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# Comparison of adenocarcinoma and adenosquamous carcinoma in patients with early-stage cervical cancer after radical surgery

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## HIGHLIGHTS

- Outcomes of adenocarcinoma and adenosquamous carcinoma of the cervix were compared.
- The clinicopathologic characteristics of the two histologic types were similar.
- Histologic type had no impact on patterns of recurrence and survival outcomes.

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## ABSTRACT

*Objective.* To compare outcomes after radical hysterectomy in patients with stage IB1 adenocarcinoma (AdCa) and adenosquamous carcinoma (AdSCCa) of the uterine cervix.

*Methods.* We performed a retrospective analysis of 265 patients with AdCa and 72 patients with AdSCCa. Demographic, clinicopathologic, surgical, and follow-up data were compared.

*Results.* There were no differences in demographic and clinicopathologic characteristics between the two histologic types (AdCa vs. AdSCCa). Only mean size of tumor and lymphovascular space invasion was larger and more frequent in AdSCCa (2.7 cm vs 2.3 cm, P = 0.019 & 29.2% vs 14.7%, P = 0.008). After a median follow-up time of 68 months, 39 (14.7%) and 13 (18.1%) AdCa and AdSCCa patients, respectively, had recurrent disease (P = 0.467), and 33 (12.5%) and 11 (15.3%) patients, respectively, died of their disease (P = 0.555). 5-year RFS rates were 89% and 85% (P = 0.582), respectively, and 5-year OS rates were 93% and 89% (P = 0.787). Histologic type had no clinical impact on RFS and OS in multivariate analysis adjusting for significant prognostic factors. There were no differences in pattern of recurrence and time to recurrence between the two histologic types. When patients were stratified into three risk groups according to the criteria of GOG protocols 92 and 109, histologic type had no clinical impact on RFS and OS in any of the risk groups.

*Conclusion.* There are no differences in clinicopathologic factors, patterns of recurrence, time to recurrence, RFS and OS between patients with AdCa and AdSCCa.



## Introduction

Cervical cancer is the second most common cancer and the most common cause of cancer deaths in women worldwide [1]. In Korea, it is the seventh most common cancer and the ninth most common cause of cancer deaths in women, and 3728 new cases and 989 deaths from cervical cancer were recorded in 2011 [2,3]. Although the incidence of cervical cancer is decreasing owing to the introduction of nation-wide organized screening programs in developed countries, it remains an important health problem for women. Squamous cell carcinoma (SCCa), although varying in frequency between populations, is the most common histologic type of cervical cancer; it accounts for approximately 75% of all cases [4], although its incidence is decreasing [5]. Adenocarcinoma (AdCa) is the second most common histologic type of cervical cancer, accounting for 15% of all cases [4], but its absolute and relative incidences are increasing, especially in women aged 20–40 [5]. In older reports, 5% of all cervical cancers were AdCa [6], whereas in more recent reports the incidence was as high as 18.5–27% [7,8]. Adenosquamous carcinoma (AdSCCa) is a mixture of malignant glandular and squamous components consisting of intermingled AdCa and SCCa. It occurs in 2–3% of patients with cervical cancer, and its incidence is increasing, along with that of AdCa [5]. Many studies have suggested that patients with early-stage AdCa and AdSCCa have poorer

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**Table 1**
Clinicopathologic factors in the adenocarcinoma and adenosquamous carcinoma groups (n = 337).

| Characteristic | | Total (n = 337) | Adenocarcinoma (n = 265) | Adenosquamous carcinoma (n = 72) | P-value |
|---|---|---|---|---|---|
| Age (years), mean (range) | | 46.2 (25–76) | 46.1 (27–73) | 46.7 (25–76) | 0.633 |
| | ≤47 years, n (%) | 197 (58.5) | 159 (60) | 38 (52.8) | 0.283 |
| | >47 years, n (%) | 140 (41.5) | 106 (40) | 34 (47.2) | |
| Parity, n (%) | ≤2 | 236 (70) | 184 (69.4) | 52 (72.2) | 0.772 |
| | >2 | 101 (30) | 81 (30.6) | 20 (27.8) | |
| BMI (kg/m$^2$), mean (range) | | 23.8 (17.1–42.2) | 23.6 (17.1–35.2) | 24.4 (17.5–42.2) | 0.086 |
| | ≤24 kg/m$^2$, n (%) | 195 (57.9) | 159 (60) | 36 (50) | 0.140 |
| | >24 kg/m$^2$, n (%) | 142 (42.1) | 106 (40) | 36 (50) | |
| Size of tumor (cm), mean (range) | | 2.4 (0.2–7.3) | 2.3 (0.2–7.3) | 2.7 (0.2–8.0) | 0.019 |
| | ≤2 cm, n (%) | 163 (48.4) | 134 (50.6) | 29 (40.3) | 0.144 |
| | >2 cm, n (%) | 174 (51.6) | 131 (49.4) | 43 (59.7) | |
| LVSI, n (%) | Negative | 277 (82.2) | 226 (85.3) | 51 (70.8) | 0.008 |
| | Positive | 60 (17.8) | 39 (14.7) | 21 (29.2) | |
| DOI, n (%) | ≤1/2 | 190 (56.4) | 156 (58.9) | 34 (47.2) | 0.083 |
| | >1/2 | 147 (43.6) | 109 (41.1) | 38 (52.8) | |
| Parametrium, n (%) | Negative | 302 (89.6) | 240 (90.6) | 62 (86.1) | 0.279 |
| | Positive | 35 (10.4) | 25 (9.4) | 10 (13.9) | |
| Resection margin, n (%) | Negative | 332 (98.5) | 261 (98.5) | 71 (98.6) | 1.000 |
| | Positive | 5 (1.5) | 4 (1.5) | 1 (1.4) | |
| Lymph node, n (%) | Negative | 285 (84.6) | 229 (86.4) | 56 (77.8) | 0.096 |
| | Positive | 52 (15.4) | 36 (13.6) | 16 (22.2) | |
| Adjuvant therapy, n (%) | Not done | 225 (66.8) | 186 (70.2) | 39 (54.2) | 0.069 |
| | Chemotherapy | 26 (7.7) | 19 (7.2) | 7 (9.7) | |
| | Radiotherapy | 37 (11) | 27 (10.2) | 10 (13.9) | |
| | CCRT | 49 (14.5) | 33 (12.5) | 16 (22.2) | |

