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Cutaneous Angiosarcoma of Head and Neck: A New Predictive Score for Locoregional Metastasis[1,2]

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Abstract

OBJECTIVES: Cutaneous angiosarcoma of head and neck (cAS-HN) is a malignant neoplasm with deficient data on prognostic factors. The aim of this study is to present our monocenter database on cAS-HN so far and a new predictive score for locoregional metastasis (LRM). *METHODS:* Retrospectively, tumor characteristics and outcome of 103 consecutive patients with cAS-HN were analyzed. The main predictors of LRM (identified by univariate and multivariate statistics) were combined to a LRM risk score. The prognostic values of stratification into high-, medium-, and low-risk groups concerning disease-specific survival (DSS), distant metastasis (DM), and progression-free survival (PFS) were evaluated. *RESULTS:* LRM ($n = 29$) and control ($n = 74$) groups differed significantly concerning several tumor characteristics and outcome (DM, PFS, and DSS). Patients developing LRM showed 3-, 5-, and 10-year survival rates of 32%, 16%, and 11% (mean DSS time of 36.7 months [95% confidence interval (CI) 20.5-52.8]) compared to 81%, 73%, and 69% (mean DSS time of 292.4 months [95% CI 208.4-376.5]) in controls without LRM ($P < .001$). The main predictors were American Joint Committee on Cancer (AJCC) stage, tumor extent, and origin of the primary tumor. The LRM risk score revealed significant higher values for the LRM group [7.14 (SD 1.46) *vs* 4.88 (SD 1.89), $P < .001$]. The high-risk group showed significantly higher risk for DM and more unfavorable DSS and PFS. *CONCLUSION:* The LRM risk score is a simple way to estimate the risk for LRM and DM, to stage patients, and to determine treatment options.

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Introduction

Angiosarcomas of head and neck (AS-HN) are approximately 1% to 2% of all head and neck soft tissue sarcomas, rare malignant mesenchymal tumors originating in the endothelium of blood vessels, and due to their common benign visual appearances are difficult to diagnose. Sixty percent are cutaneous angiosarcomas (cAS), mainly found in the capillitium and face in people older than 70 years (cAS-HN) [1,2].

Treatment options vary depending on medical findings such as metastases and the patient's condition. As most studies have approved, initial treatment of choice is surgery combined with adjuvant radiotherapy [3–6].

Five-year disease-specific survival (DSS) rates vary between 46% and 62%. Important prognostic factors are extent of primary tumor, resection status, histologic tumor differentiation, and metastases [1–3].

Due to aggressive growth and delayed diagnosis, mainly, in AS, 16% to 45% of patients are diagnosed with initial distant metastasis (DM) [7–10]. In their study on cAS-HN, Guadagnolo et al. [3] excluded patients with initial metastases. Here, 25 patients (36%) developed DM, especially in the lung. Eleven patients (16%) had

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nodal relapse. Deyrup et al. [1] reported on 15 patients of 69 (22%) who developed metastases. Both studies found no significant predictive factors for metastasis. Of 80 patients with cAS-HN in our Cancer Centre, we described 13 with initial DM, 16 with secondary DM, and 27 with locoregional metastasis (LRM). [2] In this study, we add 23 further consecutive patients to broaden the database. In our abovementioned previous study, prevalence of LRM was only reported shortly in a descriptive manner. Assessment of risk factors for LRM and development of risk stratification were not performed at all. Analyzing LRM risk may be of prognostic and therapeutic relevance in this rare tumor entity.

Patients and Methods

Patients

Consecutive patients with cAS-HN treated surgically between 1980 and 2013 were retrospectively identified from our institutional database. This study was approved by the local ethics committee (Ethical Committee of the Westphalian Wilhelms-University Muenster, Approval No. 2014-528-f-S) and was conducted in accordance with the Guidelines for Good Clinical Practice and in compliance with the Declaration of Helsinki. All participating patients provided written informed consent.

