American Journal of Otolaryngology–Head and Neck Medicine and Surgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

American Journal of Otolaryngology–Head and Neck Medicine and Surgery

journal homepage: www.elsevier.com/locate/amjoto

Sarcomatoid larynx carcinoma differential clinical evolution, on field statistical considerations

Filippo Ricciardiello [a,*], Marco Bocchetti [b,c], Raul Pellini [d], Remo Palladino [e], Michele Caraglia [b,c], Amedeo Boscaino [f], Gerardo Petruzzi [d], Francesco Jacopo Romano [g], Bruno Chiurazzi [g], Raffaele Addeo [h], Salvatore Mazzone [a], Massimo Mesolella [i], Flavia Oliva [a], Brigida Iorio [j]

[a] Ear, Nose, and Throat Unit, AORN "Antonio Cardarelli", Naples, Italy
[b] Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[c] Biogem Scarl, Molecular Oncology and Precision Medicine Laboratory, Via Camporeale, 83031 Ariano Irpino, Italy
[d] Department of Otolaryngology-Head and Neck Surgery, IRCCS Regina Elena National Cancer Institute, Rome, Italy
[e] Otolaryngology, P.O. Umberto I, Nocera Inferiore, Salerno, Italy
[f] U.O.C. Pathology Unit, AORN "Antonio Cardarelli", Naples, Italy
[g] U.O.C. Oncology Unit, AORN "Antonio Cardarelli", Naples, Italy
[h] Oncology Unit, Day Hospital, San Giovanni di Dio Hospital, ASL Napoles 2 Nord, Frattamaggiore, Italy
[i] Department of Neuroscience, Reproductive and Odontostomatological Science, Ear Nose and Throat Unit, University of Naples 'Federico II', Naples, Italy
[j] Department of Otolaryngology, Pellegrini Hospital, ASL Napoli 1 Centro, Naples, Italy

ARTICLE INFO

Keywords:
Larynx
Spidle cell carcinoma
Squamous cell carcinoma
Survival
Statistical analysis

ABSTRACT

Spindle cell larynx carcinoma (SpCC) represents around 3% of laryngeal cancers. It is originated by a single cancer stem cell undergoing epithelial to mesenchymal transition. This explains the aggressiveness, the peculiar resistance to conventional therapy and the frequent relapses. We focused on this particular cancer subset characteristics in patients, in early and advanced stages primarily aiming to define and highlight the differences with Laryngeal Squamous Cell Carcinoma (LSCC) focusing on clinical features, treatments, follow-up and survival in a patient's cohort composed by comparable cases from two subgroups.

1. Introduction

Spindle cell carcinoma (SpCC) is an uncommon variant of conventional squamous cell carcinoma (SCC). The World Health Organization Classification of Head and Neck Tumors (2017) highlights that SpCC is a monoclonal neoplasm originating from a non-committed stem cell, giving rise to both epithelial and mesenchymal components. Recent studies suggest that the characteristic spindle cell phenotype of the neoplastic cells in SpCC is the result of epithelial-mesenchymal transition [1]. It has been considered a biphasic tumor composed by a squamous cell carcinoma and a malignant spindle cell component with a mesenchymal appearance, mutated from an epithelial clone [2]. Histologically, a blending of squamous cells and spindle cells is often observed, and they may present different arrangements with storiform, solid, and fascicular appearances [3]. Immunohistochemical studies on epithelial and mesenchymal markers (such as AE1/AE3, epithelial membrane antigens, vimentin, desmin, and S-100) are essential to diagnose the tumor, although they may vary widely. Overall, immunohistochemistry is an important tool for diagnosis although it is not infallible. Misdiagnosis could be avoided coupling ultrastructural investigation [4]. SpCC is considered a highly malignant variant of squamous cell carcinoma, it is quite rare and comprises 2% to 3% of all laryngeal cancers [5]. The oral cavity is the next most frequent site for this tumor, affecting the lower lips, tongue and buccal mucosa [6]. Typically, these tumors onset is more frequent in older patients with a significant smoking history [7]. In this study, we analyzed the aggressiveness of laryngeal SpCC in a group of 17 patients (sarcomatoid subgroup A) compared with a homogeneous group of 17 patients affected by laryngeal SCC (non-sarcomatoid subgroup B) to determine all the peculiarities associated to this particular, rare and aggressive carcinoma aiming to discuss about therapeutic schemes adopted, survival and recurrence.

