Received: 8 January 2024 | Revised: 18 March 2024 | Accepted: 29 March 2024

DOI: 10.1002/hed.27767

CLINICAL REVIEW

WILEY

Analysis of local, regional, and distant recurrence of disease in mucoepidermoid tumors of larynx: A systematic review

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Funding information
Italian Ministry of Health, Grant/Award Number: RC-2024-2790136

Abstract

The aim of this systematic review is to analyze epidemiology, clinical presentation, histopathological features, treatment and oncological outcomes in laryngeal mucoepidermoid cancer (MEC) in order to improve the knowledge on the management of such a rare malignant neoplasm. Specifically, authors highlight patients' and tumors' features about local, regional, and distant recurrence of disease. PRISMA 2020 guidelines were applied in this systematic literature review. A computerized search was performed using the Embase/Pubmed, Scopus, and Cochrane databases, for articles published from 1971 to December 2023. A descriptive and univariate analysis including selected papers with low or intermediate risk of bias was performed. Twenty-seven papers (11 case series and 16 case reports) were included in this review. Fifty-six patients were included in the analyses, with a mean age of 56.7 years; 84% of them were males. Most patients (86%) underwent a primary surgical approach. Clinical stage was reported as follows: early stage (26 patients) and locally advance and advanced stage (19 patients). Overall survival (OS) and disease-free survival (DFS) at 2 years was 80% and 78%, respectively. The mean time to local recurrence was 18.7 months (range 8–36 months). The survival after recurrence is about 85% and 70% at 5 years, respectively. The mean time of lymph node recurrence was 14.7 months (range 7–19 months). Finally, the mean time of distant recurrence was 15 months (range 7–36 months) with a poor prognosis: all patients died due to the disease in a range of 0–7 months after metastasis

Abbreviations: ACC, adenoid cystic carcinoma; CHT, chemotherapy; CHT-RT, chemo-radiotherapy; CT, computed tomography; DFS, disease-free survival; FT, feeding tube; MEC, mucoepidermoid carcinoma; MRI, magnetic resonance imaging; OS, overall survival; RT, radiotherapy; SCC, squamous cell carcinoma; TL, total laryngectomy; WHO, World Health Organization.

evidence. Laryngeal MEC is a rare neoplasm of minor salivary glands in the larynx. No guidelines or indications about the management of this neoplasm are reported in the literature. The lower incidence of regional recurrence of the disease and the better OS and DFS underline how the prognosis of MEC is more favorable respect to other malignant histotypes.

KEYWORDS

cancer, head and neck, larynx, mucoepidermoid, oncological outcomes

1 | INTRODUCTION

Mucoepidermoid carcinoma (MEC) is one the most common malignant salivary gland tumor accounting for 10%–15% of all salivary gland neoplasms and 30% of all salivary malignancies followed by adenoid cystic carcinoma (ACC).[1–3] Based on its specific clinical and histological features,[4] the World Health Organization (WHO) in 2005 and then in 2017 recognized MEC as a malignant glandular epithelial neoplasm characterized by mucous, intermediate, and epidermoid cells, with columnar, clear cell, and oncocytoid features.[5] The literature reported mainly case reports and small case series on MEC of larynx. Accordingly, larynx is not considered a common site of disease of MEC. Their localization depends on the distribution of laryngeal subepithelial glands and intraepithelial mucous glands. The most common sites include the floor of the laryngeal ventricle, false vocal folds, and anterior commissure, whereas the true vocal folds are only exceptionally involved.[6] They most commonly show as a submucosal mass with an intact overlying mucosa. The spread may also occur under an intact mucosal lining, preventing it from early detection.[7] Because of the rarity of these cases, diagnostic and therapeutic decisions are made empirically from case to case.[8] However, surgical resection with the goal of disease-free margins is considered the golden standard. Adjuvant therapies, such as radiotherapy (RT), chemo-radiotherapy (CHT-RT), and chemotherapy (CHT), are employed in the treatment of MEC affecting salivary glands.[9,10] However, no clinical trial data are available, and any significant associated survival benefit in this population is still to be observed.[11] No consistent data are available about not surgical primary/isolated treatment modality in laryngeal MEC.

This systematic review is meant to improve the knowledge of laryngeal MEC management by presenting an extensive overview on the epidemiology, clinical presentation, histological features, treatment, and oncological outcomes of laryngeal MEC. Consequently, the main aim of our paper is to highlight patients' and tumors' features about local, regional, and distant recurrence of such a disease, thus offering the first systematic review on laryngeal MEC in the literature.

