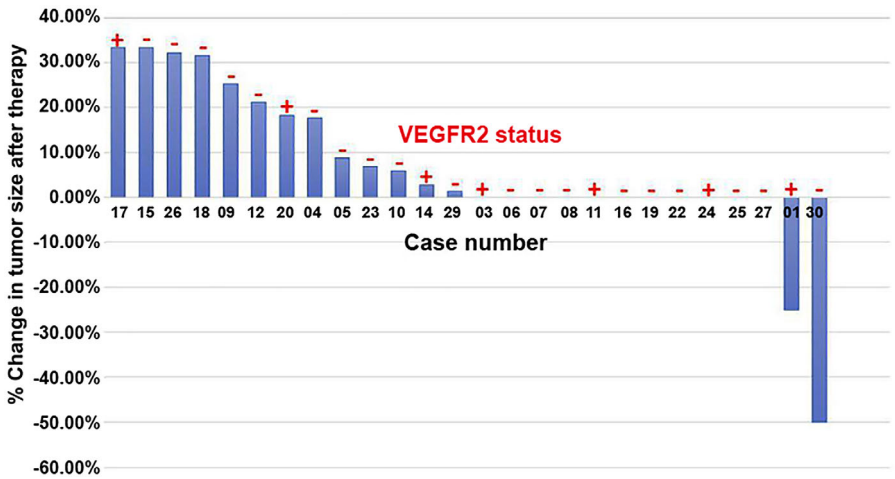

Figure 2. Waterfall plot illustrating the response to treatment in the 26 patients included in the efficacy analysis. The response to treatment was measured radiographically as the percentage change in tumor size after therapy, evaluated as recommended by RECIST version 1.1. Tumor expression of VEGFR2 (positive or negative) is shown in red.
Abbreviation: VEGFR2, vascular endothelial growth factor receptor-2.

Outcome Notes

Among 32 patients screened for inclusion, 30 were included in the safety and survival analyses (i.e., received apatinib), and 26 were included in the efficacy analysis (at least one imaging follow-up). Median follow-up time and exposure to apatinib were 5.34 months and 72 days, respectively. Among 26 patients included in the efficacy analysis, 2 showed partial remission (7.7%) and 14 had stable disease (53.8%). The overall response rate was 7.7%, and the disease control rate was 61.5%. Median PFS and OS were 4.63 months (95% confidence interval, 2.11–7.16 months) and 6.57 months (4.90 months to not estimable), respectively. Fifteen patients (50.0%) experienced treatment-related AEs, most commonly hypertension (26.7%), diarrhea (20.0%) and hand-foot-skin reaction (10.0%). No patients had grade ≥4 treatment-related AEs.

Adverse Events							
All Cycles							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Proteinuria	97%	3%	0%	0%	0%	0%	3%
Fatigue	93%	7%	0%	0%	0%	0%	7%
Hypertension	74%	20%	3%	3%	0%	0%	26%

Mucositis oral	97%	3%	0%	0%	0%	0%	3%
Nausea	93%	7%	0%	0%	0%	0%	7%
Anemia	93%	7%	0%	0%	0%	0%	7%
Noncardiac chest pain	97%	3%	0%	0%	0%	0%	3%
Back pain	93%	7%	0%	0%	0%	0%	7%
Diarrhea	80%	13%	7%	0%	0%	0%	20%
Skin and subcutaneous tissue disorders—hand-foot-skin reaction	90%	7%	3%	0%	0%	0%	10%
Investigations—esophagostoma	97%	0%	3%	0%	0%	0%	3%

Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Esophageal cancer is the ninth most common cancer worldwide and one of the leading causes of cancer-related mortality [1, 2]. China has a higher incidence of esophageal cancer than Western countries, and more than 50% of all new cases are diagnosed in China [3]. Esophageal squamous cell carcinoma (ESCC) accounts for most cases [2, 4]. Various risk factors for ESCC have been proposed, including advanced age, smoking, alcohol consumption, and caustic injury to the esophagus [5, 6]. At the time of diagnosis, approximately half of patients with esophageal cancer present with metastatic disease, which is associated with a poor prognosis. Indeed, the 5-year overall survival (OS) is 15%–25% in all patients with esophageal cancer and less than 4% in those with metastatic disease [1, 2, 4, 5].

