


# Clinicopathological Features and Survival of Adolescent and Young Adults with Cervical Cancer

Cancer Control  
Volume 28: 1–11  
© The Author(s) 2021  
Article reuse guidelines:  
[sagepub.com/journals-permissions](https://sagepub.com/journals-permissions)  
DOI: 10.1177/10732748211051558  
[journals.sagepub.com/home/ccx](https://journals.sagepub.com/home/ccx)  


Shuya Pan<sup>1</sup>, Wenxiao Jiang<sup>1</sup>, Shangdan Xie<sup>1</sup>, Haiyan Zhu<sup>2</sup>, and Xueqiong Zhu<sup>1</sup> 

## Abstract

**Purpose:** To explore clinicopathological characteristics and their prognostic value among young patients with cervical cancer (who are aged  $\leq 25$  years old).

**Methods:** The Surveillance, Epidemiology, and End Results Program (SEER) database was used to extract data on cervical cancer patients. They were then stratified by age as young women ( $\leq 25$  years old) and old women (26–35 years old) and analyzed for clinicopathology characteristics and treatment modalities. Prognosis was analyzed using Kaplan–Meier survival curve, as well as hazard ratios using Cox regression modeling. The nomogram was developed based on Cox hazards regression model.

**Results:** Compared to 26–35 years old women, patients aged  $\leq 25$  years tended to be white ethnicity, unmarried, had earlier stage of disease. There was also a better prognosis among younger cohort. Grade, FIGO stage, histologic subtypes, and surgical modalities influenced the survival outcomes of young patients. Among young cohorts, surgery prolonged the survival time of IA-IIA stage patients while surgical and non-surgical management presented no statistically prognostic difference among patients at IIB-IVB stage. Besides, the nomogram which constructed according to Cox hazards regression model which contained independent prognosis factors including FIGO stage, surgery type, and histologic type of tumor can robustly predict survival of young patients.

**Conclusion:** Cervical cancer patients  $\leq 25$  years old were uncommon and lived longer than the older patients. Among these young patients at IA-IIA stage, surgical treatment could be more effective at preventing death than non-surgery. The nomogram could perfectly predict the prognosis of young adults and adolescents with cervical cancer.

## Keywords

cervical cancer, young patients, prognosis, nomogram, Surveillance, Epidemiology, and End Results

## Introduction

Cervical cancer is the fourth most common and lethal cancer among women. It is estimated that there were approximately 570,000 new cases and 311,000 cancer-related deaths in 2018 worldwide, most of which occurred in the developing country.<sup>1</sup> In addition, in the United States, cervical cancer was the second leading cause of cancer related death among women aged 20–39 years, with 10 deaths per week.<sup>2</sup> Furthermore, an increasing number of young women have been diagnosed with cervical cancer according to epidemiologic studies.<sup>3–5</sup>

As has been proposed from previous studies, the morbidity and mortality of cervical cancer have been marked decreased in the United States over the past few decades<sup>6–8</sup> due to the

<sup>1</sup>Center for Uterine Cancer Diagnosis & Therapy Research of Zhejiang Province, Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Wenzhou Medical University, People's Republic of China, Wenzhou, China

<sup>2</sup>Department of Gynecology, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, People's Republic of China, Shanghai, China

### Corresponding Authors:

Xueqiong Zhu, Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Wenzhou Medical University, People's Republic of China, No. 109 Xueyuan Xi Road, Wenzhou, Zhejiang 325027, China. Email: [zjwzqxq@163.com](mailto:zjwzqxq@163.com)

Haiyan Zhu, Department of Gynecology, Shanghai First Maternity and Infant Hospital, No. 2699 Gaoke West Road, Pudong, Shanghai, 200126, China. E-mail: [zhuhaiyandoc@sina.com](mailto:zhuhaiyandoc@sina.com)



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE

and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

availability of the HPV vaccination and adoption of cervical screening. Although, for young women especially adolescents, starting screening earlier than 21 years old was believed to obtain more harm than benefits.<sup>9</sup> In addition, the treatment options for young adults and adolescents with cervical cancer is complicated because preservation of fertility is of great importance and should be considered to young patients<sup>(10-12)</sup>. Hence, it is of importance to explore the clinicopathological characteristics and find a meaningful method to predict the prognosis of young women with cervical cancer.

Accordingly, in the present study, the clinical characteristics, treatment modalities, and prognosis of cervical cancer patients  $\leq 25$  years old were analyzed and their difference with patients at 26–35 years old were evaluated.

## Patients and Methods

### Patients

The information of the patients was obtained from the latest version of Surveillance, Epidemiology, and End Results (SEER) cancer registry database, which covers nearly 28% of the US population. The incidence rate of cervical cancer (ICD-O-3 C53.0-C53.1, C53.8-C53.9) from 2004 to 2016 was acquired from the rate session of SEER\*Stat 8.3.6. Furthermore, case listing session was used to identify all cervical cancer patients who were diagnosed from 2004 to 2016, and patients diagnosed  $>35$  years old were excluded.

### Variables

Patients' characteristics were analyzed under following parameters: age, year of diagnosis, race (white, black, and other), FIGO stage (I, II, III, and IV), grade (well differentiated, moderately differentiated, poorly differentiated, and undifferentiated), tumor histology (squamous, adenocarcinomas, and others including uncommon subtypes such as complex epithelial neoplasms, small cell carcinoma and adenosquamous cell carcinoma), tumor size ( $\leq 4$  cm and  $>4$  cm), nodal status (node positive, node negative), numbers of positive lymph nodes (1, 2, 3, and  $\geq 4$ ) and survival. Besides, the FIGO stage was classified according to the FIGO cancer report 2018<sup>13</sup> based on the TNM stage provided by SEER database. In addition, treatment modalities such as the administration of site-specific surgery, radiotherapy, and chemotherapy were also included. As for surgical approaches, they were classified into 2 groups: hysterectomy including simple hysterectomy, modified radical or radical hysterectomy, hysterectomy not otherwise specified and pelvic exenteration; local tumor resection including conization alone or trachelectomy. Besides, "total hysterectomy without removal of tubes and ovaries" (surgery code 30) and "hysterectomy without removal of tubes and ovaries" (surgery code 61) were classified into hysterectomy without ovarian removal; on the other hand, "total hysterectomy with removal of tubes and ovaries" (surgery code 40) and "hysterectomy with removal of

tubes and ovaries" (surgery code 62) were classified into hysterectomy with ovarian removal. Patients were then stratified by age into young patients ( $\leq 25$  years old) and old patients (26–35 years old). It is worth mention because of the limitation of rate session of SEER database, which groups patients every 5 years from the age of 0 onward, such as 0–4, 5–9, and 10–14. The age groups were "<25 years old" and "25-34 years old" when analyzing incidence rate of cervical cancer patients.