2 | MATERIALS AND METHODS

2.1 | Search strategy and information sources

PRISMA 2020 guidelines were applied in this systematic literature review.[12] A computerized search was performed using the Embase/Pubmed, Scopus, and Cochrane databases, for articles published from 1971 to December 2023. The search string for each database is reported in Table 1.

2.2 | Study selection and data extraction

After running the above search string in December 2023, the abstracts and titles obtained were screened independently by two of the authors (F.C. and P.G.), who subsequently met and discussed disagreements on citation inclusion. Inclusion criteria for abstract selection were the adoption of the English language and the subjects being affected by laryngeal MEC. We excluded studies with no abstract, or adopting languages other than English, or not describing any information about

TABLE 1 Search string for each database.

Database	Search string	Articles found
Embase/ Pubmed	"mucoepidermoid* carcinoma" OR "mucoepidermoid* tumor" OR "mucoepidermoid* neoplasm") AND "laryn*"	272
Scopus	"mucoepidermoid*" AND "laryn*"	169
Cochrane	"mucoepidermoid*" AND "laryn*"	4

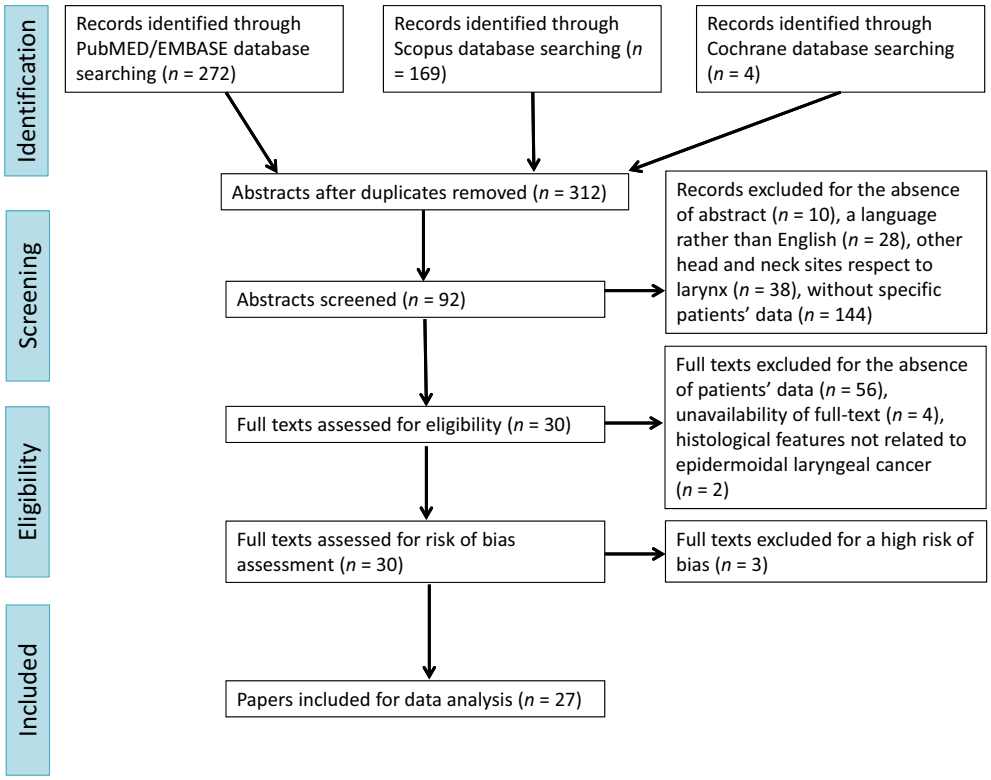

FIGURE 1 Flow chart of the study. [Color figure can be viewed at wileyonlinelibrary.com]

laryngeal MEC. The same authors screened the full texts identified by such criteria, and then they met and discussed disagreements on article inclusion. Inclusion criteria for full-text selected articles were the same as the above described for abstract selection, and additionally the following one: studies including individual information on cases affected by laryngeal MEC. Exclusion criteria were: articles without patients' related data as well as articles not reporting histological diagnosis of laryngeal MEC. A further manual check of the references included in the articles was performed. Details on the study selection process are reported in the PRISMA flow chart in Figure 1.

Information from each study was extracted using a standardized data extraction form, including: the article title, the first author name, year of publication, study type, number of patients with laryngeal MEC, demographics, site of tumor, clinical and diagnostic information, clinical and pathological stage, need of adjuvant therapies, functional outcomes (length of hospitalization, need of tracheotomy, decannulation time, use a feeding tube [FT], time of removal of FT, postoperative complications) and oncological outcomes (time of follow-up; overall survival; disease-specific survival; local, regional, and distant control of disease).

