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Endostar, an Antiangiogenesis Inhibitor, Combined With Chemoradiotherapy for Locally Advanced Cervical Cancer

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This phase II randomized clinical trial aimed to assess the efficacy and toxicity of Endostar, an antiangiogenesis inhibitor, combined with concurrent chemoradiotherapy (CCRT) for locally advanced cervical cancer (LACC). Patients with LACC were randomly assigned to either CCRT plus Endostar (CCRT+E arm) or CCRT alone (CCRT arm). All patients received pelvic intensity-modulated radiation therapy (IMRT) and brachytherapy. Weekly cisplatin was administered concurrently with IMRT. Patients in the CCRT+E arm also received concurrent Endostar every 3 weeks for two cycles. The primary endpoint was progression-free survival (PFS) and acute toxicities. The exploratory endpoint was the impact of vascular endothelial growth factor receptor-2 (VEGFR2) expression on long-term survival. A total of 116 patients were enrolled. Patients in the CCRT+E arm and in the CCRT arm had similar acute and late toxicity profile. The 1- and 2-year PFS were 91.4% versus 82.1% and 80.8% versus 63.5% ($p=0.091$), respectively. The 1- and 2-year distance metastasis-free survival (DMFS) were 92.7% versus 81.1% and 86.0% versus 65.1% ($p=0.031$), respectively. Patients with positive VEGFR2 expression had significant longer PFS and overall survival (OS) compared with those with negative VEGFR2 expression. Patients in the CCRT+E arm had significantly longer PFS, OS, and DMFS than those in the CCRT arm when VEGFR2 expression was positive. In conclusion, CCRT plus Endostar significantly improved DMFS but not PFS over CCRT alone. The addition of Endostar could significantly improve survival for patients with positive VEGFR2 expression.

Key words: Cervical cancer; Antiangiogenesis; Radiation therapy; Concurrent chemotherapy; Randomized controlled trial

INTRODUCTION

Cervical cancer is one of the most common gynecologic malignances, with an estimated 520,000 new cases and 260,000 deaths worldwide per year. It is the second most commonly diagnosed cancer and third leading cause of cancer death among females in less developed countries. Early screening techniques have been widely practiced in recent years, which contribute to the decline of the incidence. However, among the young female population, there is a tendency for increased incidence¹. Approximately 70% of the patients are staged as locally advanced disease upon diagnosis. Therefore, cervical cancer remains one of the serious threats to women's health².

Radiation therapy (RT) is a paramount approach as the initial treatment option for locally advanced cervical cancer (LACC). The 5-year survival rates for stage IB2, IB3, IIB, IIIA, IIIB, IIIC1, IIIC2, and IVA were 83.3%, 76.1%, 63.9%, 40.7%, 41.4%, 60.8%, 37.5%, and 24.0%, respectively, according to a recent published study on prognostic performance of the 2018 International Federation of Gynecology and Obstetrics (FIGO) Staging System³. To further improve the treatment outcome for patients with locally advanced disease is the direction of joint efforts of physicians worldwide. Concurrent chemoradiotherapy (CCRT) achieved a significantly higher survival rate over RT alone, which is confirmed by five randomized studies that enrolled nearly 2,000 patients⁴⁻⁸. In 1999, the

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US National Cancer Institute (NCI) issued an alert that chemoradiotherapy should be considered for all patients with LACC, reassuring that CCRT is a standard treatment approach for these patients⁹.

In 1971, Judah Folkman first proposed a novel concept that tumor growth depends on the process of angiogenesis, which forms the theoretical foundation of tumor growth control¹⁰. Angiogenesis is considered to be associated with tumor growth, metastasis, recurrence, and prognosis. At present, targeting cellular signal transduction pathway involving vascular endothelial growth factor (VEGF) has been one of the main strategies to treat malignant tumors. There are at least four isoforms of VEGF (A, B, C, and D), of which VEGFA is a key angiogenic factor inducing angiogenesis. The main VEGF-associated receptors are VEGFR1, VEGFR2, and VEGFR3. Binding of VEGF to VEGFR2 is considered as the most important signal pathway in the process of tumor angiogenesis, and blocking the binding could potentially enhance the antitumor effects^{11,12}. A study using an *in vivo* nude mice model found that, compared with normal cervical tissues, tissues from cervical cancer expressed an upregulated VEGFR2 protein level, which is positively correlated with advanced stage, lymph node metastasis, and poor prognosis¹³.

In recent years, chemoradiotherapy combined with antiangiogenesis has become a hot research arena in LACC. Bevacizumab, as an anti-VEGF agent that binds to VEGF-A and prevents it from interacting with VEGFR1 and VEGFR2, has been proven to be able to shrink tumor size, delay tumor growth, and prevent metastases in cervical cancer. In August 2014, bevacizumab was approved by the US Food and Drug Administration (FDA) to be used in metastatic or recurrent cervical cancer¹⁴. Some studies also examined the combination of chemotherapy and RT. For example, in a phase II study (RTOG 0417), newly diagnosed cervical cancer staged as IB–IIIB were treated with bevacizumab plus chemoradiotherapy¹⁵. The results showed that this combination was safe and feasible. Improvements in 2-year and 3-year overall survivals were observed, compared with the results of another study—RTOG 9001—in which patients were treated with chemoradiotherapy alone (2-year overall survival: 81.3% vs. 59.8%; 3-year overall survival: 80.2% vs. 76.8%)¹⁵.

Endostar is an independently developed recombinant human endostatin in China. As an important antiangiogenesis agent, Endostar plays a critical role in the VEGF signal pathway through inhibiting the tyrosine phosphorylation of KDR/VEGFR2 and the expression of VEGFR2 induced by VEGF¹⁶. Research on mouse xenograft model for cervical cancer has found that the addition of Endostar to CCRT could dramatically decrease the tumorigenic activity of tumor cells, lower the incidence of lymph node metastases, and inhibit tumor angiogenesis¹⁷. In a randomized controlled trial, 52 patients with

LACC were randomly assigned to either CCRT arm or Endostar+CCRT arm. Patients in the Endostar+CCRT arm had significantly higher complete response rate and overall response rate than those in the CCRT arm (complete response rate: 73.1% vs. 34.6%; overall response rate: 96.2% vs. 76.9%). Besides, the 1-year overall survival rate was also significantly different, favoring the Endostar+CCRT arm¹⁸. However, in the era of precision RT represented by IMRT and 3D-CRT, the role of Endostar combined with chemoradiotherapy in LACC is largely unknown. To specifically address this issue, we designed the current study.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

In this prospective, randomized phase II study, patients with LACC were randomly assigned in a 2:1 ratio to receive CCRT plus Endostar (CCRT+E arm) or CCRT alone (CCRT arm). The inclusion criteria were as follows: Ages between 18 and 70 years old; histologically proven and newly diagnosed cervical squamous carcinoma or adenocarcinoma; stages between IB2-IVA according to the FIGO Staging System (version 2014); performance status (PS) score 0-1; measurable lesion; no distant metastases confirmed by abdominal ultrasound, chest computed tomography (CT), and bone emission computed tomography (ECT); life expectancy ≥ 6 months; signed study-specific consent form; white blood cell count $\geq 4.0 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$; normal prothrombin time; and values of liver and renal functions $\leq 1.25 \times$ upper normal limits. The exclusion criteria were as follows: distant metastases upon diagnosis; coexistence of other malignancy; prior treatment with antitumor therapies, including RT, chemotherapy, and targeted therapy; contraindication to RT or chemotherapy, including severe infection, myocardial infarct, severe arrhythmia, severe cerebrovascular disease, mental disorder, and uncontrolled diabetes; lactating women; and patients currently in other clinical trials. The trial was registered with the Chinese Clinical Trial Registry (ChiCTR2000040892).

External Beam RT

External beam RT used in the study was step-and-shoot IMRT technique. Ninety minutes before CT simulation and each subsequent treatment, patients were asked to empty their rectum and bladder, and then drink 500 ml of water and hold the urine. During the simulation, patients were required to lie down on a wide-bore CT simulator couch (Somatom Sensation Open, Siemens Medical Solutions, Erlangen, Germany) in a prone position with two arms crossed upward and holding the contralateral elbow. Tailored thoracoabdominal thermoplastic masks were designed to cover the scanning area (from upper abdomen to upper third of thigh). Radiopaque markers

were placed on the edge of the anus and vaginal orifice. Intravenous contrast-enhanced CT using a 4-mm slice from the upper border of the L1 vertebra to 2 cm below the ischial tuberosity was performed for planning. Scanning range was extended to 4 cm below the vulva if the whole length of the vagina or inguinal lymph node was involved.

Gross tumor volume (GTV) was defined as any primary disease and involved lymphadenopathy. There were three clinical target volumes (CTV1, CTV2, and CTV3). CTV1 included the GTV, uterus, and cervix. CTV2 included the parametrial and paravaginal tissues, ovaries, and vagina according to the involvement (i.e., upper half if no vagina involvement or only slight involvement; upper two thirds if upper vagina involvement; or entire vagina if more vagina involvement). CTV3 included the common iliac, internal iliac, external iliac, and presacral lymph nodes. Planning target volumes (i.e., PTV1, PTV2, and PTV3) were formed by adding 5- to 10-mm margins to CTVs in three dimensions.

The plans were designed and optimized using the Pinnacle inverse planning system. The prescribed radiation dose delivered to PTV1, PTV2, and PTV3 were 50–54 Gy, 45–48.6 Gy, and 45–48.6 Gy, respectively, in 25–27 fractions. A boost dose was added to the positive pelvic lymph node to ensure the total dose reached 60 Gy. Verification based on cone-beam computed tomography (CBCT) or electronic portal imaging device (EPID) was required before treatment. This was done prior to the first treatment and every week thereafter. If CBCT was used, consecutive verifications were performed for the first five fractions, and if the setup error was not significant, weekly verification was considered appropriate.

