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Stage I uterine carcinosarcoma: Matched cohort analyses for lymphadenectomy, chemotherapy, and brachytherapy

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HIGHLIGHTS

- 42% of women with stage I carcinosarcoma received no adjuvant chemotherapy or radiotherapy.
- Lymphadenectomy, multiagent chemotherapy, and brachytherapy were each associated with increased survival.
- Hazard of death decreased 3% (1–5%) per each 5 lymph nodes removed up to 15–20 removed nodes.
- Hazard of death increased 5% (4–7%) per each 1 cm increase in tumor size.

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ABSTRACT

Objective. To determine if lymphadenectomy, chemotherapy and radiotherapy are associated with survival benefit among women with stage I uterine carcinosarcoma.

Methods. Women with stage I uterine carcinosarcoma ($n = 5614$) were identified from the 1998–2013 National Cancer Data Base. Kaplan-Meier survival estimates and Cox proportional-hazards regression models were used to evaluate predictors of overall survival. Effects of these predictors were also estimated using propensity score matched analyses for lymphadenectomy, adjuvant chemotherapy, and radiotherapy.

Results. 42.0% (2360/5614) of women in the cohort received no adjuvant radiation or chemotherapy. Black race and positive surgical margin status were associated with decreased survival by multivariable Cox regression. Among women with pathologically node-negative disease, the hazard of death increased 5% (4–7%) per each one centimeter increase in tumor size ($P = 1.9 \times 10^{-10}$). From matched cohort analyses, omitting lymphadenectomy was associated with decreased median (interquartile range) survival: 45.2 (36.4–57.6) versus 73.9 (63.8–91.6) months, hazard ratio (HR) (95% CI) 1.38 (1.20–1.59), $P = 9.4 \times 10^{-6}$. Hazard of death decreased by 3% (1–5%) for each five lymph nodes removed ($P = 0.01$). Multiagent chemotherapy and vaginal brachytherapy were associated with decreased hazard of death (HR (95% CI) 0.62 (0.54–0.73), $P = 1.1 \times 10^{-9}$ and HR (95% CI) 0.83 (0.70–0.97), $P = 0.02$, respectively). Highest five-year survival was observed after brachytherapy and multiagent chemotherapy (74.1% (68.3–80.3%), $P < 2.0 \times 10^{-16}$).

Conclusion. Lymphadenectomy to at least 15–20 removed nodes is associated with increased survival of women with node-negative uterine carcinosarcoma. Adjuvant "cuff and chemo" with vaginal brachytherapy and multiagent chemotherapy is associated with increased survival.

1. Introduction

Uterine carcinosarcoma is a rare tumor with a poor prognosis even when identified at an early stage. Carcinosarcoma is most often diagnosed in the 7th decade of life [1]. Women often present with bleeding and may have an enlarged uterus [1]. Approximately 25% and 30% of women have distant metastases or lymph node involvement, respectively, at presentation [1]. Overall survival at five-years has been reported at 50–60% for stage I/II disease and as low as 10–20% for stages III and IV [1].

Surgery consisting of at least hysterectomy and bilateral salpingo-oophorectomy is considered standard-of-care [1]. Survival benefit associated with use of adjuvant therapies for uterus-confined

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carcinosarcoma is unclear. Previous analyses of 1099 and 1819 women with stage I carcinosarcoma from the surveillance, epidemiology, and end results (SEER) database showed a survival benefit of lymphadenectomy in one study and contradictory results about a possible survival benefit of adjuvant radiotherapy [2,3]. The negative radiotherapy associations in these studies may have been underpowered [2,3]. There is currently a lack of consensus on the optimal treatment regimen for these patients including the best use of chemotherapy or radiotherapy. In particular, there is no clinical trial evidence to suggest a survival benefit of adjuvant chemotherapy or radiotherapy for stage I uterine carcinosarcoma.

We analyzed overall survival of a large cohort of women with stage I uterine carcinosarcoma to test associations of adjuvant treatments with survival and to generate hypotheses about survival associations of lymphadenectomy and adjuvant therapies. These hypotheses were then tested using a series of matched cohort analyses.

1.1. Methods and materials

1.1.1. Data source

We performed an observational retrospective cohort analysis of women with stage I uterine carcinosarcoma from the 1998–2013 National Cancer Data Base (NCDB). The NCDB, established jointly by the American Cancer Society and Commission on Cancer of the American College of Surgeons in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the US annually [4]. Individual-level data is prospectively collected by professional registrars and is audited [4]. Local institutional review board approval is not required for NCDB analyses. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each Commission on Cancer accredited hospital.

