Cutaneous Angiosarcoma of the Scalp

A Multidisciplinary Approach

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BACKGROUND. Angiosarcoma is a malignant tumor of vascular endothelial cells that arises in the head and neck. It is a rare, difficult to treat, and lethal tumor.

METHODS. Clinical data from patients who were diagnosed with angiosarcoma of the scalp between 1975 and 2002 at the University of Michigan were reviewed. Analysis was performed to assess for factors impacting time to recurrence and survival.

RESULTS. The study was comprised of 29 patients with a median age of 71.0 years. Most patients presented after a delay in diagnosis with either a bruise-like macule (48.3%) or a nonbruise-like nodule (51.7%). Seventy-five percent of patients had pathologic Stage T2 disease, and 76% of patients had high-grade tumors. Virtually all patients underwent surgical excision (96.6%); however, negative surgical margins were achieved in only 21.4% of patients. Multiple lesions on presentation were associated with a shorter time to recurrence ($P = 0.02$). The median actuarial survival was 28.4 months. Younger patients and patients with Stage T1 disease had improved survival ($P = 0.024$ and $P = 0.013$, respectively). Radiation therapy was associated significantly with a decreased chance of death (hazard ratio, 0.16; $P = 0.006$).

CONCLUSIONS. Although surgery remains the first option for the treatment of patients with angiosarcoma of the scalp, achieving negative margins often is impossible. Patients who are younger and who have less extensive disease fare better. Postoperative radiation therapy should be employed routinely, as it may lead to improved survival. ***Cancer* 2003;98:1716-26.**

KEYWORDS: scalp, angiosarcoma, resection, radiation.

A malignant tumor of vascular endothelial cells that can occur in any region of the body, angiosarcoma usually affects the face and scalp region, most often in elderly patients.[1,2] Overall, sarcomas occur uncommonly in the head and neck, constituting less than 1% of all head and neck malignancies.[3] According to Aust et al., fewer than 5% of soft tumor sarcomas occur in the head and neck, with only approximately 10% classified as angiosarcomas.[4] Angiosarcomas of the face and scalp are insidious, and their clinical presentation varies widely. In their early stages, they frequently appear clinically innocent and even may show benign capillary hemangioma-like structures histologically.[5–8] This pattern, however, is deceiving, because angiosarcomas usually have an aggressive course. Tumor cells are located mainly in the dermis and may extend into the subcutaneous tissue. Angiosarcoma has a tendency for metastasis by lymphatic or hematogenous routes, and late local recurrence and metastasis after years of apparent remission and successful local control are well documented.[9,10] The overall prognosis for patients with angiosarcoma of

the head and neck remains dismal, with a reported 5-year survival rate of approximately 10%.[1,10–12]

Given the rarity of the tumor, relatively little is known concerning the features, natural history, or optimal treatment of face and scalp angiosarcomas. Although surgical resection remains the cornerstone of therapy, because of the pattern of diffuse, clinically undetectable spread, the disease is very difficult to resect completely.[1,12] In recent years, the treatment of patients with angiosarcomas has undergone considerable change, including the increased use of more limited surgery followed by multimodal therapy involving radiation and chemotherapy.[2,7,10,11,13]

Reports concerning the treatment of head and neck angiosarcomas are infrequent in the medical literature. Most information comes from small case reports that, because of the rarity of angiosarcoma, group all angiosarcomas of the head, scalp, and neck together. There is no empiric evidence, however, to suggest that angiosarcomas of the general head and neck region behave in the same manner as scalp angiosarcomas. Furthermore, given the small numbers, previous studies have been unable to analyze how clinical and therapeutic variables may impact the time to recurrence and overall survival in patients with scalp angiosarcoma. In this report, we present a retrospective study of 29 patients with angiosarcoma *solely* of the scalp. To our knowledge, this study represents the largest series of scalp angiosarcomas reported to date. Our study was undertaken to assess the results achieved using a multimodal treatment strategy in caring for patients with angiosarcoma of the scalp at the University of Michigan.

MATERIALS AND METHODS

The clinical data on all patients with angiosarcoma of the scalp that were diagnosed and confirmed histologically at the University of Michigan between 1975 and 2002 were reviewed. Only scalp angiosarcomas were included in the review. Patients with angiosarcomas involving other areas of the head and neck were excluded from this study. Clinical information was obtained by a retrospective review of the patient's records as well as a query of the tumor registry. The records were examined for the following data: age at diagnosis, gender, race, clinical site of tumor presentation, type of primary and secondary treatments, disease-free survival, and overall survival. Histologic diagnosis and tumor grade were confirmed by a review of the available pathology by a single University of Michigan pathologist (A. F. P.). All patients had their surgical procedures performed at the University of Michigan.

Every individual had undergone a full evaluation, including a history and physical examination, prior to treatment. Treatment plans were individualized based on extent of disease, histopathologic grade, and stage of the disease.

All patients who received radiation therapy were treated at the University of Michigan Medical Center or one of its radiation oncology affiliates. Patients received whole-scalp radiation therapy with opposed photon fields treating the forehead, vertex, and posterior aspect of the scalp (a rind of scalp from the lateral view close to the midsagittal plane) that were matched to en face electron fields directed toward the lateral scalp, as described previously.[14] The whole scalp was treated generally to a dose in the range of 60 Gray (Gy) (in 1.8–2.0 Gy fractions) with a boost to sites of macroscopic disease, bringing the total dose to 60–72 Gy. In addition, a beam arrangement comprised entirely of matched electron beams to a similar whole-scalp and total boost dose was used occasionally, as described previously.[15]

Distributions of survival and time to recurrence were analyzed in relation to each of the above-mentioned factors. Univariate tests (log-rank tests) were used to determine differences in these distributions by any of the factors. Factors that appeared to have a significant impact on time to recurrence or survival were entered into a Cox proportional hazards model to test for significant effects, simultaneously adjusting for multiple factors. Model selection was performed to find the set of effects that all had a significant association with time to recurrence or survival.

