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 radiothrapy 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[1]. Approximately 10–25% of cervical cancer is adenocarcinoma (AC), and squamous cell carcinoma (SCC) is the most prevalent histological classification[2,3]. Additionally, the prevalence of cervical AC has been reported to increase in multiple regions[4], the proportion of which has been demonstrated to double in the last ten years[5]. However, knowledge of cervical AC is currently limited to small case series, with unclear clinicopathological features and standard treatment[6,7].

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[8], 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 [4,9,10]. 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[4,10]. Therefore, it is significant to examine the prognostic indicators forAC, 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[11], reports tumor data on approximately 30% of the US population by selecting relevant registries to represent population diversity[12]. As such, SEER is a valuable database to study such rare tumors[13,14]. 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 8140–8490[15,16].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 researches[6,21].

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 ≤ 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 (52.20%) 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 stutus	
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 stutus, 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).

Table 2
Univariate and multivariate analyses of cancer special survival (CSS) and overall survival (OS) for patients.

Variables	CSS			OS		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	P-value	HR(95%CI)	*P*-value	*P*-value	HR(95%CI)	*P*-value
Year at diagnosis	0.788		NI	0.591		NI
2004–2007						
2008–2011						
2012–2015						
Insured stutus	0.063		0.123	0.033		0.151
uninsured/unknown		Reference			Reference	
any medicaid/insured		0.883(0.754,1.034)□			0.898(0.776,1.040)	
Marital status	< 0.001		< 0.001	< 0.001		< 0.001
unmarried		Reference			Reference	
married		0.754(0.649,0.876)			0.739(0.643,0.849)	
Age	< 0.001		< 0.001	< 0.001		< 0.001
≤ 45		Reference			Reference	
□45		1.551(1.297,1.856)			1.938(1.633,2.300)	
Race	< 0.001		0.434	< 0.001		0.183
black		Reference			Reference	
white		0.867(0.699,1.077)	0.197		0.831(0.682,1.013)	0.067
other		0.876(0.656,1.171)	0.372		0.839(0.641,1.096)	0.198
Grade	< 0.001		< 0.001	< 0.001		< 0.001
grade I/II		Reference			Reference	
grade III/IV		2.110(1.757,2.534)	< 0.001		2.052(1.731,2.431)	< 0.001
unknown		1.153(0.940, 1.414)	0.171		1.165(0.967, 1.403)	0.109
FIGO stage	< 0.001		< 0.001	< 0.001		< 0.001
stage I		Reference			Reference	

Variables	CSS			OS		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	P-value	HR(95%CI)	*P*-value	*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	
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	
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	
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	
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	

Variables	CSS			OS		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	P-value	HR(95%CI)	*P*-value	*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)	0.05	1.12 (0.74, 1.70)	0.05

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[2,3]. AC is the second most common primary cervical cancer, secondly only to SCC [22].Previous studies predominantly enrolling patients with SCC have provided most of our knowledge about the treatment of cervical cancer[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 [25]. For this purpose, by including a total of 3102 cervical AC patients, we aimed atdescribing the clinicopathological features and treatment, as well as examining prognostic indicators for cervical AC.

Depth of cervical invasion, tumor size, FIGO stage, nodal status [26,27], tumor grade and patient age[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[7]. Surgery and radiotherapy are recommended as the primary therapeutic regimes for early-stage cervical cancer in accordance with NCCN guidelines [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[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[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[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[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[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[13,34]; Secondly,

information on human papilloma virus 18 subtype[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.

