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Review

Leiomyosarcoma: Prognostic outline of a rare head and neck malignancy

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ABSTRACT

Soft tissue sarcomas (STS) are mesenchymal malignant neoplasms with a broad spectrum of biologic behaviour. Most STS show predilection for extremities with rarity in head and neck. Leiomyosarcoma (LMS) is an extremely rare STS in head and neck due to the paucity of smooth muscles in this anatomical region. Owing to its rarity, diagnosis of LMS is often delayed or is often misdiagnosed. Our study aimed to evaluate clinico-demographic factors determining clinical course of primary head-neck LMS. Further, we also assessed cases of secondary head-neck LMS and LMS due to other causes to compare their clinical outcome with primary head-neck LMS. In primary LMS cases, intraoral LMS showed slightly better prognosis than extraoral LMS. Survival analysis revealed that prognosis of primary LMS was significantly better than secondary LMS. No significant difference in survival was seen between primary LMS and LMS due to other causes. These observations indicate that site of origin appears to determine the clinical behaviour of LMS. Results showed that size, recurrence and metastasis are important prognostic variables. Though large tumor size was associated with poor prognosis, tumor aggressiveness may not be directly proportional to its size. Surgical management with or without adjuvant therapy was associated with favourable outcome. As several factors are associated with prognostic outcome of head-neck LMS, multimodality therapy approach after careful analysis of various prognostic variables in each case on an individual basis is essential.

Introduction

Soft tissue sarcomas (STS) are heterogeneous and aggressive malignant neoplasms comprising of tumors demonstrating broad range of differentiation such as smooth muscle, skeletal muscle, adipocytes, vascular and neural tissues while few cases lack specific differentiation. STS account for more than 10% of pediatric and less than 1% of adult solid malignancies. These tumors usually originate in lower extremities and rarely in head and neck region [1–5]. Their clinical course varies widely owing to several internal (tumor size, histopathological grade, lymphatic or hematogenous dissemination) and external (diagnostic approach, therapeutic effectiveness, patient care) factors [6].

Leiomyosarcoma (LMS) constitutes approximately 7% of all STS. It has been categorized into site-specific subgroups owing to remarkable clinical and biological dissimilarity. LMS most often occur in gastrointestinal tract, uterus and retroperitoneal structures with rarity in head and neck region due to the paucity of smooth muscles [1,4,7]. It is an aggressive tumor that frequently shows recurrence with regional or distant metastasis [8]. Though rare, head-neck is also a site for metastatic spread of primary LMS elsewhere [9–11]. In addition, LMS in head and neck also develops due to other causes. These include LMS associated with previous histologically distinct tumor, late sequelae of cancer therapy, immunodeficiency, and environmental exposure [12–15].

Several treatment modalities such as surgery with or without radio/chemotherapy have been considered for LMS [9,16]. However, its optimal management is still unclear. It is, therefore, essential that head-neck LMS cases are documented and followed up precisely. These intricacies prompted us to study clinico-pathological aspects of head-neck LMS cases reported in last 18 years with a focus on therapeutic modalities and prognosis.

Materials & methods

Data collection

A systematic search of literature on PubMed database was carried to retrieve cases of head-neck LMS reported from January 2000 till February 2018. The key terms used in different combinations (using Boolean logic) were: ('head' OR 'neck' OR 'pharynx' OR 'thyroid' OR 'larynx' OR 'maxillofacial' OR 'oral cavity' 'nasal' OR 'paranasal' OR 'face') AND ('leiomyosarcoma') OR ('second tumor') OR ('secondary

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leiomyosarcoma'). We categorised head-neck LMS into primary head-neck LMS, secondary head-neck LMS and primary LMS due to other cause (LDOC) which included LMS associated or occurring after treatment of an unrelated tumor and LMS in immunocompromised cases.

Clinical and demographic characteristics of all cases (such as age, sex, site metastasis, treatment modality, recurrence) were assessed carefully. Based on site primary head-neck LMS was categorised as intraoral (IO) involving maxilla, mandible, intraoral regions; and extraoral (EO) LMS. Age was categorised into children and young adult (≤25 years), middle aged adult (> 25 to ≤50 years) and old age (> 50 years). Size of the tumor was defined as small (< 2 cm), intermediate (2–4 cm) and large (> 4 cm). Treatment was categorised into surgery with/without neck dissection, radiotherapy and chemotherapy, radiotherapy or chemotherapy, surgery with chemotherapy or radiotherapy and only biopsy or palliative care or no treatment. Metastasis and recurrence were identified as present or absent. Cases were categorised as alive or dead based on follow-up. Reports in which data for a particular variable was not given were labelled as 'missing'.

