Clinicopathological Characteristics and Prognostic Factors for Cervical Adenocarcinoma: A Population-Based Study

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Abstract

Objective: We aimed to assess the clinicopathological features and determine prognostic factors of cervical adenocarcinoma (AC).

Methods: Relevant data were extracted from Surveillance, Epidemiology and End Results (SEER) database from 2004 to 2015. The log-rank test and Cox proportional hazard analysis were utilized to identify independent prognostic factors.

Results: A total of 3102 patients were identified. The higher proportion of patients with early FIGO stage (stage I: 69.4%; stage II: 14.1%), low pathological grade (grade I/II: 49.1%) and tumor size ≤4cm (46.8%). The 5- and 10-year CSS rates were 74.47% and 70.00%. Meanwhile, the 5- and 10-year OS rates were 71.52% and 65.17%. Multivariate analysis found that married, surgery as well as chemotherapy were independent favorable prognostic indicators. Additionally, aged ≥45, grade III/IV, tumor size ≥4cm, advanced FIGO stage, pelvic lymph node metastasis (LNM) were unfavorable prognostic factors (all P<0.001). Stratified analysis found that patients without surgery could benefit significantly from chemotherapy and radiotherapy. In addition, chemotherapy could significantly improved survival in stage II-IV patients and radiotherapy only improved stage III patients (all P<0.01).

Conclusion: Marital status, age, grade, tumor size, FIGO stage, pelvic LNM, surgery and chemotherapy were significantly associated with prognosis of cervical AC.

Introduction

Uterine cervix carcinoma is a threatening cause of cancer-related death in females, which is reported to have approximately 311,000 death cases and 570,000 new cases in 2018. Approximately 10–25% of cervical cancer is adenocarcinoma (AC), and squamous cell carcinoma (SCC) is the most prevalent histological classification. Additionally, the prevalence of cervical AC has been reported to increase in multiple regions, the proportion of which has been demonstrated to double in the last ten years. However, knowledge of cervical AC is currently limited to small case series, with unclear clinicopathological features and standard treatment.

The standard therapeutic regimen of cervical AC is currently the same standard as SCC, which includes radical hysterectomy along with adjuvant radiotherapy (RT), radical hysterectomy or primary RT for early-stage cancer. In addition, concurrent chemoradiotherapy (CCRT) is prevalently recommended and promoted for locally advanced cancer as well as early-stage FIGO lesions, which gives rise to equivalent outcomes. Nevertheless, cervical cancer in both cervical SCC and AC patients even with the same FIGO stage still have disparate prognostic outcomes. At present, whether the standard therapeutic regimen is equally suitable for SCC and AC patients has been questioned due to poorer prognostic outcomes of AC patients than SCC. Therefore, it is significant to examine the prognostic indicators for AC, aiming at establishing a framework for new therapeutic strategies.

The NCI-supported Surveillance, Epidemiology and End Results (SEER) database, the most authoritative and largest cancer dataset in North America, reports tumor data on approximately 30% of the US population by selecting relevant registries to represent population diversity. As such, SEER is a valuable database to study such rare tumors. Therefore, a retrospective study was conducted by collecting eligible patients from SEER database, aiming at summarizing clinical features, survival and treatment for patients with cervical AC to delineate prognostic factors.
Materials And Methods

Ethics statement

To acquire relevant data from the database, we signed the SEER Research Data Agreement (No.19817-Nov2018) and further searched for data based on the approved guidelines. All extracted data were publicly accessible and de-identified, and data analysis was considered to be non-human subjects by Office for Human Research Protection. Thus, no approval was requested by institutional review board.

Study population

SEER*State v8.3.6 (released on August 8, 2019) was utilized for selecting and identifying qualified subjects, which includes 18 SEER regions from 1998 to 2015 (2018 submission). The inclusion criteria were as follows: (1) primary cervical AC patients; (2) the diagnosis of cervical AC was based on ICD-O-3; coded as 8140–849015,16. Patients were eliminated if they had: (1) more than one malignancies; (2) reported diagnosis source from autopsy or death certificate or without pathological diagnosis; (3) without certain necessary clinicopathological data, including surgical style as well as FIGO stage; (4) without prognostic information. The rest of subjects were enrolled as the initial cohort of SEER.

