

Original Article

Histologic Subtypes, Treatment Patterns, and Survival Outcomes in Cervical Cancer: A Population-based SEER Study

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ABSTRACT

Aim: Cervical cancer comprises histologically distinct subtypes whose independent prognostic significance remains uncertain. This study aimed to characterize clinicopathologic features, treatment patterns, and survival outcomes according to histologic subtype in a large population-based cohort.

Methods: Using the Surveillance, Epidemiology, and End Results Research Data, 17 registries database, we identified 62,048 women diagnosed with cervical cancer from 2004 to 2023 for inclusion in this retrospective cohort study. Five histologic categories were defined for classification: squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, neuroendocrine/small cell carcinoma, and other/rare histologic subtypes. Overall survival (OS) and cancer-specific survival (CSS) were estimated using the Kaplan-Meier method and compared using multivariable Cox regression, Fine-Gray competing-risk analysis, and stage-stratified models with formal histology-by-stage interaction testing.

Results: Squamous cell carcinoma accounted for the largest share of cases (64.9%), while adenocarcinoma accounted for 24.2% of cases. In univariable analysis, adenocarcinoma was associated with lower risk of death than squamous cell carcinoma [OS hazard ratio (HR) 0.69], but after multivariable adjustment, this reversed to a higher risk [adjusted HR (aHR) 1.11 for OS, 1.20 for CSS, both $p < 0.001$]. This association differed by stage: adenocarcinoma showed a lower risk in localized disease (aHR 0.90, $p = 0.018$) but a higher risk in regional and distant disease (both $p < 0.001$); this pattern was confirmed by formal interaction testing ($p < 0.001$). Neuroendocrine/small cell carcinoma carried the highest adjusted risk among all subtypes at every stage (aHR 2.20 for OS and 2.29 for CSS) and had the greatest burden of distant metastasis, with a 5-year OS of 29.4%.

Conclusion: The prognostic significance of cervical cancer histologic subtype depends on disease stage, with adenocarcinoma showing associations opposite those of squamous cell carcinoma in localized versus advanced disease. Neuroendocrine/small-cell carcinoma carries the poorest prognosis at all stages and warrants dedicated treatment strategies.

Keywords: Cervical cancer, histologic subtype, neuroendocrine carcinoma, SEER, survival, prognosis

Introduction

Cervical cancer remains the fourth most common malignancy among women worldwide, with an estimated 662,301 new cases and 348,874 deaths in 2022 [1]. Screening programs and human papillomavirus vaccination have reduced incidence in many countries, but the disease burden remains

disproportionately high in regions where these interventions have not achieved full coverage [2].

Cervical cancer is not a single disease entity. Squamous cell carcinoma accounts for the majority of cases, while adenocarcinoma, adenosquamous carcinoma, neuroendocrine/small cell carcinoma, and other rare histologic subtypes together represent a clinically significant minority

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[3]. Screening has preferentially reduced the incidence of squamous lesions, and as a result, the relative proportion of adenocarcinoma within the overall case mix has increased even as absolute case numbers have declined [4].

The prognostic significance of histologic subtype remains unresolved. Several population-based cohorts have reported that adenocarcinoma is associated with worse survival than squamous cell carcinoma, particularly among patients treated with concurrent chemoradiation for locally advanced disease [4]. Other analyses using propensity score matching for stage and treatment found no independent survival difference between the two subtypes [5]. These conflicting findings indicate that the prognostic weight of histologic subtype, independent of stage and treatment, has not been consistently established.

Rarer histologic subtypes remain poorly characterized due to their low incidence. Neuroendocrine and small cell carcinoma of the cervix account for less than 2% of cervical malignancies, yet these tumors demonstrate early lymphovascular invasion, a high burden of distant metastasis, and markedly reduced survival, with reported 5-year overall survival (OS) below 35% in most series [6]. Because prospective trial data are lacking for this population, treatment decisions are largely extrapolated from squamous cell carcinoma and adenocarcinoma paradigms, an approach that has not been formally validated [6].

This study examined the relationship between histologic subtype and patient characteristics, treatment patterns, and survival outcomes in a large, contemporary cohort of patients with cervical cancer.

Methods

Study Design and Data Source

Data for this population-based retrospective cohort were drawn from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, which aggregates incidence, clinicopathologic, first-course treatment, and survival information from cancer registries throughout the United States. We accessed the incidence, SEER Research Data, 17 registries, november 2025 submission (2000-2023) through SEERStat software. This registry set, which records one entry per tumor, represents roughly 26.5% of the United States population, according to 2020 census figures. This study used de-identified, publicly available data from the SEER Research Data (17 registries) database. This study was based exclusively on de-identified data obtained from the SEER Research Data database. Institutional ethics committee approval was not required for this secondary data analysis. Informed consent was not required because the study used de-identified registry data without direct patient contact.

Study Population

The initial SEER data extraction included female patients diagnosed with malignant cervical cancer between 2000 and 2023. Cases were restricted to patients for whom cervical

cancer was recorded either as one primary only or as the first of two or more primary cancers, based on the SEER sequence number variable. Male patients, cases with non-malignant tumors, and cases with non-cervical primary sites were excluded during the SEER*Stat selection stage.

Although the initial extraction covered 2000-2023, the primary analytic cohort was restricted to patients diagnosed between 2004 and 2023 because the combined summary stage with expanded regional codes variable is available only from 2004 onward. After excluding patients diagnosed between 2000 and 2003, the final analytic cohort included 62,048 patients.

For metastatic-site analyses, patients with distant-stage disease diagnosed from 2010 to 2023 were evaluated separately because SEER site-specific metastasis variables for bone, brain, liver, and lung are available only from 2010 onward. Distant lymph-node and other metastasis variables were analyzed in the 2016-2023 subset, consistent with their availability in SEER.

Histologic Subtype Classification

Histologic subtype was assigned using International Classification of Diseases for Oncology-third edition (ICD-O-3) morphology codes recorded in the "Histologic Type ICD-O-3" and "ICD-O-3 Hist/behav" variables. Each patient was categorized into one of five mutually exclusive groups: squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, neuroendocrine/small cell carcinoma, or other/rare histology. Squamous cell carcinoma served as the reference group in survival models because it was the most common histologic subtype.

Covariates

Descriptive and multivariable analyses included the following variables: age group at diagnosis, year of diagnosis, race/ethnicity, marital status, county-level median household income, rural-urban continuum, primary cervical site, tumor grade, tumor size, summary stage, primary tumor surgery, radiation therapy, and chemotherapy.

Age was categorized as <40, 40-59, 60-74, and ≥75 years. Year of diagnosis was grouped as 2004-2008, 2009-2013, 2014-2018, and 2019-2023. For the multivariable Cox regression models, the year of diagnosis was recategorized into three broader periods (2004-2009, 2010-2015, and 2016-2023) to preserve adequate event counts within each period stratum for the less common histologic subtypes; the finer four-period grouping was retained for descriptive characterization of the cohort. The summary stage was categorized as localized, regional, distant, or unknown/unstaged. Tumor size was categorized as ≤20 mm, 21-40 mm, 41-60 mm, >60 mm, microscopic focus, and unknown/missing. Treatment variables were derived from SEER first-course treatment recodes, including primary tumor surgery, radiation therapy, and chemotherapy. Because the SEER chemotherapy and radiation variables include "no/unknown" categories, these variables were interpreted as indicating treatment receipt versus no/unknown rather than as confirmed absence of therapy.

Outcomes

The primary outcomes were OS and cancer-specific survival (CSS). OS was defined as the time from diagnosis to death from any cause. CSS was defined as the time from diagnosis to death attributable to cervical cancer according to the SEER cause-specific death classification, with deaths from other causes censored. Survival time was measured in months using the SEER survival months variable. Patients with zero-month survival were recoded as 0.5 months for time-to-event analyses.

Statistical Analysis

Baseline clinicopathologic characteristics and treatment patterns were summarized according to histologic subtype. Categorical variables were presented as frequencies and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous or ordinal time-related variables were summarized using the median and interquartile range, and compared using the Kruskal-Wallis test when appropriate.