2.3 | Quality assessment

Two authors (F.C. and P.G.) independently assessed the quality of the included studies using an assessment tool for case series and case reports,[13] which considers four domains (selection, ascertainment, causality, and reporting) and provides eight questions to aid a quality score. Studies were rated as having a low, moderate, or high risk of bias according to the description thereof (Table 1). The articles with a high risk of bias were excluded from the analysis.

2.4 | Data analysis

Patients' level data were extracted and summarized. Categorical variables were presented as frequency and percentage. Continuous variables were presented as mean and range. In order to evaluate survival to recurrence of tumor, a Kaplan–Meier analysis was performed, showing survival curve to recurrence event in the study group. The statistical analyses were carried out by means of STATA v.14 (StataCorp LLC, College Station, TX).

3 | RESULTS

Running the search strings reported in Table 1, a total of 272, 169 and 4 manuscripts were identified in Embase/PubMed, Scopus, and Cochrane databases, respectively. Subsequently the removal of duplicates was performed and 312 papers were selected. After the abstract selection, 92 articles were selected for full-text screening. The other 270 articles were excluded due to the absence of abstracts (10), the adoption of a language other than English (28), descriptions of head and neck tumors' sites other than larynx (38), and papers without specific patients' data (144). The full-text screening restricted eligibility to 30 papers. The other 62 articles were excluded due to the absence of specific patients' data (56), the unavailability of full-text (4) or histological features not related to laryngeal MEC (2). Finally, full texts were processed for a risk of bias evaluation: as a result, three articles were excluded for a high risk of bias (Table 2). Therefore, the intended analysis could be finally carried out on 27 articles. The selection process of the papers is summarized in the PRISMA flow chart in Figure 1. Twenty-seven papers (11 case series and 16 case reports) were included in this review. The papers were published between 1975 and 2023. The general characteristics of each study were summarized in Table 3. The total amount of patients included was 56. The largest study population consisted of 12 patients.

3.1 | Epidemiology and clinical presentation of laryngeal MEC

The sex of the 56 included patients was stratified as follow: females were 8/50 (16%), males 42/50 (84%). The sex was unknown in six patients. Mean age reported was 56.7 years (range 13–77). Twenty-seven patients had symptoms or signs at diagnosis, such as hoarseness (20 patients), dyspnea (5 patients), painful swallowing (5 patients), sore throat (2 patients), neck mass (2 patients), hemoptysis (1 patient), and stridor (1 patient). Radiological imaging data were reported in seven cases: computed tomography (CT) and magnetic resonance imaging (MRI) were performed in four and three patients, respectively. Supraglottis was the most involved area of the larynx (32 cases), followed by glottis (18 cases) and subglottic area (6 cases). Twenty-nine patients out of 56 (52%), 14/56 (25%) patients, 8/56 (14%) patients, and 5/56 (9%) patients were, respectively, affected by cT1, cT2, cT3, and cT4a clinical stage of primary tumor, according to AJCC/TNM classification VIII edition.[14] Furthermore, lymph node clinical status was reported in 45 patients, as cN1 (5 patients), cN2a (1 patient), cN2b (1 patient), and cN2c (3 patients). For none of the patients clinical information was reported about distant metastasis at diagnosis of the primary. Finally, clinical stage was stratified as follows: stage I (11 patients), stage II (15 patients), stage III (12 patients), and stage IVA (7 patients).

3.2 | Management and histological features of laryngeal MEC

Most patients (86%) underwent a primary surgical approach, which consisted in total laryngectomy (TL) (31 cases), supraglottic laryngectomy (11 cases), other partial laryngectomy (3 cases), and cordectomy (3 cases). The other eight patients underwent exclusive radiotherapy. A lymph nodal dissection was performed in 20/56 (36%) patients. Five/twenty (25%) and 15/20 (75%) patients underwent monolateral and bilateral dissection, respectively. Mean hospitalization time was 16.2 days (range 12–20 days). Histological data of primary tumors were reported in 50/56 patients. Primary tumor was classified as follows: pT1 (23 patients), pT2 (14 patients), pT3 (8 patients), pT4a (4 patients), and pT4b (1 patient). Ten patients were affected by lymph nodal metastasis: pN1 (3 patients), pN2a (3 patient), pN2b (1 patient), pN2c (3 patients). Pathological stage of patients was reported in 21/56 cases, for which it was stratified as follows: stage I (no patient), stage II (8 patients), stage III (7 patients), and stage IVA (6 patients). Information about tumoral grading was reported in 25/56 (45%) patients, most of which were represented by a well-differentiated histology: 12/25 (50%) cases. Six/twenty-five (20%) patients had a moderate differentiated histology and 7/25 (30%) patients presented a poor differentiated histology. Surgical margins were negative in almost all of patients (95%). Adjuvant therapy was performed in 13/50 (26%) patients; of these, 9 and 4 underwent CHT-RT and RT, respectively.

