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The importance of surgery in scalp angiosarcomas

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Abstract

Background: Scalp angiosarcomas (SA) are rare, representing < 1% of soft tissue sarcomas. The optimal management of these tumors is unknown, with management based on small case series. We sought to assess the impact of different therapies on overall survival (OS), the practice patterns nationally, and identify factors associated with OS for non-metastatic scalp angiosarcomas.

Methods: A prospectively maintained database was used to identify non-metastatic scalp angiosarcomas who received some form of definitive therapy. Logistics regression, Kaplan-Meier, and Cox proportional-hazard models were utilized.

Results: A total of 589 patients met study entry criteria with a median follow-up of 4.2 years. The majority (482 patients, 81.8%) had upfront definitive resection and an additional 317 patients (65.8%) received postoperative radiation. Of the 107 patients who didn't have surgery, the majority (65 patients, 60.7%) received definitive radiation and 42 patients (39.3%) received radiation and chemotherapy. One-year and five-year survival estimates for patients not receiving definitive surgery were 68.0% (95%CI: 57.5–76.4) and 18.0% (95%CI: 10.2–27.5) respectively compared to 78.2% (95%CI: 74.0–81.9) and 34.1% (95%CI: 28.9–39.3) for patients receiving

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Author contributions

RJC: all aspects; JMS: data collection, statistical analysis; MLY: planning, review; NM: planning, review; DKM: planning, review; JJB: planning, review; JLC: planning, review; KDG: planning, review; TWG: planning, data collection, review; KRP: all aspects.

Conflicts of interest/disclosures

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.suronc.2018.07.010>.

definitive surgery ($p < 0.01$). On multivariable analysis, age ≥ 65 years, tumor size ≥ 5 cm, and not receiving definitive surgery was associated with worse OS.

Conclusions: The majority of patients with non-metastatic scalp angiosarcomas had upfront definitive surgery, with a subsequent improvement in OS, including when accounting for other patient and tumor factors. Postoperative radiation was frequently given. Our large series confirmed age and tumor size as prognostic factors for this rare disease.

Keywords

Angiosarcoma; National cancer data base; Scalp sarcoma; Head and neck sarcomas

1. Introduction

Angiosarcomas of the head and neck represent about 15% of all head and neck sarcomas and 1% of all soft tissue sarcomas, most commonly arising on the scalp [1–3]. Given the rarity of this disease there is limited evidence for the optimal treatment strategy, mostly derived from case series, which suggest that surgical resection with wide margins followed by postoperative radiation is the optimal management [4–8]. The role of chemotherapy is unclear, with some studies suggesting a benefit concurrently or after radiation [9,10]. Angiosarcomas arise from blood or lymphatic vessels and biologically have a propensity for insidious local infiltration [10]. Angiosarcomas are aggressive tumors that recur both locally, distantly, and have risk of spread to draining lymphatics [11–13]. Given these aggressive characteristics, estimated survival rates at 5 and 10 years are 34% and 14% respectively [14].

Given the rarity of angiosarcomas of the scalp, the optimal management is unclear. To further understand practice patterns of therapy in the United States (US) and to determine the impact of these therapies on overall survival (OS), we utilized the National Cancer Data Base (NCDB) to identify a large cohort of patients with non-metastatic scalp angiosarcomas who had complete treatment records. Our goals were to identify demographic, tumor, and treatment related factors associated with the receipt of different therapies as well as determine the impact of these therapies on OS.

2. Methods

2.1. Patient selection

The NCDB captures 70% of newly diagnosed cancers in the US. The database reports on Commission on Cancer accredited facilities and includes demographic, socioeconomic, and disease characteristics as well as detailed surgical and radiation treatment information.

The sarcoma NCDB file was queried for patients diagnosed between 2004 and 2014. Our inclusion criteria included only patients with nonmetastatic angiosarcomas of the scalp who received some form of de-finitive therapy. We excluded patients with incomplete treatment records and patients who had a previously diagnosed malignancy (Supplemental Fig. 1). Staging was via modern guidelines [15]. The following patient characteristics were examined: age, sex, race, insurance status (uninsured, private, or government), Charlson-Deyo comorbidity [16,17] score, county of residence (urban, rural, or metro as defined by

