ORIGINAL RESEARCH ARTICLE

Influence of gemcitabine combined with lobaplatin interventional embolization on vaginal flora and biofilm formation in patients with advanced cervical cancer

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Abstract

This study aimed to evaluate the therapeutic effect of Gemcitabine (GEM) combined with Lobaplatin (LOB) interventional embolization in patients with locally advanced cervical cancer. Sixty patients were randomly assigned to a therapy group (30 cases) treated with GEM+LOB interventional embolization and a control group (30 cases) treated with GEM+LOB intravenous drip. The curative effect and changes in vaginal flora and biofilm formation were assessed using bioinformatics methods and ultraviolet spectrophotometry. The therapy group showed significantly better outcomes (P <0.05), with substantial changes in vaginal flora. The proportion of Gardnerella vaginalis (Gv) in the therapy group decreased from 43.51% before treatment to 13.54% after treatment, and the rate of Gv's cell membrane formation was significantly shortened. However, no significant differences were found in colony content or cell membrane formation delay between the two groups. GEM+LOB interventional embolization not only improved treatment efficacy and survival prognosis in patients with locally advanced cervical cancer but also modulated vaginal microbiota imbalance and inhibited biofilm formation of Gv. These findings provide a new theoretical basis for optimizing clinical treatment strategies for cervical cancer and exploring the relationship between cancer therapy and vaginal microecological balance. *(Afr J Reprod Health 2026; 30 [3]: 38-50).*

Keywords: Gemcitabine combined with Lobaplatin interventional embolization; advanced cervical cancer; vaginal flora: biofilm formation

Résumé

Cette étude visait à évaluer l'effet thérapeutique de la Gemcitabine (GEM) combinée à l'embolisation interventionnelle du Lobaplatin (LOB) chez des patients atteints d'un cancer du col de l'utérus localement avancé. Soixante patients ont été répartis de façon aléatoire dans un groupe thérapeutique (30 cas) traité avec GEM+LOB embolisation interventionnelle et un groupe témoin (30 cas) traité avec GEM+LOB goutte à goutte intraveineuse. L'effet curatif et les changements dans la flore vaginale et la formation de biofilm ont été évalués à l'aide de méthodes de bioinformatique et de spectrophotométrie ultraviolette. Le groupe thérapeutique a montré des résultats significativement meilleurs (P < 0,05), avec des changements substantiels de la flore vaginale. La proportion de Gardnerella vaginalis (Gv) dans le groupe de traitement a diminué, passant de 43,51% avant le traitement à 13,54% après le traitement, et le taux de formation de la membrane cellulaire de Gv a été considérablement réduit. Toutefois, aucune différence significative n'a été observée entre les deux groupes quant au contenu des colonies ou au délai de formation dela membrane cellulaire. L'embolisation interventionnelle GEM+LOB a non seulement amélioré l'efficacité du traitement et le pronostic de survie chez les patients atteints d'un cancer du col de l'utérus localement avancé, mais a également modulé le déséquilibre du microbiote vaginal et inhibé la formation de biofilm de Gv. Ces résultats fournissent une nouvelle base théorique pour optimiser les stratégies de traitement clinique du cancer du col de l'utérus et explorer la relation entre le traitement du cancer et l'équilibre microécologique vaginal.

Mots-clés: Gemcitabine combinée à l'embolisation interventionnelle Lobaplatin; Cancer du col de l'utérus avancé; Flore vaginale: formation de biofilm.*(Afr J Reprod Health 2026; 30 [3]: 38-50).*

Introduction

Cervical cancer is the second largest female malignant tumor after breast cancer. In recent years, the incidence has remained high and shows an upward trend, and the age of onset has gradually become younger [1]. At present, cervical cancer is mainly staged using the relevant indicators of the

International Federation of Obstetrics and Gynecology (FIGO) clinical staging[2].Locally advanced cervical cancer (LACC) usually refers to patients with cervical cancer at stage IB2 to IVA. Clinically, however, phases IB2 and IIA2 are generally regarded as research objects.This is because these stages represent a transition from early localized cervical cancer to widely advanced disease, characterized by high clinical incidence and ongoing controversy regarding optimal treatment strategies, making them critical targets for exploring therapeutic breakthroughs.LACC generally refers to patients with stages IB2 to IVA.

According to the FIGO clinical staging criteria for cervical cancer, the definitions and key features of each stage within this range are as follows: Stage IB2: tumor confined to the cervix with a maximum diameter ≥4 cm, without parametrial, vaginal, or distant organ involvement; Stage IIA: tumor invades the vaginal mucosa but does not involve the parametrium, further subdivided into IIA1 (tumor maximum diameter <4 cm) and IIA2 (tumor maximum diameter ≥4 cm); Stage IIB: tumor involves the parametrium but does not extend to the pelvic sidewall; Stage IIIA: tumor involves the lower third of the vagina without pelvic sidewall involvement; Stage IIIB: tumor extends to the pelvic sidewall or causes hydronephrosis/non-functioning kidney due to ureteral obstruction; Stage IVA: tumor invades adjacent organs (*e.g.*,bladder mucosa, rectal mucosa) or extends beyond the true pelvis, without evidence of distant metastasis[3]. At present, surgical techniques, radiotherapy, and chemotherapy have made progress in the treatment of cervical cancer. However, due to its large local tumor volume, difficult surgical resection, and proneness to tumor recurrence and metastasis, the 5-year survival rate of LACC is still very low, which makes the treatment of LACC an important area of cancer research[4].Since 2008, it has been identified that the primary cause of cervical cancer is high-risk human papillomavirus (HR-HPV).

Cervical cancer is recognized as an infectious disease[5]. Although the current HPV vaccine research and development is progressing well, and a variety of vaccines have been successfully marketed, it has not significantly reduced the incidence of cervical cancer. A more effective treatment method needs to be explored. There are many treatment methods for cervical cancer in China, including surgical treatment, radical radiotherapy, and preoperative adjuvant chemotherapy.Neoadjuvant chemotherapy (NACT) is chemotherapy before surgery or radical radiotherapy. The purpose is to reduce the scope of the lesion, increasing the sensitivity of radiotherapy, improving the short-term curative effect, and preventing the tumor from metastasizing to a distant place. NACT is frequently adopted in China, but there is a huge controversy in clinical research on the long-term efficacy of NACT[6]. Some scholars argue that NACT may alter the pathological characteristics of cervical cancer tissues. Following NACT, tumor cells may exhibit shrinkage, degeneration, or even necrosis. These changes can interfere with the pathological examination and analysis of subsequent surgical resection specimens, making it difficult for pathologists to accurately identify and evaluate actual high-risk factors (such as lymph node metastasis, deep stromal invasion, and lymphovascular space involvement).

