Salivary gland carcinomas (SGCs) are highly heterogeneous histopathological entities that arise in either the major or minor salivary glands. Although uncommon, these tumours exhibit considerable aggressiveness, unpredictable progression, and significant mortality. The fifth edition of the World Health Organisation classification of head and neck tumours distinguishes between 24 salivary gland malignancies. This may lead to difficulties in terms of diagnostic accuracy and suitable therapeutic selection. Mucoepidermoid carcinoma occurs most frequently and is characterised by gradual disease progression. Although salivary duct carcinoma, myoepithelial carcinoma, and carcinoma ex pleomorphic adenoma are rarely detected, they contribute to poor patient outcomes. Currently, attempts have been made to establish molecular characterisation of SGCs to improve differential diagnosis and create targeted treatments. This study aimed to summarise current knowledge regarding genetic variations in the most common salivary gland malignancies.

Key words: salivary gland carcinoma, molecular landscape, genetic alterations, NGS.

Contemp Oncol (Pozn) 2024; 28 (3): 201–216
DOI: https://doi.org/10.5114/wo.2024.144288

Review paper

Molecular landscape of salivary gland malignancies. What is already known?

Julia Pikul, Anna Rzepakowska

Department of Otorhinolaryngology, Head and Neck Surgery, Medical University of Warsaw, Warsaw, Poland

Introduction

Malignancies of the salivary glands are rare and account for approximately 5–8.5% of all head and neck cancers (HNC) [1–3]. Their occurrence is rare, with an annual incidence of 0.69 cases per 100,000 [4, 5]; however, the mortality rate is 40% [1]. Moreover, an increase of approximately 50% in both morbidity and mortality is predicted in the near future [6]. Salivary gland cancers (SGCs) are characterised by miscellaneous disease courses and clinical behaviours that contribute to unfavourable patient outcomes [2]. Among SGCs, more than 20 histopathological varieties have been classified by the World Health Organisation. Mucoepidermoid carcinoma (MEC) is the most common type of cancer, followed by acinic cell carcinoma (AcCC), adenoid cystic carcinoma (AdCC), carcinoma ex-pleomorphic adenoma (Ca *ex* PA), and adenocarcinoma (AC) [2, 7, 8]. The number of histopathological features interfering with benign lesions might also contribute to misdiagnosis and inappropriate management [9–11]. The incidence of these tumours is greater in males, and the risk of development increases with age. Former exposure to radiotherapy is also a well-known risk factor [3, 12–15]. A history of other cancers, including HNC, and occupational hazards are also associated with SGC incidence [3, 13]. In contrast to HNC risk factors, neither alcohol consumption nor tobacco use increases the risk of salivary gland malignancies [12, 13]. Numerous other causative factors have been proposed; however, studies are limited, and the results are inconclusive. Suspicious lesions, especially those with rapid growth, associated painful swelling, facial nerve palsy, or ulceration, indicate malignancy and should be investigated by imaging methods, preferably multiparametric magnetic resonance imaging.

Preoperative fine-needle aspiration enables the differentiation between benign and malignant tumours as well [2, 3, 16]. Radical surgical excision is the standard management option. Owing to tumour advancement and histopathological features, patients must receive further adjuvant radiotherapy or chemoradiotherapy [5, 16]. Park *et al.* reported disease recurrence in more than 50% of SGCs, despite radical primary treatment [17]. Distant metastases (DMs) occur in 10–40% of cases, frequently in the lungs (more than 50%), bones (40%), and liver (20%). Metastasis development is related not only to tumour type and stage but also to genetic alterations in tumour cells. These factors are therefore responsible for poor patient outcomes despite radical treatment [18–20].

Currently, the value of genetic analysis with next-generation sequencing (NGS) is particularly highlighted in SGCs. This will not only improve the knowledge about the molecular background of the pathologies but also enable the introduction of targeted therapies, especially for recurrent diseases, advanced stages, and drug-resistant cases [16, 21–24]. Additionally, it might be a pivotal tool in differential diagnosis, especially in ambiguous cases [25]. A summary of the clinical characteristics of SGCs with respect to incidence, histological subtype, predominant location, and survival is presented in Table 1. The most common genetic rearrangements in SGCs are listed in Table 2. The purpose of this paper was to review genetic variations,

Table 1. Clinicopathological features of salivary gland malignancies

Parameters	Mucoepi-dermoid carcinoma	Adenoid cystic carcinoma	Acinic cell carcinoma	Salivary duct carcinoma	Myoepi-thelial carcinoma	Epithelial-myoepithelial carcinoma	Secretory carcinoma	Carcinoma ex-pleomorphic adenoma	Clear cell carcinoma	Intraductal carcinoma	Adeno-carcinoma	Poly-morphous adeno-carcinoma	Micro-secretory adeno-carcinoma
Histopathological variant/growth pattern	Oncocytic Clear-cell Sclerosing Low-grade Intermediate-grade High-grade	Cribriform Tubular Solid	Solid papillary-cystic Follicular Microcystic Low-grade Intermediate-grade High-grade	Cribriform Solid Cystic Papillary	Solid Trabecular Reticular	Sebaceous Oncocytic Double-clear	Microcystic Tubular Solid	Myoepithelial carcinoma Salivary duct carcinoma Adenoid Epithelial-myoepithelial carcinoma	Single cells Nested Solid Sheet-like Cords Trabeculae	Intercalated duct type Apocrine Hybrid Oncocytic Low-grade Intermediate-grade High-grade	Variety of growth patterns	Lobular Trabecular Microcystic Cribriform Papillary	Variety of growth patterns
Incidence per 1,000,000 (% of all SGC)	0.62–1.80 (9–30)	0.41–1.72 (6–25)	0.41–1.73 (6–17)	0.27–0.69 (4–10)	0.14–0.83 (2–12)	0.34 (< 5)	0.14–0.27 (2–4)	0.20–1.10 (3–16)	< 300 cases were described	< 200 cases were described	0.14–1.24 (2–18)	~1%	A few cases
Predominant location Other location	Major salivary glands (90% in the parotid glands)	Submandibular glands or minor salivary glands Lung, breast	Major salivary glands (87% in the parotid glands)	Major salivary glands	Major salivary glands	Major salivary glands	Major salivary glands	Major salivary glands	Intraoral minor salivary glands	Major salivary glands	Major salivary glands	Minor salivary glands	Minor salivary glands
5-year survival (%)	37.5–100	60–90	33–96	20–50	50–64	80–96	~95	25–96	No data	No data	43–81	75–100	No data
References	[2, 26–28]	[2, 51, 185, 186]	[2, 73, 185, 186]	[2, 185]	[88, 185, 187]	[143, 185]	[152, 154, 183, 185]	[2, 69, 185, 186]	[168]	[176, 185]	[69, 185]	[2, 105, 185, 188]	[189]

SGCs – salivary gland carcinomas

Table 2. The most frequent genetic alterations in salivary gland carcinomas

Histopathological type	Fusions	Other genetic changes	References
Mucoepidermoid carcinoma (MEC)	***CRTC1-MAML2,*** 56–88%	***TP53,*** 21–42% ***CDKN2A,*** 42–56% ***CDKN2B,*** 31% ***BAP1,*** < 21% ***PIK3CA,*** 17–21% ***HRAS,*** < 14%	Saade *et al*. [31] Kang *et al*. [34] Seethala *et al*. [35] Zerdan *et al*. [47] Wang *et al*. [48] Morita *et al*. [49]
Acinic cell carcinoma (AcCC)	***SCPP* gene cluster – *NR4A3,*** > 80%	***CDKN2A/B*** high percentage in high-grade tumours and metastases cases ***ATM,*** 7–14% ***PTEN,*** 10–12%	Haller *et al*. [75] Dogan *et al*.[78] Ross *et al*. [69]
Adenoid cystic carcinoma (AdCC)	***MYB-NFIB,*** 60–80% *MYBL1-NFIB,* *MYBL1-YTHDF3*	***NOTCH*** signalling pathway, ~ 40% (***NOTCH1,*** 26%) R/M primary tumours, ~ 13 (***NOTCH1,*** 8.5) ***KDM6A,*** ~ 15 ***BCOR,*** 13–17 ***ARID1A,*** 7–14	Wagner *et al*. [61] Ho *et al*. [59] Lee *et al*. [66] Ross *et al*. [69] Wang *et al*. [68]
Adenocarcinoma (AC)			
Polymorphous adenocarcinoma (PAC)		***PRKD1*** hotspot mutation, 50–73%	Andreasen *et al*. [108] Weinreb *et al*. [107]
Cribriform adenocarcinoma (CA)	***PRKD1-3*** fusions, > 80%		Weinreb *et al*. [115]
Microsecretory adenocarcinoma (MiAC)	***MEF2C-SS18,*** ~ 90%		Skálová *et al*. [39]
Basal cell adenocarcinoma (BCAC)		***CYLD*** mutation, 29%	Rito *et al*. [190]
Mucinous adenocarcinoma (MAC)		***AKT1 E17K*** mutation, 100% ***TP53*** mutation, 88%	Rito *et al*. [190] Rooper *et al*. [191]
Salivary duct carcinoma (SDC)		***TP53,*** 39–60% ***HRAS,*** 11–49% ***ERBB2,*** 10–100% ***NF1,*** 7–20% ***PIK3CA,*** 19–47% ***PTEN,*** 6–13.5% ***AR*** overexpression	Dalin *et al*. [126] Ku *et al*. [140] Kohsaka *et al*. [136] Dogan *et al*. [127] Mueller *et al*. [123]
Myoepithelial carcinoma (MECA) *de novo* MECA ex PA	*TGFBR3-PLAG1,* 25% ***FGFR1-PLAG1,*** 29%	Various copy number alternations	Dalin *et al*. [88]
Epithelial-myoepithelial carcinoma (EMC)		***HRAS,*** 27–87% ***PIK3CA,*** 22–40% ***AKT1,*** 6.5–20%	Urano *et al*. [146] Grünewald *et al*. [148] Chiosea *et al*. [149] Nakaguro *et al*. [150]
Secretory carcinoma (SC)	***ETV6-NTRK3,*** > 95%		Baněčková et al. [192]
Carcinoma ex-pleomorphic adenoma (CA ex PA)	***PLAG1/HMGA2*** rearrangements	***TP53,*** 55–100% ***ERBB2,*** 39–57% ***PIK3CA,*** 8–42% ***HRAS,*** 4–23%	Stenman *et al*. [72] Dalin *et al*. [88] Chiosea *et al*. [128] Grünewald *et al*. [141] Dogan *et al*. [127] Kohsaka *et al*. [136]
Clear cell carcinoma (CCC)	***EWSR1-ATF1,*** > 90%		Antonescu *et al*. [170]
Intraductal carcinoma (IC)	***RET* rearrangements,** ~ 45% ***NCOA4-RET*** (mainly in intercalated subtype) ***MYO18A-ALK***	***HRAS*** ***PIK3CA*** High percentage (only in apocrine subtype)	Skálová *et al*. [179] Weinreb *et al*. [180] Hsieh *et al*. [182] Majewska *et al*. [183]

including novel findings, in the most known histopathological types of SGCs.

A comprehensive literature search was performed in the PubMed database. We analysed the full texts of the articles published in English in the period 1984–2024. The exclusion criteria were as follows: languages other than English, only abstracts available, papers concerning HNC holistically without specific analysis of SGCs, and analysis

of malignant transformation of benign lesions, e.g. pleomorphic adenoma.

