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Collet-Sicard Syndrome: A scoping review

Autor

**Nombre completo del autor o autores**

Rafael Alberto Aponte-Caballero; Maria de los Ángeles Castiblanco ; Juan Felipe  
Abaunza Camacho

Director

**William Mauricios Riveros Castillo; Javier Mauricio Saavedra**

**Neurocirugía**

**Escuela de Medicina y Ciencias de la Salud**

**Programa de Neurocirugía**

**Universidad del Rosario**

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## Title Page

### Collet-Sicard Syndrome: A scoping review

#### Author information

Maria Paula Aguilera-Pena<sup>1\*</sup>, Maria A. Castiblanco<sup>1,2,3,4\*</sup>, Valentina Osejo-Arcos<sup>1,2,3,4</sup>, Rafael Aponte-Caballero<sup>1,2,3,4</sup>, Santiago Gutierrez-Gomez<sup>1,2,3,4</sup>, Juan Felipe Abaunza-Camacho<sup>1,2,3,4</sup>, Natalia Guevara-Moriones<sup>1</sup>, Camilo Armando Benavides-Burbano<sup>1,2,3,4</sup>, William M. Riveros-Castillo<sup>1,2,3,4</sup>, Javier M. Saavedra<sup>1,2,3,4</sup>

1. Center for Research and Training in Neurosurgery (CIEN), Bogotá, Colombia.
2. Neurosurgery Department, Hospital Universitario Samaritana, Bogotá, Colombia.
3. Neurosurgery Department, Hospital Universitario Mayor-Mederi, Bogotá, Colombia.
4. Universidad del Rosario, School of Medicine, Bogotá, Colombia.

\* This author contributed equally to this work

#### ORCID

- mariapaulaaguilerap@gmail.com; <https://orcid.org/0000-0001-7361-6891>
- mariadelosangeles.castiblancoa@gmail.com; <https://orcid.org/0000-0003-1955-265X>
- valentina.osejo@urosario.edu.co; 0000-0002-2037-0506
- rafaaponte3@hotmail.com; <https://orcid.org/0000-0002-2740-8837>
- santiago.gutierrezgo@urosario.edu.co; <https://orcid.org/0000-0003-1326-8308>
- juan.abanza@urosario.edu.co; <https://orcid.org/0000-0002-8465-6351>
- nataliam-guevara@juanncorpas.edu.co;
- cabenavides@fucsalud.edu.co; <https://orcid.org/my-orcid?orcid=0000-0001-7354-6248>
- mauroneuro@yahoo.com; <https://orcid.org/0000-0003-3978-2153>
- javiermsaavedra@gmail.com; <https://orcid.org/0000-0001-9935-3903>

#### CORRESPONDING AUTHOR:

Maria Paula Aguilera-Pena

[mariapaulaaguilerap@gmail.com](mailto:mariapaulaaguilerap@gmail.com)

Center for Research and Training in Neurosurgery (CIEN), Bogotá, Colombia.

E-mail: [mariapaulaaguilerap@gmail.com](mailto:mariapaulaaguilerap@gmail.com)

Tel: +1 786 777 9489

## Abstract

Collet-Sicard syndrome (CSS) is the unilateral palsy of the cranial nerves (CN) IX, X, XI, and XII. To our knowledge, no review describes the characteristics of patients diagnosed with CSS. Therefore, this review aims to collect and describe all cases in the literature labeled as CSS.

We performed a scoping review of the literature and conducted a database search in Embase and PubMed. We included articles and abstracts with case reports or case series of patients with CSS diagnosis. We classified the cases into two groups: “CSS”, referring to patients presenting exclusively with IX-XII nerve involvement, and “CSS-plus”, which corresponds to cases with CSS and other neurological impairments.

We included 135 patients from 126 articles, of which 84 (67.7%) were male. The most common clinical manifestations reported were dysphagia and dysphonia. The most common etiology was tumoral in 53 cases (39.6%) and vascular in 37 cases (27.6%). Half of the patients underwent conservative treatment, and the majority showed partial or total improvement. The most frequent anatomic space was the jugular foramen (44.4%) and the parapharyngeal retrostyloid space (28.9%). Approximately 21% of the patients had other CN impairments, with the seventh and eighth CN most frequently compromised.

We conclude that although there is a need for greater rigor in CSS reporting, the syndrome has a clear utility in the localization of jugular foramen and parapharyngeal retrostyloid space pathology.

**Keywords:** Collet-Sicard syndrome, Review, Scoping Review, Tumor

## INTRODUCTION

Collet-Sicard Syndrome (CSS) was first described in 1915 by a French otolaryngologist called Frédéric Justin Collet, who named this clinical entity <sup>[20,27]</sup>. Independently, in 1917, the French radiologist and neurologist Jean-Athanase Sicard described the same syndrome <sup>[27,113]</sup>. CSS is defined as unilateral palsy of the cranial nerves (CN) IX, X, XI, and XII. This syndrome includes dysphagia, absent gag reflex, impaired taste and sensation over the posterior third of the tongue, dysphonia, tongue deviation, paralysis of the palate, hemianesthesia of the larynx, pharynx, and soft palate, weakness of trapezius, and sternocleidomastoid muscle <sup>[121,128]</sup>

CSS is a rare entity. No prevalence or incidence is reported in the literature. This syndrome has various etiologies, including malignant and benign neoplasms, vascular disease, and trauma, among others <sup>[2]</sup>. To our knowledge, no review describes the characteristics of patients diagnosed with CSS. Thus, this scoping review aims to collect and describe all cases in the literature labeled as CSS.

## MATERIALS & METHODS:

We carried out a Scoping Review of the Literature. This study was conducted and reported in accordance with the PRISMA extension for Scoping Reviews (PRISMA-ScR 2018) [125]. We conducted a database search in October 2021 using Embase terms "'collet Sicard syndrome'/exp OR 'collet Sicard syndrome'" and PubMed terms "Collet Sicard" OR "Collet Sicard Syndrome". We did not limit the search according to publication date. We included articles and abstracts written in English, Spanish, Portuguese, German, and French, with case reports or case series of patients with a Collet-Sicard diagnosis. We excluded review articles without any patient description. A total of 231 articles were extracted from both databases and gray literature; 88 were duplicated, and 18 fulfilled the exclusion criteria. Only 126 articles fulfilled the inclusion criteria and 135 patients were included in the analysis (Appendix 1).