Intracavitary Brachytherapy

High-risk CTV (HR-CTV) was defined as any macroscopic tumor found in imaging studies and examination, and intermediate risk CTV (IR-CTV) included significant microscopic disease and initial tumor extension before external beam RT. Doses to HR-CTV and IR-CTV were assessed by D_{90} and D_{100} (minimal doses received by 90% and 100% of volumes, respectively). High-dose volume was assessed by V_{150} and V_{200} (volumes receiving 150% and 200% of prescribed doses, respectively). Doses to organs at risk (OARs) were assessed by $D_{0.1}$, $D_{1\text{ cc}}$, $D_{2\text{ cc}}$, $D_{5\text{ cc}}$, and $D_{10\text{ cc}}$ (maximal doses received by 0.1, 1, 2, 5, and 10 cc volumes, respectively). The fractionation for the high-dose rate brachytherapy was 24 Gy in four fractions.

Chemotherapy and Antiangiogenesis Therapy

Weekly cisplatin (40 mg/m²) with IV hydration and diuretics (mannitol and furosemide) was injected intravenously for 5 weeks. Antiemetic was administered prior to

the use of cisplatin. Patients in the CCRT+E arm received two planned cycles of continuous infusion by micro-pumps with Endostar at a dose of 7.5 mg/m²/day from day 1 to day 14, repeated every 3 weeks during IMRT.

Assessment of Treatment Response and Toxicity Evaluation

Treatment response after treatment was evaluated by CT/MRI images according to the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. Acute toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. They were assessed weekly during the treatment, and up to 3 months after the treatment. Late toxicities were assessed based on the Toxicity Criteria of Radiation Therapy Oncology Group (RTOG) and defined as any toxicities related to treatment occurring later than 3 months after treatment. The frequency of evaluation for survival and toxicity was every 3 months for the first 2 years after the treatment and every 6 months thereafter. The confirmation of disease recurrence was mainly based on symptoms, physical examination, and imaging studies, and pathological biopsy was performed when necessary.

Study Endpoints

The primary endpoints were progression-free survival (PFS) and acute toxicities. The secondary endpoints were overall survival (OS), distant metastasis-free survival (DMFS), and locoregional recurrence-free survival (LRRFS). The exploratory endpoint was the impact of VEGFR2 expression on long-term survival. OS was calculated from the date of randomization to the date of death or the last follow-up visit. PFS, DMFS, and LRRFS were calculated from the date of randomization to the date of disease progression, distant metastasis, and local/regional recurrence, respectively.

Assessment of VEGFR2 Expression by Immunohistochemistry

VEGFR2 expression was examined by using paraffin-embedded tissue sample with a 5- μ m section obtained from biopsy. The immunohistochemistry slides were independently examined by two senior pathologists. If there were discrepancies between the two independent pathologists, discussions among senior pathologists in the Pathology Department will be held to make a final decision on VEGFR2 expression. Assessment criteria were as follows: According to the number of positive cells, $\leq 10\%$ positive cells were regarded as grade 0, 10% to 50% grade 1, 51% to 79% grade 2, and $\geq 80\%$ grade 3. According to staining intensity, colorless was regarded as grade 0, pale or whitish yellow (weakly positive) as grade 1, yellow (positive) as grade 2, and brown (strongly positive) as grade 3. Staining index counts were calculated according

to the following formula: Staining index = grade according to the percentage of positive cells × grade according to staining intensity. A staining index of ≥ 3 was regarded as positive¹⁵.

Sample Size Calculation

For LACC patients treated with CCRT, the 2-year PFS is about 70%, according to the RTOG 0417 and 9001 clinical studies. In the present study, sample size calculation was performed assuming a projected 2-year PFS of 90% for patients assigned to the CCRT+E arm and 70% for those assigned to the CCRT arm. With a two-sided type I error of 0.05 and a power of 80%, a randomization ratio of 2:1 between the experimental and control arms, 3 years of accrual, 1 year of follow-up, and with a 10% dropout rate taken into account, the intended number of randomly assigned patients were 74 for the CCRT+E arm and 36 for the CCRT arm.

Statistical Analyses

Statistical analyses were performed using SPSS version 22 software (SPSS, Inc., Chicago, IL, USA). Survival curves were estimated using the Kaplan–Meier method, and comparisons were made using the log-rank test. A two-tailed value of $p < 0.05$ was considered statistically significant. The comparison of clinical characteristics between the two arms was based on a *t*-test for continuous variables, and Pearson's chi-square test or Fisher

exact test was used to evaluate the association between categorical variables.

RESULTS

Patient Baseline Characteristics

Between January 2017 and January 2020, a total of 143 patients were screened, 116 of whom were eligible for the study and randomized into the CCRT+E arm and the CCRT arm, with sample sizes of 78 and 38, respectively. For the intention-to-treat (ITT) population, the median age was 55 years old, ranging from 36 to 70 years old. PS score was 0 in 27 patients (23.3%) and 1 in 89 patients (76.7%). Ninety-eight patients (84.5%) had squamous cell carcinoma, and 18 (15.5%) had adenocarcinoma. One hundred and twelve patients (96.5%) were staged as IIA or above, including 14 patients (12.1%) in IIA, 66 patients (56.9%) in IIB, 16 patients (13.8%) in IIIA, 14 patients (12.1%) in IIIB, and 2 patients (1.7%) in IVA. Fifty-nine patients (50.9%) had pelvic lymph node metastases, and 9 (7.8%) had para-aortic lymph node metastases. No significant differences were found in age, PS score, stage, histological type, pelvic lymph node metastasis, and para-aortic lymph node metastasis between the two arms (Table 1). Among the 116 patients, 83 (71.6%) were found to have positive VEGFR2 expression, and 33 (28.4%) had negative VEGFR2 expression.

In the CCRT+E arm, two patients left the study before the start of the treatment due to uncontrolled high blood

Table 1. Baseline Characteristics of Patients

Characteristic	All Patients (<i>N</i> = 116)	CCRT+E Group (<i>N</i> = 78)	CCRT Group (<i>N</i> = 38)	<i>p</i> Value
Age (years)				0.984
Median	55.0	55.0	55.0	
Range	36.0–70.0	36.0–70.0	40.0–70.0	
ECOG PS				0.694
0	27 (23.3%)	19 (24.3%)	8 (21.1%)	
1	89 (76.7%)	59 (75.7%)	30 (78.9%)	
FIGO stage				0.226
IB2	4 (3.4%)	2 (2.6%)	2 (5.3%)	
IIA	14 (12.1%)	10 (12.8%)	4 (10.5%)	
IIB	66 (56.9%)	46 (58.9%)	20 (52.6%)	
IIIA	16 (13.8%)	13 (16.7%)	3 (7.9%)	
IIIB	14 (12.1%)	6 (7.7%)	8 (21.1%)	
IVA	2 (1.7%)	1 (1.3%)	1 (2.6%)	
Pelvic metastasis				0.556
Yes	59 (50.9%)	38 (48.7%)	21 (55.3%)	
No	57 (49.1%)	40 (51.3%)	17 (44.7%)	
Para-aortic metastasis				0.716
Yes	9 (7.8%)	7 (9.0%)	2 (5.3%)	
No	107 (92.2%)	71 (91.0%)	36 (94.7%)	
Histological type				0.955
Squamous cell	98 (84.5%)	66 (84.6%)	32 (94.7%)	
Adenocarcinoma	18 (15.5%)	12 (15.4%)	6 (5.3%)	

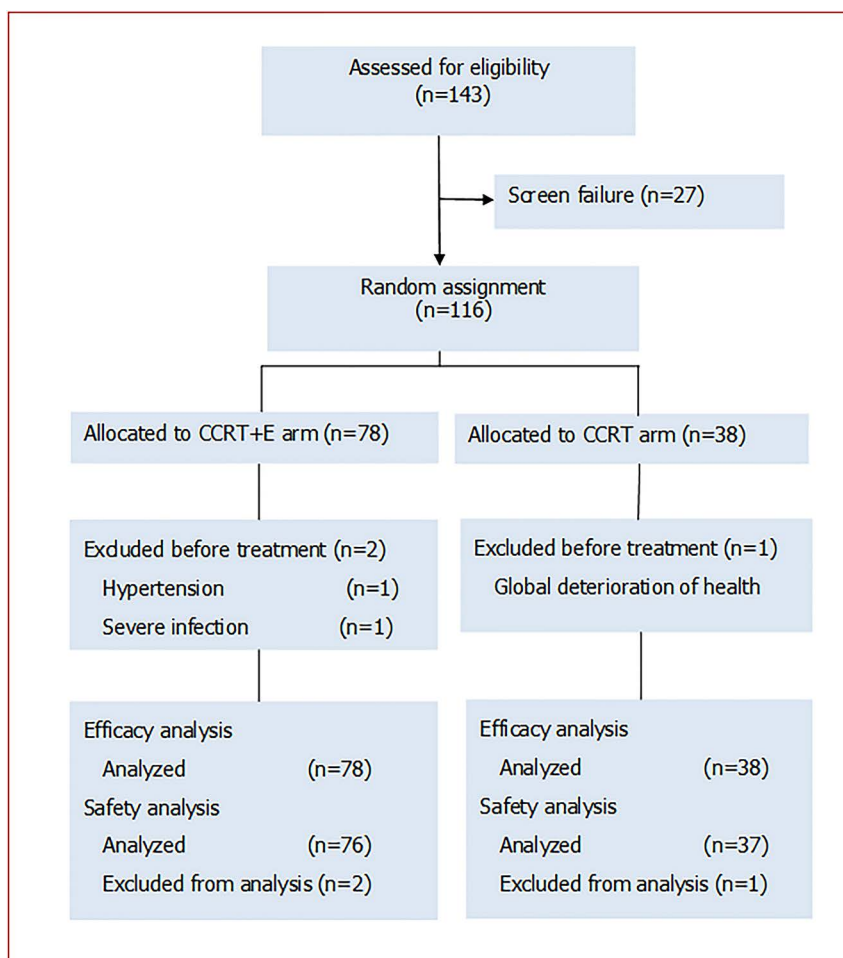


Figure 1. CONSORT flowchart.

pressure in one patient and infection in the other, whereas in the CCRT arm, one patient was withdrawn from the study before the start of the treatment due to global deterioration of health condition. The ITT population for the CCRT+E and CCRT arms were 78 and 38 patients, respectively. Efficacy evaluation was based on the ITT population (Fig. 1).

