Clinical Efficacy and Safety of Apatinib for Maintenance Treatment in Patients with Advanced Esophageal Squamous Cell Carcinoma

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Research article

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Abstract

Background: To investigate the clinical efficacy,safety and prognostic factors of the therapy that apatinib is used for maintenance treatment in patients with advanced esophageal squamous cell carcinoma.

Methods: We select 46 patients with advanced esophageal squamous cell carcinoma treated with radiotherapy and chemotherapy in our hospital from January 2017 to February 2019, all of them were treatment with apatinib. Analysis the clinical efficacy, adverse reactions and prognostic factors. Meanwhile, the expression of patients'VEGFR-2、NF-kB was detected by immunohistochemical SABC method,and the microvessel density and microlymphatic tube density were counted.Analysis of the relationship between indicators and MVD, MLVD counts and the efficacy of apatinib.

Results: We found that oral treatment of apatinib in VEGFR-2、NF-kB positive group was better than that in negative group. The partial remission rate of patients was 26.09%; the disease control rate was 67.39%.The main adverse reactions were hypertension (60.87%); hand and foot syndrome (34.77%); proteinuria (36.96%). The degree of adverse reactions was mainly grade 1~2. The median progression-free survival was 3.7 months and the median overall survival was 7.2 months. Log-Rank univariate analysis showed that the degree of adverse reactions and ECOG score were related to OS in patients with advanced esophageal squamous cell carcinoma.Cox multivariate regression analysis showed that the degree of adverse reactions and ECOG score were independent factors affecting OS in patients with advanced esophageal squamous cell carcinoma.

Conclusion: Positive expression of VEGFR-2 and NF-kB can be used as a biological reference target for targeted treatment of oral apatinib. Apatinib has a certain clinical effect in the maintenance treatment of advanced esophageal squamous cell carcinoma patients after treatment, with mild adverse reactions and high safety.

Background

Esophageal cancer is one of the most common malignant tumors of the digestive tract[1]. Surgery is still the treatment of choice for patients with esophageal cancer,but more than 40% of patients have postoperative local or regional recurrence. Postoperative local recurrence and lymph node metastasis are the main reasons for the failure of surgical treatment[2]. These patients do not have a uniform standard treatment. Radiotherapy and chemotherapy are the main treatments for advanced esophageal cancer or postoperative recurrence and metastasis[3]. For patients with advanced esophageal cancer, due to the poor effect of radiotherapy and chemotherapy, targeted therapy has become the research direction for the treatment of advanced esophageal cancer.

Compared with cytotoxic drugs,molecular targeted drugs have less side effects, convenient administration and good tolerance.In recent years,targeted therapy has attracted much attention, among which anti-angiogenic targeted drugs have become one of the research hotspots[4]. Apatinib is a small molecule tyrosine kinase inhibitor that selectively inhibits Vascular Endothelial Growth Factor Receptor 2(VEGFR-2) activity and blocks signal transduction after binding to Vascular Endothelial Growth Factor (VEGF), which inhibits endothelial cell proliferation and migration, thereby inhibiting tumor angiogenesis[5-6]. In theory, anti-angiogenic tumor treatment strategies have a broad anti-tumor spectrum, low resistance to drug resistance and easy access to target. Therefore, the research on anti-angiogenic tumor biotherapy has become a hot topic in recent ten years[7].

This study will investigate the clinical efficacy, safety, and prognostic factors of apatinib for maintenance therapy in patients with advanced esophageal squamous cell carcinoma(ESCC). To confirm that apatinib can benefit for the patients with advanced esophageal cancer in maintenance therapy after radiotherapy and chemotherapy. We hope that for patients with esophageal squamous cell carcinoma, if we can find a breakthrough to improve the prognosis by individualized treatment strategies through new effective treatment targets, even if it only improves the overall survival rate by 1%, we can save the valuable lives of many patients with esophageal cancer every year.