The search was performed with the following keywords: "salivary gland carcinoma", "genetic alterations", "molecular abnormalities", "NGS", "targeted therapy", "precision therapy", "mucoepidermoid carcinoma", "acinic cell carcinoma", "adenoid cystic carcinoma", "carcinoma ex-pleomorphic adenoma", "Ca *ex* PA", "adenocarcinoma", "salivary duct carcinoma", "myoepithelial carcinoma", "epithelial-myoepithelial carcinoma", "secretory carcinoma", "polymorphous adenocarcinoma", "cribriform adenocarcinoma", "microsecretory adenocarcinoma", "basal cell adenocarcinoma", "mucinous adenocarcinoma", "clear cell carcinoma", and "intraductal carcinoma".

The results of the search are presented in relation to the histopathological types of SGCs.

Mucoepidermoid carcinoma

Mucoepidermoid carcinoma is the predominant salivary gland neoplasm and is detected in more than 30% of all salivary malignancies [26]. Generally, it is characterised by gradual growth, rare recurrence, and favourable patient outcomes. However, this type of cancer can be highly heterogeneous and can present as low-, intermediate-, or high-grade cancer, with the latter being associated with poor outcomes. Additionally, the mean age at diagnosis is lower than that of other subtypes and ranges from 45 to 49 years [2, 26–29].

Chromosomal translocation t(11;19)(q14-21; p12-13) is unique for MEC and results in CREB regulator transcriptional coactivator (*CRTC1*) (also known as *MECT1*)-mastermind-like transcriptional coactivator 2 (*MAML2*) oncogene fusion. It has been detected in more than 80% of patients with this cancer subtype. This alteration leads to cell proliferation and survival through autocrine amphiregulin (AREG)/epidermal growth factor receptor (EGFR) signalling [30–35]. Chen *et al*. revealed that aberrantly activated AREG-EGFR signalling in CRTC1-MAML2-positive MEC cells made them highly sensitive to EGFR inhibition, suggesting benefit from EGFR-targeted therapies, e.g. cetuximab [36]. However, the results of further studies were unsatisfactory, and Ni *et al.* proposed simultaneous therapy with erlotinib-EGFR inhibitors and Notch inhibitors as more effective [32]. Since *MAML2* is involved in NOTCH signalling pathway activation [33, 37, 38], this drug combination becomes more target specific. The other translocation, t(11;19)(q21;q26), results in a *CRTC3-MAML2* fusion product that is detected in 6% of cases [30, 39, 40]. Another rare change is the translocation t(6;22)(p21;q12), which promotes *ESWR1–POU5F1* fusion [40]. Previously, the *CRTC1-MAML2* fusion product was considered a positive prognostic factor [41–43]. However, further research did not reveal significant differences in survival between patients with and without the translocation [31, 44, 45]. In contrast, Anzick *et al.* revealed that adverse outcomes in patients with translocations might be related to other genetic alterations, such as *CDKN2A* deletion [46]. However, copy number variations (CNVs) and somatic mutations associated with this alteration have not been frequently analysed in MEC. Zerdan *et al*. performed NGS analysis of 118 MEC tumours and reported *CDKN2A* abnormalities in 53% of the cohort. Other frequent changes included those in *TP53* (41%), *CDKN2B* (31%), *BAP1* (19%), *PIK3CA* (17%), *TERT* (15%), and *HRAS* (14,5%) [47]. Similar observations regarding the most common variations were reported by Wang *et al.* [48]. In contrast, the analysis of comparable sample sizes by Morita *et al.* revealed that *HRAS* mutations are rarely detected [49]. On the other hand, Kang *et al.* reported whole-exome sequencing results for 18 MEC tumours, and the second most frequent variation after *TP53* was the *POU6F2* gene (17%) [34]. In addition, alterations in *BRCA2* and *ERBB2* are quite common in MEC (17% and 13%, respectively) [30]. Although *NF1* alterations are not frequently detected, Kato *et al.* reported *NF1* and *TP53* commutation [47, 50]. However, the significance of these findings remains unclear. Further studies are needed to obtain a more in-depth molecular inquiry into MEC molecular pathogenesis, especially in cases with poor outcomes.

Adenoid cystic carcinoma

Adenoid cystic carcinoma frequently arises in the submandibular or minor salivary glands. Its occurrence in the parotid gland is rare. Although AdCC is known as a histopathological type with indolent growth, it tends to recur, with perineural invasion and DM, especially to the lungs [51–54]. Cases of relapse and metastasis (R/M) are frequently incurable because of a lack of effective systemic therapies, despite ongoing clinical trials. Therefore, there is an urgent need to verify the possibility of using targeted treatment.

The activating neurogenic locus notch homologue protein 1 (*NOTCH1*) mutation and v-myb avian myeloblastosis viral oncogene homologue (*MYB*) overexpression are related to AdCC development, progression, perineural invasion, and even chemoresistance, which predisposes patients to unfavourable outcomes [30, 55–58]. In contrast, Ho *et al.* did not find a correlation between mutational *MYBs* and either R/M or survival [59]. In approximately 80% of cases, *MYB* alternations present as the t(6;9)(q22-23;p23-24) translocation, which involves the *MYB* proto-oncogene and the nuclear factor 1B gene (*NFIB*) transcription factor, leading to overexpression of the fusion product and worsening the prognosis [30, 60, 61]. *MYB NFIB* translocation is associated with high MYB expression. This translocation disrupts the MYB 3′ UTR, a microRNA regulatory site responsible for downregulating *MYB*. The existence of additional mechanisms for *MYB* overexpression in AdCC was investigated, revealing alternate rearrangements that translocate super-enhancers in the *NFIB* and *TGFBR3* loci to the *MYB* locus. The MYB protein binds these super-enhancers, which in turn physically interact with the *MYB* promoter, drive its overexpression, and establish a positive feedback loop [62].

To emphasise the importance of *MYB* gene activity, it coordinates the upregulation of pivotal targetable genes involved in several functions related to carcinogenesis, such as apoptosis (*API5, BCL2, BIRC3, HSPA8,* and *SET*),

cell cycle control (*CCNB1, CDC2,* and *MAD1L1*), cell growth and angiogenesis (*MYC, KIT, VEGFA, FGF2,* and *CD53*), and cell adhesion (CD34) [63, 64]. Notably, in 35% of *MYB-NFIB* fusion-negative tumours, *MYBL1* alterations were identified [65]. Interestingly, *MYB/MYBL1* rearrangements were not very common in R/M AdCCs (22%). In contrast, NOTCH signalling pathway alterations were noted in approximately 40% of R/M cases (with NOTCH1 mutations observed in 26% of these), while only 13% of primary tumours demonstrate increased signalling in the pathway (NOTCH1 mutations in 8.5%) [59, 66].

Notably, Ho *et al.* also reported frequent alterations in R/M AdCC among genes involved in chromatin remodelling: *KDM6A, KMT2C/MLL3, ARID1A, ARID1B, BCOR, MLL2/KMT2D*, and *CREBBP,* with increased frequency compared with primary tumours. *TERT* promoter mutations were found in > 10% of the R/M patients. Interestingly, *NOTCH1* and *MYB/MYBL1* fusions are practically undetectable in these lesions [59]. In parallel, Stephens *et al.*, in addition to significant *MYB* activation, reported *SPEN* gene alterations (negative NOTCH signalling regulators) in more than 20% of the study cohort [67]. Similar findings regarding *NOTCH1, KDM6A, ARID1A, BCOR, CREEB,* and *TERT* have been previously reported. Less frequently detected alterations were in *MLL2, RUNX1, PTEN, BAP1, PIK3CA, CDKN2A, ACTB, MGA, CTNNB1, FOXD1*, *IGFR1, MUC5B, OBSCN*, *PIK3R1, SPHKAP, TTN FGFR2,* and *BRAF* [68, 69]. In contrast, *TP53* mutations are rarely found in AdCCs, including R/M cases. Compared with tumours with favourable outcomes, recurrent and metastatic tumours harbour notably greater loads of mutations. Thus, the options of targeted therapies are quite extensive for verifying their efficiency in advanced stages [56, 70, 71].

Acinic cell carcinoma

The characteristics of AcCC are generally similar to those of MEC. However, some cases of aggressive metastatic AcCC have been reported recently [72–74]. Current knowledge regarding the molecular alterations in AcCC has not yet been properly established.

Haller *et al.* detected rearrangement t(4;9)(q13;q31), which results in secretory Ca-binding phosphoprotein (*SCPP*) gene cluster (*STATH, HTN1, HTN3, ODAM, FDCSP*, and *MUC7*) and nuclear receptor subfamily 4 group A member 3 (*NR4A3*) fusion in most tumours of the analysed cohort (more than 80%). The former translocation is unique to AcCC and allows for differentiation of AcCC from mammary analogue secretory carcinoma (MASC), particularly in cases with high-grade transformation. Moreover, the resulting fusion gene acts as an oncogenic driver, with the NR4A3 transcription factor being upregulated due to the translocation of active enhancers from the SCPP gene cluster (which is highly expressed in salivary glands) to the region upstream of NR4A3 [75, 76]. The second most common fusion involves the histatin 3 and Myb/SANT-like DNA-binding domain containing 3 genes (*HTN3-MSANTD3*) (t(4;9)(q13.3;q31.1)), which have been described in a few cases (4–8%) [75–77]. According to the authors, the former translocation is exceptional for AcCC and provides an effective differential diagnosis of MASC, especially in cases with high-grade transformation. Moreover, NR4A3 might be considered an oncogenic driver through enhancer hijacking, whereby *NR4A3* is upregulated [75, 77]. In a recent study, Ross *et al.* reported *CDKN2A* and *CDKN2B* alterations in 76% and 45% of patients with relapses or metastases, respectively [69]. Simultaneously, Dogan *et al.* performed a genetic analysis and reported that the *CDKN2A/B* gene changed solely in high-grade tumours (58% of this group), whereas in the disease course with distant metastasis, these rearrangements were found in nearly 90% of the patients [78], confirming them as a negative prognostic factor. Notably, for tumours with identified negative markers, there are targetable treatment options based on CDK4/6 inhibitors, immunotherapy, or DNA methyltransferase inhibitors [79, 80]. Moreover, in advanced AcCC, other genetic changes have also been observed [78]. The most common rearrangements were related to *ATM* (7–14%), *PTEN* (10–12%), *FBXW7*, and *TP53* rearrangements, whereas alterations in *BRAF*, *NF1*, *HRAS*, *NOTCH1*, *TERT*, *ARID2*, *BIRC3*, *MTAP*, and *FAT1* were less common [69, 78]. Importantly, some of these alterations may provide opportunities for utilising precision therapy.

Carcinoma ex-pleomorphic adenoma

Carcinoma *ex* PA is a rare primary SGC arising from a preexisting PA. It is estimated that 5–15% of benign pleomorphic adenomas undergo malignant transformation to carcinoma (Ca *ex* PA) [81, 82]. Thus, the detection of the benign part of the tumour might lead to a final misdiagnosis, but rapid growth and other symptoms should indicate suspicion of malignancy [83]. Although salivary duct carcinoma, myoepithelial carcinoma (MECA), and adenocarcinoma not otherwise specified (NOS) are considered the most commonly detected malignant components of Ca *ex* PA, other types of SGC histopathology have also been described [84–89]. The pleomorphic adenoma gene 1 (*PLAG1*) and the high-mobility group AT-hook 2 (*HMGA2*) genes are most frequently altered in both PAs and Ca *ex* PAs [90], but not typical for primary salivary duct carcinoma (SDC), MECA, or AC. Katabi *et al.* presumed that rearrangements in these genes were specific to both PA or Ca *ex* PA and could distinguish Ca *ex* PA from its *de novo* counterparts [91]. Nonetheless, further investigations have shown their occurrence in *de novo* lesions [88]. Carcinoma *ex* PA tumours have abundant copy number alterations (CNAs) that are suspected to be involved in the malignant transformation from benign lesions. The most common loss of heterozygosity is the amplification of 12q genes (*HMGA2*, *MDM2*), deletions of 5q, gains of 8q12.1 (*PLAG1*) and 8q22.1-q24.1 (*MYC*), and amplification of 17 chromosomes (*ERBB2*) [88, 92–94]. Table 3 lists the most commonly detected genetic alterations, including fusions and histopathological subtypes of Ca *ex* PA, reported in the literature.

