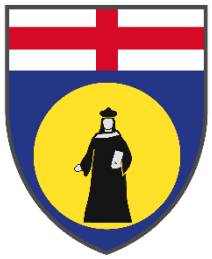

UNIVERSITÀ DEGLI STUDI DI GENOVA

SCUOLA DI SCIENZE MEDICHE E FARMACEUTICHE
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TESI DI SPECIALIZZAZIONE

Rare Laryngeal tumors: a Retrospective Bicentric Study on 74 Patients and Systematic Review

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INTRODUCTION

Head and neck cancer ranks as the seventh most common cancer worldwide, encompassing a diverse group of tumors affecting the upper aerodigestive tract [1]. Within this category, laryngeal cancer (LC) stands out as the most prevalent neoplasm, accounting for 30%-40% of head and neck malignancies and representing the most common cancer in the field of otolaryngology [2]. Each year, approximately 184,615 new cases of LC are diagnosed globally, making up 1.1% of all cancer cases, and it results in 99,840 deaths, representing 1% of all cancer-related fatalities [2]. Squamous cell carcinoma (SCC), originating from the laryngeal epithelium, is the predominant histological type, comprising 85-90% of all LC [3, 4]. More rarely, a minority of cases will suffer from non squamous cell tumors, thus originating from laryngeal minor salivary glands, connective tissue, muscles, cartilage, vascular, lymphatic, and neural tissues [5].

Laryngeal malignant salivary gland tumors (LMSGT) account for less than 1% of all laryngeal malignancies [6], with adenoid cystic carcinoma (ACC) being the most common (32-69%), followed by mucoepidermoid carcinoma (15-35%) [7].

Laryngeal neuroendocrine carcinomas (LNC) account for about 0,6-1% of all laryngeal neoplasm [8, 9] and they are usually classified according to their grade of differentiation. Specifically, they are categorized into well-differentiated LNC, also known as typical carcinoid, moderately differentiated LNC, referred to as atypical carcinoid, and poorly differentiated LNC, which are further divided into small-cell and large-cell neuroendocrine carcinomas [10].

Among laryngeal sarcomas (LS), chondrosarcoma is by far the most common histology, being also the most common non-squamous cell tumor of the larynx. Chondrosarcoma accounts for 0.1-1% of all laryngeal neoplasms [11].

Among rare laryngeal tumors, primary laryngeal mucosal melanoma (LMM) represents the rarest entity, making it difficult to find accurate data in literature on the actual incidence. This may be partly due to the fact that, as the disease often presents at a metastatic stage with distant spread, it becomes challenging to identify primary cases and their site of origin. Mucosal Melanoma (MM) of the head and neck accounts for only 0.5-3% of all MM cases, with LMM, representing just 3.8% to 7.4% of these cases [12].

Due to the rarity of these diseases, case reports, case series, and single-center experiences represent the main contributions in the literature for defining treatment and sharing clinical insights. In this scenario, clinicopathological features, treatment protocols, prognostic factors, and survival data are limited, and a consensus on the best management for these lesions is still to be determined.

In this study, we evaluate the surgical and oncological outcomes within a cohort of patients diagnosed with rare laryngeal tumors, who received treatment at two renowned Italian tertiary cancer centers. Additionally, we present a comprehensive and up-to-date systematic review of the literature concerning rare laryngeal tumors, with the aim of elucidating significant perspectives in this challenging area of head and neck cancers'pathology.

MATERIALS AND METHODS

Study population

We retrospectively evaluated patients affected by non-SCC malignant laryngeal tumors, treated between 1995 and 2022 at two Italian institutions, both tertiary cancer centers: the Unit of Otolaryngology and Head and Neck Surgery - European Institute of Oncology, IRCCS and the Unit of Otolaryngology – Head and Neck Surgery - IRCCS Ospedale Policlinico San Martino – University of Genova.

Inclusions criteria were the following: 1) primary malignant laryngeal neoplasm; 2) non-metastatic at the time of diagnosis; 3) tumor with final histology of sarcoma, neuroendocrine carcinoma, malignant salivary gland tumor, and mucosal melanoma; 4) at least one year of follow up (FU) after treatment; 5) patients treated with curative intent.

Exclusion criteria were the following: 1) laryngeal SCC or other histology apart from the above mentioned; 2) other sites of origin besides the larynx; 3) patients metastatic at presentation; 4) patients younger than 18 years-old.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee (ID LAR_MULTI).

Diagnostic work-up and treatment protocol

Clinical evaluation was performed preoperatively with a flexible video-endoscope under white light (WL) and bioendoscopy (NBI, Olympus Medical System Corporation, Tokyo, Japan; Storz Professional imaging Enhancement System (SPIES) filters (Karl-Storz, Tuttlingen, Germany, Pentax i-Scan high-definition, video-endoscopic system, Japan). Based on the subsite and histology, patients underwent either a head and neck magnetic resonance imaging (MRI) or a computed tomography (CT) scan with contrast enhancement. In advanced-stage cases a PET or a whole body CT scan was also performed to assess the presence of distant metastases.

Patients were staged or re- staged if old cases, according to the eighth edition of the Union for International Cancer Control —American Joint Committee on Cancer TNM staging system [13]. All

cases were discussed by the dedicated multidisciplinary team composed by surgeons, radiotherapists, oncologists, radiologists and pathologists, in order to define treatments and care. Surgical treatments were always conducted with radical intent and included: transoral laser microsurgery (TOLMS), open partial horizontal laryngectomies (OPHL), total laryngectomy (TL), and cricotracheal resection and anastomosis (CTRA), with or without neck dissection, following NCCN guidelines [14]. Formal indications to any adjuvant treatment were released on the base of the final histopathological report and further multidisciplinary board discussion.

Data collection and outcomes

Data collected included demographic characteristics (age, gender), initial clinical variables (tumor histology, grading, pT, pN, and margin status), treatment-related information (type of treatment, and any adjuvant treatment), status at last follow-up, and additional data on whether the patient underwent total laryngectomy. Recurrence data included presence and location of recurrence. We then divided the data and results into four subgroups: LS, LNC, LMSGT, and LMM.

The primary survival endpoints were overall survival (OS) and recurrence free survival (RFS). Secondary endpoint was total laryngectomy-free survival (TLFS).

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 [15]. A comprehensive search on PubMed, and Embase was conducted on April 2024, using the following queries:”('larynx cancer'/exp OR 'larynx cancer') AND ('adenocarcinoma'/exp OR adenocarcinoma OR 'typical carcinoid'/exp OR 'typical carcinoid' OR 'atypical carcinoid'/exp OR 'atypical carcinoid' OR 'small cell neuroendocrine' OR scnc OR 'large cell neuroendocrine carcinoma'/exp OR 'large cell neuroendocrine carcinoma' OR lcnc OR 'nut midline carcinoma'/exp OR 'nut midline carcinoma' OR nutmc OR 'melanoma'/exp OR melanoma OR 'adenoid cystic carcinoma'/exp OR 'adenoid cystic carcinoma' OR 'rhabdomyosarcoma'/exp OR rhabdomyosarcoma OR 'rhabdo-myosarcoma' OR 'malignant fibrous histiocytoma'/exp OR 'malignant fibrous histiocytoma' OR mfh OR 'lymphoma'/exp OR lymphoma OR 'mucoepidermoid tumor'/exp OR 'mucoepidermoid tumor' OR 'acinar cell carcinoma'/exp OR 'acinar cell carcinoma' OR 'salivary gland cancer'/exp OR 'salivary gland cancer' OR 'neuroendocrine tumor'/exp OR 'neuroendocrine tumor' OR 'myoepithelial carcinoma'/exp OR 'myoepithelial carcinoma') AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)”.

Selection criteria

Original papers in English, published until April 2024 were considered. Inclusion criteria were: 1) cohort study as study design, reporting cases of primary malignant laryngeal neoplasm, belonging to one of the following categories: LS, LNC, LMSGT and LMM; 2) at least one year of FU after treatment; 3) patients treated with curative intent; 4) papers reporting survival data in terms of OS, disease specific survival (DSS), RFS and TLFS. Exclusion criteria were: a) impossibility to extrapolate specific data on treatments and survival of patients; b) pediatric cohorts; c) case reports; d) all cases not meeting the above inclusion criteria. Two authors (PB and CM) independently screened all titles and abstracts, and full-texts were obtained for publications that fulfilled inclusion criteria. The references of all selected articles were reviewed to identify additional relevant articles and other papers found with manual search were also included if relevant.

Data extraction

For each study included, the relevant features (publication year, country, study design) were collected along with demographics, tumor features, mean follow-up, and OS, DSS, RFS and TLFS rates, when available. PB extracted data from eligible articles and created a dedicated database, one for each group of histologies.

Statistical Analysis

Descriptive statistics were used to present patient and tumor characteristics. Data were presented as absolute and relative frequencies (percentage) for categorical variables or median and interquartile range (IQR) for continuous variables.

Survival distributions for both OS and RFS were estimated using the Kaplan-Meier method, and the log-rank test was employed to compare survival curves across groups. Continuous variables were dichotomized based on their median values.

Results from Cox proportional hazard models of factors found to be significant in univariate analysis were presented as hazard ratios (HRs) with 95% confidence intervals (CIs), and p-values < 0.05 were considered statistically significant.

A Multivariable Cox proportional hazards model was applied to adjust the effect of pT combined on RFS for age considered as continuous variable following their statistical significance in a univariate analysis based on the log-rank test.

All the statistical analyses were performed using R software (http://www.r-project.org) version 4.3.0 and, particularly, the packages "*survival*" and "*survminer*".

RESULTS

Patients

The study cohort characteristics are detailed in Table 1. The analysis included 74 patients with four distinct tumor types: sarcomas (N=34, median follow-up 5.28 years), neuroendocrine carcinomas (N=25, median follow-up 2.10 years), salivary gland tumors (N=13, median follow-up 3.97 years), and melanomas (N=2).

Among the sarcoma group there were 22 chondrosarcomas, 2 solitary fibrous tumors, 2 malignant fibrous histiocytomas, 2 leiomyosarcomas, 2 synovial sarcomas, 1 rhabdomyosarcoma, 1 liposarcoma, 1 Kaposi sarcoma and 1 osteosarcoma. Among the neuroendocrine group 3 were well-differentiated, 3 moderately-differentiated, 16 poorly-differentiated and 3 were LNC not further specified. Lastly, in the LMSGT group 6 were adenoid cystic carcinoma, 5 mucoepidermoid carcinoma, 1 adenocarcinoma and 1 lymphoepithelial carcinoma.

The median age at treatment was 59 years (IQR: 55–68) for sarcomas, 68 years (IQR: 59–73) for neuroendocrine tumors, and 63 years (IQR: 45–69) for salivary gland tumors, while the two patients affected by LMM were 63 and 57 years old. The majority of patients with LS were male (68%), together with LNC patients (80%), compared to 46% in salivary gland tumors, and both patients with melanoma.

Surgery was the predominant treatment across all groups, with 73 out of 74 patients undergoing surgery. Only 1 out of 25 patients with neuroendocrine tumors was treated with chemoradiotherapy.