Methods

Patient characteristics

This study retrospectively analyzed 46 cases of advanced esophageal cancer diagnosed in our hospital from January 2017 to February 2019 by pathological histology or cytology. Chest CT、abdominal CT、bone scans and brain MR、neck lymph node color ultrasound were routinely performed before treatment.The inclusion criteria were as follows: All patients received systemic radiotherapy and chemotherapy; age20-80years; expected lifetime≥3months; Pathological tissue type: esophageal squamous cell carcinoma; Eastern Cooperative Oncology Group (ECOG) score ≤2; no serious coronary heart disease, arrhythmia, heart failure and other heart diseases; no obvious abnormal liver and kidney function. All patients signed informed consent.

Patients selected according to AJCC pathological stages: 18 cases in stage III and 28 cases in stage IV; 35 males,11 females; Median age 62(range:40-80 years); 27 patients with smoking history and 19 patients without smoking history; 32 cases with drinking history and 14 cases without drinking history; ECOG physical condition score0~1 were 36 cases and score 2 were 10 cases; 9 patients with upper esophageal neoplasms, 26 patients with middle segment and 11 patients with lower segment; 35 cases with lymph node metastasis and 11 cases without lymph node metastasis. The disease characteristics of these esophageal carcinoma patients are listed in Table 1.

Table 1
Demographics and baseline characteristics of patients

Baseline characteristics	Number of patients n (%)
Sex	
Male	35(76.09)
Female	11(23.91)
Pathological	Squamous Cell Carcinoma
Age (years)	
65	17(36.96)
≥65	29(63.04)
Drinking History	
YES	32(69.57)
NO	14(30.43)
Smoking History	
YES	27(58.70)
NO	19(41.30)
Location of primary tumor	
Upper	9(19.57)
Middle	26(56.52)
Lower	11(23.91)
ECOG performance status	
0-1	36(78.26)
2	10(21.74)
Lymph node metastasis	
Present	35(76.09)
Absent	11(23.91)
Stage	
III	18(39.13)
IV	28(60.87)

Treatment schedule

All 46 patients were treated with oral apatinib (250 mg qd po) within 2 weeks after chemoradiotherapy,and the dose was increased to 500 mg qd po after 1 week of tolerance. Continue medication until the disease progresses or intolerable toxic side effects occur. Patients measured their blood pressure once a week and reviewed electrocardiogram,blood routine,urine routine, liver and kidney function every 2 weeks. 4 weeks (28 days) is a treatment cycle, the efficacy was evaluated after 1

treatment cycle, and the evaluation is performed every 4 weeks thereafter.The clinical efficacy was evaluated according to blood routine, liver and kidney function, tumor markers, CT, skull MRI and whole body bone scan.

All selected patients' pathological specimens were fixed with 10% formalin solution,5um continuous thick sections. Adopt immunohistochemical SABC method. Main steps: paraffin specimen sections, xylene dewaxing, gradient alcohol hydration, 0.3% H2O2 blocking endogenous peroxidase, DNA coloration.VEGFR-2 plus EDTA antigen repair solution for high temperature repair. PBS was used as a negative control instead of the primary antibody. The expression of VEGFR-2 in esophageal cancer was detected by immunohistochemical SABC method and the Microvascular Density(MVD)、Micro-lymphatic Vessel Density(MLVD) were counted.

The clinical efficacy evaluation was determined according to the RECIST1.1[8] solid tumor objective curative effect evaluation standard,which was evaluated after 4 weeks of treatment and re-evaluated every 4 weeks. Effect evaluation: divided into complete response(CR, complete response), partial response(PR, partial response), stable disease(SD, stable disease)and disease progression(PD, progressive disease). Objective response rate (ORR)=complete number of cases(CR)+ partial response (PR) /total number of cases(CR+PR+SD+PD)×100%. Disease control rate(DCR)=complete number of cases(CR)+partial response(PR)+stable disease(SD)/total number of cases (CR+PR+SD+PD)×100%. Treatment-related adverse reactions were classified as 0-4 according to NCICTC4.0 version. Observe the efficacy and safety of patients.

VEGFR-2 and Nuclear Factor Kappa B(NF-kB)-positive substances are mainly localized in the cytoplasm and are brown-yellow granular.Ten visual fields were randomly selected under high magnification(x400),and the percentage of positive cells was calculated in each field. The number of positive cells in the whole section was ≥5%, which was judged as positive, and <5%was negative[9]. MVD is judged first at the low magnification (x100), to observe the highest blood vessel density in the tumor. The single endothelial cells or endothelial cell clusters stained in the tumor area as a microvessel were counted, 5-7 red blood cell sizes were counted. And then the number of microvessels in five visual fields was randomly calculated under high magnification(x200), take the average value.

