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Review Article

## Secretary carcinoma in labial minor salivary gland of pediatric patients. A systematic Review.

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### ABSTRACT

#### Background:

Secretary carcinoma (SC), formerly referred to as mammary analogue secretary carcinoma (MASC), is a rare malignant salivary gland neoplasm most frequently identified in the parotid gland but also reported in minor salivary glands. It is strongly associated with the ETV6:NTRK3 fusion, which has therapeutic implications due to the advent of TRK inhibitors. Pediatric SC is exceedingly rare, with even fewer cases reported in the labial minor salivary glands, making systematic analysis crucial.

#### Objective:

To synthesize available evidence on pediatric SC of the labial minor salivary glands, focusing on presentation, diagnosis, management, and outcomes.

#### Methods:

Electronic databases (PubMed, Scopus, Google Scholar) were searched until 2025. Studies were included if they described SC of the labial minor salivary glands in patients aged  $\leq 18$  years with histopathologic and immunohistochemical confirmation. Two case reports met the inclusion criteria.

#### Results:

Both patients presented with upper lip masses. A 9-year-old girl had a well-circumscribed, 2 cm lesion confirmed as SC (CK7+, mammaglobin+, S100+); managed by excision with margin extension, she remained disease-free at 36 months. A 17-year-old male had a high-grade SC of the philtrum with nodal metastasis, treated by wide excision, bilateral selective neck dissection, and adjuvant chemoradiotherapy; he remained disease-free at 6 months. Both tumors displayed classical SC morphology, though molecular fusion testing was not universally performed.

#### Conclusions:

Pediatric labial SC is exceptionally rare but clinically significant. It should be considered in the differential diagnosis of circumscribed pediatric lip nodules. Management is primarily surgical, with aggressive multimodal therapy indicated for high-risk disease. Awareness is vital to avoid misdiagnosis as acinic cell carcinoma and to facilitate timely recognition of ETV6-NTRK3 fusions, which may enable targeted therapies.

**Keywords:** Secretary carcinoma, labial minor salivary glands, pediatric patients.

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## INTRODUCTION

Secretory carcinoma (SC) of the salivary glands is a recently recognized malignant neoplasm that has gained attention due to its distinctive histologic appearance and recurrent gene fusion<sup>[1]</sup>. Originally described by Skálová and colleagues, it was initially termed mammary analogue secretory carcinoma (MASC) because of its morphologic and immunohistochemical resemblance to secretory carcinoma of the breast<sup>[2]</sup>. World Health Organization (WHO) formally adopted the term secretory carcinoma<sup>[3]</sup>, and the 2022 fifth edition of the WHO Classification reaffirmed its status as a distinct diagnostic entity<sup>[4]</sup>.

Histologically, SC is characterized by microcystic, tubular, and papillary growth patterns, often containing abundant intracellular and extracellular eosinophilic secretions that are periodic acid-Schiff–diastase (PAS-D) positive<sup>[5]</sup>. Immunohistochemistry (IHC) typically demonstrates strong and diffuse positivity for S100 protein, mammaglobin, and cytokeratin 7 (CK7), while being negative for DOG1, distinguishing it from acinic cell carcinoma (AcICC). This immunoprofile is highly supportive of the diagnosis, particularly when coupled with morphology<sup>[4]</sup>.

At the molecular level, SC is defined by the ETV6::NTRK3 translocation, resulting from the t (12;15)(p13;q25) chromosomal rearrangement. This gene fusion activates tyrosine kinase signaling pathways, driving oncogenesis. Less common ETV6 partners, including RET, MAML3, and MET, have also been described<sup>[1,7]</sup>. The molecular profile is not only diagnostically valuable but also therapeutically relevant, as NTRK fusion–positive tumors are targetable with TRK inhibitors such as larotrectinib and entrectinib, which are approved for pediatric use in advanced or unresectable disease<sup>[8]</sup>.

From an epidemiological perspective, SC is rare, accounting for less than 0.3% of all salivary gland malignancies<sup>[9]</sup>. The majority of cases occur in adults, with a predilection for the parotid gland, followed by other major and minor salivary gland sites<sup>[10]</sup>. Pediatric SC is even more uncommon, with only a handful of cases reported globally. A systematic review in 2021 identified just 13 pediatric cases, most involving the parotid gland and only a single case in the buccal mucosa. Importantly, no pediatric labial cases were recorded at that time, underscoring the rarity of this presentation<sup>[10,11]</sup>.

