

The extra 1.5 cm makes the differences: reduced incidence of vaginal intraepithelial neoplasia after modified hysterectomy for CIN3/adenocarcinoma in situ (AIS) patients

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Abstract

Objectives

To assess whether modified hysterectomy can improve locoregional control compared to the standard extrafascial hysterectomy for cervical high grade intraepithelial neoplasia 3 (CIN3)/adenocarcinoma in situ (AIS) patients.

Methods

A total of 135 CIN3/AIS patients from May 2014 to March 2018 were enrolled and randomized to different hysterectomy group and finally 128 patients were eligible for analysis, in which 60 patients received standard extrafascial hysterectomy and 68 patients received modified hysterectomy by removing extra 1.5cm of vagina. Intra-operative variables including operative time, estimated amount of blood loss, urinary catheter time, hospital stay time and postoperative complications, most importantly the postoperative recurrence and disease free survival (DFS) were compared and analyzed.

Results

Age, BMI and histology grade were comparable between these two groups. No significant differences were found at median surgical times, blood loss and postoperative hospital stay neither laparoscopically nor abdominally, and neither was found about the incidences of fistulas, or other surgical complications. No incidences of prolonged urinary retention were found in both groups. With a median follow-up of 47.3 months (range 11–64 months), the modified hysterectomy group had a significantly improved in DFS rate compared to the standard extrafascial hysterectomy group ($P=0.026$). No disease related death occurred in the follow-up time.

Conclusion

With similar intra-operative variables operative time, modified hysterectomy appeared to provide the most reliable specimens and significantly reduced the postoperative vaginal recurrence rate for CIN3/AIS patients who choose remove their uterus when compared with standard extrafascial hysterectomy.

Introduction

Cervical intraepithelial neoplasia (CIN), which occurs in the transformation zone of the cervix, is the most common pre-malignant lesion. According to these atypical squamous changes by their depth, it can be described as CIN 1, 2 or 3 and some of these lesions will develop into squamous cancer if progresses. Thus, when high grade CIN is identified, it should be treated, which includes different techniques, such as ablation, cold knife conization (CKC), loop electrosurgical excision procedure (LEEP), etc. and choice of

treatment depends on the grade and extent of the disease with most techniques achieving a success rate of 90% for eradicating CIN [1–3].

Hysterectomy in treatment of CIN2 + is not recommended by ASCCP and European guidelines, as study has shown that the therapeutic efficacy of conservative therapies is almost identical to hysterectomy but with less complications [4–6] and hysterectomy is only considered when repeat diagnostic excision is not feasible for treatment of recurrent or persistent biopsy-confirmed CIN2-3. Hysterectomy for CIN is also a known risk factor for the subsequent development of vaginal intraepithelial neoplasia (VAIN), with historical recurrence rates ranging from 0.9–6.8% [7–9]. Nevertheless, in many developing countries including China, many histology-confirmed CIN3 lesions are treated with hysterectomy [10]. Without doubt, this treatment can not reach the expectant treatment effect for both the doctor and patients due to the potential incidence of vaginal intraepithelial neoplasia after hysterectomy, and will certainly increase the treatment cost to the patients for following further treatment, and seriously affect the quality of life of the patients.

In order to improve the prognosis and reduce the incidence rate of subsequent vaginal recurrence, we modified the standard extrafascial hysterectomy for CIN3/AIS patients who asked for removing their uterus by removing extra 1.5cm vaginal fornix and assessed the outcomes with patients received standard extrafascial hysterectomy in order to identify the best treatment strategy for CIN3/AIS patients demanding to remove their uterus.

Materials And Methods

1. Patients and procedures

From May 2014 to March 2018, 135 patients histologically diagnosed with CIN3//adenocarcinoma in situ (AIS) at the Department of Gynecologic Oncology of the Affiliated Tumor Hospital of Zhengzhou University School of Medicine got enrolled. The inclusion criteria were: (1) age 30–70 years old; (2) with definite histological diagnosis; (3) have completed childbearing; (4) acceptable liver, renal, cardiovascular pulmonary and other major organ functions. Exclusion criteria including: (1) age < 30 or > 70 years; (2) desire future fertility (3) any lung, liver, or cardiovascular pulmonary and other major organ dysfunctions; (4) with a history of VAIN or concomitant VAIN; (5) invasive cervical cancer. Women were grouped randomly according to a computer-generated random numeric table produced by SPSS in order to minimize the selection bias, and a random allocation number was determined with a telephone call prior to surgery. Seven patients with incomplete follow-up were not included.