Follow-up

The patients were followed up by telephone or out-patient service The deadline for follow-up is 30 January 2020. Progress-free survival refers to the period from the day the patient begins medication until the tumor progresses, the patient is lost to follow-up or dies. The overall survival time refers to the time from the day the patient started medication to the patient's missing visit or death.

Statistical analysis

SPSS 20.0 software was used for data analysis, and Log-Rank method was used for univariate analysis of factors affecting prognosis. $P<0.05$ was considered statistically significant.

Results

Efficacy

The efficacy of all 46 patients can be evaluated after the treatment. Among them, 2(4.35%) patient had attained complete response (CR) and 10(21.74%) patients had achieved partial response (PR), whereas 19(41.30%) and 15(32.61%) patients showed stable disease (SD) and progressive disease (PD), respectively. Objective response rate was 26.09%, and disease control rate was 67.39%, Data are listed in Table 2, Figure1.

Table 2
Objective response according to RECIST criteria

Type of response	Number（%）
Complete response (CR)	2(4.35)
Partial response (PR)	10(21.74)
Stable disease (SD)	19(41.30)
Progerssion disease (PD)	15(32.61)
Objective response (CR+PR)	12(26.09)
Disease control rate (CR+PR+SD)	31(67.39)

In 46 cases of esophageal squamous cell carcinoma, the expressions of VEGFR-2 and NF-kB were related to lymph node metastasis (P<0.05), but were not related to patient age, gender, smoking history, drinking history, tumor site, ECOG and stage (P>0.05). MVD of esophageal squamous cell carcinoma was related to lymph node metastasis (P<0.05), and was not related to gender, age, drinking history, smoking history, tumor location, degree of differentiation, and stage (P>0.05). The MLVD in the center of the tumor has nothing to do with gender, age, lymph node metastasis, tumor location, degree of differentiation, and stage (P>0.05), as shown in Table 3.

Table 3

The relationship between the expression of VEGFR-2、NF-kB , MVD 、MLVD and clinicopathological characteristics features

Clinicopathological features	n	VEGFR-2 +n(%)	P	NF-kB +n(%)	P	MVD x±s	P	MLVD x±s	P
Sex			0.894		0.500		0.514		0.472
Male	35	23(65.71)		15(42.86)		35.00±16.23		4.00±9.44	
Female	11	7(63.64)		6(54.55)		34.00±14.64		5.00±8.42	
Age (years)			0.567		0.804		0.496		0.647
<65	17	12(70.59)		8(47.06)		34.00±16.22		5.00±9.64	
≥65	29	18(62.07)		13(44.83)		43.65±14.98		4.00±7.86	
Drinking			0.759		0.082		0.297		0.548
YES	32	23(71.88)		14(43.75)		35.60±16.25		4.50±6.87	
NO	14	7(50.00)		7(50.00)		39.35±17.46		5.30±6.42	
Smoking			0.953		0.250		0.975		0.718
YES	27	15(55.56)		14(51.85)		31.21±4.93		5.00±9.22	
NO	19	15(78.95)		7(36.84)		30.58±4.21		4.50±8.73	
Location			0.088		0.141		0.357		0.671
Upper	9	7(77.78)		4(44.44)		31.26±4.95		5.56±6.85	
Middle	26	21(80.77)		15(57.69)		30.99±4.97		4.80±4.97	
Lower	11	2(18.18)		2(18.18)		29.28±4.06		5.56±6.85	
ECOG			0.650		0.097		0.995		0.205
0-1	36	24(66.67)		15(41.67)		30.95±4.91		5.00±8.64	
2	10	6(60.00)		6(60.00)		30.65±4.39		3.00±7.56	
Lymph node metastasis			0.014		0.020		0.042		0.120
Present	35	27(77.14)		19(54.29)		43.00±16.06		6.22±4.08	
Absent	11	3(27.27)		2(18.18)		27.50±5.22		8.17±2.12	
Stage			0.567		0.082		0.462		0.346
III	18	11(61.11)		10(55.56)		30.46±4.15		5.00±10.04	
IV	28	19(67.86)		11(39.29)		31.14±4.91		4.50±8.57	

The expression of MVD in VEGFR-2 and NF-kB positive patients was significantly higher than that in negative patients ($P<0.05$). The expression of MLVD in VEGFR-2, NF-kB positive and negative patients was not statistically significant ($P> 0.05$), as shown in Table 4.

