Int J Clin Exp Med 2020;13(12):9818-9825
www.ijcem.com /ISSN:1940-5901/IJCEM0119182

Original Article

Prognosis investigation in young patients with cervical adenocarcinoma undergoing cold knife conization and factors influencing postoperative recurrence

Jinmei Yu, Meiyan Zou, Xia Li, Zhiqiang Qiao, Yunting An

Department of Oncology, Jiangxi Maternal and Child Health Hospital, Nanchang 330006, Jiangxi Province, China

Received July 29, 2020; Accepted September 16, 2020; Epub December 15, 2020; Published December 30, 2020

Abstract: Objective: To explore the prognosis of young patients (≤ 35 years old) with cervical adenocarcinoma *in situ* (ACIS) after cold knife conization (CKC). Methods: One hundred young patients with ACIS who underwent CKC in our hospital from April 2014 to April 2017 were selected as research subjects. According to whether the patients needed supplementary treatment after CKC, they were divided into two groups: the follow-up group (without supplementary treatment, n = 60) and the surgery group (with supplementary treatment, n = 40). The clinical treatment efficacy, complications, adverse psychological moods and quality of life between the two groups were compared. The two groups of patients were followed up for 3 years, and the number of patients who died, had recurrence, or developed into invasive adenocarcinoma was recorded, and the risk factors leading to recurrence were analyzed. Results: The clinical efficacy evaluation results of the two groups were similar, and no deaths occurred during the 3-year follow-up. In addition, although the number of patients with recurrence and development of invasive adenocarcinoma in the follow-up group was higher than that in the surgery group, there was no significant difference in comparison. The follow-up group had lower SDS and SAS scores than the surgery group, while having a higher quality of life score than the surgery group. The incidence of postoperative complications in the follow-up group was lower than that in the surgery group. Conclusion: There is no need to supplement hysterectomy for young ACIS patients with negative margin after CKC.

Keywords: Cervical adenocarcinoma *in situ*, cold knife conization, hysterectomy

Introduction

Cervical cancer is the fourth most common malignant tumor among women, with an estimated 570,000 new cases in 2018 [1]. Cervical adenocarcinoma *in situ* (ACIS) refers to adenocarcinoma which is confined to the epithelial layer of the cervical endometrium where the crypt does not penetrate the basement membrane nor invade deeply; it is a precancerous lesion of cervical invasive carcinoma [2, 3]. In recent years, due to the infection of human papillomavirus (HPV) and the increase of oral contraceptives, the incidence of ACIS has clearly increased and the affected individuals tend to be younger [4]. ACIS is multifocal and "jumping lesion". The lesion location is not easy to find and may be high in the cervical canal. It is difficult to find through cervical cytology, cervical biopsy under colposcope and scratching of the cervical canal, but it is often found in pathology or follow-up after conization due to atypical hyperplasia of the cervical squamous epithelium. Therefore, ACIS should be treated with caution [5, 6].

At present, hysterectomy is the standard treatment for ACIS [7]. However, since the uterus is an important reproductive organ of women, patients are not only under great psychological pressure after hysterectomy, but also lose their fertility, leading to the occurrence of negative emotions, which will adversely affect the postoperative recovery and quality of life of patients [8, 9]. As ACIS patients tend to be younger, more and more patients have fertility requirements; conservative treatment is the preferred method for these patients [10]. Loop electrosurgical excision procedure (LEEP) and cold knife conization (CKC) are two most commonly

used conservative treatments at present. Since CKC can provide conical specimens with relatively great depth and large volume, it is more commonly used than LEEP [11]. Although conservative treatment can preserve the uterine and reproductive functions of patients, ACIS is often multifocal, and the focus at the highest position may be neglected, or any residual focus in deep tissue cracks may be left at the apex of conization, which may lead to recurrence and a risk of deterioration [12]. Therefore, many patients still undergo hysterectomy after conservative treatment such as LEEP and CKC. It has been reported that patients with negative margin after conization can be treated by conization alone [13]. Other studies have shown that cervical conization and hysterectomy have the same effect on ACIS patients. Therefore, they concluded that conservative treatment with strict follow-up is a reasonable treatment choice for all ACIS patients, not only those who want to preserve fertility [14]. This suggests that patients with ACIS who have negative pathological results after CKC may not need supplemental hysterectomy therapy, but more data from clinical studies is still needed.

