A systematic review of secretory carcinoma of the salivary gland: where are we?

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Objective. The aim of this systematic review was to describe the epidemiology, diagnostic criteria, differential diagnosis, treatment, prognostic factors, and treatment outcomes of secretory carcinoma.

Study Design. A comprehensive search of Lilacs, PubMed, Science Direct, and Web of Science databases was conducted to identify all case reports, letter to the editor, and histopathologic reclassifications regarding salivary gland secretory carcinoma published in English, Spanish, French, and Portuguese.

Results. The final analysis included 119 studies, which totaled 642 secretory carcinoma diagnoses, with 239 case reports and 403 diagnostic reclassifications, mostly in the United States. The age range was 5 to 87 years, and cases were predominantly in males (58.7%) and mostly affecting the parotid glands (73.7%). The disease usually presents as a slow-growing, painless mass. The main differential diagnosis is acinic cell carcinoma, and the tumor is usually treated with surgery. The prognosis is considered favorable, although there have been reports of local recurrences, distant metastases, and deaths.

Conclusions. It is important that clinicians become aware of this salivary gland neoplasm and report clinical data, clinical course, management and long-term follow-up. There is an urgent need to conduct more clinical trials, especially on tropomyosin receptor kinase (TRK) inhibitors and other potential target therapy modalities. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;132: e143–e152)

Skalova et al., in 2010,[1] proposed a new name for tumors of the salivary gland—*mammary analogue secretory carcinoma of salivary glands* (MASC). This tumor is characterized by the presence of a translocation t(12;15)(p13;q25), which leads to fusion of the *ETV6* gene on chromosome 12 and the neurotrophic tropomyosin receptor kinase 3 (*NTRK3*) gene on chromosome 15. Before the initial description, these salivary gland tumors were mostly diagnosed as acinic cell carcinomas (AciCCs) or adenocarcinomas.[2]

The updated *World Health Organization Classification of Head and Neck Tumors* (4th edition, 2017) changed the initial MASC designation, which is now referred to as *secretory carcinoma* (SC), to standardize nomenclature for these tumors occurring at different organ sites.[3] Thus, the aim of this systematic review was to describe the clinical and epidemiologic characteristics, diagnostic criteria, differential diagnosis, treatment, prognostic factors, and treatment outcomes of the SC.

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MATERIALS AND METHODS

Strategy for identification of studies

The strategy for this systematic review was to identify research articles indexed in electronic databases, such as Lilacs, PubMed, Science Direct, and Web of Science. The key term used was "secretory carcinoma of salivary gland," and the search was performed on October 16, 2019. In addition, a manual search was carried out with evaluation of the bibliographies of the selected studies to identify articles that were considered potentially relevant to the topic.

Criteria for selection of studies

Case reports, case series, and letters to the editor, as well as histopathologic reclassification studies in humans, reporting on cases of salivary gland SCs were analyzed. Publications in English, Spanish, French, and Portuguese were considered. Literature reviews or diagnostic tests, studies

Statement of Clinical Relevance

Secretory carcinoma of the salivary gland is a rare malignant neoplasm with an overall favorable prognosis, even though local recurrences, distant metastases, and deaths have been reported. For more aggressive tumors, surgical removal is followed by chemotherapy/target therapy and radiotherapy, alone or in combination.

dealing with primary SC in other locations or in animals, articles in other languages, and articles from before 2010 (year of publication of the first study on SC of the salivary gland[1]) were excluded.

Methods of revising the eligibility criteria for inclusion

The selection of studies was accomplished by a single investigator. The identification was based on titles and abstracts obtained via database search, which resulted in 383 studies (PubMed = 319; Science Direct = 39; Web of Science = 24; and Lilacs = 1). During the selection process, 32 duplicate articles were excluded, and 252 did not meet the pre-established inclusion criteria. Thus, 99 indexed articles were selected for full reading. Of these, 2 were excluded because they were not available for downloading (both were meeting abstracts), and 1 was excluded because it was only available in the Chinese language. Twenty-two articles were identified from verification of cross-references within the article's bibliography, and 1 was excluded because the full text was unavailable. Thus, 119 studies were included for the final analysis (Figure 1).