* Corresponding author.
E-mail address: filippouricciardiello@virgilio.it (F. Ricciardiello).

https://doi.org/10.1016/j.amjoto.2021.102934
Received 14 December 2020;
Available online 27 January 2021
0196-0709/

2. Materials and methods

2.1. Inclusion criteria

Patients cohort was selected among patients of Ear-nose-throat (ENT) Unit at Cardarelli Hospital, Naples (Italy) and from "Regina Elena" National Cancer Institute, Rome (Italy) from 1st January 2002 to 31st October 2019. Patients enrolled in the study underwent to ENT examination by laryngoscopy, neck and chest CT with intravenous contrast, biopsy with histological examination that confirmed laryngeal cancer diagnosis. Patients with laryngeal cancer were treated with cordectomy performed with CO2 laser aid or open laryngectomy (subtotal or total); elective or curative neck dissection was performed, only 2 patients in each group were treated with chemoradiotherapy protocol. In the post-operative period, patients underwent oncological follow-up, examinations by ENT specialist by direct fiber optic laryngoscopy and video recording in accordance with the timetable guidelines for each tumor stage, annual neck and chest CT and total body PET for both loco-regional and distance disease recurrence monitoring. pTNM was evaluated according to TNM criteria (VIII edition) [8]. Patients with follow-up lower than 12 months were excluded from the study. Our study dataset was composed by 34 laryngeal carcinoma cases in total (26 M and 8F), split in two subgroups: Subgroup A, composed by 17 SpCC diagnosed patients while Subgroup B composed by 17 LSCC diagnosed patients according to the inclusion criteria stated above. Sarcomatoid (Subgroup A) population was composed by 17 cases with definitive sarcomatoid larynx carcinoma diagnosis, enrolled between 1st January 2002 to 31st October 2019. In order to highlight SpCC features, Subgroup A was compared to a specular non-sarcomatoid squamous infiltrating laryngeal carcinoma group (Subgroup B) with negative anamnesys of any other malignancies and no exposure to environmental risk factors. The Subgroup B was formed by patients sharing similarities in staging and treatment strategies with Subgroup A: the demographic characteristics staging, grading treatment strategies and RT for each patient subgroup are described in Tables 1 and 2. The study was in accordance with the Institutional Ethics Committee guidelines, Italian law, and the Declaration of Helsinki, as required for studies based on retrospective analyses on routine archival formalin-fixed, paraffin-embedded tissues. All patients provided written informed consent regarding the use of these data for research purposes.

2.2. Statistical analysis

We evaluated survival through Kaplan-Meier method, mortality risk through COX univariate statistical analysis considering the following variables: staging, grading, treatment strategy and RT treatment. Moreover, we analyzed all the significant variable influencing survival through a multivariate and Hazard Risk (HR) analysis and we calculated the Odd Ratio risk (OR) and Relative Risk (RR) of death in both groups. Odd Ratio risk (OR) was also evaluated for nodal recurrence and tumor recurrence (N Recurrence and T Recurrence).

Follow-up period for both subgroups was compared through Wilcoxon/Mann-Whitney test for independent and non-parametric variables using Med-Calc software, version 9.3.7.0. We applied the Kaplan-Meier method, normalizing the different categories by the long-rank Mantel-Haenszel test in order to study overall and disease-specific survival (OS and DSS, respectively) in each subgroup and to compare those data between the two subgroups. Moreover, we calculated the additional risk of T and N recurrence and mortality in SpCC patients compared with LSCC by Odds Ratio (OR). A Cox proportional hazard model was used to study the simultaneous contribution of multiple factors to mortality risk. The assessed variables were staging, grading, treatment strategies and disease-specific survival in each subgroup. We performed multivariate Cox regression analysis for all the significant variables found in univariate analysis to underline HR of patients with sarcomatoid carcinoma and SCC. In each test, p-value <0.05 was considered statistically significant.

