Comparison of Survival Outcomes in Early Stage Invasive Adenocarcinoma with Squamous Cell Carcinoma of the Uterine Cervix

Marut Yanaranop MD*,***,
Suphet Tuipae MD*,***, Saranyu Nakrangsee MD**,***

** Department of Obstetrics and Gynecology, Rajavithi Hospital, Bangkok, Thailand.*
*** Department of Pathology, Rajavithi Hospital,Bangkok, Thailand*
**** College of Medicine, Rangsit University, Bangkok, Thailand*

Background: *Invasive adenocarcinoma (AC) is the second most common carcinoma of the uterine cervix; however, it is not clear whether this histologic type influences survival outcomes.*
Objective: *To evaluate the survival outcomes of patients with invasive AC compared to those with squamous cell carcinoma (SCC) in early stage cervical cancer following radical hysterectomy.*
Material and Method: *A historical cohort study was conducted of 316 Thai women with cervical cancer clinical stage IA2-IIA (120 AC and 196 SCC) who underwent radical hysterectomy from January 1 to December 31, 2000.*
Results: *With a median follow-up of 65.23 months, the estimated 5-year recurrence-free survival (RFS) and overall survival (OS) for patients with AC did not significantly differ from those with SCC (90.3% vs. 93.1%, p = 0.301 and 90.9% vs. 93.5%, p = 0.342 respectively). Using Cox regression analysis, cervical stroma invasion (CSI) and lymphovascular space invasion (LVSI) were the significant prognostic factors for RFS, whereas CSI was the only significant prognostic factor for OS. Women with AC who had two prognostic factors showed significantly lower 5-year RFS than those with SCC (69.5% vs. 86.3%, p = 0.035).*
Conclusion: *Survival and recurrence were not different for surgically treated cervical cancer in women with early stage AC or SCC.*

Keywords: *Cervical cancer, Adenocarcinoma, Squamous cell carcinoma, Radical hysterectomy, Survival*

J Med Assoc Thai 2017; 100 (Suppl. 1): S77-S86
Full text. e-Journal: *http://www.jmatonline.com*

Carcinoma of the uterine cervix is the fourth most common malignancy in women worldwide[1], with an estimated 528,000 newly-diagnosed cases and 266,000 deaths in 2012[2]. Although the incidence of cervical cancer has shown a relative decline over the past 40 years, the relative proportion and absolute incidence of cervical adenocarcinoma (AC) compared with squamous cell carcinoma (SCC) have increased. During the past decade, the incidence of adenocarcinoma of the uterine cervix has increased from approximately 5% to more than 25% of cervical cancers[3-5].

Most of our knowledge of the treatment of cervical cancer comes from studies in which the majority of the patients had SCC. No prospective study has focused on treatment of AC as a sole histology, and it remains controversial whether patients with AC have a worse prognosis. It is not clear whether this histologic type influences outcomes or spread patterns. Several studies have described factors contributing to poor prognosis of AC, including pelvic lymph node metastasis, lymphovascular space invasion (LVSI), histologic grade, tumor size, ovarian metastasis, low sensitivity to radiation and diagnosis of bulky tumor[6-8]. Most studies have identified prognostic factors in patients with AC of the uterine cervix who underwent irradiation; however, the most effective treatment for AC of the uterine cervix has not yet been established. The standard treatment, which consists of surgery and/or radiation therapy, is similar for patients with cervical AC and those with SCC. Subset analysis of 50 patients with AC from a randomized trial of stage IB-IIA cervical cancer appeared to reveal a significant advantage for patients who had surgery, compared to

Correspondence to:
Yanaranop M, Department of Obstetrics and Gynecology, Rajavithi Hospital, 2 Phyathai Road, Rajathewi, Bangkok 10400, Thailand.
Phone: +66-2-3548165-74 ext. 3226, Fax: +66-2-3548084
E-mail: myanaran@hotmail.com

those who had radiotherapy alone, in both overall survival (OS) (70% vs. 59%, $p = 0.05$) and disease-free survival (DFS) (66% vs. 47%, $p = 0.02$)[9]. A systematic review by the Cochrane Gynecological Cancer Group recommended surgery for early stage AC of the uterine cervix[10]. Therefore, patients with AC of the uterine cervix should more frequently undergo surgery in order to improve prognosis.

This retrospective study was undertaken to compare the survival outcomes of patients with stage IA2-IIA invasive AC of the uterine cervix treated with radical hysterectomy and those with SCC, and to determine the prognostic factors.