RESULTS

Demographics and Presentation

The study group was comprised of 18 men and 11 women (male:female ratio, 1.6:1.0). The median age at presentation was 71.0 years (range, 33–90 years). There was no difference in the median age at which male and female patients presented. All the patients were white except for one patient of Asian descent. No patient had a past history of radiation therapy. Follow-up ranged from 3.2 months to 106.0 months (median, 18.3 months) (Table 1).

Most patients presented with a significant delay in diagnosis. The median time to diagnosis was 5.1 months, with a range from no delay up to 12 months. There was no difference in the time to diagnosis with regard to gender. It is known that angiosarcoma presents in a variety of manners, with an appearance suggesting an infectious condition,[16,17] an angiomatous lesion,[18] or a posttraumatic bruise. Our experience was similar. Most patients presented with either a bruise-like macule (n = 14 patients; 48.3%) or an otherwise nonbruise-like, nodular lesion (n = 15 pa-

TABLE 1
Patient Characteristics (n = 29 patients)

Characteristic	No. (%)
Age (yrs)	
Median	71.0
Range	33–90
Gender	
Female	11 (37.9)
Male	18 (62.1)
Follow-up (mos)	
Median	18.3
Range	3.2–106.0
Delay in diagnosis (mos)	
Median	5.1
Range	0–12
Total no. of lesions on presentation	
One lesion	17 (58.6)
One lesion plus satellitosis	4 (13.8)
Multifocal disease	8 (27.6)
T classification of disease	
Initial clinical T1	18 (62.1)
Initial clinical T2	11 (37.9)
Final pathologic T1	7 (24.1)
Final pathologic T2	21 (72.5)
No pathologic T stage available (no surgery)	1 (3.4)
Grade of angiosarcoma	
Low	6 (20.7)
High	19 (65.6)
Unknown (no surgery)	1 (3.4)
Not available for review	3 (10.3)

tients; 51.7%) on their scalp. In the majority of patients, the lesion was painless (n = 23 patients; 79.3%). Other symptoms included intermittent bleeding (n = 7 patients; 24.1%), edema (n = 2 patients; 6.9%), and ulceration (n = 1 patient; 3.4%).

The average lesion size on clinical appearance was 5.9 cm × 4.7 cm, with the smallest lesion measuring 1 cm × 1 cm and the largest, which involved nearly the entire scalp, measuring 20 cm × 10 cm. Eighteen patients presented with clinical T1 disease (greatest dimension < 5.0 cm), and 11 patients presented with clinical T2 tumors (greatest dimension ≥ 5.0 cm). Most scalp angiosarcomas presented as single lesions (n = 17 patients; 58.6%). Four patients presented with solitary lesions but also had associated satellitosis. Of the eight patients who presented with multifocal disease, five patients had clinical T2 tumors.

An insidious tumor, scalp angiosarcoma is difficult to stage accurately. In the current series, a review of the clinical staging versus final pathologic staging demonstrated little concordance. Twelve of 18 patients (56%) who were initially staged with clinical T1 disease were later staged with pathologic T2 disease. Thus, the majority of patients actually had pathologic T2 disease (21 of 28 patients), not T1 disease, as initial clinical staging had indicated. One patient did not undergo surgery and, thus, did not have pathologic stage determined.

Histologic diagnoses were reviewed by a single University of Michigan pathologist in 25 patients for whom diagnostic material still was available for review. Nineteen of those 25 tumors were graded histologically as high grade (76%), and 6 tumors were low grade (24%) (Fig. 1).

PATTERNS OF TREATMENT

Twenty-eight of 29 patients (96.6%) underwent wide local surgical excision as their primary mode of treatment (Table 2). One patient was deemed unresectable on initial presentation and proceeded directly to radiation therapy. The surgical procedure utilized in resecting the scalp angiosarcoma varied considerably. Of 28 patients who underwent surgery, 20 patients had frozen section margins performed in the operating room to assist in determining the extent of the resection. Eleven patients had positive frozen margins, all of which were confirmed later on final pathology. In contrast, of the 9 patients who had negative intraoperative frozen margins, it was determined later that 6 patients (67%) actually had positive margins on permanent sections. Therefore, in the current study, intraoperative frozen sectioning had a sensitivity of 64.7%, a positive predictive value of 100%, but a negative predictive value of only 33.3% (Table 3).

The propensity of scalp angiosarcoma to exhibit a diffuse pattern of clinically undetectable spread makes resection difficult and extensive, and it almost always necessitates reconstruction rather than primary closure. In our series, the average surgical defect left after wide local excision was 14.3 cm × 11.8 cm, with the smallest resection measuring 3.5 cm × 2.5 cm and the largest spanning 28.0 cm × 27.0 cm. In every instance, primary closure was not possible, and a reconstruction was necessary. In 2 patients, this involved a tissue flap, whereas, in the other 26 patients, reconstruction consisted of a split-thickness skin graft (STSG). The timing of the reconstruction varied, with some surgeons choosing immediate reconstruction and other surgeons electing delayed reconstruction. Delayed reconstruction involved placement of homograft or a similar biologic dressing on the surgical site until permanent pathology results were obtained. Delayed reconstruction postpones definitive grafting until the final pathologic status of the surgical margins is known, thus avoiding the need to disrupt a recently placed graft in the event a reexcision is required.