Treatment Compliance

Overall, patient compliance to the designated treatment was well maintained. All patients completed the planned external beam RT and brachytherapy. The median overall treatment time (OTT) was 53.5 days (range, 42–90 days) in the CCRT+E arm and 55 days (range, 43–73 days) in the CCRT arm. OTT did not differ significantly between the two arms ($p=0.704$). Sixty-eight patients (85.9%) in the CCRT+E arm completed ≥ 4 cycles of chemotherapy, 42 of whom (53.8%) completed 5 cycles; 31 patients (81.6%) in the CCRT arm completed ≥ 4 cycles of chemotherapy, 17 of whom (44.7%) completed 5 cycles.

Sixty-seven patients (87.2%) in the CCRT+E arm completed 2 cycles of Endostar.

Early Treatment Response

Among 113 patients eligible for evaluation, complete response (CR) and partial response (PR) were observed in 107 patients (94.8%) and 3 patients (2.6%), respectively. Three patients experienced disease progression. In the CCRT+E arm, 73 (96.0%) and 2 (2.6%) patients achieved CR and PR, respectively, and 1 patient had progressive disease, whereas in the CCRT arm, 34 (91.9%) patients and 1 (2.7%) patient achieved CR and PR, respectively, and 2 patients had progressive disease. No significant difference was found in the early treatment response between the two arms ($p=0.527$).

Follow-Up Time and Patterns of Treatment Failure

The median follow-up time for the ITT population was 22 months (IQR: 11–31 months). In the CCRT+E arm, the median follow-up time was 22 months (IQR: 11–30

months), whereas in the CCRT arm, it was 23 months (IQR: 10–32 months). For the ITT population, 21 (18.1%) patients experienced treatment failure, 3 (2.6%) of whom had locoregional failure alone, 10 (8.6%) of whom had distant metastases alone, and 8 (6.9%) of whom had both locoregional failure and distant metastases. Eighteen (15.5%) patients died, one half in each arm.

Survival Analysis

There was a trend toward an improvement in PFS in the CCRT+E arm, but it did not meet the study endpoint. The 1- and 2-year PFS in the CCRT+E arm and the CCRT arm were 91.4% versus 82.1% and 80.8% versus 63.5% (HR: 0.496; 95% CI: 0.204–1.205; $p=0.091$), respectively. Significant difference in DMFS was found between the two arms, with 1- and 2-year DMFS of 92.7% versus 81.1% and 86.0% versus 65.1% (HR: 0.378; 95% CI: 0.139–1.010; $p=0.031$), respectively. With regard to OS and LRRFS, there were no significant differences between the two arms. The 1- and 2-year OS for the two

arms were 94.1% versus 84.7% and 85.6% versus 70.0% (HR: 0.569; 95% CI: 0.220–1.471; $p=0.212$), respectively. The 1- and 2-year LRRFS for the two arms were 97.2% versus 97.0% and 90.4% versus 80.1% (HR: 0.524; 95% CI: 0.160–1.727; $p=0.256$), respectively (Fig. 2).

Univariable and Multivariable Analysis

On univariable analysis, stage, OTT, cycles of chemotherapy, pelvic lymph node metastasis, para-aortic lymph node metastasis, and expression of VEGFR2 were predictive of PFS. On multivariable analysis, however, only stage, OTT, cycles of chemotherapy, para-aortic lymph node metastasis, and expression of VEGFR2 were independent predictors for PFS. Patients who were staged as IB2–IIB, had an OTT of no more than 56 days, completed >3 cycles of chemotherapy, had no metastasis to the para-aortic lymph node, or expressed positive VEGFR2 had a significantly longer PFS (Table 2). Figure 3 shows the impact of age, PS score, stage, and histological type on PFS, and Figure 4 shows the impact of cycles of

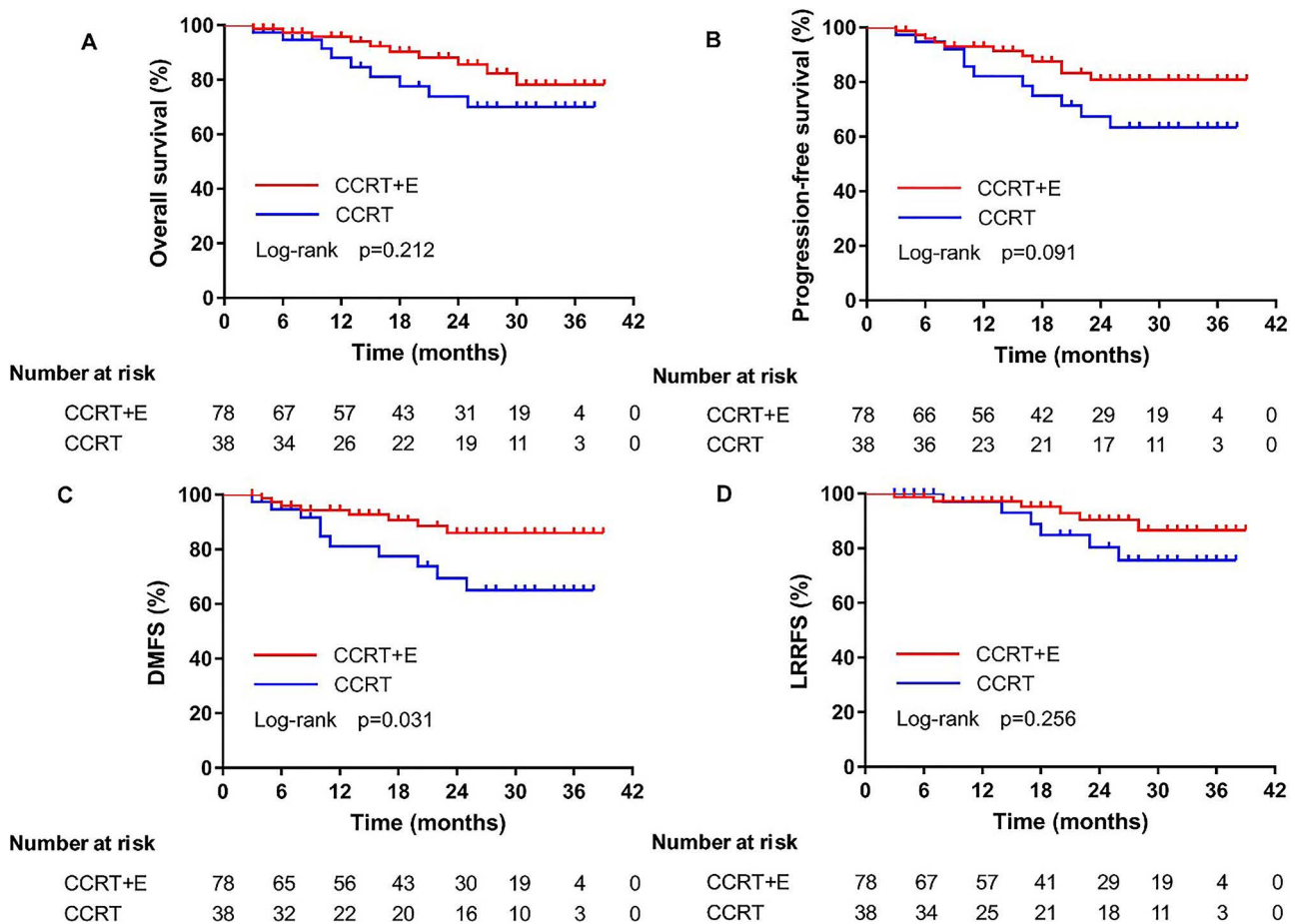


Figure 2. Comparison of long-term treatment outcomes between the concurrent chemoradiotherapy plus Endostar (CCRT+E) arm and the CCRT arm by Kaplan–Meier survival analysis: overall survival (OS) (A), progression-free survival (PFS) (B), distance metastasis-free survival (DMFS) (C), and locoregional recurrence-free survival (LRRFS) (D).

