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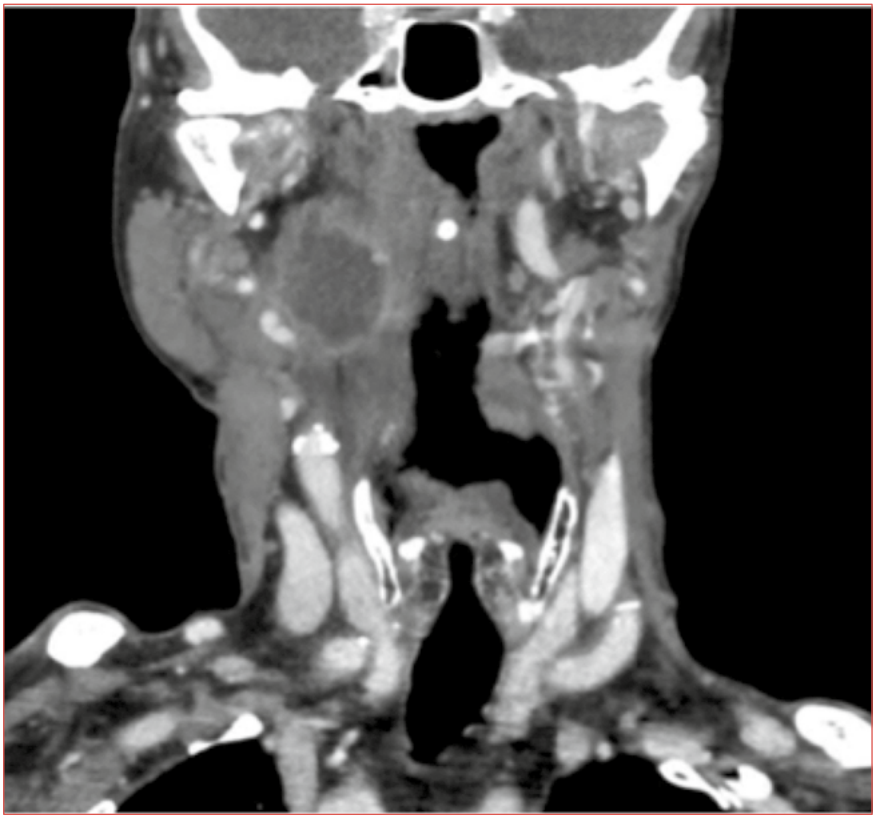
Squamous cell carcinoma metastatic to the lymph nodes of the parapharyngeal space: case series and systematic review



Cover figure. CT scan with contrast. Coronal view. Right parapharyngeal squamous cell carcinoma metastasis infiltrating the superior pharyngeal constrictor muscle.

Matteo Fermi[1,2], Cecilia Botti[1], Francesco Chiari[1], Andi Abeshi[1], Livio Presutti[1,2], Matteo Miglio[3], Francesco Mattioli[3], Daria Maria Filippini[2,4], Sara Valerini[3], Daniele Marchioni[3], Gabriele Molteni[1,2], Edoardo Serafini[3]

[1] Otorhinolaryngology and Audiology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [2] Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, Università di Bologna, Bologna, Italy; [3] Department of Otorhinolaryngology - Head and Neck Surgery, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy; [4] Division of Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

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Correspondence
Francesco Chiari
E-mail: francesco.chiari.med@gmail.com

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Summary

Objective. Parapharyngeal space (PPS) is a rare and unusual site of head and neck squamous cell carcinoma (SCC) metastases. Treatment strategy for PPS metastases is still not well defined. This research aims to investigate the clinical implications and oncological outcomes of SCC metastases in PPS.

Material and methods. A systematic review was conducted according to PRISMA criteria. The authors considered only articles reporting the history and treatment of patients with PPS SCC metastases. A retrospective chart review was conducted in two tertiary referral academic centers collecting data of patients with diagnosis of PPS SCC metastases between 2010 and 2023 to study their outcome based on clinical presentation and treatment strategy.