Consequently, these critical high-risk factors may be obscured and remain undetected during pathological assessment. However, some scholars found that preoperative NACT didn't significantly improve the long-term prognosis of cervical cancer patients compared with direct surgery[7].

Some pointed out that compared with radiotherapy, the risk of death after NACT combined with surgery was reduced, and the 5-year survival rate was significantly improved[8]. It is known that the main drug routes of NACT include systemic intravenous chemotherapy and arterial interventional embolization chemotherapy.The efficacy difference between the two administration routes has long been a focus of clinical debate.Intravenous chemotherapy is simple to perform but requires systemic drug metabolism, resulting in lower local drug concentrations at the tumor site.

In contrast, transarterial interventional embolization delivers drugs directly to the tumor-feeding arteries, theoretically enhancing local therapeutic efficacy.Studies confirmed that the short-term effect of arterial interventional chemotherapy was better than that of intravenous chemotherapy, which can directly reduce the size of the lesion and reduce the incidence of adverse

reactions. However, whether interventional embolization chemotherapy has a long-term effect requires further research. Therefore, this work aimed to explore the long-term effect of interventional embolization.

The Gemcitabine (GEM) used in this study is a cell cycle anti-metabolic drug, a newly synthesized cytosine nucleoside derivative, and was first used to treat non-small cell lung cancer. In recent years, it has been widely used in a variety of hematological malignancies and solid tumors. When the drug enters the human body, it will form GEM diphosphate (dFdCTP) and GEM triphosphate (dFdCTP) under the activation of deoxycytidine kinase. These two metabolites will enter the cell to inhibit DNA replication, thereby playing an anti-tumor effect [9].

Lobaplatin (LOB), as the only platinum type that can be completely dissolved at a therapeutic dose, has good anti-cancer activity, which doesn't damage liver function, and has mild adverse reactions. It is a new type of anti-tumor drug for injection. In addition, it can be used in combination with a variety of chemotherapy drugs and is currently one of the commonly used drugs for interventional embolization[10]. Therefore, the efficacy of GEM combined with LOB interventional embolization in the treatment of 60 patients with LACC was evaluated. Moreover, the patient's survival rate, recurrence and metastasis rate, long-term treatment effect, and the occurrence of adverse reactions after treatment were observed and analyzed. It was hoped to explore the effectiveness and safety of GEM combined with LOB interventional embolization.

Recent studies reported that HR-HPV infection, pre-cervix lesions, and the formation of cervical cancer were closely related to the changes of vaginal flora. Among which, changes in the number of vaginal lactobacilli, *Gardnerella vaginalis* (Gv), *etc.* caused imbalance of the flora, then leading to vaginal, cervical, and even pelvic diseases. Among these, Gv plays a particularly critical role.

Not only is it a hallmark strain of vaginal microbiota imbalance, but it also secretes toxic substances that suppress local immune responses. More importantly, the biofilm formed by Gv can tightly adhere to the cervical surface, providing a sanctuary for persistent HR-HPV infection and thereby accelerating the progression of cervical cancer. Cervical cancer was considered to be related to the imbalance of vaginal flora [11]. In this work, patients with LACC were treated with GEM combined with LOB interventional embolization. The number and diversity of vaginal flora were determined before and after treatment, and the biofilm formation rate of typical strains were compared. It was hoped to explore the effect of interventional embolization on the vaginal flora of patients with cervical cancer.

Methods

Screening of study participants

All experimental procedures in this study were conducted at Xi'an Daxing Hospital. Sixty women were recruited, all of whom had been diagnosed with LACC in Xi'an Daxing hospital from October 20, 2019 to November 20, 2020. The women ranged in age from 47-74 years old, and had an average age of 60.65±8.69 years old.

A random number table method was used to enroll the patients into a therapy group (30 cases) and control group (30 cases). The specific randomization procedure was as follows: after confirming that all patients met the inclusion criteria and were free of exclusion criteria, the research team assigned a unique sequence number to each patient in the order of enrollment. Standard random number tables were then used to generate random numbers corresponding to each sequence number. Patients with odd random numbers were allocated to the therapy group , while those with even numbers were assigned to the control group.

The entire randomization process was conducted by an independent statistician not involved in patient recruitment or treatment to avoid selection bias. Patients in therapy group received GEM combined with LOB interventional embolization every day, while those in control group received GEM+LOB intravenous drip, with both treatments lasting for 3 weeks. This study was reviewed and approved by the Medical Ethics Committee of Xi'an Daxing Hospital (Approval No.: [XDH032]; Date of Approval: [September 10, 2019]). Prior to enrollment, all patients and their families were fully informed of the study's purpose, procedures, potential risks, and benefits.

Written informed consent was obtained from each patient and their family members. The study was conducted in strict accordance with the principles of the *Declaration of Helsinki*.

Inclusion criteria were as follows:

1. Cervical cancer tumor diameter not less than 4cm
2. Eastern Cooperation Oncology Group (ECOG) score not less than 2 points[12]
3. Patients without obvious abnormalities in the heart, lung, liver, kidney function, and the bone marrow, and with no other tumor complications
4. patients' condition was in line with various surgical treatment indicators, and patients' physical condition being able to withstand two courses of chemotherapy.

The exclusion criteria were as follows:

1) women who had drug contraindications to GEM, LOB, or other related therapeutic drugs; 2) those patients with severe infections, diabetes, mental disorders, cardiovascular and cerebrovascular diseases, or other system diseases at the same time; 3) patients with a history of radiotherapy and chemotherapy.