In this study, ACIS patients with negative pathological results after CKC were recruited. By comparing the prognostic outcomes of these patients without total hysterectomy with those with total hysterectomy, the need for total hysterectomy was explored, so as to find the best treatment method that is both effective in treating the disease and preserving the physiological and psychological functions of the young patients.

Data and methods

Research subjects

A total of 100 young patients with ACIS who underwent CKC in Jiangxi Maternal and Child Health Hospital from April 2014 to April 2017 were selected as research subjects. According to whether the patients needed supplementary treatment after CKC, they were divided into two groups: the follow-up group (without supplementary treatment, n = 60) and the surgery group (with supplementary treatment, n = 40). Inclusion criteria: All patients were confirmed with ACIS by preoperative biopsies, aged between 18 to 35 years, underwent CKC successfully, with negative excised specimens, and had good follow-up conditions. Exclusion criteria: Patients had incomplete clinical data, heart, liver, kidney or other important organ dysfunction, mental disorder or difficulty in communicating, or complicated with various tumors. All patients signed the informed consent, and this study was approved by the Ethics Committee of our hospital.

Therapeutic method

After admission, both groups were treated with CKC. The treatment operation was performed by doctors with more than 5 years of surgical experience in our hospital. The operation was as follows: adrenaline saline (0.2:100) was injected in the direction of 3 o'clock and 9 o'clock in the cervix, the suture was marked in the direction of 12 o'clock, and then a circular incision was made 5 mm outside the iodine-free area of the cervical canal with a sharp knife, which was taken as the bottom of the vertebral body. The lesion was cut conically towards the cervical canal with a cone height of 20-25 mm and width of 20-25 mm, and the range was adjusted according to the pathological changes and the specific conditions of patients. Then, the wound was sutured with absorbable thread No. 1 for hemostasis, and the wound was compressed with iodophor gauze. After 24 hours, it was taken out, and the resected specimen was submitted for examination as a whole. After successful completion of CKC in the surgery group, supplementary treatment (total hysterectomy) was performed 3 weeks later. The two groups of patients were followed up for 3 years after surgery, and the number of patients who died, had recurrence, or developed into invasive adenocarcinoma was recorded.

Outcome measures

Six months after CKC operation, the clinical curative effect was evaluated. Markedly effective: the cervix was smooth, and no lesions were found by cervical TCT and colposcopy. Effective: the degree of cervical erosion was reduced, and the scope of lesions was reduced. Ineffective: the lesion scope has not decreased or expanded. The number of cases of death, recurrence, and progression to invasive adenocarcinoma were recorded 3 years after surgery in both groups. The postoperative complica-

Table 1. Comparison of general data of patients in the two groups [n (%)] (x ± sd)

Group	Surgery group (n = 40)	Follow-up group (n = 60)	χ^2/t	P
Cultural level			0.246	0.620
≥ high school	18 (45.00)	24 (40.00)		
< high school	22 (55.00)	36 (60.00)		
Affected glands			0.304	0.581
With	12 (30.00)	15 (25.00)		
Without	28 (70.00)	45 (75.00)		
Presence or absence of children			0.097	0.755
Present	7 (17.50)	12 (20.00)		
Absent	33 (82.50)	48 (80.00)		
Preoperative HPV			0.035	0.852
Positive	10 (25.00)	16 (26.67)		
Negative	30 (75.00)	44 (73.33)		
Marital status			0.280	0.870
Unmarried	12 (30.00)	21 (35.00)		
Married	22 (55.00)	31 (51.67)		
Divorced	6 (15.00)	8 (13.33)		
Smoking history			0.554	0.457
With	15 (37.50)	27 (45.00)		
Without	25 (62.50)	33 (55.00)		
Number of conception			0.240	0.624
≤ 2	18 (45.00)	30 (50.00)		
> 2	22 (55.00)	30 (50.00)		
Menopause			0.043	0.835
Present	8 (20.00)	11 (18.33)		
Absent	32 (80.00)	49 (81.67)		
Age (years)			0.109	0.742
< 30	22 (55.00)	35 (58.33)		
≥ 30	18 (45.00)	25 (41.67)		
BMI (kg/m^2)	22.54±2.75	22.89±3.18	1.041	0.301

tions of the two groups were recorded, including postoperative bleeding, cervical adhesion, cervical stenosis, postoperative infection and urinary system diseases (incontinence/frequent micturition/dysuria). Six months after surgery, the anxiety and depression of patients were evaluated by self-rating anxiety scale (SAS) [15] and self-rating depression scale (SDS) [16]. The total score was 100 points, and a higher score indicated more serious anxiety. Six months after surgery, QLQ [17] was used to evaluate patients' quality of life, including 6 items: general health (GH), role physical (RP), physical function (PF), social function (SF), role emotional (RE) and mental health (MH). Each item was 100 points, and the higher the score, the better the quality of life.