Extraction and synthesis of data

From the selected studies, information about the country, number of reported cases, diagnostic reclassification, patient gender and age, tumor location and size, symptomatology, time of evolution, treatment received, occurrence of cervical or distant metastases, recurrences, and deaths caused by the tumor were analyzed. Whenever possible, authors were contacted by email to obtain missing data.

RESULTS

A total of 119 studies were analyzed, resulting in the identification of 642 cases of SC (a detailed description of the articles is provided in Supplementary Table I). Of these articles, 74 were case reports (239 cases), and 45 were diagnostic reclassifications (403 cases) (Table I).

Epidemiology

Most cases were reported in the United States,[2,4-49] followed by Japan,[50-64] the Czech Republic,[1,65-67] China,[68-73] the United Kingdom,[74-76] The Netherlands,[77] and South Korea.[78-81] Cases were also reported from Australia,[82-84] Brazil,[85-88] Canada,[89-91] Chile,[92] Ecuador,[93] Finland,[94] France,[95,96] Germany,[97,98] India,[99-102] Iran,[103] Italy,[104] Mexico,[105,106] Pakistan,[107-109] Poland,[110] Singapore,[111-113] South Africa,[114] Spain,[115–117] and Taiwan[118-120] (see Table I).

SC mainly affects people 40 to 50 years of age (average age 45 years),[45,89] and it is quite uncommon in pediatric patients.[20] Just over 30 pediatric cases (individuals less than 18 years of age) have been published.[7,9,12,15,20,24,25,32,38,40,52,55,56,58,60,63,67,76,78,79,89,91,96,100-102,107,108,110,118–120] The youngest patient reported was a 5-year-old girl in the United States,[12] and the oldest was an 87-year-old female in Australia.[83]

From the included studies, 340 (58.7%) male patients and 239 (41.3%) female patients presented with SC (approximate male to female ratio 1.4:1) (Table II). Furthermore, gender information was not provided for 63 cases. With regard to gender distribution, there is no consensus in the literature; however, some authors reported an equal gender distribution,[1,76,82] whereas others observed higher frequency of this tumor in men.[2,31,74,79,89,103] Similarly, Boon et al., reported a male to female ratio of 1.2:1.[77]

Diagnosis

To achieve correct diagnosis of SC, it is essential to rule out other tumors of the salivary gland. SC represents 5% of all malignant salivary gland tumors.[82] The lesion usually presents itself as a painless, slow-growing mass, which the patient may have been aware of for months or perhaps even years before it is finally detected on physical examination.[20] In some cases, the lesions are associated with some degree of

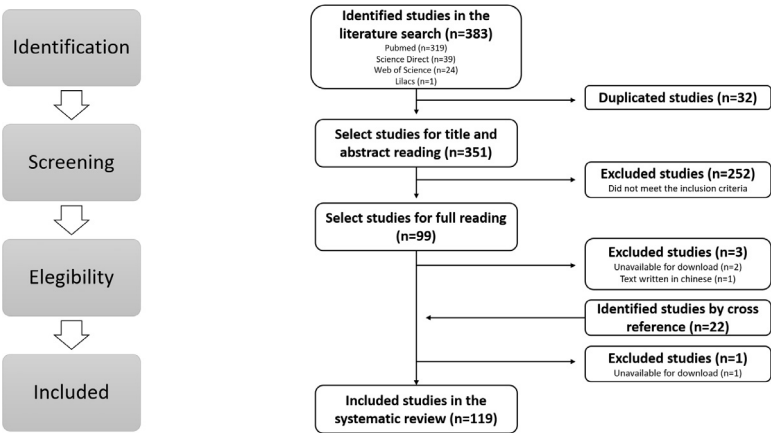

Fig. 1. Criteria of eligibility for articles identified for the systematic review.

Table I. Number of papers and cases of SC published as case reports and diagnostic reclassification studies by country, until October 16, 2019