Table 2. Uni- and Multivariable Analyses for Progression-Free Survival

Subgroup	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Treatment				
CCRT	1.000		1.000	
CCRT+E	0.576 (0.249–1.335)	0.199	0.332 (0.132–1.836)	0.219
Age (years)				
<60	1.000		1.000	
≥60	1.703 (0.727–3.988)	0.220	1.646 (0.662–4.091)	0.283
ECOG PS				
0	1.000		1.000	
1	2.490 (0.735–8.430)	0.143	0.816 (0.216–3.074)	0.764
FIGO stage				
IB2–IIB	1.000		1.000	
IIIA–IVA	3.415 (1.471–7.921)	0.004	3.605 (1.174–8.003)	0.022
Histological type				
Squamous cell	1.000		1.000	
Adenocarcinoma	1.435 (0.529–3.892)	0.478	0.987 (0.311–3.131)	0.982
Overall treatment time				
≤56 days	1.000		1.000	
>56 days	3.461 (1.451–8.253)	0.005	4.197 (1.589–11.083)	0.004

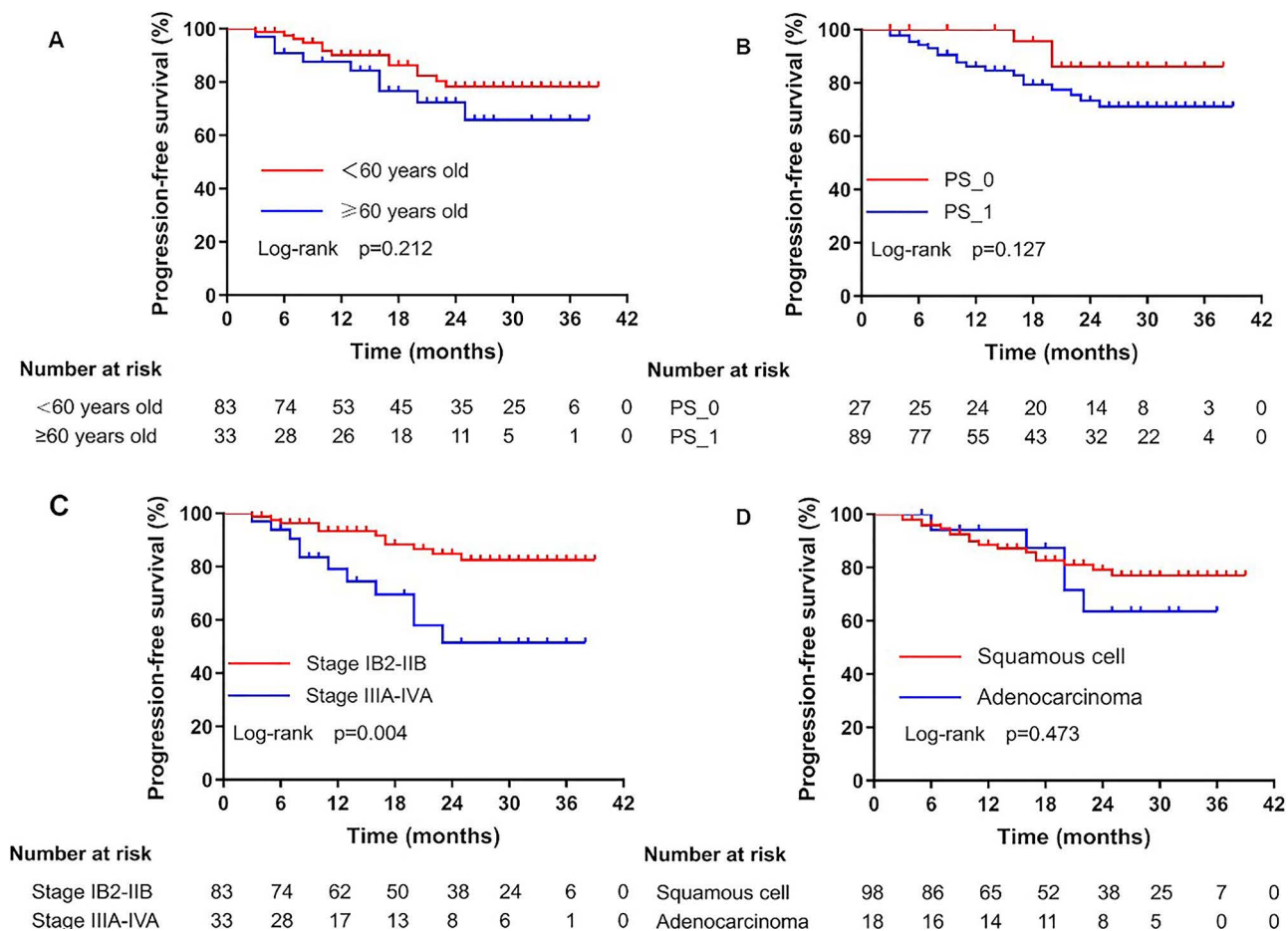


Figure 3. Progression-free survival for the intention-to-treat (ITT) population stratified by age (A), ECOG PS (B), 2014 International Federation of Gynecology and Obstetrics (FIGO) staging (C), and histological type (D).

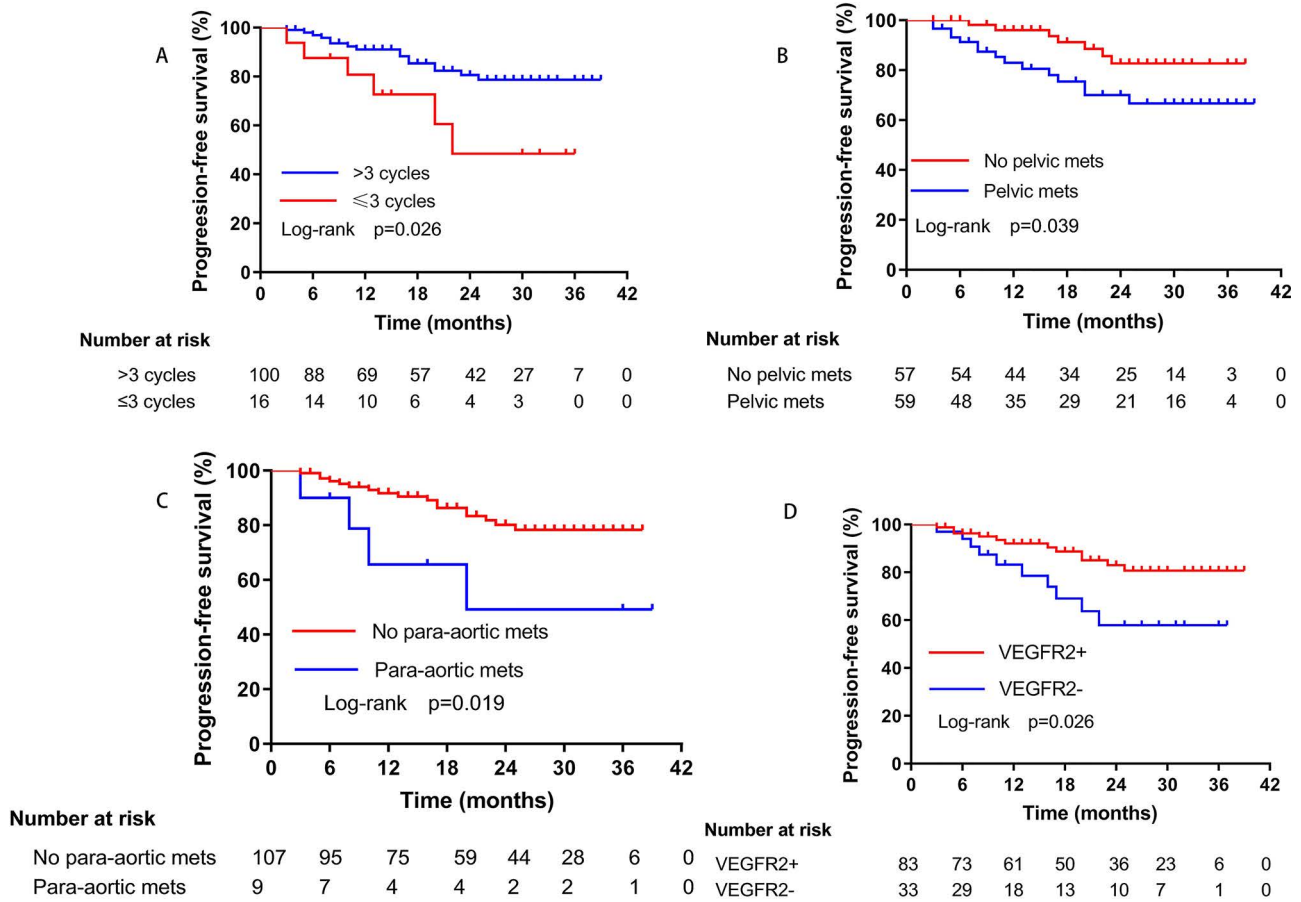


Figure 4. Progression-free survival for the ITT population stratified by cycles of chemotherapy (A), pelvic lymph node metastasis (B), para-aortic lymph node metastasis (C), and VEGFR2 expression (D).

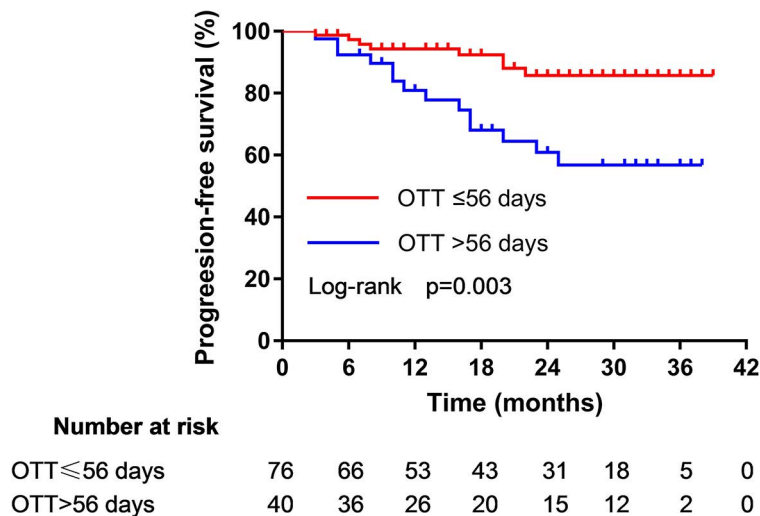


Figure 5. Progression-free survival for the ITT population stratified by overall treatment time (OTT).

chemotherapy, pelvic lymph node metastasis, para-aortic lymph node metastasis, and VEGFR2 expression on PFS. Figure 5 shows the impact of OTT on PFS.