Results. The retrospective chart review showed that the oropharynx was the most frequent primary tumour site. The advanced stage at the time of diagnosis was related to poorer survival and higher recurrence rates. A significant difference in 2-year overall survival in the subgroup of patients who

experienced PPS metastases within the primary treatment and those who experienced PPS metastases as regional recurrence (66.7 *vs* 30.8%) was observed. Similar low survival rates were reported in the literature review with a mean overall and disease-free survival of 19.8 and 8.6 months, respectively. **Conclusions**. PPS metastases are associated with a dismal prognosis, especially when diagnosed as regional recurrence after primary treatment, due to patients' poor general conditions and difficulty of treatment.

Key words: parapharyngeal space, SCC, parapharyngeal metastasis, parapharyngeal tumour

Introduction

The parapharyngeal space (PPS) is a deep anatomical region of the neck, which is further divided into pre- and post-styloid compartments by the styloid process and tensor-vascular-styloid fascia [1]. The PPS contents include several visceral and neurovascular structures, from which tumours can originate occupying one or both the PPS compartments. Tumours of the PPS are rare, accounting for 0.5% of all head and neck neoplasms. Most of these tumours are benign (80%) and arise from the parotid deep lobe (i.e., pleomorphic adenomas) and the nerves within the post-styloid space (i.e., schwannomas) [2,3]. PPS malignancies include primary tumours arising from the PPS, tumours arising from adjacent anatomic spaces involving the PPS (i.e., nasopharynx, oropharynx, parotid gland) and PPS lymph node metastases [2,3]. PPS nodal metastases are usually secondary to malignancies of the upper airway tract, although localisation of thyroid papillary carcinoma is also possible [4]. However, the mechanism of the metastatic spread to the PPS is not well understood due to its rarity and the limited available clinical data [5]. Clinical detection of PPS metastases is difficult due to the absence of early symptoms, which are often manifested when the PPS mass becomes larger than 2.5-3 cm [5]. Moreover, most of these symptoms and signs (i.e., hoarseness, dysphagia, dyspnoea, serous otitis media, etc.) are not specific for this anatomical region and might be misdiagnosed by the clinician, determining a delay in diagnosis and treatment [6]. Computed tomography (CT) scan, magnetic resonance imaging (MRI), and 18 fluorodeoxyglucose positron emission tomography (18FDG-PET) are the gold standard imaging studies for the diagnosis of PPS tumors (Cover figure). The adoption of fine needle aspiration cytology (FNAC) is limited by the deep localization of PPS neoplasm, which makes it difficult to be properly assessed. Nevertheless, whenever technically feasible, FNAC can reach a high diagnostic accuracy (90-95%) [7,8]. The treatment of PPS metastases is not standardised and requires a multidisciplinary discussion that must consider the patient's general condition, previous oncologic treatments, and PPS neoplasm staging. However, most cases are managed with surgery or chemo/radiation (CHT-RT). The surgical treatment aims to completely remove the PPS metastasis, possibly with nervous function preservation and adequate vascular control. Different surgical approaches have been suggested such as the transcervical, transcervical-transparotid, infratemporal, transnasal, transmandibular-transvestibular, and various combinations of them [3,9,10-12]. CHT-RT is usually employed for the management of unresectable lesions, as adjuvant treatment, or in cases with a high risk of cranial nerves or internal carotid artery injury during surgery. This paper aims to retrospectively review the cases of head and neck squamous cell carcinomas (HNSCC) metastatic to the lymph nodes of the PPS managed in two academic tertiary care centres and to perform a systematic review of the literature to investigate the clinical implications of PPS metastases in patients diagnosed with HNSCC. In addition, we provide data about the therapeutic approach for PPS metastases and the oncological outcomes of these patients.

Material and methods

Study design of retrospective study

The retrospective multicentric study was performed in two tertiary academic centres.

Patient selection

A chart review involving all patients diagnosed from January 2010 to December 2023 with PPS SCC lymph node metastasis was performed. Data regarding the clinical and radiological presentation of PPS metastasis, primary tumour site, staging, time to regional recurrence in the PPS, therapeutic strategy, and outcomes were collected. Treatment response was interpreted according to the Response Evaluation Criteria In Solid Tumors (RECIST) [14].