Sarcomas were most frequently Grade 1 (59%), followed by Grade 2 (29%) and Grade 3 (12%). Among patients with neuroendocrine tumors, 52% had Grade 3 tumors, 32% had Grade 2, and 16% had Grade 1. In contrast, 46% of salivary gland tumors were Grade 1, with fewer patients in Grade 2 (23%) and Grade 3 (31%).

In terms of organ preservation, total laryngectomy (whether as initial treatment or for recurrence), was performed in 38% of LS patients, in 24% of LNC patients, in 15% of LMSGT patients, and in 50% of LMM patients.

At the last follow-up, among sarcoma patients, 29 (84.9%) were alive (27 with NED and 2 AWD), while 5 (14.7%) had died (2 DOD and 3 DOC). Among patients with neuroendocrine tumors, 7 patients (28%) were still alive, 6 (24%) with no evidence of disease (NED) and 1 (4%) alive with disease (AWD), while 18 (72%) had died, 17 (70,8) from the disease (DOD) and 1 (4%) from other causes (DOC). In the salivary gland group, 11 patients (84.7%) were still alive (10 with NED and 1 AWD), while 2 patients (15%) had died, both for disease. Of the two patients observed with

melanoma, one experienced DOD 19 months after treatment due to lung metastases, while the other was AWD with lung metastases and awaiting the initiation of non-surgical treatment.
Recurrence rates were higher in patients with neuroendocrine tumors (72%) compared to those with salivary gland tumors (54%) and sarcomas (24%). Additionally, both patients observed with melanoma experienced recurrence.
The survival data analysis reported below exclude melanomas due to the limited sample size.

Overall Survival Analysis – Sarcomas

A Kaplan-Meier survival analysis was conducted on a cohort of 34 sarcomas patients to evaluate overall survival outcomes over time (Figure 1). During the follow-up period only 5 deaths were observed. The median survival time was not reached, indicating that the majority of patients did not experience mortality during the follow-up period. The median follow-up time among those who did not experience the event was 5.55 years.
Log-rank tests were conducted to identify potential prognostic and confounding factors (Table 2), with age variable dichotomized according to its median value. Statistically significant differences in OS were observed between the age groups (p-value = 0.04).
Specifically, the group aged ≤ 59 years had 1 event among 17 patients, with the median survival time not reached, while the group aged > 59 years experienced 4 events out of 17 patients, with a median survival of 9.95 years (95% CI: 9.95 - NA).

Overall Survival Analysis – Neuroendocrine carcinomas

A Kaplan-Meier survival analysis was conducted on a cohort of 25 patients with neuroendocrine tumors to evaluate overall survival outcomes over time (Figure 2). During the follow-up period, a total of 18 events (deaths) were observed. The median survival time was estimated at 2.89 years (95% CI: 1.66-NA). Most deaths occurred within the first three years of follow-up. The median follow-up time among those who did not experience the event was 4.4 years.
Log-rank tests were conducted to identify potential prognostic and confounding factors (Table 3). A borderline significant difference was observed for pT (p-value = 0.06) and grading when considered combined (p-value = 0.06).
More deaths were reported in the early years, among patients with pT=3 compared to the other two groups. In particular, the group with pT=1 had 7 event out of 9 patients, with a median survival of 3.59 years (95% CI: 1.66 - NA), and the group with pT=2 experienced 2 events out of 4 patients, with a median survival of 3.25 years (95% CI: 2.10 - NA), while the group with pT=3 experienced 8 events out of 11 patients, with a lower median survival of only 1.13 years (95% CI: 0.67 - NA), (Figure 3).

When combining the pT=1 and pT=2 groups, the difference becomes statistically significant (p-value = 0.02, Table 4), with the merged group showing a median survival of 3.59 years (95% CI: 2.10 - NA) (Figure 4).

Overall Survival Analysis – Salivary gland tumors

A Kaplan-Meier survival analysis was conducted on a cohort of 13 patients with salivary gland tumors to evaluate overall survival outcomes over time (Figure 5). During the follow-up period, only 2 events (deaths) were observed. The median survival time could not be determined due to the low number of events; however, the lower confidence limit was estimated at 5.41 years, The median follow-up time among those who did not experience the event was 3.97 years.

Log-rank tests were performed to identify potential prognostic and confounding factors, but none reached statistical significance (data not shown).

Recurrence-Free Survival Analysis – Sarcomas

A Kaplan-Meier survival analysis was conducted to evaluate RFS in a cohort of 34 sarcoma patients (Figure 6). During the follow-up period, 8 recurrences were observed, all of which occurred within the first four years after treatment. The median RFS was not reached, indicating that the majority of patients did not experience recurrence during the follow-up period. The median follow-up time was 4.10 years.

Log-rank tests were conducted to assess the impact of various prognostic factors on RFS, including age, sex, tumor grade, pT, and whether patients underwent total laryngectomy. The analysis was also stratified by sites of recurrence: local, regional, and distant recurrence. However, no statistically significant associations were found for any of the variables in relation to recurrence-free survival (Table 4).

Recurrence-Free Survival Analysis – Neuroendocrine carcinomas

A Kaplan-Meier survival analysis was conducted on a cohort of 25 patients with neuroendocrine tumors to evaluate RFS. The analysis revealed that the majority of the 18 recurrences occurred within the first two years of follow-up, and by 8 years, no patients remained at risk. The median RFS was estimated at 1.04 years (95% CI: 0.75-5.47), and the median follow-up time was 0.84 years (Figure 7).

Log-rank tests were conducted to identify potential prognostic and confounding factors, across different recurrence site stratifications: local recurrence, regional recurrence, and distant recurrence.

Significant associations were observed only for distant recurrence, in relation to age, pT, and total laryngectomy (Table 5).

Younger patients (aged ≤ 68 years) presented a higher incidence of distant recurrence, with 10 events out of 13 patients, compared to those aged > 68 years, who had 3 events out of 12 patients, with a p-value of 0.04 (Figure 8).

Furthermore, patients with pT=3 tumors had the highest risk of distant recurrence, with 8 events out of 11 patients, compared to 2 events out of 9 patients for pT=1 and 3 events out of 4 patients for pT=2, with a p-value of 0.01 (Figure 9). When the pT=1 and pT=2 groups were combined and compared with the pT=3 group, the difference in recurrence-free survival became more significant (p-value = 0.00), indicating that pT=3 tumors are associated with a significantly higher recurrence risk (Figure 10).

Lastly, patients who underwent total laryngectomy had a significantly higher risk of distant recurrence (p-value = 0.02), with 5 out of 6 patients experiencing distant recurrence compared to 8 out of 19 patients who did not undergo the procedure (Figure 11).

In the Multivariable Cox proportional hazards model, the analysis revealed that patients with pT3 tumors had a more than sixfold increased likelihood of relapse compared to those with pT1 or pT2 stages (HR = 6.58, 95% CI: 1.82–23.8, p = 0.004), independent of age (Table 6).

Recurrence-Free Survival Analysis – Salivary gland tumors

A Kaplan-Meier survival analysis was conducted on a cohort of 13 patients with salivary gland tumors to evaluate RFS (Figure 12). During the follow-up period, a total of 7 recurrences were observed, all occurring within the first 5 years. The median time to first recurrence was estimated at 3.27 years (95% CI: 1.57 - NA). The median follow-up time was approximately 2.11 years.

Log-rank tests were performed for various prognostic factors, across different recurrence stratifications: local recurrence, regional recurrence, and distant recurrence. The only variable that reached statistical significance was age concerning local recurrence. Among young patients (aged ≤ 63 years), there were no events (0 recurrences out of 7 patients), whereas among patients aged > 63 years, 3 out of 6 patients experienced local recurrence, with a p-value of 0.02 (Figure 13). However, given the small sample size, the lack of significance in other variables may be due to insufficient statistical power.

Systematic review

The initial search in PubMed and EMBASE produced a total of 7171 articles, 6201 and 970 respectively.

196 articles written in other languages other than English were excluded. After filtering the initial search results on title 1579 articles remained. Of these, 214 remained after filtering on abstract. The entire text of these articles was analyzed and 25 met the inclusion criteria for our study (see Fig. 14 for complete flow diagram for study selection). In particular 10 concerning LS [16–25], 7 concerning LNC [9, 26–31] and 8 concerning LMSGT [32–39]. No paper regarding LMM met the inclusion criteria for this study.

Data are presented in Table 7, 8 and 9, one for each histological group. For sarcomas the median age of presentation ranged between 50 and 65 years. The mean FU ranged between 55,5 and 276 months. One paper [17] presented two different cohorts, one treated with conservative surgery and one with total laryngectomy and are therefore reported separately in Table 7. Most studies concerned chondrosarcomas only, while 2 [20, 22] included all types of sarcomas. The 5-years OS, DSS and DFS in all studies ranged between 48-100%, 78,9-90% and 30-67,6% respectively. In the neuroendocrine group the median age ranged between 57 and 64 years. One paper [29] presented three different cohorts, one concerning early staged, one locally advanced and one metastatic LNC. Another paper [30] presented three different cohorts depending on different stages (I-II, III-IVa-IVb and IVc). These cohorts are reported separately in Table 8. The mean FU ranged between 16 and 24 months. Most studies reported cases of poorly differentiated LNC exclusively, while 3 [9, 28, 31] included all types of LNC. The 5-years OS and DSS in all studies ranged between 9-73,9% and 30,2-60% respectively.

Regarding LMSGT, the median age ranged between 49 and 65 years. The mean FU ranged between 23 and 102 months. Three studies [32, 35, 36] reported cases of adenoid cystic carcinoma exclusively, 3 [34, 37, 38] included mixed hystologies among LMSGT, 1 [33] only adenocarcinoma not otherwise specified and 1 [39] cases of adenoid cystic carcinoma and adenocarcinoma not otherwise specified together. The 5- and 10-years OS in all studies ranged between 45,2-72,6% and 46-61% respectively, while 5 and 10-years DSS ranged between 42,8-83% and 45,3-67,9% respectively.

DISCUSSION

This study presents a comprehensive analysis of rare laryngeal tumors, including sarcomas, neuroendocrine carcinomas, malignant salivary gland tumors, and mucosal melanomas, through a retrospective bicentric study and a systematic review. The findings contribute valuable insights into the clinicopathological features, survival outcomes, and recurrence patterns of these rare entities, underlining both their heterogeneity and clinical challenges.

The present analysis highlights LNC as the most aggressive histology compared to LS and LMSGT, with a median survival of approximately 2.89 years. The same group shows also higher mortality and recurrence rate, in correlation with higher pT stage. In a meta-analysis by Van der Laan et al. [10], a recurrence rate for LNC was reported to range between 35% and 81%, depending on the histology, which aligns with our observed rate of 72%. This result, being closer to the higher end of the reported range, can be attributed to the large proportion of poorly differentiated cases (64%) included in our cohort.

In our study LNC showed also a predominance of metastases with a distant recurrence rate of 52% (compared to loco and regional of 18% for both). This trend finds confirmation in literature with a reported rate of 42.0% to 57.1% for distant metastases in patients with an atypical carcinoid tumor or poorly differentiated subtype [10]. Additionally, our results show that 68% of patients died due to the disease, confirming its aggressiveness and poor prognosis, with a reported 5-year OS ranging between 13,3-73,9% [9, 26–29] with higher limit values found in papers that consider all grades tumors [9, 28] and lower limit values reported when considering only poorly differentiated ones [26].

