Breast Angiosarcoma: a SEER Population- Based Study

Zhengshui Xu
Xi'an Jiaotong University Medical College First Affiliated Hospital https://orcid.org/0000-0003-0934-3205

Xiaopeng Li
Xi'an Jiaotong University Medical College First Affiliated Hospital

Jing Guo
Xi'an Jiaotong University Medical College First Affiliated Hospital

Liyue Yuan
Xi'an Jiaotong University Medical College First Affiliated Hospital

Zilu Chen
Xi'an Jiaotong University Medical College First Affiliated Hospital

Jianbao Zheng
Xi'an Jiaotong University Medical College First Affiliated Hospital

Xuejun Sun
Xi'an Jiaotong University Medical College First Affiliated Hospital

Junhui Yu (yujunhui@mail.xjtu.edu.cn)
Xi'an Jiaotong University Medical College First Affiliated Hospital https://orcid.org/0000-0002-6270-7891

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Abstract

Background

Breast angiosarcoma is a rare malignancy with poor survival. Due to the paucity of data, the generation of high-quality evidence for its high-risk features and the impact of treatment modalities on survival have been hampered.

Objective

To examine high-risk features and the impact of treatment modalities on disease-specific survival (DSS) in breast angiosarcoma and differences between breast angiosarcoma cases with and without other prior cancers.

Methods

In this retrospective study, patients with breast angiosarcoma diagnosed from 1975 to 2016 were identified from the Surveillance, Epidemiology, and End Results database. Cox proportional hazards regression analysis adjusted for age, race, decade at diagnosis, location, pathologic grade, extent of disease, tumor size, and therapy to model DSS outcomes. Propensity score matching analyses were performed to adjust for the differences between breast angiosarcoma cases with and without other prior cancers to compare their DSS values. A Kaplan-Meier curve was used to visualize the cumulative survival probability.

Results

Of 648 patients with breast angiosarcoma, 55.4% had a prior cancer diagnosis. Older (age ≥ 70) patients were more likely to have breast angiosarcoma with prior cancer than younger patients (64.3% versus 21.8%). Via multivariate analysis, pathologic grade and extent of disease were identified to be significantly associated with DSS in breast angiosarcoma. In matched data, breast angiosarcoma patients with prior cancer had a better DSS than those without prior cancer (HR = 0.60, 95%CI 0.38–0.96, p = 0.0389). In breast angiosarcoma patients without prior cancer, patients with larger tumor size receiving surgery plus radiation or/and chemotherapy might have a better survival than those patients receiving surgery only (HR = 0.38, 95%CI 0.14–0.99, p = 0.0128). DSS is not impacted by the current therapeutic strategies in unselected breast angiosarcoma patients.

Conclusions

Breast angiosarcoma patients with prior cancer have a better DSS than those without prior cancer. Additionally, some breast angiosarcoma cases with prior cancer may be cutaneous angiosarcomas. Pathologic grade and extent disease are high-risk features. DSS is not impacted by the current therapeutic strategies in unselected breast angiosarcoma patients.

Introduction

Breast angiosarcoma is an aggressive, malignant endothelial cell tumor of vascular or lymphatic origin that accounts for less than 2% of all soft tissue sarcomas.[1, 2] Although most angiosarcomas take place spontaneously, lymphoedema and radiotherapy (RT) are two main causal etiological factors in the development of angiosarcomas.[2–8] If angiosarcomas arise in breast, it is hard to difference between cutaneous angiosarcomas of breast and primary parenchymal angiosarcomas of breast.[1, 2, 8, 9] Additionally, cutaneous angiosarcomas of breast commonly arise from the dermis and subcutis of the RT field and periphery of the resection margins.[8–11] Nearly 40% of RT-related cutaneous angiosarcomas of the breast do not involve the breast parenchyma.[8] Most breast angiosarcoma patients who had other prior cancers and received radiation and/or breast resection could be classified as having cutaneous angiosarcomas of breast. [4, 6, 8, 12, 13] Furthermore, patients who had been diagnosed with breast cancer and received mastectomy without remaining breast parenchyma should definitively be classified as having cutaneous angiosarcomas of breast [4, 14]. Hence, in this study, we considered the differences between breast angiosarcoma patients without or with prior cancers.