Covariates and endpoint

The following clinicopathological parameters were analyzed: year of diagnosis (2004–2007, 2008–2011, 2012–2015)17; marital status (unmarried, married) (unmarried status included widowed, single, divorced and separated)18,19; race (black, white or others); insured status (uninsured/unknown, any medicaid/insured); age (≤ 45, >45); grade (grade I/II, grade III/IV, unknown); FIGO stage (stage I, II, III, IV)20; tumor size (≤ 4 cm, >4 cm, unknown); pelvic lymph node (LN) dissections (none or biopsy, removal of 1 to 3 regional LNs, removal of ≥ 4 regional LNs), pelvic lymph node metastasis (LNM) (positive, negative and unknown); surgery (no surgery, local tumor excision, total hysterectomy), chemotherapy (no/unknown, yes); radiotherapy (no/unknown, yes). Median age at diagnosis of our study was 45 years old, which was also used as the cutoff value of age classification. Meanwhile, the classification of tumor size and age was based on previous researches6,21.

The endpoint of our research included overall survival (OS) and cancer-specific survival (CSS). The former was defined as the duration from diagnosis to all-cause death, and the latter was referred to the duration from diagnosis to cervical AC-caused death.

Statistical analyses

Kaplan-Meier (K-M) method was employed to estimate the univariate analysis, followed by log-rank test for assessing the differences of CSS and OS in different FIGO stages. If variables had $P$ values $\leq 0.1$ in univariate analysis, they were incorporated into multivariate Cox proportional hazard analysis. In addition, stratified analysis was performed by using Cox regression analysis. SPSS software (SPSS Inc., Chicago, USA, version 19.0) was utilized for statistical analysis, and GraphPad Prism 5 was utilized for plotting survival curves. A two-sided $P < 0.05$ was considered as statistically significant.

Results

Patients’ Characteristics
A total of 3102 cervical AC patients were identified, including 2153 (69.4%) patients with stage I, 437 (14.1%) patients with stage II, 401 (12.9%) patients with stage III as well as 111 (3.6%) patients with stage IV. The detailed screening process was shown in Fig. 1. Patient features and therapy regimens were listed in Table 1. To be specific, the median age was 45 years (range: 6–98 years). Among them, 11 cases (0.4%) were ≤ 18 years old, 1618 (52.2%) were ≤ 45 years old, and 422 cases (13.6%) were ≥ 65 years old. Most of cervical AC cases were low pathological grade (grade I/II: 49.1%), tumor size ≤ 4 cm (46.8%) and treated by surgery (69.4%). More patients received ≥ 4 pelvic LN dissection (47.6%) and 12.6% of them had positive pelvic LN.
Table 1
The clinicopathological characteristics and treatment of the included 3102 cervical adenocarcinomas patients.

| Variable              | N (%)       |
|-----------------------|-------------|
| Year at diagnosis     |             |
| 2004–2007             | 893 (28.8%) |
| 2008–2011             | 1062 (34.2%)|
| 2012–2015             | 1147 (37.0%)|
| Insured status        |             |
| uninsured/unknown     | 838 (27.0%) |
| any medicaid/insured  | 2264 (73.0%)|
| Marital status        |             |
| unmarried              | 1512 (48.7%)|
| married                | 1590 (51.3%)|
| Age                   |             |
| ≤ 45                  | 1618 (52.2%)|
| >45                   | 1484 (47.8%)|
| Race                  |             |
| black                 | 237 (7.6%)  |
| white                 | 2493 (80.4%)|
| other                 | 372 (12.0%) |
| Grade                 |             |
| grade I/II            | 1524 (49.1%)|
| grade III/IV          | 769 (24.8%) |
| unknown               | 809 (26.1%) |
| FIGO stage            |             |
| stage I               | 2153 (69.4%)|
| stage II              | 437 (14.1%) |
| stage III             | 401 (12.9%) |
| stage IV              | 111 (3.6%)  |
| Tumor size            |             |
| ≤ 4 cm                | 1453 (46.8%)|
| Variable                                | N (%)     |
|-----------------------------------------|-----------|
| 4 cm                                    | 722 (23.3%)|
| unknown                                 | 927 (29.9%)|
| Surgery                                 |           |
| no surgery                              | 948 (30.6%)|
| local tumor excision                    | 367 (11.8%)|
| total hysterectomy                       | 1787 (57.6%)|
| Lymph node dissection                   |           |
| none or biopsy                          | 1553 (50.1%)|
| 1 to 3                                  | 72 (2.3%)  |
| ≥ 4                                     | 1477 (47.6%)|
| Pelvic lymph node metastasis            |           |
| negative                                | 1407 (45.4%)|
| positive                                | 206 (6.6%)  |
| unknown                                 | 1489 (48.0%)|
| Chemotheray                             |           |
| no/unknown                              | 1968 (63.4%)|
| yes                                     | 1134 (36.6%)|
| Radiotherapy                            |           |
| no/unknown                              | 1845 (59.5%)|
| yes                                     | 1257 (40.5%)|

