



# Effect of tibolone on the survival of early stage cervical adenocarcinoma patients

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## Objective

Gynecologic oncologists are uncertain about the safety of tibolone application in cervical adenocarcinoma (AC) patients. This study examined the possible adverse effects of tibolone on the survival of cervical AC patients.

## Methods

Medical records of 70 cervical AC patients with International Federation of Gynecology and Obstetrics stages IA to IB were reviewed. A bilateral salpingo-oophorectomy was performed in all patients, and survival outcomes between tibolone users (n=38) and non-users (n=32) were compared.

## Results

A comparison of the tibolone users with non-users revealed similar clinicopathological variables. Progression-free survival ( $P=0.34$ ) and overall survival ( $P=0.22$ ) were similar in the users and non-users. The risks of progression (hazard ratio [HR], 1.71; 95% confidence interval [CI], 0.46–6.37;  $P=0.43$ ) and death (HR, 1.59; 95% CI, 0.06–45.66;  $P=0.79$ ) were also similar in both groups.

## Conclusion

Tibolone has no adverse effect on the survival of cervical AC patients and can be administered safely to this population. These findings may be helpful in improving the quality of life of cervical AC patients.

**Keywords:** Uterine cervical neoplasm; Adenocarcinoma; Tibolone; Prognosis; Survival

## Introduction

Cervical cancer is the fourth most common cancer and the fourth leading cause of cancer death in females worldwide 2012 [1]. In Korea, cervical cancer is the seventh most common female malignancy, with more than 3,000 women diagnosed annually, accounting for 3.3% of new female cancer cases [2]. Squamous cell carcinoma (SCC) is the most common histologic type; however, the prevalence of adenocarcinoma (AC) has increased over the last several decades, accounting for approximately 25% of cases [3].

The treatment of cervical AC is similar to that of SCC. Cervical cancer patients can enter menopause either through a bilateral salpingo-oophorectomy (BSO) or concurrent chemoradiotherapy (CCRT). Menopause can cause estrogenic deficiency symptoms and affect the quality of life. Postmenopausal hormone therapy (HT) is the most effective treatment

for vasomotor symptoms and reduces the risk of osteoporosis [4,5].

The risk of lymph node metastasis (LNM) is higher and prognosis is poorer in cervical AC than in SCC [6]. Therefore, the

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likelihood of CCRT and menopause is higher in cervical AC patients than in SCC patients. On the other hand, many gynecologic oncologists are uncertain about the safety of HT in cervical AC patients.

Tibolone is a synthetic steroid with estrogenic, androgenic, and progestogenic properties; it has been used as an alternative to estrogen therapy. To the best of the authors' knowledge, there has been no study on the effects of tibolone on the survival of cervical AC patients. Therefore, in this study, the authors retrospectively analyzed the data of cervical AC patients who were or were not treated with tibolone, to determine if tibolone had an adverse effect on the survival of cervical AC patients.

## Materials and methods

### 1. Case selection

This retrospective study group comprised cervical AC patients with International Federation of Gynecology and Obstetrics (FIGO) stage IA to IB treated with a radical hysterectomy, BSO, and retroperitoneal lymph node dissection at Gil Medical Center (GMC) in Incheon, South Korea, between January 2002 and December 2015. Patients with squamous, adenosquamous, or other histologies except for AC were excluded.

Using electronic patient records, data for the following parameters were collected: age, FIGO stage, histology, parametrial spread (PM), LNM, resection margin (RM), lymphovascular space invasion (LVSI), depth of invasion (DOI), tumor size, adjuvant treatment regimens, HT prescription, time to progression, and date of death or last record notation. The 2009 FIGO staging system was implemented.

During the study period, 104 patients with histologically confirmed cervical AC presented at GMC. The patients were excluded if they had incomplete data, did not undergo BSO, had received HT other than tibolone, or were over 70 years of age. Thirty-eight patients who received tibolone were identified from the records (defined as users). To compare the rate and pattern of recurrence, the data of 32 patients who had not received hormonal therapy (defined as non-users) were analyzed. The cases and controls were not matched.