We collected data considering the cervical spaces described by *Varoquaux et al.* and *Kamalian et al.*, who divided them into suprahyoid and infrahyoid [48,127]. Suprahyoid spaces regarded for the analysis were: prevertebral space, parotid space, masticator space, retropharyngeal space, pharyngeal mucosal space, and parapharyngeal space. Tenso-vascular-styloid fascia divided this last space into pre-styloid and retro-styloid spaces (PRS). The retro-styloid space refers to the carotid sheath in the suprahyoid space [48] (Figure 2).

Furthermore, we assigned an additional classification to CSS etiologies, considering those cases that started outside of the cranium as extracranial, those that formed within the bone such as metastases, as intraosseous, and those that started within the cranium as intracranial. More than one label could be attached to the same case if more than one of the aforementioned spaces was compromised.

Two independent reviewers (MP and MA) extracted the data from each article and the discrepancies were solved in a discussion between them. Data were recorded in a Microsoft Office 365, Microsoft Inc., Redmond, Washington, United States Excel spreadsheet. We classified the cases into two groups: "CSS", which refers to patients presenting exclusively with IX-XII cranial nerve involvement, and "CSS-plus", which corresponds to cases presenting with the original syndrome description and other neurological impairments.

For the statistical analysis, the normal distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test. Variables with normal distribution were described with mean and standard deviation, while those with non-normal distribution were described with median and interquartile range. Categorical variables were described with their absolute and relative frequencies. The differences in categorical variables were assessed with  $\chi^2$  test and Fisher's exact test, and the U Mann-Whitney test was used for continuous variables. Statistical significance was met at  $p < 0.05$ . Data was analyzed using

the SPSS, International Business Machines Corporation, Armonk, New York, United States, personal license Version 26 for Mac iOS.

## RESULTS

We included a total of 126 articles and 135 patients diagnosed with CSS (Figure 1, PRISMA diagram). Of them, 84 (67.7%) were male, with a median age at diagnosis of 55 [IQR, 41.0 - 67.0]; 40 (32.3%) were female, with a median age of 50 [IQR, 37.0 - 62.0]. The most common clinical manifestations were dysphagia (n=92, 68.15%), dysphonia (n=78, 57.78%), tongue deviation (n=60, 44.44%), palate paralysis (n=54, 40.00%), and trapezius weakness (n=48, 35.56%) (Table 1).

The principal etiology was tumoral with 53 cases (39.6%), with glomus jugulare (n=10, 18.9%) and metastatic prostate adenocarcinoma (n=8, 15.1%) as the most frequent. This is followed by vascular etiology, with 37 cases (27.6%). Internal carotid dissection was the most reported cause in this subgroup (n=20, 54.1%), followed by jugular thrombosis (n=5, 13.5%). Traumatic etiology was the third most common cause of CSS with 32 cases (23.9%), in which condylar (n=17, 53.1%) and Jefferson fracture (n=7, 21.9%) represented the most frequent trauma-related injuries. Other congenital, iatrogenic, and infectious causes were less frequent. Half of the patients underwent conservative treatment, and the majority showed partial or total improvement. Follow-up was made in 48.1% of patients. Additional CN impairment was present in 21% of patients. Other general characteristics of the patients included are shown in Table 1.

Table 2 shows the anatomic distribution and its main etiologies. The most common anatomic spaces were the jugular foramen (44.4%), and the parapharyngeal retrostyloid space (28.9%). The jugular foramen was most commonly affected by tumors (53.3%), and the PRS by vascular pathology (61.5%) (Figure 2). The prevertebral anatomic space was most commonly affected by traumatic injury (74%). Most of these lesions were located in the extracranial (41.4%) and intraosseous (30.8%) regions.

Table 1 shows the characteristics of CSS compared to CSS-plus. Approximately 21% of the patients had other CN impairments, with the seventh and eighth CNs most frequently affected (Table 3).

## DISCUSSION

We conducted a scoping review to characterize CSS, focusing on the affected anatomical spaces and clinical characteristics. Since its first description in 1915, we found 126 studies describing CSS in 135 patients.

### *Etiology:*

Gutierrez et al. described in 2015 the main characteristics of 51 cases of CSS extracted from PubMed. They reported that the most common etiology was metastasis, while our study found that glomus jugulare was the most frequent etiology in the tumoral group. In contrast to Gutierrez et al., we also found congenital disease (Developmental abnormalities of the craniocervical junction, Eagle's syndrome) as a possible cause [49,77,115].

We found that the most prevalent tumoral causes were glomus jugulare and metastatic tumors. Glomus jugulare represents 0.6% of all head and neck tumors [50]. Although rare, glomus jugulare neoplasm is the most frequent tumor of the jugular foramen, constituting 60-80% of all such cases [46]. In concordance with Jaiswal et al. we found glomus jugulare predominantly in females [46]. Its usual clinical presentation consists of pulsatile tinnitus, hearing loss, vertigo, and in some cases, lower CN impairment [46,60]. However, we believe its slow-growing and locally invasive behavior explains why it is the most frequent cause of CSS, given the close vicinity between the jugular and hypoglossal canal.

Among metastatic tumors, prostate and breast cancer were the most frequent primary neoplasms that presented with CSS, in alignment with Opie et al. [80]. This finding is probably related to prostate adenocarcinoma being the most frequent primary tumor metastasizing to the skull base [36,58].

Internal carotid artery dissection represented the most common cause within the vascular etiology group. Carotid dissection occasionally presents with paresis of the cranial nerves and, to a greater extent, with lower cranial nerve compromise, with the XII CN being the most affected one [37,39,69,121]. In the literature, we found two hypotheses explaining the physiopathology of lower CN palsy secondary to internal carotid dissection. The first is localized ischemia of the small vessels affecting the lower cranial nerves [37,39]. The second and most accepted hypothesis is intramural hematoma formation due to arterial dissection. This hematoma can compress the lower cranial nerves leading to CSS [37,39,116].

