Oncol Ther (2026) 14:575–595
https://doi.org/10.1007/s40487-026-00447-6

REVIEW

Evolving Concepts in Salivary Duct Carcinoma: A Narrative Review

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Received: April 13, 2026 / Accepted: May 19, 2026 / Published online: June 5, 2026

ABSTRACT

Salivary duct carcinoma (SDC) is an aggressive neoplasm that typically involves the major salivary glands. This rapidly growing tumor is known to recur and metastasize to the neck nodes and to distant sites. Given its poor prognosis, researchers have focused on identifying factors and driver genomic alterations that may account for its behavior, ultimately yielding potential therapeutic targets. This review summarizes the growing body of knowledge on SDC since the publication of the latest *WHO Classification of Tumors of the Head and Neck*. Updates on emerging subtypes, immunohistochemical profiles, molecular alterations, and potential therapeutic targets are succinctly presented. Findings from studies on tumor immune

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microenvironment (TIME), which may have implications for the treatment and prognosis of SDC, are also discussed in this narrative review.

Keywords: Salivary duct carcinoma; Molecular landscape; Tumor immune microenvironment; Androgen receptor; HER2 expression; Genetic alterations

Key Summary Points

Salivary duct carcinoma (SDC) is a rapidly growing malignancy with high recurrence and metastatic potential, particularly to cervical lymph nodes, and also to distant sites.
Understanding of the pathogenesis of SDC has significantly improved since the publication of the fifth edition of the *WHO Classification of Head and Neck Tumors*.
The identification of new morphologic subtypes and novel driver molecular alterations may contribute to prediction of clinical behavior, ultimately yielding potential therapeutic targets.
While the prognosis of SDC remains poor, recognizing factors that impact disease-free (DFS) and overall survival (OS) will further refine personalized patient care.

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INTRODUCTION

Salivary gland carcinomas (SGCs) are among the most diverse malignancies, with a remarkable range of histomorphologic features and biological behavior [1]. The fifth edition of the *WHO Classification of Head and Neck Tumors* recognizes 21 malignant epithelial neoplasms arising from the salivary glands [2]. Of these tumors, arguably the most aggressive is salivary duct carcinoma [3]. Salivary duct carcinoma (SDC) is defined by the WHO as "an aggressive carcinoma resembling mammary ductal carcinoma, most typically with an apocrine phenotype." It may arise de novo or from a pre-existing pleomorphic adenoma (SDC ex PA) [4].

The majority of SDCs involve the major salivary glands, particularly the parotid gland [2, 5]. In recent years, unusual locations in the head and neck region have been reported, such as the inferior turbinate [6] and the tip of the tongue [7]. The clinical presentation of SDC is typically characterized by a rapidly growing mass. SDC has a marked sex predilection, with up to 80% of cases presenting in male individuals [8, 9]. It may present with additional signs and symptoms such as facial nerve palsy, pain, and enlarged lymph nodes [4].

According to the European Society for Medical Oncology-European Reference Network on Rare Adult Solid Cancers (ESMO-EURACAN) guidelines, the standard treatment for SDC is surgery with radiotherapy. In case of clinical or radiologic evidence of lymph node involvement, tumor resection is performed with a comprehensive neck dissection. This is followed by radiotherapy, provided there are no distant metastases. However, despite treatment, approximately 50% of patients will develop recurrences or metastases (R/M) [10].

The aggressive behavior of SDC can be attributed to frequent recurrences and distant metastases. The regional lymph nodes, liver, lung, bone, and brain are the most common sites of metastases [9, 10]. Malignant pleural effusion secondary to SDC, i.e., pleuritis carcinomatosa, has been reported [13]. Cutaneous lymphangitis carcinomatosa has also been reported in 5% of patients with SDC [14]. The cutaneous

manifestations can be variable, and metastatic SDC can present as erythematous plaques or hemorrhagic papules, associated with varying degrees of edema and induration, mimicking erysipelas [15]. Metastatic SDC has also been documented to arise in scald injuries and irradiated skin fields following radiation therapy [16, 17]. In both cases, alterations in the microenvironment are presumed to play a role in the metastatic process. In most reported cases of metastatic SDC, patients had a prior diagnosis of SDC, and immunohistochemistry (IHC) panels consisting of androgen receptor (AR) and breast markers, such as GCDFP-15, were usually sufficient to confirm the diagnosis [13, 18, 19].

Since the release of the fifth edition of the *WHO Classification of Head and Neck Tumors*, a remarkable number of publications have focused on SDC. Given the aggressiveness of the tumor, most of these articles have centered on the molecular pathology of SDC. This review summarizes the most significant developments in terms of SDC morphology, molecular pathology, and targeted therapy.