All the patients have a cold knife conization procedure prior to hysterectomy and the pathology of cone specimen was reviewed by gynecologic pathologists to confirm margin involvement and exclude the presence of micro-invasive disease. The Institutional Ethics Review Board of the Affiliated Cancer Hospital of Zhengzhou University reviewed and approved this study (IRB Number: 15CT062) and all participants were well informed and provided written informed consent.

2. Surgical technique

In standard extrafascial hysterectomy with or without bilateral salpingo-oophorectomy group, following the establishment of pneumoperitoneum, a camera was placed through the umbilicus and two 10 mm and two 5 mm trocars were inserted into the abdomen. The round ligaments were transected, the vesicouterine fold was incised, and the bladder was mobilized down to the level of the vagina. The uterosacral and cardinal ligaments are dissected and cut following the extraction of the uterine corpus. The uterine artery and vein were transected at the point. Vaginal fornices were delineated and circular colpotomy was performed using unipolar hook cautery and all the specimens were retrieved from the vagina. As for abdominal total hysterectomy, vertical midline incision was made and the round ligaments were transected, the vesicouterine fold was opened, and the bladder was mobilized down to the level of the vagina. The infundibulopelvic ligaments were transected when bilateral salpingo-oophorectomy was performed and a minimal part of vagina is resected at fornix level.

In modified hysterectomy group, all the procedures were same except bladder was further mobilized down to the level of the vagina and a colpotomy cup was used to ensure 1.5 cm vaginal margin. Vaginal length was ascertained intraoperatively after taking the uterus out and the mean length at each case were recorded. The vaginal cuff was closed using running suture. Surgical outcomes including length of operating time, blood loss, intraoperative and postoperative complications were all recorded. Operative time was calculated from the entry of the Veress needle to the last suture on skin incision and from cutting and to skin closure. Blood loss was estimated by the waste irrigation fluid volume (mL) minus the volume of normal saline used for irrigation (mL). After surgery, a pelvic catheter remained for 48 hours and antibiotics were given 48 hours for both surgical procedures. Patients were assessed daily until discharge from the hospital. The perioperative results included the operative time, amount of blood loss, urinary catheter time and the length of postoperative hospital stay and surgery complications.

3. Follow up

Follow-ups were conducted through outpatient rechecks. The blinded follow-up was performed by visiting different doctors. Patients receive recommends to return for clinical visits every three months for the first 2 years of follow-up and subsequently every six months until 5 years. Cytology and HPV test were done annually. Disease-free survival (DFS) was defined as the time from diagnosis to disease progression or the time of the first failure (loco regional or distant), and overall survival (OS) was defined as the time from the initial diagnosis until death from any cause. When there is suspicious lesion, colposcopy and endocervical sampling was taken for biopsy.

4. Statistical analyses

The χ^2 test and independent sample *t* test for proportions were used to analyze differences in the distributions of the different variables between groups. The results are expressed as the mean \pm SD. Kaplan-Meier estimates of DFS and comparisons between the survival curves of each were performed using Log-rank tests. All analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY,

United States). All reported *P* values are two-sided, and *P*-values of 0.05 or lower were considered to be statistically significant.

Result

In terms of age, body mass index (BMI), the patients in modified hysterectomy and standard extrafascial hysterectomy group were comparable. The median age and BMI at modified hysterectomy and standard extrafascial hysterectomy group were 48.6 ± 9.3 and 51.1 ± 9.5 years, 25.3 ± 3.6 and 24.5 ± 3.5 kg/m², and no significant differences were found (*P* = 0.800 and 0.854). Residual lesions were found at nine patients and seven patients in their hysterectomy specimens at modified and standard extrafascial hysterectomy group. The data for both groups are shown in Table 1. The excised vagina length was 1.5 ± 0.31 cm.

Table 1

Clinical and pathologic characteristics at modified hysterectomy and standard extrafascial hysterectomy group

Characteristic	Modified hysterectomy group (n = 68)	Standard hysterectomy group (n = 60)	<i>P</i> value
Age, years	48.6 ± 9.3	51.1 ± 9.5	0.800
BMI (kg/m ²)	25.3 ± 3.6	24.5 ± 3.5	0.854
Hysterectomy			0.852
Abdominal	23(33.8%)	19(36.9%)	
Laparoscopic	45(66.2%)	41(63.1%)	
Cone margins			0.804
Negative	59	51	
Positive	9	9	

1. Operative time, intraoperative blood loss and complications

In the modified hysterectomy group, 45(66.2%) underwent a modified laparoscopic hysterectomy and one laparoscopic procedure converted to laparotomy due to adhesion from previous surgery. 23(33.8%) procedure was completed by laparotomy. In the standard extrafascial hysterectomy removing group, 39(65%) underwent a laparoscopic hysterectomy, in which two cases underwent conversion to abdominal

hysterectomy due to adhesion from previous surgery. 21 (35%) hysterectomy were completed by laparotomy.

