Original Study

Grade and Prognosis in Localized Primary Angiosarcoma

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Abstract

Primary angiosarcoma of the breast is an extremely rare cancer with poor prognosis. We queried the Surveillance, Epidemiology, an End Results database and found 226 cases between 1990 and 2006, with a median age of 49 years. Histologic grade was a significant predictor of outcome and the use of adjuvant radiation therapy did not confer any survival benefit for patients with localized disease.

Background: Primary angiosarcoma of the breast (PAOB) is rare and institutional series have provided conflicting data on the effect of grade on prognosis. **Patients and Methods:** Using a case listing session of Surveillance, Epidemiology, and End Results (SEER) 18 (1973-2010) we examined outcomes for patients with PAOB. Analyses were conducted with SEER*Stat 8.1.2, Microsoft Excel 2007, and GraphPad Prism 6. Comparisons were made using the Fisher exact test and log rank test (Mantel−Cox); P values were 2-sided. **Results:** Two hundred twenty-six women with PAOB were identified; median age was 49 (range, 15-107) years and 82% (185) were white. Seventy-two percent (162) had localized disease, 15% (34) regional disease, 7% (16) distant disease, and 6% (14) had unknown staging. Fourteen percent (32) had Grade 1, 24% (55) Grade 2, 30% (68) Grade 3 disease, and grade was unknown in 32% (72) of patients. Median overall survival (OS) for patients with localized, regional, and distant disease was 172, 24, and 16 months, respectively ($P < .001$). Median OS for patients with localized Grade 1 and 2 disease was not reached versus 36 months for Grade 3 disease ($P < .001$); 3-year OS was 89% (78) versus 47% (32). There was a strong trend for patients with Grade 3 disease to undergo mastectomy (44%, n = 30 vs. 23%, n = 20; $P = .070$) and 24% (55) of all patients received radiation. Radiation did not improve survival for localized Grade 1 and 2 disease ($P = .676$), or Grade 3 disease ($P = .589$); surgery and grade subgroups were too small for meaningful comparisons regarding radiation. **Conclusion:** Histologic grade is a significant predictor of survival for patients with localized PAOB. Regardless of grade, adjuvant radiation did not confer a survival benefit for patients with localized disease.

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Introduction

Primary angiosarcoma of the breast (PAOB) is a rare malignancy, constituting < 0.05% of all primary breast cancers.[1] PAOB needs to be differentiated from secondary angiosarcomas that arise in the breast after radiation exposure or lymphedema (Stewart Treves

syndrome).[2,3] Although secondary angiosarcomas arise in the cutaneous tissue and might secondarily invade the breast parenchyma, PAOB is a malignant vascular neoplasm that arises within the breast parenchyma.

Compared with secondary angiosarcomas of the breast, PAOB tends to occur in younger women and is a very aggressive tumor with a poor prognosis.[4] Institutional case series and retrospective studies have attempted to define prognostic factors for PAOB. Tumor size has consistently been shown to be associated with outcome.[4-6] Histologic grade as an indicator of prognosis, however, has been fraught with controversies. Although it was described as a prognostic variable in many studies,[7-9] others have not found a statistically significant effect of grade on survival.[6,10]

Because of the rarity of the disease the data to guide treatment of PAOB is mainly derived from retrospective studies and has been a matter of much debate. Surgical resection of the tumor remains the mainstay of therapy[1] and the role of adjuvant

radiation therapy, although not as clear, seems to be generally accepted.[4,11,12]

We queried the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute to examine outcomes of patients with PAOB. We investigated survival in patients stratified according to stage and grade and evaluated the influence of radiation therapy.

Patients and Methods

Patients

The population-based SEER database of the US National Cancer Institute includes data from 27 population-based registries, 9 from 1990 to 1999 and 18 from 2000 to 2009 that includes approximately 26% of US cancer patients.[13] The SEER database classifies cancer histology and topography information on the basis of the third edition of the International Classifications of Diseases for Oncology.

SEER*Stat software (version 8.1.2) was used with the case listing sessions on SEER 18 (1973-2010) to retrieve deidentified individual level data. Cases were selected by primary site breast (C500-C506, C508-C509) and angiosarcoma (9120/3) in women. Patients of all ages with pathologically confirmed angiosarcoma of the breast diagnosed between 1990 and 2009 were included. We excluded patients who had more than 1 primary malignancy.