After careful assessment of the retrieved data, distribution of head-neck LMS was as follows: (a) 189 cases of primary head-neck LMS out of which 79 were IO and 110 were EO; (b) 35 cases of secondary LMS; and (c) 34 cases of LDOC (Fig. 1). Any discrepancy was resolved by mutual consensus of the authors. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed [17].

Statistical analysis

The data was analysed using Statistical software IBM SPSS statistics 20.0 (IBM Corporation, Armonk, NY, USA) and depicted using tables, graphs and charts. P value of less than 0.05 was considered to be statistically significant. In the present study descriptive and inferential statistical analyses were carried out. Chi square test was used to find significance of study parameters on categorical scale. Hazard ratio of death from disease was performed using univariate & multivariate Cox Regression analysis with reference category for each factor. Kaplan-Meier analysis was used to estimate mean survival time.

Results

Demographics

The demographic features are mentioned in Table 1.The mean age at diagnosis of primary IO and EO LMS was 42 and 58 years respectively. The incidence of primary head-neck EO LMS (58%) was slightly more than primary IO LMS (42%). There was no gender based difference in primary IO LMS (male-49.4%, female-50.6%), however primary EO LMS showed slight male proclivity (M-54.5%, F-45.5%). Primary IO LMS was reported approximately 4 times more in children and young adults while primary EO LMS was 1.7 times more common in old age group. Approximately 50% of primary EO LMS and only 29.4% IO LMS were larger than 4 cm in greatest dimension (Table 2). The most common site for primary IO LMS was maxilla (26.5%) followed by mandible (22.8%), palate (13.9%), tongue (12.6%) and buccal mucosa (6.3%). In EO LMS thyroid (19%), larynx (16.2%) and nasal-paranasal area (13.5%) constituted maximum number of cases followed by intracranial (10.8%) and auricular region (5.4%).

Table 1
Demographic details of primary leiomyosarcoma.

Variables	Sub-groups	n	%
Age	1–25	26	13.8
	> 25 to ≤50	62	32.8
	> 50	101	53.4
Gender	Male	99	52.4
	Female	90	47.6
Site	Intraoral	79	41.8
	Extraoral	110	58.2
Size	< 2 cm	26	13.8
	2–4 cm	61	32.3
	> 4 cm	58	30.7
	'Missing'	44	23.3
Treatment	Surgery with/without neck dissection	104	55.0
	Radiotherapy + Chemotherapy	5	2.6
	Radiotherapy or Chemotherapy	1	0.5
	Surgery with chemotherapy or radiotherapy	73	38.6
	Only biopsy/Palliative/No treatment	3	1.6
	'Missing'	3	1.6
Recurrence	Present	34	18.0
	Absent	97	51.3
	'Missing'	58	30.7
Metastasis	Present	45	23.8
	Absent	96	50.8
	'Missing'	48	25.4
Follow up	Dead	52	27.5
	Alive	135	71.4
	'Missing'	2	1.1

The mean age at diagnosis for secondary head-neck LMS was 60.4 years while it was 47.1 years for LDOC. The incidence of secondary head-neck LMS was 2.5 times more common in females and was seen only in middle aged adults (23%) and old age (77%). Out of 35 cases of secondary LMS only 25.7% (9/35case) were reported intraorally while 74.3% (24/35 case) were EO. Further, 66.67% of cases showing IO secondary LMS died due to disease while 54% succumbed to secondary LMS in EO region.

We found that males were two times more likely than females to develop LDOC. It was more prevalent in old age (4.75 times) than young age individuals. More than two-third (72%) of LDOC were reported extraorally while only 28.1% were intraoral.

Univariate and multivariate analysis

To determine the prognostic implication of demographic variables, univariate and multivariate Cox regression analysis was performed. The relative hazard value was high for middle aged adults and old age individuals, female gender, extraoral site, large tumor size, no treatment or only palliative care and radiotherapy and/or chemotherapy, presence of metastasis and recurrent tumor (Table 3).