Statistical analysis

SPSS 21.0 was used for statistical analysis of the data collected in this study, and GraphPad 7 software package was used to draw the required images. Chi-square test or Fisher's precise test was applied to compare the counting data. Independent sample t test was applied to compare the measurement data between the two groups. Multivariate Logistic regression was utilized to analyze the risk factors of recurrence. With $P < 0.05$, there was a statistical difference.

Results

Comparison of general data

There were statistically significant differences between the two groups in general data and pathological data such as cultural level, affected glands, presence or absence of children, preoperative HPV, marital status, smoking history, number of conception, menopause, age and BMI ($P > 0.05$). As shown in **Table 1**.

Comparison of clinical efficacy

Evaluation of clinical efficacy of the two groups indicated that there were no ineffective cases in the surgery group and 5 cases (8.33%) in the follow-up group, but there was no significant difference in the total effective rate between the two groups ($P > 0.05$). As shown in **Table 2**.

Comparison of patient prognosis

During the 3-year follow-up; in the follow-up group it was found that no patients died, 12 patients (20.00%) had recurrence, and 1

Table 2. Comparison of clinical efficacy

Group	Markedly effective	Effective	Ineffective	Total effective rate
Surgery group (n = 40)	32 (80.00)	8 (20.00)	0 (0.00)	40 (100.00)
Follow-up group (n = 60)	45 (75.00)	10 (16.67)	5 (8.33)	55 (91.67)
χ^2	-	-	-	2.074
p	-	-	-	0.061

Table 3. Comparison of prognosis results of patients [n (%)]

Group	Death	Recurrence	Invasive adenocarcinoma
Surgery group (n = 40)	0 (0.00)	4 (10.00)	0 (0.00)
Follow-up group (n = 60)	0 (0.00)	12 (20.00)	1 (1.67)
χ^2	-	1.786	0.673
p	-	0.181	0.412

patient's condition (1.67%) developed into invasive adenocarcinoma. In the surgery group, there was no case of death nor progression to invasive adenocarcinoma, but 4 cases (10.00%) had recurrence. There was no remarkable difference between the two groups in recurrence and development into invasive adenocarcinoma (P > 0.05). As shown in **Table 3**.

Comparison of incidence of complications

By recording the complications of the two groups, it was found that the complications such as postoperative bleeding, cervical adhesion, cervical stenosis and postoperative infection were similar in the two groups (P > 0.05). However, the incidence of urinary system diseases (incontinence/frequent micturition/dysuria) and the total number of affected people in the surgery group were evidently higher than those in the follow-up group (P < 0.05). As shown in **Table 4**.

Comparison of SDS and SAS scores

The evaluation of patients' negative emotions showed that the scores of SDS and SAS in the follow-up group were lower than those in the surgery group (P < 0.05). As shown in **Figure 1**.

Comparison of quality of life

Quality of life improvement was assessed in both groups, and the results showed that the scores of GH, RP, PF, SF, RE and MH in QLQ in the follow-up group were higher than those in surgery group (P < 0.05). As shown in **Figure 2**.

Analysis of related factors affecting patients' recurrence

Patients with recurrence within 3 years after surgery were enrolled in recurrent group (n = 16), and patients without recurrence were enrolled in non-recurrent group (n = 84). Univariate analysis of general data and pathological data showed that patients with affected glands, HPV positive before surgery, smoking history and extent of lesion ≥ 2 quadrants had higher recurrence rates (P < 0.05). As shown in **Table 5**.

Multivariate analysis of recurrence of patients

The factors with statistical significance in Result 2.7 were taken as independent variables and the recurrence of patients as dependent variables to conduct multivariate Logistic regression analysis. The results showed that affected glands, preoperative HPV positive and extent of lesion ≥ 2 quadrants were all risk factors for the recurrence of ACIS patients, while smoking history was not the risk factor for the recurrence of ACIS patients. As shown in **Table 6**.