### Statistical Analysis

Further comparison of the qualitative data was done using the chi-squared ( $\chi^2$ ) and Fisher's Exact probability tests. The differences of cause-specific survival (CSS) and overall survival (OS) between the age of  $\leq 25$  and 26–35 were estimated using the Kaplan–Meier method and the comparison of the CSS and OS between 2 age groups was conducted by the log-rank test. Multivariate Cox proportional hazards model analyses were then performed to explore the risk factors for OS in women who under or at 25 years old. When  $P$ -value was  $\leq .05$ , it was considered statistically significant. All statistical analyses above were performed using the SPSS statistical software package (version 26.0; IBM Corporation, Armonk, NY, USA).

### Nomogram

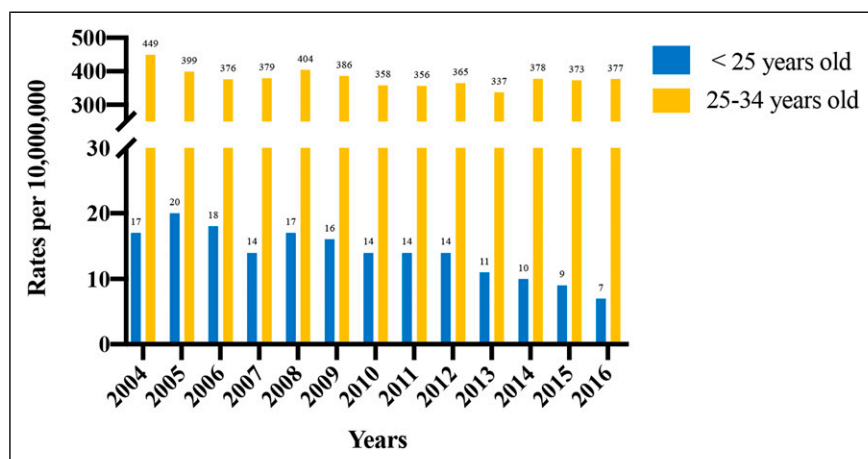
The univariate prognostic factors of OS and CSS were determined by the Kaplan–Meier estimates and the log-rank test, respectively. Variables with  $P < .05$  were included into the multivariable Cox hazards model. Of note, because the information of tumor size and nodal status is already contained within FIGO stage, they were not entered as a predictor in the final model in order to avoid issues of multicollinearity. Using a forward stepdown selection process, the final model selection was determined

The nomogram model was created based on the independent prognostic factors previously obtained by multivariate Cox hazards model and was then validated in 2 ways. First, the performance of prognostic nomogram was evaluated using concordance index (C-index), which ranged from .5 to 1.0 and was positively correlated with the accuracy of the prediction.<sup>14</sup> Second, the calibration curve was employed to display concordance probabilities of prognostic nomogram based on 1000 bootstrap resamples. In an ideal calibration curve, the predicted probabilities were agreed with the actual probabilities.<sup>14</sup> The nomogram and calibration curve were plotted by rms package of RStudio software (version 2.2.5033).

## Results

### Incidence and Survival of all Cervical Patients Stratified by Age

The incidence of cervical cancer in patients stratified by age from 2004 to 2016 was examined. As it is depicted in the



**Figure 1.** Tendency of incidence rate of cervical cancer patients stratified by age from 2004 to 2016.

columns (Figure 1), the incidence of patients was in decline in <25 years old patients. Although the fluctuation of case number in <25 years group was slight, the morbidity dropped by over than 50%.

Data was evaluable for a total of 7,372 patients with cervical cancer  $\leq 35$  years old between the years 2004 and 2016. Survival curves for all patients are depicted in Figure 2. A statistically differences according to the age groups was seen, with a better CSS rate and OS rate of young age group than their older counterparts ( $P = .042$  and  $.028$  for CSS and OS, respectively). The median follow-up of CSS was 68 months in patients  $\leq 25$  years old vs 53 months in patients at 26–35 years old. Furthermore, the 5-year CSS of young patients and old patients was 85.2% and 82.3%, respectively, while 10-year CSS was 84.6% and 80.2%. As for OS, the overall 5-year survival rate was 83.7% for younger group and 80.9% for older group, and overall 10-year survival rate was 82.6% and 77.6%, respectively.

Interestingly, when comparing age groups among different histologic type, the results were different (Supplementary Figure 1). Among patients diagnosed with squamous cell cancer, young patients performed a better prognosis compared with old patients, while no statistically significant difference was observed between 2 age groups among patients diagnosed with adenocarcinoma and other rare histologic subtypes. On the other hand, when FIGO stage was controlled, there was no significantly statistically difference in CSS and OS between young and old age group among each FIGO stage (Supplementary Figure 2).

### Demographic and Clinicopathological Characteristics of Patients

As shown in Table 1, the cohort included 799 patients (10.84%) at 25 years old or younger and 6,573 (89.16%) at 26–35 years old, with a median age of 24 and 32, respectively. Significant difference was found in the race, marital status, grade, histologic type, nodal status, and