The median surgical time at modified hysterectomy and standard extrafascial hysterectomy was 89.8 ± 13.9 min vs 87.1 ± 13.7 min and 93.4 ± 21.7 min vs 89.6 ± 24.3 min. Time consumption was increased at modified hysterectomy group but not significantly different was found ($P= 0.531$ and 0.447). The average bleeding volumes in the group of abdominal and laparoscopic were 102 ± 42.6 vs 98.5 ± 35.9 mL and 74.8 ± 25.9 vs 73.3 ± 23.7 mL. No significant difference was found for either measures ($P= 0.618$ and 0.848). No intraoperative bleeding occurred in either group, and none of the patients received intra-operative or post-operative blood transfusions.

The median catheter indwelling time at modified hysterectomy and standard extrafascial hysterectomy was 2.1 ± 0.34 vs 2.1 ± 0.3 ds and 1.8 ± 0.7 vs 1.7 ± 0.7 ds. No significant difference between the two groups ($P= 0.610$ and 0.509). The hospital stay time at modified hysterectomy and standard extrafascial hysterectomy was 7.0 ± 0.9 vs 7.1 ± 1.0 ds and 4.6 ± 1.6 vs 4.9 ± 1.8 ds. No significant difference was observed between patients who received a modified hysterectomy and those who did not ($P= 0.863$ and 0.539). One case of ureteral injury occurred at modified hysterectomy group and one case of delayed ueterovaginal fistula was observed at standard extrafascial hysterectomy resulting from ischemic necrosis. Overall incidence of any complication was not found to be significant (NA and $P = 0.489$). No prominent differences were significant related to operative related characteristics and incidences of complications (Table 2).

Table 2
 Characteristics of the operations and incidences of complications at modified hysterectomy and standard hysterectomy group..

	Modified hysterectomy group (n = 68)	Standard hysterectomy group (n = 60)	P value
Operating time (min)	89.8 ± 13.9	87.1 ± 13.7	0.531
Abdominal	93.4 ± 21.7	89.6 ± 24.3	0.447
Laparoscopic			
Blood loss (mL)	102.8 ± 42.6	98.5 ± 35.9	0.618
Abdominal	74.8 ± 25.9	73.3 ± 23.7	0.848
Laparoscopic			
Catheter time (day)	2.1 ± 0.34	2.1 ± 0.3	0.610
Abdominal	1.8 ± 0.7	1.7 ± 0.7	0.509
Laparoscopic			
Hospital stay (day)	7.0 ± 0.9	7.1 ± 1.0	0.863
Abdominal	4.6 ± 1.6	4.9 ± 1.8	0.539
Laparoscopic			
Operative complication			
Injury*	1(1.5%)	0(0%)	NA
Fistula**	0(0%)	1(1.7%)	0.489
* Injury including uratus, ladder and bowel			
** Fistula including vesicovaginal, ureterovaginal and rectovaginal fistula			

2. Recurrence

The mean follow-up for the patients in this study was 47.3 months (range 11–64 months), and the last follow-up was concluded in March 2019. During the postoperative follow-up, five patients at standard hysterectomy group (three patients undergone laparoscopic hysterectomy and two undergone abdominal hysterectomies) experienced vaginal recurrences, including one patient with invasive vaginal cancer, three patients with VAIN3 at vaginal stump, one case of VAIN2. The postoperative recurrence rates were 8.3%. No case of VAIN at the modified hysterectomy group observed. The correlation of recurrence and section margin, and pre- and post- high-risk HPV status was concluded in Table 3. Significant difference at

disease-free survivals was found ($P= 0.026$, log-rank test) which are reported in Fig. 1. No case of distant metastasis and disease-related death were observed at all the patients.

Table 3
HPV status at pre-treatment and posttreatment patients.