**Patient Survival**

The median survival time was 45.0 months. The 3-, 5- and 10-year CSS rates were 77.97%, 74.47% and 70.00%. Meanwhile, the 3-, 5- and 10-year OS rates were 75.56%, 71.52% and 65.17%. KM curves stratified by FIGO stage were displayed in Fig. 2A (CSS) and Fig. 2B (OS). Notably, patients with stage III and IV had significantly poorer prognosis than those with stage I and II (P<0.0001 for both). The 5-year CSS and OS rate for patients with stage I were 90.43% and 88.08%; stage II: 55.53% and 53.19%; stage III: 23.95% and 20.45%; and stage IV: 9.77% and 8.90%.

**Prognostic factors of survival**

Univariate analysis revealed that insured status, marital status, age, race, grade, tumor size, FIGO stage, surgery, number of pelvic lymph node dissections, pelvic lymph node metastasis, chemotherapy and radiotherapy were prognostic indicators for CSS and OS (all P<0.05). Moreover, multivariate analysis revealed that married status (HR: 0.754, 95%CI: 0.649–0.876, P<0.001) and surgery [(local tumor excision) HR: 0.532, 95%CI: 0.395–0.717, P<0.001; (total hysterectomy) HR: 0.439, 95%CI: 0.336–0.574, P<0.001] were independent favorable prognostic factors.
of CSS. However, age ≥ 45 (HR: 1.551, 95% CI: 1.297–1.856, \( P < 0.001 \)), grade III/IV (HR: 2.110, 95% CI: 1.757–2.534, \( P < 0.001 \)), tumor size ≥ 4 cm (HR: 1.467, 95% CI: 1.163–1.850, \( P < 0.001 \)), advanced FIGO stage (\( P < 0.001 \)), pelvic LNM (HR: 2.874, 95% CI: 2.064–4.003, \( P < 0.001 \)) were independent unfavorable prognostic indicators. The results of multivariate analysis in OS were similar. Besides, chemotherapy (HR: 0.699, 95% CI: 0.579–0.843, \( P < 0.001 \)) was also an independent favorable prognostic factor for OS (Table 2).
| Variables                  | CSS |                  |                  | OS |                  |                  |
|---------------------------|-----|------------------|------------------|----|------------------|------------------|
|                           | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis | P-value | HR(95%CI) | P-value | HR(95%CI) | P-value |
| Year at diagnosis         | 0.788 | NI               | 0.591            |     | NI               |
| 2004–2007                 |     |                  |                  |     |                  |                  |
| 2008–2011                 |     |                  |                  |     |                  |                  |
| 2012–2015                 |     |                  |                  |     |                  |                  |
| Insured status            | 0.063 | 0.123            | 0.033            |     | 0.151            |
| uninsured/unknown         | Reference | Reference | Reference |
| any medicaid/insured      | 0.883| 0.898(0.776, 1.040) |               |     |                  |                  |
| Marital status            | < 0.001 | < 0.001 | < 0.001 | < 0.001 |                  |                  |
| unmarried                 | Reference | Reference | Reference |
| married                   | 0.754| 0.739(0.643,0.849) |               |     |                  |                  |
| Age                       | < 0.001 | < 0.001 | < 0.001 | < 0.001 |                  |                  |
| ≤ 45                      | Reference | Reference | Reference |
| <45                       | 1.551| 1.938(1.633,2.300) |               |     |                  |                  |
| Race                      | < 0.001 | 0.434 | < 0.001 | 0.183 |                  |                  |
| black                     | Reference | Reference | Reference |
| white                     | 0.867| 0.831(0.682,1.013) |               |     | 0.067            |
| other                     | 0.876| 0.839(0.641,1.096) |               |     | 0.198            |
| Grade                     | < 0.001 | < 0.001 | < 0.001 | < 0.001 |                  |                  |
| grade I/II                | Reference | Reference | Reference |
| grade III/IV              | 2.110| 2.052(1.731,2.431) |               |     |                  |                  |
| unknown                   | 1.153| 1.165(0.967, 1.403) |               |     | 0.109            |
