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REVIEW

Aggressive Subtypes of Laryngeal Chondrosarcoma and their Clinical Behavior: A Systematic Review

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ABSTRACT

Introduction: Laryngeal chondrosarcoma (CS) is a rare indolent malignant tumor. High-grade (G3), dedifferentiated (DD), and myxoid (MY) CSs are considered more aggressive subtypes due to their metastatic potential and relatively poor outcomes. The aim of this systematic review is to evaluate treatment modalities and survival outcomes in patients affected by these rarer CS subtypes.

Methods: Papers published from January 1, 2000, to August 25, 2024, describing cases of laryngeal G3, DD, and MY CS were included.

Results: A total of 38 patients (15 G3, 13 DD, and 10 MY) were selected. Cricoid cartilage was the most common site of origin. Total laryngectomy (TL) was often performed. Primary conservative approaches in 42.8% of patients were followed by loco-regional recurrence.

Conclusions: Aggressive subtypes of CS require a radical approach because of the higher rate of loco-regional and distant recurrences compared

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to low-grade CS. TL with radical intent is the most common treatment, and adjuvant therapy should be considered after careful multidisciplinary discussion.

Keywords: High grade; Dedifferentiated; Myxoid; Chondrosarcoma; Laryngeal tumors

Key Summary Points

Chondrosarcoma (CS) is a malignant tumor arising from cartilaginous tissue; its occurrence in the larynx is rare (< 1% of all laryngeal malignancies) and typically arises within the hyaline cartilages, especially the cricoid.

Even though the latest World Health Organization Classification of Head and Neck Tumors states that "tumor location, grade, subtype, and therapy do not seem to influence outcome (other than possibly for dedifferentiated tumors)," this assumption may be hampered by the exceedingly rare occurrence of the most aggressive forms of these sarcomas (5% of all laryngeal CS), involving high grade (G3), dedifferentiated (DD), and myxoid (MY) variants.

The aim of the present systematic review is therefore to evaluate treatment modalities and survival outcomes in patients affected by the aggressive subtypes of laryngeal CS, including G3, DD, and MY, as described in the available literature.

A comprehensive search was conducted on August 25, 2024, including original papers in English, published since January 1, 2000 and describing cases of G3, DD, and MY laryngeal CS; among 1565 articles, a total of 21 articles and 38 patients were selected.

Surgery is the mainstay of therapy, and total laryngectomy is the most frequent treatment for aggressive CS; the role of adjuvant radiotherapy is discussed since CSs are classically considered radioresistant tumors. When comparing the prognosis and survival rates of G3, DD, and MY variants to those of low-grade CS, they are poorer, with higher rates of recurrences. and distant metastases even after radical treatment

INTRODUCTION

Chondrosarcoma (CS) is a malignant tumor arising from cartilaginous tissue. It is the most common non-soft tissue sarcoma among adults [1]. While it may frequently occur in the long bones, pelvis, and ribs, its occurrence in the larynx is rare, constituting < 1% of all laryngeal malignancies and around 1–2% of CS in the whole body [2]. Laryngeal CS is more prevalent in older adults, with a peak of incidence in the 5th and 7th decades. It has a higher predilection for males, with a male-to-female ratio of 3:1 [3–5]. CS typically arises within the hyaline cartilages, especially the cricoid (about 75%), and, less frequently, the thyroid, arytenoids, or epiglottis [6, 7].

According to the World Health Organization (WHO) Classification of Head and Neck Tumors (2024) [8], CSs are usually classified as low- (G1), intermediate- (G2), and high-grade (G3) tumors, although 95% are well-differentiated lesions [3, 7, 9–11], often misdiagnosed initially as benign chondroma [7]. However, when G3 CSs are diagnosed, they may represent a significant clinical challenge due to their unpredictable and, possibly, more unfavorable behavior and poor prognosis [3]. Dedifferentiated (DD) CS, in particular, is known to be an aggressive malignancy, even though rare, characterized by the presence of a high-grade undifferentiated sarcoma component (rarely with heterologous elements, e.g., rhabdomyoblastic) associated with a lower-grade cartilaginous one [6]. A poorer prognosis is also related to an additional subtype of conventional CS, the myxoid (MY)

variant, considered a high-grade lesion due to its unpredictable behavior and higher tendency to recur, apparently linked to the amount of cellular component and inversely related to the myxoid content (prognosis being more favorable in the presence of reduced cellularity and abundant myxoid matrix) (Fig. 1) [12].

Surgical resection remains the first choice of treatment and should be based whenever possible on organ-sparing (transoral or open) approaches [7, 9, 10, 13–16], while total laryngectomy (TL) should be reserved only for large lesions, involving more than one cartilage, or presenting an aggressive histology. Although rare, such aggressive subtypes of CS are of clinical relevance as their management may differ substantially from G1–G2 lesions, with no shared guidelines available to date.

The aim of the present systematic review is therefore to evaluate treatment modalities and survival outcomes in patients affected by the rare aggressive subtypes of laryngeal CS, including G3, DD, and MY, as described in the available literature.