	Case report		*Diagnostic reclassification*		*Total*	
Country	*No. of articles*	*No. of cases*	*No. of articles*	*No. of cases*	*No. of articles*	*No. of cases*
United States*	33	140	14	130	47	270
Japan	9	9	6	47	15	56
Czech Republic	2	5	2	41	4	46
China	2	2	4	40	6	42
United Kingdom†	1	9	2	26	3	35
The Netherlands‡	0	11	1	20	1	31
South Korea	1	2	3	27	4	29
Canada	2	8	1	13	3	21
Taiwan§	2	10	1	6	3	16
Pakistan‖	2	8	1	6	3	14
Brazil	1	1	3	12	4	13
Australia¶	2	4	1	7	3	11
France**	1	10	1	1	2	11
Iran	0	0	1	10	1	10
Germany	1	3	1	4	2	7
Poland	0	0	1	7	1	7
India	4	6	0	0	4	6
Mexico	1	1	1	4	2	5
Spain	2	3	1	2	3	5
Singapore	3	2	0	0	3	2
Chile	1	1	0	0	1	1
Ecuador	1	1	0	0	1	1
Finland	1	1	0	0	1	1
Italy	1	1	0	0	1	1
South Africa	1	1	0	0	1	1
TOTAL	**74**	**239**	**45**	**403**	**119**	**642**

There were 10 cases reported by Chiosea et al.,[48] which were reported again; also, 4 tumors by Griffith et al.,[9] and 3 cases by Griffith et al.,[8] were excluded, because they were repeated from the article by Chiosea et al.[2] There was 1 case reported by Petersson et al.,[112] which was repeated by Petersson et al.[113]

*Chiosea et al.,[2] (9 case reports and 27 diagnostic reclassification).
†Khurram et al.,[76] (7 case reports and 4 diagnostic reclassification).
‡Hsieh et al.,[119] (8 case reports and 6 diagnostic reclassification).
§Din et al.,[107] (6 case reports and 5 diagnostic reclassification).
‖Boon et al.,[77] (11 case reports and 20 diagnostic reclassification).
¶Luk et al.,[82] (2 case reports and 7 diagnostic reclassification).
**Projetti et al.,[96] (9 case reports and 1 diagnostic reclassification).

discomfort,[40,77,89,97] tenderness,[4,112,119] facial paresthesia,[27] and facial paralysis.[2,38,74] Less frequently, more aggressive behavior can be observed, and in some cases, pain, skin infiltration, and ulceration have been reported.[18,110]

Cases can be diagnosed as early as 1 month.[55,64,68,97,108,117,119] At the other end of the scale, late diagnosis can occur from 10 years[91,119] to 30 years[1] in the evolution of the disease.

SCs are usually unique, floating, unencapsulated lesions but are well delineated, have white-gray, brown, or yellow coloration and may present as prominent cystic lesions filled with secretions.[28,102] According to Bishop et al., SCs developing in the minor salivary glands tend to be smaller compared with those affecting the major salivary glands, such as the parotid and submandibular glands, presenting mean sizes of 0.9 cm and 2.2 cm, respectively.[121] Corroborating this information, the smallest tumor, measuring 0.3 cm, was identified in the upper lip of a 62-year-old woman in the United States[46] and the largest a 20-cm tumor affecting the parotid gland of a 15-year-old boy in India.[100]

Lymph node involvement is present in several cases.[1,2,8,10,14,15,18,22,25,27,48,51,60,63,64,67,74,91,92,103,106,110-112,118,119] Chiosea et al. observed that about one-quarter of their cases presenting with SC had lymph node involvement, and despite the small number of cases analyzed, lymph node metastases appeared to be more common in SC than in AciCC.[48]

Based on its anatomic pathology features, SC is not highly infiltrative, particularly in cases where SC is predominantly macrocystic. The pattern of growth is variable, and SCs could present as tubules or microcysts, papillae, or macrocysts, and perineural invasion

Table II. Clinical and epidemiologic characteristics of the cases included in the study, until October 16, 2019

Variable	*n (%)*
Age (years), minimum − maximum	5−87
Gender*	
Male	340 (58.7)
Female	239 (41.3)
Location†	
Parotid gland	444 (73.7)
Submandibular gland	39 (6.5)
Unspecified—buccal mucosa	23 (3.9)
Unspecified—major salivary gland	19 (3.1)
Upper lip/lip mucosa	16 (2.7)
Soft palate	11 (1.8)
Hard palate	9 (1.5)
Lower lip/lip mucosa	8 (1.3)
Unspecified—lip	8 (1.3)
Unspecified—minor salivary gland	8 (1.3)
Others‡	17 (2.9)
Total	**642 (100)**