Table 4
The Relationship between the expression of VEGFR-2 、NF-kB and MVD 、MLVD（x±s

Group	n	MVD	P	MLVD	P
VEGFR-2			P<0.05		P>0.05
+	30	35.23±6.28		5.00±8.42	
-	16	26.34±3.56		3.00±8.57	
NF-kB			P<0.05		P>0.05
+	21	25.10±1.27		4.50±8.64	
-	25	26.12±3.35		5.00±9.04	

The effective rates of VEGFR-2 and NF-kB positive patients were 30.00% (9/30) and 28.57% (6/21), which were significantly higher than the negative expression of 18.75% (3/16) and 16.00% (4 /25), the difference is statistically significant (P<0.05)

Patients had a median PFS of 3.7 months and a median OS of 7.2 months. Univariate analysis of clinical features and PFS and OS was performed in 46 patients with advanced esophageal cancer. There was no correlation between gender, drinking history, and tumor location with PFS and OS. Cox regression model analysis showed that the score of ECOG,the extent of adverse reactions after taking apatinib were independent factors affecting PFS and OS in patients, as shown in Table 5.

Table 5

Analysis for factors associated with overall survival and disease-free survival in patients with ESCC

Variable	mPFS (months)	P	Multivariate Hazard ratio(95%CI)	P	mOS (months)	P	Multivariate Hazard ratio(95%CI)	P
Sex		0.744	0.982(0.336-2.866)	0.973		0.588	0.747(0.348-1.604)	0.455
Male	3.53				7.20			
Female	3.49				7.75			
Adverse events		0.002	2.828(1.171-6.829)	0.021		0.036	2.781(1.163-6.649)	0.022
I-II	3.31				7.94			
III-IV	3.77				5.82			
Drinking		0.224	0.516(0.206-1.295)	0.159		0.291	0.651(0.296-1.434)	0.287
YES	3.10				5.82			
NO	4.13				8.50			
Smoking		0.474	1.221(0.590-.528)	0.590		0.058	1.824(0.666-4.999)	0.242
YES	4.01				8.50			
NO	4.02				5.00			
Location		0.544	1.207(0.450-3.239)	0.709		0.297	1.581(0.974-2.678)	0.063
Upper	3.53				7.21			
Middle	3.60				7.30			
Lower	3.49				6.01			
ECOG status		0.004	1.981(1.034-3.796)	0.039		0.024	1.963(1.015-3.799)	0.045
0-1	4.36				7.01			
2	3.18				7.48			

Adverse events

The main adverse events occurred during the treatment included Hematological toxicity, Gastrointestinal reactions, Hypertension, Proteinuria, Hand-foot syndrome, etc. The degree of adverse reactions is mainly grade 1-2. After symptomatic treatment, they all improved, and no treatment-related deaths occurred.The details of the adverse events by grade and incidence were showed in Table 6, Figure2.

Table 6
Common adverse events during treatment

Adverse events	No of patients (%)			
	Grade1	Grade2	Grades3	Grade4
Hematotoxicity	13(28.26)	7(15.22)	1(2.17)	0(0.00)
Gastrointestinal	5(10.87)	3(6.52)	0(0.00)	0(0.00)
Hypertension	16(34.78)	9(19.57)	2(4.35)	1(2.17)
Proteinuria	9(19.57)	5(10.87)	3(6.52)	0(0.00)
Hand-foot syndrome	8(17.39)	6(13.04)	1(2.17)	1(2.17)
Fatigue	3(6.52)	2(4.35)	0(0.00)	0(0.00)

Discussion

Esophageal cancer is a more common malignant tumor in the world. Radical resection is feasible for patients with early esophageal cancer. Because the early symptoms are not typical, most patients only come to hospital when they have symptoms. Therefor, fewer patients are diagnosed at the early stageand and feasible surgery patients are less, only about 20%. For patients with esophageal cancer who can not be surgically resected, multidisciplinary comprehensive treatment should be adopted, in which the 5-year survival rate<10% for radiotherapy and 6.4% for chemotherapy-based systemic therapy.The 5-year survival rate of esophageal cancer is low, only 10% -25%[10].