Subgroup Analysis

On subgroup analysis, there was an improvement in PFS for patients who were ≥60 years old, had PS score 1, classified as any stage, had any histological type, had >56 days of OTT, received >3 cycles of chemotherapy, developed pelvic lymph node metastasis or para-aortic lymph node metastasis, or had positive VEGFR2 expression, favoring CCRT+E, whereas an improvement in PFS was found in patients who were <60 years old, or had negative VEGFR2 expression, favoring CCRT (Fig. 6).

Impact of VEGFR2 Expression on Long-Term Outcome

Patients with positive VEGFR2 expression had significantly longer PFS and OS, with 1- and 2-year PFS of 96.3% versus 87.3% and 83.0% versus 57.9% (HR: 0.385; 95% CI: 0.166–0.893; *p*=0.026), respectively, and with 1- and 2-year OS of 94.6% versus 89.7% and

87.2% versus 66.4% (HR: 0.365; 95% CI: 0.129–1.035; *p*=0.022), respectively, compared with those with negative VEGFR2 expression. However, the expression of VEGFR2 had no significant impact on LRRFS and DMFS (Fig. 7).

Overall, 70.5% and 73.7% of patients had positive VEGFR2 expression in the CCRT+E arm and in the CCRT arm, respectively. In the CCRT+E arm, patients with positive VEGFR2 expression had significantly longer PFS, OS, LRRFS, and DMFS, compared with those with negative VEGFR2 expression. The 1- and 2-year PFS were 98.1% versus 81.7% and 91.3% versus 56.6% (HR: 0.135; 95% CI: 0.035–0.515; *p*=0.006), respectively; the 1- and 2-year OS were 97.8% versus 81.3% and 94.0% versus 65.3% (HR: 0.160; 95% CI: 0.040–0.645; *p*=0.022), respectively; the 1- and 2-year LRRFS were 100.0% versus 90.6% and 96.8% versus 72.7% (HR: 0.161; 95% CI: 0.025–1.039; *p*=0.015), respectively; the 1- and 2-year DMFS were 89.1% versus 85.9% and 91.3% versus 73.1% (HR: 0.224; 95% CI: 0.047–1.062; *p*=0.024), respectively (Fig. 8). In the CCRT arm,

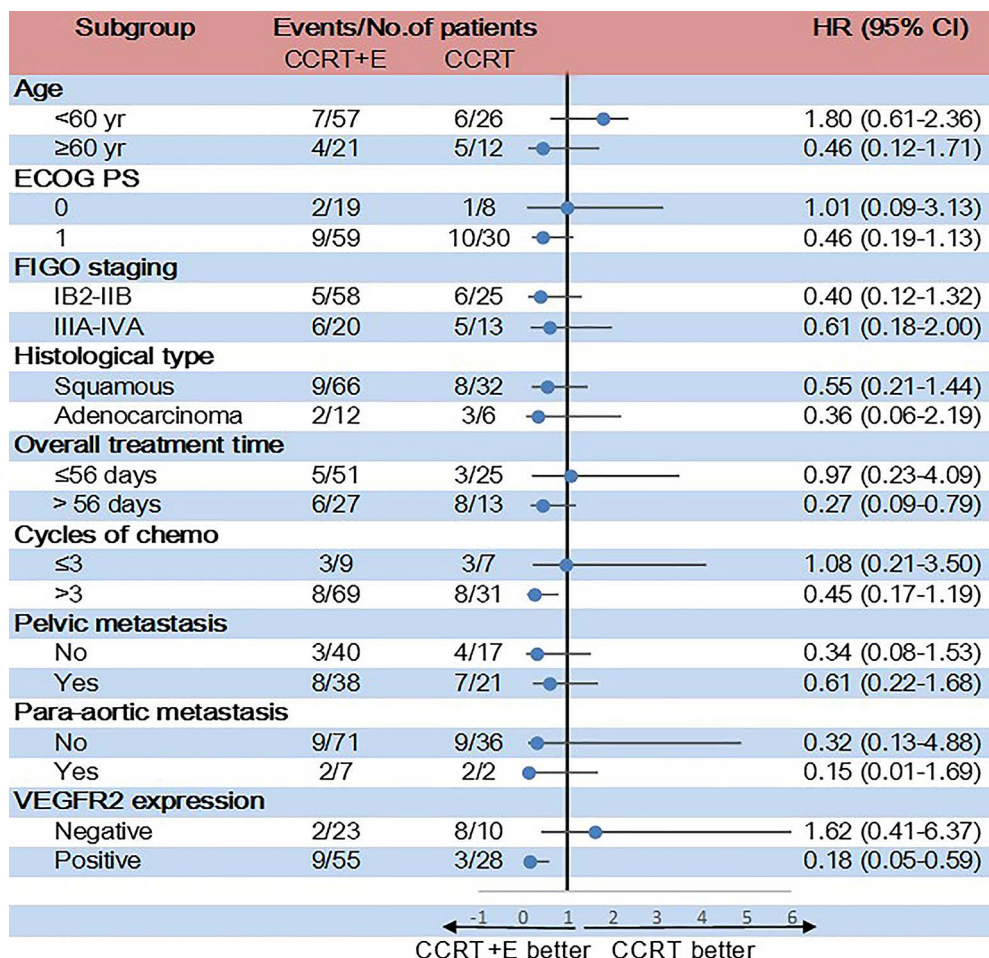


Figure 6. Subgroup analysis of progression-free survival for the ITT population.

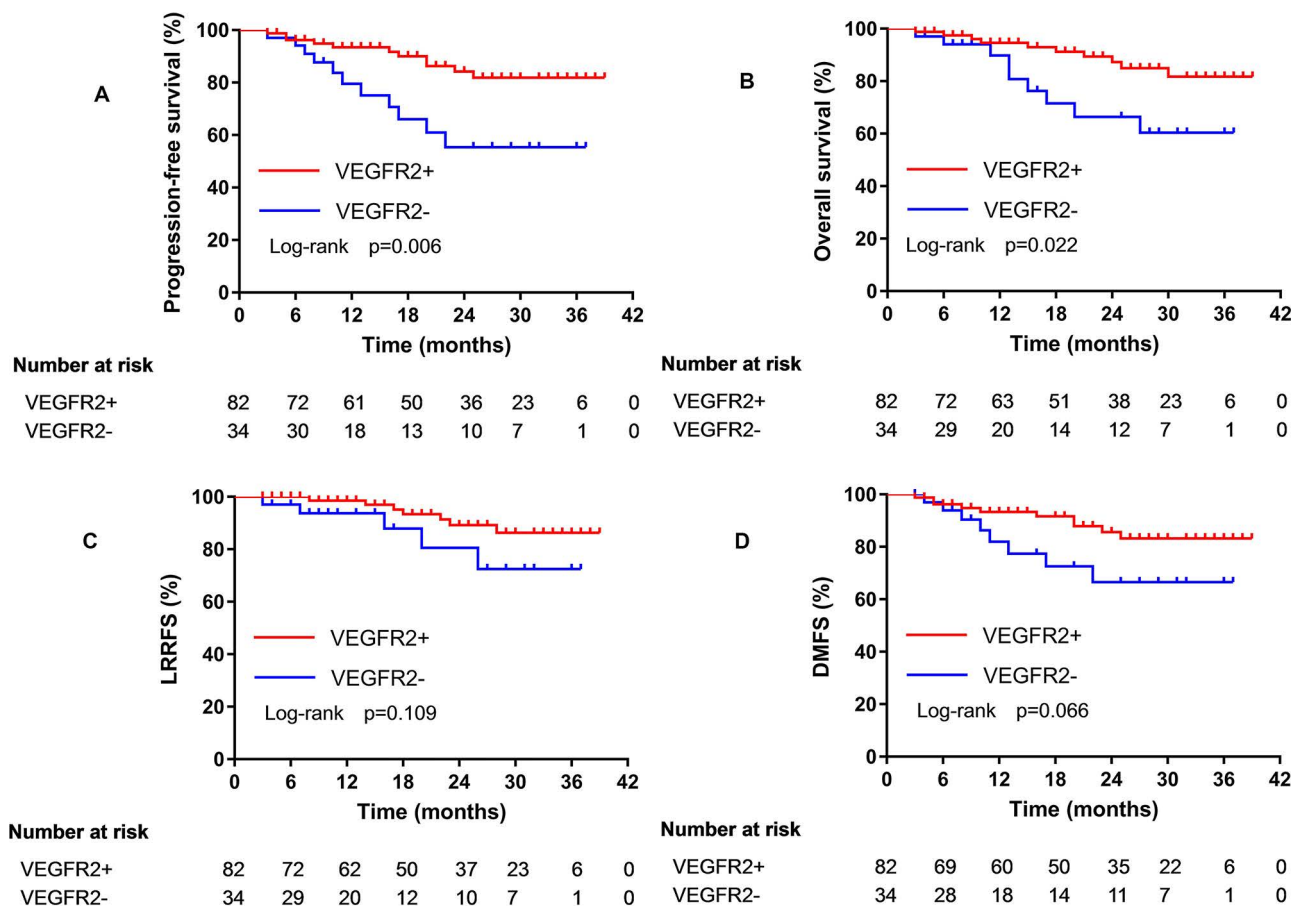


Figure 7. The impact of VEGFR2 expression on survival outcome in the ITT population: PFS (A), OS (B), LRRFS (C), and DMFS (D).

although patients with positive VEGFR2 expression had lower PFS, OS, LRRFS, and DMFS in general, compared with those with negative VEGFR2 expression, no statistical significance was found (Fig. 9).