Radiotherapy and chemotherapy are the main treatment methods for patients with advanced esophageal cancer or postoperative recurrence and metastasis. Concurrent chemoradiation therapy (CCRT) has been shown to prolong survival and reduce disease persistence and recurrence [7, 8], but the long-term result remains unsatisfactory [9]. Thus, there has been great interest in the development of novel agents with limited toxicity that target the mechanisms of tumor growth and metastasis. Several targeted therapies are now available that inhibit molecules that contribute to carcinogenesis, such as human epidermal growth receptor 2, vascular endothelial growth factor receptor-2 (VEGFR2), programmed cell death-1 receptor, and endothelial growth factor receptor [10].

The VEGFR2 is commonly expressed in esophageal cancer tissue and is thought to contribute to tumor angiogenesis and dissemination [11]. Apatinib is a novel inhibitor of angiogenesis that targets the intracellular adenosine triphosphate–binding site of VEGFR2 [12]. Apatinib has shown positive results as a second- or further-line treatment in patients with ESCC [13–16]. The overexpression of VEGF in esophageal cancer may be associated with a poor prognosis [17, 18]. However, no studies published to date have examined whether tumor expression of VEGFR2 affects the clinical response of esophageal cancer to apatinib.

The aims of this study were to assess the efficacy and safety of apatinib as a single agent in patients with metastatic, unresectable cancer of the esophagus or esophagogastric junction for whom standard second-line therapy had failed or was not suitable and to examine whether the clinical response to apatinib was related to VEGFR2 expression.

This prospective, single-arm, open-label, investigator-initiated phase II study included patients with advanced cancer of the esophagus or esophagogastric junction admitted to Tianjin Medical University Cancer Institute and Hospital (Tianjin, China) between August 2017 and January 2019.

The study was approved by the institutional ethics committee of Tianjin Medical University Cancer Institute and Hospital (E2017107). The trial was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before the initiation of any study related procedure. This study is registered at ClinicalTrials.gov (NCT03285906).

The objective of the study was to evaluate whether apatinib monotherapy might be an effective and safe second- or further-line treatment in patients with metastatic, unresectable cancer of the esophagus or esophagogastric junction. The main findings were that 7.7% of patients showed partial response (PR) and 53.8% had stable disease (SD) after apatinib monotherapy, with an overall response rate (ORR) of 7.7% and a disease control rate (DCR) of 61.5%. Median progression-free survival (PFS) and overall survival (OS) were 4.63 months and 6.57 months, respectively. Although half the patients experienced treatment-related adverse events (AEs), all were grade ≤3. Taken together, our findings suggest that apatinib may be effective and safe as a second- or further-line treatment for advanced esophageal cancer.

Apatinib is an anticancer agent with oral bioavailability that selectively targets VEGFR2 to exert antiangiogenic and antiproliferative effects [12, 21]. Apatinib has been demonstrated to have promising activity against gastric, breast, and lung tumors [12]. Moreover, a retrospective analysis concluded that apatinib (500 mg daily) combined with docetaxel may be effective as a second-line treatment for advanced esophageal cancer, with a median PFS of nearly 6 months, an ORR of 88.9%, and a DCR of 93.3% [14]. However, very few previous studies have explored the use of

apatinib monotherapy in the setting of advanced cancer of the esophagus or gastroesophageal junction. In a multicenter, phase III trial of patients in China with advanced gastric or gastroesophageal junction adenocarcinoma, administration of apatinib monotherapy (850 mg daily) was associated with significant improvements in OS (6.5 vs. 4.7 months) and PFS (2.6 vs. 1.8 months) when compared with placebo [13]. In another study, the use of apatinib monotherapy (500 mg daily) as a second- or further-line treatment for advanced ESCC resulted in a PR rate of 24.2%, SD rate of 50.0%, progressive disease (PD) rate of 25.8%, ORR of 24.2%, DCR of 74.2%, median PFS of 115 days, and median OS of 209 days [16]. The current phase II trial, which also used a daily apatinib dose of 500 mg, reported a PR rate of 7.7%, SD rate of 53.8%, PD rate of 30.8%, clinical progression rate of 7.7%, ORR of 7.7%, DCR of 61.5%, median PFS of 4.63 months, and median OS of 6.57 months. Thus, the findings of our study are broadly consistent with those of previous clinical investigations, indicating that apatinib monotherapy (at a daily dose of 500 mg) may be an effective second- or further-line treatment for advanced esophageal cancer.

