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Case Report

Comprehensive diagnosis and treatment of ductal carcinoma of the submandibular gland: case report and literature review

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Abstract: Salivary duct carcinoma (SDC) is a rare malignant tumor of the salivary gland and is most commonly found in the parotid gland, followed by the submandibular gland. Due to its rarity, there is no consensus on its treatment. Surgical resection is currently the only curative treatment. Considering its high degree of malignancy, extensive tumor resection and postoperative adjuvant radiotherapy are recommended. We report a rare case of SDC of the submandibular gland. A 62-year-old man presented to our hospital with complaints of swelling in the right submaxillary area for 4 months, rapidly growing, with pain for 10 days. After admission, fine needle aspiration (FNA) revealed right submandibular gland ductal carcinoma. Considering its aggressiveness, large size, and invasion of parapharyngeal and oral floor soft tissues, the patient received two cycles of neoadjuvant chemotherapy followed by extended surgical resection. Postoperatively, the patient received four cycles of concurrent chemoradiotherapy, followed by afatinib targeted therapy. No recurrence or metastasis was observed in a 45-month follow-up. Thus we present a comprehensive treatment for salivary duct carcinoma combining neoadjuvant chemotherapy with surgery, postoperative concurrent radiotherapy, and chemotherapy followed by afatinib targeted therapy.

Keywords: Submaxillary gland, ductal carcinoma, salivary gland, salivary gland malignancy

Introduction

Salivary duct carcinoma (SDC) is a high-grade malignant tumor originating from reserve cells of the interlobular ductal secretory ducts of the salivary gland or malignant transformation of the secretory ducts of pleomorphic adenomas, accounting for approximately 5-10% of all salivary gland malignancies [1]. SDC of the salivary gland was first reported by Kleinsasser in 1968 who noted that it is morphologically similar to high-grade ductal carcinoma in situ of the breast. In 1991, the World Health Organization (WHO) officially classified it as a separate type of tumor in the classification of salivary gland tumors [2]. SDC is one of the most aggressive salivary gland tumors and is most commonly found in the parotid, followed by the submandibular gland, sublingual gland, and palate [3]. Most patients come to the hospital with a late stage malignant tumor with cervical lymph node metastasis. Despite surgery and adjuvant chemotherapy, the overall prognosis is poor. Most patients will have local recurrence or distant metastasis within 2-3 years after surgery and eventually die from tumor metastasis or multi-organ failure [4]. Because of its low incidence rate, worldwide SDC reports rely on small-scale case reports, which can lead to contradictory conclusions and fail to provide effective guidance for diagnosis and treatment. Moreover, SDC has poor response to surgery, radiotherapy, chemotherapy or other treatments. Therefore, comprehensive treatments such as HER2 targeted treatments and receptor tyrosine kinase inhibitors are gaining attention. Many case reports describe successful cases such as targeted therapy and immunotherapy. The purpose of this study is to report the clinical and pathologic characteristics, treatment process, and prognosis of a patient with ductal carcinoma of the submandibular gland admitted to our department, to provide a better understanding of the disease and information for the personalized treatment of SDC.