Of 28 patients who underwent surgery, 21 patients underwent immediate reconstruction, whereas only 7 patients underwent delayed reconstruction. Of the 21

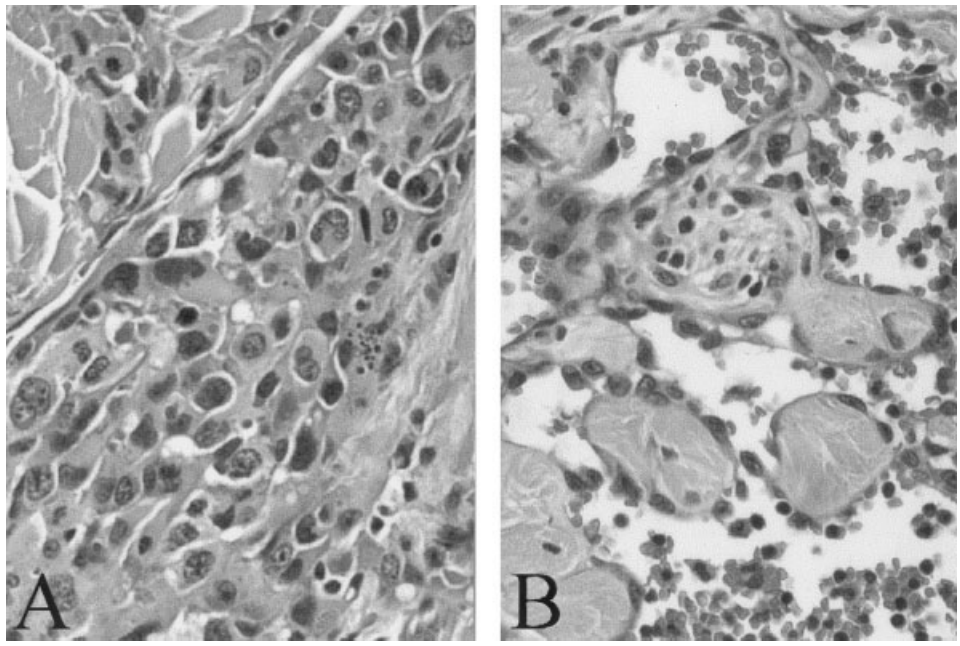

FIGURE 1. Light microscopy of scalp angiosarcoma. (A) High-power magnification of a high-grade scalp angiosarcoma showing marked nuclear pleomorphism with numerous mitotic figures. (B) High-power magnification of a low-grade scalp angiosarcoma demonstrating enlarged endothelial cells bulging into the vascular spaces, which contain red blood cells.

TABLE 2
Patterns of Treatment (n = 29 patients)

Treatment	No. (%)
Primary therapy	
Surgical excision	28 (96.6)
Radiation therapy	1 (3.4)
Median size of surgical defect (cm)	14.3 × 11.8
Smallest defect	3.5 × 2.5
Largest defect	28.0 × 27.0
Timing of reconstruction	
Immediate	21 (75.0)
Delayed	7 (25.0)
Type of reconstruction	
Split thickness skin graft	26 (92.9)
Tissue flap	2 (7.1)
Status of margin at conclusion of surgery(s)	
Negative	6 (21.4)
Positive	22 (78.6)
Postoperative radiation therapy	
No	6 (20.7)
Yes	23 (79.3)
Postoperative chemotherapy	
None	21 (72.5)
Initial adjuvant therapy	1 (3.4)
Salvage therapy	7 (24.1)

TABLE 3
Results of Intraoperative Frozen Margin Assessment (n = 20 patients)[a]

Frozen section findings	Final pathology findings	
	Positive	Negative
Positive	11	0
Negative	6	3

[a] Sensitivity, 64.7%; specificity, 50.0%; positive predictive value, 100%; negative predictive value, 33.3%.

patients who underwent immediate reconstruction, 11 patients (52%) required at least 1 additional operative reexcision after the pathology report showed residual disease at the margins. Four of those patients underwent three repeat attempts at reresection. In each of those patients, the *immediate* reconstruction required revision or a completely new STSG at the time of the subsequent resection. In the delayed reconstruction group, 4 of 7 patients (57%) required a second reexcision. Those patients, however, avoided the morbidity associated with a graft revision or a second STSG, because they underwent reconstruction only after final pathologic margins had been reviewed.

Despite the wide margins of excision and the multiple attempts at reexcision, surgery alone frequently failed to eradicate scalp angiosarcoma. In the 28 patients who underwent surgical resection, only 6 patients had negative pathologic margins at the completion of their surgeries (21.4%). Roughly 80% of patients, some of whom had undergone multiple operations and large disfiguring resections, still had residual disease at their surgical margins. Because of this inability of surgery to eradicate local disease successfully, adjuvant therapies have been adopted, including radiation and, to a lesser degree, chemotherapy.

Wide-field radiation therapy is a rational therapeutic approach for scalp angiosarcoma. The clinically involved dermis and a very generous margin of surrounding skin can be treated, while the brain and

other normal tissues are spared. In the current series, 23 of 29 patients received radiation therapy (79%). For 1 patient, this represented primary therapy for a lesion that was deemed unresectable, whereas in the other 22 patients, it was used as adjuvant therapy. Of the 22 patients with positive margins after surgery, 17 patients received radiation therapy (77%). It is noteworthy that all six patients who had negative surgical margins underwent wide-field radiation therapy.