Inclusion criteria for this study were histopathologic secured sporadic cAS-HN and a minimum follow-up time of 6 months. Exclusion criteria were patients suffering from multiple cancers of the head and neck, patients after other malignancies in the head and neck, and patients who had already received cancer or lymph node surgery (e.g., neck dissection). Patients with cAS-HN arising in lymphoedema or after radiation were also excluded from the study. All patients received complete appropriate staging, including ultrasonography of relevant lymph node levels and abdomen and radiologic imaging [computed tomography (CT) or magnetic resonance imaging (MRI) of head, neck, thorax, and abdomen]. Follow-up care (clinical examination, ultrasonography, CT, or MRI in case of suspicious findings) was conducted every 3 months in the first 2 years and every 6 months thereafter. Patients who developed regional LRM during the observation period were classified as the LRM group, and those without LRM were classified as the control group.

Methods

Relevant characteristics and parameters for analysis were performed comparable to our previous research and are displayed in detail in Table 1. The main outcome parameters were local relapse (LR), LRM, DM, progression-free survival (PFS), and DSS.

For continuous variables, the Mann-Whitney U test was used as a non-parametric test for abnormally distributed data. Categorical variables were analyzed using the chi-square test and Fisher exact test. DSS (time from first diagnosis to tumor-dependent death; data on patients without tumor-dependent death were censored at the last follow-up time), PFS [time from first diagnosis to disease progression (LR, LRM, and DM)], LRM time (time from first diagnosis to LRM), and DM time (time from first diagnosis to DM) were calculated using the Kaplan-Meier method, and group differences were analyzed using the log-rank test.

Binary logistic regression analysis (BLR) was used to model the predictors of LRM. Potential predictors identified by univariate analysis were entered into a stepwise backward procedure using $P < .05$ for entry and $P > .1$ for removal. To create a prediction model for LRM, only preoperative assessable variables with significant group differences ($P < .05$) were considered to be suitable for inclusion in the BLR. Intraoperative or postoperative parameters were excluded from the BLR, even if statistically significant. To overcome risk of overmodeling, we decided to insert only the following three variables into BLR: localization of the primary tumor, tumor extent, and AJCC stage. AJCC stage can be interpreted as a composite variable that includes information on tumor dimension and depth (T classification), nodal disease at first diagnosis (N classification), DM at first diagnosis (M classification), and histologic grading. Because occurrence of LRM is a time-dependent variable, we also modeled prediction of LRM time using Cox regression analysis (CRA). The same three variables that were inserted into BLR were used for CRA. Development of the prediction models was performed considering the suggestions of Harrell et al. [11].

Creation of an easy to use LRM risk score was performed by combining the BLR- and CRA-confirmed predictors of LRM occurrence. Instead of taking BLR equation itself for risk assessment, we decided to develop a point assessment for each predictor to enable easy and quick routine assessment for the clinician (Table 3). By receiver operating characteristic curve analysis and Youden index calculation, an optimal cut-off value for the LRM risk score was defined, and for clinical and prognostic purposes, the study population was stratified to a three-scale (low, medium, and high) risk group assessment. Prognostic relevance of LRM risk groups on DSS, PFS, and DM time was calculated according to Kaplan-Meier including the log-rank test for the whole study population ($n = 103$) and for a smaller sample ($n = 90$) after exclusion of patients with primary DM (M1, $n = 13$).

All statistical analyses were performed by a statistician using the Statistical Package for Social Sciences, version 18.0 (SPSS Inc, Chicago, IL).

Results

Overview

In our study, we included 103 patients with cAS-HN, of these 65 males and 38 females. Mean age at first diagnosis was 72.1 ± 13.5 years, and mean follow-up time was 57.4 ± 83.2 months. Concerning the overall survival status, 52 people died, while 51 survived, leading to a mean overall survival status of 155.3 months [95% confidence interval (CI) 102.6-207.98, median 58.8 (95% CI 49.2-68.5)]; 3-, 5-, 10-, and 20-year survival rates were 61%, 49%, 37%, and 26%. Focusing on the DSS status, 40 patients died because of the tumor and 12 due to other reasons. Mean DSS was 220.2 months (95% CI 153.1-287.3), and median DSS was 174.1 months (95% CI 11.5-336.8) with 3-, 5-, 10-, and 20-year survival rates of 66%, 55%, 50%, and 44%.

Initial Nodal Disease (N1)

Comparing patients with N1 ($n = 10$) to those with N0 ($n = 93$), gender, age, localization, and tumor size did not differed significantly ($P > .05$). Concerning one region of tumor extent, 2 of 57 patients were diagnosed with N1, while in cAS-HN of two or more regions, 8 of 46 cases were affected ($P = .040$). Of 23 superficial cAS-HN (TIa and IIa), none was found to be N1, whereas of 80 deep tumors (TIb and TIIb) 10 were diagnosed to be N1 ($P = .112$).