Currently, breast angiosarcomas without and with prior cancer are managed similarly, and the treatment is mainly based on experience with other kinds of soft tissue sarcomas. Surgical intervention is the most common frontline option, while RT and chemotherapy have also been used.[2, 6, 15–17] However, the impact of different management strategies is still unclear. Herein, we tried to compare the impacts of different management strategies on prognosis in breast angiosarcoma patients without or with prior cancer. Additionally, we sought to define high-risk factors in each group.

Methods

Data were extracted from the Surveillance, Epidemiology, and End Results Program (SEER) database, a national registry that has been funded by the National Cancer Institute since 1971, using the SEER-18 registry [18]. SEER*Stat Version 8.3.6 was used to identify patients diagnosed with breast angiosarcoma between 1975 and 2016 according to the International Classification of Diseases for Oncology, 3rd edition morphological code. The study was subject to approval by the First Affiliated Hospital of Xi'an Jiaotong University's Review Board and to a Data Use Agreement with NCI.

Data extraction, collection and exclusion

Patients were classified by whether they had a prior cancer. The relevant information, as follows, was entered into our previously prepared tables:

Primary outcomes: number of patients, number of patients in each group, age, race, decade at diagnosis, location, pathologic grade, extent of disease, tumor size, and therapy.

Secondary outcomes: comparison of disease-specific survival (DSS) between breast angiosarcoma patients without and with prior cancer and the impact of different therapies on disease-specific survival (DSS).

The detailed data regarding age, decade at diagnosis, location, pathologic grade, extent of disease, tumor size, and therapy are presented in Table 1. The length of DSS was calculated from the date of diagnosis of breast angiosarcoma to the date of death or the end of the observation period. Patients who died from other causes other than breast angiosarcoma were censored considered as living.

Table 1
Characteristics of patients with breast angiosarcoma based on existence of a prior cancer (N = 648)

	No Prior (case, %)	With Prior (case, %)	P-Vaule
no.	289	359	
Age at diagnosis			< 0.001
<50	137 (47.7)	15 (4.2)	
50–69	89 (30.8)	113 (31.5)	
≥70	63 (21.8)	231 (64.3)	
Race			< 0.001*
White	232 (80.3)	330 (91.9)	
Other	54 (18.7)	29 (8.1)	
Unknown	3 (1.0)	0 (0)	
Decade at Diagnosis			< 0.001
1975–1986	50 (17.3)	2 (0.6)	
1987–1996	42 (14.5)	17 (4.7)	
1997–2006	83 (28.7)	140 (39.0)	
2007–2016	114 (39.4)	200 (55.7)	
Location			< 0.001
Nipple	1 (0.3)	7 (1.9)	
Central portion	17 (5.9)	31 (8.6)	
Inner quadrant	50 (17.3)	38 (10.6)	
Outer quadrant	49 (17.0)	42 (11.7)	
[a]Dualquadrants	76 (26.3)	61 (17.0)	
[b]Multiquadrants	96 (33.2)	180 (50.1)	
Pathologic Grade			< 0.001
Well differentiated	43 (14.9)	26 (7.2)	
Moderately differentiated	66 (22.8)	38 (10.6)	
Poorly differentiate/ Un- differentiated	101 (34.9)	202 (56.3)	
Unknown	79 (27.3)	93 (25.9)	

	No Prior (case, %)	With Prior (case, %)	P-Vaule
[c]Extent of Disease			< 0.001
Localized	99 (34.3)	180 (50.1)	
Regional	9 (3.1)	52 (14.5)	
Distant	10 (3.5)	10 (2.8)	
Unknown	171 (59.2)	117 (32.6)	
Tumor Size			< 0.001
≤50 mm	62 (21.5)	122 (34.0)	
>50 mm	51 (17.6)	74 (20.6)	
Unknown	176 (60.9)	163 (45.4)	
Therapy			< 0.001
Surgery Only	146 (50.5)	232 (64.6)	
Surgery + Radiation	41 (14.2)	31 (8.6)	
Surgery + Chemotherapy	48 (16.6)	54 (15.0)	
Surgery + Radiation + Chemotherapy	37 (12.8)	15 (4.2)	
[d]No Surgery	17 (5.9)	27 (7.5)	

*Fish test

[a]More than one quandrant but less than half breast size

[b]Entire breast: ¾ or more of breast involved with tumor, or multiple tumors in different subsites

[c]Extent of Disease: Local: tumor spread limited to the organ of origin; Regional: beyond the limit of the organ of origin; Distant: distant lymph node metastasis and distant metastasis

[d]No Surgery: only Radiation or/and Chemotherapy; no any therapy

If patients were duplicates, male, or treated without any therapy, they were excluded.