Compared with radiation therapy, chemotherapy was used much more sparingly, with only 7 patients receiving chemotherapeutic agents (24%): 6 patients for recurrent disease and 1 patient for initial adjuvant therapy (Table 2). The range of chemotherapeutic agents used was comprised of systemic interferon α-2b, cyclophosphamide, paclitaxel, 5-fluorouracil, cisplatin, and etoposide. Investigational gene therapy was offered to two patients with recurrent disease and involved direct intralesional injection of the cDNA for interferon α-2b.

Patterns of Recurrence and Overall Survival

At a median follow-up of 18.2 months, tumor had recurred in 21 patients (72.4%). Local failure was defined as recurrence at the primary site with or without distant disease. Overall, local recurrence developed in 17 patients, 4 of whom also had evidence of distant metastases. An additional four patients developed recurrences with distant metastases alone. Sites of known metastases included the lung in five patients, the lymph nodes in two patients, and bone. Two patients presented with bilateral pneumothoraces as the initial manifestation of their metastatic angiosarcoma of the scalp. Interestingly, bilateral pneumothorax as a presenting feature of metastatic angiosarcoma of the scalp has been reported previously.[19,20]

In the univariate analysis, the only factor that significantly differentiated distributions of time to recurrence was whether the patient presented with one lesion or more than one lesion (Table 4). Figure 2 shows that patients who presented with a single lesion had a longer median disease-free survival (16.1 months) compared with patients who presented with multiple lesions (7.7 months; $P = 0.02$). Other factors, such as age at presentation, clinical or pathologic T classification, tumor grade, and margin status, did not have a significant impact on the time to recurrence in the univariate analysis (all $P > 0.05$). Although radiation therapy did not significantly impact the time to overall recurrence (local disease plus distant disease), it did prolong the time to local recurrence ($P = 0.03$). In the multivariate analysis, the total number of lesions on presentation affected the time to recurrence significantly. Those patients who had more than 1 lesion on presentation were significantly more likely to have a shorter time to recurrence compared with patients who had less disease (hazard ratio [HR], 3.4; 95% confidence interval [95% CI], 1.2–9.8; $P = 0.01$). Radiation therapy also maintained significance with

TABLE 4
Univariate Analysis of Clinicopathologic Factors in the Subgroup of Patients with Recurrent Cutaneous Angiosarcoma (n = 21 patients)

Feature	No. of patients	Median DFS (mos)	P value (log-rank test)
Age			
≤ 70 yrs	6	15.2	0.74
> 70 yrs	15	10.1	—
Presentation			
Single lesion	13	16.1	0.02
Multiple lesions	8	7.7	—
Clinical stage			
T1	11	14.2	0.18
T2	10	8.9	—
Pathologic stage			
T1	2	14.9	0.98
T2	19	10.2	—
Tumor grade[a]			
Low	4	16.6	0.14
High	14	9.9	—
Margin status			
Negative	1	5.5	0.14
Positive	20	10.2	—
Radiation therapy			
No	5	8.2	0.96
Yes	16	10.7	—

DFS: disease-free survival.
[a] Three patients had no diagnostic material available for review and were excluded from the analysis.

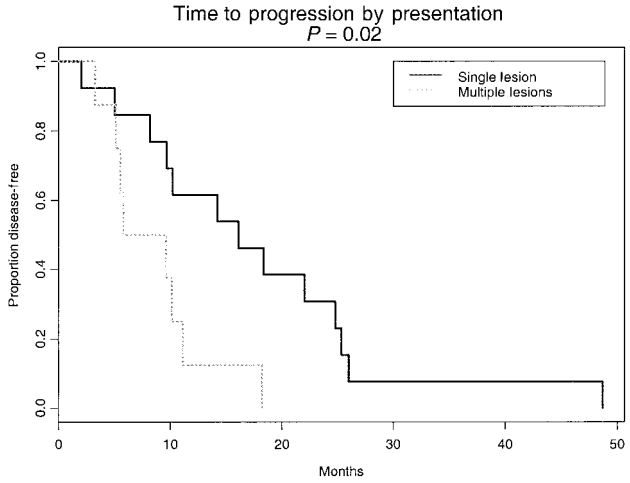

FIGURE 2. The burden and distribution of disease at presentation impacts recurrence. Patients who had multiple lesions had a shorter median disease free survival compared with patients who had one lesion at the time of presentation ($P = 0.02$).

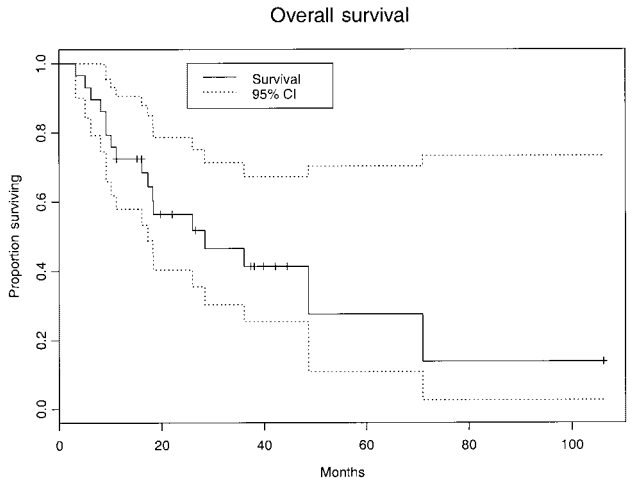

FIGURE 3. The median actuarial survival for patients with angiosarcoma of the scalp was 28.4 months. The 95% confidence intervals (95% CI) for the overall survival curve are relatively wide, suggesting that certain clinical or therapeutic variables may have a differential impact on survival.

regard to local (but not overall) recurrence on multivariate analysis (HR, 0.6; 95% CI, 0.2–0.83; $P = 0.04$).

