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Head and neck

Adenosquamous cell carcinoma of the head and neck: a retrospective single institution series

Carcinoma adenosquamoso del distretto testa-collo: studio retrospettivo monocentrico

Gabriele Zigliani[1], Sara Migliorati[1], Elisa Marazzi[1], Mara Arcuri[1], Michele Tomasoni[1], Simonetta Battocchio[2], Alberto Paderno[1], Davide Lancini[1], Alberto Deganello[3], Cesare Piazza[1]

[1] Department of Otorhinolaryngology – Head and Neck Surgery, ASST Spedali Civili, Department of Surgical and Medical Specialties, Radiological Sciences and Public Health, University of Brescia, School of Medicine, Brescia, Italy; [2] Department of Pathology, ASST Spedali Civili, University of Brescia, School of Medicine, Brescia, Italy; [3] Department of Otorhinolaryngology – Head and Neck Surgery, IRCCS National Cancer Institute, Milan, Italy

SUMMARY

Objectives. Head and neck adenosquamous cell carcinoma (HN-ASCC) is a rare, aggressive neoplasm, with limited data reported in the literature. The aim of this study was to assess tumour behaviour and prognostic factors impacting overall survival (OS) in a retrospective, single institution series.

Methods. A retrospective study on patients affected by HN-ASCC who were treated surgically between 2002 and 2019 at the Department of Otorhinolaryngology – Head and Neck Surgery of the University of Brescia was conducted. Demographics, clinical data, OS, and relative prognostic factors were analysed.

Results. The study included 32 patients, with a median age of 66 years, mostly males (84.4%) and untreated (68.8%). Adjuvant treatments followed surgery in 28.1% of patients. Compared to conventional SCC, ASCC showed a higher proportion of cases arising in the larynx (40.6%); no difference was found in other features. Advanced (pT3-4) local stage at presentation (p = 0.023), perineural invasion (PNI, p = 0.01), and positive margins (p = 0.007) were independent negative prognostic factors for OS.

Conclusions. HN-ASCC is a rare, aggressive cancer, most frequently arising in the larynx of elderly males, usually diagnosed in an advanced local stage. OS is generally poor, affected by local advanced stage, PNI, and positive resection margins.

KEY WORDS: adenosquamous cell carcinoma, head and neck, survival, prognosis, recurrence

RIASSUNTO

***Obiettivo**. Il carcinoma adenosquamoso del distretto testa-collo (HN-ASCC) è una neoplasia rara e aggressiva, con pochi dati riportati in letteratura. Lo scopo del presente lavoro è quello di valutare il comportamento di questa neoplasia e i fattori prognostici che ne influenzano la sopravvivenza cruda mediante uno studio retrospettivo su una serie monocentrica.*

***Metodi**. Il lavoro, retrospettivo, ha reclutato pazienti affetti da HN-ASCC trattati chirurgicamente dal 2002 al 2019 presso la Clinica Otorinolaringoiatrica dell'Università degli Studi di Brescia. Sono stati analizzati i dati demografici, clinici, di sopravvivenza cruda e i relativi fattori prognostici.*

***Risultati**. Lo studio ha incluso 32 pazienti di età mediana pari a 66 anni, per lo più maschi (84,4%), mai trattati prima (68,8%). Il trattamento adiuvante è stato somministrato dopo la chirurgia nel 28,1% dei casi. Confrontato col più frequente SCC, l'ASCC insorge maggiormente a livello laringeo (40,6%); non sono state riscontrate altre differenze. Lo stadio locale avanzato (pT3-4) alla diagnosi (p = 0,023), l'infiltrazione perineurale (p = 0,01) e i margini positivi (p = 0,007) sono risultati fattori prognostici negativi indipendenti per la sopravvivenza cruda.*

***Conclusioni**. L'HN-ASCC è una neoplasia rara, aggressiva, per lo più a origine laringea e in pazienti anziani, maschi, in stadio localmente avanzato alla diagnosi. La sopravvivenza cruda è solitamente scarsa e condizionata dallo stadio localmente avanzato, dalla presenza di invasione perineurale e dai margini positivi.*