| FIGO stage                | < 0.001 | < 0.001 | < 0.001 | < 0.001 |                  |                  |
| stage I                   | Reference | Reference | Reference |
| Variables                        | CSS               | OS               |
|---------------------------------|-------------------|------------------|
|                                 | Univariate        | Multivariate     | Univariate        | Multivariate     |
|                                 | analysis          | analysis         | analysis          | analysis         |
|                                 | $P$-value         | HR(95%CI)        | $P$-value         | HR(95%CI)        | $P$-value         |
| stage II                        | 2.359(1.848,3.012)| $<0.001$        | 1.933(1.547,2.415)| $<0.001$        |
| stage III                       | 4.805(3.796,6.083)| $<0.001$        | 3.946(3.192,4.878)| $<0.001$        |
| stage IV                        | 8.235(6.139,11.047)| $<0.001$        | 6.410(4.882,8.417)| $<0.001$        |
| Tumor size                      | $<0.001$         | $<0.001$        | $<0.001$         | $<0.001$        |
| ≤ 4 cm                          | Reference         | Reference        | Reference         | Reference        |
| ≤ 4 cm                          | $1.467(1.163,1.850)$| 0.001        | $1.383(1.120,1.707)$| 0.003        |
| unknown                         | $1.562(1.245,1.959)$| $<0.001$    | $1.488(1.215,1.823)$| $<0.001$    |
| Surgery                         | $<0.001$         | $<0.001$        | $<0.001$         | $<0.001$        |
| no surgery                      | Reference         | Reference        | Reference         | Reference        |
| local tumor excision            | $0.532(0.395,0.717)$| $<0.001$    | $0.489(0.370,0.646)$| $<0.001$    |
| total hysterectomy              | $0.439(0.336,0.574)$| $<0.001$    | $0.372(0.289,0.479)$| $<0.001$    |
| Lymph node dissection           | $<0.001$         | 0.055           | $<0.001$         | 0.076           |
| none or biopsy                  | Reference         | Reference        | Reference         | Reference        |
| 1 to 3                          | $1.475(0.795,2.736)$| 0.218        | $1.632(0.902,2.955)$| 0.106        |
| ≥ 4                             | $0.800(0.486,1.318)$| 0.382        | $0.981(0.610,1.578)$| 0.936        |
| Pelvic lymph node metastasis    | $<0.001$         | $<0.001$        | $<0.001$         | $<0.001$        |
| negative                        | Reference         | Reference        | Reference         | Reference        |
| positive                        | $2.874(2.064,4.003)$| $<0.001$    | $3.007(2.222,4.069)$| $<0.001$    |
| unknown                         | $1.732(1.041,2.882)$| $<0.001$    | $1.901(1.172,3.083)$| 0.009        |
| Chemotheray                     | $<0.001$         | 0.100           | $<0.001$         | $<0.001$        |
| no/unknown                      | Reference         | Reference        | Reference         | Reference        |
| Variables | CSS | | OS | |
| --- | --- | --- | --- | --- |
| | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
| | $P$-value | HR(95%CI) | $P$-value | HR(95%CI) | $P$-value | HR(95%CI) | $P$-value |
| yes | 0.840(0.682,1.034) | 0.699(0.579,0.843) |
| Radiotherapy | $< 0.001$ | 0.231 | $< 0.001$ | 0.356 |
| no/unknown | Reference | Reference | |
| yes | 0.880(0.715,1.084) | 0.913(0.753,1.107) |

Abbreviation: CSS: cancer-specific survival; OS: overall survival; NI, not included in the multivariate survival analysis;

Stratified analysis of the effect of chemotherapy and radiotherapy on survival

In order to explore the benefits of chemotherapy and radiotherapy, we conducted stratified analysis of patients with different FIGO stage and surgical style. As a result, patients with stage III/IV could significant benefit from chemotherapy (both CSS and OS), and stage II patients could benefit in terms of OS. Meanwhile, patients without surgery could also benefit significantly from chemotherapy and radiotherapy. In addition, only patients with stage III could benefit significantly from radiotherapy (Table 3 and Table 4).
Table 3
Stratified analysis of cancer-specific survival (CSS) and overall survival (OS) for chemotherapy in different FIGO stage and surgery style.

