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Clinicopathological characteristics and outcome of 31 patients with *ETV6-NTRK3* fusion gene confirmed (mammary analogue) secretory carcinoma of salivary glands

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ABSTRACT

Objectives: In 2010, a new subtype of salivary gland cancer (SGC), (mammary analogue) secretory carcinoma (SC), was defined, characterized by the *ETV6-NTRK3* fusion gene. As clinical behavior and outcome data of this histological subtype tumor are still sparse, we aimed to describe the clinicopathological course and outcome of a series of translocation positive SC patients.

Patient and methods: We re-evaluated the pathological diagnosis of a subset of SGCs, diagnosed in 4 of 8 Dutch head and neck centers. Subsequently, tumors with a morphological resemblance to SC were tested for the *ETV6-NTRK3* fusion gene using RT-PCR. Furthermore, patients prospectively diagnosed with SC were included. The clinical characteristics and outcomes were retrieved from the patient files.

Results: Thirty-one patients with *ETV6-NTRK3* fusion gene positive SC were included. The median age was 49 years, 17 patients (55%) were male. Eighteen tumors (58%) arose in the parotid gland. One patient presented with lymph node metastasis. All patients underwent tumor resection and 4 patients had a neck dissection. Four patients had re-resection and 15 patients (48%) received postoperative radiotherapy. One patient developed a local recurrence, no regional recurrences or distant metastases were observed. After a median follow-up of 49 months the 5- and 10-year overall survival were 95%, the 5- and 10-year disease free survival were 89%.

Conclusion: The clinical course of SC is favorable with a low rate of locoregional recurrence and excellent survival. Given the low incidence of nodal metastases, elective neck treatment, i.e. surgery and/or radiotherapy, does not seem to be indicated.

Introduction

Salivary gland cancers comprise a wide histological spectrum with more than twenty different subtypes [1]. In 2010, a new entity of salivary gland cancer was described by Skálová et al., characterized by the presence of the *ETV6-NTRK3* fusion gene [2]. The histopathological appearance resembles secretory carcinoma of the breast, and both tumors share the *ETV6-NTRK3* fusion gene, hence the proposed name was mammary analogue secretory carcinoma (MASC). In the updated 2017 WHO classification, MASC is acknowledged and referred to as 'secretory

carcinoma', to standardize nomenclature amongst different organ sites [1].

The morphological features of secretory carcinoma include a variety of architectural growth patterns, intracytoplasmic vacuoles, lack of intracytoplasmic zymogen granules in a mucinous or hemosiderin-laden histiocyte-rich background [3]. Immunohistochemical markers such as S100, vimentin, STAT5a, MUC4 and mammaglobin may be helpful in preselecting patients with suspected secretory carcinoma, but none of these markers can fully confirm the diagnosis. However, the presence of the *ETV6-NTRK3* fusion gene is pathognomonic [4]. The

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most important entities in the differential diagnosis of secretory carcinoma are acinic cell carcinoma (AcicC), polymorphous adenocarcinoma (PAC), and adenocarcinoma not otherwise specified (NOS). Although in salivary gland cancer the presence of the fusion gene is specific for secretory carcinoma, the *ETV6-NTRK3* fusion gene has also been demonstrated in several other solid and hematological malignancies, such as secretory carcinoma of the breast, papillary thyroid carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myeloid leukemia and sino-nasal low-grade adenocarcinoma [5–8].

In recent years, several reports have been published on characteristic histopathological features of secretory carcinoma within the many subtypes of SGC, but little is known about the clinical behavior of this new entity, including the outcome of these patients. A review of 279 cases showed a male to female ratio of 1.5:1 and occurrence mostly (68%) in the parotid gland [9]. Disease free survival (DFS) in secretory carcinoma patients was reported to be similar to DFS in AcicC in a comparison in respectively 29 and 38 patients [10]. The aim of the current study is to focus on clinical behavior and outcome of patients with secretory carcinoma.

