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Laryngeal soft tissue sarcoma: A systematic review and individual patient data analysis of 300 cases

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Abstract

Background: Laryngeal sarcoma is rare. We performed a systematic review and individual patient analysis to evaluate the patterns of care, prognostic factors, and role of radiotherapy in laryngeal soft tissue sarcoma.

Methods: A systematic search on PubMed and Google scholar was done. An individual patient data analysis was done.

Results: Of the 300 cases of laryngeal sarcoma, 80% underwent surgery. 44% underwent larynx preservation surgery and 25% received radiotherapy with surgery. Median progression free survival (PFS) was 48 months and overall survival (OS) of 224 months for the entire cohort. Patients with large primary, cartilage invasion, and positive margins had numerically worse PFS. Cartilage invasion and primary tumor size >3 cm were the most common risk factors for adjuvant radiation therapy. Patients receiving radiotherapy were not associated with better survival.

Conclusion: Laryngeal sarcoma associated with a good survival. Larynx preservation surgery is feasible in nearly half patients. Adjuvant radiotherapy may be warranted in patients poor prognostic factors.

KEYWORDS

larynx, patterns of care, radiotherapy, sarcoma

1 | INTRODUCTION

Head and neck is an unusual site for soft tissue sarcoma and accounts for less than 10% of all sarcomas.[1,2] Laryngeal soft tissue sarcoma (LSTS) is quite rare and accounts for less than 1% of laryngeal tumors.[1,3] Owing to rarity, information on histology, clinical features, and treatment options are sparse. Management of laryngeal sarcoma poses unique challenge for all relevant specialities. Respiratory distress or stridor being the commonest presentation, many patients require emergency tracheostomy and unplanned surgery. Unlike other sites of soft tissue sarcoma, obtaining adequate surgical margins in larynx often requires total laryngectomy and thus complete functional loss. This unfortunately goes against the standard practice in soft tissue sarcoma of organ preservation surgery followed by adjuvant radiation. In patients who undergo organ preservation surgery, role of adjuvant radiation and chemotherapy is also inconclusive in laryngeal sarcoma. There is also limited information on patterns of recurrence. Present systematic review and individual patient data analysis are aimed at identifying patterns of care, comparing effect of organ preservation surgery versus total laryngectomy and effect of adjuvant therapy on survival and recurrence patterns.

1.1 | Methodology

A comprehensive search of PubMed and Google scholar with the following MesHand text terms "larynx sarcoma, laryngeal sarcoma, larynx non-epithelial tumor, larynx AND sarcoma, laryngeal AND sarcoma" was done independently to retrieve all possible publications in laryngeal sarcoma by authors AR and YI. The search engines were screened till September 2020. Search result was restricted to articles published in English language and related to human studies only. After collecting patient data with laryngeal sarcoma from systematic search, duplicate entries were removed by mutual discussion. After the initial search, the abstracts were read, and relevant publications were sorted for extraction of data. Individual patient information was retrieved from full papers of case reports and case series. Abstracts were used to obtain information and corresponding authors were communicated by email to retrieve information, wherever full paper could not be retrieved. References in articles were cross-checked not to miss any article in our search process. Individual patient data were entered in a pre-designed excel sheet. PRISMA flow chart depicts data synthesis from the eligible studies (see supporting information). Categorical variables were summarized by frequency and percentage and quantitative variables by the median and range. Overall survival (OS) was calculated from the date of diagnosis to the date of documented death respectively. Statistical analyzes were done using the MedCalc version 19.2.6 software. Univariate analysis was done using the log-rank test and multivariate analysis done using the Cox-regression analysis. A p-value of <0.05 was considered significant.

2 | RESULTS

2.1 | Patient demography and treatment details

Non-rhabdomyosarcoma non-Ewing's laryngeal sarcoma (NRNELSTS) constituted 81% (n = 300) of all LSTS (n = 372). Median age of presentation was 53 years (range: 2 months–87 years). There was a clear male preponderance seen in NRNELSTS (male to female ratio of 4:1). Most common presentation was hoarseness seen in 44% of patients and16% patients presented with respiratory distress or stridor (Table 1). Median symptom duration was 4 months (range: 2 days–72 months). Smoking history was present in only 5% patients (n = 15). Supraglottis (n = 116) was the commonest location of tumor followed by glottis (n = 96). Cartilage invasion at presentation was documented in 13 (4.3%) patients only. Three (1%) patients presented with metastatic disease. Commonest histology was synovial sarcoma (n = 64) followed