EXTENDING THE SPECTRUM OF THE HISTOPATHOLOGIC FEATURES OF SDC

SDC typically presents as a firm, infiltrative mass that involves surrounding tissues. The conventional histology of SDC is a tumor composed of malignant cells with large pleomorphic nuclei, coarse chromatin, and prominent nucleoli. The eosinophilic, abundant cytoplasm has characteristic apocrine features. Architecturally, tumor cells form complex solid, cribriform, and papillary-cystic patterns (Fig. 1). Comedo-type necrosis is a usual finding and contributes to

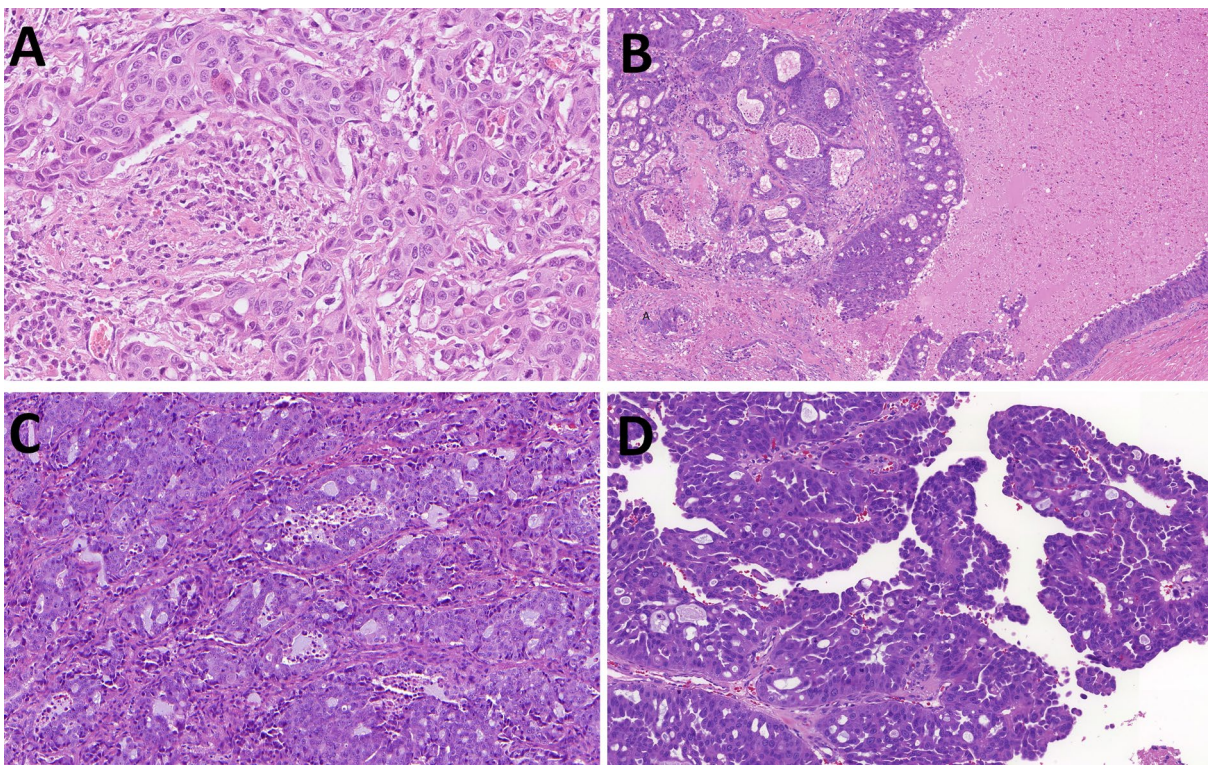

Fig. 1 A variety of architectural patterns may be seen in salivary duct carcinoma. These include **a** solid (×40), **b** cystic to macrocystic (×4), **c** cribriform (×10), and **d** papillary architecture (×10). Perineural invasion and necrosis are seen in **a** and **b**, respectively

the tumor's striking resemblance to mammary ductal carcinoma [4].

Based on morphology, several subtypes of SDC are recognized (Fig. 2). The tumor may present with markedly atypical spindle-shaped cells and heterologous mesenchymal differentiation (sarcomatoid) (Fig. 2a) [19], pools of extracellular mucin (mucin-rich) (Fig. 2b) [20], and small nests of tumor cells with retraction artifacts (micropapillary) (Fig. 2c) [21]. Similar to the micropapillary subtype of invasive ductal carcinoma of the breast, the micropapillary subtype of SDC has an "inside-out pattern" when stained with EMA. Other subtypes are basal-like (amphophilic cytoplasm) (Fig. 2d) and oncocytic (abundant eosinophilic cytoplasm) (Fig. 2e) [22]. These five subtypes (sarcomatoid, mucin-rich, micropapillary, basal-like, and oncocytic) are recognized in the current WHO classification [4, 23]. Areas of conventional SDC are usually readily identified and make the diagnosis straightforward. Because more than one subtype may be present in a given tumor, no minimum morphologic threshold is required to report a specific subtype, although some authors recommend a 50% cutoff for the oncocytic subtype [24, 25]. Micropapillary SDC is known to have the worst prognosis, but the biologic behavior of all subtypes remains to be further studied [22].