Statistical analysis

The analyses were conducted with GraphPad Prism 8.0 (GraphPad Software, La Jolla, California) and IBM SPSS Statistics version 26.0 (IBM Corp, Armonk, NY). Categorical variables were presented as rates, while continuous variables as mean (± standard deviation - SD). Comparisons of

data sets of continuous variables with normal distributions were performed with a two-tailed Student t-test. A paired or Independent-samples Student t-test was used, as appropriate. Wilcoxon test was performed for data sets with non-normal distributions. Chi-square or Fisher's exact tests were used to compare categorical variables, as appropriate, and odds ratios (OR) for variables affecting survival or recurrence were obtained. Overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) were calculated at 2 years. Endpoints were obtained as the length of time from the date of diagnosis to the date of: i) death by any cause (OS); ii) death from the disease (DSS); iii) local, regional, or distant recurrence (DFS). OS, DSS, and DFS curves were represented by Kaplan-Meier graph product limit estimate.

Research methodology

A literature search using the electronic databases Embase, PubMed, and the Cochrane library was performed according to PRISMA-guided systematic searches by two independent investigators (FC and ES). The investigators independently identified, selected, and qualitatively assessed the studies. Disagreements on search strategy, article inclusion, and data extraction were resolved by a third investigator (MF). The following string was run on the above-mentioned databases: ("parapharyngeal space" OR "parapharynx") AND ("squamous cell carcinoma" OR "metastases" OR "metastasis" OR "epidermoid carcinoma").

The search was limited to articles in English published between January 1970 and December 2023. Reference lists of the included studies were checked for additional literature.

Study selection

Only articles on diagnosis and treatment of PPS squamous cell carcinoma metastasis were included in the review process. Studies reporting clinical, radiological, and therapeutic information were deemed suitable for further inclusion. Manuscripts dealing with PPS histologies other than SCC or those with PPS directly involved by SCC arising from one of the surrounding anatomical structures (e.g., nasopharynx, oropharynx) were excluded. Moreover, the review process excluded all studies not reporting the distinction between primary PPS SCCs and SCCs metastatic to the lymph node of the PPS.

A flow diagram reporting the study selection method was created according to the PRISMA statement (Fig. 1).

Study quality assessment

Two authors (FC and MF) independently assessed the quality of the included studies using an assessment tool [13], which considers 4 domains (selection, ascertainment, causality, and reporting) and provides 8 questions to calculate the quality score. Studies were rated as low [15-19], moderate [20-26], or high quality based on evaluation of risk of bias according to the description.

Data collection

Data from all the studies included in the systematic review process were extracted and pooled for qualitative and quantitative analysis. Data regarding demographics, the clinical and radiological presentation of the PPS metastases, staging at clinical presentation of the primary tumour, salvage treatment protocol, and post-treatment oncological outcome were collected.

Results

Retrospective chart review

The retrospective patient's cohort consisted of 23 patients (69.6% males, mean age 54.2 years +/- 11.4) who were diagnosed with HNSCC metastatic to the lymph nodes of the PPS.

Most patients (30.4%) had primary SCC arising from the oropharynx, followed by the nasopharynx (21.7%), oral cavity (17.4%), larynx (13%) and hypopharynx (8.7%).

In two patients (8.7%) the primary tumour was not recognised and was subsequently classified as carcinoma of unknown primary (CUP).

Eight patients (35%) experienced PPS metastasis at the time of diagnosis of the primary tumour, while 15 (65%) developed PPS metastasis during the follow-up as a regional recurrence of an HNSCC.

Most of the above-mentioned primaries presented as advanced stage HNSCCs, being stage III and IV in 17.4% and 60.8%, respectively. Moreover, only 26.1% of these patients had no lymph node metastasis at clinical presentation.

