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Systematic or Meta-analysis Studies

Small cell and large cell neuroendocrine carcinoma of the larynx: A comparative analysis☆

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ABSTRACT

The poorly differentiated neuroendocrine carcinomas (NECs) of the larynx are rare tumors that comprise of a small cell-type (SCNEC) and a large cell-type (LCNEC). In order to consolidate the current knowledge about their characteristics and management a systematic review of the available literature was performed. The PubMed/Medline and Scopus databases search resulted in 141 articles published between 1972 and 2019, describing 273 patients: 230 cases were of SCNEC histology (84.2%) and 43 cases were LCNECs (15.8%). Comparing both histological entities, patients with LCNECs were older (63.2 vs. 58.7 years, $p = 0.036$) than SCNEC patients and had more often primary tumor in a supraglottic larynx (79.5 vs. 56.1%, $p = 0.039$), advanced-stage neck disease (N2-3, 56.8 vs. 40%, $p = 0.061$), surgery-based treatment (83.7 vs. 51.9%, $p < 0.001$) and had no radiotherapy (44.2 vs. 29%, $p = 0.071$). At presentation, systemic metastases were diagnosed in 12.1% of the patients, whereas disease relapse was experienced by two-thirds (65.3%) of those initially staged M_0; systemic relapse, alone or in combination with local/regional recurrence, was the most frequent type of failure (in 71.9%). On multivariate analysis, more advanced disease stage and SCNEC histology adversely influenced disease-specific survival. Wide variations in the pattern of care, including radiotherapy doses and chemotherapy regimens, were found among long-term survivors without known disease at ≥ 24 months of follow-up (N = 36). We conclude that the most effective treatment for poorly differentiated NECs has yet to be determined.

Introduction

Neuroendocrine tumors of the larynx constitute a rare and morphologically heterogeneous group of tumors. They are characterized by the presence of neurosecretory granules and share a characteristic immune profile. According to the 2017 WHO proposed classification, the poorly differentiated neuroendocrine carcinomas (NECs) comprise the poorly differentiated neuroendocrine carcinomas of a small cell-type (SCNEC) and a large cell-type (LCNEC) (Fig. 1). The other two tumors of epithelial origin are the well differentiated neuroendocrine carcinoma and the moderately differentiated neuroendocrine carcinoma [1].

In the larynx, a small cell-type poorly differentiated NEC was first described by Olofsson and Van Nostrand in 1972 [2], whereas the large cell-type NEC has only recently been characterized as a histological entity that was previously classified with the poorly differentiated NEC group [3]. Historically, LCNEC cases were not distinguished from atypical carcinoids and both were classified as moderately differentiated NECs. However, the observed differences in biologic behavior and the

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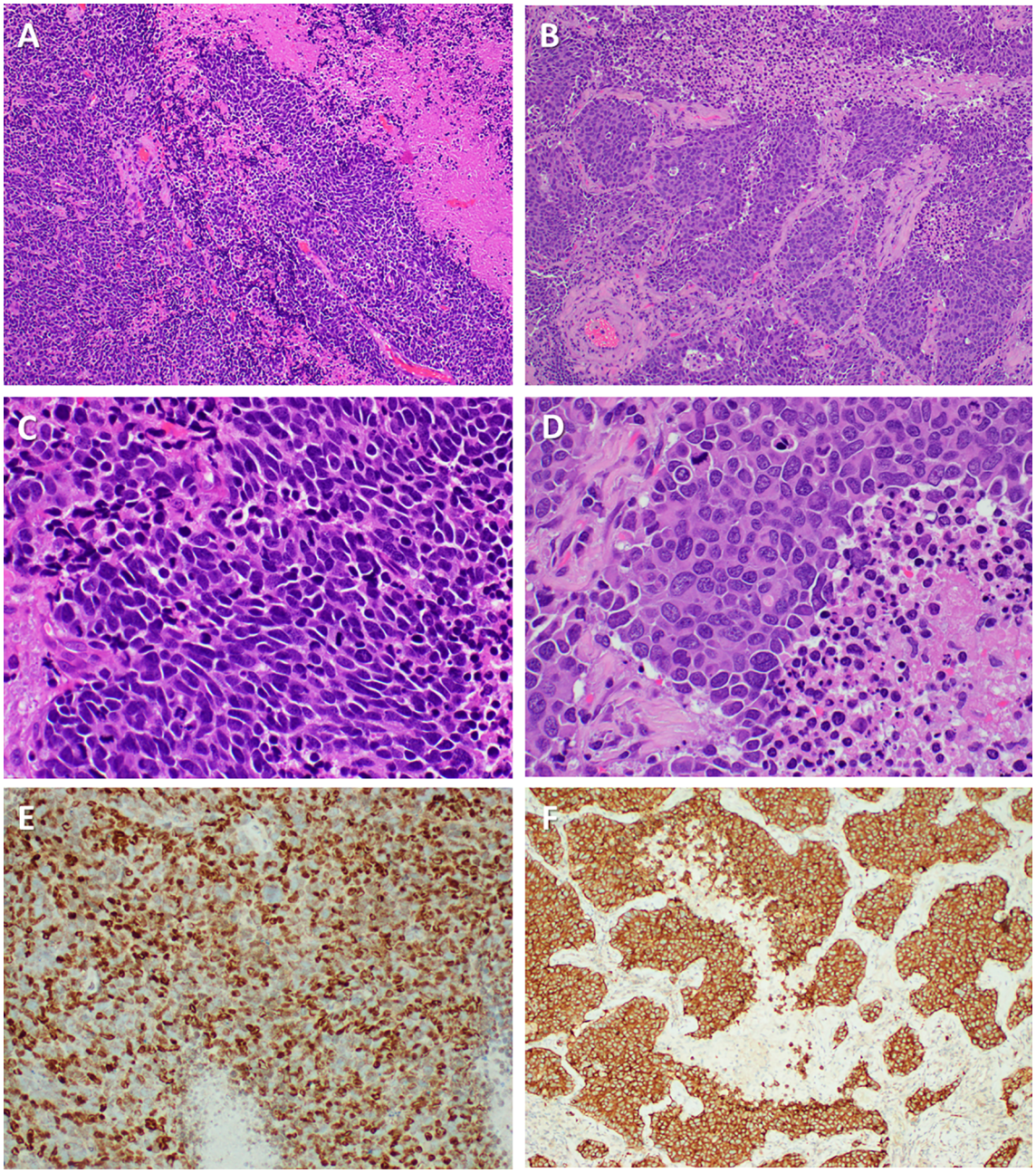