Material and Method

The ethics committee of Rajavithi Hospital reviewed and approved this study (No. 85/2009). The medical records were reviewed of stage IA2-IIA cervical cancer patients who had been histologically diagnosed with AC or SCC after radical hysterectomy and pelvic lymphadenectomy (RHPLN) at Rajavithi Hospital between January 1, 2000 and December 31, 2009. Patients with history of pre-operative radiotherapy and/or chemotherapy were excluded. Pathologic slides were reviewed by 2 pathologists, one with 10 and one with 15 years' experience, and histologic variables were confirmed. If pathologic diagnoses were discordant, the final agreement was a consensus reached by the two pathologists. Tumors were staged according to the International Federations of Gynecology and Obstetrics (FIGO) clinical staging system of the uterine cervix 2009[11]. Tumor size was determined from the pathologic slides, and depth of invasion (DOI) was measured from the base of the surface epithelium to the deepest malignant cells. LVSI was considered to be present only if viable tumor cells were present inside an endothelium-lined space within an area of stroma in the uterine cervix. Uterine corpus invasion was defined histologically as a tumor extending over the histologic internal os and invading the endometrium and/or myometrium of the uterine corpus.

The criteria for administration of post-operative concurrent chemoradiation therapy (CCRT) included positive lymph node involvement, inadequate surgical margin, and parametrial invasion. Cisplatin at a dosage of 40 mg/m^2 or carboplatin at a dosage of target area under the concentration versus time curve (AUC) of 2 mg/mL/min was given every week for six cycles. Radiation therapy alone was given to patients who refused chemotherapy or had poor performance status. Whole pelvis radiation therapy (WPRT) consisting of external-beam irradiation of 50 Gy was delivered to the whole pelvis with a 10-MV x-ray by parallel-opposed anteroposterior fields or four-field box technique. The daily fraction was 2.0 Gy, five fractions per week. In case of para-aortic or common iliac node metastasis, extended-field radiation therapy (EFRT) was administered via box portals for 50 Gy with the fractionation of 2.0 Gy daily, five fractions per week. High-dose rate brachytherapy using vaginal colpostat or cylinder with Iridium-192 source was given to patients whose vaginal margin was not free from tumor. The usual dose per fraction prescribed at 0.5 cm depth from the vaginal stump was 6 Gy given in 3 fractions.

After completion of treatment, all patients underwent follow-up evaluation every 3 months during the first year, every 4 months during the second year, then every 6 months until the fifth year, and every year thereafter. Recurrence was defined either by pathologic proof of recurrence or by imaging study showing regrowth of the tumor or enlargement of lymph nodes.

Overall survival (OS) was defined as the duration from the first day of surgical treatment until death, regardless of the causes of mortality. Recurrence-free survival (RFS) was calculated as the duration from the first day of surgical treatment to the first time of tumor recurrence or death. In the case of patients who were lost to follow-up, RFS and OS data were censored at the time of patients known to be still alive since the last follow-up. For the patients alive at the time of the study, survival data were right-censored at 31 December 2014.

Sample size calculation was based on the formula for two sample comparison of proportion using 1-tail alpha equal 0.05 and power 90%, $n = [Z_a(2P(1-P))^{1/2} + Z_b((P_1(1-P_1)+P_2(1-P_2))^{1/2}]^2/(P_1-P_2)^2$ [12]. Overall survival of AC and SCC of the uterine cervix from a study of Irie et al[13] was used for calculation. At least 113 participants per groups were needed, and 119 participants per groups were initially required to compensate for the expected 5% dropout rate.

Statistical analysis was undertaken using STATA 14 (StataCorp, College Station, TX). Participants' baseline characteristics were described using frequency and percentages for categorical data, and mean and standard deviation (SD) for continuous data. Clinicopathologic variables were compared using the Chi-square test or the Student's t-test when appropriate. RFS and OS distributions were calculated by the Kaplan-Meier method. Univariate and multivariate survival analysis for the significant prognostic factors of RFS and OF were executed with log-rank test and

the Cox proportional hazards regression model. The stability of the model was certified by using the likelihood ratio purposeful selection step-backward methods. Stratified Cox analysis was used for analysis of effect modifiers compared between the AC and SCC groups. A probability value of <0.05 was considered statistically significant.

Results

During the study period, 326 patients with stage IA2-IIA cervical cancer histologically diagnosed as AC or SCC underwent primary surgical treatment including radical hysterectomy and pelvic lymphadenectomy. Six patients histologically diagnosed with adenosquamous carcinoma and four with undifferentiated carcinoma were excluded. Finally, 316 patients, 120 (38%) with AC and 196 (62%) with SCC, were included in this study.

The clinicopathologic and treatment characteristics of the patients are summarized in Table 1. The mean age of all patients at first presentation was 46.1±8.8 years. There were no statistically significant differences in term of age, clinical staging, DOI, level of cervical stroma invasion (CSI), LVSI, parametrium invasion and uterine corpus invasion. The tumor size (mm) of the SCC group was significantly higher than that of the AC group (25.4±15.2 vs. 19.0±11.8, $p<0.001$). Positive vaginal surgical margins were found in two patients in the SCC group and one in the AC group. Oophorectomy was performed in 70 AC and 116 SCC patients. Ovarian metastasis was found in only one patient (0.9%) in the SCC group. Histologic diagnosis of AC included endocervical (108 cases), endometrioid (6 cases), villoglandular (2 cases), clear cell (2 cases) and signet ring cell type (2 cases). Histologic diagnosis of SCC included keratinizing (33 cases), non-keratinizing (155 cases) and papillary type (8 cases).