Survival outcomes were estimated using the Kaplan-Meier method; median follow-up was estimated using the reverse Kaplan-Meier method. OS and CSS curves were compared across histologic subtypes using the log-rank test. Survival probabilities at 1, 3, and 5 years were reported with 95% confidence intervals (CIs) calculated using Greenwood's standard errors and log-log transformation.

Univariable Cox proportional hazards regression models for OS and CSS were fitted and are presented as supplementary analyses. Multivariable Cox proportional hazards models were then constructed to estimate adjusted hazard ratios and 95% CIs for OS and CSS. Covariates were selected a priori based on clinical relevance and data availability rather than on statistical significance in univariable analyses. The multivariable models included histologic subtype, age group, year of diagnosis, race/ethnicity, marital status, county-level household income, rural-urban continuum, primary cervical site, summary stage, tumor grade, tumor size, primary tumor surgery, radiation therapy, and chemotherapy. The proportional hazards assumption was evaluated using Schoenfeld residuals and visual inspection of log-minus-log survival plots where applicable.

To assess the robustness of the CSS findings in the presence of competing mortality, a Fine-Gray competing-risk regression model was performed for cervical cancer-specific mortality, treating death from other causes as a competing event [7]. Results were reported as adjusted subdistribution hazard ratios with 95% CIs. Stage-stratified multivariable Cox models were also fitted separately for patients with localized, regional, and distant disease to evaluate whether the prognostic association of histologic subtype differed by disease extent. Interaction terms between formal histology and summary stage were added to the adjusted Cox models, and the global interaction effect was assessed using a joint Wald test. Patients with unknown or unstaged disease were excluded from the interaction analysis.

Statistical significance was defined as a two-sided p value below 0.05. All analyses were performed using Python 3.12, with data handling and statistical computation carried out using the pandas, NumPy, SciPy, lifelines, and statsmodels packages. Competing-risk analyses were performed using a Fine-Gray subdistribution hazards implementation, consistent with the cmprsk methodology. Figures were generated using Matplotlib.

Results

Study Population and Baseline Characteristics

Between 2004 and 2023, 62,048 women diagnosed with cervical cancer met the inclusion criteria for the analytic cohort (Figure 1). Squamous cell carcinoma was the most common histologic subtype ($n=40,245$, 64.9%), followed by adenocarcinoma ($n=15,026$, 24.2%), other/rare histologic subtypes ($n=3,961$, 6.4%), adenosquamous carcinoma ($n=1,889$, 3.0%), and neuroendocrine/small cell carcinoma ($n=927$, 1.5%).

Baseline clinicopathologic characteristics differed significantly across histologic subtypes (Table 1). Summary stage differed by histologic subtype; with distant-stage disease at diagnosis was most frequent in neuroendocrine/small-cell carcinoma (39.9%) and in other/rare histologies (22.5%), compared with 14.1% for squamous cell carcinoma and 11.7% for adenocarcinoma ($p<0.001$). Tumor size also differed by histologic subtype, with tumors >60 mm most frequent in neuroendocrine/small cell carcinoma (27.1%) and tumors ≤ 20 mm most frequent in adenocarcinoma (29.6%). Tumor grade differed by histologic subtype: grade III/IV (poorly differentiated) histology was most frequent in neuroendocrine/small cell carcinoma (16.5%) and least frequent in adenocarcinoma (5.2%) among subtypes with recorded grade. The primary cervical site also differed by histologic subtype, with endocervical origin most frequent in adenocarcinoma (53.2%) and least frequent in squamous cell carcinoma (8.9%).

Treatment Patterns

Treatment patterns varied significantly according to histologic subtype (Table 2). Primary tumor surgery was performed most frequently in adenocarcinoma (69.9%) and least frequently in other/rare histology (33.0%) and in neuroendocrine/small cell carcinoma (39.2%). Chemotherapy was administered to 80.3% of patients with neuroendocrine/small cell carcinoma, compared with 37.6% of patients with adenocarcinoma. Radiation therapy was administered to 61.2% of patients with adenosquamous carcinoma and to 30.0% of patients with other or rare histologies. Median time from diagnosis to treatment initiation ranged from 19 days (other/rare histology) to 28 days (adenocarcinoma and adenosquamous carcinoma) ($p<0.001$).

Survival Outcomes by Histologic Subtype

Median follow-up, estimated using the reverse Kaplan-Meier method, was 107 months (95% CI, 106-109) for the overall

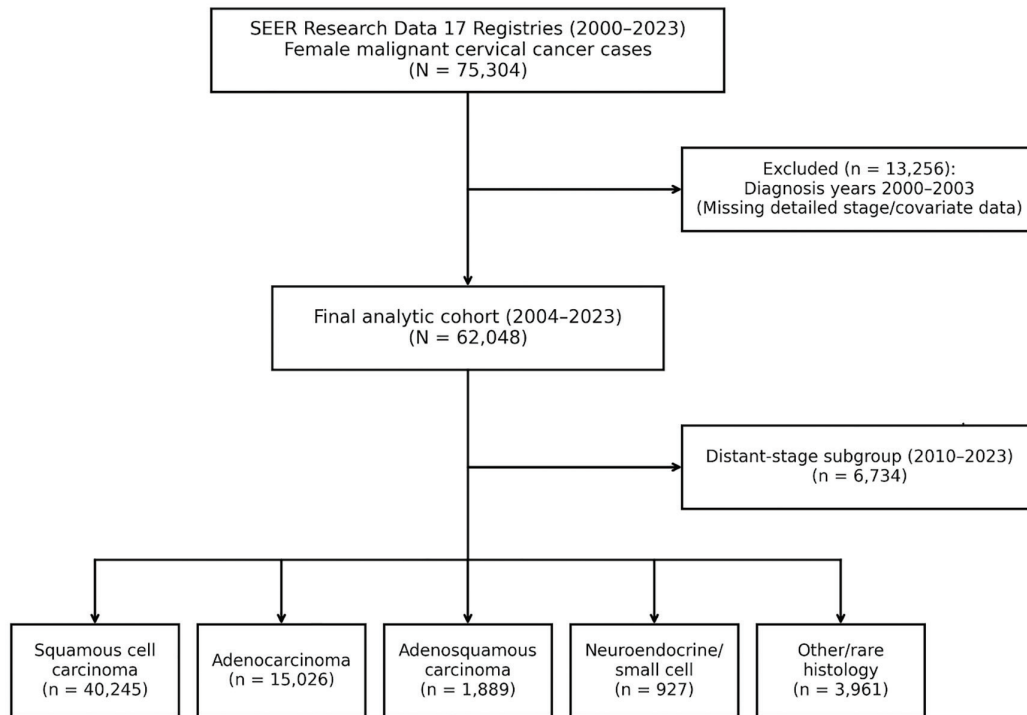


Figure 1. Study flow diagram. Flow diagram showing cohort selection from the SEER Research Data 17 Registries database and classification according to histologic subtype
SEER: Surveillance, Epidemiology, and End Results

Table 1. Baseline clinicopathologic characteristics of patients with cervical cancer according to histologic subtype, SEER 2004-2023

Characteristic	Category	Total (n=62,048)	Squamous cell carcinoma (n=40,245)	Adenocarcinoma (n=15,026)	Adenosquamous carcinoma (n=1,889)	Neuroendocrine/ small cell carcinoma (n=927)	Other/rare histology (n=3,961)	p value
Age group, years	<40	16,893 (27.2)	10,952 (27.2)	4,330 (28.8)	573 (30.3)	269 (29.0)	769 (19.4)	<0.001
	40-59	28,805 (46.4)	18,635 (46.3)	7,347 (48.9)	947 (50.1)	412 (44.4)	1,464 (37.0)	
	60-74	11,660 (18.8)	7,656 (19.0)	2,527 (16.8)	287 (15.2)	181 (19.5)	1,009 (25.5)	
	≥75	4,690 (7.6)	3,002 (7.5)	822 (5.5)	82 (4.3)	65 (7.0)	719 (18.2)	
Year of diagnosis	2004-2008	15,739 (25.4)	10,506 (26.1)	3,343 (22.2)	647 (34.3)	194 (20.9)	1,049 (26.5)	<0.001
	2009-2013	15,007 (24.2)	9,729 (24.2)	3,624 (24.1)	481 (25.5)	212 (22.9)	961 (24.3)	
	2014-2018	15,871 (25.6)	10,091 (25.1)	4,027 (26.8)	437 (23.1)	282 (30.4)	1,034 (26.1)	
	2019-2023	15,431 (24.9)	9,919 (24.6)	4,032 (26.8)	324 (17.2)	239 (25.8)	917 (23.2)	
Race/ethnicity	Non-Hispanic White	31,280 (50.4)	19,543 (48.6)	8,363 (55.7)	922 (48.8)	452 (48.8)	2,000 (50.5)	<0.001
	Non-Hispanic Black	7,852 (12.7)	5,815 (14.4)	1,055 (7.0)	200 (10.6)	130 (14.0)	652 (16.5)	
	Non-Hispanic American Indian/ Alaska Native	591 (1.0)	401 (1.0)	124 (0.8)	18 (1.0)	5 (0.5)	43 (1.1)	
	Non-Hispanic Asian or Pacific Islander	6,196 (10.0)	3,906 (9.7)	1,598 (10.6)	224 (11.9)	128 (13.8)	340 (8.6)	
	Hispanic, all races	15,638 (25.2)	10,296 (25.6)	3,731 (24.8)	523 (27.7)	209 (22.5)	879 (22.2)	
	Non-Hispanic unknown race	491 (0.8)	284 (0.7)	155 (1.0)	2 (0.1)	3 (0.3)	47 (1.2)	

