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Significance of lymph node metastasis on survival of women with uterine adenosarcoma

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HIGHLIGHTS

- Uterine adenosarcoma (UAS) has a low incidence rate (<3%) of lymph node metastasis.
- Nodal metastasis is an independent risk factor for survival in uterine UAS.
- Deep invasion, large tumor, and sarcomatous overgrowth increase nodal metastasis.

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ABSTRACT

Objective. Uterine adenosarcoma (UAS) is a rare gynecologic malignancy and the significance of lymph node metastasis on survival has not been well studied.

Methods. A retrospective study was performed utilizing the Surveillance, Epidemiology, End Results Program to examine UAS (n = 994), endometrial stromal sarcoma (ESS, n = 2910), and uterine leiomyosarcoma (LMS, n = 5506) diagnosed between 1973 and 2013. The impact of lymph node metastasis on cause-specific survival (CSS) was cross-compared by multivariable analysis. Systematic literature review was conducted to examine the impact of nodal metastasis on progression-free survival (PFS) in UAS.

Results. UAS had the lowest incidence of lymph node metastasis among the sarcoma subtypes examined (UAS 2.9%, LMS 3.4%, and ESS 6.6%, $P < 0.001$). Lymph node metastasis was independently associated with decreased CSS in all three tumor types (all, $P < 0.01$); however, magnitudes of statistical significance of lymph node metastasis for CSS were similar across the three tumor types: adjusted-hazard ratio (aHR) for UAS 2.34, ESS 2.43, and LMS 2.10. Systematic literature review identified 230 unique cases of surgically treated UAS. On multivariable analysis, lymph node metastasis (aHR 4.72) had the greatest degree of significance for PFS compared to other tumor factors including sarcomatous overgrowth (aHR 2.88), heterologous elements (aHR 2.08), and deep myometrial invasion (aHR 1.51). Large tumor, deep myometrial invasion, and sarcomatous overgrowth were associated with increased risk of lymph node metastasis (all, $P < 0.05$).

Conclusion. While uterine adenosarcoma had a low incidence of lymph node metastasis, the impact of lymph node metastasis on survival was comparable to ESS or LMS.

1. Introduction

Uterine sarcoma is a rare gynecologic malignancy, comprising approximately 3% of all uterine tumors. In 2016, an estimated 1800 new cases of uterine sarcoma are anticipated in the United States [1,2]. From 1988 to 2001, the rate of death from uterine sarcoma has increased from 7.6 to 9.1% of all uterine malignancies [3]. The most common histologic subtypes in uterine sarcoma are leiomyosarcoma (LMS, 63%) followed by endometrial stromal sarcoma (ESS, 21%) [4]. Uterine adenosarcoma (UAS), first described approximately four decades ago [5], is a rare histology type accounting for 2–5% of all uterine sarcomas [1].

The International Federation of Gynecology and Obstetrics (FIGO) revised a new classification and staging system for uterine sarcomas in

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2009 designed to reflect their unique biological characteristics across each sarcoma [6], and specific criteria are currently used to stage UAS. In contrast to LMS and ESS, UAS commonly arises from the endometrium and is histologically characterized by an admixture of benign glandular epithelial and a malignant stromal sarcomatous components [5,7]. The majority of UAS are low-grade and have a low malignant potential, with 5-year cause-specific survival (CSS) approaching 48–79% [8–11]. Due to the rarity of UAS, epidemiology, clinical manifestations, and the impact of lymph node metastasis in patients with this tumor remained understudied. Available evidence examining lymph node metastasis in UAS has primarily been derived from case reports of which making their findings difficult to adopt in general population [9,10,12]. The aim of this study was to examine the significance of lymph node metastasis on survival outcome of women with UAS.

2. Materials and methods

2.1. Study design and eligibility

University of Southern California Institutional Review Board (IRB) exempted the use of publicly available deidentified data, The Surveillance, Epidemiology, and End Results (SEER) Program database for this study. SEER is a population-based database launched in 1973 that is supported and managed by the National Cancer Institute in the United States. The SEER database covers approximately 27.8% of the US population from 11 states and 7 areas. SEER*Stat 8.3.2 was used to sort the dataset (1973–2013), accessed on May 18, 2016.

Cases were examined for eligibility in this study by a diagnosis within the category "Corpus uteri/Uterus NOS," which was then limited to those subcategorized by malignancy. Within the extracted dataset, uterine sarcoma cases were identified and grouped into UAS, ESS and LMS by histology codes. Patients with endometrial cancer, carcinosarcoma, tumors metastatic to the uterus, and other rare sarcoma subtypes (liposarcoma, rhabdomyosarcoma, or other histologic types of sarcoma) were excluded. Variables obtained from the database included patient demographics, tumor characteristics, treatment patterns, and survival outcome. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were consulted for this observational study [13].