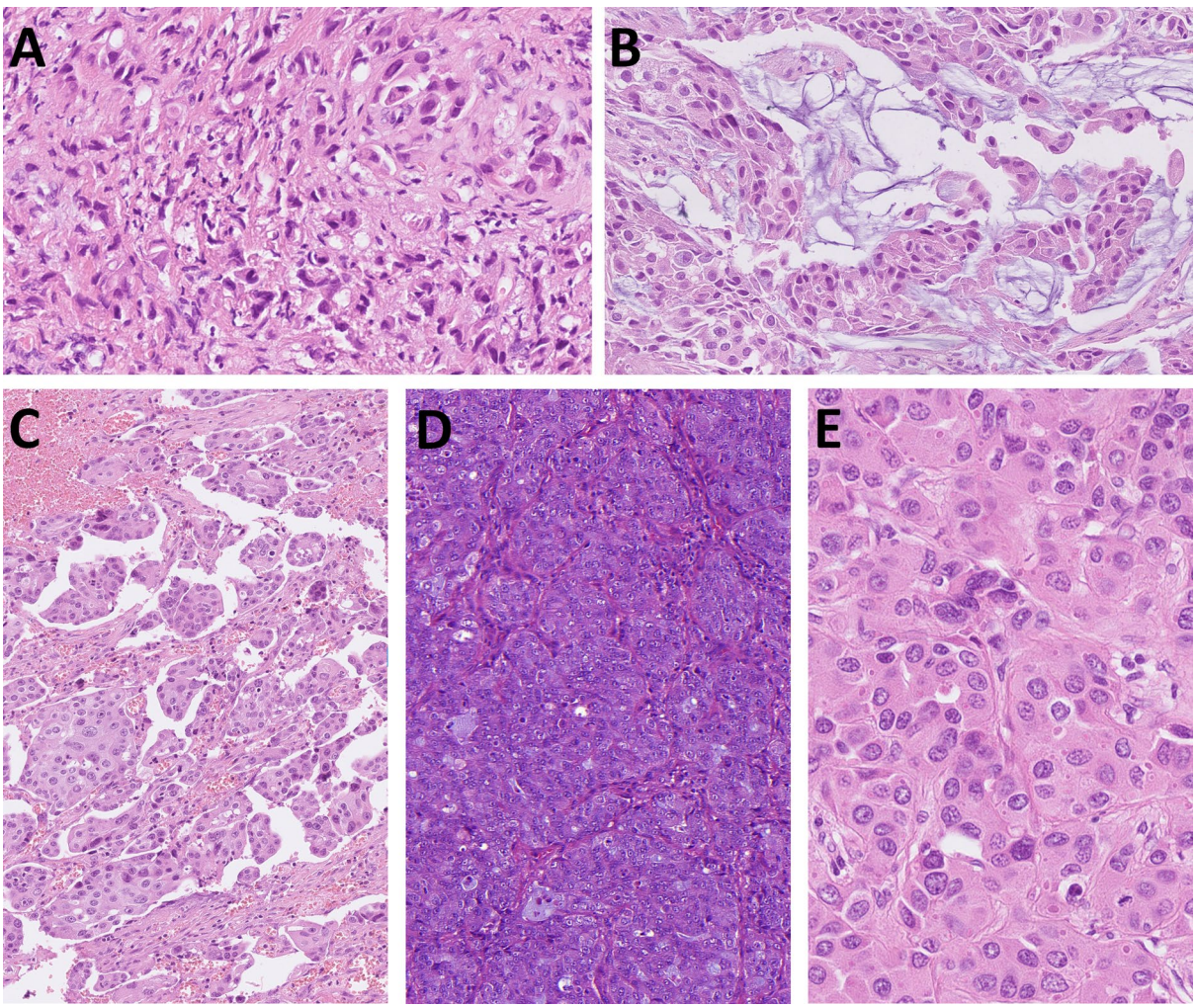

Fig. 2 Subtypes of salivary duct carcinoma: **a** sarcomatoid (×20), **b** mucin-rich (×20), **c** micropapillary (×10), **d** basaloid (×4), and **e** oncocytic (×40)

Emerging subtypes include squamous [26], rhabdoid [27], macrocystic [28], mucocyte-rich/extracellular mucin-poor [29], signet ring [30], and SDC with osteoclast-like giant cells [22]. It is of note that metastases from SDC of the different subtypes, particularly SDC with squamous differentiation, may present with a pure ductal histomorphology [26].