Treatment methods

Seldinger technique[13] was adopted to perform internal iliac artery puncture and intubation for patients in the treatment group. Under the guidance of angiography technology, the tumor blood vessels and uterine arteries were identified. 1250 mg/m^2 GEM and 80 mg/m^2 LOB were injected into the body at the same time, gelatin sponge was utilized for interventional embolization. The administration was given once a week for three weeks was a course of treatment. The treatment lasted for two courses,
The treatment time of control group was the same. On the first day of each course of treatment, 80 mg/m^2 of LOB and 250 mg/m^2 of GEM were injected intravenously for 30 minutes. On the first day of the second week, 250 mg/m^2 of GEM was injected intravenously for 30 minutes. All patients received targeted cervical cancer surgery after chemotherapy. The specific surgical procedure was determined based on the clinical stage after NACT and the status of residual lesions: 1) For stage IB2–IIA2 patients who achieved partial or complete response (tumor diameter reduced to <4 cm with no parametrial invasion) after chemotherapy, radical hysterectomy with pelvic lymphadenectomy was performed; 2) For stage IIB–IIIB patients with significant shrinkage of parametrial lesions after chemotherapy, modified radical hysterectomy with pelvic lymphadenectomy was performed; 3) For stage IVA patients with effective chemotherapy response and limited adjacent organ involvement (*e.g.*, superficial bladder mucosa invasion), extended radical hysterectomy was performed, combined with partial resection of affected adjacent organs and pelvic lymphadenectomy when necessary. A summary record of the review of all patients was made within two years after the operation. Moreover, it was necessary to calculate the probability of recurrence and metastasis of patients with cervical cancer, so did the average survival time.

Observed indicators included two aspects: 1.patients' one-year survival rates, two-year survival rates, and local recurrence or metastasis rate;

2. evaluation of treatment effect, which was classified into four levels as follows. i: complete remission, short diameter of pathological lymph node was less than 10mm, tumor disappeared completely, and no new lesions were generated; ii: partial remission, the product of the maximum tumor diameter and the maximum vertical diameter was reduced by more than half; iii: stable, the product of the largest tumor diameter and the largest vertical diameter was reduced by 25% to 50%; iv: progression, the product of the maximum diameter of the tumor and the maximum vertical diameter increased by more than 25%.

Collection of vaginal secretions and analysis of flora

With the patient's consent the vaginal secretions were collected. After routinely disinfecting the vaginal opening, a disposable sterile vaginal dilator was utilized to dilate the vagina. The purpose of this procedure was to fully expose the cervix and posterior vaginal fornix (rather than dilating the cervical canal), ensuring that sterile swabs can accurately collect secretions from these target sites while avoiding contamination during the sampling process. Sterile cotton swabs with secretions of the cervix and posterior fornix of the vagina were placed in a sterile test tube. After passing through

liquid nitrogen, they were transferred to a refrigerator at -80℃ for storage. The collected samples were extracted with the vaginal swab DNA extraction kit (Beijing Bioteke Biotechnology Co., Ltd.) for bacterial genome extraction, and the specific operations were carried out in accordance with the kit instructions. The extracted DNA was diluted and taken as the template for PCR amplification, and then the product was subjected to gel electrophoresis. The results were analyzed by bioinformatics. The default indices of the MiSeq remained unchanged, and original sequencing was performed. The adapter sequence and low-quality sequence were removed during preprocessing. Thereafter, analysis of the main components of the sample flora and analysis of the difference of the bacterial colony, etc. were carried out. The data analysis process was shown in Figure 1.

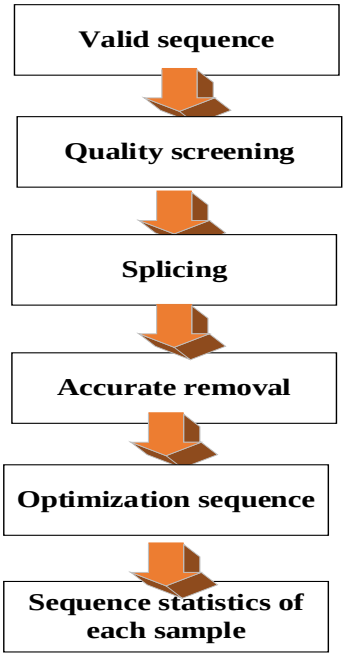


Figure 1: The flow charts of the patient's vaginal flora detection.

Statistical methods

In this study, SPSS 21.0 was employed to calculate and analyze the data. The calculated data conforming to the normal distribution was represented by the mean ± standard deviation ($\bar{x} \pm s$), and the non-conforming calculated data was represented by the percentage (%). The *t* test was adopted for two independent samples, the Mann-Whitney U test was applied to the diversity index, and α=0.05 was set as the test level. $P<0.05$ indicated that the difference was statistically considerable.

Ethical considerations

The study had been approved by the Medical Ethics Committee of the Hospital, and the patients and their families understood the research situation and signed informed consent forms, respectively.

Results

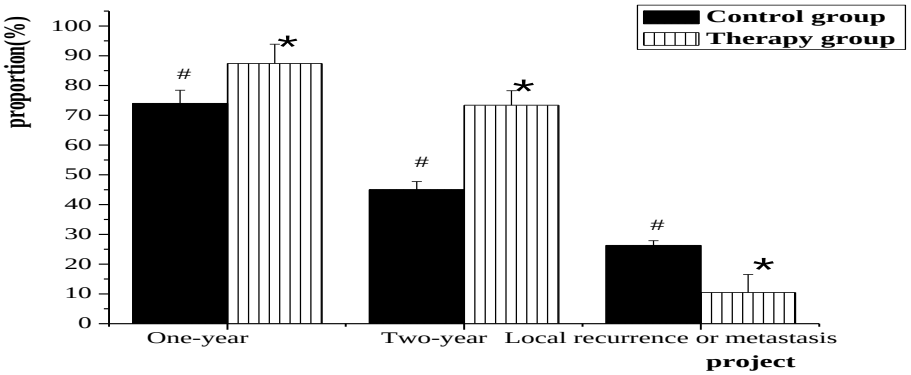
Comparison of clinical efficacy

A total of 60 patients with LACC that met the criteria were included, and the age ranged from 47 to 74 years. There were 30 cases in the therapy group, of which 19 cases were 55-69 years old, 7 cases were 70-76 years old, and 4 cases were 76-80 years old. 30 cases were in control group, of which 17 cases were 55-69 years old, 8 cases were 70-76 years old, and 5 cases were 76-80 years old.