All 316 patients received pelvic lymphadenectomy, and pelvic node metastasis was found in 10 AC and 21 SCC patients (8.3% vs. 10.7%, $p = 0.620$). While para-aortic node sampling was performed on 4 AC and 8 SCC patients, metastatic para-aortic nodes were observed only in three of the SCC cases group. All patients with para-aortic node metastasis had accompanying pelvic node metastasis.

Forty-four patients with lymph node metastasis, parametrial invasion and positive vaginal resected margin received adjuvant CCRT. Sixteen patients with deep CSI and/or LVSI and/or large tumor size more of than 4 cm received WPRT. All 5 patients with metastatic para-aortic or common iliac nodes received EFRT. All 3 patients with positive

Table 1. Patients' characteristics and treatment outcomes of clinical stage IA2-IIA adenocarcinoma and squamous cell carcinoma of the uterine cervix

Variables	AC (n = 120)	SCC (n = 196)	*p*-value
Age (years)	45.8±8.5	46.3±8.9	0.610
BMI (kg/m^2)	24.8±3.2	24.3±2.7	0.128
Parity	2.9±1.3	2.4±1.2	0.129
FIGO clinical staging			0.070
IA2	6 (5.0)	18 (9.2)	
IB1	100 (83.3)	138 (70.4)	
IB2	10 (8.3)	32 (16.3)	
IIA	4 (3.3)	8 (4.1)	
Operation			0.662
Modified RHPL	1 (0.8)	4 (2.0)	
RHPL	115 (95.8)	184 (95.8)	
RHPL and para-aortic node sampling	4 (3.3)	8 (4.1)	
Number of pelvic nodes	21.3±6.8	20.5±7.7	0.350
Number of para-aortic nodes	1.3±0.5	4±2.5	0.055
Adjuvant therapy			0.572
WPRT	3 (17.6)	13 (29.5)	
CCRT	12 (70.6)	28 (63.6)	
CCRT + EFRT	2 (11.8)	3 (6.8)	
Tumor size (mm)	19.0±11.8	25.4±15.2	<0.001*
<20 mm	68 (56.7)	75 (38.3)	<0.001*
20-39 mm	44 (36.7)	78 (39.8)	
≥40 mm	8 (15.8)	43 (21.9)	
Depth of invasion (mm)			0.245
<5 mm	44 (36.7)	60 (30.6)	
5-9.9 mm	41 (34.2)	61 (31.1)	
≥10 mm	35 (29.2)	75 (38.3)	
Cervical stroma invasion			0.181
Inner third	62 (51.7)	90 (45.9)	
Middle third	27 (22.5)	36 (18.4)	
Outer third	31 (25.8)	70 (35.7)	
LVSI	30 (25.0)	67 (34.2)	0.111
Parametrium invasion	4 (3.3)	18 (9.2)	0.079
Uterine corpus invasion	6 (5.0)	24 (12.2)	0.053
Pelvic node metastasis	10 (8.3)	21 (10.7)	0.602

Values are presented as n (%) and mean ± SD. * Significant at $p<0.05$.

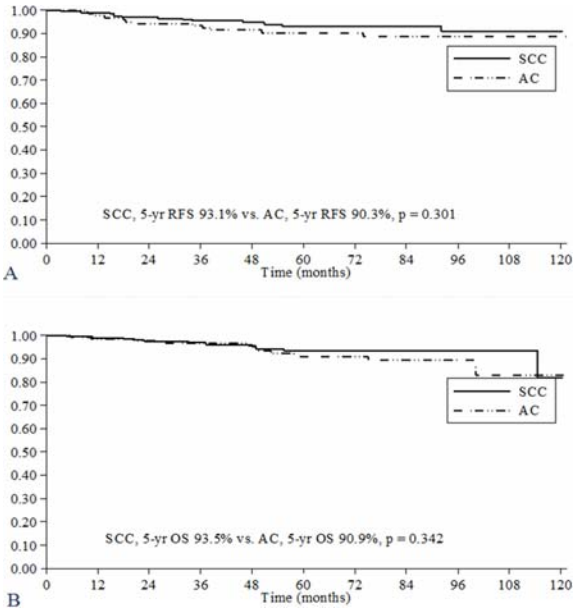
AC = Adenocarcinoma; BMI = Body mass index; CCRT = Concurrent chemoradiation therapy; EFRT = Extended-field radiation therapy; FIGO = International federation of gynecology and obstetrics; LVSI = Lymphovascular invasion; RHPL = Radical hysterectomy and pelvic lymphadenectomy; SCC = Squamous cell carcinoma; SD = Standard deviation; WPRT = Whole pelvis radiation therapy

vaginal resected margin were also given vaginal brachytherapy.