Patients and methods

In four hospitals in the Netherlands, patients with subsets of salivary gland cancer (AcicC, PAC and adenocarcinoma) were retrospectively evaluated for morphological resemblance to secretory carcinoma by pathologists (U.F, L.S, E.B. and S.M.W.) from 2000 until 2016. Patients suspected of secretory carcinoma were tested for the presence of the *ETV6-NTRK3* fusion gene. The *ETV6-NTRK3* fusion gene was analyzed using reverse transcriptase-polymerase chain reaction (RT-PCR). RNA was extracted from formalin-fixed and paraffin-embedded tissues (FFPE) using RNA-Bee-RNA isolation reagent (Bio-Connect BV, Huissen, the Netherlands) according to standard procedures. RNA quantity and quality were determined by NanoDrop measurement (Fisher Scientific, Landsmeer, the Netherlands) and, subsequently, cDNA synthesis was performed using Superscript II (Invitrogen Life Technologies Europe, Bleiswijk, the Netherlands) and random hexamers (Promega Nederland, Leiden, the Netherlands).

The cDNA was tested by the reverse transcription-polymerase chain reaction (RT-PCR) for the *HMBS* (hydroxymethylbilase synthase) housekeeping gene using the primers forw150 5'-TGCCAGAGAAGAGT GTGGTG-3', rev150 5'-ATGATGGCACTGAACTCCTG-3', forw250 5'-CTGGTAACGGCAATGCGGCT-3', rev250 5'-TTCTTCTCCAGGGCATG TTC-3'.

For detection of the *ETV6-NTRK3* fusion, the following primers were used: *ETV6* forward primer P385: 5'-ACCACATCATGGTCTCTGTCT CCC-3' and *NTRK3* reverse primer P386: 5'-CAGTTCTCGCTTCAGCAC GATG-3'. The PCR products were analyzed by agarose gel electrophoresis.

Patients who were prospectively diagnosed with secretory carcinoma were also included. For both retrospective and prospective cases, the presence of the *ETV6-NTRK3* fusion gene was mandatory for inclusion in this study. Patients' characteristics regarding clinical presentation, diagnosis, treatment and follow-up were collected by evaluating medical records. According to the Dutch guidelines, review by a medical ethical committee was not necessary due to the retrospective nature of this study (www.federa.org).

Resection margins were categorized as free (> 5 mm), close (1–5 mm) or involved (< 1 mm) based on the pathology reports. For further survival analysis, close and involved margins were grouped as 'not free'.

For the prospectively collected cases the date of diagnosis was defined as first date of histopathological confirmation of the diagnosis secretory carcinoma. In retrospective cases, the date of obtaining the original histopathological material was used as date of diagnosis.

Statistics

Overall survival (OS) is defined as the time from date of diagnosis until date of death of any cause. Patients alive at the last known follow-up date were censored. DFS is defined as the time from date of surgery until date of recurrence (local or regional recurrence or distant metastasis) or death of any cause, whichever comes first. Patients alive without disease recurrence at last known follow-up were included in the analysis as censored. OS and DFS were estimated using Kaplan Meier survival curves. Statistical analysis was performed using SPSS data analysis software version 22.0.

Results

Patients and tumor characteristics

In total, 42 patients were tested; 3 patients tested negative, for 6 patients the fusion gene could neither be confirmed nor invalidated, in 33 patients we confirmed the presence of the *ETV6-NTRK3* fusion gene. Unfortunately, clinical records were not available for 2 of the 33 confirmed patients; thus, a total of 31 patients with *ETV6-NTRK3* fusion gene positive secretory carcinoma were included. The median age at diagnosis was 49 years (range 19–83 years), 17 patients (55%) were male. Eighteen tumors (58%) were located in the parotid gland, one in the submandibular gland, and the remaining 12 tumors in the minor salivary glands. The primary site of the minor salivary gland tumors were the lip (n = 5), the oral mucosa (n = 2), the soft palate (n = 1), the hard palate (n = 1) and the remaining three could not be further specified. Nineteen patients (61%) had T1 tumors, 10 patients (32%) T2 tumors; for 2 patients the T-classification was not available. Only one patient presented with regional lymph node metastasis, none of the patients had distant metastasis at diagnosis. In most patients, the presenting symptom was a painless mass (22 patients). One patient presented with a painful swelling and one with a non-healing wound. For the remaining 9 patients no symptoms could be retrieved from the medical records. The median time from start of symptoms to diagnosis was 14 months (range 6 weeks–20 years).

Eleven patients were prospectively diagnosed with secretory carcinoma between 2011 and 2016. The remaining 20 patients were retrospectively diagnosed with secretory carcinoma, confirmed by the presence of the *ETV6-NTRK3* fusion gene. The initial diagnosis of these patients was between 2000 and 2012. Of these 20 patients, 16 patients were previously diagnosed with AcicC, three as PAC and one as adenocarcinoma NOS.