Statistical analysis

Categorical variables are presented as numbers and percentages. Chi-square tests and t-tests were performed for descriptive analyses. The Cox proportional hazards regression analysis was adjusted for age, race, decade at diagnosis, location, pathologic grade, extent of disease, tumor size, and therapy to model DSS outcomes. If there were inherent differences between breast angiosarcoma patients without and with prior cancer in terms of baseline patient characteristics, we used propensity score matching

analyses [19] with the Statistical Package for the Social Sciences software, version 22.0 (SPSS, Chicago, IL, USA) to adjust for these differences. A Kaplan-Meier curve was used to visualize the cumulative survival probability. Statistical analysis was performed using GraphPad Prism 7 software (GraphPad Software, San Diego, CA). All P values were 2-sided, with a value < 0.05 considered statistically significant.

Results

Patient characteristics

In total, the number of breast angiosarcoma patients diagnosed between 1975 and 2016 was 672. After we excluded 15 duplicates, 3 male patients and 6 patients who had not received any therapy, 648 patients were identified, of which 359 had a prior cancer diagnosis (Table 1). The amount of patients steadily increased over the last three decades of age, especially the amount of breast angiosarcoma patients with prior cancer.

Older (age≥70) patients were more likely to have breast angiosarcoma with prior cancer. Examinations of pathologic grade showed higher tumor grade in breast angiosarcomas with prior cancer than in those without prior cancer (grade 3: 56.3% versus 34.9%). This result suggests that breast angiosarcoma with prior cancer shows a more aggressive tumor phenotype than those without prior cancer. Furthermore, finding a larger extent of disease and a greater tumor size in breast angiosarcomas with prior cancer than in those without prior cancer may have strengthened our suggestion above, but we could not determine these results because of missing data. However, breast angiosarcoma patients without prior cancer were more likely to receive combination surgery with radiation or/and chemotherapy (43.6%) than those with prior cancer (27.8%). Overall, surgery alone was the most common treatment modality in both breast angiosarcomas with (64.6%) and without (50.5%) prior cancer (Table 1).

Disease-specific survival and high-risk features

In the multivariate analysis, pathologic grade and extent of disease were significantly associated with DSS in breast angiosarcoma (Table 2). However, there was still a small difference between angiosarcomas with and without prior cancer; mainly in the subgroup of extent of disease, regional disease was an independent risk factor in breast angiosarcomas with prior cancer (HR 3.05, 95%CI 1.77-7.70, p<0.001) but not in breast angiosarcomas without prior cancer (HR 1.78, 95%CI 0.59-5.15, p=0.309). In the subgroup of pathologic grade, having unknown data was also an independent risk factor in breast angiosarcomas with prior cancer (Table 2).

Table 2 Multivariate analysis of disease-specific survival in breast angiosarcoma

