Research Article

The sealing effect of the magnetic-sealing uterine manipulator in patients with early-stage cervical cancer

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Running title: Sealing effect of MUM

Abstract

Objective: To assess the sealing effect of a Magnetic-Sealing Uterine Manipulator (MUM) in isolated uterus.

Design: Non - intervention study.

Setting: This study was conducted at the First Affiliated Hospital of Xi'an Jiaotong University from November 2019 to April 2021.

Population: Patients with early-stage cervical cancer who underwent radical laparotomy hysterectomy.

Methods: The MUM closure test (group 2) and the control test (right-angle forceps closure tests, group 1 and 3) were carried out in an isolated uterus.

Main outcome measure: DNA ploidy analysis system was used to analyze the exfoliated cells. Statistical analysis was performed using Wilcoxon signed rank test to assess the sealing effect of MUM.

Results: We identified 36 patients. None regional node metastasis was found in all cases and only one of their tumors was larger than 4.0 cm. The mean numbers of exfoliated tumor cells in groups 1, 2, and 3 were 1, 1, and 2, respectively. There was no significant difference in the number of exfoliated cells between group 1 and group 3 ($p=0.476$). We merged the results of group 1 and 3. Furthermore, there was significant difference between right-angle forceps closure tests and MUM closure test ($p=0.022$).

Conclusion: The sealing effect for MUM was better than the right-angle forceps. The MUM can effectively seal the cervical cancer cells in the cup cover and avoid the dissemination of tumor cells.

Keywords: cervical cancer; magnetic-sealing uterine manipulator; minimally invasive surgery; exfoliated cells; iatrogenic dissemination

Tweetable abstract: The magnetic-sealing uterine manipulator is a safe and valuable option for women with early-stage cervical cancer during minimally invasive surgery.

Introduction

In the past two decades, minimally invasive or open abdominal radical hysterectomy (RH) has become the main operation method for women with early-stage cervical cancer [1]. Scholars have pointed out that minimally invasive surgery (MIS) have advantages such as less blood loss, fewer transfusions, shorter hospital stays, fewer-needed adjuvant therapies, and lower medical costs when compared with open surgery [2-5]. Also, the MIS reduces the incidence of short-term complications, including postoperative pelvic floor dysfunction, nerve damage, digestive and urogenital system complications [6-8]. Considering these advantages, patients tend to choose the MIS.

However, doctors in the M.D. Anderson Cancer Center (MDACC) found that minimally invasive RH was associated with lower rates of disease-free survival and overall survival than open abdominal RH among women with early-stage cervical cancer [9, 10]. Then, the MDACC stopped MIS and switched to open surgery for cervical cancer. The National Comprehensive Cancer Network (NCCN) guidelines (Version 3. 2019) quickly demonstrated that patients should be informed of results in the studies, and their choices should be respected [11].

Since then, many scholars have indicated that lower rates of survival during MIS were correlated with the iatrogenic dissemination of cervical cancer. The potential reasons for dissemination were CO_2 pneumoperitoneum, steep Trendelenburg position, and uterine manipulator [2, 12, 13]. Recently, uterine manipulator was considered as the main reason because the routine use of it increases the probability of intra-abdominal overflow after cancer resection [14]. Moreover, “vaginal cuff closure” is used to replace uterine manipulator during MIS in some studies [15-17]. Successful results have been reported, but there are limitations, such as potential risk of the spillage of tumor cells, tissue tearing by the sutures leading to inadvertent bleeding [18], lack of control, unclear exposure and difficult operation. Thus, new effective instrument is needed.

Considering unique advantages of uterine manipulator [19] and magnetic technology[20], our team designed a uterine manipulator which had the property of anti-dissemination of tumor cells by magnetic force — a magnetic-sealing uterine manipulator (MUM). The use of it could completely seal the cervix in cup cover, avoiding contact between tumor and pelvic cavity. This device has been patented

(CN201910478230.1). To evaluate the clinical applicability of MUM, we used right-angle forceps closure test as control test. Because during open abdominal RH, right-angle forceps were used to seal cervical cancer cells [11]. All tests were performed on isolated uteruses, being collected from patients who underwent open abdominal RH.