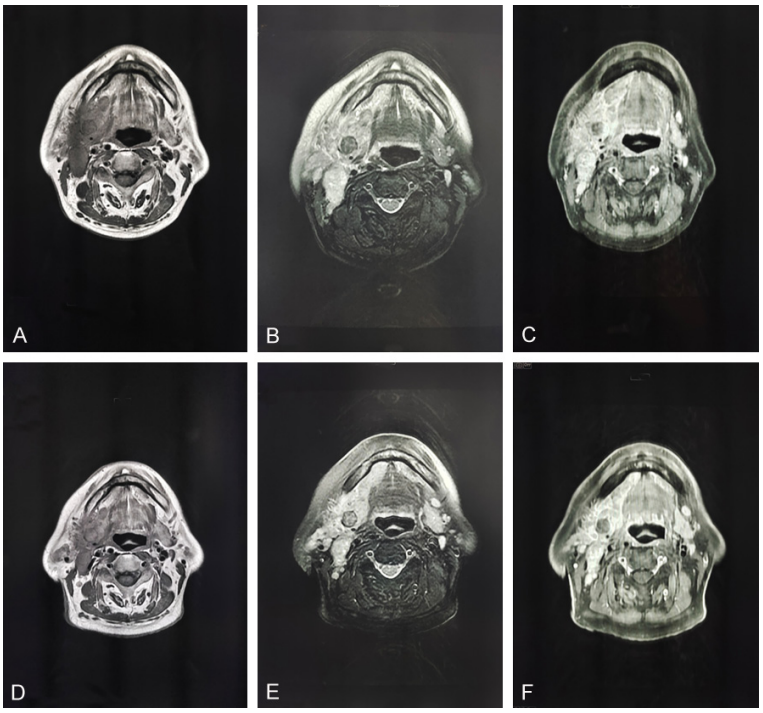

Figure 1. (A-C) Prior to chemotherapy, MRI demonstrates a soft tissue mass in the right submandibular gland area, with obscure margin and uneven signals. TIW1 (A) shows low signal and T2W1 (B) shows slightly higher signal. Enhancement scan (C) demonstrates it was enhanced unevenly, the boundary between the mass and the deep muscles in the right oral floor and the right parapharyngeal space was unclear. (D-F) After two cycles of chemotherapy, the tumor was slightly smaller than before.

Case report

In January 2019, a 62-year-old man was referred to our hospital with the complaints of swelling in the right submaxillary area for 4 months and a rapidly growing swelling with pain for 10 days. The patient had a medical history of chronic obstructive pulmonary disease for two years and hypertension for ten years. Physical examination revealed that the right submandibular area was visibly swollen, the skin surface was dark red, the skin temperature was slightly elevated, and a mass of approximately 6.0 cm × 5.0 cm × 4.0 cm could be palpated. It was hard, fixed, tender, and its boundary was unclear. The tongue had deviated to the right, the first two-thirds of the tongue was numb, and the lower lip was not skewed. A hard mass was palpable on the right side of the floor of the mouth and in the parapharynx. The mass entered the posterior part of the ascending ramus of the mandible, and its upper border was not palpated. In the right submandibular and neck regions, several enlarged lymph nodes in II-V areas could be palpated. They were hard, poorly defined, and poorly mobile, with the larger one measuring 3.0 × 2.0 cm in diameter. A soft tissue mass was detected in the right submandibular gland area on maxillofacial enhanced CT, threrfore, we considered the possibility of submandibular adenocarcinoma. Multiple lymphadenopathies in the right parapharyngeal space, right cervical I and II areas, and the right clavicle area made us consider metastasis. The enhanced MRI showed that the right submandibular gland area occupied space, so we considered the possibility of malignant lesions, multiple metastases in right cervical area II, right parapharyngeal space, right infratemporal fossa space, and right oropharyngeal fundus. Additionally, the adjacent right floor of the mouth and the deep muscles of the right parapharyngeal space may have been involved (**Figure 1**). Next, we performed a PET/CT examination, which indicated signs of a malignant tumor in the right submandibular gland, invading the adjacent medial pterygoid muscle. Multiple lymph nodes were seen in the right parapharyngeal space, right neck I, II, and right clavicular region, and metastasis was considered; multiple lymph nodes were seen in the left submandibular and submental region. FDG uptake suggested possible reactive hyperplasia.

On admission, the diagnosis was right submandibular gland tumor, which was considered malignant with cervical lymph node metastasis. Fine needle aspiration (FNA) was performed under local anesthesia. The histopathological examination revealed microscopically that there were clusters of atypical cells with indistinct borders, large nuclei, visible nucleoli, and easily visible mitotic figures. Immunohistochemistry revealed the following: AE1/AE3 (+), CK7 (+), p53 (mutant +), Ki-67 (about 80% +), AR (+), Her-2 (1+), GCDFP15 (+), S-100 (-), P63 (-), DOG-1 (-), CD117 (-), P40 (-),