Baseline characteristics of all patients are shown in Table 1.

Primary treatment

Primary treatment for all 31 patients consisted of surgery. Seventeen patients had a surgical resection of the affected salivary gland, and in four of them surgery also included a neck dissection (only one patient had tumor positive lymph nodes). Eleven patients had either a local excision, excision or incision biopsy of the tumor. For three patients, the exact type of surgery could not be determined. Seven patients (23%) had involved resection margins, nine patients had closely excised tumors (29%) and 13 (42%) had free resection margins. In two patients, information about resection margins was not available. Four patients (13%) had additional surgery, because of involved resection margins (2), a close excision margin (1) and an uncertain margin after excision biopsy. Fifteen patients (48%) received postoperative radiotherapy: all seven patients with involved resection margins, six out of nine patients with closely excised tumors and two patients with free resection margins. One of the patients with free resection margins had a difficult preparation of the facial nerve during surgery, and was therefore treated with postoperative radiotherapy. For the other patient with free resection margins the exact reason for

Table 1
Patients' and tumor characteristics.

Median age , in years [range]	49 [19–83]
Gender , n (%)	
Male	17 (55)
Female	14 (45)
Tumor localization , n (%)	
Major salivary glands	
- Parotid	18 (58)
- Submandibular gland	1 (3)
- Sublingual gland	0 (0)
Minor salivary glands	12 (39)
Method of diagnosis of secretory carcinoma , n (%)	
Prospective	11 (35)
Retrospective	
- Acinic cell carcinoma	16 (52)
- Polymorphous adenocarcinoma	3 (10)
- Adenocarcinoma, not otherwise specified	1 (3)
Signs and symptoms , n (%)	
Painless mass	22 (71)
Painful mass	1 (3)
Non-healing wound	1 (3)
Unknown	7 (23)
Median duration of symptoms , (range)	14 months (6 weeks–20 years) ^a
TNM stage , n	
T1/T2/T3/T4/Tx	19/10/0/0/2
N0/N1/N2/N3	30/0/1/0
M0/M1	31/0
Surgery , n (%)	
Yes	31 (100)
No	0 (0)
Resection margins , n (%)	
Free (> 5 mm)	13 (42)
Not Free	
- Close (1–5 mm)	9 (29)
- Involved (< 1 mm)	7 (23)
Not available	2 (6)
Revision surgery , n (%)	
Yes	4 (13)
No	27 (87)
Postoperative radiotherapy , n (%)	
Yes	15 (48)
No	16 (57)

^a Based on 20 patients.

postoperative radiotherapy could not be retrieved from the patient files. Of the four patients who underwent re-excision, two patients additionally underwent postoperative radiotherapy. The characteristics of patients with postoperative radiotherapy and patients with surgery only are summarized in Table 2. The median dose of radiotherapy was 66 Gy (range 60–66 Gy). More detailed information about the radiotherapy target volume was available in eight out of 15 patients with radiotherapy. In four patients, the target volume included the ipsilateral neck; in the other four patients, only the surgical bed was irradiated. None of the patients received chemotherapy.

Disease recurrence

Only one patient (4%) had a local recurrence, occurring 50 months after primary surgery (resection margins of the primary surgery were not available), without postoperative radiotherapy. The patient remained disease-free during the 40 months following surgical resection of the recurrence. None of the patients had a regional recurrence or distant metastasis.

Survival

After a median follow up time of 49 months, 1 patient died (without

Table 2

Characteristics of patients with secretory carcinoma with *ETV6-NTRK3* fusion gene mutation receiving postoperative radiotherapy versus patients with surgery only.