Table 1. Continued

Characteristic	Category	Total (n=62,048)	Squamous cell carcinoma (n=40,245)	Adenocarcinoma (n=15,026)	Adenosquamous carcinoma (n=1,889)	Neuroendocrine/ small cell carcinoma (n=927)	Other/rare histology (n=3,961)	p value
Marital status	Married	25,411 (41.0)	15,241 (37.9)	7,608 (50.6)	865 (45.8)	393 (42.4)	1,304 (32.9)	<0.001
	Single/never married	18,946 (30.5)	13,056 (32.4)	3,837 (25.5)	562 (29.8)	291 (31.4)	1,200 (30.3)	
	Divorced/ separated/widowed	13,573 (21.9)	9,277 (23.1)	2,575 (17.1)	367 (19.4)	197 (21.3)	1,157 (29.2)	
	Unmarried/ domestic partner	425 (0.7)	302 (0.8)	98 (0.7)	12 (0.6)	3 (0.3)	10 (0.3)	
	Unknown	3,693 (6.0)	2,369 (5.9)	908 (6.0)	83 (4.4)	43 (4.6)	290 (7.3)	
County-level median household income	<\$75,000	20,414 (32.9)	14,087 (35.0)	4,159 (27.7)	548 (29.0)	300 (32.4)	1,320 (33.3)	<0.001
	\$75,000-\$99,999	28,173 (45.4)	18,056 (44.9)	7,005 (46.6)	929 (49.2)	414 (44.7)	1,769 (44.7)	
	≥\$100,000	13,449 (21.7)	8,094 (20.1)	3,860 (25.7)	412 (21.8)	213 (23.0)	870 (22.0)	
	Unknown/missing	12 (0.0)	8 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	
Rural-urban continuum	Metropolitan ≥1 million	37,887 (61.1)	23,992 (59.6)	9,596 (63.9)	1,262 (66.8)	593 (64.0)	2,444 (61.7)	<0.001
	Metropolitan <1 million	16,937 (27.3)	11,240 (27.9)	3,949 (26.3)	456 (24.1)	238 (25.7)	1,054 (26.6)	
	Nonmetropolitan	7,104 (11.4)	4,927 (12.2)	1,463 (9.7)	165 (8.7)	96 (10.4)	453 (11.4)	
	Unknown/missing	120 (0.2)	86 (0.2)	18 (0.1)	6 (0.3)	0 (0.0)	10 (0.3)	
Primary cervical site	Endocervix	12,422 (20.0)	3,577 (8.9)	7,996 (53.2)	386 (20.4)	101 (10.9)	362 (9.1)	<0.001
	Exocervix	1,795 (2.9)	1,465 (3.6)	217 (1.4)	41 (2.2)	18 (1.9)	54 (1.4)	
	Cervix uteri, NOS	46,609 (75.1)	34,299 (85.2)	6,619 (44.1)	1,409 (74.6)	786 (84.8)	3,496 (88.3)	
	Overlapping lesion	1,222 (2.0)	904 (2.2)	194 (1.3)	53 (2.8)	22 (2.4)	49 (1.2)	
Summary stage	Localized	27,048 (43.6)	16,314 (40.5)	8,785 (58.5)	809 (42.8)	206 (22.2)	934 (23.6)	<0.001
	Regional	22,699 (36.6)	16,945 (42.1)	3,879 (25.8)	748 (39.6)	315 (34.0)	812 (20.5)	
	Distant	8,982 (14.5)	5,670 (14.1)	1,764 (11.7)	288 (15.2)	370 (39.9)	890 (22.5)	
	Unknown/unstaged	3,319 (5.3)	1,316 (3.3)	598 (4.0)	44 (2.3)	36 (3.9)	1,325 (33.5)	
Tumor grade	Grade I/well differentiated	32,496 (52.4)	20,993 (52.2)	8,960 (59.6)	1,188 (62.9)	421 (45.4)	934 (23.6)	<0.001
	Grade II/moderately differentiated	5,787 (9.3)	4,326 (10.7)	1,343 (8.9)	92 (4.9)	6 (0.6)	20 (0.5)	
	Grade III/IV/poorly- undifferentiated	4,557 (7.3)	3,130 (7.8)	778 (5.2)	199 (10.5)	153 (16.5)	297 (7.5)	
	Unknown/blank	19,208 (31.0)	11,796 (29.3)	3,945 (26.3)	410 (21.7)	347 (37.4)	2,710 (68.4)	
Tumor size	≤20 mm	12,806 (20.6)	7,673 (19.1)	4,442 (29.6)	375 (19.9)	103 (11.1)	213 (5.4)	<0.001
	21-40 mm	9,370 (15.1)	5,734 (14.2)	2,854 (19.0)	403 (21.3)	132 (14.2)	247 (6.2)	
	41-60 mm	9,965 (16.1)	7,153 (17.8)	1,982 (13.2)	371 (19.6)	153 (16.5)	306 (7.7)	
	>60 mm	8,918 (14.4)	6,431 (16.0)	1,345 (9.0)	256 (13.6)	251 (27.1)	635 (16.0)	
	Microscopic focus	1,135 (1.8)	885 (2.2)	164 (1.1)	7 (0.4)	0 (0.0)	79 (2.0)	
	Unknown/missing	19,854 (32.0)	12,369 (30.7)	4,239 (28.2)	477 (25.3)	288 (31.1)	2,481 (62.6)	

Values are presented as number (%). Percentages are column percentages within each histologic subtype unless otherwise indicated. The study cohort included female patients diagnosed with malignant cervical cancer between 2004 and 2023 in the SEER Research Data 17 Registries database, restricted to one primary only or first of two or more primary cancers. Histologic subtypes were grouped using ICD-O-3 morphology codes. Summary stage was based on the SEER Combined Summary Stage with Expanded Regional Codes variable. County-level median household income and rural-urban continuum were derived from SEER county attributes. P values were calculated using the χ^2 test or Fisher's exact test, as appropriate.