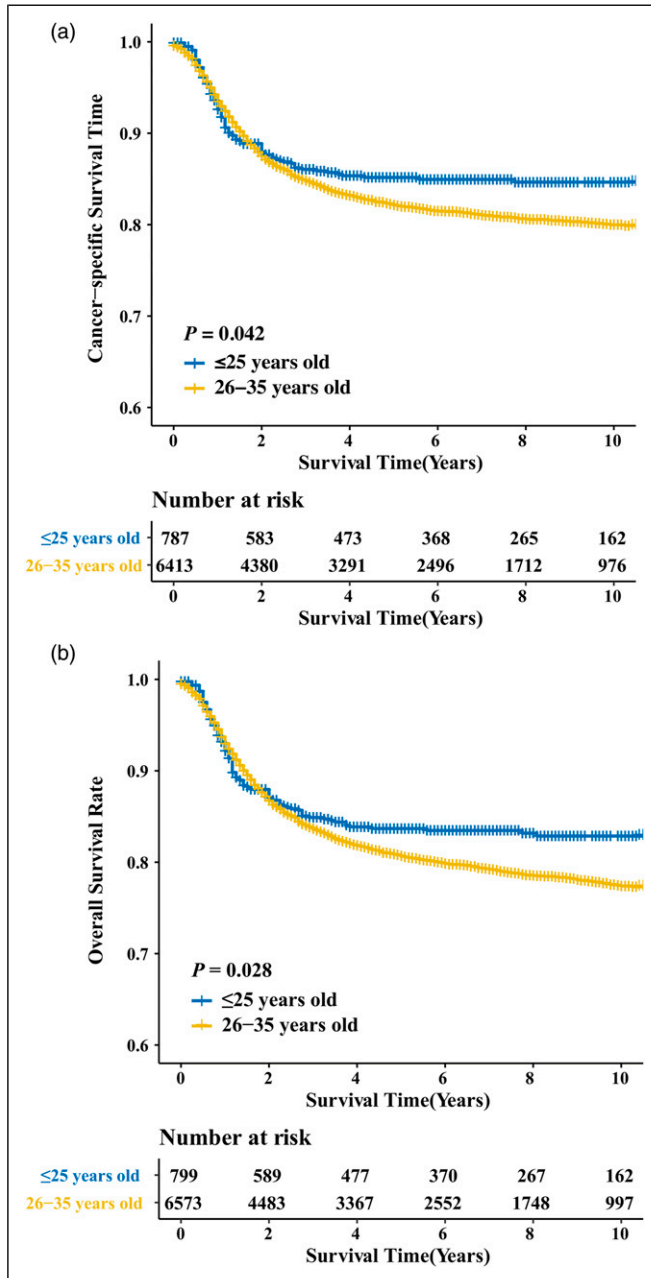
treatment modalities between  $\leq 25$  and 26–35 years old patients (all  $P < .05$ ). Specifically, squamous carcinomas were the most frequent histologic type in both age groups (70.2% and 67.6%, respectively), and fewer young patients were diagnosed with adenocarcinomas than old patients (17.8% vs 24.2%). Additionally, patients  $\leq 25$  years old were less likely to be diagnosed with positive lymph nodes than that in the patients at 26–35 years old (15.4% vs 19.3%). However, there was no significant difference between the 2 age groups in FIGO stage and number of positive lymph nodes.

Compared with patients diagnosed at 26–35 years old, though no statistically significant difference was observed, more patients  $\leq 25$  years old were diagnosed at FIGO I stage (71.6% vs 68.1%). The fraction of patients in FIGO I stage was in decline with increasing age among all cervical cancer, which further confirmed that younger patients with cervical cancer were more likely to be diagnosed at earlier stage (Supplementary Figure 3).

The differences of treatment modalities between the 2 groups are presented in Table 1. The younger group had a higher percentage of undergoing surgery than the older group (78.0% vs 73.9%,  $P = .014$ ), but presented a lower proportion in receiving radiotherapy (29.3% vs 36.6%,  $P < .001$ ).

### Univariate and Multivariate Survival Analysis for Young Cervical Cancer Patients

Since the disparity of CSS and OS among  $\leq 25$  years old patients in our results can be negligible, survival analysis of OS was then performed to explore the risk factors in women who under or at 25 years old. The univariate analysis of the younger cohort for survival significance with Kaplan–Meier method (Table 2) showed that FIGO stage, nodal status, treatment modalities as well as tumor size, grade and histologic type of tumors were significantly associated with the OS in cervical cancer patients  $\leq 25$  years old ( $P$  all  $< .005$ ).



**Figure 2.** Comparison of survival rates of cervical cancer patients between patients  $\leq 25$  and 26–35 years old. (a) Cancer-specific survival; (b) overall survival.

However, race and marital status did not significantly influence OS of the patients  $\leq 25$  years old with cervical cancer.

Multivariate analysis was performed with variables including grade, FIGO stage, histologic type, and surgery type of the patients with cervical cancer patients using Cox proportional hazards model and revealed that histologic type, FIGO stage, and surgery were independent prognostic factors for the OS rate of cervical cancer patients  $\leq 25$  years old (Figure 3). Specifically, compared to squamous cell neoplasms, other subtypes demonstrated a hazard ratio of 2.67 ( $P = .031$ ),

whereas adenocarcinomas demonstrated no significant impact ( $P = .905$ ).

### Influence of Surgery on Overall Survival Rate Among Young Cervical Patients

As shown in Table 3, the majority (89.8%) of young cervical cancer patients at earlier stage (IA-IIA) underwent surgery. However, among advanced stage (IIB-IVB) cervical cancer, most patients (56.1%) did not undergo cancer-directed surgery and received treatment with radiotherapy or chemotherapy and 43.3% of patients received operation and adjuvant radiation or chemotherapy. The prognostic effects of surgery according to the 2 groups were also examined using multivariate Cox proportional hazards model with variables including tumor size, FIGO stage, histologic type, and surgery of the cervical cancer patients. Among IA-IIA patients, the OS of patients who underwent surgery was significantly better than patients who did not undergo surgery ( $P = .01$ , HR = .261). To further find out whether surgical procedures affect survival outcomes of patients at IA-IIA stage, survival rates of different surgical modalities were analyzed and it was found that there was no statistically significant difference among the 5-year OS rate between local tumor excision and hysterectomy ( $P = .101$ ) (Figure 4). With regard to patients at IIB or more advanced stage, no significant difference was found in OS between different surgery group ( $P = .433$ ). At the same time, the impact of ovarian removal in young cervical cancer patients was explored (Figure 5). As depicted in the survival curve, among patients underwent hysterectomy, ovarian removal significantly improved the OS time of cervical cancer patients diagnosed  $\leq 25$  years old ( $P = .045$ ).

### Construction and Validation of Nomogram of Young Patients

According to the previous Cox proportional hazards model, the independent prognostic factors were FIGO stage, histologic type, and surgery. Therefore, a nomogram was developed with these variables to predicting OS of cervical patients  $\leq 25$  years old (Figure 6). The nomogram illustrated that FIGO stage had the greatest impact to the prognosis, followed by tumor grade and histologic type. Each prognostic factor determined a score on the point scale. By positing the total score on the total point scale, the probability of 1-year, 3-year, and 5-year OS can be estimated. For instance, a young cervical cancer patient diagnosed squamous cell cancer at FIGO II stage has undergone hysterectomy. The total score of her was 102 (27 from histologic type, 32.5 from surgery type and 42.5 from FIGO stage respectively); by positing the total score on the scale, we got the predicted survival probabilities of 1 year-, 3 year-, and 5 year- (>90%, 82%, and 76.4%, respectively).