the US Census Bureau), year of diagnosis, percentage of residents without a high school degree in patient's census tract (< 14, 14–19.9, 20–28.9, and ≥ 29% quartiles), median income of patient's census tract (< 30,000, 30,000–35,999, 36,000–45,999, and ≥ 46,000 dollars as determined by the American Community Survey), and distance from the patient's zip code to treatment facility (< 10 miles, 10–50 miles, or ≥ 50 miles). The following tumor characteristics were examined: tumor size (< 5 cm or ≥ 5 cm) and stage group (II or III). Treatment characteristics examined included: facility type (academic or community program), facility location (northeast, south, midwest, and west), treatment center volumes (high vs. Low volume defined using the 80th percentile for the number of cases treated at each facility), use of neck dissection, surgical margins, time from diagnosis to surgical resection (0–3 months, 3–6 months, or ≥ 6 months), receipt of postoperative radiation, and receipt of postoperative chemotherapy.

2.2. Statistical methods

Statistical analysis was conducted using SAS Version 9.4 (Cary, NC) and SAS macros [18]. Univariable logistic regression models were fit to determine predictors of receiving definitive surgery. The collinearity of among all variables was checked by removing any variance inflation factors greater than ten. Separate univariable and multivariable analyses were performed to determine factors associated with receipt of postoperative radiation and postoperative chemotherapy in patients who underwent upfront definitive surgical resection. OS was defined as months from diagnosis to death or last follow up. Univariable and multivariable Cox proportional hazard models for OS were generated in two analyses: one for all patients receiving definitive therapy and one only in patients who received upfront surgery. Note that surgery specific variables (e.g. pathological stage, margin status) could only be included in models restricted to patients receiving definitive surgery. Kaplan-Meier curves were generated for OS stratified by receipt of surgery with comparisons using log-rank tests. For all analyses a $p < 0.05$ was considered statistically significant. For each Cox survival model, the proportional hazard assumption was assessed by plotting the logarithms of the cumulative baseline hazard rate for each level of each covariate after adjusting for the effects of other variables if applicable.

3. Results

3.1. Patient characteristics

A total of 589 patients met study entry criteria (Supplemental Fig. 1). The median follow-up was 4.2 years (range 0.4–9.2 years). A total of 482 patients (81.8%) received definitive surgery, with an additional 317 patients (65.8%) receiving postoperative radiation. Of the 107 (18.2%) patients who did not have definitive resection, 65 patients (60.7%) were treated with definitive radiation alone and 42 patients (39.3%) received radiation and chemotherapy. The median delivered radiation dose was 60.0 Gy (range 45.0 Gy–74.0 Gy). The median number of fractions delivered was 30 (range 23–37). Supplemental Table 1 summarizes the radiation modalities used and Supplemental Table 2 summarizes the radiation target volumes. Table 1 summarizes the study population.

3.2. The impact of definitive surgery

Patients treated with definitive radiation or definitive chemoradiation were more likely to have tumors ≥ 5 cm (OR = 2.26, 95%CI:1.26–4.05, $p < 0.05$) compared with patients treated with definitive surgery, otherwise there were no other patient, tumor, treatment characteristic differences (all $p > 0.10$).

One-year and five-year survival estimates for patients not receiving definitive surgery were 68.0% (95%CI: 57.5–76.4) and 18.0% (95%CI:10.2–27.5) respectively compared to 78.2% (95%CI: 74.0–81.9) and 34.1% (95%CI: 28.9–39.3) for patients receiving definitive surgery ($p < 0.01$, Fig. 1). On univariate analysis for OS, age ≥ 65 years, black race, living in a census tract with a median income $< \$30,000$, tumor size ≥ 5 cm, and not receiving definitive surgery were associated with worse OS while male sex, having private insurance, and living 10–50 miles from their treatment facility were associated with improved OS (Table 2). On multivariable analysis, only age ≥ 65 years, tumor size ≥ 5 cm, and not receiving definitive surgery remained associated with worse OS (Table 2).

3.3. The impact of postoperative therapies

On univariable analysis of patients receiving definitive surgery, living within 10 miles of a patient's treatment facility, tumor size ≥ 5 cm, and positive surgical margins were associated with receipt of postoperative radiation (all $p < 0.05$). On multivariable analysis, only positive surgical margins (OR = 1.34, 95%CI: 1.10–1.57, $p < 0.05$) remained associated with receipt of postoperative radiation. On uni-variable analysis, tumor size ≥ 5 cm, pathological stage III, and living within 10 miles of a patient's treatment facility were associated with the receipt of postoperative chemotherapy (all $p < 0.05$). On multivariable analysis, only tumor size ≥ 5 cm and living within 10 miles of a patient's treatment facility remained associated with receipt of postoperative chemotherapy (all $p < 0.05$).