Fig. 1. Histological comparison of poorly differentiated neuroendocrine carcinomas of the larynx. SCNEC showing a hypercellular neoplastic proliferation with solid growth and areas necrosis (A, hematoxylin and eosin stained slide, 10 × 10 magnification). Tumor cells exhibit scant cytoplasm, indistinct cellular boarders, and oval to spindled nuclei with densely hyperchromatic chromatin. Nuclear molding, increased mitotic activity and apoptotic bodies are easily identified (C, hematoxylin and eosin stained slide, 10 × 40 magnification). Tumor cells show diffuse nuclear INMS-1 immunoreactivity confirming neuroendocrine differentiation (E, immunohistochemical stained slide, 10 × 20 magnification). LCNEC showing nested growth with peripheral palisading and focal rosette formation (B, hematoxylin and eosin stained slide, 10 × 10 magnification). Tumor cells exhibit moderate eosinophilic cytoplasm and round to oval nuclei with vesicular chromatin and distinct nucleoli. Numerous mitosis, apoptotic bodies and comedo necrosis are identified (D, hematoxylin and eosin stained slide, 10 × 40 magnification). Tumor cells show diffuse cytoplasmic synaptophysin immunoreactivity confirming neuroendocrine differentiation (F, immunohistochemical stained slide, 10 × 20 magnification).

patients' outcomes between the two morphologic entities prompted Green et al in 2005, employing the 2004 WHO criteria for pulmonary LCNECs, to describe a rare case of LCNEC arising in the larynx [4]. From its first description, several reviews and a meta-analysis of reported SCNEC cases diagnosed in the larynx were published [5–12]; however, only two publications summarized literature reports on laryngeal LCNECs [12,13].

The clinical course of poorly differentiated laryngeal NECs is characterized with non-specific symptoms, early and rapid disease progression, usually with systemic dissemination, and short survival times. Analyzing the 2004–2012 data from the National Cancer Database (NCDB) that covers approximately 70% of the US cancer incidence, Pointer et al identified 853 head and neck SCNEC cases, with the larynx being involved in 34.9% of patients [14]. At presentation, stage III-IVB disease and systemic metastases were diagnosed in 70.6% and 25.8% of these patients, respectively; the median overall survival (OS) was 17.9 months and a 2-year OS 40.6%. Recent meta-analysis of laryngeal NECs, covering a period between 1972 and 2013, reported a

5-year disease specific survival (DSS) of 19.3% for SCNEC and 15.3% for LCNEC [12].

The objective of the present review was to systematically evaluate the available literature on poorly differentiated NECs of the larynx in order to consolidate the current knowledge about the characteristics and management of SCNECs and LCNECs.

Methods

Literature search strategy

In March 2019, a three step strategy of the literature search was employed. In the first step, a comprehensive literature search of the PubMed/Medline and Scopus databases was performed, using the following search terms: “laryngeal neoplasms”, “laryngeal cancer”, “larynx neoplasms”, “cancer of the larynx”, “large cell carcinoma”, “LCNC”, “small cell carcinoma”, “SCNC”, “oat cell carcinoma”, “neuroendocrine”, “neuroendocrine”, “high-grade”, and “poorly differentiated”. The query was created by assigning the title, abstract and keywords/MeSH fields to all terms and combining them with the Boolean operators OR and AND.