No substantial difference was found in the general information of the two groups of patients in age and gender ($P>0.05$), indicating that the two groups of patients were comparable in sociodemographic characteristics.Comparisons of survival rate and recurrence and metastasis rate between the therapy group and control group were shown in Figure 2. The one-year survival rate and two-year survival rate of the therapy group was higher in those of control group, while the recurrence and metastasis rate of cervical cancer was significantly lower in that of the control group ($P<0.05$). The comparison between the therapy group and control groups after treatment was shown in Table 1. The treatment effect of the therapy group was generally better than that of control group, with significant differences ($P<0.05$).

Comparison of adverse reactions between the two groups of patients

Patient's adverse reactions were recorded during the treatment period and during the review and follow-up period. The main manifestations were certain gastrointestinal reactions, decreased white blood cells, decreased platelets, liver and kidney damage, neurotoxicity, *etc.* The specific conditions were shown in Table 2.



*Note: * indicated P<0.05 in contrast to control group; # indicated P<0.05 in contrast to that before treatment*.

Figure 2: Comparison of patient survival rate, recurrence, and metastasis rate.

Table 1: Comparison of curative effect between two groups of patients

Therapeutic efficacy evaluation	Control group (n=30)	Therapy group (n=30)	Statistic (χ^2)	*P*
Complete response (CR)	4 (13.33)	8 (26.67)	χ^2=4.28	0.234
Partial response (PR)	13 (43.33)	16 (53.33)	-	-
Stable disease (SD)	9 (30.00)	5 (16.67)	-	-
Progressive disease (PD)	4 (13.33)	3 (10.00)	-	-
Overall response rate (ORR = CR + PR)	17 (56.67)	24 (80.00)	χ^2=4.52	0.034

Table 2: Comparison of adverse reactions between the two groups of patients

Adverse event categories	Control group (n=30)	Therapy group (n=30)	Statistic (χ^2)	*P*
Gastrointestinal reactions (nausea, vomiting, etc.)	11 (36.67)	13 (43.33)	0.38	0.538
Leukopenia	9 (30.00)	10 (33.33)	0.09	0.764
Thrombocytopenia	6 (20.00)	8 (26.67)	0.45	0.502
Hepatic and renal impairment	3 (10.00)	4 (13.33)	0.15	0.698
Neurotoxicity (numbness, tingling, etc.)	2 (6.67)	3 (10.00)	0.22	0.639
Overall incidence of adverse events	21 (70.00)	24 (80.00)	0.98	0.322

Sequencing information of vaginal flora of two groups of patients

After DNA sequence analysis of the obtained samples, a total of 4331 sequences were obtained. After all the data were processed, *denovo* mode was adopted for cluster analysis, and then representativesequences were selected for classification in GAST mode. Alpha diversity is an indicator that describes the number and distribution of flora in a microecosystem.Usually,chao index, ace index, shannon index,and simpson index are used for analysis. Chao index and ace index reflect the abundance of the sample community, while Shannon index and simpson index reflect the overall diversity of the community. The results in Figure 3 showed that there was little difference in the abundance of vaginal flora between the two groups of patients before and after treatment, which was not statistically significant (P <0.05).

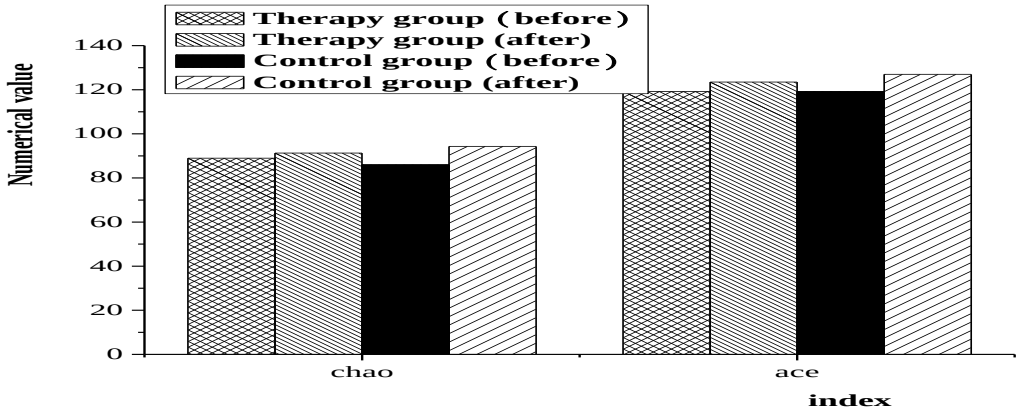


Figure 3: Comparison of chao and ace indexes between the two groups of patients

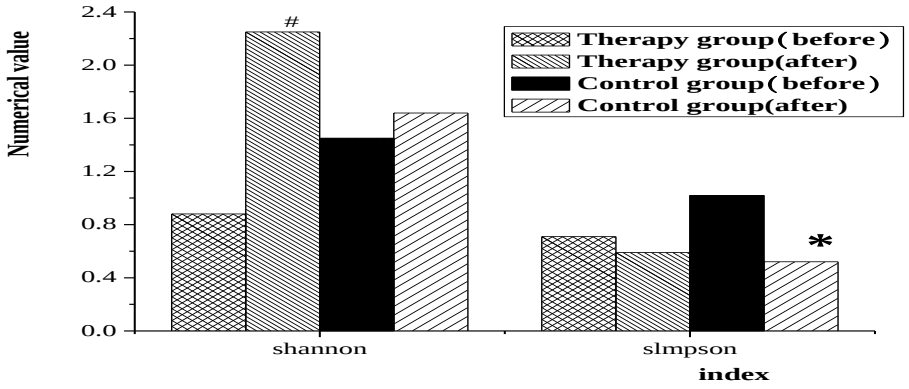


Figure 4: Comparison of shannon and simpson indexes between the two groups of patients

However, the shannon index of vaginal flora in the therapy group changed greatly before and after treatment, with considerable difference (P <0.05). The change of Shannon index before and after treatment in control group was not significant (P >0.05). Figure 4 showed that the simpson index of control group changed dramatically before and after treatment, with remarkable differences (P <0.05), while the difference of the simpson index before and after the therapy group was not considerable (P >0.05).Note: # indicated P<0.05 in contrast to that of therapy group before treatment; * indicated P<0.05 in contrast to that of control group before treatment.