PAROLE CHIAVE: *carcinoma adenosquamoso, testa-collo, sopravvivenza, prognosi, recidiva*

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Correspondence
Gabriele Zigliani
Department of Otorhinolaryngology – Head and Neck Surgery, ASST Spedali Civili, Department of Surgical and Medical Specialties, Radiological Sciences and Public Health, University of Brescia, School of Medicine, Brescia, Italy, piazzale Spedali Civili 1, 25123 Brescia, Italy
Tel. +39 030 3995319
E-mail: gabriele.zigliani@gmail.com

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Introduction

Head and neck adenosquamous cell carcinoma (HN-ASCC) is a rare, aggressive neoplasm; the most frequently involved site is the larynx, followed by the oral cavity, oropharynx, hypopharynx, nasopharynx, and nasal cavity [1,2]. It is usually diagnosed in the 6th and 7th decades with a male prevalence [2-4]. Due to its exceptional rarity, information about its diagnosis, description, and treatment strategies are based on case reports and small clinical series.

ASCC was first described by Gerughty et al. [5] in 1968, with 80% of patients having distant metastasis at diagnosis; it has been considered as a variant of mucoepidermoid carcinoma (MEC) until Evans [6], in 1984, suggested that ASCC should be deemed as an independent histology due to its local aggressiveness, early tendency to distant spreading, and poor prognosis [4,7]. At histologic analysis, ASCC shows both squamous and adenomatous malignant components. The former usually predominates, it can be in situ or invasive, and range from well to poorly differentiated. The latter have a tubular, alveolar, and/or glandular morphology. Mucin production is typically present, but is not a requirement for diagnosis in the presence of true gland formation [8]. Perineural invasion is typically present [3].

Despite the lack of scientific evidence, ASCC appears to be strongly related to alcohol abuse and smoking habits, although HPV may also take part in its pathogenesis [2,4]. Symptoms are related to the site affected and include painful ulcers, hoarseness, dysphagia, dyspnoea, obstruction, and haemoptysis [3]. Histopathological differential diagnosis includes muco-epidermoid carcinoma, adenoid squamous cell carcinoma, metastatic adenocarcinoma, necrotising sialo-metaplasia, and squamous cell carcinoma [3].

Because of its rarity, there are no specific guidelines for the management of ASCC. Most authors recommend early and aggressive surgical resection followed by adjuvant treatments [3,4], even though the beneficial role of radiation therapy (RT) and associated chemotherapy (CHT) in the adjuvant setting has not been clearly demonstrated.

Materials and methods

A retrospective analysis of consecutive patients affected by primary HN-ASCC who were treated surgically from January 2002 to November 2019 was conducted at the Department of Otorhinolaryngology – Head and Neck Surgery, University of Brescia, Italy. Inclusion criteria were: a) histopathological diagnosis of HN-ASCC originating from the oral cavity, oropharynx, larynx, hypopharynx, or sinonasal cavities performed or confirmed at our Institution; b) primary or salvage surgery with curative intent; c) availability of comprehensive demographics and histopathological details. Patients with distant metastasis at diagnosis were excluded. Clinical, radiological, histopathological reports, and mortality registries were consulted. Demographics, clinical, tumour-, treatment-related characteristics, and information on follow-up were retrieved and collected in an anonymised database. Patients were followed after surgery with a standard protocol, which involved endoscopic examination every 2 months for the first year, 4 months during the second year, and 6 months thereafter. Radiological evaluation (CT scan or MRI) of the head and neck was performed every 4 months in the first 2 years, 6 months from the third to the fifth year. Chest and abdomen CT scan (or a PET) was also obtained yearly.

Data from a historic cohort of patients affected by Stage II-IV SCC of the oral cavity, oropharynx, larynx and hypopharynx treated by upfront surgery at our Institution between 2009 and 2019, meeting the same inclusion/exclusion criteria of the ASCC cohort, were also retrieved.

