Original Article

Outcomes of head and neck angiosarcoma with different treatment modalities: a 20-year single institutional experience

Yen Sin Koh[1], Jason Yongsheng Chan[2,3]^, Wen Shen Looi[1], Mohamad Farid[2,3], N Gopalakrishna Iyer[4], Ci-An Gerald Tay[4], Kiattisa Sommat[1], Ru Xin Wong[1]^

[1]Division of Radiation Oncology, National Cancer Centre, Singapore, Singapore; [2]Division of Medical Oncology, National Cancer Centre, Singapore, Singapore; [3]SingHealth Duke-NUS Blood Cancer Centre, Singapore, Singapore; [4]Department of Head and Neck Surgery, National Cancer Centre and Singapore General Hospital, Singapore, Singapore

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Correspondence to: Ru Xin Wong. Division of Radiation Oncology, National Cancer Centre, 11 Hospital Cres, Singapore 169610, Singapore. Email: wong.ru.xin@singhealth.com.sg.

Background: Cutaneous angiosarcoma (AS) is an aggressive entity and commonly presents in the head and neck region of elderly patients. We present our experience with various treatment modalities and approaches herein.

Methods: A retrospective chart review of patients with AS of the head and neck treated over a 20-year period in a single institution was undertaken.

Results: A total of 88 patients with a mean age of 74 years were included. Seventy-four patients had scalp primary. Thirty-one patients were metastatic at diagnosis. The median overall survival (OS) for metastatic and localized AS were 6.9 and 20.4 months respectively. For localized AS, 21 patients underwent curative surgery; 14 patients had negative margins, 7 patients had adjuvant radiotherapy and 15 patients had locoregional disease as first site of relapse. For palliative treatment, 64 patients received chemotherapy due to unresectable or relapsed disease; the most common chemotherapy agent was taxanes. Additionally, 51 patients received palliative radiotherapy and 6 patients received photodynamic therapy (PDT). Of patients who had palliative chemotherapy and/or radiotherapy, most patients demonstrated response. Fourteen patients did not receive surgery but had OS of more than two years. Patients with surgery had lower 2-year progression-free survival (62.8% *vs.* 35.0%, P=0.026) but higher OS (64.6% *vs.* 42.0%, P<0.001), compared to no surgery. In univariable analysis, blood inflammatory markers showed an association with OS. In multivariable analysis, only age and stage predicted for OS.

Conclusions: AS of the head and neck is aggressive. Although surgery was associated with better OS, this could have been confounded by performance status and smaller tumours. In view of high locoregional relapse rates despite resection, morbid surgery should not be undertaken for tumours that require extensive resection. Some patients experienced extended survival with a conservative approach of chemotherapy with or without local consolidation therapy.

Keywords: Head; neck; scalp; face; angiosarcoma (AS)

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^ ORCID: Ru Xin Wong, 0000-0002-4973-7404; Jason Yongsheng Chan, 0000-0002-4801-3703.

Introduction

Angiosarcoma (AS) is a rare cancer of the vascular endothelium, constituting 1.6–5.0% of all cutaneous soft tissue sarcomas. It commonly occurs in the head and neck region (1,2). The disease usually presents innocuously as a benign bruise-like lesion, often covered by the hairline (2,3), making diagnosis challenging. Surgically, it is difficult to achieve negative margins due to multifocality and subclinical infiltration (2,4). The disease often metastasizes to regional nodes and distant sites (lung, liver and bone) (1,4). As a result, the outcomes for head and neck AS are often poor, with 5-year survival ranging from 10% to 54% (2).

Due to its rarity (4), there is a paucity of related literature. As most studies were presented as case reports and series, there is a lack of established management consensus. While some studies advocated surgery with adjuvant radiotherapy (2,5-8), many other studies showed otherwise, particularly for larger tumors (1,4,6,7,9). For example, a study interrogated the SEER database and concluded that surgery and radiotherapy were not associated with survival (10). A few authors also demonstrated extended survival in selected patients, who only received chemotherapy with or without local radiotherapy (2,5-7).