Analysis of the structure of vaginal flora in two groups of patients

Sequencing was performed on the V4 sequence of 16S rRNA of vaginal microorganisms in all collected samples. The results showed that before and after treatment, a total of 20 bacterial phyla were detected in the vaginal microbial samples of the two groups of patients. The relative abundance of the phyla of the two groups of patients changed greatly before and after treatment. The most significant change was the decrease in the population of Firmicutes and the increase of the population of Firmicutes. The relative abundance of

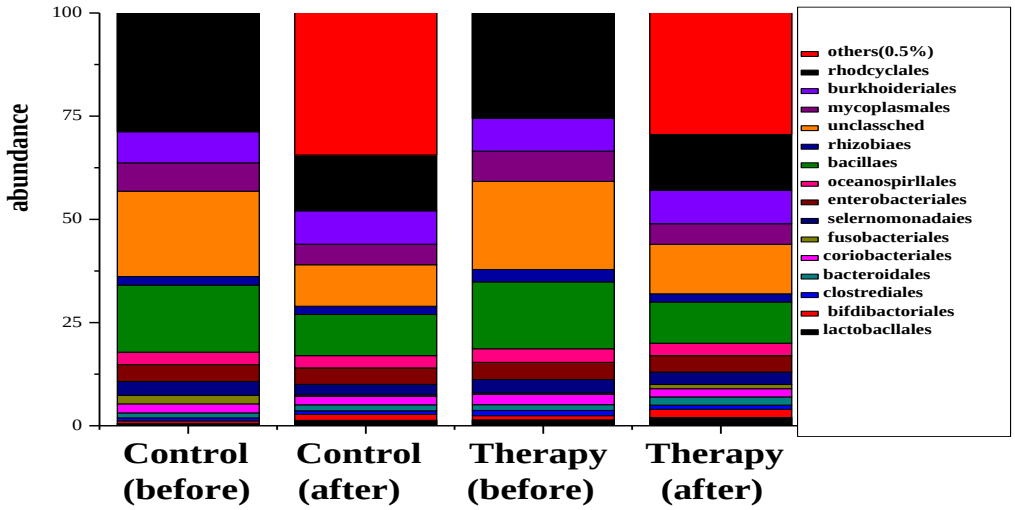
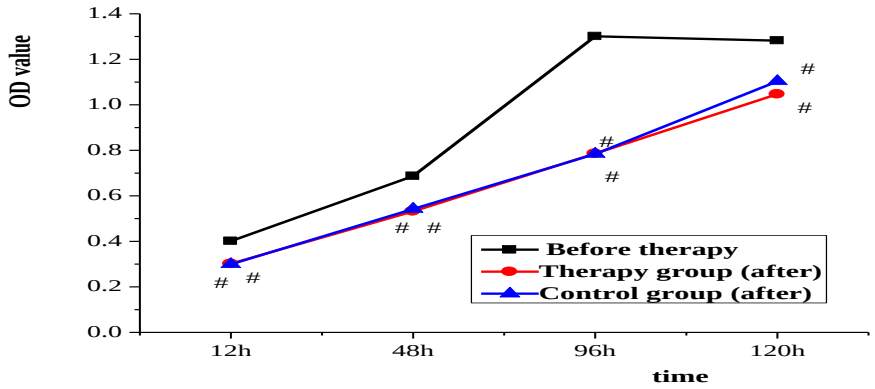


Figure 5: Comparison of the distribution of vaginal colonies between groups before and after therapy

Figure 6: SEM image of vagina Gv ATTCC14018



Note: # indicated P<0.05 in contrast to that before treatment.

Figure 7: Comparison of Gv biofilm formation speed before and after treatment

Actinobacteria, Bacteroides, Proteobacteria, Aseptomyces, and Fusobacteria increased. Further analysis of the two groups of vaginal flora was conducted at the genus level (Figure 5). Before treatment, the relative abundance of vaginal Gv was higher than the normal range, reaching 21.42%. The content of Lactobacillus was obviously inferior to the normal value, accounting for only 42.96%. These two were the main bacterial genera that constituted the vaginal flora. Lactobacillus was the dominant genus in the vaginal flora of the therapy group and control group after treatment, accounting for 74.33%. It also included other genus such as Gv, Streptococcus, and Prevotella, but the content was relatively small. The analysis of the difference on the colony groups showed that vaginal Gv was the main different bacteria of cervical cancer before and after the treatment.

Comparison of biofilm formation between the two groups of patients

In detection of the rate of biofilm formation, Gv biofilm was taken as the reference for comparison. The Gv obtained from the two groups of patients before and after treatment was first observed with a scanning electron microscope (SEM), and the results are shown in Figure 6. Then, a 96-well plate was utilized as a carrier for culture, and the crystal violet assay was implemented to detect the formation of vaginal Gv biofilm (Figure 7). The average biofilm formation speed of Gv before treatment in the therapy group and control group was faster than that after treatment, with substantial differences (P <0.05). After treatment, the average biofilm formation speed of the therapy group and control group was not significantly different (P >0.05). It was shown that the treatment of GEM combined with LOB in LACC can significantly slow down the formation of biofilms and can delay the spread of cancer cells. In addition, there was not much difference between intravenous injection and interventional embolization to delay the speed.