NOS: Not otherwise specified, SEER: Surveillance, Epidemiology, and End Results, ICD-O-3: International Classification of Diseases for Oncology-third edition

Table 2. Treatment patterns of patients with cervical cancer according to histologic subtype, SEER 2004-2023

Characteristic	Category	Total (n=62,048)	Squamous cell carcinoma (n=40,245)	Adenocarcinoma (n=15,026)	Adenosquamous carcinoma (n=1,889)	Neuroendocrine/ small cell carcinoma (n=927)	Other/ rare histology (n=3,961)	p value
Primary tumor surgery	Surgery performed	32,905 (53.0)	19,523 (48.5)	10,506 (69.9)	1,206 (63.8)	363 (39.2)	1,307 (33.0)	<0.001
	No surgery	28,488 (45.9)	20,590 (51.2)	4,471 (29.8)	680 (36.0)	560 (60.4)	2,187 (55.2)	
	Unknown	655 (1.1)	132 (0.3)	49 (0.3)	3 (0.2)	4 (0.4)	467 (11.8)	
Radiation therapy	Radiation given	33,078 (53.3)	24,027 (59.7)	6,168 (41.0)	1,157 (61.2)	538 (58.0)	1,188 (30.0)	<0.001
	No/unknown radiation	28,970 (46.7)	16,218 (40.3)	8,858 (59.0)	732 (38.8)	389 (42.0)	2,773 (70.0)	
Chemotherapy	Chemotherapy yes	29,888 (48.2)	21,260 (52.8)	5,651 (37.6)	1,042 (55.2)	744 (80.3)	1,191 (30.1)	<0.001
	No/unknown chemotherapy	32,160 (51.8)	18,985 (47.2)	9,375 (62.4)	847 (44.8)	183 (19.7)	2,770 (69.9)	
Surgery- radiation sequence	No radiation and/or no surgery	48,959 (78.9)	31,791 (79.0)	11,673 (77.7)	1,224 (64.8)	724 (78.1)	3,547 (89.5)	<0.001
	Radiation after surgery	11,669 (18.8)	7,612 (18.9)	2,951 (19.6)	593 (31.4)	177 (19.1)	336 (8.5)	
	Radiation before surgery	1,146 (1.8)	673 (1.7)	326 (2.2)	61 (3.2)	23 (2.5)	63 (1.6)	
	Radiation before and after surgery	193 (0.3)	116 (0.3)	61 (0.4)	9 (0.5)	0 (0.0)	7 (0.2)	
	Other/unknown sequence	81 (0.1)	53 (0.1)	15 (0.1)	2 (0.1)	3 (0.3)	8 (0.2)	
Regional lymph node surgery	None/not performed or not applicable	39,901 (64.3)	28,377 (70.5)	7,157 (47.6)	891 (47.2)	628 (67.7)	2,848 (71.9)	<0.001
	1 to 3 regional lymph nodes removed	1,539 (2.5)	871 (2.2)	508 (3.4)	64 (3.4)	30 (3.2)	66 (1.7)	
	4 or more regional lymph nodes removed	17,393 (28.0)	9,505 (23.6)	6,435 (42.8)	849 (44.9)	229 (24.7)	375 (9.5)	
	Sentinel lymph node biopsy±lymph node removal	1,394 (2.2)	678 (1.7)	621 (4.1)	55 (2.9)	14 (1.5)	26 (0.7)	
	Biopsy/aspiration only	317 (0.5)	237 (0.6)	48 (0.3)	7 (0.4)	4 (0.4)	21 (0.5)	
	Unknown/not applicable	1,504 (2.4)	577 (1.4)	257 (1.7)	23 (1.2)	22 (2.4)	625 (15.8)	

Table 2. Continued

Characteristic	Category	Total (n=62,048)	Squamous cell carcinoma (n=40,245)	Adenocarcinoma (n=15,026)	Adenosquamous carcinoma (n=1,889)	Neuroendocrine/ small cell carcinoma (n=927)	Other/ rare histology (n=3,961)	p value
Reason no cancer- directed surgery	Surgery performed	32,905 (53.0)	19,523 (48.5)	10,506 (69.9)	1,206 (63.8)	363 (39.2)	1,307 (33.0)	<0.001
	Not recommended	26,132 (42.1)	19,028 (47.3)	4,028 (26.8)	634 (33.6)	521 (56.2)	1,921 (48.5)	
	Not recommended/ contraindicated	901 (1.5)	653 (1.6)	146 (1.0)	18 (1.0)	16 (1.7)	68 (1.7)	
	Recommended but not performed, unknown reason	681 (1.1)	432 (1.1)	132 (0.9)	11 (0.6)	10 (1.1)	96 (2.4)	
	Recommended but refused	375 (0.6)	218 (0.5)	88 (0.6)	6 (0.3)	4 (0.4)	59 (1.5)	
	Recommended, unknown if performed	360 (0.6)	238 (0.6)	74 (0.5)	10 (0.5)	9 (1.0)	29 (0.7)	
	Patient died before surgery	33 (0.1)	16 (0.0)	6 (0.0)	0 (0.0)	0 (0.0)	11 (0.3)	
	Unknown/DCO/ autopsy only	661 (1.1)	137 (0.3)	46 (0.3)	4 (0.2)	4 (0.4)	470 (11.9)	
Time from diagnosis to treatment, days	Median (IQR)	26 (0-49)	26 (0-49)	28 (0-50)	28 (6-47)	23 (10-41)	19 (0-41)	<0.001

Values are presented as number (%) unless otherwise indicated. Percentages are column percentages within each histologic subtype. P values were calculated using the χ^2 test for categorical variables and the Kruskal-Wallis test for time from diagnosis to treatment. "No/unknown chemotherapy" and "No/unknown radiation" reflect SEER treatment recode categories and should not be interpreted as confirmed absence of treatment in every case.

DCO: Death certificate only, IQR: Interquartile range, SEER: Surveillance, Epidemiology, and End Results

cohort. A total of 23,568 deaths from any cause (38.0%) and 17,841 cervical cancer-specific deaths (28.8%) occurred during follow-up (Table 3).

Five-year OS was highest for adenocarcinoma (74.6%, 95% CI, 73.8-75.3) and lowest for neuroendocrine/small cell carcinoma (29.4%, 95% CI, 26.3-32.6). Five-year OS for squamous cell carcinoma, adenosquamous carcinoma, and other/rare histologies was 65.4%, 62.2%, and 41.1%, respectively. Five-year CSS rates followed a similar pattern, ranging from 78.2% (95% CI, 77.5-78.9) for adenocarcinoma to 32.7% (95% CI, 29.4-36.1) for neuroendocrine/small cell carcinoma. Kaplan-Meier curves for overall and cancer-specific survival differed significantly across histologic subtypes, as assessed by the log-rank test ($p < 0.001$ for both comparisons) (Figure 2).

Survival also differed significantly by age group (Figure 3) and by diagnosis era (Figure 4). Five-year OS ranged from 80.9% in patients <40 years to 26.6% in patients ≥ 75 years (log-rank $p < 0.001$). Across diagnostic eras, 5-year OS ranged from 65.0% (2009-2013 and 2014-2018) to 66.8% (2019-2023) (log-rank $p = 0.010$) (Supplementary Table 1).

Univariable and Multivariable Cox Regression Analysis

In univariable analysis, adenocarcinoma was associated with lower risk of death compared with squamous cell carcinoma

for both OS (HR 0.69, 95% CI, 0.67-0.72) and CSS (HR 0.73, 95% CI, 0.70-0.76) (Supplementary Table 2). After adjustment for age, year of diagnosis, race/ethnicity, marital status, income, rural-urban continuum, primary cervical site, summary stage, tumor grade, tumor size, and treatment variables, this association reversed: adenocarcinoma was associated with a higher risk of death relative to squamous cell carcinoma for both OS (aHR 1.11, 95% CI, 1.06-1.15, $p < 0.001$) and CSS (aHR 1.20, 95% CI, 1.15-1.25, $p < 0.001$) (Table 4).

Neuroendocrine/small cell carcinoma showed the highest adjusted risk among all histologic subtypes for both OS (aHR 2.20, 95% CI, 2.03-2.38) and CSS (aHR 2.29, 95% CI, 2.10-2.49). Adenosquamous carcinoma (aHR 1.39, 95% CI, 1.29-1.49 for OS; aHR 1.50, 95% CI, 1.39-1.62 for CSS) and other/rare histologies (aHR 1.70, 95% CI, 1.62-1.78 for OS; aHR 1.83, 95% CI, 1.74-1.93 for CSS) also showed a higher adjusted risk relative to squamous cell carcinoma ($p < 0.001$ for all comparisons).