At the second step, the results were manually filtered by reviewing the titles and abstracts. Eligibility criteria included: (i) a full length journal article, a case report, letter to the editor, or a short communication (meeting abstracts and review articles were excluded); (ii) a clear description of the histologic diagnosis (SCNEC or LCNEC); and (iii) written in English or any other non-Chinese language.

Finally, the selected publications underwent a detailed reading to extract information on patients, disease, and treatment characteristics and outcome. At this stage, the lists of references in these publications were reviewed for applicable papers potentially missed during the literature search. Due to the wide time span covered and, consequently, a high variability in reporting the T-, N-, and M-stage of the disease at presentation, the UICC TNM staging system as well as a simplified classification system were used: stage I – tumor limited to the larynx; stage II – neck involved (regional disease); stage III – systemic metastases.

Statistical analyses

For comparative analyses, the χ-square test, χ-square test for trends and *t*-test for unpaired samples were used. Survival estimates were obtained by the method of Kaplan-Meier with a log-rank comparison to examine the difference between the survival curves. The end-point of the survival analysis was DSS (death from disease was considered as an event) which was calculated from the date of the diagnosis. The initially planned analysis of the disease-free survival was omitted due to a lack of relevant data. The multivariate analysis was performed for the identification of independent prognosticators for DSS using Cox Proportional Hazard models with backward stepwise selection. Prior to the regression analysis, a correlation between all the studied independent variables and dependent variable were tested in order to avoid a multi-collinearity of the independent variables. All statistical tests were 2-sided and a p-value < 0.05 was considered significant.

Results

Results of the literature search

The initial PubMed and Scopus databases search yielded 431 publications. After the titles and abstracts review, 237 publications were selected for full text reading and a detailed eligibility assessment. This process resulted in the exclusion of an additional 117 publications. Furthermore, a reference lists search, which was also part of the eligibility assessment, resulted in an additional 21 publications that underwent a full text review and fulfilled inclusion criteria. Finally, 141 articles describing 273 patients were selected for systematic review [2,4,5,7,8,13,15–149] (Fig. 2).

Out of 273 poorly differentiated NECs of the larynx reported between 1972 and 2019, 230 cases were of SCNEC histology (84.2%, reported in 128 publications: [2,5,7,8,15–63,65–90,92,94–103,105–112,114,116–118,120–139,141,143,145–147,149]) and 43 cases were LCNECs (15.8%, reported in 20 publications: [4,13,64,82,91,93,104,113,115,118,119,124,125,137,138,140,142,144,146,148]). The number of relevant publications and the number of described SCNEC cases varied somewhat through the studied period. Due to a confusion of terminology and the uncertainty of early studies, the majority of LCNEC cases were reported after the year 2000 (Fig. 3).

Clinical characteristics

The collected information on a patients’ gender and age, smoking status, primary tumor location in the larynx, disease stage and outcome was shown in Table 1. When SCNEC and LCNEC literature cases were compared by means of various characteristics, the two histological entities seemed to share the majority of features. However, at presentation, patients with LCNECs were significantly older that those with SCNECs (63.2 vs. 58.7 years, $p = 0.036$), had a higher proportion of supraglottic tumors (79.5 vs. 56.1%, $p = 0.039$), more advanced neck disease ($N_{2\text{-}3}$, 56.8 vs. 40%, $p = 0.061$), and were treated with surgery-based (83.7 vs. 51.9%, $p < 0.001$) treatment protocols and without radiotherapy (RT) (44.2 vs. 29%, $p = 0.071$).

Treatment outcome and survival

The frequency and the pattern of a disease relapse, as well as the survival status at the end of the follow-up, were comparable between the two groups (Table 1). At presentation, 12.1% of the reported patients had systemic metastasis. In two-thirds (65.3%) of the patients without systemic metastases at diagnosis the disease relapsed during or after treatment. The most frequent type of failure was a systemic relapse (in 71.9%), alone or in combination with local/regional tumors’ re-appearance. No difference in OS were observed between SCNEC and LCNEC groups when all patients with pertinent information on survival ($N = 249$) were considered (at 2 years, 37 vs. 57%; at 5 years, 17 vs. 38%; $p = 0.087$), as well as after limiting the analysis to the period 2000–2019 ($N = 129$; at 2 years, 49 vs. 55%; at 5 years, 24 vs. 38%; $p = 0.628$). In the SCNEC group, patients reported after the year 2000 had significantly improved OS compared to those described in older publications ($N = 208$; at 2 years, 49 vs. 28%; at 5 years, 24 vs. 12%; $p = 0.014$).