Discussion

China, as a region with a high incidence of cervical cancer, reports over 100,000 new cases annually, with an incidence rate exceeding 13%. Among these, LACC presents significant clinical challenges due to large tumor volume, high surgical difficulty, and elevated risk of recurrence and metastasis, resulting in persistently low 5-year survival rates, making it a major focus and difficulty in clinical treatment [14,15]. Currently, the standard treatment for LACC primarily involves radiotherapy combined with intravenous chemotherapy. However, this approach has notable limitations. Intravenous chemotherapeutic agents undergo systemic metabolism, and the local tumor drug concentration is only one-fifth to one-third of the systemic levels. This not only leads to suboptimal lesion control but also frequently causes severe systemic toxicities such as myelosuppression and gastrointestinal reactions. Some patients are forced to discontinue treatment due to intolerable adverse effects. In this context, transarterial interventional embolization chemotherapy has gradually been applied in LACC treatment, leveraging its advantage of targeted drug delivery. This study employed a regimen of GEM combined with LOB delivered via interventional embolization, wherein chemotherapeutic agents were administered directly into the tumor-feeding arteries through catheterization, effectively bypassing hepatic first-pass metabolism. Efficacy data demonstrated that the total response rate in the therapy group (interventional embolization) was significantly higher than that in the control group (intravenous chemotherapy) ($P < 0.05$). Moreover, the 1-year and 2-year survival rates were markedly improved compared to the control group ($P < 0.05$). These results not only validate the advantage of interventional embolization in short-term lesion control but also provide, for the first time, direct evidence of its value in achieving long-term survival benefits in LACC, addressing a gap in previous research that emphasized short-term efficacy over long-term prognosis [16]. Notably, this study also revealed that interventional embolization therapy modulates the vaginal microecology of patients. After treatment, the proportion of Gv in the therapy group decreased to 13.54%, and the biofilm formation rate was significantly reduced ($P < 0.05$), whereas no significant change was observed in the control group ($P > 0.05$). Previous studies have indicated that Gv biofilm can tightly adhere to the cervical epithelium, providing a sanctuary for HR-HPV, suppressing local immune cell activity, and accelerating cervical carcinogenesis and tumor progression. Therefore, the inhibitory effect of interventional embolization on Gv may represent a microecological mechanism underlying its

enhanced efficacy. This finding, which has not been reported in similar studies, opens a new direction for LACC treatment by combining tumor-targeted therapy with microecological modulation.

Recent studies mentioned that the process of cervical cancer was that when the vaginal flora was imbalanced, apoptosis was inhibited and escaped the immune system tracking after the cervical epithelial cells were continuously infected by HR-HPV. As a result, the original cell cycle was out of control and the cells appeared immortalized [17]. As the body's immune system's defense function gradually collapsed, the body's susceptibility to HR-HPV increased, and the process of cervical cancer accelerated. Some studies also suggested that cervical cancer was closely related to the number of suspicious bacteria. Vaginal Gv, as a common strain found in female HR-HPV infection, can secrete vaginal cytolysin to inhibit the secretion of immunoglobulin A antibodies in the vagina and reduces the occurrence of local immune reactions, thereby increasing the carcinogenic potential of HR-HPV infection[18,19].

In recent years, studies revealed that 16RsDNA sequencing results of vaginal swabs of patients with cervical cancer showed that Gv in the vaginal flora of patients increased significantly at the level of genus and species [20]. Vaginal Gv is one of the most common bacteria in the vaginal secretions of patients with cervical cancer, and is considered to be an important factor in inducing cervical cancer.[21] OaKley *et al*.[22] found that vaginal Gv had a strong biofilm formation ability and adhered tightly to the surface of the cervix, which had a strong cytotoxic effect on the cervical epithelium. It was a key synergistic factor that caused the host to be infected with HR-HPV for a long time, accelerated the cancerization of cervical epithelial cells, and promotes tumor metastasis. Huang *et al*.[23] adopted fluorescence in situ hybridization to detect vaginal Gv biofilm, which contained a large number of bacteria. Zhai *et al*.[24] confirmed that epithelial cells adhered to vaginal Gv biofilm through pathological sections and scanning electron microscopy. In this experiment, after GEM combined with LOB interventional embolization, the Gv content of the vaginal flora of patients with LACC decreased, and the rate of biofilm formation decreased accordingly. The results indicated that the good effects of GEM combined with LOB interventional embolization may be related to changes in the vaginal flora and changes in the rate of biofilm formation caused by them. Previous studies on interventional chemotherapy for LACC have predominantly focused on the efficacy of single-agent regimens or short-term lesion changes, with limited attention to microecological impacts. This study employed a combination regimen of GEM and LOB, leveraging the synergistic antitumor mechanisms of these agents, inhibiting DNA replication and disrupting DNA structure, respectively, to enhance therapeutic efficacy. The favorable safety profile of LOB, characterized by mild hepatotoxicity, further ensured treatment safety. Moreover, this study is the first to incorporate evaluation indicators for Gv and biofilm formation, addressing a critical gap in research on the microecological regulatory effects of interventional therapy. These findings provide a novel perspective for understanding the multidimensional mechanisms of LACC treatment.

Strengths

This study directly compares GEM+LOB interventional embolization with conventional intravenouschemotherapy in patients with locally advanced cervical cancer, providing clear evidence of superioltherapeutic efficacy and improved short-term survival. lt is also one of the few studies tosimultaneously assess treatment outcomes together with changes in vaginal microecology,demonstrating reductions in Gardnere/la vaginalis abundance and biofilm formation. The use ofstandardized sequencing methods, clear efficacy criteria, and consistent statistical analysis furtherstrengthens the reliability of the findings.

Limitations

The study is limited by its single-center design and relatively small sample size, which may affectgeneralizability,. The follow-up period was only two years, preventing evaluation of long-termsurvival outcomes. Additionally, the study did not investigate the molecular mechanisms underlvingchanges in vaginal flora or biofilm inhibition, and did not account for potential confounders thatmay influence microbiota composition.

Conclusıon

In this work, the efficacy of GEM combined with LOB interventional embolization in 60 patients with LACC was evaluated. Moreover, the patient's survival, tumor recurrence and metastasis, and adverse reactions were observed after treatment. It was found that GEM combined with interventional embolization can effectively prolong the survival time of patients, which also improved the distribution of vaginal flora of patients and delayed the biofilm formation of vaginal Gv cells. The core strengths of this study are reflected in three aspects: First, it addresses a critical clinical challenge in LACC by integrating the efficacy of interventional embolization with vaginal microecological modulation.

