Received: 11 April 2023 | Revised: 23 August 2023 | Accepted: 22 October 2023

DOI: 10.1002/hed.27566

ORIGINAL ARTICLE

WILEY

Prognostic role of the MRI-based involvement of superior pharyngeal constrictor muscle in oropharyngeal squamous cell carcinoma

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Section Editor: Matthew Old

Abstract

Objectives: The aim of this study was to determine the impact of the involvement of the superior pharyngeal constrictor muscle (SPCM) evaluated by magnetic resonance imaging (MRI) on outcome in oropharyngeal squamous cell carcinomas (OPSCCs).

Methods: A retrospective study including consecutive patients with OPSCC treated with curative intent.

Results: A total of 82 consecutive patients with OPSCC met inclusion criteria. At multivariate analysis, patients with SPCM infiltration were at significantly higher risk of death (HR: 3.37, CI: 1.21–9.38) and progression (HR: 3.39, CI: 1.38–8.32). In a multivariate model conditioned on HPV status, a significantly higher risk of death and progression was observed by combining both SPCM and HPV status with patients harboring an HPV-negative OPSCC with SPCM infiltration showing the poorest outcome.

Conclusion: MRI evidence of SPCM involvement significantly and independently increases the risk of death and progression in subjects with OPSCC. Considering both MRI-assessed SPCM infiltration and HPV status significantly improved risk stratification in these malignancies.

KEYWORDS

HPV, squamous cell carcinoma, superior pharyngeal constrictor muscle, surgery, survival

1 | INTRODUCTION

Oropharyngeal cancers are a group of malignant diseases that account for approximately 100 000 new cases and 50 000 deaths worldwide each year. Oropharyngeal squamous cell carcinomas (OPSCCs) represents more than 90% of these malignancies.[1]

In addition to the stage and the involved subsite, the prognosis of OPSCC critically depends on human papillomavirus (HPV) status, the strongest prognostic biomarker

for this cancer. As different aspects of the disease including category T, N, and the presence of extracapsular lymph node extension have a different prognostic impact in HPV-positive and HPV-negative OPSCC, the VIII edition of the TNM Staging System of Head and Neck Tumors incorporated a separate staging algorithm for $p16^{INK4a}$-positive OPSCCs.[2] Positive immunostaining for cyclin-dependent kinase inhibitor $p16^{INK4a}$ is, indeed, considered a surrogate marker for transforming HPV infection in OPSCC.[3]

However, both subgroups are quite heterogeneous and roughly 20% of all patients with HPV-driven OPSCC develop recurrent disease within 5 years after diagnosis.[4] It is, therefore, of paramount importance to identify clinical and biological predictors that can improve prognostic stratification in these malignancies. With the aim to reduce toxicity while maintaining efficacy, numerous trials are currently underway to assess the non-inferiority of de-intensified treatments in HPV-driven OPSCCs.[5] A strict selection of patients eligible for such trails is consequently crucial.

Several structures, such as the epiglottis, larynx, extrinsic tongue muscles, medial pterygoid, hard palate, and mandible, can shift a tumor from an early to an advanced T category when involved.[6,7] However, the involvement of the superior pharyngeal constrictor muscle (SPCM) is not considered in the AJCC's staging system. Despite this, the SPCM, by forming the posterior and lateral walls of the oropharynx, acts as a barrier separating the organ from the parapharyngeal and prevertebral spaces, potentially preventing cancer invasion into these areas.[9] Moreover, SPCM invasion significantly influences the selection of surgical approaches and reconstructive strategies.[8–10]

Hence, the aim of this study was to examine the correlation between SPCM infiltration by cancer, as assessed by magnetic resonance imaging (MRI), and the neck lymph node status at the time of diagnosis. Additionally, the study aimed to assess the impact of this infiltration on the outcome of both HPV-driven and non-HPV-driven OPSCC.