	Postoperative radiotherapy n = 15	Surgery only n = 16
Median age , in years [range]	52 [20–83]	46 [19–68]
Gender , n (%)		
Male	8 (53)	9 (56)
Female	7 (47)	7 (44)
Tumor localization , n (%)		
Major salivary glands		
Parotid	11 (73)	7 (44)
- Submandibular gland	1 (7)	0 (0)
- Sublingual gland	0 (0)	0 (0)
Minor salivary glands	3 (20)	9 (56)
Method of diagnosis of secretory carcinoma , n (%)		
Prospective	5 (33)	6 (38)
Retrospective	10 (67)	10 (63)
- Acinic cell carcinoma	10 (67)	6 (38)
- Polymorphous adenocarcinoma	0 (0)	3 (19)
- Adenocarcinoma, NOS	0 (0)	1 (6)
Signs and symptoms , n (%)		
Painless mass	12 (80)	10 (63)
Painful mass	0 (0)	1 (6)
Non-healing wound	0 (0)	1 (6)
Unknown	3 (20)	4 (25)
Median duration of symptoms , (range)	2 years (6 weeks–20 years)	6 months (3 months–2 years)
TNM stadium , n		
T1/T2/T3/T4/Tx	7/7/0/0/1	12/3/0/0/1
N0/N1/N2/N3	14/0/1/0	16/0/0/0
M0/M1	15/0/0/0	16/0/0/0
Surgery , n (%)		
Yes	15 (100)	16 (100)
No	0 (0)	0 (0)
Resection margins , n (%)		
Free (> 5mm)	2 (13)	11 (69)
Not Free		
- Close (1–5 mm)	6 (40)	3 (19)
- Involved (< 1 mm)	7 (47)	0 (0)
Not available	0 (0)	2 (13)
Additional resection , (n%)		
Yes	2 (13)	2 (13)
No	13 (87)	14 (87)

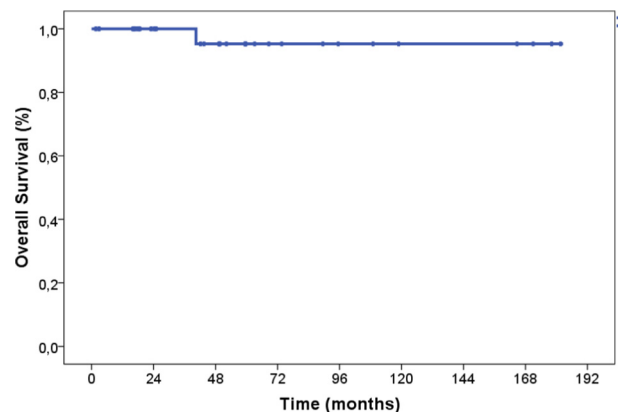


Fig. 1a. Overall survival of all secretory carcinoma patients.

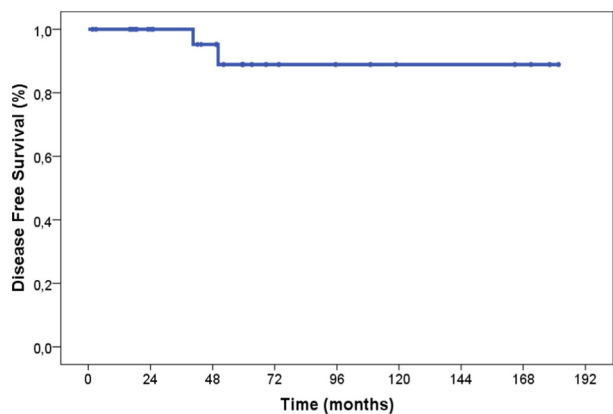


Fig. 1b. Disease Free Survival all secretory carcinoma patients.

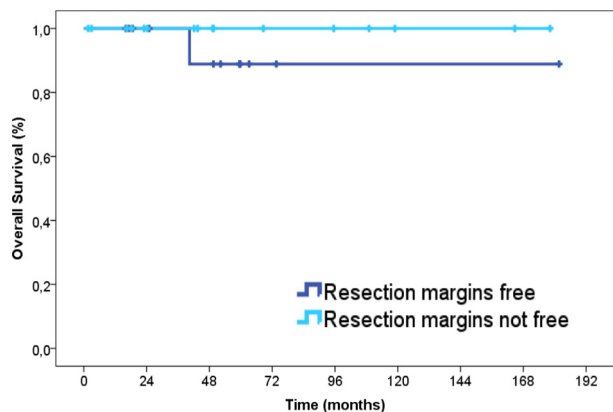


Fig. 1c. Overall survival categorized by resection margins being free or not free.