The majority of patients with esophageal squamous cell carcinoma in China are moderately sensitive to chemotherapy. First-line chemotherapy regimen for esophageal cancer is mainly based on platinum or fluorouracil combination, and its effective rate can reach 40%-60%. After the failure of first-line chemotherapy, in the choice of second-line chemotherapy regimen,you can choose a single drug, such as yew drugs and irinotecan; dual-drug combinations can also be selected, such as docetaxel combined with platinum,docetaxel combined with fluorouracil, irinotecan combined with fluorouracil; or a three-drug combination regimen[11]. However, these drugs have limited benefit in the treatment of late esophageal cancer after failure of first-line chemotherapy.

Molecular targeted therapy has the advantages of strong specificity and small side effects, and has become an effective method for the treatment of advanced esophageal cancer. The molecular basis of targeted therapy for advanced esophageal cancer mainly includes Epidermal Growth Factor Receptor(EGFR), Human Epidermalgrowth Factor Receptor-2(HER-2) and VEGF. Vascular endothelial growth factor and their receptors(VEGF/VEGFRs) are important cytokines in tumor angiogenesis, which can promote the proliferation of blood vessels as well as lymphatic endothelial cells to form new vessels and then promote the growth and metastasis of tumor cells[12]. VEGF is a signal peptide structural glycoprotein that exerts biological effects by binding the KDR/FLt domain on VEGFR outside the membrane of endothelial cells and constitutes the tumor angiogenesis pathway, forming a series of signal transduction mechanisms, inducing the formation of blood vessels and lymphatic vessels, and promoting tumor growth. VEGF are expressed in most solid human tumors, mainly located in the cytoplasm and cell membrane of tumor cells, and are more concentrated in the marginal region of the tumor than in the central region [13]. VEGFR1 mainly regulates the migration of monocytes and macrophages; VEGFR2 plays an important role in the occurrence and generation of blood vessels; VEGFR3 is mainly related to the formation of lymphatic vessels; VEGF expresses its activity by binding to VEGFR-2[14]. Studies have shown that the overexpression rate of VEGF in esophageal squamous cell carcinoma was 24% -74%.

VEGFR-2 is mainly expressed in endothelial cells, and its expression is closely related to angiogenesis and cell mitosis. VEGFR-2 overexpression can not only promote angiogenesis ,but also promote cell mitosis[15]. Therefore, VEGFR-2

expression plays a crucial role in neovascularization of tumors[16]. When VEGF specifically binds to VEGFR-2, the VEGFR-2 is activated, which in turn occurs a series of signal transduction responses that promotes tumor cell growth,proliferation and migration[17]. Apatinib is a novel oral small molecule antiangiogenic preparation that can highly selectively bind and inhibit vascular endothelial cell growth factor receptor-2. Apatinib can compete with VEGF to combine with VEGFR-2. The combination of apatinib and VEGFR-2 reduces and inhibits the combination of VEGF and VEGFR-2, thereby inhibits the autophosphorylation of VEGFR-2 and the growth of tumor cells and neovascularization [18].