The involvement of labial minor salivary glands is exceedingly rare in both adults and children. Adult lip cases have been described, including those by Kratochvil et al<sup>[12]</sup>, but pediatric reports only began to emerge recently. These

cases broaden the clinical spectrum of pediatric SC and highlight the need for awareness of this rare entity in children presenting with lip nodules.

Clinically, SC often presents as a slowly enlarging, painless mass, which can mimic benign salivary tumors or inflammatory lesions. Without careful histopathologic evaluation and IHC confirmation, misdiagnosis as acinic cell carcinoma or mucoepidermoid carcinoma is possible, potentially leading to inappropriate management. Recognizing SC is particularly critical in children, where surgical morbidity and long-term treatment implications must be weighed carefully<sup>[13]</sup>.

Given the rarity of SC in pediatric labial minor salivary glands and the emerging significance of targeted therapy in fusion-positive tumors, synthesizing available evidence is essential. This systematic review aims to consolidate the clinical, diagnostic, and therapeutic characteristics of pediatric labial SC to support clinicians in timely recognition and optimal management of this rare malignancy.

## MATERIALS AND METHODS

This systematic review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines<sup>[14]</sup> (Figure 1). The review protocol was prospectively registered with PROSPERO (Registration ID: CRD420251134650). A comprehensive search strategy was applied to identify all published reports of secretory carcinoma (SC) arising in labial minor salivary glands of pediatric patients.

### Search strategy and information sources

Electronic databases, including PubMed/MEDLINE, Scopus, Google Scholar, and Web of Science, were systematically searched from inception until 2025. The search terms combined both free-text keywords and controlled vocabulary (MeSH terms where applicable) and included the following: “secretory carcinoma”, “MASC”, “mammary analogue secretory carcinoma”, “ETV6-NTRK3”, “labial”, “lip”, “minor salivary glands”, “pediatric”, “child”, and “adolescent”. Boolean operators “AND” and “OR” were used to combine terms. Reference lists of included studies and relevant reviews were also manually screened to ensure no additional eligible studies were missed.



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presentation, tumour site and size, histology and IHC profile, molecular confirmation where available, treatment modality, use of adjuvant therapy, and follow-up outcomes. Given the rarity of cases and descriptive nature of available evidence, a qualitative synthesis was performed instead of meta-analysis. Data extraction was performed by two reviewers working independently. Each reviewer extracted all variables from the eligible reports using a predefined form. Extracted data were cross-checked, and disagreements were resolved through discussion.

The primary outcomes were clinical characteristics (site, size, duration of symptoms), diagnostic findings (histology, immunohistochemistry, molecular testing), treatment modality, and follow-up outcomes, including recurrence or metastasis. Additional variables extracted included patient age, sex, tumor grade, and margin status. All available information corresponding to these domains was recorded from each study. Other extracted variables included patient age, sex, presenting symptoms, tumor grade, when reported, margin status, and complications. All available results that corresponded to these domains were collected from each study.

### Effect Measures

Given that all eligible reports were descriptive case reports, no effect measures such as risk ratios or mean differences were applicable. Findings were synthesized narratively.

### Risk of bias

As evidence was limited to case reports, the risk of bias was qualitatively assessed using **CARE guidelines** for case reporting (clarity, completeness, diagnostic rigor).

### Study selection

All titles and abstracts were independently screened by two reviewers to identify potentially relevant reports. The full texts of shortlisted articles were then retrieved and evaluated for eligibility. Disagreements were resolved through discussion and consensus.

### Inclusion criteria

- Pediatric patients (age  $\leq 18$  years).
- Primary diagnosis of secretory carcinoma involving the labial minor salivary glands (upper or lower lip, philtrum).
- Histopathologic confirmation of SC with supportive immunohistochemistry (e.g., S100, mammaglobin, CK7) and/or molecular testing for ETV6 fusions.
- Case reports, case series, and observational studies published in English.

### Exclusion criteria

- SC is located in non-labial sites (parotid, buccal mucosa, palate, submandibular gland, etc.).
- Studies without sufficient diagnostic evidence (absence of histopathology or immunohistochemistry).
- Non-original articles such as reviews, editorials, or conference abstracts without full clinical data.