The C-index for the nomogram was .84 (95% CI, .82–.86), which implied that the probability of the agreement between forecast and actual was 84%. To further validate the performance

**Table 1.** Distribution of Cervical Cancer Patients' Demographic and Clinicopathological Characteristics by Age Group.

Clinical Characteristics	≤25 years old (n = 799)		26–35 years old (n = 6573)		P Value
	N	% <sup>a</sup>	N	% <sup>a</sup>	
Median age (years)	24		32		
Race/ethnicity					.003*
Black	125	15.9	779	12.1	
White	609	77.4	5172	80.3	
Others	53	6.7	491	7.6	
Unknown	12		131		
Marital status					<.001*
Unmarried	273	36.6	2678	43.8	
Married	473	63.4	3442	56.2	
Unknown	53		453		
FIGO <sup>b</sup> stage					.162
I	449	71.6	3863	68.1	
II	42	6.7	425	7.5	
III	91	14.5	998	17.6	
IV	45	7.2	361	6.4	
Unknown	172				
Grade					<.001*
I: Well differentiated	72	15.8	826	18.7	
II: Moderately differentiated	160	35.2	1898	42.9	
III: Poorly differentiated	203	44.6	1596	36.1	
IV: Undifferentiated; anaplastic	20	4.4	104	2.4	
Unknown	344		2149		
Histologic type					.002*
Squamous cell neoplasms	493	70.2	4266	67.6	
Adenocarcinomas	125	17.8	1529	24.2	
Others	84	12.0	512	8.1	
Unknown	97		266		
Tumor size					.182
≤4 cm	265	64.8	2650	68.0	
>4 cm	144	35.2	1245	32.0	
Unknown	390		2678		
Nodal status					.016*
Node positive	101	15.4	1094	19.3	
Node negative	554	84.6	4567	80.7	
Unknown	144		912		
Numbers of PLNS <sup>c</sup>					.598
1	25	47.2	272	41.4	
2	15	28.3	164	25.0	
3	5	9.4	92	14.0	
≥4	8	15.1	129	19.6	
Unknown	48		5916		
Surgery					.014*
Performed	623	78.0	4860	73.9	
Not performed	176	22.0	1713	26.1	
Radiation					<.001*
Yes	234	29.3	2404	36.6	
No	565	70.7	4169	63.4	
Chemotherapy					.054
Yes	243	30.4	2223	33.8	

(continued)

**Table 1.** (continued)

Clinical Characteristics	≤25 years old (n = 799)		26–35 years old (n = 6573)		P Value
	N	% <sup>a</sup>	N	% <sup>a</sup>	
No	556	69.6	4350	66.2	

\*P ≤ .05 a. %, valid percent  
b. FIGO, International Federation of Gynecology and Obstetrics  
c. PLNS, positive lymph nodes

**Table 2.** Univariate Analysis of Overall Survival in Cervical Cancer Patients ≤25 Years Old.

Clinical Characteristics	3-year OS <sup>a</sup>		5-year OS	
	%	P	%	P
Race/ethnicity		0.0096		.134
Black	78.9		77.8	
White	85.8		84.7	
Others	88.1		85.7	
Marital status		0.298		.767
Unmarried	86.8		84.1	
Married	83.6		82.9	
Grade		<.001*		<.001*
I: Well differentiated	96.5		96.5	
II: Moderately differentiated	84.6		84.6	
III: Poorly differentiated	66.3		64.2	
IV: Undifferentiated; anaplastic	65		65	
FIGO <sup>b</sup> stage		<.001*		<.001*
I	95.5		94	
II	61.7		61.7	
III	55.9		55.9	
IV	25.8		25.8	
Histologic type		.001*		.001*
Squamous cell neoplasms	84.9		84	
Adenocarcinomas	89.3		86	
Others	69.3		67.7	
Surgery		<.001*		<.001*
Not performed	68.1		67.4	
Performed	91.3		89.9	
Radiation		<.001*		<.001*
No	96.4		95.2	
Yes	57.1		55.8	
Chemotherapy		<.001*		<.001*
No	96.6		95.6	
Yes	58.2		56.2	
Tumor size		<.001*		<.001*
≤4 cm	91		89	
>4 cm	53.9		52	
Nodal status		<.001*		<.001*
Node negative	90.6		89.5	
Node positive	47.2		45.5	

of the prognostic predicted model, the calibration curves were plotted. It can be observed that the 1 year-, 3 year-, and 5 year-actual calibration was very close to the perfect calibration, which suggested that there was a satisfactory agreement between prediction and observation (Supplementary Figure 4).

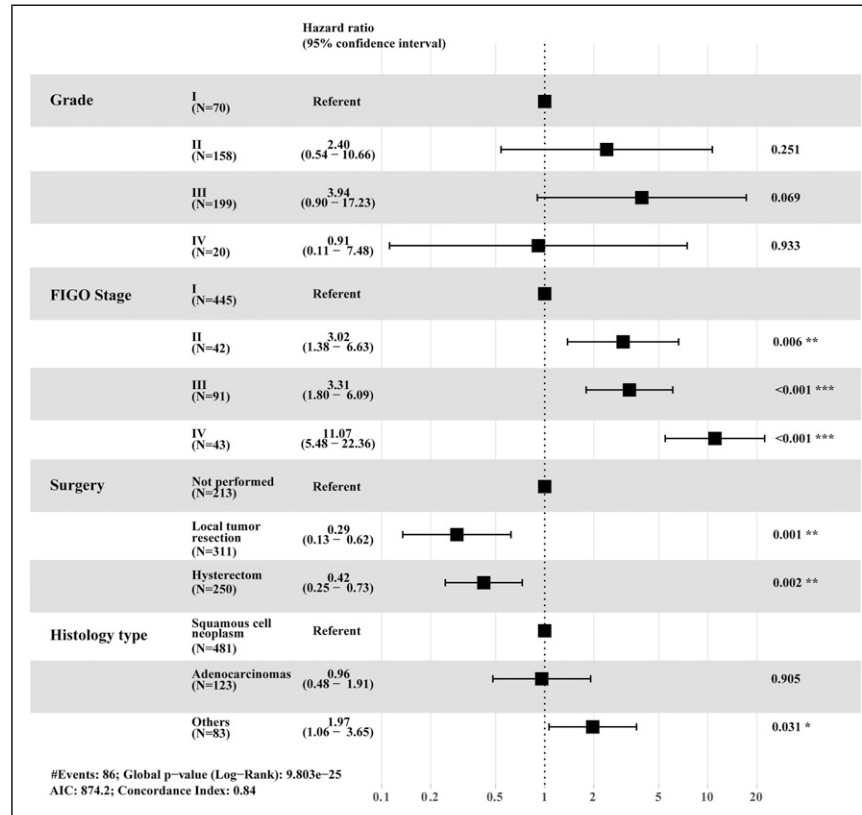
## Discussion

This research represented the largest series to date analyzing the prognostic factors and their prognostic value of adolescents and young adult patients with cervical cancer.