The median follow-up period of surviving patients was 65.23 months (5-122 months). The estimated 5-year RFS and OS for patients with AC did not significantly differ from that of patients with SCC as shown in Fig. 1 (90.3% vs. 93.1%, $p = 0.301$; 90.9% vs. 93.5%, $p = 0.342$, respectively).

Stratified survival analysis compared the clinicopathologic variables of the AC and SCC groups (Table 2 and 3) and found that clinical staging, tumor size, DOI, level of CSI, LVSI, uterine corpus invasion, and adjuvant therapy were the significant prognostic factors for RFS (Table 2), while for OS (Table 3) tumor size, DOI, level of CSI, LVSI, pelvic node metastasis, and adjuvant therapy were identified as the significant prognostic factors. After adjusting clinicopathological characteristics, the Cox proportional hazard regression model identified LVSI and middle/outer third CSI as independent prognostic factors for RFS, and middle/outer third CSI for OS (Table 4). Stratified analysis compared the clinicopathologic variables and number of risk factors (LVSI, middle/outer third CSI) of the AC and SCC groups and found a significant difference between RFS in patients with AC who had two risk factors and those with SCC (5-year RFS; 69.5% vs. 86.3%, $p = 0.035$) (Fig. 2). However, there was no significant difference between RFS in the AC and SCC group when there were no risk factors, one risk factor, and clinicopathologic variables.

Table 5 shows the recurrence rate of each carcinoma group. Out of 120 patients with AC, 12 (10%) suffered from tumor recurrence, and of the 196 patients with SCC, 13 (6.6%) suffered tumor recurrence. Locations of distant recurrence in 6 AC patients were bone (2 cases), lung (1), peritoneal spread (1), inguinal and para-aortic nodes (1), and inguinal and supraclavicular nodes (1). The locations of distant recurrence in 9 SCC patients were supraclavicular nodes (4 cases), para-aortic nodes (2 cases), liver (1), bone (1) and peritoneal spread (1). Although the locoregional and non-nodal distant failures were higher in patients with AC than in those with SCC, no statistically significant difference was found between recurrence rates and locations of initial failure sites in the two groups.



AC = Adenocarcinoma; OS = Overall survival; RFS = Recurrence-free survival; SCC = Squamous cell carcinoma

Fig. 1 A) Recurrence-free and B) overall survival curves of clinical stage IA2-IIA adenocarcinoma and squamous cell carcinoma of the uterine cervix following radical hysterectomy.

Discussion

AC is the second most common carcinoma of the uterine cervix[3]. Although most studies have reported that AC carried a worse prognosis with 10 to 20% differences in 5-year OS compared with SCC[6,8,14,15], some studies have found that histologic type had no significant effect on survival[16-21]. In the present study, there was no significant difference between RFS and OS rates in the AC and SCC groups. Multivariate analysis identified LVSI and middle/outer third CSI as independent prognostic factors for RFS, while finding middle/outer third CSI as independent prognostic factors for OS. These comparable survival outcomes of AC and SCC were reported in studies by Grisaru et al[18], Fregnani et al[20], and Kasamatsu et al[21]. In contrast, Yamauchi et al[8] showed that histology of AC was an independent significant prognostic factor for stage I-II cervical cancer patients compared with those with SCC. They also reported that patients with AC who received postoperative radiotherapy alone had a significantly poorer prognosis than those with SCC.

Pelvic node metastasis in the AC and SCC groups was not significantly different in the present study, consistent with the studies of Davy et al[15] and Lee et al[19]. In contrast, some studies have reported higher incidence of metastatic lymph nodes as a particularly important prognostic factor in AC of the

Table 2. Analysis of recurrence-free survival of clinical stage IA2-IIA cervical cancer stratified by histologic types of adenocarcinoma and squamous cell carcinoma