Among other covariates, distant-stage disease carried the highest adjusted hazard for both outcomes: OS aHR 7.74 (95% CI, 7.37-8.13) and CSS aHR 12.48 (95% CI, 11.74-13.27), both relative to localized stage. Receipt of chemotherapy (OS aHR 0.68, 95% CI, 0.65-0.70; CSS aHR 0.67, 95% CI, 0.65-0.70) and receipt of radiation therapy (OS aHR 0.84, 95% CI, 0.81-0.87; CSS aHR 0.78, 95% CI, 0.75-0.82) were each associated with

Table 3. Survival outcomes according to histologic subtype, SEER 2004-2023

Characteristic	Category	Total (n=62,048)	Squamous cell carcinoma (n=40,245)	Adenocarcinoma (n=15,026)	Adenosquamous carcinoma (n=1,889)	Neuroendocrine/ small cell carcinoma (n=927)	Other/rare histology (n=3,961)	p value
Follow-up, months	Median (reverse Kaplan-Meier, 95% CI)	107 (106-109)	108 (106-110)	102 (100-104)	134 (128-142)	93 (83-104)	120 (115-126)	
Overall survival event	Death from any cause, n (%)	23,568 (38.0)	15,438 (38.4)	4,261 (28.4)	817 (43.3)	637 (68.7)	2,415 (61.0)	<0.001
Overall survival	Median, months (95% CI)	197 (192-203)	185 (180-192)	Not reached	177 (149-201)	18 (16-20)	23 (20-26)	<0.001
Overall survival	1-year OS (95% CI)	84.6% (84.3-84.9)	85.8% (85.5-86.2)	89.9% (89.4-90.4)	85.8% (84.1-87.3)	61.0% (57.7-64.1)	57.4% (55.8-58.9)	
Overall survival	3-year OS (95% CI)	70.9% (70.5-71.3)	71.2% (70.7-71.7)	79.7% (79.0-80.3)	68.3% (66.0-70.4)	33.7% (30.6-36.9)	45.1% (43.5-46.7)	
Overall survival	5-year OS (95% CI)	65.4% (65.0-65.8)	65.4% (64.9-65.9)	74.6% (73.8-75.3)	62.2% (59.9-64.5)	29.4% (26.3-32.6)	41.1% (39.5-42.7)	
Cancer- specific survival event	Death attributable to cervical cancer, n (%)	17,841 (28.8)	11,350 (28.2)	3,287 (21.9)	656 (34.7)	573 (61.8)	1,975 (49.9)	<0.001
Cancer- specific survival	Median, months (95% CI)	Not reached	Not reached	Not reached	Not reached	20 (18-23)	38 (32-47)	<0.001
Cancer- specific survival	1-year CSS (95% CI)	86.6% (86.3-86.9)	87.7% (87.4-88.0)	91.2% (90.8-91.7)	87.3% (85.7-88.8)	64.1% (60.8-67.2)	62.0% (60.4-63.5)	
Cancer- specific survival	3-year CSS (95% CI)	74.6% (74.2-74.9)	75.0% (74.6-75.5)	82.2% (81.6-82.9)	71.4% (69.2-73.5)	37.0% (33.7-40.4)	50.3% (48.6-51.9)	
Cancer- specific survival	5-year CSS (95% CI)	70.4% (70.0-70.8)	70.7% (70.3-71.2)	78.2% (77.5-78.9)	66.3% (63.9-68.5)	32.7% (29.4-36.1)	47.0% (45.3-48.7)	

Values are presented as number (%) or Kaplan-Meier estimates with 95% confidence intervals (CI) unless otherwise indicated. Follow-up was estimated using the reverse Kaplan-Meier method and is presented as median months with 95% confidence interval. OS was defined from diagnosis to death from any cause; CSS was defined from diagnosis to death attributable to cervical cancer, with deaths from other causes censored. Survival probabilities are Kaplan-Meier estimates at 12, 36, and 60 months. Confidence intervals for Kaplan-Meier estimates were calculated using Greenwood standard errors with log-log transformation. P values for event distributions were calculated using the χ^2 test; p values for survival comparisons were based on the log-rank test across histologic subtypes.

CSS: Cancer-specific survival, OS: Overall survival, SEER: Surveillance, Epidemiology, and End Results

a lower adjusted risk. No clinically meaningful violation of the proportional hazards assumption was observed for the primary exposure variable.

Competing-risk Analysis

In the Fine-Gray competing-risk model for cervical cancer-specific mortality, adjusted subdistribution hazard ratios were consistent in direction and magnitude with those from the cause-specific Cox model. Adenocarcinoma had a higher adjusted subdistribution hazard than squamous cell carcinoma (sHR 1.18, 95% CI, 1.13-1.23, $p<0.001$), and neuroendocrine/small cell carcinoma had the highest adjusted subdistribution hazard among all subtypes (sHR 2.03, 95% CI, 1.87-2.21, $p<0.001$) (Supplementary Table 3).

Stage-stratified Analysis and Histology-by-Stage Interaction

The adjusted association between histologic subtype and survival varied according to summary stage (Supplementary Table 4). Among patients with localized disease, adenocarcinoma was associated with a lower adjusted risk of overall mortality compared with squamous cell carcinoma (aHR 0.90, 95% CI, 0.83-0.98, $p=0.018$), while the association

with CSS was not statistically significant (aHR 1.03, 95% CI, 0.92-1.15, $p=0.626$). Among patients with regional disease, adenocarcinoma was associated with a higher adjusted hazard for both OS (aHR 1.21, 95% CI, 1.14-1.28) and CSS (aHR 1.30, 95% CI, 1.22-1.39, both $p<0.001$). Among patients with distant-stage disease, adenocarcinoma was associated with a higher adjusted risk of poorer OS (aHR 1.13, 95% CI, 1.05-1.21) and of CSS (aHR 1.15, 95% CI, 1.07-1.23, both $p<0.001$). Neuroendocrine/small cell carcinoma demonstrated the highest adjusted hazard ratio in each stage stratum, ranging from aHR 1.73 (distant stage, OS) to aHR 5.89 (localized stage, CSS).

Formal interaction testing confirmed that the association between histologic subtype and survival differed significantly according to summary stage for both OS (Wald $\chi^2=215.25$, 8 degrees of freedom, $p<0.001$) and CSS (Wald $\chi^2=252.55$, 8 degrees of freedom, $p<0.001$) (Supplementary Table 5).

Metastatic subgroup Analysis

Among 6,734 patients with distant-stage disease diagnosed from 2010 to 2023, the distribution of metastatic sites differed significantly across histologic subtypes (Supplementary Table

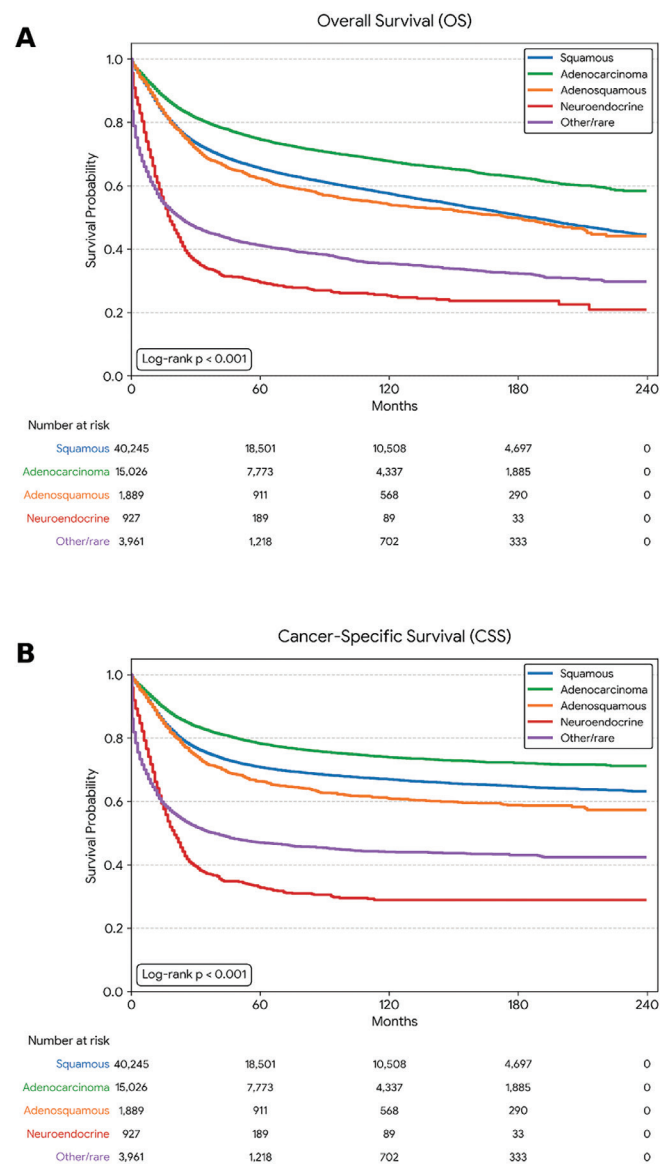


Figure 2. Kaplan-Meier survival curves according to histologic subtype in cervical cancer. Kaplan-Meier curves showing OS (A) and cancer-specific survival (CSS) (B) according to histologic subtype among patients with cervical cancer diagnosed between 2004 and 2023 in the SEER database. Overall and CSS differed significantly across histologic subtypes, as assessed by the log-rank test ($p < 0.001$ for both comparisons). Squamous cell carcinoma, the most common histologic subtype, was used as the reference group in subsequent Cox regression analyses. Neuroendocrine-small-cell carcinoma and other rare histologies demonstrated the poorest survival outcomes