Methods

Patients

Patients with following characteristics were included in the study: women who underwent open abdominal RH and pelvic lymphadenectomy, with pathological diagnosis, and Federation International of Gynecology and Obstetrics (FIGO) 2018 stages IA, IB, or IIA. We excluded patients who underwent conservative treatments, or were diagnosed with cervical intraepithelial neoplasia. Patients with endometrial cancer or endometrial cancer that had metastasized to the cervix or vaginal walls were also excluded. All patients were treated at the First Affiliated Hospital of Xi'an Jiaotong University from November 2019 to April 2021, and the basic information of the patients was obtained through the electronic medical record system.

MUM and specimen collection

The MUM consists of a buckled - magnet chain and a cup. A magnet was embedded at the end of the chain, and at the top of the chain was a square buckle (Figure 1A and C). The cup of the MUM was a conventional cup cover for the uterine manipulator (Figure 1B and C).

The process of collecting exfoliated cells of the isolated uterus was as follows. After the patient's vagina was severed, the bilateral fallopian tubes and vagina were closed by two titanium clips and right-angle forceps, respectively. The isolated uterus was immersed in normal saline after removal from the patient's body. Firstly, we carried out the right-angle forceps closure test as group1 (Figure 1D). Then, we removed the right-angle forceps, placed the cup of MUM at the vaginal fornix, made the buckled-magnet chain bypass the square buckle, and wrapped it around the outside of the vaginal wall in turn. Therefore, the vaginal wall was tightly enclosed between the buckled-magnet chain and the cup. After that, we carried out the MUM closure test as group 2 (Figure 1E and F). To eliminate the influence of the operation, we reconducted the right-angle forceps closure test as group 3 (Figure 1G). Before each operation, we flushed the isolated uterus with normal saline.

DNA ploidy analysis

Exfoliated cells were enriched after removing red blood cells and centrifuging, and then the cells were made into slides [21]. Each slide was fixed with Bohm-Sprenger

fixative fluid and stained with Feulgen-staining. Finally, the cancer cells in the sample were counted by the DNA ploidy analysis system (McAudi Medical Diagnostic System Co., Ltd. Xiamen. 20182220121).

Sample size calculation

According to the inclusion and exclusion criteria, 6 patients were enrolled through preliminary experiments. The number of tumor cells of 6 patients is shown in sTable 1. The Student's *t* test showed no statistical difference between group 1 and group 3 ($p = 0.069$), so we merged them. Through the results of the preliminary experiment, we obtained mean $(\bar{X}_i)$ and standard deviation (S_i) of each group. The influencing factors of sample size estimation included α (type I error) and β (type Ⅱ error). Sample size was calculated by following formula. The ψ parameter was related to the degree of freedom (υ_1 *and* υ_2). When we set parameters $\alpha = 0.05,\ \beta = 0.10,\ \upsilon_1 = k - 1 = 1,\ v_2 = \infty,\ \psi_{0.05,0.10(1,\infty)} = 3.24$, we got $n_{(1)} = 12$. When we set parameters $\alpha = 0.05,\ \beta = 0.10,\ \upsilon_1 = k - 1 = 1,\ v_2 = k(n_{(1)} - 1),\ \psi_{0.05,0.10(1,22)} = 3.39$, we got $n_{(2)} = 13$. These steps were repeated until the results were stable. Finally, we got $n = 13$. Therefore, the study required at least 13 samples to prove the effectiveness of MUM.

$$\mathrm{n} = \frac{\psi^2(\Sigma S_i^2/k)}{\Sigma(\bar{X}_i - \bar{X})^2/(k-1)}$$

k: number of groups; $\bar{X}_i$: mean of each group;
$\bar{X}$: mean of three groups; S_i: standard deviation