| Variables          | CSS          | OS            |
|--------------------|--------------|---------------|
|                    | HR(95CI)     | P-Value       | HR(95CI)     | P-Value       |
| FIGO stage         |              |               |              |               |
| stage I            | 2.02 (1.28, 3.18) | < 0.01       | 1.30 (0.90, 1.88) | < 0.05       |
| stage II           | 0.66 (0.42, 1.04) | < 0.05       | 0.52 (0.35, 0.79) | < 0.01       |
| stage III          | 0.56 (0.42, 0.75) | < 0.001      | 0.51 (0.39, 0.67) | < 0.001      |
| stage IV           | 0.34 (0.21, 0.55) | < 0.001      | 0.33 (0.21, 0.52) | < 0.001      |
| Surgery            |              |               |              |               |
| no surgery         | 0.73 (0.58, 0.91) | < 0.01       | 0.62 (0.50, 0.76) | < 0.001      |
| local tumor excision | 1.39 (0.62, 3.12) | < 0.05       | 0.99 (0.49, 2.01) | < 0.05       |
| total hysterectomy  | 4.23 (2.51, 7.11) | < 0.001      | 2.68 (1.69, 4.25) | < 0.001      |

Adjustment variables: Marital status; Age; Grade; Tumor size; Pelvic lymph node metastasis; Radiotherapy.

Table 4
Stratified analysis of cancer-specific survival (CSS) and overall survival (OS) for radiotherapy in different FIGO stage and surgery style.

| Variables          | CSS          | OS            |
|--------------------|--------------|---------------|
|                    | HR(95CI)     | P-Value       | HR(95CI)     | P-Value       |
| FIGO stage         |              |               |              |               |
| stage I            | 1.28 (0.80, 2.05) | < 0.05       | 1.40 (0.95, 2.07) | < 0.05       |
| stage II           | 0.91 (0.55, 1.52) | < 0.05       | 0.96 (0.60, 1.54) | < 0.05       |
| stage III          | 0.54 (0.40, 0.71) | < 0.001      | 0.56 (0.42, 0.73) | < 0.001      |
| stage IV           | 0.78 (0.49, 1.24) | < 0.05       | 0.80 (0.51, 1.25) | < 0.05       |
| Surgery            |              |               |              |               |
| no surgery         | 0.59 (0.47, 0.75) | < 0.001      | 0.62 (0.50, 0.77) | < 0.001      |
| local tumor excision | 7.04 (2.47, 20.11) | < 0.001     | 5.57 (2.29, 13.53) | < 0.001      |
| total hysterectomy  | 0.97 (0.62, 1.53) | < 0.001      | 1.12 (0.74, 1.70) | < 0.001      |

Discussion
This population-based research revealed the clinicopathological features as well as survival of patients with cervical AC. Cervical AC constitutes only approximately 20%-25% of all cervical carcinomas\textsuperscript{2,3}. AC is the second most common primary cervical cancer, secondly only to SCC\textsuperscript{22}. Previous studies predominantly enrolling patients with SCC have provided most of our knowledge about the treatment of cervical cancer\textsuperscript{23,24}. However, the different outcomes for AC have been rarely reported. Furthermore, prospective studies have not focused on the treatment of AC as the only histology. Consequently, our understanding of the natural history, prognosis factors and optimal management of cervical AC is limited\textsuperscript{25}. For this purpose, by including a total of 3102 cervical AC patients, we aimed at describing the clinicopathological features and treatment, as well as examining prognostic indicators for cervical AC.

Depth of cervical invasion, tumor size, FIGO stage, nodal status\textsuperscript{26,27}, tumor grade and patient age\textsuperscript{28,29} were the most widely studied clinicopathological parameters for cervical AC. Although these studies are most based on small sample, single center retrospective studies, the results are basically consistent with ours. In addition, we also found that marital status is an independent prognostic factor for cervical AC.

The same therapeutic strategy is recommended for SCC and AC according to the present guidelines. Nevertheless, there have been no consistent data concerning the therapeutic efficacy in different histological classification\textsuperscript{7}. Surgery and radiotherapy are recommended as the primary therapeutic regimes for early-stage cervical cancer in accordance with NCCN guidelines\textsuperscript{8}. In addition, the 5-year OS rates for stage IA1 and stage IA2 lesions were 96.5% and 99.4% for radical hysterectomy, 96.6% and 100% for local excision, 98.4% and 96.9% for simple hysterectomy in a study enrolling 1567 patients with cervical AC\textsuperscript{30}. Our study also found that surgery is an independent favorable prognostic factor.