Primary Breast Angiosarcoma Diagnosis

All the retrieved PAOB cases were categorized as local, regional, or distant (based on the American Joint Committee on Cancer 6th edition staging manual). Histologic grade was determined from the database to describe the tumors and differentiated (Grade 1), moderately differentiated (Grade 2), or poorly differentiated (Grade 3).

Outcome Measurements

The primary objective was to evaluate overall survival (OS; months) in localized PAOB stratified according to histologic grades and stage. For localized PAOB, we further conducted a comparative analysis using data on radiation therapy and surgery and additional outcome measures included OS in localized disease with or without radiation therapy.

Statistical Analysis

Overall survival curves were analyzed using the log rank test (Mantel−Cox). The sample sizes were expected to be small because of the rarity of PAOB so comparisons of OS were done using the Fisher exact test. This allowed us to examine the contingency between survival according to grade, stage, and radiation therapy. All P values were 2-sided with a value $< .05$ considered statistically significant. Analyses were conducted with Microsoft Excel 2007 and GraphPad Prism 6.

Results

Two hundred twenty-six women with PAOB were identified between 1990 and 2006 in the SEER database; 119 patients had complete grade and stage information. Overall, 14% had Grade 1, 24% had Grade 2, and 30% Grade 3 disease, and in 32% the histologic grade was unknown. Median age was 49 years (range,
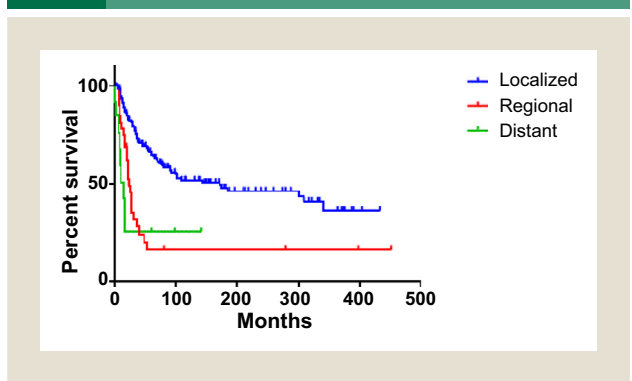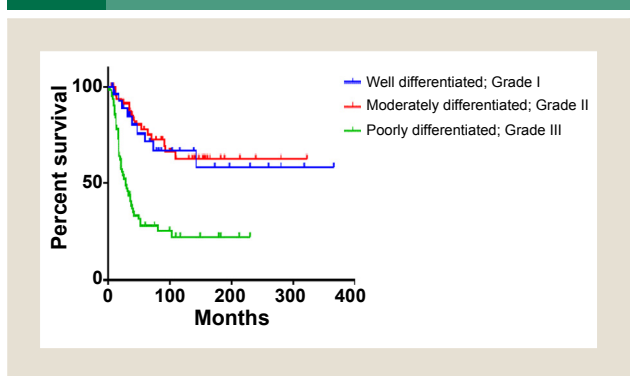
15-107 years) and 82% of the patients were white. Seventy-seven percent (n = 93) had localized disease, 16% (n = 20) had regional disease, and 7% (n = 6) had distant disease. Patients who presented with more advanced stage disease had higher grade lesions: patients with localized disease had Grade 1 (25%), Grade 2 (38%), and Grade 3 disease (37%); patients with regional disease had Grade 1 (10%), Grade 2 (15%), and Grade 3 disease (75%); patients with distant disease had Grade 2 (17%) and Grade 3 disease (83%).

Median OS for patients with localized, regional, and distant disease was significantly different ($P < .001$); 172, 24, and 16 months, respectively (Figure 1). In a comparison of median OS between all grades (Figure 2) significantly worse survival for patients with Grade 3 lesions was demonstrated although these patients clearly tended to present with more advanced disease. Specifically examining localized disease (Figure 3), Grade 3 lesions again had poor outcomes, with 60-month OS being 79% and 75% for Grade 1 and 2 versus 36% for Grade 3 tumors ($P < .001$). Of the 20 patients with regional disease, only 3 had Grade 1 and 2 had Grade 2 lesions, making further analysis according to stage and grade futile. Similarly, only 6 patients had distant disease and complete grade information precluding meaningful analysis.

Patients with localized Grade 1 lesions received surgery 91% of the time with no difference in outcomes whether they received a mastectomy (67%) or lumpectomy (33%; 5-year OS of 81%