2.2. Clinical information

Patient demographics abstracted included age and year at diagnosis, ethnicity, marital status and registration area. Tumor characteristics included histologic subtype, stage, grade, tumor size, depth of myometrial tumor invasion, and lymph node status. In this study, the ICD-O-3 SEER Site/Histology Validation List and the World Health Organization histological classification were used for grouping histologic subtypes as shown in Table S1 [14]. Stage was reclassified according to the American Joint Committee on Cancer 7th Edition staging criteria [15].

Treatment patterns included type of hysterectomy-based surgery and postoperative radiotherapy. Lymph node metastasis was evaluated by the results from Regional Lymph Node section. If not specified in this section, lymph node metastasis was considered no lymph node assessment. For survival outcome, both cause-specific survival (CSS) and all-cause mortality (overall survival [OS]) were collected. CSS were defined as the time interval between the initial tumor diagnosis and the date of death from uterine sarcoma. OS were defined as the time interval between the initial tumor diagnosis and the date of death from any causes. Patients were censored if alive at the last follow-up.

2.3. Systematic review

To evaluate progression-free survival (PFS) in women with UAS, we conducted a comprehensive systematic literature search per the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for systematic review [16]. A public search engine PubMed/MEDLINE was utilized with the entry keyword "uterine adenosarcoma" limited to English literature (searched on September 20, 2016). Eligible publications included case reports, case series, and cohort study, of UAS received hysterectomy. The references listed in each identified article were also reviewed and eligible studies were enrolled in the analysis. Among these, publications lacking sufficient patient demographics, hysterectomy status, histology results, treatment details, survival outcome and follow-up were excluded from the analysis. Age, area and year of publication, surgical pathology results (stage, depth of myometrial tumor invasion, sarcomatous overgrowth, sarcoma element [homologous *versus* heterologous], and lymph node status), treatment pattern (hysterectomy type, adjuvant radiotherapy, and adjuvant chemotherapy), and survival outcome for PFS were abstracted from the publication. Sarcomatous overgrowth was defined by >25% of the tumor consisting of a sarcomatous component based on prior study [10,17,18].

2.4. Statistical analysis

The primary interest of analysis was to examine characteristics and CSS of women with node-positive UAS. The secondary interest of analysis was to compare the impact of nodal metastasis on PFS to other tumor factors in women with surgically-treated UAS.

Continuous variables were assessed by one-way ANOVA or Kruskal-Wallis H test, and expressed as mean (± standard deviation) or median (range) as appropriate. Ordinal and categorical variables were analyzed using the chi-square test, and magnitude of statistical significance was expressed with odds ratio (OR) and 95% confidence interval (CI). Univariable and multivariable analyses for survival outcome were performed by log-rank test and a Cox proportional hazard regression test, respectively. Covariates included in the final multivariable model consisted of patient demographics, tumor factors and treatment patterns. Endpoint probability for survival was expressed as a hazard ratio (HR) with 95%CI.

The Joinpoint Regression Program (version 4.3.1.0) provided by the National Cancer Institute was utilized for evaluation of temporal (calendar year) trends in UAS [19]. Time point data were examined every calendar year to identify temporal change. The presence of annual trend was examined with a linear segmented regression test, and log-transformation was performed to determine annual percent change of the slope.

The variance inflation factor (VIF) was determined among the covarates in the multivariable analysis, and VIF ≥2.0 was interpreted as multicollinearity (myometrial invasion, tumor size and nodal metastasis for cancer stage). Survival curves were constructed with Kaplan-Meier method. All statistical tests were two-tailed, and $P < 0.05$ was considered to be statistically significant. Statistical Package for the Social Sciences (SPSS, version 24.0, Chicago, IL) was used for the analysis.

3. Results

Selection criteria are shown in Fig. 1. There were 10,577 cases of uterine sarcoma identified during the study period and there were 1167 cases excluded due to a diagnosis of rhabdomyosarcoma, liposarcoma, and other sarcoma histologic types. The remaining 9410 cases were eligible for the analysis, divided into three subgroups: UAS (n = 994), ESS (n = 2910), and LMS (n = 5506).

Demographics and clinical characteristics of patients with UAS, ESS, and LMS are listed in Table 1. Compared to ESS and LMS, patients with UAS were more likely to be over age 60 years, Caucasian, single, and to have undergone simple hysterectomy (all, $P < 0.001$). Tumor characteristics associated with UAS included early-stage disease (56.3%), <50% myometrial invasion (39.5%), and small tumor size (all, $P < 0.001$). UAS had the lowest incidence of lymph node metastasis among the three tumor types (UAS 2.9%, LMS 3.4%, and ESS 6.6%, $P < 0.001$).

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