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# Neurological Complications in Benign Parapharyngeal Space Tumors – Systematic Review and Meta-Analysis

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## Abstract

**Introduction** Parapharyngeal space tumors with complex anatomy and diverse histology have remained a challenging phenomenon for treating physicians.

**Objectives** We have conducted a comprehensive web search on the PubMed, Web of Science, EMBASE, Cochrane Library, Biomedical Literature Database (CBM), and Clinicaltrials.gov databases to determine the factors that are associated with postoperative complications in parapharyngeal space tumors.

**Data Synthesis** Two researchers reviewed all identified articles independently with a third reviewer for adjudication. Patient demographics and other clinicopathological characteristics were explored. The systematic review has identified 631 benign parapharyngeal space tumors with neurogenic and salivary tissue histology in 13 studies, with a mean age of $42.9 \pm 7.76$ years old and a median follow-up of $40.98 \pm 19.1$ months. Salivary gland (50.8%) and neurogenic (49.1%) tumors were the most common histological entities. Tumor size, location, histology, deep parotid lobe involvement, and proximity to great vessels or to the skull base were the deciding factors in selecting the surgical approach. The factors considered to select the surgical approach do not seem to have a correlation with the outcome in terms of neurological sequalae ($p = 0.106$). Tumors with neurogenic histology have significantly increased chances of developing neurological complication (OR 6.07; $p = 0.001$).

**Conclusion** Neurologic complications are significantly associated with neurogenic benign tumors rather than surgical approach.

**Keywords**
- cancer of head and neck
- parapharyngeal space
- neurologic manifestations

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## Introduction

The parapharyngeal space (PPS) is an imaginary inverted pyramidal space with an extension from the skull base to the hyoid bone divided by the Riolan bundle into pre- and poststyloid compartments.[1–3] Of all head and neck cancers, PPS tumors account for 0.5% and most of them are benign (80%), with diverse histology. Pleomorphic adenoma is the most common benign tumor of salivary gland origin occupying mostly the prestyloid compartment, and schwannomas are the most common neurogenic entities residing in the poststyloid space.[4] The correct histopathological diagnosis of these lesions may not be achieved due to their complex anatomical location, relying more on image findings (computed tomography [CT], magnetic resonance imaging [MRI], or angiography) for preliminary diagnosis. This may also help in identifying the anatomical extent of the growth.[1] Surgery has remained as the primary treatment modality if not contraindicated by gross intracranial tumor extension or by comorbidities pushing toward other nonsurgical treatment options.[5] A lot of literature including case series and reports has been published regarding PPS tumors with diverse benign and malignant histology, including all the deep lobe parotid, infratemporal fossa tumors, as well as carotid body paragangliomas that, by definition, may not fall into the precise anatomical parapharyngeal space. Accurately placing these lesions into the true PPS may have clinical implication in terms of choosing the right surgical approach.[6] The systematic reviews published for PPS lesions have already mentioned this issue and have presented the recent updates on presentation, histological diagnosis, surgical approaches, and complications. We have aimed our study more on the surgical approaches for the resection of benign PPS tumors and associated neurologic sequelae. A thorough search was conducted by reviewing all the available relevant published data to focus on the rationale behind the selection of different surgical approaches and associated neurological complications.

## Review of the Literature

### Literature Search for Data Collection

We have performed an extensive search in the PubMed, Cochrane Library, Web of Science, EMBASE, Biomedical Literature Database (CBM), and Clinicaltrials.gov databases with reference to PPS tumors. Articles fulfilling the search criteria with keywords such as *parapharyngeal space* or *transmandibular* or *benign parapharyngeal space tumor* or *trans-cervical* or *lip split mandibulotomy* or *mandibular swing* were included in the first instance and the search was concluded on May 25, 2019. The analysis included systematic reviews, retrospective studies, and literature reviews pertaining to open surgical management of primary parapharyngeal space tumors published from 1989 to 2019. No publication focused on the management of benign parapharyngeal space tumors was found due to the rarity of the disease. The studies with management of PPS tumors including series with $\geq$ 10 patients were also incorporated. Data was collected including age and gender of the patients, year of publication, histopathological classification, surgical approaches, and complications. The exclusion criteria were case reports /series addressing malignant pathology only, treatment modalities other than surgery, single-case reports or case series with $<5$ patients, nonprimary PPS tumors, tumors with nasopharyngeal, intracranial, or infratemporal fossa extensions, studies comparing approaches such as robotic/lateral skull, studies that provide data using single modality with no comparisons, letters to the editors, meeting abstracts, and editorials.