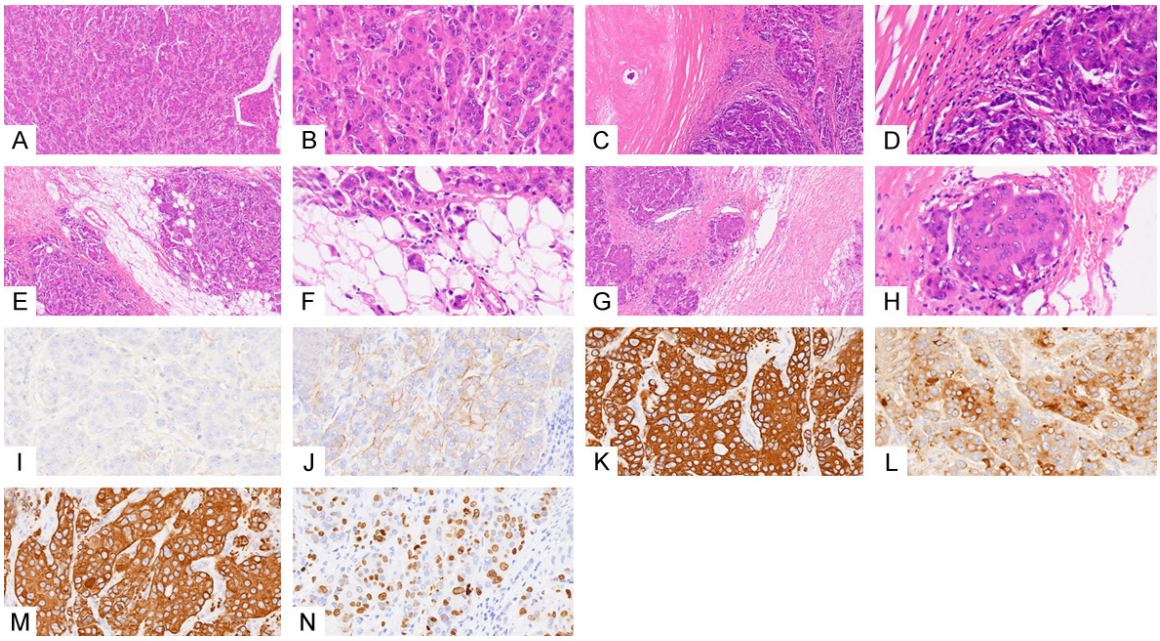

Figure 2. Histologic findings of the tumor. A. H&E of the salivary duct carcinoma (magnification × 10). B. Tumor cells are diffusely distributed and arranged in solid clusters, and lumps, and in some areas, the cells are arranged in cord-like, adenoid, and small clumps. High power microscopy shows the sheet of cells with polymorphic nuclei, eosinophilic cytoplasm, and prominent nucleoli, and pathological mitosis can be seen (magnification × 40). C. H&E of the salivary duct carcinoma (magnification × 10). D. Tumor cells infiltrate surrounding tissues and nerves (magnification × 40). E. H&E of the salivary duct carcinoma (magnification × 10). F. Tumor cells infiltrate surrounding adipose tissues (magnification × 40). G. H&E of the salivary duct carcinoma (magnification × 10). H. Tumor cells infiltrate surrounding blood vessels (magnification × 40). I. Immunohistochemistry with DOG-1 (-) (magnification × 40). J. Immunohistochemistry with HER-2 (2+) (magnification × 40). K. Immunohistochemistry with CK19 (+) (magnification × 40). L. Immunohistochemistry with GCDFP-15 (+) (magnification × 40). M. Immunohistochemistry with CK7 (+) (magnification × 40). N. Immunohistochemistry with Ki-67 about 70% (magnification × 40).

CK5 (-), ER (-), and PR (-) (**Figure 2**). The final diagnosis was right submandibular gland ductal carcinoma. Considering the high aggressiveness, large size, and invasion of parapharyngeal and oral floor soft tissues, with cervical lymph node metastasis, surgery could not guarantee safe margins to achieve R0 resection. The multi-disciplinary team (MDT) suggested neoadjuvant chemotherapy, then assessed tumor changes, and decided on the next steps in the treatment plan. Thus, we administered two cycles of nedaplatin + paclitaxel chemotherapy (nedaplatin 30 mg, d1-d3, paclitaxel 75 mg/m^2, d1). After two cycles of chemotherapy, the patient reported that the swelling in the right submandibular region was significantly reduced and the pain was relieved. On visual inspection, the right submandibular swelling was improved, and was smaller and more mobile. Enhanced CT showed a mass in the right submandibular gland area, multiple lymph node enlargements in the right cervical region II, right parapharyngeal space, right submandibular, and right oropharyngeal floor possible metastasis, and right mandible invasion. MRI showed a right submandibular gland area mass, right neck area II, right parapharyngeal space nodule, slightly reduced compared to before chemotherapy and right infratemporal fossa space, and right oropharyngeal floor multiple lymph node metastasis with no significant changes. No distant metastasis was found by PET-CT. MDT consultation revealed that clinical symptoms were relieved by neoadjuvant chemotherapy; however, imaging examination did not show significant reduction of the tumor. After comprehensive consideration, extended surgical resection was recommended. The right submandibular ductal carcinoma was resected under general anesthesia, the right mandibular bone was partially resected, and bilateral radical neck dissection was performed. Pathology showed that SDC was multi-nodular in growth, involving nerves. Cancer thrombi were seen in the veins, and cancer infiltration was seen on the surface of the bone tissue of the mandible.

