

Mammary analogue secretory carcinoma of a salivary gland of the hard palate with contralateral cervical lymph node metastases: A case report

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Abstract. Mammary analogue secretory carcinoma (MASC) is a rare malignant tumour of the salivary glands, with only few cases reported in the literature to date. Initial preoperative staging is crucial for all patients with an oral malignancy to visualize the tumour, detect lymph node or distant metastases and plan therapeutic interventions. In the case presented herein, radiological imaging revealed a tumour of the right hard palate with suspected positive contralateral lymph nodes. Therefore, local tumour resection comprising hemimaxillectomy and bilateral neck dissection was performed. The diagnosis of MASC was finally based on characteristic histopathological and immunohistochemical findings, such as S100 protein and mammaglobin positivity. The diagnosis of MASC may be challenging, as such findings lack specificity. To confirm the diagnosis, molecular genetic examinations may be performed to detect a highly specific ETV6-NTRK3 fusion gene. Depending on the results of these examinations, surgery, alone or combined with adjuvant radiation or chemoradiation, is the recommended approach. In summary, MASC should be treated similarly to other low-grade salivary gland tumours, such as acinic cell carcinoma, as they exhibit biological and histopathological similarities.

Introduction

Mammary analogue secretory carcinoma (MASC) is a rare tumour of the head and neck region first described in 2010 by Skálová *et al* (1). As of 2017, MASC has been listed in the Classification of Head and Neck Tumours by the World Health Organization (2). MASC is a malignancy of the salivary glands, predominantly observed in the parotid gland, with an incidence rate of 4-4.5% among all malignant salivary gland tumours (3-5). However, when considering only tumours of the small salivary glands, the incidence of MASC is markedly lower (4). MASC usually occurs at a mean age of 45 years and is slightly more common among men (6).

To diagnose MASC, microscopic examination is necessary. On histopathological examination, the tumour typically displays cystic, tubular and solid areas with infiltration. Most MASCs consist of relatively monomorphic cells with a moderate amount of vacuolated eosinophilic cytoplasm. On immunohistochemical examination, the tumour shows immunoreactivity for S-100, mammaglobin, MUC4 and CK7 (3). Mammaglobin and S100 protein show high sensitivity (95%), but are not specific for MASC (6-8). By contrast, an ETV6-neurotrophic receptor tyrosine kinase (NTRK)3 fusion gene is highly specific for MASC, at least considering salivary gland malignancies. This translocation can be detected by fluorescence *in situ* hybridization (FISH) or PCR analysis and confirms the diagnosis of MASC (1,3,9-11). In addition to NTRK1 and NTRK2, NTRK3 is a membrane-bound receptor and part of the NTRK neurotrophin receptor family, which is involved in neuronal cell differentiation and proliferation. Mutations play an important role in carcinogenesis, such as that in secretory breast carcinomas, medulloblastomas and MASCs (11). Approximately 300 cases of MASC have been reported in the literature to date. Due to this limited number of cases, no consistent data concerning treatment procedures and outcomes have been published. The majority of MASCs are considered as low-grade malignancies, they are treated by radical resection and have a good prognosis (10). According to the previously reported cases, patients with MASC have a 5-year overall survival rate of 95% and a 5-year disease-free survival rate of 89%, with a

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Abbreviations: AC, adenocarcinoma; AcICC, acinic cell carcinoma; CAC, cystadenocarcinoma; FDG, [¹⁸F]-fluorodeoxyglucose; FISH, fluorescence *in situ* hybridization; MASC, mammary analogue secretory carcinoma; MuC, mucoepidermoid carcinoma; PET, positron emission tomography; TRK1, tyrosine kinase inhibitor; US, ultrasound

Key words: mammary analogue secretory carcinoma, salivary gland cancer, neck dissection, oral cancer, oral cavity, lymph node metastases, head and neck, cancer

low incidence of nodal metastases (12). However, cases with high-grade transformation, lymph node and distant metastases have rarely been described (13). The case of a patient with MASC of the hard palate with bony infiltration and contralateral cervical lymph node metastases is described in the present study. This combination is extraordinarily rare and, to the best of our knowledge, has not been described in the literature to date (5). The aim of the present study was to focus on treatment procedures recommended for high-risk patients, discuss the benefits of selective neck dissection and adjuvant chemoradiation, and discuss novel treatment options with entrectinib, larotrectinib and other tyrosine kinase inhibitors (TRKIs) for patients with inoperable tumours or under palliative care.

