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Original Research Article

Applicability of perfusion-weighted imaging in evaluating the curative effect of endostar combined with neoadjuvant chemotherapy in advanced cervical cancer

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Abstract

Purpose: *To investigate the applicability of perfusion-weighted imaging (PWI) in evaluating the curative effect of endostar (EN) combined with neoadjuvant chemotherapy (NAC) in advanced cervical cancer.*
Methods: *Between January 2021 and December 2022, 85 patients from Gansu Provincial Maternity and Child-care Hospital, China with advanced cervical cancer received NAC intravenously and underwent pre and post-chemotherapy PWI. Neoadjuvant chemotherapy (NAC) consisted of paclitaxel (135 - 175 mg/m^2) and carboplatin (300 - 400 mg/m^2). The NAC regimen comprised three courses, with each course lasting three weeks. General data, gross tumor volume (GTV), maximum signal intensity loss rate (MSILR), tumor regression rate (TRR), and post-chemotherapy MSILR reduction were compared between effective and non-effective groups.*
Results: *There was a significant difference in International Federation of Gynecology and Obstetrics (FIGO) staging, pathological types and proportion of lymph node metastasis between effective and non-effective groups ($p < 0.05$). At the end of 3 cycles of chemotherapy, ORR was 72.94 %. After treatment with EN combined with NAC, GTV and MSILR in effective group were significantly lower compared to non-effective group ($p < 0.05$). After chemotherapy, the mean relative ratio (MRR) and MSILR in effective group were significantly higher compared to non-effective group ($p < 0.05$). Also, MSILR before treatment (EN combined with NAC) was positively correlated with TRR after chemotherapy in patients with advanced cervical cancer ($p < 0.05$).*
Conclusion: *Perfusion-weighted imaging effectively changes tumor volume in patients with advanced cervical cancer after treatment with EN combined with NAC, and this has high application in evaluating the drug's curative effect.*

Keywords: *Perfusion-weighted imaging, Endostar, Neoadjuvant chemotherapy, Advanced cervical cancer, Maximum signal intensity loss rate*

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INTRODUCTION

Cervical cancer is a common malignant tumor of the female reproductive system, and early symptoms in patients are often not obvious. By the time symptoms such as vaginal bleeding and bloody discharge appear, most cases are already in advanced stages, making treatment challenging and prognosis relatively poor [1].

In recent years, with advances in oncological research, neoadjuvant chemotherapy (NAC) has emerged as the preferred method for clinical treatment of advanced cervical cancer, as it effectively eliminates subclinical tumor cells, reduces metastasis, and decreases local recurrence [2,3]. Endostar (EN), through its inhibitory effect on endothelial cell proliferation and reduction of tumor neovascularization, has shown the ability to induce tumor cell apoptosis. When used in conjunction with NAC, it enhances the sensitivity of the body to chemotherapeutic drugs and improves survival rate [4].

Previous clinical evaluations of the efficacy of EN combined with NAC in solid tumor patients have largely relied on morphological changes, which have limitations due to delayed response and limited evaluation effectiveness [5]. Perfusion-weighted imaging (PWI) is a functional imaging method that provides a quantitative assessment of tissue microvascular distribution and perfusion at the molecular level. It offers advantages such as high spatial and temporal resolution and no radiation exposure. It has been widely used in the diagnosis, treatment response evaluation, and prognosis assessment of solid tumors [6,7]. The main focus of this study is to investigate the applicability of PWI in evaluating the efficacy of EN combined with NAC in the treatment of advanced cervical cancer. It aims to provide reliable imaging references for the assessment of treatment response in patients with advanced cervical cancer.

METHODS

Study subjects

A total of 85 patients with advanced cervical cancer, admitted to Gansu Provincial Maternity and Child-care Hospital, China from January 2021 to December 2022, were selected for the study. This study was approved by the Hospital's Ethics Committee (approval no. 2021GSMCLL0113) and was conducted by following the guidelines of Declaration of Helsinki [8]. All patients and their families were informed and provided consent forms to sign after accepting to participate in the study.