Patients with N1 died more often tumor-dependently ($P = .013$). Mean DSS in N1 patients was 15.4 months (95% CI 7.6-23.2) compared with mean DSS of 238 months (95% CI 166.4-310.1) in

Table 1. Comparison of Assessed Variables between the LRM and Control Groups

Parameter		Control (n = 74)	LRM Group (n = 29)	Significance (P Value)
Age				
<70 years	n (%)	23 (31.1)	5 (17.2)	.219
≥70 years	n (%)	51 (68.9)	24 (82.8)	
Gender				.262
Male	n (%)	44 (59.5)	21 (72.4)	
Female	n (%)	30 (40.5)	8 (27.6)	
Disease-specific death				<.001
No	n (%)	56 (75.7)	7 (24.1)	
Yes	n (%)	18 (24.3)	22 (75.9)	
Origin of primary tumor/localization				.030
Face	n (%)	46 (62.2)	11 (37.9)	
Scalp	n (%)	28 (37.8)	18 (62.1)	
Extent of primary tumor				.004
One region	n (%)	48 (64.9)	9 (31.0)	
Two or more regions	n (%)	26 (35.1)	20 (69.0)	
Primary tumor site				.566
Scalp	n (%)	16 (21.6)	10 (34.5)	
Lower third of the face	n (%)	1 (1.4)	1 (3.5)	
Midface including nose	n (%)	27 (36.5)	7 (24.1)	
Upper third of the face	n (%)	9 (12.2)	2 (6.9)	
Ear and periauricular	n (%)	6 (8.1)	1 (3.5)	
More than one region: face or scalp	n (%)	11 (14.9)	5 (17.2)	
More than one region: face and scalp	n (%)	4 (5.4)	3 (10.3)	
Dimension of primary tumor				<.001
<5 cm	n (%)	41 (55.4)	3 (10.3)	
≥5 cm	n (%)	33 (44.6)	26 (89.7)	
T classification				<.001
Ia	n (%)	16 (21.6)	0	
Ib	n (%)	24 (32.4)	3 (10.3)	
IIa	n (%)	7 (9.5)	0	
IIb	n (%)	27 (36.5)	26 (89.7)	
Tumor depth				<.001
Superficial (Ia, IIa)	n (%)	23 (31.1)	0	
Deep (Ib, IIb)	n (%)	51 (68.9)	29	
N classification				<.001
pN0	n (%)	73 (98.6)	20 (69.0)	
pN1	n (%)	1 (1.4)	9 (31.0)	
M classification				.001
pM0	n (%)	70 (94.6)	20 (69.0)	
pM1	n (%)	4 (5.4)	9 (31.0)	
Resection status				<.001
R0	n (%)	49 (66.2)	3 (10.3)	
R1	n (%)	22 (29.7)	23 (79.3)	
R2	n (%)	3 (4.1)	3 (10.4)	
Safety margin				.567
<1 cm	n (%)	29	1	
≥1 cm	n (%)	20	2	
LR				.117
No	n (%)	49 (66.2)	14 (48.3)	
Yes	n (%)	25 (33.8)	15 (51.7)	
DM				<.001
No	n (%)	62 (83.8)	6 (20.7)	
Yes	n (%)	12 (16.2)	23 (79.3)	
Treatment protocol				.001
Surgery alone	n (%)	30 (40.5)	4 (13.8)	
Surgery + adjuvant radiotherapy	n (%)	36 (48.6)	12 (41.4)	
Surgery + adjuvant CT	n (%)	1 (1.4)	5 (17.2)	
Surgery + combined radiochemotherapy	n (%)	3 (4.1)	6 (20.6)	
Radiotherapy alone	n (%)	2 (2.7)	1 (3.5)	
CT alone	n (%)	0 (0)	1 (3.5)	
Combined radiochemotherapy	n (%)	2 (2.7)	0 (0)	

N0 (P < .001). Eighty percent of patients with N1 died, whereas 65.5% of patients with N0 survived (P < .001). Patients with N1 showed also a high significance for initial and secondary DM (9 of 10 people with N1, P < .001).