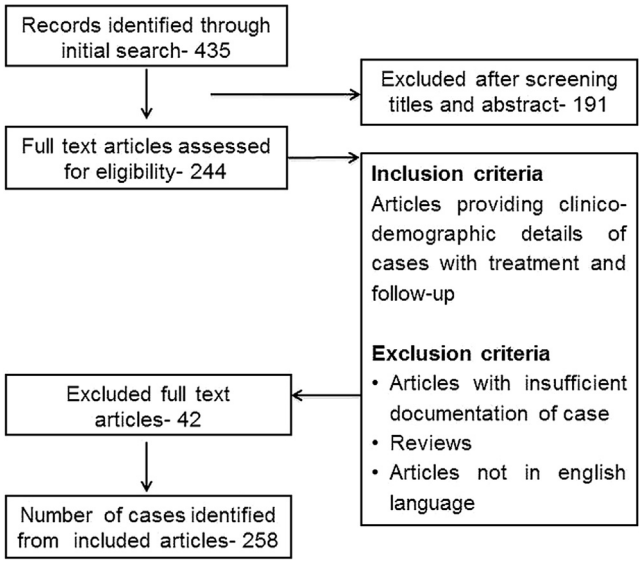

Fig. 1. Flow diagram depicting search strategy and results.

Table 2
Baseline characteristics of primary intraoral and extraoral leiomyosarcoma.

	Primary Intraoral LMS		Primary Extraoral LMS		P value
	No.	%	No.	%	
Age					
1–25	19	73.1	7	26.9	< 0.001*
> 25 to ≤50	30	48.4	32	51.6	
> 50	30	29.7	71	70.3	
Sex					
Male	39	39.4	60	60.6	0.482
Female	40	44.4	50	55.6	
Size (cm)					
< 2	12	46.2	14	53.8	0.027*
2–4	36	59	25	41	
> 4	20	34.5	38	65.5	
Treatment					
Surgery with/without neck dissection	42	40.4	62	59.6	0.792
Radiotherapy + Chemotherapy	3	60	2	40	
Radiotherapy or Chemotherapy	0	0	1	100	
Surgery with chemotherapy or radiotherapy	32	43.8	41	56.2	
Only biopsy/Palliative/No treatment	1	33.3	2	66.7	
Recurrence					
Present	15	44.1	19	55.9	0.663
Absent	47	48.5	50	51.5	
Metastasis					
Present	20	44.4	25	55.6	0.465
Absent	49	51	47	49	
Status					
Dead	21	40.4	31	59.6	0.819
Alive	57	42.2	78	57.8	

Kaplan-Meier analysis

Kaplan-Meier method was used to estimate survival function with respect to clinico-demographic variables (Fig. 2). The Kaplan-Meier estimates revealed lower survival time (94.983 months, 95%CI 67.381–122.584) for old age as compared to children, young adults and middle aged individuals. Based on size of primary LMS, large tumor size (> 4 cm) (49.954 months, 95%CI 37.987–61.921) followed by small tumor (< 2 cm) (79.564 months, 95%CI 40.797–118.331) was associated with decreased survival. Surgical management of LMS with (118.554 months, 95%CI 88.700–148.409) or without (121.883 months, 95%CI 96.275–147.492) chemo/radiotherapy was found to produce the most favourable outcome. Results showed that radiotherapy and/or chemotherapy alone was not effective in primary head-neck LMS (Table 4). Further, absence of recurrence (152.396 months, 95%CI 131.537–173.254) and metastasis (82.170 months, 95%CI 72.095–92.245) was associated with higher survival time as compared to recurrent (57.874 months, 95%CI 25.202–90.547) and metastatic (55.624 months, 95%CI 28.299–82.949) group respectively.

Discussion

LMS accounts for 1–4% of head-neck sarcomas. It originates from smooth muscle or primitive multipotent mesenchymal cells. It is an aggressive malignant neoplasm characterized by complex genetic abnormalities [18]. The present analysis described clinico-demographic details of 258 head-neck LMS cases reported in last 18 years. The occurrence of primary EO LMS was more than primary IO LMS with a highly significant difference between age groups. There was no significant difference in percentage of cases presenting with metastasis or recurrence between primary IO and EO LMS. However, univariate and multivariate Cox regression analysis showed that EO LMS was slightly more aggressive than IO LMS, but the results were not significant. Overall, tumor size, non-surgical management, recurrence and metastasis were indicators of poor outcome.