2 | MATERIALS AND METHODS

In this retrospective study, patients diagnosed with OPSCCs at the Clinic of Otolaryngology-Head and Neck Surgery, University of Trieste, Trieste, Italy between 2005 and 2021 were considered for the inclusion in this study. The study protocol was approved by the University Ethics Committee on Clinical Investigation (N.89/2018) in compliance with the Helsinki Declaration. The study included all consecutive patients that met the following inclusion criteria: (a) age ≥18 years; (b) pathologically confirmed invasive primary OPSCC arising from tonsillar complex (i.e., palatine tonsil and tonsillar fossae), posterior wall, or soft palate subsites; (c) available formalin-fixed paraffin-embedded (FFPE) specimens of the neoplastic lesion or availability of both high-risk HPV-DNA and $p16^{INK4a}$ status; (d) absence of distant metastases; (e) surgical or nonsurgical treatment with curative intent. Alive patients with a follow-up shorter than 12 months were excluded. All cases, initially staged according to the 7th edition of AJCC TNM, were subsequently restaged following the guidelines of the 8th edition. Irrespective of HPV status, a multidisciplinary team decided on treatment planning according to TNM staging and NCCN guidelines.[11] The infiltration of the SPCM did not play a role in the choice of a surgical versus nonsurgical treatment. Information on patients' demographic characteristics, tumor features, tumor HPV status, staging, and treatment was gathered.

2.1 | SPCM infiltration assessment

The SPCM infiltration was evaluated by MRI. Particularly, on axial T2WI, tumor spread through the SPCM was jointly determined by two radiologists, both with >15 years of experience in head and neck imaging, who were blinded to the results of the histopathological assessment. Irregular contour, thinning, intensity inhomogeneity of the SPCM compared to the contralateral side, or cancer protrusion into the parapharyngeal fat were considered diagnostic criteria for SPCM infiltration (Figure 1A,B).

2.2 | Neck status assessment

In patients undergoing surgical treatment, the neck status was determined based on histological findings obtained from neck dissection specimens. In nonsurgical patients, the neck status was determined based on positron emission tomography (PET) findings, following the results of Ng et al., who demonstrated the higher sensitivity of PET in comparison to MRI and computed tomography for identifying neck metastases.[12] Lymph nodes with elevated metabolism (SUVmax >4) where considered as pathological.[13]

2.3 | HPV-DNA testing and $p16^{INK4a}$ immunostaining

Search and typing of HPV DNA sequences were performed using the Linear Array HPV Detection and