In this study, time trend analyses revealed that the morbidity of young patients was in decline from 2000 to 2016, which is similar to the decreased occurrence rate and mortality of cervical cancer patients in many populations worldwide.<sup>15,16</sup> It mostly attributed to the development of HPV vaccine<sup>1</sup> and cervical cancer screening.<sup>9</sup> In many countries, it is currently recommended that women started routinely cervical screening at 25 years old.<sup>17-21</sup> Particularly, some guidelines also recommend that women should started screening at the age of 20 or 21<sup>9,22-24</sup>. However, what age cervical cancer screening should begin at remains further discussion. Previous study revealed that cervical screening in women aged 20–24 has no significant effect on decreasing incidence rate.<sup>25</sup> Also, the benefit of screening before 25 years old cannot balance against the potential harms and the false-positive results may cause overtreatment.<sup>21</sup> Therefore, it needs more research to identify the optimal age when starting screening.

As for the survival rate of young women with cervical cancer, some previous studies showed that age does not affect the prognosis of cervical cancer patients,<sup>26-28</sup> while other studies argued that younger patients show a better survival rate.<sup>12,29</sup> In this study, young cervical cancer patients live longer than the older. The differences might ascribe to the different age boundaries among different research.

In further exploring the prognostic factors of cervical cancer among patients ≤25 years old, univariate and multivariate analysis revealed that grade, FIGO stage, histologic type, tumor size, nodal status as well as patterns of treatment could influence the survival outcomes of young cervical cancer. These findings were consistent with those among older



**Figure 3.** Forest plot based on Cox hazards model of adolescent and young adult patients with cervical cancer.

**Table 3.** Influence of surgery on overall survival rate among young cervical cancer patients in multivariate Cox hazards model.

	N	%	HR <sup>a</sup> (95% CI <sup>b</sup> )	P
IA-IIA				.010*
Surgery performed	414	89.8	.261 (.093–.728)	
Surgery not performed	47	10.2	Referent	
Total	461	100.0	/	
IIB-IVB				.433
Surgery performed	71	43.3	.769 (.399–1.483)	
Surgery not performed	92	56.1	Referent	
Unknown	1	0.6	/	
Total	164	100.0	/	

\*P ≤ .05. a. HR, hazard ratio; b. CI, confidence interval.

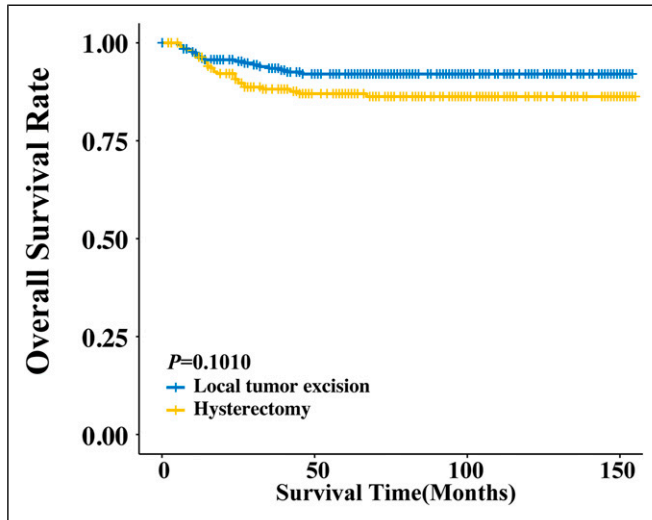
patients according to several previous reports.<sup>30–32</sup> Interestingly, we found that although histologic type did influence the survival outcome of cervical cancer patients ≤25 years old, there were no significant survival differences between adenocarcinoma and squamous cell cancer women. It was contrast to previous researches where squamous cell cervical cancer had a better prognosis than the adenocarcinoma presented.<sup>33–35</sup> This result may be explained by the fact that the majority of the patients in this age group were diagnosed at FIGO I stage. Among women at FIGO I stage, the squamous

cell carcinoma showed no survival advantage over adenocarcinoma according to several previous findings.<sup>36–39</sup>

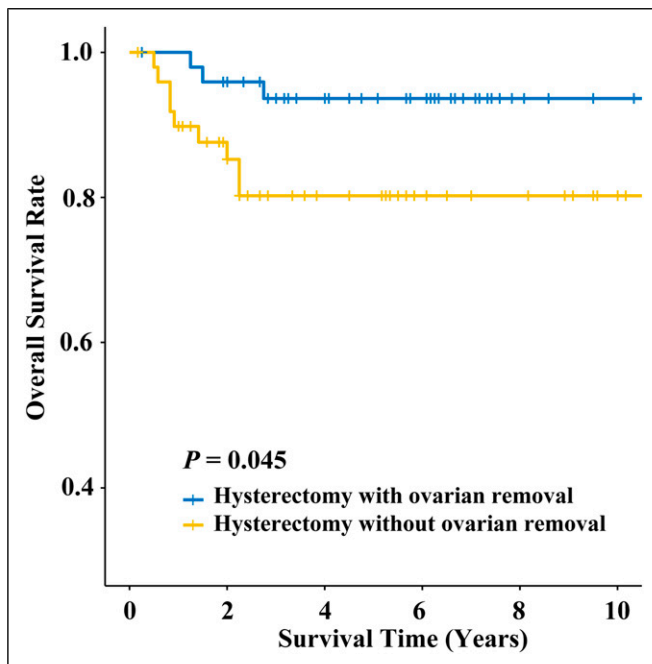
Findings from previous studies showed that regardless of age, women ≤35 years old generally presented a higher frequency of adenocarcinoma compared with patients >35 years old,<sup>40,41</sup> while the most common histological type was squamous cell carcinoma.<sup>40–43</sup> However, these previously published series did not mention the distribution of histologic type in patients at 26–35 years old. Our study showed that adenocarcinoma presented a lower incidence in patients ≤25 years old. In addition, squamous cell cancer was indeed the most frequent type of histology in cervical cancer both in patients at ≤25 and 26–35 years old.

In the distribution of stages, no statistically significant difference was found between patients ≤25 and 26–35 years in a cross-sectional study by *Vale et al.*<sup>19</sup> Consistently, in this study, the proportion of stage I in the younger was not significantly higher than that of older patients. Besides, the present study found that earlier stage patients showed a better survival rate when compared with more advanced stage. Consequently, younger patients may present a better prognosis than their older counterparts. Furthermore, in comparison with older patients, younger women were more willing to receive cervical screening.<sup>44</sup>

*Pelkofski et al.*<sup>43</sup> analyzed the characteristics of cervical cancer patients ≤25 years old and >25 years old, indicating that cervical cancer among the younger patients was more aggressive.



