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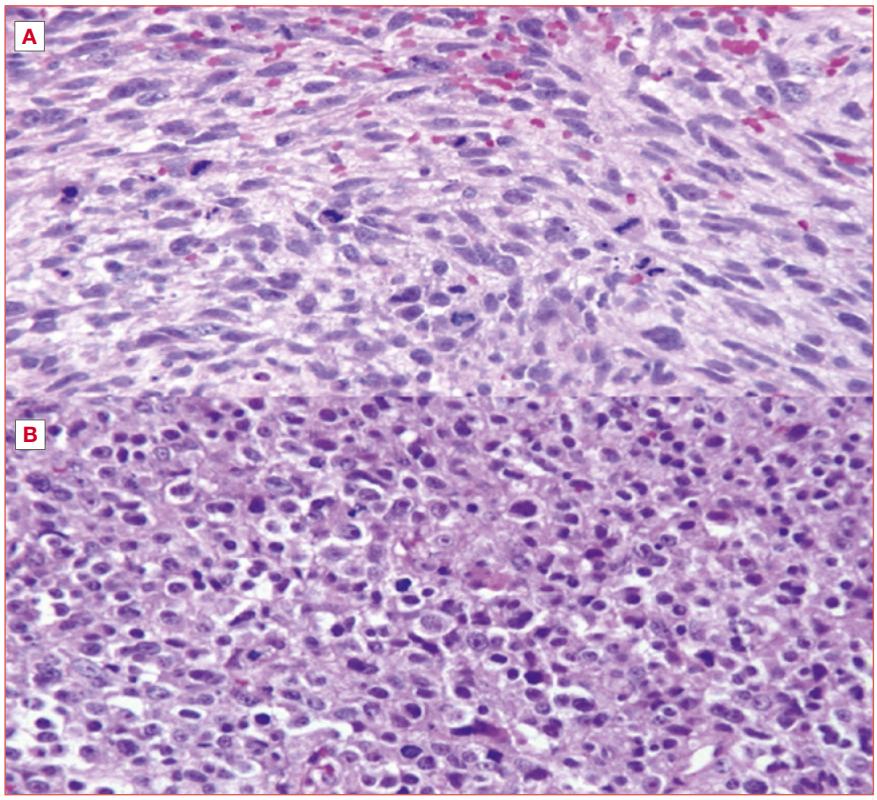
Regional and distant metastases from laryngeal chondrosarcoma: a systematic review



Cover figure. A-B) Histological images in haematoxylin and eosin of dedifferentiated laryngeal chondrosarcoma (courtesy of Dr. Lester D.R. Thompson, USA).

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This paper was written by members and invitees of the International Head and Neck Scientific Group (IHNSG)

Summary

Objective. Laryngeal chondrosarcomas (LCS) are rare malignancies, constituting approximately 0.5% of all primary laryngeal tumours. These predominantly slow-growing, low-grade tumors can sometimes exhibit a more aggressive clinical course with higher rates of local recurrence and possible regional and/or distant metastases. The true occurrence of metastatic LCS is not well defined in the literature due to limited and scattered data. This systematic review aims to analyse the metastatic behaviour of LCS, focusing on patterns of spread, therapeutic options, and clinical outcomes.

Methods. A systematic review was conducted according to the PRISMA guidelines searching on PubMed, Web of Science, and Scopus databases. Studies included cases of LCS with regional and/or distant metastasis.

Results. A total of 44 articles describing 53 cases of metastatic LCS were included. The mean age of patients was 63.5 years. Aggressive subtypes of LCS (high grade, dedifferentiated, and myxoid variants) accounted for 54.3% of metastatic cases. Distant metastases were observed in 71.7% of patients, with lungs being the most common site. Regional lymph nodes involvement was documented in 37.7% of cases. Surgery was the primary treatment, with total laryngectomy being the

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most common approach. Radiotherapy was administered as adjuvant treatment in 24.5% of patients. At last follow-up, 49% of patients had died from the disease, and 9.4% had persistent disease.
Conclusions. Although LCS is typically indolent, patients with metastatic disease present significant clinical challenges. The true metastatic rate remains uncertain due to the scattered distribution of data. Aggressive subtypes of LCS exhibit a greater propensity for metastasis, underscoring the need for closer surveillance and individualised treatment strategies.