Robotic and endoscopic approaches have not been included in the review as most of the published literature have addressed PPS tumors with open surgical access. Furthermore, the endoscopic approaches may still need to be validated for reproducibility and effectiveness to be labeled as the standard of care. We had to incorporate different benign histologies since the numbers are very small and the surgical management of these tumors has been based more on the location of the tumor rather than on the tissue of origin.

### Data Extraction

Data extraction and quality assessment of all included studies were independently performed by 2 authors (Faisal M. and Erovic B. M.). Controversies were solved by discussion or by consultation with another author (Seeman R.). Basic information such as patient demographics, histopathology, presenting complaints, surgical approaches, and postoperative complications were recorded. All included papers were clinical studies focusing on the surgical management of PPS tumors using different approaches and their postoperative complications or sequelae. The present study did not require approval and was granted exemption from the Ethical Review Board of the Evangelical Hospital, Vienna, Austria, and of the Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan.

### Data Analysis and Statistical Methods

IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The independent *t*-test was used to compare the means of two normally distributed groups (salivary versus neurogenic tumors). The Pearson correlation coefficient was calculated to determine the correlation between the tissue of origin of the tumor and postoperative complications. Binary logistic regression analysis was performed to measure the odds of having neurological complications in salivary and neurogenic PPS tumors. A $p\text{-value} < 0.05$ was considered statistically significant. GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) was used to draw the bar charts.

### Search Findings

A total of 2,674 articles were identified with the database search using keywords as mentioned in the methodology section. 1,852 articles remained after removal of duplicates. Next, the articles were screened by title and abstract reading to select the relevant studies, and 745 remained

in this step. The short case series reporting $< 5$ patients were further excluded. After full-text revision, 679 articles were excluded for reasons described in the Plasma flowchart. Hence, 13 studies, all published in English, with a total of 631 participants, were included for further evaluation.[6–18] We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the study selection procedure was illustrated by the PRISMA flow diagram (►**Fig. 1**). Three studies were conducted in USA, two in Spain, two in China, and one each in Egypt, India, Israel, Brazil, Italy, and Japan.[6–18] A total of 631 patients were recruited from studies published between 1996 and 2017.

### Study Cohort

There were 631 patients with benign histology (either salivary or neurogenic in origin). The mean age at presentation was $42.9 \pm 7.76$ years old, with a median follow-up of $40.98 \pm 19.1$ months. Baseline characteristics and demographics along with presenting complaints, histological variation, and complications of cumulative data have been further expressed (►**Table 1**). The patients were categorized into 2 groups based on the tissue of origin, such as neurogenic ($n = 310$) and salivary (321) and were subsequently compared based on subsequent complications. The primary surgical approaches used were (i) transcervical (60%), (ii) cervicoparotid (30%) including dissection and exposure of the facial nerve trunk and associated branches, and (iii) transmandibular (10%) comprising mandible split for access and tumor resection (►**Fig. 2**). The transcervical approach was favored in 9 out of 13 studies compared with 4 studies in which the cervicoparotid access was used. None of the studies has given clear preference to the use of the transmandibular approach. The most common neurogenic tumor found was schwannoma (54%) followed by paraganglioma (43%) (►**Fig. 2**). The distribution of complications based on