3.3 | Oncological outcomes of laryngeal MEC

Mean follow-up time was 45.2 months (range 1–180 months). The 2 years overall survival (OS) and disease-free survival were 80% and 78%, respectively. Indeed, patients affected by recurrence of T, N, and M were 7, 6, and 5, respectively.

Table 4 resumes the main features of patients affected by tumoral recurrence of MEC. The mean time of recurrence was 18.7 months (range 8–36 months). Most patients were males (5/6), with supraglottic (3/7) or

TABLE 2 Tool for evaluating the methodological quality of case reports and case series.

Authors	Year	Selection	Ascertainment	Causality	Reporting	Risk of bias
Shonai	1998	1	1	1	1	1
Skliris	2023	1	1	1	1	1
Ferlito	1981	1	0	0	1	3
Damiani	1981	1	1	1	1	1
Cumberworth	1989	1	1	1	1	1
Hamlin	1986	1	0	0	1	3
Tandon	1985	1	1	1	1	1
Okinaka	1984	1	1	1	1	1
Seo	1980	1	1	1	1	1
Binder	1980	1	1	1	1	1
Gatti	1980	1	1	1	1	1
Kaznelson	1979	1	1	1	1	1
Koike	1979	1	1	1	1	1
Tomita	1977	1	1	1	1	1
Spiro	1976	1	1	1	1	1
Sessions	1975	1	1	1	1	1
Davis	1975	1	1	1	1	1
Thomas	1971	1	1	1	1	1
Mitchell	1988	1	1	1	1	1
Alimoglu	2011	1	1	1	1	1
Gomes	1990	1	1	1	1	1
Calis	2006	1	1	1	1	1
Nielsen	2012	1	0	1	1	1
Luna-Ortiz	2009	1	1	1	1	1
Prgomet	1981	1	1	1	1	1
Tanaka	2010	1	0	0	1	3
Zhang	2014	1	1	1	1	1
Karatayli-Ozgursoy	2016	1	1	1	1	1
Mahlsted	2002	1	1	1	1	1
Yilmaz	2013	1	1	1	1	1
Shonai	1998	1	1	1	1	1
Skliris	2023	1	1	1	1	1
Ferlito	1981	1	0	0	1	3
Damiani	1981	1	1	1	1	1
Cumberworth	1989	1	1	1	1	1
Hamlin	1986	1	0	0	1	3
Tandon	1985	1	1	1	1	1
Okinaka	1984	1	1	1	1	1
Seo	1980	1	1	1	1	1
Binder	1980	1	1	1	1	1
Gatti	1980	1	1	1	1	1
Kaznelson	1979	1	1	1	1	1
Koike	1979	1	1	1	1	1
Tomita	1977	1	1	1	1	1

Note: Eight items can be categorized into four domains: selection, ascertainment, causality, and reporting. For each domain we defined if items related were respected (1) or not (0). Final results differentiate case reports or series into three categories of risk of bias, as low risk (4), intermediate risk (3), high risk (0,1,2).

TABLE 3 Cohort's features.

Variable		Nr cases
Patient features	Total patients	50
	Males: nr pts (%)	42 (81%)
	Females: nr pts (%)	8 (19%)
	Mean age: years (range)	56.7 (13–77)
Symptoms/signs	Hoarseness: nr pts (%)	20 (74%)
	Dyspnoea: nr pts (%)	5 (19%)
	Painful swallowing: nr pts (%)	5 (19%)
	Sore throat	2 (7%)
	Neck mass	2 (7%)
	Haemoptysis	1 (3%)
	Stridor	1 (3%)
Radiological tools	CT: nr pts (%)	4 (57%)
	MRI: nr pts (%)	3 (43%)
Tumor sites	Supraglottis: nr pts (%)	32 (57%)
	Glottis: nr pts (%)	18 (32%)
	Subglottis: nr pts (%)	6 (14%)
Clinical stage	cT1: nr (%)	29 (52%)
	cT2: nr (%)	14 (25%)
	cT3: nr (%)	8 (14%)
	cT4a: nr (%)	5 (9%)
	cN0: nr (%)	35 (78%)
	cN+: nr (%)	10 (22%)
	cN1: nr (%)	5 (11%)
	cN2a: nr (%)	1 (2%)
	cN2b: nr (%)	1 (2%)
	cN2c: nr (%)	3 (5%)
	M: nr (%)	0 (0%)
	Stage I	11 (24%)
	Stage II	15 (33%)
	Stage III	12 (27%)
	Stage IVA	7 (16%)
Therapeutic approach	Surgical approach: nr (%)	48 (86%)
	Total laryngectomy: nr (%)	31 (55%)
	Supraglottic laryngectomy: nr (%)	11 (18%)
	Other partial laryngectomy: nr (%)	3 (6%)
	Cordectomy: nr (%)	3 (6%)
	Exclusive radiotherapy: nr (%)	8 (14%)
	Monolateral neck dissection: nr (%)	5 (9%)
	Bilateral neck dissection: nr (%)	15 (27%)
	Mean hospitalization time: days (range)	16.2 (12–20)
Pathological stage	pT1: nr (%)	23 (46%)
	pT2: nr (%)	14 (28%)
	pT3: nr (%)	8 (16%)