Interestingly most of the patients in our study diagnosed with CSS due to internal carotid artery dissection had some recovery, supporting the compressive mechanism because compression has a better prognosis than ischemia <sup>[39]</sup>. The parapharyngeal retrostyloid space was the most frequent anatomical space affected in the vascular group. In this space, we can find the lower cranial nerves, sympathetic chain, and the carotid sheath, which in turn contains the cervical or C1 segment of the internal carotid artery according to the Bouthillier classification. This anatomical proximity explains how intramural hematoma formation causes compression in the last four CNs <sup>[116]</sup> (Figure 4).

Lastly, the third most frequent etiology was traumatic. This group had two predominant injuries: condyle fracture and Jefferson fracture. Jefferson fracture or atlas fracture represents 1% of all spinal injuries <sup>[109]</sup>. A study made by Domenicucci et al. evaluated post-traumatic CSS cases. The most frequent mechanism of injury for the Jefferson fracture is the axial loading along the axis of the cervical spine, which can happen in conjunction with mechanisms of lateral bending and rotation<sup>[27]</sup>. The last four cranial nerves pass through the space between the transverse process of the atlas and the styloid process. In a Jefferson fracture, the transverse process comes closer to the styloid process compressing and stretching those cranial nerves resulting in CSS <sup>[27]</sup> (Figure 3). On the other hand, condyle fracture, when there is dislocation of this structure, causes tearing of the lower cranial nerves, making the recovery of these patients more difficult compared with the Jefferson fracture <sup>[27]</sup>.

### *Cranial nerve and clinical manifestations*

The typical clinical manifestations of CSS described by Lian et al. were vocal cord paralysis, dysphagia, impairment of taste in the posterior third of the tongue, weakness of the tongue, and sternocleidomastoid <sup>[1,64]</sup>. However, in our study, the most frequent clinical manifestations were dysphagia, dysphonia, tongue deviation, palate paralysis, and trapezius weakness. We consider that the variability in the clinical manifestations can contribute to initial misdiagnosis and a delay in achieving a correct diagnosis.

Twenty-nine patients (21%) presented other cranial nerve impairments in addition to IX, X, XI, and XII. The VII CN was the most frequent additional CN affected in cases reported as CSS. In our review, it was affected in 17 patients (12.6%) <sup>[21,49,50,71,90,111,112,118,124,132,135]</sup>. Most of them (11 cases, 64.7%) presented an extracranial lesion, where the extratemporal course of the VII CN begins, in close proximity to the jugular foramen and PRS <sup>[52]</sup>. In five (29%) of these extracranial cases, there was more than one type of injury; within this subgroup, a concomitant intraosseous lesion was the most frequent (4 cases, 23.5%). The remaining cases of patients presenting with facial palsy had intraosseous compromise (9 cases, 52.9%), followed by intracranial injury alone (3 cases, 17.5%).

A group of patients with CSS and hearing loss did not have VIII CN impairment, but conductive hearing loss secondary to otitis media [50,104,105,106,108,112,123]. Therefore, when a patient presents with CSS and hearing loss, it is crucial to evaluate the auditory system and not assume that the hearing loss is a consequence of VIII CN damage.

Higher cranial nerve involvement (i.e. oculomotor, trochlear, trigeminal, and abducens) was observed in patients with systemic diseases such as granulomatosis with polyangiitis or in high-energy traumatic brain injury [10,23,63,86].

#### *Compromised Anatomical spaces:*

The most common anatomical spaces impaired in CSS were the jugular foramen and the parapharyngeal retrostyloid space. This result concurs with the most frequent etiologies found, considering that glomus jugulare and internal carotid dissection are usually located in those spaces. However, an important percentage (41 patients, 30%) of cases comprised other anatomical spaces.

In contrast to previous literature, the cases we found did not have retroparotid space compromise. Collet was the first and only author to mention the retroparotid space in connection with CSS in 1915. Since then, the term has been used in learning books and case reports of Villaret syndrome, but not in CSS cases [14,31,114]. Our findings suggest that PRS describes more thoroughly one of the spaces affected in CSS than the term “retroparotid space” does. Therefore, we suggest that this last term should be discontinued.

There was no statistically significant difference between CSS and CSS-plus in terms of etiology, clinical manifestations, anatomical space, and treatment. This means that the impairment of other CN, in addition to the IX-XII, does not affect the disease course. Indeed, there was no statistically significant difference between the impairment of VII-XII, VIII-XII, or IX-XII CN.

The only statistically significant difference between the two groups was sympathetic fiber impairment; however, the compromise of the last four CNs and ipsilateral sympathetic impairment is known as Villaret syndrome [14,31], which leads us to understand that the cases with these clinical characteristics were mislabeled as CSS.

The limitations of this study are: first, the sample size is small, which may explain the absence of any statistically significant differences. Second, we did a systematic literature search of all the cases, however, some cases could be published in non-indexed journals, and some diagnosed cases in clinical practice may not be published, possibly leading to underestimation.

In conclusion, CSS is a rare pathology. The most commonly affected anatomical locations are the jugular foramen and parapharyngeal retrostyloid space. Hence, pathologies in those spaces should be ruled out in patients presenting with CSS. Tumoral etiology should also be considered in patients with clinical signs of lower CN impairment without a history of trauma. Furthermore, we found a lack of standardization when reporting the syndrome in the literature, which makes apparent the need for greater rigor in reporting CSS.

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None

#### CONFLICT OF INTEREST

None

#### Declarations

Ethical approval

This review did not require approval by an ethics committee

#### Competing interests

The authors don't have any competing interests to disclose.

#### Authors contributions

Maria Paula Aguilera-Pena and Maria A. Castiblanco: Conceptualization, Literature search, study selection, Writing, and analysis. Valentina Osejo-Arcos: Literature search, Prepare figures 1-4, Prepare tables 1-3, Writing. Santiago Gutiérrez-Gómez: Writing - Review and editing. Rafael Aponte-Caballero: Writing - Review and editing. Juan F. Abaunza-Camacho: Writing - Review and editing. Natalia Guevara-Moriones: Illustrations. Camilo Armando Benavides-Burbano: Review and editing, Supervision. William M. Riveros-Castillo: Supervision, Project Administration. Javier M. Saavedra: Writing - Review & Editing, Supervision.