With regard to survival, at last follow-up, 17 patients had died of disease (58.6%), and 12 patients (41.4%) remained alive. The overall median actuarial survival was 28.4 months (Fig. 3). Univariate analysis revealed that age at presentation, T classification, and radiation therapy all were significant factors affecting overall survival (Table 5). Patients who were age 70 years and younger at presentation had a significantly better median survival (71 months) compared with patients older than 70 years (18.2 months; $P = 0.024$) (Fig. 4). T classification also was found to be an important prognostic factor that significantly affected overall survival. Patients who had T1 disease had a significantly improved median survival compared with patients who had T2 disease, regardless of whether this variable was considered as clinical or pathologic T staging (Fig. 5). Patients with clinical T1 disease had a median actuarial survival of 48.7 months, whereas patients with clinical T2 disease had a survival of 11.1 months ($P < 0.0001$). The effect of T classification was even more pronounced when pathologic T classification was considered. The median survival of patients with pathologic T2 disease was 18.2 months, whereas the median survival of patients with pathologic T1 disease had not been reached ($P = 0.013$). Finally, univariate analysis revealed that postoperative radiation therapy also was a significant factor with regard to overall survival. Patients who received radiation therapy had a median survival almost 4 times longer than patients who did not receive radiation therapy (36.1 months vs. 9.2 months, respectively; $P = 0.033$) (Fig. 6). Other factors, such as number of lesions at presentation, tumor grade, and margin status, did not affect survival significantly. On univariate analysis, however, there was a strong trend suggesting that patients with negative

TABLE 5
Univariate Analysis of Factors Affecting Overall Survival ($n = 29$ patients)

Factor	No. of patients	Median DFS (mos)	*P* value (log-rank test)
Age			
≤ 70 yrs	12	71.0	—
> 70 yrs	17	18.2	0.024
Presentation			
Single lesion	17	28.4	—
Multiple lesions	12	11.1	0.31
Clinical stage			
T1	18	48.7	—
T2	11	11.1	< 0.001
Pathologic stage[a]			
T1	7	NR	—
T2	21	18.2	0.013
Tumor grade[b]			
Low	6	48.7	—
High	19	28.4	0.59
Margin status[a]			
Negative	6	NR	—
Positive	22	26.0	0.064
Radiation therapy			
No	5	9.2	—
Yes	24	36.1	0.033

DFS: disease-free survival; NR: not reached.
[a] One patient did not undergo surgery and thus was not included in the analysis of pathologic stage.
[b] Four patients had no diagnostic material available for review and were excluded from the analysis.

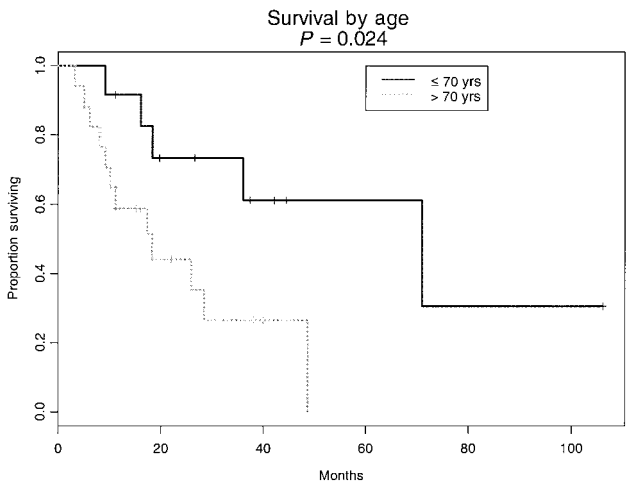

FIGURE 4. Patients who were younger at the time of presentation (age 70 years or younger) had a significantly better median survival (71 months) compared with older patients (older than 70 years; median survival, 18.2 months; $P = 0.024$).

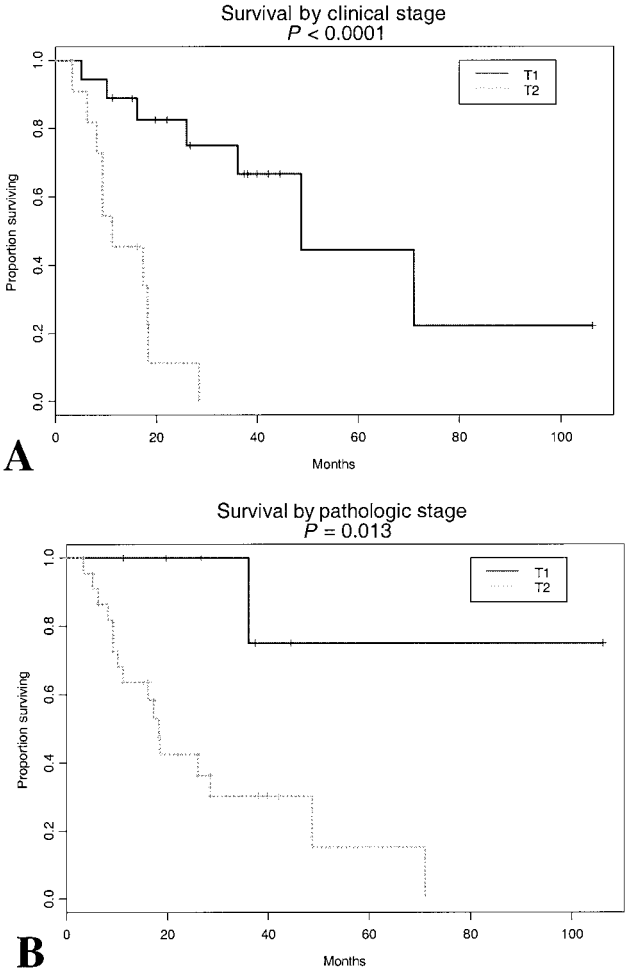

FIGURE 5. Patients who had T1 disease had a significantly improved median survival compared with patients who had T2 disease. Although the effect of T classification was significant for both (A) clinical staging and (B) pathologic staging ($P < 0.0001$ and $P = 0.013$, respectively), the long-term effect of T classification was more pronounced when pathologic T classification was considered (B).