Statistical analysis

Variables included in the analysis were expressed in terms of median, interquartile range (IQR), range of values, and percentages. The main demographics (age at surgery, gender) and pathological features (site of origin, pT, pN, margin status) were compared between the cohorts of SCC and ASCC using Mann-Whitney, chi-square, and Fisher exact-tests, as appropriate. The time at risk was computed from the date of surgery to the date of death, first relapse of disease (any site), or latest available follow-up (censored data). Outcomes of interest were overall survival (OS), defined as the time from surgery to death from any cause, and relapse-free survival (RFS), defined as the time from surgery to disease relapse (any site).

Univariate analysis was conducted using Cox proportional hazard model. Results were expressed as hazard ratio (HR) with 95% confidence intervals (CI). Survival curves and the relative 95% CI were plotted using the Kaplan Meier method and compared with the log-rank test. Five-year survival estimates and the relative 95% CI were reported at the univariate analysis. Multivariable analysis was conducted using a Cox proportional hazard model selecting the most relevant variables with a clinical application. Shoenfeld's residuals were tested to assess the proportional hazard assumption. Multicollinearity between variables was excluded by testing the variance inflation factor (vif); a vif < 5 was considered acceptable. Statistical analysis was performed using R (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria); p-values < 0.05 (two-tailed) were considered statistically significant.

Results

Clinical features

Thirty-two patients were included in the current study, and 27 (84.4%) were males; the median age at surgery was 66 years (IQR = 11), ranging from 47 to 86 years. In 10 cases (31.2%), surgery was performed as salvage treatment for local recurrence after previous (CHT)RT (70%), surgery alone (20%), or surgery and adjuvant RT (10%). Among the 22 treatment-naïve patients receiving upfront surgery, data on pre-operative biopsy was available in 17 cases. Most patients were diagnosed with conventional SCC (75%), whereas only 25% of cases were correctly diagnosed as ASCC from the beginning: in one case, pre-operative biopsy misdiagnosed ASCC for MEC. In 4 cases, pre-operative biopsy was not performed since transoral base of tongue or transoral laryngeal microsurgery (TOLMS) was scheduled, with frozen sections obtained intra-operatively to confirm malignancy. For one patient, data on pre-operative diagnosis was not available. The most involved site was the larynx (40.6%), followed by the oropharynx (21.9%), hypopharynx, oral cavity, and sinonasal cavities (12.5% each).

Among treatment-naïve patients, 13 (59.1%) were cN0: in 5 cases (38.5%) an elective neck dissection was performed, with a rate of occult nodal metastasis of 40% (2 cases, both classified as pN1); in the remaining 8 cases (61.5%), an exclusive nodal recurrence with a disease-free interval (DFI) of 35 months was observed in only one patient (12.5%) who was later successfully treated with surgery. Most tumours were locally advanced (17 patients were diagnosed as pT3-4a, 53.1%), whereas the presence of nodal metastases was observed in 37.5% of patients: 12.5% were classified as pN1, 9.4% as pN2b, and 15.6% as pN3b. Perineural (PNI) and lympho-vascular invasion (LVI) were reported in 56.2% and 43.8% of cases, respectively. Surgical resection with negative surgical margins (R0, with a distance from the lesion > 5 mm for open surgery) was obtained in 18 cases (56.2%), while positive surgical margins were detected in 14 (43.8%) patients. There were no R0 close margins.

Overall, adjuvant treatment was administered to nine patients (28.4%). Among primary tumours, RT was performed in 16.7%, whereas no case of re-RT after salvage surgery was recorded. Further details are available in Table I.

Table I. Descriptive statistics of the cohort.