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Figures

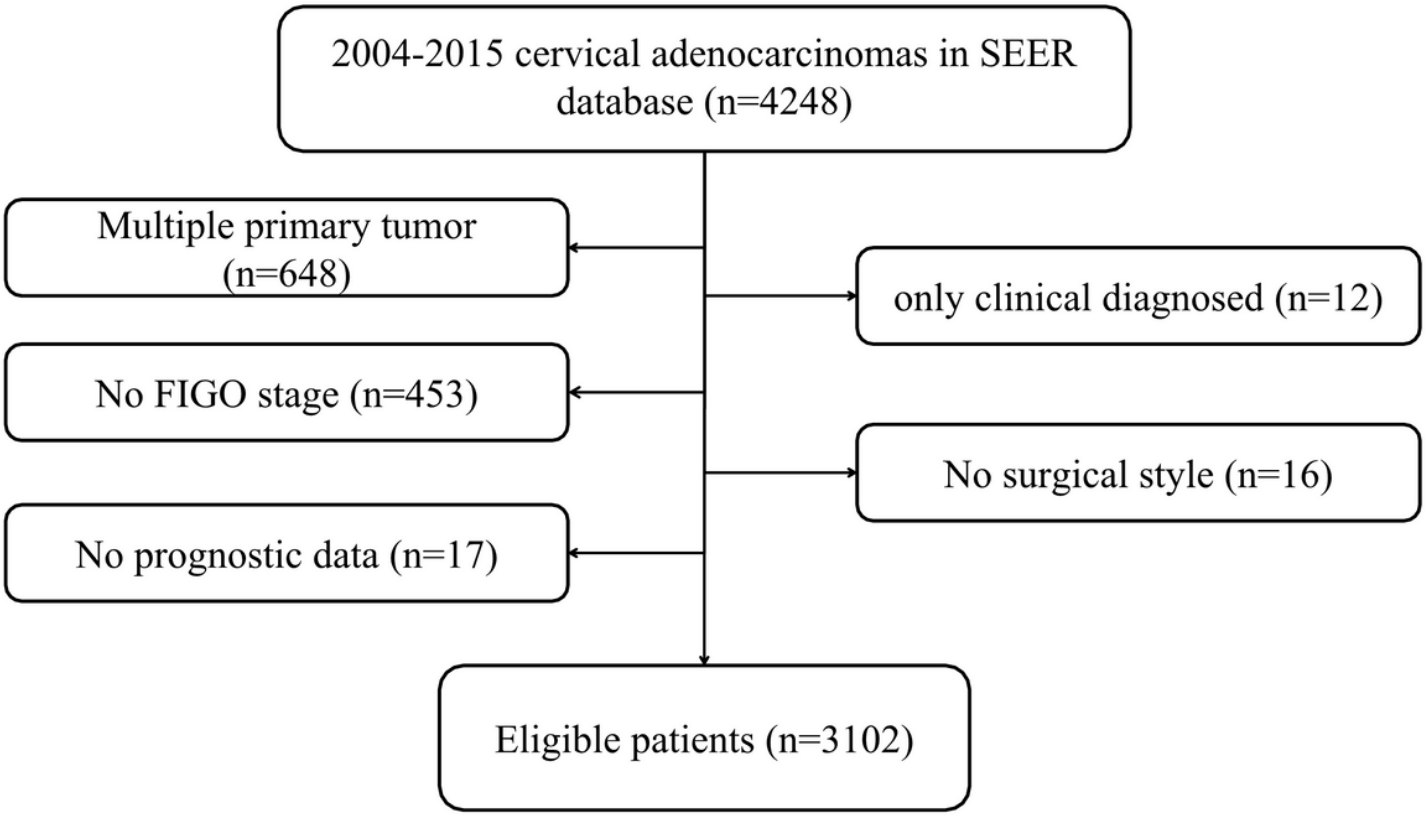

Figure 1

Flow chart of patient screening process.

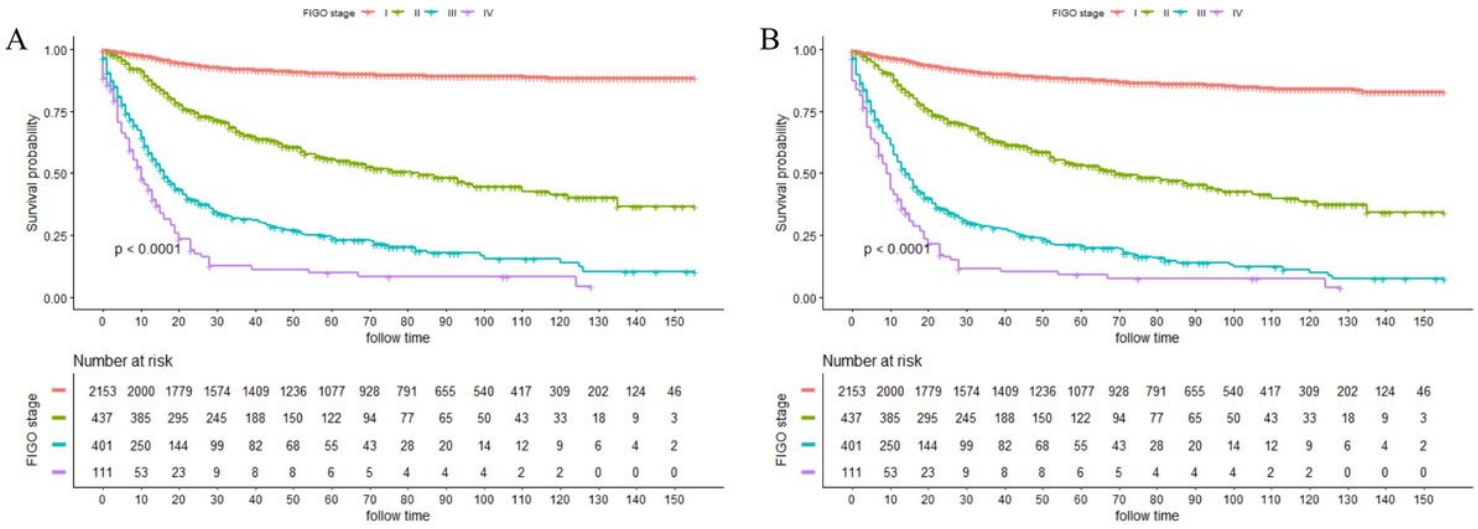

Figure 2

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