surgical margins fared better compared with patients who were left with positive margins after surgery (median survival not reached vs. 26 months, respectively; $P = 0.064$). At last follow-up, 5 of 6 patients (83.3%) who had negative surgical margins were alive and free of disease. In comparison, only 2 of 22 patients (9.1%) who had positive surgical margins were alive and disease free.

On multivariate analysis, T classification and radiation therapy status were the only factors that were associated significantly with survival. Patients who had pathologic T2 scalp angiosarcoma had a greater likelihood of death compared with patients who had T1 lesions (HR, 12.0; 95% CI, 3.3–43.5; $P = 0.0002$). In the current series, 5 of 7 patients (71.4%) who had a T1

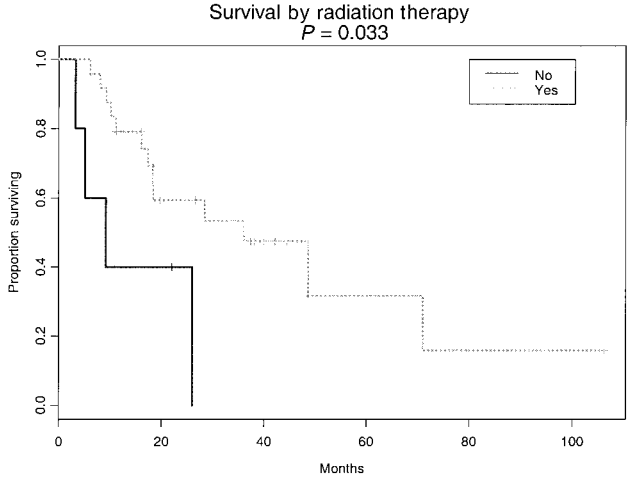

FIGURE 6. Patients who received postoperative radiation therapy had a median survival that was almost 4 times longer compared with patients who did not receiving radiation therapy (36.1 months vs. 9.2 months, respectively; $P = 0.033$).

angiosarcoma were alive and disease free at last follow-up, compared with only 2 of 21 patients (9.5%) who had T2 tumors. Multivariate analysis also showed a protective effect for radiation therapy. Patients who received postoperative radiation therapy had a significantly reduced risk of death compared with patients who did not receive radiation therapy (HR, 0.16; 95% CI, 0.04–0.59; $P = 0.006$). All seven patients who were disease free at the most recent follow-up both underwent surgery and received radiation therapy. No patients who underwent surgery alone remained free of disease.

Of the 12 patients who were alive at last follow-up, 7 patients were free of disease. According to both univariate and multivariate analyses, tumor grade had no affect on survival or time to recurrence. Five of seven patients who were disease free at last follow-up had high-grade tumors, whereas two patients had low-grade tumors. The five patients who were alive but had recurrent disease were treated in a variety of manners: surgery alone (one patient); surgery and chemotherapy (one patient); surgery, radiation, and chemotherapy (one patient); and surgery, radiation, chemotherapy, and gene therapy (two patients). In the current study, the effects of chemotherapy on time to recurrence and survival could not be assessed, because chemotherapy was used as primary therapy in only one patient. In the remaining patients who received chemotherapy as salvage therapy, the regimens varied widely.

DISCUSSION

Angiosarcomas are rare vascular tumors, the cells of which manifest many of the morphologic and functional properties of normal epithelium. Angiosarcomas may vary from highly differentiated tumors to those with significant anaplasia, sometimes making these tumors difficult to differentiate from melanomas or carcinomas. Although angiosarcomas may occur in any location in the body, they rarely arise from major vessels. In contrast to the deep location of most soft tissue sarcomas, angiosarcomas, instead, have a predilection for the skin and superficial soft tissue. Although chronic lymphedema is the most widely recognized predisposing factor in angiosarcoma of the skin and soft tissue, according to Weiss and Goldblum, only approximately 10% of these tumors actually are associated with the condition.[21] In fact, the most common form of angiosarcoma is cutaneous angiosarcoma not associated with lymphedema.

Recognized as a distinctive subgroup of angiosarcoma, scalp angiosarcoma usually occurs in elderly white men with an estimated male-to-female ratio of 3:1 and an average age at presentation of 63 years.[4,21] The current series confirmed this predilection for elderly white men. In the current study, the group was comprised of 18 men and 11 women (a male:female ratio of 1.6:1.0) with a median age at presentation of 71.0 years. All the patients were white except for one patient of Asian descent.

Clinically, the appearance of cutaneous angiosarcomas is quite variable. The lesion may be single or multifocal; bluish or violaceous; nodules, plaques, or flat infiltrating areas; and they occasionally can bleed or ulcerate.[22,23] Most early lesions begin as ill-defined, bruise-like areas with an indurated border. More advanced lesions can be elevated, nodular, or occasionally ulcerated. Our experience was similar, with most patients presenting with either a bruise-like macule or an otherwise nonbruise-like, nodular lesion on their scalp. In the great majority of patients, the lesion was painless (79.3%). Other symptoms included intermittent bleeding (7 patients), edema (2 patients), and ulceration (1 patient).