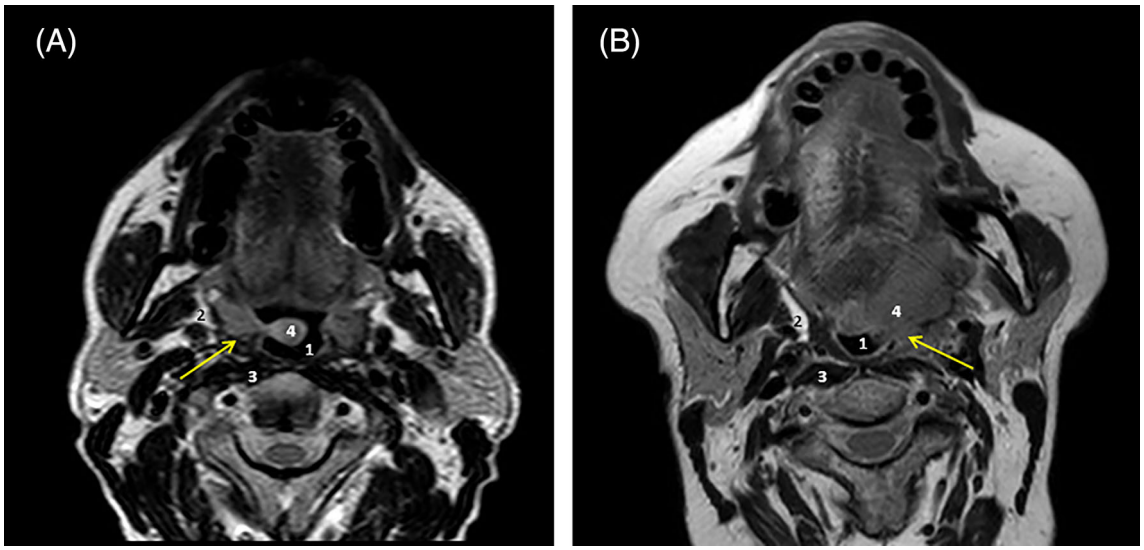

FIGURE 1 Pretreatment MR imaging in patients with OPSCCs. (A) Axial T2WI of a 72-year old male with right-tonsillar SCC (arrow) showing no signs of SPCM: note the normal contour and thickness of the SPCM similar to the contralateral side. (B) Axial T2WI of a 68-year old male with left-tonsillar SCC revealing thinning of the SPCM due to the tumor (arrow) and protrusion of the tumor into the parapharyngeal space. 1: pharyngeal lumen; 2: parapharyngeal space; 3: prevertebral muscles; 4: primary tumor. MR, magnetic resonance; OPSCC, oropharyngeal squamous cell carcinoma; SPCM, superior pharyngeal constrictor muscle [Color figure can be viewed at wileyonlinelibrary.com]

Genotyping Test (Roche Molecular Systems, Milan, Italy), as described by the manufacturer. The expression of $p16^{INK4a}$ protein was performed on formalin-fixed paraffin-embedded sections by immunostaining using the BD Pharmingen IHC Detection kit, according to the manufacturer's instructions. The expression results were scored as positive by using a 70% cut-point and considering nuclear and cytoplasmic stain distribution. A tumor was defined as HPV-driven when double positive for high-risk HPV-DNA and $p16^{INK4a}$ overexpression.[14]

2.4 | Statistical analysis

Sociodemographic and clinical characteristics were summarized as percentage or median values, with interquartile range (Q1–Q3). The association between SPCM infiltration and clinical characteristics was evaluated through Fisher's exact test; agreement between MRI and histological and was evaluated through Cohen's kappa coefficient.

For each patient, the time at risk was calculated from the date of treatment (i.e., date of surgery or date of radio-chemotherapy completion) to the event date or last follow-up, whichever occurred first. The event of interest was death for overall survival (OS), and progression or death for progression-free survival (PFS). Survival probabilities were calculated according to Kaplan–Meier method, and differences across strata were evaluated through the log-rank test.[15] Hazard ratios (HR) and the corresponding 95% CI were calculated using Cox proportional hazards models, adjusting for sex and age, plus clinically relevant covariates (i.e., oropharyngeal subsite, stage, and treatment)[15] Statistical analysis was performed using SAS 9.4 and R software 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

A total of 82 consecutive patients with primary OPSCC (median [range] age, 65 [42–88] years; 56 [68.3%] males) met inclusion criteria and were analyzed. Sociodemographic and clinical characteristics are shown in Table 1. Most of cases were tumors arising from the tonsillar complex (73.0%) and were stage III-IVb tumors (67.1%). Overall, 30 cases were HPV-driven (36.6%) based on the double positivity for high-risk HPV-DNA and $p16^{INK4a}$ overexpression. Forty-three patients (52.5%) were submitted to up-front surgery.

3.1 | SPCM infiltration and status of neck lymph nodes

Based on MRI findings, the SPCM was involved by the tumor in 45 cases (54.9%). In the surgical group, the concordance between MRI findings and histological

TABLE 1 Socio-demographic and clinical characteristics

Characteristics	*n* (%)
Sex	
Woman	26 (31.7)
Man	56 (68.3)
Age (years)	
<65	41 (50.0)
≥65	41 (50.0)
Median (Q1–Q3)	65 (58–71)
Oropharyngeal subsite	
Soft palate	10 (12.2)
Tonsillar complex	60 (73.2)
Posterior wall	12 (14.6)
T categories	
T1	12 (14.6)
T2	14 (17.1)
T3	20 (24.4)
T4	36 (43.9)
N categories	
N0	18 (22.0)
N1	21 (25.6)
N2	33 (40.2)
N3	10 (12.2)
Cancer stage	
I	12 (14.6)
II	15 (18.3)
III	16 (19.5)
IVa-IVb	39 (47.6)
HPV status	
Negative	52 (63.4)
Positive	30 (36.6)
Treatment	
Surgery alone	19 (23.2)
Surgery + (chemo)-radiotherapy	24 (29.3)
(Chemo)-radiotherapy	39 (47.6)
SPCM infiltration	
No	37 (45.1)
Yes	45 (54.9)