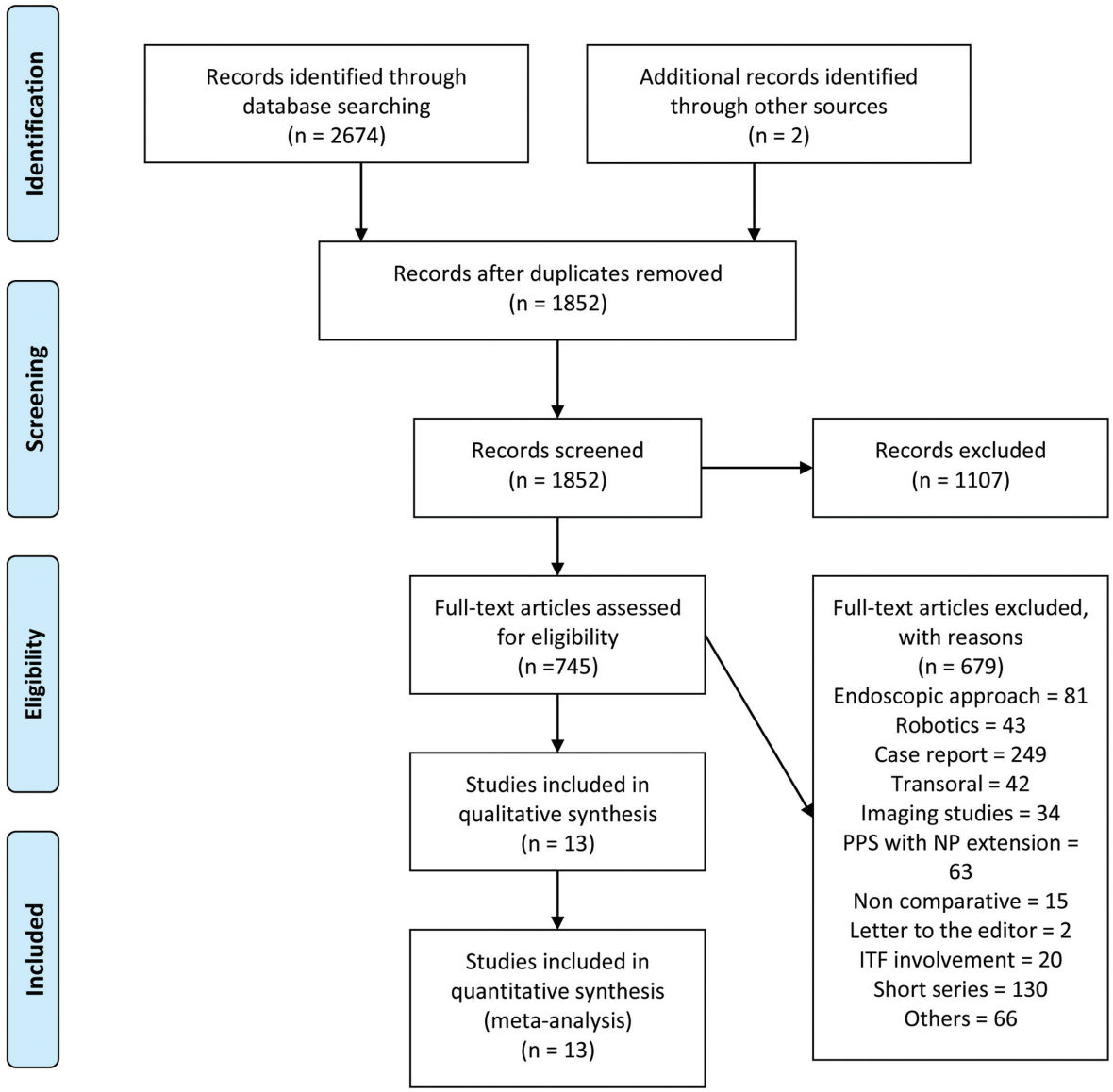


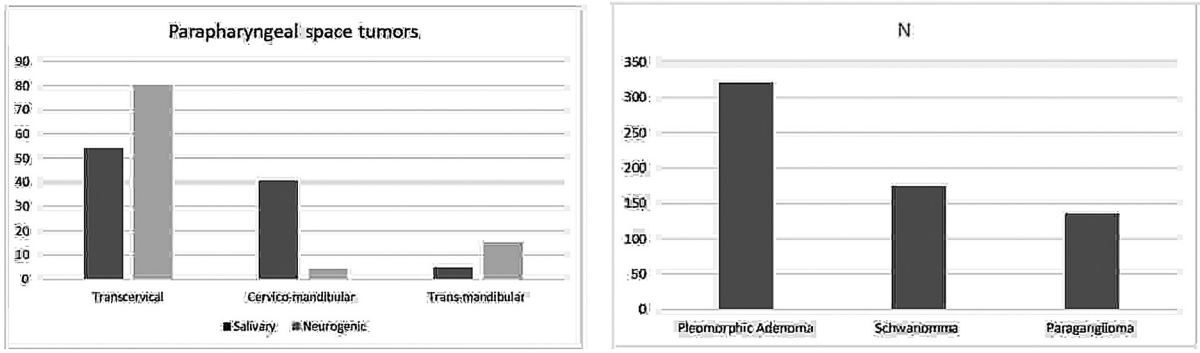

**Fig. 1** Flow diagram; the flow diagram was adapted according to the PRISMA recommendations.

**Table 1** Demographics and baseline characteristics of cumulative studies

| Author | Year of publication | Country | Sample size (*n*) | Mean age (years old) | M:F ratio* | Presenting complaints | Mean follow-up (months) |
|---|---|---|---|---|---|---|---|
| Cohen et al. | 2005 | USA | 89 | 47 | 2.3:1 | No symptom 25.3% | 28 |
| Attia et al. | 2004 | Egypt | 8 | 37 | 1:1.9 | Neck swelling 72% | 21 |
| Miller et el. | 1996 | USA | 37 | 48 | 1:1 | Pharyngeal mass 45% | 35 |
| Hazarkia et al. | 2004 | India | 38 | 33 | 1.5:1 | Neck swelling 53.5% | 39 |
| Zhi et al. | 2008 | China | 113 | 36 | 1.3:1 | Neck swelling 72.8% | 36 |
| Malone et al. | 2001 | USA | 18 | 53 | 1:1.9 | Not mentioned | 24 |
| Khafif et al. | 2005 | Israel | 31 | 46 | 1:1.6 | Not mentioned | 35 |
| Tincani et al. | 1999 | Brazil | 16 | 53 | 2.2:1 | Pharyngeal mass 68% | 60 |
| Cassoni et al. | 2014 | Italy | 49 | 38 | 1:1.4 | Pharyngeal mass 68.3% | 91 |
| Iglesias et al. | 2015 | Spain | 28 | 42 | 1:1.5 | Pharyngeal mass 71% | 48 |
| Ijichi et al. | 2017 | Japan | 26 | 43 | 1:2.1 | Neck swelling 34.4% | 29 |
| Shi et al. | 2017 | China | 130 | 45 | 1:1 | Pharyngeal/Neck swelling 55% | 45 |
| Grili et al. | 2017 | Spain | 58 | 47 | 1:1 | Pharyngeal mass 26% | Not mentioned |

Abbreviations: F, female; M, male.




**a** Distribution of surgical approaches based on tissue of tumor origin

**b** Distribution of PPS tumor histology based on salivary and neurogenic tissue

**Fig. 2** Distribution of parapharyngeal space tumors based on surgical approach and tumor histology.

salivary or neurogenic histology has been represented for all the studies included in the review.

The 148 patients with neurogenic complication among 310 neurogenic tumors (mean: 11.38; standard deviation [SD]: 11.81) were compared against 41 patients with neurological complication among 321 salivary gland tumors and demonstrated a significantly increased rate of nerve-related complications ($t = 2.42$; $p < 0.05$). Among the neurologic complications, the most encountered were vocal cords palsy (73%), Horner syndrome (9%), hypoglossal nerve injury (6%), and first bite syndrome (4%) (►**Table 2**).

