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CASE REPORT

Metastatic Laryngeal Minor Salivary Gland Carcinoma to the Liver: Successful Treatment with Anti-EGFR-Based Combination Therapy - A Case Report and Literature Review

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Abstract: Laryngeal minor salivary gland carcinoma is a rare malignancy, accounting for less than 1% of laryngeal cancers. We present a case of a 43-year-old male with a history of surgically resected laryngeal ductal carcinoma who developed liver metastases. Initial pathology from the liver lesion was inconclusive, leading to a misdiagnosis of intrahepatic cholangiocarcinoma. After progression on first-line chemotherapy and immunotherapy, the diagnosis was revised to metastatic laryngeal minor salivary gland carcinoma, supported by positive EGFR expression. Second-line treatment with the anti-EGFR agent cetuximab, combined with immunotherapy and chemotherapy (sindilizumab, albumin-bound paclitaxel, and S-1), resulted in a sustained partial response. This case highlights the diagnostic challenges of this rare tumor and suggests the potential efficacy of anti-EGFR therapy in EGFR-expressing metastatic laryngeal salivary gland carcinoma. Given the rarity and aggressive nature of primary laryngeal salivary duct carcinoma, it remains a significant challenge for both diagnosis and treatment. The current case underscores the difficulty in identifying the primary tumor site, especially when metastasis occurs. Additionally, the effectiveness of anti-EGFR therapy in EGFR-expressing tumors offers a promising treatment avenue. Further research is essential to establish standardized treatment protocols, identify predictive biomarkers, and optimize combination strategies for this uncommon malignancy.

Keywords: laryngeal minor salivary gland carcinoma, secondary liver malignancy, anti-EGFR therapy, immune checkpoint inhibitors, case report

Introduction

Laryngeal cancer accounts for about 5% of head and neck tumors, with squamous cell carcinoma being the most common type, representing around 95% of single laryngeal malignancies. Other less common types include neuroendocrine tumors, small salivary gland tumors, soft tissue sarcomas, bone/cartilage sarcomas, malignant melanomas, and lymphomas.[1] In accordance with the WHO Histological Classification of Salivary Gland Tumours, salivary gland tumours are categorised as adenoid cystic carcinoma, mucoepidermoid carcinoma and adenoalveolar cell carcinoma, among others.[2] Laryngeal minor salivary gland carcinoma is rare, comprising less than 1% of laryngeal malignancies.[3] It is more common for minor salivary gland carcinoma of the larynx to occur in the supraglottic and subglottic regions. The distribution of salivary glands in the larynx is closely related to the anatomical subdivisions of the larynx. The density of these glands gradually decreases from the supraglottic to the glottic and subglottic regions, with the total distribution density of the glands being approximately 23–47 glands per cm². A substantial number of minor salivary glands are situated in the supraglottic region, including the ventricular band, aryepiglottic folds and epiglottis. Additionally, the

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subglottic and glottic regions may also exhibit salivary gland distribution.[4] For laryngeal minor salivary gland tumors, the primary treatment is surgical resection to control local and regional lesions. In cases of unresectable or distant metastases, targeted therapies such as trastuzumab, androgen deprivation systemic therapy, and anti-EGFR therapy may be effective treatment options. To the best of our knowledge, only three prior cases of primary laryngeal salivary gland carcinoma have been reported in the English literature, including one sarcomatoid variant.[5–7] The present case, therefore, adds to a very limited body of knowledge concerning this formidable entity in a critical anatomical location.