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6). Liver metastases were most frequent in neuroendocrine/small cell carcinoma (37.2%) and least frequent in squamous cell carcinoma (12.1%, $p < 0.001$). Bone metastases followed a similar pattern, occurring in 31.0% of neuroendocrine/small cell carcinoma cases compared with 15.1% of adenocarcinoma cases ($p < 0.001$). Multiple metastatic sites (bone, brain, liver, or lung) were recorded in 29.3% of neuroendocrine/small cell carcinoma cases, compared with 12.3% of squamous cell carcinoma cases.

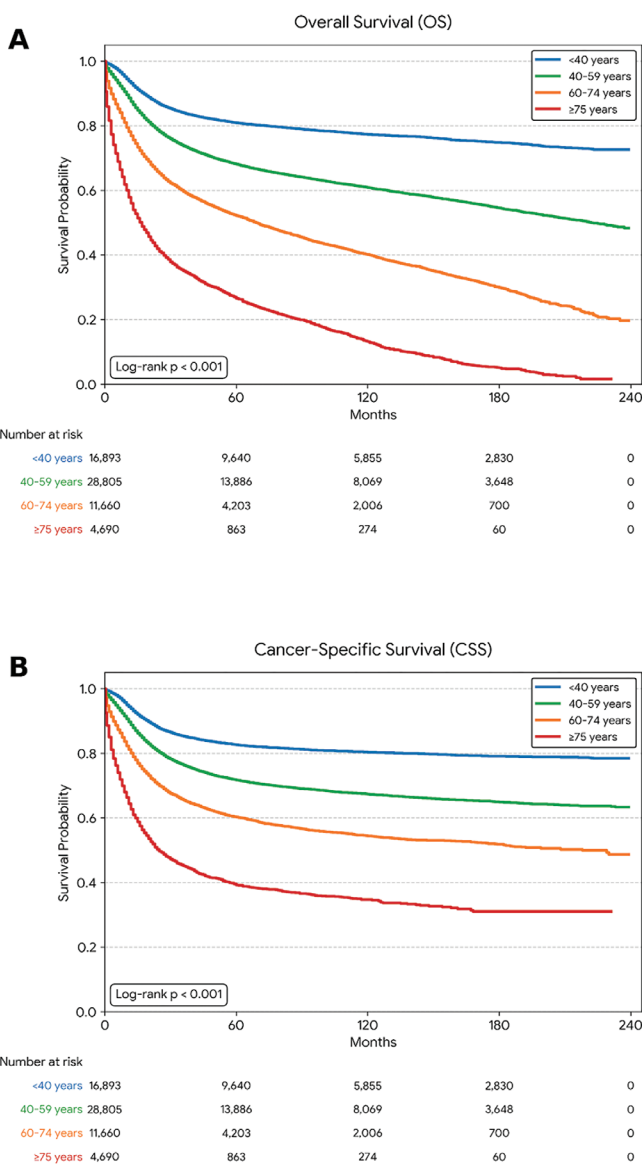


Figure 3. OS and CSS according to age group in patients with cervical cancer, SEER 2004-2023. Kaplan-Meier curves showing (A) OS and (B) CSS according to age group. Survival decreased progressively with increasing age. Log-rank tests demonstrated statistically significant differences among age groups in both overall and CSS ($p < 0.001$). Numbers at risk are shown at 0, 60, 120, 180, and 240 months

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Within the metastatic subgroup, 3-year OS was 9.0% (95% CI, 5.9-12.9) for neuroendocrine/small cell carcinoma compared with 26.2% (95% CI, 24.8-27.7) for squamous cell carcinoma, and 26.8% (95% CI, 24.3-29.4) for adenocarcinoma (log-rank $p < 0.001$) (Supplementary Table 7). The presence of liver metastasis (3-year OS 6.6% versus 27.0% without liver metastasis) and the presence of brain metastasis (3-year OS 6.9% versus 24.4% without brain metastasis) were each associated with significantly lower survival in this subgroup (log-rank $p < 0.001$ for both).

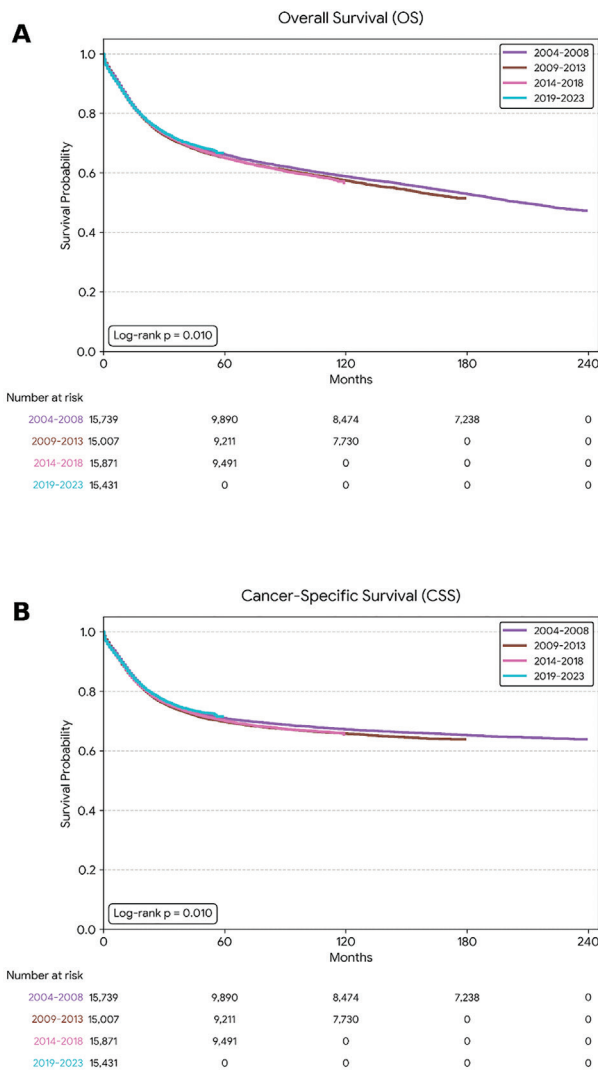


Figure 4. OS and CSS according to diagnosis era in patients with cervical cancer, SEER 2004-2023. Kaplan-Meier curves showing (A) OS and (B) CSS according to diagnosis era. Years of diagnosis were grouped into four approximately 5-year calendar periods: 2004-2008, 2009-2013, 2014-2018, and 2019-2023. Survival differed significantly across diagnostic eras for both overall and CSS, as assessed by the log-rank test ($p=0.010$). Number-at-risk values are shown at 0, 60, 120, 180, and 240 months. Later diagnosis eras have shorter maximum follow-up periods owing to the SEER 2023 study cutoff; therefore, long-term survival estimates for recent eras should be interpreted cautiously

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Discussion

In this population-based cohort of 62,048 women with cervical cancer, histologic subtype was independently associated with overall and CSS after adjustment for stage, treatment, and sociodemographic factors. Adenocarcinoma showed a favorable unadjusted association with survival but an unfavorable association after adjustment; this reversal was not uniform across disease stages. Neuroendocrine/small cell carcinoma carried the highest adjusted risk of death among all histologic subtypes at every stage of the disease and had

the highest burden of distant metastasis at diagnosis. The prognostic effect of histologic subtype differed significantly according to summary stage, as confirmed by formal interaction testing.