Adjuvant therapy was administered according to the surgeons' preferences. Adjuvant chemotherapy, which consisted of either single platinum or platinum-based combination therapy, began within 4 weeks after radical surgery. Adjuvant

radiation or CCRT with weekly cisplatin (50 mg/m<sup>2</sup>) was administered to patients by using the four-field box technique with a 10 MeV Lineac for a total dose of 45–50 Gy. Adjuvant radiation or CCRT was started within 4 to 6 weeks after radical surgery. After treatment completion, all patients were examined every 3 months for the first 2 years and every 6 months thereafter. A physical examination was performed and vaginal cytology was evaluated at every visit. Computed tomography was performed every 6 to 12 months or when clinically indicated.

### 2. Statistical analysis

The association between the prognostic factors, including tibolone, and the survival outcome was determined using the Kaplan-Meier method with the log-rank test and multivariate Cox proportional hazard analysis with the hazard ratio (HR) and 95% confidence interval (CI). The Pearson's  $\chi^2$  test or Fisher's exact test was used to compare the characteristics. Statistical analyses were performed using IBM SPSS software ver. 21.0 (SPSS, Inc., an IBM Company, Chicago, IL, USA). The null hypothesis of no difference was rejected for *P*-values less than 0.05 or equivalent, if the 95% CIs of the risk point estimates were excluded.

### 3. Ethics

Approval was obtained in advance from the Institutional Review Board of GMC, Korea (No. GBIRB 2017-105) and informed consent requirement was waived because the current study was conducted as a retrospective review.

## Results

The clinicopathological variables examined, including age, FIGO stage, PM, LNM, RM, LVSI, DOI, tumor size, and regimens of adjuvant therapy, were similar in the users and non-users (Table 1).

The median length to date of the last record notation was 60 months (range: 12–60 months) in the users and 53 months (range: 12–60 months) in the non-users. Progression-free survival (PFS) was similar in the users and non-users (*P*=0.34) (Fig. 1). The univariate analysis revealed that among the clinicopathologic factors, the FIGO stage, PM, LNM, LVSI, DOI, and tumor size were significantly associated with the PFS, whereas tibolone use, age, and RM were not. Multivari-

**Table 1.** Comparison of clinicopathological factors based on postmenopausal hormone therapy use

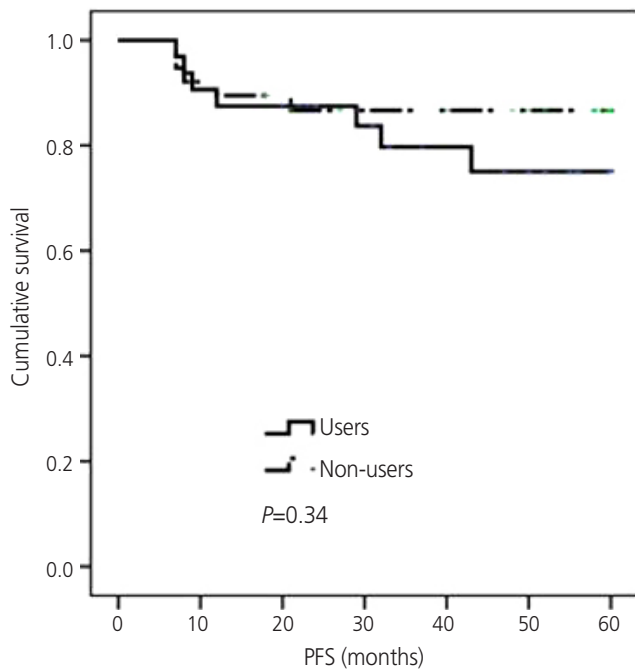
Variables	Users (n=38)	Non-users (n=32)	P-value
Age			0.28
≤50	25 (65.8)	9 (28.1)	
>50	13 (34.2)	23 (71.9)	
FIGO Stage			0.77
IA1	5 (13.2)	2 (6.3)	
IA2	0 (0)	0 (0)	
IB1	27 (71.1)	25 (78.1)	
IB2	4 (10.5)	5 (15.6)	
IIA	2 (5.3)	0 (0)	
PM			0.06
Negative	34 (89.5)	26 (81.3)	
Positive	4 (10.5)	6 (18.7)	
LNM			0.11
Negative	34 (89.5)	24 (75.0)	
Positive	4 (10.5)	8 (25.0)	
RM			0.21
Negative	34 (89.5)	30 (93.8)	
Positive	4 (10.5)	2 (6.2)	
LVSI			0.06
Negative	29 (76.3)	21 (65.6)	
Positive	9 (23.7)	11 (34.4)	
DOI			0.74
≤One half	23 (60.5)	12 (37.5)	
>One half	15 (39.5)	20 (62.5)	
Tumor size (cm)			0.13
≤4	23 (60.5)	24 (75.0)	
>4	15 (39.5)	8 (25.0)	
Adjuvant therapy			0.37
None	20 (52.6)	18 (56.3)	
RT only	2 (5.3)	0 (0)	
Chemotherapy only	14 (36.8)	5 (15.6)	
CCRT	2 (5.3)	9 (28.1)	

Values are presented as number (%).