Case Presentation

The patient is a 43-year-old male with an Eastern Cooperative Oncology Group (ECOG) score of 1, who was admitted to the hospital with a chief complaint of right abdominal pain for a duration of over ten days, and with evidence of hepatic occupancy for eight days. The patient underwent surgery for laryngeal cancer at Peking Tongren Hospital in April 2021. The postoperative pathology report revealed the presence of ductal carcinoma in the larynx, with invasion of the thyroid cartilage plate. Additionally, tumour involvement was observed in the metanephric and cricocephalic spaces bilaterally, along with the presence of an intralesional tumour thrombus. However, no evidence of cancer metastasis was identified in the peri-tracheal lymph nodes (0/4). Genetic analysis revealed the presence of wild-type RAS and the absence of ERBB2 amplification. The patient was subsequently treated with postoperative adjuvant radiotherapy at a dose of 66Gy delivered in 33 fractions. After admission, a CT (Computed Tomography) scan of the cervicothoracic and abdominopelvic regions was conducted in December 2023, revealing multiple occupying lesions in the liver. In January 2024, a CT scan-guided liver puncture was performed. The pathology of the puncture showed adenocarcinoma. Immunohistochemistry did not demonstrate clear evidence of marker expression, suggesting an uncertain histological origin. The immunohistochemical analysis revealed that the tumor was negative for AR (androgen receptor), positive for EGFR, and HER2 (Human Epidermal Growth Factor Receptor 2) (1+). A consultation at Peking Union Medical College Hospital in Beijing in January 2024 yielded the following results: The liver puncture tissue showed features of adenocarcinoma, which was difficult to differentiate with certainty. The immunohistochemical analysis revealed that the tumor was GCDFP-15 (Partially +), Ki-67 (index 40%), AR (-), CgA (-), Syn (-), GATA3 (+), ER (-), S-100 (-), Mammaglobin (+). In combination with additional immunohistochemistry, the results did not completely exclude cholangiocarcinoma. Further refinement of PET/CT (Positron Emission Tomography/Computed Tomography) in January 2024 revealed multiple occupations in the liver parenchyma, high metabolism, and the presence of malignant lesions (Figure 1). Additionally, there were multiple enlarged lymph nodes in the hepatic portal region and retroperitoneum, high metabolism, and the possibility of metastasis. The preliminary diagnosis was intrahepatic cholangiocarcinoma, stage IV, MSS (Microsatellite Stable) type, HER2 (1+); laryngeal cancer after surgery. The first-line treatment was given with sindilizumab combined with the GP regimen (Gemcitabine plus cisplatin), based on the ToPAZ-1/KN966 trial data. The evaluation of PD (liver) was reviewed after two cycles. The treatment plan was modified, with the liver lesion now considered to be metastatic. This resulted in a revised diagnosis of laryngeal minor salivary gland carcinoma, stage IV, HER2 (1+), AR (-), EGFR (+), RAS wild-type, MSS type. The second-line treatment comprised sindilizumab combined with cetuximab and an AS regimen (Albumin-bound paclitaxel plus S-1). The assessment of PR was sustained during this period (Figure 2). The patient is currently undergoing irregular follow-up, with no evidence of tumor progression.

Discussion

Non-squamous cell carcinoma of the larynx accounts for a mere 5% of laryngeal cancers. Its pathological types are primarily neuroendocrine tumours, minor salivary gland tumours, soft tissue sarcomas, bone/chondrosarcomas, malignant melanomas and lymphomas.[1] Salivary gland carcinomas account for less than 3% of head and neck tumours.[8] They are classified into major and minor salivary gland carcinomas, with less than 20% of cases arising from minor salivary glands.[9] A study by Shen et al found that 281 of 2123 salivary gland tumours in Southwest China over an 11-year period were from minor salivary glands, accounting for 13.2% of the tumours.[10] The major salivary glands in the human body are the parotid, submandibular and sublingual glands. Enlarged masses of these glands are typically benign. The minor salivary glands, on the other hand, are distributed widely throughout the body. They are found in the oral cavity and pharynx, as well as the upper respiratory and gastrointestinal tracts. Tumorous lesions of this type are usually malignant.