All authors reviewed the manuscript

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## Availability of data and materials

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Fig 1. PRISMA flow diagram

Fig 2. Relationship of the retrostyloid parapharyngeal space with adjacent cervical spaces

Axial cut at the level of the parotid gland. 1. Masticatory space, 2. Parotid space, 3. Parapharyngeal mucosal space, 4. Parapharyngeal prestyloid space, 5. Parapharyngeal restrotyloid space, 6. Pharyngeal mucosal space, 7. Prevertebral space. 8. Parotid duct 9. Masseter muscle 10. Mandible 11. Medial pterygoid muscle 12. Parotid gland 13. Stylopharyngeal muscle, Styloglossus muscle, Stylohyoid muscle 14. Styloid process 15. External carotid artery 16. Internal carotid artery. 17. Retromandibular vein 18. Facial nerve 19. Hypoglossal nerve 20. Accessory nerve 21. Internal jugular vein 22. Cervical sympathetic trunk 23. Digastric muscle 24. Sternocleidomastoid muscle 25. Longissimus muscle 26. Glossopharyngeal nerve 27. Vagus nerve. Illustration created using Procreate version 5.3.4

Fig 3. Relationship between the styloid process and Jefferson fracture

A Jefferson fracture decreases the space between the right lateral mass and the ipsilateral styloid process, where the IX, X, XI CN are located. Illustration created using Procreate version 5.3.4

Fig 4. Anatomical relationships of the lower cranial nerves and surrounding structures

1. Hipoglossal nerve; 2. Hipoglossal canal; 3. Occipital condyle; 4. Glossopharyngeal nerve; 5. Vagus nerve; 6. Inferior petrosal sinus; 7. Posterior meningeal artery; 8. Accessory nerve; 9. Carotid artery; 10. Jugular foramen; 11. Internal jugular vein; 12. Styloid process. Illustration created using Procreate version 5.3.4

**Table 1. Comparison between CSS and CSS-plus**

|  | <b>Total N(%)</b> | <b>CSS</b>        | <b>CSS-plus</b> | <b>P</b>     |
|--|-------------------|-------------------|-----------------|--------------|
|  | <b>N (%)</b>      | <b>N (%)</b>      | <b>N (%)</b>    | <b>value</b> |
|  |                   | <b>106 (78.5)</b> | <b>29 (21)</b>  |              |

|                                          |                     |                              |                              |              |
|------------------------------------------|---------------------|------------------------------|------------------------------|--------------|
| <b>Age*</b>                              | <b>53 (37 - 63)</b> | <b>53.50 (38.25 - 62.00)</b> | <b>55.00 (37.00 - 67.00)</b> | <b>0.956</b> |
| <b>Sex</b>                               |                     |                              |                              | <b>0.077</b> |
| <b>Female</b>                            | <b>40 (32.3)</b>    | <b>29 (28.7)</b>             | <b>11 (47.8)</b>             |              |
| <b>Male</b>                              | <b>84 (67.7)</b>    | <b>72 (71.3)</b>             | <b>12 (52.2)</b>             |              |
| <b>General Cause</b>                     |                     |                              |                              | <b>0.245</b> |
| <b>Congenital</b>                        | <b>3 (2.2)</b>      | <b>2 (1.9)</b>               | <b>1 (3.4)</b>               |              |
| <b>Iatrogenic</b>                        | <b>5 (3.7)</b>      | <b>5 (4.8)</b>               | <b>0 (0.0)</b>               |              |
| <b>Infectious</b>                        | <b>4 (3.0)</b>      | <b>2 (1.9)</b>               | <b>2 (6.9)</b>               |              |
| <b>Trauma</b>                            | <b>32 (23.9)</b>    | <b>27 (25.7)</b>             | <b>5 (17.2)</b>              |              |
| <b>Tumor</b>                             | <b>53 (39.6)</b>    | <b>38 (36.2)</b>             | <b>15 (51.7)</b>             |              |
| <b>Vascular</b>                          | <b>37 (27.6)</b>    | <b>31 (39.5)</b>             | <b>6 (20.7)</b>              |              |
| <b>Space</b>                             |                     |                              |                              |              |
| <b>Jugular Foramen</b>                   | <b>60 (44.4)</b>    | <b>45 (42.5)</b>             | <b>15 (51.7)</b>             | <b>0.373</b> |
| <b>Parapharyngeal Retrostyloid Space</b> | <b>39 (28.9)</b>    | <b>31 (29.2)</b>             | <b>8 (27.6)</b>              | <b>0.861</b> |
| <b>Prevertebral Space</b>                | <b>27 (20.0)</b>    | <b>24 (22.6)</b>             | <b>3 (10.3)</b>              | <b>0.142</b> |
| <b>Prestyloid Parapharyngeal Space</b>   | <b>19 (14.1)</b>    | <b>13 (12.3)</b>             | <b>6 (20.7)</b>              | <b>0.193</b> |
| <b>Hypoglossal Foramen</b>               | <b>12 (8.9)</b>     | <b>9 (8.5)</b>               | <b>3 (10.3)</b>              | <b>0.498</b> |
| <b>Foramen Magnum</b>                    | <b>4 (3.0)</b>      | <b>3 (2.8)</b>               | <b>1 (3.4)</b>               | <b>0.625</b> |
| <b>Parotid Space</b>                     | <b>2 (1.5)</b>      | <b>1 (0.9)</b>               | <b>1 (3.4)</b>               | <b>0.385</b> |
| <b>Retropharyngeal Space</b>             | <b>1 (0.7)</b>      | <b>0 (0.0)</b>               | <b>1 (3.4)</b>               | <b>0.215</b> |
| <b>Side</b>                              |                     |                              |                              | <b>0.845</b> |
| <b>Left</b>                              | <b>69 (56.6)</b>    | <b>55 (56.1)</b>             | <b>14 (58.3)</b>             |              |
| <b>Right</b>                             | <b>53 (43.4)</b>    | <b>43 (43.9)</b>             | <b>10 (41.7)</b>             |              |
| <b>Treatment</b>                         |                     |                              |                              |              |
| <b>Surgical</b>                          | <b>24 (18.3)</b>    | <b>17 (16.3)</b>             | <b>7 (25.9)</b>              | <b>0.190</b> |
| <b>Conservative</b>                      | <b>73 (55.7)</b>    | <b>58 (55.8)</b>             | <b>15 (55.6)</b>             | <b>0.984</b> |
| <b>Radiotherapy</b>                      | <b>23 (17.6)</b>    | <b>16 (15.4)</b>             | <b>7 (25.9)</b>              | <b>0.158</b> |
| <b>Endovascular</b>                      | <b>7 (5.3)</b>      | <b>4 (3.8)</b>               | <b>3 (11.1)</b>              | <b>0.135</b> |