Inclusion criteria

Patients who met the diagnostic criteria for cervical cancer [9] confirmed by clinical-pathological examination, clinical International Federation of Gynecology and Obstetrics (FIGO) stage ranging from IB3 to IIA2, patients receiving neoadjuvant chemotherapy (NAC) with Endostar (EN), patients with an expected survival period of more than 3 months, and complete clinical data.

Exclusion criteria

Patients with concurrent hematologic disorders, recurrent cervical cancer; intolerance to NAC, contraindications to magnetic resonance imaging (MRI) examination, and concurrent malignant tumors or psychological/psychiatric disorders.

Chemotherapeutics

All patients completed NAC with EN. Endostar (EN) (Shandong Xiansheng Maidijin Biopharmaceutical Co. Ltd, National Medical Products Administration number) was administered intravenously at a dose of 15 mg once daily for three weeks as one course of treatment, with a total of three courses. The NAC regimen included paclitaxel (CPSC Cenway (Tianjin) Pharmaceutical Co. Ltd, National Medical Products Administration number H20183044) combined with carboplatin (Shanghai Acebright Pharmaceuticals Group Co. Ltd., National Medical Products Administration number H20203353. Prednisolone (20 mg) (Zhejiang Xianju Pharmaceutical Co. Ltd, National Medical Products Administration number H33021207) was orally administered 12, 3, and 1 h before paclitaxel chemotherapy, so as to enhance self-tolerance. Diphenhydramine (20 mg) (Shandong Xinhua Pharmaceutical Co. Ltd, National Medical Products Administration number H37020713) was administered by intramuscular injection 30 mins before chemotherapy to prevent allergic reactions. Paclitaxel injection (135-175 mg/m^2) was diluted in 500 mL of 5 % glucose solution and administered intravenously once daily, and carboplatin injection (300 - 400 mg/m^2) was diluted in 500 mL of 5 % glucose solution and administered intravenously once daily. Each course of treatment lasted three weeks, and a total of three courses were administered.

Evaluation of parameters/indices

Chemotherapeutic efficacy

Chemotherapeutic efficacy was classified into complete response (CR) defined as the complete disappearance of tumor lesions as confirmed by imaging examination after chemotherapy; partial response (PR) defined as a significant reduction in tumor diameter by more than 50 % compared to before chemotherapy; stable disease (SD) defined as tumor size reduction of less than 30 % after chemotherapy; and progressive disease

(PD) define as tumor size increase of 20 % or more after chemotherapy [10].

The overall response rate (ORR) was calculated using Eq 1.

ORR = CR + PR + SD …….. (1)

Patients who had their ORR calculated were classified as responders and placed in the effective group, while those whose ORR could not be calculated were classified as non-responders (non-ORR) and placed in the non-effective group.

Perfusion-weighted imaging examination and image analysis

All the patients underwent examinations before and after chemotherapy using a magnetic resonance image (MRI) scanner (Siemens AVONTOM 1.5T MRI scanner). An 8-channel phased-array body coil was selected. Conventional axial T1-weighted imaging parameters were set as follows: Time of Repetition (TR) = 658 ms, Time of Echo (TE) = 100 ms, slice thickness = 6.0 mm, field of view = 300 mm × 300 mm. Parameters for sagittal T2-weighted imaging were set as follows: TR = 3000 ms, TE = 104 ms, slice thickness = 3.0 mm, field of view = 260 mm × 260 mm. Parameters for high-resolution axial T2-weighted imaging were set as follows: TR = 4000 ms, TE = 100 ms, slice thickness = 3 mm, field of view = 200 mm × 180 mm, matrix = 320 × 320. Patients were positioned in a supine position, and a dose of 0.2 mL/kg of gadolinium-based contrast agent was injected intravenously at a rate of 2.5 mL/s, followed by a flush with 15 mL of normal saline.