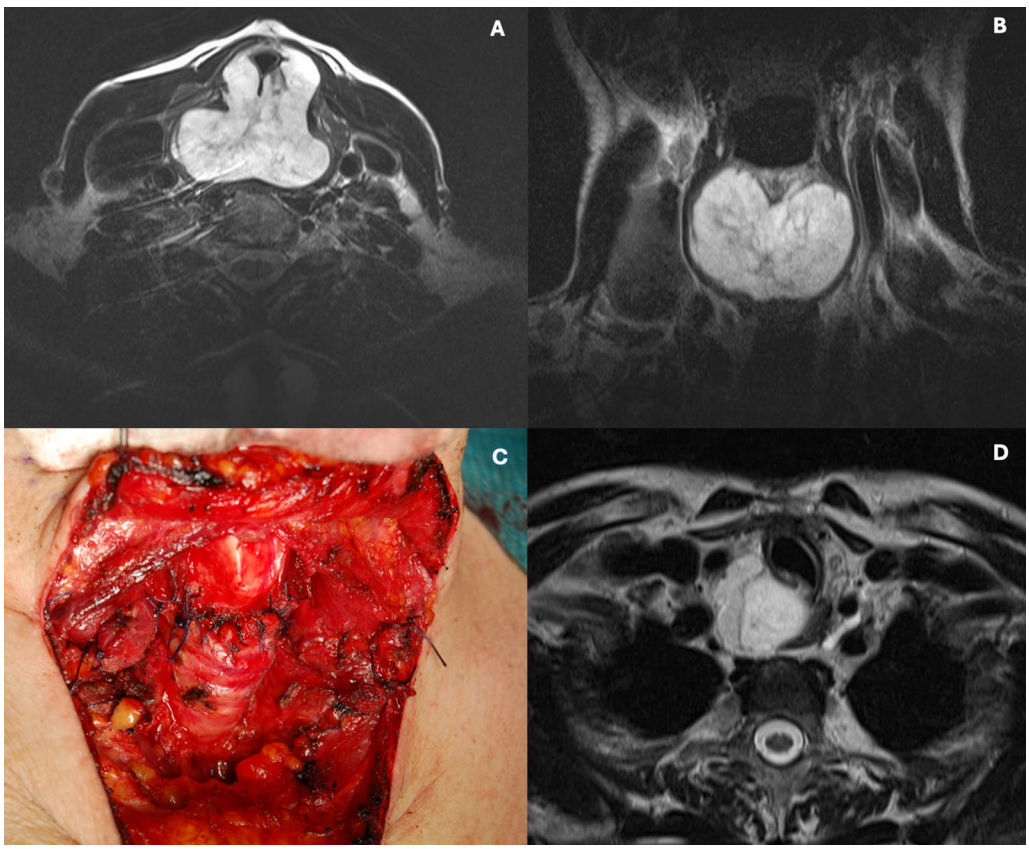

Fig. 1 A 60-year-old male complaining of dysphagia, hoarseness, and dyspnea was diagnosed with a > 4 cm cricoid CS at MR (**A** axial and **B** coronal T2-weighted sequences). He was submitted to subtotal cricoidectomy with thyro-crico-tracheal anastomosis (**C** surgical field at the end of the procedure) during which a fleshy consistence of the tumor raised the question of its possible dedifferentiation. A final histopathologic diagnosis of MY CS with abundant cellularity and areas of necrosis was rendered, and TL was proposed but the patient refused. Six months later, he started complaining again of dyspnea and dysphagia, and a new MR showed persistent disease at the level of the cervico-mediastinal junction (**D** axial T2-weighted sequence). A TL was then performed, but the patient died 12 months later of uncontrolled mediastinal disease

METHODS

Search Strategy

This systematic review was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist and statement recommendations [17]. A comprehensive search on PubMed, Web of Science, and Scopus was conducted on August 25, 2024, using the following queries: "(Chondrosarcoma or chondrosarcomas or chondrosarcomatoid or sarcoma or sarcomas) and (larynx or laryngeal) and (dedifferentiated or myxoid or undifferentiated or aggressive or G3 or G4 or high grade)."

Selection Criteria

Original papers in English, published from January 1, 2000, to August 25, 2024, describing cases of G3, DD, and MY laryngeal CS, were considered. Exclusion criteria were G1–G2 CS, impossibility to extrapolate specific data on treatments or survival of patients from composite series, pediatric cohorts, non-human studies, reviews, and articles without full text available.

Two researchers (CP and CM) independently screened all titles, read the abstracts, and subsequently excluded those not fulfilling the inclusion criteria. Next, both authors analyzed the full text and decided whether the publication should be included or not, according to the above-mentioned criteria. A third investigator (MT) acted as a mediator in cases of dispute. The references of all selected articles were also reviewed to identify additional relevant articles.

Data Extraction

The features of each study included were: authors' name, publication year, country, study design, period of observation, gender, and age at presentation. We also collected data on presenting symptoms, tumor characteristics (subsite, histologic subtype, dimensions, and margins status), regional or distant involvement at diagnosis, treatment modality, mean follow-up, recurrence rate (local, regional or distant), and cause of death. Two authors (CP and CM) independently extracted data from eligible articles and created a dedicated database in Microsoft Excel. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Quality Assessment

The quality of each study included was independently estimated by two authors (CM and MT) through the Joanna Briggs Institute (JBI) checklist [18] for case series. A senior author (CP) was consulted in case of discrepancies.