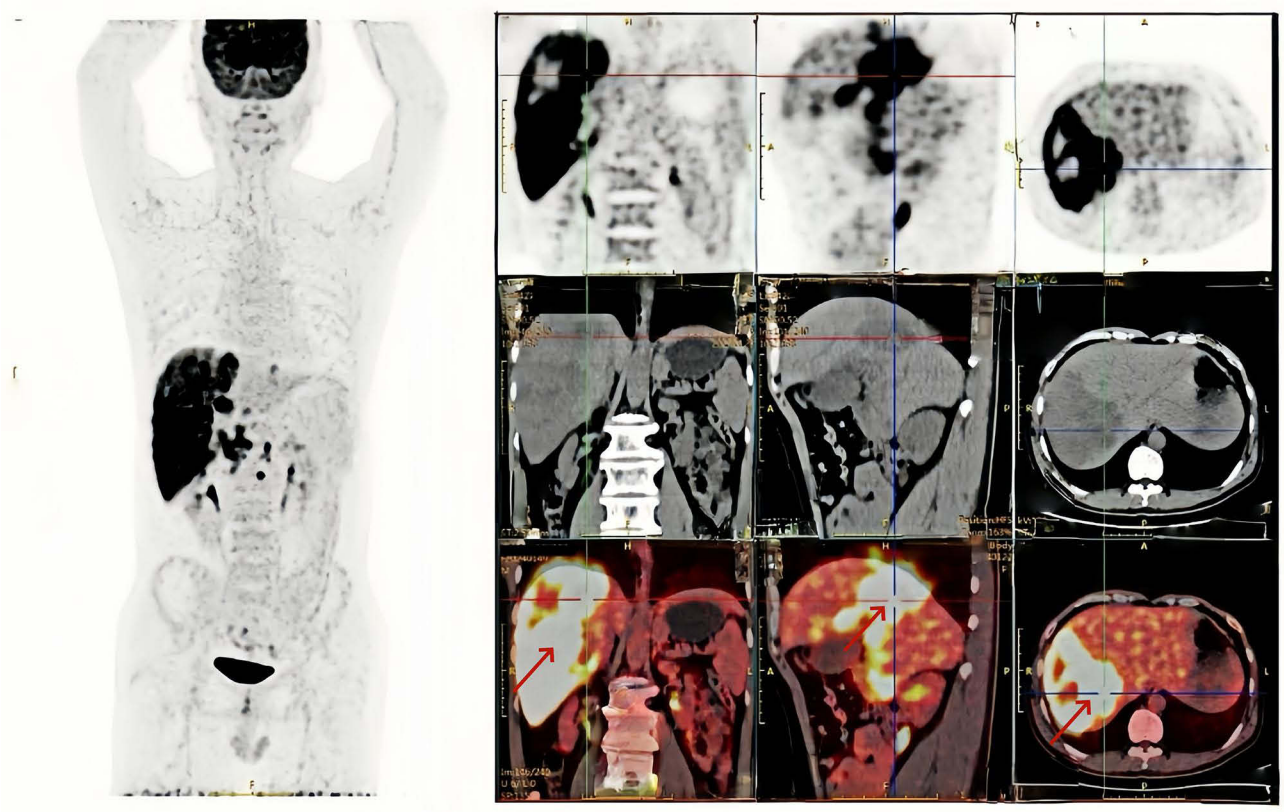

Figure 1 The patient's PET/CT image.
Note: Red arrows indicate hepatic lesions (SUVmax, 19.5).