Key words: chondrosarcoma, larynx, metastases, lymph nodes

Introduction

Laryngeal chondrosarcomas (LCS) are rare tumours accounting for about 0.5% of all laryngeal primary tumours, even though they represent the most frequent non-epithelial malignancy of this organ [1]. These tumours predominantly affect the cricoid cartilage and are more commonly observed in patients between the age of 50 and 70 years, but may also occur in younger subjects [2]. Treatment is mainly based on laryngeal-sparing surgical excision, which can be achieved endoscopically via transoral laser microsurgery (TLM) or by a number of open-neck conservative techniques, reserving upfront total laryngectomy (TL) to quite advanced, recurrent, or aggressive lesions, affecting older patients who are no more amenable of organ preservation strategies [3-8]. Chemotherapy (CHT) and radiotherapy (RT) are not recommended as upfront treatments [9], although successful definitive proton therapy has been recently reported [10].
Generally, LCS are slow-growing tumours with relatively low malignant potential. However, high-grade (G3), dedifferentiated (DD), and myxoid (MY) LCS are considered more aggressive subtypes due to their higher rates of local recurrence, distant metastases (DM), and relatively poor prognosis [8] (Cover figure). Metastases from LCS have been described in the literature in up to 10% of cases, although some studies reported a lower incidence of 1.9% [1]. Metastatic patterns of LCS are typically haematogenous with lung and bone being the most prevalent metastatic sites. Considering the cervical lymph nodes, regional metastases are rare, and neck dissection must be reserved for cases in which diagnostic imaging suggests clinical lymph node(s) involvement [11].
Limited and scattered data, mostly in form of case reports, regarding metastatic LCS are available in the literature. The aim of this review is therefore to provide a comprehensive analysis of the metastatic behaviour of LCS, with a focus on its patterns of spread, therapeutic options, and clinical outcomes.

Materials and methods

Search strategy

This systematic review was conducted following the guidelines outlined in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist and statement [12]. A thorough literature search was performed across PubMed, Web of Science, and Scopus in February 2025 using the query: "(Chondrosarcoma or chondrosarcomas or chondrosarcomatoid or sarcoma or sarcomas) and (larynx or laryngeal) and (metastasis or lymph nodes or lymph node or node or nodes or lymphatic or metastatic or neck metastasis or regional metastasis or neck or distant metastasis)".

Selection criteria

Original research articles in English and Italian, published until February 2025 that reported cases of LCS with regional involvement and/or DM at diagnosis or during follow-up were included. Studies were excluded if they involved non-human subjects, or lacked specific data from composite series or were reviews or articles without full-text availability. Two independent researchers (CM and AF) screened all titles, reviewed abstracts, and excluded studies that did not meet the inclusion criteria. Full-text articles were then assessed to determine their eligibility based on the predefined criteria. In cases of disagreement, a third investigator (CP) acted as a mediator to reach a consensus. Additionally, references of all selected articles were examined to identify further relevant studies.

Data extraction

The data extracted from each included study comprised the authors' names, year of publication, journal, as well as number of cases, and gender and age of patients at presentation. Additionally, we gathered information on tumour characteristics (site of origin and histologic subtype), presence and site of regional and/or distant spread at diagnosis or during follow-up, therapeutic approach, length of follow-up, and status at the last control. Two authors (CM and AF) independently reviewed and extracted data from the selected articles, compiling the information into a dedicated Microsoft Excel database. This article is based on previously published research and does not involve any new studies with human participants or animals conducted by the authors.

Results

General findings

The initial search returned 4,581 articles. All details about

identification, screening, and inclusion/exclusion criteria are reported in Figure 1. A total of 44 articles [1,5,11,13-53], case reports and case series, were selected. In total, 53 patients with metastatic LCS were included in the present systematic review.

Demographics and tumour characteristics

Demographics were stated for almost all patients, except for 15 cases [5,14,24,34,42,46,47,50,51]. Mean age of our population was 63.5 years (range, 38-82). When reported, the male to female ratio was 2 to 1, counting 26 males and 12 females. Excluding 16 cases (30.2%) [14,22,28,34,38,41,42,46,47,50,51], whose exact origin was not specified, the cricoid was the most common site of origin of LCS (n = 25, 67.6%) [1,5,13,15,17-21,23,26,30,31,37,39,40,43,45,49,52,53]. Among these, in one case (2.7%) each, cricoid was involved with the thyroid [45] and the arytenoid [53], respectively. Rarely, the primary site was the epiglottis (n = 3, 8.1%) [24,25,27], arytenoid (n = 1, 2.7%) [32], or corniculate cartilage (n = 1, 2.7%)[16]. Histological subtypes were reported in 35 cases [1,5,11,17-19,25-33,35-40,43-45,48-50,52,53]. Only 5 patients (14.3%) had a well-differentiated (G1) LCS [21,26,48,50,52], while nearly half had an aggressive subtype ([G3, DD, or MY], n = 19, 54.3%) [1,17-19,25,27,28,30-32,35-38,43,44,53]. Details are reported in Table I.