Other centers had reported different treatment strategies as well. A European study examined the possibility of neoadjuvant chemotherapy for non-metastatic patients with AS (8). Various experimental techniques like photodynamic therapy (PDT) had been utilized for skin relapses too (11). A few recent publications also advocated for personalized medicine through molecular profiling (9,12). Researchers from the Angiosarcoma Project found UV-related mutational signatures in AS. These signatures were similar in other skin cancers, such as melanoma, and might explain the immunotherapy sensitivity of AS (13).

However, most of these studies were in Western context. These studies generally had patients with smaller and more operable tumors (2,11,12). For instance, a study in Mayo clinic reported that 73% of patients (n=40/55) with localized AS had multimodality therapies including surgery, with a 5-year locoregional control and overall survival (OS) of 18% and 38% respectively (2). In contrast, a few Asian series reported relatively lower survival outcomes (14-16). Given the dismal survival outcomes of Asian patients, it is essential to examine this disease in the Asian setting.

Hence, we aim to contribute to the literature our experience on head and neck AS, within a single Asian tertiary center. We will report outcomes from various treatment modalities and explore the prognostic significance of blood inflammatory markers. We present the following article in accordance with the STROBE reporting checking (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-40/rc).

Methods

This was a retrospective cohort study from a larger prospectively collected sarcoma database. Patients with scalp and face AS treated in National Cancer Centre Singapore were included. The year of diagnosis ranged from 1999 to 2020. The study was approved by institutional review board (Singhealth IRB 2018/3065, 2018/2020), with waiver of consent for patients lost to follow up, and written informed consent obtained from the patients whenever possible. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Tumor size was categorized at 5-cm cut-off, in accordance with the American Joint Committee on Cancer (AJCC) TNM criteria. Patients were classified as metastatic if extensive multifocal lesions or distant metastases were presented at diagnosis. Blood biomarkers (hemoglobin, platelets, and white cell count) were collected at time of diagnosis to generate inflammatory ratios. Relapses were diagnosed based on computed tomography (CT) scan or clinical assessment of lesion size and numbers. Death-related data was obtained from the National Registry.

Statistical analysis

Survival outcomes examined for the study were OS and progression free survival (PFS). To determine significant factors for survival outcomes, univariable and multivariable cox proportional hazard model analyses were performed. The following variables were examined as potential factors for survival outcomes: age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, tumor size, metastatic at diagnosis, sex, surgery and blood biomarkers. OS was defined as the time of diagnosis to time of last follow up/death. PFS was defined as the time of diagnosis to time of first recurrence/last follow up. Outcomes were also described for three sub-groups of patients: (I) patients who underwent surgery with a curative intent; (II) patients with localized tumours without radical resection; (III) patients with *de novo* metastases.

All statistical analyses were done using R (Version 4.0.3), assuming the tests were two-sided and at 5% significance level.

Table 1 Characteristics of all patients with angiosarcoma (n=88)

Variable	n (%)
Mean age at diagnosis (SD) (n=88)	73.7 (12.2)
Sex (n=88)	
Female	26 (29.5)
Male	62 (70.5)
Ethnicity (n=88)	
Chinese	78 (88.6)
Malay	6 (6.8)
Indian	1 (1.1)
Others	3 (3.3)
ECOG Performance Status at diagnosis (n=82)	
0	34 (41.5)
1	33 (40.2)
2	6 (7.3)
3	5 (6.1)
4	4 (4.9)
Mets at diagnosis (n=86)	
No	55 (64.0)
Yes	31 (36.0)
Size of tumor (n=86)	
<5 cm	22 (25.6)
≥5 cm	33 (38.4)
Metastatic	31 (36.0)
Site of tumor (n=88)	
Scalp	74 (84.1)
Face and neck	14 (15.9)
Grade (n=41)	
2	20 (48.8)
3	21 (51.2)
Median OS in months (95% CI)	14.7 (10.4–21.2)

n represents the sample size. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; SD, standard deviation.