Variables	AC (n = 120)		SCC (n = 196)		HR	95% CI	*p*-value
	n	Event (%)	n	Event (%)			
Overall	120	12 (10.0)	196	13 (6.6)	1.51	0.69, 3.32	0.301
Age (years)	120	12 (10.0)	196	13 (6.6)	1.00	0.96, 1.05	0.983
BMI (kg/m^2)	120	12 (10.0)	196	13 (6.6)	0.96	0.83, 1.11	0.565
FIGO staging							
IA2-IB1	106	8 (7.5)	156	7 (4.5)	1		
IB2-IIA	14	4 (28.6)	40	6 (15.0)	3.72	1.66, 8.35	0.001*
Tumor size (mm)							
<20 mm	68	3 (4.4)	75	2 (2.7)	1		
20-39 mm	44	7 (15.9)	78	5 (6.4)	3.20	1.12, 9.14	0.030*
≥40 mm	8	2 (25.0)	43	6 (13.9)	6.53	2.06, 20.65	0.001*
Depth of invasion							
<5 mm	44	1 (2.3)	60	1 (1.7)	1		
5-9.9 mm	41	4 (9.8)	61	3 (5.0)	3.72	0.77, 17.90	0.102
≥10 mm	35	7 (20.0)	75	9 (12.0)	8.92	2.04, 38.93	0.004*
Cervical stroma invasion							
Inner third	62	1 (1.6)	90	1 (1.1)	1		
Middle/outer third	58	11 (19.0)	106	12 (11.3)	12.29	2.89, 52.25	0.001*
LVSI							
Negative	90	3 (3.3)	129	4 (3.1)	1		
Positive	30	9 (30.0)	67	9 (13.4)	6.53	2.70, 15.77	<0.001*
Parametrium invasion							
Negative	116	12 (10.3)	178	10 (5.6)	1		
Positive	4	0 (0.0)	18	3 (16.7)	2.20	0.65, 7.45	0.205
Uterine corpus invasion							
Negative	114	9 (7.9)	172	9 (5.2)	1		
Positive	6	3 (50.0)	24	4 (16.7)	4.26	1.74, 10.39	0.001*
Pelvic node metastasis							
Negative	110	9 (8.2)	175	11 (6.3)	1		
Positive	10	3 (30.0)	21	2 (9.5)	2.64	0.99, 7.05	0.053
Adjuvant therapy							
No	103	7 (6.8)	152	8 (5.3)	1		
Yes	17	5 (29.4)	44	5 (11.4)	3.32	1.48, 7.45	0.004*

AC = Adenocarcinoma; BMI = Body mass index; CI = Confidence interval; FIGO = International federation of gynecology and obstetrics; HR = hazard ratio; LVSI = Lymphovascular space invasion; SCC = Squamous cell carcinoma
* Significant at $p<0.05$

uterine cervix compared to SCC. Irie et al[13] reported a significantly higher positive rate of lymph nodes in patients with AC than in those with SCC of stage IB-IIB disease (31.6% vs. 14.8%, $p = 0.010$). Nakanishi et al[22] identified lymph node metastasis as a prognostic variable for stage Ib AC of the uterine cervix. Five-year OS and RFS of patients with AC in the presence of lymph node metastasis were significantly poorer than those with SCC (63.2% vs. 83.6%, $p>0.001$ and 47.4% vs. 80.6%, $p = 0.002$ respectively). Shingleton et al[16] did not find a statistically significant difference between survival in the two histologic types; however, subset analysis suggested that AC patients with positive nodes had a worse OS than SCC patients (33% vs. 76%, $p<0.001$). This discrepancy is probably due to the number of patients, the difference in histological subtypes of AC, stage and adjuvant treatments.

Ovarian metastasis of AC was not found in the present study. Only one case of ovarian metastasis was observed in the SCC group: this patient was in FIGO stage IB2 accompanied with pathological parametrium invasion, uterine corpus invasion and

Table 3. Analysis of overall survival of clinical stage IA2-IIA cervical cancer stratified by histologic types of adenocarcinoma and squamous cell carcinoma

Variables	AC (n = 120)		SCC (n = 196)		HR	95% CI	*p*-value
	n	Event (%)	n	Event (%)			
Overall	120	11 (9.2)	196	12 (6.1)	1.49	0.66, 3.38	0.342
Age (years)	120	11 (9.2)	196	12 (6.1)	0.98	0.93, 1.03	0.434
BMI (kg/m^2)	120	11 (9.2)	196	12 (6.1)	0.90	0.77, 1.05	0.171
FIGO staging							
IA2-IB1	106	9 (8.5)	156	8 (5.1)	1		
IB2-IIA	14	2 (14.3)	40	4 (10.0)	1.97	0.77, 1.08	0.159
Tumor size (mm)							
<20 mm	68	3 (4.4)	75	2 (2.7)	1		
20-39 mm	44	7 (15.9)	78	6 (7.7)	3.42	1.20, 9.75	0.021*
≥40 mm	8	1 (12.5)	43	4 (9.3)	4.14	1.15, 14.87	0.029*
Depth of invasion							
<5 mm	44	1 (2.3)	60	0 (0.0)	1		
5-9.9 mm	41	3 (7.3)	61	5 (8.2)	7.67	0.96, 61.53	0.055
≥10 mm	35	7 (20.0)	75	7 (9.3)	15.71	2.05, 120.68	0.008*
Cervical stroma invasion							
Inner third	62	1 (1.6)	90	1 (1.1)	1		
Middle/outer third	58	10 (17.2)	106	11 (10.4)	11.20	2.61, 48.04	0.001*
LVSI							
Negative	90	4 (4.4)	129	5 (3.9)	1		
Positive	30	7 (23.3)	67	7 (10.4)	3. 89	1.65, 9.16	0.002*
Parametrium invasion							
Negative	116	11 (9.5)	178	10 (5.6)	1		
Positive	4	0 (0.0)	18	2 (11.1)	1.29	0.30, 5.65	0.732
Uterine corpus invasion							
Negative	114	9 (7.9)	172	10 (5.8)	1		
Positive	6	2 (33.3)	24	2 (8.3)	2.36	0.79, 7.09	0.125
Pelvic node metastasis							
Negative	110	8 (7.3)	175	9 (5.1)	1		
Positive	10	3 (30.0)	21	3 (14.3)	3.75	1.46, 9.59	0.006*
Adjuvant therapy							
No	103	6 (5.8)	152	8 (5.3)	1		
Yes	17	5 (29.4)	44	4 (9.1)	3.13	1.34, 7.29	0.008*