Inter-Arm Comparison of Long-Term Outcome for Patients With Positive or Negative VEGFR2 Expression

Patients in the CCRT+E arm had significantly longer PFS, OS, and DMFS than those in the CCRT arm when VEGFR2 expression was positive. The 1- and 2-year PFS were 98.1% versus 81.1% and 91.3% versus 68.3% (HR: 0.180; 95% CI: 0.055–0.588, $p=0.004$), respectively; the 1- and 2-year OS were 97.8% versus 84.8% and 94.0% versus 72.1% (HR: 0.216; 95% CI: 0.063–0.736; $p=0.012$), respectively; the 1- and 2-year DMFS were 98.1% versus 80.1% and 91.3% versus 71.2% (HR: 0.195; 95% CI: 0.056–0.677; $p=0.007$), respectively. However, no significant difference was found in LRRFS between the two arms (Fig. 10).

No significant differences were found in PFS, OS, LRRFS, and DMFS between the CCRT+E and CCRT

arms when VEGFR2 expression was negative. The 1- and 2-year PFS were 75.8% versus 83.3% and 56.6% versus 55.5% (HR: 1.621; 95% CI: 0.413–6.368; $p=0.536$), respectively; the 1- and 2-year OS were 91.3% versus 100.0% and 65.3% versus 80.0% (HR: 2.530; 95% CI: 0.527–12.150; $p=0.364$), respectively; the 1- and 2-year LRRFS were 90.6% versus 100.0% and 72.7% versus 100.0% (HR: 1.727; 95% CI: 0.256–11.660; $p=0.620$), respectively; the 1- and 2-year DMFS were 85.8% versus 83.3% and 73.1% versus 55.5% (HR: 0.950; 95% CI: 0.181–4.990, $p=0.951$), respectively (Fig. 11).

Acute and Late Toxicities

Patients in the both arms had similar acute and late toxicity profile. The most frequently seen acute toxicities included bone marrow suppression, nausea, diarrhea, and fatigue, manifested mainly as grade I or II. The most commonly observed late toxicities were injuries to the skin and subcutaneous tissue, leg edema and pain, irradiation enteritis, irradiation cystitis, and uronephrosis. The incidences of toxicities in the CCRT+E arm and the

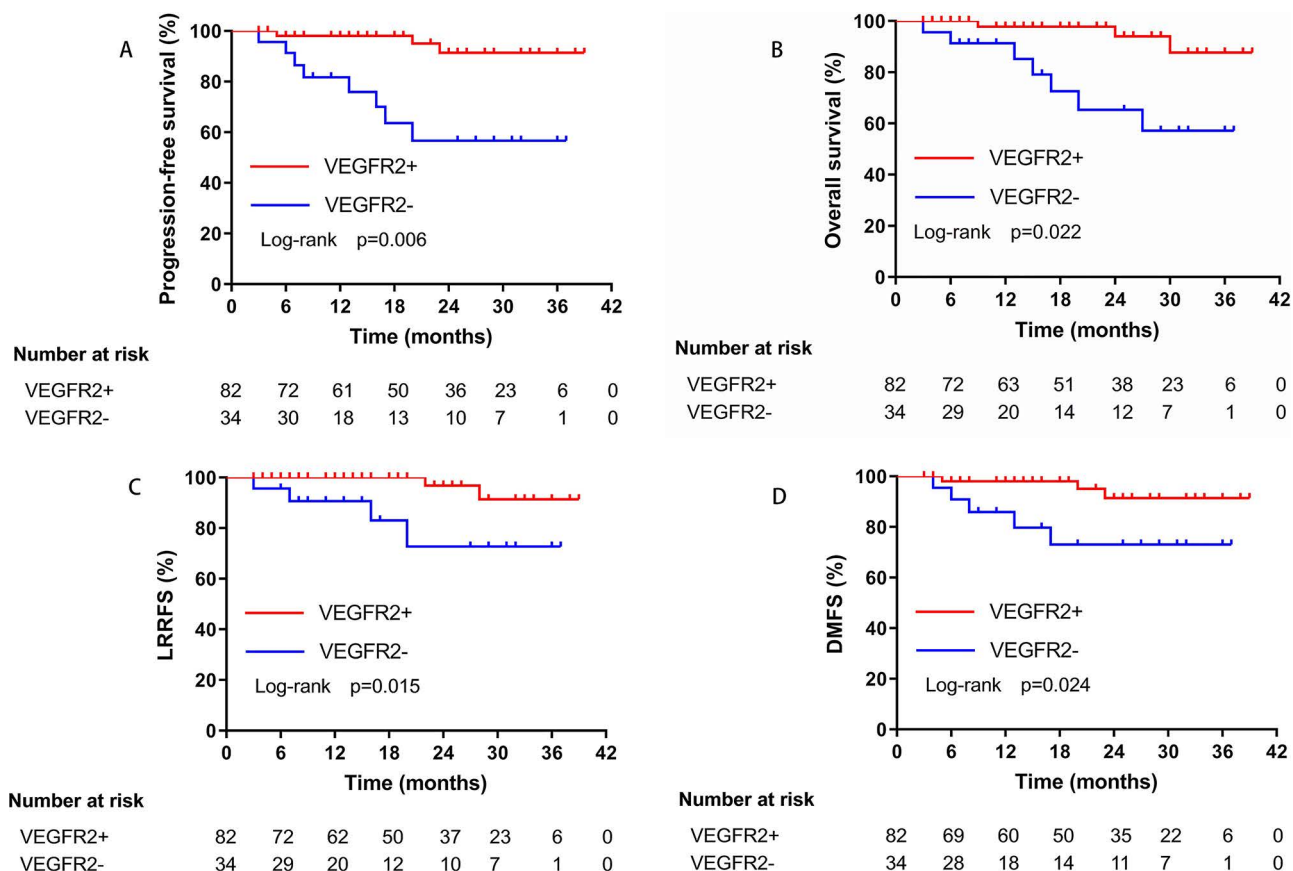


Figure 8. The impact of VEGFR2 expression on survival outcomes in the CCRT+E arm: PFS (A), OS (B), LRRFS (C), and DMFS (D).

CCRT arm ranged from 3.9% to 10.5% and from 2.7% to 13.5%, respectively (Table 3).

DISCUSSION

CCRT consisting of RT and cisplatin-based chemotherapy as a standard treatment approach for LACC (FIGO staging IB2–IVA) has been practiced for nearly 20 years, based on several randomized controlled trials and various meta-analyses. CCRT decreases the risk of death by 30–50%, and improves survival by 10–12%^{4,5,7,8}. A meta-analysis published in 2010 demonstrated that, in addition to an improvement in PFS, CCRT significantly reduced the risk of local recurrence and distant metastases.

Despite all of these efforts, approximately 30% of the patients will eventually experience treatment failure. Improving treatment outcome further by adding other cytotoxic agents to CCRT is limited. With the in-depth insight into molecular biology and molecular pathology during tumorigenesis, progression, and metastasis, the effectiveness of targeted therapy has been proven in a variety of tumor types. It improves the quality of life of patients with advanced disease, prolongs survival

with tolerable toxicities, and becomes a new treatment approach following surgery, RT, and chemotherapy.

Numerous clinical studies along with standard clinical practice have confirmed the appropriateness of an antiangiogenesis strategy for cancer treatment and the effectiveness of angiogenesis inhibitors. In recent years, the addition of angiogenesis inhibitors to chemoradiotherapy has become a new research interest in patients with LACC. Bevacizumab, as an anti-VEGF antibody, has been proven to be able to shrink the tumor size, delay tumor growth, and inhibit tumor metastasis. In a phase II clinical trial (COG-0227C), patients with refractory or recurrent cervical cancer received bevacizumab. The median PFS and OS were 3.4 months and 7.29 months, respectively¹⁹. GOG240 is a randomized phase III study on bevacizumab for cervical cancer patients in an adjuvant setting and also a 2×2 factorial design experiment. A total of 452 patients with stage IV, refractory/recurrent disease were treated with chemotherapy alone or a combination of chemotherapy and bevacizumab. Prolonged median OS and PFS were observed, favoring the combination arm (17 months vs. 13.3 months, *p*=0.0035; 8.2 months