As the vast majority of patients with LNC died from distant metastasis, a radical excision of the tumor permitted good locoregional control of the disease, these patients benefitted from a good quality of life. This aspect seems fundamental as not only patients avoided tracheotomy and PEG due to cancer progression, also they showed augmented compliance to post operative medical oncological treatments.

LS and LMSGT on the other hand have shown a more favorable prognosis, in terms of both mortality as well as recurrence rate.

In our cohort sarcomas showed relatively favorable overall survival with just 5 deaths observed during the FU time, only 2 patients out of 34 (8%) died because of the disease and 79% of them was alive and disease-free at last FU. These results are coherent with literature, reporting a 5-years OS ranging between 48-100% [16–18, 33–39] if we consider papers reporting all sarcomas [16–25] and a range of 79,4-100% [16, 33–39] if we consider only papers reporting chondrosarcomas [16–19, 21, 23–25]. The latter histology represented the majority in our study (22 out of 34) with grade 1 being the most represented among sarcomas (59%), thus justifying the favorable survival emerged. Regarding recurrence, we observed an overall recurrence rate of 24%, with local recurrences accounting for 24%, regional recurrences for 8%, and distant recurrences also for 8%, with only two patients developing distant metastases and with locoregional recurrences all treated with surgery. Notably, while eight patients experienced local recurrence, only two ultimately died from the disease. This highlights that effective locoregional control of the disease can be achieved through surgery without adversely impacting overall survival. The same result was observed by Thomson et al [23],

in a series of 111 patients affected by laryngeal chondrosarcomas, with a reported recurrence rate of 18%. In their study, increasing tumor grade was associated with a higher chance of developing a recurrence, but this did not affect the overall survival rate [23].

The absence of significant associations between clinical or pathological variables and overall survival (OS) or recurrence-free survival (RFS) in our cohort may be attributed to the limited sample size. Indeed, larger studies have demonstrated that higher tumor grade is an independent predictor of both worse OS [18] and RFS [23], a relationship that may not have been evident in our smaller cohort.

LMSGT exhibited a favorable prognosis, with only two observed deaths during follow-up. In this subgroup the majority was represented by adenoid cystic carcinoma and mucoepidermoid carcinoma (85%), with grade 1 representing 46% of cases. Literature confirms the good prognosis of this disease, with a reported range in terms of 5y-OS and DSS of 45,2-72,6 and 42,8-83% [32–39] respectively when comprising all histologies and 64-72,6 and 69-77,3% [32, 35, 36, 39] respectively when comprising adenoid cystic carcinoma solely.

Regarding ACC, Mur et al. [32] found how low-grade disease was associated with better DSS compared to high-grade disease with a 5-year DSS of 95.2% versus 38.7%.

In our cohort, there were a total of seven recurrences: three local and four distant. Two patients ultimately succumbed to the disease, one with adenoid cystic carcinoma (ACC) and the other with adenocarcinoma. Notably, all three local recurrences were successfully treated with surgery, and these patients remained free of disease at their last follow-up. This underscores that local recurrence does not necessarily impact survival and highlights surgery as an effective treatment approach for managing such recurrences. Age was the only variable found to be statistically associated with local recurrence in our study, while no other significant associations were identified for overall survival (OS) or recurrence-free survival (RFS). This lack of statistical relationships may be attributed to the limited sample size of our LMSGT cohort. Conversely, larger studies on adenoid cystic carcinoma of the head and neck have demonstrated that histologic grade serves as a significant prognostic factor for recurrence [40, 41].

The final subgroup in our cohort consisted of patients with mucosal melanoma, an exceptionally rare entity within the already uncommon group of laryngeal tumors. Given the limited sample size of only two cases in our study, statistical analysis could not be conducted. Nevertheless, the aggressive nature and poor prognosis of this malignancy were evident, as one patient succumbed to the disease, while the other remains alive but with metastatic progression. In a recent systematic review on LMM by Fernandez et al. [42], with 44 cases presented, they reported a 5y-OS and -RFS of 12% and 10% respectively, with the most frequent cause of death being distant metastasis (55% of cases). Notably, no significant association was found between type of treatment and OS nor DSF time and also the

type of surgery was not associated with DSF time. Only the presence of metastasis was significantly associated with both OS and DFS time. This highlights the paramount importance of accurate preoperative staging in these patients and the need for thoughtful selection of the surgical approach. The chosen procedure should aim to achieve oncologic radicality, considering the relatively low local recurrence rate (33.3%) [42], while prioritizing the preservation of quality of life, given the poor overall prognosis associated with this disease.

In terms of laryngeal preservation 30% of our patients underwent total laryngectomy, whether as primary treatment or as treatment for recurrence. The sarcoma group showed the highest rate of total laryngectomy (38%), compared to LNC (24%) and LMSGT (15%) a result that finds confirmation in a systematic review by A.C. Iglesias et al. [43] in which TL emerged as the treatment of choice in 34% of patients.

Across all four histological subtypes analyzed, surgical treatment proved to be effective in achieving locoregional disease control without precluding the possibility of salvage surgery in cases of local recurrence. This flexibility underscores the role of surgery not only in establishing primary disease control but also in offering a viable pathway for subsequent interventions, preserving long-term quality of life even in the face of recurrent disease.

CONCLUSIONS

This study provides a detailed analysis of rare laryngeal tumors, specifically focusing on sarcomas, neuroendocrine carcinomas, malignant salivary gland tumors, and mucosal melanomas. Through a retrospective analysis and systematic review, the findings underscore the heterogeneity of these tumor types and the distinct challenges they pose in terms of management, survival, and recurrence.

LNC emerged as the most aggressive histology, with poor overall survival and high recurrence rates, predominantly due to distant metastases. LS, the most prevalent subgroup, exhibited the most favorable prognosis among the studied groups, with a high percentage of patients alive and disease-free at follow-up and low incidence of recurrences. LMSGT, which demonstrated relatively favorable outcomes in terms of survival, had a higher recurrence rate compared to LS. Despite the very small sample size, the aggressive behavior and poor prognosis of LMM were clearly evident.

Future studies should aim to expand sample sizes and explore novel therapeutic strategies tailored to these rare tumor types. Additionally, focus on quality-of-life outcomes, particularly in preserving laryngeal function, will be essential in refining treatment protocols and enhancing patient care.

TABLES

Table 1. Characteristics of the study cohort, including demographic information and clinical variables

Characteristics	Sarcomas N = 34[1]	Neuroendocrine N = 25[1]	Salivary N = 13[1]
Age	59 (55, 68)	68 (59, 73)	63 (45, 69)
Sex			
Female	11 (32%)	5 (20%)	7 (54%)
Male	23 (68%)	20 (80%)	6 (46%)
Treatment			
Chemoradiotherapy	0 (0%)	1 (4.0%)	0 (0%)
Surgery	34 (100%)	24 (96%)	13 (100%)
Grading			
1	20 (59%)	4 (16%)	6 (46%)
2	10 (29%)	8 (32%)	3 (23%)
3	4 (12%)	13 (52%)	4 (31%)
Total laryngectomy	13 (38%)	6 (24%)	2 (15%)
Status at last follow-up			
NED	27 (79%)	6 (24%)	10 (77%)
AWD	2 (5.9%)	1 (4.0%)	1 (7.7%)
DOD	2 (5.9%)	17 (68%)	2 (15%)
DOC	3 (8.8%)	1 (4.0%)	0 (0%)
Recurrence	8 (24%)	18 (72%)	7 (54%)

[1] Median (Q1, Q3); n (%)

AWD: alive with disease; DOD: dead of disease; DOC: dead of other causes; NED: no evidence of disease.

Table 2. Summary of survival events and log-rank test p-values based on patient demographic information and clinical variables in patients with Sarcomas

	N	Events	p-value*
Age			
<= 59	17	1	0.04
> 59	17	4	
Sex			
Female	11	2	0.81
Male	23	3	
Grading			
1	20	2	
2	10	2	0.32
3	4	1	
Grading combined			
1 and 2	30	4	0.24
3	4	1	
pT			
1	14	2	
2	15	3	0.70
3	5	0	
pT combined			
1 and 2	29	5	0.46
3	5	0	
Total laryngectomy			
Yes	13	2	0.51
No	21	3	

* log-rank test

Table 3. Summary of survival events and log-rank test p-values based on patient demographic information and clinical variables in patients with Neuroendocrine Laryngeal Tumor.

	N	Events	p-value*
Age			
<= 68	13	10	0.57
> 68	12	8	
Sex			
Female	5	5	0.68
Male	20	13	
Grading			
1	4	3	0.12
2	8	4	
3	13	11	
Grading combined			
1 and 2	12	7	0.06
3	13	11	
pT			
1	9	7	0.06
2	4	2	
3	11	8	
pT combined			
1 and 2	13	9	0.02
3	11	8	
Total laryngectomy			
Yes	6	4	0.47
No	19	14	

* log-rank test

Table 4. Summary of recurrence events and log-rank test p-values based on patient demographic information and clinical variables in patients with Sarcomas

		Local recurrence		Regional recurrence		Distant recurrence	
	N	Events	p-value*	Events	p-value*	Events	p-value*
Age							
<= 59	17	4	0.95	2	0.21	1	0.96
> 59	17	4		0		1	
Sex							
Female	11	3	0.58	0	0.37	1	0.48
Male	23	5		2		1	
Grading							
1	20	3		1		0	
2	10	4	0.39	1	0.81	2	0.09
3	4	1		0		0	
Grading combined							
1 and 2	30	7	0.98	2	0.60	2	0.57
3	4	1		0		0	
pT							
1	14	4		2		1	
2	15	3	0.81	0	0.21	1	0.81
3	5	1		0		0	
pT combined							
1 and 2	29	7	0.90	2	0.54	2	0.52
3	5	1		0		0	
Total laryngectomy							
Yes	13	3	0.76	0	0.35	1	0.64
No	21	5		2		1	

* log-rank test

Table 5. Summary of recurrence events and log-rank test p-values based on patient demographic information and clinical variables in patients with Neuroendocrine Laryngeal Tumor.

		Local recurrence		Regional recurrence		Distant recurrence	
	N	Events	p-value*	Events	p-value*	Events	p-value*
Age							
<= 68	13	4	0.82	4	0.61	10	0.04
> 68	12	3		3		3	
Sex							
Female	5	2	0.70	3	0.18	3	0.84
Male	20	5		4		10	
Grading							
1	4	2		2		1	
2	8	4	0.07	3	0.53	3	0.23
3	13	1		2		9	
Grading combined							
1 and 2	12	6	0.03	5	0.31	4	0.10
3	13	1		2		9	
pT							
1	9	2		3		2	
2	4	3	0.20	3	0.36	3	0.01
3	11	2		1		8	
pT combined							
1 and 2	13	5	1.00	6	0.32	5	0.00
3	11	2		1		8	
Total laryngectomy							
Yes	6	5	0.31	1	0.64	5	0.02
No	19	2		6		8	

* log-rank test

Table 6. Cox Proportional Hazards Model with Age and pT variables in patients with Neuroendocrine Laryngeal Tumor.