Results

A total of 88 patients were included in the study. *Table 1* summarized the patients' characteristics. The mean age was 73.7 years [Standard deviation (SD): 12.2]. Most patients were male (n=62), ethnic Chinese (n=78), and with ECOG 0–1 (n=67). Thirty-one patients were metastatic at diagnosis. Fifty-five patients had localized disease at diagnosis and two patients did not have staging assessment due to frailty. Of patients without distant metastases, 22 patients had tumor smaller than 5 cm; 33 patients had large or extensive disease. Most patients (n=74) had primary tumor arising from the scalp. The median follow-up was 12.8 months [interquartile range (IQR): 5.7–25.9 months]. The 2- and 5-year OS were 37.5% (95% CI: 28.4–49.5%) and 14.7% (95% CI: 8.13–26.6%) respectively. The median OS was 14.7 months (95% CI: 10.4–21.2 months) (*Figure 1A*).

Types of treatment

Surgery

Twenty-one patients underwent surgery with curative intent: seven patients with R1, the rest R0. One patient had initial nodal dissection. Another patient had nodal dissection upon relapse. At time of study, all patients had relapsed, except for two patients who were disease free. For these two patients, they had small tumors that were excised completely without adjuvant treatment. For first site of relapse, 15 cases were locoregional. Additionally, one case had local and distant relapse simultaneously; three cases had distant relapse.

Radiotherapy

Seven patients had adjuvant radiotherapy: five cases after R0 and two cases after R1. Fifty-one patients had palliative radiotherapy, either sequentially after chemotherapy, or by itself. Of assessable patients, none had lesions that progressed during treatment; all had documented response or stable disease. The median RT dose given for adjuvant RT was 56 Gy (IQR: 55–60 Gy) and the median RT fraction was 29 (IQR: 22–30). The palliative regimen ranged from single hypo-fractionated (e.g., single 8 Gy) to high dose conventional treatments (e.g., 60 Gy in 30 fractions).

Chemotherapy

None received (neo)adjuvant chemotherapy. Chemotherapy was administered for unresectable disease, or upon relapse (n=64). Most patients were given taxanes (n=36). Subsequently, 18 patients were given 2nd line chemotherapy, 13 patients were given 3rd-line chemotherapy and three patients were given 4th line chemotherapy. Of 35 assessable patients after first line chemotherapy, six patients had documented progression of lesions, 23 patients had good