In the present study, treatment-related AEs were observed in 50.0% of patients, and these were most commonly hypertension (26.7%), diarrhea (20.0%), and hand-foot-skin reaction (10.0%). The majority of AEs were grade 1 in severity; only one patient experienced a grade 3 AE (hypertension), and no patients had grade ≥4 treatment-related AEs. A previous study of apatinib monotherapy for advanced ESCC described hand-foot-skin reaction (51.6%), proteinuria (24.2%), and hypertension (21.0%) as the most common AEs, with acceptable grade 3/4 toxicities in 59.7% of patients [16]. Another study of apatinib monotherapy also described proteinuria (47.7%), hypertension (35.2%) and hand-foot-skin reaction (27.8%) as the most common nonhematologic AEs, and the toxicity profile was deemed to be acceptable [13]. The AEs observed in this study are comparable to those observed in previous research, indicating that apatinib has an acceptable toxicity profile when used as a single agent for the management of advanced esophageal cancer. Nevertheless, two cases of death due to massive hemoptysis have been reported after therapy with apatinib, which was speculated to have resulted from bronchial artery erosion by tumor [22]. This would suggest that apatinib should be used with caution in patients with large vessels or airways eroded by tumor [1].

Several clinical studies have investigated the use of anti-angiogenic agents in advanced gastric/gastroesophageal junction cancer [9, 23–25]. The expression of VEGFR2 in esophageal cancer tissue is thought to contribute to tumor angiogenesis and dissemination [11]. Furthermore, VEGF overexpression in esophageal cancer appears to be associated with a poor prognosis [17, 18]. Because apatinib selectively targets VEGFR2, the present study investigated whether tumor expression of VEGFR2 might be associated with a longer PFS or OS in patients treated with apatinib. Although we found no significant association of VEGFR2 expression with PFS or OS, there appeared to be a trend toward a longer PFS in patients with VEGFR2-positive tumor (p = .097; Table 2). Because of the small sample size, it cannot be excluded that our study was underpowered to detect a real association between VEGFR2 expression and PFS, particularly as all the patients in our study had a poor clinical status due to advanced disease that had failed to respond to previous therapy. We also observed no significant association of Eastern Cooperative Oncology Group performance status score with PFS or OS, in contrast to a previous investigation [16].

This study has several limitations. First, this was a single-center study, so the generalizability of the results is not known. Second, the sample size was small, so the analysis may have been underpowered to detect some real effects. Third, this was an open-label study, which may have introduced bias into the estimates of treatment effect. Fourth, we did not include a comparator group (e.g., placebo). Large-scale, multicenter, randomized controlled trials are needed to confirm and extend our findings.

In conclusion, the results of this prospective, single-arm, open-label, investigator-initiated phase II study indicate that apatinib may be effective and safe as a second- or further-line treatment for advanced esophageal cancer.

Acknowledgments

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Disclosures

The authors indicated no financial relationships.

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Tables and Figures

Table 1. Demographic and clinical characteristics of the 30 study participants

Characteristic	Value
Age, median (range), years	60 (23–72)
Sex	
Male	26 (87)
Female	4 (13)
Tumor location	
Cervical	1 (3)
Upper thoracic	5 (17)
Mid-thoracic	15 (50)
Mid-to-lower thoracic	2 (7)
Lower thoracic	7 (23)
Tumor histology	
Squamous cell carcinoma	2 (7)
Adenocarcinoma	28 (93)
Tumor differentiation	
Well differentiated	0 (0)
Moderately differentiated	16 (53)
Poorly differentiated	13 (43)
Not differentiated	1 (3)
Disease status	
Initially metastatic	30 (100)
Recurrence after potentially curative therapy	17 (57)
Prior chemotherapy	30 (100)
Yes	29 (97)
No	1 (3)

Data are presented as *n* () unless otherwise stated.