Abbreviations: HPV, human papillomavirus; SPCM, upper pharyngeal constrictor muscle.

examination was 90.7% (K Cohen [95% CI]: 0.79 [0.59–0.98]) with three cases MRI positives and histologically negatives, attributed to peritumoral edema, and one case MRI negative and histologically positive for SPCM infiltration. The prevalence of SPCM infiltration increased by T category, being 2.2%, 8.9%, 24.4%, and 64.4% in T1, T2, T3, and T4 lesions, respectively ($p < 0.001$). Patients with SPCM infiltration were more likely to present involvement of the regional lymph nodes compared to patients with SPCM uninvolved by tumor (84.4% vs. 70.3%; $p = 0.180$). When stratifying for HPV-status, the association between SPCM infiltration and neck metastases at diagnosis was stronger in non-HPV-driven cancers ($p = 0.065$), whereas no association emerged from HPV-driven cancers ($p = 1.000$; Table 2).

3.2 | SPCM status and outcome

Patients with SPCM infiltration exhibited a poorer prognosis compared to those without infiltration, with a dramatic decline in both PFS and OS during the first year following treatment (Figure 2A,B). This association was further confirmed in the multivariate analysis demonstrating that patients with SPCM infiltration faced a significantly higher risk of both death (HR: 3.37, 95% CI: 1.21–9.38) and progression (HR: 3.39, 95% CI: 1.38–8.32) in comparison to patients without infiltration (Table 3). Patients with non-HPV-driven OPSCC had a worse PFS and OS (Figure 2C,D). At the multivariate analysis, patients with non-HPV-driven tumors were confirmed to have a significantly higher risk of progression (Table 3).

When analyzing the impact of SPCM infiltration separately in patients with HPV-driven and non-HPV-driven OPSCC, it was observed that SPCM infiltration worsened the the PFS (Figure 2E) and OS (Figure 2F) in both groups: patients with non-HPV-driven cancer with SPCM infiltration reporting the worst prognosis (5-year OS: 31.8% and 5-year PFS: 29.9%) compared to patients with HPV-driven cancer without SPCM infiltration (5-year OS and PFS: 88.9%; $p < 0.001$; Figure 2E,F). These results were confirmed in a multivariate model, where patients with non-HPV-driven cancer and SPCM infiltration exhibited a 9-fold higher risk of death (95% CI: 1.47–57.57) and a 15-fold higher risk of progression (95% CI: 2.64–82.74) compared to patients with HPV-driven cancer without SPCM infiltration (Table 3). Notably, among patients with HPV-driven cancer, SPCM infiltration significantly impacted the prognosis, with a 5-year OS of 64.0% and 89.9% in patients with and without SPCM infiltration, respectively (Figure 2F). Similar results emerged for PFS (Figure 2E).

Among patients with SPCM infiltration, a nonsignificant better PFS (Figure 3A) and OS (Figure 3B) was observed in cases treated by surgery followed by (chemo)-radiotherapy compared to those treated by surgery or (chemo)radiotherapy alone.

TABLE 2 Associations between SPCM infiltration and N status at diagnosis

	SPCM infiltration, *n* (%)		
N status	**No**	**Yes**	**Total**
All patients	37	45	
N negative	11 (29.7)	7 (15.6)	18 (22.0)
N positive	26 (70.3)	38 (84.4)	64 (78.0)
Fisher's exact test, $p = 0.180$			
HPV-negative patients	22	30	
N negative	9 (40.9)	5 (16.7)	14 (26.9)
N positive	13 (59.1)	25 (83.3)	38 (73.1)
Fisher's exact test, $p = 0.065$			
HPV-positive patients	15	15	
N negative	2 (13.3)	2 (13.3)	4 (13.3)
N positive	13 (86.7)	13 (86.7)	26 (86.7)
Fisher's exact test, $p = 1.000$			

Abbreviations: HPV, human papillomavirus; SPCM, upper pharyngeal constrictor muscle.