Univariate analysis showed a trend of improved DSS in patients treated between 2000 and 2019 ($p = 0.013$), of a younger age (≤ 59 years, $p = 0.064$), non-smokers ($p = 0.160$), with LCNECs ($p = 0.127$), the primary tumor in the supraglottis or glottis ($p = 0.023$), less advanced tumor stage (refers to stage-N, stage-M, overall TNM, and a simplified 3-level classification system; for all, $p < 0.001$), and in those treated with a combination of RT and chemotherapy (ChT), with or without surgery ($p = 0.144$). Only gender and T-stage failed to exert any impact on DFS in univariate analysis.

Due to the highly significant correlation between stage-defining variables, i.e. stage-N, stage-M, and the overall stage, and the higher percentage of missing data on the TNM stage category, a simplified 3-level classification system for stage description was tested in the multivariate analysis. In the Cox model, several variables were incorporated: period (before 2000 vs. 2000–2019), age (≤ 59 vs > 59 years), smoking status (non-smokers vs. smokers), histology (SCNEC vs. LCNEC), the primary tumor site (supraglottis and glottis vs. subglottis and multiple sites), overall tumor stage (I vs. II vs. III), and therapy (RT + ChT $\pm$ surgery vs. others). With the backward stepwise method, the disease stage and histology were the only statistically significant variables retained in the final model with age appearing as statistically

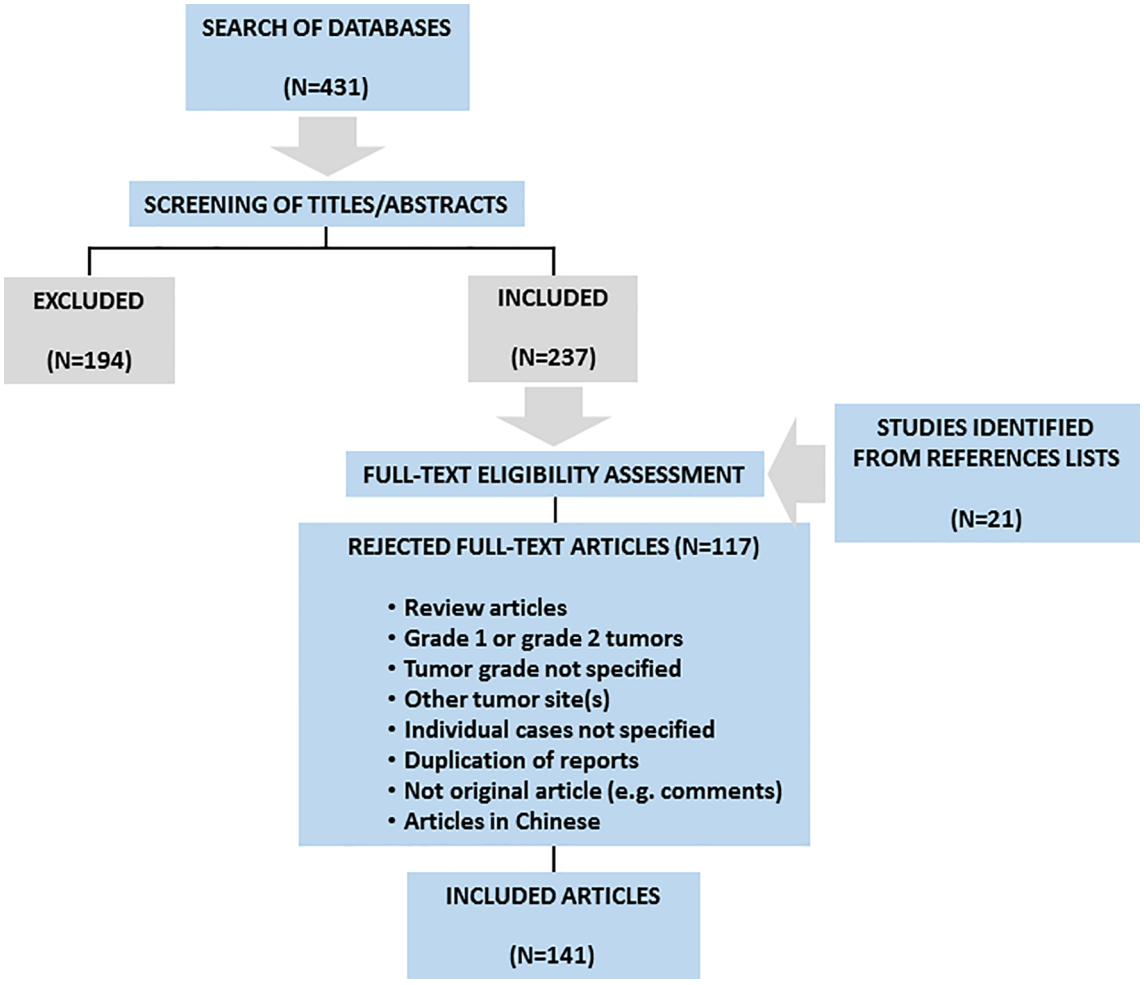

Fig. 2. Three-step strategy of the literature search.

marginally significant (Table 2).