Through comparing the GEM+LOB interventional regimen versus conventional intravenous chemotherapy, the study not only confirms the superior efficacy of interventional therapy but also reveals its inhibitory effects on Gv and biofilm formation, providing dual-dimensional evidence (tumor control + microecological improvement) for LACC treatment, with a highly innovative study design. Second, the data collection and analysis were rigorously conducted: therapeutic efficacy was evaluated using internationally standardized tumor response criteria (CR, PR, SD, PD); microbiota detection followed standardized experimental protocols; and statistical methods employed chi-square tests to ensure scientific validity in intergroup comparisons, resulting in high reliability of the findings. Third, the conclusions directly address clinical needs by clarifying applicable scenarios and operational considerations for the interventional embolization regimen, offering concrete guidance for clinicians in selecting LACC treatment strategies, thus demonstrating significant translational value. However, this study has several limitations that should be addressed in future research: First, the sample size was small (n=60) and derived from a single center, with patient age concentrated between 47–74 years, potentially introducing selection bias. Subsequent studies should involve multicenter, large-sample (n>200) cohorts with age stratification (<50, 50–65, >65 years) to validate the findings. Second, the follow-up period was limited to 2 years, preventing assessment of the long-term impact of interventional embolization on 5-year survival in LACC patients.

Extended follow-up to 5 years is necessary to further confirm the durability of therapeutic efficacy. Third, the molecular mechanisms by which GEM+LOB inhibits Gv biofilm formation were not thoroughly investigated. Future in vitro studies should analyze the effects of these drugs on Gv quorum sensing signaling pathways and the expression of biofilm matrix synthesis-related genes (*e.g.*, *epsA*, *bap*) to provide molecular-level evidence for optimizing treatment strategies.

Clinically, this study confirms that GEM+LOB interventional embolization can serve as a preferred neoadjuvant treatment option for LACC. It is recommended that clinicians preoperatively identify tumor-feeding arteries via MRI and CTA, and develop individualized protocols through collaboration between interventional radiology and gynecologic oncology departments. For patients with high Gv prevalence (>40%), local lactobacillus formulations may be combined post-intervention to further optimize vaginal microecology and enhance therapeutic benefits. Simultaneously, a comprehensive adverse event monitoring system should be established post-intervention, with particular attention to embolization-related complications (e.g., post-embolization syndrome, vascular injury) to ensure treatment safety. For healthcare policy formulation, this study provides evidence for standardizing LACC treatment strategies. Health authorities should consider incorporating GEM+LOB interventional embolization into clinical guidelines for LACC (especially regarding referral criteria for primary hospitals) to promote its adoption in medically qualified institutions. Furthermore, addressing the limitations of single-center design and small sample size requires policy-driven initiatives (*e.g.*, dedicated research grants) to support multicenter, large-sample studies. This will further validate the generalizability of the protocol and strengthen evidence-based support for improving LACC diagnosis and treatment quality.

Author contributions

Dahai Li designed the study, performed the clinical procedures, collected and analyzed the patient data,

and drafted the manuscript. He also supervised the data interpretation regarding vaginal flora and biofilm formation. All aspects of the study were coordinated and overseen by Dahai Li, who approved the final version of the manuscript.

References

1. Zeng Q, Feng K, Yu Y,Lv Y. Hsa_Circ_0000021 Sponges miR-3940-3p/KPNA2 Expression to Promote Cervical Cancer Progression. *Curr Mol Pharmacol.* 2024;17:e170223213775.doi:10.2174/1874467216666230217151946
2. Parikh Nisha, Parmar Srushti, Dave Bhavarth, Mohammad Kaif and Parikh Palak, Comprehensive Review on Analytical and Bioanalytical Methods for Quantification of Anti-angiogenic Agents used in Treatment of CervicalCancer, *Current Pharmaceutical Analysis*; Volume 19, Issue 10, Year 2023, e081123223291. doi: 10.2174/0115734129270020231102081109
3. Gennigens C, De Cuypere M, Hermesse J, Kridelka F, Jerusalem G. Optimal treatment in locally advanced cervical cancer. *Expert Rev Anticancer Ther*. 2021 Jun;21(6):657-671. doi: 10.1080/14737140.2021.1879646. Epub 2021 Mar 11. PMID: 33472018.
4. Xin Mi, Caiyi Chen, Chen Feng, Yingying Qin, Zi-Jiang Chen, Yajuan Yang and Shidou Zhao, The Functions and Application Prospects of Hepatocyte Growth Factor inReproduction, *Current Gene Therapy*; Volume 24, Issue 5, Year 2024, e230224227382. DOI: 10.2174/0115665232291010240221104445
5. Bule YP, Silva J, Carrilho C, Campos C, Sousa H, Tavares A and Medeiros R. Human papillomavirus prevalence and distribution in self-collected samples from female university students in Maputo. *Int J Gynaecol Obstet.* 2020 May;149(2):237-246. doi: 10.1002/ijgo.13126. Epub 2020 Mar 25. PMID: 32086940.
6. Wei Zheng, Haixia Mu, Jing Chen, Chunjie Wang and Li Hou, Circ_0002762 Regulates Oncoprotein YBX1 in Cervical Cancer viamir-375 to Regulate the Malignancy of Cancer Cells, *Protein & Peptide Letters*; Volume 30, Issue 2, Year 2023, e040123212381. DOI: 10.2174/0929866530666230104155209
7. Xiaojuan Ding, Ailing Wan, Xin Qi, Ke'er Jiang, Zhao Liu and Buze Chen, ZNF695, A Potential Prognostic Biomarker, Correlates with Im muneInfiltrates in Cervical Squamous Cell Carcinoma and Endoce rvicalAdenocarcinoma: Bioinformatic Analysis and Experimental Verification, *Current Gene Therapy*; Volume 24, Issue 5, Year 2024, e010324227572. DOI: 10.2174/0115665232285216240228071244
8. Kang GU, Jung DR, Lee YH, Jeon SY, Han HS, Chong GO and Shin JH. Potential Association between Vaginal Microbiota and Cervical Carcinogenesis in Korean Women: A Cohort Study. *Microorganisms.* 2021 Jan 31;9(2):294. doi: 10.3390/microorganisms9020294. PMID: 33572693; PMCID: PMC7912413.
9. Akilli H, Tohma YA, Bulut AN, Karakas LA Haberal AN, Kuscu UE and Ayhan A. Comparison o no adjuvant treatment and radiotherapy in early-stage cervical carcinoma with intermediate risk factors. *Int J Gynaecol Obstet.* 2020 Jun;149(3):298-302. doi: 10.1002/ijgo.13147. Epub 2020 Apr 22. PMID: 32246761.
10. Nunes de Arruda F, da Costa S, Bonadio R, Dornellas A, Pereira D, de Bock GH and Del Pilar Estevez Diz M. Quality of life of locally advanced cervical cancer patients after neoadjuvant chemotherapy followed by chemoradiation versus chemoradiation alone (CIRCE trial): a randomized phase II trial. *Int J Gynecol Cancer.* 2020 Jun;30(6):749-756. doi: 10.1136/ijgc-2019-001134. Epub 2020 Apr 21. PMID: 32321767; PMCID: PMC7362881.
11. Shah SS, Senapati S, Klacsmann F, Miller DL, Johnson JJ, Chang HC and Stack MS. Current Technologies and Recent Developments for Screening of HPV-Associated Cervical and Oropharyngeal Cancers. *Cancers (Basel).* 2016 Sep 9;8(9):85. doi: 10.3390/cancers8090085. PMID: 27618102; PMCID: PMC5040987.
12. Feng T, Shou HF, Yuan SH, Tang HR, Lyu XJ, Yin ZM, Lou HM, Ni J. [Treatment and prognosis analysis of 488 patients with FIGO 2018 stage IIIc squamous cervical cancer]. *Zhonghua Fu Chan Ke Za Zhi*. 2023 May 25;58(5):359-367. Chinese. doi: 10.3760/cma.j.cn112141-20230128-00028. PMID: 37217343.
13. Furusaka T, Asakawa T, Tanaka A, Matsuda H, Ikeda M. Efficacy of multidrug superselective intra-arterial chemotherapy (docetaxel, cisplatin, and 5-fluorouracil) using the Seldinger technique for tongue cancer. *Acta Otolaryngo*l. 2012 Oct;132(10):1108-14. doi: 10.3109/00016489.2012.684702. PMID: 22998559.
14. Sodhani P, Gupta S, Gupta R, Mehrotra R. Bacterial Vaginosis and Cervical Intraepithelial Neoplasia: Is there an Association or is Co-Existence Incidental? *Asian Pac J Cancer Prev.* 2017 May 1;18(5):1289-1292. doi: 10.22034/APJCP.2017.18.5.1289. PMID: 28610416; PMCID: PMC5555537.
15. Pereira E, Nair N, Gorski J, Schwartz M.A.,Zakashansky K.,Dottino P., Kolev V. and Hayes M.P.The addition of chemotherapy to adjuvant radiotherapy in patients with intermediate-risk stage IB cervical cancer and the effect on survival[J]. *Gynecologic Oncology*, 2017, 145:134.
16. Sabera K, Farzana S, Annekathryn G. Role of Neoadjuvant Chemotherapy in Treatment of Cervical Cancer: A Case Series of Thirty-Eight Patients Treated at Bangabandhu Sheikh Mujib Medical University in Dhaka, Bangladesh[J]. *Open Journal of Obstetrics and Gynecology*,2018;8(5):446-455.
17. Kone ES, Balili AD, Paparisto PD, Ceka XR, Petrela ED. Vaginal Infections of Albanian women Infected with HPV and their impact in intraepithelial cervical lesions evidenced by Pap test. J *Cytol.* 2017 JanMar;34(1):16-21. doi: 10.4103/0970-