**Figure 4.** Comparison of survival rates of overall survival (OS) rates according to different surgical approaches in adolescent and young adult patients with IA-IIA stage cervical cancer who only received operation ( $P = .101$ ).



**Figure 5.** Comparison of survival rates of overall survival (OS) rates according to whether ovarian removal was conducted among young adult patients with hysterectomy ( $P = .045$ ).

However, there were only 17 patients  $\leq 25$  among the cohort in the prior research. On the contrary, our study addressed that the histologic subtype, clinical stage, and nodal status of the young patients showed significant survival benefits compared to the older group with 799 cases brought into our study.

Our nomogram indicating that among variables that impact the prognosis of young cervical patients, FIGO stage had the

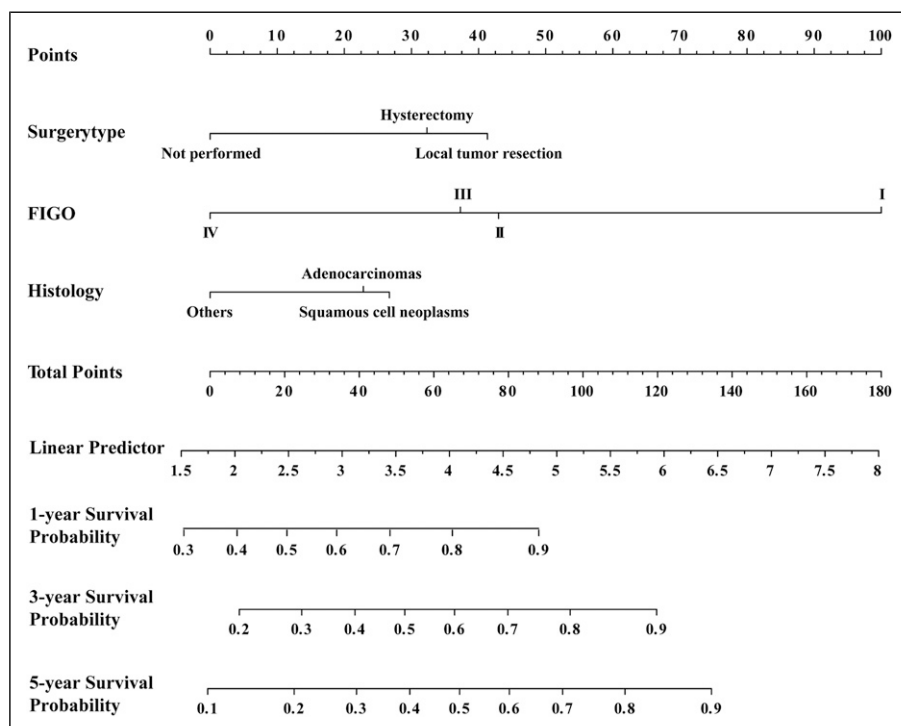
most significant influence, followed by histologic type and surgery, successively. The C-index was very close to 1.0, and the calibration curve was perfectly in agreement with actual prediction curve, which indicated that these 4 factors can precisely predict the survival outcome of young cervical patients.

The optimum treatment for cervical cancer patients diagnosed at early stage has remained a source of controversy. Previous study conducted in cervical cancer patients at Ib stage by *Volterrani et al* showed that surgical treatment did not improve the prognosis compared to radiotherapy or chemotherapy.<sup>45</sup> On the other hand, it has also been suggested that surgery presented a survival advantage over radiotherapy or chemotherapy as primary treatment at early-stage cervical cancer.<sup>46,47</sup> Our univariate analysis confirmed the association between surgical treatment and improved survival in young patients at IA-IIA stage, which was consistent with the advised treatment according to the FIGO cancer report 2018.<sup>13</sup> As for surgical modalities, radical hysterectomy and pelvic lymphadenectomy are the standard surgical modalities to treat early-stage cervical cancer, but impaired fertility of patients.<sup>48</sup> Previous research revealed that there was no statistically significant difference between uterine preservation surgery and hysterectomy at earlier stage among cervical cancer patients of all ages.<sup>47</sup> In agreement with this historical study, our study unveiled that hysterectomy showed no statistically significant benefit in comparison with local tumor resection in IA-IIA cervical cancer patients at 25 years old or younger. Results presented here suggested that young women with earlier stage cervical cancer who desire preserving fertility can take local tumor surgery into consideration.

As for stage IIB-IVB of the disease, it is well acknowledged that definitive chemoradiotherapy is the standard initial treatment for cervical cancer,<sup>49</sup> and combined therapy was not recommended by the FIGO cancer report 2018 since surgery with adjuvant radiotherapy is believed to increase morbidity.<sup>13</sup> Consistent with these viewpoints, in our multivariate analysis of the advanced cohort, surgery was not an independent prognostic factor, which proved that no significant difference of the OS was found between patients received combined treatment and patients who did not undergo any type of operation but received radiation or (and) chemotherapy. In addition, there were nearly half of the patients at stage IIB-IVB who underwent surgery in our research. With the publication of the new FIGO classification for cervical cancer, patients at stage I and II with lymph node metastases were reclassified into stage III.<sup>50</sup> Most of them had received hysterectomy, which may explain the reason for the large proportion of patients at stage IIB-IVB undergoing surgery in this study.

In the current study, there are a number of strengths and limitations that warrant careful consideration. First, this is currently the largest study concentrating on female cervical cancer  $\leq 25$  years old, including clinical factors such as FIGO stage, histology, and grade. Second, we used data from the SEER, the largest tumor registry in the United States, which





**Figure 6.** Overall survival (OS)-associated nomogram for adolescent and young adult patients with cervical cancer.

provide valuable evidence about the treatment of cervical cancer in young women. One of the primary limitations of this study is its retrospective nature, causing difficulty to rule out selection bias. In addition, patients with unclear FIGO stage were not included in our cohort, which may lead to bias to our results. Because the SEER database lack of the HPV infection information, further work is required to better understand the relationship of HPV infection and the characteristics as well as modalities of younger patients with cervical cancer.