Myoepithelial carcinoma

The incidence of MECA is estimated to be very low, at 2% among all SGCs. Nonetheless, because of the difficulty of proper diagnosis, the actual number of cases is predicted

Table 3. Malignant component of carcinoma ex pleomorphic adenoma as reported in respective studies

Gene	Identified malignant component in Ca *ex* PA	References
Genes fusions		
CTNNB1-PLAG1	MECA, SDC ~ 30%	Asahina *et al*. [193], Skálová *et al*. [194], Dalin *et al*. [126]
FBXO32-PLAG1	ND	Bubola *et al*. [195]
FGFR1-PLAG1	MECA, SDC, ND	Dalin *et al*. [88], Chiosea *et al*. [128], Skálová *et al*. [194], Bubola *et al*. [195]
LIFR-PLAG1	MECA, SDC	Skálová *et al*. [194], Dalin *et al*. [126]
MEG3-PLAG1	ND	Bubola *et al*. [195]
ND4-PLAG1	MECA	Dalin *et al*. [88]
PLAG1-NFIB	ND	Bubola *et al*. [195]
TGFBR3-PLAG1	MECA	Dalin *et al*. [88], Rupp *et al*. [196]
HMGA2-CNOT2	ND	Bubola *et al*. [195]
HMGA2-NFIB	ND	Bubola *et al*. [195]
HMGA2 fusions	MECA	Dalin *et al*. [88]
Oher PLAG1 fusions	MECA	Dalin *et al*. [88]
HMGA2-WIF1	ND, Adenoid cystic carcinoma with sarcomatoid transformation, MECA	Persson *et al*. [92] Katabi *et al*. [197]
ETV6-RET	SC	Smith *et al*. [198]
ZCCHC7-NTRK2	ND (recurrence and metastatic case)	Pircher *et al*. [199]
Somatic gene mutations		
TP53	SDC, MECA	Chiosea *et al*. [128], Grünewald *et al*. [141], Dogan *et al*. [127], Rupp *et al*. [196], Dalin *et al*. [126], Kohsaka *et al*. [136], Mueller *et al*. [123]
PIK3CA	SDC, MECA, EMC	Chiosea *et al*. [128], Dogan *et al*. [127], Dalin *et al*. [88], Hallani *et al*. [144], Dalin *et al*. [126], Kohsaka *et al*. [136], Mueller *et al*. [123]
HRAS	SDC, MECA, EMC	Chiosea *et al*. [128], Dogan *et al*. [127], Dalin *et al*. [88], Hallani *et al*. [144], Dalin *et al*. [126]
ERBB2	SDC (gain/amp)	Chiosea *et al*. [128], Dogan *et al*. [127], Dalin *et al*. [126], Kohsaka *et al*. [136], Mueller *et al*. [123]
AKT1	SDC	Dalin *et al*. [126]
ALK	SDC	Mueller *et al*. [123]
APC	SDC	Dogan *et al*. [127], Mueller *et al*. [123]
AR	SDC	Dogan *et al*. [127]
ARID1A	SDC	Kohsaka *et al*. [136]
ASXL1	SDC	Dogan *et al*. [127]
ATM	SDC, MECA	Chiosea *et al*. [128], Dalin *et al*. [88], Mueller *et al*. [123]
ATR	MECA	Dalin *et al*. [88]
AURKA	SDC	Dogan *et al*. [127]
BAP1	SDC	Dogan *et al*. [127]
BRAF	SDC	Chiosea *et al*. [128], Kohsaka *et al*. [136]
BRCA1	MECA	Dalin *et al* [88]
BRCA2	SDC	Dogan *et al*. [127], Kohsaka *et al*. [136]
BTK	SDC	Dogan *et al*. [127]
CCNE1	SDC	Dogan *et al*. [127], Mueller *et al*. [123]
CCND3	SDC	Mueller *et al*. [123]
CDH1	SDC	Dogan *et al*. [127]
CDK4	SDC	Grünewald *et al*. [141], Mueller *et al*. [123]
CDK6	SDC	Mueller *et al*. [123]
CDK12	SDC	Dogan *et al*. [127]
CDKN1B	SDC	Dogan *et al*. [127]
CDKN2A	SDC	Chiosea *et al*. [128], Mueller *et al*. [123]

Table 3. Cont.

Gene	Identified malignant component in Ca *ex* PA	References
CHEK2	SDC	Mueller *et al*. [123]
CREBBP	MECA, SDC	Dalin *et al*. [88], Mueller *et al*. [123]
CTCF	SDC	Dogan *et al*. [127]
DNMT1, DNMT3A, NMT3B	SDC	Dogan *et al*. [127]
DOCK7	SDC	Dalin *et al*. [126]
EGFR	SDC	Dogan *et al*. [127]
EP300	SDC	Mueller *et al*. [123]
ERBB3	SDC	Dogan *et al*. [127]
EWSR1	MECA (clear cell)	Skálová *et al*. [194]
FANCA, FANCC	SDC	Dogan *et al*. [127]
FASN	SDC	Dalin *et al*. [126]
FAT1	SDC, MECA	Dogan *et al*. [127], Dalin *et al*. [88]
FAT4	MECA	Dalin *et al* [88]
FBXW7	SDC	Dogan *et al*. [127], Mueller *et al*. [123]
FGFR1	MECA, SDC	Dalin *et al*. [88], Dalin *et al*. [126], Mueller *et al*. [123]
FGFR2	MECA	Dalin *et al*. [88]
FGFR3	SDC	Chiosea *et al*. [128]
FGFR4	SDC	Mueller *et al*. [123]
FH	SDC	Dogan *et al*. [127]
FLCN	SDC	Dogan *et al*. [127]
FOXA1	SDC	Dalin *et al*. [126], Kohsaka *et al*. [136]
GATA2	SDC	Dogan *et al*. [127]
HMGA2	ND	Persson *et al*. [92]
HNF1A	SDC	Dogan *et al*. [127]
JUN	SDC	Dogan *et al*. [127]
KDR	SDC	Dalin *et al*. [126]
KIT	SDC	Mueller *et al*. [123]
KMT2A	SDC	Dogan *et al*. [127], Kohsaka *et al*. [136]
KMT2B	SDC	Dalin *et al*. [126]
KMT2C	SDC	Dogan *et al*. [127], Dalin *et al*. [126], Kohsaka *et al*. [136]
KMT2D	SDC	Kohsaka *et al*. [136]
LIFR	MECA	Dalin *et al*. [88]
MAP2K2	SDC	Kohsaka *et al*. [136]
MAP3K1	SDC	Dogan *et al*. [127]
MDM2	ND, SDC	Persson *et al*. [92], Mueller *et al*. [123]
MET	MECA	Dalin *et al*. [88]
MLH3	SDC	Dalin *et al*. [126]
MML2	MECA	Dalin *et al*. [88]
MN1	MECA	Dalin *et al*. [88]
MSH5	SDC	Dalin *et al*. [126]
MTOR	SDC	Dalin *et al*. [126]
MYC	SDC	Dogan *et al*. [127]
NCOA1, NCOA2	MECA	Dalin *et al*. [88]
NCOR1	SDC	Dogan *et al*. [127], Dalin *et al*. [126]
NF1	SDC	Dogan *et al*. [127], Dalin *et al*. [126], Kohsaka *et al*. [136], Mueller *et al*. [123]
NOTCH1	MECA, SDC	Dalin *et al*. [88], Mueller *et al*. [123]
NOTCH2-3	SDC	Mueller *et al*. [123]

Table 3. Cont.

Gene	Identified malignant component in Ca *ex* PA	References
NSD1	SDC	Dalin *et al*. [126]
PIK3R1	SDC	Dogan *et al*. [127]
PTEN	SDC	Chiosea *et al*. [128], Dogan *et al*. [127], Kohsaka *et al*. [136]
PTPN11	SDC	Dogan *et al*. [127]
PTPRS	SDC	Dogan *et al*. [127]
RAD51C	SDC	Dogan *et al*. [127]
RET	SDC	Dalin *et al*. [126]
RICTOR	SDC	Mueller *et al*. [123]
ROS1	SDC	Mueller *et al*. [123]
RTEL1	SDC	Dogan *et al*. [127]
SF3B1	SDC	Dalin *et al*. [126]
SMAD4	SDC	Dalin *et al*. [126]
SMARCA4	MECA, SDC	Dalin *et al*. [88], Dalin *et al*. [126]
TSC2	SDC	Mueller *et al*. [123]
ZFHX3	SDC	Kohsaka *et al*. [136]

EMC – epithelial-myoepithelial carcinoma, MECA – mucoepidermoid carcinoma, ND – no data available, SDC – salivary duct carcinoma

to be greater [10, 95]. The tumour might occur as a *de novo* lesion or arise from the malignant transformation of a PA or myoepithelioma [96]. These data suggest that MECA *ex* PAs are more frequently detected than *de novo* lesions [88, 97]. However, the conclusion regarding which component is characterised by more aggressive behaviour or poorer patient outcomes remains debatable [95, 97–100]. In most cases, this subtype of cancer is associated with adverse patient results, including early local and DM [10, 88, 95]. Myoepithelial carcinoma is one of the most commonly confirmed components of Ca *ex* PAs [89, 101].

Salivary gland MECA rarely occurs; therefore, few genetic studies of this type are available. Dalin *et al.* analysed 40 tumours with divisions on either the MECA *de novo* or the MECA *ex* PA, as well as cases with and without recurrence. In MECA *ex* PA, more genetic alterations, including fusions, somatic mutations, and CNVs, were found. According to the authors, CNVs are responsible for the malignant transformation of the PA into the MECA *ex* PA and are also associated with a worse prognosis. *FGFR1-PLAG1* fusion was the most commonly (18%) identified in the MECA *ex* PA, followed by *TGFBR3-PLAG1* but with no evidence of their prognostic value. Furthermore, *EWSR1-ATF1* was described only in the MECA *de novo,* with or without recurrence [88]. In contrast to the research conducted by Skálová *et al*., *EWSR1* rearrangements were found frequently in the clear cell component of MECA both in *de novo* cases and those arising from the PA, but the fusion partner genes were not identified [102]. In the aforementioned study, *PIK3CA* was present only in patients without relapse, whereas *FGFR2* mutations were found in patients with recurrence [88]. The findings are summarised in Table 4. *FGFR2* mutations were also described in 2 patients after radical PA excision, in which the MECA rapidly developed. In both PAs and MECAs (without the PA component), *FGFR2* point mutations were confirmed, which might be indicative of an aggressive disease course [103]. Recently, Gandhi *et al.* reported a novel *CTCF-NCOA2* fusion in a single MECA patient [104]. Furthermore, Cormier *et al.* presented a novel *TERT* promoter mutation in metastatic MECA *ex* PA (the tumour was previously misdiagnosed as PA) [9].

Adenocarcinoma

Polymorphous adenocarcinoma

Polymorphous adenocarcinoma (PAC) is a rare, slow-growing malignant tumour. It mainly arises from the minor salivary glands (second most common histopathological type), particularly those localised on the hard palate. There is a higher prevalence in women than in men, and patient outcomes are defined as one of the most favourable outcomes among SGCs [105, 106].