The median survival of patients receiving postoperative radiation was 3.6 years (95%CI: 2.6–5.1) compared to 2.8 years (95%CI: 2.3–3.3) for those not receiving postoperative radiation ($p = 0.27$). The median survival of patients receiving postoperative chemotherapy was 3.5 years (95%CI: 2.2–4.5) compared to 3.0 years (95%CI: 2.5–3.5) for those not receiving postoperative chemotherapy ($p = 0.40$).

On univariable analysis of OS among patients receiving definitive surgery, age ≥ 65 years, living in a census tract with a median income $< \$30,000$, tumor size ≥ 5 cm, positive margins at surgery were associated with worse OS while male sex, having private insurance, and living within 10 miles of a patient's treatment facility were associated with better OS (all $p < 0.05$). On multivariable analysis of the same population, only tumors ≥ 5 cm (HR = 1.72, 95%CI: 1.23–2.42, $p < 0.01$) and positive surgical margins (HR = 1.52, 95%CI:1.06–2.18, $p = 0.02$) remained associated with worse OS. Notably neither receipt of postoperative radiation (HR = 0.98, 95%CI:0.82–1.34, $p = 0.59$) nor receipt of postoperative chemotherapy (HR = 0.88, 95%CI: 0.64–1.20, $p = 0.33$) were associated with OS. On exploratory subset analysis, receipt of postoperative radiation was not associated with improved OS amongst patients with positive margins at surgery ($p = 0.10$) or amongst patients with tumors ≥ 5 cm ($p = 0.16$).

4. Discussion

To the author's knowledge this is the largest series of non-metastatic scalp angiosarcomas reported in the literature and the first to utilize the NCDB. Given the rarity of disease, lack of Phase III data and few Phase II trials, our series helps illuminate practice patterns in the US as well as examines OS outcomes. In this sampling of 70% of cancer diagnoses in the US, we saw that 81.8% of patients received upfront definitive surgery, with the 65.8% of these patients receiving postoperative radiation and 23.0% receiving postoperative chemotherapy. We found that de-finitive surgery is the most important factor for improving OS in patients with non-metastatic scalp angiosarcomas. This series also con-firmed other known negative prognostic factors for this rare disease including older age at diagnosis and larger tumor size. Postoperative radiation nor postoperative chemotherapy was associated with improved OS, which may be related to non-balanced patient groups.

Treatment for angiosarcomas in national guidelines is usually lumped together with other soft tissue sarcomas, such as National Comprehensive Cancer Network (NCCN) guidelines [19]. Based on case series, radical surgery with wide margins is recommended. However, given the invasive and multifocal nature of angiosarcomas [20–22] as well as their proximity to critical structures for scalp primaries [4,5,23], negative margins are often difficult to achieve. For example, a series of 29 patients from the University of Michigan found that 28 patients(96.6%) were able to undergo upfront surgery but 22 patients (78.6%) had positive margins [23]. A series of 28 patients of angiosarcomas of the head and neck from UCLA found that 21 (75%) received upfront surgery with “a significant portion” having residual tumor [4]. A series of 56 patients of angiosarcomas of the scalp and/or face from the Mayo Clinic found that 44 (78.9%) got upfront surgery with 12 patients (27%) having positive margins even after re-resection [7]. Our series confirmed the importance of definitive surgery in a population database setting, with markedly improved survival outcomes for patients receiving definitive surgery (Fig. 1). Our series also is in line with case series as most patients (81.8%) could receive upfront surgery with a significant portion (42.2%) having positive margins. Omitting surgery was associated with worse OS even when balancing for other factors (HR = 1.46, 95%CI: 1.10–1.93, $p < 0.01$).