The factors considered for selecting surgical approaches in 13 studies on PPS tumors were categorized into size, location, histology, proximity to greater vessels or to the base of skull, histology, and deep parotid lobe involvement (►**Table 3**). Each factor was given a score and the combined scores were compared with the percentage of complications to assess if any of these factors considered before surgery would have an effect in the outcome in terms of complication rates. The correlation coefficient suggested a small degree of positive correlation that is not statistically significant ($p = 0.930$). The tissue of origin (neurogenic versus salivary) seems to have a positive correlation with more complications related to neurogenic tumors (Pearson coefficient: 0.662; $p = 0.019$) (►**Fig. 3**). The binary logistic regression showed a significantly increased likelihood of developing postoperative neurological complications in tumors with neurogenic histology ($p = 0.0001$) (►**Table 2**). We performed a meta-analysis assessing neurological complications among the groups with both salivary and neurogenic tissues of origin. Due to a heterogeneity < 50%, a fixed term model was used. Neurological deficit was observed in 48% of patients with neurogenic histology (148/310), while only 13% of the patients with salivary tumor developed neurological deficit. The pooled relative risk (RR) was 2.41 (95% confidence interval [CI]: 1.80–3.23; $p = 0.001$) (►**Fig. 4**).

**Table 2** Determinants of selection of surgical approaches in cumulative studies

| Author | Size | Location | Proximity to great vessels | Proximity to the skull base | Histology | Parotid lobe involvement |
|---|---|---|---|---|---|---|
| Cohen et al.[7] | No | No | Yes | Yes | No | Yes |
| Attia et al.[8] | Yes | Yes | Yes | No | Yes | No |
| Miller et el.[9] | Yes | Yes | Yes | No | Yes | No |
| Hazarkia et al.[10] | No | No | Yes | Yes | Yes | Yes |
| Zhi et al.[11] | Yes | Yes | Yes | No | Yes | No |
| Malone et al.[12] | No | No | No | No | Yes | No |
| Khafif et al.[13] | Yes | No | Yes | No | Yes | No |
| Tincani et al.[14] | No | Yes | No | No | Yes | No |
| Cassoni et al.[15] | No | No | No | No | Yes | Yes |
| Iglesias et al.[16] | Yes | Yes | Yes | No | Yes | No |
| Ijichi et al.[17] | Yes | Yes | No | No | Yes | No |
| Shi et al.[18] | Yes | Yes | Yes | Yes | Yes | No |
| Grili et al.[6] | Yes | Yes | Yes | No | Yes | No |

**Table 3** Complications of surgical removal of neurogenic tumors

| Neurological complications | n | % | |
|---|---|---|---|
| VC paralysis | 109 | 73 | |
| Hoarseness | 5 | 3.3 | |
| Hypoglossal nerve injury | 10 | 6.7 | |
| Horner syndrome | 14 | 9.39 | |
| First bite syndrome | 6 | 4 | |
| Pharyngoparalysis | 2 | 1.3 | |
| CN V palsy | 3 | 2 | |
| Total | 149 | | |
| | **Univariate Analysis** | | |
| **Variable** | **OR** | **p-value** | **95%CI** |
| Histology (N versus S) | 6.0 | 0.001 | 4.083–9.026 |

Abbreviations: CI, confidence interval; CN, cranial nerve; N, neurogenic; OR, odds ratio; S, salivary; VC, vocal cords.