RESULTS

General Findings

The initial search returned 1565 articles. All details about identification, screening, and inclusion/exclusion criteria are reported in Fig. 2. A total of 21 articles [3, 19–38], including both case reports and case series, for a total of 38 patients, were included in the present systematic review, comprising 15 G3 [3, 21–23, 26, 27, 31, 34, 36–38], 13 DD [3, 19, 21, 23–25, 29, 30, 32, 33, 35], and 10 MY [3, 20, 28] (Table 1).

Quality Assessment

Detailed scores according to the JBI checklist [18] for each case series considered in the systematic review are reported in Table S1. All manuscripts included were retrospective case series [3, 21–23, 26, 27, 29, 31, 38].

Demographics and Tumor Characteristics

Demographics were reported for most patients (26 of 38, or 68.4%). The mean age was 59.6 (range 24–88) years, and there was a clear male predominance (22 of 26, or 84.6%).

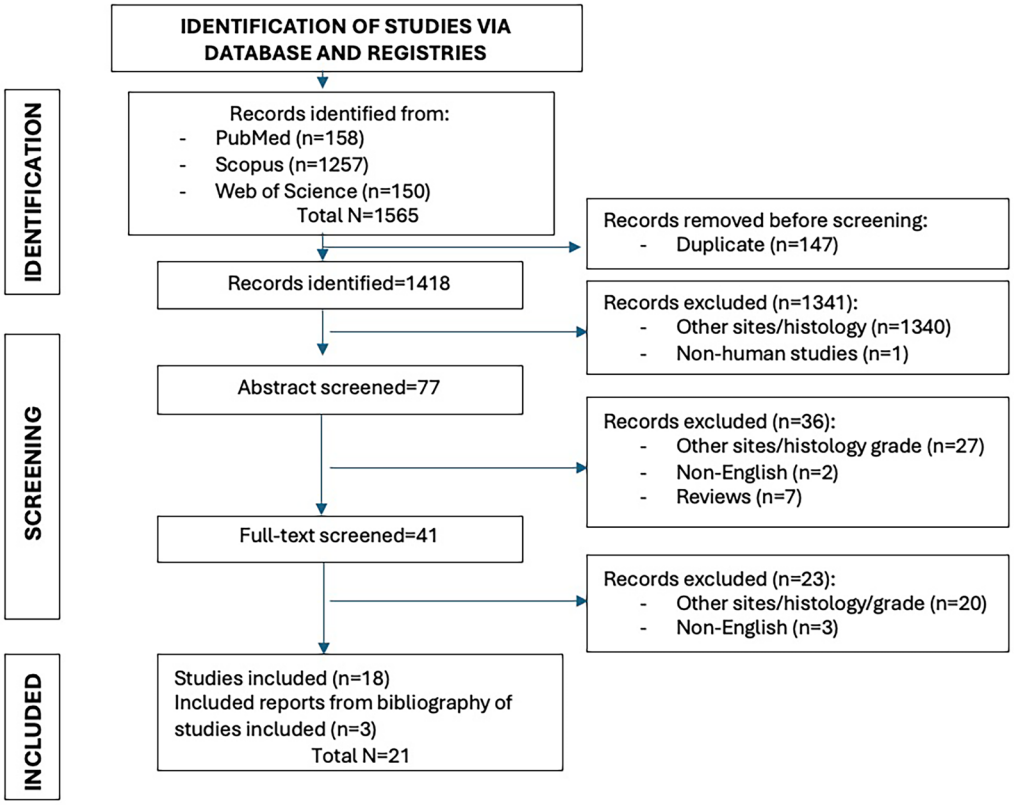

Fig. 2 Articles selection. Original papers in English, published from January 1, 2000, to August 25, 2024, describing cases of high-grade (G3), dedifferentiated (DD), and myxoid (MY) laryngeal chondrosarcoma, (CS) were included

Excluding 14 cases (36.8%) [3, 27, 29] whose exact origin was not specified, the cricoid was the most common site of origin (16 patients, or 66.7%) [3, 21, 23, 26, 28, 30–35, 38], while in 2 (8.3%) [24, 37] both the cricoid and the thyroid were involved. The hyoid bone was involved in three (12.5%) patients [21, 27, 36]. Only in one (4.1%) [21] was the site of origin the epiglottis, an elastic cartilage rarely involved by CS. This patient (affected by a DD CS) was also the only case of regional preoperative involvement diagnosed at first treatment [21]. None of the patients had distant metastases detected before surgery. The most common presenting symptom was worsening hoarseness, rarely associated with dyspnea. Interestingly, six (15.8%) patients reported symptoms such as neck mass, pain, and hemoptysis, which are rarely reported in G1–G2 CS. All patients underwent preoperative diagnostic imaging, CT, MR, or both. Of 14 patients whose gross tumor dimensions were reported [3, 19–22, 24, 25, 28, 30, 32, 34–36], 9 (64.3%) [3, 19–22, 24, 33, 36] were ≥ 4 cm in their largest diameter. Demographics and tumor features are presented in Table 2.