Interestingly, most of the PPS metastases (60.9%) were diagnosed through cross-sectional imaging, since no presenting symptom or sign (e.g., cranial nerve palsies) was reported. Most of these lesions were diagnosed during oncological follow-up as regional recurrence (65%) after a mean of 11.7 months +/- 5.8. The remaining PPS SCC metastases (35%) were diagnosed at the time of the primary tumour staging. Most of these PPS lesions were confined within the prestyloid compartment (43.5%) or the retrostyloid compartment (21.7%), while the remaining involved both compartments. The diagnosis of SCC PPS metastasis was achieved through cross-sectional imaging (e.g., CT or MRI) or radiometabolic imaging (e.g., 18-FDG PET) in

most of the patients (95.7%). Due to technical and anatomical limitations related to the PPS anatomy, a FNAC was performed only in 3 cases (13%), achieving a diagnosis of SCC in only one case. Among patients who experienced PPS SCC metastasis within the primary tumour presentation, 6 (75%) underwent CHT-RT while the remaining 2 (25%) underwent upfront surgery using a transparotid-transcervical approach and adjuvant CHT-RT. All these patients achieved complete response after treatment except for one who had CUP (cT0 cN2b) and underwent CHT-RT, experiencing disease progression after treatment and dying of disease. None of the patients, who had complete response, experienced further loco-regional or distant failure after a mean of 20 months +/- 11. Among patients who experienced PPS SCC metastasis as regional recurrence after primary treatment, 6 underwent salvage surgical treatment (20% salvage surgery, 13.4% salvage surgery and adjuvant CHT-RT), one (6.7%) exclusive CHT-RT and one (6.7%) exclusive RT, while the remaining 4 patients underwent first-line medical treatment (13.3% CHT, 6.7% immunotherapy, 6.7% CHT-immunotherapy). Three patients (20%) underwent only best supportive care due to poor general conditions or unresectable disease.

Considering the disease extent of patients with PPS metastases as regional recurrence, 6 (40%) presented PPS metastases as the only site of recurrence, while all the others presented PPS metastases synchronous with other sites (27% primary site + PPS, 27% neck lymph node + PPS, 6.7% distant metastases + PPS). The oncologic outcome achieved was less satisfactory since only 38.5% of the patients achieved a complete response after salvage treatment. Moreover, only 14.3% of these patients were free from disease and only 33.3% of them were still alive after a mean follow-up of 44.9 months +/- 38.3.

Comparing the 2-year OS rates in the subgroup of patients who experienced PPS metastases within the primary tumour presentation and those who experienced PPS metastases as regional recurrence, a substantial difference (66.7 *vs* 30.8%) was observed, albeit not reaching statistical significance ($p = 0.08$, OR 6.7, CI 90% 0.9-49.2). On the other hand, a statistically significant difference ($p = 0.02$) was observed in the 2-year DSS (83.3 *vs* 33.3%), with an OR of 0.71 (CI 90% 0.01-0.7) for the subgroup of patients who experienced PPS metastases within the primary tumour presentation. The clinical characteristics of patients are summarised in Table I.

Systematic literature review

A total of 12 studies met the inclusion criteria for the systematic review process (Fig. 1) [15-26]. They were published between 1982 and 2016. One of the articles was a case report, while the remaining 11 were retrospective case series including patients affected by PPS SCC metastases.

Quality assessment reported a high risk of bias in 5 studies (41.7%) and an intermediate risk of bias in 7 (58.3%).

The entire study population consisted of 22 patients (12 males, 3 females, and 7 not specified) affected by PPS SCC metastases (Tab. II). The mean age of the patient cohort was 60 years (range 32-83).

Histopathological diagnosis was achieved in 12 of 22 patients (54.5%) via ultrasound-guided FNAC.

Most of the primary tumours were oropharyngeal (15 patients – 68.2%), being the soft palate the most frequent anatomic subsite involved (6 patients). The remaining primaries originated from the hypopharynx (2 patients – 9.1%), larynx (2 patients – 9.1%), and paranasal sinuses (1 patient – 4.5%). There was also a case of CUP origin. Considering data availability regarding the preoperative staging, 11 patients (68.7%) had locally advanced stage primary tumours (T3 or T4) and 12 patients (75%) had cervical lymph node metastases at diagnosis of the primary tumour.

