RESEARCH ARTICLE

Does Microinvasive Adenocarcinoma of Cervix Have Poorer Treatment Outcomes than Microinvasive Squamous Cell Carcinoma?

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Abstract

Background: To compare the pathological findings and oncologic outcomes of stage IA cervical carcinoma patients, between adenocarcinoma and squamous cell carcinoma cases. Materials and Methods: A total of 151 medical records of stage IA cervical carcinoma patients undergoing primary surgical treatment during 2006-2013 were reviewed. Information from pathological diagnosis and recurrence rates were compared with descriptive statistical analysis. The Kaplan-Meier method and Cox proportional hazards model were used for survival analysis. Results: The median age was 48.9 years. There was no significant difference in rates of lymph node, parametrium, uterine, vaginal, or ovarian metastasis, when comparing adenocarcinoma with squamous cell carcinoma. Overall recurrence rates of adenocarcinoma (5.7%) and squamous cell carcinoma (2.6%) were not statistically significant different, even when stratified by stage. When comparing progression free survival with squamous cell carcinoma, adenocarcinoma had an HR of 0.448 (0.073-2.746), p=0.386. Conclusions: Microinvasive adenocarcinoma of cervix has similar rate of extracervical involvement and oncologic outcomes to squamous cell carcinoma.

Keywords: Cancer - cervix - histopathology - adenocarcinoma - microinvasion

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Introduction

Cervical carcinoma is the worldwide burden disease which incidence of 528,000 and 266,000 patients death a year (Globocan, 2012). It is the second most common Thai female cancer, with 22 new cases and 12 death cases per day (Attasara and Sriplung, 2013). The global incidence of squamous cell carcinoma has progressively declined due to the cervical cancer screening program. The proportion of adenocarcinoma has increased to 20-25% of cervical carcinoma cases (Fujiwara et al., 2014). The clinical staging and primary treatment are accordance with the International Federation of Gynecology and Obstetrics (FIGO) recommendations, which are similar for both squamous and glandular lesions (Percorelli et al., 2009; Denny and Quinn, 2015). FIGO definition of microinvasion is tumor invade cervical stroma in depth ≤5 mm and width ≤7 mm, lymph-vascular space invasion (LVSI) status is negligible. Conization is the standard method for diagnosis and staging of microinvasive cervical carcinoma.

For stage IA1 patients without LVSI, simple hysterectomy is a proper management but if LVSI present, the proper surgical treatment procedures will be modified radical hysterectomy and pelvic lymphadenectomy (MRHPL) which are the same procedures for stage IA2 cervical carcinoma (Percorelli et al., 2009; Shepherd, 2012; Denny and Quinn, 2015). Due to difficulty in evaluating depth of invasion in adenocarcinoma, some surgeons consider performing the more extended surgical procedure than squamous cell carcinoma, which is radical hysterectomy with pelvic lymphadenectomy (RHPL) as the treatment of choice for all microinvasive adenocarcinoma patients. However, a study in 77 patients with stage IA adenocarcinoma revealed no difference in rate of parametrium or pelvic lymph node involvement when compared with squamous cell carcinoma in previous studies (Oster et al., 1997). Another study in 68 patients with early stage I cervical adenocarcinoma found pelvic node metastatic rate of 1.9%, and recurrent rate of 4.4% at median follow-up time of 40 months, which is similar to squamous cell carcinoma in other studies (Covens et al., 1999). The majority of studies have shown that the 5-year overall survival (OS) rate of adenocarcinoma was less than squamous cell carcinoma by approximately 10-20%, and stated that adenocarcinoma is a negative prognostic factor for both early and advanced stages (Gien et al., 2010; Park et al., 2012; Galic et al., 2015). However, some studies have shown in the opposite way (Hou et al., 2011; Spoozak et al., 2012; Winer et al., 2015).

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For avoiding unnecessary aggressive procedures, the authors would like to compare between adenocarcinoma and squamous cell carcinoma of patients with stage IA cervical carcinoma in the aspects of *i)*. the rate of extracervical involvement in surgical treatment specimens, and *ii)*. the oncologic outcomes.