The unadjusted survival advantage for adenocarcinoma observed in this cohort is consistent with earlier population-based reports [4]. However, once stage, treatment, and other covariates were accounted for, adenocarcinoma was associated with higher risk of death than squamous cell carcinoma, aligning with findings from concurrent chemoradiotherapy cohorts in which adenocarcinoma showed poorer response to radiotherapy-based treatment than squamous cell carcinoma [8,9]. This adjusted association was not consistent across stage strata in the present cohort: adenocarcinoma was associated with lower risk in localized disease, but with higher risk in regional and distant disease. This pattern provides a plausible explanation for the divergent conclusions reported in prior studies, whose cohorts differed in stage distribution and treatment composition. Studies restricted to patients treated with chemoradiation for locally advanced disease, where adenocarcinoma is relatively underrepresented and biologically distinct, have more often reported an adverse association, while studies with a broader stage mix, including a larger share of surgically treated localized adenocarcinoma, have reported neutral or favorable associations [4,5,8,9]. Part of the heterogeneity within the adenocarcinoma group may also reflect the coexistence of human papillomavirus (HPV)-associated and HPV-independent histologic variants, the latter of which have been associated with more advanced stage at diagnosis and reduced sensitivity to chemoradiotherapy [10]. SEER data do not include HPV or p16 status; therefore, this distinction could not be directly evaluated in the present cohort.

Adenosquamous carcinoma has similarly been associated with adverse survival in population-based SEER analyses, independent of stage and treatment [10]. In the present cohort, the association between adenosquamous histology and OS was weaker than its association with CSS, likely because competing non-cancer mortality attenuates the OS estimate in this subgroup; this effect is removed when cancer-specific death is examined separately.

Prior reports on neuroendocrine/small cell carcinoma outcomes align with the markedly poor prognosis we observed for this histology in the present cohort [6,11]. This subtype is currently managed largely by extrapolation from small-cell lung cancer treatment paradigms, given the shared aggressive biologic behavior and absence of dedicated randomized trials in the cervical population [11]. The consistently elevated risk of neuroendocrine/small cell carcinoma across every stage stratum in the present analysis, including localized disease, is in line with the view that this histology behaves as a systemic disease at diagnosis regardless of anatomic extent [11].

Treatment patterns differed substantially across histologic subtypes. Primary tumor surgery was least frequently performed in patients with neuroendocrine/small-cell carcinoma and other rare histologies, a pattern that parallels

Table 4. Multivariable Cox regression analysis for overall and CSS, SEER 2004-2023

Variable	Category	Overall survival aHR (95% CI)	p value	Cancer-specific survival aHR (95% CI)	p value
Histologic subtype	Squamous cell carcinoma	1 [Reference]		1 [Reference]	
	Adenocarcinoma	1.11 (1.06-1.15)	<0.001	1.20 (1.15-1.25)	<0.001
	Adenosquamous carcinoma	1.39 (1.29-1.49)	<0.001	1.50 (1.39-1.62)	<0.001
	Neuroendocrine/small cell carcinoma	2.20 (2.03-2.38)	<0.001	2.29 (2.10-2.49)	<0.001
	Other/rare histology	1.70 (1.62-1.78)	<0.001	1.83 (1.74-1.93)	<0.001
Age group, years	<40	1 [Reference]		1 [Reference]	
	40-59	1.47 (1.42-1.53)	<0.001	1.24 (1.19-1.30)	<0.001
	60-74	2.17 (2.08-2.27)	<0.001	1.51 (1.44-1.59)	<0.001
	≥75	3.67 (3.49-3.87)	<0.001	2.33 (2.20-2.48)	<0.001
Year of diagnosis	2004-2009	1 [Reference]		1 [Reference]	
	2010-2015	0.99 (0.96-1.02)	0.454	0.98 (0.95-1.02)	0.377
	2016-2023	0.95 (0.91-0.99)	0.009	0.93 (0.89-0.97)	<0.001
Race/ethnicity	Non-Hispanic White	1 [Reference]		1 [Reference]	
	Non-Hispanic Black	1.12 (1.08-1.17)	<0.001	1.10 (1.05-1.15)	<0.001
	Non-Hispanic American Indian/Alaska Native	1.09 (0.94-1.25)	0.247	1.12 (0.96-1.32)	0.151
	Non-Hispanic Asian or Pacific Islander	0.85 (0.82-0.90)	<0.001	0.87 (0.83-0.92)	<0.001
	Hispanic, all races	0.86 (0.83-0.89)	<0.001	0.85 (0.82-0.89)	<0.001
	Non-Hispanic unknown race	0.21 (0.14-0.30)	<0.001	0.13 (0.08-0.23)	<0.001
Marital status	Married	1 [Reference]		1 [Reference]	
	Single/never married	1.18 (1.14-1.22)	<0.001	1.16 (1.12-1.21)	<0.001
	Divorced/separated/widowed	1.23 (1.19-1.28)	<0.001	1.18 (1.13-1.22)	<0.001
	Unmarried/domestic partner	1.12 (0.92-1.38)	0.265	1.04 (0.83-1.31)	0.707
	Unknown	0.93 (0.87-0.99)	0.020	0.87 (0.81-0.94)	<0.001
County-level median household income	≥\$100,000	1 [Reference]		1 [Reference]	
	\$75,000-\$99,999	1.13 (1.09-1.17)	<0.001	1.12 (1.08-1.17)	<0.001
	<\$75,000	1.24 (1.19-1.29)	<0.001	1.21 (1.15-1.27)	<0.001
Rural-urban continuum	Metropolitan ≥1 million	1 [Reference]		1 [Reference]	
	Metropolitan <1 million	0.99 (0.95-1.02)	0.383	0.97 (0.94-1.01)	0.190
	Nonmetropolitan	1.00 (0.95-1.05)	0.939	0.96 (0.91-1.01)	0.141
	Unknown/missing	0.90 (0.64-1.26)	0.549	0.88 (0.60-1.30)	0.519
Primary cervical site	Cervix uteri, NOS	1 [Reference]		1 [Reference]	
	Endocervix	0.86 (0.82-0.89)	<0.001	0.85 (0.81-0.89)	<0.001
	Exocervix	0.82 (0.75-0.90)	<0.001	0.81 (0.72-0.90)	<0.001
	Overlapping lesion	1.02 (0.93-1.12)	0.636	1.05 (0.94-1.17)	0.381
Summary stage	Localized	1 [Reference]		1 [Reference]	
	Regional	2.70 (2.58-2.82)	<0.001	3.99 (3.77-4.24)	<0.001
	Distant	7.74 (7.37-8.13)	<0.001	12.48 (11.74-13.27)	<0.001
	Unknown/unstaged	2.10 (1.97-2.25)	<0.001	2.75 (2.54-2.99)	<0.001
Tumor grade	Grade I/well differentiated	1 [Reference]		1 [Reference]	
	Grade II/moderately differentiated	0.79 (0.74-0.85)	<0.001	0.77 (0.71-0.83)	<0.001
	Grade III/IV/poorly-undifferentiated	0.99 (0.93-1.05)	0.741	0.98 (0.92-1.05)	0.621
	Unknown/blank	0.85 (0.83-0.88)	<0.001	0.83 (0.80-0.86)	<0.001

Table 4. Continued

Variable	Category	Overall survival aHR (95% CI)	p value	Cancer-specific survival aHR (95% CI)	p value
Tumor size	≤20 mm	1 [Reference]		1 [Reference]	
	21-40 mm	1.50 (1.41-1.60)	<0.001	1.83 (1.68-2.00)	<0.001
	41-60 mm	1.68 (1.57-1.79)	<0.001	2.12 (1.95-2.31)	<0.001
	>60 mm	2.00 (1.87-2.13)	<0.001	2.63 (2.42-2.87)	<0.001
	Unknown/missing	1.81 (1.71-1.92)	<0.001	2.36 (2.18-2.55)	<0.001
Primary tumor surgery	Surgery performed	1 [Reference]		1 [Reference]	
	No surgery	2.13 (2.06-2.21)	<0.001	2.16 (2.07-2.25)	<0.001
	Unknown	6.60 (5.98-7.28)	<0.001	7.20 (6.45-8.05)	<0.001
Radiation therapy	No/unknown radiation	1 [Reference]		1 [Reference]	
	Radiation given	0.84 (0.81-0.87)	<0.001	0.78 (0.75-0.82)	<0.001
Chemotherapy	No/unknown chemotherapy	1 [Reference]		1 [Reference]	
	Chemotherapy yes	0.68 (0.65-0.70)	<0.001	0.67 (0.65-0.70)	<0.001