Characteristic	**N**	**Event N**	**HR**[1]	**95% CI**[1]	**p-value**
Age	24	13	0.96	0.91, 1.01	0.106
pT combined					
pT=1 or pT=2	13	5	—	—	
pT=3	11	8	6.58	1.82, 23.8	**0.004**

[1] HR = Hazard Ratio, CI = Confidence Interval

Table 7. Studies included in the systematic review of laryngeal sarcomas

Author	PY	Country	No. cases	Median FUP time	Median age	1y-OS	2y-OS	5y-OS	1y-DSS	5y-DSS	1y-DFS	2y-DFS	5y-DFS	1y-TLFS	2y-TLFS	5y-TLFS	Note
Pierre Gazda	2024	France	74	55,5	65		98,6	89,5				86,8			73,6	61,7	Condrosarcomas
Marianne Schleich	2024	France	31	96	62			100						96		75	Condrosarcomas (conservative treatment)
Marianne Schleich	2024	France	12	60	62			83									Condrosarcomas (total laryngectomy)
Vidit M. Talati	2021	USA	348		62,8			88,2									Condrosarcomas
Janet O. Adeola	2021	USA	274		62			89									Condrosarcomas
Luna-Ortiz	2017	Mexico	11		53,8			48					30				All sarcomas
Dubal	2014	USA	143		61				96,5	88,6							Condrosarcomas
Liu	2006	Taiwan	10	92	62			76		90							All sarcomas
Thompson	2002	USA	111	120	64			79,4		78,9							Condrosarcomas
Thomè	1998	Brazil	6	276	50			100									Condrosarcomas
Lewis	1997	USA	44	132	63			90,1					67,6				Condrosarcomas

Table 8. Studies included in the systematic review of laryngeal neuroendocrine carcinoma

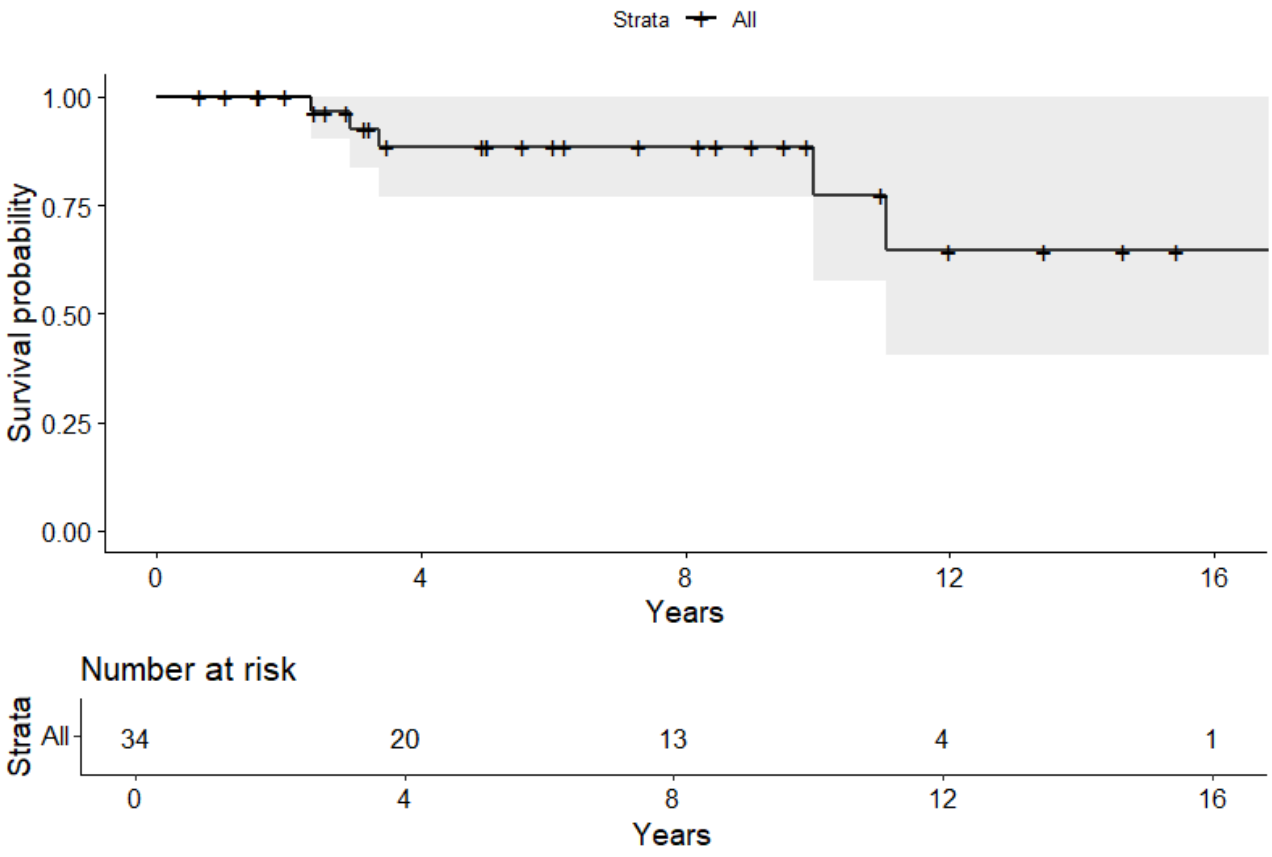
Author	PY	Country	No. cases	Median FUP time	Median age	1y-OS	2y-OS	3y-OS	5y-OS	1y-DSS	2y-DSS	5y-DSS	1y-DFS	2y-DFS	1y-TLFS	Note
Guimaraes Sousa	2021	USA	15	17,8	58				13,3				50	12,5		Poorly differentiated
Strojan	2021	Slovenia	11		64		72		49		87	60				Poorly and moderately differentiated
Le Chen	2019	China	26	24	61			76,9	69,2							All grades
Lin	2018	USA	47	16	61				34							Poorly differentiated early stage
Lin	2018	USA	133	16	61				26							Poorly differentiated locally advanced
Lin	2018	USA	53	16	61				9							Poorly differentiated metastatic
Pointer	2017	USA	64		60		65.3									Poorly differentiated stage I/II
Pointer	2017	USA	160		60		42.3									Poorly differentiated stage III/IVa/IVb
Pointer	2017	USA	73		60		14.2									Poorly differentiated stage Ivc
Ghosh	2015	USA	185		61							30,2				All grades
Zhu	2015	China	14		57		84,4		73,9							All grades

Table 9. Studies included in the systematic review of laryngeal malignant salivary gland tumors

Author	PY	Country	No. cases	Median FUP time (months)	Median age	2y-OS	5y-OS	10y-OS	1y-DSS	2y-DSS	5y-DSS	10y-DSS	Note
Mur	2020	USA	89	102	57		72,6	61,2			77,3	67,9	Adenoid Cystic Carcinoma
Spinnazzi	2016	Italy	111		65				80,8		60,1	53	Adenocarcinoma not otherwise specified
Baddour	2015	USA	229								52,6	45,3	All histologies
Dubal	2015	USA	69		56				98,4		69,1	50,9	Adenoid Cystic Carcinoma
Moukarbel	2008	Canada	15	84	49		64	46			69	49	Adenoid Cystic Carcinoma
Wang	2006	Taiwan	11	95	65		71	57			83	63	All histologies
Alavi	1999	USA	12	23	61	56,5	45,2						All histologies
Cohen	1985	USA	18		62					70,6	42,8		Adenoid Cystic Carcinoma and Adenocarcinoma