4 | DISCUSSION

In the present study, the infiltration of the SPCM emerged as a negative prognostic factor for patients with OPSCC, leading to worse OS and PFS outcomes in both HPV-driven and non-HPV-driven cancers. In particular, SPCM infiltration helped in identifying patients with HPV-driven cancers with a higher hazard of recurrence and death.

Up to now, SPCM has primarily been investigated for its surgical significance, serving as a critical landmark in transoral surgery and as a determining factor for predicting the deep margin status in surgically resected OPSCC.[6,16,17]

In this study we aimed to consider the clinical and oncological impact of the infiltration of this structure in patients with OPSCC arising from tonsillar complex, soft palate, and posterior walls of the oropharynx. We excluded OPSCCs arising from the base of the tongue because, given their more distant relationship with the SPCM, the subset characterized by muscle infiltration would likely have been in a significantly more advanced stage, potentially biasing the results.

Despite few other studies having investigated this aspect in the recent past, their focus has been on early stages disease or without considering the interference of the HPV-status.[18,19] Since HPV-driven and non-HPV-driven OPSCC are two biologically and clinically different diseases,[20] considering the HPV status in these malignancies is imperative. Moreover, this study reports the largest series of patients in which the prognostic role of the SPCM in OPSCC was investigated.

First, we observed a trend in the association between SPCM infiltration and neck metastases at diagnosis only in non-HPV-driven cancers. The link between SPCM infiltration and neck nodes status was already investigated by other authors who reported that N-positive status were significantly correlated with an increased risk of SPCM invasion or penetration.[18] Furthermore, patients with SPCM infiltration were reported to be at higher risk for multiple lymph node metastasis even in early squamous cell carcinoma of the tonsil.[18,19] Our observation of a closer link between muscle infiltration and the presence of lymph node metastases restricted to subjects with HPV-negative carcinoma may be at least partially explained by the different biology conferred by HPV infection on OPSCC.[20] HPV-driven tumors are indeed particularly prone to metastasize to cervical lymph nodes even when in a very early stage and their clinical presentation as cervical metastases from unknown primary is rather pathognomonic.[21,22] These tumors seem to originate from the cryptic tonsillar epithelium, characterized by a porous basement membrane that facilitates the migration of neoplastic cells.[23] Consistently, invasion and even metastasis have been observed in lesions that histologically appear "in situ."[24] Thus, the invasion of surrounding structures including SPCM is probably less relevant on the risk of metastatic colonization of cervical lymph nodes in subjects with HPV-driven OPSCC.

Second, regarding the prognostic impact of SPCM infiltration, its involvement was significantly and independently associated with a higher risk of death and progression regardless of stage and treatment modality. In a previous investigation,[19] it was observed that locoregional