LRM in Clinical Course

Table 1 presents differences between the LRM group and the controls. We found significant differences between both groups concerning the dimensions of the primary tumor, TNM classification, tumor depth, resection status, DM, and treatment protocol.

Kaplan-Meier analysis of DSS showed 3-, 5-, and 10-year survival rates of 32%, 16%, and 11% for the LRM group compared to 81%, 73%, and 69% in the control group (P < .001). Mean DSS with LRM was 36.7 months (95% CI 20.5-52.8, median 17.9), pointing out a high significance (P < .001) compared to DSS without LRM

Table 2. Statistical Details of the Calculated Prediction Models (BLR and CRA) and Its Variables

Included Variable	Significance (*P* Value)	Wald	*df*	Exp(*B*)	95% CI of exp(*B*)
BLR					
Localization	(.061)	3.502	1	2.830	0.952-8.410
EPT	(.074)	3.201	1	2.724	0.909-8.162
AJCC stage	(.063)	10.471	5		
IA *versus* IV	(.999)	0.000	1	0.000	—
IB *versus* IV	(.027)*	4.876	1	0.132	0.022-0.797
IIA *versus* IV	(.003)**	8.941	1	0.052	0.007-0.360
IIB *versus* IV	(.087)	2.924	1	0.278	0.064-1.206
III *versus* IV	(.443)	0.587	1	0.442	0.055-3.568
CRA					
Localization	(.022)*	5.226	1	2.537	1.142-5.636
EPT	(.023)*	5.184	1	2.663	1.146-6.187
AJCC stage	(<.001)***	23.148	5		
IA *versus* IV	(.975)	0.001	1	0.000	—
IB *versus* IV	(.001)**	11.757	1	0.084	0.020-0.347
IIA *versus* IV	(<.001)***	16.566	1	0.032	0.006-0.167
IIB *versus* IV	(.001)**	11.619	1	0.189	0.072-0.492
III *versus* IV	(.167)	1.913	1	0.380	0.096-1.498

Significance, statistical significance. *$P < .05$, **$P < .01$, ***$P < .001$, *df*, degree of freedom. Localization, scalp/neck *versus* face. EPT, extent of primary tumor: one *versus* more than one anatomic region.

[mean DSS 292.4 (95% CI 208.4-376.5, median 245.9)]. Twenty-three of 29 cases with LRM developed DM ($P < .001$).

Multivariate Regression Analyses

BLR (prediction of LRM) and CRA (prediction of LRM time) both proved the prognostic value of all three inserted variables (localization, tumor extent, and AJCC stage), and all three variables were included into the BLR and CRA equation models (Table 2). The BLR model showed good quality with a Nagelkerke's *R*-square (a marker of inclusion and prognosis quality) of 0.400 and accurate classification (predicted *vs* observed LRM, respectively; no LRM) of 83.5% of all patients. A value of exp(*B*) (odds ratio) <1 indicates a reduced risk, whereas values >1 indicate an increased probability. Therefore, localization of cAS-HN at the scalp and/or neck and tumor extent over more than one region increase risk of LRM development and correlate with shorter LRM time. Compared to AJCC stage IV, especially patients with AJCC stages IA, IB, and IIA showed significantly reduced risk for LRM occurrence.

LRM Risk Score and Risk Stratification

The three included parameters in the BLR and CRA were combined to develop a clinically applicable predictive score for LRM risk (LRM risk score; Table 3). The mean LRM score was significantly higher in the LRM group [7.14 (SD 1.46; 95% CI 6.58-7.69)] than in the control group [4.88 (SD 1.89; 95% CI 4.44-5.32); $P < .001$].

Table 3. Design and Algorithm for Calculation of the LRM Risk Score Based on Characteristics of the Primary Tumor (Localization and Extent over Anatomic Regions) and AJCC Stage

Predictive Variable	Assessed Points					Value
	0	1	2	3	4	
Localization		Face	Capillitium and neck			1-2
Tumor extent		One region		More than one region		1, 3
AJCC stage	IA	IIA	IB	IIB	III, IV	0-4
Total						2-9

Table 4. Distribution of LNM Risk Scores with regard to LRM Occurrence and Stratification into LRM Risk Groups