Table 1
Sarcomatoid group (A).

Patient	Staging	Grading	Treatment	RT	Follow-up	Death
1	IV	IV	Lsub	Yes	18	Yes
2	II	IV	Lsub		60	
3	IV	IV	Lsub	Yes	20	Yes
4	IV	IV	Lsub	Yes	15	Yes
5	IV	IV	Lt	Yes	22	Yes
6	IV	IV	Lt	Yes	16	Yes
7	IV	IV	Lt	Yes	23	Yes
8	III	IV	ChRT	Yes	12	Yes
9	IV	IV	Lt	Yes	15	Yes
10	IV	IV	Lt	Yes	10	Yes
11	IV	IV	Lt	Yes	22	Yes
12	IV	IV	ChRT	Yes	15	Yes
13	IV	IV	Lt	Yes	20	Yes
14	IV	IV	Lt		18	Yes
15	III	IV	Lt		36	
16	IV	IV	Lt	Yes	28	Yes
17	II	IV	Cordectomy		14	

Staging TNM VIII edition; Lsub: subtotal Laryngectomy; Lt: total Laryngectomy; ChRT: chemoradioterapy treatment.

Table 2
Non-sarcomatoid group (B).

Patient	Staging	Grading	Treatment	RT	Follow-up	Death
1	IV	III	Lsub	Yes	47	
2	II	III	Lsub		23	
3	IV	III	Lsub	Yes	36	
4	III	III	Lsub	Yes	25	
5	IV	III	Lt	Yes	30	
6	IV	IV	ChRT	Yes	24	Yes
7	IV	III	Lt	Yes	24	
8	IV	III	Lt	Yes	68	
9	IV	III	Lt	Yes	48	
10	IV	III	Lt	Yes	12	
11	IV	III	ChRT		12	Yes
12	IV	III	Lt	Yes	12	
13	III	III	Lt		36	
14	IV	III	Lt	Yes	15	Yes
15	IV	IV	Lt	Yes	20	Yes
16	IV	III	Lt	Yes	32	
17	II	III	Cordectomy		25	

Staging TNM VIII edition; Lsub: subtotal Laryngectomy; Lt: total Laryngectomy; ChRT: chemoradiotherapy treatment.

3. Results

3.1. Demographic and clinical characteristics of the patients

The study cohort was formed by 34 cases of laryngeal carcinoma (26 M and 8F) divided into two subgroups: 17 cases of sarcomatoid carcinoma (SpCC) (A) and 17 cases of LSCC (B). Sarcomatoid subgroup (A) was composed by 13 males and 4 females with a median age of 71 years (range: 38–82 years); non-sarcomatoid subgroup (B) by 13 males and 4 females with a median age of 71 years (range: 40–82 years). No differences were recorded in staging distribution between the two subgroups: both subgroups had 2 patients with stage II, 2 with stage III and 13 with stage IV according to VIII edition of TNM [7], respectively. On the other hand, histological grading was different between the two subgroups: in subgroup A all 17 patients had an Undifferentiated G4 (High grade) carcinoma while in subgroup B 15 patients showed G3 carcinoma and 2 patients had an undifferentiated G4 (High grade) carcinoma.

3.2. Patients management

In each group, 2 patients were treated exclusively with chemoradiotherapy and had no surgical treatments, 1 patient underwent

complete cordectomy, 4 patients subtotal laryngectomy and 10 patients total laryngectomy. For the surgical treatments a neck dissection was required, as well. RT treatment was performed as adjuvant in 13 patients in the sarcomatoid group and 11 patients in non-sarcomatoid one. Chemoradiotherapy was also combined with RT as a treatment strategy (ChRT) for some patients. Follow-up was completed in all patients in accordance with the timetables provided for in the guidelines. In sarcomatoid subgroup, median follow-up was 14.32 months in squamous subgroup 20.67 months. The follow-up analysis did not show any statistically significant difference between these two subgroups (p = 0.0629), using Wilcoxon/Mann-Whitney test for independent and non-parametric variables. Therefore, sarcomatoid and squamous subgroups were homogeneous for demographic features, staging and treatment strategy using Wilcoxon/Mann-Whitney (Treatment strategy p = 0.5582 and staging p = 1). Patient outcome for both groups is summarized in Tables 1 and 2.