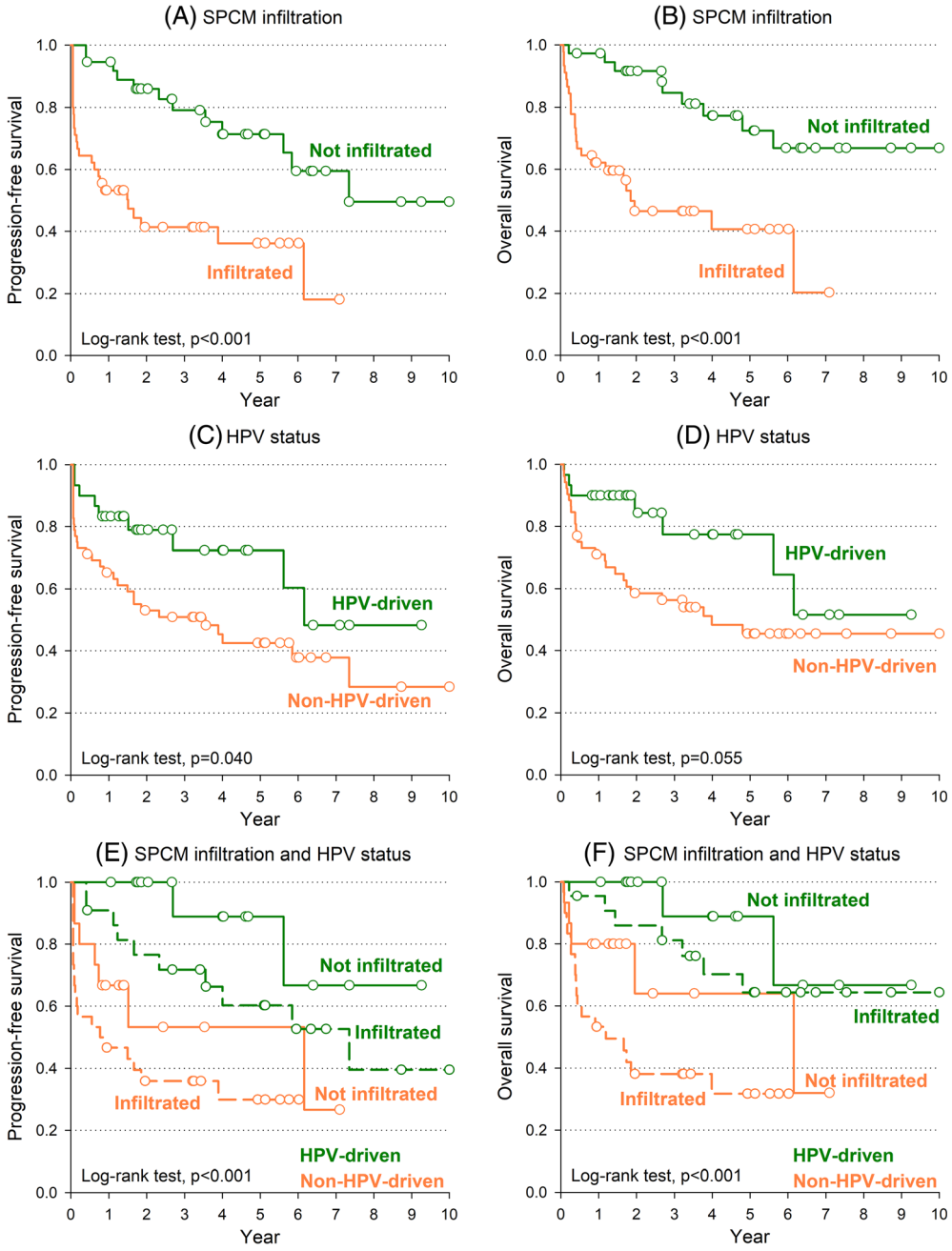

FIGURE 2 Kaplan–Meier estimates of progression free survival and overall survival according to superior pharyngeal constrictor muscle invasion status (A, B), HPV status (C, D), and interaction (E, F). HPV, human papillomavirus; SPCM, superior pharyngeal constrictor muscle [Color figure can be viewed at wileyonlinelibrary.com]

recurrence was significantly correlated with invasion of the SPCM at univariate analysis. Since that time, the prognostic impact of SPCM invasion in OPSCC has not been reevaluated. Our observation of an association between SPCM infiltration and the risk of progression, regardless of stage, suggests that this anatomical region may be a crucial site for neoplastic spread and dissemination.

In the last decade, high-risk HPV infection has been identified as a common cause of, and an important prognostic factor in oropharyngeal cancer.[25] To our knowledge, this is the first study that highlights role of SPCM in OPSCC in relation to HPV status. In the present study, the determination of HPV-status was based on double positivity for high-risk HPV-DNA sequences and $p16^{INK4a}$ overexpression. While the 8th edition of the TNM Staging System of Head and Neck Tumours discriminates HPV-positive and HPV-negative OPSCC based on $p16^{INK4a}$ alone, which is considered a surrogate marker of transforming HPV infection, an upregulation of $p16^{INK4a}$ was identified in 8%–20% of tumors with no evidence of HPV transforming infection.[26]

Conversely, double positivity for HPV-DNA/$p16^{INK4a}$ showed the strongest diagnostic accuracy in determining HPV-status in OPSCC in clinical setting.[14] Interestingly, in the multivariate model conditioned on HPV status, a

TABLE 3 Hazard ratio (HR) and corresponding 95% confidence interval (CI) for overall survival and progression-free survival according to SPCM infiltration and HPV status