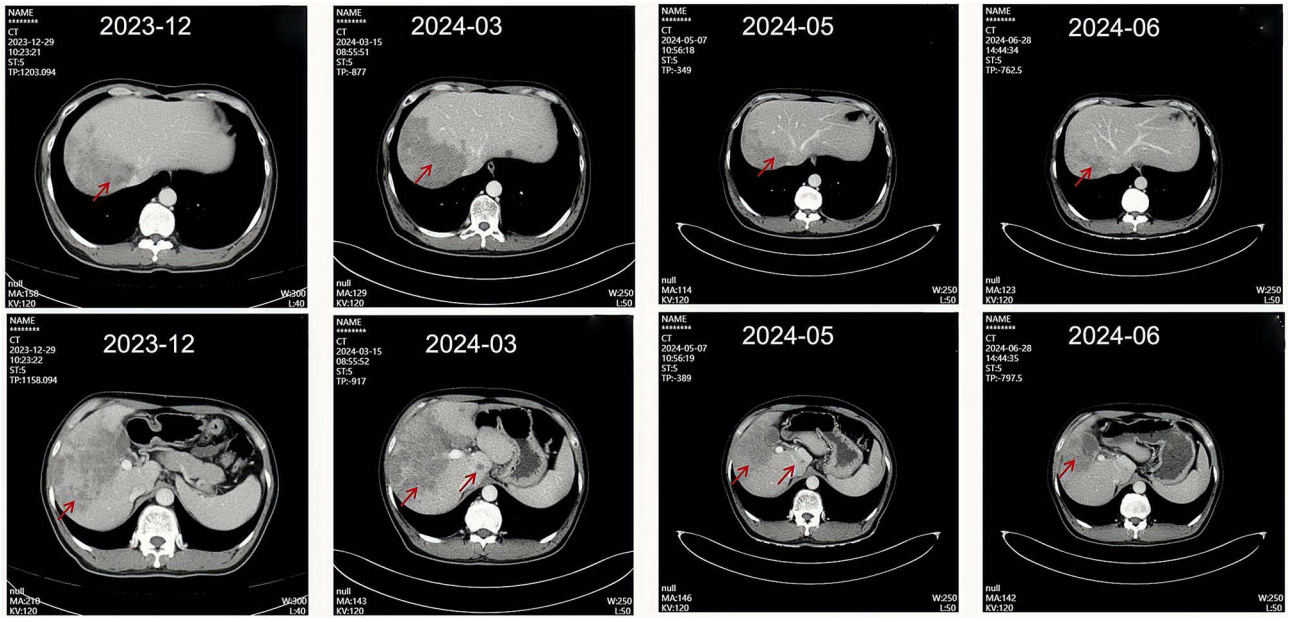

Figure 2 Previous imaging review of liver lesions of the patient.
Notes: First-line therapy: From December 2023 to March 2024 (sindilizumab plus GP). Second-line therapy: From March 2024 to September 2024 (Sintilimab combined with cetuximab plus the AS regimen). Red arrows indicate hepatic lesions.
Abbreviations: GP, Gemcitabine plus cisplatin; AS, Albumin-bound paclitaxel plus S-1.

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The primary sites of minor salivary gland carcinomas are similar in the literature, with the most common site being the oral cavity, followed by the oropharynx, the nasal cavity and sinuses, the trachea, and the larynx.[11] Laryngeal salivary gland carcinoma accounts for less than 1% of cases.[3] The clinical presentation of laryngeal minor salivary gland carcinoma is contingent upon the location of the tumour, its extent of lesion invasion, and the biological behaviour exhibited by different pathological types. Laryngeal minor salivary gland carcinomas are most commonly found in the ventricular girdle, aryepiglottic folds and anterior subconjunctival region. However, they rarely occur in the vocal folds. Therefore, it is important to consider the possibility of laryngeal minor salivary gland carcinoma when dealing with submucosal masses in the supraglottic and subglottic regions. The pathological types of minor salivary gland carcinoma are complex, with more than 20 distinct types. The most prevalent pathological types include adenoid cystic carcinoma, adenocarcinoma, mucoepidermoid carcinoma, and malignant mixed tumour, among others. Salivary duct carcinoma (SDC)represents approximately 10% of cases and is characterised by histological features that are similar to those observed in invasive ductal carcinoma of the breast. The term "salivary duct carcinoma" is employed due to the analogous histological characteristics observed in breast invasive ductal carcinoma.[12,13] The behavior of salivary gland tumors is well-documented to be highly aggressive, with a strong propensity for local recurrence, distant metastasis, and a consequently poor prognosis.[5,6] However, the extremely limited number of laryngeal cases makes its natural history in this specific site difficult to predict.