## Conclusions

The incidence rate of cervical cancer was in decline from 2004 to 2016. Although there was a low proportion of patients aged  $\leq 25$  in cervical cancer patients, this group tended to be less aggressive, with a better prognosis than their older counterparts. Moreover, greater attention should be paid to cervical carcinoma patients with unusual histologic subtypes, higher clinical stage, poor differentiation grade, and lymph node metastasis, as these factors predict significantly shorter survival times. In addition, different surgical approaches had no significant effect on prognosis for stage IA-IIA among young cervical cancer patients. Furthermore, we developed a well validated nomogram to predict the prognosis of patients aged  $\leq 25$  years old.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was supported by Science and Technology Planning Project of Wenzhou city (No.ZS2017006) and Center for Uterine Cancer Diagnosis & Therapy Research of Zhejiang Province. The sponsor had no involvement in the collection, analysis, and interpretation of data or in the writing of the article.

## Ethics Approval

All data in this article are achieved from SEER database, which have passed the ethical application.

## ORCID iD

Xueqiong Zhu  <https://orcid.org/0000-0002-8389-928X>

## Supplementary Material

Supplementary material for this article is available online.

## References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J Clin.* 2018;68(6):394-424. doi:10.3322/caac.21492
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA A Cancer J Clin.* 2020;70(1):7-30. doi:10.3322/caac.21590

3. Patel A, Galaal K, Burnley C, et al. Cervical cancer incidence in young women: a historical and geographic controlled UK regional population study. *Br J Cancer*. May 22 2012;106(11):1753-1759. doi:10.1038/bjc.2012.148
4. Li S, Hu T, Lv W, Zhou H, Li X, Yang R, et al. Changes in prevalence and clinical characteristics of cervical cancer in the people's republic of China: a study of 10,012 cases from a nationwide working group. *Oncol*. 2013;18(10):1101-1107. doi:10.1634/theoncologist.2013-0123
5. Motoki Y, Mizushima S, Taguri M, et al. Increasing trends in cervical cancer mortality among young Japanese women below the age of 50 years: an analysis using the Kanagawa population-based cancer registry, 1975-2012. *Cancer Epidemiology*. Oct 2015;39(5):700-706. doi:10.1016/j.canep.2015.08.001
6. Jemal A, Simard EP, Dorell C, et al. Annual report to the nation on the status of cancer, 1975-2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. *J Natl Cancer Inst*. 2013;105(3):175-201. doi:10.1093/jnci/djs491
7. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: a review of current American cancer Society guidelines and current issues in cancer screening. *CA A Cancer J Clin*. 2018;68(4):297-316. doi:10.3322/caac.21446
8. Van Dyne EA, Henley SJ, Saraiya M, Thomas CC, Markowitz LE, Benard VB. Trends in human papillomavirus-associated cancers - United States, 1999-2015. *MMWR. Morb and Mortal Wkly Rep*. Aug 24 2018;67(33):918-924. doi:10.15585/mmwr.mm6733a2
9. USPST F, Curry SJ, Krist AH, et al. Screening for cervical cancer. *J Am Med Assoc*. Aug 21 2018;320(7):674-686. doi:10.1001/jama.2018.10897
10. Meanwell CA, Kelly KA, Wilson S, et al. Young age as a prognostic factor in cervical cancer: analysis of population based data from 10 022 cases. *Br Med J*. 1988;296(6619):386-391. doi:10.1136/bmj.296.6619.386
11. Ioka A, Tsukuma H, Ajiki W, Oshima A. Influence of age on cervical cancer survival in Japan. *Jpn J Clin Oncol*. 2005;35(8):464-469. doi:10.1093/jjco/hyi125
12. Quinn BA, Deng X, Colton A, Bandyopadhyay D, Carter JS, Fields EC. Increasing age predicts poor cervical cancer prognosis with subsequent effect on treatment and overall survival. *Brachytherapy*. 2019;18(1):29-37. doi:10.1016/j.brachy.2018.08.016
13. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynecol Obstet*. Oct 2018;143(Suppl 2):22-36. doi:10.1002/ijgo.12611
14. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol*. 2008;26(8):1364-1370. doi:10.1200/JCO.2007.12.9791.
15. Feldman S, Cook E, Davis M, et al. cervical cancer incidence among elderly women in massachusetts compared with younger women. *J Low Genit Tract Dis*. Oct 2018;22(4):314-317. doi:10.1097/LGT.0000000000000435.
16. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA A Cancer J Clin*. 2019;69(1):7-34. doi:10.3322/caac.21551
17. Popadiuk C, Decker K, Gauvreau C. Starting cervical cancer screening at 25 years of age: the time has come. *Can Med Assoc J*. 7 2019;191(1):E1-E2. doi:10.1503/cmaj.181312
18. Elfström KM, Arnheim-Dahlström L, von Karsa L, Dillner J. Cervical cancer screening in Europe: quality assurance and organisation of programmes. *Eur J Cancer*. 2015;51(8):950-968. doi:10.1016/j.ejca.2015.03.008
19. Vale DB, Cavalcante LA, Andrade LALDA, Teixeira JC, Menin TLDR, Zeferino LC. Stage and histology of cervical cancer in women under 25 years old. *J Gynecol Oncol*. 2019;30(4):e55. doi:10.3802/jgo.2019.30.e55
20. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening. *Obstet Gynecol*. 2015;125(2):330-337. doi:10.1097/AOG.0000000000000669
21. Recommendations on screening for cervical cancer. *Can Med Assoc J*. 2013;185(1):35-45. doi:10.1503/cmaj.121505
22. Herbert A, Smith JHF. Women under 25 should be offered screening. *BMJ*. Feb 10 2007;334(7588):1-273. doi:10.1136/bmj.39115.406771.1F
23. The Committee on Practice Bulletins—Gynecology in collaboration with David Chelmow. Practice bulletin no. 168 summary: cervical cancer screening and prevention. *Obstet Gynecol*. Oct 2016;128(4):923-925. doi:10.1097/AOG.0000000000001699
24. Min K-J, Lee YJ, Suh M, et al. The Korean guideline for cervical cancer screening. *J Gynecol Oncol*. 2015;26(3):232-239.
25. Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. *BMJ*. Jul 28 2009;339:b2968. doi:10.1136/bmj.b2968
26. de Rijcke JM, van der Putten HWHM, Lutgens LCHW, et al. Age-specific differences in treatment and survival of patients with cervical cancer in the southeast of the Netherlands, 1986-1996. *Eur J Cancer*. Oct 2002;38(15):2041-2047. doi:10.1016/s0959-8049(02)00315-5
27. Póká R, Juhász B, Lampé L. Cervical cancer in young women: a poorer prognosis? *Int J Gynecol Obstet*. 1994;46(1):33-37. doi:10.1016/0020-7292(94)90306-9
28. Isla-Ortiz D, Palomares-Castillo E, Mille-Loera JE, et al. Cervical cancer in young women: do they have a worse prognosis? A retrospective cohort analysis in a population of Mexico. *Oncol May 10 2020*;25(9):e1363-e1371. doi:10.1634/theoncologist.2019-0902.
29. Seamon LG, Tarrant RL, Fleming ST, et al. Cervical cancer survival for patients referred to a tertiary care center in Kentucky. *Gynecol Oncol*. 2011;123(3):565-570. doi:10.1016/j.ygyno.2011.09.008
30. Nogueira-Rodrigues A, de Melo AC, Garces AHI, et al. Patterns of care and outcome of elderly women diagnosed with cervical cancer in the developing world. *Int J Gynecol Cancer*. Sep 2016;26(7):1246-1251. doi:10.1097/IGC.0000000000000756
31. Wang C, Yang C, Wang W, et al. A prognostic nomogram for cervical cancer after surgery from SEER database. *J Cancer*. 2018;9(21):3923-3928. doi:10.7150/jca.26220
32. Zhang S, Wang X, Li Z, Wang W, Wang L. Score for the overall survival probability of patients with first-diagnosed distant metastatic cervical cancer: a novel nomogram-based risk