In the current series, we found that multifocality was associated with a decreased disease-free survival (HR, 3.4; $P = 0.02$). Patients who had more than one lesion on presentation had a median disease-free survival less than one-half that of patients with only one lesion (Fig. 2). Extensive local growth and multifocality is common with scalp angiosarcoma and has been reported elsewhere in the literature.[23,24] Some authors have postulated that multiple lesions on presentation may be due to a delay in the clinical diagnosis of scalp angiosarcoma, which allows the lesion to progress unfettered, resulting in an eventual worse prognosis.[25,26] In the current series, the median delay in diagnosis was 5.1 months; however, in 2 patients, diagnosis was delayed for 1 year. Because scalp angiosarcomas can be difficult to diagnose clinically, coupled with the fact that missed diagnoses may lead to a worse prognosis, a high index of suspicion should be maintained, and there should be a low threshold to biopsy any persistent, atypical scalp lesions.

Advanced age also was associated with a poor prognosis. Patients who were older than 70 years at presentation had a significantly worse median survival (18.2 months) compared with younger patients (71 months; $P = 0.024$) (Fig. 4). Wilson-Jones was the first to distinguish a unique form of angiosarcoma developing in the face and scalp of elderly individuals.[27] It has been noted that this form of angiosarcoma, known as *senile angiosarcoma* or *malignant angioendothelioma*, carries a particularly poor prognosis.[3,27] The reason for this association remains unclear but may be due to a longer undetected disease interval or, perhaps, a different tumor biology in a relatively more immunocompromised, elderly host. More studies clearly are needed to elucidate the correlation between advanced age and the poorer prognosis seen in older patients with scalp angiosarcoma.

Microscopically, angiosarcomas often extensively involve the dermis, with poorly differentiated tumors also invading deep structures, such as fascia and subcutis. The histopathologic features of angiosarcoma are diverse. Three histologic patterns occur: vascular channels, sheets of cells, and cells with undifferentiated morphologic features. Low-grade angiosarcomas are well differentiated lesions that retain some of the functional and morphologic properties of normal vascular endothelium.[24] In poorly differentiated (high-grade) tumors, sheets of pleomorphic cells may resemble a carcinoma.[21] High-grade lesions also may have areas of hemorrhage, disordered architecture, and large cells with hyperchromatic, pleomorphic nuclei.[24] The cells often display prominent mitotic activity. Both low-grade lesions and high-grade lesions often display extensive local growth, with margins that frequently are difficult to define clinically and surgically. Although tumor grade is an important prognostic factor in patients with other types of sarcoma, some reports have found that prognosis is independent of grade in patients with angiosarcoma.[3] In the current study, histologic grade was not correlated with disease free survival or overall survival. On both univariate and multivariate analysis, tumor grade did not affect time to recurrence or overall survival ($P = 0.59$). In fact, of the 12 patients who were alive at the most

recent follow-up, 8 patients had high-grade tumors, and 5 of 7 seven patients who were completely disease free also had high-grade tumors. Similarly, Holden et al. reported that histopathologic features did not appear to be correlated with survival outcome.[1]

Other factors, including the size of the angiosarcoma lesion, have been considered with regard to prognosis. Weiss and Goldblum postulated that stage is a more potent predictor of survival, indicating that patients who had tumors measuring < 5 cm in greatest dimension had a significantly better prognosis compared with patients who had larger lesions.[21] In the current series, two things were obvious with regard to T classification: Not unexpectedly, the clinical T classification of scalp angiosarcomas was very inaccurate. Greater than 50% of patients were upstaged based on pathologic findings compared with the initial clinical staging. This highlights the clinical difficulty not only in diagnosing scalp angiosarcoma but also in accurately estimating the extent of disease. Second, pathologic T classification was a stronger indicator of long-term prognosis compared with histologic grade (Fig. 5). Whereas tumor grade was not associated with overall survival, disease stage had a significant impact on patient survival. We showed that both clinical and pathologic T1 classification were associated with longer overall survival. The effect, as expected, was more pronounced when pathologic T classification was considered compared with clinical T classification. The median survival of patients with clinical T1 disease was 48.7 months, whereas patients with pathologic T1 disease had not achieved their median survival at last follow-up. This improvement in survival with regard to pathologic T classification versus clinical T classification undoubtedly is related to a stage-shift phenomenon in which some patients with clinical T1 disease actually had pathologic T2 disease. Corroborating what we report here, others also have noted the importance of tumor stage in relation to prognosis. Holden et al. analyzed patients with tumors measuring < 5 cm, 5–10 cm, and > 10 cm and demonstrated a statistically significant correlation between tumor size and survival rate.[1] Additional studies also have reported improved survival rates for patients with primary tumors that measure < 5 cm.[7,12] Thus, it appears that one of the most important factors in determining the prognosis of patients with scalp angiosarcoma is the stage of the lesion.

To our knowledge, the optimum treatment for patients with cutaneous scalp angiosarcoma has not been defined. Generally, radical surgery and postoperative radiation therapy are advocated to treat patients with these tumors.[1,7,12] Wide surgical excision to histologically negative margins always should be the goal. Although, in the current study, negative surgical margins were not associated statistically with improved survival, there was a strong trend ($P = 0.064$). Our inability to recognize a difference between the margin positive group and the margin negative group may derive from the lack of statistical power due to the small sample size in the study. Despite this limitation, it should be noted that 5 of 7 patients (71.4%) who were alive and disease free at last follow-up had negative margins at the conclusion of their surgery.

