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Survival of women with Mullerian adenosarcoma: A National Cancer Data Base study

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HIGHLIGHTS

- Each cm increase of tumor size was associated with decreased OS of women with uterine or cervical adenosarcoma.
- Metastasis, positive surgical margin, increased age, comorbidities and radiotherapy were associated with decreased OS.
- Primary site, chemotherapy use, race, insurance status and income were not associated with OS.

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ABSTRACT

Objective. To determine overall survival (OS) and factors associated with OS of women with Mullerian adenosarcoma.

Methods. Women with adenosarcoma of the uterus, cervix or ovary (n = 2205) were identified from the 1998–2011 National Cancer Data Base. Kaplan-Meier and multivariate Cox proportional-hazards survival analyses were performed to test for associations of potential explanatory variables with OS. A subset analysis of women with uterine adenosarcoma was also performed. Analyzed confounders included age, insurance status, income, race, surgical margin status, nodal and distant metastasis, surgical procedure type, and treatment with radiation and/or chemotherapy.

Results. Primary sites were uterus (n = 1884), cervix (n = 229) and ovary (n = 92), representing 0.43% of uterine, 0.16% of cervical, and 0.04% of ovarian cancers in the NCDB. Only 36/1176 (3.1%) and 2.5% (33/1,342) had nodal and/or distant metastasis, respectively, at diagnosis. Distant metastasis, positive surgical margin, increased age, higher composite comorbidity score and adjuvant radiotherapy were independently associated with decreased OS. Primary site, lymph node status, surgical procedure, chemotherapy use, race, insurance status and income quartiles were not significantly associated with OS. Each 1 cm increase in tumor size was associated with increased hazard for death (HR (95% CI) 1.06 (1.01–1.12), p = 0.018) among women with uterine adenosarcoma.

Conclusion. Complete surgical resection remains the only treatment with well-evidenced OS benefit among women with Mullerian adenosarcoma. Early surgical resection may increase survival of Mullerian adenosarcoma.

1. Introduction

Adenosarcoma is a rare gynecologic tumor most often arising from the uterus, and less frequently from the ovary or cervix. It is characterized by a low grade stromal sarcoma with a benign glandular epithelial component, and often has a good prognosis. However, some tumors demonstrate sarcomatous overgrowth (>25% of the total tumor volume consists of pure sarcoma) which portends a more malignant and aggressive course with a higher rate of recurrence and death [1–3]. Current treatment recommendations include hysterectomy and bilateral salpingo-oophorectomy. Due to the rarity of this histology, only a few case reports and series provide data on the roles of pelvic and para-aortic lymphadenectomy and adjuvant treatment including chemotherapy and radiation. To better understand factors associated with prognosis of Mullerian adenosarcoma, we performed an analysis of cases from the National Cancer Data Base (NCDB).

2. Methods and materials

The NCDB is a population-based national cancer registry created by the American Cancer Society and American College of Surgeons and includes data for about 70% of all cancers diagnosed nationally [4].

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Deidentified, individual-level NCDB data is entered by professional cancer registrars and is audited for correctness [4]. Cases of adenosarcoma (ICD-O-3 histology code 8933) were queried from the 1998–2011 uterine (n = 441,863), ovarian (n = 223,017), and cervical (n = 146,698) cancer NCDB datasets. Race was coded as white, black, other or unknown since the number of cases for specific racial groups other than white and black were low. Recorded tumor size values >35.0 cm were not included in statistical analyses as these cases were few (n = 18) and the accuracy of coding for very large tumor sizes seemed questionable. TMN, AJCC, and FIGO staging variables were too sparsely recorded for adenosarcoma cases to be included. Alternatively, lymph node status and distant metastases were included as surrogate staging variables. The most invasive surgical procedure for treatment of the primary site was coded using the site-specific RX_SUMM_SURG_PRIM_SITE codes. Surgical codes were grouped for each primary site. Procedures performed for cervical adenosarcomas were classified as none/autopsy, local procedure (conization, endocervical curettage, biopsy and trachelectomy), hysterectomy, hysterectomy with salpingo-oophorectomy, radical hysterectomy, exenteration, or surgery not specified. Procedures performed for ovarian adenosarcomas were classified as none/autopsy, local procedure (salpingo-oophorectomy), or hysterectomy with salpingo-oophorectomy (including procedures coded as debulking). Procedures performed for uterine adenosarcomas were classified as none/autopsy, local excision (biopsy, polypectomy, and myomectomy), hysterectomy (without or unknown if salpingo-oophorectomy), hysterectomy with salpingo-oophorectomy, radical hysterectomy, exenteration, surgery not specified, or unknown/death certificated only. Adjuvant radiation and chemotherapy variables were analyzed as a categorical variable with levels yes, no or unknown.