Discussion

According to this study, for patients with negative margin after CKC, supplementary hysterectomy had no remarkable effects on improvement of patient prognosis, but the psychological mood and quality of life of patients undergoing CKC alone were better than those with supplementary hysterectomy. Affected glands, preoperative HPV positivity, smoking history and extent of lesion ≥ 2 quadrants were all risk factors leading to recurrence of ACIS patients.

ACIS is a precancerous lesion of invasive cervical cancer, which poses a great threat to the life and health of women all over the world [18]. Fortunately, there are a variety of methods to treat ACIS, and they have a good therapeutic effect. However, the clinical treatment of ACIS

Table 4. Comparison of incidence of complications [n (%)]

Group	Surgery group (n = 40)	Follow-up group (n = 60)	χ^2	p
Postoperative bleeding	4 (10.00)	2 (3.33)	1.891	0.169
Cervical adhesion	0 (0.00)	1 (1.67)	0.673	0.412
Cervical stenosis	0 (0.00)	1 (1.67)	0.673	0.412
Postoperative infection	3 (7.50)	3 (5.00)	0.266	0.606
Incontinence/frequent micturition/dysuria	4 (10.00)	0 (0.00)	6.250	0.012
Total number of people affected	11 (27.50)	7 (11.67)	4.078	0.044

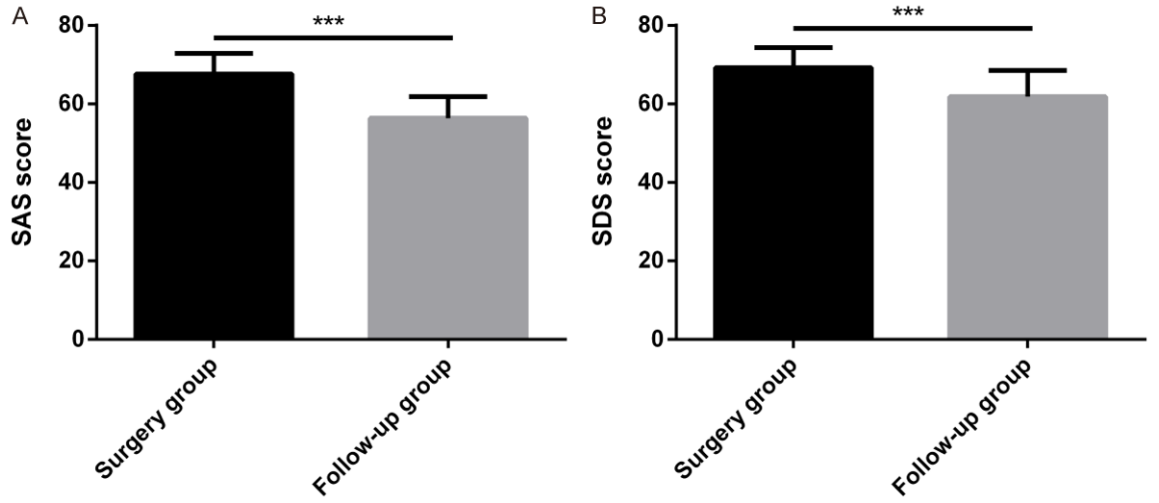

Figure 1. Comparison of SDS and SAS scores. A. Comparison of SDS score between the two groups. B. Comparison of SAS score between the two groups. Note: *** denotes P < 0.001.