The impact of histology and type of treatment was further explored by stratifying patients according to the disease stage as prognostically the most important variable. When compared by histologic type, only in patients with a regionally advanced disease (overall stage II) the DSS rates were found to be significantly different (SCNEC vs. LCNEC: at 2 years, 25 vs. 76%; at 5 years, 12 vs. 54%; p = 0.005). However, none of the treatment scenarios exerted a survival benefit in any of the stage categories. Furthermore, we analyzed the long-term survivors without a known disease at ≥24 months of follow-up (N = 36) according to the therapy they received. Table 3 lists the types of treatments and the main characteristics of RT and ChT in patients with stage I and stage II disease.

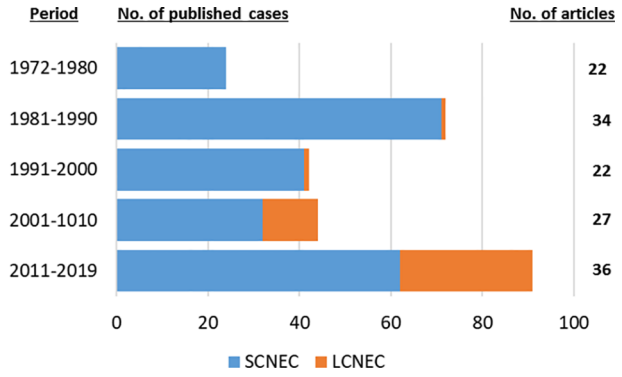

Fig. 3. Cases of poorly differentiated neuroendocrine carcinomas of the larynx reported in the literature, 1972–2019 (SCNEC, small cell neuroendocrine carcinoma, LCNEC – large cell neuroendocrine carcinoma).

Discussion

Non-squamous cell carcinomas represent approximately 1% of malignant laryngeal tumors. Of the non-squamous cell cancers of the larynx, 37% are NECs, followed in frequency by bone/cartilage sarcomas, and minor salivary gland tumors [150]. However, the proportions of individual histological entities included in the NEC group are not well defined. Individual case descriptions or small literature series cannot be a reliable source to address this question due to the high probability of publication bias. On the other hand, a population based study, the SEER database analysis, came out with conflicting results, presenting atypical carcinoids, which are historically the most common, as the least prevalent type [152]. In the Padua University hospital registry, SCNEC of the larynx accounted for 0.43% of 3284 primary and secondary laryngeal and hypopharyngeal malignant tumors diagnosed between 1966 and 1984 [7].

Historically, laryngeal SCNEC is a well-recognized histopathological entity with 230 cases described in the literature [2,5,7,8,15–63, 65–90,92,94–103,105–112,114,116–118,120–139,141,143,145–147, 149]. On the other hand, the LCNEC was formally distinguished from atypical carcinoid tumors only in 2017, when the WHO defined criteria

Table 1
Poorly differentiated neuroendocrine carcinoma of the larynx: clinical characteristics and outcome.

Characteristic	All (N = 273)	SCNEC (N = 230)	LCNEC (N = 43)	p-value
Gender				
female	60	49	11	n.s.
male	201	169	32	
unknown	12	12	0	
Age*	59.4, 0.79 (16–91)	58.7, 0.87 (16–91)	63.2, 1.71 (31–83)	0.036
Smoking status				
non-smokers	23	18	5	n.s.
smokers	171	146	25	
unknown	79	66	13	
Primary tumor site				
supraglottis	160	129	31	0.009
glottis	27	22	5	supraglottis vs. others, 0.039
subglottis	40	37	3	
multiple	19	19	0	
unknown	27	23	4	
Stage T				
T_1	33	28	5	n.s.
T_2	63	53	10	
T_3	53	40	13	
T_{4a+4b}	26	20	6	
unknown	98	89	9	
Stage N				
N_0	104	90	14	n.s.
N_1	20	18	2	N_{0-1} vs. N_{2-3}, 0.061
N_2	83	64	19	
N_3	10	8	2	
N_+, not specified	27	23	4	
unknown	29	27	2	
Stage M				
M_0	241	204	37	n.s.
M_1	33	27	6	
unknown	2	2	0	
Stage TNM				
I	18	15	3	n.s.
II	29	24	5	
III	27	25	2	
IVa + b	103	82	21	
IVc	33	27	6	
unknown	63	57	6	
Stage				
I	94	80	14	n.s.
II	119	97	22	
III	33	27	6	
unknown	27	26	1	
Therapy				
no treatment	12	12	0	0.009
RT	25	22	3	with RT vs. w/o RT, 0.071
ChT	16	16	0	with S vs. w/o S, < 0.001
RT + ChT	67	63	4	
S	48	33	15	
S + RT	35	29	6	
S + ChT	16	12	4	
S + RT + ChT	46	35	11	
unknown	8	8	0	
Treatment outcome				
no relapse	74	62	12	n.s.
relapse	139	119	20	
M + at diagnosis	33	27	6	
unknown	27	22	5	
Site of relapse (N = 139)				
local/regional	39	34	5	n.s.
systemic	75	67	8	
systemic/local/regional	25	18	7	
Survival status				
NED	67	56	11	n.s.
AWD	25	18	7	
DOD	153	131	22	
DOC	11	10	1	
unknown	17	15	2	