The results from the current study indicate that survival time in primary head-neck LMS was significantly associated with tumor size and it was least in cases with large tumor (> 4 cm). However, intermediate size tumor (2–4 cm) showed better survival as compared to small tumors (< 2 cm). This is intriguing as larger tumor size is generally related to poor clinical outcome owing to increased incidence of local and distant metastasis [19]. The fact that large tumors are

Table 3
Hazard ratio of death from Primary leiomyosarcoma.

Variable	Univariate			Multivariate		
	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age						
> 25 to ≤50	2.640	0.779–8.951	0.119	2.543	0.746–8.669	0.136
> 50	2.624	0.795–8.659	0.113	2.420	0.714–8.199	0.156
Sex						
Male	0.809	0.461–1.420	0.460	0.805	0.458–1.414	0.450
Site						
Intraoral	0.747	0.417–1.338	0.326	0.744	0.415–1.333	0.320
Size						
2–4 cm	0.564	0.214–1.481	0.245	0.575	0.218–1.520	0.265
> 4 cm	1.479	0.625–3.501	0.374	1.463	0.617–3.468	0.388
Treatment						
Radiotherapy + Chemotherapy	4.772	1.596–14.266	0.005*	4.679	1.535–14.262	0.007*
Radiotherapy or Chemotherapy	21.714	2.710–174.014	0.004*	21.157	2.595–172.510	0.004*
Surgery with chemotherapy or radiotherapy	1.484	0.796–2.768	0.215	1.481	0.793–2.763	0.218
Only biopsy / Palliative / No treatment	65.096	14.762–287.056	< 0.001**	63.746	14.237–285.420	< 0.001**
Recurrence						
Present	8.264	3.457–19.754	< 0.001**	8.403	3.493–20.217	< 0.001**
Metastasis						
Present	9.728	4.408–21.469	< 0.001**	9.473	4.285–20.942	< 0.001**

* $p < 0.05$ – Significant
** $p < 0.001$ – Highly significant.