Metastatic patterns

All LCS selected had distant and/or regional metastasis at diagnosis or during follow-up. Thirty-eight patients (71.7%) had LCS with DM [1,11,13,15,17,19-24,26-28,31-36,38-44,46,48-53]. In details, when specified, DM were detected at diagnosis and during follow-up in 4 (7.5%) [17,39,46,52] and 28 (52.9%) patients [1,5,11,13,15,20-23,26,28,31-33,35,36,38,40-44,48-50,53], respectively. During follow-up, when available, the mean time of DM detection was 23.8 months (range, 3-84). The most common sites of DM were lungs, described in 29 patients (54.7%) [1,5,11,15,17,19,21-24,26-28,31,32,35,36,38-41,44,48,50,52,53]. Other rare sites were bone (n = 4, 7.5%) [31,39,41,43], brain (n = 2, 3.8%) [32,34], kidney (n = 1, 1.9%) [19], and liver (n = 1, 1.9%) [48]. Regional lymph nodes involvement was reported in 20 patients (37.7%) [14-16,18,19,25-27,29-31,45-47,49,53]. It was observed in 6 (11.3%) at diagnosis [18,25,45,46] and in 7 (13.2%) during follow-up [15,16,30,31,49,53] with a mean time of 12.8 months (range, 5-24). Additional details are reported in Table I.

Treatment and follow-up

Surgery was performed in nearly all patients (77.4%), except for 11 whose treatment was not specified [14,24,42,46,47,50,51], and