Radiotherapy is an alternative option for patients not fit for surgery or who refuse surgery. For patients with stage IB2-IVA cervical cancer, concurrent cisplatin based-chemoradiotherapy plus brachytherapy is the standard therapeutic regimen\textsuperscript{7}. Our study found that for patients without surgery, radiotherapy and chemotherapy can bring significant survival benefits. However, in terms of tumor stage, only patients with stage III can gain significant survival benefits from radiotherapy. The worse efficacy of cervical AC is possibly caused by insensitivity of radiotherapy. Cervical AC patients have been reported to have poorer complete response (CR) as well as local control rates, therefore requiring longer time to obtain CR than SCC populations following CCRT or definitive radiotherapy\textsuperscript{23,31,32}. Similarly, local failure is also more common in cervical AC patients. In addition, Hu revealed higher probability of distant failure in AC patients\textsuperscript{10}. In consideration of poor outcomes of patients with cervical AC, more effective protocols are required for these patients. Adjuvant chemotherapy or neoadjuvant is a possible strategy. According to a Chinese clinical trial, 880 patients with FIGO stage IIB-IVA cervical AC were randomly assigned to receive only CCRT or CCRT with one cycle of neoadjuvant chemotherapy and two cycles of consolidation chemotherapy. Subsequently, patients treated by CCRT along with chemotherapy had better OS, DFS and local control after a median follow-up of 60 months. The above outcomes implicate that combined CCRT and chemotherapy is promising to enhance the survival of patients with cervical AC\textsuperscript{33}.

The NCI-supported SEER database is the most authoritative and largest source for tumor incidence and survival. The large-scale, publicly available SEER dataset can be reliably used to guide anti-cervical AC therapy. As far as we know, our research includes the largest subjects to investigate prognostic parameters for cervical AC in the past ten years. Inevitably, there are also several limitations in our study. Firstly, selection bias and the effects of inaccessible variables from the SEER dataset are unavoidable due to the nonrandomized nature of our research\textsuperscript{13,34}; Secondly,
information on human papilloma virus 18 subtype\textsuperscript{7,35} were inaccessible from SEER database, which are considered as valuable indicators for survival of cervical cancer. Thirdly, SEER fails to provide all data to completely address our hypothesis, such as detailed information on chemotherapy and radiotherapy. Nevertheless, the currently accessible information from SEER database could fit our objectives. While the above-mentioned issues should be further investigated.

**Conclusions**

Marital status, age, grade, tumor size, FIGO stage, pelvic LNM, surgery and chemotherapy were significantly associated with prognosis of cervical AC. Patients without surgery could significantly benefit from chemotherapy and radiotherapy. Stage II-IV patients could significant benefit from chemotherapy. In addition, only stage III patients could get significant survival benefit from radiotherapy. This is the largest series to discuss clinicopathological characteristics and outcomes for patients with cervical AC, and these results are vital to disease management and future prospective studies for this rare cancer.

**Declarations**

**Funding**

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**Conflict of interest**

All authors declare that they have no conflicts of interest.

**Author contributions**

Min Wang conceived the study and searched the database and literature. Zhen-huan Zhou and Min Wang discussed and analyzed the data. Min Wang wrote the manuscript. Wei-wei Han revised the manuscript. All authors approved the final version.

**References**

1. Bray, F. et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians* \textbf{68}, 394-424, doi:10.3322/caac.21492 (2018).

2. Siegel, R. L., Miller, K. D. & Jemal, A. Cancer Statistics, 2017. *CA: a cancer journal for clinicians* \textbf{67}, 7-30, doi:10.3322/caac.21387 (2017).

3. Alfsen, G. C., Thoresen, S. O., Kristensen, G. B., Skovlund, E. & Abeler, V. M. Histopathologic subtyping of cervical adenocarcinoma reveals increasing incidence rates of endometrioid tumors in all age groups: a population based study with review of all nonsquamous cervical carcinomas in Norway from 1966 to 1970, 1976 to 1980, and 1986 to 1990. *Cancer* \textbf{89}, 1291-1299 (2000).

4. Williams, N. L., Werner, T. L., Jarboe, E. A. & Gaffney, D. K. Adenocarcinoma of the cervix: should we treat it differently? *Curr Oncol Rep* \textbf{17}, 17, doi:10.1007/s11912-015-0440-6 (2015).
5. Cracchiolo, B., Kuhn, T. & Heller, D. Primary signet ring cell adenocarcinoma of the uterine cervix - A rare neoplasm that raises the question of metastasis to the cervix. *Gynecol Oncol Rep* **16**, 9-10, doi:10.1016/j.gore.2016.01.004 (2016).