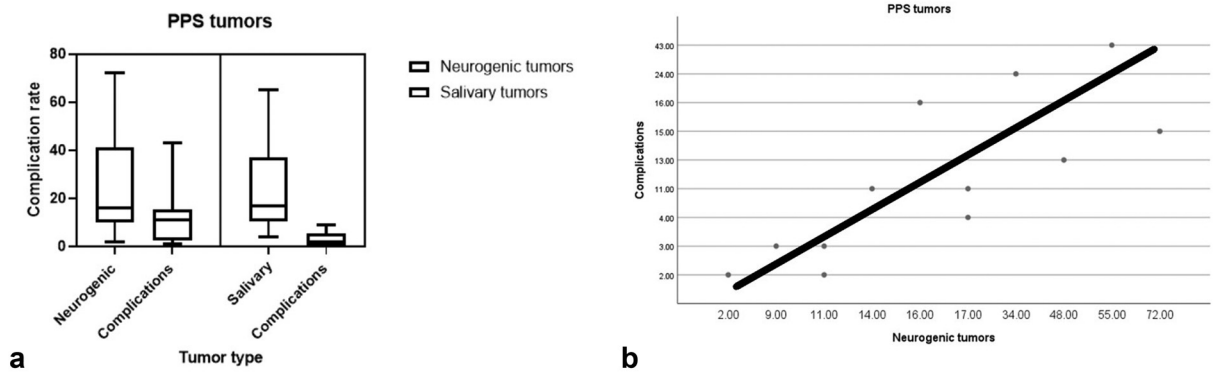



**Fig. 3** Comparison of complication rates based on tissue of origin in PPS tumors. Note: Pearson correlation = 0.686; $p = 0.019$.

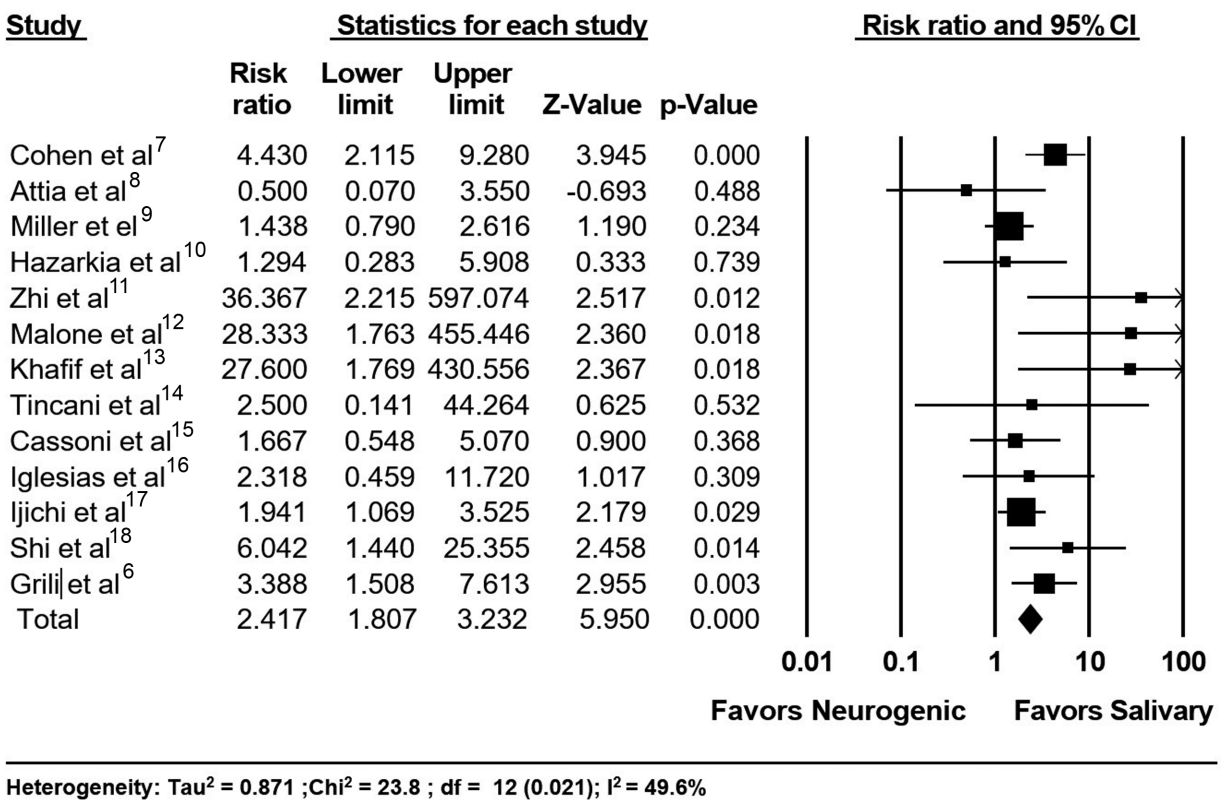



**Fig. 4** Meta-analysis – Neurogenic histology and risk of neurogenic complications.

### Quality of Studies

The risk of bias of the included works has been assessed in eight categories using the ACROBAT-NRSI tool recommended by the Cochrane group and an overall score was calculated indicating the quality of each analyzed study (►**Table 4**).