The preferred treatment is complete surgical excision, with lymph node dissection warranted in the event of regional nodal metastasis. Patients with low-grade tumours are more likely to achieve a cure through surgical intervention. However, even in such cases, post-operative radiotherapy is an essential component of treatment. Furthermore, biologically targeted therapeutic agents may offer a promising treatment avenue in the future.[14] Distant metastatic sites of salivary gland carcinoma are predominantly lung (80%), bone (15%), liver and others (5%).[15] The five-year overall survival (OS) rate is less than 40%.[13] For patients exhibiting distant metastases, the most efficacious preceding chemotherapy regimen was the TC regimen (paclitaxel plus carboplatin), with an objective response rate of approximately 30%.[16]

Given the high expression levels of HER-2 and AR in SDC, an increasing number of studies have been undertaken to investigate the potential of targeted therapy against these two receptors. Recent studies have demonstrated that targeted therapy with trastuzumab in advanced metastatic SDC patients with positive HER-2 expression also exhibits a favourable clinical response and prolongs their survival.[16,17] In a multicentre Phase II clinical trial, investigators observed favourable outcomes in 43 patients diagnosed with advanced SDC and exhibiting positive HER2 expression. These patients were treated with docetaxel in conjunction with trastuzumab, resulting in an objective response rate of 70.2%.[18] The remarkable effectiveness of innovative antibody-drug conjugates (ADCs), including trastuzumab deruxtecan (T-DXd), in treating HER2-positive solid tumours, has generated new hope for patients with this condition. In accordance with this, the NCCN guidelines have incorporated HER2-targeted therapy into the recommended treatment options for HER2-positive salivary gland carcinoma, emphasising the necessity for individualised drug selection based on testing results.[19,20]

Furthermore, the majority of SDCs express the AR. In a study by Williams et al, 179 out of 183 patients were found to be positive for the AR receptor,[21] indicating a high prevalence of this phenomenon. The genetic alterations of the androgen receptor observed in SDC specimens include mutations and additional copies of the gene, as opposed to gene amplification, which is a characteristic of prostate cancer.[22,23] Preclinical studies of SDC cell lines have demonstrated that androgens can promote cell growth. Furthermore, the proliferation of SDC cells can be attenuated by inhibiting or knocking down the androgen receptor.[22,24] In patients with androgen receptor-positive metastatic SDC, androgen receptor blockers (such as bicalutamide) have demonstrated efficacy in improving the clinical benefit rate.[25] However, the mechanisms of resistance and adverse effects of targeted or targeted combination chemotherapy require further investigation.

Furthermore, EGFR is another growth factor that is frequently overexpressed in SDC. A high proportion of SDC specimens examined exhibited elevated EGFR expression. The prognostic significance of EGFR in SDC remains uncertain, with some studies indicating that EGFR status is an independent predictor of disease-free survival,[26] while the majority of studies have not identified a significant prognostic effect.[27,28] Hitre et al evaluated the efficacy and safety

of cetuximab in combination with platinum-based chemotherapy or radiotherapy in patients with adenoid cystic carcinoma (ACC) expressing EGFR, all of whom were treated with cetuximab, with locally advanced patients treated with both radiotherapy and cisplatin-based chemotherapy, and distantly metastatic patients treated with cisplatin and 5-fluorouracil-based chemotherapy. The results of the study showed that cetuximab in combination with chemotherapy or radiotherapy showed good efficacy in both locally advanced and distantly metastatic ACC patients, with an objective response rate of approximately 42%.[29]

In this case, it was challenging to ascertain the primary focus of the liver lesion. The patient was initially diagnosed with primary intrahepatic cholangiocellular carcinoma and treated with immunotherapy in combination with a GP regimen. However, the efficacy of this treatment was unsatisfactory. Subsequently, the patient's liver lesion was considered to be a metastasis of laryngeal cancer. The efficacy of an anti-EGFR-based targeted combination therapy was remarkable. In conclusion, malignant tumours of laryngeal salivary gland origin are exceedingly uncommon, with salivary duct carcinoma of the laryngeal minor salivary glands being an even rarer occurrence. The current clinical experience with this type of disease is limited. Further study is warranted on the use of trastuzumab and androgen deprivation systemic therapy in patients with unresectable or distant metastases. The identification of biomarkers that can predict which patients are likely to respond to this treatment is also a priority area of research. Furthermore, anti-EGFR therapy may prove an efficacious treatment for patients exhibiting EGFR expression.