Case report

A 44-year-old Caucasian woman initially presented at the Department of Oral and Maxillofacial Plastic Surgery of the University Hospital of Wuerzburg (Wuerzburg, Germany) in June 2018. The patient reported painless swelling in the area of the right hard palate (Fig. 1). A biopsy had already been performed at a private practice office, and histopathological examination revealed a carcinoma with immunoreactivity for CK7, S100 and mammaglobin. No irregularities and no radiotherapy of the head and neck region were noted in the patient's history.

The staging procedures included clinical examination, ultrasound (US) of the neck, MRI, cone beam CT and [^{18}F]-fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT).

The MRI examination revealed a tumour measuring 18x16x12 mm, with invasion of the right maxillary sinus and suspected retropharyngeal and cervical lymph nodes on the left side on FDG-PET/CT. By contrast, CT and MRI showed bilateral suspected lymph nodes (Figs. 2-4). A secondary suspected pharyngeal lesion at the tongue base was also identified.

Based on the aforementioned findings, the patient underwent local resection of the hard palate tumour, with a clinical safety distance of 10 mm, along with bilateral radical neck dissection (levels I-V) with temporary tracheotomy. Plastic reconstruction of the hard palate was performed during the same operation using a radial forearm flap. Biopsies of the suspected lesion in the pharynx showed no signs of malignancy. Histopathological examination of the specimen revealed a tumour with a diameter of 13 mm, with the closest margins at 3 mm, medullary bone invasion and two (2/37) lymph node metastases on the contralateral side of the neck at level Va. No metastases were detected on the ipsilateral side of the neck. Histopathological examination of the tumour revealed microcystic, tubular and solid areas with infiltration. The tumour cells were monomorphic and round-oval, with a moderate amount of vacuolated eosinophilic cytoplasm (Figs. 5 and 6). On immunohistochemical examination, the tumour was positive for CK7, S100, mammaglobin, GATA3, GCDF-P15 and pan-cytokeratin (AE1/3). P16 expression in tumour cells, partial reactivity of SOX10 and specific reactivity for CD117 were also detected. The Ki-67 index was low (<5%). FISH analysis performed using an ETV6 break-apart



Figure 1. Painless swelling (~1x1 cm) in the right hard palate with ulceration due to the biopsy performed in the private surgery practice. Apart from the lesion, the oral mucosa appeared normal. Dental status: Tooth 23 was retained. Apart from that finding, the dental chart was inconspicuous, without any signs of loosening teeth.

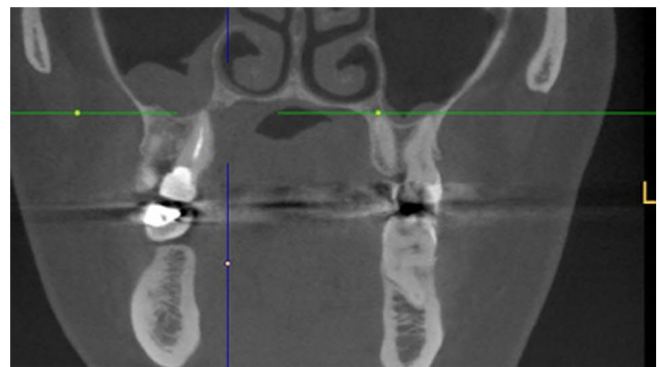


Figure 2. Cone beam CT revealed bone invasion in the right hard palate. The mucosa of the right maxillary sinus exhibited reactive changes.

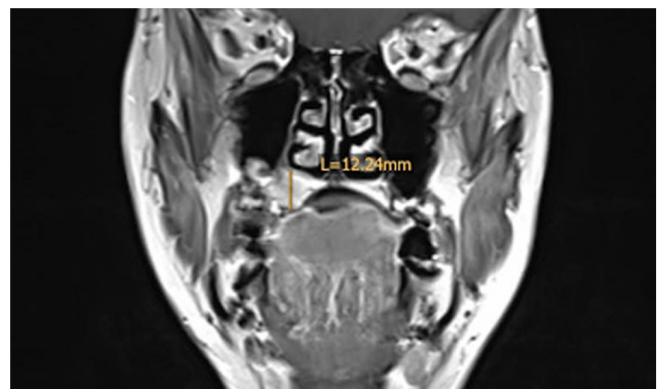


Figure 3. MRI examination revealed a tumour measuring 18x16x12 mm in the right hard palate. Suspected lymph nodes were observed on both sides of the neck.