Materials and Methods

Patients with stage IA cervical adenocarcinoma and squamous cell carcinoma who scheduled for surgical treatment between January 1, 2006, and December 31, 2013 were retrospective reviewed after approval by Siriraj Institutional Review Board (COA no.Si563/2014). Survival data was collected until December 31, 2015. The surgical procedure for stage IA1 without LVSI was simple hysterectomy. While the procedures for stage IA1 with LVSI present or stage IA2, was MRHPL or RHPL according to clinician preference. The surgical procedures were stepped up one higher stage for those who had invasive lesions at cone margins. Hysterectomy would be abandoned in cases of frozen section histology confirmed for extracervical metastasis.

Patients' characteristics, FIGO clinical staging, histopathology of conization and subsequent surgical specimens, and survival data were retrieved from the medical records of studied patients. Pathology reports and slides were reviewed by a gynecopathologist. Microscopic findings including, tumor type, tumor grade, tumor size, LVSI, surgical margins, parametrial involvement and metastasis were completed. Adenocarcinoma included mucinous adenocarcinoma and adenosquamous carcinoma.

Collected data was analyzed using SPSS software version 21.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used for the baseline characteristics. Patients' characteristic, histopathology of surgical treatment specimens, the rates of extracervical lesions, and recurrent rates between adenocarcinoma and squamous cell carcinoma were analyzed by two-sided χ^2 and Fisher exact tests as appropriate. One-way ANOVA was used for comparing mean age between adenocarcinoma and squamous cell carcinoma group. Kaplan-Meier method was used for created survival curves. Log-Rank Mantel-Cox method was used to identify associated of FIGO staging, surgical procedures with progression free survival (PFS) between adenocarcinoma and squamous cell carcinoma groups. A P-value of less than 0.05 was considered statistical significance.

Results

Total 151 patients were included for study. Demographic and tumor data were presented in Table 1. Median age of patients was 47 years (interquartile range [IQR], 42-55). Median parity was 2 (IQR, 2-3). Median body mass index was 24.1 kg/m^2 (IQR, 21.3-27.6). Fifty nine patients (39.1%) were postmenopause. Four patients (3%) were a smoker. Diabetes mellitus was taken from the history of 17 patients (11.3%). Most patients (80.8%) were asymptomatic and came to the hospital for cervical cancer screening by their own preference. Abnormal cervical cytology was detected in 130 patients, which were high-grade intraepithelial lesion (HSIL) in 75 patients, squamous cell carcinoma in 29 patients, atypical squamous cell-cannot exclude HSIL (ASC-H) in 10 patients, atypical glandular cells-not otherwise specified (AGC-NOS) in 5 patients, atypical glandular cells-favor neoplasia (AGC-FN) in 3 patients, adenocarcinoma in situ (AIS) in 3 patients, low-grade squamous intraepithelial

Table 1. Demographic Data, Tumor Characteristic and Postoperative Radiation Ratea of All 151 Studied Patients, Comparing Adenocarcinoma to Squamous Cell Carcinoma

Variables	Adenocarcinoma (N=35)	Squamous cell carcinoma (N=116)	P-value
Age, yr	44.9±7.3	49.9±10.7	0.987
Postmenopause	8 (22.9)	51 (44.0)	0.025
Parity ≥3	7 (20.6)	48 (41.7)	0.025
Body mass index, kg/m^2			0.011
<18.5	6 (17.6)	3 (2.6)	
18.5-24.9	18 (52.9)	63 (54.8)	
25.0-29.9	7 (20.6)	38 (33.0)	
≥30.0	3 (8.9)	11 (9.6)	
FIGO stage			0.062
IA1	22 (62.9)	91 (78.4)	
IA2	13 (37.1)	25 (21.6)	
Hysterectomy type			0.048
Abandoned	1 (2.9)	2 (1.7)	
Simple hysterectomy	11 (31.4)	65 (56.0)	
MRHPL	2 (5.7)	9 (7.8)	
RHPL	21 (60.0)	40 (34.5)	
Lymphadenectomy	23 (65.7)	56 (48.3)	0.07

*FIGO, the International Federation of Gynecology and Obstetrics; MRHPL, modified radical hysterectomy and pelvic lymphadenectomy; RHPL, radical hysterectomy and pelvic lymphadenectomy

Table 2. Pathological Results of Surgical Treatment Specimens and Postoperative Radiation Therapy of All 151 Studied Patients, Comparing Adenocarcinoma To Squamous Cell Carcinoma