In the right cervical area V 2/6 lymph nodes were positive. In the II, III, and IV areas, 5/17 lymph nodes were positive. 13 lymph nodes in the left cervical area did not show metastasis, and all surgical margins were negative.

Gross inspection showed that the right submandibular gland resection specimen had a piece of irregularly shaped solid masses attached to the bone, with a size of 10.0 cm × 9.0 cm × 4.0 cm. There was an incision along the maximum diameter. Bone tissue size was 6.0 cm × 5.0 cm × 2.0 cm. The size of surrounding salivary gland tissue was 8.0 cm × 7.0 cm × 4.0 cm forming an irregular solid mass, some of which may be accompanied by cystic change or necrosis. The lesion boundary was unclear, but a malignant component could be seen on the surface of the mandible. The tumor invaded the adjacent pterygoid muscle and the right parapharyngeal space tissue. The section of the tumor tissue was gray-white, the texture was medium, and a small capsule could be seen locally.

Microscopic analysis revealed that the tumor cells were arranged in solid clusters, and in some areas, the tumor cells were arranged in cord-like, adenoid form, or small clumps. High-power microscopy showed that the tumor cells were round, oval, or polygonal, with abundant eosinophilic cytoplasm. Occasionally, the phenomenon of parietal pulp secretion and cytoplasmic vacuolization changes were seen. They had large, round or oval nuclei, deep staining, obvious nucleoli, high nucleocytoplasmic ratio, and frequent mitotic figures. Fibrosis and hyaline degeneration in the tumor stroma with lymphocytic infiltration may also occur. SDC tumor cells often infiltrated surrounding tissues, blood vessels, lymphatic vessels, and nerves. Immunohistochemistry: AR (+), Her2 (2+), Ki-67 (approx. 80% +). Genetic testing showed mutations ERBB2-p.Asp769His, ERBB2-p.His878Tyr, and no HER-2 amplification.

Tumor stage was determined as pT4bN2bM0. Postoperatively, four cycles of concurrent chemoradiotherapy were administered to the tumor area and lymph node metastasis area, followed by oral afatinib targeted therapy (40 mg/day, 22 months in total). No recurrence or metastasis was observed at the 45-month follow-up.

Discussion

Salivary gland tumors constitute approximately 3% of head and neck tumors. The most common are parotid gland tumors, accounting for about 70-80%; submandibular gland tumors account for only 10%. Salivary duct carcinoma or SDC is a rare malignant tumor of the salivary gland, most commonly found in the parotid gland (about 70%), followed by the submandibular gland (about 20-25%), sublingual gland, and minor salivary gland [5]. SDC predominantly affects men and is more common in middle-aged and elderly people. According to the literature, the age of onset is approximately 60-70 years, with a male-to-female incidence rate of about 3:1 [6]. SDC often presents as a rapidly enlarging mass in the parotid and submandibular regions within a short period of time, and the disease duration is usually six months. Local pain and facial nerve palsy may accompany the mass in the parotid gland, while the mass in the submandibular region may be accompanied by palsy of the lingual and sublingual nerves. Approximately 20% of SDCs develop from pre-existing benign lesions such as pleomorphic adenomas, thus the disease course is longer and the prognosis of cancerous changes originating from pleomorphic adenomas is better than that of new SDCs [7]. SDC is characterized by high malignancy, aggressiveness, rapid disease progression, lymph node involvement, high rates of local recurrence and distant metastasis, and high mortality rate. Local lymph nodes and even distant metastases are often revealed during consultation. According to related studies, about 54%-82% of the patients had metastases in the cervical lymph nodes at the first visit, the rate of distant metastases during treatment and follow-up could reach up to 18%-63%, and the most common distant metastatic sites were lung and bone [8, 9]. Uijen et al. [10] reported that some SDC patients had distant metastases at the first visit, and that approximately 50% of patients with no distant metastases at follow-up developed distant metastases with a median duration of only 16 months and the common distant metastatic sites were lung (approx. 54%), bone (approx. 46%), and, in a few patients, the brain (approx. 18%). In our case, the tumor was located in the right submandibular gland, which is the second most common localization of SDC. The patient age