Variables		N	%
Age (years)	≤ 65	15	46.9%
	> 65	17	53.1%
Gender	Female	5	15.6%
	Male	27	84.4%
Presentation	Primary	22	68.7%
	Recurrence	10	31.3%
Previous treatment (for recurrent ASCC)	CHTRT	7	70%
	Surgery + RT	1	10%
	Only surgery	2	20%
Subsite	Sino-nasal	4	12.5%
	Oral cavity	4	12.5%
	Oropharynx	7	21.9%
	Hypopharynx	4	12.5%
	Larynx	13	40.6%
pT classification	pT1	6	18.8%
	pT2	9	28.1%
	pT3	6	18.8%
	pT4a	11	34.3%
pN classification	pN0	20	62.5%
	pN1	4	12.5%
	pN2b	3	9.4%
	pN3b	5	15.6%
Presence of nodal metastasis	No	19	59.4%
	Yes	13	40.6%
Staging	I-II	15	46.9%
	III-IV	17	53.1%
PNI	Absent	14	43.8%
	Present	18	56.2%
LVI	Absent	18	56.2%
	Present	14	43.8%
Margins	R0	18	56.2%
	R1	14	43.8%
Adjuvant treatment	None	21	70%
	RT	5	16.7%
	CHTRT	4	13.3%
	Missing data	(2)	

ASCC: adenosquamous cell carcinoma; CHTRT: chemo-radiotherapy; LVI: lympho-vascular invasion; PNI: perineural invasion; RT: radiotherapy.

Overall survival and analysis of prognosticators

Follow-up data were available for 30 patients, with a median follow-up of 39 months (range, 1-149). At the end of the study, 13 (43.4%) patients died of disease: all experienced recurrence, with a median DFI of 8.5 months (range, 3-41): loco-regional recurrence occurred in 11 cases (36.7%), whereas distant metastases were diagnosed in 2 (6.7%). Five-year OS and RFS were 49.3% (95% CI, 33.5%-72.5%) and 53% (95% CI, 36.1%-77.7%), respectively (Fig. 1).

Univariate analysis according to OS showed that PNI (HR = 4.62, p = 0.011), LVI (HR = 2.71, p = 0.052), presence of positive resection margins (HR = 3.04, p = 0.026), and advanced local disease (pT3-4, HR = 4.14, p = 0.018)

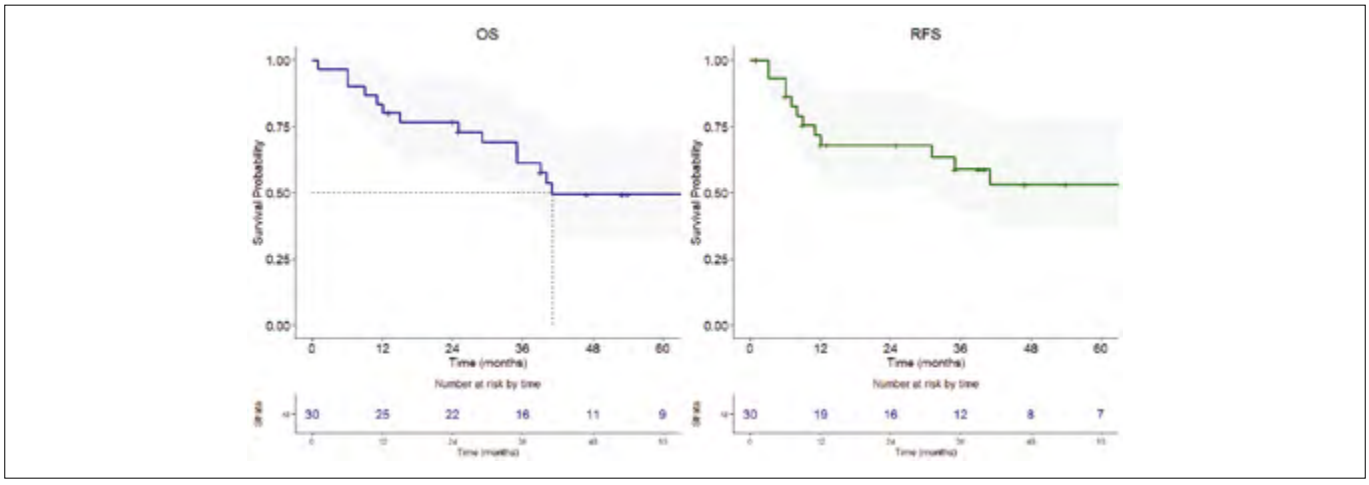

Figure 1. Kaplan Meier curves showing overall survival (OS) and recurrence free survival (RFS).

were significantly associated with worse OS (Fig. 2). Multivariate analysis confirmed PNI (HR = 7.81, p = 0.01), presence of positive margins (HR = 7.80, p = 0.007), and pT3-4 (HR = 4.69, p = 0.023) as independent prognostic factors (Tab. II).