probe was positive. Considering the findings of histopathological and immunohistochemical examinations, and the FISH results with proof of a break in the ETV6-gene (12q13), the diagnosis of MASC was confirmed (Figs. 5-8). Based on these findings, the tumour stage was defined as follows: pT4a, pN2c (2/37), pL0, pV0 and pPn0 (8th Edition of the

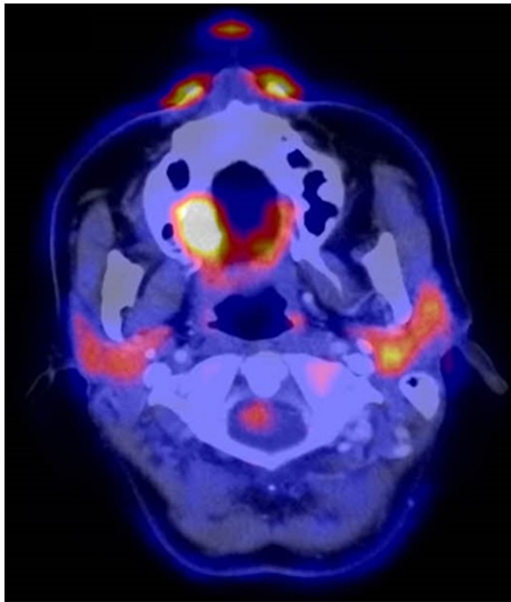


Figure 4. Positron emission tomography-CT revealed an FDG-avid tumour mass in the right hard palate and contralateral cervical lymph node metastases. A second FDG-avid lesion in the pharynx exhibited no sign of malignancy on biopsy. FDG, [^{18}F]-fluorodeoxyglucose.

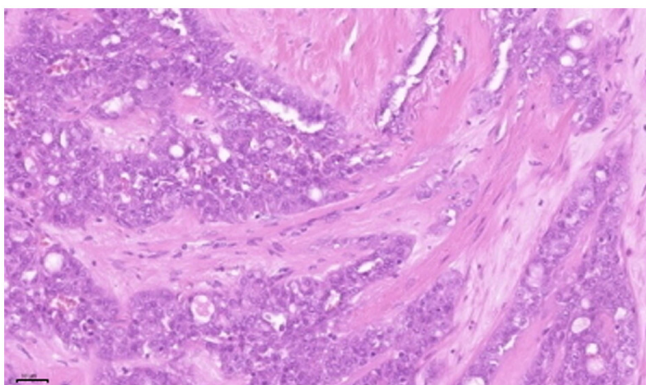


Figure 5. HE staining of the resectate (magnification, x20; scale bar, 50 μm). On microscopic examination, the tumour was solid, microcystic and tubular, with fibrous septa. The tumour cells appeared monomorphic and round-oval, with small nucleoli and fine granular chromatin. The cytoplasm was weakly eosinophilic and partly vacuolated.

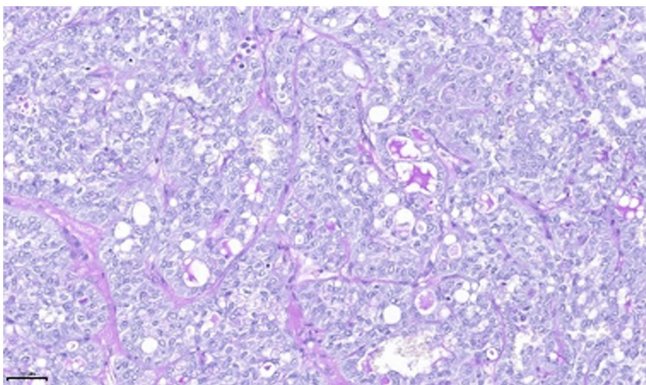


Figure 6. PAS staining of the resectate (magnification, x20; scale bar, 50 μm). Eosinophilic and PAS-positive secretions are evident in the microcystic areas. PAS, Periodic acid-Schiff.