NF-kB, as a multidirectional functional transcription factor, often exists as a heterodimer in many cells in the body and plays an important role in many diseases. Recently, it has been found that NF-KB is highly expressed in a variety of tumors and can induce-regulation of some anti-apoptotic genes and inhibit apoptosis. Paeeez[19] confirmed that the existence of activated NF-KB pathways in esophageal squamous cell carcinoma cell lines, and activated NF-KB plays an important role in the survival and proliferation of esophageal squamous cell carcinoma cells. The results of this study showed that NF-KB was closely related to lymph node metastasis in esophageal cancer ($P<0.05$). Moreover, the MVD of the NF-KB positive group was significantly higher than that of the negative group, but there was no statistically significant difference in intratumoral MLVD between the two groups, indicating that NF-KB is involved in the development of esophageal cancer development and plays an important role in promoting angiogenesis and lymph node metastasis, may induce the production of tumor vessels and promote tumor metastasis by regulating VEGF and IL-8 expression related to angiogenesis. Immunohistochemistry and immunoblotting methods found that chromosome region maintenance 1(CRMl) is highly expressed in esophageal squamous cell carcinoma. CRMl gene silencing can cause apoptosis of squamous cell carcinoma.NF-KB is affected by CRMl genes during the development, invasion and metastasis of esophageal squamous cell carcinoma. The results of our experiment showed that the positive effective rate of NF-KB esophageal cancer was significantly higher than that of negative expression, suggesting that NF-KB could be a potential molecular target for the evaluation of the efficacy of apatinib targeted therapy.Existing studies have suggested that some drugs can exert effects by interfering with NF-KB,inhibit the development of malignant tumors and can be used in the treatment of esophageal cancer[20]. Studies have found that for patients with advanced gastric cancer and adenocarcinoma of the esophagogastric junction with higher VEGFR-2 positive expression, oral apatinib can significantly prolong PFS and OS in patients. The results of this study found that VEGFR-2 positive expression in esophageal cancer benefited significantly, and the expression rate of VEGFR-2 in esophageal cancer with lymph node metastasis was significantly higher than that in patients without lymph node metastasis. The MVD of VEGFR-2 positive group was also significantly higher than that of negative group.However,in esophageal cancer VEGFR-2 positive and negative expression tissues,there was no significant difference in the MLVD count of the tumor center region, indicating that VEGFR-2 may promote lymph node metastasis by inducing lymphatic formation in the peripheral region rather than in the central region, and the specific mechanism needs to be further studied.

The main adverse reactions of apatinib in the treatment of malignant tumors include hypertension, proteinuria, hand and foot skin reaction and so on. The results of our study showed that the main adverse reactions were hypertension(60.87%); hand and foot syndrome(34.77%); proteinuria (36.96%). The degree of adverse reactions was mainly grade 1-2, and all patients could tolerate. Because the adverse reactions of apatinib drugs were dose-restrictive, all were relieved after active symptomatic treatment, and there did not appear serious adverse event.In the phase II/III clinical study of apatinib, it was found that the incidence of hypertension was 36.32%, the incidence of proteinuria was 44.36%, and the incidence of hand and foot skin reaction was 27.35%[21]. Most patients have mild to moderate blood pressure elevation, which can be better controlled after taking antihypertensive drugs. Some patients with proteinuria usually present around 3 weeks after taking apatinib and are reversible, and usually does not require special treatment. The occurrence of hand and foot skin reaction is generally occur 2-3 weeks after taking apatinib,and symptomatic supportive treatment is available[22].

To date, apatinib has been studied in phase I/II/III trials and has shown positive results in a variety of tumors, such as gastric cancer, breast cancer, lung cancer, and esophageal cancer. Phase II clinical studies of these tumors suggest that

apatinib can significantly prolong PFS in patients, and patients' ORR and DCR also increase to varying degrees[23-24], suggest that the application of apatinib in patients with multiple advanced malignancies who failed after standard regimen treatment can still achieve better results[25-26]. In 2017, a study reported the efficacy of apatinib in advanced esophageal squamous cell carcinoma. Among the 62 patients given 500mg/days, 15 patients had PR and 31 patients achieved SD, the disease control rate was 74.2%. The median of PFS and OS was 3.8 and 7.0 months,respectively. Compared with second-line chemotherapy,apatinib is more effective in advanced esophageal squamous cell carcinoma[27]. The results of a phase II study at the 14th esophageal cancer conference showed that patients with metastatic esophageal squamous cell carcinoma after failure of first-line or multi-line chemotherapy, the objective remission rate and disease control rate after apatinib were 12% and 60%, respectively. The progression-free survival period and the overall survival period reached 3.2 and 5.3 months, respectively, consistent with the results of many previous studies. Another study showed that apatinib was safe and feasible for advanced esophageal squamous cell carcinoma with better survival benefit and lighter toxic response than traditional second-line chemotherapy, and was considered to be suitable for second-line or subsequent treatment of esophageal squamous cell carcinoma[28]. In this experiment, the patient's partial response rate was 26.09%, the disease control rate was 67.39%, the median progression-free survival was 3.7 months and the median overall survival was 7.2 months. Univariate and multivariate analysis showed that the prognosis of patients was related to the degree of adverse reactions and ECOG scores after taking apatinib, and the results were consistent with other research reports,suggesting that apatinib is important for the maintenance treatment of advanced esophageal squamous cell carcinoma after radiotherapy and chemotherapy.