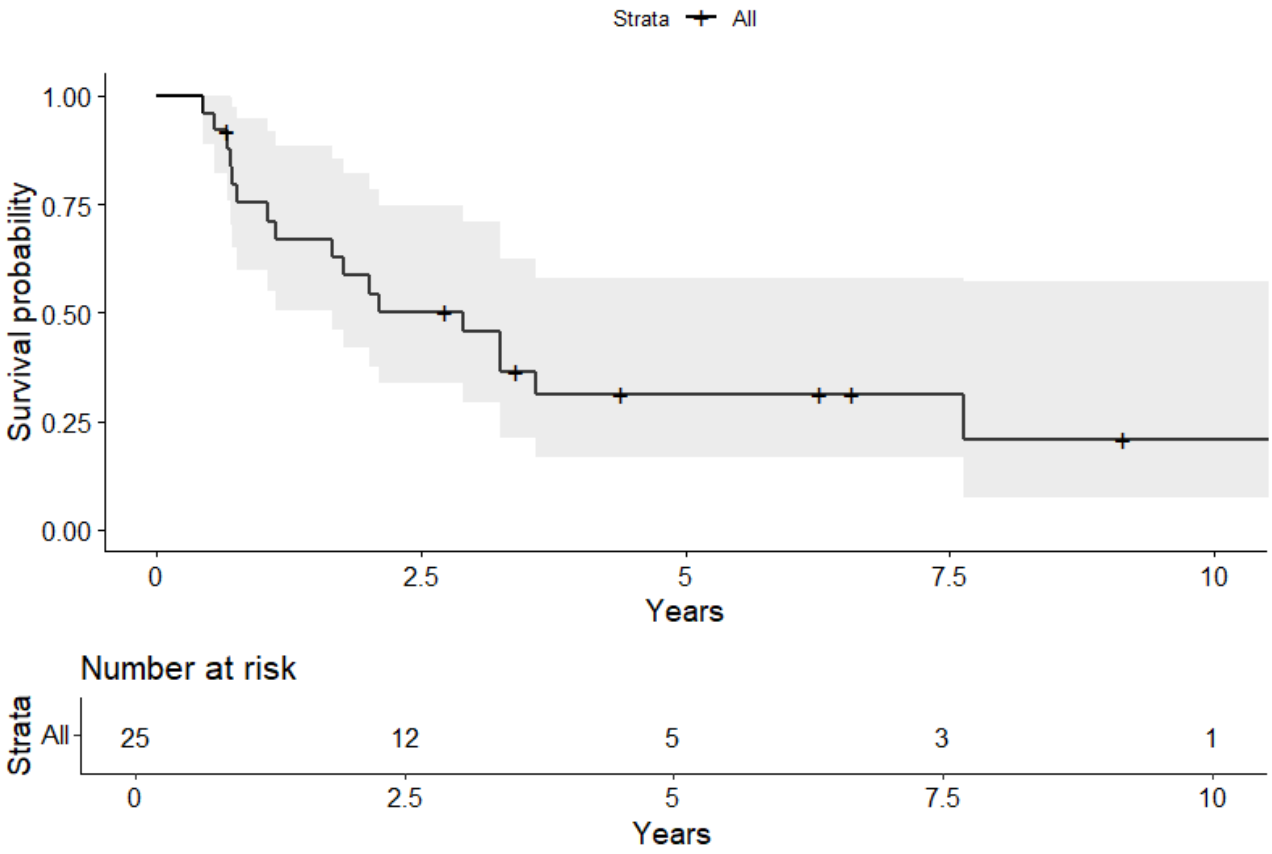
FIGURES

Figure 1. Kaplan-Meier curve for Overall Survival (OS) in patients with Sarcomas



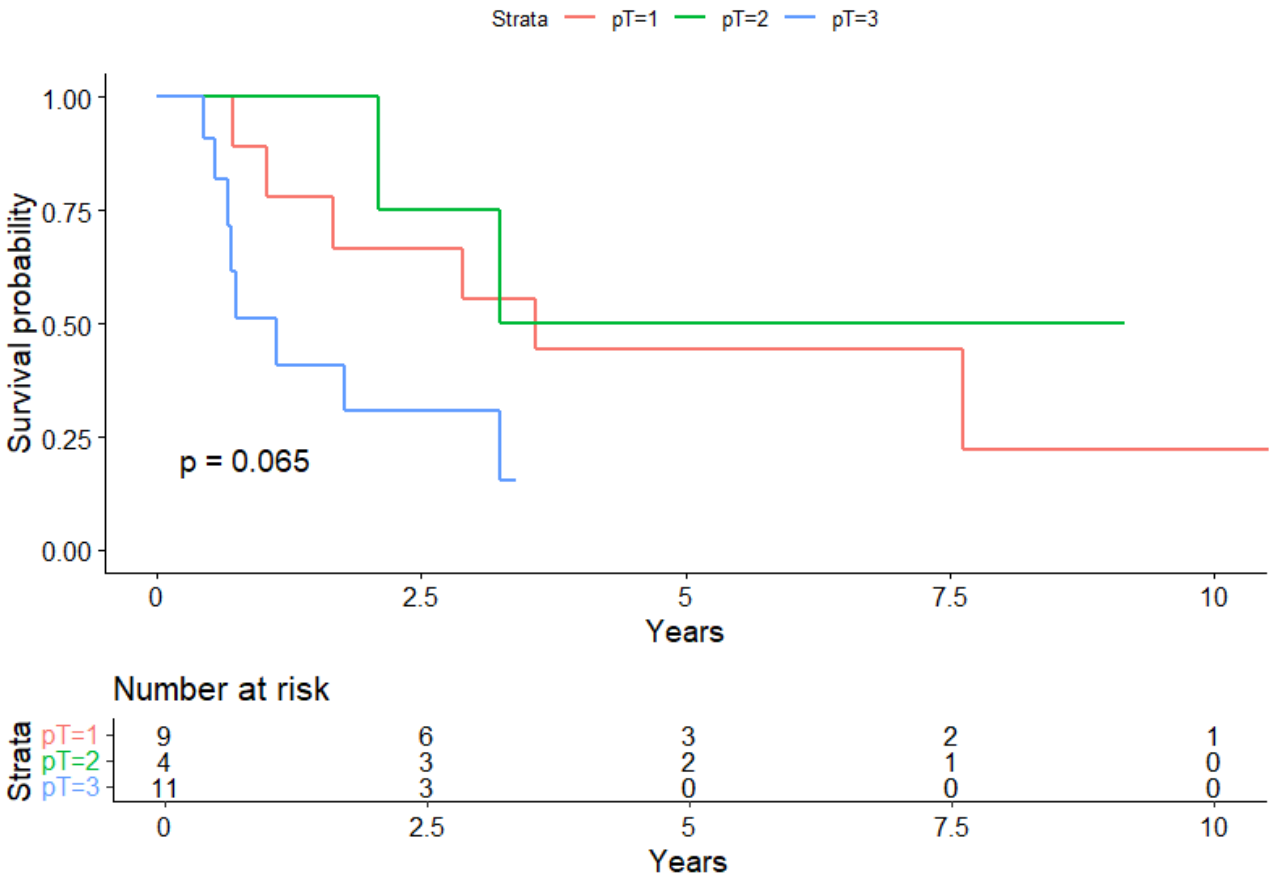
N	Events	Median	0.95 LCL	0.95 UCL
34	5	NA	11	NA

Figure 2. Kaplan-Meier curve for Overall Survival (OS) in patients with Neuroendocrine Laryngeal Tumor.



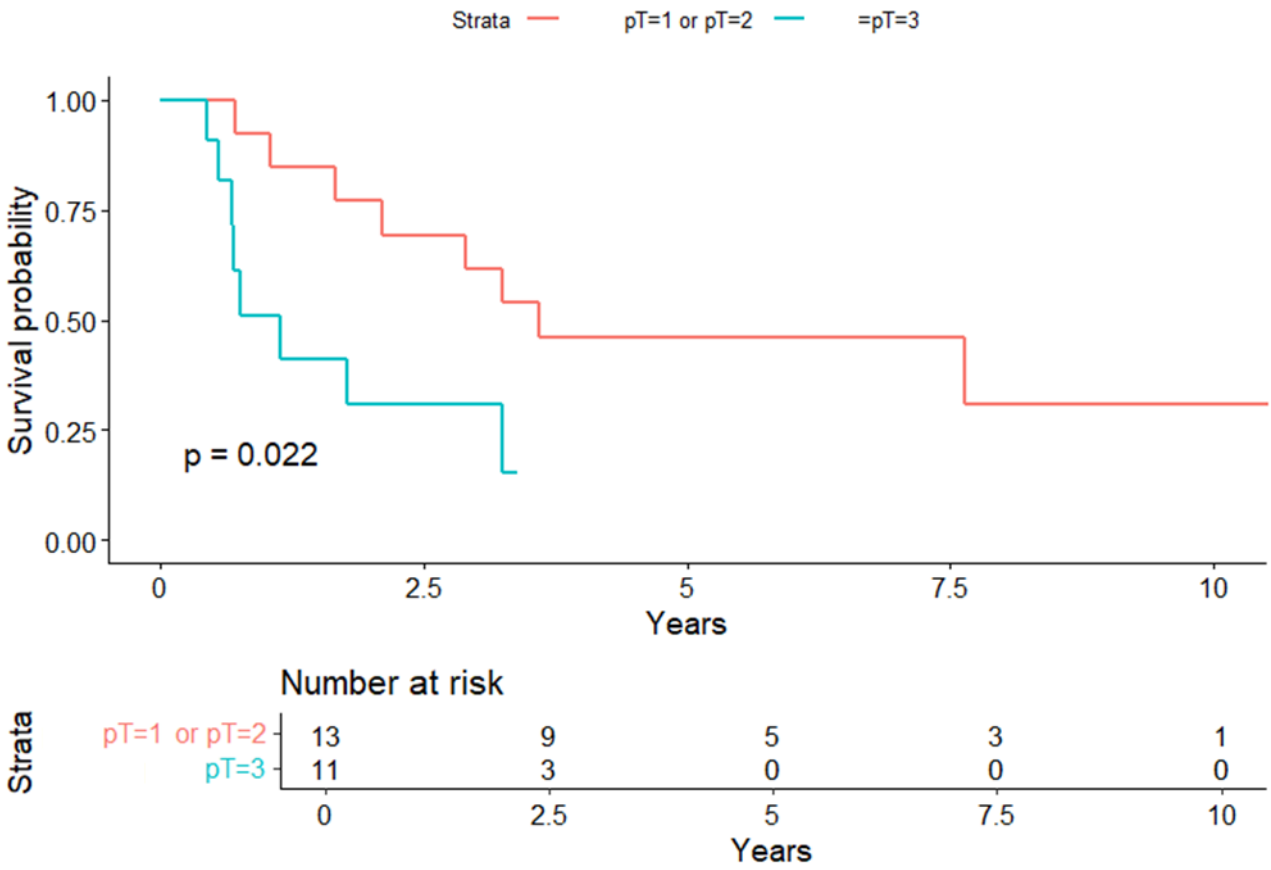
N	Events	Median	0.95 LCL	0.95 UCL
25	18	2.89	1.66	NA

Figure 3. Kaplan-Meier survival curves and log-rank test based on pT groups in patients with Neuroendocrine Laryngeal Tumor.



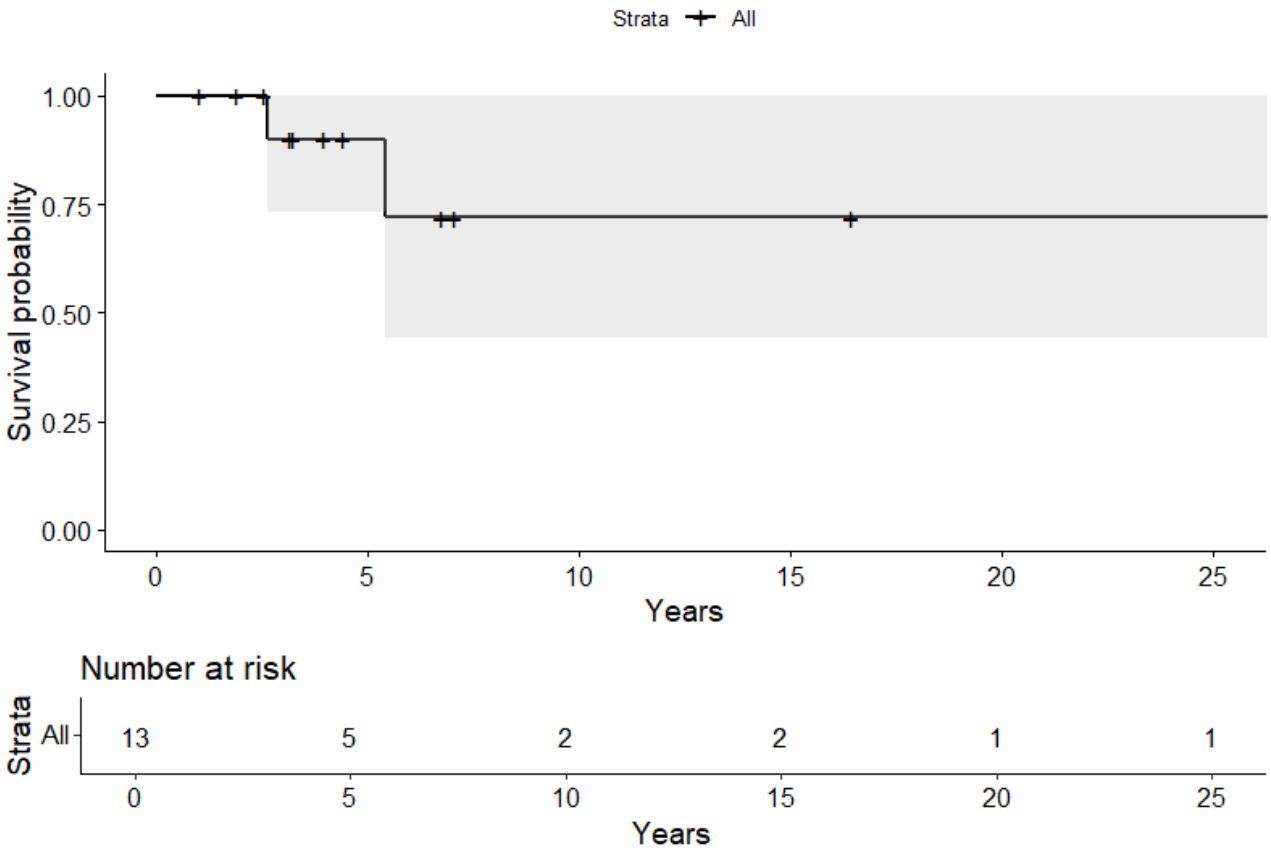
	N	Events	Median	0.95 LCL	0.95 UCL
pT=1	9	7	3.59	1.66	NA
pT=2	4	2	3.25	2.10	NA
pT=3	11	8	1.13	0.67	NA

Figure 4. Kaplan-Meier survival curves and log-rank test based on pT groups in patients with Neuroendocrine Laryngeal Tumor, with pT=1 and pT=2 combined into a single group