TABLE 3 (Continued)

Variable		Nr cases
	pT4a: nr (%)	4 (8%)
	pT4b: nr (%)	1 (2%)
	pN0: nr (%)	40 (80%)
	pN+: nr (%)	10 (20%)
	Stage I: nr (%)	0 (0%)
	Stage II: nr (%)	8 (38%)
	Stage III: nr (%)	7 (33%)
	Stage IVA: nr (%)	6 (26%)
	R+: nr (%)	0 (0%)
	G1: nr (%)	12 (48%)
	G2: nr (%)	6 (24%)
	G3: nr (%)	7 (28%)
Adjuvant therapy	None: nr (%)	37 (74%)
	Yes: nr (%)	13 (26%)
	CH-RT: nr (%)	9 (18%)
	CH: nr (%)	4 (8%)
Oncological outcomes	Overall survival 2 years	80%
	Disease-free survival 2 years	78%
	Mean follow-up time: months (range)	45.2 (1–180)
	Recurrence of T: nr (%)	7 (12%)
	Mean time of recurrence of T: days (range)	18.7 (8–36)
	Recurrence of N: nr (%)	6 (10%)
	Mean time of recurrence of N: days (range)	14.7 (10–19)
	Recurrence of M: nr (%)	5 (8%)
	Mean time of recurrence of M: days (range)	15 (7–36)

Abbreviations: Nr, number; pts, patients.

glottis (3/7) tumors in accordance with the current cohort of patients. Four/seven patients underwent RT as primary treatment. The OS after recurrence treatment is about 85% and 70% at 5 years (Figure 2), respectively.

Table 5 highlights the main features of patients affected by lymph-node metastasis of MEC. The mean time of regional recurrence was 14.7 months (range 7–19 months). Four/six patients were males and only 1 case was affected by subglottic MEC in accordance with the current cohort of patients. In a single case a patient underwent a lymph node dissection associated with total laryngectomy, followed by contralateral metastases after 7 months. Four patients underwent a curative lymph node dissection and they died for other causes or were alive at the least follow-up time. However, two patients underwent palliative care due to contemporary distant metastases.

Finally, Table 6 describes the relevant features of patients affected by distant metastasis. The mean time of recurrence for them was 15 months (range 7–36 months). Three of out of 5 patients were males, 3/5 presented a supraglottic cancer and the other ones had a glottic or subglottic tumor. All patients died for the disease (4/5) or other causes (1/5) in a range of 0–7 months after metastasis evidence. local-advance and advance stage.

4 | DISCUSSION

Malignant neoplasms arising from minor salivary glands are very rare in the larynx and include 0.1%–1% of all laryngeal neoplasms.[7] Adenocarcinoma, ACC, and MEC can be considered the most common histotypes.[15] The literature reported less than 80 laryngeal MEC cases and

TABLE 4 Patients features about T recurrence of disease.

Pts	First author (y of publication)	Sex (age at diagnosis)	Site of tumor	Clinical stage	First treatment (adj therapy)	Histological features	Time of recurrence	Treatment of T recurrence	Other recurrences	Follow-up
1	Damiani (1981)	Male (67 y)	Supraglottic	cT2 cN0 M0, stage II	TL	pT2 pNX M0	36 m	Palliative RT on T and M recurrence	Recurrence on N (19 m) and M (36 m)	DOD at 3 y
2	Okinaka (1984)	Male (51 y)	Glottic	cT1a cN0 M0, stage I	Cordectomy	pT1a pNX M0	10 m	PL	No	NA
3	Seo (1980)	Female (76 y)	Subglottic	cT4a cN0 M0, stage III	RT	NA	10 m	TL	Recurrence on N (17 m) and M (17 m)	DOC at 24 m
4	Koike (1979)	Male (64 y)	Glottic	cT1a cN0 M0, stage I	RT	NA	12 m	NA	Recurrence on M (12 m)	DOD at 12 y
5	Koike (1979)	Male (45 y)	Glottic	cT1a cN0 M0, stage I	RT	NA	36 m	NA	No	NA
6	Nielsen (2012)	Male (61 y)	Supraglottic	cT3 cN0 M0, stage III	RT	G1	8 m	NA	No	NA
7	Mahlstedt (2002)	Unknown (56 y)	Supraglottic	cT3 cN0 M0, stage III	TL + LND	pT3 pN0 M0, G3	60 m	NA	No	NA