### Data extraction and synthesis

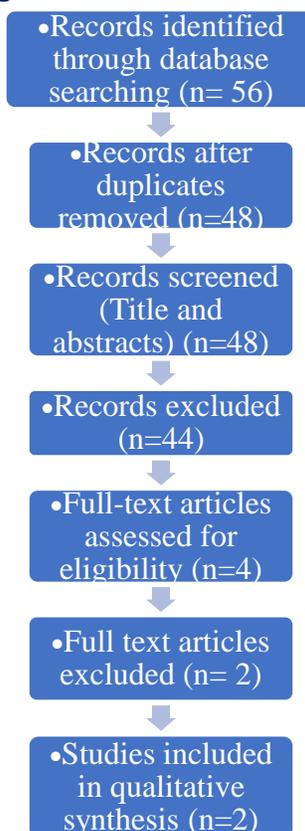
Data from each eligible study were extracted into a structured table, including patient demographics, clinical

## RESULTS

### Case identification



**Figure 1: PRISMA Flowchart**



Two reports met eligibility criteria:

1. **De Melo et al. (2025)**<sup>[15]</sup> – 9-year-old girl, upper lip SC.
2. **Asuquo et al. (2024)**<sup>[16]</sup> – 17-year-old male, philtrum SC.



**Table 1: Case characteristics**

Author (Year)	Study	Age/Sex	Site	Size	Histology/IHC	Molecular Testing	Treatment	Adjuvant	Follow-up/Outcome
De Melo et al. (2025) <sup>[15]</sup>	Secretory Carcinoma in a Labial Minor Salivary Gland of a Pediatric Patient.	9/F	Upper lip	2 cm	Microcystic nests, eosinophilic PAS-D+ secretions; CK7+, S100+, mammaglobin+	Not reported	Excision + margin extension	None	Disease-free, 36 months
Asuquo et al. (2024) <sup>[16]</sup>	Secretory Carcinoma of the Philtrum of the Upper Lip: A Case Study	17/M	Philtrum (upper lip)	~2.5 cm	SC morphology; high-grade; IHC limited due to resource constraints	Not performed	Wide excision + bilateral selective neck dissection	Cisplatin chemoradiotherapy	Disease-free, 6 months

No additional reports met the inclusion criteria, and no full-text articles were excluded after review. The two included patients were 9 and 17 years old. Both tumors involved the upper lip region. The median tumor size was approximately 2 to 2.5 cm. One lesion demonstrated low-grade morphology with no nodal disease, while the second showed high-grade features with cervical lymph node metastasis. Surgical excision was performed in both patients; one required margin extension, and the other underwent bilateral selective neck dissection with adjuvant chemoradiotherapy. At follow-up, both patients remained disease-free, with reported durations of 6 and 36 months.

Synthesis eligibility was determined by comparing each report against the prespecified criteria, including patient age, labial site involvement, diagnostic confirmation, and completeness of clinical information. Only studies fulfilling all criteria were incorporated into the narrative synthesis. Assessment of reporting bias was limited because all available evidence consisted of isolated case reports. Missing information, such as molecular testing, was attributed to incomplete reporting rather than selective outcome omission.

**Table 2 summarizes the clinical features, diagnostic details, treatment approaches, and outcomes of the included cases.**

**Table 2: Summary of Pediatric Secretory Carcinoma Cases by Anatomic Site**

Site (Pediatric)	Age Range (years)	Number of Reported Cases*	Clinical Behavior	Treatment Modalities	Outcomes Reported
Parotid gland	5 – 17	~10–11 (majority of pediatric SC cases)	Mostly indolent, slow-growing; occasional nodal disease	Superficial/total parotidectomy ± selective neck dissection	Favorable in most cases; long-term disease-free survival reported



<b>Buccal mucosa</b>	12	1	Localized, low-grade lesion	Local excision	Disease-free at follow-up
<b>Palate</b>	10–13	1–2	Small, slow-growing nodules; low-grade	Wide local excision	No recurrence reported
<b>Labial (upper lip/philtrum)</b>	9, 17	2 (De Melo 2025; Asuquo 2024)	Variable: one indolent (9F, upper lip, cured with excision), one aggressive (17M, philtrum, high-grade with nodal metastasis)	Local excision ± margin extension; neck dissection + chemoradiotherapy in advanced cases	Indolent case: disease-free at 36 months; aggressive case: disease-free at 6 months (short follow-up)