N – number of patients, n.s. – not significant, RT – radiotherapy, ChT – chemotherapy, S – surgery, NED – no evidence of disease, AWD – alive with disease, DOD – dead of disease, DOC dead of other causes, w/o – without.
* Mean, standard error of the mean (range).

Table 2
Results of multivariate analysis.

	Disease-free survival		
Variable	HR	95% CI	p-value
Stage			
I vs. II	1.84	1.12–3.03	0.016
II vs. III	6.76	3.37–13.57	< 0.001
Histology			
SCNEC vs. LCNEC	0.48	0.25–0.92	0.027
Age			
≤59 vs. ≥ 60 years	1.54	0.99–2.40	0.056

SCNEC – small cell neuroendocrine carcinoma, LCNEC – large cell neuroendocrine carcinoma, HR – hazard ratio, CI – confidence interval.

for its recognition and classified these tumors, together with SCNECs, in the poorly differentiated category of NECs [15]. Since the first attempt of Green at al in 2005, who used the established lung criteria for the characterization of the LCNEC, only 39 cases were collected and an additional 4 cases were retrospectively identified from previous reports [4,13,64,82,91,93,104,113,115,118,119,124,125,137,138,140,142,144,146,148].

The histogenesis of NECs originated in the larynx is not clear [152]. These tumors could arise from the neuroendocrine cells located in the laryngeal mucosa and, possibly, glandular epithelia [51,153]. However, the role of the pre-existing differentiated neuroendocrine cells as the possible origin of the NECs was questioned because such cells are common in the subglottic part of the larynx and the NECs are usually growing in supraglottis sites [154]. Alternatively, the combination of yet unidentified innate genetic/molecular events and alterations in the laryngeal microenvironment may have resulted in the acquisition of neuroendocrine phenotypes by reserve or by undifferentiated, basal cells of laryngeal epithelia, followed by their clonal proliferation [152]. The high proportion of patients with a history of smoking (88.1% of literature cases) supports this hypothesis.

A clinical presentation of poorly differentiated laryngeal NECs is similar to the case of a conventional squamous cell carcinoma growing in the corresponding part of the larynx. Thus, symptoms reported by the patients depend merely on the subsite involved and the extent of the disease and include swallowing difficulties, breathing problems and/or hoarseness of varying degrees and in different combinations. An association between laryngeal NECs and paraneoplastic syndromes was rarely but well documented and may have diagnostic implications. In 2016, Ferlito et al reviewed the literature and described 10 such cases, 5 of them had SCNECs [155]. According to our analysis and population-based studies, a typical patient with poorly differentiated NECs is an almost 60-year-old man, smoker, with the primary tumor in the supraglottis [151]. In general, diagnostics' procedures in these patients follow the algorithms used in patients with other laryngeal malignancies. Anatomical imaging (CT, MRI) are useful to demonstrate the local extension of the disease although small primary tumors may only be localized by endoscopic assessment. A strong tendency to systemic

Table 3
Treatment details in long-term survivals with poorly differentiated neuroendocrine carcinomas of the larynx reported in the literature (i.e. without known disease present at ≥ 24 months of follow-up).

