Treatment of Angiosarcoma of the Head and Neck: A Systematic Review

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PRACTICE **POINTS**

- Angiosarcoma is a rare tumor that is difficult to treat, with multiple treatment options being utilized.
- Within this systematic review, wide local excision (WLE) combined with radiotherapy (RT), chemotherapy, and immunotherapy, as well as Mohs micrographic surgery (MMS), offered the longest mean (SD) overall survival time.
- When clinicians are tasked with treating primary cutaneous angiosarcoma of the head and neck, they should consider MMS or WLE combined with RT.

Primary cutaneous angiosarcoma (cAS) of the head and neck is a rare sarcoma with a poor prognosis and limited treatment options. We conducted a systematic review of treatments used for head and neck cAS and determined the treatment modalities that offer the longest mean overall survival (OS). Forty publications totaling 1295 patients were included. Both surgical and nonsurgical modalities have shown potential efficacy in the treatment of cAS; however, limited data preclude definitive recommendations. Multidisciplinary management of cAS should be considered to tailor treatment on a case-by-case basis.

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Cutaneous angiosarcoma (cAS) is a rare malignancy arising from vascular or lymphatic tissue. It classically presents during the sixth or seventh decades of life as a raised purple papule or plaque on the head and neck areas.[1] Primary cAS frequently mimics benign conditions, leading to delays in care. Such delays coupled with the aggressive nature of angiosarcomas leads to a poor prognosis. Five-year survival rates range from 11% to 50%, and more than half of patients die within 1 year of diagnosis.[2-7]

Currently, there is no consensus on the most effective treatments, as the rare nature of cAS has made the development of controlled clinical trials difficult. Wide local excision (WLE) is most frequently employed; however, the tumor's infiltrative growth makes complete resection and negative surgical margins difficult to achieve.[8] Recently, Mohs micrographic surgery (MMS) has been postulated as a treatment option. The tissue-sparing nature and intraoperative margin control of MMS may provide tumor eradication and cosmesis benefits reported with other cutaneous malignancies.[9]

Nearly all localized cASs are treated with surgical excision with or without adjuvant treatment modalities; however, it is unclear which of these modalities provide a survival benefit. We conducted a systematic review of the literature to compare treatment modalities for localized cAS of the head and neck regions and to compare treatments based on tumor stage.

METHODS

A literature search was performed to identify published studies indexed by MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and PubMed from January 1, 1977, to May 8, 2020, reporting on cAS and treatment modalities used. The search was conducted in accordance with the Preferred Reporting Items for

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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Systematic Reviews and Meta-Analysis guidelines.[5] Data extracted included patient demographics, tumor characteristics (including T1 [≤5 cm] and T2 [>5 cm and ≤10 cm] based on the American Joint Committee on Cancer soft tissue sarcoma staging criteria), treatments used, follow-up time, overall survival (OS) rates, and complications.[10,11]

Studies were required to (1) include participants with head and neck cAS; (2) report original patient data following cAS treatment with surgical (WLE or MMS) and/or nonsurgical modalities (chemotherapy [CT], radiotherapy [RT], immunotherapy [IT]); (3) report outcome data related to OS rates following treatment; and (4) have articles published in English. Given the rare nature of cAS, there was no limitation on the number of participants needed.