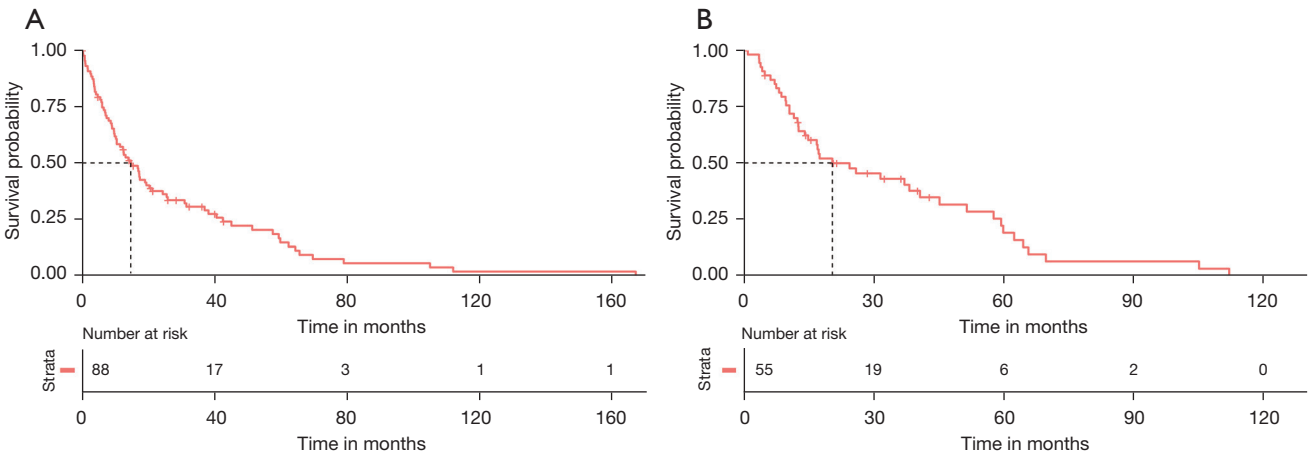

Figure 1 Overall Survival for patients with (A) angiosarcoma (n=88); (B) non-metastatic angiosarcoma (n=55).

response, six patients had stable lesions.

PDT

Six patients had PDT for cutaneous relapses. Five patients had locoregional or distant progressive disease. One had abscopal effect with partial response of distant disease after primary site PDT.

Outcomes of patients with localized disease

Table 2 summarized the patients' characteristics with localized (non-metastatic) disease at presentation (n=55). Thirty-seven patients passed away from AS. The 2-year and 5-year OS were 49.9% (95% CI: 37.9–65.7%) and 18.9% (95% CI: 9.6–37.1%) respectively. The median OS was 20.4 months (95% CI: 14.8–45.1 months) (*Figure 1B*). The 2-year and 5-year PFS were 51.2% (95% CI: 36.6–71.6%) and 20.4% (95% CI: 8.5–48.7%) respectively. The median PFS was 26.3 months (95% CI: 19.2–37.4 months).

Twenty-one patients had surgery with curative intent. Of these patients, 14 patient had negative margins and seven patients had adjuvant radiotherapy. More local relapses were observed for patients with adjuvant radiotherapy (57.1%), as compared to those without adjuvant radiotherapy (35.7%). Patients with adjuvant radiotherapy had better OS as compared to those without adjuvant radiotherapy (log-rank test P=0.002).

When the patients were stratified by surgery, patients who had surgery with curative intent were younger [mean age: 70.1 (surgery) *vs.* 75.1 (no surgery), P=0.142], with better ECOG [ECOG 0: 84.2% (surgery) *vs.* 35.5% (no surgery), P<0.01] and smaller tumour size [tumour size <5 cm: 71.4% (surgery) *vs.* 21.2% (no surgery), P<0.01].

Outcomes of patients with de novo metastases

For patients with metastatic disease at presentation (n=31, *Table 3*), the mean age is 73.6 (SD: 10.8) years. Most of the patients were ECOG 1 (n=16). All but one patient died from AS. The median follow-up was 6.9 (IQR: 2.6–19.2) months. The median OS was 6.9 (95% CI: 3.7–19.0) months. In terms of treatments given, 17 patients had palliative radiotherapy and 17 patients had palliative chemotherapy. Among the patients who had palliative chemotherapy, most demonstrated response. Among patients who were given palliative RT and assessable (n=8), all had response to the treatment.

Selected non-surgical patients with extended survival

Among patients who did not have surgery with a curative intent, 14 patients had OS of more than two years. The median age was 72. Four patients were metastatic at diagnosis, six patients had large tumours, three patients had small tumours of <5 cm. For treatment, six patients received chemoradiotherapy, two patients received chemoradiotherapy with PDT, one patient received chemotherapy with PDT, three patients received chemotherapy alone, two patients only had palliative radiotherapy. At initial biopsy, seven patients had well differentiated AS, seven patients were grade 2 and two patients were grade 3. Seven patients did not have their tumour grade assessed. For survival outcomes, 11 patients passed away from AS, one patient passed away from

Table 2 Characteristics of patients with localized angiosarcoma (n=55)