Conventional SDC is characterized by positive AR immunoexpression in about 90% of SDCs, consistent with an apocrine immunophenotype [8, 31]. GATA3 immunoexpression is characteristically positive [29]. Diffuse and strong HER2 expression is present in about one-third of cases [5, 12, 32, 33]. Cytokeratin CK7 is reliably positive, while SOX10 and S100 are negative. Immunostaining for p63 assists in identifying the intraductal component by staining the myoepithelial cells underlying the neoplastic cells. Recent studies have shown some variations in the immunoprofiles of SDC subtypes. Among the SDC subtypes in the WHO classification, sarcomatoid SDCs do not express AR and HER2 in their neoplastic cells with spindle morphology. The basal-type SDC subtype is positive for p63 but negative for AR, which may represent a diagnostic pitfall [22]. In the emerging SDC subtypes, AR immunoexpression in SDCs with squamous differentiation is variable, while such cells with squamous morphology express the classical markers CK5/6, p63, and p40. Most SDCs with rhabdoid features express AR and HER2, while e-cadherin expression is decreased or lost in more than 90% of such cases (Fig. 3) [27].

Immunostains, including HES1, BAP1, and p53, have been investigated for their ability to identify subtypes, to differentiate between de novo cases of SDC and SDC ex PA, and for prognostication. HES1, which labels intercalated duct cells, is highly expressed in SDC, although it has not been thoroughly investigated in other SGCs [34]. BAP1 expression may be lost in SDC ex PA [35]. Cytoplasmic staining of p53 in SDC has been shown to be associated with truncating

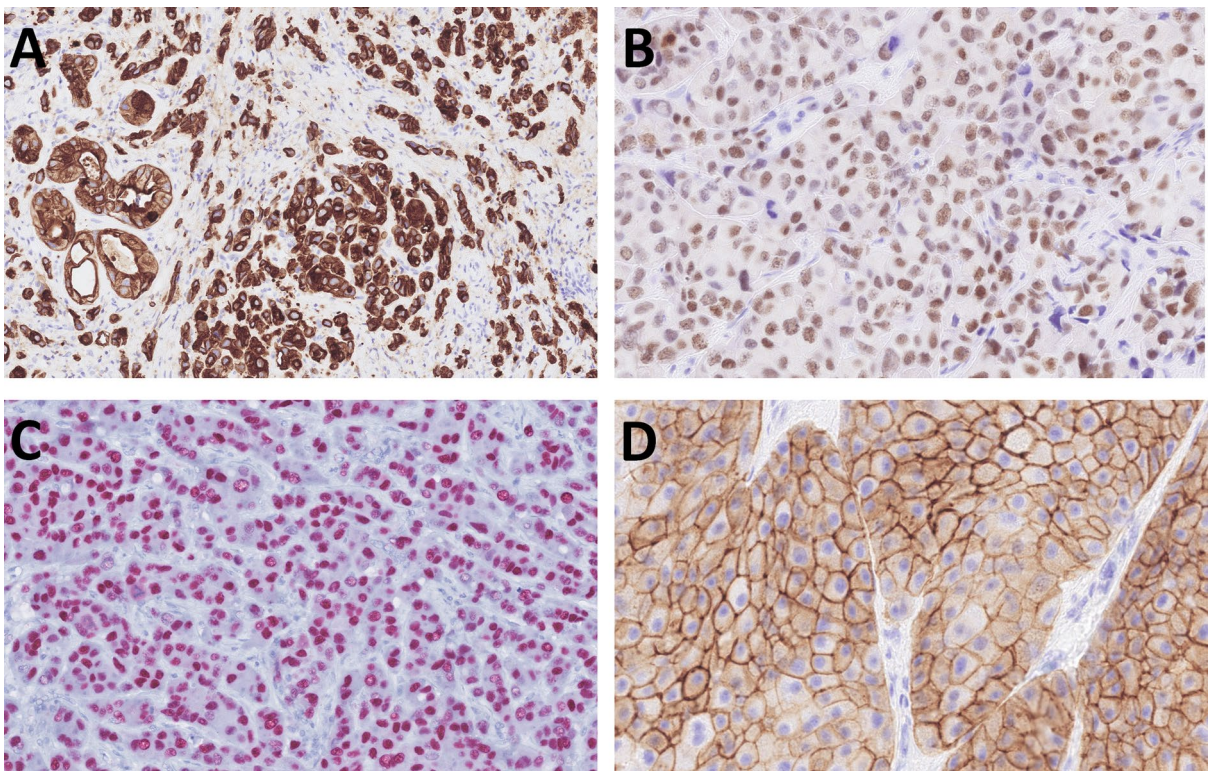

Fig. 3 Salivary duct carcinoma is positive for **a** CK7 (×10), **b** GATA3 (×20), and **c** AR (×20). One-third of cases may be positive for **d** HER2 (×40)

mutations in *TP53* [36]. The patient cohort in the study by Utsumi et al. (2025) further demonstrated that SDCs with cytoplasmic p53 staining have shorter disease-free survival (DFS), suggesting the use of p53 as a prognostic marker [22].