Treatment

Treatment modalities were described in all studies and are detailed in Table 2. Surgery was always performed with curative intent. Excluding cases whose type of surgery was not specified ($n = 9$) [3, 28], TL was the most common treatment, performed in 20 patients (69% of cases for which the type of surgery was described) [3, 19, 21–24, 26, 28, 30, 31, 33, 35, 37, 38]. Fifteen (75%) [3, 22–24, 26, 28, 31, 33, 37] of these underwent primary TL, whereas for 5 (25%) [19, 21, 30, 35, 38] TL was a salvage procedure after failure of other conservative treatments (radiotherapy [RT], open partial laryngectomies, or

Table 1 General features of the 21 articles included in the systematic review

Study no.	First author	Year	Country	Journal	Type of study	No. of pts	Histopathologic variants
1	Faquin et al.[a] [19]	2000	USA	Diagn Cytopathol	CR	1	DD
2	Uygur et al. [20]	2001	Turkey	J Laryngol Otol	CR	1	MY
3	Thompson and Gannon[‡] [3]	2002	USA	Am J Surg Pathol	CS	14	4 G3, 2 DD, 8 MY
4	Saleh et al. [21]	2002	France	Eur Arch Otorhinolaryngol	CS	2	1 DD, 1 G3
5	Jones et al. [22]	2003	USA	J Otolaryngol	CS	1	G2–G3
6	Casiraghi et al. [23]	2004	France, Italy, USA	Ann Diagn Pathol	CS	3	1 G3, 2 DD
7	Rinaggio et al. [24]	2004	USA	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	CR	1	DD
8	Sauter et al. [25]	2007	Germany	Anticancer Res	CR	1	DD
9	Obeso et al. [26]	2010	Spain	Acta Otorrinolaringol Esp	CS	1	G3
10	Goda et al. [27]	2011	Canada	Cancer	CS	1	G3
11	Babarovic et al. [28]	2012	Croatia	Indian J Pathol Microbiol	CR	1	MY
12	Buda et al. [29]	2012	Israel	Isr Med Assoc J	CS	1	DD
13	Purohit et al. [30]	2014	Switzerland	Laryngoscope	CR	1	DD
14	Oliveira et al. [31]	2014	Portugal	Braz J Otorhinolaryngol	CS	1	G3
15	Fidai et al. [32]	2016	USA	Head Neck Pathol	CR	1	DD
16	Magliocca et al. [33]	2017	USA	Ann Diagn Pathol	CR	1	DD
17	Waters et al. [34]	2018	Ireland	J Surg Case Rep	CR	1	G3
18	Chen et al. [35]	2018	China	Postgrad Med	CR	1	DD
19	Bian et al. [36]	2018	China	Int J Clin Exp Med	CR	1	G2–G3
20	Galletti et al. [37]	2019	Italy	BMJ Case Rep	CR	1	G3
21	Zeitels and Baird[§] [38]	2022	USA	Laryngoscope	CS	2	1 G3, 1 G2–G3

CR, case report; CS, case series; DD, dedifferentiated; CS, chondrosarcoma; G2–G3 intermediate-high-grade; G3, high-grade; CC, clear cell; MY, myxoid

[a]This case has also been presented in another paper by Sakai et al. [39]

[b]This series also includes two case reports presented separately by Garcia et al. [40] with more details

[c]This series includes one case report presented separately by Zeitels et al. 2011 [41] with more details

endoscopic debulking). Among all TLs, 11 were performed for G2–G3/G3 lesions (73.3% of all G2–G3/G3 CS), 8 for DD (61.5% of them), and 1 for MY (10%, but for 80% of MY the type of surgery was not reported) [3].

Primary conservative approaches were applied to 14 (48.3%) patients [3, 19–21, 25, 29, 30, 32, 34–36, 38]. In particular, open partial procedures were performed in 12 (41.4%) [3, 19–21, 30, 32, 34, 35, 38], while 2 (6.9%) underwent transoral laser microscopic surgery (TOLMS) [25, 29]. Among all patients treated with a conservative approach, six (42.8%) had a loco-regional recurrence [19, 21, 30, 35, 38], and five (35.7%)

Table 2 Demographics, tumor characteristics, treatment, and oncologic outcomes of the present systematic review

Authors	Year	No. of pts	Histology	Age, gender	Presenting symptoms	Cartilage of origin	Maximal diameter (cm)	Regional and distant metastases	Treatment	Adjuvant treatment	Recurrence, time, site	Oncologic outcome (months)
Faquin et al. [19]	2000	1	DD	74, M	Rapidly enlarging neck mass	T	4.5	No	Partial resection RT and debulking—TL	No	NA	NA
Uygur et al. [20]	2001	1	MY	77, M	Neck pain	T	7	No	PL	No	No	NED, 8
Thompson and Gannon [3]	2002	14	4 G3	NA	NA		–	No	4 TL	No	NA	1 NED, 204; 3 DOC, 162
			2 DD	67, M	Hoarseness	C	4	No	Wide resection	No	No	NED, 136
				41, M	Hoarseness, dysphagia	C	5	No	TL	No	No	NED, 91
			8 MY	NA	NA	NA	–	No	S	4 RT	Yes, L (1 patient)	2 DOD, (1 postop and 1 18); 6 NED, 52.8

