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Significance of uterine corpus tumor invasion in early-stage cervical cancer

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Abstract

Objective: To examine characteristics and survival outcomes of women with surgically-treated cervical cancer exhibiting uterine corpus tumor invasion.

Methods: We utilized The Surveillance, Epidemiology, and End Results Program to identify cervical cancer patients who underwent hysterectomy between 1973 and 2003. Logistic regression models were used to identify risk factors for uterine corpus tumor invasion on multivariable analysis. Association of uterine corpus tumor invasion and cause-specific survival (CSS) from cervical cancer was examined with Cox proportional hazard regression models on multivariable analysis.

Results: We identified 837 (4.9%) cases of uterine corpus invasion and 16,237 (95.1%) cases of non-invasion. Median follow-up time was 14.0 years. There were 1642 deaths due to cervical cancer. Uterine corpus invasion was independently associated with older age, non-squamous histology, high-grade tumors, large tumor size, and nodal metastasis on multivariable analysis (all, $P < 0.001$). On univariable analysis, uterine corpus tumor invasion was significantly associated with decreased CSS compared to the non-invasion (5-year rates, 79.0% *versus* 94.5%, $P < 0.001$). After controlling for other significant prognostic factors, uterine corpus tumor invasion remained an independent prognostic factor for decreased CSS (adjusted-hazard ratio 1.45, 95% confidence interval 1.21–1.74). Among stage T1b cases (n = 6730), uterine corpus tumor invasion remained an independent prognostic factor for decreased CSS (adjusted-hazard ratio 1.95, 95%CI 1.47–2.60). Uterine corpus tumor invasion was significantly associated with decreased CSS in stage T1b1 disease (74.5% *versus* 90.7%, $P < 0.001$) and in stage T1b2 disease (67.0% *versus* 79.5%, $P = 0.01$).

Conclusion: Uterine corpus tumor invasion is an independent prognostic factor for decreased survival of women with early-stage cervical cancer.

Keywords: Cervical cancer; Uterine corpus; Lymph node metastasis; Survival outcome

Introduction

In 2016, approximately 1 in 160 women are estimated to develop invasive cervical cancer in the United States, and roughly 4100 women will die of cervical cancer in this given year.[1] The survival rate of women with cervical cancer has not changed in the past four decades,[1] and therefore, understanding the pattern of tumor spread is valuable to improve the prognosis of women with cervical cancer.

Cervical cancers typically spread loco-regionally *via* direct tumor invasion, laterally into the parametria, distally into the upper vagina, and less often anterior-posteriorly into the bladder or rectum.[2] The current staging system for cervical cancer incorporates these anatomical sites of direct tumor extension, and the presence of tumor invasion

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into these anatomical sites are associated with decreased survival outcome.[3]

Another potential anatomical direction of direct tumor extension in cervical cancer is into the uterine corpus. One could theorize that uterine corpus tumor invasion is reflective of aggressive tumor behavior associated with decreased survival in women with cervical cancer due to the established association that loco-regional tumor extension of cervical cancer to the adjacent organs with decreased survival outcome.[3] However, uterine corpus tumor invasion has not been incorporated into the current cervical cancer staging system.[4] Previous studies examining the survival outcome related to uterine corpus tumor invasion had relatively small sample sizes that make the findings difficult to adopt in a general population.[5–10]

The objective of the study was *(i)* to identify contributing factors for uterine corpus tumor invasion in surgically-treated cervical cancer, and *(ii)* to examine survival outcome of women in whom the tumor exhibits uterine corpus invasion by examining a population-based database.

Materials and methods

Data source and eligibility

We utilized The Surveillance, Epidemiology, and End Results Program (SEER) that is the largest population-based tumor registry in the United States.[11] The SEER database was launched in 1973, supported and managed by the National Cancer Institute.[11] This database covers approximately 27.8% of the US population from 11 States and 7 areas. The SEER database is publicly available and deidentified, and the University of Southern California Institutional Review Board exempted the use of such database. We used The STROBE guidelines to direct the observational study.[12]

We used SEER*Stat 8.3.2 to extract the dataset for SEER18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases by using selection codes for "Cervix Uteri", "malignancy", and "female sex". Within the extracted cases, women with cervical cancer who underwent hysterectomy between 1973 and 2003 were included in the study. During this study period, uterine corpus invasion was routinely coded in the 2-digit EOD system (code 70, 74, 77, 79, 80, 84, 87, and 89) between 1973 and 1982, the 4-digit EOD system (code 3) between 1983 and 1987, and the EOD-10 system (code 30, 35, 36, and 37) between 1988 and 2003. After year 2004, the pathology coding system does not include uterine corpus invasion, and therefore, cases were excluded from the study. Cases with uterine sarcomas, metastatic tumors to the uterine cervix, and radiotherapy prior to the hysterectomy were excluded.

Clinical information

Variables abstracted from the SEER database were patient demographics, tumor characteristics, treatment patterns, and survival outcome. Patient demographics included age (<40, 40–49, 50–59, and ≥60), and calendar year at diagnosis (1973–1979, 1980–1989, 1990–1999, and 2000–2003), ethnicity (White, Black, Hispanic, Asian, and others), marital status (single, married, and others), and registered area (East, Central, and West). Tumor characteristics included cancer T stage (T1a, T1b, T2a, and T2b), histologic subtype (squamous, adenocarcinoma, adenosquamous, and others), tumor grade (1, 2, and 3), tumor size (≤2.0, 2.1–4.0, 4.1–6.0, and >6.0 cm), and pelvic lymph node status (metastasis *versus* non-metastasis). Histologic subtypes were grouped per the ICD-0-3 site/histology validation list and World Health Organization (WHO) histological classification (Table S1). Treatment pattern included type of hysterectomy (simple, radical, and others) and adjuvant radiotherapy (whole pelvic radiotherapy, intracavitary brachytherapy, and others). Survival outcomes were examined for cervical cancer-specific survival and overall survival from all causes. Cause-specific survival was defined as the time interval between the date of cervical cancer diagnosis and date of death due to cervical cancer. Overall survival was defined as the time interval between cervical cancer diagnosis and the data of death from any cause. Patients were censored if alive at the last follow-up.

Statistical analysis

The primary interest of the analysis was to examine characteristics of women with cervical cancer in whom the tumor invaded the uterine corpus. The secondary interest of analysis was to examine survival outcomes of women with cervical cancer whose tumors had uterine corpus invasion. Cases with uterine corpus tumor invasion were compared to cases without uterine corpus tumor invasion. Statistical significance of continuous variables was assessed by the Student *t* test. Ordinal and categorical variables were assessed with the chi-square test. Binary logistic regression models were used for multivariable analysis to determine independent risk factors for uterine corpus tumor invasion, and magnitude of statistical significance was expressed with adjusted-odds ratio (aOR) with 95% confidence interval (CI). Patient demographics, and tumor characteristics, and treatment patterns were entered in the final model. Model fitting was examined by Hosmer–Lemeshow goodness-of-fit test.

We examined survival outcome with the Kaplan–Meier method to construct survival curves,[13] and statistical significance between the curves were assessed with the log-rank test for univariable analysis. Cox proportional hazard regression models were used to identify the independent prognostic factors for Cause-specific survival and overall survival in multivariable analysis,[14] and magnitude of statistical significance was expressed with adjusted-hazard ratio (aHR) with 95%CI. Covariates entered in the final model were the significant covariates in univariable analysis with *P*-value cutoff being less than 0.05. The variance

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