MOLECULAR ALTERATIONS IN SDC

It is recognized that tumor mutation burden in SDCs may be extremely high [37]. A large number of molecular alterations can be present in a single case of SDC. A comprehensive review by Pikul and Rzepakowska (2024) indicates that the most common alteration is the *TP53* mutation, which is reported in more than half of SDC cases. Other commonly encountered molecular alterations are *HER2/ERBB2* amplification (the second most common, approximately 30%), *FGFR1* amplification, *PIK3CA* mutation, *HRAS* mutation, copy number gains in *AR*, loss of *PTEN* or *CDKN2A*, rearrangements of *PLAG1* and *HMGA2* (in SDC ex PA), and *BRAF* pathogenic variants. *ALK* fusions and *ETV6::NTRK3* fusions have also been reported [4]. None of these molecular alterations is entirely specific to SDC, but *ERBB2* amplification is unique for SDC amongst salivary gland tumors. This amplification, however, does not result from an increase in gene copy number but is due to epigenetic alterations in the form of gene promoter hypomethylation [1]. Table 1 shows the different molecular alterations associated with SDC that have been reported in the literature.

The apocrine subtype of intraductal carcinoma (IDC) reportedly has high rates of mutations in *PIK3CA* and *HRAS*. This suggests that IDC could be a true carcinoma in situ related to SDC. However, a true neoplastic nature of the myoepithelial cell layer of IDC, as considered by some authors, would rule out that possibility [2, 38]. In addition, *HRAS* mutations are mostly seen in de novo SDCs, which supports the carcinoma in situ status of apocrine IDC [37, 39].

A few novel molecular alterations in SDC have been recently described. These include *EGFR* mutation, which is more commonly expressed in SDC ex PA [40]; concurrent *RAD50* and *POLE* mutations [29]; and *CDH1* biallelic inactivation [41]. Interestingly, SDC was reported in a patient with a germline mutation in *NF1*, which might work synergistically with *TP53* in the pathogenesis of SDC [42].

Other genetic aberrations reported include *SZT2::MAST2* fusion [43]; *MET* fusions (*KMT2C::MET*, *PCM1::MET*) in a case of SDC with IDC [44]; *MLH1* mutation [45]; *CDK12* co-amplification with *HER2*, which might herald poor prognosis [46]; *FGFR3::TACC3* fusion [47]; and *LAT1* overexpression, which is a potential target for boron neutron capture therapy [48].

Additional cases of *ALK* fusions consistent with those published in the fifth edition of the WHO classification have been reported since 2023. A classic fusion seen in non-small cell lung carcinoma, *EML4::ALK* fusion, was also reported in a patient with metastatic SDC. The patient had a complete response at 8 months after initiating alectinib therapy [11]. *HNRNPH3::ALK* fusions have also been described [49]. These cases further reinforce the potential impact of performing molecular testing on a case-to-case basis.

Recently, potential SDC biomarkers have been identified through bioinformatics analyses of differentially expressed genes and through an analysis of copy number alterations (CNAs). These biomarkers include *FOXM1*, a transcription factor that is aberrantly expressed in solid tumors and is involved in cancer cell proliferation [50]. SDC ex PA displays unique CNAs, including *GRB7* and *RPSAP52* amplifications, which may account for the differences in its biologic behavior from de novo SDCs [51].

Although some molecular alterations imply a characteristic morphology, occasional discordance between histology and molecular profile of some SDC cases may exist. One such example is a patient with biallelic inactivation of *CDH1*, a gene that encodes for e-cadherin, but the SDC of this patient had no rhabdoid features [41]. Another case of SDC had signet ring cells and an *AKT1* mutation, which is classically seen in mucinous adenocarcinomas [30].

Molecular testing is not mandatory to make a diagnosis of SDC, but patients may benefit from targeted therapy based on molecular findings [4].