Table 2 continued

Authors	Year	No. of pts	Histology	Age, gender	Presenting symptoms	Cartilage of origin	Maximal diameter (cm)	Regional and distant metastases	Treatment	Adjuvant treatment	Recurrence, time, site	Oncologic outcome (months)
Saleh et al. [21]	2002	2	DD	38, M	Neck mass, dysphonia	E + H	4	Regional disease at diagnosis and regional recurrence after the first treatment	PL + mRND RND S (subcutaneous nodule)	RT (after PL)	Yes, 2 m and 120 m, R	NED, 132
			G3	53, M	Dyspnea, neck pain	C	–	No	Laryngofissure + tumor excision TL	RT (after TL)	Yes, 12 m, L	NED, 180
Jones et al. [22]	2003	1	G2–G3	72, M	Dysphonia	T	7	Lung metastases at recurrence	TL	RT	Yes, 12 m, D	DOD,12
Casiraghi et al. [23]	2004	3	G3	60, M	Hoarseness	C	–	No	TL + ND	No	NA	LFU, 7
			DD	61, M	Dyspnea	C	–	No	TL + ND	No	No	NED, 60
			DD	58, M	Hoarseness	C	–	No	TL	No	Yes, NA	DOD, 24

Table 2 continued

Authors	Year	No. of pts	Histology	Age, gender	Presenting symptoms	Cartilage of origin	Maximal diameter (cm)	Regional and distant metastases	Treatment	Adjuvant treatment	Recurrence, time, site	Oncologic outcome (months)
Rinaggio et al. [24]	2004	1	DD	60, M	Hoarseness, dyspnea	T + C	4.5	Lung metastases at recurrence	TL + TT + bilateral ND	RT	Yes, NA, D	DOD, 3
Sauter et al. [25]	2007	1	DD	66, M	Hoarseness	Posterior part of VC	1	No	TOLMS	No	No	NED, 3
Obeso et al. [26]	2010	1	G3	63, M	Dysphonia	C	–	No	TL	CRT	Yes, NA	DOD, 8
Goda et al. [27]	2011	1	G3	38, M	NA	LARYNX + H	–	Lung metastases at recurrence	S	RT	Yes, 12 m, D	NED, 119
Babarovic et al. [28]	2012	1	MY	65, M	Dysphonia	C	3	No	TL	RT	No	NED, 24
Buda et al. [29]	2012	1	DD	24, M	Hoarseness, dyspnea	NA	–	No	TOLMS	CHT	Yes, 96 m, L	NED, 168
Purohit et al. [30]	2014	1	DD	69, M	Dysphonia	C	3	No	CTRA TL	CRT (after TL)	Yes, 5 m, L	NED, 7

Table 2 continued

Authors	Year	No. of pts	Histology	Age, gender	Presenting symptoms	Cartilage of origin	Maximal diameter (cm)	Regional and distant metastases	Treatment	Adjuvant treatment	Recurrence, time, site	Oncologic outcome (months)
Oliveira et al. [31]	2014	1	G3	73, M	Dysphonia, dyspnea	C	–	No	TL	No	No	NED, 84
Fidai et al. [32]	2016	1	DD	55, M	Dyspnea	C	3.1	No	PL + ND	No	No	NED, 8
Magliocca et al. [33]	2017	1	DD	76, F	Dysphonia, dyspnea	C	–	Bone and soft tissues metastases at recurrence	TL	RT	Yes, NA, D	DOD, 8
Waters et al. [34]	2018	1	G3	64, M	Dysphonia	C	2	No	PL	RT	No	NED, NA
Chen et al. [35]	2018	1	DD	59, M	Hemoptysis, dyspnea	C	5	No	2 partial resections of laryngeal neoplasm misdiagnosed as giant cell granuloma and aneurysmal bone cyst TL	No	No	NED, 9

Table 2 continued

Authors	Year	No. of pts	Histology	Age, gender	Presenting symptoms	Cartilage of origin	Maximal diameter (cm)	Regional and distant metastases	Treatment	Adjuvant treatment	Recurrence, time, site	Oncologic outcome (months)
Bian et al. [36]	2018	1	G2–G3	42, F	Neck mass	H	4.9	No	Transcervical resection (subtotal excision of the hyoid bone)	No	No	NED, 23
Galletti et al. [37]	2019	1	G3	88, M	Dysphonia	T + C	–	No	TL	No	No	NED, 18
Zeitels and Baird [38]	2022	2	G3	63, F	Dysphonia	C	–	No	PL TL	RT (after TL)	No	NA
			G2–G3	44, M	Hoarseness, dysphagia	C	–	Mediastinal lymph nodes at recurrence	PL + aortic homograft	No	Yes, 12 m, D	AWD, 36

DD, dedifferentiated; CS, chondrosarcoma; G2–G3 intermediate-high-grade; G3, high-grade; CC, clear cell; MY, myxoid; F, female; M, male; T, thyroid cartilage; C, cricoid cartilage; E, epiglottis; H, hyoid bone; VC, vocal cord; NA, not available; ADJ, adjuvant therapy; TL, total laryngectomy; PL, partial laryngectomy; TOLMS, transoral laser microsurgery; CTRA, crico-tracheal resection and anastomosis; TT, total thyroidectomy; mRND, modified radical neck dissection; ND, neck dissection; TT, total thyroidectomy; S, surgery; RT, radiotherapy; CHT, chemotherapy; CRT, chemoradiotherapy; m, months; L, local; R, regional; D, distant; AWD, alive with disease; NED, no evidence of disease; DOD, dead of disease; DOC, dead from other causes; LFU, lost to follow-up

underwent TL for local recurrence after a mean follow-up of 35.6 (range 5–108) months [19, 21, 30, 35, 38].