Image processing software was used to process acquired images. Tumor volume was manually determined on the largest cross-sectional area of the tumor, and a region of interest (ROI) was delineated. The ROI encompassed the entire lesion area, and projections were made in three directions (left-right, superior-inferior, anterior-posterior) within the ROI. Sum of each voxel was recorded as gross tumor volume (GTV). Maximum signal intensity loss rate (MSILR) was recorded on high-resolution T2-weighted images before and after NAC. Tumor regression rate (TRR) was calculated using Eq 2.

TRR = ((V0-V1)/V0)100 …….. (2)

Where V0 is the pre-chemotherapy volume and V1 is the post-chemotherapy volume [9].

Tumor volume and maximum signal intensity loss rate

Tumor volume (GTV) and maximum signal intensity loss rate (MSILR) before and after chemotherapy were compared between effective and non-effective groups. Tumor regression rate (TRR) and MSILR loss rate after chemotherapy were also compared between these two groups [7].

Statistical analysis

Data analysis was performed using Statistic Package for Social Science (SPSS) 22.0 statistical software (IBM, Armonk, NY, USA). Measurement data were expressed as mean ± standard deviation (SD). Differences were analyzed using t-tests. Count data were expressed as percentages (%), and differences were analyzed using chi-square tests. Pearson correlation analysis was used to examine the relationship between pre-chemotherapy MSILR and post-chemotherapy TRR in patients with advanced cervical cancer receiving EN combined with NAC. $P < 0.05$ was considered statistically significant.

RESULTS

Effect of EN combined with NAC

Effectiveness of EN combined with NAC was evaluated at the end of 3 cycles of chemotherapy. Complete response (CR) rate was 22.35 % (19/85), partial response (PR) rate was 29.41 % (25/85), stable disease (SD) rate was 21.18 % (18/85), progressive disease (PD) rate was 27.06 % (23/85), and overall response rate (ORR) was 72.94 % (62/85).

General characteristics

There were no statistically significant differences in age and body mass index (BMI) between effective and non-effective groups ($p > 0.05$). However, there were statistically significant differences in FIGO stage, histological type, and percentage of lymph node metastasis in both groups ($p < 0.05$) (Table 1).

Changes in GTV and MSILR

Before EN was combined with NAC, there was no significant difference in GTV between the effective and non-effective groups ($p > 0.05$). However, MSILR in the effective group was significantly lower compared to non-effective group ($p < 0.05$).

Table 1: Comparison of general characteristics between effective and non-effective groups (mean ± SD)

Group	Number of case	Age (years)	BMI (kg/m^2)	FIGO staging (IB_3/IIA_2)	Pathological pattern	Lymph node metastasis (Positive/negative)
Effective	62	49.12±4.28	23.27±3.36	34/28	45/17	20/42
Non-effective	23	47.65±3.90	23.02±3.15	7/16	9/14	13/10
t/χ^2		1.440	0.310	4.001	8.102	4.158
P-value		0.154	0.758	0.045	0.004	0.041

Table 2: Changes in GTV and MSILR before and after EN Combined with NAC (mean ± SD)

Group	Number of cases	GTV (cm^3)		MSILR (%)	
		Prechemotherapy	Post-chemotherapy	Prechemotherapy	Post-chemotherapy
Effective	62	35.72±4.96	2.93±0.58*	44.76±3.51	14.36±2.05*
Non-effective	23	36.04±5.11	38.74±5.36	40.90±2.87	39.67±2.42
T-value		0.262	52.309	4.716	48.122
P-value		0.794	0.000	0.000	0.000

*$P < 0.05$ vs. before chemotherapy

After EN was combined with NAC chemotherapy, both GTV and MSILR in the effective group were significantly lower compared to before treatment ($p < 0.05$). In the non-effective group, GTV was higher and MSILR was lower after chemotherapy, but the differences were not statistically significant ($p > 0.05$). The GTV and MSILR in the effective group after chemotherapy were significantly lower compared to non-effective group ($p < 0.05$) (Table 2).