## Discussion

Benign tumors are the most common entity (80–90%) found in the PPS, with the parotid gland as the most common site of origin.[19–21] The PPS is divided into two compartments by an osteomuscular aponeurotic sheath originating at the styloid process. The prestyloid space contains components such as the deep lobe of the parotid gland, fat and lymphatic nodes, inferior, lingual, and temporal auricular alveolar nerves. The retrostyloid space encloses neurovascular structures such as the carotid artery, the jugular vein, the cervical sympathetic chain, and cranial nerves IX, X, XI, and XII, suggesting a more diverse histology from this compartment.[22] Parapharyngeal space tumors must be clearly identified, since erroneous anatomical boundaries may have resulted in the inclusion of adjacent tumors in some of the published literature, such as deep lobe tumors, which should only be considered if the location is retromandibular. Similarly, lesions at the foramen ovale must be a part of infratemporal fossa tumors while carotid body paragangliomas below the posterior digastric body must not be considered a part of PPS tumors.[23] Due to their complex anatomical location and diverse histology, precise approaches to PPS tumors have remained a controversial debate.[24,25] Complete excision with minimal morbidity should be the aim of the operating surgeon, particularly when dealing with benign PPS tumors. Size, location (pre- or poststyloid), proximity to the skull base and to the vascular bundle, extension to the deep lobe of the parotid, and imaging-based position (superior/middle/inferior) of the lesions are some of the key factors considered preoperatively to select a surgical approach.[7,13,15]

The inclusion of mandibulotomy has raised many concerns, such as facial scar, orocervical fistula, prolonged operating time, malocclusion, trismus, delay in resuming regular diet, risk of exposure of the fixation plate, and temporomandibular joint (TMJ) dysfunction.[26–28] The most used approach to access PPS tumors published in the literature was the transcervical, either alone or in combinations. In the cumulative series of 631 patients, this approach has been utilized for 60% of cases, addressing both salivary and extraparotid neurogenic tumors. The facial nerve may not need to be exposed to further extend the dissection and exposure. Due to excessive push and pull, neuropraxia may occur in the postoperative setting. The identification of the facial nerve may increase the access to large-sized and superiorly-placed PPS tumors. The rationale behind the use of the transcervical approach in our cumulative search was small (preferably $< 8$cm), benign, prestyloid extraparotid tumors in the lower PPS. Further exposure can be achieved

**Table 4** Quality of included studies using ACROBAT-NRSI* version 10

| Assessment of bias | Selection of population | Assessment of exposure | Outcome of interest | Match with prognostic variables | Assessment of prognostic factors | Assessment of outcome | Adequate follow up | Cointervention between groups | Overall score |
|---|---|---|---|---|---|---|---|---|---|
| Cohen et al.[7] | Low risk | Medium | Low risk | Medium risk | Low risk | Low risk | Low risk | High risk | Medium |
| Attia et al.[8] | Low risk | Low risk | Low risk | Medium risk | Low risk | Low risk | Low risk | Low risk | Medium |
| Miller et al.[9] | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk | High risk | High |
| Hazarkia et al.[10] | Low risk | Low risk | Low risk | Medium risk | Low risk | Low risk | Low risk | High risk | Medium |
| Zhi et al.[11] | Medium risk | Low risk | Low risk | Medium risk | Low risk | Low risk | Low risk | High risk | Medium |
| Malone et al.[12] | Low risk | Low risk | Low risk | Medium risk | Low risk | Low risk | Low risk | Medium risk | Medium |
| Khafif et al.[13] | Low risk | Low risk | Low risk | Medium risk | Low risk | Low risk | Low risk | Medium risk | Medium |
| Tincani et al.[14] | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | High risk | High risk | High |
| Cassoni et al.[15] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Medium risk | Medium |
| Iglesias et al.[16] | Medium risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk | Medium risk | Medium |
| Ijichi et al.[17] | Low risk | Low risk | Low risk | Medium risk | Low risk | Low risk | Low risk | Medium risk | Medium |
| Shi et al.[18] | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk | High risk | Medium |
| Grili et al.[6] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Medium risk | Medium |

*A Cochrane risk of bias assessment tool for nonrandomized studies of interventions.

by division of posterior belly of the digastric muscle and removal of the submandibular gland on occasion.