1.1.2. Cohort selection

Women with ICD-O-3 histology codes (8950/8951/8980/8981) for stage I uterine carcinosarcoma with recorded clinical follow-up data were selected ($n = 5938$). Uncommon coding inconsistencies do occur in NCDB datasets. Therefore, we checked the pathologic lymph node status and distant metastasis at diagnosis status and excluded 27 cases with positive nodes and 99 cases with metastasis at diagnosis. Women with no surgery or non-staging procedures only (example: myomectomy, hysteroscopy, polypectomy) were also excluded (final cohort $n = 5614$).

1.1.3. Variable selection and definitions

Overall survival (OS) is the outcome variable. Recurrence and disease-specific survival are not available from the NCDB. Predictor variables of interest are type of radiotherapy and chemotherapy treatments received. Additional covariates were included to adjust for potential confounding during regression analyses. These covariates were age at diagnosis, Charlson/Deyo composite comorbidity score, race, community median household annual income quartile by zip code, insurance status, cancer center type, disease grade, performance of lymph node dissection, and surgical margin status. Government insurance was combined with Medicaid. Race was categorized as White, Black, Asian/Pacific Islander, Other (includes persons coded as “other” by NCDB and a small number of Native Americans with low counts) or not reported. Hispanic ethnicity was coded separately per NCDB. For Kaplan-Meier survival estimates, tumor size and age at diagnosis were categorized using their 25th and 75th percentiles. Tumor size was truncated at 45 cm since much larger sizes are less believable and may represent coding error. Tumor size was reported and analyzable for 73.4% (4120/5614) of the cohort. Charlson/Deyo composite comorbidity score were recorded beginning in 2003 and was only available for 77.5% (4352/5614) of the cohort. Standard NCDB variable definitions are publicly available online at the American College of Surgeons.

1.1.4. Statistical analyses

Women who received any palliative treatment or who were coded as experiencing thirty-day mortality were excluded from survival analyses ($n = 55$). Median OS times and five-year survival probabilities were estimated using the method of Kaplan-Meier and compared with the log-rank test. A multivariable Cox proportional-hazards model of OS was built by backward selection with removal of non-significant covariates to evaluate survival by lymph node status and adjuvant treatment types of radiotherapy and chemotherapy, adjusting for possible confounders and using robust standard errors clustered on hospital identification codes. Initial variables included age at diagnosis, Charlson/Deyo composite comorbidity score, history of prior malignancy, race, Hispanic ethnicity, median household annual income by zip code, insurance status, cancer center type, disease grade, lymph node status, surgical margin status, and chemotherapy and radiotherapy variables. The proportional-hazards assumption was checked, and the model was stratified by age categories, prior malignancy, tumor size categories, and grade to avoid violation of the proportional-hazards assumption. The Analysis of Deviance table was used to confirm that all variables in the final model were significant. Goodness of fit of the final model was confirmed with deviance residuals. Relative hazard of death among women with pathologically node-negative disease as a function of tumor size was estimated using restricted cubic splines.

1.1.5. Matched cohort analyses

To reduce the effects of possible biases, we used propensity score methods which reduce the effects of confounding in observational studies by mimicking a randomized trial where exposed versus unexposed cohorts are matched on the potential confounders prior to analysis [5]. Separate matched cohort analyses were performed to examine the association of overall survival with (1) lymphadenectomy versus no lymph node dissection, (2) multiagent chemotherapy versus no chemotherapy, and (3) brachytherapy versus no radiotherapy. One-to-one or one-to-two nearest-neighbor propensity score matching was performed to generate the cohorts. Cohorts were matched using age, race, Hispanic ethnicity, income quartile, insurance status, comorbidity score, prior malignancy status, cancer center type, tumor size, grade, lymph node status (for chemotherapy and radiotherapy cohorts), surgical margin status, chemotherapy (for lymphadenectomy and radiotherapy cohorts) and radiotherapy exposure (for lymphadenectomy and chemotherapy cohorts). Women without recorded tumor size were excluded, except for the radiotherapy matched cohorts where one-to-two matching and tumor size categories (including women without known tumor size) were used to maintain statistical power.

Characteristics were compared between matched cohorts using Fisher's exact tests for categorical variables and Mann-Whitney *U* tests for ordinal or numeric variables. Five-year survival rates of matched cohorts were estimated by Kaplan-Meier analyses and compared using the log-rank test. Hazard ratios were estimated using multivariable Cox proportional-hazards models which included the propensity score and all variables used for cohort matching. Non-significant variables were removed by backward selection. The proportional-hazard assumption was checked and models were stratified as needed. Goodness of fit was verified by examining deviance residuals. Any significantly ($P < 0.05$) imbalanced characteristics and the actual propensity scores were included in all final Cox models even if not significantly associated with survival. As an alternative method of adjusting for the probability of treatment group assignment for each case, sensitivity analyses were also done using inverse probability weighting of the final multivariable Cox model of each matched cohort. All tests were two-tailed. Statistical analyses were performed in R using the MatchIt, survival and rms packages [6–9].