Variable	n (%)
Mean age at diagnosis (SD) (n=55)	72.9 (12.2)
ECOG Performance Status at diagnosis (n=51)	
0	27 (52.9)
1	17 (33.3)
2	4 (7.8)
3	1 (2.0)
4	2 (3.9)
Size of tumor (n=55)	
<5 cm	22 (40.0)
≥5 cm	33 (60.0)
Site of tumor (n=55)	
Scalp	46 (83.6)
Face & neck	9 (16.4)
Death (n=55)	
No	13 (23.6)
Yes	42 (76.4)
Death due to angiosarcoma (n=42)	
No	5 (11.9)
Yes	37 (88.1)
Relapse (Locoregional or Distant) (n=55)	
No	30 (54.5)
Yes	25 (45.5)
Median OS in months (95% CI)	20.4 (14.8–45.1)
Median PFS in months (95% CI)	26.3 (19.2–37.4)
Patients with surgery (Curative intent) (n=21)	
Surgical margins (n=21)	
R0	14 (66.7)
R1	7 (33.3)
Adjuvant radiotherapy (n=21)	
Yes	7 (33.3)
No	14 (66.7)

n represents the sample size. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; SD, standard deviation.

Table 3 Characteristics of patients with metastatic angiosarcoma (n=31)

Variable	n (%)
Mean age at diagnosis (SD) (n=31)	73.6 (10.8)
ECOG Performance Status at diagnosis (n=29)	
0	7 (24.1)
1	16 (55.2)
2	2 (6.9)
3	3 (10.3)
4	1 (3.4)
Site of tumor (n=31)	
Scalp	27 (87.1)
Face & neck	4 (12.9)
Grade (n=12)	
2	2 (16.7)
3	10 (83.3)
Death due to angiosarcoma (n=31)	
No	1 (3.2)
Yes	30 (96.8)
Median OS in months (95% CI)	6.9 (3.7–19.0)
Palliative Radiotherapy (n=31)	
No	14 (45.2)
Yes	17 (54.8)
Palliative Chemotherapy (n=31)	
No	14 (45.2)
Yes	17 (54.8)

n represents the sample size. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; SD, standard deviation.

subdural hemorrhage, and two patients were alive at time of analysis. Amongst dead patients (n=12), the median OS was 47.0 months.

OS and PFS for the different groups of patients

For overall survival of patients with (I) *de novo* metastatic AS; (II) curative surgery for localized disease; (III) no

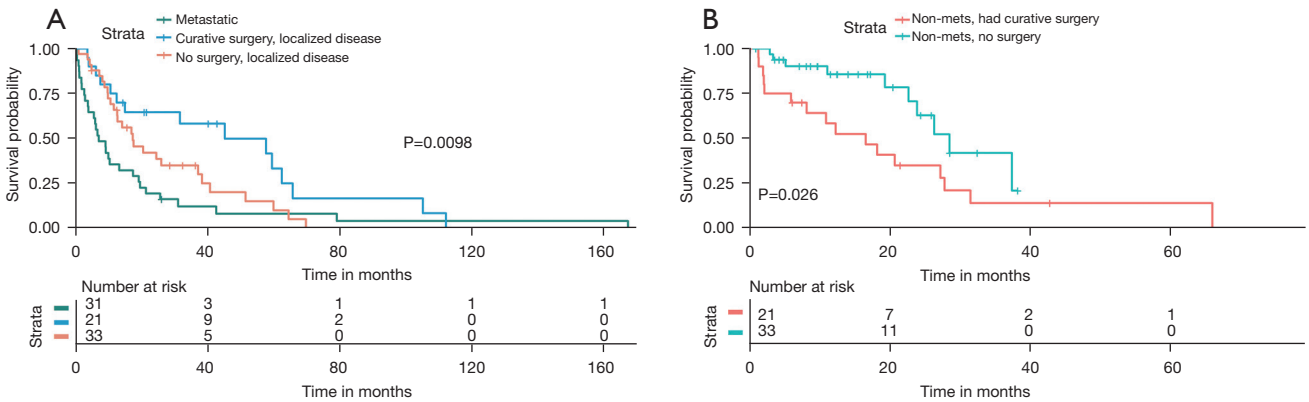

Figure 2 Overall survival and progression free survival for different groups of patients based on treatment receipt. (A) Overall survival of patients with metastatic disease, curative surgery and localized disease, no survey and localized disease. (B) Progression free survival of patients with non-metastatic and had curative surgery, patients with non-metastatic and no surgery.