Table 1 Molecular alterations reported in salivary duct carcinoma (adapted from Skálová et al. [2] and Pikul and Rzepakowska [37])

Commonly reported altered genes in salivary duct carcinoma		
Gene	**Frequency**	**References**
TP53 mutation	39–68%	[36, 109–115]
HRAS mutation	11–49%	[110, 112–114, 116–121]
NF1 mutation	7–20%	
ERBB2 amplification	10–100%	[110, 112–114, 117, 120]
PIK3CA mutation	18–47%	[110, 112–114, 116–121]
PTEN mutation	6–13.5%	[109, 110, 112–114, 116–120]
PLAG1 rearrangements	22–73%	[122, 123]
HMGA2 rearrangements	18–44%	[122, 123]
Other uncommonly altered genes in salivary duct carcinoma		
Pathway	**Gene**	**References**
DNA damage pathway	*ATM*	[109–115]
	BRCA2	
	CHEK2	
	MDM2	
	MDM4	
	MLH3	
	MLH5	
MAPK	*BRAF*	[110, 112–114, 116–120]
	KRAS	
	NRAS	
RTK	*ALK*	[110, 112–114, 117, 120]
	EGFR	
	ERBB3-4	
	FGFR1-2	
	FGFR4	
	FLT3	
	JAK2	
	KDR	
	KIT	

Table 1 continued

Other uncommonly altered genes in salivary duct carcinoma		
Pathway	**Gene**	**References**
	MET	
	NTRK2	
	PDGFRA	
	RET	
PI3K/AKT/mTOR	*AKT1-3*	[109, 110, 112–114, 116–120]
	PIK3R1	
	RICTOR	
	RPTOR	
	TSC2	
Androgen signaling	*FASN*	[112, 117]
	FOXA1	
Histone modification	*KDM6A*	[110, 112, 113, 117]
	KMT2A	
	KMT2C	
	KMT2D	
	KMT2E	
	NSD1	
Cell cycle	*CDK4*	[110, 112–114, 117, 118]
	CDK6	
	CDK12	
	CDKN1A	
	CDKN1B	
	CDKN2A	
	CCNE1	
	CCND1-3	
	RB1	
NOTCH	*CREBBP*	[113, 114]
	EP300	
	FBXW7	
	NOTCH1-3	

Table 1 continued

Other uncommonly altered genes in salivary duct carcinoma		
Pathway	**Gene**	**References**
SWI/SNF complex	*ARID1A*	[110, 112, 114, 117]
	SMARCA4	
	SMARCB1	
WNT-β-catenin	*APC*	[113, 114, 117]
	CDH1	
	CTNNB1	
	FAT1	
Other genes	*ABL1*	[110, 112–114, 117, 118]
	AURKA	
	BCOR	
	CCND1	
	CCNE1	
	FLCN	
	GNAS	
	IDH1/IDH2	
	IGFR1	
	IKBKE	
	KLF5	
	AMP	
	MAP2K1	
	MAP2K4	
	MITF	
	MPL	
	MYC	
	PRDM1	
	SMAD4	
	SMO	
	STK11	
	TNIK	
	VHL	
	ZFHX3	

Table 1 continued

Other uncommonly altered genes in salivary duct carcinoma		
Pathway	**Gene**	**References**
	POLE	[29]
	LAT1	[48]
	FOXM1	[50]
	GRB7	[51]
	RPSAP52	
Fusions	*ETV6::NTRK3*	[110, 112, 117, 124]
	ABL1::PPP2R2C	
	BCL6::TRADD	
	HNRNPH3::ALK	
	EML4::ALK	
	RAPGEF6::ACSL6	
	SZT2::MAST2	[43]
	FGFR3::TACC3	[47]
Other reported genetic alterations in salivary duct carcinoma ex pleomorphic adenoma		
CTNNB1::PLAG1		[117, 125, 126]
FGFR1::PLAG1		[109, 116, 124, 126]
LIFR::PLAG1		[117, 126]
ASXL1		[110]
BAP1		
BTK		
CTCF		
DNMT1, DNMT3A, DNMT3B		
FANCA, FANCC		
FH		
GATA2		
HNF1A		
JUN		
MAP3K1		
PTPN11		
PTPRS		

Table 1 continued

Other reported genetic alterations in salivary duct carcinoma ex pleomorphic adenoma	
RAD51C	
RTEL1	
DOCK7	[117]
MSH5	
MTOR	
SF3B1	
NCOR1	[110, 117]
ROS1	[114]

THE ROLE OF TUMOR MICROENVIRONMENT IN SDC

Several studies have focused on evaluating tumor immune microenvironment (TIME) of SGCs. TIME is composed of the stroma and cells, such as fibroblasts and leukocytes, that may play a role in the pathogenesis and progression of SDC. This makes the TIME a potential target for immune checkpoint inhibitors (ICIs).

On the basis of the patterns of immune cell infiltration, SGCs may be classified as immune-desert (not responsive to ICIs), immune-inflamed (potentially responsive to ICIs), and immune-excluded [52]. SDCs are considered immune-excluded tumors, i.e., immune cells infiltrate their stroma but not the malignant cells. The response of immune-excluded tumors to ICIs is not yet well established. However, one study notes that SDCs are relatively immunogenic and may therefore benefit from immunotherapy [53].

