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Adjuvant radiation therapy in uterine carcinosarcoma: A population-based analysis of patient demographic and clinical characteristics, patterns of care and outcomes

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HIGHLIGHTS

- Longer survival was observed in patients who received adjuvant radiation therapy.
- African Americans had worse survival than non-African Americans.
- Access to radiation therapy was not affected by race.
- Longer survival was observed in the more recent cohort of patients.

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ABSTRACT

Objective. To examine clinical and demographic characteristics of a population-based cohort of patients with uterine carcinosarcoma (UCS), to assess access to treatment and survival patterns.

Methods. Surveillance, Epidemiology and End Results database was queried for patients diagnosed in 1999–2010 and treated with surgery with or without adjuvant radiation therapy (aRT). The Kaplan–Meier method was used to estimate survival functions, and Cox proportional hazards regression - to analyze the effect of covariates on survival.

Results. 2342 patients were eligible. African Americans presented with more advanced AJCC stages than other races (35.4% vs. 29.1%; $p < 0.01$). African Americans vs. others, and women diagnosed in 1999–2004 vs. in 2005–2010, received aRT at a similar rate: 36.5% vs. 39.9% (p = NS), and 39.5% vs. 38.9% (p = NS), respectively. There was a trend towards higher aRT utilization among patients younger than 65 vs. older (41.4% vs. 37.5%; $p < 0.06$). We observed better overall and cause-specific survival in the aRT group: 42 vs. 22 ($p < 0.0001$) and 57 vs. 28 months ($p < 0.0001$), respectively. Black race, diagnosis in 1999–2004, advanced stage and age ≥ 65 years carried a higher risk of UCS death.

Conclusions. We observed greater survival rate in the aRT group. African Americans were more likely to present with later stage disease and die of UCS than non-African Americans. Age and stage, but not race, influenced receipt of aRT. Patients treated more recently survived longer.

1. Introduction

Carcinosarcoma of the uterus (UCS; alternatively termed malignant mixed Mullerian tumor, mixed mesodermal sarcoma, and metaplastic carcinoma) is a gynecologic neoplasm that accounts for fewer than 5% of all uterine malignancies but is estimated to be responsible for up to 16% of uterine cancer deaths [1,2]. The outcomes are particularly dismal in African American women [1,3–5]. An incomplete understanding of histopathogenesis of this tumor is reflected in the lack of agreement in approach to clinical treatment.

The tumor is simultaneously composed of distinct carcinomatous and sarcomatous elements, and was, until recently, grouped with the uterine sarcomas for research and treatment purposes. However, there is now ample histopathological and molecular evidence that the sarcomatous component derives from the carcinomatous precursor through metaplastic transformation [6–8]. It is carcinoma, not sarcoma,

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that dominates the invasive foci and the metastatic lesions. The histological characteristics of the carcinomatous component of the primary tumor are predictive of distant spread [8–10]. The epithelial component is thus currently believed to confer most of the clinical characteristics to this aggressive tumor. The epithelial origin is acknowledged in the new FIGO staging system, where UCS is grouped with carcinomas [11,12]. Nonetheless, it is important to bear in mind that in historical literature UCS was invariably combined for analysis with true sarcomas (i.e. tumors of mesodermal origin).

The treatment strategies are evolving along with the knowledge of the biological characteristics of this malignancy. Surgery is the backbone of treatment, and surgical approaches take into account the tendency of this tumor, even at early stages, to involve pelvic and paraaortic lymph nodes, and the peritoneum [13,14]. Significant controversy exists regarding optimal adjuvant therapy, the need for which is highlighted by the high rate of both locoregional and distant recurrence (15–35% and 40–60%, respectively) [5,15,16]. The role of adjuvant radiation therapy in the management of UCS has been the subject of an active debate. Several retrospective case series and small randomized studies reported a high incidence of postoperative local recurrence. Addition of aRT was associated with a decrement in the rate of local failure, but without impact on survival [2,15,16,18,21].

Owing to the rarity of UCS, small study sample size is a common limitation. The present retrospective observational study examined the use of aRT in a large group of UCS patients whose cases were deposited into the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, analyzed clinical and demographic characteristics of this patient cohort and explored associations between the treatment and patient attributes and outcomes.

Caution should be exercised when reading and interpreting our study, which is subject to biases characteristic of all retrospective studies. With selection, observation and recording biases at play, associations reported herein might have been affected by unrecognized and unidentified confounding factors. Therefore, no causal relationships between interventions or patient characteristics and outcomes should be inferred.