*\*Based on systematic review by Vasanthi & Ramadoss (2021)<sup>[10]</sup> & recent reports<sup>[15,16]</sup>.*

## DISCUSSION

Secretory carcinoma (SC) is a distinct salivary gland malignancy that has been increasingly recognized since its first description in 2010[1]. Although originally reported in adults, pediatric cases have gradually been documented, though they remain rare. Within this already limited population, tumors arising in the **labial minor salivary glands** are exceptionally uncommon. To date, only two such pediatric cases [15,16] have been described in the literature, both of which were included in this review. By examining these alongside previously reported pediatric SC cases in other salivary sites, important insights into clinical presentation, diagnostic strategies, management, and outcomes can be drawn.

### Clinical presentation and spectrum of disease

Pediatric SCs across all sites most frequently present as **slowly enlarging, painless masses**, often with a history spanning several months [10]. The two labial cases followed this general trend but demonstrated strikingly different biological behaviors. The 9-year-old girl presented with a small, circumscribed nodule of the upper lip and had an indolent course with long-term disease-free survival after conservative surgery [15]. In contrast, the 17-year-old male developed a high-grade tumor in the philtrum with cervical lymph node metastasis, requiring neck dissection and adjuvant chemoradiotherapy [16]. This contrast illustrates the **heterogeneity of pediatric SC**, which can behave either as a low-grade, indolent malignancy or as an aggressive tumor with nodal spread, even within the same anatomic region.

When viewed in the context of broader pediatric SC literature, most reported cases involve the **parotid gland**, followed by isolated occurrences in the **buccal mucosa** and **palate**. These tumors are generally low- to intermediate-grade and managed successfully with surgery, often without

the need for adjuvant therapy [17]. Compared to these, the labial cases highlight that while SC usually follows a favorable course, **aggressive transformation can occur** in pediatric patients, particularly in older adolescents [15].

### Diagnostic considerations

Accurate diagnosis of SC relies on a combination of histomorphology, immunohistochemistry (IHC), and molecular testing [18]. Histologically, both labial cases demonstrated the typical microcystic/tubular growth patterns with PAS-D-positive eosinophilic secretions, which are highly characteristic of SC. Immunohistochemical staining is critical in differentiating SC from morphologic mimics[15,16]. The tumor cells typically express S100, mammaglobin, and CK7, a profile observed in the De Melo case [15]. In contrast, the Asuquo case was diagnosed largely on morphology due to limited IHC and molecular resources [16]. This underscores a significant diagnostic challenge in low-resource settings, where the absence of molecular confirmation may increase the risk of misclassification, especially with acinic cell carcinoma (AciCC), mucoepidermoid carcinoma, or polymorphous adenocarcinoma.

The gold standard remains detection of the ETV6::NTRK3 fusion, present in the majority of cases [19]. Although molecular confirmation was not available for both labial reports, its recognition is vital not only for diagnostic certainty but also for therapeutic decision-making.

### Treatment strategies and outcomes

Surgical excision with negative margins is the mainstay of treatment for pediatric SC across all anatomic sites. In the labial series, the indolent case was successfully treated with simple excision and margin extension, while the high-grade case necessitated bilateral selective neck dissection and adjuvant cisplatin-based chemoradiotherapy. This mirrors



the broader pediatric experience, where surgery alone is usually curative in low-grade tumors, but nodal involvement or high-grade transformation requires more aggressive multimodal management[15,16].

Outcomes for pediatric SC are generally favorable, with long-term disease-free survival reported in most cases. However, the aggressive behavior of the adolescent labial case highlights the need for careful staging and individualized treatment planning. Importantly, follow-up durations in published reports remain relatively short, and late recurrences cannot be excluded.

### Role of targeted therapy

The presence of NTRK gene fusions in SC has significant therapeutic implications. TRK inhibitors such as larotrectinib and entrectinib have shown remarkable efficacy in pediatric patients with NTRK fusion-positive malignancies, often with durable responses and favorable safety profiles[20]. While none of the pediatric SC cases reviewed to date have been treated with targeted agents, molecular confirmation of ETV6::NTRK3 fusions should be pursued wherever possible to preserve this treatment option in recurrent, unresectable, or metastatic disease. This approach may be particularly relevant for aggressive tumors such as the high-grade labial case reported in 2024[16].