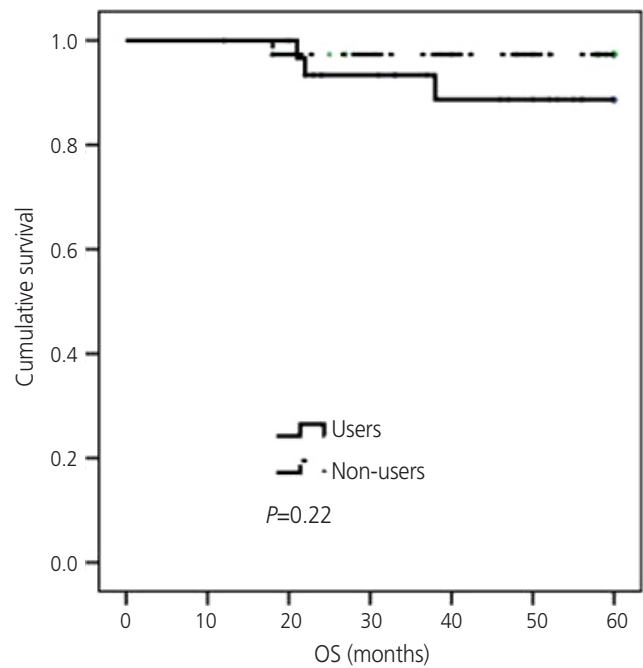
FIGO, International Federation of Gynecology and Obstetrics; PM, parametrial spread; LNM, lymph node metastasis; RM, resection margin; LVSI, lymph-vascular space invasion; DOI, depth of invasion; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

ate analysis showed that the risk of progression in users was similar to that in non-users (HR, 1.71; 95% CI, 0.46–6.37;  $P=0.43$ ). On the other hand, PM (HR, 3.83; 95% CI, 1.04–14.10;  $P=0.04$ ) and LNM (HR, 12.49; 95% CI, 3.02–51.56;  $P<0.01$ ) were significant prognostic factors (Table 2).

The overall survival (OS) did not appear to be affected by tibolone use ( $P=0.22$ ) (Fig. 2). The univariate analysis showed that PM, LNM, RM, LVSI, DOI, and tumor size were significantly associated with the OS, whereas tibolone use, age, and FIGO stage were not. The Cox proportional hazards



**Fig. 1.** Progression-free survival associated with tibolone use. PFS, progression-free survival.



**Fig. 2.** Overall survival associated with tibolone use. OS, overall survival.

**Table 2.** Prognostic factors for progression-free survival

Prognostic factors	HR	95% CI	P-value
Univariate analysis for prognostic factors for PFS			
Tibolone use	0.59	0.19–1.76	0.34
Age	1.67	0.34–8.10	0.26
FIGO stage	0.06	0.01–0.51	0.02
PM	10.0	3.02–33.14	<0.01
LNM	13.0	4.2–40.23	<0.01
RM	1.03	0.01–3.73	0.14
LVSI	4.40	1.62–11.94	<0.01
DOI	4.89	1.64–14.60	<0.01
Tumor size	1.67	1.25–1.80	0.02
Cox proportional hazards analysis including significant high-risk factors from univariate analysis and tibolone			
Tibolone use	1.71	0.46–6.37	0.43
PM	3.83	1.04–14.10	0.04
LNM	12.49	3.02–51.56	<0.01

HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; FIGO, International Federation of Gynecology and Obstetrics; PM, parametrial spread; LNM, lymph node metastasis; RM, resection margin; LVSI, lymph-vascular space invasion; DOI, depth of invasion.

model showed that there were no significant prognostic factors for OS. The risk of death in the users was not significantly higher than that in the non-users (HR, 1.59; 95% CI, 0.06–45.66;  $P=0.79$ ) (Table 3).