Treatment	Stage I ($T_{any}N_0M_0$)		Stage II ($T_{any}N_+M_0$)	
	N	Details (follow-up)[Ref]	N	Details (follow-up, mos)[Ref]
RT	0		0	
RT + ChT	4	T_xN_0 n.s. (78 mos)[34] T_xN_0 n.s. (87 mos)[36] T_xN_0 50 Gy, VIN-BCNU-CTX-MEL (54 mos)[42] T_2N_0 70 Gy, weekly CPx6 (24 mos)[131]	4	T_3N_{2c} CTX-VIN-MTX-CCNU for 18 mos, 40 Gy (28 mos)[35] T_2N_+ 60, ChT n.s. (73 mos)[36] T_3N_{2b} concurrent CaPEx3 + 60 Gy, adjuvant CP-CPT-11x3 (54 mos)[103] T_4N_{2b} induction CPEx4, concurrent 66 Gy + CPE × 3 (26 mos)[145]
SURG	6	T_xN_0 TLE (90 mos)[5] T_xN_0 TLE + bilateral RND (42 mos)[49] T_1N_0 TLE + RND (26 mos)[59] T_2N_0 TLE + RND (25 mos)[61] T_1N_0 transoral CO_2 laser (36 mos)[133] T_2N_0 n.s. (41 mos)[137]	2	T_2N_1 TLE + left ND (28 mos)[81] T_xN_+ TLE + ipsilateral mRND (24 mos)[90]
SURG + RT	1	T_2N_0 preoperative RT 11.4 Gy, TLE + left RND (90 mos)[2]	3	T_xN_{2b} TLE + bilateral ND, 50 Gy (52 mos)[65] T_xN_{2c} pLE + bilateral mRND, RT n.s. (48 mos)[106] T_3N_{2b} TLE + mRND, 60 Gy (105 mos)[124]
SURG + ChT	1	T_2N_0 TLE, POMACE regimen (34 mos)[70]	3	T_3N_{2b} neoadjuvant ChT n.s., TLE + bilateral mRND (168 mos)[13] $T_{4a}N_{2c}$ n.s. (31 mos)[119] T_3N_{2b} n.s. (24 mos)[119]
SURG + RT + ChT	4	T_2N_0 pLE, 50 Gy + CTX-DOX-MTX per 4 weeks × 9 (60 mos)[74] T_2N_0 n.s. (48 mos)[118] T_2N_0 pLE, postoperative CRT (n.s.) (26 mos)[129] T_2N_0 transoral laser, postoperative CaPEx6, 50 Gy (99 mos)[134]	4	T_3N_2 n.s. (81 mos)[118] T_3N_{2b} TLE + bilateral ND, concurrent CPEx2 + 50 Gy, adjuvant CPEx2 (36 mos)[126] T_2N_{2c} n.s. (29 mos)[138] T_xN_+ n.s. (34 mos)[140]

RT – radiotherapy, ChT – chemotherapy, SURG – surgery, N – number of patients, CP – cisplatin, VIN – vincristine, BCNU – lomustin, CTX – cyclophosphamide, MEL – melphalan, n.s. – not specified, TLE – total laryngectomy, (m)RND – (modified) radical neck dissection, pLE – partial laryngectomy, DOX – doxorubicin, MTX – methotrexate, CRT – chemoradiation, CaPE – carboplatin-etoposide, CCNU – lomustine, CPT-11 – irinotecan, CP – cisplatin, CPE – cisplatin-etoposide, ND – neck dissection.

dissemination with distant metastasis found in one quarter of patients at their first presentation prompted a meticulous staging with a preferred use of FDG-PET/CT [14,120,132,156,157].

Imaging findings are non-specific and cannot lead to a definitive diagnosis. Histologic verification of the lesion is mandatory (Fig. 1). SCNEC is characterized by a submucosal cellular proliferation typically in association with surface ulceration. The tumor cells grow in solid nests, sheets or ribbons, and are small to medium in size with scant cytoplasm. Characteristically, the nuclei of SCNEC are oval to spindle with dense hyperchromatic chromatin, lack distinct nucleoli and show nuclear molding [158]. Marked crush artifact and extravasated nuclei acids coating adjacent vessels, referred as Azzopardi phenomenon, are features of SCNEC. The diagnosis of LCNEC requires the presence of neuroendocrine architecture, including organoid nesting, trabecular growth, rosettes, and peripheral palisading. The tumor cells are medium to large in size with moderate to abundant cytoplasm. In contrast to SCNEC, the nuclei are round and exhibit vesicular chromatin with easily identified nucleoli [13]. Both, SCNEC and LCNEC, show confluent areas of tumor necrosis, apoptotic bodies and increased mitotic activity, easily exceeding more than 10 mitoses per 10 high-power fields [159]. Poorly differentiated NECs are immunoreactive for cytokeratins and SCNEC often show a characteristic perinuclear (punctate) staining patter (especially with low-molecular weight). According to the 2017 WHO classification of Head and Neck Tumors, at least one positive neuroendocrine marker (synaptophysin, chromogranin or CD56) is required for the diagnosis of SCNEC and LCNEC [1,159]. The latter statement is controversial as some experts advocate for the documentation of two positive neuroendocrine markers. In addition, INSM-1, is emerging as a more specific marker of neuroendocrine differentiation [160]. Immunostaining for p16 can be observed in both SCNEC and LCNEC, however it should be stressed that p16 positivity in laryngeal NEC is not an effective surrogate marker for HPV infection [137]. As of today, few studies have addressed a possible relationship between high-risk HPV and laryngeal NEC. Based on the available data, limited by small sample size, incomplete tumor sampling and concerns about methodology, there is no etiological viral effect [161,162]. In rare occasions, composite tumors may appear in the larynx, consisting of a SCNEC combined with a squamous cell carcinoma or adenocarcinoma [44,53,57,61,71,73,88,94,99,136,149], although a five-components' combination, also including chondrosarcoma and rhabdomyosarcoma parts, has been described [65]. In addition, a squamous cell carcinoma was found in synchrony with LCNECs [140].