	No prior		With prior	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age at diagnosis				
<50	ref		ref	
50-69	1.15 (0.72-1.85)	0.55	1.24 (0.36-4.31)	0.737
≥70	1.19 (0.66-2.14)	0.56	2.00 (0.60-6.69)	0.263
Race				
White	ref		ref	
Others	0.83 (0.46-1.50)	0.529	1.46 (0.72-2.96)	0.299
Decade at Diagnosis				
2007-2016	ref		ref	
1997-2006	0.53 (0.26-1.10)	0.087	0.75 (0.44-1.28)	0.29
1987-1996	0.75 (0.30-1.90)	0.544	0.80 (0.25-2.61)	0.715
1975-1986	0.99 (0.38-2.58)	0.984	No calculating	
Location				
Outer quadrant	ref		ref	
Inner quadrant	0.89 (0.44-1.79)	0.733	2.25 (0.96-5.24)	0.061
Central portion	0.58 (0.19-1.78)	0.341	0.46 (0.16-1.34)	0.155
Dualquadrants	1.43 (0.78-2.63)	0.244	1.34 (0.60-2.96)	0.477
Multiquadrants	1.08 (0.57-2.04)	0.805	0.89 (0.43-1.83)	0.754
Nipple	No calculating		2.11 (0.44-10.19)	0.351
Pathologic Grade				
Well differentiated	ref		ref	
Moderately differentiated	1.15 (0.55-2.41)	0.72	2.06 (0.55-7.70)	0.285
Poorly differentiate / Un-differentiated	2.52 (1.25-5.09)	0.01	3.87 (1.31-11.42)	0.014
Unknown	1.17 (0.54-2.50)	0.693	3.69 (1.23-11.10)	0.02
Extent of Disease				

Localized	ref		ref	
Regional	1.78 (0.59-5.15)	0.309	3.05 (1.77-7.70)	<0.001
Distant	4.62 (1.66-12.87)	0.003	7.14 (2.56-11.42)	<0.001
Unknown	1.32 (0.27-6.37)	0.729	1.43 (0.68-11.10)	0.344
Tumor Size				
≤50mm	ref		ref	
>50mm	1.72 (0.81-3.66)	0.157	1.55 (0.85-2.81)	0.153
Unknown	1.48 (0.33-6.60)	0.61	1.68 (0.88-3.22)	0.119
Therapy				
Surgery Only	ref		ref	
Surgery + Radiation	0.99 (0.54-1.80)	0.96	1.22 (0.59-2.50)	0.596
Surgery + Chemotherapy	1.03 (0.58-1.85)	0.914	0.81 (0.41-1.60)	0.538
Surgery + Radiation + Chemotherapy	1.37 (0.75-2.49)	0.301	0.88 (0.34-2.29)	0.796
No Surgery	0.90 (0.29-2.76)	0.849	1.73 (0.77-3.90)	0.185

[a]More than one quandrant but less than half breast size

[b]Entire breast: ¾ or more of breast involved with tumor, or multiple tumors in different subsites

[c]Extent of Disease: Local: tumor spread limited to the organ of origin; Regional: beyond the limit of the organ of origin; Distant: distant lymph node metastasis and distant metastasis

[d]No Surgery: only Radiation or/and Chemotherapy; no any therapy

DSS did not differ significantly between breast angiosarcoma patients without and with prior cancer (HR=0.367, 95%CI 0.67-1.16, p=0.369), as shown in Figure 1A. However, there were inherent differences in baseline patient characteristics between the two groups, and propensity score matching analyses were performed to adjust for these differences to compare disease-specific survival (DSS). We matched the two groups at a 1:1 ratio according to age, pathologic grade, extent of disease and tumor size (supplementary Table S1 and Table S2). Surprisingly, in the matched data, breast angiosarcoma patients with prior cancer had a better DSS than those without prior cancer, with (HR=0.6, 95%CI 0.38-0.96, p=0.0389), as shown in Figure 1B.

Treatment outcomes

In breast angiosarcoma patients without and with prior cancer, the DSS associated with surgery only did not differ significantly from that of other treatment modalities (Table 2). There were also no significant

differences between surgery only and surgery plus radiation or/and chemotherapy in terms of pathologic grade, extent of disease, or tumor size, as shown in Figure 2 and Figure 3. However, in breast angiosarcomas without prior cancer, patients with larger tumor size receiving surgery plus radiation or/and chemotherapy had a better survival than those patients receiving surgery only (HR=0.38, 95%CI 0.14-0.99, p=0.0128), as shown in Figure 3F.