The treatment performed on the primary tumour was reported in 7 studies (58.3%), being surgery followed by adjuvant RT in 10 patients (45.5%). Considering the data availability regarding the time of diagnosis, PPS metastases were detected within primary tumour diagnosis in 3 patients (30%). The remaining cases (70%) experienced PPS metastasis as a regional recurrence. In the latter cases, PPS SCC metastases occurred 11.8 months after primary tumour treatment on average.

Treatments for PPS SCC metastases were reported by 10 studies (83.3%), for a total of 16 patients (72.7%). The most frequently performed treatment was exclusive RT in 9 patients (56.2%), followed by salvage surgery in 5 (31.2%), and CHT-RT in 2 (12.6%).

Survival rates were reported in 6 studies (50%), on 14 patients (63.6%), for a mean OS and DFS of 19.8 and 8.6 months, respectively.

Discussion

The overall outcome of patients with locally advanced head and neck SCC is poor and, even after multimodality treatments, around 40–50% of patients experience disease recurrence [27,28]. Regional lymph node metastases have been widely demonstrated to be a major prognostic factor in head and neck cancers [21]. Ninety-three percent of HNSCC asymptomatic recurrences after definitive RT and CHT-RT are local or regional and mainly occur within the first 2 years after initial

Table I. Clinical data of retrospective chart review patients.

	Primary final stage	Primary tumour site	Symptoms	PPS subsite	Primary tumour treatment	Recurrence involvement sites	PPS recurrence treatment	Type of response to treatments	2-yr OS
Primary PPS SSC diagnosis	Stage II: 1	CUP: 2	Hypoacusis: 1	Prestyloid: 4	CHT-RT: 6	/	/	No response: 2	66.7%
	Stage III: 2	OP: 2	Pain: 2	Retrostyloid: 2	Surgery + RT: 1			Partial response: 2	
	Stage IV: 5	NP: 3	Nasal obstruction: 1	Pre- and retrostyloid: 2	Surgery + CHT-RT: 1			Complete response: 4	
		OC: 1							
Recurrent PPS SSC diagnosis	Stage II: 3	L: 3	Dysphagia: 2	Prestyloid: 6	Surgery: 5	PPS alone: 6	Surgery: 3	No response: 4	30.8%
	Stage III: 2	OP: 5	Pain: 2	Retrostyloid: 3	RT: 3	PPS + T site: 4	First line CHT: 2		
	Stage IV: 10	NP: 2	Trismus: 1	Pre- and retrostyloid: 6	CHT-RT: 3	PPS + LC lymph-node: 4	RT: 2	Partial response: 4	
		HP: 2			Surgery + RT: 2	PPS + distant metastasis: 1	CHT-RT: 1	Complete response: 5	
		OC: 3			Surgery + CHT-RT: 2		Surgery + CHT-RT: 1		
							Surgery + CHT-RT: 1		
							CHT + immunotherapy: 2		
							Best supportive care: 3		

PPS: parapharyngeal space; SCC: squamous cell cancer; OS: overall survival; CUP: carcinoma of unknown primary; CHT-RT: chemo-radiotherapy; CHT: chemotherapy; RT: radiotherapy; OC: oral cavity; NP: nasopharynx; OP: oropharynx; HP: hypopharynx; L: larynx; LC: laterocervical; yr: year.

treatment [27,29,30]. Since regional recurrences typically develop along the Robbins neck node levels, most of the literature focuses on their management. Therefore, there are no extensive reports focusing on the impact and prognostic significance of metastatic HNSCC in the PPS. The retrospective cohort analysed herein confirms the results of the literature review reporting oropharyngeal SCC as the most common primary SCC site associated with PPS metastasis. Upon separately analysing cases of PPS metastasis in the context of HNSCCs, our findings revealed a prevalence of oropharyngeal SCC specifically in instances of regional recurrence (33%). However, no significant differences were observed in terms of the site of origin for cases where metastasis occurred during the primary tumour presentation. Thus, the risk of PPS metastasis at initial diagnosis might be related to the advanced stage of the disease and genetic or biological features rather than the subsite of origin. Commonly, oropharyngeal SCC metastasizes to lymph nodes of levels I-IV except for those