Elevated expression of certain IHC markers, such as CD8, FOXP3, PD1, CTLA4, LAG3, and PD-L1, in the TIME was associated with a more aggressive histology and poorer outcomes [42, 54]. Analysis of the exact location of these markers, i.e., within the center or at the periphery of the tumor, may also play a role in SDC behavior. Expression of PD1 and PD-L1 by peripheral SDC tumor cells, for instance, was shown to be associated with a higher tumor stage [55].

Aside from the presence of immune cells, the collagenized stroma of SDCs harbors an increased number of matrix cancer-associated fibroblasts (mCAFs). Mayer et al. (2025) demonstrated that mCAFs are significantly associated with tumor R/M [56]. Increased deposition of collagen may be associated with aggressive behavior and chemoresistance [57]. One study focused on the expression of markers, such as PSMA, in the tumor neovasculature; however, no relationship between these markers and SDC prognosis was found [58].

Other studies have investigated proteins produced by tumor cells that may play a role in how a tumor interacts with the native stroma. Some tumors express aberrant forms of MUC1 glycoprotein, which is involved in proliferation, invasion, and metastasis. SDC cells express an aberrant form of MUC1, termed Tn-MUC1, which is associated with poor prognosis [59]. Another glycoprotein of interest is tissue factor (TF), which is expressed in SDC and other SGCs such as mucoepidermoid carcinoma (MEC) and secretory carcinoma (SC). TF is implicated in tumor growth, angiogenesis, and metastasis, and it creates a TIME that is able to evade T cells by impeding their infiltration and function [60]. Nectin-4, a transmembrane protein that activates the PI3K/AKT pathway, resulting in VEGF overexpression and promotion of angiogenesis, is overexpressed in 25% of SDC tumors. Immunotherapy with enfortumab vedotin targets nectin-4 [61]. Similar to antigens within the TIME, these

aberrantly expressed proteins might serve as potential therapeutic targets.

PRECISION MEDICINE IN THE MANAGEMENT OF SDC

Recurrences and distant metastases eventually develop in 54% of patients with SDC, despite the current standard of treatment with curative intent, i.e., surgery followed by radiotherapy. Because of the dismal prognosis of SDC associated with R/M, systemic therapy is usually required [10]. Comprehensive genomic profiling has shown that among salivary gland tumors, SDC has the highest mutation burden, with a median of 15 mutations per case [37]. *TP53* and *HER2* were the most frequently mutated genes in both primary and metastatic or recurrent SDCs (RM-SDC). From a therapeutic perspective, HER2 status, along with AR expression, may be suitable in stratifying patients [62–68].

Among SGCs, SDC is the most commonly studied in terms of molecular-matched therapies [69]. The currently accepted optimal approach in HER2+ and AR+ R/M-SDCs includes HER2-targeted therapy, such as trastuzumab and bevacizumab, preferably in combination with a taxane [69]. This is followed, when progression occurs, by AR blockade, with medications such as bicalutamide and triptorelin. This approach resulted in an increase in median overall survival to 45 months, versus 21 months in historical controls [70, 71]. Earlier phase II trials showed that the median progression-free survival (mPFS) for SDC is 8.8 and 8.9 months for combined AR blockade and trastuzumab–docetaxel, respectively [70, 72]. In a more recent study, two pooled phase I studies using the antibody–drug conjugate trastuzumab–deruxtecan showed an improved mPFS of 20.5 months [73]. Most of these clinical trials were performed in high-income countries; further studies involving institutions from low- to middle-income countries are recommended.

Determination of HER2 status in SDCs makes use of the 2018 ASCO/CAP guidelines for HER2 expression [74, 75]. Patients with HER2-low SDC, i.e., those with IHC 1+ or 2+/ISH–, tend to have fewer distant metastases and represent more often cases of de novo origin [20, 65]. Furthermore, in these patients, Ki-67 is low, and there is intermediate p53 expression in the HER2-low group, compared with HER2-positive patients. Studies show that in patients receiving AR-targeted therapy, HER2-low cases have better progression-free survival (PFS) and objective response rates (ORR) than patients with HER2-positive SDC [66]. Genetically more complex cases may require a different approach. The study by Rieke et al. (2023) on a limited number of patients with genomic complexity (AR+, *HRAS/PIK3CA* co-mutated) and AR-targeted therapy reported mixed results (partial response, stable disease, progressive disease) [76].

Other treatment options being explored include *EGFR*-based therapies such as near-infrared photoimmunotherapy [40], PD-L1-based immunotherapy [77], and ICIs such as nivolumab [78]. A small number of patients may respond to ICIs [79]. More robust studies are needed to establish the true benefit of other treatment options, as most of these studies involved only a single or a small number of patients [7, 40, 45, 52, 76–78, 80–95].