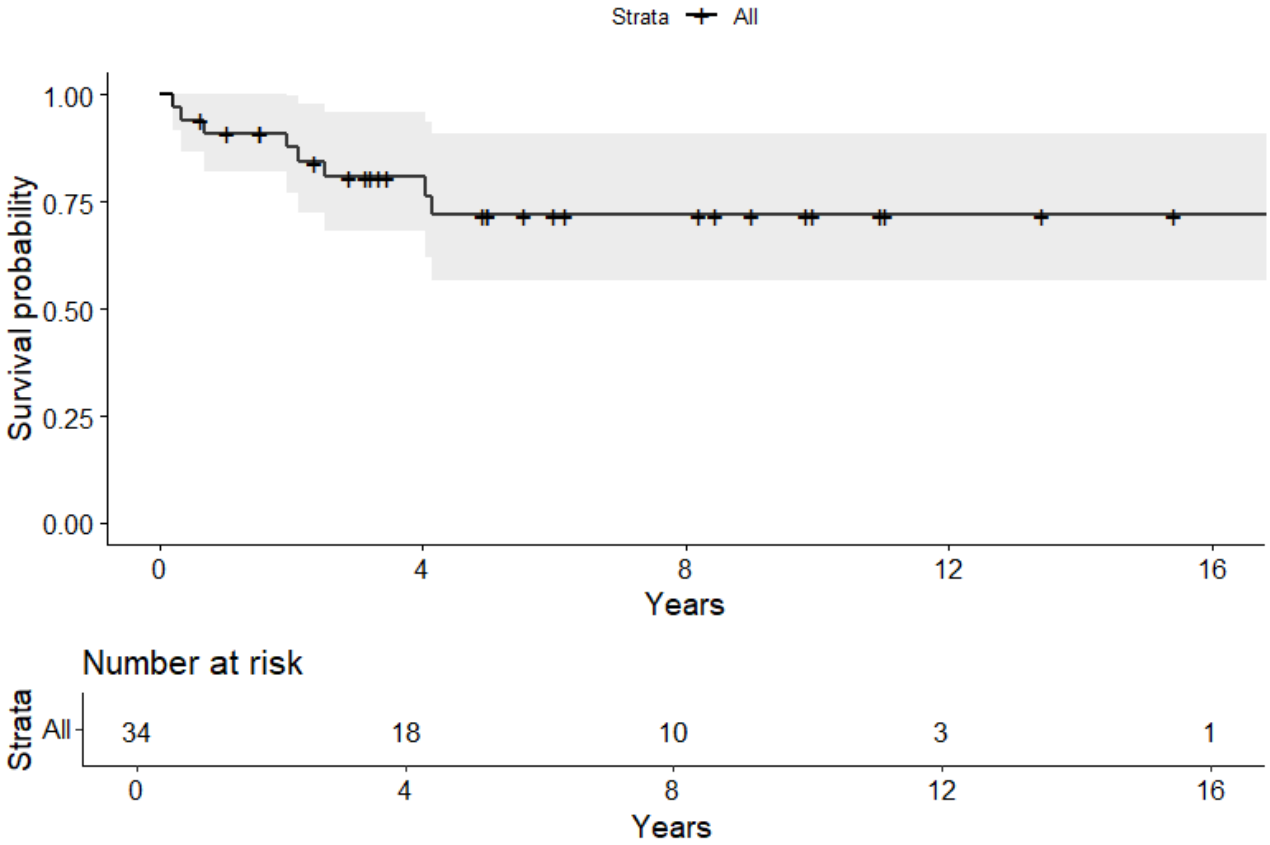
	N	Events	Median	0.95 LCL	0.95 UCL
pT=1 or pT=2	13	9	3.59	2.10	NA
pT=3	11	8	1.13	0.67	NA

Figure 5. Kaplan-Meier curve for Overall Survival (OS) in patients with Laryngeal Salivary gland tumors



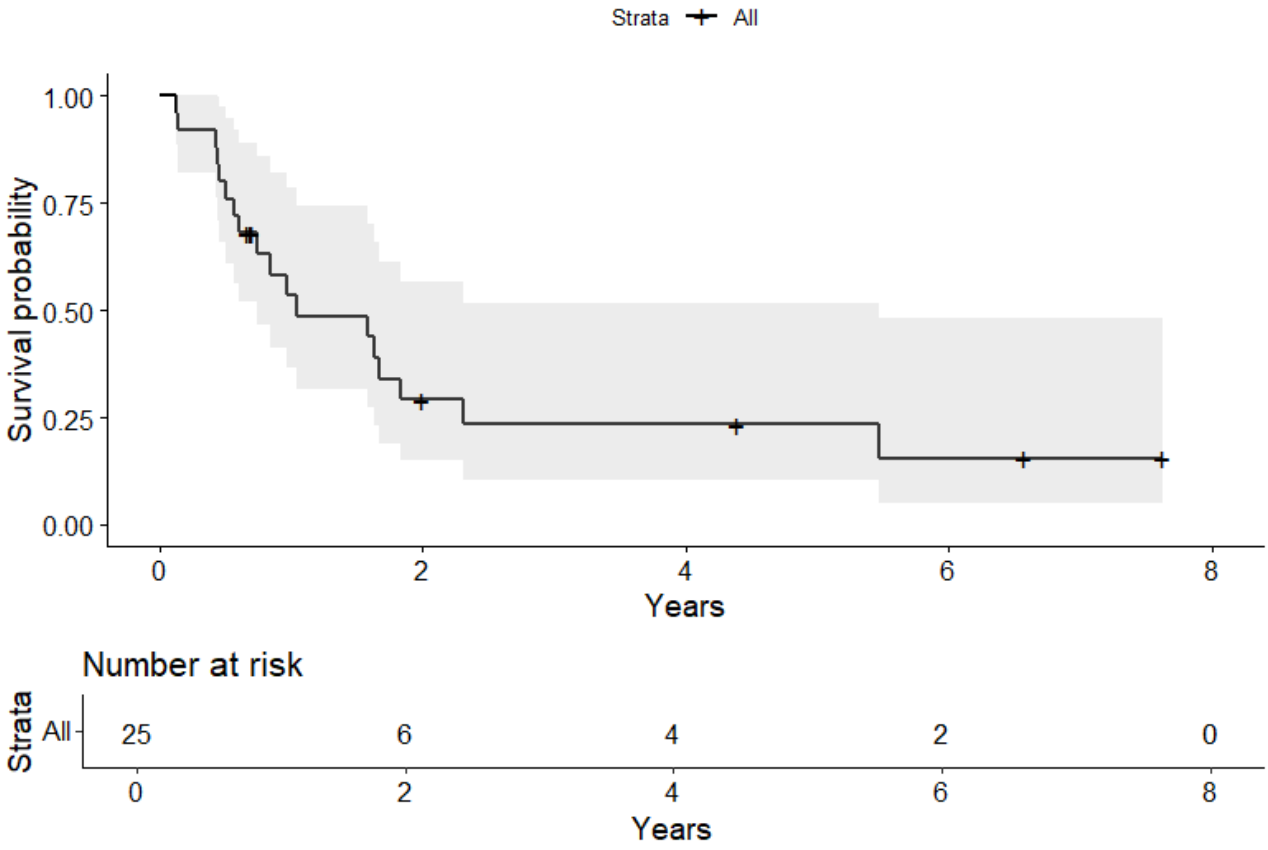
N	Events	Median	0.95 LCL	0.95 UCL
13	2	NA	5.41	NA

Figure 6. Kaplan-Meier curve for Recurrence-Free Survival (RFS) in patients with Sarcomas



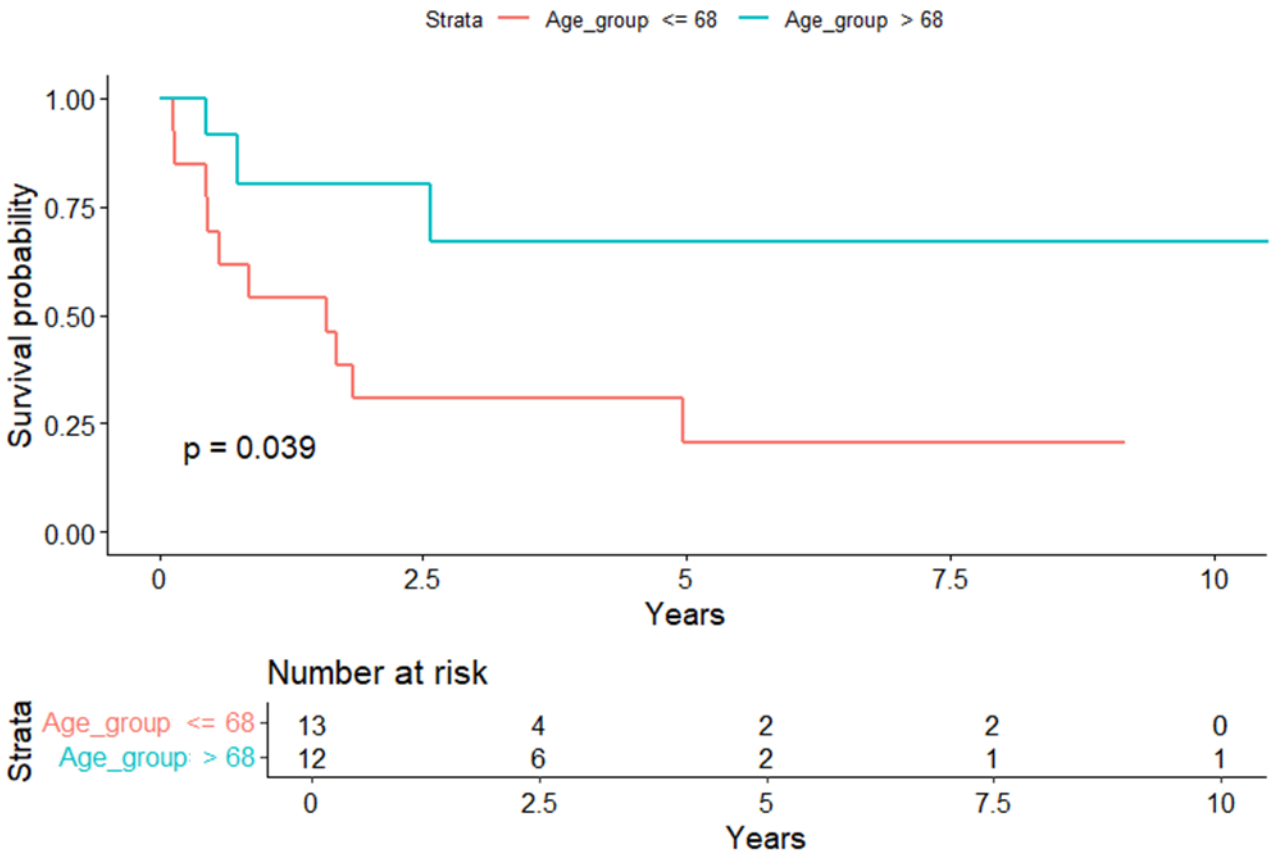
N	Events	Median	0.95 LCL	0.95 UCL
34	8	NA	NA	NA

Figure 7. Kaplan-Meier curve for Recurrence-Free Survival (RFS) in patients with Neuroendocrine Laryngeal Tumor.