Abbreviations: adj, adjuvant; CHT, chemotherapy; DOC, died for other causes; DOD, died of disease; LND, lateral neck dissection; m, months; NA, not available data; NED, no evidence of disease; PL, partial laryngectomy; Pts, patients; RT, radiotherapy; TL, total laryngectomy; y, years.

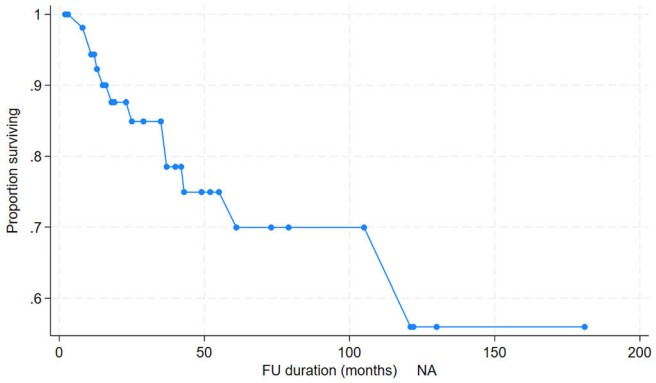

FIGURE 2 Kaplan–Meier curve underlines the survival of patients after a local recurrence of disease. [Color figure can be viewed at wileyonlinelibrary.com]

the current analysis selected 56 of them. The selection process excluded some papers due to the lack of data needed to carry on this systematic review.

Due to the rarity of this histotype in the larynx, an accurate diagnosis is fundamental. Three different types of cells make up MEC: squamous cells, mucous cells and intermediate cells.[16] According to the ratio of solid to cystic elements, neural invasion, necrosis, mitosis, and cellular anaplasia, these tumors are usually classified as low, medium, or high grade.[17] The most frequent grading histotype is the high-grade differentiated one.[18] According to it, 12/25 (50%) cases that were reported presented a well-differentiated histology.

Most patients in a group were males (81%); this is deemed to be an incongruent piece of data with reference to patients affected by salivary glands MEC, which was characterized by a weak prevalence of females.[4] At the same time, there is not a consistent difference in terms of mean age at onset between laryngeal MEC (60 years) and salivary glands ones (55 years).[4] According to the other histological types of laryngeal cancer, supraglottic and glottic are the most affected sites by laryngeal MEC, which is 57% and 32%, respectively. Hoffman et al.[19] highlighted how a larger number of laryngeal cancer cases originate from the glottic region (approximately 65%), followed by the supraglottic area (about 30%). Steuer et al.[20] underlined that the most frequent symptoms of laryngeal malignancies include hoarseness, sore throat, dysphagia, and impairment in voice quality with no differences between various histotypes of laryngeal malignances. Clinical stage of tumor at diagnosis was homogenously distributed, with a weak prevalence of early stage (60%). The most relevant part of patients (80%) did not present clinical nodal disease during radiological staging. These data were similar to those reported by the American Cancer Society.[21]

TABLE 5 Patients features about N recurrence of disease.

Pts	First author (y of publication)	Sex (age at diagnosis)	Site of tumor	Clinical stage	First treatment (adj therapy)	Histological features	Time of recurrence	Treatment of N recurrence	Other recurrences	Follow-up
1	Damiani (1981)	Male (61 y)	Supraglottic	cT2 cN0 M0, stage II	TL	pT2 pNx M0	16 m	LND	No	NED at 10 y; DOC at 11 y
2	Damiani (1981)	Male (67 y)	Supraglottic	cT2 cN0 M0, stage II	TL	pT2 pNx M0	19 m	LND	Recurrence on T (36 m) and M (36 m)	DOD at 3 y
3	Cumberworth (1989)	Female (41 y)	Glottic	cT1a cN0 M0, stage I	RT	G1	14 m	LND	No	NED at 17 m
4	Seo (1980)	Female (76 y)	Subglottic	cT4a cN0 M0, stage III	RT	NA	17 m	Palliative treatments	Recurrence on T (10 m) and M (17 m)	DOC at 24 m
5	Blinder (1980)	Male (55 y)	Glottic	cT1b cN0 M0, stage I	TL	pT3 pNx M0, G2	12 m	LND + RT	No	NED at 24 m
6	Spiro (1976)	Male (59 y)	Supraglottic	cT1 cN0 M0, stage III	TL + LND	pT1 pN1 M0, stage III	7 m	Palliative treatments	Recurrence on M (7 m)	DOD at 7 m