*Information not available in 63 cases.
†Information not available in 40 cases.
‡Others = unspecified palate (4 cases; 0.68%), accessory parotid gland (3 cases; 0.52%), alveolar mucosa (2 cases; 0.34%), buccal mucosa (2 cases; 0.34%), base of tongue (1 case; 0.17%), corners of the mouth (1 case; 0.17%), floor of the mouth (1 case; 0.17%), parapharynx (1 case; 0.17%), tongue (1 case; 0.17%) and unspecified oral cavity (1 case; 0.17%).

is rarely identified. Secretions are almost always present in the microcysts and/or macrocysts and their appearance ranges from slightly rosy and sparkling to brightly eosinophilic and colloidal. Tumor cells have an apocrine appearance, with eosinophilic granular cytoplasm often having a vacuolated or "bubbly" quality, which can confer the appearance of clear cells. The tumor nuclei are oval, with open chromatin, single variable prominent nuclei, and low rates of mitosis and rarely have necrosis.[121] Microscopically, SCs have a lobulated growth pattern and are composed of microcellular and glandular spaces, with abundant homogenous or bubbling secretory eosinophilic material positive for periodic acid-Schiff (PAS), mucicarmine, mucin 1 cell surface associated (MUC1), and MUC4.[1,20] The cytopathologic findings in SC are very similar to the histologic ones. They usually present moderate to high level of cellularity, with an epithelial cell predominance and vacuolated metachromatic material on the cytoplasm. The nuclei present fine chromatin and pinpoint nucleoli. Tumor cells may be arranged in papillary, cystic, tubular, and solid growth arrangements, and the extracellular material contains granular debris and histiocytes.[17,53] The final diagnosis of SC cannot be achieved through cytology alone.[53]

Immunohistochemical analysis presents positivity for mammaglobin, S-100 protein, cytokeratins (CKs) 7, 8, 18, and strong vimentin; however, DOG1, CK 5/6, p40, and p63 (which can be focally positive) are negative [7,8,82,101]. SC typically harbors a balanced chromosome translocation, t(12, 15)(p13; q25), resulting in the formation of the *ETV6-NTRK3* fusion gene encoding a chimeric oncoprotein-tyrosine kinase (TRK). Chromosomal alteration can be detected by using *ETV6* fluorescent in situ hybridization or through detection of the *ETV6-NTRK3* fusion transcript by reverse transcription polymerase chain reaction.[121] In addition, non-NTRK fusion types, such as ETV6-MET,[27] ETV6-MAML3,[10] ETV6-RET,[40] and unknown ETV6 partners (ETV6-X), have already been identified in SC.[67] Most of the pathology laboratories are not sufficiently equipped to detect the *ETV6-NTRK3* fusion gene, and, when this is the case, SC can be confirmed with immunohistochemistry (IHC) combined with the anatomopathologic features.[46] Given the reality of the limited capacity of many pathology laboratories, especially in developing countries, such as Brazil, it might be important to diagnose SC via pathology and IHC with a minimum amount of stains to reduce costs. Pan-TRK antibody is helpful when looking to rule out AciCC, which is the main differential diagnosis. Nevertheless, pan-TRK may be negative even for SC when a non-TRK fusion partner is present. In such cases, PCR have to be considered.[122]

Differential diagnosis

Retrospective studies have shown that the main differential diagnosis is AciCC, but there are other tumors of the salivary gland, such as low-grade salivary duct carcinoma; adenocarcinoma/cystadenocarcinoma, not otherwise specified (NOS); and low-grade mucoepidermoid carcinoma (MEC), which have also been misdiagnosed as SC.[123]

Clearly, SC is said to be more frequently found in nonparotid sites, especially in the minor salivary glands in comparison with AciCC.[2,13,48] However, the results of this systematic review suggest that SC is still much more common in the major salivary glands, especially in the parotid gland. In addition, studies have found that AciCC affects women more frequently, whereas SC has been showing a discrete male predilection.[2]

Histologically, SC is considered a "zymogen poor" AciCC or an intercalated duct-cell-predominant variant.[10] The neoplastic cells of SC resemble intercalated duct cells and have low-grade nuclei with distinct nuclear membranes and centrally located nucleoli. The architectural patterns of SC (microcystic, papillary−cystic, follicular, and solid) overlap with those of AciCC. However, large serous acinar cells with cytoplasmic zymogen granules positive for PAS, which is typical of AciCC, are absent in SC.[33] IHC can be helpful in the differential diagnosis because SC is typically mammaglobin positive, DOG1 negative, and S100 and

vimentin positive, whereas AciCC usually shows an inverted pattern.[79,123] In addition, most classic AciCCs are easily distinguishable from SCs even at the morphologic level.[124]