Variables	Adenocarcinoma (N=35)	Squamous cell carcinoma (N=116)	P-value
Residual diseases (n=151)			
No residual diseases	19 (54.3)	52 (44.8)	0.603
HSIL/AIS lesions	7 (20.0)	30 (25.9)	
Invasive lesions	9 (25.7)	34 (29.3)	
Parametrium metastasis (n=71)	0/22	1/49 (0.9)	0.077
Pelvic node metastasis (n=79)	0/23	2/56 (3.6)	0.153
Surgical margins involvement (n=148)	1/34 (2.9)	4/114 (3.5)	0.813
Ovarian metastasis (n=101)	0/19	0/82	0.071
Uterine metastasis (n=148)	0/34	4/114 (3.5)	0.42
Vagina metastasis (n=74)	1/23 (4.3)	3/51 (5.9)	0.13
Present of LVSI (n=148)	2/34 (5.8	8/114 (7.0)	0.71
Postoperative radiotherapy (n=151)	2/35 (5.7)	10/116 (8.6)	0.402

*AIS, adenocarcinoma in situ; HSIL, high grade squamous intraepithelial neoplasia; LVSI, lymph-vascular space invasion

lesion (LSIL) in 3 patients, and atypical squamous cells of undetermined significance (ASC-US) in 2 patients. Diagnostic conization was done by loop electrosurgical excision procedure (LEEP) for 135 patients (89.4%) and by cold knife conization method for 16 patients (10.6%). Of 113 patients staged as IA1, 34 patients were without disease at conization margins, 51 patients had high-grade lesions (HSIL/AIS), and 28 patients had carcinoma at margins. Of 38 patients with stage IA2 disease, 6 patients were without disease at conization margins, 7 patients had high-grade lesions at conization margins, and 25 patients presented carcinoma at margins. Pathological results of surgical treatment specimens and postoperative radiation rate were showed in Table 2. Microscopic examination revealed residual carcinoma in 43 patients (28.5%), high-grade lesions in 37 patients (24.5%), and no residual cervical neoplasia in 71 patients (47%). The current study had a postoperative radiation rate of 5.7% and 8.6% for stage IA1 and IA2, respectively without significant difference between adenocarcinoma and squamous cell carcinoma.

Median follow-up duration of 52.7 months (range 0-111.1 months), all patients were survived. Median progression free survival (PFS) for all 151 patients was 51.4 months (range 0-111.1 months), with overall recurrent rate of 3.3% as showed in Table 3. When considered by FIGO stage; 2/113 of IA1 (1.8%) and 3/38 of IA2 (7.9%) had recurrence of disease. Of 5 recurrent patients, 2 squamous cell carcinoma and 2 adenocarcinoma patients had loco-regional recurrence, another squamous cell carcinoma patient had distant metastasis.

Correlation of median PFS of studied patients categorized by FIGO stage, histologic type and surgical procedures was presented in Table 4. Recurrent rate for adenocarcinoma was 5.7%, whereas 2.6% for squamous cell carcinoma with no statistically significant difference (p=0.365). Comparison between stage IA1 adenocarcinoma and squamous cell carcinoma patients who underwent simple hysterectomy and stage IA2 who underwent RHPL, showed similar PFS duration. Eleven of stage IA1 adenocarcinoma patients underwent simple hysterectomy compared with 65 of stage IA1 squamous cell carcinoma patients, had PFS of 50 months and 42.5 months, respectively. Twelve adenocarcinoma patients with stage IA2 underwent RHPL versus 22 squamous cell carcinoma patients with stage IA2, had PFS of 62.3 versus 58.1 months. Kaplan-Meier analysis of cancer-specific PFS for stage IA was showed in Figure 1. When compared PFS with squamous cell carcinoma, adenocarcinoma had HR of 0.448 (0.073-2.746), p=0.386.