Abbreviations: adj, adjuvant; CHT, chemotherapy; DOC, died for other causes; DOD, died of disease; LND, lateral neck dissection; m, months; NA, not available data; NED, no evidence of disease; PL, partial laryngectomy; Pts, patients; RT, radiotherapy; TL, total laryngectomy; y, years.

TABLE 6 Patients features about M recurrence of disease.

Pts	First author (y of publication)	Sex (age at diagnosis)	Site of tumor	Clinical stage	First Treatment (adj therapy)	Histological features	Time of recurrence	Treatment of T recurrence	Other recurrences	Follow-up
1	Damiani (1981)	Male (67 y)	Supraglottic	cT2 cN0 M0, stage II	TL	pT2 pNx M0	36 m	Palliative RT on T and M recurrence	Recurrence on N (19 m) and T (36 m)	DOD at 36 m with metastasis at lung
2	Damiani (1981)	Female (75 y)	Supraglottic	cT2 cN0 M0, stage II	TL (RT)	pT2 pNx M0	10 m	CHT	No	DOD at 10 m with metastasis at esophagus
3	Seo (1980)	Female (76 y)	Subglottic	cT4a cN0 M0, stage III	RT	NA	10 m	TL	Recurrence on T (10 m)	DOC at 17 m
4	Koike (1979)	Male (64 y)	Glottic	cT1a cN0 M0, stage I	RT	NA	12 m	NA	Recurrence on T (12 m)	DOD at 12 m
5	Spiro (1976)	Male (59 y)	Supraglottic	cT1 cN0 M0, stage III	TL + LND	pT1 pN1 M0, stage III	7 m	Palliative treatments	Recurrence on M (7 m)	DOD at 7 m with bone metastasis

Abbreviations: adj, adjuvant; CHT, chemotherapy; DOC, died for other causes; DOD, died of disease; LND, lateral neck dissection; m, months; NA, not available data; NED, no evidence of disease; PL, partial laryngectomy; Pts, patients; RT, radiotherapy; TL, total laryngectomy; y, years.

The treatment of laryngeal MEC depends on medical experience—due to the lack of data reporting outcomes—according to the type of surgical or not surgical management. The most relevant group of patients had undergone surgical procedures according to the management of salivary glands MEC. Postoperative RT was usually indicated in salivary glands cases of advanced tumor stage, high-grade tumor, perineural or lymphovascular invasion, close or positive resection margins, or lymph node involvement.[9] The use of CHT-RT was associated with a better local control with no difference in the OS compared to patients receiving RT only.[10] Regarding surgical procedures, TL is the most used procedure to remove laryngeal MEC. Nowadays, TL is considered a well-established surgical procedure for treating patients with advanced laryngeal carcinoma, which are not amenable to more conservative techniques, or in cases where primary organ-preserving treatments failed.[22] Nevertheless, most included papers were published before the replacement of TL for open partial laryngectomy and above all the minimally invasive techniques, which may account for the huge use of TL to treat laryngeal MEC cases. Furthermore, the lack of knowledge of oncological outcomes of laryngeal MEC might contribute to the surgical choice of a more radical approach.

The EUROCARE-5 population-based study[23] analyzed about 250 000 head and neck cancer cases from 86 cancer registries. That study stratified the recurrence of the disease of laryngeal cancer as follows: 56% local recurrence, 36% regional recurrence, and 8% metastatic recurrence, with a 5 years overall survival of 74, 37, and 7 months after recurrence diagnosis, respectively. The current analysis is in line with such trend. Most patients affected by local recurrence underwent RT to heal MEC, while the other three patients underwent surgical treatments such as TL and cordectomy. All cases were treated according to laryngeal guidelines based on laryngeal squamous cell carcinoma (SCC). Four out of 34 (12%) cases affected by an early stage of the disease and 3/13 (23%) cases affected by local and advanced stage of the disease had local and regional recurrences of the disease. These data are in line with EUROCARE-5 ones.[23] Five patients were alive at the last follow-up after local recurrence evidence.[8,24–26] However, two patients presented lymph node or distant hematogenous metastasis at the time of diagnosis of recurrence and both of them died for the disease.[27,28] The survival rate after diagnosis of local recurrence is 85% and 75% at 5 years, respectively (Figure 2). This upshot is in accordance with the 5 years overall survival rate detected for laryngeal cancer.[23] A regional recurrence of disease is described in 9% of patients, less than the average value of laryngeal cancer lymph node recurrence.[27–31] However, a distant