Neck dissection was primarily performed in 17.2% of patients ($n=5$) and secondarily in 3.5% ($n=1$) for a suspicious regional recurrence. Margin status was reported in nine studies [21, 27, 28, 32–34, 36–38], R0 in five cases [32, 33, 36–38], and R1 in 3 [21, 27, 34] (both after TL or open procedures). The only R2 was reported in the neck, in relation to the carotid artery and vagal nerve [28].

Sixteen patients (42.1%) were subjected to adjuvant treatments: 15 (39.5%) had RT [3, 21, 22, 24, 26–30, 33, 34, 38], in 2 of whom it was associated with chemotherapy (CHT) [26, 30], while 1 (2.5%) received only adjuvant CHT [29]. All details are described in Table 2.

Follow-Up and Outcomes

Follow-up data were reported for 36 patients and were missing in 2 studies [19, 38]. The mean follow-up was 54.7 (range 3–204) months. Ten patients died (27.8%), seven (19.5%) of disease (13.3% of all G2–G3/G3, 23.1% of all DD, and 20% of all MY) [3, 22–24, 26, 33], and three (8.3%) of other causes [3]. Among patients dead of disease, one MY died in the immediate postoperative period [3], two DD and one G3 had distant metastasis after having undergone primary TL [23, 24, 33], and one MY had local relapse treated with surgery [3].

More than half of the patients (24, or 66.7%) were alive without evidence of disease (mean follow-up, 68.7 months; range 3–204). Recurrences were reported for 12 patients [3, 21–23, 26, 27, 29, 30, 33, 38] within a mean of 21.6 months: 5 cases of G2–G3/G3 (after a mean time of 12 months), 6 DD (after a mean of 34.3 months), and 1 patient with MY (after an unspecified follow-up).

Five loco-regional recurrences were reported, and all (except for one in which the type of surgery was not specified) had been previously treated with primary conservative surgery [3, 21, 29, 30]. In contrast, five cases of distant metastases (3 G2–G3/G3 and 2 DD) were reported, the majority of which were treated with TL [22, 24, 27, 33, 38]. Only two patients underwent palliative lung metastasectomy [27, 38], while the other three died of disease [22, 24, 33]. Details are reported in Table 2.

DISCUSSION

CS are cartilage-forming malignant mesenchymal tumors infrequently occurring in the head and neck region (1–12%) and particularly rare in the larynx [42]. A diagnosis of laryngeal CS was first made in 1935 by New [43], and its etiology has since then remained essentially unknown [6]. About 95% of CS are low-intermediate grade (G1–G2) tumors [34, 44]. Even though the latest WHO Classification of Head and Neck Tumors (2024) [8] states that "tumor location, grade, subtype, and therapy do not seem to influence outcome (other than possibly for dedifferentiated tumors)," this assumption may be hampered by the exceedingly rare occurrence of the most aggressive forms of CS, per se already an infrequent diagnosis. In fact, laryngeal G3 CS represents a very rare (or absent) occurrence even in the largest series in the literature [3, 7, 9–11], and this means that even tertiary, academic, head and neck cancer referral centers may encounter such clinical scenarios once per decade or even less often. Histologic grade is the most significant prognostic factor for metastatic relapse, occurring in about 70% of G3 [45–47] and 31% of MY CS [48] at all sites. Such figures are lacking for laryngeal CS because of their intrinsic rarity even though the clinical impression is that certain subtypes even in this location may display a more aggressive behavior with higher rates of loco-regional and distant recurrences compared to their well-differentiated counterparts.

The MY subtype, originally believed to be a slow-growing and low-grade CS, showed high rates of local recurrence and distant metastasis in long-term follow-up studies [12, 49], especially when associated with high cellularity and low myxoid content [12]. Distant metastases are more common than regional ones, and most metastatic CSs are poorly differentiated or DD [50].

Aggressive subtypes of laryngeal CS, due to higher rates of metastasis and poorer prognosis (5-year overall survival [OS] < 10–25% for DD at all sites) [46, 47], emphasize the need for comprehensive removal of the lesion at its first presentation. This means that an organ-sparing surgical philosophy (i.e., TOLMS or open partial laryngectomies) can be adopted if it is aimed at obtaining the most representative sample of the lesion (within R0 or R1 margins) and rule out its possible aggressive nature. In case of a final histopathologic diagnosis of a G1–G2 lesion, such an approach can be reasonably followed by close endoscopic and/or radiologic surveillance, whereas when a G2–G3/G3, DD, and possibly also MY CS have been identified, a more aggressive surgical resection should be discussed with the patient in a multidisciplinary environment.

Unfortunately, due to the rarity of laryngeal G3, DD, and MY CS, the published literature is scarce and generally represented by case reports or very small retrospective case series, based on which strong recommendations are difficult to formulate.

Patient and Tumor Characteristics

In line with the available literature [3, 23], the aggressive subtypes of laryngeal CS occurred more frequently among males older than 50 years, differently from CS arising in other head and neck subsites (skull base or maxillofacial bones) that most commonly occur in 50-year-old or younger women. Local symptoms of G3, DD, and MY may not be different from their less aggressive counterparts and usually include hoarseness, along with progressive dyspnea and dysphagia, the latter especially frequent when the neoplasm has a posterior location compressing the post-cricoid portion of the hypopharynx. However, if not involving the glottis by ankylosing a crico-arytenoid joint, these tumors may remain asymptomatic for long periods and sometimes be incidentally discovered during endoscopic or intubation procedures. A non-negligible subgroup of aggressive CS may also exhibit unusual symptoms such as an enlarging neck mass, pain, and hemoptysis at diagnosis, which are not reported in the most common G1–G2 lesions.