### Comparison with adult labial SC

Adult cases of labial SC, first reported in 2010, have generally followed a more indolent course, managed successfully with local excision and demonstrating good outcomes[10]. Pediatric labial tumors appear to share the same morphologic and immunophenotypic features but show a broader biological spectrum, with at least one case demonstrating high-grade transformation and nodal metastasis[15,16]. This raises the possibility that pediatric age, along with tumor grade and nodal status, may influence prognosis more significantly than in adults.

### Summary

In summary, pediatric SC of the labial minor salivary glands is an exceptionally rare but important clinical entity. Its presentation ranges from indolent, circumscribed nodules to high-grade, metastatic disease. Diagnosis requires careful histopathologic and immunohistochemical evaluation, ideally supplemented by molecular confirmation of ETV6 gene fusions. Treatment should be tailored to the disease extent, with conservative excision sufficient for low-grade tumors and multimodal therapy warranted in aggressive

cases. The identification of NTRK fusions highlights the potential of TRK inhibitors as future therapeutic options in children. Greater awareness of this rare tumor will help avoid misdiagnosis and ensure timely, effective management.

### Historical timeline of recognition and classification

- **2010** – Skálová et al. first describe “MASC,” highlighting its morphologic and immunophenotypic overlap with breast secretory carcinoma[2].
- **2011–2013** – Subsequent reports validate MASC as a unique entity, distinct from acinic cell carcinoma (AciCC), despite their clinical and histological similarities.[21,22]
- **2014–2016** – Increasing case reports establish the **ETV6::NTRK3 fusion** as the defining molecular hallmark of MASC, shared with breast secretory carcinoma[23].
- **2017 WHO Classification (4th edition)** – The entity is officially renamed **secretory carcinoma (SC)** of the salivary glands, emphasizing its unique identity[1].
- **2022 WHO Classification (5th edition)** – SC is reaffirmed as a distinct salivary malignancy, with refined diagnostic and molecular criteria, including recognition of variant fusion partners (RET, MAML3, MET)[24].
- **2021 Pediatric Systematic Review** – Vasanthi & Ramadoss compile **13 pediatric SC cases**, almost exclusively in the parotid, noting the absence of labial cases[10].
- **2024–2025** – First pediatric **labial SC cases** are reported: a **17-year-old male** with a high-grade philtral tumor and a **9-year-old girl** with a low-grade upper lip lesion. These represent the **first documented pediatric labial presentations** of SC[15,16].

### Conclusions

Pediatric SC of the labial minor salivary glands is exceedingly rare but clinically important. It presents as a circumscribed lip nodule, often painless, and may be misdiagnosed as acinic cell carcinoma. Correct diagnosis requires a combination of morphology and IHC, supported by molecular testing where available. Surgery achieves good outcomes in localized disease, while high-grade or



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advanced cases may require multimodal therapy. With the identification of ETV6::NTRK3 fusions, TRK inhibitors offer promising therapeutic options in refractory pediatric SC.

### Limitations and future perspectives

The current evidence is limited by the very small number of cases, all of which are **case reports** with variable diagnostic work-up, treatment strategies, and follow-up durations. Publication bias must also be considered, as unusual or aggressive cases are more likely to be reported. Future research should focus on the development of **multi-institutional registries** or collaborative case series to aggregate pediatric SC cases across anatomic sites. This would enable a clearer understanding of prognostic factors, refine treatment protocols, and assess the long-term role of molecular-targeted therapies in this rare disease.

### Clinical Recommendations

- **Maintain suspicion** of SC in pediatric labial nodules.
- **Perform IHC** with S100, mammaglobin, CK7; exclude AcicC with DOG1.
- **Order ETV6 fusion testing** where feasible to confirm diagnosis and establish eligibility for TRK inhibitors.
- **Surgical excision** with negative margins is the mainstay of therapy.
- **Neck management/adjuvant therapy** is indicated for high-grade or metastatic disease.
- **Long-term follow-up** is essential due to the risk of recurrence or late metastasis.

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The study was not funded.

### Conflict of interest.

There is no conflict of interest.

### Availability of data.

Data used in this study are available upon request from the corresponding author.

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