Comparison of clinical features and prognosis of 'conventional' SCC and ASCC

Fourteen patients with treatment-naïve Stage II-IV ASCC of the oral cavity, oropharynx, larynx, and hypopharynx were compared to an historic retrospective cohort of patients affected by treatment-naïve conventional SCC and submitted to upfront surgery (n = 305). No significant differences were found considering age at diagnosis (p = 0.686), gender (p = 0.994), margin status (p = 0.101), pT classification (p = 0.590), and presence of nodal metastasis (p = 0.684), whereas ASCC were significantly more common in the larynx and rarely observed in the oral cavity compared to SCC (p = 0.013). Further details are shown in Table III.

No significant differences between the cohorts of stage I-IV 'conventional' SCC and ASCC (Fig. 3) were found both in terms of OS (52.5%, 95% CI, 47.0%-58.8% *vs* 46.2%, 95% CI, 25.7%-83.0%; p = 0.576) and RFS (61.6%, 95% CI, 56.0%-67.8% *vs* 51.3%, 95% CI, 29.6%-88.8%, p = 0.571).

Discussion

The author who first described HN-ASCC suggested the origin of such a rare lesion from sero-mucinous glands of the upper aero-digestive tract [5]. Evans [6] then ascertained

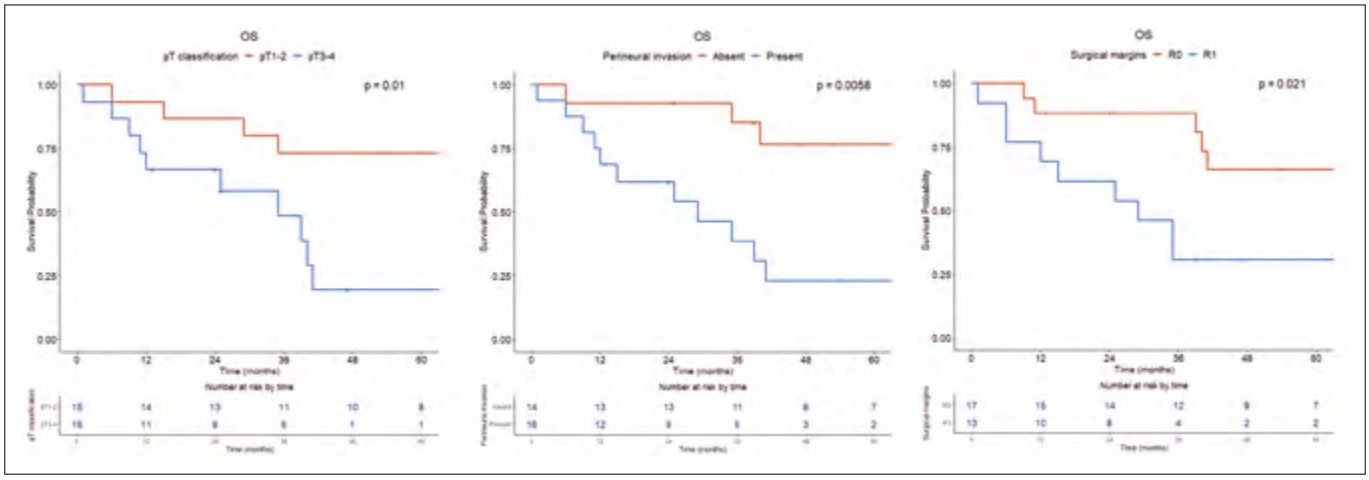

Figure 2. Kaplan Meier curves showing overall survival (OS) according to pT classification (pT1-2 *vs* pT3-4), PNI (Pn0 *vs* Pn1), and surgical margins (R0 *vs* R1).

Table II. Univariate and multivariate analysis showing the prognostic role of demographics, treatment and pathological-related variables in terms of OS.