|                                      |                  |                   |                  |              |
|--------------------------------------|------------------|-------------------|------------------|--------------|
| <b>Chemotherapy</b>                  | <b>5 (3.8)</b>   | <b>1 (1.0)</b>    | <b>4 (14.8)</b>  | <b>0.006</b> |
| <b>Improvement</b>                   |                  |                   |                  | <b>0.103</b> |
| <b>Total</b>                         | <b>22 (23.4)</b> | <b>16 (21.3)</b>  | <b>6 (31.6)</b>  |              |
| <b>Partial</b>                       | <b>54 (57.4)</b> | <b>47 (62.7)</b>  | <b>7 (36.8)</b>  |              |
| <b>None</b>                          | <b>18 (19.1)</b> | <b>12 (16.0)</b>  | <b>6 (31.6)</b>  |              |
| <b>Sympathetic</b>                   | <b>5 (3.7)</b>   | <b>1 (1.0)</b>    | <b>4 (14.3)</b>  | <b>0.007</b> |
| <b>Follow up</b>                     | <b>65 (87.8)</b> | <b>49 (87.5)</b>  | <b>16 (88.9)</b> | <b>0.621</b> |
| <b>Signs and Symptoms</b>            |                  |                   |                  |              |
| <b>Dysphagia</b>                     | <b>92 (68.1)</b> | <b>76 (71.70)</b> | <b>16 (55.2)</b> | <b>0.365</b> |
| <b>Hoarseness or Dysphonia</b>       | <b>78 (57.8)</b> | <b>67 (63.21)</b> | <b>11 (37.9)</b> | <b>0.812</b> |
| <b>Tongue Weakness or Deviation</b>  | <b>60 (44.4)</b> | <b>50 (47.17)</b> | <b>10 (34.5)</b> | <b>0.606</b> |
| <b>Palate deviation or paralysis</b> | <b>54 (40.0)</b> | <b>44 (41.51)</b> | <b>10 (34.5)</b> | <b>0.863</b> |
| <b>Trapezius Weakness</b>            | <b>48 (35.6)</b> | <b>39 (36.79)</b> | <b>9 (31.0)</b>  | <b>0.679</b> |
| <b>Paralysis of the vocal cord</b>   | <b>43 (31.8)</b> | <b>33 (31.13)</b> | <b>10 (34.5)</b> | <b>0.508</b> |
| <b>Gag reflex absent</b>             | <b>42 (31.1)</b> | <b>34 (32.08)</b> | <b>8 (27.6)</b>  | <b>0.800</b> |
| <b>Dysarthria</b>                    | <b>37 (27.4)</b> | <b>30 (28.30)</b> | <b>7 (24.1)</b>  | <b>0.779</b> |
| <b>Weak Sternocleidomastoid</b>      | <b>31 (23.0)</b> | <b>27 (25.47)</b> | <b>4 (13.8)</b>  | <b>0.894</b> |
| <b>Tongue atrophy</b>                | <b>28 (20.7)</b> | <b>20 (18.87)</b> | <b>8 (27.6)</b>  | <b>0.494</b> |
| <b>Sternocleidomastoid atrophy</b>   | <b>15 (11.1)</b> | <b>11 (10.38)</b> | <b>4 (13.8)</b>  | <b>0.860</b> |
| <b>Shoulder weakness</b>             | <b>13 (9.6)</b>  | <b>10 (9.43)</b>  | <b>3 (10.3)</b>  | <b>0.737</b> |
| <b>Trapezius atrophy</b>             | <b>13 (9.6)</b>  | <b>9 (8.49)</b>   | <b>4 (13.8)</b>  | <b>0.864</b> |
| <b>Loss sensation larynx</b>         | <b>9 (6.7)</b>   | <b>7 (6.60)</b>   | <b>2 (6.9)</b>   | <b>0.673</b> |
| <b>Tongue Fasciculations</b>         | <b>9 (6.7)</b>   | <b>7 (6.60)</b>   | <b>2 (6.9)</b>   | <b>0.589</b> |
| <b>Taste impairment</b>              | <b>5 (3.7)</b>   | <b>5 (4.72)</b>   | <b>0 (0.0)</b>   | <b>0.424</b> |

\* Median (IQR)

**Table 2.**  
**Anatomic Space**  
**and General**  
**Cause**

| Anatomic Space                    | Tumor     | Vascular  | Trauma    | Infectious* | Iatrogenic | Congenital | Total     |
|-----------------------------------|-----------|-----------|-----------|-------------|------------|------------|-----------|
|                                   | N (%)     | N (%)     | N (%)     | N (%)       | N (%)      | N (%)      | N (%)     |
| Jugular Foramen                   | 32 (53.3) | 12 (20.0) | 11 (18.3) | 3 (5.0)     | 2 (3.3)    | 0 (0.0)    | 60 (44.4) |
| Parapharyngeal Retrostyloid Space | 5 (12.8)  | 24 (61.5) | 4 (10.3)  | 2 (5.1)     | 2 (5.1)    | 2 (5.1)    | 39 (28.9) |
| Prevertebral Space                | 6 (22.2)  | 0 (0.0)   | 20 (74.0) | 1 (3.7)     | 0 (0.0)    | 0 (0.0)    | 27 (20.0) |
| Prestyloid Parapharyngeal Space   | 11 (57.9) | 3 (15.8)  | 2 (10.5)  | 0 (0.0)     | 2 (10.5)   | 1 (5.3)    | 19 (14.1) |
| Hypoglossal Foramen               | 8 (66.7)  | 1 (8.3)   | 2 (16.7)  | 1 (8.3)     | 0 (0.0)    | 0 (0.0)    | 12 (8.9)  |
| Foramen Magnum                    | 2 (50.0)  | 0 (0.0)   | 1 (25.0)  | 1 (25.0)    | 0 (0.0)    | 0 (0.0)    | 4 (3.0)   |
| Parotid Space                     | 2 (100.0) | 0 (0.0)   | 0 (0.0)   | 0 (0.0)     | 0 (0.0)    | 0 (0.0)    | 2 (1.5)   |
| Retropharyngeal Space             | 1 (100.0) | 0 (0.0)   | 0 (0.0)   | 0 (0.0)     | 0 (0.0)    | 0 (0.0)    | 1 (0.7)   |