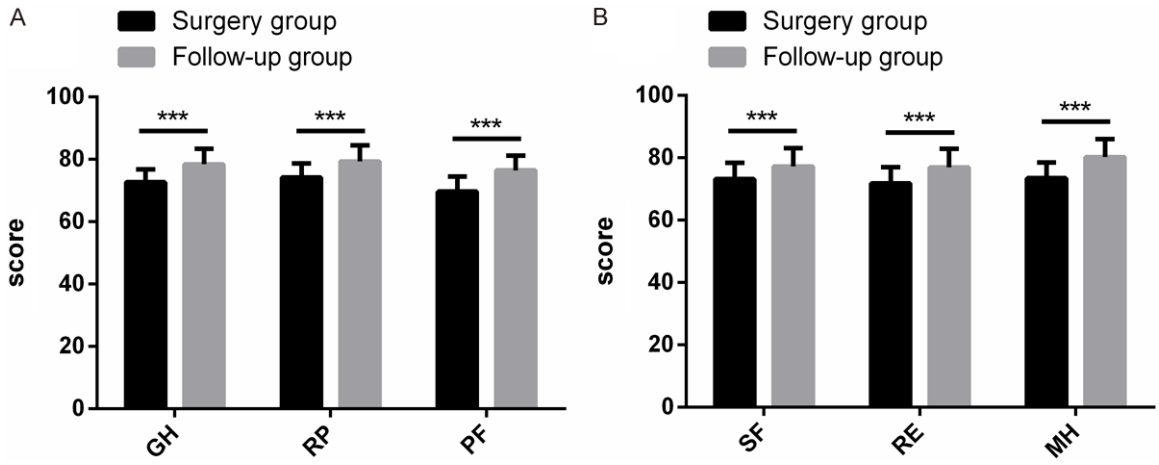

Figure 2. Comparison of quality of life score. A. Comparison of GH, RP, and PF scores between the two groups. B. Comparison of SF, RE, and MH scores between the two groups. Note: *** denotes P < 0.001.

is controversial, and it is difficult for patients to choose between hysterectomy and conservative treatment [19]. The former will cause patients to lose their uterus, while the latter is considered to have a higher risk of recurrence/residual. Recent studies have concluded that conservative treatment with strict follow-up is a reasonable treatment option for all patients with ACIS, not only those who want to preserve their fertility [14, 20]. There is also a point of

Table 5. Analysis of related factors affecting recurrence of patients [n (%)]

Group	Recurrent group (n = 16)	Non-recurrent group (n = 84)	χ^2/t	p
Affected glands			12.179	< 0.001
With	10 (62.50)	17 (20.24)		
Without	6 (37.50)	67 (79.76)		
Preoperative HPV			9.059	0.003
Positive	9 (56.25)	17 (20.24)		
Negative	7 (43.75)	67 (79.76)		
Smoking history			5.595	0.018
With	11 (68.75)	31 (36.90)		
Without	5 (31.25)	53 (63.10)		
Number of conception			1.605	0.205
≤ 2	10 (62.50)	38 (45.24)		
> 2	6 (37.50)	46 (54.76)		
Menopause			0.446	0.505
Present	1 (25.00)	15 (17.86)		
Absent	12 (75.00)	69 (82.14)		
Extent of lesion			6.895	0.009
≥ 2 quadrants	10 (62.50)	24 (28.57)		
1 quadrant	6 (37.50)	60 (71.43)		
Age (years)			1.364	0.243
< 30	7 (43.75)	50 (59.52)		
≥ 30	9 (56.25)	34 (40.48)		

Table 6. Multivariate analysis of recurrence of patients

Variable	β	S.E	Wals	P	OR	95% CI
Affected glands	0.832	0.351	4.748	0.011	1.768	1.026-0.514
Smoking history	1.305	0.589	2.061	0.084	1.018	0.879-2.205
HPV positive before operation	1.046	0.494	7.135	0.002	2.008	1.033-3.942
Extent of lesion ≥ 2 quadrants	0.443	0.627	7.125	0.003	2.746	1.874-4.468

view that patients with negative margin after conization can be treated by conization alone [13], suggesting that there is no need for subsequent supplementary hysterectomy. This study mainly compared the prognosis of patients with negative margin after CKC without supplementary hysterectomy and supplementary hysterectomy. The results showed that the clinical treatment efficacy evaluation results of the two groups were similar, and no death occurred in either of the two groups during the 3-year follow-up. In addition, although the number of patients with recurrence and development of invasive adenocarcinoma in the follow-up group was higher than that in the surgery group, there was no remarkable difference in comparison. The above results indicated that for ACIS patients with negative margin of CKC, supplementary hysterectomy did not significantly improve the prognosis. Because of the disease itself or related treatment, ACIS patients will have some negative emotions and decline in quality of life. This situation is particularly obvious in patients who have undergone hysterectomy because they have lost their uterus [21]. In evaluating the psychological emotions and quality of life of patients in the two groups, the scores of SDS and SAS in the follow-up group were lower than those in the surgery group, while scores of quality of life were higher than those in the surgery group. As an important organ in women, losing the uterus will lead to various complications. By comparing the postoperative complications between the two groups, it was found that the incidence of postoperative complications in the follow-

up group was better than that in the surgery group. The above results suggested that for ACIS patients with negative margin after CKC, hysterectomy does not improve the prognosis of patients, plus it also has a negative impact on thepsychological mood and quality of life.