Variables		Logrank test		Cox proportional hazard regression model		Cox proportional hazard regression model	
		5-year OS (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	< 65	52.4% (30.6%-89.6%)	0.316	1.67 (0.61-4.58)	0.323		
	> 65	46.8% (27.0%-81%)					
Gender	Female	75.0% (42.6%-100%)	0.205	3.44 (0.45-26.23)	0.233		
	Male	44.4% (27.9%-70.6%)					
Presentation	Primary	52.2% (33.7%-80.8%) 42.0% (18.4%-95.6%)	0.238	1.79 (0.68-4.76)	0.241	2.56 (0.62-10.60)	0.195
	Recurrence	42.0% (18.4%-95.6%)					
Previous RT	No	56.4% (37.4%-84.8%)	0.198	1.90 (0.71-5.12)	0.204	0.93 (0.18-4.76)	0.932
	Yes	35.0% (14.3%-85.8%)					
Subsite	Sino-nasal	100% (100%-100%)	0.844*	1.10 (0.15-8.21)	0.922		
	Oral cavity	66.7% (30.0%-100%)	(2y-OS)	1.44 (0.19-10.70)	0.724		
	Oropharynx	57.1% (30.1%-100%)		1.39 (0.26-7.20)	0.704		
	Hypopharynx	50.0% (18.8%-100%)		1.10 (0.15-8.20)	0.922		
	Larynx	91.7% (77.3%-100%)					
pT	pT1-2	73.3% (54%-99.5%)	**0.010**	4.14 (1.28-3.4)	**0.018**	4.69 (1.24-17.79)	**0.023**
	pT3-4	19.4% (5.7%-65.6%)					
Nodal metastases	No	62.5% (28.1%-78.3%)	0.779	0.86 (0.32-2.34)	0.768	1.84 (0.46-7.31)	0.387
	Yes	32.5% (32.5%-95.0%)					
PNI	Pn0	76.6% (56.6%-100%)	**0.006**	4.62 (1.42-15.06)	**0.011**	**7.81 (1.61-37.83)**	**0.010**
	Pn1	23.2% (8.75%-61.6%)					
LVI	Lv0	62.2% (42.2%-91.7%)	**0.044**	2.71 (0.99-7.44)	0.052		
	Lv1	29.7% (11.7%-75.1%)					
Margins	R0	66.2% (45.7%-95.8%)	**0.021**	3.04 (1.14-8.12)	**0.026**	**7.80 (1.73-35.13)**	**0.007**
	R1	30.8% (13.6%-69.5%)					
Adjuvant RT	No	53.9% (35.5%-81.8%)	0.735	1.23 (0.38-3.96)	0.725		
	Yes	43.8% (18.9%-100%)					

LVI: lympho-vascular invasion; PNI: perineural invasion; RT: radiotherapy.