Weinreb *et al.* revealed a *PRKD1* p.E710 hotspot mutation in nearly 73% of tumours, and these observations were not identified in other SGCs. Thus, this alteration is unique to PAC and may be useful for differentiating it from its mimics [107, 108]. Notably, in cribriform adenocarcinoma (CA), *PRKD1-3* fusions are the most common. CA is classified as an aggressive variant of PAC with a high predisposition to metastasis [109–112]. Among the fusion partners *ARID1A, ATL2, DDX3X, PPP2R2A, PRKAR2A, SNX9,* and *STRN3* (cases with high-grade transformation) should be mentioned [113–116]. However, the type of genomic alteration is not specific for any AC subtype, and occasionally, either *PRKD1-3* fusions or *PRKD1* rearrangements are found in PAC and CA, respectively [109]. Therefore, differentiation between these 2 variants with various behaviours might be challenging.

Adenocarcinoma not otherwise specified

Tumours with a histopathological diagnosis of adenocarcinoma NOS constitute a heterogeneous group that has not

Table 4. Genetic rearrangements in the mucoepidermoid carcinoma de novo and the mucoepidermoid carcinoma ex pleomorphic adenoma presented in the study by Dalin *et al*. in relation to oncological outcomes

MECA *de novo*		MECA *ex* PA	
No recurrence	**Recurrence**	**No recurrence**	**Recurrence**
TGFBR3-PLAG1	*HMGA2* fusions	*TGFBR3-PLAG1*	*FGFR1-PLAG1*
Other *PLAG1* fusions	*EWSR1-ATF1*	*FGFR1-PLAG1*	Other *PLAG1* fusions
EWSR1-ATF1	*FGFR1*	Other *PLAG1* fusions	*HMGA2* fusions
MSN-ALK	*FGFR2*	*HMGA2* fusions	*FGFR2*
PIK3CA	*SMARCA4*	*HRAS*	*MAML2*
MAML2	*PCM1*	*PIK3CA*	*NOTCH1*
NOTCH1	*TRIP11*	*FGFR1*	*ATM*
ATM		*LIFR*	*ATR*
KMT2C		*MET*	*BRCA1*
SETD2		*MAML2*	*MN1*
		ATR	*COL2A1*
		CREBBP	*FAT1*
		NCOA1	*FAT4*
		NCOA2	

MECA – mucoepidermoid carcinoma, PA – pleomorphic adenoma

yet been well characterised. For example, *NTRK2-ZCCHC7* and *SS18-ZBTB7A* fusions have been described [116, 117]. In R/M cases, *TP53* (55%), *PIK3CA*, *HRAS*, *CDKN2A*, *ERBB2*, *PTEN*, *NF1*, and *ARID1A* alterations were observed with considerable frequency [69].

On the basis of genetic pattern analysis, microsecretory adenocarcinoma has been distinguished from NOS. Microsecretory adenocarcinoma harbours *MEF2C-SS18* fusion in approximately 90% of cases [39, 118].

The most common alterations in basal cell adenocarcinoma and mucinous adenocarcinoma are shown in Table 1.

Salivary duct carcinoma

Salivary duct carcinoma is one of the most aggressive SGCs, with either early relapse or frequent DM. It is also associated with significant mortality. Predilection in elderly males with a smoking history is usually combined with advanced-stage presentation and parotid gland localisation [119–123]. The estimated morbidity is 5.5–12% [124, 125]. Moreover, SDCs *ex* PAs have also been detected [122, 126–128]. Table 2 provides genetic information for this subtype.

In addition to the microscopic structure resembling high-grade ductal carcinoma of the breast, SDC is also characterised by the overexpression of human epidermal growth factor receptor 2 (*HER2*). Instead of oestrogen and progesterone receptor positivity, androgen receptor (AR) expression is detected in 75–98% of cases [122, 126, 129, 130]. Notably, *AR* is seldom detectable in other SGCs [131]. However, studies are inconclusive regarding the prognostic value of the AR [129, 131, 132]. Nevertheless, Kawakita *et al.* showed in a retrospective study that the utilisation of HER2-targeted therapy and androgen deprivation therapy significantly improved patients results compared with conventional therapy management [133]. The anti-HER2 therapies that induce improvement in clinical responses in SDC patients use trastuzumab in combination with chemotherapy (i.e. taxanes, capecitabine, carboplatin, eribulin) or with another anti-HER2 targeted agent (i.e. pertuzumab). Further expectations and therapeutic advances are related to novel anti-HER2 drugs such as antibody-drug conjugates (i.e. trastuzumab emtansine, trastuzumab deruxtecan) introduced in this setting [134].

In recent years, genetic knowledge about SDC has increased profoundly, but it still has not been comprehensively investigated. The tumour mutation burden is extremely high in most SDC cases, in contrast to other SGCs. Vos *et al.* evaluated therapy with nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) in patients with metastatic SGC. Although the efficacy was limited in AdCC, with infrequent responses, they found it promising for non-AdCC SGCs, particularly salivary duct carcinomas [135]. Genetic fusions are not recurrent events in this subtype, whereas somatic mutations as well as CNVs are considerably more common [123, 126, 136]. Moreover, most of them provide opportunities for the utilisation of targeted treatment for this unpredictable cancer [30, 127, 137–139]. *TP53, HRAS, PIK3CA,* and *ERBB2* (*HER*) rearrangements are the most common, and some of them are related to poor outcomes [123, 126–128, 136, 140, 141]. Interestingly, although *HRAS* mutations constitute the majority of *de novo* lesions, they are rare in SDC *ex* PAs [123, 126, 127, 136]. Data regarding the molecular landscape of SDCs are presented in Table 5.

Epithelial-myoepithelial carcinoma

Epithelial-myoepithelial carcinoma (EMC) is rarely detected, and it was first reported by Donath *et al.* in 1972. Previously, it appeared under other terminology of adenomyoepithelioma or clear cell adenoma. The tumour consists of a dual cell population that forms a double layer: inner ductal cells and outer myoepithelial cells [142–144]. Notably, various histological subtypes of EMCs exist, including sebaceous, oncocytic, and double-clear subtypes.

Table 5. The genetic pathways most commonly affected in salivary duct carcinoma

Pathway	Genes	References
DNA damage	*TP53* (39–60%), *ATM, BRCA2, CHEK2, MDM2, MDM4, MLH3, MLH5*	[123, 126, 127, 136, 140, 141]
MAPK	*HRAS* (11–49%), *NF1* (7–20%), *BRAF, KRAS, NRAS*	[123, 125, 126, 127, 128, 136, 137, 140]
RTK	*ERBB2* (10–100%), *ALK, EGFR, ERBB3-4, FGFR1-2, FGFR4, FLT3, JAK2, KDR, KIT, MET, NTRK2, PDGFRA, RET*	[123, 126, 127, 136, 137, 140]
PI3K/AKT/mTOR	PIK3CA (19–47%), *PTEN* (6–13.5%), *AKT1-3, PIK3R1, RICTOR, RPTOR, TSC2*	[123, 125, 126, 127, 128, 136, 137, 140]
Androgen signalling	*AR, FASN, FOXA1*	[126, 136]
Histone modification	*KDM6A, KMT2A, KMT2C, KMT2D, KMT2E, NSD1*	[126, 127, 136, 140]
Cell cycle	*CDK4, CDK6, CDK12, CDKN1A, CDKN1B, CDKN2A, CCNE1, CCND1-3, RB1*	[123, 126, 127, 136, 140, 141]
NOTCH	*CREBBP, EP300, FBXW7, NOTCH1-3*	[123, 140]
SWI/SNF complex	*ARID1A, SMARCA4, SMARCB1*	[123, 126, 127, 136]
WNT-β-catenin	*APC, CDH1, CTNNB1, FAT1*	[123, 126, 140]
Other	*ABL1, AURKA, BCOR, CCND1, CCNE1, FLCN, GNAS, HMGA2, IDH1-2, IGFR1, IKBKE, KLF5, AMP, MAP2K1, MAP2K4, MITF, MPL, MYC, PRDM1, SMAD4, SMO, STK11, TNIK, VHL, ZFHX3*	[123, 126, 127, 136, 140, 141]
Fusions	*ETV6-NTRK3, ABL1-PPP2R2C, BCL6-TRADD, HNRNPH3-ALK, EML4-ALK, RAPGEF6-ACSL6*	[126, 127, 195]

Thus, the differential diagnosis could pose difficulties [145, 146]. Morbidity predominates in females more than males. Most commonly, the parotid gland is affected, and the tumour is characterised by a high overall survival rate. Although DM rarely occur, relapses are common [143, 147].

HRAS (27–87%) was described as the most frequently mutated gene in EMC [146, 148–150]. In the studies conducted by Urano *et al.* and Nakaguro *et al.,* these findings were not detected in EMCs *ex* PAs [146, 150]. In parallel, Hallani *et al.* did not prove *HRAS* alterations for *de novo* EMC [144]. *PIK3CA* and *AKT1* have been reported quite commonly in EMC (22–40% and 6.5–20%, respectively) [146, 148]. *CTNNB1, FBXW7,* and *TP53* rearrangements and *SMARCB1* deletions have been reported in single cases (the last 3 in high-grade tumours) [144, 148]. Mäkelä *et al.* described rare metastatic EMC in a 36-year-old woman, where in addition to *HRAS* mutation, *ARID1B, ATR, CDK12, ERBB4, MAPK1, NANOG, NOTCH2, PIK3R1,* and *RPTOR* alterations were detected [151].

Secretory carcinoma

Secretory carcinoma (SC) (previously known as mammary analogue secretory carcinoma) is a novel salivary gland tumour that was described by Skálová *et al.* in 2010 [152]. Most of these tumours were previously classified as AcCC [153]. The age at diagnosis is relatively low (mean 45 years), including paediatric patients. There is a greater predilection in men, and the disease course is indolent, with favourable patient outcomes [154, 155].

Secretory carcinoma has a significant histological and molecular resemblance to breast secretory carcinoma. It is characterised by harbouring the same translocation t(12;15)(p13;q25), resulting in the *ETV6-NTRK3* fusion gene encoding a chimeric oncoprotein-tyrosine kinase (unlike AcCC) [152, 155, 156]. Other *ETV6* fusion partners have also been discovered, including *ETV6-MAML3* [157], *ETV6-MET* [158], and *ETV6-RET* [157, 159]. Notably, some of these genes remain unknown (*ETV6-X*) [160]. Recently, other novel fusions, such as *VIM-RET* [161], *CTNNA1-ALK* [162], and dual fusion, *ETV6-RET* and *EGFR-SEPT14,* were identified in an 18-year-old male [159]. *ETV6-NTRK3* and *MYB-SMR3B* fusions were found in recurrent high-grade submandibular tumours [161]. Only a few studies have analysed genetic rearrangements other than fusions. Na *et al.* identified pathogenic *PRSS1* mutations, mainly in patients with an aggressive disease course and recurrence, whereas other findings were classified as likely pathogenic or of uncertain significance [163]. In contrast, Skálová *et al.* analysed 3 tumours with high-grade transformation and did not detect the most commonly occurring genetic alterations associated with poor outcomes (*TP53, CTNNB1, EGFR, CCND1*) [164].