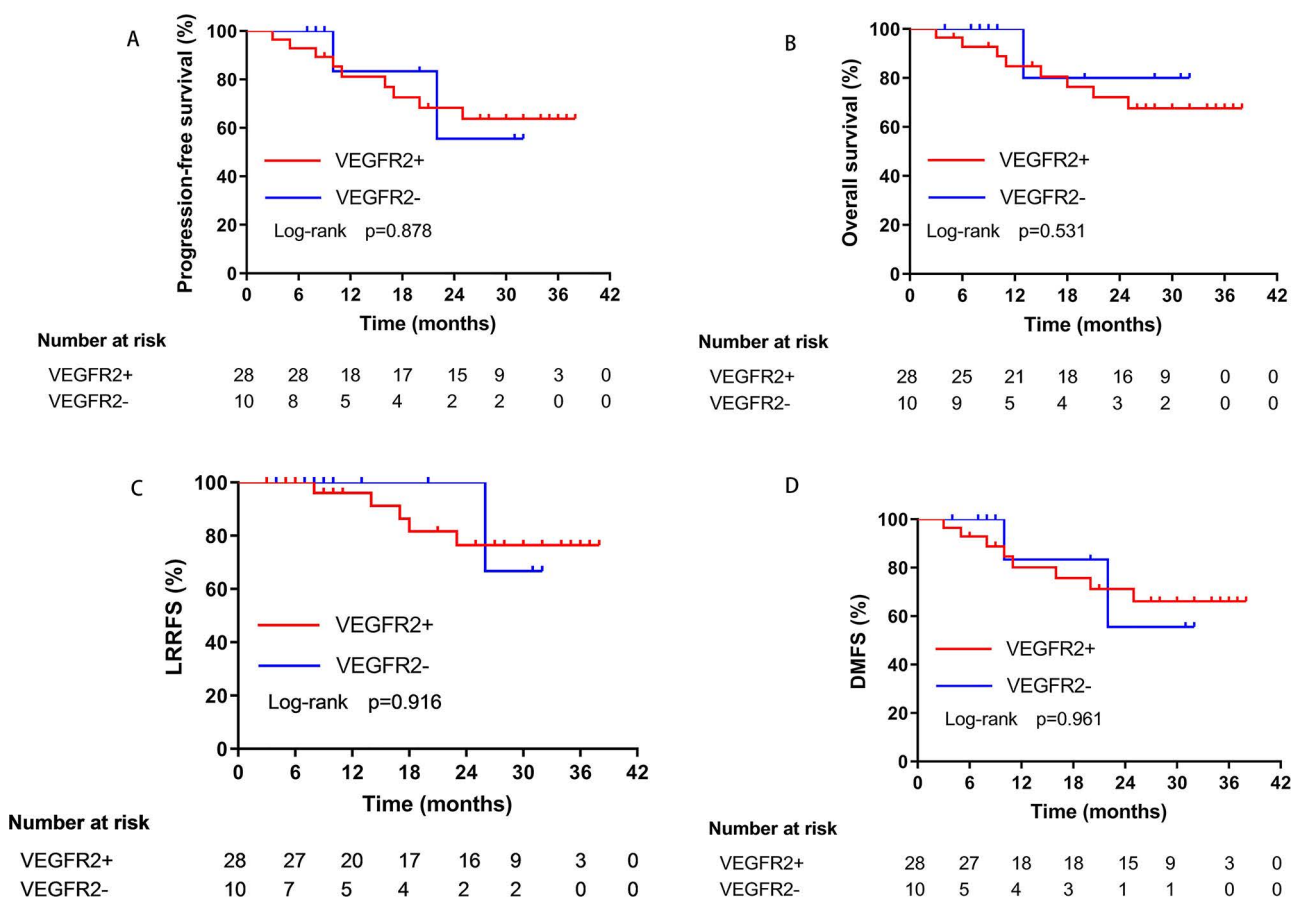


Figure 9. The impact of expression of VEGFR2 on survival outcomes in the CCRT arm: PFS (A), OS (B), LRRFS (C), and DMFS (D).

vs. 5.9 months, $p=0.0002$)²⁰. Some studies also investigated the combination of bevacizumab and chemoradiotherapy. For example, in a phase II clinical trial (RTOG 0417), newly diagnosed cervical cancer patients with stages IB–IIIB disease received bevacizumab combined with chemoradiotherapy¹⁵. This study showed that bevacizumab combined with chemoradiotherapy was safe and feasible. This regimen improved the 2- and 3-year OS, comparing with the results of RTOG 9001 (2-year OS: 59.8% vs. 81.3%; 3-year OS: 80.2% vs. 76.8%).

As an antiangiogenesis agent, Endostar is an independently developed recombinant human endostatin in China. Endostar has been shown in an in vivo mouse cervical tumor xenograft model to significantly reduce tumor growth and the risk of metastases to lymph nodes, and inhibit tumor angiogenesis when it is added to CCRT¹⁷. Ke et al. conducted a small randomized trial in which 52 LACC patients were assigned into the CCRT arm or the CCRT+Endostar arm¹⁸. Significantly higher CR and objective response (OR) rates were observed in the CCRT+Endostar arm (73.1% vs. 34.6%; 96.2% vs. 76.9%). Moreover, patients in the CCRT+Endostar arm

had a significantly higher 1-year OS (100% vs. 86.4%). However, a few aspects should be noted when one interprets the results. First, in the Ke et al. study, patients were treated with two-dimensional, four-field with box-shaped RT technique. Second, regarding brachytherapy technique, two-dimensional brachytherapy based on X-ray was used in the Ke et al. study. Finally, the commonly used dosage of cisplatin in the concurrent setting is once a week or every 3 weeks. However, weekly cisplatin administration is more convenient and less toxic. In the Ke et al. study, cisplatin was administered using a dose of 20 mg/m²/week, which results in a much lower dose-intensity level.

In an era of IMRT and three-dimensional brachytherapy, whether the addition of Endostar to the standard treatment regimen could improve treatment outcome is largely unknown. To directly address this issue, a well-designed clinical trial is required. To the best of our knowledge, however, there have been no randomized controlled trials that has been conducted, to date, except for the one presented herein. In our study, the addition of Endostar to CCRT had a trend to improve PFS, but did not meet the

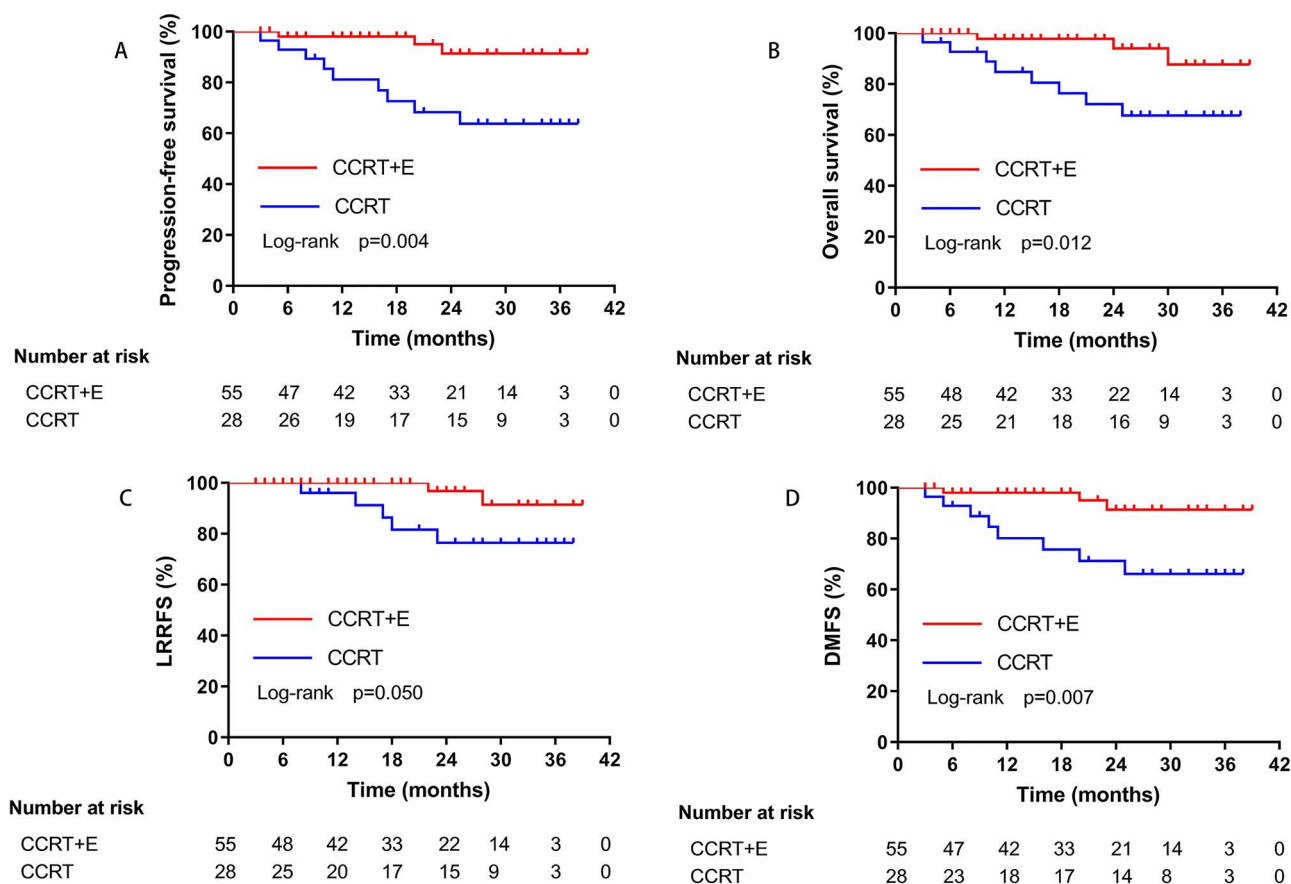


Figure 10. Comparison of survival outcomes between the CCRT+E arm and the CCRT arm when VEGFR2 is positive: PFS (A), OS (B), LRRFS (C), and DMFS (D).

confirmed PFS. The 1- and 2-year PFS in the CCRT+E arm and the CCRT arm were 91.4% versus 82.1% and 80.8% versus 63.5% (HR: 0.496; 95% CI: 0.204–1.205; $p=0.091$), respectively. However, significant differences in DMFS were found between the two arms, with 1- and 2-year DMFS of 92.7% versus 81.1% and 86.0% versus 65.1% (HR: 0.378; 95% CI: 0.139–1.010; $p=0.031$), respectively.

Regarding the impact of clinicopathological factors on PFS, there are a number of reports that assessed a variety of factors, including the status of metastases to pelvic or para-aortic lymph nodes, tumor-related neutrophil density within a tumor, stage, tumor size, concurrent chemotherapy, histological type, ratio of platelet, and lymphocyte prior to treatment, and factors associated with RT like OTT^{21–27}. In the present study, multivariable analysis revealed that FIGO stage, cycles of chemotherapy, OTT, para-aortic lymph node metastasis, and expression of VEGFR2 were independent predictors for PFS. However, treatment modalities, age, PS score, histological type, and pelvic lymph node metastasis had no significant impact on PFS.