AC = Adenocarcinoma; BMI = Body mass index; CI = Confidence interval; FIGO = International federation of gynecology and obstetrics; HR = hazard ratio; LVSI = Lymphovascular space invasion; SCC = Squamous cell carcinoma
* Significant at $p<0.05$

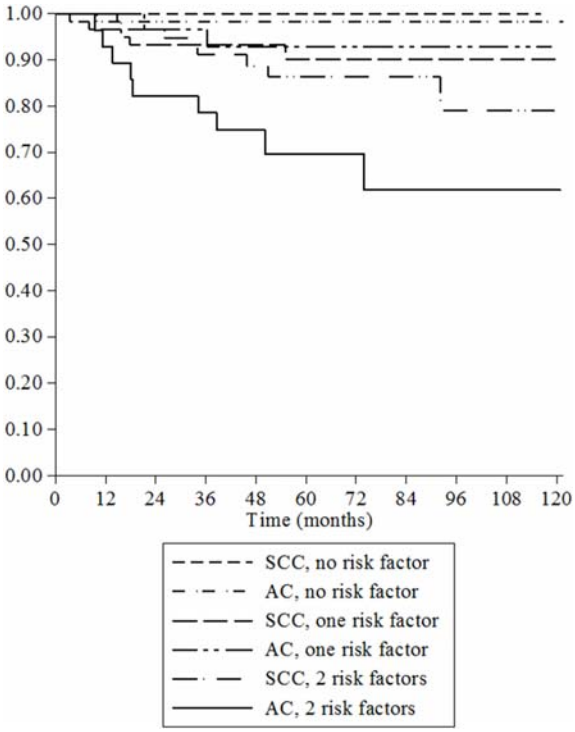
pelvic node metastasis. In contrast, in 1,347 stage I-IIB cervical cancer patients, Shimada et al[23] found more frequent ovarian metastasis in patients with AC than in those with SCC (5.31% vs. 0.79%, $p<0.001$).

There were no significant differences between the recurrence rates and sites in the patients in the two histological groups, which were classified into locoregional and distant recurrences in this study; however, patients with AC were identified as having higher distant non-nodal metastasis than those with SCC, whereas patients with SCC were identified as having higher distant nodal metastasis. A similar finding was reported in a study by Shimada et al[23]. In SCC with distant recurrence, 8 of 9 patients had recurrence of extrapelvic lymph nodes, whereas, in AC with distant recurrence, 7 of 9 patients had hematogenous metastasis, suggesting that routes of spread may differ: SCC predominantly disseminates lymphatically, whereas AC may do so hematogenously. Although further investigation is still needed, taking into account data in the present study and the previous literature, radical hysterectomy followed by adjuvant

Table 4. Multivariate Cox proportional hazards model for recurrence-free and overall survival of clinical stage IA2-IIA adenocarcinoma and squamous cell carcinoma of the uterine cervix following radical hysterectomy

Variables	RFS			OS		
	Adjusted HR	95% CI	*p*-value	Adjusted HR	95% CI	*p*-value
Histology						
SCC	1			1		
AC	1.94	0.88, 4.27	0.100	1.73	0.76, 3.94	0.189
Cervical stroma invasion						
Inner third	1			1		
Middle/outer third	6.81	1.45, 31.86	0.015*	10.93	2.55, 46.79	0.001*
LVSI						
Negative	1			1		
Positive	3.16	1.24, 8.05	0.016*	1.72	0.71, 4.18	0.229

AC = Adenocarcinoma; CI = Confidence interval; HR = Hazard ratio; LVSI = Lymphovascular space invasion; OS = Overall survival; RFS = Recurrence-free survival
* Significant at $p<0.05$



AC = Adenocarcinoma; SCC = Squamous cell carcinoma

Fig. 2 Recurrence-free survival stratified by risk factors (lymphovascular space invasion and cervical stroma invasion).

therapy is still considered the standard treatment option for early stage AC of the uterine cervix with equivalent results for SCC. In this study, presence of two risk factors in patient with AC had interaction effect on RFS. The 5-year RFS in patients with AC who had both LVSI invasion and middle/outer CSI was significantly lower than in those with SCC. Therefore, the criteria for the option of adjuvant therapy in patients with AC may differ from its choice for those with SCC. Additional adjuvant chemotherapy is suggested for patients with AC who have two risk factors and should be investigated in a prospective study.