Testing for *ETV6-NTRK3* gene rearrangements is critical for SC patients care since entrectinib, an inhibitor of tropomyosin receptor kinase (TRKs), has been reported to be effective and safe in treating solid tumours with NTRK fusion genes. In an integrated analysis of phase 1–2 trials (STARTRK-1, STARTRK-2, and ALKA-372-001) of solid tumours with the NTRK fusion gene, the response rate to the TRK inhibitor entrectinib was 57%, and the median progression-free survival was 11.2 months [165]. Another TRK inhibitor, larotrectinib, is also effective in the treatment of solid tumours with the NTRK fusion gene [166]. Other potential therapies for SC patients with identified oncogenic RET fusions, namely ETV6-RET , are selpercatinib and pralsetinib selective RET inhibitors, currently under preclinical and clinical testing [167].

Clear cell carcinoma

Clear cell carcinoma (CCC) (previously known as hyalinising clear cell carcinoma) is an indolent low-grade tumour that typically arises from the intraoral minor salivary glands. There is a higher prevalence in females, whereas relapses and metastases are rare [168].

Considering the occurrence of clear cells in other SGCs, differential diagnosis may be a challenge [169]. Antonescu *et al.* first described genetic rearrangement in the CCC-*EWSR1-ATF1* fusion *t*(12;22)(q13;q12). It occurs in more than 90% of cases, and, being unique for CCC, it is therefore a helpful differentiation tool [170]. *EWSR1-CREB1, EWSR1-CREM,* and *SMARCA2-CREM* fusions have been reported in single cases thus far [171–173].

Intraductal carcinoma

Intraductal carcinoma (IC) is a rare salivary gland tumour that affects mainly the parotid gland, with features similar to mammary atypical ductal hyperplasia or ductal carcinoma *in situ* of the breast [174, 175]. Recent studies have classified 4 distinctive subtypes: intercalated duct type, apocrine, hybrid, and oncocytic [176].

RET rearrangements, including recurrent *NCOA4-RET* (intercalated, oncocytic, seldom hybrid), *TRIM27-RET* (hybrid, apocrine), and *TRIM33-RET* (oncocytic) rearrangements, have been detected [177–179]. In contrast, *RET* gene alterations have not yet been confirmed in the apocrine subtype [180].

The relationship between IC and SDC remains controversial, even though they are considered diverse entities. Intraductal carcinoma, especially invasive apocrine IC, is a precursor for more aggressive cancers, such as SDC [174, 176, 180]. Nevertheless, this issue requires further investigation. Molecular evidence of resemblance to SDC revealed a high occurrence of *HRAS* and *PIK3CA* hotspot mutations in apocrine IC [174, 180–182]. Additionally, *ATM, SPEN*, and *TP53* mutations and either *DFFA-ARID1A* or *KIF13B-EPB41L4B* fusions were found in this subtype [174,180]. In parallel, *BRAF* V600E mutations in the oncocytic subtype and novel fusions of *TUT1-ETV5* and *KIAA1217-RET* in intercalated duct variants and hybrid intercalated duct tumours with invasive growth have also been identified [178, 179].

Furthermore, Majewska *et al.* reported an *MYO18A-ALK* fusion in intercalated duct-type IC in elderly patients after radical excision and no disease relapse during follow-up [183].

Recently, Watanabe *et al.* presented a case of a 59-year-old male with high-grade intercalated-type IC and DM. Despite radical excision and postoperative radiotherapy, the patient developed multiple DM. Genetic analysis revealed a *CTNNA1-ALK* fusion and *TP53* mutation. Despite further ALK-TKI therapy, the patient's condition declined, and NGS analysis of the blood samples revealed a novel *PIK3CA* mutation (*ALK* fusion was not detected). The importance of this shift remains uncertain. Nevertheless, treatment failure might be related to novel alterations and the predominance of other abnormalities in recurrent tumour tissue [184].

Conclusions

Salivary gland carcinomas are rare entities with unpredictable disease courses. The diversity of both the histological architecture and molecular alterations is distinct among individual subtypes, which leads to diagnostic difficulties. Moreover, because of the rare incidence of SGCs, multicentre clinical trials are urgently needed to provide targeted therapeutic options. Currently, the value of genetic analysis has been highlighted, particularly in terms of the possibilities of precision therapies and in light of the insufficient effectiveness of standard treatment options. Knowledge of the molecular landscape of SGC, especially related to outcome predictors, will provide novel and precise methods for diagnosis and therapy in the future.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209-249.
2. Young A, Okuyemi OT. Malignant Salivary Gland Tumors. StatPearls. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.: Treasure Island (FL), 2022.
3. Gatta G, Guzzo M, Locati LD, McGurk M, Prott FJ. Major and minor salivary gland tumours. Crit Rev Oncol Hematol 2020; 152: 102959.
4. Global Cancer Observatory. International Agency for Research on Cancer. Cancer Today.
5. Van Herpen C, Poorten VV, Skalova A, et al. Salivary gland cancer: ESMO-European Reference Network on Rare Adult Solid Cancers (EURACAN) Clinical Practice Guideline for diagnosis, treatment and follow-up. ESMO Open 2022; 7: 100602.
6. Global Cancer Observatory. International Agency for Research on Cancer. Cancer Tomorrow. Available from: https://gco.iarc.fr/tomorrow/en.
7. Son E, Panwar A, Mosher CH, Lydiatt D. Cancers of the major salivary gland. J Oncol Pract 2018; 14: 99-108.
8. Speight PM, Barrett AW. Salivary gland tumours: diagnostic challenges and an update on the latest WHO classification. Diagn Histopathol 2020; 26: 147-158.
9. Cormier C, Agarwal S. Myoepithelial carcinoma ex-pleomorphic adenoma: a rare pathology misdiagnosed as pleomorphic adenoma; with a novel TERT promoter mutation and high PD-L1 expression. Head Neck Pathol 2022; 16: 322-330.
10. Xu B, Mneimneh W, Torrence DE, et al. Misinterpreted myoepithelial carcinoma of salivary gland: a challenging and potentially significant pitfall. Am J Surg Pathol 2019; 43: 601-609.
11. Hernandez-Prera JC, Skálová A, Franchi A, et al. Pleomorphic adenoma: the great mimicker of malignancy. Histopathology 2021; 79: 279-290.
12. Spitz MR, Tilley BC, Batsakis JG, Gibeau JM, Newell GR. Risk factors for major salivary gland carcinoma. A case-comparison study. Cancer 1984; 54: 1854-1859.
13. Radoï L, Barul C, Menvielle G, et al. Risk factors for salivary gland cancers in France: Results from a case-control study, the ICARE study. Oral Oncol 2018; 80: 56-63.
14. Spitz MR, Fueger JJ, Goepfert H, Newell GR. Salivary gland cancer. A case-control investigation of risk factors. Arch Otolaryngol Head Neck Surg 1990; 116: 1163-1166.
15. Salivary Gland Cancer: Risk Factors. CancerNet Editorial Board 05/2020.
16. Geiger JL, Ismaila N, Beadle B, et al. Management of salivary gland malignancy: ASCO Guideline. J Clin Oncol 2021; 39: 1909-1941.
17. Park GC, Roh JL, Cho KJ, et al. Incidence and risk factors of late recurrence in patients with salivary gland cancer. Clin Otolaryngol 2017; 42: 416-424.
18. Glazer TA, Shuman AG. Distant metastases and palliative care. Adv Otorhinolaryngol 2016; 78: 182- 188.
19. Nam SJ, Roh JL, Cho KJ, Choi SH, Nam SY, Kim SY. Risk factors and survival associated with distant metastasis in patients with