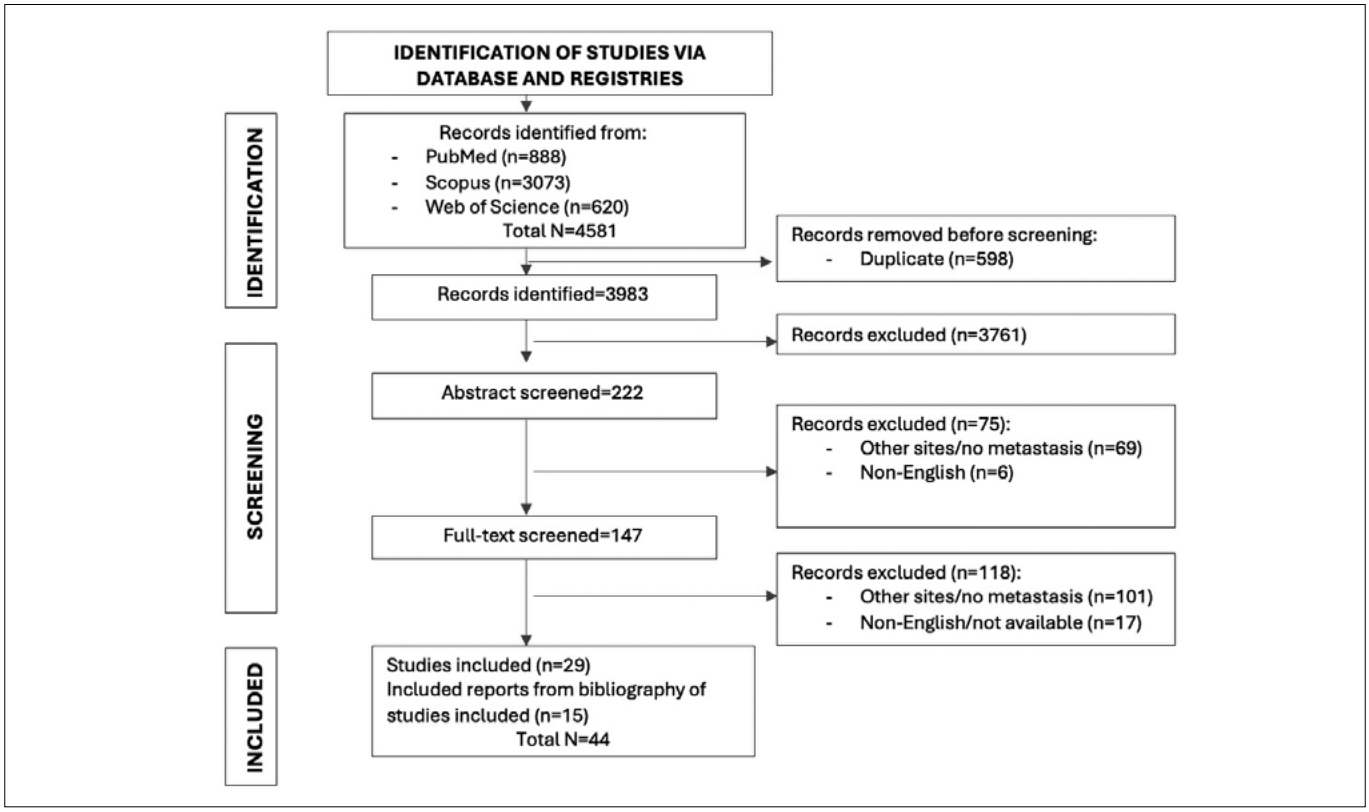

Figure 1. Selection process of original papers published until February 2025, describing cases of metastatic LCS.

one (1.9%) who was managed with palliative care alone [50]. The most common treatment was TL performed in 37.7% (n = 20) of cases as primary treatment [1,11,15,16,21,25,26,28,29,31,32,35-37,40,43-45], and in 20.8% (n = 11) [5,13,18,19,23,30,31,33,48,53] as secondary treatment after failure of previous conservative surgical techniques. Conservative surgical approaches, including partial laryngectomies or local resections, were performed in 6 (11.3%) patients [17,20,22,27,41,49]. Thirteen (24.5%) received adjuvant RT after surgery [1,11,16,18,28,35,35,36,38,43,44,48,49], while 3 patients underwent RT with palliative intent [22,31,39]. Mean follow-up, when available, was 50.2 months (range, 0-360 months). At the last follow-up, more than half of our popu-

Table I. Demographics, tumour characteristics, metastatic pattern, treatment, and oncologic outcomes of cases included in the present systematic review (n = 53).