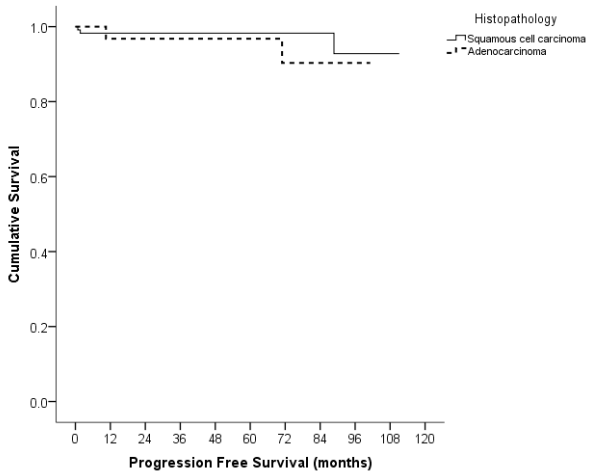

Figure 1. Progression Free Survival of Stage IA Cancers Classified by Histopathology

Table 3. Correlation of Recurrence Rate of Adenocarcinoma and Squamous Cell Carcinoma of 151 Studied Patients Stratified by FIGO Stage

FIGO stages	Adenocarcinoma	Squamous cell carcinoma	P-value
	(N=35)	(N=116)	
IA1 (n=113)	0/22	2/91 (2.2)	0.483
IA2 (n=38)	2/13 (15.4)	1/25 (4.0)	0.217
Total	2/35 (5.7)	3/116 (2.6)	

FIGO, the International Federation of Gynecology and Obstetrics

Discussion

While adenocarcinoma and squamous cell carcinoma share many similar epidemiological features, adenocarcinoma has different by associated with obesity, exogenous estrogen, younger age, and not linked to smoking (Gien et al., 2010; Hou et al., 2011; Fujiwara et al., 2014). The present study found that the proportion of adenocarcinoma was 23.2% of all microinvasive cases and adenocarcinoma had a tendency to occur in younger age, and had underwent more aggressive surgical treatment than squamous cell carcinoma with statistical significance (p=0.048), which are similar to the previous study (Galic

Table 4. Median Progression Free Survival of Adenocarcinoma and Squamous Cell Carcinoma of 151 Studied Patients Categorized by FIGO Stage and Surgical Treatment Procedures

FIGO stages	Adenocarcinoma		Squamous cell carcinoma		P-value
	Surgical procedures	PFS (mo)	Surgical procedures	PFS (mo)	
IA1 (n=113)	SH (n=11)	50	SH (n=65)	42.5	0.69
	MRHPL (n=2)	67.8	MRHPL (n=7)	61.4	n/a
	RHPL (n=9)	72.9	RHPL (n=18)	52.6	n/a
	Abandoned (n=0)	-	Abandoned (n=1)	1	n/a
IA2 (n=38)	MRHPL (n=0)	-	MRHPL (n=2)	34.9	n/a
	RHPL (n=12)	62.3	RHPL (n=22)	58.1	0.401
	Abandoned (n=1)	10.5	Abandoned (n=1)	111.1	n/a

FIGO, the International Federation of Gynecology and Obstetrics; MRHPL, modified radical hysterectomy and pelvic lymphadenectomy; PFS, progression free survival; RHPL, radical hysterectomy and pelvic lymphadenectomy; SH, simple hysterectomy; n/a, data were not analysis due to small sample; p-value was calculated by Log Rank Mantel-cox method

et al., 2012). Moreover, squamous cell carcinoma patients had significantly high number of multiparity (p=0.025). Furthermore, the current study found that squamous cell carcinoma had a higher proportion of stage IA1 disease than adenocarcinoma with marginal statistical significance (78.4% vs 62.9%, p= 0.062) which showed discrepancy with data from the United States that represented no difference for stage distribution (Spoozak et al., 2012).

RHPL is often considered as the appropriate treatment for patients with stage IA cervical adenocarcinoma. The more radical surgery, the more surgical morbidity including hemorrhage and transfusion, fistula, long-term bowel and bladder dysfunction, and sexual dysfunction was occurred (Magrina et al., 1995; Landoni et al., 2001; Reade et al., 2013). In 1997, a study of 77 stage IA adenocarcinoma patients, was not found lymph node metastasis in 48 patients who underwent lymphadenectomy, no parametrium involvement in 26 patients, no adnexal metastasis in 23 patients who underwent salpingo-oophorectomy, and not found skip lesion (Oster et al., 1997), with concordance with following study (Poynor et al., 2006). Japanese study of 41 IA1 and 38 IA2 adenocarcinoma patients, reported both lymph node metastasis and parametrium metastasis for 1.4% (Kasamatsu et al., 2002). Reynolds et al. (2010), studied 52 IA1 and 14 IA2 adenocarcinoma patients, found only one patient had pelvic lymph node metastasis and without recurrence at all during 80 months of follow-up period. Also, they performed meta-analysis of 367 stage IA adenocarcinoma patients, revealed no lymph node metastasis, or parametrium involvement, or recurrence disease (Reynolds et al., 2010). The largest review of stage IA adenocarcinoma by the Surveillance, Epidemiology, and End Results databased (SEER) including 202 stage IA1 and 248 stage IA2, reported lymph node metastasis rate of 1.3% and 3.5%, respectively. The recurrence rate was 1.6% and 2.8%, respectively (Hou et al., 2011). A recent study of 10 women with stage IA1 with LVSI and 40 women with stage IA2 cervical adenocarcinoma, the authors reported positive pelvic nodes in 2 patients, no parametrium metastasis, 1 patient had recurrence of disease, and no disease related death (Yoneda et al., 2015). Hence, microinvasive adenocarcinoma had low rate of extracervical metastasis.