- assessment system. *Front in Oncol.* 2019;9:1106. doi:10.3389/fonc.2019.01106
33. Huang Y-T, Wang C-C, Tsai C-S, et al. Clinical behaviors and outcomes for adenocarcinoma or adenosquamous carcinoma of cervix treated by radical hysterectomy and adjuvant radiotherapy or chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* Oct 1 2012;84(2):420-427. doi:10.1016/j.ijrobp.2011.12.013
  34. Galic V, Herzog TJ, Lewin SN, et al. Prognostic significance of adenocarcinoma histology in women with cervical cancer. *Gynecol Oncol.* May 2012;125(2):287-291. doi:10.1016/j.ygyno.2012.01.012
  35. Noh JM, Park W, Kim YS, et al. Comparison of clinical outcomes of adenocarcinoma and adenosquamous carcinoma in uterine cervical cancer patients receiving surgical resection followed by radiotherapy: a multicenter retrospective study (KROG 13-10). *Gynecol Oncol.* 2014;132(3):618-623. doi:10.1016/j.ygyno.2014.01.043
  36. Teke F, Yoney A, Teke M, et al. Lack of any impact of histopathology type on prognosis in patients with early-stage adenocarcinoma and squamous cell carcinoma of the uterine cervix. *Asian Pac J Cancer Prev.* 2014;15(6):2815-2819. doi:10.7314/apjcp.2014.15.6.2815.
  37. Jung EJ, Byun JM, Kim YN, et al. Cervical adenocarcinoma has a poorer prognosis and a higher propensity for distant recurrence than squamous cell carcinoma. *Int J Gynecol Cancer.* 2017; 27(6):1228-1236. doi:10.1097/IGC.0000000000001009
  38. Intaraphet S, Kasatpibal N, Siriaunkgul S, et al. Prognostic impact of histology in patients with cervical squamous cell carcinoma, adenocarcinoma and small cell neuroendocrine carcinoma. *Asian Pac J Cancer Prev.* 2013;14(9):5355-5360. doi:10.7314/apjcp.2013.14.9.5355
  39. Nakanishi T, Wakai K, Ishikawa H, et al. A comparison of ovarian metastasis between squamous cell carcinoma and adenocarcinoma of the uterine cervix. *Gynecol Oncol.* 2001;82(3): 504-509. doi:10.1006/ygyno.2001.6316
  40. Yang L, Jia X, Li N, Chen C, Liu Y, Wang H. Comprehensive clinic-pathological characteristics of cervical cancer in southwestern China and the clinical significance of histological type and lymph node metastases in young patients. *PLoS One.* 2013; 8(10):e75849. doi:10.1371/journal.pone.0075849.
  41. Cai H-B, Liu X-M, Huang Y, et al. Trends in cervical cancer in young women in Hubei, China. *Int J Gynecol Cancer.* Oct 2010; 20(7):1240-1243. doi:10.1111/igc.0b013e3181eccc79
  42. Kong Y, Zong L, Yang J, Wu M, Xiang Y. Cervical cancer in women aged 25 years or younger: a retrospective study. *Cancer Manag Res.* 2019;Volume 11:2051-2058. doi:10.2147/CMAR.S195098
  43. Pelkofski E, Stine J, Wages NA, Gehrig PA, Kim KH, Cantrell LA. cervical cancer in women aged 35 years and younger. *Clin Therapeut.* 2016;38(3):459-466. doi:10.1016/j.clinthera.2016.01.024
  44. Touch S, Oh J-K. Knowledge, attitudes, and practices toward cervical cancer prevention among women in Kampong Speu Province, Cambodia. *BMC Cancer.* 2018;18(1):294. doi:10.1186/s12885-018-4198-8
  45. Volterrani F, Feltre L, Sigurta' D, Di Giuseppe M, Luciani L. Radiotherapy versus surgery in the treatment of cervix stage Ib cancer. *Int J Radiat Oncol Biol Phys.* 1983;9(12):1781-1784. doi:10.1016/0360-3016(83)90344-9
  46. Rungruang B, Courtney-Brooks M, Beriwal S, et al. Surgery versus radiation therapy for stage IB2 cervical carcinoma: a population-based analysis. *Int J Gynecol Cancer.* 2012;22(3): 484-489. doi:10.1097/IGC.0b013e31823f890f
  47. Bansal N, Herzog TJ, Shaw RE, Burke WM, Deutsch I, Wright JD. Primary therapy for early-stage cervical cancer: radical hysterectomy vs radiation. *Am J Obstet Gynecol.* 2009;201(5): e1-485. doi:10.1016/j.ajog.2009.06.015
  48. Bentivegna E, Gouy S, Maulard A, Chargari C, Leary A, Morice P. Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review. *Lancet Oncol.* 2016;17(6): e240-e253. doi:10.1016/S1470-2045(16)30032-8.
  49. Koh W-J, Abu-Rustum NR, Bean S, et al. Cervical cancer, version 3.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw.* 2019;17(1):64-84. doi:10.6004/jnccn.2019.0001
  50. de Gregorio A, Widschwendter P, Ebner F, et al. Influence of the new FIGO classification for cervical cancer on patient survival: a retrospective analysis of 265 histologically confirmed cases with FIGO stages IA to IIB. *Oncology.* 2020;98(2):91-97. doi:10.1159/000503149