LRM Risk Score	LRM Risk Group	Control Group (*n* = 74)	LRM Group (*n* = 29)
		n (%)	*n* (%)
2	Low	6 (100.0)	–(0.0)
3	Low	18 (94.7)	1 (5.3)
4	Low	10 (100.0)	–(0.0)
Total low risk (*n* = 35)		34 (97.1)	1 (2.9)
5	Medium	9 (75.0)	3 (25.0)
6	Medium	16 (76.2)	5 (23.8)
Total medium risk (*n* = 33)		25 (75.8)	8 (24.2)
7	High	8 (61.5)	5 (38.5)
8	High	5 (31.3)	11 (68.8)
9	High	2 (33.3)	4 (66.7)
Total high risk (*n* = 35)		15 (42.9)	20 (57.1)

Receiver operating characteristic curve analysis revealed an optimum cut-off value of 6.5 to differentiate between patients with or without LRM. Patients with an LRM risk score ≥7 (7-9) were classified as the high-risk group (LRM risk >30%), while those with an LRM score <7 (2-6) showed a lower risk for LRM (area under the curve: 0.819, 95% CI 0.732-0.906). From a clinical point of view, the latter group can be further divided into a low-risk group (LRM risk <10%) and a medium-risk group (LRM risk 10-30%). Table 4 shows distribution of LRM risk score values, the risk stratification, and prevalence of LRM within these subgroups.

Prognostic Value of LRM Risk Stratification

After stratifying the study population according to the LRM risk score into low, medium, and high risks, we found significant differences between these groups concerning time-dependent outcome variables (Table 5). Patients with high LRM risk had a significantly shorter time to DM (DM time; Figure 1), PFS

Table 5. Time to Distant Dissemination (DM Time), PFS Time, and DSS Time with regard to LRM Risk Stratification Based on the LRM Risk Score

	LRM Risk Group		
	Low	Medium	High
Total collective (n = 103)			
DM time (months)			
Mean	377.9	213.6	29.1
Median	—	—	23.2
95% CI	269.7-486.2	145.6-281.5	18.9-39.4
PFS time (months)			
Mean	243.7	134.8	17.5
Median	132.1	16.5	10.9
95% CI	141.3-346.2	70.6-199.1	9.5-25.6
DSS time (months)			
Mean	331.9	198.2	31.3
Median	—	—	23.7
95% CI	222.7-441.2	128.8-267.6	10.7-41.8
Without M1 (n = 90)			
DM time (months)			
Mean	377.9	211.6	40.0
Median	—	—	36.0
95% CI	269.7-486.2	143.4-279.8	27.1-52.9
PFS time (months)			
Mean	243.7	130.5	22.7
Median	132.1	13.3	12.4
95% CI	141.3-346.2	66.7-194.2	11.9-33.5
DSS time (months)			
Mean	331.9	197.4	41.9
Median	—	—	40.7
95% CI	222.7-441.2	128.0-266.9	27.7-56.1

DM time, time to DM.