**Note:** Cases could present with one or more spaces affected simultaneously

**\*Not including viral infection**

**Table 3. Additional cranial nerve impairment**

|               |  |
|---------------|--|
| Cranial Nerve |  |
|---------------|--|

|                                |                  |
|--------------------------------|------------------|
| <b>Facial Nerve</b>            | <b>17 (12.6)</b> |
| <b>Vestibulocochlear Nerve</b> | <b>8 (5.9)</b>   |
| <b>Trochlear Nerve</b>         | <b>3 (2.2)</b>   |
| <b>Trigeminal Nerve</b>        | <b>2 (1.5)</b>   |
| <b>Abducens Nerve</b>          | <b>2 (1.5)</b>   |
| <b>Oculomotor Nerve</b>        | <b>1 (0.8)</b>   |
| <b>Optic Nerve</b>             | <b>1 (0.8)</b>   |

## APPENDIX

| <b>Appendix 1. Selected Studies</b>         |             |                             |                        |
|---------------------------------------------|-------------|-----------------------------|------------------------|
| <b>Author</b>                               | <b>Year</b> | <b>Publication Type</b>     | <b>Number of Cases</b> |
| <b>Ordoñez-Granja et al <sup>[81]</sup></b> | <b>2020</b> | <b>Article</b>              | <b>1</b>               |
| <b>Shahrkini et al <sup>[109]</sup></b>     | <b>2020</b> | <b>Article</b>              | <b>1</b>               |
| <b>Ganesh et al <sup>[35]</sup></b>         | <b>2019</b> | <b>Article</b>              | <b>1</b>               |
| <b>Simões et al <sup>[115]</sup></b>        | <b>2019</b> | <b>Article</b>              | <b>1</b>               |
| <b>Dey et al <sup>[25]</sup></b>            | <b>2019</b> | <b>Article</b>              | <b>1</b>               |
| <b>Krishnan et al <sup>[54]</sup></b>       | <b>2019</b> | <b>Article</b>              | <b>1</b>               |
| <b>Zamudio Moya et al <sup>[136]</sup></b>  | <b>2019</b> | <b>Letter to the editor</b> | <b>1</b>               |
| <b>Komune et al <sup>[53]</sup></b>         | <b>2019</b> | <b>Conference Abstract</b>  | <b>1</b>               |
| <b>Behravesht et al <sup>[10]</sup></b>     | <b>2019</b> | <b>Conference Abstract</b>  | <b>1</b>               |
| <b>Subha et al <sup>[118]</sup></b>         | <b>2018</b> | <b>Article</b>              | <b>1</b>               |
| <b>Saliou et al <sup>[99]</sup></b>         | <b>2018</b> | <b>Article</b>              | <b>1</b>               |
| <b>Erben et al <sup>[28]</sup></b>          | <b>2018</b> | <b>Article</b>              | <b>1</b>               |
| <b>Peters et al <sup>[86]</sup></b>         | <b>2018</b> | <b>Article</b>              | <b>1</b>               |
| <b>Oushy et al <sup>[83]</sup></b>          | <b>2018</b> | <b>Article</b>              | <b>1</b>               |
| <b>Sanchez-Lars et al<sup>[100]</sup></b>   | <b>2017</b> | <b>Letter to the editor</b> | <b>1</b>               |
| <b>Mayer et al <sup>[70]</sup></b>          | <b>2017</b> | <b>Article</b>              | <b>1</b>               |
| <b>Barbiero et al <sup>[7]</sup></b>        | <b>2017</b> | <b>Article</b>              | <b>1</b>               |
| <b>Neo et al <sup>[76]</sup></b>            | <b>2017</b> | <b>Article</b>              | <b>1</b>               |

|                                             |             |                             |          |
|---------------------------------------------|-------------|-----------------------------|----------|
| <b>Kang et al <sup>[49]</sup></b>           | <b>2016</b> | <b>Article</b>              | <b>1</b> |
| <b>Schuster et al <sup>[105]</sup></b>      | <b>2016</b> | <b>Conference Abstract</b>  | <b>1</b> |
| <b>Jaiswal et al <sup>[46]</sup></b>        | <b>2016</b> | <b>Article</b>              | <b>1</b> |
| <b>Neo et al <sup>[76]</sup></b>            | <b>2016</b> | <b>Conference Abstract</b>  | <b>2</b> |
| <b>Schuster et al <sup>[106]</sup></b>      | <b>2016</b> | <b>Conference Abstract</b>  | <b>1</b> |
| <b>Mnari et al <sup>[71]</sup></b>          | <b>2016</b> | <b>Article</b>              | <b>1</b> |
| <b>Domenicucci et al <sup>[27]</sup></b>    | <b>2015</b> | <b>Article</b>              | <b>1</b> |
| <b>Rebattu et al <sup>[93]</sup></b>        | <b>1925</b> | <b>Article</b>              | <b>1</b> |
| <b>Bolender et al <sup>[12]</sup></b>       | <b>1978</b> | <b>Article</b>              | <b>1</b> |
| <b>Young et al <sup>[134]</sup></b>         | <b>1992</b> | <b>Article</b>              | <b>1</b> |
| <b>Legros et al <sup>[63]</sup></b>         | <b>2000</b> | <b>Article</b>              | <b>1</b> |
| <b>Caroli et al <sup>[17]</sup></b>         | <b>2005</b> | <b>Article</b>              | <b>1</b> |
| <b>Kwon et al<sup>[57]</sup></b>            | <b>2011</b> | <b>Article</b>              | <b>1</b> |
| <b>Gutierrez Rios et al <sup>[38]</sup></b> | <b>2015</b> | <b>Letter to the editor</b> | <b>1</b> |
| <b>Yüce et al <sup>[135]</sup></b>          | <b>2015</b> | <b>Article</b>              | <b>1</b> |
| <b>Barna et al <sup>[7]</sup></b>           | <b>2015</b> | <b>Article</b>              | <b>1</b> |
| <b>Taga-Senirli et al<sup>[119]</sup></b>   | <b>2014</b> | <b>Article</b>              | <b>1</b> |
| <b>Nunes et al <sup>[77]</sup></b>          | <b>2013</b> | <b>Conference Abstract</b>  | <b>1</b> |
| <b>Oliveira et al <sup>[79]</sup></b>       | <b>2013</b> | <b>Conference Abstract</b>  | <b>1</b> |
| <b>Zelenak et al <sup>[137]</sup></b>       | <b>2013</b> | <b>Article</b>              | <b>1</b> |
| <b>Mayer et al <sup>[70]</sup></b>          | <b>2017</b> | <b>Article</b>              | <b>2</b> |
| <b>Smith et al <sup>[116]</sup></b>         | <b>2013</b> | <b>Article</b>              | <b>1</b> |
| <b>Khalid et al <sup>[50]</sup></b>         | <b>2013</b> | <b>Article</b>              | <b>1</b> |
| <b>Dettling et al <sup>[24]</sup></b>       | <b>2013</b> | <b>Article</b>              | <b>1</b> |
| <b>Climans et al <sup>[19]</sup></b>        | <b>2013</b> | <b>Letter to the editor</b> | <b>1</b> |
| <b>Lakshminaray et al <sup>[59]</sup></b>   | <b>2013</b> | <b>Conference Abstract</b>  | <b>1</b> |
| <b>Tanaka et al <sup>[120]</sup></b>        | <b>2012</b> | <b>Conference Abstract</b>  | <b>1</b> |
| <b>Hayward et al <sup>[43]</sup></b>        | <b>2012</b> | <b>Article</b>              | <b>1</b> |
| <b>Rajput et al <sup>[90]</sup></b>         | <b>2011</b> | <b>Article</b>              | <b>1</b> |