curative surgery for localized disease (*Figure 2A*), there was a significant difference in OS among the three groups (P<0.001). Patients with curative surgery for localized disease had the highest OS, while patients with metastatic AS had lowest OS. For patients with curative surgery for localized disease, the 2- and 5-year OS were 64.6% (95% CI: 46.6–89.6%) and 33.2% (95% CI: 15.7–70.3%) respectively. Pertaining to patients with no curative surgery for localized disease, the 2-year and 5-year OS were 42.0% (95% CI: 27.6–63.9%) and 10.0% (95% CI: 2.81–35.6%) respectively.

Of patients with localized tumours, the 2-year PFS of patients with no curative surgery was significantly higher than those with curative surgery (62.8% *vs.* 35.0%, P=0.026) (*Figure 2B*).

Cox proportional hazard model for OS and PFS

Univariable analysis of OS for all patients (*Table 4*) revealed that age [hazard ratio (HR): 1.04; 95% CI: 1.02–1.07], ECOG (HR of ECOG 1 *vs.* ECOG 0: 2.08; 95% CI: 1.22–3.57, HR of ECOG 2–4 *vs.* ECOG 0: 3.84; 95% CI: 1.99–7.43), tumor size (HR of metastatic *vs.* <5 cm: 2.50; 95% CI: 1.40–4.53), metastasis at diagnosis (HR of metastasis *vs.* no metastasis: 1.90; 95% CI: 1.18–3.06), grade of tumour (HR of grade 3 *vs.* grade 2: 2.24; 95% CI: 1.10–4.56) and surgery (HR of surgery *vs.* no surgery: 0.49; 95% CI: 0.28–0.88) were significant predictors for OS (*Table 4*). When these predictors were included in the multivariable model (*Table 4*), only age (HR: 1.04; 95% CI: 1.01–1.07) and metastasis at diagnosis (HR: 1.98; 95% CI: 1.09–3.61) were shown to be significant (*Table 4*).

Univariable analysis of PFS for patient with localized AS showed that only surgery was a significant predictor for PFS (HR of surgery *vs.* no surgery: 2.30; 95% CI: 1.15–4.60).

Cox proportional hazard model for OS with regards to blood biomarkers

Lower hemoglobin level (HR: 0.79; 95% CI: 0.68–0.92) and lower lymphocyte:monocyte ratio (LMR) (HR: 0.81; 95% CI: 0.67–0.97) were significantly associated with worse survival (*Table 5*). When hemoglobin, LMR, age and metastatic status were included in the multivariable analysis of OS (*Table 5*), the blood biomarkers no longer predicted for survival.

Discussion

Our study presented the following key findings: (I) 2- and 5-year OS of patients with head and neck AS were guarded 37.5% and 14.7%; (II) patients who underwent surgery with a curative had worse PFS but better OS; (III) most surgical patients experienced locoregional recurrences as first site of relapse; (IV) some non-surgical patients were able to survive beyond two years; (V) there were good responses on taxanes; (VI) only age and clinical stage were significant predictors of OS.

Our study demonstrated that AS is aggressive, as its 2-year (49.9%) and 5-year OS (18.9%) of localized disease were dismal. These findings were in line with some of the existing literature (1,15,16). However, our study had