3.3. Statistical analysis

Analyzing Odd Ratio mortality risk between sarcomatoid and non-sarcomatoid group we found an increased risk in sarcomatoid group of 11.6667 (95% CI = 2.1254 to 64.0411; z statistic = 2.828) with a statistically significative p-value (p = 0.0047). The Relative Risk is 2.8824 (95% CI = 1.2234 to 6.7910; z statistic = 2.421) with a statistically significative p-value (p = 0.0155). In sarcomatoid group relapse risk was 82.35%, occurred in 14 patients; in non-sarcomatoid group was 29.41%, occurred in 5 patients. The Odd Ratio recurrence risk on N in sarcomatoid group was calculated to be 11.20 (95% CI = 2.2035 to 56.9266; z statistic = 2.912) with a statistically significative *p*-value (p = 0.0036). Laterocervical lymph nodes recurrence happened in 12 patients (70.59%) in sarcomatoid group and in 3 patients (17.65%) in non-sarcomatoid group. Moreover, in sarcomatoid group, the Odd Ratio risk for recurrence on T was calculated to be 3.12 (95% CI = 0.5129 to 19.0385; z statistic = 1.236) without a statically significative p-value (p = 0.2165). The recurrence on T occurred in 5 patients (29.41%) in sarcomatoid group and in 2 patients (11.76%) in non-sarcomatoid group. Noteworthy, in 3 sarcomatoid patients we recorded a recurrence simultaneously on T and N while it happened in just 1 patient in non-sarcomatoid group. The survival analysis (OS and DSS) evidenced 18 months median survival in sarcomatoid subgroup (A) with 14 patients' death for cancer and 1 for other diseases (Fig. 1). In non-sarcomatoid subgroup (B), 3 patients died for cancer originating in laryngeal site, and 1 for other disease and median survival was 19.5 months (Fig. 2). In sarcomatod subgroup (A) median survival correlated

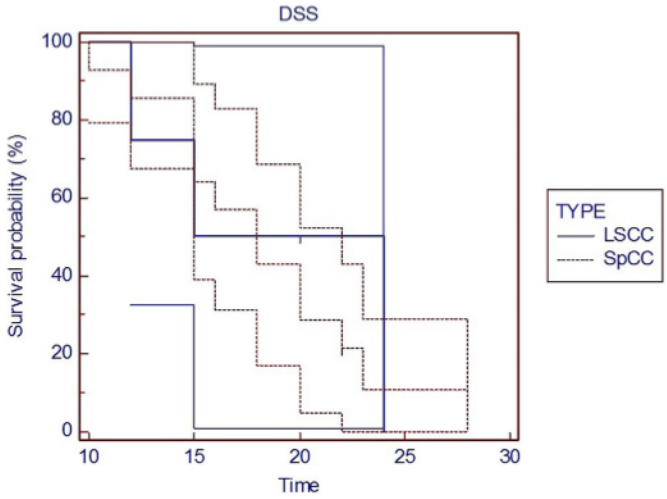

Fig. 2. Specific disease survival (DSS) in sarcomatoid and non sarcomatoid group (Chi-square 0.1540 DF 1 p = 0.6947 Hazard ratio 0.7926 95% CI 0.2190 to 2.7507).