Survival analyses were performed for women with recorded vital status and follow-up time (n = 1337, (60.6%) of the total adenosarcoma cohort). Disease-specific survival and disease recurrence are not available in the NCDB. Median Kaplan-Meier OS times were estimated for presumed explanatory variables. Univariate Cox regression analyses were also performed to test presumed explanatory variables for association with OS. A multivariate Cox proportional hazards regression model was created using all presumed explanatory variable with a univariate association with OS ($p < 0.10$). To avoid regression coefficient estimation errors due to small numbers of cases for some levels of explanatory variables, some categorical variables were combined or omitted as follows. Surgical margin statuses were classified as negative, positive, or unknown. Government insurance (n = 6) was combined with Medicaid insurance status. These combinations are supported by examining Kaplan-Meier curves for the combined categories. Cases with radiation status unknown (n = 15), and surgical procedure listed as exenteration (n = 5), surgery NOS (n = 10), or unknown/death certificate (n = 3) were omitted. The ability to perform multivariate regression was limited by data missing for vital status for many patients with a documented metastasis status. Since stage was not reported for these cases and metastasis status was very significantly associated with OS times, the decision was made to include metastasis status in the multivariate model while accepting that the final model would then include fewer cases. The multivariate Cox proportional hazards regression model was built by stepwise selection. The proportional hazards assumption was checked at each step. No variables required stratification. Interactions between significant main-effect covariates were tested. The Analysis of Deviance table verified that all terms in the model significantly improved the model. Goodness of fit was confirmed by plotting and quantitatively evaluating the deviance residuals. A similar Cox model was created with only the uterine adenosarcoma cases. The number of women with cervical or ovarian adenosarcoma was too low to develop multivariate Cox regression models in these cohorts. Univariate regressions were performed to test associations of explanatory variables with OS among women with cervical or ovarian adenosarcoma. Restricted mean survival (RMS) curves were plotted from the Cox proportional-hazards regression of OS as a function of tumor size for women with adenosarcoma grouped by primary site [5,6]. For RMS calculations, a restriction time of 175 months was chosen to match the longest follow up time of the cohort. Survival analyses were performed in R using the "survival" package [7,8].

3. Results

3.1. Patient and disease characteristics

A total of 2205 cases of adenosarcoma were reported from 722 hospitals throughout the United States. Primary disease sites were uterus (n = 1884), cervix (n = 229) and ovary (n = 92), representing 0.43% of uterine, 0.16% of cervical, and 0.04% of ovarian cancers in the NCDB, respectively. A similar number of cases were treated in the community (n = 1185) and at academic (n = 969) centers. Patient and disease characteristics for the cohort are shown in Table 1 (online only). The distribution of cases by age at diagnosis spans a wide range of ages from <20 to >80 years (Fig. S1). Mean age at diagnosis of cervical adenosarcoma (48.3 (±13.6)) was younger compared to women with uterine (58.6 (±15.4)) or ovarian (56.5 (±13.0)) adenosarcoma (one-way ANOVA, $p < 2 \times 10^{-16}$). The distribution of cases by tumor size for each primary site is shown in Fig. S2. Cervical tumors were also diagnosed at a smaller median size of 3.0 (2.0–5.0) cm compared to uterine (5.9 (3.5–8.7) cm) and ovarian tumors (10.2 (6.0–16.0) cm) (Kruskal-Wallis, $p < 2 \times 10^{-16}$). Of cases with reported lymph node status, 36/1176 (3.1%) had at least 1 positive lymph node. This corresponded to 3.4% (34/1009) of the uterine adenosarcoma cases. Only 2.5% (33/1342) of all cases with a recorded status for metastasis had a distant metastasis at the time of diagnosis including 1/140 cervical, 1/53 ovarian and 31/1149 uterine adenosarcomas. Median tumor size was larger among women with versus without distant metastasis at diagnosis (8.5 (5.2–12.2) versus 5.9 (3.5–8.5) cm, Mann-Whitney *U* test, p = 0.007).

3.2. Primary and adjuvant treatment modalities

Most women underwent total or radical hysterectomy with or without salpingo-oophorectomy (1983/2205, 90%) with negative surgical margins (1755/2205, 79.6%). Few women underwent surgery for a distant lymph node or metastatic lesion (138/2205, 6.3%). Radiation was given to 11.4% (26/229) of women with cervical adenosarcoma, 11.9% (11/92) with ovarian adenosarcoma, and 18.2% (342/1884) with uterine adenosarcoma. Only 5 women (1 with cervical and 4 with uterine) received preoperative radiation. All other radiation was administered as adjuvant, post-surgical therapy. Adjuvant chemotherapy was administered to 44.6% (41/92) of women with ovarian, 4.8% (11/229) with cervical and 8.7% (164/1884) with uterine adenosarcoma.

3.3. Survival analyses

Of women with a reported vital status, 32.6% (436/1338) were deceased. Median follow-up time was 70.9 (28.4–102.8) months. Kaplan-Meier median OS time estimates and univariate hazard ratios for OS are shown in Table 1 for all tested explanatory variables. Reflecting the often long survival times of women with completely surgically resected adenosarcoma, the Kaplan-Meier estimate of median OS time could not be estimated for many comparison groups, nor could bounds of 95% CIs be estimated for many groups with long median OS times (particularly for small groups). Women with ovarian adenosarcoma, positive lymph nodes, distant metastasis at diagnosis, or greater than microscopic residual disease had particularly short survival times (Fig. 1). A highly significant (likelihood ratio test, $p < 2 \times 10^{-16}$) Cox model of OS was created and included explanatory variables metastasis status, margin status, age at diagnosis, comorbidity score and radiotherapy, all significantly associated with OS (Table 2). By multivariate Cox regression, primary site, lymph node status, tumor size, surgical procedure, chemotherapy use,