2. Materials and methods

The data for this study were extracted from Statistics, Epidemiology and End Results (SEER) database run by the National Cancer Institute. This federally funded database collects and makes publicly available de-identified data on cancer incidence, prevalence, diagnosis, treatment and mortality. The participant registries conform to high standards in compilation, processing and storage of the epidemiologic information. SEER data have formed the basis of at least 5000 scientific publications. The latest group of registries encompasses approximately 30% of the US population from 18 geographic areas. The cancer site and histology are reported according to the International Classification of Diseases for Oncology (ICD-O) edition contemporaneous with the diagnosis [19].

A unique record is created for each tumor. It contains information about the patient's gender, age, ethnicity, date of diagnosis, stage, tumor histology and grade, modalities of treatment, date of last contact, and cause of death (if applicable). These de-identified, retrospective data are freely available to the public. Scientific studies involving these data are exempt from full review by the institutional review boards.

Eligibility criteria in our study were as follows: year of diagnosis: between 1999 and 2010; sex: female; age: 18 to 85+; race: African American, White, American Indian/AK natives and Asians/Pacific islanders; site of malignancy: uterus; histology: Müllerian mixed tumor *or* carcinosarcoma; stage according to the American Joint Commission on Cancer (AJCC): I–IV; surgery performed either as a definitive treatment or as part of a regimen that incorporated aRT; type of radiation: external beam, records of patients who underwent any other type of radiation were excluded from analysis; and vital status: alive or dead. Race was divided into two categories: African Americans and non-African Americans; the latter comprised Whites, American Indians/AK Natives and Asians/Pacific Islanders — the patient numbers for separate minority race categories were too small for a meaningful individual statistical analysis. We excluded subjects with multiple malignancies, unknown race, age, and cancer stage, unknown vital status, unknown radiation treatment status (even if primary surgery was performed), and those who had undergone neoadjuvant or intraoperative radiation or any form of brachytherapy alone. Age was arbitrarily dichotomized into <65 vs. ≥65 years. Patients were split into two cohorts based on the quinquennium of diagnosis: those diagnosed between years 1999 and 2004, and 2005 and 2010 with the goal of exploring temporal changes in the rates of survival.

The primary endpoint variables were the overall survival (OS) and cause-specific survival (CSS), and were defined in accordance with the SEER criteria. Subjects who were alive as of last follow-up were considered censored for OS. Subjects who were alive, or dead due to other causes as of last follow-up, were considered censored for CSS.

The Kaplan–Meier product limit method was used to estimate survival and the log-rank test was used to compare survival between groups. Ninety-five percent confidence intervals (95% CI) for survival rates were calculated using Greenwood's formula for computing the standard error. OS and CSS were compared separately, according to each of the patient characteristics (age group, African-American race, year of diagnosis and AJCC stage at diagnosis) and according to radiation treatment group (aRT vs. no aRT).

Multivariable analysis was performed using Cox proportional hazards regression to evaluate the association with the survival time (OS and CSS, separately) of aRT status, age group, race, year of diagnosis and AJCC stage. A backward selection algorithm was then applied in order to arrive at a more parsimonious model. 95% confidence intervals (CI) for adjusted hazard ratios were calculated to assess the precision of the obtained estimates. All analyses were generated using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). The sample size in the study was a sample size of convenience and was not based on any formal statistical power calculations.

3. Results

3.1. Demographics

A total of 5647 patients diagnosed with carcinosarcoma of the uterus between the years 1999 and 2010 were identified in the SEER database. 3305 patients were excluded from analysis due to one or more of the following factors: for 1949 patients cancer stage was unknown; in 1288 carcinosarcoma was a second malignancy; 699 patients either had no surgery, or it was unknown whether they received surgery, or they received only non-destructive local procedures such as cryosurgery or myomectomy, or sequence of surgery with radiation was unknown; for 342 patients radiation was “recommended, unknown if received”; 426 patients received radiation therapy with “implants or isotopes” either alone or in combination with external beam radiation; 30 had “Radiation, NOS” and 31 had “unknown radiation”. The final cohort that was used for analysis consisted of 2342 patients. Mean age at diagnosis was 67 years (range, 23–85). The demographic and treatment characteristics of the study cohort are summarized in Table 1.

The majority of women (69.6%) presented with the American Joint Commission on Cancer (AJCC) stage I disease. There was a significant association between race and the AJCC stage at presentation: African Americans were more likely to present with a more advanced AJCC stage (II—IV) than non-African Americans (Whites and Other races): 35.4% vs. 29.1% ($p < 0.0005$).

There was no significant difference between women diagnosed in the period of 1999–2004 and women diagnosed during the period of 2005–2010 with respect to receiving adjuvant external beam radiation therapy (aRT): 39.5% vs. 38.9%; p = NS. There was no significant difference between African-Americans and non-African Americans with

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