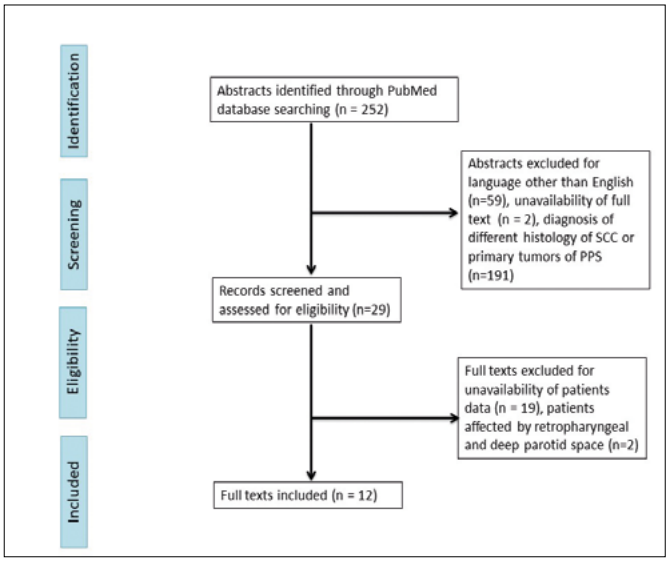

Figure 1. Flow-chart of the study.

Table II. Clinical, radiological and therapeutic data of included cases.

Authors	Year	Patients	ID	Age	Sex	Related symptoms and signs	
Sobol et al. [22]	1982	1	1	62	M	Diaphoresis, nausea, headache, left neck and ear pain, Horner syndrome, mass in the left part of the oropharynx and lateral pharyngeal wall	
Talmi et al. [31]	1992	2	1	NA	NA	SIADH (paraneoplastic)	
			2	NA	NA	SIADH (paraneoplastic)	
Richardson et al. [21]	1993	3	1	60	M	Severe pain in the left side of the neck, drop attacks, hypotension	
			2	66	M	Discomfort in throat, compressing the posterior and right pharyngeal wall	
			3	65	M	NA	
Fried et al. [23]	1998	1	1	71	M	Severe right-side temporal headaches	
Umeda et al. [24]	2002	4	1	83	M	NA	
			2	54	F	NA	
			3	32	F	NA	
			4	62	M	NA	
Douglas et al. [16]	2005	6	1	NA	NA	NA	
			2	NA	NA	NA	
			3	NA	NA	NA	
			4	NA	NA	NA	
			5	NA	NA	NA	
			6	NA	NA	NA	
Ohki et al. [20]	2005	1	1	54	M	Pain of left ear, throat and neck, trismus	
Koenigsberg et al. [15]	2007	1	1	56	M	NA	
Dimitrijevic et al. [6]	2010	3	1	NA	NA	NA	
			2	NA	NA	NA	
			3	NA	NA	NA	
Dallan et al. [18]	2016	1	1	51	M	NA	

PPS: parapharyngeal space; FNAC: fine needle aspiration cytology; OS: overall survival; DFS: disease free survival; DSS: disease specific survival; M: male; F: female; NA: not available; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; SCC: squamous cell cancer; CHT-RT: chemo-radiotherapy; CHT: chemotherapy; RT: radiotherapy; SIADH: syndrome of inappropriate antidiuretic hormone secretion; PNS: paranasal sinuses; OP: oropharynx; HP: hypopharynx; L: larynx.