to staging was 12 months for stage III and 18 months for stage IV (Fig. 3) (is worth to mention that just 1 stage III patient died). While in non-sarcomatoid subgroup (B) median survival for stage III was 20 months, and for stage IV 15 months (Fig. 4). Cox proportional hazard model was used to verify if staging, grading, treatment strategy and RT were independent prognostic factors both for SpCC patients (subgroup A) and for LSCC patients (subgroup B). Univariate analysis showed that treatment strategy (Chi-square 4.4520 DF 1; p = 0.0349 Hazard ratio 5.9935 95% CI 0.7517 to 47.7854); staging (Chi-square 5.0095 DF 1; p = 0.0252) and RT (Chi-square 5.1091 DF 1; p = 0.0238) but not grading (Chi-square 2.6711 DF 1; *p* = 0.1022) correlated to decreased survival only in sarcomatoid patients (subgroup A) (Table 3). Univariate analysis in non-sarcomatoid soubgroup (B) was not significative in staging (Chi-square 1.1540 DF 1; p = 0.6947), grading (Chi-square 0.7492 DF 1; p = 0.3867) and treatment strategy (Chi-square 0.02717 DF 1; p = 0.8691). Multivariate analysis (Table 4) of the same variables found to be significant at univariate analysis in the sarcomatoid subgroup (A), were not statistically significant covariates although tending to the worse prognosis; therefore, radiotherapy is not confirmed as an independent variable (Chi-square 5.4902 DF 3; p = 0.0642). It was not possible to perform multiparametric analysis in LSCC group (subgroup B) because no variable was significant in univariate analysis.

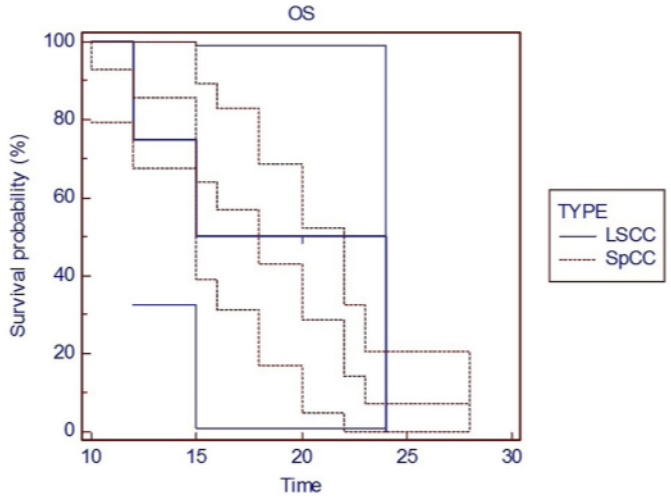

Fig. 1. Overall survival in sarcomatoid and non sarcomatoid group (Chi-square 0.2632 DF 1; p = 0.6079 Hazard ratio 0.7424 95% CI 0.2080 to 2.5063).

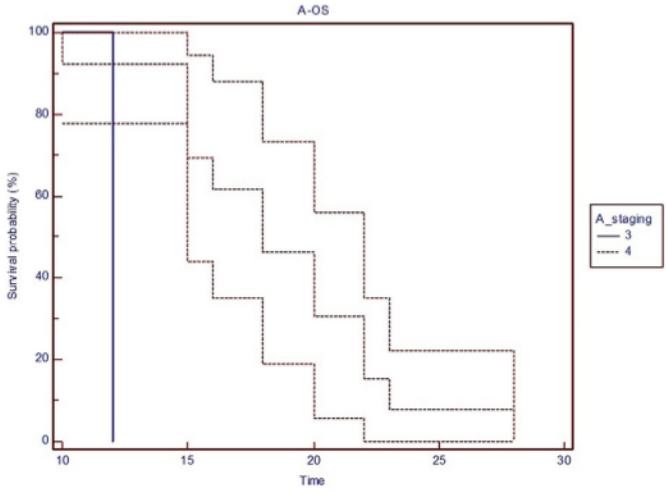

Fig. 3. Overall survival in sarcomatoid group (Chi-square 5.2814 DF 1 p = 0.0216 Hazard ratio 7.1823 95% CI 2.4903 to 97,764.1571).