Conclusion

Survival and recurrence rates were comparable for surgically treated cervical cancer in patients with early stage adenocarcinoma and those with squamous cell carcinoma. The independent significant risk factors for tumor recurrence were positive LVSI and middle/outer third CSI.

What is already known on this topic?

AC is the second most common carcinoma of the uterine cervix and the relative proportion of AC has increased in recent years. The prognoses and survival outcomes remain controversial as to whether patients with AC have a worse prognosis than those with SCC.

What this study adds?

The survival outcomes of patient with early-stage AC of uterine cervix are not significant different from those with SCC. LVSI and level of CSI are the

Table 5. Recurrence rates of clinical stage IA2-IIA adenocarcinoma and squamous cell carcinoma of the uterine cervix following radical hysterectomy

Recurrence	AC (n = 120)	SCC (n = 196)	*p*-value
Total recurrence (%)	12 (10.0)	13 (6.6)	0.282
Locoregional recurrence (%)	10 (8.3)	7 (3.6)	0.069
Vagina	4*	2	
Pelvis	8	5	
Distant recurrence (%)	6 (5.0)	9 (4.6)	0.869
Nodal extra-pelvis	2	6	
Non-nodal extra-pelvis	4	3	

AC = Adenocarcinoma; SCC = Squamous cell carcinoma
* 2 cases found both vagina and pelvic recurrence

significant prognostic factors of RFS; however, patients with AC who have two risk factors exhibit the interaction effect on RFS. Recurrent patterns are different in patients with AC and those with SCC, and AC predominantly disseminates hematogenously whereas SCC does so lymphatically.

Acknowledgements

This present study was supported by a research fund of Rajavithi Hospital.

Potential conflicts of interest

None.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-86.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.
3. Wang SS, Sherman ME, Hildesheim A, Lacey JVJr, Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. Cancer 2004; 100: 1035-44.
4. Bray F, Carstensen B, Moller H, Zappa M, Zakelj MP, Lawrence G, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev 2005; 14: 2191-9.
5. Adegoke O, Kulasingam S, Virnig B. Cervical cancer trends in the United States: a 35-year population-based analysis. J Womens Health (Larchmt) 2012; 21: 1031-7.
6. Eifel PJ, Burke TW, Morris M, Smith TL. Adenocarcinoma as an independent risk factor for disease recurrence in patients with stage IB cervical carcinoma. Gynecol Oncol 1995; 59: 38-44.
7. Ishikawa H, Nakanishi T, Inoue T, Kuzuya K. Prognostic factors of adenocarcinoma of the uterine cervix. Gynecol Oncol 1999; 73: 42-6.
8. Yamauchi M, Fukuda T, Wada T, Kawanishi M, Imai K, Hashiguchi Y, et al. Comparison of outcomes between squamous cell carcinoma and adenocarcinoma in patients with surgically treated stage I-II cervical cancer. Mol Clin Oncol 2014; 2: 518-24.
9. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997; 350: 535-40.
10. Baalbergen A, Veenstra Y, Stalpers L. Primary surgery versus primary radiotherapy with or without chemotherapy for early adenocarcinoma of the uterine cervix. Cochrane Database Syst Rev 2013; (1): CD006248.
11. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009; 105: 103-4.
12. Bernard R. Fundamentals of biostatistics. 5th ed. Pacific Grove, CA: Duxbury-Thomson Learning Publisher; 2000.
13. Irie T, Kigawa J, Minagawa Y, Itamochi H, Sato S, Akeshima R, et al. Prognosis and clinicopathological characteristics of Ib-IIb adenocarcinoma of the uterine cervix in patients who have had radical hysterectomy. Eur J Surg Oncol 2000; 26: 464-7.
14. Takeda N, Sakuragi N, Takeda M, Okamoto K,