First author	Year	No. of cases	Age (y)	Gender	Site	Histological subtype	Treatment	N+/M+	N+ AT diagnosis	M+ AT diagnosis	Status FU	Mean FU (m)	N+ during FU	Site	Time (m)	M+ during FU	Site	Time (m)
Ungerecht [13]	1951	1	62	M	C	NR	Laryngofissure and TL 7 m later	M+	NR	NR	NR	NR	NR	NR	NR	YES	LUNGS	NR
Frenzel [14]	1953	1	NR	NR	NR	NR	NR	C. NODES	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sirota [15]	1958	1	65	M	C	NR	TL	C. NODES, LUNGS, RENAL ARTERY	NR	NR	DOD	28	YES	C. NODES	NR	YES	LUNGS AND RENAL ARTERY TUMOUR EMBOLUS	24
Bronzini [16]	1959	1	72	M	COR	NR	TL + RT; left RND +RT 7 m later	C. NODES, WIDESPREAD	NR	NR	DOD	18	YES	C. NODES	NR	NO	None	0
Ghalib *[17]	1969	1	74	F	C	G2-G3	TT + excision soft tissue mass; tracheotomy 1 d later	LUNGS	NO	YES	DOD	30	NR	NR	NR	NR	NR	NR
Al-Saleem [18]	1970	1	70	F	C	G3/DD	Several endoscopic resections; TL + RT for N+ 1 m later	C. NODES	YES	NO	DOD	8	NR	NR	NR	NR	NR	NR
Huizenga and Balogh *[19]	1970	1	68	M	C	G3	Laryngofissure; TL 5 y later; local excision 3 y later; RT 9 y later	LUNG, KIDNEY, AND NECK	NR	NR	DOD	NR	NR	NR	NR	NR	NR	NR
Hyams and Rabuzzi [20]	1970	1	71	F	C	NR	2 local resection; tracheotomy for recurrence 23 y later; RT	SUBCUTANEOUS THORACIC AND ABDOMINAL NODULES	NO	NO	DOD	360	NO	None	0	YES	SUBCUTANEOUS THORACIC AND ABDOMINAL NODULES	NR
Hellquist [21]	1979	1	65	F	C	G1	Tracheotomy; TL 1 m later	LUNGS, SPLEEN	NO	NO	DOD	42	NO	None	0	YES	LUNGS, SPLEEN	36
Harwood [22]	1980	1	75	M	NR	NR	Excision; palliative RT for lung metastases	LUNGS	NR	NR	NR	NR	NR	NR	NR	YES	LUNGS	NR
Ferlito [11]	1984	1	74	M	T	G2	TL + RT	LUNGS	NO	NO	DOD	30	NO	None	0	YES	LUNGS	12
Escher [23]	1984	1	53	M	C	NR	Laryngofissure; multiple resections 4, 5, and 6 y later; then after TL 1 y later	LUNGS	NR	NR	AWD	138	NR	NR	NR	YES	LUNGS	NR
Gray [24]	1984	1	NR	NR	E	NR	NR	LUNGS	NR	NR	DOD	Fulminating fatal outcome	NR	NR	NR	NR	NR	NR
Kasanzew [25]	1988	1	46	F	E	G3	Tracheotomy followed by TL + bilateral VI level dissection; left RND	PARALAYNGEAL NODES	YES	NO	NED	6	NO	None	0	NO	None	0
Hakky [26]	1989	1	56	M	C	G1	TL + ND	C. NODES, LUNGS	NR	NR	NED	36	NR	NR	NR	YES	LUNGS	36
Jacobs [27]	1989	1	52	M	E	G2/G3	PL + right mRND; segmental lobectomy 3 y later	C. NODES, LUNGS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nicolai [28]	1990	1	74	M	NR	DD	TL + RT	LUNGS	NO	NO	DOD	30	NO	None	0	YES	LUNGS	12
Glaubiger [29]	1991	1	57	M	T	G2	TL + PP + TT + left mRND + right RND	C. AND MEDIASTINAL NODES	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Brandwein [30]	1992	1	69	M	C	DD	PL; TLM; TL; tracheal resection; RT	C. NODES	NO	NO	DOC	216	YES	C. NODES	18	NO	None	0
Nakayama [31]	1993	2	58	F	C	DD	TL; excision of stomal recurrence 4 m later; ND 1 m later; excision of recurrence 5 y later	C. NODES	NO	NO	DOC	168	YES	C. NODES	5 (4 regional recurrences during subsequent 8 y)	NO	None	0
			62	F	C	DD	Tracheotomy + laryngofissure; TL + excision distal clavicle 21 m later; palliative RT (bone) 3 m later; further RT on chest wall later on	CLAVICLE, C. NODES, LUNGS, BONES (VERTEBRAL), LEFT ANTERIOR CHEST WALL	NO	NO	AWD	NR	YES	C. NODES	24	YES	DISTAL CLAVICLE, LUNGS AND BONES, LEFT ANTERIOR CHEST WALL	21 (distal clavicle), 24 (lungs and vertebral)
Moran [32]	1993	1	61	F	ARY	MY	TL	LUNGS, BRAIN	NO	NO	DOD	15	NO	None	0	YES	LUNGS, BRAIN	15

Table I. Demographics, tumour characteristics, metastatic pattern, treatment, and oncologic outcomes of cases included in the present systematic review (n = 53).