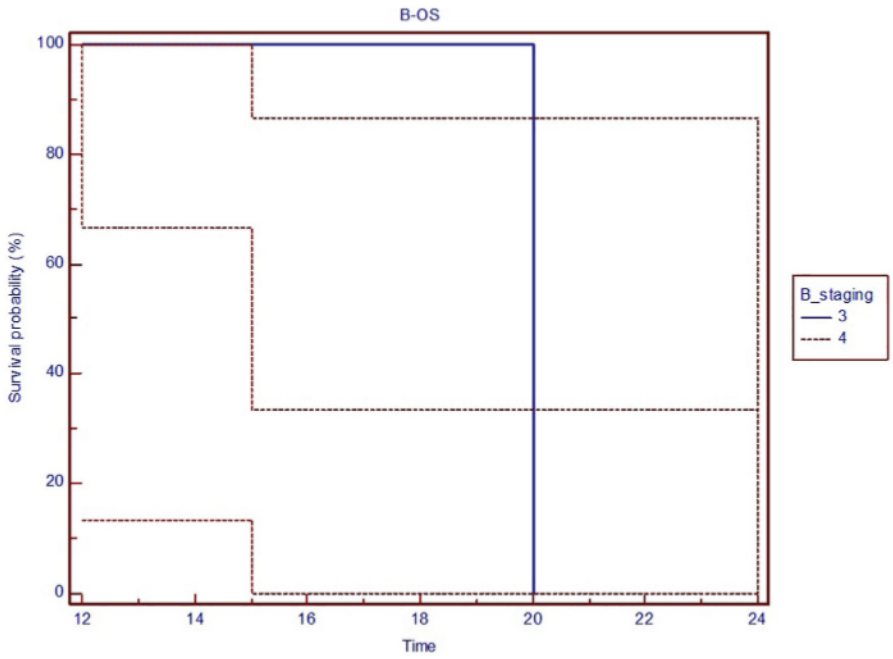

Fig. 4. Overall survival in nonsarcomatoid group (Chi-square 0.01053 DF 1 p = 0. 9183 Hazard ratio 0.8974 95% CI 0.07891 to 9.8432).

Table 3
Univariate Cox's analysis in sarcomatoid group.

Covariate	P	Chi-square	HR	95% CI of HR
Staging	0.0252	5.0095	4.2557	0.7141 to 25.3611
Grading	0.1022	2.6711	3.1541	0.6798 to 14.6344
Treatment strategy	0.0349	4.4520	5.9935	0.7517 to 47.7854
RT	0.0238	5.1091	6.5152	0.8269 to 51.3328

Table 4
Multivariate Cox's analysis in sarcomatoid group.

Covariate	P	SE	B	HR	95% CI of HR
Staging	0.5441	1.3186	0.7999	2.2254	0.1701 to 29.1121
Treatment strategy	0.5458	1.5731	0.9502	2.5861	0.1204 to 55.5713
RT	0.5379	1.5975	0.9839	2.6749	0.1187 to 60.2767

4. Discussion

In 2017 WHO clarified sarcomatoid nomenclature to unify the different definitions found in the previous articles. Sarcomatoid carcinoma is a high-grade variant of squamous cell head and neck carcinoma. It may arise in any squamous epithelium, but is most commonly found in the oral cavity or larynx. Thompson et al. [2] reported that recurrences developed in 45% of their 187 patients with laryngeal sarcomatoid carcinoma; surgical eradication, tumor stage, and tumor location (glottic vs other location) were significant prognostic factors. 25% of patients treated with radiation alone died for cancer, 18.9% of patients treated by surgery alone had the same outcome. Ballo et al. [3] reported positive outcomes in 28 glottic stage I or II sarcomatoid carcinoma cases treated with definitive radiotherapy. Gamez et al. [7] observed a 5-year OS of 80% for stage I sarcomatoid tumors versus 84% for squamous cell carcinomas. For other stages (II–IV), the 5-year overall survival rates were 43% for sarcomatoid tumors versus 51% for squamous cell carcinomas. They recommend multimodal therapy for advanced stages. Surgery is the best choice for laryngeal sarcomatoid carcinoma [9]. According to Dubal et al. [10], the radiotherapy role remains less clear. Radiotherapy treated cases had a 5-year DSS of 75.6%, which did not differ significantly from cases who did not receive any radiotherapy treatment (75.8%). It is important to note that the best prognosis was observed when surgery was used in combination with radiotherapy (84.2%), but this DSS rate was very similar to cases treated with surgery alone without radiotherapy (84.0%). Patients who received radiotherapy alone had the worst favorable outcomes (5-year DSS of 60.5%). Moreover, they reported that survival in glottic early-stage carcinoma was 84%, but became 51.9% in non-glottic ones. All those findings suggest that Spindle Cell Carcinoma evolution is similar to the squamous cell carcinoma in the early stages, while it is far more aggressive in the advanced stages. Our study is in accordance with the previously discussed literature since we are not able to distinguish a peculiar clinical pattern between Spindle Cell Carcinoma and Squamous Cell Carcinoma of the Larynx in the early stage. This changes when grading and staging increases. Survival and aggressiveness of Spindle originated malignancy is significantly increased compared to SCC, as showed by survival analysis, resistance to therapies and recurrence. It is important to note that the "early" Spindle Cell Larynx Carcinoma diagnosis, by both immunohistochemistry and ulstrastructural investigation might represent a crucial point to define a precise therapeutic and surgical approach, avoiding unimpactful approaches only causing side effects to the patients and delaying the effective tumor attack.