TABLE 1 Demographic and treatment features of laryngeal sarcoma

Demographic features	No. of patient (n)	Percentage (%)
Laryngeal soft tissue sarcoma (LSTS)		
Non-rhabdomyosarcoma non-Ewing's laryngeal sarcoma (NRNELSTS)	300	81
Ewing's /rhabdomyosarcoma	72	19
Sex (n = 300)		
Males	222	73.6
Females	53	18
Not described	25	8.3
Presenting complaints (n = 300)		
Hoarseness	130	44
Stridor/respiratory distress	46	16
Dysphagia	20	6.7
Swelling/mass	7	2
Others	23	7
Unknown	74	20
Sub-sites (n = 300)		
Supra-glottis	116	39.6
Glottis	96	33
Sub-glottis	15	5
Larynx-NOS	50	15
Not described	29	7
Histology		
Synovial sarcoma	64	22.7
Leiomyosarcoma	57	19.7
Fibrosarcoma	49	16
Liposarcoma	46	14.7
Surgery (n = 300)		
Yes	240	80
No	28	9
Not described	32	11
Extent of surgery (n = 240)		
Radical	135	56
Conservative	105	44
Radiotherapy		
Radical	12	
PORT	68/240	27
PORT following		
Radical surgery	38/135	28
Conservative surgery	26/105	25

by leiomyosarcoma ($n = 57$) and fibrosarcoma ($n = 49$) (Figure 1). A total of 240 (80%) patients underwent surgery for treatment of NRNELSTS while 28 (9%) patients did not undergo surgery. 105 (44%) patients underwent larynx preservation surgery while 135 (56%) patients underwent total laryngectomy. Positive or close margins were found in six patients. Adequate information on treatment was not available in 11% patients. Twenty-six (25%) patients who underwent larynx preservation surgery received adjuvant radiation while 38 (28%) patients who underwent total laryngectomy received adjuvant radiation. Median dose of adjuvant radiation was 60 Gy (range: 33.5–75 Gy). Twelve (44%) of 27 patients, who did not undergo surgery, were treated with radiation. The median dose of definitive radiotherapy was 60 Gy (Range: 19.3–76.5 Gy). Adjuvant chemotherapy was given in five patients while neo-adjuvant chemotherapy was used for one patient. Demographic and treatment details are summarized in Table 1.

2.2 | Survival analysis

Median progression free survival (PFS) of entire cohort was 48 months (95% CI: 29–84 months). Median overall survival (OS) was 224 months (95% CI: 224–396 months) for the entire cohort (Figure 2).

2.3 | Prognostic factors

On univariate analysis histology, size ≥3 cm, cartilage invasion, and positive margin were associated with numerically worse PFS. Median PFS for patients with cartilage invasion was 16 months versus 36 months for patients with no cartilage involvement ($p = 0.646$). Location of primary was not found to be a prognostic factor (Table 2).

2.4 | Effect of radiationand type of surgery on progression free survival and overall survival

There was no difference in PFS or OS based on type of surgery, that is, conservative versus radical surgery on univariate analysis (Figure 3). There was no difference in OS or PFS on addition of radiotherapy to surgery (Table 2) (Figure 4). But chi-squared test showed higher proportion of patients with above prognostic factors received radiation (Table 3). Multivariate analysis failed due to lack of events.

2.5 | Recurrence patterns in laryngeal sarcoma

A total of 67 (23%) patients experienced documented recurrence. Local or loco-regional recurrence was seen in

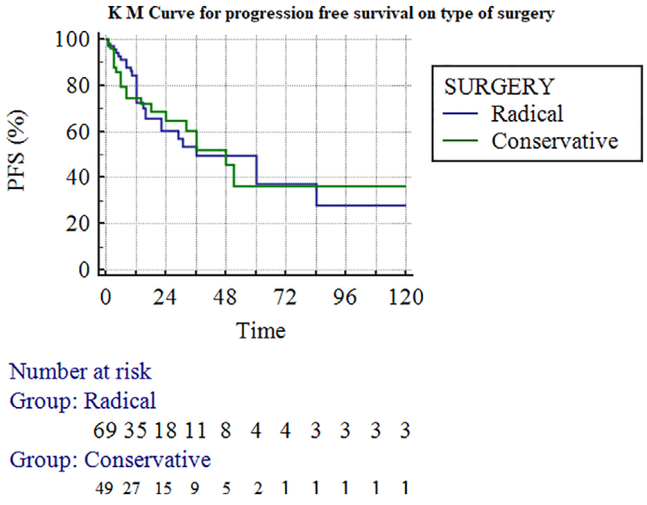

FIGURE 2 Kaplan Meier curve comparing progression free survival between radical and conservative surgery [Color figure can be viewed at wileyonlinelibrary.com]