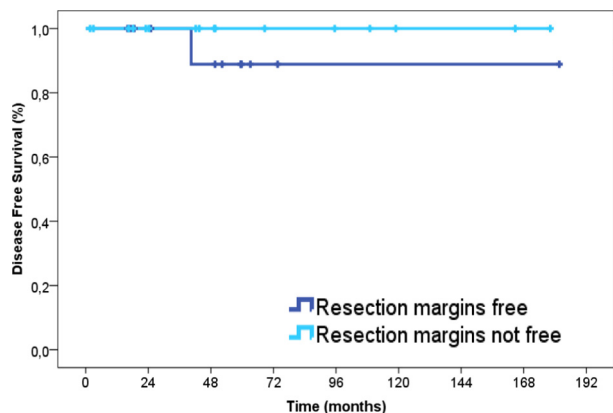


Fig. 1d. Disease free survival categorized by resection margins being free or not free.

signs of disease recurrence). The estimated 5- and 10-year OS were 95%. The 5- and 10-year disease-free survival were 89%. OS and DFS are displayed in Figs. 1a–1f.

The estimated 5-year OS and DFS were 89% for patients with free resection margins, and 100% for patients with resection margins that were not free (either close or involved), respectively.

The estimated 5-year OS and DFS of patients treated with surgery and radiotherapy were both 89%, for patients treated with surgery only these were 100% and 89%, respectively.

The OS and DFS for patients according to resection margins and radiotherapy are also illustrated in Figs. 1a–1f.

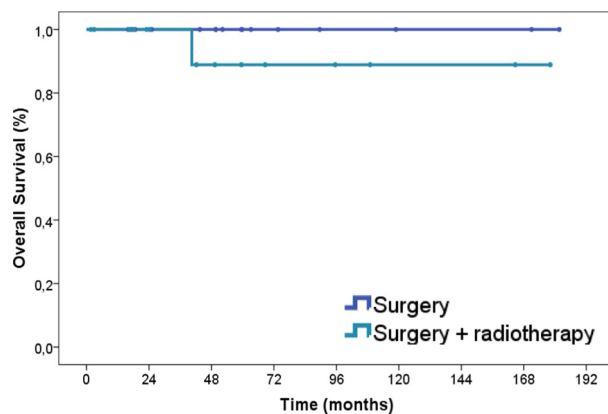


Fig. 1e. Overall survival categorized by primary treatment with surgery versus surgery and radiotherapy.

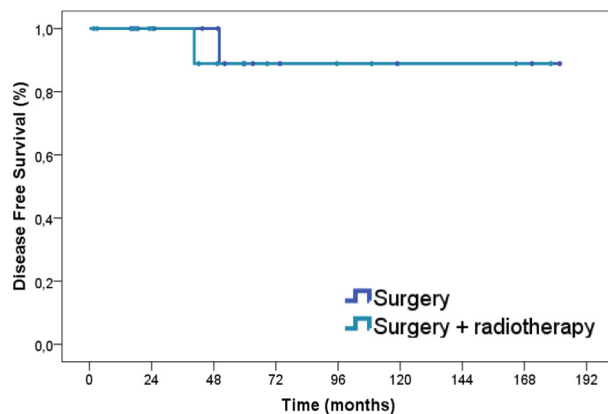


Fig. 1f. Disease free survival categorized by primary treatment with surgery versus surgery and radiotherapy.

Discussion

In this report of 31 patients with *ETV6-NTRK3* fusion gene positive secretory carcinoma, we presented the clinical spectrum of secretory carcinoma. The outcome of disease was favorable and only one of the patients had local recurrence of the disease.

There was a male to female ratio of 1.2:1, which is in accordance with most reports showing a larger proportion of male patients. In a literature review of 279 cases, the male to female ratio was 1.5:1 [9].

As for secretory carcinoma of the breast, in secretory carcinoma pediatric cases may be encountered [11,12]. However, we had no pediatric cases, but we did encounter 6 adolescent and young adults (18–35 years).

We only observed T1 and T2 tumors in our cohort, although T₃ and T₄ tumors were described by others [2,10]. Only one patient of our series had cervical lymph node metastasis at time of diagnosis, and was surgically treated. In another described series of 36 secretory carcinoma patients, 18 patients had a neck dissection, of which 4 patients had tumor positive lymph nodes [10].

In the current study, the largest proportion of retrospective cases of secretory carcinoma were previously classified as AcicCC and the remaining cases were mostly identified as PAC. AcicCC was therefore the most important differential diagnosis in this report. AcicCC may be morphologically differentiated by structural and cytologic diversity and by the presence of large serous acinar cells containing zymogen granules which are absent in secretory carcinoma.