5. Conclusion

In our study we analyzed many advanced staged and few early staged patients (2 in each group), and, in accordance with the discussed literature, we observed the same outcome in sarcomatoid and non-sarcomatoid group in early-stage (2 sarcomatoid patients with a stage 2 cancer are alive at 14 and 60 months, similarly 2 non-sarcomatoid ones at 23 and 25 months). Mortality risk, described by OR, showed 11.66 times increased risk in sarcomatoid patients due to the aggressiveness in advanced stages. Nodal recurrence risk also happens 11.20 times more frequently in sarcomatoid patients. Cox's univariate model showed that, only in sarcomatoid group, staging, treatment strategy and radiotherapy were correlated to decreased survival; radiotherapy trend is correlating to poor prognosis. In sarcomatoid group, single patient

analysis clarified that radiotherapy is associated with a worse prognosis while patients did not receive radiotherapy had better survival. This might possibly due to the combination of the increased cancer resistance to radiation and the treatment toxicity.

Funding

This paper was not funded.

CRediT authorship contribution statement

FR Conceptualization and study plan BI Statistical analysis and manuscript draft MB and MC revision and formatting RP, RP, AB, GP, FJR, BC, RA, SM, MM, FO patient clinical informations and supervision.

Declaration of competing interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

[1] Gale N, Poljak M, Zidar N. Update from the 4th edition of the World Health Organization classification of head and neck Tumours: what is new in the 2017 WHO blue book for Tumours of the Hypopharynx, larynx, trachea and Parapharyngeal space. Head Neck Pathol 2017;11(1):23–32.

[2] Thompson LD, Wieneke JA, Miettinen M, Heffner DK. Spindle cell (sarcomatoid) carcinomas of the larynx: a clinicopathologic study of 187 cases. Am J Surg Pathol 2002;26(2):153–70.

[3] Ballo MT, Zagars GK. Radiation therapy for soft tissue sarcoma. Surg Oncol Clin N Am 2003;12(2):449–67 [vii].

[4] Marioni G, Bottin R, Staffieri A, Altavilla G. Spindle-cell tumours of the larynx: diagnostic pitfalls. A case report and review of the literature. Acta Otolaryngol 2003;123(1):86–90.

[5] De Stefani A, Boffano P, Bongioannini G. Review of histologic and immunohistochemical features of spindle cell carcinomas (carcinosarcomas) of the larynx. J Craniofac Surg 2014;25(5):e430–3.

[6] Ellis GL, Corio RL. Spindle cell carcinoma of the oral cavity. A clinicopathologic assessment of fifty-nine cases. Oral Surg Oral Med Oral Pathol 1980;50(6):523–33.

[7] Gamez ME, Jeans E, Hinni ML, et al. Outcomes and patterns of failure of sarcomatoid carcinoma of the larynx: the Mayo Clinic experience. Laryngoscope. 2018;128(2):373–7.

[8] Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC Cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67(2):93–9.

[9] Li YJ, Li WY, Wang J, Gao ZQ, Qi F, Jiang H. Clinic features of laryngeal carcinosarcoma and sarcomatoid carcinoma. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2017;52(5):385–7.

[10] Dubal PM, Marchiano E, Kam D, et al. Laryngeal spindle cell carcinoma: a population-based analysis of incidence and survival. Laryngoscope. 2015;125(12):2709–14.

/