Laryngoscopy followed by computed tomography (CT) and/or magnetic resonance (MR) are fundamental diagnostic evaluations allowing definition of the cartilaginous nature of the lesion due to its pathognomonic appearance at imaging, even though its grading requires assessment of the entire lesion, which can be difficult in small biopsy samples in particular [9]. From a histopathologic point of view, we confirm the exceedingly rare incidence of the more aggressive subtypes of CS, with only 38 patients documented in a literature review spanning 24 years [3, 19–38]. Preoperative diagnosis of CS can be difficult outside high-volume referral centers and can sometimes be misdiagnosed or, more frequently, down-graded based on small biopsy specimens that are not representative of the entire lesion. In our systematic review, one case [35] was first diagnosed as a reparative giant-cell granuloma and aneurysmal bone cyst arising from the cricoid, and only after several recurrences and TL was it correctly identified as a DD CS.

Preoperative CTs and/or MRs are definitely useful to make a presumptive diagnosis of cartilaginous tumor and evaluate its site of origin, three-dimensional extent, and dimensions but are usually not able to establish a differential diagnosis among different subtypes and the degree of biologic aggressiveness. In particular, CT detects “popcorn” calcification and MR identifies high-intensity signals in T2, which are both highly specific for CS [51]. The association of radiologic characteristics, large dimensions (> 4 cm), clinical data (such as rapid growth or soft tissues involvement and atypical symptoms), and histologic evaluation of a large sample is helpful in establishing the correct diagnosis. A representative biopsy or, even better, definitive histologic evaluation of the entire surgical specimen allows assessment of the possible coexistence of areas with varying degrees of differentiation.

According to the literature, CSs arise from hyaline cartilage, and the cricoid is the most common site of origin (66.7% in our study population compared to 75% commonly reported in the literature, also including the less aggressive

subtypes) [23]. In particular, the posterior lamina of the cricoid cartilage accounts for most of the malignancies [3], probably in association with an age-related ossification phenomenon, classically starting where the posterior crico-arytenoid muscles insert [52]. We found only one case (4.1%) originating at the level of the epiglottis [23], in line with the 3% involvement of the epiglottis or accessory cartilages reported previously [25]. However, due to the frequently large dimensions of aggressive CS at diagnosis, the precise site of origin of these tumors often remains unknown.

Treatment

Surgery is the mainstay of treatment. A conservative approach is often chosen for G1–G2 CS when at least one crico-arytenoid joint, posterior crico-arytenoid muscle, and recurrent laryngeal nerve can be safely preserved together with a reasonable laryngeal function [7, 16, 53, 54]. The reason is the indolent, non-aggressive, and non-metastatic course of these lesions that allows even multiple, repeated conservative resections without affecting OS. However, a different approach must be considered for the more aggressive subtypes. A surgically conservative approach should be applied only for diagnostic purposes but, once a G3, DD, or even MY CS has been diagnosed, their relatively poor prognosis and higher local and distant recurrence rates should prompt a more radical approach. Indeed, TL was the most common treatment (69%), performed in 73.3% of G2–G3/G3, 61.5% of DD, and 10% of MY (the type of surgical approach was not available for 80% of MY) [3]. Among the patients treated with conservative approaches, 42.8% had loco-regional recurrences [19, 21, 30, 35, 38].

In 1973 [55], Jones gave some useful indications for TL as treatment of CS. According to his view, TL should be applied to tumors with extensive laryngeal involvement and ensuing inability to preserve airway patency, recurrences after previous treatments, and dedifferentiated histology (such as in the present systematic review). Aggressive CS subtypes and bilateral massive involvement of the posterior lamina of the cricoid cartilage or both cricoarytenoid joints make TL the first choice of treatment, particularly in the presence of DD CS. In this review, primary surgical conservative approaches were proposed in 48.3% of patients [3, 19–21, 25, 29, 30, 32, 34–36, 38], but 42.8% experienced loco-regional recurrences and 35.7% underwent TL for local recurrence after a mean of 35.6 months [19, 21, 30, 35, 38].

Controversy still exists regarding laryngeal function-sparing excision versus TL for treatment of laryngeal CS. When feasible, a conservative approach in G1–G2 CS is better because it seems that the ultimate cure rate after TL performed for recurrent disease is comparable to that of primary TL (77 vs. 86%) [40, 56, 57]. In general, transoral treatment is possible only for small lesions or to debulk large tumors and get a proper diagnosis, with laser, allowing better control of resection and bleeding. In the literature, series of CS [7] treated with TOLMS are reported but mostly concerning G1–G2 CS. Indeed, herein TOLMS was performed in only two patients [25, 29]. On the other hand, several different open partial laryngeal resections have been described, while the aim of systematizing their use and indications is far from the scope of this paper. No guidelines are available for regional surgical treatment, but lymphatic spread of laryngeal CS seems to have a low incidence.