Discussion

Breast angiosarcoma is the second most common among all angiosarcomas. [1, 3, 20–25] The increasing incidence rate of breast angiosarcoma may be attributed to the worldwide use of radiotherapy in breast cancer.[2, 13, 26, 27] If angiosarcomas arise in breast, it is hard to differentiate between cutaneous angiosarcomas of breast and primary parenchymal angiosarcomas of breast.[1, 2, 8, 9] Combined with the conclusions of previous studies, [8, 9, 28] we also conclude that some breast angiosarcoma cases with prior cancer should be classified as cutaneous angiosarcomas of breast. We found that higher tumor grade, larger extent of disease and greater tumor size were more common in breast angiosarcoma patients with prior cancer than in breast angiosarcoma patients without prior cancer, which suggests that breast angiosarcoma with prior cancer shows a more aggressive tumor phenotype than those without prior cancer. Furthermore, finding a larger extent of disease and a greater tumor size in breast angiosarcomas with prior cancer than in those without prior cancer may have strengthened our suggestion above, but we could not determine these results because of missing data. However, in matched data, breast angiosarcoma patients with prior cancer had a better DSS than those without prior cancer. Hence, we suggest that breast angiosarcoma patients without prior cancer, at least some of them, have different origins of disease than breast angiosarcoma patients with prior cancer. Additionally, cutaneous angiosarcomas had a better survival rate than de novo angiosarcomas.[29] These results deeply support that a portion of breast angiosarcoma cases with prior cancer should be classified as cutaneous angiosarcoma of the breast.

In our study, we found that both pathologic grade and distant disease were closely associated with DSS in breast angiosarcoma, which was supported by previous studies.[4, 6, 15–17] However, we further found that regional disease was the independent risk factor in breast angiosarcoma patients with prior cancer but not in breast angiosarcoma patients without prior cancer. Unknown pathologic grade data were associated with decreased DSS in breast angiosarcoma patients with prior cancer, which might be due to the large amount of patients with grade 3 disease in our study (accounting for 56.3% of the present data). We found that age and tumor size were not associated with survival outcomes, which was inconsistent with previous studies.[14, 15, 17, 30] In previous studies, researchers focused more on the relationship between age and overall survival. However, in our study, patients who died from causes other than breast angiosarcoma were considered as living. The different definitions of survival might be responsible for the different results. However, we suggest that we should focus on death from breast angiosarcoma when the effects of other causes, such as age and other diseases, on survival cannot be excluded.

Currently, surgical intervention is the most common frontline option for breast angiosarcoma, and this intervention is based on the therapeutic strategies used in breast cancer. Additionally, mastectomy and breast conservative surgery are the most popular options,[4, 10, 12, 15, 17, 31–34] but the impacts of them are still unclear.[6, 30] Because of the high rate of local recurrence, extensive surgery with resection of a larger region of skin has been proposed.[7, 11, 35] Interestingly, low lymph node involvement is not common in breast angiosarcoma; therefore, routine axillary dissection may not be necessary.[10, 26] Therefore, the best surgical approach is still unknown.

The chemotherapy strategies used for breast angiosarcoma, including anthracyclines or taxanes, are mainly based on experience with other kinds of soft tissue sarcomas.[29, 36] The benefit of chemotherapy and/or radiotherapy for breast angiosarcoma is still unclear, but the side effects of these therapies are well known. On the one hand, some studies have demonstrated that chemotherapy and/or radiotherapy have benefits in patients with breast angiosarcoma,[14, 36, 37] whereas several researchers reported that adjuvant therapies had no or even a negative effect on prognosis.[13, 17, 29] Furthermore, we found that chemotherapy and/or radiotherapy had no benefit in unselected breast angiosarcoma patients. In further research, we found that patients with larger tumor size receiving surgery plus radiation and/or chemotherapy might have a better survival than those patients receiving surgery only in breast angiosarcoma without prior cancer, which is similar to the findings of Shearwood McClelland III and colleagues.[6] Manisha Palata reported that hyperfractionated radiotherapy for angiosarcoma provided a high rate of local control after breast-conserving therapy. [26] From the above results, we conclude that adjuvant therapies play an important role in the treatment of breast angiosarcoma. However, the “3Ws” (how to use, when to use, and who is needed) may be key considerations in the future.