carcinoma of the salivary gland. Ann Surg Oncol 2016; 23: 4376-4383.
20. Mimica X, McGill M, Hay A, et al. Distant metastasis of salivary gland cancer: Incidence, management, and outcomes. Cancer 2020; 126: 2153-2162.
21. Morganti S, Tarantino P, Ferraro E, D'Amico P, Duso BA, Curigliano G. Next Generation Sequencing (NGS): A Revolutionary Technology in Pharmacogenomics and Personalized Medicine in Cancer. Adv Exp Med Biol 2019; 1168: 9-30.
22. Mosele F, Remon J, Mateo et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol 2020; 31: 1491-1505.
23. Hussen BM, Abdullah ST, Salihi A, et al. The emerging roles of NGS in clinical oncology and personalized medicine. Pathol Res Pract 2022; 230: 153760.
24. Kamps R, Brandão RD, Bosch BJ, et al. Next-generation sequencing in oncology: genetic diagnosis, risk prediction and cancer classification. Int J Mol Sci 2017; 18.
25. Skálová A, Stenman G, Simpson RHW, et al. The role of molecular testing in the differential diagnosis of salivary gland carcinomas. Am J Surg Pathol 2018; 42: e11-e27.
26. Sama S, Komiya T, Guddati AK. Advances in the treatment of mucoepidermoid carcinoma. World J Oncol 2022; 13: 1-7.
27. Peraza A, Gómez R, Beltran J, Amarista FJ. Mucoepidermoid carcinoma. An update and review of the literature. J Stomatol Oral Maxillofac Surg 2020; 121: 713-720.
28. Coca-Pelaz A, Rodrigo JP, Triantafyllou A, et al. Salivary mucoepidermoid carcinoma revisited. Eur Arch Otorhinolaryngol 2015; 272: 799-819.
29. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. Head Neck Surg 1986; 8: 177-184.
30. Vathiotis IA, Johnson JM, Argiris A. New systemic therapies in salivary gland cancer. In: Vermorken JB, Budach V, Leemans CR, Machiels J-P, Nicolai P, O'Sullivan B (eds). Critical issues in head and neck oncology. Springer International Publishing, Cham 2023, 327-345.
31. Saade RE, Bell D, Garcia J, Roberts D, Weber R. Role of CRTC1/MAML2 translocation in the prognosis and clinical outcomes of mucoepidermoid carcinoma. JAMA Otolaryngol Head Neck Surg 2016; 142: 234-240.
32. Ni W, Chen Z, Zhou X, et al. Targeting Notch and EGFR signaling in human mucoepidermoid carcinoma. Signal Transduct Target Ther 2021; 6: 27.
33. Coxon A, Rozenblum E, Park YS, et al. Mect1-Maml2 fusion oncogene linked to the aberrant activation of cyclic AMP/CREB regulated genes. Cancer Res 2005; 65: 7137-7144.
34. Kang H, Tan M, Bishop JA, et al. Whole-exome sequencing of salivary gland mucoepidermoid carcinoma. Clin Cancer Res 2017; 23: 283-288.
35. Seethala RR, Dacic S, Cieply K, Kelly LM, Nikiforova MN. A reappraisal of the MECT1/MAML2 translocation in salivary mucoepidermoid carcinomas. Am J Surg Pathol 2010; 34: 1106-1121.
36. Chen Z, Chen J, Gu Y, et al. Aberrantly activated AREG-EGFR signaling is required for the growth and survival of CRTC1-MAML2 fusion-positive mucoepidermoid carcinoma cells. Oncogene 2014; 33: 3869-3877.
37. Tonon G, Modi S, Wu L, et al. t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. Nat Genet 2003; 33: 208-213.
38. O'Neill ID. t(11;19) translocation and CRTC1-MAML2 fusion oncogene in mucoepidermoid carcinoma. Oral Oncol 2009; 45: 2-9.
39. Skálová A, Hyrcza MD, Leivo I. Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Salivary Glands. Head Neck Pathol 2022; 16: 40-53.
40. Kaur K, Mehta S, Vanik S, et al. The evolving role of molecular pathology in the diagnosis of salivary gland tumours with potential pitfalls. Eur Arch Otorhinolaryngol 2022; 279: 3769-3783.
41. Okabe M, Miyabe S, Nagatsuka H, et al. MECT1-MAML2 fusion transcript defines a favorable subset of mucoepidermoid carcinoma. Clin Cancer Res 2006; 12: 3902-3907.
42. Miyabe S, Okabe M, Nagatsuka H, et al. Prognostic significance of p27Kip1, Ki-67, and CRTC1 MAML2 fusion transcript in mucoepidermoid carcinoma: a molecular and clinicopathologic study of 101 cases. J Oral Maxillofac Surg 2009; 67: 1432-1441.
43. Behboudi A, Enlund F, Winnes M, et al. Molecular classification of mucoepidermoid carcinomas prognostic significance of the MECT1-MAML2 fusion oncogene. Genes Chromosomes Cancer 2006; 45: 470-481.
44. Birkeland AC, Foltin SK, Michmerhuizen NL, et al. Correlation of Crtc1/3-Maml2 fusion status, grade and survival in mucoepidermoid carcinoma. Oral Oncol 2017; 68: 5-8.
45. van Weert S, Lissenberg-Witte BI, Bloemena E, Leemans CR. Mucoepidermoid carcinoma of the head and neck: CRTC1/3 MAML 2 translocation and its prognosticators. Eur Arch Otorhinolaryngol 2022; 279: 2573 2581.
46. Anzick SL, Chen WD, Park Y, et al. Unfavorable prognosis of CRTC1-MAML2 positive mucoepidermoid tumors with CDKN2A deletions. Genes Chromosomes Cancer 2010; 49: 59-69.
47. Bou Zerdan M, Kumar PA, Zaccarini D, Ross J, Huang R, Sivapiragasam A. Molecular targets in salivary gland cancers: a comprehensive genomic analysis of 118 mucoepidermoid carcinoma tumors. Biomedicines 2023; 11.
48. Wang K, McDermott JD, Schrock AB, et al. Comprehensive genomic profiling of salivary mucoepidermoid carcinomas reveals frequent BAP1, PIK3CA, and other actionable genomic alterations. Ann Oncol 2017; 28: 748-753.
49. Morita M, Murase T, Okumura Y, et al. Clinicopathological significance of EGFR pathway gene mutations and CRTC1/3-MAML2 fusions in salivary gland mucoepidermoid carcinoma. Histopathology 2020; 76: 1013-1022.
50. Kato S, Elkin SK, Schwaederle M, et al. Genomic landscape of salivary gland tumors. Oncotarget 2015; 6: 25631-25645.
51. Cantù G. Adenoid cystic carcinoma. An indolent but aggressive tumour. Part A: from aetiopathogenesis to diagnosis. Acta Otorhinolaryngol Ital 2021; 41: 206-214.
52. Sung MW, Kim KH, Kim JW, et al. Clinicopathologic predictors and impact of distant metastasis from adenoid cystic carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 2003; 129: 1193-1197.
53. Liu X, Yang X, Zhan C, Zhang Y, Hou J, Yin X. Perineural invasion in adenoid cystic carcinoma of the salivary glands: where we are and where we need to go. Front Oncol 2020; 10: 1493.
54. Cordesmeyer R, Schliephake H, Kauffmann P, et al. Clinical prognostic factors of salivary adenoid cystic carcinoma: A single-center analysis of 61 patients. J Craniomaxillofac Surg 2017; 45: 1784-1787.
55. Ferrarotto R, Mitani Y, Diao L, et al. Activating NOTCH1 mutations define a distinct subgroup of patients with adenoid cystic carcinoma who have poor prognosis, propensity to bone and liver metastasis, and potential responsiveness to Notch1 inhibitors. J Clin Oncol 2017; 35: 352-360.
56. Sahara S, Herzog AE, Nör JE. Systemic therapies for salivary gland adenoid cystic carcinoma. Am J Cancer Res 2021; 11: 4092-4110.
57. Ferrarotto R, Mitani Y, McGrail DJ, et al. Proteogenomic analysis of salivary adenoid cystic carcinomas defines molecular subtypes and identifies therapeutic targets. Clin Cancer Res 2021; 27: 852-864.
58. Xu LH, Zhao F, Yang WW, et al. MYB promotes the growth and metastasis of salivary adenoid cystic carcinoma. Int J Oncol 2019; 54: 1579-1590.
59. Ho AS, Ochoa A, Jayakumaran G, et al. Genetic hallmarks of recurrent/metastatic adenoid cystic carcinoma. J Clin Invest 2019; 129: 4276-4289.
60. Weaver AN, Lakritz S, Mandair D, Ulanja MB, Bowles DW. A molecular guide to systemic therapy in salivary gland carcinoma. Head Neck 2023; 45: 1315-1326.
61. Wagner VP, Bingle CD, Bingle L. MYB-NFIB fusion transcript in adenoid cystic carcinoma: current state of knowledge and future directions. Crit Rev Oncol Hematol 2022; 176: 103745.
62. Drier Y, Cotton MJ, Williamson KE, et al. An oncogenic MYB feedback loop drives alternate cell fates in adenoid cystic carcinoma. Nature Genetics 2016; 48: 265-272.

63. Stenman G, Andersson MK, Andrén Y. New tricks from an old oncogene: gene fusion and copy number alterations of MYB in human cancer. Cell Cycle 2010; 9: 2986-2995.
64. Persson M, Andrén Y, Mark J, Horlings HM, Persson F, Stenman G. Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. Proc Natl Acad Sci U S A 2009; 106: 18740-18744.
65. Mitani Y, Liu B, Rao PH, et al. Novel MYBL1 Gene Rearrangements with Recurrent MYBL1-NFIB Fusions in Salivary Adenoid Cystic Carcinomas Lacking t(6;9) Translocations. Clin Cancer Res 2016; 22: 725 733.
66. Lee RH, Wai KC, Chan JW, Ha PK, Kang H. Approaches to the management of metastatic adenoid cystic carcinoma. Cancers (Basel) 2022; 14.
67. Stephens PJ, Davies HR, Mitani Y, et al. Whole exome sequencing of adenoid cystic carcinoma. J Clin Invest 2013; 123: 2965-2968.
68. Wang S, Yu Y, Fang Y, et al. Whole-exome sequencing reveals genetic underpinnings of salivary adenoid cystic carcinoma in the Chinese population. J Genet Genomics 2020; 47: 397-401.
69. Ross JS, Gay LM, Wang K, et al. Comprehensive genomic profiles of metastatic and relapsed salivary gland carcinomas are associated with tumor type and reveal new routes to targeted therapies. Ann Oncol 2017; 28: 2539-2546.
70. Chae YK, Chung SY, Davis AA, et al. Adenoid cystic carcinoma: current therapy and potential therapeutic advances based on genomic profiling. Oncotarget 2015; 6: 37117-37134.
71. Dillon PM, Chakraborty S, Moskaluk CA, Joshi PJ, Thomas CY. Adenoid cystic carcinoma: a review of recent advances, molecular targets, and clinical trials. Head Neck 2016; 38: 620-627.
72. Vander Poorten V, Triantafyllou A, Thompson LD, et al. Salivary acinic cell carcinoma: reappraisal and update. Eur Arch Otorhinolaryngol 2016; 273: 3511-3531.
73. Al-Zaher N, Obeid A, Al-Salam S, Al-Kayyali BS. Acinic cell carcinoma of the salivary glands: a literature review. Hematol Oncol Stem Cell Ther 2009; 2: 259-264.
74. Dublin JC, Oliver JR, Tam MM, et al. Nodal metastases in pediatric and adult acinic cell carcinoma of the major salivary glands. Otolaryngol Head Neck Surg 2022; 167: 941-951.
75. Haller F, Bieg M, Will R, et al. Enhancer hijacking activates oncogenic transcription factor NR4A3 in acinic cell carcinomas of the salivary glands. Nat Commun 2019; 10: 368.
76. Andreasen S, Varma S, Barasch N, et al. The HTN3-MSANTD3 fusion gene defines a subset of acinic cell carcinoma of the salivary gland. Am J Surg Pathol 2019; 43: 489-496.
77. Haller F, Skálová A, Ihrler S, et al. Nuclear NR4A3 immunostaining is a specific and sensitive novel marker for acinic cell carcinoma of the salivary glands. Am J Surg Pathol 2019; 43: 1264-1272.
78. Dogan S, Xu B, Rana S, et al. Loss of CDKN2A/B is a molecular marker of high-grade histology and is associated with aggressive behavior in acinic cell carcinoma. Mod Pathol 2023; 36: 100150.
79. Kreuger IZM, Slieker RC, van Groningen T, van Doorn R. Therapeutic strategies for targeting CDKN2A loss in melanoma. J Invest Dermatol 2023; 143: 18-25.e11.
80. Zhao R, Choi BY, Lee MH, Bode AM, Dong Z. Implications of genetic and epigenetic alterations of CDKN2A (p16(INK4a)) in cancer. EBioMedicine 2016; 8: 30-39.
81. Hellquist H, Paiva-Correia A, Vander Poorten V, et al. Analysis of the clinical relevance of histological classification of benign epithelial salivary gland tumours. Adv Ther 2019; 36: 1950-1974.
82. Valstar MH, de Ridder M, van den Broek EC, et al. Salivary gland pleomorphic adenoma in the Netherlands: A nationwide observational study of primary tumor incidence, malignant transformation, recurrence, and risk factors for recurrence. Oral Oncol 2017; 66: 93-99.
83. Gupta A, Koochakzadeh S, Neskey DM, Nguyen SA, Lentsch EJ. Carcinoma ex pleomorphic adenoma: A review of incidence, demographics, risk factors, and survival. Am J Otolaryngol 2019; 40: 102279.
84. Antony J, Gopalan V, Smith RA, Lam AK. Carcinoma ex pleomorphic adenoma: a comprehensive review of clinical, pathological and molecular data. Head Neck Pathol 2012; 6: 1-9.
85. Park KS, Kim JH, Lee DH, Lee JK, Lim SC. Carcinoma ex pleomorphic adenoma of the parotid gland. Am J Otolaryngol 2022; 43: 103389.
86. Suzuki M, Matsuzuka T, Saijo S, et al. Carcinoma ex pleomorphic adenoma of the parotid gland: a multi-institutional retrospective analysis in the Northern Japan Head and Neck Cancer Society. Acta Otolaryngol 2016; 136: 1154-1158.
87. Nandini DB, Singh WT, Aparnadevi P, Ningombam DS. Epithelial-myoepithelial carcinoma ex pleomorphic adenoma of the parotid gland with unique histologic differentiation: a rare case report. J Oral Maxillofac Pathol 2022; 26: S34-s39.
88. Dalin MG, Katabi N, Persson M, et al. Multi-dimensional genomic analysis of myoepithelial carcinoma identifies prevalent oncogenic gene fusions. Nat Commun 2017; 8: 1197.
89. Katabi N, Gomez D, Klimstra DS, Carlson DL, Lee N, Ghossein R. Prognostic factors of recurrence in salivary carcinoma ex pleomorphic adenoma, with emphasis on the carcinoma histologic subtype: a clinicopathologic study of 43 cases. Hum Pathol 2010; 41: 927-934.
90. Stenman G. Fusion oncogenes in salivary gland tumors: molecular and clinical consequences. Head Neck Pathol 2013; 7 Suppl 1: S12-19.
91. Katabi N, Ghossein R, Ho A, et al. Consistent PLAG1 and HMGA2 abnormalities distinguish carcinoma ex-pleomorphic adenoma from its de novo counterparts. Hum Pathol 2015; 46: 26-33.
92. Persson F, Andrén Y, Winnes M, et al. High-resolution genomic profiling of adenomas and carcinomas of the salivary glands reveals amplification, rearrangement, and fusion of HMGA2. Genes Chromosomes Cancer 2009; 48: 69-82.
93. Bell D, J NM, Rao PH, El-Naggar AK. t(3;8) as the sole chromosomal abnormality in a myoepithelial carcinoma ex pleomorphic adenoma: a putative progression event. Head Neck 2013; 35: E181-183.
94. El-Naggar AK, Callender D, Coombes MM, Hurr K, Luna MA, Batsakis JG. Molecular genetic alterations in carcinoma ex-pleomorphic adenoma: a putative progression model? Genes Chromosomes Cancer 2000; 27: 162-168.
95. Xu B, Katabi N. Myoepithelial Carcinoma. Surg Pathol Clin 2021; 14: 67-73.
96. Lavareze L, Scarini JF, de Lima-Souza RA, et al. Clinicopathological and survival profile of patients with salivary gland myoepithelial carcinoma: A systematic review. J Oral Pathol Med 2023; 52: 101-108.
97. Kong M, Drill EN, Morris L, et al. Prognostic factors in myoepithelial carcinoma of salivary glands: a clinicopathologic study of 48 cases. Am J Surg Pathol 2015; 39: 931-938.
98. Su YX, Roberts DB, Hanna EY, et al. Risk factors and prognosis for myoepithelial carcinoma of the major salivary glands. Ann Surg Oncol 2015; 22: 3701-3707.
99. Di Palma S, Guzzo M. Malignant myoepithelioma of salivary glands: clinicopathological features of ten cases. Virchows Arch A Pathol Anat Histopathol 1993; 423: 389-396.
100. Soluk-Tekkeşin M, Wright JM. The World Health Organization Classification of Odontogenic Lesions: a summary of the changes of the 2017 (4th) edition. Turk Patoloji Derg 2018; 34.
101. Haltiner CC, Betz S, Smith J, Nelson B, Ambrosio AA. Carcinoma ex-pleomorphic adenoma diagnosis during global health engagement operations. Mil Med 2021; 186: 828-832.
102. Skálová A, Weinreb I, Hyrcza M, et al. Clear cell myoepithelial carcinoma of salivary glands showing EWSR1 rearrangement: molecular analysis of 94 salivary gland carcinomas with prominent clear cell component. Am J Surg Pathol 2015; 39: 338-348.
103. Pikul J, Rzepakowska A, Machnicki M, Stokłosa T. FGFR2 point mutation in 2 cases of pleomorphic adenoma progressing to myoepithelial carcinoma. Contemp Oncol (Pozn) 2023; 27: 211-216.
104. Gandhi J, Mantilla JG, Ricciotti RW, Chen EY, Liu YJ, Bandhlish A. Myoepithelial carcinoma of theparotid gland with a novel CTCF: NCOA2 fusion. Genes Chromosomes Cancer 2023; 62: 161-166.
105. Patel TD, Vazquez A, Marchiano E, Park RC, Baredes S, Eloy JA. Polymorphous low-grade adenocarcinoma of the head and neck: A population-based study of 460 cases. Laryngoscope 2015; 125: 1644 1649.