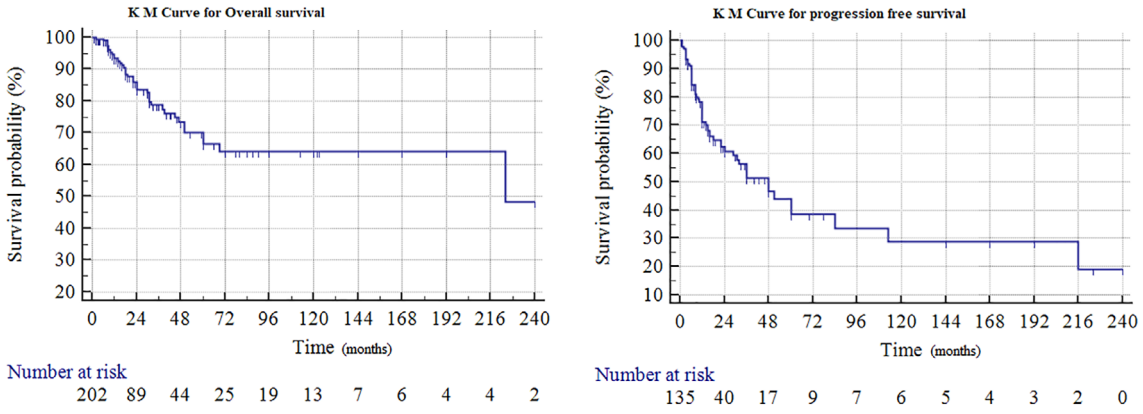

FIGURE 1 Kaplan Meier curve representing overall and progression free survival of entire cohort [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Univariate analysis of prognostic and treatment factors on survival

Factors	Median PFS (months)	95% CI (months)	*p*-value	Median OS (months)	95% CI (months)	*p*-value	Remarks
Histology							
Fibrosarcoma	22	10.5–22		50	38–224		Fibrosarcoma worse OS than leiomyosarcoma or synovial sarcoma
Leiomyosarcoma	24	8–24	$p = 0.563$	Not reached		$p = 0.045$	
Synovial sarcoma	36	12–51		Not reached			
Cartilage invasion							
Yes	16	4–113	$p = 0.646$	Not reached		$p = 0.484$	Cartilage invasion associated with numerically worse PFS
No	36	16–36		50	10–50		
Margin status							
Negative	Not reached		$p = 0.286$	69	32–69	$p = 0.618$	Positive margins associated with numerically worse OS
Positive	36	6–36		24	24–24		
Size							
<3 cm	Not reached		$p = 0.153$	Not reached		$p = 0.558$	
>3 cm	29	16–32		39	30–39		
Conservative surgery							
No RT	Not reached		$p = 0.220$	Not reached		$p = 0.767$	
RT	36	14–51		Not reached			
Radical surgery							
No RT	29	15–60	$p = 0.955$	Not reached		$p = 0.716$	
RT	36	16–60		Not reached			

36 patients while distant metastases occurred in only 20 patients. Overall median time of recurrence was 12 months (range 1–216 months). Median time for local and distant recurrence was similar (12 months). Commonest site of distant failure was lung ($n = 14$) followed by bone ($n = 6$). For 27 (75%) of 36 patients of locoregional failure, salvage surgery was attempted.

3 | DISCUSSION

Sarcomas (non-RMS, non-Ewing's) are commonly found to arise from the extremities. Malignant tumors, which arise from head and neck, are usually of epithelial origin and squamous cell carcinoma (SCC) is the most common histology.[4,5]Sarcomas make a very small fraction of head and neck tumors. As laryngeal sarcoma is less common, its behavior, optimum treatment, and outcome remain elusive and merits to be looked in. As we embarked on the systematic review and individual patient data analysis, we found only a handful of cases (372 cases) of laryngeal sarcoma. Point should be made that nearly 80% of laryngeal sarcomas are non-rhabdomyosarcoma non-Ewing's. We restricted our further analysis to NRNELSTS as treatment and prognosis vary considerably in Ewing's sarcoma and rhabdomyosarcoma. The present analysis clearly highlights that LSTS present in the sixth decade of life with hoarseness (44%), which is quite like the presentation of SCC of larynx.[5] Age of presentation in our study is like that found in a SEER database analysis where in