Statistical analysis

Quantitative data were expressed as mean values ± standard deviation (SD). We used Wilcoxon signed rank test to analyze significant differences between the right-angle forceps closure test and the MUM closure test. Data were analyzed using Statistical Package for the Social Sciences version 18.0 software (SPSS Inc., Chicago, IL, USA). For all analyses, $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 39 patients with cervical cancer were enrolled. Querying the electronic medical record system, we obtained the following information from each patient: age, histological type, differentiated grade, FIGO stage, tumor size and lymph node metastasis (Table 1). Three patients were excluded, whose postoperative pathology were stage IIIC. Mean age of patients was 44 years (range, 29 – 56 years). Among the 36 patients, 77.78% were diagnosed squamous carcinoma. FIGO stage IA and IB presented in 91.67% of all patients. None regional node metastasis was found in all cases and only one diameter of their tumors was larger than 4.0 cm.

The number of exfoliated tumor cells

Using DNA ploidy analysis technology, we determined the number of exfoliated tumor cells from each sample. Theoretically, the DNA index of normal cells was 1 – 2. Given that cells with DNA index ≥ 2.5 were generally defined as diseased cells, these were regarded as exfoliated tumor cells in this study. During the first right-angle forceps closure test, two tumor cells were found in one sample (Figure 2). The number of exfoliated tumor cells from each patient, according to group assignment, was plotted as a stacking bar graph (Figure 3). In 80.56% of the samples, the number of exfoliated tumor cells in group 2 was less than that in group 1 or group 3. Further, in nineteen samples, the number of exfoliated tumor cells in group 2 was zero.

Data calculation

Statistical analysis showed that the mean numbers of exfoliated tumor cells in groups 1, 2, and 3 were 1, 1, and 2, respectively. According to the statistical analysis performed by the Wilcoxon signed rank test, there was no significant difference in the number of exfoliated cells between group 1 and group 3 ($p = 0.476$). Therefore, we merged the results of group 1 and group 3 as group 4. Statistical analysis showed significant difference between group 2 and group 4 ($p = 0.022$). In summary, the sealing effect for MUM was better than that of the right-angle forceps.

Discussion

Main Findings

In this study, no significant difference was observed in the number of exfoliated tumor cells between the first right-angle forceps closure test and the second right-angle forceps closure test. This finding successfully ruled out the effects of manipulation during the experimental procedure. More importantly, there was significantly difference between right-angle forceps closure tests and MUM test. And fewer exfoliated tumor cells were collected in the MUM closure tests than in the right-angle forceps closure tests. This proved that, during MIS, the tumor cells were effectively sealed in the cup cover by the MUM. This method had better effects than the right-angle forceps for open abdominal radical hysterectomy in patients with early-stage cervical cancer.

Strengths and Limitations

We firstly designed this new uterine manipulator, the MUM, that can be used during MIS. We preserved the advantages of the traditional uterine manipulator, but also overcame the dissemination of tumor cells by introducing a buckled-magnet chain. Through this study, we demonstrated that the use of the MUM had value in clinical application.

Admittedly, there are several limitations to the present work. Firstly, the result did not conform to a normal distribution. The inspection efficiency of outcomes might have been influenced by the non-parametric test. Secondly, a single-center research design might lead to selection bias. Also, the surgery was performed by different surgeons, and the length of the removed vaginal wall might also affect the number of exfoliated tumor cells. To ensure homogeneity of the subject cohort, we enrolled patients according to strict inclusion and exclusion criteria. Moreover, we added the second right-angle forceps closure test, after the MUM closure test, to avoid random errors from the experimental conditions. As Wilcoxon signed rank test showed, there was no significant difference between the two right-angle forceps closure tests. This finding implied that the results were credible.

Interpretation

With the results of the Laparoscopic Approach to Carcinoma of the Cervix trials, many research teams put forward a variety of measures to solve the dissemination of tumor cells during MIS. Some researchers reported that the lower rates of overall survival in minimally invasive RH, compared to open abdominal RH, were associated with the use of a uterine manipulator [14], FIGO stage, and tumor size [12, 22]. Further retrospective studies showed similar oncological results after abdominal or laparoscopic RH in tumors of < 2.0 cm for early-stage cervical cancer [23-26]. Yuting Liu *et al*. showed that the surgical routes and the learning curve of laparoscopic RH affected the survival outcomes of patients with early-stage cervical cancer. The authors further suggested that operators should strengthen their skills [27]. While most studies are retrospective, further studies are needed to verify these conclusions.