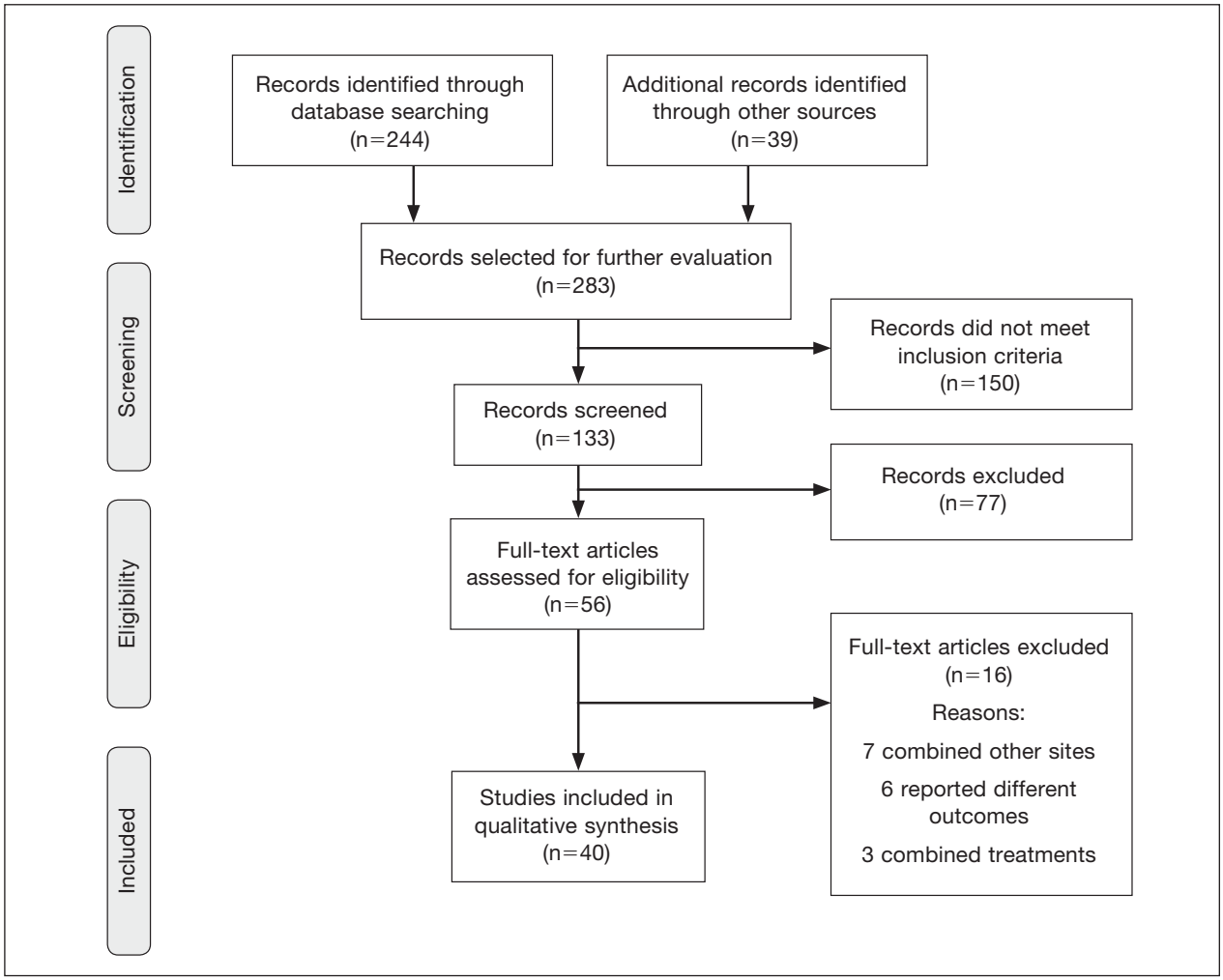
The Newcastle-Ottawa scale for observational studies was used to assess the quality of studies.[12] Higher scores indicate low risk of bias, while lower scores represent high risk of bias.

Continuous data were reported with means and SDs, while categorical variables were reported as percentages. Overall survival means and SDs were compared between treatment modalities using an independent sample *t* test with $P<.05$ considered statistically significant. Due to the heterogeneity of the data, a meta-analysis was not reported.

RESULTS

Literature Search and Risk of Bias Assessment

There were 283 manuscripts identified, 56 articles read in full, and 40 articles included in the review (Figure). Among the 16 studies not meeting inclusion criteria, 7 did not provide enough data to isolate head and neck cAS cases,[1,13-18] 6 did not report outcomes related to the current review,[19-24] and 3 did not provide enough data to isolate different treatment outcomes.[25-27] Among the included studies, 32 reported use of WLE: WLE alone (n=21)[2,7,11,28-45]; WLE with RT (n=24)[2,3,11,28-31,33-36,38-41,43-51]; WLE with CT (n=7)[2,31,35,39,41,48,52]; WLE with RT and



Flow diagram depicting search strategy and study inclusion from a literature search performed to identify published studies indexed by MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and PubMed from January 1, 1977, to May 8, 2020, reporting on cutaneous angiosarcoma and treatment modalities used.

CT (n=11)[2,29,31,33-35,39,40,48,52,53]; WLE with RT and IT (n=3)[35,54,55]; and WLE with RT, CT, and IT (n=1).[53] Nine studies reported MMS: MMS alone (n=5)[39,56-59]; MMS with RT (n=3)[32,50,60,61]; and MMS with RT and CT (n=1).[51]

Risk of bias assessment identified low risk in 3 articles. High risk was identified in 5 case reports,[57-61] and 1 study did not describe patient selection.[43] Clayton et al[56] showed intermediate risk, given the study controlled for 1 factor.

Patient Demographics

A total of 1295 patients were included. The pooled mean age of the patients was 67.5 years (range, 3–88 years), and 64.7% were male. There were 79 cases identified as T1 and 105 as T2. A total of 825 cases were treated using WLE with or without adjuvant therapy, while a total of 9 cases were treated using MMS with and without adjuvant therapies (Table). There were 461 cases treated without surgical excision: RT alone (n=261), CT alone (n=38), IT alone (n=35), RT with CT (n=81), RT with IT (n=34), and RT with CT and IT (n=12)(Table). The median follow-up period across all studies was 23.5 months (range, 1–228 months).