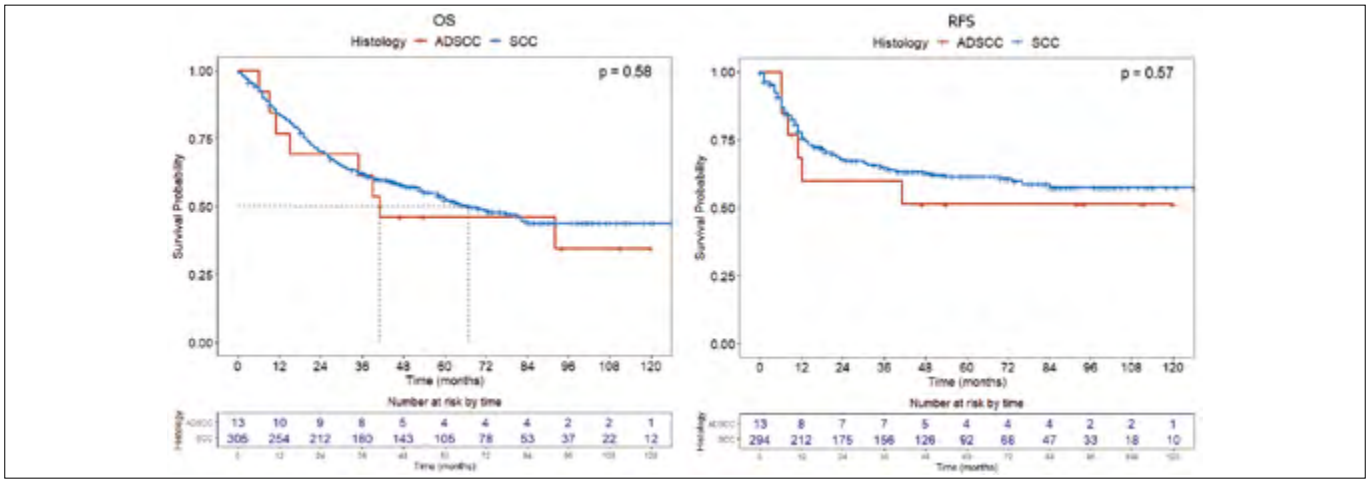

Figure 3. Kaplan Meier curves comparing overall survival (OS) and recurrence free survival (RFS) between stage II-IV oral cavity, oropharyngeal, hypopharyngeal and laryngeal SCC and ASCC.

Table III. Differences in most relevant demographics and pathological variables between the retrospective cohorts of patients affected by treatment-naïve, Stage II-IV primary ASCC and conventional SCC of the head and neck treated in our centre.

Variables		ASCC	SCC	P-value
Median age (range) - years		67.5 (52-84)	67 (26-91)	0.686
Gender	Female	3 (21.4%)	77 (25.2%)	0.994
	Male	11 (78.6%)	228 (74.8%)	
pT	pT1	0 (0%)	11 (3.6%)	0.590
	pT2	6 (42.9%)	84 (27.6%)	
	pT3	3 (21.4%)	70 (23%)	
	pT4	5 (35.7%)	139 (45.8%)	
Site	Hypopharynx	3 (21.4%)	32 (10.5%)	**0.013**
	Larynx	5 (35.7%)	94 (30.8%)	
	Oral cavity	3 (21.4%)	164 (53.8%)	
	Oropharynx	3 (21.4%)	15 (4.9%)	
Nodal metastasis	No	6 (42.9%)	157 (52.1%)	0.684
	Yes	8 (57.1%)	144 (47.9%)	
Extranodal extension	No	5 (62.5%)	47 (34.3%)	0.135
	Yes	3 (37.5%)	90 (65.7%)	
Margins	R0	8 (57.1%)	158 (77.8%)	0.101
	R1	6 (42.9%)	45 (22.2%)	

the distinct histopathological features of ASCC, and Alos [10] described the related immunohistochemical diagnostic criteria: CEA, CK7, and CAM5.2 reflect adeno-carcinomatous and glandular components; CK20 is absent, while the squamous component expresses CK5/6 and p63. Histopathological diagnosis based on small pre-operative biopsy can often be mistaken with MEC, but mostly with SCC: this might be due to either the small portion of tissue picked up with biopsy (the glandular component is always deeper than the SCC component, and therefore a superficial biopsy might lead to uncomplete diagnosis), and the uncommon occurrence of HN-ASCC.

Historically, consensus in the previous literature reported that ASCC has a poor prognosis with a tendency for lymphatic metastasis [11]. Because of its rarity, retrospective series from the literature do not include a large number of patients, except for the cohort study by Lee et al. (provided by the SEER database), with more than 200 cases collected over 40 years [7].