In poorly differentiated NECs, various treatment combinations and drugs' regimens were tested with variable success. The high propensity to disseminate in other organs infers that systemic drugs should be part of any treatment strategy used in these tumors, with the possible exception of small primary tumors without neck involvement. Our analysis showed that 46.9% of the cases developed distant metastasis and of all relapses, 71.9% had a systemic component. Indeed, analyzing the literature cases, van der Laan et al came to the conclusion that patients with SCNECs seem to benefit most from a combination of RT and ChT [12]. Based on our results, we cannot confirm their finding, as the disease stage and histological type were the only significant variables retained in the multivariate model; the type of treatment failed to show any prognostic relevance. When reviewing treatment details in long-term survivors, it appears that different treatment scenarios can be applied with curative intent, including surgery alone. However, with the advancement of the stage of the disease, a clear shift from unimodal surgical treatment towards a more aggressive multimodal combinations is evident (Table 3). Depending on the intensity of the systemic regimens, RT doses of 40 Gy to 70 Gy [35,131] in the definitive setting and between 50 Gy and 60 Gy in the postoperative setting, were successfully used in these patients [65,74,124,126,134]. Although a wide range of different ChT regimens were implemented over many years, combinations based on platinum compounds and etoposide, modeled after the small cell lung carcinoma regimen, seems to predominate in more recent cases [103,126,131,134,145]. Other systemic options currently under intensive research in small cell lung cancer, including checkpoint inhibitors administered in different combinations with RT and/or ChT, will probably in the future also find a place in the management of

laryngeal poorly differentiated NECs [163]. At present, no clear evidence-based guidelines could be generated and the selection of treatment regimen remains in the domain of personal experiences and the attitude of treating clinicians. However, in view of the above observations, early and aggressive multimodal treatment regimens with systemic component, appear warranted in this disease, while surgery should be reserved only for early stage primary tumors without a regional spread. Prophylactic brain irradiation, which was occasionally used in the past, does not appear to play a role in this disease [8,30,35,42,44,45,164,165]. In the present analysis, isolated brain metastases were reported in only 5 out of 100 patients with specified site of relapse, confirming that this type of failure is uncommon [5,54,107,143,145].

An intriguing finding of our analysis is that clinical profile as well as survival differences exist between SCNECs and LCNECs. Patients with LCNECs are older, with the primary tumor more often located in the supraglottis, and tend to have a more advanced neck disease (stage N_{2-3}). In these patients, the risk of dying of index cancer is reduced by 52% compared to those with SCNECs. The significant difference in survival between the two histological types was observed only in patients with a regionally advanced disease. Clinicians should be aware of the diversity that exists between the two histological entities of the poorly differentiated category of NETs when discussing disease characteristics and prognosis with their patients and during the treatment decision-making process, particularly in view of the aggressiveness of the different therapy scenarios proposed to the patient. Howewer, it should be noted that observed differences between the histological entities are derived from the comparison of a small number of LCNECs with much larger group of SCNECs; with accumulation of LCNEC and a more balanced comparison, this picture may change.

We are aware that the present analysis has several shortcomings that are common to similar systematic reviews of the literature. Summarizing the results of numerous case reports and the small series of patients published by different authors and institutions, and a study period of several decades, inherently biased by significant qualitative differences in the diagnosis and therapy, may easily lead to wrong or misleading conclusions. Also the fact that only a limited number of real-life cases have been reported in the literature, which are, or are not, representative (i.e. publication bias), can blur the picture. This is especially true for LCNEC, because of the confusions in terminology many cases remain hidden in the atypical carcinoid group. However, the rarity of these tumors prevents any prospective evaluation of different therapies: an orchestrated collection of retrospective data from multiple institutions seems to be the best way to improve our knowledge about these interesting tumors.

Conclusions

A poorly differentiated NEC is a rare tumor and its incidence is not well determined. Due to the high propensity to regional and systemic spread, a thorough diagnostic workup is crucial in these patients. The most effective treatments have yet to be determined; at present, it appears that only early and aggressive therapies, employing different treatment modalities, may potentially be considered curative. There are important differences between the associated histological entities, with LCNECs being prognostically more favorable than SCNECs.

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Declaration of Competing Interest

The authors have declared no conflicts of interest.

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