|                                            |             |                             |          |
|--------------------------------------------|-------------|-----------------------------|----------|
| <b>Petrović et al <sup>[87]</sup></b>      | <b>2011</b> | <b>Article</b>              | <b>1</b> |
| <b>Opie et al <sup>[80]</sup></b>          | <b>2010</b> | <b>Article</b>              | <b>1</b> |
| <b>Battaglia et al <sup>[9]</sup></b>      | <b>2009</b> | <b>Article</b>              | <b>1</b> |
| <b>Sibai et al <sup>[112]</sup></b>        | <b>2009</b> | <b>Article</b>              | <b>1</b> |
| <b>Lee et al <sup>[61]</sup></b>           | <b>2009</b> | <b>Article</b>              | <b>1</b> |
| <b>Romero Muñoz et al <sup>[96]</sup></b>  | <b>2009</b> | <b>Conference Abstract</b>  | <b>1</b> |
| <b>Lucato et al <sup>[67]</sup></b>        | <b>2008</b> | <b>Article</b>              | <b>1</b> |
| <b>Erol et al <sup>[30]</sup></b>          | <b>2007</b> | <b>Article</b>              | <b>1</b> |
| <b>Chacon et al <sup>[18]</sup></b>        | <b>2006</b> | <b>Article</b>              | <b>1</b> |
| <b>Basu et al <sup>[8]</sup></b>           | <b>2006</b> | <b>Article</b>              | <b>1</b> |
| <b>Mohr et al <sup>[73]</sup></b>          | <b>2006</b> | <b>Article</b>              | <b>1</b> |
| <b>Shine et al<sup>[111]</sup></b>         | <b>2005</b> | <b>Article</b>              | <b>1</b> |
| <b>Garcia-Escriva et al<sup>[34]</sup></b> | <b>2005</b> | <b>Article</b>              | <b>1</b> |
| <b>Jimenez-Caballero<sup>[47]</sup></b>    | <b>2004</b> | <b>Article</b>              | <b>1</b> |
| <b>Hsu et al <sup>[45]</sup></b>           | <b>2004</b> | <b>Article</b>              | <b>1</b> |
| <b>Rao et al <sup>[91]</sup></b>           | <b>2004</b> | <b>Article</b>              | <b>1</b> |
| <b>Walker et al<sup>[130]</sup></b>        | <b>2003</b> | <b>Article</b>              | <b>1</b> |
| <b>Willy et al <sup>[132]</sup></b>        | <b>2003</b> | <b>Article</b>              | <b>1</b> |
| <b>Paparounas et al<sup>[84]</sup></b>     | <b>2003</b> | <b>Article</b>              | <b>1</b> |
| <b>Heckmann et al <sup>[44]</sup></b>      | <b>2000</b> | <b>Letter to the editor</b> | <b>1</b> |
| <b>Schmidt et al <sup>[103]</sup></b>      | <b>2000</b> | <b>Article</b>              | <b>2</b> |
| <b>Satoh et al <sup>[101]</sup></b>        | <b>2000</b> | <b>Article</b>              | <b>1</b> |
| <b>Connolly et al <sup>[22]</sup></b>      | <b>2000</b> | <b>Article</b>              | <b>1</b> |
| <b>Rüegg et al <sup>[97]</sup></b>         | <b>1999</b> | <b>Article</b>              | <b>1</b> |
| <b>Krystkowiak et al <sup>[55]</sup></b>   | <b>1998</b> | <b>Article</b>              | <b>1</b> |
| <b>Larson et al <sup>[60]</sup></b>        | <b>1997</b> | <b>Article</b>              | <b>1</b> |
| <b>Rees et al<sup>[94]</sup></b>           | <b>1997</b> | <b>Article</b>              | <b>1</b> |
| <b>Tappin et al<sup>[121]</sup></b>        | <b>1996</b> | <b>Article</b>              | <b>1</b> |
| <b>Ruiz et al <sup>[98]</sup></b>          | <b>1995</b> | <b>Article</b>              | <b>1</b> |