Considering the uterine manipulator could potentially influence the prognosis of patients during MIS [14], some scholars evaluated the safety of MIS without the application of the uterine manipulator. A nationwide population-based cohort study by Emilia Alfonzo *et al.* found that the disease-free survival and overall survival rate were not significantly different between patients who underwent robotic and open abdominal RH with early-stage cervical cancer [28]. To our knowledge, some researchers used "vaginal cuff closure" to replace the uterine manipulator during MIS, and obtained better prognosis compared with open abdominal RH [15-17]. Recently, Seiji Mabuchi *et al.* developed a novel manipulation device, the U-traction, which could be used during MIS with safety and utility [18]. These studies indicated that the traditional uterine manipulator was a risk factor for poor prognosis in patients with early-stage cervical cancer treated with MIS. However, these methods had some disadvantages: potential risks spillage of tumor cells, tissue tearing by the sutures leading to inadvertent bleeding, injury of the blood vessels located in the abdominal wall [18], lack of control, unclear exposure and difficult operation. Moreover, the advantages of the uterine manipulator cannot be ignored. Over the past few decades, the uterine manipulator was regarded as the best way to mobilize the uterus during surgery. The use of the manipulator could provide a clear surgical field by exposing the pelvis and impelling the uterus away from important anatomic structures [19]. Regrettably, there is a lack of relevant studies which attempted to improve upon uterine manipulation.

In recent years, the application of magnetic surgery has developed rapidly. Lirui Zhang *et al.* successfully used an internal grasper and magnetic anchoring guidance system to perform single-port laparoscopic surgeries in 18 patients with benign

gynecological diseases[29]. Also, magnetic pressing technology had been successfully used for vascular anastomosis[30, 31], digestive tract anastomosis[32], and rectovaginal fistula repair[33], etc. Positive results were obtained in those studies and researchers pointed out that magnetic technology had the advantages of minimally invasive, efficient, and safe[20, 34-36]. Based on the above advantages, we added a buckled-magnet chain to traditional uterine manipulator. Through the magnetic attraction, the vaginal wall was mechanically fixed between cup cover and buckled-magnet chain. To evaluate the clinical applicability of MUM, we used the number of exfoliated tumor cells on isolated uteruses to compare the sealing effect between the MUM and right-angle forceps closure tests. The results showed that the MUM was better than the right-angle forceps in avoiding the spread of tumor cells.

Although statistical analysis showed an exciting result, the absolute number of tumor exfoliated cells through DNA ploidy analysis was not much different. However, it at least proved that compared with the control group, the sealing effect of MUM was not worse than that of the control group. MUM had certain application potential. In our study, 25 patients had tumor 2 cm or smaller (Table 1), which might impact applicability of the study to other cervical cancer tumors larger than 2 cm. Because of the small sample size, we did not perform a stratified analysis. Moreover, our study was just a hypothesis generating to initially evaluate the sealing effect of the MUM. We think that further efforts are required to improve the MUM and match the corresponding laparoscopy instruments. And then we will apply for human experiments to evaluate the sealing effect of MUM in laparoscopic surgery in larger prospective studies.

Conclusions

We effectively sealed the cervical cancer cells by the MUM. The MUM provides a good opportunity for women with early-stage cervical cancer to benefit from MIS in the future.

Disclosure of interests

The authors have declared that no potential conflicts of interest exist.