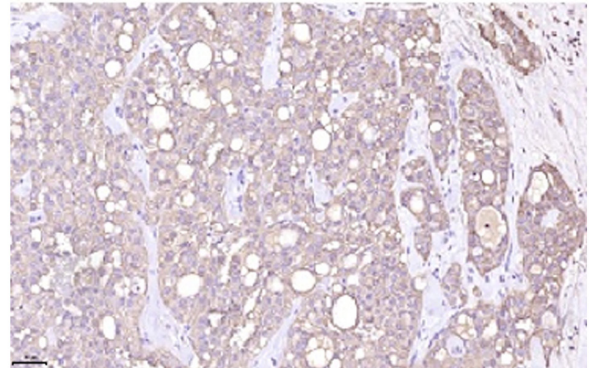
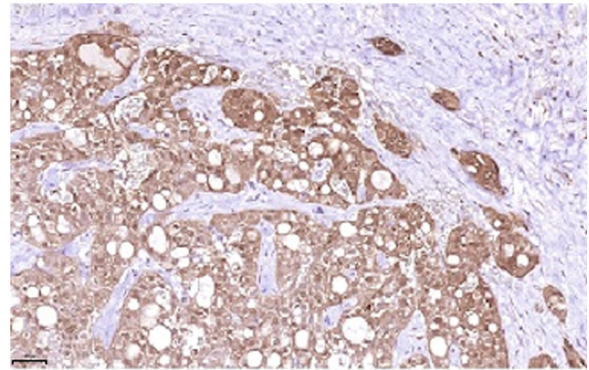


Figure 7. Immunohistochemical examination of the resectate (magnification, x50; scale bar, 50 μm) revealed specific positivity for S100 (top panel) and specific cytoplasmic positivity for mammaglobin (bottom panel).

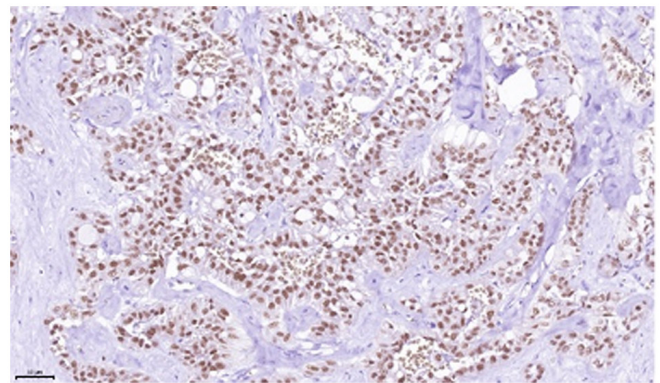


Figure 8. Immunohistochemical examination of the resectate (magnification, x50; scale bar, 50 μm) revealed specific nuclear positivity for GATA3.

TNM Classification, 2017) (14). Due to the several high-risk characteristics of this tumour, including bone invasion and contralateral nodal metastases, adjuvant radiochemotherapy with 30 rounds of radiation (dynamic volumetric modulated arc therapy; 54.00/66.00 Gy) and cisplatin (a cumulative dose of 200 mg/m^2 body surface area) was performed. A radiation dose of 54.00 Gy was delivered to the area of lymphatic cervical drainage, and 66 Gy was delivered to the area of the tumour in the hard palate.

The postoperative course was uneventful, and the patient has visited our outpatient centre regularly to date (last follow-up visit, March 2021), without signs of recurrence. The postoperative clinical examination revealed limited abduction

of the shoulder and limited opening of the mouth, for which physiotherapy and exercises were performed.

Discussion

MASC is a rare type of head and neck cancer that mostly affects the major salivary glands. As a malignant tumour, preoperative staging examinations are necessary, including clinical examination, radiological imaging, and histological, immunohistochemical and molecular genetic examinations.

In the case presented herein, preoperative imaging revealed a tumour measuring 18x16x12 mm, with bony infiltration of the right hard palate and cervical lymph node metastases. Suspected lymph node metastases were shown on both sides of the neck on MRI and CT scans. By contrast, FDG-PET/CT scan only showed suspected lymph nodes on the contralateral side of the neck. There were no signs of distant metastases.