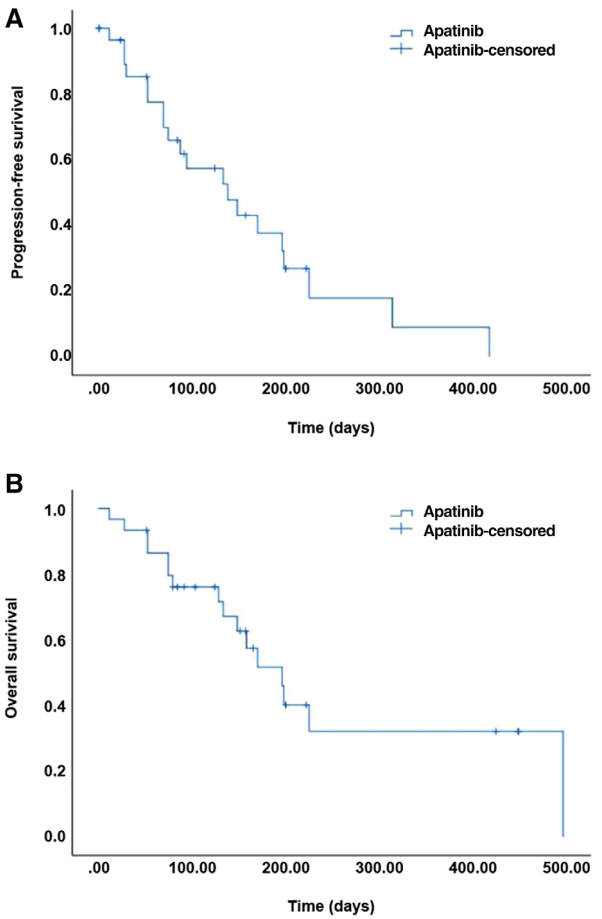

Figure 3. Survival analysis for patients with esophageal cancer treated with apatinib. **(A):** Kaplan-Meier curve showing progression-free survival. **(B):** Kaplan-Meier curve showing overall survival.