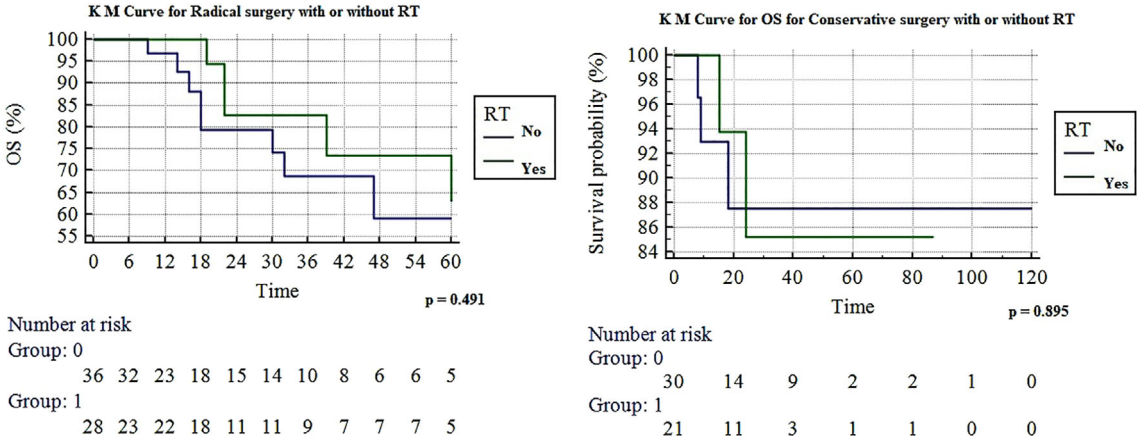

FIGURE 3 Kaplan Meier curve comparing overall survival after radiotherapy with radical and conservative surgery [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 4 Graphical representation of distribution of laryngeal sarcoma histology [Color figure can be viewed at wileyonlinelibrary.com]

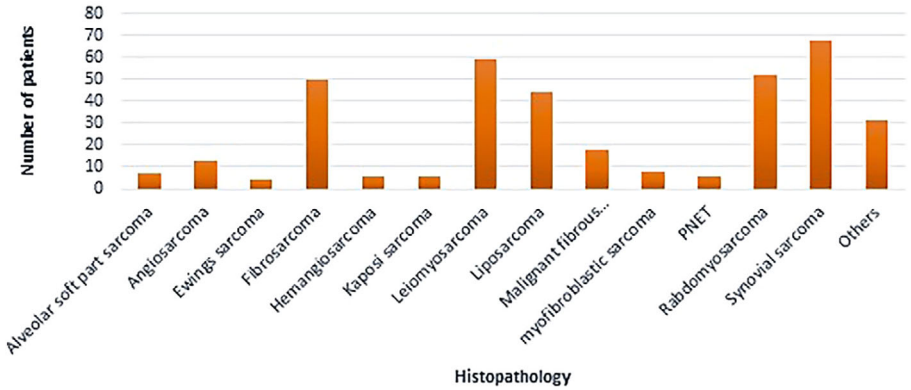

TABLE 3 Chi-squared test to assess selection bias of patients for radiotherapy (RT)

Prognostic factors	No RT	RT given	*p*-value
Cartilage invasion			
No	3	7	$p = 0.2043$
Yes	10	9	
Margin			
Negative	16	13	$p = 0.1188$
Positive	1	4	
Size			
< 3 cm	18	8	$p = 0.0096$
>3 cm	9	18	

>75% patients presented between 50 and 80 years of age.[6] Stridor was the presenting complaint in 16% cases and another 6% presented with dysphagia, but presentation with a lymph node was quite rare seen in <5% cases. Contradictory to our finding, the SEER database analysis found >80% patients presenting with lymph nodes. One possible reason could be a higher percentage of carcinosarcoma in the SEER database analysis and different distribution of various histologies between the two studies. Other possible reason could be reporting bias in various case reports and series in our study. Male patients were affected four times more commonly than females in the present study, which closely corroborates with SEER data as well as in large single institutional series of laryngeal sarcoma[6-8] Only 5% cases had history of smoking in our analysis. Hence, it appears reasonable to consider a differential of LSTS whenever a non-smoker is being evaluated for hoarseness without any palpable neck node and a lesion is found in the larynx. The present analysis also highlights that these tumors arise equally from supra glottis larynx or glottic larynx and 13 patients had documented cartilage invasion. Hence, it appears important to include MRI of the neck to diagnose the extension of the disease. The most common site of metastases appears to be lung followed by bone. Therefore, CT chest in the initial work up may be warranted and clinicians must have in mind the chance of bone metastases during follow up. The dictum in recent years for laryngeal cancers has