Histological examination revealed a malignant tumour of a minor salivary gland, and immunohistochemical examinations confirmed the diagnosis of MASC by showing the typical characteristics of this entity. To verify the diagnosis of MASC, several differential diagnoses had to be excluded. In a retrospective review, Chiosea *et al* (15) reported that 11 of 89 (12.4%) patients with MASC were incorrectly diagnosed with acinic cell carcinoma (AciCC), and 14 of 37 (37.8%) patients were incorrectly diagnosed with adenocarcinoma (AC). In particular, MASC and AciCC share histological similarities. Although AciCC is characterized by basophilic cytoplasm and zymogen granules, MASC cells typically have eosinophilic cytoplasm and no zymogen granules, which was consistent with the histopathological findings of the present case. However, zymogen-poor AciCCs are very difficult to differentiate from MASCs (1,6,16). Strong S100 protein and mammaglobin expression levels may help differentiate between the two entities, as these findings exclude AciCC (6,10,17). Another important differential diagnosis of MASC is AC, which can express S100 and mammaglobin and is typically observed in the minor glands (6). Other differential diagnoses, such as cystadenocarcinoma (CAC) and mucoepidermoid carcinoma (MuC), must also be considered (6). Due to these findings in some cases, histopathological and immunohistochemical examinations do not ensure the accurate diagnosis of MASC. In these cases, detection of the t(12;15)(p13;q25) translocation (ETV6-NTRK3 fusion gene) may help differentiate between MASC and other similar tumours (3,6). The ETV-6 gene encodes a tyrosine kinase that regulates cell proliferation and differentiation. Considering only salivary gland neoplasms, this translocation is highly specific for MASC (3,7). In the case presented herein, immunohistochemical and molecular genetic examinations confirmed the diagnosis of MASC.

As the existing literature is limited, no consistent therapy guidelines are currently available for this tumour entity. In the literature, the majority of the patients received treatment based on histochemical similarities and similar growth patterns analogous to other low-grade malignancies or AciCC, and underwent surgery with or without adjuvant radiation or chemoradiation (6,10,13). In a review of the literature, primary radiotherapy or chemoradiation were not considered as common therapeutic options (17). Therefore, only one

case report was found concerning a patient with MASC who was treated with primary radiotherapy. That patient had a locally advanced MASC of the parotid gland, without nodal or distant metastases. The patient received radiation (66 Gy) with cetuximab and achieved stable disease. Cetuximab is an EGFR-TRKI which, along with other TRKIs, may be useful for treating MASC (18).

For sufficient tumour resection, a clinical safety margin of 10 mm is considered to be appropriate, and it is obligatory in head and neck squamous cell carcinoma according to German guidelines (19). Currently, no valid data are available on whether selective neck dissection in patients with a negative nodal status improves patient outcomes and overall survival. In the present case, two nodal metastases were identified at level Va on the contralateral side of the neck, although MASC is normally a low-grade malignancy and nodal metastases are rare. Chiosea *et al* (15) reported cervical nodal metastases in 6/34 patients (17.6%). In another study, 4/18 (22%) patients had nodal metastases (6), which were mostly observed in patients with a higher T stage (T3 or T4) and submandibular gland tumours (17). Owing to the small number of cases in those studies, a distinct recommendation for neck dissection cannot be given. However, the data indicate that patients may benefit from selective neck dissection, even when imaging examinations are negative for nodal metastases. Levels I, II, III and Va are more likely to be affected by nodal metastases from MASC, similar to other oral malignancies (20,21). For cases with a positive nodal status, uni- or bilateral neck dissection of levels I-V should be performed, and adjuvant radiation or chemoradiation is necessary due to the more aggressive tumour behaviour (22). In cases of a low-grade malignancy without nodal metastases, surgery alone may be sufficient (6). Based on the MRI and CT findings in the present case, bilateral radical neck dissection was performed. Histopathological examination of the resectate detected two (2/37) lymph node metastases corresponding to the lesions on FDG-PET/CT on the contralateral, but not the ipsilateral, side of the neck. Lymph nodes on the ipsilateral side may have appeared enlarged and suspicious on MRI and CT due to the preoperative biopsy performed in a private practice. Of note, a biopsy should be preferably performed after imaging examinations to prevent the detection of false-positive lymph nodes and overtreatment (23). In the present case, nodal dissection of the lower ipsilateral levels may have been prevented by this approach, further demonstrating the higher specificity of FDG-PET/CT for detecting cervical nodal metastases compared with CT and MRI (24,25). Currently, FDG-PET/CT is not routinely performed in patients with head and neck cancer due to the lack of clear recommendations, limited availability and high cost.

Due to the positive nodal status, the patient received adjuvant chemoradiation with cisplatin and 66 Gy. It is unclear whether chemoradiation is superior to radiation. In a study by Sethi *et al* (17), only 2/86 (2.3%) of patients with MASC received adjuvant chemotherapy, in contrast to 21/86 (24.4%) patients who received radiation without chemotherapy. This approach is supported by a review in 2019 comparing the treatments received by 7,342 patients with salivary gland cancer. The patients were separated into different subgroups

by histological subtype. The patients had AciCC (20.6%) and mucoepidermoid carcinoma (36.4%), but not MASC. The treatment differed significantly across the subgroups. Overall, 42% of the patients with AciCC received surgery and adjuvant radiation, and only 4% received surgery and adjuvant chemotherapy. In this subgroup, the 2- and 5-year overall survival rates for surgery plus radiotherapy vs. surgery plus chemoradiation were 95 and 84% vs. 81 and 63%, respectively (26). If these data are extrapolated to MASC, the treatment for which is similar to that for AciCC, there is no scientific evidence supporting the benefit of adjuvant chemotherapy. Thus, adjuvant radiation appears to be appropriate for high-risk patients with nodal metastases.