From 2002, our Institution had 32 patients diagnosed with ASCC, showing a large proportion of males, mostly (81.2%) in their 7th-9th decades, confirming previous observations reporting a higher incidence in the elderly [5,8], even if age appears to play a major negative role in survival, as demonstrated by Lee et al. [7] Nevertheless ASCC can occur in younger patients, as previously reported [11-13]. The relative frequency of the sites of origin was confirmed by our data, showing the larynx as the most involved site, followed by the oropharynx, whereas the oral cavity, hypopharynx, and sinonasal tract were less frequently involved. Interestingly, the site of origin was the only feature that significantly differed from the historic cohort of conventional SCC, showing a drastically higher and lower proportion of laryngeal and oral cavity ASCC, respectively. No difference in terms of age, gender, margin status, pT and pN categories, five-year OS and RFS was found, although the small sample size of our series limits us from drawing solid conclusions. We have not yet identified specific risk factors for the onset of this neoplasm; alcohol and smoking, as for conventional SCC, can be however involved in laryngeal ASCC [2,4], while the role of HPV remains unclear. In the cohorts of Masand et al. [8] and Mehrad et al. [12], evidence of HPV DNA or p16 was rarely reported, but better prognosis was hypothesised since no recurrence was observed in these patients after adequate treatment.

The main contribution provided by our cohort study is that locally advanced disease, and the presence of PNI and positive margins of resection, are independently associated with worse outcomes. Tumour staging has a strong impact on prognosis, as demonstrated by Lee et al. [7]. In our cohort, patients affected by locally advanced disease, with tumor in pT3-4 categories, showed a significant reduction of 5-year OS (19.4%) compared to pT1-2 (73.3%), confirming its prognostic role as an independent factor at multivariable analysis (HR = 4.69).

Conversely, the presence of nodal metastasis, although a common occurrence (37.5%), was not associated with a

decrease in OS at either univariate or multivariate analysis. We did not find any report in the literature to confirm this unusual result; the exiguous number of patients involved in this study could also explain this discrepancy from previous studies. Unfortunately, the rarity of this cancer histotype makes comparison between larger series difficult to realise.

As previously described by Sheahan [13] and Keelawat [1], patients with tumour showing PNI experienced a significant decrease in 5-year OS (23.2% *vs* 76.6%), thus confirming it as an independent negative prognosticator at multivariate analysis (HR = 7.81). PNI could explain both marked tumour aggressiveness and consequent poor prognosis, although Kass and colleagues [14] demonstrated that there was no difference in PNI on prognosis between ASCC and conventional SCC. Even if statistical significance was not met, the rate of positive margins was higher in the ASCC group in comparison to the historical SCC cohort (43% *vs* 22%), reinforcing the need of obtaining wider macroscopic margins in healthy appearing tissue when resecting ASCC. In fact, the presence of positive surgical margins was significantly associated with a reduction in 5-year OS (30.8% *vs* 66.2%), with an independent prognostic role at multivariable analysis (HR = 7.80), underlying the dramatic importance of radical excision of these lesions, even at cost of sacrificing aesthetic and functional outcomes.

On the other hand, age at diagnosis (cut-off 65 years), presentation (up-front surgery for untreated tumour *vs* salvage surgery for local recurrence), site of origin, and adjuvant treatments were not significantly associated with a change in OS. The non-significant role of age may be due to the advanced age of many patients, whereas the site of origin may not play a prognostic role since it could be counterbalanced by the ability of the surgeon to perform radical resections. As shown by other studies [15,16], the protective role of adjuvant treatments in terms of OS has not been demonstrated, although this is probably biased by the small number of patients studied.

The main limitations of the current study are its retrospective nature and the small number of ASCC patients secondary to the rarity of this neoplasm. However, our series deepens the features of an uncommon histopathological entity in the head and neck district, identifies precise factors affecting outcome, and assesses tumour behaviour through a congruous lapse of time.

Conclusions

HN-ASCC is a rare, aggressive tumor arising from the epithelium of the upper aero-digestive tract. It most frequently originates in the larynx of elderly males and is diagnosed at an advanced local stage. Compared to conventional SCC, ASCC did not show a significant increase in nodal metastases at diagnosis. OS is generally poor and significantly affected by local advanced stage, PNI, and positive resection margins. The beneficial role of adjuvant (CHT)RT has not been demonstrated.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

MT, GZ: concept; GZ, EM, MA, SM: data collection; GZ, EM, MA, SM, MT: writing – original draft; CP, AP, DL, AD: writing – review and editing.

Ethical consideration

This study was approved by the Institutional Ethic Committee (CE Spedali Civili, Brescia) (protocol number: 4267). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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