Postoperative radiation is routinely recommended for angiosarcomas because of high-risk of recurrence [7,8,19,23,24]. Several case series have found that postoperative radiation improves local control and OS [7,23]. For example, in the series from the Mayo Clinic, radiation therapy was associated with improved 5-year locoregional control (12% vs. 20%) and higher 5-year recurrence free survival (12% vs. 19%) [7]. In the University of Michigan series, radiation therapy was associated with a decreased chance of death (HR = 0.16) [23]. However, there are case series that do not suggest a benefit to postoperative radiation [21,22,25]. In a series of 8 resected scalp angiosarcomas, postoperative radiation was given to 5 patients, with 3 of these patients failing locally compared to none in the other cohort [21]. In a series of 121 resected angiosarcomas from France, 32 patients (26%) received postoperative radiation with doses from 50 to 60 Gy, which was not associated with disease outcomes [22]. Given the heterogeneity of these case series, as angiosarcomas of all subsites tend to be lumped together and small numbers given the rarity of the disease, it is difficult to elucidate specifics for treatment. In our series of 482 resected scalp angiosarcomas, the

majority received postoperative radiation (65.8%) with a median dose of 60 Gy. Another confounding variable is the method of radiation delivery. Over the last two decades there has been substantial advances in radiation delivery, transitioning from two-dimensional planning to intensity modulated radiotherapy. In many subsites, these more modern radiation techniques are linked with lower toxicity, improved cancer-control outcomes, and improved survival. Supplemental Table 1 summarizes the radiation modality for our population, showing the heterogeneity in modality for this rare disease. Our series cannot comment on the impact of radiation modality on survival. Radiation target volumes are also not well defined for this rare disease, and in Supplemental Table 2 we demonstrate that about half of patients received radiation treatment to regional nodes but we cannot comment on the impact of nodal treatment on OS outcomes. Our series did not find an OS benefit to postoperative radiation (HR = 0.98, 95%CI: 0.82–1.34, $p = 0.59$) but this group was enriched with patients with positive margins and given the lack of local and locoregional control data in the NCDB, routinely omitting postoperative radiation should not be recommended based on this series.

The use of postoperative chemotherapy is evolving in scalp angiosarcomas, with rationale given the risk of metastasis in these patients [12,13]. A series of 55 angiosarcoma patients treated in Japan with surgery and chemotherapy (with or without radiation) found that the combination of surgery and chemotherapy was associated with a better prognosis [25]. However a meta-analysis of soft tissue sarcomas in adults found that in 14 trials with adjuvant doxorubicin-based chemotherapy there was a local recurrence-free interval (HR = 0.73) and distant recurrence-free interval (HR = 0.70) benefit to chemotherapy without a corresponding statistically significant OS benefit (HR = 0.89) [26]. Further complicating analyses is the limited number of angiosarcomas on these larger studies given the rarity of the histology. In our series of national practice patterns in the US, we found that 23% of resected patients received postoperative chemotherapy. Our series did not find an OS benefit to postoperative chemotherapy (HR = 0.88, 95%CI: 0.64–1.20, $p = 0.33$) but these patients were enriched with tumors ≥ 5 cm and given the lack of locoregional and distant metastasis failure information in the NCDB, we cannot fully elucidate the role of postoperative chemotherapy for scalp angiosarcomas.

Our series confirmed known prognostic factors for scalp angiosarcomas in a larger population. Tumor size ≥ 5 cm is a known poor prognostic factor not only for angiosarcomas, but also for all soft tissue sarcomas [12,14,23], and is a cutoff in previous and current staging guidelines [15,27]. Our series found that patients with tumors ≥ 5 cm were more likely to not receive definitive surgery (OR = 2.26, 95%CI: 1.26–4.05, $p < 0.05$) and were associated with worse OS on univariable and multivariable analysis (HR = 1.74, 95%CI: 1.32–2.28, $p < 0.01$) amongst all patients. Additionally, tumor size ≥ 5 cm was associated with the receipt of postoperative chemotherapy and was independently associated with worse OS when examining only patients who received definitive surgery (HR = 1.72, 95%CI: 1.23–2.42, $p < 0.01$). Our series also confirmed previous studies showing that older age is a poor prognostic factor [22,23], with patients diagnosed at ages 65 years or older associated with worse OS on multivariable analysis (HR = 2.90, 95%CI: 1.71–4.94, $p < 0.01$).