Unfortunately, in our study, we found that almost all of the current therapeutic strategies available had no significant effect on the DSS in patients with breast angiosarcoma, and similar results were found in cutaneous angiosarcoma.[3] Recently, due to the endothelial cell basis of tumors of vascular or lymphatic origin in breast angiosarcoma, inhibitors of vascular endothelial growth factor receptor (VEGFR) have been approved for treatment.[29, 37–39] In a phase I/II study, the combination of carotuximab with pazopanib was effective and resulted in durable complete responses and encouraging progression-free survival, especially in patients with cutaneous lesions.[37, 38] However, a randomized phase II trial showed that paclitaxel administered once per week with bevacizumab showed no superior benefit over paclitaxel without bevacizumab in patients with advanced angiosarcoma. In several cases, CTLA-4 inhibitors, PD-1 directed therapy, proton beam therapy and photodynamic therapy showed therapeutic benefits,[40–43] and these might be potential future options. There is a compelling need to explore novel therapeutic strategies for breast angiosarcoma.

There were several limitations in our study. First, due to its retrospective nature, potential selection bias cannot be excluded. Second, the data in our study were collected completely from the SEER database. Third, sometimes it is hard to differentiate between cutaneous angiosarcomas of breast and primary parenchymal angiosarcomas of breast, which may impact all related studies. The details of surgical

intervention, chemotherapy and radiotherapy were not included in the SEER data, so further research on the impact of treatment modalities is not possible.

Conclusion

Breast angiosarcoma patients with prior cancer have a better DSS than those without prior cancer. A portion of breast angiosarcoma cases with other prior cancers may be cutaneous angiosarcomas. Pathologic grade and extent disease, but not age and tumor size, have a close association with DSS in breast angiosarcoma. DSS is not impacted by the current therapeutic strategies in unselected breast angiosarcoma patients.

Declarations

Data Availability Statement

The data used to support the findings of this study are included within the article and the Surveillance, Epidemiology, and End Results database.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

Disclaimer

The study was subject to approval by the first hospital of Xi'an Jiaotong University's Review Board and to a Data Use Agreement with NCI.

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Figures

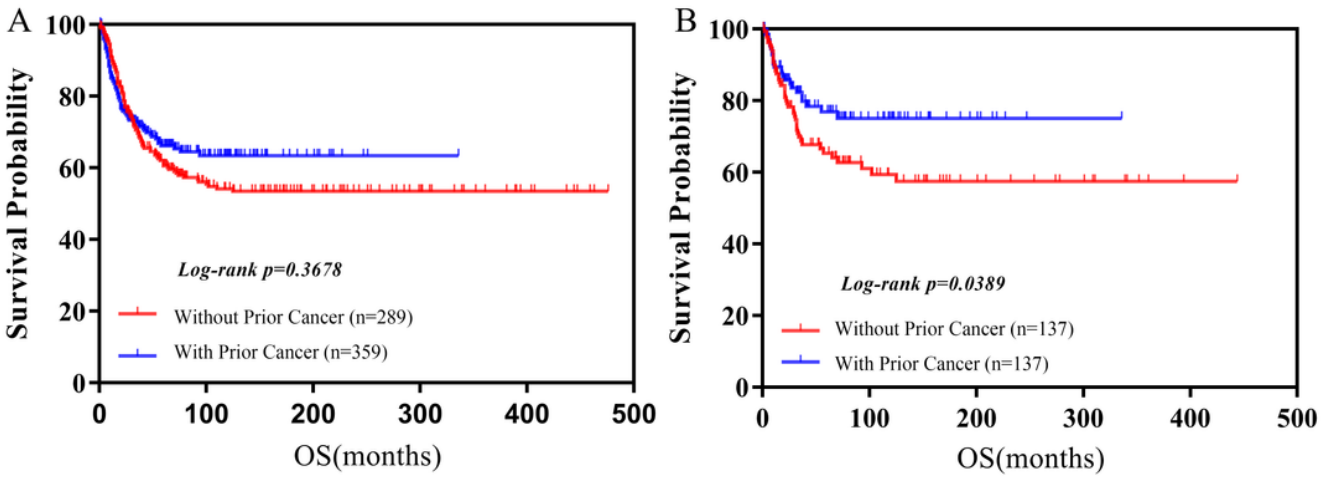

Figure 1

Kaplan-Meier curves to compare DSS between breast angiosarcoma patients without versus with prior cancer. (A) unadjusted data. (B) matched groups. DSS: disease-specific survival