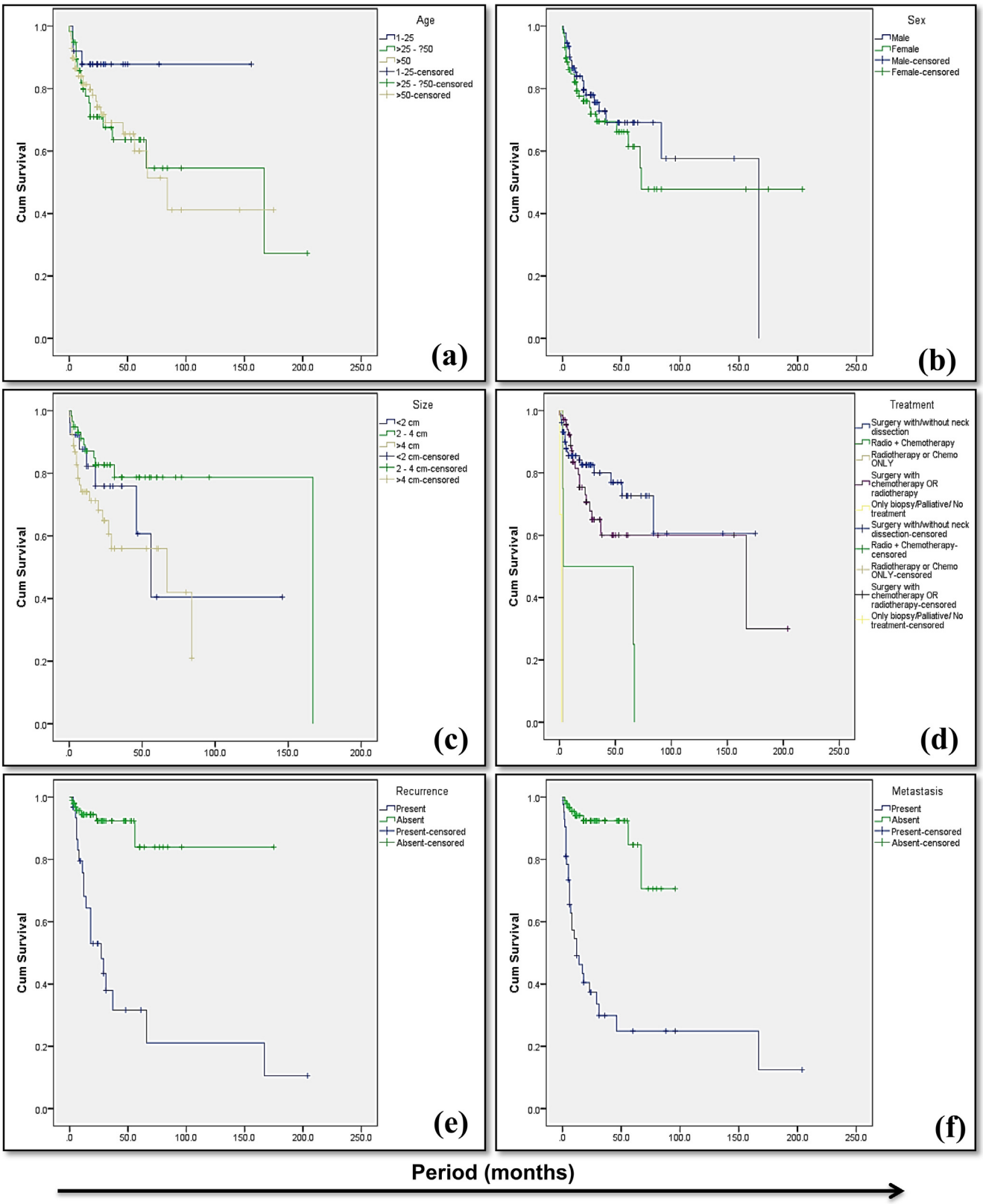

Fig. 2. Kaplan-Meier plots for survival of cases with primary head-neck leiomyosarcoma.

generally treated aggressively by clinicians may explain this finding. But this holds true up to a point where increasing size of sarcoma becomes an independent prognostic factor [19–23]. We found in our analysis that the mainstay of treatment in small size LMS was surgical excision without chemotherapy or radiotherapy (77% cases) while in only 15% cases adjuvant treatment was given. However, in cases with intermediate tumor size approximately 38% were given chemotherapy or radiotherapy along with surgery, while 60.6% cases underwent only surgical management. Further, in cases with large tumor size approximately 50% cases received adjuvant therapy and 38.5% were treated

Table 4
Mean survival time in patients with primary LMS using Kaplan-Meier analysis.

	Estimate (months)	95% Confidence Interval		P value
		Lower Bound	Upper Bound	
Age				
1–25	137.716	118.315	157.118	0.239
> 25 to ≤50	112.397	79.488	145.306	
> 50	94.983	67.381	122.584	
Overall	114.877	91.097	138.657	
Sex				
Male	110.801	86.471	135.131	0.457
Female	113.964	82.913	145.015	
Overall	114.877	91.097	138.657	
Site				
Intraoral	116.544	93.439	139.650	0.322
Extraoral	110.921	80.531	141.310	
Overall	114.877	91.097	138.657	
Size				
< 2 cm	79.564	40.797	118.331	0.036*
2–4 cm	134.278	114.619	153.938	
> 4 cm	49.954	37.987	61.921	
Overall	95.895	71.830	119.960	
Treatment				
Surgery with/without neck dissection	121.883	96.275	147.492	< 0.001*
Radiotherapy + Chemotherapy	34.875	0.000	70.665	
Radiotherapy or Chemotherapy	3.000	3.000	3.000	
Surgery with chemotherapy or radiotherapy	118.554	88.700	148.409	
Only biopsy/Palliative/No treatment	1.443	0.352	2.534	
Overall	115.334	91.458	139.209	
Recurrence				
Present	57.874	25.202	90.547	< 0.001*
Absent	152.396	131.537	173.254	
Overall	128.083	99.353	156.812	
Metastasis				
Present	55.624	28.299	82.949	< 0.001*
Absent	82.170	72.095	92.245	
Overall	117.775	90.982	144.569	

Table 5
Mean survival time in patients with secondary LMS and LDOC compared to primary LMS using Kaplan-Meier analysis.