Table 4 Cox proportional hazard model for Overall survival

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis (n=88)	1.04 (1.02–1.07)	<0.001	1.04 (1.01–1.07)	0.015
ECOG Performance Status (Reference =0) (n=82)				
1	2.08 (1.22–3.57)	<0.001	1.68 (0.91–3.08)	0.097
2–4	3.84 (1.99–7.43)	<0.001	2.31 (0.98–5.42)	0.055
Tumor size (Ref: <5 cm) (n=86)				
≥5 cm	1.74 (0.93–3.24)	0.082		
Metastatic	2.50 (1.40–4.53)	0.003		
Metastasis at diagnosis (Reference: no) (n=86)				
Yes	1.90 (1.18–3.06)	<0.001	1.98 (1.09–3.61)	0.025
Margin (Reference: negative) (n=20)				
Positive	3.00 (1.00–9.04)	0.051		
Sex (Reference: female) (n=88)				
Male	0.89 (0.54–1.45)	0.632		
Grade (Reference: Grade 2) (n=41)				
Grade 3	2.24 (1.10–4.56)	0.026		
Surgery (Reference: No) (n=84)				
Yes	0.49 (0.28–0.88)	0.017	1.09 (0.52–2.28)	0.825

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

Table 5 Cox proportional hazard model for overall survival based on blood biomarkers

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Hemoglobin (n=67)	0.79 (0.68–0.92)	0.003	0.89 (0.74–1.08)	0.237
NLR (n=72)	1.02 (1.00–1.05)	0.062		
PLR (n=72)	1.001 (0.999–1.002)	0.568		
LMR (n=72)	0.81 (0.67–0.97)	0.025	0.84 (0.70–1.01)	0.070
Age at diagnosis (n=65)			1.04 (1.00–1.08)	0.028
Metastasis at diagnosis (Ref: No) (n=65)				
Yes			1.66 (0.93–2.95)	0.088

CI, confidence interval; HR, hazard ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet lymphocyte ratio; LMR, lymphocyte-monocyte ratio.

poorer outcomes as compared to Western reports. A study from Mayo clinic showed that the 5-years for patients with localized AS was 41% (2). Another study from University of Florida revealed that the 5-year OS of patients with AS was 54% (17).

From our study, patients who had surgery with curative intent had better OS but worse PFS. After adjusting for age, performance status and metastatic status at presentation, association of OS with surgery was not significant. The finding of worse PFS could be explained by closer

surveillance and hence earlier detection of recurrences. Non-surgical patients were also on palliative chemotherapy, which could have delayed relapses (none of our surgical patients received (neo)adjuvant chemotherapy). Some studies had similar findings, postulating that post-surgical inflammatory marks like vascular endothelial growth factor (VEGF) can cause tumours proliferation (18). Fifteen of 21 surgical patients experienced locoregional recurrences as first site of relapse. These findings support the emerging perspective that morbid surgery should be avoided due to high recurrence rate (2,8). Other studies have corroborated that risks of distant metastases and locoregional relapses after surgery were high (19). Moreover, a Canadian series could not find a difference in outcomes between surgery alone, radiotherapy alone or combined treatment (1).

In light of high relapse rates, some authors have proposed simple resection followed by adjuvant radiotherapy (2,20). However, our study implied otherwise. In our results, there was a higher proportion of relapses for surgical patients with adjuvant radiotherapy [57.1% (adjuvant radiotherapy) *vs.* 35.7% (without adjuvant radiotherapy)]. Hence, it remains debatable whether resection and adjuvant radiotherapy should be routinely offered in these patients. Such an approach can be morbid and logistically challenging, especially in elderly or frail patients. However, in smaller localized tumours, wide excision may still have a role if it can be achieved without overt complications (2,20).

Our study showed that among non-surgical patients, 14 patients managed to achieve long-term survival when treated conservatively. Other published studies also support our finding, showing that for treatment-sensitive tumours, chemotherapy and radiation effects can be long-lasting (2,5,6). Outcomes from Asian researchers have also found that many lesions were too extensive and more likely to have subclinical distant/locoregional disease. For these cases, chemotherapy and/or radiotherapy may be more suitable. For example, Fujisawa *et al*. compared patients treated with surgery *vs.* taxane-based conservative therapy and found that the latter had better outcomes (21). In another study by Fujisawa *et al.* (7), patients who had surgery had a lower 5-year OS (8%) as compared to those with chemo-radiotherapy (56%). On the contrary, a small series from Tokyo that employed high dose radiotherapy with taxane reported median survival of only 20 months, with patients succumbing to locoregional and pulmonary relapses (22). Hence, the future challenge is in profiling and predicting good responders to better customize therapy.