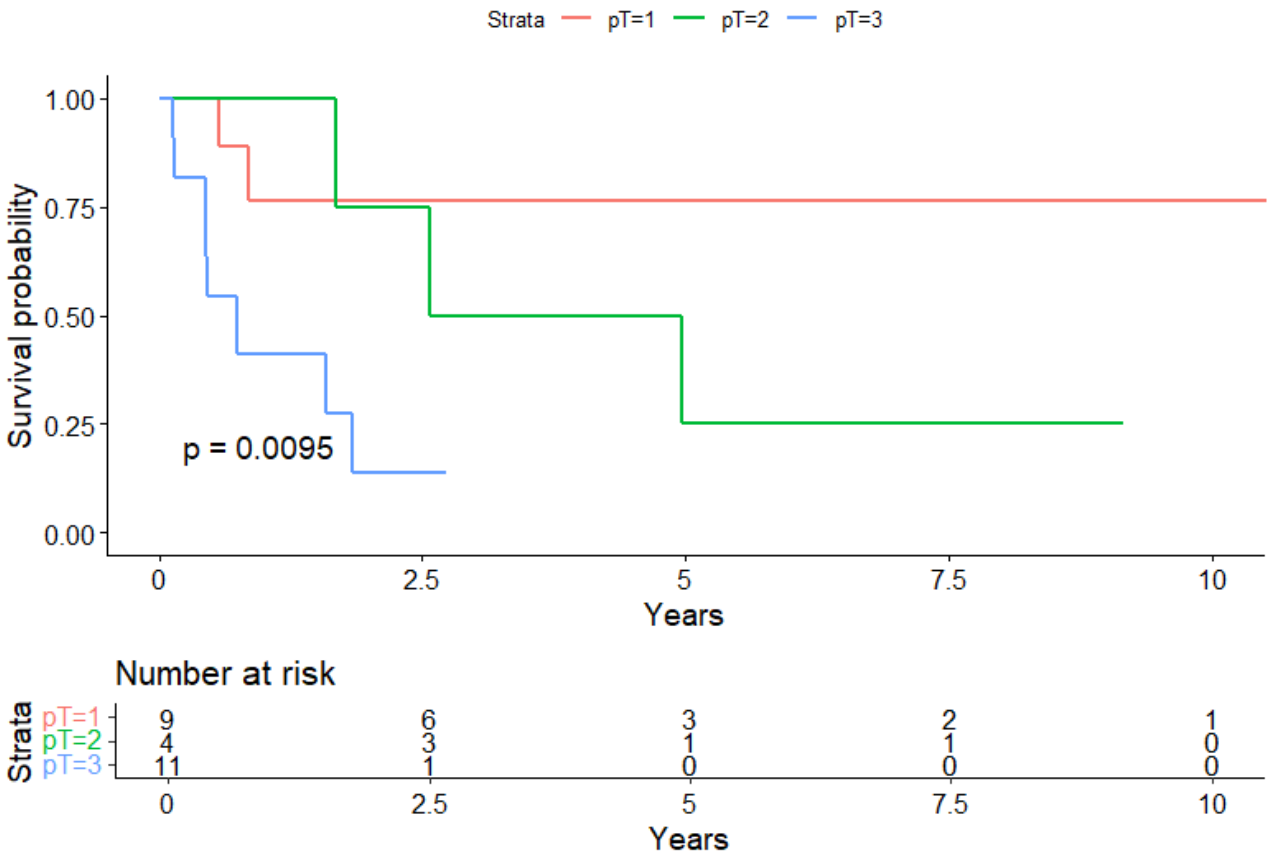
N	Events	Median	0.95 LCL	0.95 UCL
25	18	1.04	0.75	5.47

Figure 8. Kaplan-Meier survival curves and log-rank test for Recurrence-Free Survival (RFS) based on age groups divided by the median age in patients with Neuroendocrine Laryngeal Tumor.



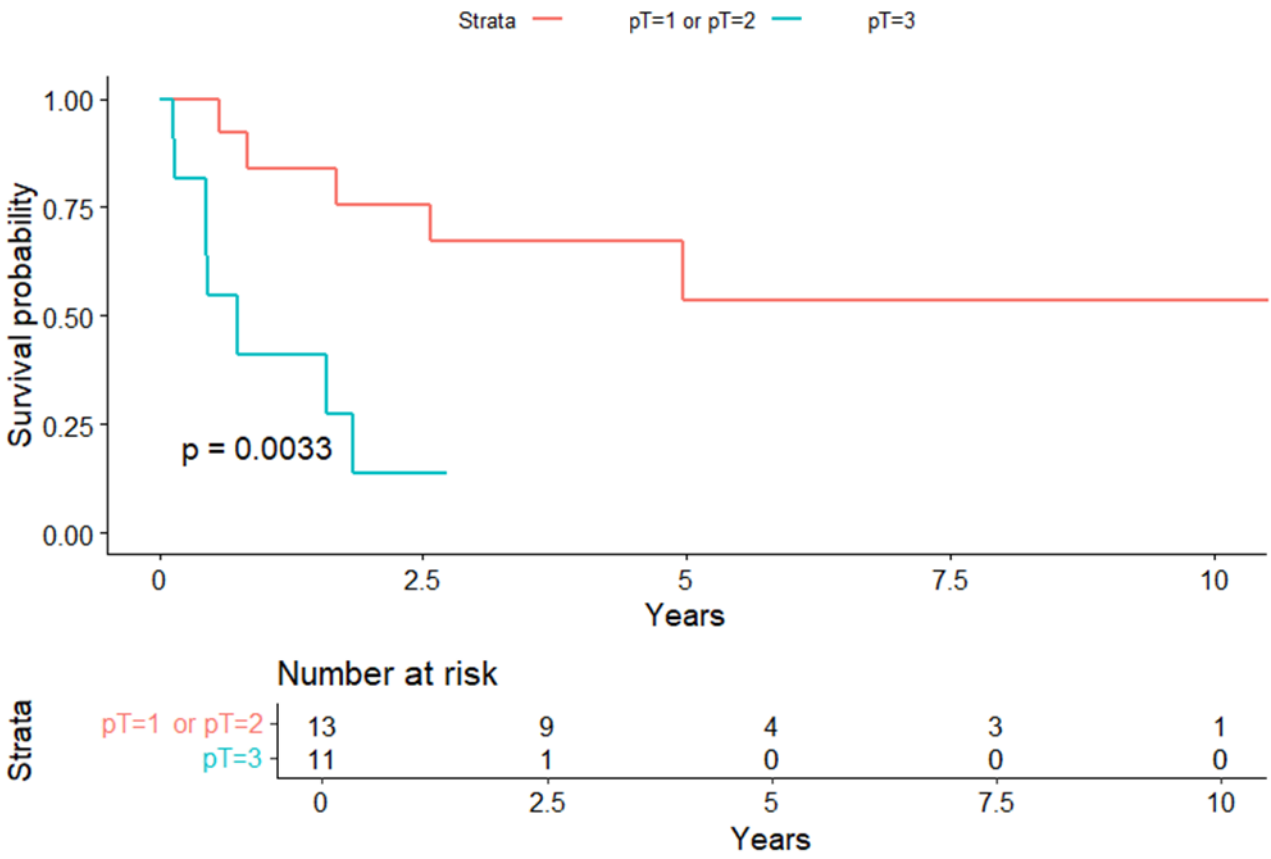
	N	Events	Median	0.95 LCL	0.95 UCL
Age group ≤ 68	13	10	1.59	0.46	NA
Age group > 68	11	3	NA	2.57	NA

Figure 9. Kaplan-Meier survival curves and log-rank test for Recurrence-Free Survival (RFS) based on pT groups in patients with Neuroendocrine Laryngeal Tumor.



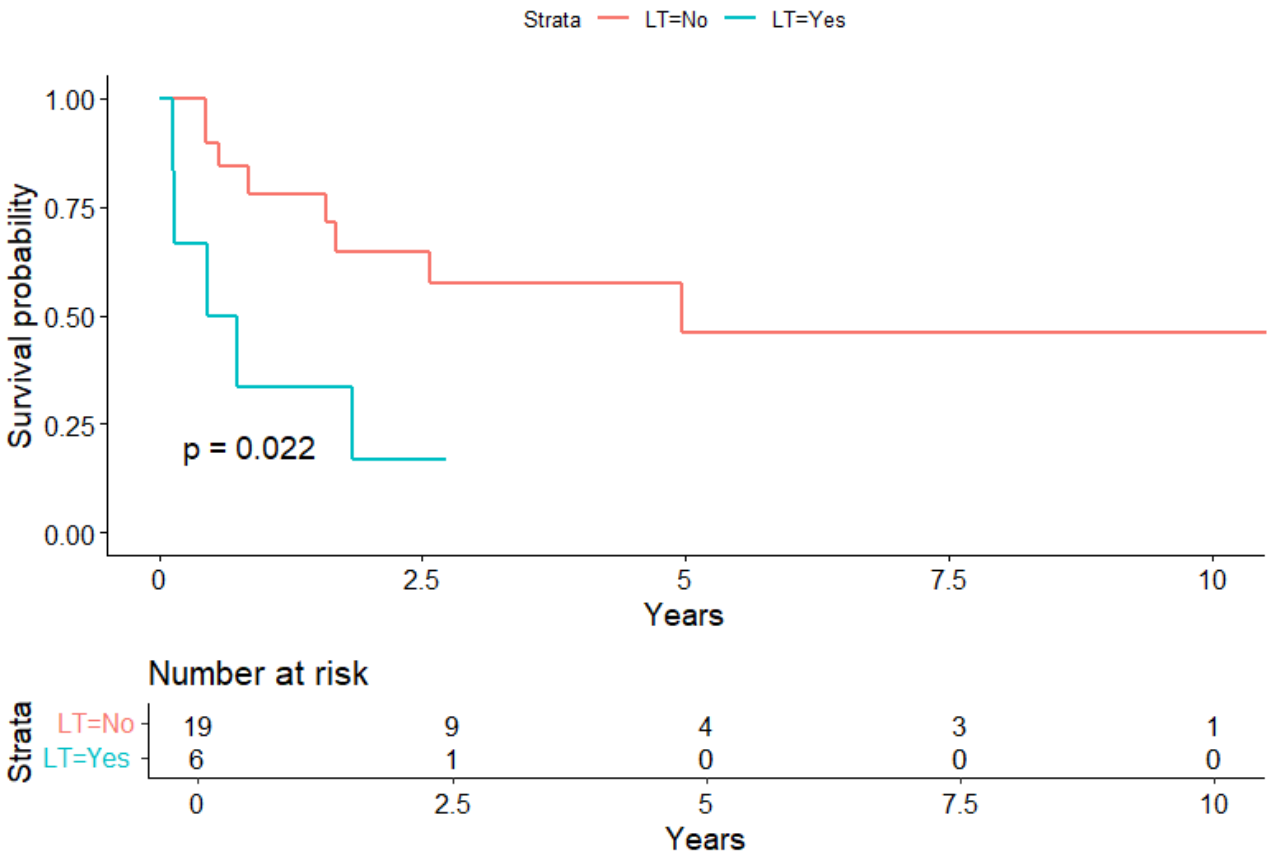
	N	Events	Median	0.95 LCL	0.95 UCL
pT=1	9	2	NA	NA	NA
pT=2	4	3	3.77	1.68	NA
pT=3	11	8	0.75	0.45	NA