106. Mimica X, Katabi N, McGill MR, et al. Polymorphous adenocarcinoma of salivary glands. Oral Oncol 2019; 95: 52-58.
107. Weinreb I, Piscuoglio S, Martelotto LG, et al. Hotspot activating PRKD1 somatic mutations in polymorphous low-grade adenocarcinomas of the salivary glands. Nat Genet 2014; 46: 1166-1169.
108. Andreasen S, Melchior LC, Kiss K, et al. The PRKD1 E710D hotspot mutation is highly specific in separating polymorphous adenocarcinoma of the palate from adenoid cystic carcinoma and pleomorphic adenoma on FNA. Cancer Cytopathol 2018; 126: 275-281.
109. Xu B, Barbieri AL, Bishop JA, et al. Histologic Classification and Molecular Signature of Polymorphous Adenocarcinoma (PAC) and Cribriform Adenocarcinoma of Salivary Gland (CASG): an international interobserver study. Am J Surg Pathol 2020; 44: 545-552.
110. Skalova A, Sima R, Kaspirkova-Nemcova J, et al. Cribriform adenocarcinoma of minor salivary gland origin principally affecting the tongue: characterization of new entity. Am J Surg Pathol 2011; 35: 1168-1176.
111. Laco J, Kamarádová K, Vítková P, et al. Cribriform adenocarcinoma of minor salivary glands may express galectin-3, cytokeratin 19, and HBME-1 and contains polymorphisms of RET and H-RAS proto oncogenes. Virchows Arch 2012; 461: 531-540.
112. Sebastiao APM, Xu B, Lozada JR, et al. Histologic spectrum of polymorphous adenocarcinoma of the salivary gland harbor genetic alterations affecting PRKD genes. Mod Pathol 2020; 33: 65-73.
113. de Jager VD, de Visscher S, Schuuring E, Doff JJ, van Kempen LC. A novel PPP2R2A::PRKD1 fusion in a cribriform adenocarcinoma of salivary gland. Genes Chromosomes Cancer 2023; 62: 297-300.
114. Owosho AA, Baker E, Wood CB, Jain R. A novel STRN3::PRKD1 fusion in a cribriform adenocarcinoma of salivary gland with high-grade transformation. Genes Chromosomes Cancer 2023; 62: 624 628.
115. Weinreb I, Zhang L, Tirunagari LM, et al. Novel PRKD gene rearrangements and variant fusions in cribriform adenocarcinoma of salivary gland origin. Genes Chromosomes Cancer 2014; 53: 845-856.
116. Freiberger SN, Brada M, Fritz C, et al. SalvGlandDx – a comprehensive salivary gland neoplasm specific next generation sequencing panel to facilitate diagnosis and identify therapeutic targets. Neoplasia 2021; 23: 473-487.
117. Bishop JA, Weinreb I, Swanson D, et al. Microsecretory adenocarcinoma: a novel salivary gland tumor characterized by a recurrent MEF2C-SS18 fusion. Am J Surg Pathol 2019; 43: 1023-1032.
118. Bishop JA, Sajed DP, Weinreb I, et al. Microsecretory adenocarcinoma of salivary glands: an expanded series of 24 cases. Head Neck Pathol 2021; 15: 1192-1201.
119. 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.
120. Johnston ML, Huang SH, Waldron JN, et al. Salivary duct carcinoma: treatment, outcomes, and patterns of failure. Head Neck 2016; 38 Suppl 1: E820-826.
121. Gilbert MR, Sharma A, Schmitt NC, et al. A 20-year review of 75 cases of salivary duct carcinoma.JAMA Otolaryngol Head Neck Surg 2016; 142: 489-495.
122. Williams L, Thompson LD, 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: 705-713.
123. Mueller SA, Gauthier MA, Blackburn J, et al. Molecular patterns in salivary duct carcinoma identifyprognostic subgroups. Mod Pathol 2020; 33: 1896-1909.
124. Luukkaa H, Klemi P, Leivo I, et al. Salivary gland cancer in Finland 1991–1996: an evaluation of 237 cases. Acta Otolaryngol 2005; 125: 207-214.
125. Luk PP, Weston JD, Yu B, et al. Salivary duct carcinoma: clinicopathologic features, morphologic spectrum, and somatic mutations. Head Neck 2016; 38 Suppl 1: E1838-1847.
126. 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: 4623-4633.
127. Dogan S, Ng CKY, Xu B, Kumar R, et al. The repertoire of genetic alterations in salivary duct carcinoma including a novel HNRNPH3-ALK rearrangement. Hum Pathol 2019; 88: 66-77.
128. Chiosea SI, Thompson LD, Weinreb I, et al. Subsets of salivary duct carcinoma defined by morphologic evidence of pleomorphic adenoma, PLAG1 or HMGA2 rearrangements, and common genetic alterations. Cancer 2016; 122: 3136-3144.
129. Boon E, Bel M, van Boxtel W, et al. A clinicopathological study and prognostic factor analysis of 177 salivary duct carcinoma patients from The Netherlands. Int J Cancer 2018; 143: 758-766.
130. Skálová A, Stárek I, Vanecek T, et al. Expression of HER-2/neu gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence in-situ hybridization and immunohistochemistry. Histopathology 2003; 42: 348-356.
131. Dalin MG, Watson PA, Ho AL, Morris LG. Androgen receptor signaling in salivary gland cancer. Cancers (Basel) 2017; 9.
132. Williams CYK, Townson AT, Terry N, Schmitt NC, Sharma A. Role of HER2 in prognosis of salivary duct carcinoma: a systematic review and meta-analysis. Laryngoscope 2023; 133: 476-484.
133. 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: 17588359221119538.
134. Filippini DM, Pagani R, Tober N, et al. HER2-targeted therapies for salivary gland cancers. Oral Oncol 2024; 148: 106612.
135. Vos JL, Burman B, Jain S, et al. Nivolumab plus ipilimumab in advanced salivary gland cancer: a phase 2 trial. Nature Medicine 2023; 29: 3077-3089.
136. Kohsaka S, Tada Y, Ando M, et al. Identification of novel prognostic and predictive biomarkers in salivary duct carcinoma via comprehensive molecular profiling. NPJ Precis Oncol 2022; 6: 82.
137. Nardi V, Sadow PM, Juric D, et al. Detection of novel actionable genetic changes in salivary duct carcinoma helps direct patient treatment. Clin Cancer Res 2013; 19: 480-490.
138. Wang H, Guo M, Wei H, Chen Y. Targeting p53 pathways: mechanisms, structures, and advances in therapy. Signal Transduct Target Ther 2023; 8: 92.
139. Hassin O, Oren M. Drugging p53 in cancer: one protein, many targets. Nat Rev Drug Discov 2023; 22: 127-144.
140. Ku BM, Jung HA, Sun JM, et al. High-throughput profiling identifies clinically actionable mutations in salivary duct carcinoma. J Transl Med 2014; 12: 299.
141. Grünewald I, Trautmann M, Busch A, et al. MDM2 and CDK4 amplifications are rare events in salivary duct carcinomas. Oncotarget 2016; 7: 75261-75272.
142. Politi M, Robiony M, Avellini C, Orsaria M. Epithelial-myoepithelial carcinoma of the parotid gland: Clinicopathological aspect, diagnosis and surgical consideration. Ann Maxillofac Surg 2014; 4: 99-102.
143. Vázquez A, Patel TD, D'Aguillo CM, et al. Epithelial-myoepithelial carcinoma of the salivary glands:an analysis of 246 cases. Otolaryngol Head Neck Surg 2015; 153: 569-574.
144. El Hallani S, Udager AM, Bell D, et al. Epithelial-myoepithelial carcinoma: frequent morphologic and molecular evidence of preexisting pleomorphic adenoma, common HRAS mutations in PLAG1-intact and HMGA2-intact Cases, and Occasional TP53, FBXW7, and SMARCB1 alterations in high-grade cases. Am J Surg Pathol 2018; 42: 18-27.
145. Kusafuka K, Yamashita M, Muramatsu A, Arai K, Suzuki M. Epithelial-myoepithelial carcinoma ex pleomorphic adenoma of the parotid gland: report of a rare case with immunohistochemical and genetic analyses. Med Mol Morphol 2021; 54: 173-180.
146. Urano M, Nakaguro M, Yamamoto Y, et al. Diagnostic significance of HRAS mutations in epithelial myoepithelial carcinomas exhibiting a broad histopathologic spectrum. Am J Surg Pathol 2019; 43: 984-994.
147. Nakaguro M, Nagao T. Epithelial-myoepithelial carcinoma. Surg Pathol Clin 2021; 14: 97-109.