Comparison Between Surgical and Nonsurgical Modalities

Wide Local Excision—Wide local excision (n=825; 63.7%) alone or in combination with other therapies was the most frequently used treatment modality. The mean (SD) OS was longest for WLE with RT, CT, and IT (n=3; 39.3 [24.1]), followed by WLE with RT (n=447; 35.9 [34.3] months), WLE with CT (n=13; 32.4 [30.2] months), WLE alone (n=324; 29.6 [34.1] months), WLE with RT and IT (n=11; 23.5 [4.9] months), and WLE with RT and CT (n=27; 20.7 [13.1] months).

Nonsurgical Modalities—Nonsurgical methods were used less frequently than surgical methods (n=461; 35.6%). The mean (SD) OS time in descending order was as follows: RT with CT and IT (n=12; 34.9 [1.2] months), RT with CT (n=81; 30.4 [37.8] months), IT alone (n=35; 25.7 [no SD reported] months), RT with IT (n=34; 20.5 [8.6] months), CT alone (n=38; 20.1 [15.9] months), and RT alone (n=261; 12.8 [8.3] months).

When comparing mean (SD) OS outcomes between surgical and nonsurgical treatment modalities, only the addition of WLE to RT significantly increased OS when compared with RT alone (WLE, 35.9 [34.3] months; RT alone, 12.8 [8.3] months; P=.001). When WLE was added to CT or both RT and CT, there was no significant difference with OS when compared with CT alone (WLE with CT, 32.4 [30.2] months; CT alone, 20.1 [15.9] months; P=.065); or both RT and CT in combination (WLE with RT and CT, 20.7 [13.1] months; RT and CT, 30.4 [37.8] months; P=.204).

Comparison Between T1 and T2 cAS

T1 Angiosarcoma—There were 79 patients identified as having T1 tumors across 16 studies.[2,31,32,34,39-41,46,48-50,53,58-60,62] The mean (SD) OS was longest for WLE with RT, CT, and

Demographics of Patients Included in a Systematic Review of the Literature on Cutaneous Angiosarcoma and Treatment Modalities

		AJCC tumor staging	
Patient Demographics	Overall (n=1295)	T1 (n=79)	T2 (n=105)
Age, y	67.5	66.2	66.4
Males, %	64.7	70.9	72.4
Location, n			
Scalp and face	257	7	17
Scalp	902	33	49
Face	57	23	20
Neck	5	0	3
Other[a]	74	16	16
Treatment, n			
WLE total	825	65	60
WLE alone	324	22	16
WLE+RT	447	30	21
WLE+CT	13	4	8
WLE+RT+CT	27	7	14
WLE+RT+IT	11	0	0
WLE+RT+CT+IT	3	2	1
MMS total	9	4	2
MMS alone	5	2	2
MMS+RT	3	2	0
MMS+RT+CT	1	0	0
Nonsurgical total	461	9	43
RT	261	1	17
CT	38	0	2
IT	35	0	0
RT+CT	81	6	23
RT+IT	34	2	0
RT+CT+IT	12	0	1

Abbreviations: AJCC, American Joint Committee on Cancer; CT, chemotherapy; IT, immunotherapy; MMS, Mohs micrographic surgery; RT, radiotherapy; WLE, wide local excision.

[a]Other sites included unspecified region generalized to the head and neck.

IT (n=2; 56.0 [6.0] months), followed by WLE with CT (n=4; 54.5 [41.0] months); WLE with RT (n=30; 39.7 [41.2] months); WLE alone (n=22; 37.2 [37.3] months); WLE with both RT and CT (n=7; 25.5 [18.7] months); RT with IT (n=2; 20.0 [11.0] months); RT with CT (n=6; 15.7 [6.8] months); and RT alone (n=1; 13 [no SD]) months)(eTable).

T2 Angiosarcoma—There were 105 patients with T2 tumors in 15 studies.[2,31,32,34,39-41,46,48-50,52,53,57,62] The mean (SD) OS for each treatment modality in descending order was as follows: RT with CT and IT (n=1; 36 [no SD reported] months); RT with CT (n=23; 34.3 [46.3] months); WLE with RT (n=21; 26.3 [23.8] months); WLE with CT (n=8; 21.5 [16.6] months); WLE alone (n=16; 19.8 [15.6] months); WLE with RT and CT (n=14; 19.2 [10.5] months); RT alone (n=17; 10.1 [5.5] months); CT alone (n=2; 6.7 [3.7] months); and WLE with RT, CT, and IT (n=1; 6.0 [no SD] months)(eTable).