There are several strengths and limitations to this study. The strengths include the largest number of non-metastatic scalp angiosarcomas in any study to date treated with modern therapy. However, like other studies utilizing registry data, the NCDB does not capture all variables, potentially leading to an inherent imbalance when comparing cohorts of patients. We preformed multivariable analysis and subset analysis to account for confounding variables, but given that this disease is rare, the numbers are small enough that imbalances likely are present. The NCDB provides detailed surgical information and radiation information such that we can accurately report definitive surgeries, margin status, and radiation dose but the database lacks chemotherapy details including types of agents and number of cycles. This series cannot comment on toxicity or quality of life outcomes as this information is not available in the NCDB. Finally, the NCDB only provides OS outcomes and does not provide information on local control, regional control, distant metastasis control, or any other disease-specific outcomes, which may limit analysis of the impact of postoperative radiation and/or chemotherapy.

In conclusion, this series serves as the largest cohort of non-meta-static scalp angiosarcomas, highlighting national practice patterns for a rare entity with current treatment guidelines based on limited cohorts or extrapolated from other soft tissue sarcoma variants. Our series emphasizes the importance of upfront definitive surgical resection, confirms that size and age are extremely important to OS outcomes, and provides information about the use of postoperative radiation and chemotherapy. Given the infrequency with which this disease is seen, our series may help provide management information for patients with non-metastatic scalp angiosarcomas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Overall survival amongst patients with non-metastatic angiosarcoma of the scalp among patients receiving definitive surgery with or without postoperative therapies versus patients receiving definitive radiation or definitive chemoradiation.

Overall survival (OS) was calculated as time from diagnosis to time to death. The number at risk is delineated above the x axis at each time point. Kaplan-Meier estimates for median OS was 1.6 years (95% CI: 1.1–2.6) for patients treated without definitive surgery versus 2.9 years (95% CI: 2.5–3.5) for patients receiving definitive surgery ($p < 0.01$). 1-year and 5-year survival estimates for patients not receiving definitive surgery was 68.0% (95% CI: 57.5–76.4) and 18.0% (95% CI: 10.2–27.5) respectively compared to 78.2% (95% CI: 74.0–81.9) and 34.1% (95% CI: 28.9–39.3) for patients receiving definitive surgery ($p < 0.01$).

Table 1

Summary of all patient, tumor, and treatment characteristics of non-metastatic scalp angiosarcomas.

Variable		N = 589	%
Patient Characteristics			
Age at Diagnosis (years)	< 65	109	18.5
	65	480	81.5
Charlson-Deyo Comorbidity Score	0	457	77.6
	1 +	132	22.4
Sex	Male	400	67.9
	Female	189	32.1
Race	White	519	88.1
	Black	46	7.8
	Other	24	4.1
Insurance Status	Uninsured	20	3.4
	Private	128	21.7
	Government (Medicare or Medicaid)	441	74.9
Percentage of Census Tract of Residence without a High-School Degree	Missing	26	–
	> = 29%	76	13.5
	20–28.9%	130	23.1
	14–19.9%	128	22.7
	< 14%	229	40.7
Median Income of Patient's Census Tract of Residence	Missing	26	–
	< \$30,000	71	12.6
	\$30,000 – \$35,999	89	15.8
	\$36,000 – \$45,999	152	27.0
	\$46,000 +	251	44.6
Distance from patient's zip code to treatment facility	< = 10 miles	245	42.2
	10–50 miles	239	41.2
	> 50 miles	96	16.6
	Missing	9	–
County Type	Metro	473	83.6
	Urban	82	14.5
	Rural	11	1.9
	Missing	23	–
Year of Diagnosis	2004–06	185	31.4
	2007–09	162	27.5
	2010–12	125	21.2
	2013–14	117	19.9
Tumor Characteristics			
Tumor Size	< 5 cm	259	60.9
	5cm	166	39.1
	Missing	164	–

Variable		N = 589	%
AJCC Pathologic Stage Group *	II	165	36.2
	III	291	63.8
	Missing	26	–
Treatment Characteristics			
Facility Type	Community Cancer Program	293	50.4
	Academic Program	288	49.6
	Missing	8	–
Facility Location	Northeast	118	20.3
	South	234	40.3
	Midwest	137	23.6
	West	92	15.8
	Missing	8	–
Treatment Center Volume	Low	241	40.9
	High	348	59.1
Treatment Paradigm	Surgery ± Postoperative Therapy	482	81.8
	Radiation Alone or	107	18.2
	Chemotherapy & Radiation		
Use of Neck Dissection *	No	398	84.7
	Yes	72	15.3
	Missing	12	–
Surgical Margins *	Negative	258	57.8
	Positive	188	42.2
	Missing	36	–
Time from Diagnosis to Surgical Resection *	0–3 months	225	49.6
	3–6 months	40	8.9
	> 6 months	188	41.5
	Missing	29	–
Receipt of postoperative radiation *	No	165	34.2
	Yes	317	65.8
Receipt of postoperative chemotherapy *	No	371	77.0
	Yes	111	23.0

* These variables reflect only patients that received definitive surgery (n = 482).