The cervicoparotid approach uses formal identification of the facial nerve trunk and is indicated for tumors in proximity to the deep lobe of the parotid gland with risk of adherence to the facial nerve. The transcervical approach only may jeopardize the preservation of the facial nerve. In our cumulative results, it is the second most used approach, which is in line with previously published data, in which the most commonly used indications for the cervicoparotid access were large, pre- or retrostyloid, deep lobe parotid, or minor salivary gland tumors, as well as neurogenic tumors with or without facial nerve involvement located in the middle to lower PPS but not involving the base of skull. Access may be further enhanced by prognathic mandibular dislocation dividing the stylomandibular ligament and the styloid muscle.

The transmandibular approach with its modifications (midline/paramedian or lateral splits) is usually performed for massive, large vascular or recurrent benign tumors placed more superiorly in the PPS. In the cumulative series, the transmandibular approach was only used in 6% of the patients, especially due to the large size of the tumors (mostly $>$ 8cm), to the vascular nature of the tumor, to superior location of the tumor in the PPS, and to proximity of the tumor to the skull base. The use of the transmandibular approach has been further limited as indicated by recent studies showing a decline in the use of the transmandibular approach (from 9 to 6%) when compared with previous reports.[29–31] Prolonged hospital stay, delay in resuming normal diet, tracheostomy covering, trismus, and associated TMJ and occlusal disturbances are some of the drawbacks of this technique.[32,33]

The cumulative studies in our cohort have depicted a significantly high number of neurogenic complications in both salivary and neurogenic tumors. Detailed analysis has shown these complications to be more common in tumors with neurogenic tissue of origin. The literature has described 5 major histological subtypes of neurogenic tumors with $>$ 90% presenting benign histology. Batsakis and Sneige[22] have reported paraganglioma to be the most common subtype, while John et al. and Danke et al. have found schwannomas to be the most commonly found histological entity.[34,35] Schwannomas arise usually from cranial nerves IX to XII or from the cervical sympathetic chain, with decreased risk of nerve injury when small. On the other hand, paragangliomas derive from the vagal nerve with a potential for intracranial extension or malignant transformation. The list of complications in our combined series included vocal cord paralysis (73%), Horner syndrome (9.3%), hypoglossal nerve injury (6.7%), and first bite syndrome (4%). The tumors with salivary histology had a complication rate of 12.8%, which is significantly lower than that of neurogenic tumors (47.7%) (t value = 2.42; $p = 0.023$). This preemptive assessment of the anticipated range of neurologic complications must be considered to educate the patients on the postoperative sequelae and, simultaneously, prepare them to facilitate rehabilitation.

Our systematic analysis may have its share of limiting factors. Most of the studies included are retrospective series with inherent biases for the selection of surgical approaches, clinical expertise, and intraoperative and postoperative care, with a variable support for postoperative rehabilitation. Most studies have omitted data on some critical factors when applying these surgical approaches, such as length of hospital stay, cost effectiveness, return to normal diet or oral feeding in the transmandibular approach, infection, time to healing, and length of the surgery.

## Final Comments

Most PPS tumors are benign (80%), with either neurogenic or vascular origin. With $< 0.5\%$ of the tumors arising from the deep parotid lobe, the transcervical approach may be an appropriate solution for these benign PPS tumors with less morbidity and complications. Cranial nerve deficits are the result of complications arising from the neurogenic tissue, irrespective of which surgical approach is used.

Conflict of Interests

The authors have no conflict of interests to declare.

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