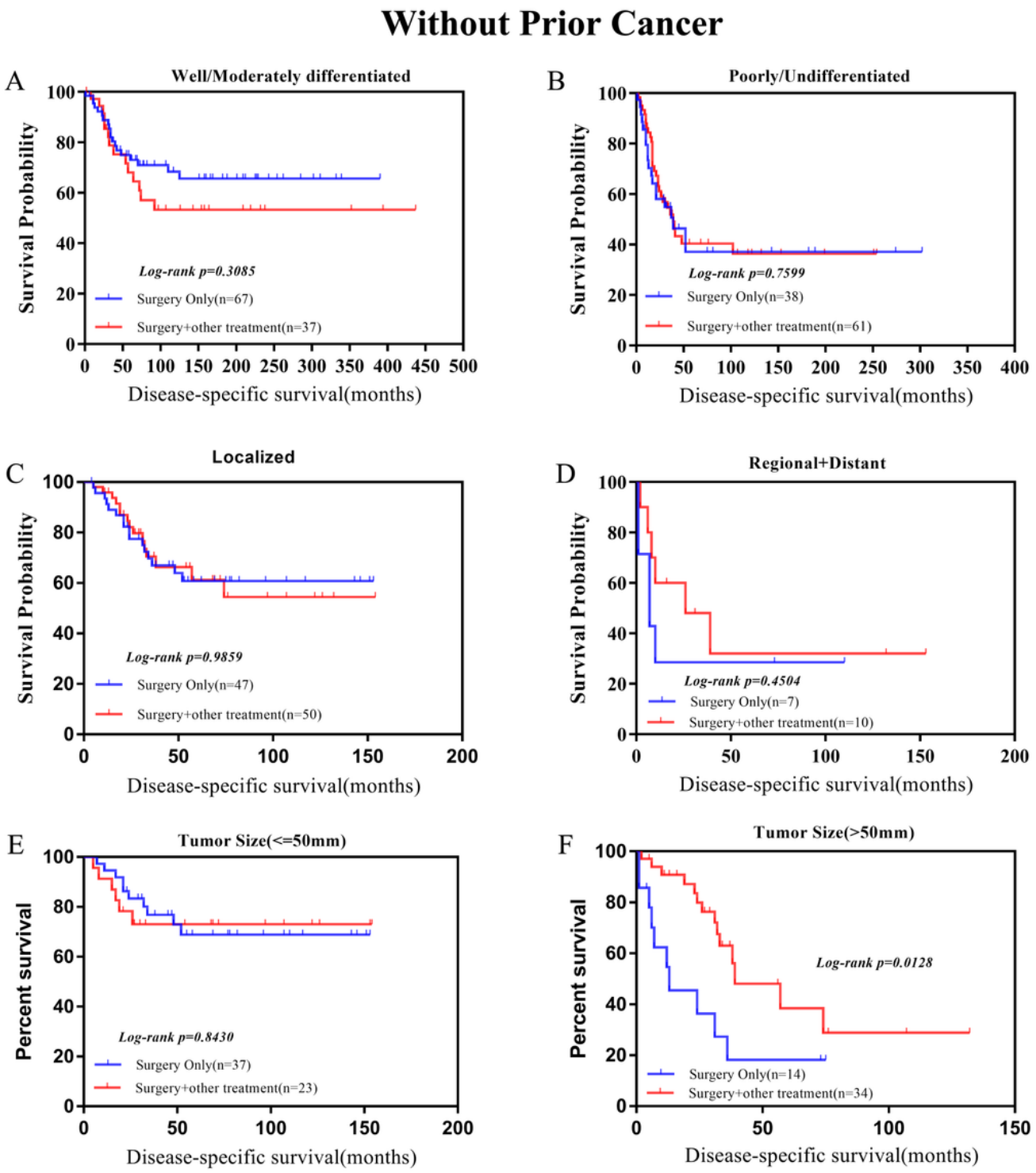

Figure 2

DSS for patients undergoing surgery only versus surgery plus radiation or/and chemotherapy in terms of pathologic grade (A), extent of disease (B), and tumor size (C) in breast angiosarcoma patients without prior cancer group. DSS: disease-specific survival