Evaluation of efficacy

With the treatment progression of EN combined with NAC treatment, MRR and MSILR loss rates in the effective group gradually increased, while the changes in MRR and MSILR loss rates in the non-effective group were not significant. The MRR and MSILR loss rates in the effective group after chemotherapy were significantly higher than those in the non-effective group ($p < 0.05$) (Table 3).

Table 3: Mean relative ratio (MRR) and MSILR loss rate in patients treated with EN Combined with NAC

Group	Number of case	MRR loss rate (%)	MSILR loss rate (%)
Effective	62	53.78±11.64	25.79±8.32
Non-effective	23	-2.55±0.83	7.90±1.63
T-value		23.100	10.203
P-value		0.000	0.000

Correlation analysis between PWI parameters

Pearson correlation analysis revealed a significant positive correlation between the PWI parameters (MSILR and TRR) before and after administration of a combination of EN with NAC in patients with advanced cervical cancer (r = 0.544, $p < 0.05$) (Figure 1).

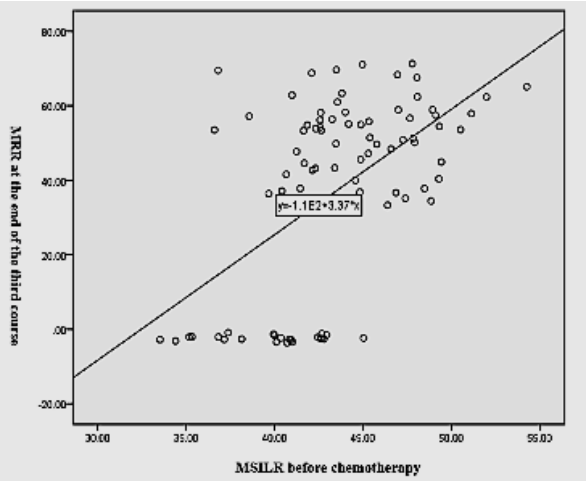

Figure 1: Correlation between MSILR and TRR before and after chemotherapy in patients with advanced cervical cancer

DISCUSSION

Advanced cervical cancer is a malignant tumor of the female reproductive system characterized by irregular vaginal bleeding, discharge, and lower abdominal pain, posing a serious threat to patients' lives and quality of life [11]. Neoadjuvant chemotherapy (NAC) has become a common approach in the clinical treatment of patients with advanced cervical cancer, as it exhibits good efficacy due to systemic cytotoxic effects of the chemotherapeutic drugs that constitute NAC with a higher reactivity and better activity when combined with anti-angiogenic targeted drugs such as Endostar [12]. Previous

clinical evaluations of treatment efficacy in cervical cancer often relied on changes in tumor morphology before and after chemotherapy, but these evaluations were susceptible to factors such as internal liquefaction necrosis of solid tumors [13]. Therefore, this study primarily investigated the applicability of perfusion-weighted imaging (PWI) in evaluating the efficacy of Endostar combined with NAC in the treatment of advanced cervical cancer.

The results of this study showed that there were no significant differences in age and BMI between effective and non-effective groups of advanced cervical cancer patients. However, significant differences were observed between the two groups in terms of FIGO stage, pathological type, and percentage of lymph node metastasis, which is consistent with a previous report [14]. This suggests that different FIGO stages, pathological types, and the presence of lymph node metastasis may be correlated with the efficacy of Endostar combined with NAC chemotherapy. In this study, the efficacy of Endostar combined with NAC was evaluated at the end of three cycles of chemotherapy. Among the 85 patients with advanced cervical cancer, the complete response (CR) rate was 22.35 %, partial response (PR) rate was 29.41 %, stable disease (SD) rate was 21.18 %, and progressive disease (PD) rate was 27.06 %. The overall response rate (ORR) was 72.94 %, indicating that Endostar combined with NAC has a definite effect on disease control in patients with advanced cervical cancer.