First author	Year	No. of cases	Age (y)	Gender	Site	Histological subtype	Treatment	N+/M+	N+ AT diagnosis	M+ AT diagnosis	Status FU	Mean FU (m)	N+ during FU	Site	Time (m)	M+ during FU	Site	Time (m)
Fichera [33]	1995	1	60	F	T	G2	Laryngofissure; TL 6 y later	M+ (PLURIVISCERAL METASTASIS)	NO	NO	DOD	6	NO	None	0	YES	PLURIVISCERAL	6
Lippert [34]	1997	1	NR	NR	NR	NR	Surgery not otherwise specified	BRAIN	NR	NR	DOD	3	NR	NR	NR	NR	NR	NR
Thompson [1]	2002	2	66	M	C	G2	TL; RT	LUNGS	NO	NO	DOD	20.4	NO	None	0	YES	LUNGS	NR
			62	M	C	MY	TL; CRT	LUNGS	NO	NO	DOD	19.2	NO	None	0	YES	LUNGS	NR
Jones [35]	2003	1	72	M	T	G2/G3	TL + RT	LUNGS	NO	NO	DOD	12	NO	None	0	YES	LUNGS	NR
Rinaggio [36]	2004	1	60	M	T	DD	Debulking and TL + TT + bilateral ND 2 w later + RT	LUNGS	NO	NO	DOD	3	NO	None	0	YES	LUNGS	3
Casiraghi [37]	2004	2	61	M	C	DD	TL + ND	NR	NR	NR	NED	60	NR	NR	NR	NR	NR	NR
			58	M	C	DD	TL	NR	NR	NR	DOD	24	NR	NR	NR	NR	NR	NR
Goda [38]	2011	1	38	M	NR	G3	Surgery not otherwise specified + RT	LUNGS	NO	NO	NED	119	NO	None	0	YES	LUNGS	12
Böscke [39]	2012	1	81	F	C	G2	Tracheotomy + palliative RT of neck, shoulder, and mediastinum	LUNGS, HUMERUS	NO	YES	DOD	2.5	NR	NR	NR	NR	NR	NR
Domínguez-Durán [40]	2014	1	60	M	C	G2	TL; CHT 1 y later	LUNGS, SKIN	NO	NO	DOD	35	NO	None	0	YES	LUNGS, SKIN	12 (LUNGS), 30 (SKIN)
Leong [41]	2014	1	39	F	NR	NR	PL + ND + RFFF	LUNGS AND PELVIS	NO	NO	DOD	25	NO	None	0	YES	LUNGS, PELVIS	25
Dubal [42]	2014	1	NR	NR	NR	NR	NR	M+	NR	NR	NR	NR	NR	NR	NR	YES	NR	NR
Magliocca [43]	2017	1	76	F	C	DD	TL + RT; palliative CHT 3 m later	SOFT TISSUE, BONES	NO	NO	DOD	8	NO	None	0	YES	SOFT TISSUES, BONES	3
Lame [44]	2017	1	65	M	T	G3	TL + bilateral ND + right thyroid lobectomy + RT	LUNGS	NO	NO	DOD	12	NO	None	0	YES	LUNGS	12
Dogan [45]	2020	1	82	M	C, T	G2	TL + left ND	C. NODES (VI LEVEL)	YES	NO	NA	NR	NR	NR	NR	NR	NR	NR
Adeola [46]	2021	4	NR	NR	NR	NR	NR	C. NODES, M+	YES, 3 pts	YES, 1 pt	NR	NR	NR	NR	NR	NR	NR	NR
Talati [47]	2022	2	NR	NR	NR	NR	NR	C. NODES	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Roch-Zniszczoł [48]	2022	1	68	M	T	G1	Tracheotomy; TL 8 m later + RT	LIVER, LUNGS	NO	NO	DOD	84	NO	None	0	YES	LIVER, LUNGS	84
Rüller [5]	2022	2	NR	NR	C	G2	Laryngofissure, 3 endoscopic debulking, TL + peristomal recurrence excision + PMMF	LUNGS	NO	NO	AWD	57.4	NO	None	0	YES	LUNGS	NR
			NR	NR	C	G2	2 endoscopic excisions, 2 laryngofissures, TL	LUNGS	NO	NO	AWD	81.3	NO	None	0	YES	LUNGS	80
Zeitels [49]	2022	1	48	M	C	G2	PL + aortic homograft; ND + RT 1 y later	NECK, MEDIASTINUM	NO	NO	AWD	36	YES	C. NODES	12	YES	MEDIASTINUM	12
Gazda [50]	2024	2	NR	NR	NR	G1/G2	1° case, NR for larynx, lung resection, pulmonary radiofrequency; 2° case, palliative care	LUNGS	NR	NR	NR	NR	NR	NR	NR	YES	LUNGS	NR
Schleich [51]	2024	1	NR	NR	NR	NR	NR	M+	NR	NR	AWD	NR	NR	NR	NR	NR	NR	NR
Mirza [52]	2025	1	77	M	C	G1	Intubation + biopsy	LUNGS + MEDIASTINAL AND HILAR LYMPHADENOPATHIES	NO	YES	DOD	During hospitalization	NO	None	0	NO	None	0
Charous [53]	2025	1	57	M	C, ARY	G3/DD	Debulking; TL 2 y later; ND 5 m later	C. NODES, DERMAL AND LUNGS	NO	NO	DOD	21	YES	C. NODES	5	YES	DERMAL, LUNGS	20