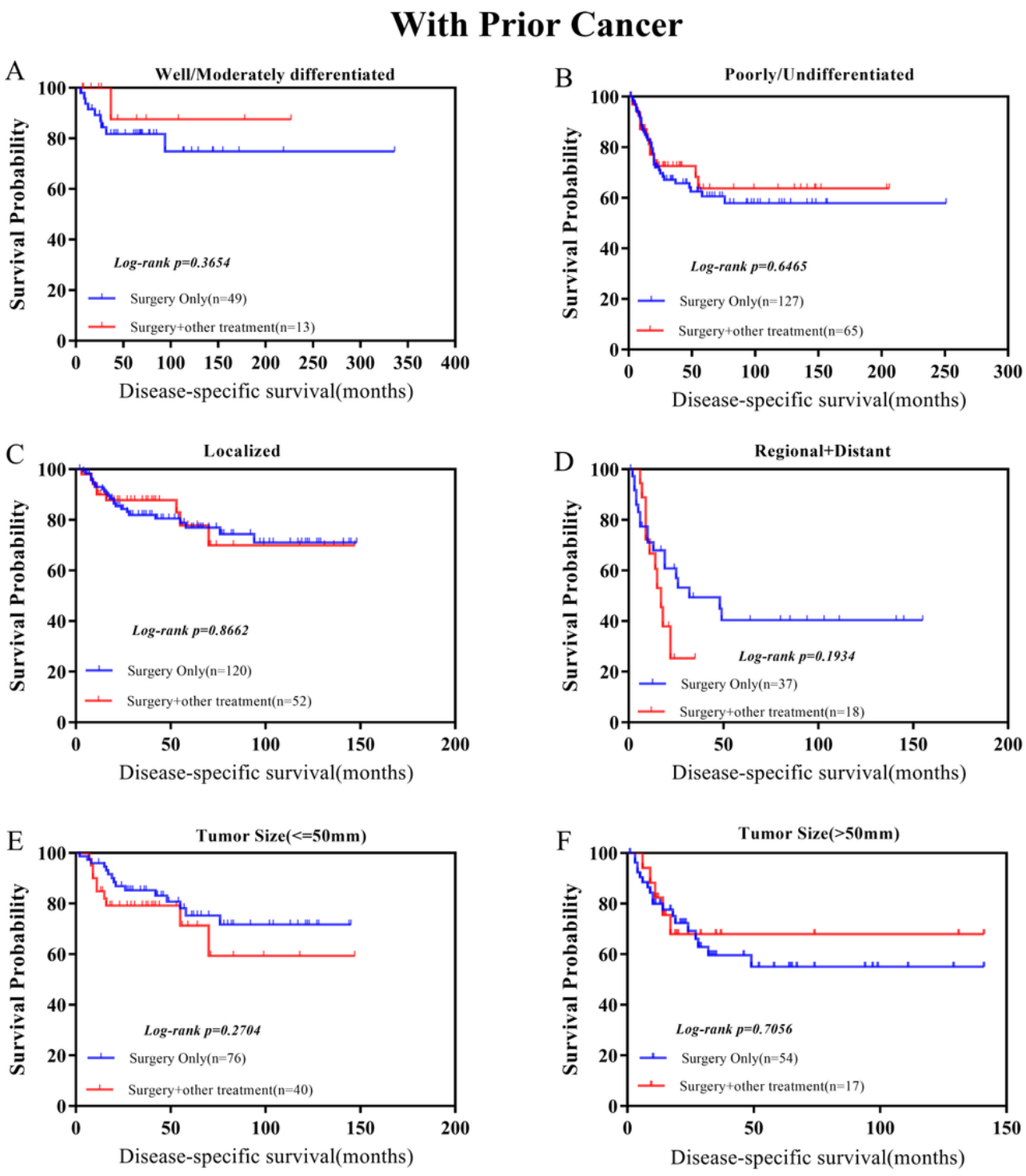

Figure 3

DSS for patients undergoing surgery only versus surgery plus radiation or/and chemotherapy in terms of pathologic grade (A), extent of disease (B), and tumor size (C) in breast angiosarcoma patients with prior cancer group. DSS: disease-specific survival

Supplementary Files

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