Among the commonly used medical imaging techniques, MRI has the highest contrast resolution for soft tissues, and PWI can monitor local tissue perfusion at the molecular and microscopic levels, providing a good evaluation of hemodynamics and functional changes in tumor lesions. It has important reference value in the assessment of NAC efficacy in malignant tumors [15,16]. Results of this study showed that there were no significant differences in gross tumor volume (GTV) between effective and non-effective groups before administration of Endostar in combination with NAC. However, the mean signal intensity ratio (MSILR) in the effective group was significantly lower compared to non-effective group. After treatment with a combination of Endostar with NAC, both GTV and MSILR in effective group were significantly lower than those before chemotherapy, while GTV and MSILR in non-effective group showed no significant differences compared to before chemotherapy. Furthermore, both GTV and MSILR in effective group after treatment with Endostar combined with NAC were significantly lower compared to those in non-effective group. A previous study indicated that MRI can assess changes in tumor lesions before and after NAC in breast cancer patients [17], which is consistent with the results of this study. This suggests that PWI effectively changes tumor lesion volume after Endostar combined with NAC in patients with advanced cervical cancer who respond well to treatment.

The results of this study showed that as the EN combined with NAC treatment progressed, loss rates of mean relative ratio (MRR) and mean signal intensity ratio (MSILR) increased gradually in the effective group. In contrast, changes in the loss rates of MRR and MSILR in non-effective group were not significant. Moreover, MRR and MSILR loss rates in the effective group after chemotherapy were significantly higher compared to those in non-effective group. This indicated that PWI can track changes in tumor lesions after Endostar combined with NAC treatment in patients with advanced cervical cancer, and MSILR and other liquid signal attenuation signals provide a better assessment of treatment efficacy at different stages. Furthermore, PWI obtains functional imaging information based on changes in signal intensity and time relationship caused by contrast agents in local tissues, allowing for effective evaluation of local tissue vitality and function. It is widely used in the differentiation of benign and malignant tumors and assessment of lesion clearance efficacy [18].

Cervical cancer lesions possess characteristics such as active tumor cell proliferation, high cell density, and small extracellular space. The cytotoxicity of Endostar combined with NAC promotes tumor cell membrane decomposition, resulting in a decrease in tumor cell density and an increase in extracellular space, which is reflected in a significant increase in MSILR [19,20]. In this study, Pearson correlation analysis was used to investigate the relationship between PWI parameters and tumor response rate (TRR) before Endostar combined with NAC was administered and after chemotherapy in the effective group. The results showed a significant positive correlation between MSILR and TRR before Endostar combined with NAC was administered and after chemotherapy, indicating that the larger the MSILR before chemotherapy, the more significant the observed tumor shrinkage, and the higher the TRR. This therefore sheds light on the applicability of MSILR as a commonly used PWI parameter in evaluating the efficacy of Endostar combined with NAC in the treatment of advanced cervical cancer.

Limitations of this study

One limitation of this study is the potential bias in results due to the small sample size. Further multi-center studies with larger sample sizes are needed to validate the findings.

CONCLUSION

Perfusion-weighted imaging (PWI) effectively changes tumor lesion volume after treatment with Endostar combined with NAC in patients with advanced cervical cancer. As related research continues in this field, PWI will provide more valuable information for diagnosing the efficacy of Endostar combined with NAC in patients with advanced cervical cancer.

DECLARATIONS

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None provided.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

Ethical Approval

This study was approved by the Ethics Committee of Gansu Provincial Maternity and Child-care Hospital, China (approval no. 2021GSMCLL0113).

Availability of Data and Materials

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

***Use of Artificial Intelligence*/Large Language Models**

None provided.

Use of Research Reporting Tools

None provided.

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