	Estimate (months)	95% Confidence Interval		P value
		Lower Bound	Upper Bound	
Site				
A.				
Primary intraoral LMS	116.544	93.439	139.650	< 0.001**
Primary extraoral LMS	110.921	80.531	141.310	
Secondary LMS	32.373	20.171	44.575	
Overall	100.583	78.818	122.349	
B.				
Primary intraoral LMS	116.544	93.439	139.650	0.561
Primary extraoral LMS	110.921	80.531	141.310	
LDOC	63.840	44.046	83.634	
Overall	114.626	92.267	136.985	

only surgically. This implies that additional treatment in intermediate size primary LMS could be the reason for better tumor control and survival as compared to small size LMS. Though, on the other hand adjuvant treatment was not found to be very effective in large size LMS indicating that increased tumor size negatively influence survival.

There are several reports in literature [24–28] which mentions that adjuvant radiotherapy and/or chemotherapy is favorable in LMS. This is particularly true for sarcomas with high risk of distant metastasis [26,29,30] and recurrence [25,26,29,30] and in cases where anatomical location of tumor restricts surgical intervention [25,28]. Moreover, with reduced survival time in small size LMS one can presume distinct genetic alterations in clinically low risk primary LMS cases [31]. This assumption has essential clinical and prognostic implication as based on size it is not possible decisively to prove the aggressive nature of LMS without long term follow-up. Thus irrespective of size adjunctive therapy must be considered in the therapeutic management of primary head-neck LMS.

The most common metastatic sites for non-head and neck primary LMS are lung, brain and bone [10–12]. Head-neck region is an extremely rare site for metastatic LMS and carries a dismal prognosis. As secondary LMS in head-neck region is exceedingly uncommon, they are often misdiagnosed [10,11]. We analysed 35 cases of secondary head-neck LMS of which approximately two-third originated from uterus and retroperitoneum. Survival analysis results (Table 5) showed that secondary head-neck LMS was associated with significant poor prognosis ($p < 0.001$) compared to primary head-neck LMS. On the other hand, in cases with LDOC though the survival time was less as compared to primary LMS, the results were not significant ($p > 0.05$). These findings raise the intriguing possibility that site of origin may be a significant factor in determining biological characteristic and behaviour of LMS [7]. Though several authors have argued over anatomical variant of LMS, whether site of origin influences its biological behaviour remains inconclusive [32–34]. Furthermore, probing at molecular level Italiano et al. [35] and others [18,36] have identified distinct subtypes of LMS with dissimilar clinical outcome. It is, therefore, not surprising that clinically indolent cases may be biologically aggressive. These complexities may pose significant management challenges.

The results of this analysis emphasizes on two clinically and prognostically relevant aspects in head-neck LMS. Firstly, aggressiveness of primary head-neck LMS may not be directly proportional to tumor size and therefore, adjuvant therapy irrespective of tumor size would ensure reduced morbimortality. Secondly, clinical behaviour of LMS depends on site of origin and as site of origin is an important prognostic factor it is necessary to recognize cases of secondary head-neck LMS for early therapeutic intervention.

The major limitation of this analysis is limited follow-up and lack of detailed and well described report of LMS cases. Also the scarcity of LMS cases in each group reduced the statistical strength to distinguish small differences, if any. Due to these limitations our results should be interpreted with caution. Nonetheless, to the best of our knowledge this is the first report to describe primary head-neck LMS with secondary LMS and LDOC for better assessment of clinical behaviour and prognostic factors influencing survival.

Conclusion

Despite limitations several trends have emerged in head-neck LMS. LMS may represent distinct disease processes based on anatomical site of origin. Treatment mode, tumor recurrence and metastasis are important determinant of clinical outcome. In addition, though the prognosis appears to be independent of tumor size, large tumor size is particularly associated with unfavourable outcome. These intricacies in head-neck LMS recommend multimodality therapy approach after careful analysis of various prognostic variables in each case on an individual basis. The rarity of LMS in head-neck region warrants further studies to characterize this disease.

Declaration of Competing Interest

None declared.

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None.

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