was 62 years, which is the age of predilection. A mass was present in the right submandibular area mass for four months, and the mass increased rapidly with pain over 10 days until hospitalization. Examination showed a right submandibular area mass, with invasion of surrounding tissues such as the right mandible and parapharyngeal space, multiple lymphadenopathies in the right neck, and possible metastasis. This was consistent with the biological characteristics of SDC reported in the literature, such as strong invasiveness and early lymph node metastasis.

For most typical SDCs, the diagnosis can be confirmed based on hematoxylin-eosin (H&E) staining, and immunohistochemistry can further confirm the diagnosis and determine prognosis, and guide treatment. In typical SDCs, CK (+), EMA (+), CK7 (+), AR (+), GCDFP15 (+), S-100 (-), P63 (-), P40 (-), CK5 (-), ER (-), PR (-). Histopathology of SDC needs to be differentiated from adenoid cystadenocarcinoma, mucoepidermoid carcinoma, and epithelial-myoepithelial carcinoma. (1) Adenoid cystadenocarcinoma: This tumor grows slowly, has a long history of disease, and often invades extensively along the nerve path, while SDC has a high degree of malignancy, a fast growth rate, and a short history of the disease. Microscopically, the tumor cells of adenoid cystic carcinoma are small, have less cytoplasm, a large nucleus, deep staining, and a larger nucleus. The tumor cells of SDC are large, eosinophilic, and have rich cytoplasm. Sometimes there may be apocrine secretion in tumor cells. The morphological characteristics of SDC are partially crossed with adenoid cystic carcinoma, but adenoid cystic carcinoma is often accompanied by myoepithelial differentiation. Immunohistochemistry shows S-100, CEA positive, CK weakly positive, and EMA negative, it can be distinguished from SDC. (2) Mucoepidermoid carcinoma: The tumor is rich in mucus, which is easily confused with the mucoid type. Under the microscope, epidermoid, intermediate, and mucoid tumor cells are found in the tumor. There can be keratinization in the epidermoid cells. The mucoid cells are columnar, the cytoplasm is transparent and basophilic. Tumor tissue usually lacks sieve and papillary structure. There are no obvious epidermoid and myxoid tumor cells in SDC tumors, and there is no keratinization in the tumor cells. Sieve structure and papillary structure are often seen in the tumor. Immunohistochemistry of mucoepidermoid carcinoma is negative for AR and HER2, and positive for CK5/6 and p63, while immunohistochemistry of SDC is usually negative for CK5/6 and p63. (3) Epithelial-myoepithelial carcinoma: The most characteristic pathological manifestation o is a double-layer glandular tubular structure. The inner layer is myoepithelial cells, and the outer layer is glandular epithelial cells. The immunohistochemical outer layer of glandular epithelial cells expresses CK, and the medial myoepithelial cells express S-100 and SMA, AR negative. (4) Pleomorphic adenoma: This tumor is common in young and middle-aged women aged 20-40 years. The tumor often contains more cartilaginous and mucus-like components and has a complete capsule, and rarely invades surrounding tissues. On the whole, it often appears as a clear and smooth mass, which can be accompanied by cystic changes, with relative characteristics. However, SDC tumor has no capsule, the focus boundary is unclear, and often invades the surrounding tissue structure, so the two are easy to distinguish. Under the microscope, pleomorphic adenoma and malignant adenocarcinoma components, the tumor cells lack much pleomorphism. In addition to the formation of adenoid and tubular structures, it can also be seen that tumor cells form cysts due to lumen expansion. Immunohistochemical staining shows that tumor cells often express positive myoepithelial markers, whereas SDC tumor cells are obvious in pleomorphism, and mitotic figures are common. Fibrous tissue hyperplasia and hyaline degeneration can be seen in the SDC tumor stroma. Immunohistochemical staining shows that tumor cells do not express myoepithelial markers. In our patient, microscopically we observed clusters of nest-like arrangement of heterogeneous cells with indistinct borders, large, deeply stained nuclei, distinct nucleoli, and easily visible mitotic figures, and immunohistochemical stainings for AE1/AE3 (+), CK7 (+), Ki-67 (approx. 80% +), AR (+), Her-2 (2+), GCDFP15 (+), and S-100 (-), which were consistent with the microscopic features and immunohistochemical expression reported in the literature. It was relatively easy to diagnose submandibular ductal carcinoma.