involving the soft palate that frequently metastasize to the retro- and parapharyngeal nodes of the retrostyloid compartment [32,33]. However, the risk of distant lymph node metastasis after previous treatment has already been described [34,35]. This risk may be associated with the altered direction of lymphatic drainage, which might be increased toward the PPS, potentially contributing to a higher incidence of nodal relapse in this region [36]. Patients who experienced PPS metastases within primary tumour presentation and those who experienced it as regional recurrence presented with advanced stage tumours at the time of diagnosis, with a high rate of nodal metastases (73.9%). Advanced tumour stage is widely recognised as a robust predictive factor for both survival and recurrence in HNSCC [37,38]. This holds even greater significance in the subset of patients herein studied, given the rarity of metastases in the PPS. The primary clinical challenge lies in the notable frequency of the absence of signs or symptoms in patients with PPS metastases. Oropharyngeal wall medialisation or neck swelling typically becomes apparent only when there are substantial metastatic volumes, and cranial nerve impairment or discomfort is uncommon even in the presence of metastatic lesions [36]. While most neck lymph node metastases might be identified during follow-up with only clinical examination, early identification of PPS metastases

	Radiology	FNAC	T	Timing of presentation of PPS metastases	Treatment of T	Treatment of PPS metastases	OS (months)	DFS/DSS (months)
	CT, Arteriography	SCC	L	12 months	Surgery + RT	Palliative RT	20	12
	NA	SCC	NA	NA	NA	NA	NA	NA
	NA	SCC	NA	NA	NA	NA	NA	NA
	CT	SCC	OP	4 years	RT + salvage surgery	NA	NA	NA
	NA	SCC	NA	NA	NA	NA	NA	NA
	CT	NA	OP	At diagnosis	CHT + RT	CHT + RT	NA	NA
	MRI	SCC	HP	6 months	CHT + salvage surgery + adjuvant RT	Stereotactic RT + CHT	24	6
	NA	SCC	OP	3 months	Surgery	Surgery	9	3
	NA	SCC	PNS	15 months	RT + CHT+ Surgery	RT	18	18
	NA	SCC	OP	NA	Surgery + RT	NA	7	NA
	NA	SCC	OP	NA	Surgery + RT	NA	8	NA
	NA	NA	OP	NA	Surgery + RT	RT	26	NA
	NA	NA	OP	NA	Surgery + RT	RT	26	NA
	NA	NA	OP	NA	Surgery + RT	RT	26	NA
	NA	NA	OP	NA	Surgery + RT	RT	26	NA
	NA	NA	OP	NA	Surgery + RT	RT	26	NA
	NA	NA	OP	NA	Surgery + RT	RT	26	NA
	CT, MRI	SCC	OP	4 months	Neoad CHT + Surgery + adjuvant CHT	RT	11	4
	CT, PET, MRI	No	OP	At diagnosis	NA	Embolization + surgery	NA	NA
	NA	SCC	NA	NA	NA	NA	NA	NA
	NA	SCC	NA	NA	NA	NA	NA	NA
	NA	SCC	NA	NA	NA	NA	NA	NA
	NA	SCC	OP	NA	NA	Surgery	NA	NA

relies mainly on radiological exams. Herein, patients were divided into two groups according to the concurrent presentation of PPS metastases during the primary tumour diagnosis or as regional recurrence after initial treatment. Both the literature review and the present case series concluded that most of patients experienced PPS metastases in a recurrent setting (70% and 65% respectively). The survival analysis showed that a significantly worse DSS was seen in patients with recurrent SCC in the PPS than in those with PPS metastasis at the time of primary tumour diagnosis and staging. The appropriate management of PPS metastases in the context of a primary tumour diagnosis or recurrent setting should be discussed case by case according to the National Comprehensive Cancer Network guidelines [39]. In our case series, 6 of 8 patients diagnosed with a primary tumour underwent CHT-RT, reflecting the predominant origin of these tumours in the pharynx. Concerning PPS metastases in a recurrent setting, the frequent concomitant presence of multiple site localisations, the high risks related to salvage treatment in a difficult anatomical area, the delay in diagnosis, and the presence of fibrosis related to previous treatments pose major issues. In our case series, the recurrence was limited to the PPS in only 40% of the patients, while the remaining 60% experienced HNSCC relapse at multiple sites contemporar-