On the basis of recent advances in the understanding of its molecular profile, in RM-SDC, a combined biomarker panel is recommended to be performed. In addition to AR expression and HER2 status, molecular markers such as *EGFR, PIK3CA*, *HRAS*, *NTRK*, and *BRAF* are studied to enhance precision in patient management on a case-to-case basis [64, 65, 96]. At the same time, certain markers may predict the response to therapy. Examples are EZH2 and H3K27me3, which, when overexpressed, are predictive of poor efficacy of AR-targeted therapy [97].

FACTORS AFFECTING PROGNOSIS IN SDC

Factors associated with a worse prognosis in SDC are well established. These include disease stage, nodal and distant metastases, perineural invasion, lymphovascular invasion, and tumor size [86, 98–101]. Histopathologic features associated with poor prognosis include prominent nuclear

pleomorphism, high tumor budding, and high poorly differentiated clusters [9]. De novo SDCs have higher rates of perineural and lymphovascular invasion compared to SDC ex PA. In one study, *EGR1*, a gene involved in neural cell proliferation, differentiation, and apoptosis, was found to have decreased expression in de novo SDC compared to SDC ex PA [102]. Nevertheless, there is no significant difference between the prognosis of de novo SDC and SDC ex PA [9]. Positive margins after resection and extranodal extension also resulted in poorer DFS [103, 104].

Several studies have explored other possible prognosticators of SDC. A study by Kajiwara et al. (2024) showed that the presence of an increased number of autonomic nerves, based on immunostaining with tyrosine hydroxylase (TH) and vesicular acetylcholine transporter (VACT), has a significant association with aggressive behavior, including advanced T/N classification, and shorter DFS and overall survival (OS) [105]. In another cohort of 61 patients with SDC, thrombocytopenia was deemed an independent predictor of poor OS [106]. Lastly, circulating tumor DNA, which is seen in advanced SDC, appears to have some correlation with radiologic response [107].

A graded prognostic assessment (GPA) in SDC was developed by Fushimi et al. (2024), incorporating the Eastern Cooperative Oncology Group performance score (ECOG-PS), HER2 status, and extent of locoregional disease. A score of 1 is given for each category when PS is greater than 1, HER2 status is negative, or uncontrolled locoregional disease is present. SDC-GPA scores of 0, 1, 2, and 3 points resulted in median OS estimates of 50.5, 16.1, 3.9, and 1.2 months, respectively [108]. With advances in molecular diagnostics, the significance of these prognostic factors might be better understood in the future.

CONCLUSION

Our understanding of the pathogenesis of SDC has significantly improved since the publication of the fifth edition of the *WHO Classification of Head and Neck Tumors*. The identification of new morphologic subtypes and novel molecular alterations, along with a better understanding of TIME, will greatly impact patient management in the era of precision medicine. While the prognosis of SDC remains poor, recognizing factors that impact the OS of these patients will further refine personalized patient care.

ACKNOWLEDGEMENTS

This article was written by members and invitees of the International Head and Neck Scientific Group.

Author Contributions. Concept and design of the work, acquisition, analysis and interpretation of data: Marvin C. Masalunga, Patrick J. Bradley, Martina Bradová, Alena Skálová, Alfio Ferlito. First draft was provided by Marvin C. Masalunga. Critical revision of the manuscript for important intellectual content and scientific integrity: Alena Skálová, Carla van Herpen, Toshitaka Nagao, Göran Stenman, Vincent Vander Poorten, Henrik Hellquist, Silvana Di Palma, Ilmo Leivo, Alfio Ferlito. All authors have read and approved the final manuscript.

Funding. This study was supported by a study grant, the Cooperatio Program—research area SURG from Charles University, Czech Republic (MB, AS), the project National Institute for Cancer Research—NICR (Programme EXCELES, ID Project No. LX22NPO5102)—funded by the European Union—Next Generation EU (AS, MB), and the Finnish Cancer Society, Finska Lakaresallskapet, the Turku University Hospital Fund, and the Maritza and Reino Salonen Foundation, Finland (IL). No funding was received for the publication of this article.

Data Availablity. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflicts of Interest. Marvin C. Masalunga has nothing to disclose. Patrick J. Bradley has nothing to disclose. Carla van Herpen has nothing to disclose. Toshitaka Nagao has nothing to disclose. Göran Stenman has nothing to disclose. Vincent Vander Poorten has nothing to disclose. Henrik Hellquist has nothing to disclose. Silvana Di Palma has nothing to disclose. Martina Bradová has nothing to disclose. Ilmo Leivo has nothing to disclose. Alena Skálová has nothing to disclose. Alfio Ferlito is an Editorial Board member of *Oncology and Therapy*. Alfio Ferlito was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethics Approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethics Committee waived the requirement for informed consent according to the Czech Law (Act. no. 373/11, and its amendment Act no. 202/17); it is not necessary to obtain informed consent in fully anonymized studies. For this type of study, consent for publication is not required.

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