Since ACIS has the characteristics of jumping multifocal distribution, there is a high risk of residual lesions [22]. Therefore, it is necessary to identify the risk factors that may lead to the recurrence of ACIS patients, so that intervention measures can be made in advance. In this study, the clinicopathological data of 100 ACIS patients was analyzed by univariate analysis. It was found that affected glands, preoperative HPV positivity, smoking history and lesion extent ≥ 2 quadrants are important factors leading to recurrence. Subsequently, through Logistic regression model analysis, we found that affected glands, preoperative HPV positive and lesion extent ≥ 2 quadrants were all risk factors for recurrence of ACIS patients. For patients with these high-risk recurrence factors, adequate attention should be paid, targeted preventive measures should be taken, and such patients should be regularly reexamined, so as to reduce the recurrence rate.

There are certain shortcomings in this study, for example: this study only had a follow-up period of 3 years, so we failed to know the longer prognosis of the patients. Secondly, we did not analyze the treatment costs of the two groups from an economic point of view. In addition, the subjects in this study were all from the same region, so our results may not be applicable to women in other regions. These shortcomings are expected to be further discussed in the follow-up study.

To sum up, there is no need to supplement hysterectomy for ACIS patients with negative margin after CKC.

Disclosure of conflict of interest

None.

Address correspondence to: Yunting An, Department of Oncology, Jiangxi Maternal and Child Health Hospital, No. 318 Bayi Avenue, East Lake Distric, Nanchang 330006, Jiangxi Province, China. Tel: +86-0791-86310931; E-mail: anyunting19@163.com

References

[1] Sakuragi N, Murakami G, Konno Y, Kaneuchi M and Watari H. Nerve-sparing radical hysterectomy in the precision surgery for cervical cancer. J Gynecol Oncol 2020; 31: e49.

[2] Cohen PA, Brand A, Sykes P, Wrede DCH, McNally O, Eva L, Rao A, Campion M, Stockler M, Powell A, Codde J, Bulsara MK, Anderson L, Leung Y, Farrell L and Stoyles P. Excisional treatment in women with cervical adenocarcinoma in situ (AIS): a prospective randomised controlled non-inferiority trial to compare AIS persistence/recurrence after loop electrosurgical excision procedure with cold knife cone biopsy: protocol for a pilot study. BMJ Open 2017; 7: e017576.

[3] Cuello MA, Espinosa ME, Orlandini EJ and Hwang DY. The value of endocervical curettage during loop electrosurgical excision procedures in predicting persistent/recurrent preinvasive cervical disease. Int J Gynaecol Obstet 2018; 141: 337-343.

[4] Bai H, Liu J, Wang Q, Feng Y, Lou T, Wang S, Wang Y, Jin M and Zhang Z. Oncological and reproductive outcomes of adenocarcinoma in situ of the cervix managed with the loop electrosurgical excision procedure. BMC Cancer 2018; 18: 461.

[5] Salani R, Puri I and Bristow RE. Adenocarcinoma in situ of the uterine cervix: a metaanalysis of 1278 patients evaluating the predictive value of conization margin status. Am J Obstet Gynecol 2009; 200: 182, e1-5.

[6] Krivak TC, Retherford B, Voskuil S, Rose GS and Alagoz T. Recurrent invasive adenocarcinoma after hysterectomy for cervical adenocarcinoma in situ. Gynecol Oncol 2000; 77: 334-335.

[7] Munro A, Codde J, Spilsbury K, Stewart CJ, Steel N, Leung Y, Tan J, Salfinger SG, Mohan GR, Semmens JB and Cohen PA. Risk of persistent or recurrent neoplasia in conservatively treated women with cervical adenocarcinoma in situ with negative histological margins. Acta Obstet Gynecol Scand 2017; 96: 432-437.

[8] Saffarieh E, Ahmadi R, Pazoki R, Yousefnezhd A and Yousefi-Sharami R. The study of life expectancy in hysterectomized women in Semnan Amir Al Momenin Hospital in 2017. J Family Med Prim Care 2020; 9: 826-829.

[9] Bahri N, Tohidinik HR, Fathi Najafi T, Larki M, Amini T and Askari Sartavosi Z. Depression following hysterectomy and the influencing factors. Iran Red Crescent Med J 2016; 18: e30493.