Conclusion

These results confirmed that a survival benefit was found in patients received maintained treatment of apatinib. However, the sample size of this study is small and there are still some limitations.In short, apatinib still has a certain clinical effect in the maintenance treatment of patients with advanced esophageal cancer,with mild adverse reactions, high safety, and more patient tolerance. The degree of adverse reactions and ECOG scores after taking apatinib were related to the patient's OS, which could prompt the patient's prognosis. Moreover, the positive expression of VEGFR-2 and NF-kB can be used as biological reference targets for oral apatinib targeted therapy. Therefore, apatinib is worthy of popularization and application in the maintenance treatment of patients with advanced esophageal squamous cell carcinoma.

Abbreviations

ESCC

Esophageal Squamous Cell Carcinoma.

MVD

Microvascular Density

MLVD

Micro-lymphatic Vessel Density

VEGF

Vascular Endothelial Growth Factor

VEGFR-2

Vascular Endothelial Growth Factor Receptor 2

NF-kB

Nuclear Factor Kappa B

CR

Complete Response

PR

Partial Response

SD

Stable Disease

PD

Progressive Disease

OS

Overall Survival

PFS

Progression-Free Survival

ORR

Objective Response Rate

DCR

Disease Control Rate

ECOG

Eastern Cooperative Oncology Group

EGFR

Epidermal Growth Factor Receptor

HER-2

Human Epidermalgrowth Factor Receptor-2

CRMI

Chromosome Region Maintenance 1

Declarations

Ethics approval and consent to participate

This article was approved by Ethics Committee of Harbin Medical University Cancer Hospital and was carried out in accordance with the World Medical Association Helsinki Declaration.

Consent to participate

Written informed consent was obtained from all participants and the study was conducted according to the bylaws of the institution. We abide by all ethical considerations and keep the patients' personal information confidential.

Consent for publication

Not applicable

Availability of data and material

All data and materials are fully available without restriction.

Competing interests

Author Guohui Liu declares that she has no conflict of interest. Author Chunbo Wang declares that he has no conflict of interest. Author Mingyan E declares that she has no conflict of interest.

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Authors' contributions

GH L participated in drafted and finalized the manuscript.

CB W **acquisition, analysis, and interpretation of data for the work**.

MY E responsible for the guidance and proofreading of the paper

All authors have contributed significantly, and that all authors read and approved the final manuscript.