	Patients	Events		HR (95% CI)	
	n	*n*	(%)	Univariate[a]	Multivariable[b]
Overall survival					
SPCM infiltration					
No	37	9	24.3	Reference	Reference
Yes	45	24	53.3	3.91 (1.79–8.57)	3.37 (1.21–9.38)
HPV status					
Positive	30	7	23.3	Reference	Reference
Negative	52	26	50.0	2.22 (0.96–5.11)	2.23 (0.81–6.17)
SPCM infiltration/HPV status					
No/positive	15	2	13.3	Reference	Reference
No/negative	22	7	31.8	2.16 (0.45–10.42)	2.96 (0.52–16.89)
Yes/positive	15	5	33.3	3.93 (0.76–20.36)	4.58 (0.73–28.83)
Yes/negative	30	19	63.3	8.30 (1.92–35.92)	9.19 (1.47–57.57)
Progression-free survival					
SPCM infiltration					
No	37	12	32.4	Reference	Reference
Yes	45	27	60.0	3.53 (1.72–7.23)	3.39 (1.38–8.32)
HPV status					
Positive	30	9	30.0	Reference	Reference
Negative	52	30	57.7	2.13 (1.01–4.49)	2.72 (1.06–6.93)
SPCM infiltration/HPV status					
No/positive	15	2	13.3	Reference	Reference
No/negative	22	10	45.5	3.34 (0.73–15.25)	5.50 (1.06–28.59)
Yes/positive	15	7	46.7	5.90 (1.21–28.76)	7.34 (1.33–40.39)
Yes/negative	30	20	66.7	9.93 (2.29–43.09)	14.79 (2.64–82.74)

Abbreviations: HPV, human papillomavirus; SPCM, upper pharyngeal constrictor muscle.

[a]Estimated from Cox proportional hazards model.

[b]Conditioned on HPV status and adjusted for sex, age, oropharyngeal subsite, cancer stage, and treatment.

significantly higher risk of death and progression was observed by combining both SPCM and HPV status, with patients who harbored an HPV-negative OPSCC and had SPCM infiltration showing the poorest outcome. Thus, considering SPCM infiltration in OPSCC may be useful to stratify patients with HPV-driven and non-HPV-driven tumors.

Particularly, SPCM could serve as an additional factor, along with smoking habits and advanced N and T categories,[25] to identify patients who, despite having an HPV-driven OPSCC, may have an adverse prognosis and therefore be ineligible for treatment de-escalation trials.

Unfortunately, due to the size of the sample and the retrospective design, we were not able to explore the impact of the different types of treatment on the prognosis of patients presenting with SPCM infiltration with adequate statistical power. However, although not statistically significant, we observed a trend towards a better prognosis in patients with SPCM infiltration who were treated with surgery followed by (chemo)-radiotherapy. This observation may provide a basis for considering prospective studies to explore the potential benefit of postoperative adjuvant treatment in cases with SPCM involvement.

The depth of invasion (DOI) has been incorporated into the current T staging system of the oral cavity cancer due to its crucial role both in the prognostication and predicting occult nodal metastases.[27–30] Determining the deep of invasion is critical in establishing treatment strategies for patients candidates to transoral surgery.[31] However, despite the wide diffusion of transoral surgical approaches, DOI is not conceptualized in OPSCC. Therefore, MRI-assessed SPCM invasion might represent a parameter similar to DOI, whose role in preoperative prognostication and treatment planning of patients with OPSCC deserves investigation.