[10] Ciavattini A, Giannella L, Delli Carpini G, Tsiroglou D, Sopracordevole F, Chiossi G and Di Giuseppe J; Italian Society of Colposcopy and

Cervico-Vaginal Pathology (SICPCV). Adenocarcinoma in situ of the uterine cervix: clinical practice guidelines from the Italian society of colposcopy and cervical pathology (SICPCV). Eur J Obstet Gynecol Reprod Biol 2019; 240: 273-277.

[11] Hanrahan AJ, Schultz N, Westfal ML, Sakr RA, Giri DD, Scarperi S, Janakiraman M, Olvera N, Stevens EV, She QB, Aghajanian C, King TA, Stanchina E, Spriggs DR, Heguy A, Taylor BS, Sander C, Rosen N, Levine DA and Solit DB. Genomic complexity and AKT dependence in serous ovarian cancer. Cancer Discov 2012; 2: 56-67.

[12] Krivak TC, Rose GS, McBroom JW, Carlson JW, Winter WE 3rd and Kost ER. Cervical adenocarcinoma in situ: a systematic review of therapeutic options and predictors of persistent or recurrent disease. Obstet Gynecol Surv 2001; 56: 567-575.

[13] Shin CH, Schorge JO, Lee KR and Sheets EE. Conservative management of adenocarcinoma in situ of the cervix. Gynecol Oncol 2000; 79: 6-10.

[14] Baalbergen A, Molijn AC, Quint WG, Smedts F and Helmerhorst TJ. Conservative treatment seems the best choice in adenocarcinoma in situ of the cervix uteri. J Low Genit Tract Dis 2015; 19: 239-243.

[15] Dunstan DA, Scott N and Todd AK. Screening for anxiety and depression: reassessing the utility of the Zung scales. BMC Psychiatry 2017; 17: 329.

[16] Liu N, Liu S, Yu N, Peng Y, Wen Y, Tang J and Kong L. Correlations among psychological resilience, self-efficacy, and negative emotion in acute myocardial infarction patients after percutaneous coronary intervention. Front Psychiatry 2018; 9: 1.

[17] Arcopinto M, Salzano A, Giallauria F, Bossone E, Isgaard J, Marra AM, Bobbio E, Vriz O, Aberg DN, Masarone D, De Paulis A, Saldamarco L, Vigorito C, Formisano P, Niola M, Perticone F, Bonaduce D, Sacca L, Colao A and Cittadini A; T.O.S.CA. (Trattamento Ormonale Scompenso CArdiaco) Investigators. Growth hormone deficiency is associated with worse cardiac function, physical performance, and outcome in chronic heart failure: insights from the T.O.S.CA. GHD Study. PLoS One 2017; 12: e0170058.

[18] van der Horst J, Siebers AG, Bulten J, Massuger LF and de Kok IM. Increasing incidence of invasive and in situ cervical adenocarcinoma in the Netherlands during 2004-2013. Cancer Med 2017; 6: 416-423.

[19] Kim ML, Hahn HS, Lim KT, Lee KH, Kim HS, Hong SR and Kim TJ. The safety of conization in the management of adenocarcinoma in situ of the uterine cervix. J Gynecol Oncol 2011; 22: 25-31.

[20] Codde E, Munro A, Stewart C, Spilsbury K, Bowen S, Codde J, Steel N, Leung Y, Tan J, Salfinger SG, Mohan GR and Cohen PA. Risk of persistent or recurrent cervical neoplasia in patients with 'pure' adenocarcinoma-in-situ (AIS) or mixed AIS and high-grade cervical squamous neoplasia (cervical intra-epithelial neoplasia grades 2 and 3 (CIN 2/3)): a population-based study. BJOG 2018; 125: 74-79.

[21] Harnod T, Chen W, Wang JH, Lin SZ and Ding DC. Hysterectomies are associated with an increased risk of depression: a population-based cohort study. J Clin Med 2018; 7: 366.

[22] Munro A, Codde J, Spilsbury K, Steel N, Stewart CJ, Salfinger SG, Tan J, Mohan GR, Leung Y, Semmens JB, O'Leary P, Williams V and Cohen PA. Risk of persistent and recurrent cervical neoplasia following incidentally detected adenocarcinoma in situ. Am J Obstet Gynecol 2017; 216: 272.e1-272.e2.