Similarly, cytology, IHC, and molecular genetics have been helpful in the differential diagnosis of low-grade MEC and SC. MEC usually presents with a cystic and solid architecture; intermediate, epidermoid, and inflammatory cells; and intracytoplasmic and intraluminal mucin secretions. Immune staining is positive for p63 and CK7 (strong) and is negative for S100, DOG-1, and mammoglobin; molecular genetics present the translocation t(11; 19)(q21;p13), which leads to the fusion gene *CRTC1-MAML2*.[7,101]

The use of mammoglobin alone is not enough to complement anatomopathology, given that it can eventually be positive for several other types of tumors.[125] If mammoglobin and DOG-1 are combined, the results are equal to those of ETV6 break-apart analysis, at least when distinguishing SC from AciCC.[29] Xu et al. recently described pan-TRK IHC has specificity of nearly 100%. This suggests that this single antibody could be an inexpensive and attractive screening tool for selecting patients suspected of having TRK fusion tumors, such as SCs, especially when harboring the most typical *ETV6-NTRK3* fusion gene.[126]

Treatment

The main treatment for SC is surgical excision, and given the high incidence of SC in the parotid glands, parotidectomy is usually the treatment of choice in such cases. Selective or radical neck dissection is commonly performed,[2,7,15,36,47,63,66,68,69,77,82,83,92,97,103,106,109-111,116,117] and in some cases, adjuvant therapy is given (chemotherapy and radiotherapy, alone or in combination), especially in cases with lymph nodes metastases, lymphatic and/or vascular invasion, positive surgical margins, and perineural invasion.[1,2,27,33,35,57,63,66,68,69,73,74,79,82,88,91,92,103,106,109-111,114-116,124]

Prognostic factors and treatment outcomes

Although data on treatments and outcomes are limited, SC appears to be a low-grade malignant neoplasm, with a favorable prognosis.[77,105] However, recurrences and local tumor metastases have already been described in a considerable number of cases.[1,27,33,39,41,63,64,66,67,77-79,91,100,103,110]

Despite the favorable prognosis, distant metastases have been reported by Gupta et al. (liver metastasis),[42] Cai et al. (lung metastasis),[73] Forner et al. (lung metastasis),[91] Baghai et al. (multiple bone metastases),[103] Cipriani et al. (pleura and thorax metastases),[43] Skalova et al. (multiple distant metastases to lungs, liver, and bones),[67] Drilon et al. (lung metastasis),[5] Stevens et al. (lung metastasis),[33] and Skalova et al. (cervical lymph nodes, pleura, pericardium, and lung metastases).[1] Moreover, some authors have reported deaths resulting from this tumor.[1,43,66,103,107,110]

The clinical course of SC is generally favorable, with excellent disease-free and overall survival rates.[127] Boon,[77] who observed 31 patients with a median follow-up duration of 49 months, reported 5- and 10-year overall survival rates of 95% and 5- and 10-year disease-free survival rates of 89%. However, even though there is no statistical significance, SC tends to be worse than AciCC with regard to prognosis.[2]

DISCUSSION

As indicated by this systematic review, the main location of SC is the parotid gland (73.7%), and secondary locations include the submandibular gland (6.5%) and unspecified areas of the buccal mucosa (< 4%) (see Table II). The literature indicates that the minor salivary glands and the submandibular gland are also reported as less frequent sites.[26,57-59,74,89,103] The most common intraoral sites are the lips, soft palate, and buccal mucosa.[2,10,12,13,35,37,46,49-51,61,62,64,76,77,98,106]

Given the recent recognition of SC, it is important to not only highlight the efforts of large centers to identify underdiagnosed cases but also the need for better understanding of this tumor. Diagnostic reclassification studies are important in the context of providing clinical and epidemiologic information about this pathology, and case reports provide specific approaches for treating this type of tumor, especially a more specific treatment for SC. In this context, molecular target therapy stands out as the treatment for SC in patients not eligible for surgery or who have indications for adjuvant treatment.