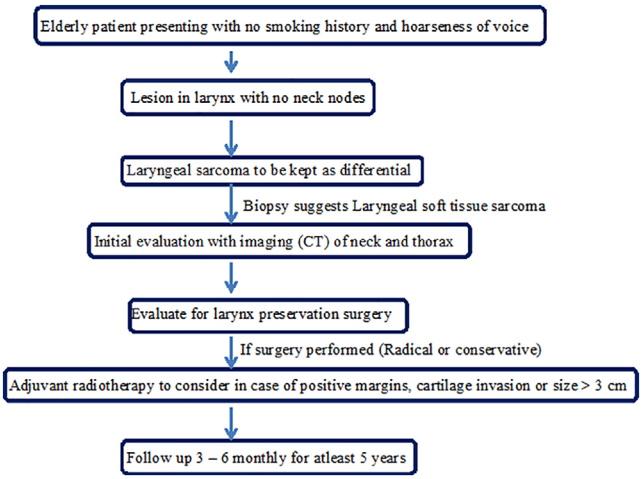

FIGURE 5 Evaluation and management algorithm laryngeal soft tissue sarcoma [Color figure can be viewed at wileyonlinelibrary.com]

been to attempt functional preservation with conservative surgery or radiotherapy. However, such approach may not be suitable for sarcoma. Surgery forms the cornerstone of therapy in LSTS as the analysis found surgical resection rate of nearly 80%. The most important highlight is that even in such rare disease nearly 44% patients underwent a larynx preservation surgery without excess R1 resection. Conservative surgical approach may also be further supported as PFS was no different compared to those of radical approach. This finding is further supported by similar findings from the SEER database analysis.[6] This may be attributed to early development of symptoms and early diagnosis unlike extremity STS. Adjuvant radiation, for extremity STS, is often advocated for high grade, deep seated and larger tumors. In the present analysis, nearly 25% patients from both conservative surgery group and laryngectomy group received adjuvant radiation to a dose of 60 Gy. On analysis of impact of adjuvant radiation on survival outcome, we found no improvement in log rank test. However, in chi-square analysis significantly higher number of patients with larger (>3 cm) tumor received adjuvant radiation, which appears to have equated survival outcome of poor risk patients with that of good risk patients and this may be considered a positive effect of adjuvant radiation. Point should also be made that nearly 50% of evaluable patients experienced local or loco-regional recurrence within 12 months and this may call for consolidation of therapy. With tumor growth in size, erosion of cartilage happens, which confers poor prognosis that appeared in the present analysis as well as patients with cartilage invasion had relatively poorer PFS (16 vs. 36 months) compared to those without cartilage erosion. However, this could not reach statistical significance because of small sample size. We also attempted to investigate the impact of histology on the outcome different prognostic variables.

Present analysis also reveals that the patients have a favorable prognosis as median PFS and OS for the entire cohort was 48 months and 224 months, though median time to local or distant metastasis is 12 months only. This also suggests that the patients merit careful regular follow-up at three monthly intervals for at least 2 years and six monthly thereafter with clinical examination. As the patients predominantly fail in lung or bone a periodic x-ray evaluation of the chest every six months may be considered. The proposed management algorithm is described in Figure 5.

This IPD clearly highlights that LSTS is a rare disease with favorable survival. These tumors present early unlike other STS and are amenable for conservative surgery also, which allows for voice preservation in many cases. Efficacy of adjuvant radiation may be limited to cases with adverse pathological factors or in patient with conservative surgery. However, point should be made that even in STS adjuvant radiation improves local disease control without much impact on survival. The present analysis is not free from limitations. Being a retrospective individual patient data analysis, it attracts all possible criticisms inherent to retrospective analysis. In addition, there are missing data for different variables, which make interpretation difficult. However, it is impossible to have large and prospective data in rare diseases. Therefore, the present analysis aims to give a broad idea about such a rare disease and may guide to reach a meaningful conclusion about management of such patients.

4 | CONCLUSION

LSTS is a rare disease with favorable survival. These tumors present early unlike other STS and are amenable for conservative surgery also, which allows for voice preservation in many cases. Adjuvant radiation may be considered for patients with high-risk factors to a dose of 60 Gy.

CONFLICT OF INTEREST

The authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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