Endostar plays a critical role in the VEGF signal pathway through inhibiting the tyrosine phosphorylation of KDR/VEGFR2 and the expression of VEGFR2 induced by VEGF¹⁶. In principle, tumors with high levels of expression of VEGF or VEGFR2 could respond well to Endostar²⁸. However, the relations between high level expression of VEGFR2 and long-term treatment outcome are ambiguous, according to the literature. Dang and colleagues²⁹ found that a high level of VEGFR2 expression was associated with a poor OS, whereas in another study, researchers found that patients with a higher-level expression of VEGFR2 had a higher response rate to the treatment³⁰. Qin et al. revealed that in cervical cancer, tumor tissues with a higher level of VEGFR2 expression had dramatically increased sensitivity to apatinib, an anti-VEGFR2 agent, and apatinib in combination with paclitaxel could strongly reduce tumor growth¹³. In the present study, positive VEGFR2 expression was observed in 70.5% and 73.7% of patients in the CCRT+E and the CCRT arms, respectively. Patients with positive VEGFR2 expression had better PFS and OS than those with negative VEGFR2 expression. For patients treated with Endostar

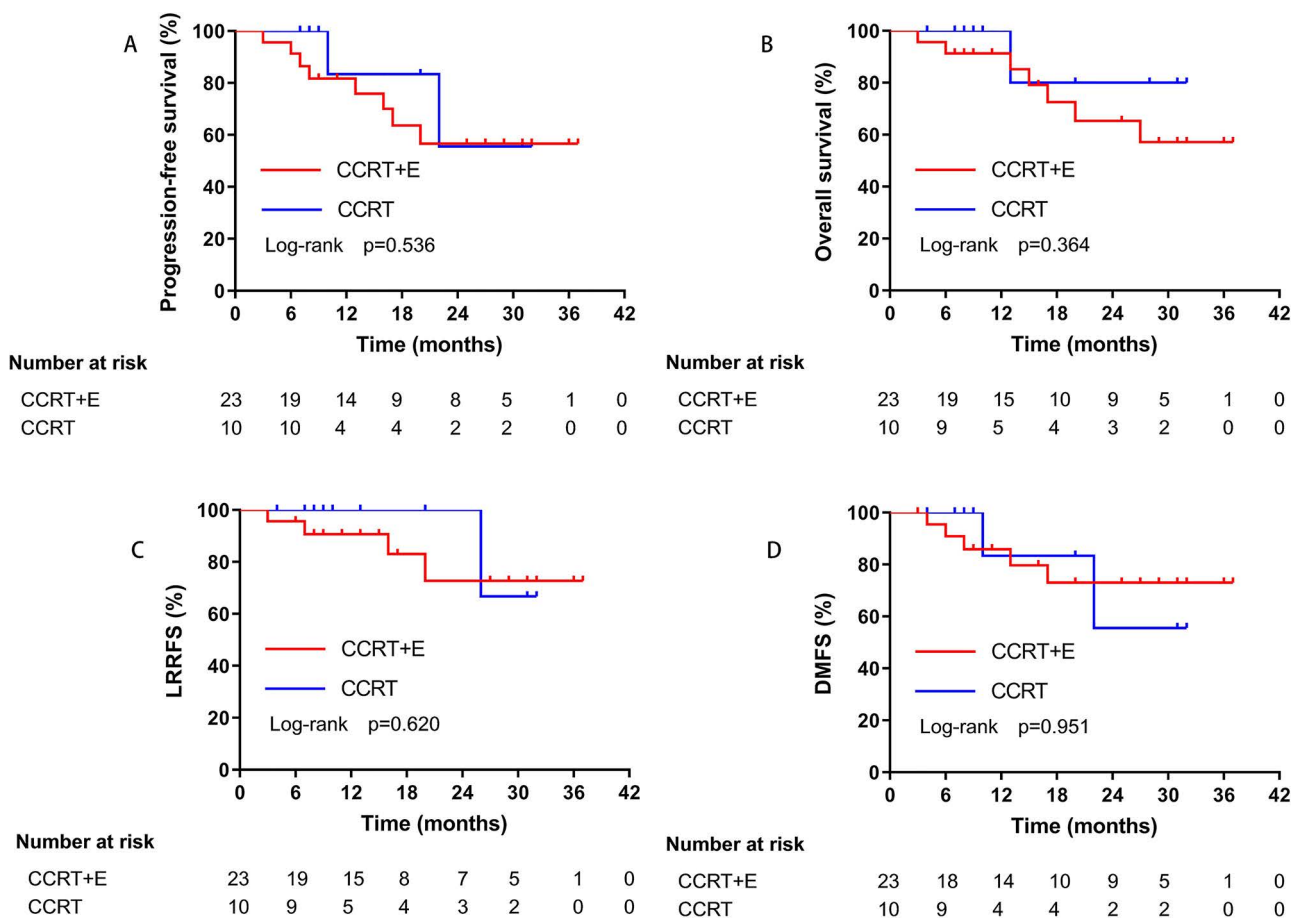


Figure 11. Comparison of survival outcomes between the CCRT+E arm and the CCRT arm when VEGFR2 is negative: PFS (A), OS (B), LRRFS (C), and DMFS (D).

and enrolled into the CCRT+E arm, improvements in PFS, OS, LRRFS, and DMFS were observed, favoring those with positive expression, whereas in the CCRT arm, although patients with positive VEGFR2 expression had worse PFS, OS, LRRFS, and DMFS than those with negative VEGFR2 expression, no statistical significances were found. For patients with positive VEGFR2 expression, the comparison of the CCRT+E arm and the CCRT arm showed that the former had significantly longer PFS, OS, LRRFS, and DMFS than the latter. However, when patients had negative VEGFR2 expression, no significant differences were found between the two arms. Results from the abovementioned studies and ours suggest that antiangiogenesis agents such as apatinib and Endostar are the key to improving the clinical outcome and stopping the malignant process for patients with a high-level expression of VEGFR2.

The role of monotherapy for cancer is often limited, and the most commonly practiced strategy to fight against cancer is the combination of various treatment modalities. When Endostar is combined with RT, the latter can cause

serious damage to the vascular endothelial cells, whereas Endostar can enhance this killing effect on the vascular endothelial cells by blocking the binding of VEGF and its receptors. The synergistic effect of RT and Endostar has been reported by a number of studies. Meng et al. conducted a study in a Lewis lung cancer mice model and found that 5 days after Endostar injection, hypoxia in tumor cells was remarkably improved, which contributed to the enhanced tumor cell killing³¹. In cervical cancer, the most recent research found that adding Endostar to neoadjuvant chemotherapy consisting of cisplatin and paclitaxel could improve the 2-year OS and PFS, compared with neoadjuvant chemotherapy alone. In addition, patients in the combination group also had a lower Ki67 and a downregulated expression of VEGFR2 gene and protein³².

Patients in both arms had similar acute and late toxicity profile. The most frequently seen acute toxicities included bone marrow suppression, nausea, diarrhea, and fatigue, manifested mainly as grades I–II. The most commonly observed late toxicities were injuries to the skin

Table 3. Acute and Late Toxicities

Toxicity	CCRT+E (n = 76)				CCRT (n = 37)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Acute toxicity								
Anemia	26 (34.2%)	15 (19.7%)	7 (9.2%)	0 (0.0%)	13 (35.1%)	5 (13.5%)	2 (5.4%)	0 (0.0%)
Thrombocytopenia	36 (47.4%)	5 (6.6%)	3 (3.9%)	0 (0.0%)	18 (48.6%)	1 (2.7%)	1 (2.7%)	0 (0.0%)
Neutropenia	11 (14.5%)	22 (28.9%)	7 (9.2%)	0 (0.0%)	4 (10.8%)	8 (21.6%)	2 (5.4%)	1 (2.7%)
Leukopenia	15 (19.7%)	45 (59.2%)	4 (5.3%)	0 (0.0%)	12 (32.4%)	14 (37.8%)	1 (2.7%)	0 (0.0%)
Vomiting	18 (23.7%)	7 (9.2%)	1 (1.3%)	0 (0.0%)	6 (16.2%)	4 (10.8%)	1 (2.7%)	0 (0.0%)
Nausea	53 (69.7%)	6 (7.0%)	1 (1.3%)	0 (0.0%)	24 (64.9%)	3 (8.1%)	0 (0.0%)	0 (0.0%)
Diarrhea	23 (30.3%)	19 (25.0%)	2 (2.6%)	0 (0.0%)	13 (35.1%)	7 (18.9%)	1 (2.7%)	0 (0.0%)
Stomatitis	3 (3.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal injury	2 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dermatitis	19 (25.0%)	5 (6.6%)	2 (2.6%)	0 (0.0%)	7 (18.9%)	1 (2.7%)	0 (0.0%)	0 (0.0%)
Allergic reaction	3 (3.9%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	2 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension	4 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatigue	39 (51.3%)	5 (6.6%)	0 (0.0%)	0 (0.0%)	20 (54.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)
Late toxicity								
Skin and subcutaneous site	8 (10.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Leg edema and pain	6 (7.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Irradiation enteritis	5 (6.6%)	2 (2.6%)	0 (0.0%)	0 (0.0%)	3 (8.1%)	2 (5.4%)	0 (0.0%)	0 (0.0%)
Irradiation cystitis	2 (2.6%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (2.7%)	1 (2.7%)	0 (0.0%)	0 (0.0%)
Uronephrosis	4 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

and subcutaneous tissue, leg edema and pain, irradiation enteritis, irradiation cystitis, and uronephrosis. The incidences in the CCRT+E arm and CCRT arm ranged from 3.9% to 10.5% and from 2.7% to 13.5%, respectively.

There are some limitations to our study. First, it was performed in a single center. In addition, the follow-up time was not sufficiently long to draw a solid conclusion. Prospective, randomized controlled, multicenter studies with large sample size is warranted to confirm the findings.

In conclusion, the preliminary results of our study suggest that the combination of CCRT plus Endostar could significantly improve DMFS but not PFS over CCRT alone. The additional Endostar could significantly improve survival for patients with positive VEGFR2 expression.

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