**Data reported by Nakayama et al. [31]; AAW; alive and well; ARY, arytenoid; AWD, alive with disease; C, cricoid cartilage; CHT, chemotherapy; C. NODES, cervical lymph nodes; COR, corniculate cartilage; CRT, chemoradiotherapy; d, days; DD, dedifferentiated LCS; DOC, died of other causes; DOD, died of disease; E, epiglottis; F, female; FU, follow-up; G1, grade 1 LCS; G2, grade 2 LCS; G3, grade 3 LCS; m, months; M, male; M+, presence of distant metastasis; mRND, modified radical neck dissection; MY, myxoid LCS; N, number; N+, presence of regional metastasis; ND, neck dissection; NED, no evidence of disease; NR, not reported; PL, partial laryngectomy; PMMF, pectoralis major myocutaneous flap; PP, partial pharyngectomy; RFFF, radial forearm free flap; RND, radical neck dissection; RT, radiotherapy; T, thyroid cartilage; TL, total laryngectomy; TLM, transoral laser microsurgery; TT, total thyroidectomy; y, years; w, weeks.*

lation had died (n = 28, 52.8%): 26 (49%) died of disease (DOD) [1,11,15-21,24,28,32-37,39-41,43,44,48,52,53] and 2 (3.8%) from other causes (DOC) [30,31]. Five patients (9.4%) were alive with disease (AWD) [5,23,31,49]. All data are reported in Table I.

Discussion

LCS is the most frequent sarcoma of the larynx [2]. Compared to chondrosarcomas of other sites of the body, laryngeal ones tend to be low-grade and less aggressive [54], even though it is not clear if this depends on an intrinsic biologic behaviour of LCS or, more probably, from their well-confined position of the larynx within the body and the consequent relatively early diagnosis due to dysphonia and dyspnoea. The prognosis of LCS is, in fact, generally favourable, due to its usual indolence and low propensity to metastatic diffusion [55]. Indeed, surgeons have seemingly prioritised preserving the larynx over reducing the recurrence rate, accepting a higher likelihood of tumour persistence/recurrence due to its low impact on overall and disease-specific survivals [56]. However, in rare cases, these tumours may progress to regional and DM. One of the largest series, involving 111 LCS diagnosed between 1970 and 1997 [1], reported a metastatic rate of 1.9%. However, still today, the true incidence of metastatic LCS remains unreliable and not well defined. Indeed, the reported percentages of metastases from LCS described in up to 10% of cases hold little significance, as they are often based on small case series or rely on data from other authors. Our systematic review provides an in-depth analysis of the metastatic behaviour of LCS, with a focus on its patterns of spread and clinical outcomes.

General findings

A total of 44 articles and 53 metastatic LCS were included in the present review [1,5,11,13-53]. In the article selection process, we excluded the case reported by Neel and Unni [57], as the authors did not conclusively determine whether the tumour found in the cervical spine was a metastasis or a further metachronous primary tumour. Moreover, it was not considered a metastasis in the more recent reviews by Lewis et al. [58] and Nakayama et al. [31].

Demographics and tumour characteristics

While the location of primary LCS is one of the most important determinants for recurrence and organ preservation, for metastatic potential no clear risk factors are known. Our population had a mean age of 63.5 years (range, 38-82) with a male predominance, and the most frequent site of origin of the tumour was at the level of the cricoid, as described for LCS series in general. No differences in terms of demographics between metastatic and non-metastatic LCS were found. According to the histopathological subtypes, G1 LCS accounted for only 14.3% of metastatic cases [21,26,48,50,52], while more than half (54.3%) of the metastatic tumours were G3, DD, and MY [1,17-19,25,27,28,30-32,35-38,43,44,53]. These findings reinforce the prognostic significance of histological grading of LCS, suggesting that aggressive subtypes necessitate closer monitoring and potentially more extensive initial treatment. Although rarely, G1 LCS can sometimes present metastasis. However, determining whether these cases were truly G1 is challenging due to the well-documented difficulties and subjectivity with high intra- and inter-observer variability in the histopathological evaluation of chondrosarcoma aggressiveness. In fact, assessing cartilaginous tumours may often be complex and time-consuming, particularly in terms of classification and grading [21].