Mohs Micrographic Surgery—The use of MMS was only identified in case reports or small observational studies for a total of 9 patients. Five cASs were treated with MMS alone for a mean (SD) OS of 37 (21.5) months, with 4 reporting cAS staging: 2 were T1[58,59] (mean [SD] OS, 37.0 [17.0] months) and 2 were T2 tumors[39,57] (mean [SD] OS, 44.5 [26.5] months). Mohs micrographic surgery with RT was used for 3 tumors (mean [SD] OS, 34.0 [26.9] months); 2 were T1[50,60] (mean [SD] OS, 42.0 [30.0] months) and 1 unreported staging (eTable).[56] Mohs micrographic surgery with both RT and CT was used in 1 patient (unreported staging; OS, 82 months).[51]

Complications

Complications were rare and mainly associated with CT and RT. Four studies reported radiation dermatitis with RT.[53,55,62,63] Two studies reported peripheral neuropathy and myelotoxicity with CT.[35,51] Only 1 study reported poor wound healing due to surgical complications.[29]

COMMENT

Cutaneous angiosarcomas are rare and have limited treatment guidelines. Surgical excision does appear to be an effective adjunct to nonsurgical treatments, particularly WLE combined with RT, CT, and IT. Although MMS ultimately may be useful for cAS, the limited number and substantial heterogeneity of reported cases precludes definitive conclusions at this time.

Achieving margin control during WLE is associated with higher OS when treating angiosarcoma,[36,46] which is particularly true for T1 tumors where margin control is imperative, and many cases are treated with a combination of WLE and RT. Overall survival times are lower for T2 tumors, as these tumors are larger and most likely have spread; therefore, more aggressive combination treatments were more prevalent. In these cases, complete margin control may be difficult to achieve and may not be as critical to the outcome if another form of adjuvant therapy can be administered promptly.[24,64]

When surgery is contraindicated, RT with or without CT was the most commonly reported treatment modality. However, these treatments were notably less effective than when used in combination with surgical resection. The use of RT alone has a recurrence rate reported up to 100% in certain studies, suggesting the need to utilize RT in combination with other modalities.[23,39] It is important to note that RT often is used as monotherapy in palliative treatment, which may indirectly skew survival rates.[2]

Limitations of the study include a lack of randomized controlled trials. Most reports were retrospective reviews or case series, and tumor staging was sparsely reported. Finally, although MMS may provide utility in the treatment of cAS, the sample size of 9 precluded definitive conclusions from being formed about its efficacy.

CONCLUSION

Cutaneous angiosarcoma is rare and has limited data comparing different treatment modalities. The paucity of data currently limits definitive recommendations; however, both surgical and nonsurgical modalities have demonstrated potential efficacy in the treatment of cAS and may benefit from additional research. Clinicians should consider a multidisciplinary approach for patients with a diagnosis of cAS to tailor treatments on a case-by-case basis.

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APPENDIX

eTABLE. Overall Survival Rates Associated With Treatment Modalities for Primary Cutaneous Angiosarcoma of the Head and Neck: T1 Tumors (≤5 cm) vs T2 Tumors (>5 cm and ≤10 cm)

	AJCC stage T1 (n=79)		AJCC stage T2 (n=105)		*t* test
Treatment	n	Mean (SD) OS, mo	n	Mean (SD) OS, mo	*P* value
WLE total	65	38.7 (38.0)	60	21.9 (18.4)	.002[a]
WLE alone	22	37.2 (37.3)	16	19.8 (15.6)	.088
WLE+RT	30	39.7 (41.2)	21	26.3 (23.8)	.187
WLE+CT	4	54.5 (41.0)	8	21.5 (16.6)	.069
WLE+RT+CT	7	25.5 (18.7)	14	19.2 (10.5)	.179
WLE+RT+CT+IT	2	56.0 (6.0)	1	6.0 (NA)	NA
MMS total	4	39.5 (24.5)	2	44.5 (26.5)	.417
MMS alone	2	37.0 (17.0)	2	44.5 (26.5)	.768
MMS+RT	2	42.0 (30.0)	0	0	NA
Nonsurgical total	9	16.3 (7.9)	43	24.4 (36.1)	.508
RT	1	13 (NA)	17	10.1 (5.5)	NA
CT	0	0	2	6.7 (3.7)	NA
RT+CT	6	15.7 (6.8)	23	34.3 (46.3)	.340
RT+IT	2	20.0 (11.0)	0	0	NA
RT+CT+IT	0	0	1	36 (NA)	NA

Abbreviations: AJCC, American Joint Committee on Cancer; CT, chemotherapy; IT, immunotherapy; MMS, Mohs micrographic surgery; NA, not applicable; OS, overall survival; RT, radiotherapy; WLE, wide local excision.

[a]Statistically significant.