In the unresectable or relapsed setting, we reported good response to taxanes. The use of taxanes was also recommended in a review article by Erikssen (23). Paclitaxel is a better tolerated agent compared to doxorubicin, especially in elderly patients who may have existing cardiac condition (23). Radiation has been reported to be ineffective as a curative monotherapy and is generally used for palliation (20). In our study, there were no instances of radiation-resistant AS. We recommend palliative chemotherapy, with or without radiotherapy for consolidation. However, we did not report on the duration of chemotherapy and did not study the utility of maintenance/extended chemotherapy, although described by small series to be useful (6).

In our study, multivariable analysis revealed that only age and stage were significant predictors for OS, similar to other studies (2). For the various blood biomarkers, hemoglobin and lymphocyte-monocyte ratio were significant prognostic factors in univariable analysis. However, they were shown not to be statistically significant in the multivariable analysis. This lack of statistical significance might be attributed to our smaller sample size.

While blood biomarkers were not significant factors in our study, recent studies had examined the molecular profiles of AS. In a larger study led by one of our co-authors, subtypes of AS are observed based on gene expressions in inflammation-related pathways (9). In another study by Chan *et al.*, it examined a large cohort of AS from which patients in this study were a subset of. He found that non-responders to chemotherapy had higher oncogenic pathway scores. Moreover, he found that high peripheral blood NLR was correlated with intra-tumoral NLR and was associated with worse outcomes (24). These findings suggest that treatments that target oncogenic pathways, such as immunotherapy, may be helpful in treating the disease. Interestingly, one of our patients had documented abscopal response after PDT, further highlighting possible immunogenicity with AS (11).

Our study has several strengths. Firstly, it contributes significantly to the limited number of smaller Asian studies. Secondly, death data was corroborated from the National Registry. Thirdly, we reported on outcomes with different modalities in both localized and metastatic patients. Lastly, it is one of the few studies that examined the characteristics and treatment responses of metastatic patients.

Limitations include the retrospective nature of our study and limited generalizability as the findings are from a single institution. Thirdly, though multivariable analyses were attempted to account for potential confounders, the

statistical power was limited by small sample size. Fourthly, it was difficult to objectively assess tumour response to various therapies as lesions were cutaneous and can be subtle, and often not obvious on imaging. Especially when assessing response after palliative radiotherapy or PDT, it could be difficult to tell dermatitis apart from disease. Lastly, we did not analyze sequencing of chemotherapy and local treatment, and cycles of chemotherapy (maintenance chemotherapy). Based on experience, most patients would receive chemotherapy first to prevent severe toxicities from concurrent multimodality treatments.

Conclusions

We showed that head and neck AS had poor outcomes. There was a high risk of locoregional relapses and AS-deaths, even in patients with localized disease and after curative surgery. Age and stage were shown to be significant factors for overall survival. Although we found that surgery was associated with better OS, it could have been confounded by other factors. The utility of adjuvant radiotherapy remains debatable as it is difficult to draw conclusions from uncontrolled retrospective series. For smaller tumours, while wide excision with or without adjuvant radiotherapy is an option, the clinical benefit of which compared to a more conservative approach with upfront chemotherapy remains unanswered. Selected patients with unresectable disease may have long lasting response from chemotherapy, with or without radiotherapy. The future challenge lies in profiling and predicting for treatment-sensitive tumours, and to determine the duration and sequencing of chemotherapy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-40/rc

Data Sharing Statement: Available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-40/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by institutional review board (Singhealth IRB 2018/3065, 2018/2020), with waiver of consent for patients lost to follow up, and written informed consent obtained from the patients whenever possible. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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