When stage IA disease was compared between adenocarcinoma and squamous cell carcinoma, the SEER data study of 3,987 women with stage IA disease included 988 adenocarcinoma (24.8%) and 2,999 squamous cell carcinoma. They revealed 0.7% of patients with stage IA1 adenocarcinoma had lymph node metastasis compared with 3.8% of squamous cell carcinoma, whereas 0.8% of stage IA2 adenocarcinoma had lymph node metastasis versus 3% for squamous cell carcinoma (Spoozak et al., 2012). The current study found that the rate of adjacent structures metastasis including parametrium, pelvic lymph node, ovary, uterus, and vagina were not significantly different between adenocarcinoma and squamous cell carcinoma. Thus, surgical treatment procedures for stage IA cervical carcinoma, even adenocarcinoma or squamous cell carcinoma should be the same.

The FIGO stage was the most important prognostic factor for treatment outcomes (Denney and Quinn, 2015). For a period of time, the negative prognostic effect of adenocarcinoma has been debating. Adenocarcinoma seemed to be a negative prognostic factor in advanced stage cervical carcinoma (Monk et al., 2007; Shimada et al., 2013), while most studies in microinvasive diseases reported no difference in oncologic outcomes when compared with squamous cell carcinoma (Hou et al., 2011; Spoozak et al., 2012; Winer et al, 2015). The current study found that the rate of 1.8% in stage IA1 and 8.6% in stage IA2 patients, compared with previous study found the recurrence rate of 3% and 5% for stage IA1 and IA2 adenocarcinoma patients, respectively (Poynor et al., 2006). Winer et al. (2015), reported similar 5-year OS rates of 98.2% for adenocarcinoma versus 95.2% for squamous cell carcinoma stage IA1-IB1 patients. Consistently, a study stated similar OS of adenocarcinoma stage IA1 with hazard ratio (HR) of 0.79 [95% confidence interval (CI), 0.21-2.94], and adenocarcinoma stage IA2 with HR of 0.51 (95% CI, 0.18-1.47), when compared to squamous cell carcinoma. Additionally, conization and hysterectomy had similar OS results for stage IA adenocarcinoma patients with HR of 0.87 (95% CI, 0.33-2.26) (Spoozak et al., 2012). As the current study revealed that histopathology type was not the prognostic factor for recurrent rate or median PFS duration in stage IA1 who underwent simple hysterectomy, and stage IA2 who underwent RHPL. For the less radical surgical procedures for treatment stage IA2 patients should warrant further study.

The current study had large number of microinvasive cervical carcinoma, which has been reported from high incidence country. Furthermore, this study compared adenocarcinoma to squamous cell carcinoma in a largest tertiary institution of Thailand. The limitation is the common drawback of retrospective design. Future studies should be focus on the practical consensus method to determine the size of cervical adenocarcinoma, for example, immunohistochemistry or molecular markers. HPV genotyping or bimolecular correlated might be a promising method to determine oncologic outcomes, and incorporate with long-term of follow-up period. Intraoperative intervention for properly selective fertility sparing surgery with devoid under treatment should be explores, for example sentinel lymph node or high accuracy of intraoperative frozen section for selective lymphadenectomy or parametrectomy.

In conclusion, microinvasive adenocarcinoma had the same rate of extracervical involvement and oncologic outcomes, when compared to squamous cell carcinoma. The results of this study will help to affirm the surgeons to choose the most appropriate surgical procedures and avoid unnecessary aggressive operation.

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