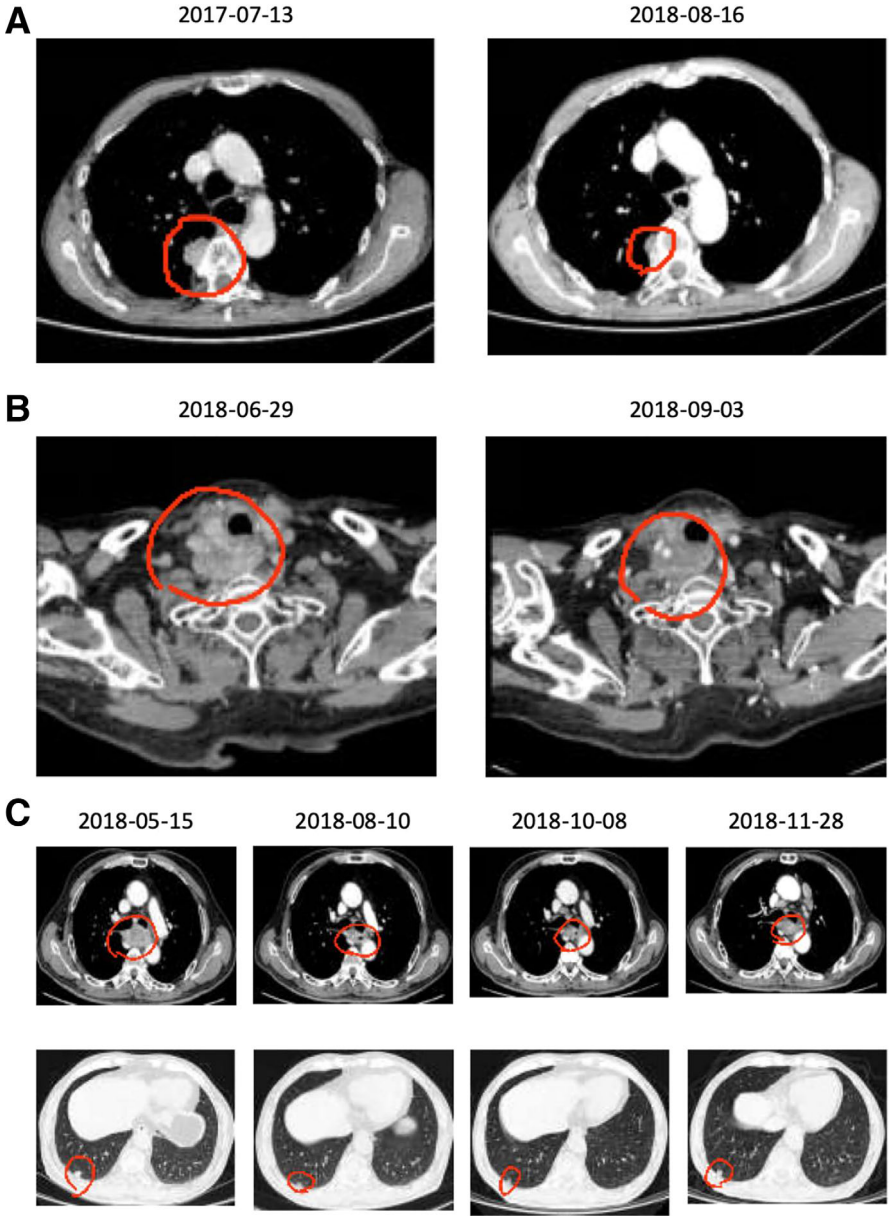

Figure 4. Representative imaging data showing the tumor response to therapy in three patients. **(A):** This 59-year-old male patient had previously received radical treatment for esophageal cancer, but a mass subsequently became evident under the right pulmonary pleura. Pathologic examination of a surgical specimen indicated squamous cell carcinoma, and metastasis was taken into consideration. The patient was enrolled into the study after failure of chemotherapy. The computed tomography (CT) images show a notable reduction in the size of the target lesion after treatment with apatinib. The progression-free survival (PFS) of this patient was >1 year. **(B):** In this 62-year-old male patient, tracheal and esophageal fistulae had formed after radical treatment of esophageal cancer, and metastasis had occurred to the neck. The patient was unable to tolerate chemotherapy. After enrollment, gastrostomy was performed, and apatinib was administered via the gastrostomy tube. The CT images show a substantial reduction in the size of the target lesion after treatment with apatinib. The PFS of the patient was >1 year. **(C):** In this 64-year-old male patient, disease recurrence and lung metastasis had occurred after radical treatment of esophageal cancer. Chemotherapy had failed, and the patient was unable to eat. The administration of apatinib via a gastrostomy tube led to a notable decrease in the size of the target lesions. The PFS of this patient was >6 months.

Table 2. Univariate analyses of PFS and OS based on different subgroups

Subgroup	PFS, median (95% CI), months	*p* value	OS, median (95% CI), months	*p* value
Sex		.593		.803
Male	3.32 (2.23–4.63)		7.69 (4.63–NE)	
Female	2.50 (1.87–4.76)		7.33 (3.09–15.38)	
Age, years		.849		.690
<65	2.94 (2.20–3.91)		7.69 (5.36–NE)	
≥65	3.22 (1.28–5.39)		8.84 (2.50–NE)	
ECOG PS		.633		.180
1	3.53 (2.14–4.63)		9.26 (6.31–15.38)	
2	2.79 (1.31–3.71)		4.76 (2.50–NE)	
Driver gene mutation		.556		.135
≥1 mutation	2.83 (2.20–4.75)		5.36 (2.92–NE)	
None/unknown	3.14 (2.10–4.17)		9.26 (6.31–NE)	
Mutation status		.097		.702
Mutation	3.91 (2.37–6.05)		7.69 (2.92–NE)	
Wild-type	2.83 (2.14–4.14)		7.33 (5.36–15.38)	

Abbreviations: 95% CI, 95% confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not estimable; OS, overall survival; PFS, progression-free survival.