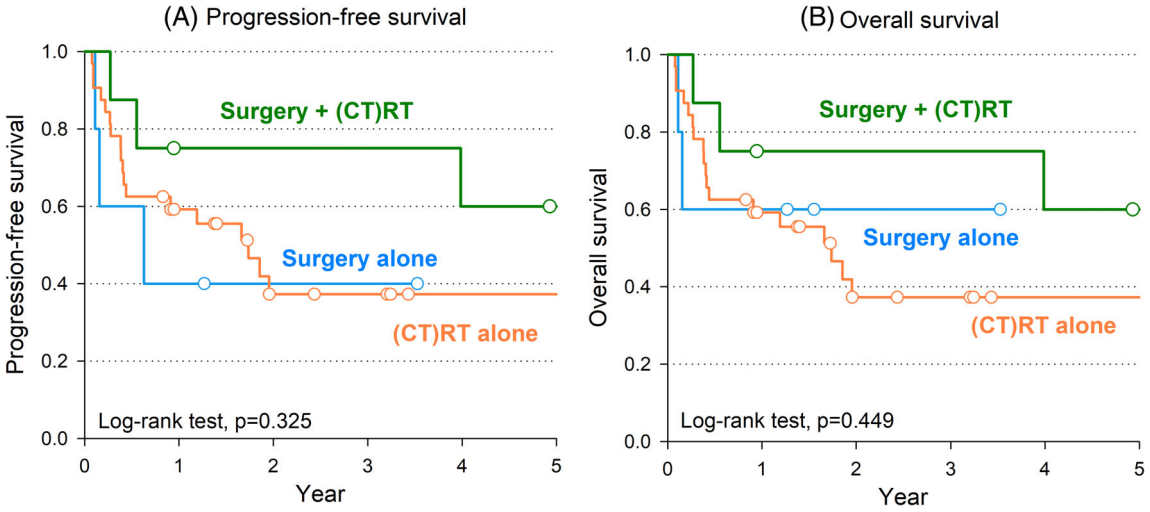

FIGURE 3 Kaplan–Meier estimates of progression free survival (A) and overall survival (B) according to treatment in patients with infiltration of the superior pharyngeal constrictor muscle. (CT)RT, (chemo)-radiotherapy [Color figure can be viewed at wileyonlinelibrary.com]

This study has some limitations. First, the retrospective nature of this research: larger prospective case-series investigations are needed to confirm the association between SPCM involvement and the outcome in OPSCC. Second, this series included both surgical and nonsurgical patients. In order to avoid bias and to homogenously evaluate the infiltration of the muscle, the assessment of SPCM infiltration was based on MRI findings. A histologically based evaluation of the tumor infiltration may provide more precise information about muscle involvement by cancer. However, radiological infiltration was assessed by expert head and neck radiologists based on MRI, representing the preoperative gold standard imaging for SPCM evaluation due to its great spatial resolution, strong soft tissue contrast and proven capacity to identify tissues and tumor margins in this area.[32–34] This was confirmed by the high rate of concordance we observed in the surgical group of the present series. Most of the discordant cases consisted of patients whose histological examination did not confirm the muscle infiltration evidenced by MRI. However, a peri-tumor inflammation that could be misunderstood as tumor infiltration may also have a prognostic significance. Cancer-associated inflammation was indeed consistently demonstrated to promote tumor progression, metastasis, and therapeutic resistance development. Recently, primary peritumoral fibroblasts were shown to promote migration of tumor cells in head and neck cancer.[35] Additionally, having a pretreatment prognostic factor may be more useful than a postoperative factor, as it may help devise optimal treatment strategies. Finally, the small sample size limits the capability to explore interaction between factors.

In conclusion, our findings showed that MRI evidence of SPCM involvement significantly and independently increases the risk of death and progression in subjects with OPSCC. Moreover, considering both SPCM and HPV status significantly improved risk stratification in these malignancies. If data are confirmed in other large case-series, it could be justified to consider the SPCM status in the OPSCC staging system.

AUTHOR CONTRIBUTIONS

Giancarlo Tirelli and Alberto Vito Marcuzzo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design*: Giancarlo Tirelli, Alberto Vito Marcuzzo, and Paolo Boscolo-Rizzo. *Acquisition, analysis and interpretation of data*: All authors. *Drafting of the manuscript*: Giancarlo Tirelli, Alberto Vito Marcuzzo, and Paolo Boscolo-Rizzo. *Critical revision of the manuscript for important intellectual content*: All authors. *Statistical analysis*: Fabiola Giudici and Jerry Polesel. *Supervision*: Giancarlo Tirelli and Paolo Boscolo-Rizzo.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Tirelli G, Marcuzzo AV, Gardenal N, et al. Prognostic role of the MRI-based involvement of superior pharyngeal constrictor muscle in oropharyngeal squamous cell carcinoma. *Head & Neck*. 2024;46(1):161-170. doi:10.1002/hed.27566