ily. In a recurrent setting, when patients are deemed operable, salvage surgery is considered the standard of care, providing durable disease control in almost 15% of patients, whereas reirradiation with or without CHT-RT is usually considered for very selected unresectable tumours [40,41]. Different surgical approaches have been proposed for PPS tumours [42-44], although low-invasive approaches are usually unsuitable for malignant disease which often require at least the transparotid-transcervical approach [3]. Malignant tumours within the PPS proliferate within a confined and narrow area bounded by bony limits. Given their inclination to expand and infiltrate adjacent structures, there is a potential for these tumours to invade major neurovascular bundles (e.g. internal carotid artery, internal jugular vein, lower cranial nerves). In this context, salvage surgery is often challenging, primarily due to fibrotic tissue resulting from previous surgical or radiation treatments. Additionally, difficulties may arise from the unresectability of the tumour from the internal carotid artery, the associated postoperative risks related to cranial nerve lesions, or the imperative to undertake extensive surgical demolitions in patients for whom such procedures are unsuitable [3]. Furthermore, recent papers have shown that the malignant nature of the tumour is an independent factor related to the presence of positive margins after surgery [45-48]. Due to these challenges, malignant lesions within the PPS are frequently deemed unresectable, leading to their management through radiation therapy for either curative or palliative purposes. Moreover, even in cases where surgery is deemed feasible, and the patient is medically suitable, postoperative complications can be severe and potentially life-threatening [3]. Some authors have proposed single or double mandibulotomy when dealing with large or malignant PPS tumors [49,50], however this procedure is associated with mandibular malunion or non-union, loss of dentition, temporomandibular joint dysfunction, and possible osteoradionecrosis in patients who previously underwent radiation therapy. Some authors have proposed reirradiation in patients unsuitable for surgery [50]. The indications are very debated among physicians as reirradiation, alone or together with chemotherapy, has a variable success rate [27] and might be associated with severe treatment-related complications such as carotid blow-out, whose risk is even higher when carotid artery encasement is present [51].

CHT-RT was the most common treatment of PPS metastasis diagnosed during the primary diagnosis due to the general high burden of disease, tumour origin, and surgery-related risks, while treatment of PPS metastasis in the recurrent group was variable due to the heterogeneity of patients. In the group of patients affected by recurrent PPS SCC within the retrospective study cohort, 7 patients (47%) could not be addressed to curative treatment due to unresectable PPS disease, poor general conditions unsuitable for irradiation or reirradiation, and were thus addressed to first-line chemotherapy, immunotherapy or best supportive care. Therefore, in cases of tumour recurrence within the PPS, the tumour burden is often so conspicuous, or the patient's general condition is so compromised that salvage treatment may become unreasonable. This situation is associated with lower rates of OS and DSS.

The systematic review herein performed is limited by the availability and heterogeneity of the data in previously published reports. All the included manuscripts were retrospective studies with diverse data collection variables and follow-up timing, among other inconsistencies. Moreover, the lack of consistent follow-up timing makes it difficult to accurately evaluate the efficacy of a management strategy.

The retrospective cohort study has a limited sample size, even if significant compared with the already published data, and the heterogeneity of treatments reported in the case series further limits the significance and generalisability of the findings. Further collaborative studies are needed to improve the level of evidence and shed light on the clinical and prognostic implications of PPS HNSCC metastases.

Conclusions

Our findings indicate that PPS metastasis in HNSCC tends to occur more frequently in the recurrent setting, attributed to anatomical lymphatic alterations following primary treatment. These metastases serve as markers of aggressive disease, characterised by challenging management and an asymptomatic presentation that contributes to diagnostic delays. The prognosis for this condition remains poor regardless of the treatment administered. While a surgical approach is generally considered the preferred management strategy, its application is hindered by factors such as unresectable lesions, the complexity of surgical procedures leading to high rates of severe complications, and the unsuitability of patients for this form of management.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

All authors contributed significantly to the creation of this manuscript, each having fulfilled the criteria as established by the ICMJE.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee (CE AVEN Emilia-Romagna: 0018649/22). Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

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