CSs have been classically considered radioresistant tumors. However, recently this concept has gradually evolved, and new radiation modalities have proven useful in these lesions, especially when resection within free margins cannot be obtained [27]. Even if not indicated for G1–G2 lesions, adjuvant RT is recommended in G3 or aggressive subtypes of CS, especially in cases with involved margins [58]. In our cohort, 42.1% of patients received adjuvant treatments, in particular RT ($n=15$) [3, 21, 22, 24, 27–29, 33, 34, 38], CRT ($n=2$) [26, 30], or CHT only ($n=1$) [29].

Even if CSs rarely are good responders to CHT and this approach is applied only for metastatic unresectable CS, DD seems to be more sensitive to CHT compared to conventional CS [1]. According to Italiano and coworkers [1], systemic conventional CHT significantly improved

survival compared to no treatment, while the number of chemotherapeutic agents used (single vs. multiple) did not significantly improve OS. Several types of CHT regimens have been used for CS, usually including anthracycline (doxorubicin), but also gemcitabine-based combinations, dacarbazine, oral etoposide, and ifosfamide [1].

Promising therapeutic modalities include the use of proton and carbon beam irradiation. However, although it has been used to treat skull base CS with a good rate of local control (92%) [59], there is currently no evidence for laryngeal tumors. Immunotherapy, particularly immune checkpoint inhibition targeting the PD-1/PD-L1 pathway, is an emerging area of clinical research. Studies have shown increased PD-1 expression in non-laryngeal CS compared to normal bone, with PD-L1 expression correlating with factors like tumor grade, size, and recurrence [60, 61]. Although PD-L1 levels and tumor mutational burden are generally low in sarcomas, an analysis of the expression of PD-L1 protein in conventional mesenchymal, clear cell, and DD CS revealed an upsurge in PD-L1 expression in 41% of DD CS [62, 63]. Clinical responses to immune checkpoint blockade remain mixed but show potential, especially in tumors with higher PD-L1 expression, but no data about laryngeal CS have been reported in the literature so far.

Oncologic Outcomes

In general, head and neck CSs have a better disease-specific survival (DSS) at 5 and 10 years (87.2% and 70.6%, respectively) compared to other sites, even if the anatomic complexity and functional density in this area often make it difficult to obtain clear resection margins. Not surprisingly, the local recurrence rate is higher than in other sites [64–67]. Laryngeal CS appears more favorable than CS in other parts of the body, even if G3 and DD behave similarly in the larynx and elsewhere, still remaining aggressive subtypes [1, 6, 19].

G3 and DD CS have a metastatic potential of 70% [42, 47, 68] and, even after radical treatment, the 10-year survival rate is around 29% [47] compared to 47.6% and 53.6% for all CS [2, 3]. The recurrence rate after surgery with or without adjuvant RT remains high (35–40%) [48]. In our systematic review, the recurrence rate was 33.3% with a mean time of 21.6 months, which is considerably shorter than the recurrence time usually reported for G1–G2 lesions [7, 9, 15]. Recurrences appeared in 33.3% of G2–G3/G3, 46.2% of DD, and 10% of MY CS. Five cases of loco-regional relapse were treated primarily with conservative surgery, while most cases with distant metastases were first treated by TL, and only two cases received palliative lung metastasectomy [27, 38]. Comparing the recurrence rate after TL performed as first-choice treatment with that after TL when other treatments had failed, the surgical curative rate was apparently not affected. In our population, all salvage TL patients, except for two whose follow-up was not available, were alive without evidence of disease, while among primary TL, except for one lost to follow-up, seven had died (4 of disease and 3 for other causes). Indeed, recurrence does not seem to affect survival and overall outcomes [57]. In our population, 66.7% of patients were alive without evidence of disease at the end of follow-up, and death from disease was rare, usually related to uncontrolled local growth or untreatable distant metastasis.

Limitations of the Present Study

Our systematic review has several limitations. First, G3, DD, and MY are very rare CS subtypes, and only case reports and limited case series are available in the literature. Among all published papers, we found only 38 patients over a literature search spanning 24 years. No randomized or large cohort studies are available (and probably never will be), and the data reported are often incomplete.

Furthermore, the rates of recurrence and survival would be more reliable if long-term follow-up was available. Indeed, due to the slow and indolent growth of these tumors, a 10–15-year follow-up is recommended for CS because of the risk of local and distant recurrence even after long periods following treatment. Another limitation is that no race or ethnicity data were collected as part of our study.

CONCLUSIONS

Aggressive subtypes of laryngeal CS include G3, DD, and MY, and their differential diagnosis from the most common G1–G2 lesions can be difficult with a definitive histopathologic report often rendered only after comprehensive removal of most of the clinically evident tumor. Surgery is the mainstay of therapy, and TL with radical intent is the most frequent treatment for aggressive CS. RT can be used in the adjuvant setting, even if CSs are classically considered radioresistant tumors. Similarly, DD CS seems to respond better to CHT compared to its less aggressive counterparts. When comparing the prognosis and survival rates of G3, DD, and MY CS to those of G1–G2 lesions, they are poorer, with higher rates of recurrences and distant metastases even after radical surgery. This contrasts what is stated in the most recent WHO "Blue Book" [8] and should raise concerns among the international head and neck community, urging more diligent tracing of such rare CS subtypes by reporting their long-term outcomes and clarifying their biologic behavior in larger cohorts than those available so far in the literature.

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Declarations

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