	Modified hysterectomy group (n = 68)	Standard hysterectomy group (n = 60)	P value
HPV at first visiting	64 (92.6%)	54 (90%)	NA
HPV at last visiting	3(4.4%)	4(6.2%)	0.714
Recurrent patients			NA

Discussion

Biopsy-confirmed CIN2-3 lesions are usually treated with LEEP or cold knife conization. Hysterectomy is denied for most CIN2 + patients and only is considered when repeat diagnostic excision is not feasible for treatment of recurrent or persistent biopsy-confirmed CIN2-3 or it is depicted as a definitive solution [11, 12]. Nevertheless, in many developing countries, due to the access of medical sources and following-up, many histology-confirmed CIN2 + lesions are treated with hysterectomy [10, 13]. However, the most serious late-complication brought by this is vaginal recurrence [14–16]. In Schockaert retrospective analysis of 3030 women with CIN2 + without history of VAIN in the University Hospital Gasthuisberg, Leuven, Belgium from 1989 to 2003, he found that incidence rate of subsequent VAIN2 + is as high as 7.4% and hysterectomy may not be considered as a definitive therapy for CIN2 + because the the high incidence rate of subsequent vaginal intraepithelial neoplasia [17].

To address this problem, we modified the standard extrafascial hysterectomy to improve locoregional control for CIN3 patients who choose have hysterectomy. The efficacy of replacing the method in terms of reducing postoperative vaginal intraepithelial neoplasia was assessed. Compared with the conventional uterus removing method, the most important finding in our study is that the postoperative vaginal recurrence rate was significant reduced due to the use of this modified method. The DFS was greatly extended with this modification than the previously defined simple hysterectomy group ($P= 0.026$). Significant reduction at vaginal recurrence in the modified group suggest that this modification per se is a definitive favorable and decisive factor that determine the prognosis of patients.

Despite the similarities of the patient populations and the surgical factors, this modified hysterectomy is not associated with an increase in operative complications, including blood loss, and hospital stay compared to a simple hysterectomy. Although the operative time was higher in patients undergoing modified hysterectomy, this difference did not reach statistical significance. Furthermore, this modified

procedure was well tolerated as reflected by the not prolonged bladder catheter retention and hospital stay times. The incidence of surgical complication between the group, such as fistulas, or other serious complications were not significantly increased. The extra procedure, therefore, has shown some benefit without any harmful effect.

By Piver-Rutledge-Smith or by Querleu and Morrows classification of hysterectomies [18, 19], as for the class I or type A hysterectomy, no vaginal portion is excised or as small as possible (less than 10mm). But narrow cut margins just near the vaginal portion cannot provide assurance that the disease has been completely excised as cervical intraepithelial neoplasia can be multifocal and discontinuous. The benefits observed in the group demonstrate that this technique is an effective means of reducing vaginal liaison after hysterectomy in patients who choose to remove their uterus, and treatment strategies, such as hysterectomy for histopathologically confirmed CIN3 liaison should be tailored [20, 21]. This modification might be recommended to clinical practitioners and hospitals where patients with CIN3 are treated sometimes to remove the uterus [22, 23].

Colposcopy, as indicated by other authors, directed vaginal multipoint biopsy should be conducted to exclude vaginal disease and patients of CIN should routinely undergo vaginal multipoint biopsy upper vagina [24]. Colposcopy is also essential for the evaluation of abnormal cytology/hrHPV tests after hysterectomy and the early detection of vaginal [25]. However, as vaginal cancer is an uncommon gynecologic malignancy and regular screening is not performed, this finding may not attribute to hysterectomy alone [26, 27]. Due to the low positive predictive value of vaginal cuff cytology for detection of vaginal cancer and the mean length of time from hysterectomy to abnormal cytology result may take many years, the final may not see yet. Our study is that several gynecologic oncologists working in our unit during the studied period performed hysterectomy, which likely resulted in variations in surgical practice. Specialized treatment centers should be acquired with this knowledge that ensures the value of this strategy for patients with CIN2+. Vaginal neoplasm is also associated with high-risk human papillomavirus, the persistence of HPV is a prognostic factor associated to the failure or recurrence after hysterectomy.

Declarations

Availability of data and materials

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

Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethics Review Board of the Affiliated Cancer Hospital of Zhengzhou University (IRB Number: 15CT062). The written informed consent was obtained from all subjects prior to participating in this study. All methods were also performed in accordance with the principles stated in the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

All the authors declare that they have no conflict of interest.