Figure 10. Kaplan-Meier survival curves and log-rank test for Recurrence-Free Survival (RFS) based on pT groups in patients with Neuroendocrine Laryngeal Tumor., with pT=1 and pT=2 combined into a single group for analysis



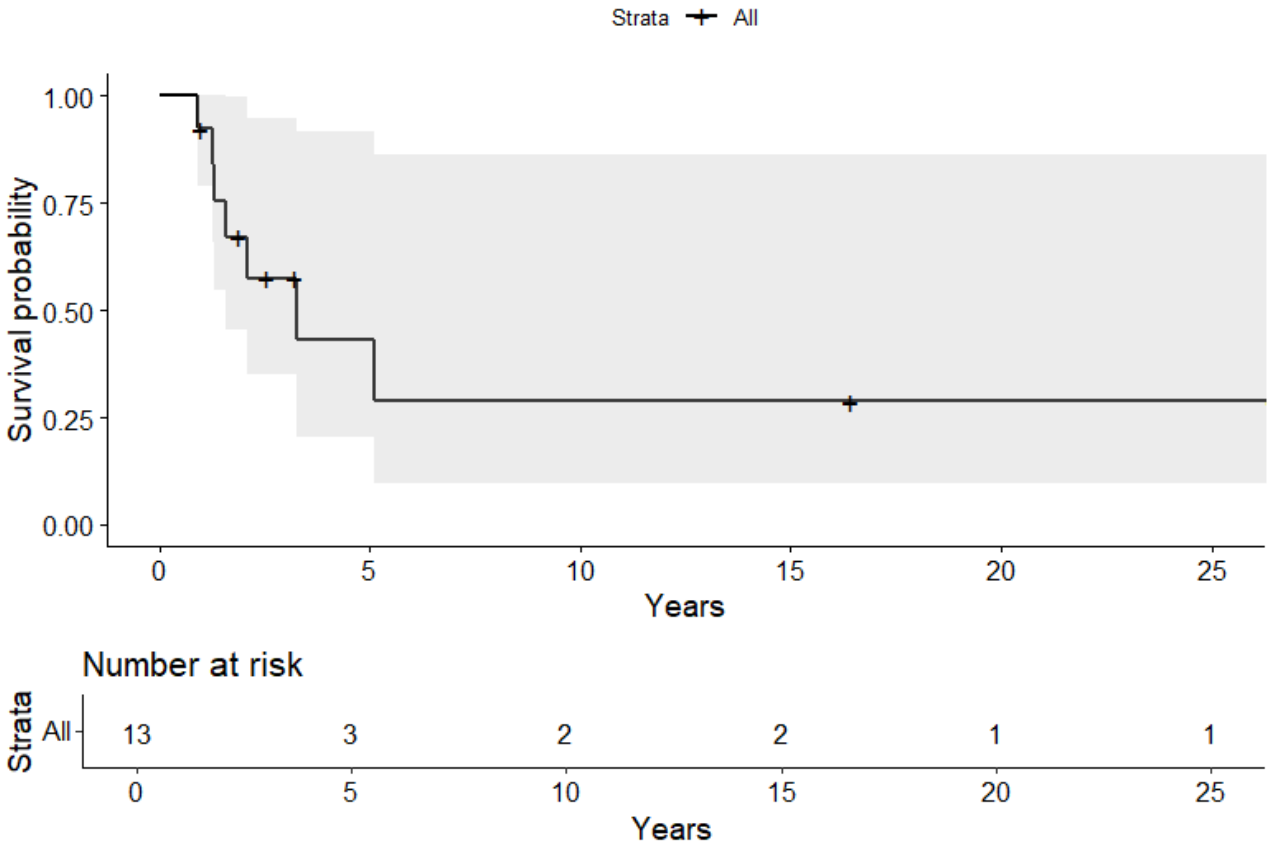
	N	Events	Median	0.95 LCL	0.95 UCL
pT=1 or pT=2	13	5	NA	2.57	NA
pT=3	11	8	0.75	0.45	NA

Figure 11. Kaplan-Meier survival curves and log-rank test for Recurrence-Free Survival (RFS) based on total laryngectomy (LT) groups in patients with Neuroendocrine Laryngeal Tumor.



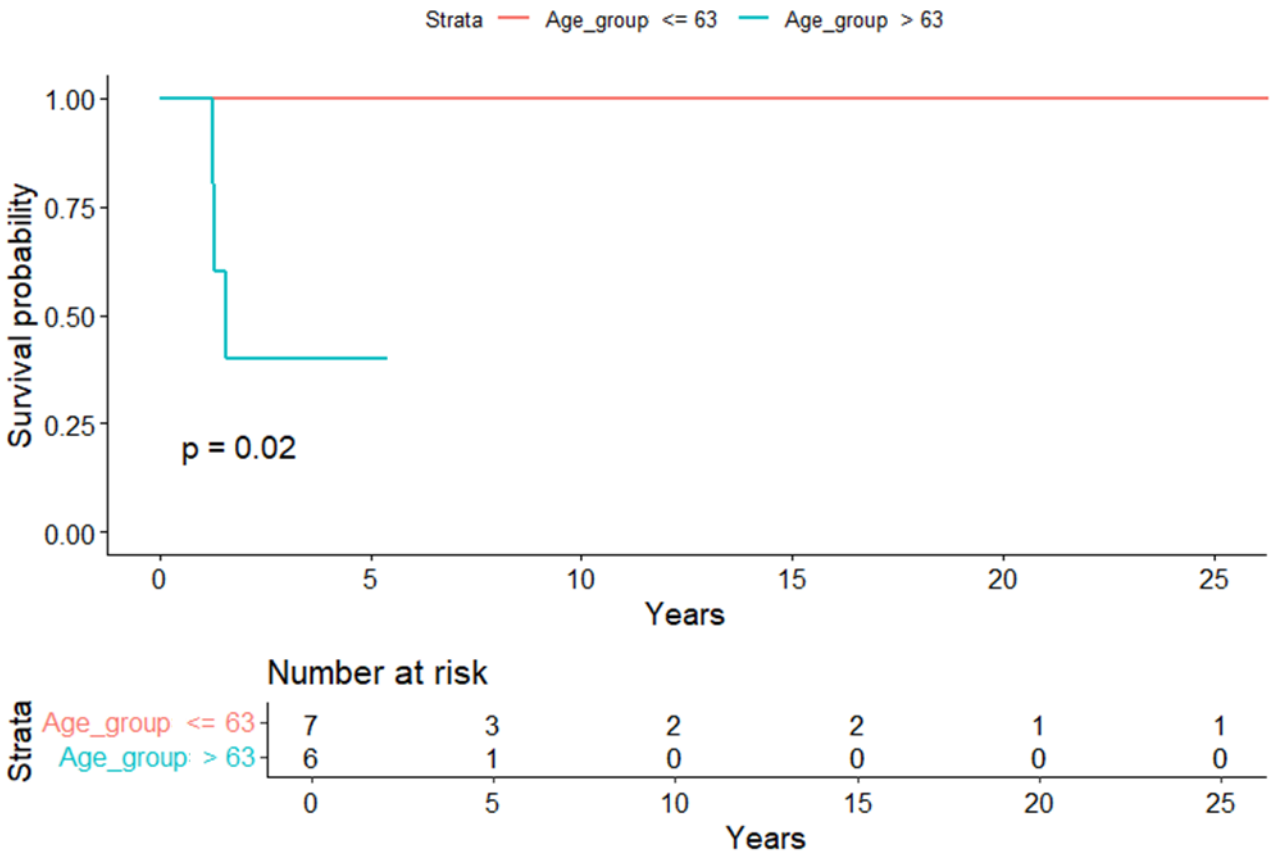
	N	Events	Median	0.95 LCL	0.95 UCL
Total laryngectomy = No	19	8	4.96	1.68	NA
Total laryngectomy = Yes	6	5	0.60	0.15	NA

Figure 12. Kaplan-Meier curve for Recurrence-Free Survival (RFS) in patients with Laryngeal Salivary gland tumors.



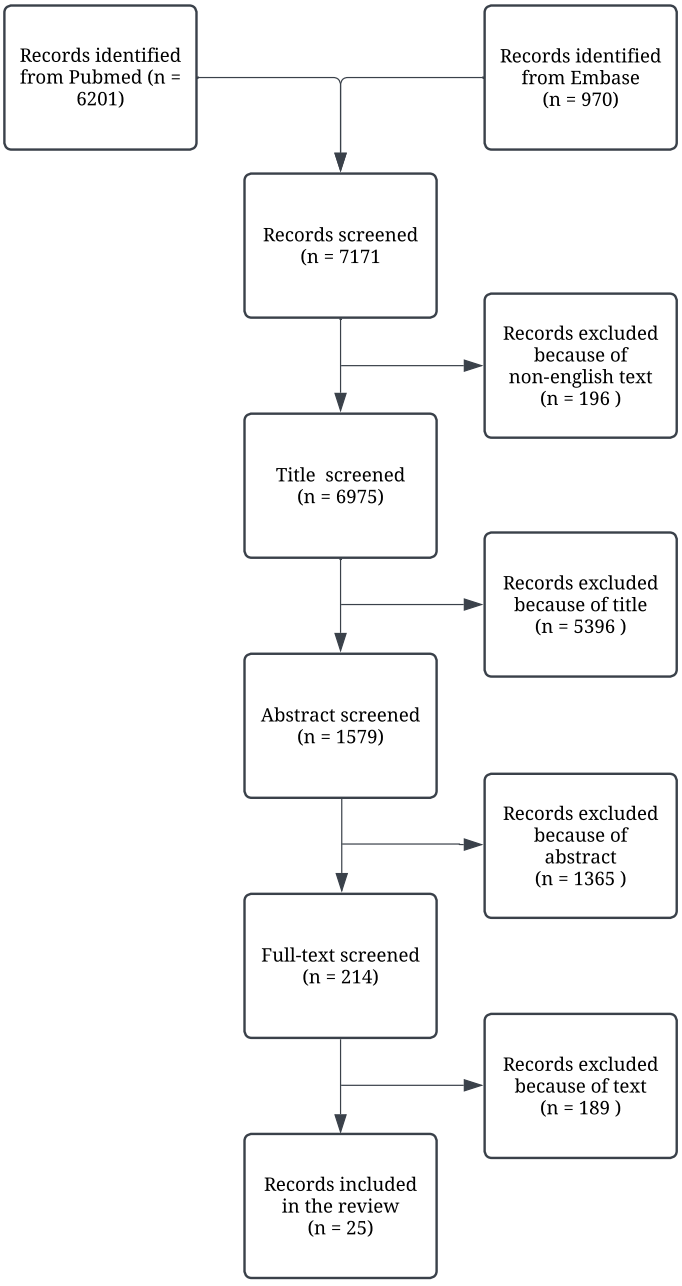
N	Events	Median	0.95 LCL	0.95 UCL
13	7	3.27	1.57	NA

Figure 13. Kaplan-Meier survival curves and log-rank test for Recurrence-Free Survival (RFS) based on age groups divided by the median age in patients with Laryngeal Salivary gland tumors.



	N	Events	Median	0.95 LCL	0.95 UCL
Age group ≤ 63	7	0	NA	NA	NA
Age group > 63	6	3	1.57	1.29	NA

Figure 14. Flow diagram for study selection



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