Expression of immunohistochemistry in SDC patients correlates with treatment and prognosis. The Her-2 expression in SDC is variable; 2+ and 3+ accounting for 16.67% and 33.33%,

respectively, and Her 2 expression is negatively correlated with disease-free survival in SDC but not with overall survival [11]. The Takase study suggested that P53 mutations are associated with poor prognosis in SDC and assessed the prognosis of SDC according to AR, Her-2, and Ki-67 expression, "Apocrine A" type (AR (+), Her-2 (-), Ki-67 <40%) had the best prognosis. Our patient's tumor was AR (+), Her-2 (2+), and Ki-67 (about 80% +), suggesting a poor prognosis [12]. GCDFP15 is often highly expressed in SDC, suggesting that there may be some similarities with the origin and pathogenesis of ductal carcinoma of the breast, and Her-2 is also highly expressed in some cases. The analysis of Williams et al. [13] showed that the AR-positive rate was 97.8% and AR negative SDC was very rare, and all previously reported AR-negative SDC was eventually classified as other tumor types. A clinical study by Kamata et al. suggested that androgens could promote SDC cellular value-added and AR receptor blockers could inhibit tumor cell proliferation and thus slow down SDC progression [14]. Ki-67 represents the value-added index of cells, and higher values represent more active cellular value-added, higher malignancy, and higher recurrence and metastasis rates. Takase's statistical analysis showed that the average Ki-67 of SDC was about 34.8%-44%, indicating highly malignant behavior of SDC [12].

SDC is aggressive, and the main treatment modality is extended resection of the tumor and cervical lymph node dissection. For tumors located in the parotid gland, the facial nerve is usually not preserved; for those in the submandibular gland, adjacent tissues should be excised in an extended manner and the invaded mandible, lingual nerve, and other tissue structures should be extended and resected together. SDC is highly aggressive and patients are often in the middle to late stage of the disease at the time of consultation. A multicenter study in Japan showed that 65%-66% of patients had tumors at stage T3 or T4 at the time of consultation [15, 16]. Two studies totaling more than 800 SDC studies showed that 40-42% of patients had tumors at T3 and T4 stages at the time of presentation [17, 18]. T3 and T4 stages were negatively associated with disease-free survival and metastasis-free survival [11]. Analysis of 22,653 parotid malignancies in the US National Cancer Database showed that the rate of lymph node metastasis in parotid SDC was 54%, much higher than the rate of lymph node metastasis in other types of parotid malignancies (about 24%) [17]. Tumor diameter >3 cm and T3 and T4 stages were risk factors for lymph node metastasis [19]. A study of 20 SDC by Gilbert [20] showed that 69% of patients had nerve invasion and 61% had lymphovascular invasion. Lymph node metastasis and nerve invasion are biological features of SDC. A study of 304 SDC cases found nerve invasion in 44% of cases and positive lymph node metastasis in 59% of cases. Cervical lymph node dissection was performed in cases where cN0 was considered preoperatively, and positive lymph node metastasis was confirmed by postoperative pathology in approximately 50% of the cases. Therefore, lymph node dissection is essential for preoperative FNA-confirmed SDC cases. It is recommended to perform at least ipsilateral lymph node dissection, and in cases where preoperative confirmation is difficult and SDC is considered intraoperatively, frozen pathology of the primary lesion and lymph nodes is feasible, and the extent of surgery is decided based on the frozen pathology results [21, 22]. Several retrospective studies support radiotherapy after SDC. Especially for cases with tumor diameter >3 cm, positive-margins, and positive lymph node metastases, radiotherapy can control local lesions and improve overall survival [22, 23]. The 2022 NCCN guidelines for head and neck tumors recommend radiotherapy after SDC regardless of tumor stage or margin status [24]. Lee et al. [25] on postoperative radiotherapy for SDC noted that adjuvant radiotherapy after surgery was beneficial for local lesion control but did not control distant metastases and did not improve survival in SDC. A retrospective study by Qian et al. [26] came to a similar conclusion that radiotherapy was useful in the local control of tumors, especially for stage T4 tumors; it also noted that stage N2-3, IV, and V lymph node metastases, cleared specimen-positive lymph nodes >8, and extra-nodal invasion were factors affecting poor prognosis. In cases where surgery is not appropriate, palliative radiotherapy and chemotherapy are recommended, but it is controversial whether chemotherapy is beneficial. There are no prospective studies on adjuvant radiotherapy and chemotherapy after surgery, and in most reports, postoperative radiotherapy is recommended, while the role of chemotherapy in adjuvant postoperative treatment is unclear. In cases of