|                                           |             |                             |          |
|-------------------------------------------|-------------|-----------------------------|----------|
| <b>Kurebayashi et al <sup>[56]</sup></b>  | <b>1995</b> | <b>Article</b>              | <b>3</b> |
| <b>Comacchio et al<sup>[21]</sup></b>     | <b>1995</b> | <b>Article</b>              | <b>1</b> |
| <b>Sharma et al <sup>[110]</sup></b>      | <b>1994</b> | <b>Article</b>              | <b>1</b> |
| <b>Prick et al<sup>[88]</sup></b>         | <b>1992</b> | <b>Letter to the editor</b> | <b>1</b> |
| <b>Wani et al <sup>[131]</sup></b>        | <b>1991</b> | <b>Article</b>              | <b>1</b> |
| <b>Silvestrini et al <sup>[114]</sup></b> | <b>1991</b> | <b>Article</b>              | <b>1</b> |
| <b>Sehitoglu et al <sup>[108]</sup></b>   | <b>1990</b> | <b>Article</b>              | <b>1</b> |
| <b>Moss et al<sup>[74]</sup></b>          | <b>1989</b> | <b>Article</b>              | <b>1</b> |
| <b>Arita et al<sup>[5]</sup></b>          | <b>1989</b> | <b>Article</b>              | <b>1</b> |
| <b>Waespe et al<sup>[129]</sup></b>       | <b>1988</b> | <b>Article</b>              | <b>1</b> |
| <b>Hashimoto et al <sup>[41]</sup></b>    | <b>1988</b> | <b>Article</b>              | <b>1</b> |
| <b>Di Stasi et al <sup>[26]</sup></b>     | <b>1986</b> | <b>Article</b>              | <b>1</b> |
| <b>Malin et al<sup>[69]</sup></b>         | <b>1984</b> | <b>Conference Abstract</b>  | <b>1</b> |
| <b>Havelius et al<sup>[42]</sup></b>      | <b>1982</b> | <b>Article</b>              | <b>1</b> |
| <b>Nagata et al <sup>[75]</sup></b>       | <b>1980</b> | <b>Article</b>              | <b>1</b> |
| <b>Mohanty et al<sup>[72]</sup></b>       | <b>1973</b> | <b>Article</b>              | <b>1</b> |
| <b>Tomio et al<sup>[124]</sup></b>        | <b>1991</b> | <b>Article</b>              | <b>1</b> |
| <b>Olazabal et al <sup>[78]</sup></b>     | <b>2014</b> | <b>Article</b>              | <b>1</b> |
| <b>Evan et al <sup>[32]</sup></b>         | <b>2021</b> | <b>Article</b>              | <b>1</b> |
| <b>Arasawa et al <sup>[4]</sup></b>       | <b>2020</b> | <b>Article</b>              | <b>1</b> |
| <b>Lian et al <sup>[64]</sup></b>         | <b>2020</b> | <b>Article</b>              | <b>1</b> |
| <b>Schuster et al <sup>[105]</sup></b>    | <b>2015</b> | <b>Article</b>              | <b>1</b> |
| <b>Rath et al<sup>[92]</sup></b>          | <b>2014</b> | <b>Conference Abstract</b>  | <b>1</b> |
| <b>Amar et al <sup>[3]</sup></b>          | <b>2012</b> | <b>Article</b>              | <b>1</b> |
| <b>Villatoro et al <sup>[128]</sup></b>   | <b>2011</b> | <b>Article</b>              | <b>1</b> |
| <b>Prashant et al <sup>[88]</sup></b>     | <b>2003</b> | <b>Article</b>              | <b>1</b> |
| <b>Kobayashi et al <sup>[51]</sup></b>    | <b>1981</b> | <b>Article</b>              | <b>1</b> |
| <b>Otto et al <sup>[82]</sup></b>         | <b>2001</b> | <b>Article</b>              | <b>1</b> |
| <b>Schattner et al <sup>[102]</sup></b>   | <b>2009</b> | <b>Article</b>              | <b>1</b> |

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|-----------------------------------------------|-------------|----------------------------|----------|
| <b>Schweinfurth et al <sup>[107]</sup></b>    | <b>1993</b> | <b>Article</b>             | <b>1</b> |
| <b>Wilson et al <sup>[133]</sup></b>          | <b>1984</b> | <b>Article</b>             | <b>1</b> |
| <b>Amar et al <sup>[3]</sup></b>              | <b>2020</b> | <b>Article</b>             | <b>1</b> |
| <b>Cabreira et al <sup>[16]</sup></b>         | <b>2020</b> | <b>Article</b>             | <b>1</b> |
| <b>Lee et al <sup>[62]</sup></b>              | <b>2017</b> | <b>Article</b>             | <b>1</b> |
| <b>Handley et al <sup>[40]</sup></b>          | <b>2010</b> | <b>Article</b>             | <b>1</b> |
| <b>Low et al <sup>[66]</sup></b>              | <b>2018</b> | <b>Article</b>             | <b>1</b> |
| <b>Al-Shabibi et al <sup>[2]</sup></b>        | <b>2021</b> | <b>Article</b>             | <b>1</b> |
| <b>Sokhi et al <sup>[117]</sup></b>           | <b>2021</b> | <b>Article</b>             | <b>1</b> |
| <b>Utheim et al <sup>[126]</sup></b>          | <b>2015</b> | <b>Article</b>             | <b>1</b> |
| <b>Erkan et al <sup>[29]</sup></b>            | <b>2016</b> | <b>Article</b>             | <b>1</b> |
| <b>Cugy et al <sup>[23]</sup></b>             | <b>2014</b> | <b>Conference Abstract</b> | <b>3</b> |
| <b>Liu et al <sup>[65]</sup></b>              | <b>2004</b> | <b>Article</b>             | <b>1</b> |
| <b>Pelliccioni et al <sup>[4]</sup></b>       | <b>1995</b> | <b>Conference Abstract</b> | <b>3</b> |
| <b>Olazabal et al <sup>[78]</sup></b>         | <b>2014</b> | <b>Article</b>             | <b>1</b> |
| <b>Bravo et al <sup>[13]</sup></b>            | <b>2018</b> | <b>Article</b>             | <b>1</b> |
| <b>Fidelis de Souza et al <sup>[33]</sup></b> | <b>2018</b> | <b>Article</b>             | <b>1</b> |
| <b>Krystkowiak et al <sup>[55]</sup></b>      | <b>1998</b> | <b>Article</b>             | <b>1</b> |
| <b>Collet <sup>[20]</sup></b>                 | <b>1915</b> | <b>Article</b>             | <b>1</b> |
| <b>Sicard <sup>[113]</sup></b>                | <b>1916</b> | <b>Article</b>             | <b>1</b> |
| <b>Benavides et al <sup>[11]</sup></b>        | <b>2021</b> | <b>Conference Abstract</b> | <b>1</b> |