Remarkably, we found that 39% of tumors occurred in the minor salivary glands. This is in agreement with data in the review of 279 secretory carcinoma patients [9]. In a Danish national cohort study 86/

97 (89%) of AcicCs presented in the parotid gland [13]. Secretory carcinoma seems to be occurring more frequently outside the parotid gland than AcicC. Therefore, if patients are diagnosed with a AcicC located in the minor salivary glands there should be a suspicion of secretory carcinoma.

Notably, eleven patients started with local excision, or incision biopsies. Although the reasons were not entirely clear, this may possibly be attributed to ambiguity on previous cytology or clinical appearance.

In this report, only one patient had a local recurrence 50 months after the primary treatment, which was successfully treated and remained disease free during follow up. Distant metastasis did not occur in our patients. However, it should be noted that one should be cautious interpreting these data, as the median follow up time in this study is only 49 months, and given the low grade behavior of secretory carcinoma, local recurrences might develop even after a more prolonged period of follow up. Actually, patients have been described in the literature diagnosed with tumors with high grade transformation, in some cases dying of disseminated disease within 2 and 6 years [14,15].

In the current study, the course of the disease is favorable in terms of OS and DFS, and appears to be comparable to outcomes of AcicC. However, it should be noted that morphologically high grade cases of secretory carcinoma were not encountered. A survival analysis of 1353 cases AcicC based on the National Cancer Data Base (NCDB) in the United States showed a 5-year overall survival of 83.3% and 5-year disease specific survival of 91.4% [16].

Although clinical outcomes between patients with AcicC and PAC versus secretory carcinoma may not differ greatly, it is important to distinguish secretory carcinoma patients from other salivary gland cancers, mainly in the case of metastatic disease. The presence of the NTRK-ETV6 fusion gene has revealed an actionable target and currently, a phase II trial with entrectinib is actively recruiting patients for those patients harboring NTRK fusion genes. Entrectinib is an orally available inhibitor of the tyrosine kinase tropomyosin-related kinases (TRK) [17].

The role of adjuvant radiotherapy is controversial for AcicC. An analysis of 1241 cases of parotid AcicC from the SEER database showed no statistical difference in overall survival for patients with surgery compared to patients undergoing surgery and adjuvant radiotherapy [18]. It should however be noted that this is most likely confounding by indication, with worst cases having received radiotherapy. In the current series, 48 percent of patients received postoperative radiotherapy. One could argue that the excellent outcomes of these secretory carcinoma patients is due to the beneficial effects of the postoperative radiotherapy or perhaps the intrinsic biological behavior of secretory carcinoma. Due to the low number of events (either local recurrences and/or death) and the differences in baseline characteristics, specifically resection margins, our data should be interpreted with caution. However, it is likely that patients with clinically N₀ disease may be spared from elective treatment, i.e. surgery or radiotherapy of the neck, given the very low incidence of nodal metastases. Future research may clarify the importance of adjuvant neck treatment for secretory carcinoma.

The limitation of this study may be the selection of patients. Secretory carcinoma has been recognized as a distinct entity of salivary gland cancer since the association with the *ETV6-NTRK3* fusion gene in 2010. Only a limited number of patients in the current series were diagnosed with secretory carcinoma prospectively. The other patients were identified after reviewing the resection specimen of a subset of salivary gland cancer and testing them for the presence of the *ETV6-NTRK3* fusion gene. Therefore, a selection bias may play a role in the data as presented in this paper. Furthermore, due to the retrospective nature of the study some cases had missing data.

However, with the presentation of 31 patients with confirmed *ETV6-NTRK3* fusion gene secretory carcinoma and detailed data on the diagnosis, treatment and outcomes, we feel this makes these results give more clinical background and a meaningful contribution to the existing

literature of secretory carcinoma.

Conclusion

We present the clinical course of 31 patients with *ETV6-NTRK3* fusion gene confirmed secretory carcinoma. The clinical course is favorable with a low rate of recurrences and an excellent overall and disease free survival after a median follow up of 49 months. Elective treatment of the neck does not seem to be indicated considering the low incidence of nodal metastases, good prognosis, and apparent low grade behavior of secretory carcinoma.

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Conflict of interest statement

S.M. Willems: Medical Advisor: MSD, Merck, AstraZeneca, Roche, Pfizer, BMS, Research Grants: AstraZeneca, Roche, Pfizer.

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