BMI, body mass index; FIGO, International Federation of Obstetrics and Gynecology; LVSI, lymphovascular space invasion; and DOI, depth of cervical stromal invasion.

prognoses than those with SCCa after radical hysterectomy [8–12] although contrary results have been reported [13–15]. Due to the relative rarity of AdCA and AdSCCa, however, the optimal management and prognostic factors for early-stage patients have not been clearly established. It is also unclear whether AdCa and AdSCCa have different prognoses because many studies did not distinguish between them, and only a few have directly compared outcomes between patients with AdCa and those with AdSCCa [16–18].

We therefore evaluated outcomes and prognostic factors in patients with FIGO stage IB1 AdCa and AdSCCa of the uterine cervix after radical hysterectomy followed by tailored adjuvant therapy.

## Materials and methods

With the approval of the Institutional Review Board of Asan Medical Center, we searched the cancer registry and computerized database of the institution to identify patients with early-stage AdCa and AdSCCa of the uterine cervix who underwent radical hysterectomy. Patients were included if they had: 1) previously untreated cervical cancer; 2) had AdCa or AdSCCa histologic types; 3) had FIGO stage IB1; and 4) had undergone radical hysterectomy by the Rutledge and Piver classification with pelvic and/or para-aortic lymphadenectomy [19]. We excluded patients who received neoadjuvant chemotherapy, radiotherapy (RT) or concurrent chemoradiation therapy (CCRT) before radical hysterectomy, patients with occult cervical cancer identified after simple hysterectomy, and patients with additional malignancies. In our center the preferred treatment for patients with FIGO stages IA2–IIA cervical cancer is radical hysterectomy; thus, almost all the patients with FIGO stage IB1 cervical cancer undergo radical hysterectomy and only a small number who are not eligible for radical surgery receive RT or CCRT. If positive pelvic or para-aortic lymph node involvement is confirmed by frozen section, our policy is to complete radical hysterectomy. Tumors were reviewed by one pathologist at our hospital who specializes in gynecologic oncology full time. Occasionally, an assistant pathologist also reviewed the findings. However, the final diagnosis was only made following agreement between both pathologists.

We retrospectively reviewed the medical records of each patient to collect demographic data, including age, parity, and body mass index (BMI); clinical data, including preoperative imaging, pelvic examination, neoadjuvant chemotherapy, surgery, and adjuvant therapy; pathologic data, including histologic type of the tumor, grade of differentiation, tumor size, depth of cervical stromal invasion (DOI), lymphovascular space invasion (LVSI), parametrial invasion, resection margin status, and lymph node status; and follow-up data, including date of recurrence, treatment at recurrence, date of last follow-up, patient status at last follow-up, and cause of death.

### *Statistical analysis*

Clinicopathologic factors, recurrence-free survival (RFS) and overall survival (OS) were compared between the AdCa and AdSCCa groups to identify any differences between the two histologic subtypes. The correlations between RFS and OS and clinicopathologic factors were examined to identify factors prognostic for RFS and OS. To determine the prognostic role of histologic type in each risk group, we stratified patients into three risk groups (low, intermediate and high) according to the criteria of two randomized controlled trials of adjuvant therapy in early-stage cervical cancer, the Gynecologic Oncologic Group (GOG) protocols 92 [20] and 109 [21]. RFS was calculated as the number of months from the date of surgery to either the date of recurrence or the date of censoring. OS was calculated as the number of months from the date of surgery to either the date of death or the date of censoring. Survival curves and rates were calculated using the Kaplan–Meier method [22]. Differences in survival were assessed using the log-rank test for categorical factors [23] and Cox's proportional hazards model for continuous factors in univariate analysis [24]. A multivariate analysis was performed using Cox's proportional hazards model to determine risk factors after adjustment for known prognostic variables. Frequency distributions were compared using Chi-squared and Fisher's exact tests, and mean and median values in the groups were compared using the Student's *t*-test and the Mann–Whitney *U*-test. A two-sided P-value less than 0.05 indicated statistical significance. Data were analyzed using SPSS software for Windows (version 11.0; SPSS Inc., Chicago, IL).