Table 2

Univariable and multivariable association of patient, tumor, and treatment characteristics with overall survival amongst all patients with non-metastatic scalp angiosarcomas.

Covariate	Level	Univariable Analysis		Multivariable Analysis*	
Patient Characteristics					
Age at Diagnosis	< 65 years	–	–	–	–
	65 years	2.21 (1.60–3.06)	< 0.01	2.55 (1.65–3.94)	< 0.01
Charlson-Deyo Comorbidity Score	0	–	–	–	–
	1 +	1.19 (0.92–1.54)	0.18	–	–
Sex	Male	0.74 (0.59–0.93)	< 0.01	0.83 (0.59–1.11)	0.19
	Female	–	–	–	–
Race	White	–	–	–	–
	Black	1.60 (1.12–2.28)	0.01	1.25 (0.77–2.01)	0.37
	Other	0.87 (0.50–1.52)	0.63	0.63 (0.27–1.48)	0.29
Insurance Status	Uninsured	0.73 (0.40–1.34)	0.63	0.90 (0.77–1.31)	0.33
	Private	0.69 (0.52–0.91)	< 0.01	0.88 (0.61–1.22)	0.23
	Government (Medicare or Medicaid)	–	–	–	–
Percentage of Census Tract of Residence without a High-School Degree	> = 29%	1.10 (0.77–1.56)	0.60	–	–
	20–28.9%	1.23 (0.93–1.62)	0.15	–	–
	14–19.9%	1.04 (0.78–1.40)	0.78	–	–
	< 14%	–	–	–	–
Median Income of Patient's Census Tract of Residence	< \$30,000	1.62 (1.17–2.24)	< 0.01	1.10 (0.71–1.71)	0.67
	\$30,000 – \$35,999	1.02 (0.73–1.42)	0.92	1.01 (0.67–1.51)	0.97
	\$36,000 – \$45,999	1.10 (0.84–1.44)	0.49	0.90 (0.65–1.25)	0.53
	\$46,000 +	–	–	–	–
Distance from patient's zip code to treatment facility	< = 10 miles	–	–	–	–
	10–50 miles	0.73 (0.58–0.93)	0.01	0.83 (0.62–1.12)	0.22
	> 50 miles	0.81 (0.59–1.11)	0.18	1.01 (0.67–1.52)	0.96
County Type	Metro	0.72 (0.34–1.53)	0.40	–	–
	Urban	0.72 (0.33–1.60)	0.42	–	–

	Univariable Analysis		Multivariable Analysis*	
Year of Diagnosis	Rural	–	–	–
	2004–06	0.86 (0.56–1.34)	0.51	–
	2007–09	0.88 (0.56–1.37)	0.57	–
	2010–12	0.77 (0.48–1.23)	0.28	–
	2013–14	–	–	–
Tumor Characteristics				
Tumor Size	< 5 cm	–	–	–
	> = 5 cm	2.05 (1.60–2.64)	< 0.01	1.74 (1.32–2.28) < 0.01
Treatment Characteristics				
Facility Type	Community Cancer Program	1.08 (0.87–1.33)	0.51	–
	Academic Program	–	–	–
Facility Location	Northeast	1.02 (0.70–1.47)	0.92	–
	South	1.03 (0.75–1.43)	0.84	–
	Midwest	1.11 (0.79–1.56)	0.55	–
	West	–	–	–
Treatment Center Volume	Low	–	–	–
	High	0.84 (0.68–1.04)	0.12	–
Treatment Paradigm	Surgery ± Postoperative Therapy	–	–	–
	Definitive Radiation or Chemoradiation	1.56 (1.21–2.02)	< 0.01	1.46 (1.10–1.93) < 0.01

Key.

NOS – Not otherwise specified.

Bold indicates statistical significance.

* Variables were subjected to backwards elimination using an alpha cutoff of 0.1 for inclusion into the multivariable model.