recurrence of the disease is described in 8% of patients, in accordance with the average value of laryngeal cancer histotypes.[25,27,29,31] A possible reason for that may be the poor trend of MEC cells to infiltrate lymphatic structures than other laryngeal histotypes. Indeed, there is no evidence of a statistical relationship between lymph-node metastasis and the site of primary tumors. The prognosis after lymph-node metastasis treatment is tolerable: 4/6 (67%) patients had no evidence of disease after 1 year of follow up, as reported in Table 5. Nevertheless, two patients underwent palliative care after nodal recurrence diagnosis due to contemporary distant hematogenous metastasis and they died for the disease.[27,31] Finally, the prognosis of patients affected by distant recurrence of disease is poor, as in the other histotypes of laryngeal cancers.[23]

The reported 2 years OS and DFS at 2 years is 80% and 78%, respectively. Due to the lack of data regarding follow up, it is not possible to have such rates at 5 and 10 years of diagnosis. However, some authors reported a 5 and 10 years OS of about 80% and 50%, respectively.[27,30,31] Damiani et al.[27] showed how in their series the 5 years OS is 100% in low grade MEC and 91% in intermediate and high grade MEC. This outcome was more satisfying compared to adeno-squamous laryngeal tumors, which were reported in the same series as 53% at 3 years of diagnosis. Rosenfeld et al.[32] first correlated the clinical outcome with histological type revealing that the low-grade MEC of salivary glands had a survival rate of 100% at 15 years of diagnosis, but at the same time the high-grade tumors had a survival rate of 39%. Oncological outcomes of this current analysis were not stratified with reference to histological tumoral features due to the lack of that information in the set of the included papers.

5 | LIMITATIONS AND FUTURE PERSPECTIVES

The systematic review reported in this paper is the first one focusing on the subject of laryngeal MEC. The related literature includes many case reports and a few case series of patients indeed. Many studies do not show exhaustive information about clinical presentation, histological features, treatment, and follow-up of patients affected by MEC. For this reason, the authors were led to exclude such papers for the analysis. In particular, the lack of sufficient data did not allow to perform an appropriate statistical analysis. In particular, the small sample and the lack of several information in many studies that were included did not allow to evaluate factors associated with the recurrence of the disease. At the same time, it was not possible to stratify oncological outcomes after the histological features of the tumor, such as grading and other prognostic factors. Nevertheless, the results can be deemed interesting to enable an overview of clinical presentations, treatment, and follow-up of MEC cases. In particular, the focus on oncological outcomes in this paper urges an effort to improve the quality of data in the current as well as near future literature through retrospective or prospective studies including a sufficient number of patients in order to enable a better knowledge of their oncological prognosis.

6 | CONCLUSIONS

Laryngeal MEC is a rare neoplasm of minor salivary glands in larynx. No guidelines or indications about the management of such a neoplasm are reported in the literature. Because of it, diagnostic and therapeutic decisions are often made empirically, case by case. Laryngeal MEC commonly affects the supraglottic region of larynx, while laryngeal SCC is frequently detected in glottic compartment. Supraglottic region is anatomically more prone to lymph-node metastases than the glottic one. Despite it, the lower incidence of regional recurrence of disease and better OS and DFS underline how the prognosis of laryngeal MEC is more favorable than other malignant histotypes as laryngeal SCC. Many studies reported how the histological low grading of the tumor was associated with a good prognosis, as in the more common parotid MEC.

ACKNOWLEDGMENT
Open access funding provided by BIBLIOSAN.

FUNDING INFORMATION
The work reported in the publication was funded by the Italian Ministry of Health, RC-2024-2790136.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available in PubMed at https://pubmed.ncbi.nlm.nih.gov/. These data were derived from the following resources available in the public domain: PubMed, https://pubmed.ncbi.nlm.nih.gov/; Scopus, https://www.scopus.com/; Cochrane, https://www.cochranelibrary.com/.

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How to cite this article: Chiari F, Di Martino G, Caporale CD, Molteni G, Presutti L, Guarino P. Analysis of local, regional, and distant recurrence of disease in mucoepidermoid tumors of larynx: A systematic review. *Head & Neck*. 2024;1-13. doi:10.1002/hed.27767