recurrence or distant metastases, chemotherapy has been attempted in some medical institutions [18]. In a retrospective study, cyclophosphamide, adriamycin, and cisplatin were used in recurrent or metastatic salivary malignancies, and SDC was more sensitive to chemotherapy compared to adenoid cystic carcinoma and mucinous epidermoid-like carcinoma [27]. SDC is more common in men and has a high rate of positive immunohistochemical AR, so androgen deprivation therapy has been applied to treat SDC, but mostly in small studies, the responses to which have varied. In a retrospective study by Locati, eight patients with recurrent, metastatic SDC were treated with androgen deprivation therapy, of whom seven had stable disease with no tumor progression and two had complete tumor remission [28]. In a study conducted by Boon on 31 patients with recurrent SDC who were given androgen deprivation therapy, four had partial tumor remission, 10 had stable tumors with no progression, and the remaining 17 had progression [29]. The expression of Her-2 in SDC is variable compared to the expression of AR. Trastuzumab, a Her-2 inhibitor, has been shown to have definite efficacy in Her-2-positive breast cancer, with higher efficiency in combination with paclitaxel, and some medical institutions have now started to experiment with trastuzumab for Her-2-positive recurrent or metastatic SDC. Limaye treated 13 SDC patients with trastuzumab; in eight of these cases it was part of postoperative adjuvant therapy (concurrent radiotherapy plus chemotherapy (paclitaxel, carboplatin, trastuzumab)) and in five it was part of palliative therapy for postoperative recurrence or metastasis (paclitaxel, carboplatin, trastuzumab), and the results showed that eight patients with adjuvant therapy had no tumor recurrence and no metastasis within two years, and the five patients with palliative therapy had tumor control and remission with a mean 18 months without significant tumor progression [30]. In a study by Takahashi, 48 Her-2-positive recurrent or metastatic salivary gland cancers are given trastuzumab and docetaxel had an overall efficacy rate of approximately 76% and a median progression-free survival of 9.8 months after treatment [31]. In a study of 323 recurrent/metastatic SDC patients, combining trastuzumab with the androgen deprivation therapy group had a significant survival benefit, and overall patient survival was significantly longer when trastuzumab or androgen deprivation therapy was administered alone [32]. Based on the retrospective studies mentioned above and the actual situation of our patient, preoperative FNA confirmed the diagnosis of SDC, two cycles of neoadjuvant chemotherapy was given followed by enlarged tumor resection and bilateral radical neck dissection, postoperative concurrent chemoradiotherapy, and oral afatinib maintenance therapy after the end of radiotherapy and chemotherapy, and at 45 months of follow-up, no recurrence or metastasis was observed.

In conclusion, SDC is a rare, highly malignant head and neck tumor prone to local recurrence and distant metastasis; early detection, early diagnosis, surgical enlarged resection, and cervical lymph node dissection are the keys to improving the prognosis of this disease. At present, the data on the analysis of SDC cases are limited. With the continuous development of chemotherapy, targeted therapy, and androgen receptor inhibitor therapy, it is expected that there will be more treatment methods to improve its prognosis in the future.

Disclosure of conflict of interest

None.

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