9371.197592. PMID: 28182076; PMCID: PMC5259924.

18. Chen YF, Tang WB, Pan XX, Wu CR, Cao Y and Yang W. Safety and efficacy of nimotuzumab combined with chemoradiotherapy in Chinese patients with locally advanced cervical cancer. *Onco Targets Ther*. 2017 Aug 17;10:4113-4119. doi: 10.2147/OTT.S133756. PMID: 28860820; PMCID: PMC5566502.
19. Pisani C, Deantonio L, Surico D, Brambilla M, Galla A, Ferrara E, Masini L, Gambaro G, Surico N and Krengli M. Quality of life in patients treated by adjuvant radiotherapy for endometrial and cervical cancers: correlation with dose-volume parameters. *Clin Transl Oncol.* 2016 Sep;18(9):901-8. doi: 10.1007/s12094-015-1458-9. Epub 2015 Nov 25. PMID: 26607932.
20. Yang K, Park W, Huh SJ, Bae DS, Kim BG and Lee JW. Clinical outcomes in patients treated with radiotherapy after surgery for cervical cancer. *Radiat Oncol J.* 2017 Mar;35(1):39-47. doi: 10.3857/roj.2016.01893. Epub 2016 Dec 12. PMID: 27927011; PMCID: PMC5398353.
21. Kwasniewski W, Wolun-Cholewa M, Kotarski J, Warchol W, Kuzma D, Kwasniewska A and Gozdzicka-Jozefiak A. Microbiota dysbiosis is associated with HPV-induced cervical carcinogenesis. *Oncol Lett*. 2018 Dec;16(6):7035-7047. doi: 10.3892/ol.2018.9509. Epub 2018 Sep 26. PMID: 30546437; PMCID: PMC6256731.
22. Oakley BB, Fiedler TL, Marrazzo JM and Fredricks DN. Diversity of human vaginal bacterial communities and associations with clinically defined bacterial vaginosis. *Appl Environ Microbiol.* 2008 Aug;74(15):4898-909. doi: 10.1128/AEM.02884-07. Epub 2008 May 16. PMID: 18487399; PMCID: PMC2519371.
23. Huang X, Li C, Li F, Zhao J, Wan X and Wang K. Cervicovaginal microbiota composition correlates with the acquisition of high-risk human papillomavirus types. *Int J Cancer.* 2018 Aug 1;143(3):621-634. doi: 10.1002/ijc.31342. Epub 2018 Mar 9. PMID: 29479697.
24. Zhai Q, Ren T, Fu Y, Zhang Z, Li L, Li Y and Meng Y. [Characteristics of cervical microecology in late reproductive-age women with different grades of cervical lesions]. *Nan Fang Yi Ke Da Xue Xue Bao*. 2020 Dec 30;40(12):1768-1775. Chinese. doi: 10.12122/j.issn.1673-4254.2020.12.11. PMID: 33380398; PMCID: PMC7835688..