Selective TRKI treatment may also be considered for therapy in patients with locally advanced, metastatic or inoperable tumours (27). For example, TRKIs as a treatment option was reported in a clinical study of 55 patients with TRK fusion-positive cancers. MASC was identified in 12 of these patients (21.81%) and was the most frequent entity. All the patients had advanced local tumour or metastases, or had already received standard therapy; therefore, they were treated with the TRKI larotrectinib. Larotrectinib at 100 mg was administered twice per day until tumour progression, the occurrence of adverse events, or withdrawal from the study. Of the 55 patients, 7 (13%) had a complete response, 34 (62%) had a partial response, 7 (13%) had stable disease, 5 (9%) had progressive disease, and 2 (4%) could not be evaluated. The overall response rate was 80%. No difference in therapy efficiency was observed across the subgroups. Of note, of the 12 patients with MASC, only 1 had progressive disease, while the remaining 11 patients exhibited a partial or complete response to larotrectinib therapy. Consistently, the European Medicines Agency approved larotrectinib for the treatment of solid tumours with NTRK gene fusion, including MASC. Another potential treatment option is entrectinib, which has also been approved for the treatment of TRK-expressing tumours. Several phase 1 and 2 studies, such as ALKA, STARTRK-1 and STARTRK-2, are investigating the potential benefits of entrectinib for the treatment of cancers with detected molecular alterations in the TRK1, TRK2 and TRK3 genes (28). STARTRK-2, in particular, includes patients with salivary gland tumours harbouring a NTRK3 gene fusion, similar to that in MASC. In addition to entrectinib and larotrectinib, which are two approved therapy options, other TRKIs, such as sitravatinib, cabozantinib, belizatinib, and several more, have been evaluated in clinical trials (29).

These data indicate a potential therapy option for patients with relapse after standard therapy, patients with inoperable tumours (locally advanced and/or metastatic), or those under palliative care (30), and underscore the significance of molecular diagnostic methods to detect the ETV6-NTRK3 fusion gene. It may be of value to re-evaluate whether this fusion gene is present in patients with inoperable salivary gland tumours and those under palliative care. This approach appears to be appropriate, as MASC is often initially misdiagnosed as AciCC, AC, CAC or MuC; thus, molecular diagnosis may uncover new therapy options.

Adequate follow-up must be applied postoperatively. A mean follow-up period of 5 years with imaging examinations

at specific intervals appears to be appropriate. We suggest that the first imaging examination be performed 6 months after surgery, followed by imaging once per year until follow-up is completed. In the first 2 years and in high-risk patients the intervals between assessments should be shorter (every 3–4 months).

This case underscores the need for sufficient staging examinations and accurate diagnosis, which are crucial for selecting the optimal therapy procedures and may uncover different (molecular) treatment options for patients receiving palliative care. If a local tumour without nodal or distant metastases is detected, surgery alone should be performed. However, when aggressive tumour behaviour and nodal metastases are observed, selective neck dissection should be considered, even when the nodal status is negative. If the nodal status is positive, ipsi- or bilateral neck dissection of levels I–V and adjuvant radiation or chemoradiation are necessary. The benefits of chemotherapy remain unclear. New molecular targeted therapies with TRKIs, such as larotrectinib and entrectinib, may be promising treatment options for patients with advanced inoperable disease and underscore the need for molecular diagnosis in selected cases.

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Availability of data and materials

Clinical data and complementary examinations are available from the corresponding author on reasonable request.

Authors' contributions

AS, RB and SH accrued all data, obtained the patient's informed consent and drafted the manuscript. AS, RB and AK have seen and can confirm the authenticity of the raw data. SS provided the histopathological information and images of the obtained resectate. All the authors have contributed to writing the manuscript. AS, RB, JH, CL, AF and UMR prepared the final version of the manuscript. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patent consent for publication

Written informed consent was obtained from the patient regarding the publication of the case details and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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