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Authors' contributions

Dr. Lei Li and Xiaoyan Song had conceived this work, analyzed and interpreted the data and draft this manuscript. Dr. Xiaojie Feng and Xiaofeng Li contributed to the implementation of the research and conducted followin-up for the patients. Dr. Zhenzhong Zhang did the statistical analysis work. Dr. Ruonan Liu and Dongxia Liang were responsible for the collection of parameters, interpreted the data and revised this manuscript. All the authors provided critical feedback and helped shape to the research, analysis and manuscript.

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Figures

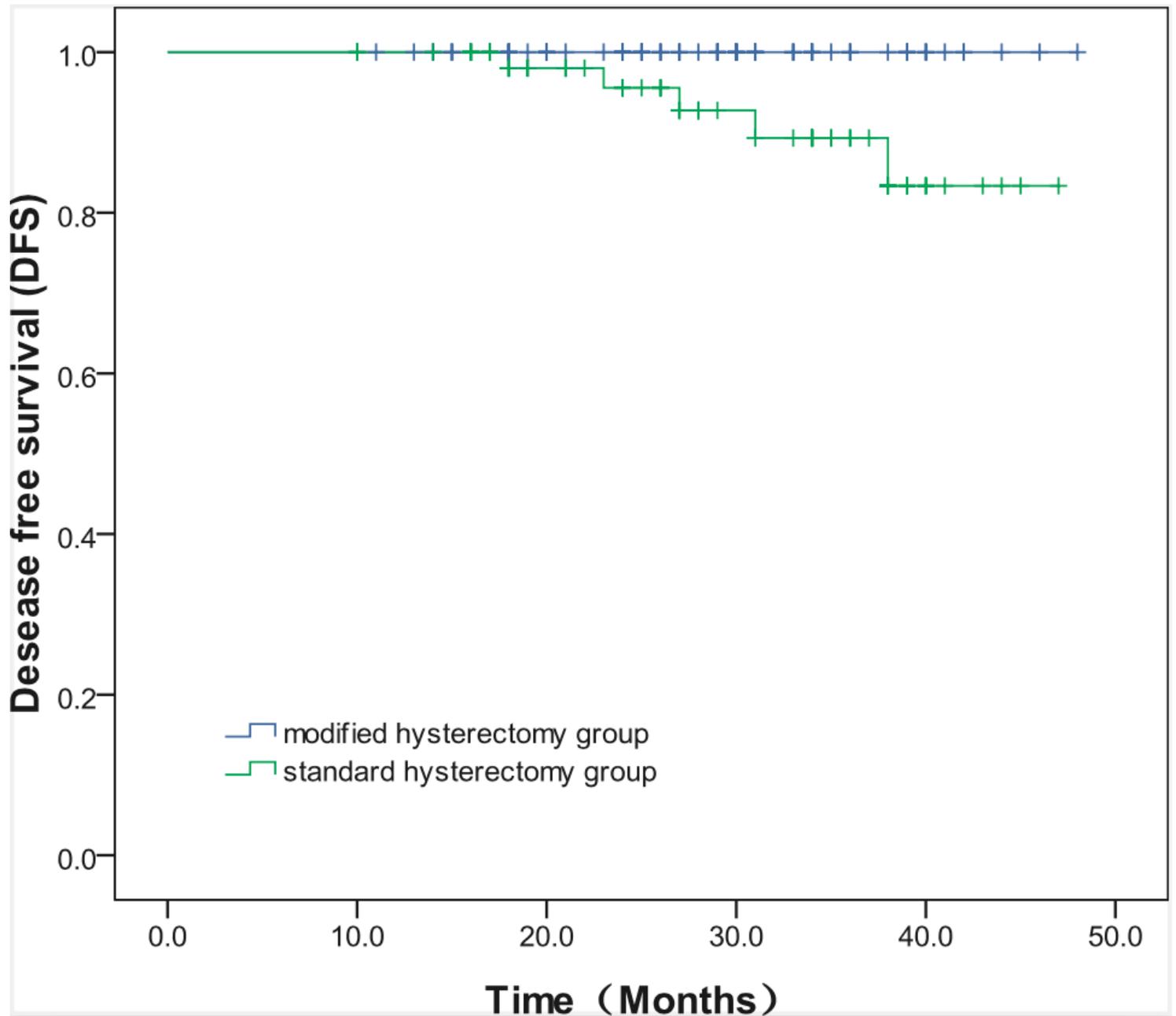


Figure 1

Kaplan-Meier survival curves for Disease free survival (DFS) at modified hysterectomy and standard extrafascial hysterectomy group and significance were found (log-rank $P=0.026$).