148. Grünewald I, Vollbrecht C, Meinrath J, et al. Targeted next generation sequencing of parotid gland cancer uncovers genetic heterogeneity. Oncotarget 2015; 6: 18224-18237.
149. Chiosea SI, Miller M, Seethala RR. HRAS mutations in epithelial-myoepithelial carcinoma. Head Neck Pathol 2014; 8: 146-150.
150. Nakaguro M, Tanigawa M, Hirai H, et al. The diagnostic utility of RAS Q61R mutation-specific immunohistochemistry in epithelial-myoepithelial carcinoma. Am J Surg Pathol 2021; 45: 885-894.
151. Mäkelä R, Arjonen A, Suryo Rahmanto A, et al. Ex vivo assessment of targeted therapies in a rare metastatic epithelial-myoepithelial carcinoma. Neoplasia 2020; 22: 390-398.
152. Skálová A, Vanecek T, Sima R, et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. Am J Surg Pathol 2010; 34: 599-608.
153. Bishop JA, Yonescu R, Batista D, Eisele DW, Westra WH. Most nonparotid "acinic cell carcinomas" represent mammary analog secretory carcinomas. Am J Surg Pathol 2013; 37: 1053-1057.
154. Ayre G, Hyrcza M, Wu J, Berthelet E, Skálová A, Thomson T. Secretory carcinoma of the major salivary gland: Provincial population-based analysis of clinical behavior and outcomes. Head Neck 2019; 41: 1227-1236.
155. Alves LDB, de Melo AC, Farinha TA, et al. A systematic review of secretory carcinoma of the salivarygland: where are we? Oral Surg Oral Med Oral Pathol Oral Radiol 2021; 132: e143-e152.
156. Tognon C, Knezevich SR, Huntsman D, et al. Expression of the ETV6-NTRK3 gene fusion as aprimary event in human secretory breast carcinoma. Cancer Cell 2002; 2: 367-376.
157. Guilmette J, Dias-Santagata D, Nosé V, Lennerz JK, Sadow PM. Novel gene fusions in secretory carcinoma of the salivary glands: enlarging the ETV6 family. Hum Pathol 2019; 83: 50-58.
158. Rooper LM, Karantanos T, Ning Y, Bishop JA, Gordon SW, Kang H. Salivary secretory carcinoma with a novel ETV6-MET fusion: expanding the molecular spectrum of a recently described entity. Am J Surg Pathol 2018; 42: 1121-1126.
159. Black M, Liu CZ, Onozato M, et al. Concurrent identification of novel EGFR-SEPT14 fusion and ETV6-RET fusion in secretory carcinoma of the salivary gland. Head Neck Pathol 2020; 14: 817-821.
160. Ito Y, Ishibashi K, Masaki A, et al. Mammary analogue secretory carcinoma of salivary glands: a clinicopathologic and molecular study including 2 cases harboring ETV6-X fusion. Am J Surg Pathol 2015; 39: 602-610.
161. Skálová A, Banečkova M, Thompson LDR, et al. Expanding the molecular spectrum of secretory carcinoma of salivary glands with a novel VIM-RET fusion. Am J Surg Pathol 2020; 44: 1295-1307.
162. Sasaki E, Masago K, Fujita S, Suzuki H, Hanai N, Hosoda W. Salivary secretory carcinoma harbouring a novel ALK fusion: expanding the molecular characterization of carcinomas beyond the ETV6 gene. Am J Surg Pathol 2020; 44: 962-969.
163. Na K, Hernandez-Prera JC, Lim JY, Woo HY, Yoon SO. Characterization of novel genetic alterations in salivary gland secretory carcinoma. Mod Pathol 2020; 33: 541-550.
164. Skálová A, Vanecek T, Majewska H, et al. Mammary analogue secretory carcinoma of salivary glands with high-grade transformation: report of 3 cases with the ETV6-NTRK3 gene fusion and analysis of TP53, β catenin, EGFR, and CCND1 genes. Am J Surg Pathol 2014; 38: 23-33.
165. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020; 21: 271-282.
166. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020; 21: 531-540.
167. Regua AT, Najjar M, Lo HW. RET signaling pathway and RET inhibitors in human cancer. Front Oncol 2022; 12: 932353.
168. Desai A, Faquin WC, Iafrate AJ, Rivera MN, Jaquinet A, Troulis MJ. Clear cell carcinoma: a comprehensive literature review of 254 cases. Int J Oral Maxillofac Surg 2022; 51: 705-712.
169. Weinreb I. Hyalinizing clear cell carcinoma of salivary gland: a review and update. Head Neck Pathol 2013; 7 Suppl 1: S20-29.
170. Antonescu CR, Katabi N, Zhang L, et al. EWSR1-ATF1 fusion is a novel and consistent finding in hyalinizing clear-cell carcinoma of salivary gland. Genes Chromosomes Cancer 2011; 50: 559-570.
171. Chapman E, Skalova A, Ptakova N, et al. Molecular profiling of hyalinizing clear cell carcinomas revealed a subset of tumors harboring a novel EWSR1-CREM fusion: report of 3 cases. Am J Surg Patho 2018; 42: 1182-1189.
172. Lanic MD, Guérin R, Sater V, et al. A novel SMARCA2-CREM fusion expending the molecular spectrum of salivary gland hyalinazing clear cell carcinoma beyond the FET genes. Genes Chromosomes Cancer 2023; 62: 231-236.
173. Gonzalez MF, Akhtar I. Hyalinising clear cell carcinoma with a novel fusion gene: Insights into the diagnosis. Cytopathology 2023; 34: 611-616.
174. Bishop JA, Gagan J, Krane JF, Jo VY. Low-grade apocrine intraductal carcinoma: expanding the morphologic and molecular spectrum of an enigmatic salivary gland tumor. Head Neck Pathol 2020; 14: 869
175. Giovacchini F, Bensi C, Belli S, et al. Low-grade intraductal carcinoma of salivary glands: A systematic review of this rare entity. J Oral Biol Craniofac Res 2019; 9: 96-110.
176. Thompson LDR, Bishop JA. Salivary gland intraductal carcinoma: how do 183 reported cases fit into a developing classification. Adv Anat Pathol 2023; 30: 112-129.
177. Skálová A, Vanecek T, Uro-Coste E, et al. Molecular profiling of salivary gland intraductal carcinoma revealed a subset of tumors harboring NCOA4-RET and novel TRIM27-RET fusions: a report of 17 cases. Am J Surg Pathol 2018; 42: 1445-1455.
178. Bishop JA, Nakaguro M, Whaley RD, et al. Oncocytic intraductal carcinoma of salivary glands: a distinct variant with TRIM33-RET fusions and BRAF V600E mutations. Histopathology 2021; 79: 338-346.
179. Skálová A, Ptáková N, Santana T, et al. NCOA4-RET and TRIM27-RET are characteristic gene fusions in salivary intraductal carcinoma, including invasive and metastatic tumors: is "intraductal" correct? Am J Surg Pathol 2019; 43: 1303-1313.
180. Weinreb I, Bishop JA, Chiosea SI, et al. Recurrent RET gene rearrangements in intraductal carcinomas of salivary gland. Am J Surg Pathol 2018; 42: 442-452.
181. Viswanathan K, Sadow PM, Maleki Z, et al. Cytomorphologic features of intraductal salivary gland carcinoma: A multi-institutional study of 13 FNA cases with histologic, molecular, and clinical correlations. Cancer Cytopathol 2021; 129: 928-946.
182. Hsieh MS, Lee YH, Jin YT, Kuo YJ. Clinicopathological study of intraductal carcinoma of the salivary gland, with emphasis on the apocrine type. Virchows Arch 2020; 477: 581-592.
183. Majewska H, Gorczyński A, Czapiewski P, et al. ALK alterations in salivary gland carcinomas. Virchows Arch 2021; 478: 933-941.
184. Watanabe T, Honma Y, Yonemori K, Sunami K, Yoshimoto S, Mori T. High-grade intraductal carcinoma of the parotid gland harboring CTNNA1::ALK rearrangement: changes in genetic status using genetic testing during treatment with an ALK inhibitor. Head Neck 2024; 46: E26-e31.
185. WHO Classification of Head and Neck Tumours, vol. 9, 2017.
186. Żurek M, Rzepakowska A, Jasak K, Niemczyk K. The epidemiology of salivary glands pathologies in adult population over 10 years in poland – cohort study. Int J Env Res Public Health 2022; 19: 179.
187. Kucharska E, Rzepakowska A, Żurek M, et al. Oncologic outcomes of the most prevalent major salivary gland cancers: retrospective cohort study from single center. Eur Arch Otorhinolaryngol 2024; 281: 4305-4313.
188. Khosla D, Madan R, Goyal S, Kumar N, Kapoor R. Polymorphous low-grade adenocarcinoma of thesalivary glands – a review. Niger Med J 2021; 62: 49-53.
189. Bishop JA, Sajed DP. Microsecretory adenocarcinoma of salivary glands. Adv Anatom Pathol 2023; 30: 130-135.
190. Rito M, Mitani Y, Bell D, et al. Frequent and differential mutations of the CYLD gene in basal cell salivary neoplasms: linkage

to tumor development and progression. Mod Pathol 2018; 31: 1064-1072.
191. Rooper LM, Argyris PP, Thompson LDR, et al. Salivary mucinous adenocarcinoma is a histologically diverse single entity with recurrent AKT1 E17K mutations: clinicopathologic and molecular characterization with proposal for a unified classification. Am J Surg Pathol 2021; 45: 1337-1347.
192. Baněčková M, Thompson LDR, Hyrcza MD, et al. Salivary gland secretory carcinoma: clinicopathologic and genetic characteristics of 215 cases and proposal for a grading system. Am J Surg Pathol 2023; 47: 661-677.
193. Asahina M, Saito T, Hayashi T, Fukumura Y, Mitani K, Yao T. Clinicopathological effect of PLAG1 fusion genes in pleomorphic adenoma and carcinoma ex pleomorphic adenoma with special emphasis on histological features. Histopathology 2019; 74: 514-525.
194. Skálová A, Agaimy A, Vanecek T, et al. Molecular profiling of clear cell myoepithelial carcinoma of salivary glands with ewsr1 rearrangement identifies frequent PLAG1 gene fusions but no EWSR1 fusion transcripts. Am J Surg Pathol 2021; 45: 1-13.
195. Bubola J, MacMillan CM, Demicco EG, et al. Targeted RNA sequencing in the routine clinical detection of fusion genes in salivary gland tumors. Genes Chromosomes Cancer 2021; 60: 695-708.
196. Rupp NJ, Höller S, Brada M, et al. Expanding the clinicopathological spectrum of TGFBR3-PLAG1 rearranged salivary gland neoplasms with myoepithelial differentiation including evidence of high-grade transformation. Genes Chromosomes Cancer 2022; 61: 94-104.
197. Katabi N, Sukhadia P, DiNapoli SE, et al. Expanding the histological spectrum of salivary gland neoplasms with HMGA2::WIF1 fusion emphasising their malignant potential: a report of eight cases. Histopathology 2024; 84: 387-398.
198. Smith ME, Surrey LF, Zhang PJ, Weinstein GS, LiVolsi VA. Molecular identification of an ETV6-RET fusion in a secretory carcinoma associated with a pleomorphic adenoma. Oral Surg Oral Med Oral Pathol Oral Radiol 2022; 134: 733-738.
199. Pircher M, Briner HR, Bonomo M, et al. Mixed response and mechanisms of resistance to larotrectinib in metastatic carcinoma ex pleomorphic adenoma of the parotid harboring an NTRK2 fusion: A case report. Medicine (Baltimore) 2021; 100: e24463.

Address for correspondence

Anna Rzepakowska
Department of Otorhinolaryngology
Head and Neck Surgery
Medical University of Warsaw
Warsaw, Poland
e-mail: arzepakowska@wum.edu.pl

Submitted: 04.07.2024
Accepted: 20.09.2024