Conclusion

Given the rarity and aggressive nature of primary laryngeal salivary duct carcinoma, it remains a significant challenge for both diagnosis and treatment. The current case underscores the difficulty in identifying the primary tumor site, especially when metastasis occurs. Additionally, the effectiveness of anti-EGFR therapy in EGFR-expressing tumors offers a promising treatment avenue. Further research is essential to establish standardized treatment protocols, identify predictive biomarkers, and optimize combination strategies for this uncommon malignancy.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. Institutional approval was not required to publish the case details.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Chiesa-Estomba CM, Barillari MR, Mayo-Yáñez M, et al. Non-squamous cell carcinoma of the larynx: a state-of-the-art review. *J Pers Med*. 2023;13(7):1084. doi:10.3390/jpm13071084
2. Ganly I, Patel SG, Coleman M, Ghossein R, Carlson D, Shah JP. Malignant minor salivary gland tumors of the larynx. *Arch Otolaryngol Head Neck Surg*. 2006;132(7):767. doi:10.1001/archotol.132.7.767
3. Alavi S, Calcaterra TC, Namazie A, Blackwell KE. Glandular carcinoma of the larynx: the UCLA experience. *Ann Otol Rhinol Laryngol*. 1999;108 (5):485–489. doi:10.1177/000348949910800512