The multivariable Cox proportional hazards models included 62,048 patients. OS events: 23,568; CSS events: 17,841. The models were adjusted for all variables shown in the table, including histologic subtype, age group, year of diagnosis, race/ethnicity, marital status, county-level household income, rural-urban continuum, primary cervical site, summary stage, tumor grade, tumor size, primary tumor surgery, radiation therapy, and chemotherapy. OS was defined as death from any cause; CSS was defined as death attributable to cervical cancer, with deaths from other causes censored. Zero-month survival was recoded as 0.5 months for time-to-event modeling.

aHR: Adjusted hazard ratio, CI: Confidence interval, CSS: Cancer-specific survival, NOS: Not otherwise specified, OS: Overall survival, SEER: Surveillance, Epidemiology, and End Results

their higher burden of distant-stage disease at diagnosis. Neuroendocrine/small cell carcinoma had the highest chemotherapy use, consistent with current practice of using platinum-etoposide regimens extrapolated from small-cell lung cancer for this histology [11]. The absence of histology-specific treatment guidelines for neuroendocrine and other rare cervical cancer subtypes, combined with their high adjusted mortality risk even after accounting for stage and treatment received, suggests that current treatment intensity may not be sufficient to overcome the underlying biologic aggressiveness of these tumors [11]. This interpretation should be considered provisional, given that SEER treatment variables capture receipt of surgery, radiation, and chemotherapy in binary form, lack information on regimen, dose, or timing, and cannot distinguish confirmed non-receipt of treatment from missing data. Racial and ethnic differences in adjusted survival observed in this cohort are consistent with prior SEER-based analyses reporting disproportionately poor outcomes for Black women with cervical cancer, particularly for adenocarcinoma [12]. Differences in insurance coverage and receipt of guideline-concordant treatment have been shown to mediate a substantial portion of this racial disparity [13]. The markedly higher adjusted mortality risk observed among older patients in this cohort parallels prior SEER-based reports of reduced surgical and adjuvant treatment utilization in elderly women with cervical cancer, independent of stage [14].

Among patients with distant-stage disease, neuroendocrine/small cell carcinoma exhibited the highest frequency of liver and bone metastases, the highest likelihood of having multiple recorded metastatic sites, and the lowest survival within this subgroup. This pattern is consistent with the propensity of neuroendocrine tumors toward early hematogenous

dissemination described in prior series [11]. The Fine-Gray competing-risk analysis produced adjusted subdistribution hazard ratios that were directionally and numerically consistent with the cause-specific Cox model, indicating that the observed associations between histologic subtype and cancer-specific mortality were not substantially distorted by competing mortality from other causes. The formal histology-by-stage interaction test provides statistical confirmation that a single hazard ratio does not adequately summarize the prognostic effect of histologic subtype across the full spectrum of disease extent, and supports stage-stratified reporting of histology-specific outcomes in future studies.

This study has several strengths, including a large, population-based sample spanning two decades, a five-group histologic classification allowing separate characterization of rare subtypes such as neuroendocrine/small cell carcinoma, and the use of complementary analytic approaches: multivariable Cox regression, Fine-Gray competing-risk analysis, stage-stratified modeling, and formal interaction testing to evaluate the robustness of the histology-survival association.

Study Limitations

Several limitations should be considered. The retrospective, registry-based design is subject to unmeasured confounding, and SEER does not capture HPV or p16 status, chemotherapy regimen, radiation dose or technique, or comorbidity burden. Histologic classification was based on registry-coded ICD-O-3 morphology and lacked central pathology review, which may have introduced misclassification, particularly for rare and morphologically heterogeneous subtypes. A substantial proportion of tumor grade and tumor size values were missing, which may have influenced the corresponding hazard

ratio estimates. Metastatic site variables were available only from 2010 onward, whereas lymph node and other metastasis variables were available only from 2016 onward, limiting these analyses to a subset of the full cohort. Survival estimates for the most recent diagnosis era are based on shorter follow-up and should be interpreted with this in mind. Finally, the findings are based on SEER-participating registries in the United States and may not be directly generalizable to populations with different screening practices, access to treatment, or healthcare systems.

Conclusion

In this population-based cohort, the prognostic significance of cervical cancer histologic subtype depended on disease stage: adenocarcinoma was associated with a favorable prognosis in localized disease but with an unfavorable prognosis in regional and distant disease, compared with squamous cell carcinoma. Neuroendocrine/small-cell carcinoma carried the highest risk of death across all stages and the greatest burden of distant metastases. These findings support stage-stratified consideration of histologic subtype in prognostic assessment. They also underscore neuroendocrine/small-cell carcinoma as a subgroup for which dedicated treatment strategies, rather than extrapolation from other histologies, should be prospectively developed and evaluated.

Ethics

Ethics Committee Approval: This study was based exclusively on de-identified data obtained from the Surveillance, Epidemiology, and End Results (SEER) Research Data database. Institutional ethics committee approval was not required for this secondary data analysis.

Informed Consent: Informed consent was not required because the study used de-identified registry data without direct patient contact.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Y., O.S., Concept: K.B., E.Y., O.S., Design: G.C.U., K.B.Y., Data Collection or Processing: K.B., G.C.U., K.B.Y., Analysis or Interpretation: G.C.U., K.B.Y., Literature Search: E.Y., K.B.Y., Writing: K.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Tables Link: <https://d2v96fxpocvxx.cloudfront.net/25021570-dd5c-48cc-b052-771af43e75cc/content-images/51c197f2-87c2-400c-81ad-d5bc01aac92b.pdf>

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74:229-263.
2. Li Z, Liu P, Yin A, et al. Global landscape of cervical cancer incidence and mortality in 2022 and predictions to 2030: the urgent need to address inequalities in cervical cancer. *Int J Cancer.* 2025;157:288-297.
3. Li Z, Lin Y, Cheng B, Zhang Q, Cai Y. Prognostic model for predicting overall and cancer-specific survival among patients with cervical squamous cell carcinoma: a SEER based study. *Front Oncol.* 2021;11:651975.
4. Lee JY, Kim YT, Kim S, et al. Prognosis of cervical cancer in the era of concurrent chemoradiation from National Database in Korea: a comparison between squamous cell carcinoma and adenocarcinoma. *PLoS One.* 2015;10:e0144887.
5. Tian T, Gong X, Gao X, Li Y, Ju W, Ai Y. Comparison of survival outcomes of locally advanced cervical cancer by histopathological types in the surveillance, epidemiology, and end results (SEER) database: a propensity score matching study. *Infect Agent Cancer.* 2020;15:33.
6. Xie N, Yu H, Lin J, Deng S, Liu L, Sun Y. A nomogram for predicting prognosis for young cervical neuroendocrine carcinoma: a SEER-based study and external validation. *Frontiers in Oncology.* 2025;15:1463422.
7. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association.* 1999;94:496-509.
8. 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. *Radiation Oncology.* 2018;13:249.
9. Rose PG, Java JJ, Whitney CW, Stehman FB, Lanciano R, Thomas GM. 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. *Gynecol Oncol.* 2014;135(2):208-212.
10. Giannella L, Grelloni C, Natalini L, et al. Molecular features of HPV-independent cervical cancers. *Pathogens.* 2025;14:668.
11. Salvo G, Gonzalez Martin A, Gonzales NR, Frumovitz M. Updates and management algorithm for neuroendocrine tumors of the uterine cervix. *Int J Gynecol Cancer.* 2019;29:986-995.
12. Cohen CM, Wentzensen N, Castle PE, et al. Racial and ethnic disparities in cervical cancer incidence, survival, and mortality by histologic subtype. *J Clin Oncol.* 2023;41:1059-1068.
13. Markt SC, Tang T, Cronin AM, et al. Insurance status and cancer treatment mediate the association between race/ethnicity and cervical cancer survival. *PLoS One.* 2018;13:e0193047.
14. Sharma C, Deutsch I, Horowitz DP, et al. Patterns of care and treatment outcomes for elderly women with cervical cancer. *Cancer.* 2012;118:3618-3626.