6. Mabuchi, Y. *et al.* Clinicopathologic Factors of Cervical Adenocarcinoma Stages IB to IIB. *International journal of gynecological cancer: official journal of the International Gynecological Cancer Society* **25**, 1677-1682, doi:10.1097/IGC.0000000000000542 (2015).

7. Gadducci, A., Guerrieri, M. E. & Cosio, S. Adenocarcinoma of the uterine cervix: Pathologic features, treatment options, clinical outcome and prognostic variables. *Critical reviews in oncology/hematology* **135**, 103-114, doi:10.1016/j.critrevonc.2019.01.006 (2019).

8. Sugalski, J. M. *et al.* National Comprehensive Cancer Network Infusion Efficiency Workgroup Study: Optimizing Patient Flow in Infusion Centers. *Journal of oncology practice* **15**, e458-e466, doi:10.1200/JOP.18.00563 (2019).

9. Chen, J. L. *et al.* Differential clinical characteristics, treatment response and prognosis of locally advanced adenocarcinoma/adenosquamous carcinoma and squamous cell carcinoma of cervix treated with definitive radiotherapy. *Acta Obstet Gynecol Scand* **93**, 661-668, doi:10.1111/aogs.12383 (2014).

10. Hu, K., Wang, W., Liu, X., Meng, Q. & Zhang, F. Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma of cervix after definitive radiotherapy or concurrent chemoradiotherapy. *Radiat Oncol* **13**, 249, doi:10.1186/s13014-018-1197-5 (2018).

11. Yu, J. B., Gross, C. P., Wilson, L. D. & Smith, B. D. NCI SEER public-use data: applications and limitations in oncology research. *Oncology (Williston Park, N.Y.)* **23**, 288-295 (2009).

12. Cahill, K. S. & Claus, E. B. Treatment and survival of patients with nonmalignant intracranial meningioma: results from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Clinical article. *Journal of neurosurgery* **115**, 259-267, doi:10.3171/2011.3.JNS101748 (2011).

13. Dudley, R. W. *et al.* Pediatric choroid plexus tumors: epidemiology, treatments, and outcome analysis on 202 children from the SEER database. *Journal of neuro-oncology* **121**, 201-207, doi:10.1007/s11060-014-1628-6 (2015).

14. Dudley, R. W. *et al.* Pediatric low-grade ganglioglioma: epidemiology, treatments, and outcome analysis on 348 children from the surveillance, epidemiology, and end results database. *Neurosurgery* **76**, 313-319; discussion 319; quiz 319-320, doi:10.1227/NEU.0000000000000619 (2015).

15. Sherman, M. E., Wang, S. S., Carreon, J. & Devesa, S. S. Mortality trends for cervical squamous and adenocarcinoma in the United States. Relation to incidence and survival. *Cancer* **103**, 1258-1264, doi:10.1002/cncr.20877 (2005).

16. Wang, S. S., Sherman, M. E., Hildesheim, A., Lacey, J. V., Jr. & Devesa, S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. *Cancer* **100**, 1035-1044, doi:10.1002/cncr.20064 (2004).

17. Wu, S. G. *et al.* Survival in signet ring cell carcinoma varies based on primary tumor location: a Surveillance, Epidemiology, and End Results database analysis. *Expert review of gastroenterology & hepatology* **12**, 209-214, doi:10.1080/17474124.2018.1416291 (2018).

18. Chen, Z. *et al.* Marital status independently predicts non-small cell lung cancer survival: a propensity-adjusted SEER database analysis. *Journal of cancer research and clinical oncology* **146**, 67-74, doi:10.1007/s00432-019-03084-x (2020).
19. Wu, S. G. et al. The Effect of Marital Status on Nasopharyngeal Carcinoma Survival: A Surveillance, Epidemiology and End Results Study. *Journal of Cancer* **9**, 1870-1876, doi:10.7150/jca.23965 (2018).

20. Oncology, F. C. o. G. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. *Int J Gynaecol Obstet* **125**, 97-98, doi:10.1016/j.ijgo.2014.02.003 (2014).

21. Yang, J., Cai, H., Xiao, Z. X., Wang, H. & Yang, P. Effect of radiotherapy on the survival of cervical cancer patients: An analysis based on SEER database. *Medicine* **98**, e16421, doi:10.1097/MD.00000000000016421 (2019).