## Discussion

For survivors of cervical cancer, quality of life is important with menopause being a major component. Estrogen and progesterone

**Table 3.** Prognostic factors for overall survival

Prognostic factors	HR	95% CI	P-value
Univariate analysis for prognostic factors for OS			
Tibolone use	2.19	0.81–5.94	0.22
Age	0.60	0.12–2.92	0.32
FIGO stage	0.17	0.02–1.58	0.16
PM	5.14	2.14–12.31	<0.01
LNM	11.74	4.70–29.30	<0.01
RM	2.99	1.66–5.39	0.04
LVSI	4.88	1.98–12.02	0.03
DOI	5.14	1.87–14.13	0.03
Tumor size	1.50	1.56–4.07	0.04
Cox proportional hazards analysis including significant high-risk factors from univariate analysis and tibolone			
Tibolone use	1.59	0.06–45.66	0.79
PM	8.26	0.40–171.01	0.17
LNM	9.79	0.48–198.11	0.14
RM	2.61	0.15–45.09	0.51

HR, hazard ratio; CI, confidence interval; OS, overall survival; FIGO, International Federation of Gynecology and Obstetrics; PM, parametrial spread; LNM, lymph node metastasis; RM, resection margin; LVSI, lymph-vascular space invasion; DOI, depth of invasion.

terone receptors are found in cervical AC [7,8]. Moreover, cervical AC appears to share some risk factors with endometrial AC. The similarities have been suggested based on the association with overweight, whereas a possible relationship with hypertension and diabetes is based on a clinical series only [9]. Therefore, many gynecologic oncologists are uncertain about the safety of HT in cervical AC patients. A Swedish population-based study reported that fewer than half of cervical cancer survivors with therapy-induced early menopause used HT, the use of which decreased with time [10]. No recommended HT regimen exists for cervical AC patients [11].

In the current study, cervical AC patients treated with tibolone, a regimen that had not been studied previously, were evaluated. Tibolone is a synthetic steroid available in many countries, including South Korea, and it has been used over 1.5 million women-years. The drug is metabolized in the gastrointestinal tract and its global effect is estrogenic in the target organs. Tibolone is effective in treating menopausal syndrome with a good tolerability profile [12]. The safety of tibolone in endometrial cancer patients and ovarian cancer patients has been assessed [13,14]. On the other hand, the safety of tibolone in cervical AC patients has not been reported. To the best of the authors' knowledge, this study is the first to examine

the effects of tibolone on the survival of cervical AC patients.

Only one study examined the effects of estrogen derivatives on the survival of cervical cancer patients. Ploch [15] reported that estrogen derivatives enabled control of most climacteric symptoms with no change in the OS or disease-free survival at 5 years. The study included cervical cancer patients diagnosed as stage I–II with no patients older than 45 years. Furthermore, all patients underwent radiotherapy only or surgery with radiotherapy. Neither the histologic subtype nor the statistical analysis method was stated clearly in the article [15].

In the current study, tibolone had no effect on the survival of AC patients. The PFS and OS were similar regardless of tibolone use. Both the univariate analysis and multivariate analysis for survival were performed. All patients reached menopause and menopause occurred naturally prior to treatment or surgically after radical surgery.

Only one study examined the association of cervical AC and HT. In a multicenter case-control study, exogenous estrogens, particularly unopposed estrogens, were positively associated with adenocarcinomas. No trends were observed with the duration of use or age at first use, but unopposed estrogens were positively associated with cervical AC [16].

Parametrial spread and LNM were significant prognostic

factors for disease-free survival in this study. The clinical stage, tumor size, and LNM are significant prognostic factors for cervical AC [3]. Nevertheless, prognostic factors can differ among studies.

This study had several limitations associated with a retrospective study. First, only early-stage patients treated with radical surgery were included; advanced-stage patients were not included. Second, the surveillance period was not long in several patients and the study size was small. Third, the current study reports the experience of a single center and there were no questionnaires on the improvement of menopausal symptoms.

In conclusion, the findings of the current study show that tibolone had no adverse effects on the survival of cervical AC patients. Thus, tibolone can be administered safely to cervical AC patients. These findings may be helpful in improving the quality of life of cervical AC patients.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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