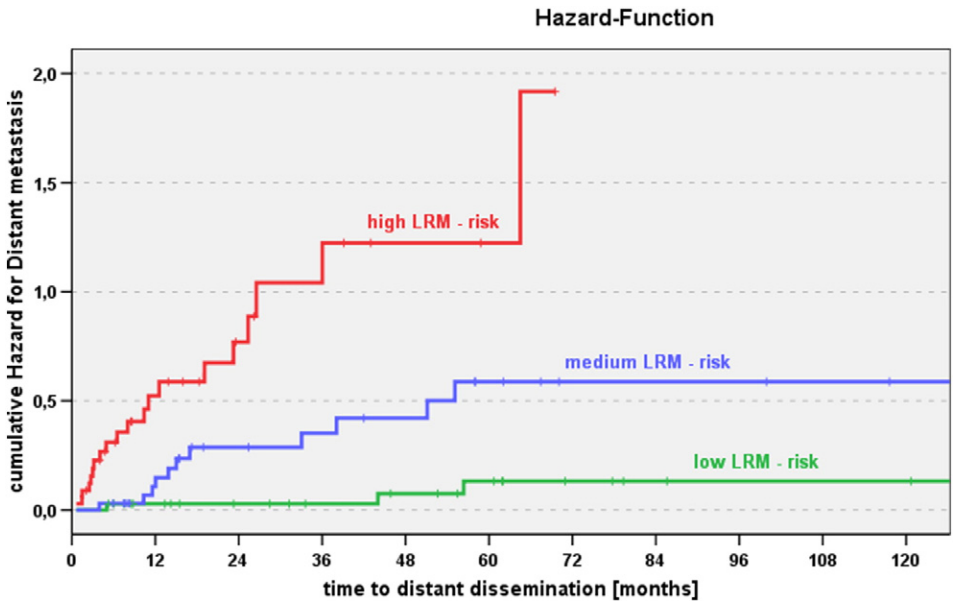

Figure 1. Cumulative hazard function for DM in different LRM risk groups. All group differences were statistically significant (high *vs* low: $P < .001$; high *vs* medium: $P = .003$; medium *vs* low: $P = .013$).

(Figure 2), and more unfavourable DSS (Figure 3). As shown in Table 5, these differences were also assessable in a smaller study sample of $n = 90$ patients after exclusion of patients who initially showed distant dissemination (M1, AJCC stage IV).

Discussion

In cAS-HN, little is known about metastatic spread. There are single case reports and studies that often include AS with origin of other body sites besides head and neck as well with AS due to radiation and lymphatic obstruction. With 103 patients, our retrospective study is the largest monocenter study on spontaneous cAS-HN to date [1,3,6].

Guadagnolo et al. [3] found a significantly reduced DSS for patients with a tumor located at the scalp and >5 cm. This correlates well with our findings concerning LRM. Apparently, tumor depth was a significant risk factor for LRM: 29 cases with a deep tumor (Ib, IIb) lead to LRM, while none of the superficial cAS-HN (in total 23) metastasized. This has not been reported previously in this way, and examining tumor depth can be done easily.

BLR and CRA found three significant parameters to predict LRM: origin and extent of primary tumor together with the AJCC stage. The big advantage of the AJCC staging is that it is a standardized and well-established method that includes multiple factors: size, depth, lymph node involvement, DM, and histologic grading. On the downside, tumor depth is equalized in AJCC because every stage includes superficial and deep tumors. Instead of AJCC, we used its single parameters alone such as tumor depth with BLR and CRA, but

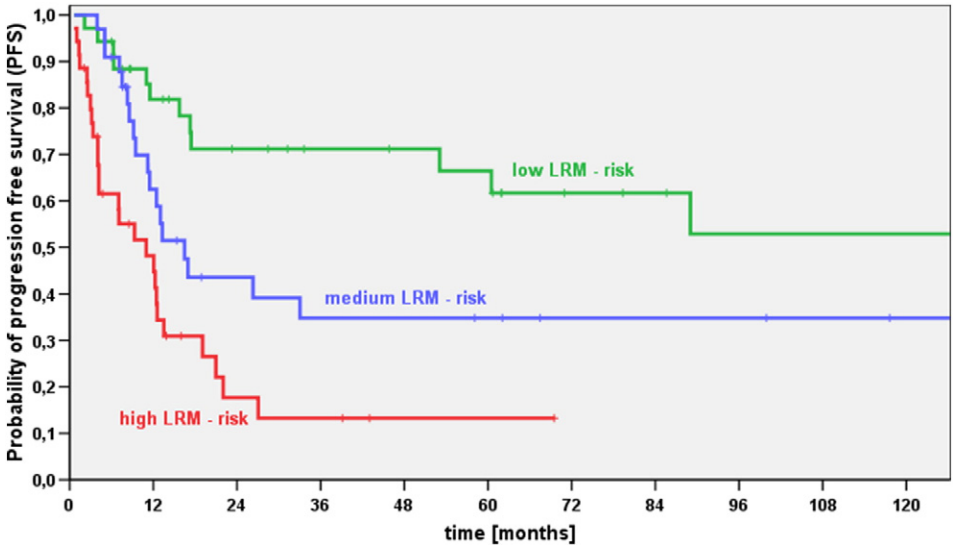

Figure 2. Kaplan-Meier curve for PFS time in different LRM risk groups. Statistically significant unfavorable outcome for the high-risk group (high *vs* low: $P < .001$; high *vs* medium: $P = .015$; medium *vs* low: $P = .056$).