4. Batsakis JG, Luna MA, El-Naggar AK. Pathology consultation: nonsquamous carcinomas of the larynx. *Ann Otol Rhinol Laryngol*. 1992;101(12):1024–1026. doi:10.1177/000348949210101212
5. Ferlito A, Gale N, Hvala H. Laryngeal salivary duct carcinoma: a light and electron microscopic study. *J Laryngol Otol*. 1981;95(7):731–738. doi:10.1017/S0022215100091350
6. Jeong HS, Son YI, Ko YH, Kim SY. Sarcomatoid salivary duct carcinoma of the larynx. *J Laryngol Otol*. 2006;120(2):154–157.
7. Goel MM, Agrawal SP, Srivastava AN. Salivary duct carcinoma of the larynx: report of a rare case. *Ear Nose Throat J*. 2003;82(5):371–373. doi:10.1177/014556130308200511
8. Mahomed Y, Meer S. Primary epithelial minor salivary gland tumors in South Africa: a 20-year review. *Head Neck Pathol*. 2020;14(3):715–723. doi:10.1007/s12105-019-01111-4
9. Shi X, Huang NS, Shi RL, Wei WJ, Wang YL, Ji QH. Prognostic value of primary tumor surgery in minor salivary-gland carcinoma patients with distant metastases at diagnosis: first evidence from a SEER-based study. *Cancer Manag Res*. 2018;10:2163–2172. doi:10.2147/CMAR.S172725
10. Shen SY, Wang WH, Liang R, Pan GQ, Qian YM. Clinicopathologic analysis of 2736 salivary gland cases over a 11-year period in Southwest China. *Acta Otolaryngol*. 2018;138(8):746–749. doi:10.1080/00016489.2018.1455108
11. Carlson ER, Schlieve T. Salivary gland malignancies. *Oral Maxillofacial Surg Clin North Am*. 2019;31(1):125–144. doi:10.1016/j.coms.2018.08.007
12. Kamitani M, Ueno S, Yamada K, Terano T, Shima M. Salivary duct carcinoma within the masseter muscle—case report. *J Oral Maxillofac Surg Med Pathol*. 2022;34(4):430–435. doi:10.1016/j.ajoms.2022.01.004
13. Schmitt NC, Kang H, Sharma A. Salivary duct carcinoma: an aggressive salivary gland malignancy with opportunities for targeted therapy. *Oral Oncol*. 2017;74:40–48. doi:10.1016/j.oraloncology.2017.09.008
14. Poorten VV, Hunt J, Bradley PJ, et al. Recent trends in the management of minor salivary gland carcinoma. *Head Neck*. 2014;36(3):444–455. doi:10.1002/hed.23249
15. Gatta G, Guzzo M, Locati LD, McGurk M, Prott FJ. Major and minor salivary gland tumours. *Crit Rev Oncol Hematol*. 2020;152:102959. doi:10.1016/j.critrevonc.2020.102959
16. Takahashi H, Tada Y, Saotome T, et al. Phase II trial of trastuzumab and docetaxel in patients with human epidermal growth factor receptor 2–positive salivary duct carcinoma. *J Clin Oncol*. 2019;37(2):125–134. doi:10.1200/JCO.18.00545
17. Wotman M, El-Naggar A, Ferrarotto R. Targeting human EGFR 2 (HER2) in salivary gland carcinoma. *Expert Rev Anticancer Ther*. 2023;23(6):573–582. doi:10.1080/14737140.2023.2208350
18. Lee J, Park S, Jung HA, et al. A Phase 2 multicenter study of docetaxel-PM and trastuzumab-pkrb combination therapy in recurrent or metastatic salivary gland carcinomas. *Cancer*. 2023;129(19):2966–2974. doi:10.1002/cncr.34892
19. Takahashi H, Tada Y, Saotome T, et al. Trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2 (HER2)-expressing salivary duct carcinoma: subgroup analysis of two Phase 1 studies [abstract]. *J Clin Oncol*. 2021;39(15_suppl):6079. doi:10.1200/JCO.2021.39.15_suppl.6079
20. Tsurutani J, Iwata H, Krop I, et al. Targeting HER2 with trastuzumab deruxtecan: a dose-expansion, Phase I study in multiple advanced solid tumors. *Cancer Discov*. 2020;10(5):688–701. doi:10.1158/2159-8290.CD-19-1014
21. Williams L, Thompson LDR, Seethala RR, et al. Salivary duct carcinoma: the predominance of apocrine morphology, prevalence of histologic variants, and androgen receptor expression. *Am J Surg Pathol*. 2015;39(5):705–713. doi:10.1097/PAS.0000000000000413
22. Mitani Y, Rao PH, Maity SN, et al. Alterations associated with androgen receptor gene activation in salivary duct carcinoma of both sexes: potential therapeutic ramifications. *Clin Cancer Res*. 2014;20(24):6570–6581. doi:10.1158/1078-0432.CCR-14-1746
23. Dalin MG, Desrichard A, Katabi N, et al. Comprehensive molecular characterization of salivary duct carcinoma reveals actionable targets and similarity to apocrine breast cancer. *Clin Cancer Res*. 2016;22(18):4623–4633. doi:10.1158/1078-0432.CCR-16-0637
24. Kamata Y, Sumida T, Murase R, Nakano H, Yamada T, Mori Y. Blockade of androgen-induced malignant phenotypes by flutamide administration in human salivary duct carcinoma cells. *Anticancer Res*. 2016;36(11):6071–6076. doi:10.21873/anticanres.11196
25. Kawakita D, Nagao T, Takahashi H, et al. Survival benefit of HER2-targeted or androgen deprivation therapy in salivary duct carcinoma. *Ther Adv Med Oncol*. 2022;14:175883592211195. doi:10.1177/17588359221119538
26. Masubuchi T, Tada Y, Maruya S, et al. Clinicopathological significance of androgen receptor, HER2, Ki-67 and EGFR expressions in salivary duct carcinoma. *Int J Clin Oncol*. 2015;20(1):35–44. doi:10.1007/s10147-014-0674-6
27. Williams MD, Roberts DB, Kies MS, Mao L, Weber RS, El-Naggar AK. Genetic and expression analysis of HER-2 and EGFR genes in salivary duct carcinoma: empirical and therapeutic significance. *Clin Cancer Res*. 2010;16(8):2266–2274. doi:10.1158/1078-0432.CCR-09-0238
28. Han MW, Roh JL, Choi SH, et al. Prognostic factors and outcome analysis of salivary duct carcinoma. *Auris Nasus Larynx*. 2015;42(6):472–477. doi:10.1016/j.anl.2015.04.005
29. Hitre E, Budai B, Takácsi-Nagy Z, et al. Cetuximab and platinum-based chemoradio- or chemotherapy of patients with epidermal growth factor receptor expressing adenoid cystic carcinoma: a phase II trial. *Br J Cancer*. 2013;109(5):1117–1122. doi:10.1038/bjc.2013.468