Metastatic pattern

In our population, all 53 cases of LCS had distant and/or regional metastasis at diagnosis or during follow-up. DM were more frequent than regional involvement (71.7% *vs* 37.7%, respectively). The timing of detection was not always specified, but, when available, regional metastasis were detected half at the diagnosis and half during follow-up with a mean time of 12.8 months. Interestingly, DM were detected at initial diagnosis in only 7.5% of cases, whereas the majority of patients (52.9%) developed them during follow-up (mean time of detection, 23.8 months), emphasising the necessity for long-term surveillance. The most common sites of DM were lungs, and rarely bones, brain, kidney or liver. In 1993, Nakayama et al. [31] published a review of the literature regarding regional metastasis and/or DM of LCS that revealed a total of 20 cases. Lavertu et al. [59] highlighted DM in 5 of the 35 cricoid cases (14%), while Thompson and Gannon [1] reported a series of 111 LCS and demonstrated that local and DM rates were exceedingly low, around 1.9%. However, accurate estimation of the incidence of metastatic LCS is seriously hampered by several issues. For instance, there is a lack of knowledge of the true total number of chondrosarcomas documented in the literature, and cases of LCS are likely more frequent than reported, as they were often classified under the broader category of cartilaginous tumours and historically misdiagnosed as chondromas [2]. The reported 10% metastasis rate in LCS is unreliable, despite being erroneously cited by several authors. Based on our data, the metastatic rate of 1.9% reported by Thompson and Gannon [1] appears to be the

most reliable estimate, even though the lack of large series or prospective studies make it impossible to define a more precise rate.

Treatment and follow-up

Surgical intervention was the primary treatment modality, with TL performed in 37.7% as the initial approach [1,11,15,16,21,25,26,28,29,31,32,35-37,40,43-45] and in 20.8% after failure of conservative surgery [5,13,18,19,23,30,31,33,48,53]. Partial laryngectomies or local resections were attempted in 11.3% [17,20,22,27,41,49] of cases, reflecting a low trend toward organ preservation in these cases. The high rate of secondary TL highlights the potential limitations of conservative approaches, particularly in aggressive tumour subtypes. According to the literature, G3 LCS, and especially DD, should be treated as separate entities from conventional chondrosarcomas because of their proclivity for more aggressive behaviours [8,26].

Thirteen (24.5%) patients had adjuvant RT after surgery [1,11,16,18,28,35,35,36,38,43,44,48,49], while 3 underwent RT with palliative intent [22,31,39]. Historically, LCS were considered as radioresistant tumours, although evidence in the literature has shown that these lesions can no longer be classified as radioresistant entities. RT could be performed in case of unfeasible surgical resection, recurrent tumours or in the adjuvant setting, in case of doubt of inadequate surgical resection [22].

Overall, the prognosis of patients with LCS is generally favourable, with 5-year survival rates exceeding 80% [56]. In our cohort, survival outcome was poor, revealing a 49% disease-specific mortality rate with a mean follow-up of 55.1 months. Disease persistence was noted in 5 patients [5,23,31,49], further underscoring the challenges in managing metastatic LCS. The occurrence of metastases significantly worsens outcomes, with survival rates dropping considerably. This emphasises the need for a more radical primary approach for specific subtypes of LCS, individualised treatment strategies, long-term follow-up, and further research into novel therapeutic options. Indeed, even if regional lymph node metastases and DM are uncommon, when present they may represent significant clinical challenges. Understanding the factors that contribute to the metastatic behaviour of LCS is crucial for risk stratification and management. Future research should focus on elucidating the molecular mechanisms underlying metastasis in LCS to develop targeted therapeutic approaches.

Conclusions

LCS is a rare tumour with generally low aggressiveness and favourable prognosis. However, it can sometimes exhibit a higher risk of local recurrence and regional and/or DM, significantly worsening outcomes. Our systematic review confirms that metastases from LCS are uncommon, with an incidence that remains difficult to determine due to the scarcity of large-scale studies. DM, primarily affecting the lungs, are more frequent than regional lymph nodes involvement and often arise several months or years after initial diagnosis, highlighting the need for extended follow-up. A better understanding of metastatic risk factors, individualised treatment approaches, and long-term follow-up strategies are essential. Future multicentre and prospective studies will be crucial in refining the management and therapeutic options for this rare but clinically important disease.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

CM, AF: article selection and data extraction; CP: mediator to reach a consensus; CP, AF, CM: study design, review drafting, and critical revision.

Ethical consideration

No formal ethics committee approval was required for this article as it is based on already published clinical data from other studies available in the literature.

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