Kuwabara M, Negishi H, et al. Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy. Acta Obstet Gynecol Scand 2002; 81: 1144-51.
15. Davy ML, Dodd TJ, Luke CG, Roder DM. Cervical cancer: effect of glandular cell type on prognosis, treatment, and survival. Obstet Gynecol 2003; 101: 38-45.
16. Shingleton HM, Bell MC, Fremgen A, Chmiel JS, Russell AH, Jones WB, et al. Is there really a difference in survival of women with squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma of the cervix? Cancer 1995; 76: 1948-55.
17. Alfsen GC,Kristensen GB, Skovlund E, Pettersen EO, Abeler VM. Histologic subtype has minor importance for overall survival in patients with adenocarcinoma of the uterine cervix: a population-based study of prognostic factors in 505 patients with nonsquamous cell carcinomas of the cervix. Cancer 2001; 92: 2471-83.
18. Grisaru D, Covens A, Chapman B, Shaw P, Colgan T, Murphy J, et al. Does histology influence prognosis in patients with early-stage cervical carcinoma? Cancer 2001; 92: 2999-3004.
19. Lee KB, Lee JM, Park CY, Lee KB, Cho HY, Ha SY. What is the difference between squamous cell carcinoma and adenocarcinoma of the cervix? A matched case-control study. Int J Gynecol Cancer 2006; 16: 1569-73.
20. Fregnani JH, Soares FA, Novik PR, Lopes A, Latorre MR. Comparison of biological behavior between early-stage adenocarcinoma and squamous cell carcinoma of the uterine cervix. Eur J Obstet Gynecol Reprod Biol 2008; 136: 215-23.
21. Kasamatsu T, Onda T, Sawada M, Kato T, Ikeda S, Sasajima Y, et al. Radical hysterectomy for FIGO stage I-IIB adenocarcinoma of the uterine cervix. Br J Cancer 2009; 100: 1400-5.
22. Nakanishi T, Ishikawa H, Suzuki Y, Inoue T, Nakamura S, Kuzuya K. A comparison of prognoses of pathologic stage Ib adenocarcinoma and squamous cell carcinoma of the uterine cervix. Gynecol Oncol 2000; 79: 289-93.
23. Shimada M, Kigawa J, Nishimura R, Yamaguchi S, Kuzuya K, Nakanishi T, et al. Ovarian metastasis in carcinoma of the uterine cervix. Gynecol Oncol 2006; 101: 234-7.

เปรียบเทียบผลลัพธ์การรอดชีวิตในผู้ป่วยมะเร็งปากมดลูกลุกลามระยะต้นชนิด adenocarcinoma กับ squamous cell carcinoma

มรุต ญาณารณพ, สุเพ็ชร ทุ้ยแป, ศรัญยู นาครังษี

ภูมิหลัง: มะเร็งปากมดลูกลุกลามชนิด adenocarcinoma เป็นมะเร็งปากมดลูกที่พบบ่อยเป็นอันดับสอง อย่างไรก็ตามยังไม่มีความแน่ชัดเกี่ยวกับอิทธิพลของชนิดทางจุลวิทยากับผลการรอดชีวิต

วัตถุประสงค์: เพื่อประเมินผลการรอดชีวิตของผู้ป่วยมะเร็งปากมดลูกลุกลามระยะต้นชนิด adenocarcinoma เปรียบเทียบกับชนิด squamous cell carcinoma ตามหลังการผ่าตัดมดลูกแบบถอนรากถอนโคน

วัสดุและวิธีการ: การศึกษาแบบ historical cohort ของสตรีไทยโรคมะเร็งปากมดลูกระยะ IA2-IIA จำนวน 316 ราย (มะเร็งชนิด adenocarcinoma 120 ราย และชนิด squamous cell carcinoma 196 ราย) ที่ได้รับการผ่าตัดมดลูกแบบถอนรากถอนโคนตั้งแต่วันที่ 1 เดือนมกราคม พ.ศ. 2543 ถึงวันที่ 31 เดือนธันวาคม พ.ศ. 2552

ผลการศึกษา: อัตราการกลับเป็นซ้ำและอัตราการรอดชีวิตที่ระยะ 5 ปี ในผู้ป่วยมะเร็งปากมดลูกชนิด adenocarcinoma ระยะต้นไม่ต่างกับชนิด squamous cell carcinoma อย่างมีนัยสำคัญทางสถิติ (ร้อยละ 90.3 กับร้อยละ 93.1 และร้อยละ 90.9 กับร้อยละ 93.5 ตามลำดับ) ด้วยระยะเวลาการตรวจติดตามมัธยฐาน 65.23 เดือน การวิเคราะห์ถดถอย Cox พบว่าระดับการกระจายเข้าในชั้นสโตรมาของปากมดลูกกับการกระจายเข้าทางเดินน้ำเหลืองและเลือด เป็นปัจจัยพยากรณ์โรคที่มีนัยสำคัญต่ออัตราการกลับเป็นซ้ำ ในขณะที่ระดับการกระจายเข้าในชั้นสโตรมาของปากมดลูกเป็นปัจจัยพยากรณ์โรคที่มีนัยสำคัญต่ออัตราการรอดชีวิต สตรีโรคมะเร็งปากมดลูกชนิด adenocarcinoma ที่มีสองปัจจัยพยากรณ์พบว่าอัตราการกลับซ้ำที่ระยะ 5 ปี ต่ำกว่าชนิด squamous cell carcinoma อย่างมีนัยสำคัญทางสถิติ (ร้อยละ 69.5 กับ ร้อยละ 86.3, p = 0.035)

สรุป: การรอดชีวิตและการกลับเป็นซ้ำไม่แตกต่างกันระหว่างสตรีโรคมะเร็งปากมดลูกระยะต้นชนิด adenocarcinoma และชนิด squamous cell carcinoma ที่เข้ารับการรักษาโดยการผ่าตัด