Author contributions

Conception and design: Yi Lv, Qiling Li; Development of methodology: Feng Ma, Rongqian Wu; Acquisition of data (acquired and managed patients, provided facilities, etc.): Xue Zhou, Dongxin Liang, Lanbo Zhao, Lu Han, Lei Wang; Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Xue Zhou, Qing Li, Shuhua Liu; Writing, review, and/or revision of the manuscript: Dongxin Liang, Lanbo Zhao, Qiling Li; Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Qiling Li; Study supervision: Yi Lv, Qiling Li.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Details of ethics approval

This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2020LSK-047) and informed written consent was obtained from all patients before the study.

Funding

This study was supported by the Clinical Research Award of the First Affiliated Hospital of Xi'an Jiaotong University, China (XJTU1AF-2018-017, XJTU1AF-CRF-2019-002), the Major Basic Research Project of Natural Science of Shaanxi Provincial Science and Technology Department (2018JM7073, 2017ZDJC-11), the Key Research and Development Project of Shaanxi Provincial Science and Technology Department (2017ZDXM-SF-068, 2019QYPY-138), the Shaanxi Provincial Collaborative Technology Innovation Project (2017XT-026, 2018XT-002), and the Medical Research Project of Xi'an Social Development Guidance Plan (2017117SF/YX011-3).

Acknowledgments

The authors thank the Center for Translational Medicine of the First Affiliated Hospital of Xi'an Jiaotong University for excellent technical assistance and support.

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Figure legends

Figure 1. The structure of MUM and the schematic of the test process. (A) The pattern diagram with the buckled-magnet chain. (B) The pattern diagram with the cup of the MUM. (C) The physical map of MUM, which includes the buckled-magnet chain and the cup. (D) and (G) The first and second right-angle forceps closure test. (E) and (F) The MUM closure test.

Figure 2. One result of DNA ploidy analysis. (A) The DNA index-quantity chart of cervical cancer cells. (B) The DNA index-area chart of cervical cancer cells. (C) The nucleus images and DNA index value diagram.

Figure 3. Several exfoliated tumor cells.

435 **Table 1**. Clinical characteristics of patients (N = 36)

Characteristic	n	(%)
Histology		
Squamous cell	28	77.78
Adenocarcinoma	7	19.44
Other	1	2.78
Grade		
Well differentiated	1	2.78
Moderately differentiated	17	47.22
Moderately-poorly differentiated	3	8.33
Poorly differentiated	7	19.45
Unknown	8	22.22
Stage		
IA	2	5.56
IB	31	86.11
IIA	3	8.33
Tumor size, cm		
≤1	16	44.44
1-2	9	25.00
>2	11	30.56
Unknown	0	0
Regional nodal metastasis		
No	36	100.00
Yes	0	0

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sTable 1. Number of exfoliated tumor cells in preliminary experiment

	Group 1	Group 2	Group 3
Pre-sample 1	0	0	1
Pre-sample 2	8	0	20
Pre-sample 3	3	3	5
Pre-sample 4	2	0	3
Pre-sample 5	6	2	8
Pre-sample 6	7	2	5

441 **sTable 2.** Number of exfoliated tumor cells

	Group 1	Group 2	Group 3
Sample 1	0	0	1
Sample 2	3	3	5
Sample 3	2	0	3
Sample 4	6	2	8
Sample 5	7	2	5
Sample 6	1	0	0
Sample 7	1	1	2
Sample 8	1	4	2
Sample 9	1	0	1
Sample 10	1	1	1
Sample 11	3	2	2
Sample 12	3	4	4
Sample 13	7	5	5
Sample 14	2	1	2
Sample 15	0	0	4
Sample 16	1	0	2
Sample 17	2	2	1
Sample 18	0	0	0
Sample 19	2	1	0
Sample 20	0	0	2
Sample 21	1	1	1
Sample 22	0	0	3
Sample 23	2	0	0
Sample 24	0	0	0
Sample 25	0	0	2
Sample 26	0	0	0
Sample 27	0	0	0
Sample 28	0	2	4
Sample 29	0	0	0
Sample 30	2	4	0
Sample 31	0	3	0
Sample 32	0	0	0
Sample 33	0	0	0
Sample 34	2	0	0
Sample 35	1	0	0
Sample 36	0	0	0

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