Achieving a negative surgical margin frequently is difficult in patients with scalp angiosarcoma because of the extensive microscopic spread that is so common in this disease. To assist in achieving negative margins, intraoperative frozen sections often are obtained to help guide the extent of the resection. We show here, however, that frozen specimens are not accurate in evaluating the extent of disease at the surgical margins. Of the nine patients who had negative intraoperative frozen margins, it was found later that six patients had positive margins on permanent sections, for an overall negative predictive value of only 33.3%. Others have reported that the use of Mohs surgery similarly does not improve the ability to define tumor free margins accurately.[28] Thus, despite multiple operations and resections, the goal of histologically negative margins remains elusive. Farhood et al., in a review of patients with head and neck sarcoma of various histologic types, reported that pathologic margins obtained by wide excision were positive in $> 50\%$ of patients.[29] In the current series, 78.6% of patients with scalp angiosarcoma still had residual disease at their surgical margins after multiple attempts at resection.

In trying to achieve a negative margin, a wound usually is created that almost never can be closed primarily. In our experience, the average surgical defect measured 14.3 cm $\times$ 11.3 cm. The reconstruction of the defect left by wide excision presents the surgeon with a dilemma. The surgeon either can carry out a primary reconstruction and potentially discover later that further excision, possibly including sacrifice of the entire reconstruction, is necessary, or the surgeon can perform a staged reconstruction after final confirmation of the margin status has been obtained. The authors prefer the latter approach. In our experience, $> 50\%$ of patients who underwent immediate reconstruction required at least 1 additional operative reexcision after the final pathology report showed positive residual disease at the margins. Four patients underwent three reoperations. In each instance, the initial reconstruction required a revision or a completely new STSG at the time of the subsequent resection. Based on this, we recommend temporary reconstruc-

tion of the scalp, either with cadaveric homograft or with a skin substitute. The homograft is placed on the wound just like a skin graft and remains in place until the pathologist ascertains the status of the margins on the surgical specimens. When the margins are reviewed, the patient is returned to the operating room to undergo reexcision (if appropriate or possible); then, permanent autologous STSG is performed.

The overall prognosis for patients with scalp angiosarcoma is poor. In our series, at last follow-up, 17 patients had died of disease (58.6%), and 12 patients (41.4%) remained alive. The overall median actuarial survival was 28.4 months. The patients who died had a median survival of 18.2 months from the time of diagnosis. This is consistent with what Holden et al. reported: Twelve percent of patients survived for 5 years, with approximately 50% of patients dying within 15 months of presentation.[1] Both age at presentation and T stage were associated significantly with improved survival, as noted above. The third factor that seemed to affect survival was whether patients received radiation therapy.

Potential treatment options for patients with scalp angiosarcoma include surgery, radiation, chemotherapy, and (more recently) gene therapy. Results with surgery alone have been disappointing, with high rates of recurrence and an inability to obtain clear surgical margins. In our series, only one patient who underwent surgery alone was alive at last follow-up, but this patient had recurrent local disease. Mark et al. reported similar disappointing results with surgery alone.[7] Given the poor results obtained with surgery alone, radiation therapy has been offered as possible adjuvant therapy. Although some authors report that radiation therapy provides no benefit,[8,27] others have suggested that surgery combined with radiation therapy offers the best prognosis.[1,2,9,11] Mark et al. reported improved disease free survival with the addition of radiation therapy to surgery.[7] Similarly, Hodgkinson et al. from the Mayo Clinic reported that the only two survivors in their series underwent surgery and received radiation therapy.[11] In our series, both univariate and multivariate analysis showed that radiation therapy strongly impacted survival. Patients who received radiation therapy had a median survival almost 4 times longer than patients who did not receive radiation therapy (36.1 months vs. 9.2 months, respectively; $P = 0.033$) (Fig. 6). The prognostic implications of radiation therapy withstood competing risk adjustment, and the multivariate analysis showed that postoperative radiation therapy had a protective effect (HR, 0.16; $P = 0.006$). It is important to note that all seven patients who were alive and disease free at the most recent follow-up underwent surgery and received radiation therapy.

The clinical roles of other adjuvant treatments, such as chemotherapy and gene therapy, are less defined.[30–32] In a series from the University of California–Los Angeles, four of six patients who underwent surgery and received radiation and chemotherapy were disease free.[7] Other investigators have concluded that, in patients with nonextremity soft tissue sarcomas, adjuvant chemotherapy offers no statistically significant benefit for survival.[31] One agent that does appear to have substantial activity is paclitaxel. In one study, a response rate of 89% was seen in patients with angiosarcoma of the scalp or face, even in those patients who were treated previously with chemotherapy or radiation therapy.[33] In our series, only one patient received chemotherapy as primary adjuvant therapy, whereas seven patients with recurrent disease received chemotherapy as salvage therapy. Several of our patients did have objective evidence of a response to chemotherapy; and it was noted that one patient responded to gene therapy, which involved direct, intralesional injection of the cDNA for interferon α-2b. This response was manifest by the disappearance of injected lesions and the regression of at least one noninjected lesion.

It appears that a combination of good clinical prognostic factors (young age at presentation, fewer lesions on presentation, small tumor size, and perhaps the ability to obtain clear margins), as well as definitive treatment with surgery and radiation, offers the best hope of cure. Surgery combined with radiation therapy, however, does not appear to cure many patients with large tumors ($>$ 5 cm) or patients with persistent, positive surgical margins. In our series, these patients had a high incidence of local recurrence, and most were dead at recent follow-up. For these reasons, there is a serious need for the development of new approaches, including more effective local and systemic therapy.

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