22. Rose, P. G. et al. Locally advanced adenocarcinoma and adenosquamous carcinomas of the cervix compared to squamous cell carcinomas of the cervix in gynecologic oncology group trials of cisplatin-based chemoradiation. *Gynecologic oncology* **135**, 208-212, doi:10.1016/j.ygyno.2014.08.018 (2014).

23. Katanyoo, K., Sanguanrungsirikul, S. & Manusirivithaya, S. Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma in locally advanced cervical cancer. *Gynecologic oncology* **125**, 292-296, doi:10.1016/j.ygyno.2012.01.034 (2012).

24. Lee, Y. Y. et al. A comparison of pure adenocarcinoma and squamous cell carcinoma of the cervix after radical hysterectomy in stage IB-IIA. *Gynecologic oncology* **120**, 439-443, doi:10.1016/j.ygyno.2010.11.022 (2011).

25. Wu, S. Y., Huang, E. Y. & Lin, H. Optimal treatments for cervical adenocarcinoma. *American journal of cancer research* **9**, 1224-1234 (2019).

26. Park, J. Y. et al. Outcomes after radical hysterectomy according to tumor size divided by 2-cm interval in patients with early cervical cancer. *Annals of oncology : official journal of the European Society for Medical Oncology* **22**, 59-67, doi:10.1093/annonc/mdq321 (2011).

27. Nosaka, K. et al. Cytoplasmic Maspin Expression Correlates with Poor Prognosis of Patients with Adenocarcinoma of the Uterine Cervix. *Yonago Acta Med* **58**, 151-156 (2015).

28. Baalbergen, A., Ewing-Graham, P. C., Hop, W. C., Struijk, P. & Helmerhorst, T. J. Prognostic factors in adenocarcinoma of the uterine cervix. *Gynecologic oncology* **92**, 262-267, doi:10.1016/j.ygyno.2003.09.001 (2004).

29. Alfsen, G. C., Reed, W., Sandstad, B., Kristensen, G. B. & Abeler, V. M. The prognostic impact of cyclin dependent kinase inhibitors p21WAF1, p27Kip1, and p16INK4/MTS1 in adenocarcinomas of the uterine cervix: an immunohistochemical evaluation of expression patterns in population-based material from 142 patients with international federation of gynecology and obstetrics stage I and II adenocarcinoma. *Cancer* **98**, 1880-1889, doi:10.1002/cncr.11727 (2003).

30. Bean, L. M., Ward, K. K., Plaxe, S. C. & McHale, M. T. Survival of women with microinvasive adenocarcinoma of the cervix is not improved by radical surgery. *American journal of obstetrics and gynecology* **217**, 332 e331-332 e336, doi:10.1016/j.ajog.2017.05.021 (2017).

31. Yokoi, E. et al. Impact of histological subtype on survival in patients with locally advanced cervical cancer that were treated with definitive radiotherapy: adenocarcinoma/adenosquamous carcinoma versus squamous cell carcinoma. *J Gynecol Oncol* **28**, e19, doi:10.3802/jgo.2017.28.e19 (2017).

32. Xiong, Y. et al. Combination of external beam radiotherapy and Californium (Cf)-252 neutron intracavity brachytherapy is more effective in control of cervical squamous cell carcinoma than that of cervical adenocarcinoma. *Medical oncology (Northwood, London, England)* **32**, 231, doi:10.1007/s12032-015-0670-3 (2015).
33. Tang, J., Tang, Y., Yang, J. & Huang, S. Chemoradiation and adjuvant chemotherapy in advanced cervical adenocarcinoma. *Gynecologic oncology* **125**, 297-302, doi:10.1016/j.ygyno.2012.01.033 (2012).

34. Hankinson, T. C. *et al.* Short-term mortality following surgical procedures for the diagnosis of pediatric brain tumors: outcome analysis in 5533 children from SEER, 2004-2011. *Journal of neurosurgery. Pediatrics* **17**, 289-297, doi:10.3171/2015.7.PEDS15224 (2016).

35. Lau, H. Y. *et al.* The relationship between human papillomavirus and Epstein-Barr virus infections in relation to age of patients with cervical adenocarcinoma. *Taiwan J Obstet Gynecol* **48**, 370-374, doi:10.1016/S1028-4559(09)60325-9 (2009).

**Figures**

![Flow chart of patient screening process.](image.png)

**Figure 1**

Flow chart of patient screening process.
Figure 2

Kaplan-Meier curves for cancer-specific survival (CSS) (A) and overall survival (OS) (B) of included patients in different FIGO stage.