The recognition of SC and the *ETV6* rearrangement test have potential value in the treatment of this tumor.[79] Recent studies have highlighted that inhibition of active *ETV6-NTRK3* is highly effective in the treatment of these patients.[2,121] In vitro studies in SC have highlighted that insulin-like growth factor receptor inhibitors may be useful in blocking the oncogenesis induced by *ETV6-NTRK3* translocation.[128] Some types of leukemia, which have the same translocation, respond well to treatment with TRK inhibitors, suggesting the possibility of using this therapy for SC as well.[2] The presence of fusions involving *NTRK* genes leads to the production of proteins that activate or overexpress kinase function, which confers oncogenic potential to the cells involved.[129] Moreover, Chi et al. have suggested that the small molecule tyrosine inhibitor PKC412 acts to block activation of *ETV6-NTRK3* and consequently to stunt cell proliferation and to induce apoptosis, indicating that target molecular therapy is a possibility for patients with this fusion gene.[130]

Drilon et al. reported a case in which target therapy with crizotinib, a multitargeted kinase inhibitor, was

Table III. Published studies on molecular target therapy of SC, until October 16, 2019

Medicine	*Year*	*Study phase*	*Status**	*No. of SC cases*	*Follow-up*	*Reference*
Crizotinib + Entrectinib	2016	Case report†	–	1	Disease progression after 18 weeks of crizotinib therapy; and asymptomatic disease progression after 10 months of entrectinib trial	Drilon et al.[5]
Entrectinib	2017	Phase I	Recruiting + ongoing	1	Up to 90% reduction in size with up to 9 months' follow-up	Drilon et al.[131]
Larotrectinib	2018	Phase I (adults); phase I/II (children); phase II (adolescents and adults)	Recruiting + ongoing	12	3 tumors had complete size response; 1 increased in size as a result of mutation associated with previous treatment; others reduced in size by > 40%	Drilon et al.[134]

*Clinical trial status information from Scott.[133]
†Case report article, where the patient was inserted in a phase I clinical trial.

associated with initial pain reduction, but progressive disease was observed over an 18-week period. For this reason, the patient was then included in a phase I clinical trial with entrectinib. After 10 months of treatment with entrectinib, asymptomatic disease progression was identified.[5] Drilon et al. presented a case of SC over a 9-month follow-up in a phase I study with entrectinib and observed a 90% reduction in tumor size.[131]

More recently, Loxo Oncology, in collaboration with Bayer AG, developed larotrectinib, a first-in-class, highly-selective, small-molecule, oral TRK inhibitor.[132] This drug produces high and long-lasting responses in adolescents and adults with NTRK-positive tumors.[133] Drilon et al. studied 55 patients, 12 of whom had SC, and observed that the overall response rate was 80% (95% confidence interval [CI] 67−90). The results of the study showed that after 1 year, 71% of responses persisted, and 55% of all patients remained progression-free. Besides that, as of the cutoff date, 86% of the treatment-responsive patients were continuing to receive treatment or were referred for surgery with curative intent.[134] Those authors agreed that prolonged therapy with larotrectinib had minimal toxic effects and that the most common side effects were fatigue, dizziness, nausea, and anemia.[134-136]

The ongoing clinical trials are in phases I, I/II, and II, including both patients under treatment and new patients (Table III). These studies have been developed mainly in the United States, Australia, Canada, Europe, Ireland, and the United Kingdom.[133] Larotrectinib was approved in the United States in November 2018, and in Brazil, it was approved on July 1, 2019 by the National Health Surveillance Agency.[137]

CONCLUSIONS

Thus, according to the findings from the studies analyzed in this systematic review, case reports and histopathology reclassification studies on SC have mainly been from the United States. The tumor usually presents itself as a slow-growing and painless mass in the parotid gland. Correct diagnosis of SC should involve histologic analysis, IHC, and fluorescent in situ hybridization, although PCR may be required, with AciCC being the main differential diagnosis. The surgical treatment used in most cases has shown to be effective, with a good prognosis and with few reported cases of recurrence, metastasis, and death. It is important that clinicians have knowledge about this rare salivary gland tumor, its clinical behavior, and the unique treatment for it. TRK inhibitors, such as entrectinib and larotrectinib, have shown positive results in pediatric and adult patients. New clinical trials must be implemented to further confirm their effectiveness.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.oooo.2020.04.007.

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