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Figures

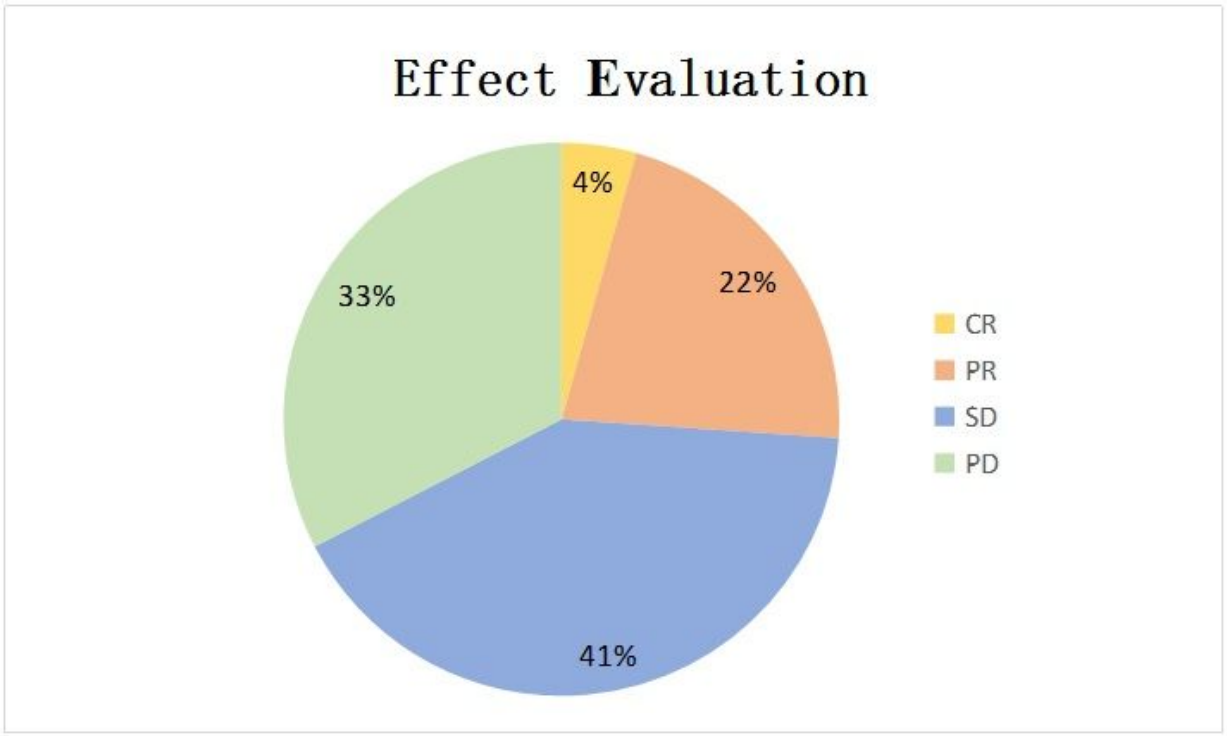
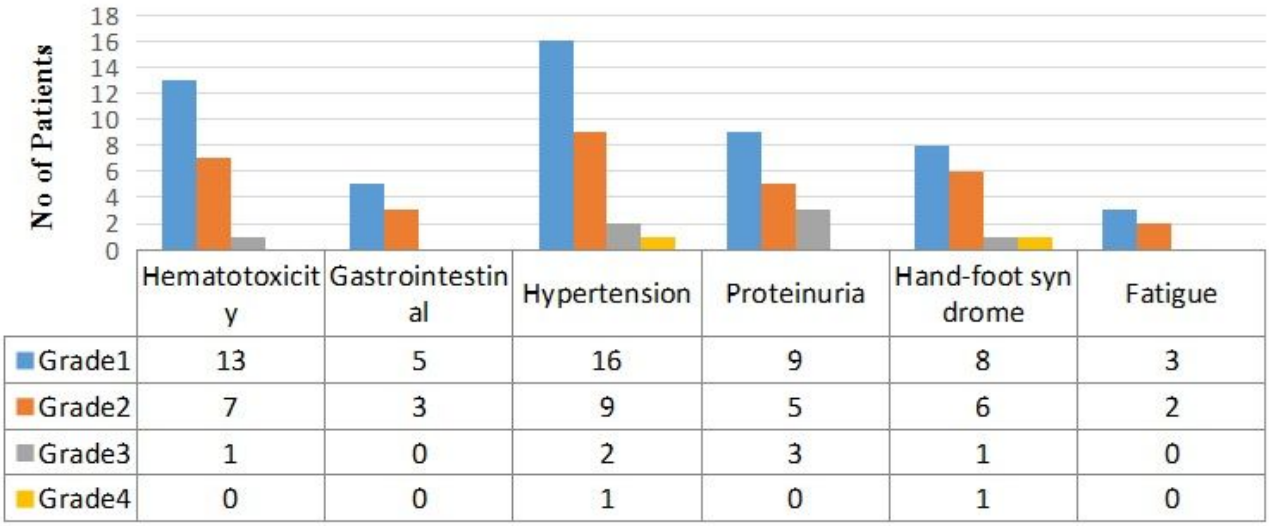


Figure 1

Evaluation of the efficacy of patients after apatinib treatment



	Hematotoxicity	Gastrointestinal	Hypertension	Proteinuria	Hand-foot syndrome	Fatigue
Grade1	13	5	16	9	8	3
Grade2	7	3	9	5	6	2
Grade3	1	0	2	3	1	0
Grade4	0	0	1	0	1	0

Figure 2

Adverse reactions during apatinib treatment