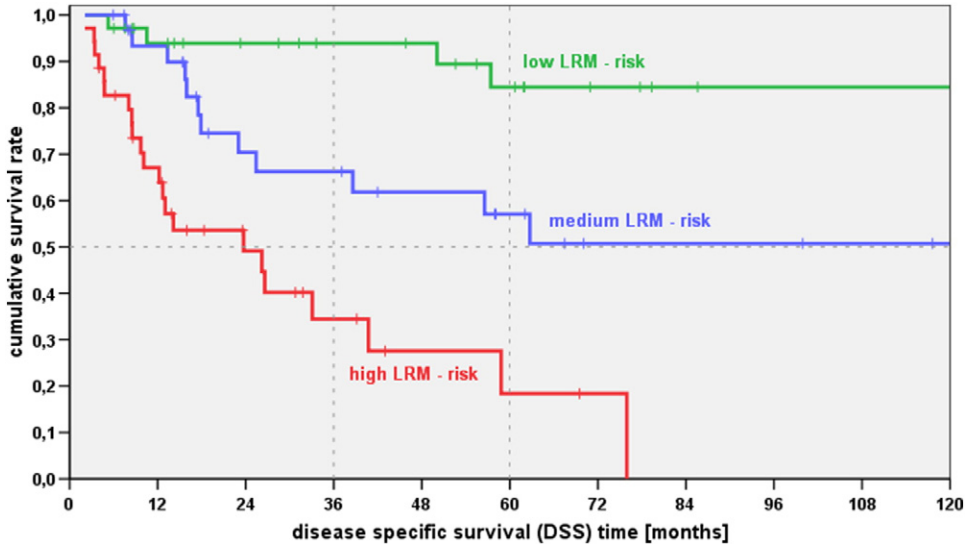

Figure 3. Kaplan-Meier curve for DSS time in different LRM risk groups. All group differences were statistically significant (high *vs* low: $P < .001$; high *vs* medium: $P = .002$; medium *vs* low: $P = .029$).

results of predicting LRM probability did not improve (data not shown). Furthermore, we choose AJCC stage instead of multiple single or further histologic parameters to avoid overmodeling.

With the three stated significant variables, we created an LRM risk score to predict the risk of LRM and its impact on DM, PFS, and DSS. We estimated three different clinical groups concerning LRM risk: low, medium, and high risks, interestingly with almost the same size (low: $n = 35$, medium: $n = 33$, high: $n = 35$). Of the low-risk group, only one person developed LRM, while of medium risk 8 patients (24.2%) and of high risk 20 patients (57.1%) were eventually diagnosed with LRM. As shown in Figures 1 to 3, the low risk group had the best results for DM, PFS, and DSS. After 30 months, e.g., hazard for DM in the high-risk group was twice as high as in the low-risk group. This kind of risk stratification was not reported previously.

There are other similar scores, for example, for metastatic colorectal cancer and prostate cancer risk assessment [12,13]. Although these tumors present total different entities, development and design of these clinical risk scores have a lot in common with our LRM score. Both scores have already proven its prediction values and its simplicity over the last decade [14,15]. This fact illustrates the possible clinical value of such risk scores.

Of course, certain limitations in this study have to be mentioned, including the retrospective design. Our LRM risk prediction score needs to be confirmed and validated internally and externally in an independent data set in further prospective controlled studies. Due to the fact that cAS-HN is a rare disease, our prediction model is only based on a discovery cohort, and a validation cohort is missing. This is a clear shortcoming of our study. Nevertheless, in our opinion, it is important to present our results to facilitate validation of our score by other researchers. Furthermore, the inclusion of patients with follow-up times less than the median time to LRM is a probable error source to the predictive model.

Conclusion

For cAS-HN, no common and consistent guidelines for diagnosis and treatment are available. Our LRM score is a simple and implementable way for the clinician to stage patients and to determine treatment options. With three parameters, the risk for LRM can be estimated and therefore the risk for DM. The medium- and high-risk groups might subsequently profit from neck dissection, local radiotherapy of draining the lymphatic area, or adjuvant CT.

Compared to other scores, it is also very simple to use and may affect the decision of treatment options. Nevertheless, additional validation of the score has to be accomplished. For the future, a coherent classification of cAS-HN patients will be possible, and because of the few numbers of affected patients, data collection of multicenter studies will be simplified. With it, further (prospective) studies especially on treatment can be arranged to find a common treatment strategy for patients with cAS-HN.

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