Published in final edited form as:

Oral Oncol. 2017 November ; 74: 40–48. doi:10.1016/j.oraloncology.2017.09.008.

Salivary Duct Carcinoma: An Aggressive Salivary Gland Malignancy with Opportunities for Targeted Therapy

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Abstract

Salivary duct carcinoma (SDC) is a rare, aggressive salivary malignancy that is often diagnosed at an advanced stage. Previously, little was known about outcomes of this disease due to its rarity. In the past several years, much has been learned about salivary duct carcinoma after publication of outcomes from several large single-institution series and national database searches. Recent studies of genomic alterations have helped elucidate the biology and pathogenesis of this aggressive disease. Here we review outcomes of the disease, effects of treatment, prognostic factors, and genomic alterations in SDC. Studies of targeted therapy and promising future directions are also discussed.

Keywords

salivary duct carcinoma; salivary malignancy; ErbB2

INTRODUCTION

Salivary duct carcinoma (SDC) was originally described by Kleinsasser and colleagues in 1968 as a salivary malignancy that histologically resembles ductal carcinoma of the breast [1]. It occurs more commonly in the parotid gland than in the submandibular or minor salivary glands [2–6]. SDC has a propensity to metastasize early to regional lymph nodes and distant sites, as well as a high rate of recurrence [3–5, 7–12]. The mainstay of therapy

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includes surgery and radiation; use of systemic therapy has been explored in some case series and small clinical trials [9, 13, 14]. Survival is poor, with most patients surviving only about three years after diagnosis [7, 12, 15–17].

Epidemiology

SDC is most frequently seen in men aged 50 or older [4, 6, 16, 18, 19] and is one of the more rare malignant salivary tumors. In one series of all salivary gland cancers during a 5-year period in Finland, it was estimated that 4–6% were SDC [20]. A review of the SEER Medicare Database found that SDC comprised 1.8% of all major salivary gland cancers included in the database [19].

Histopathologic Features

Though described as early as 1968, SDC was only recognized as a distinct tumor type by the World Health Organization in 1991 [21]. Prior to this time, SDC was not frequently diagnosed, possibly due to limited awareness of its existence as a separate histologic entity. Studies on the histopathologic features of this tumor have helped considerably to distinguish it from other salivary malignancies, and as a result SDC may be less rare than originally thought. SDC specimens show high-grade apocrine/ductal morphology [22]. Specimens commonly demonstrate papillary-cribriform growth patterns, with areas of pleomorphism and necrosis [21]. Papillary/micropapillary, sarcomatoid, mucinous, oncocytic, and basaloid morphologic variants have been described but are rare [6, 22, 23]. Another variant with a low grade histologic pattern and relatively indolent growth has also been described [24, 25], which is often mistaken for low-grade acinic cell carcinoma or mammary analog secretory carcinoma [25]. The detection of androgen receptors, expressed in the vast majority of SDC tumors, can be critical in distinguishing SDC from other tumor types [21, 22, 26].

Interestingly, a high proportion of SDC tumors are found within a benign pleomorphic adenoma; SDC tumors that are also classified as carcinoma ex pleomorphic adenoma may be frequent, with studies reporting evidence of prior pleomorphic adenoma in 20–70% of SDCs [7, 11, 27, 28]. An encapsulated, in situ form of SDC has also been described, characterized by lack of capsular invasion. This in situ variant, usually occurring within a pleomorphic adenoma, is often less aggressive than typical cases of SDC [23, 26, 29]. Griffith and colleagues characterized 117 cases of SDC ex pleomorphic adenoma and found that while most were widely invasive with aggressive clinical behavior and poor survival, the five patients who had intracapsular SDC ex pleomorphic adenoma had a more indolent course with no disease progression [30].

Many patients present with advanced T stage (i.e. T3 or T4), with figures ranging from 35–74% [2, 4–7, 9, 11, 12, 14, 15, 18, 22, 31–38]. Two separate National Cancer Data Base (NCDB) studies, each with over 400 patients, found that 40–42% of patients presented with advanced T stage [36, 38]. However, analyses of multi-institutional data in Japan revealed an advanced T stage incidence of 65–66% [35, 37].

The risk of pathologic N+ disease ranges from 47–83% in the literature [2, 4–10, 12, 14–16, 18, 19, 22, 31–40]. However, analyses using national databases or multiple institutions described an N+ incidence of 47–56% [2, 19, 35–38]. In a National Cancer Data Base

(NCDB) analysis of 22,653 patients with parotid malignancies, the risk of N+ disease and occult nodal disease were 54% and 24%, respectively, for patients with SDC, higher than that seen for any other parotid gland pathologies (mean for all parotid malignancies: 24% and 10%, respectively) [36]. Among patients with SDC, tumor size (>3cm) and histologic grade have been identified as risk factors for nodal involvement [19, 36].

Perineural invasion (PNI) and lymphovascular invasion (LVI) are noted in 28–85% [2, 5–8, 11, 12, 14, 18, 31, 32, 40] and 20–71% [2, 5–8, 11, 12, 14, 31, 32, 40] of patients, respectively. The largest single institution study of SDC was conducted at the University of Pittsburgh Medical Center and described the incidence of PNI and LVI as 69% and 61%, respectively [7].

Imaging Characteristics

On MRI, SDCs tend to have low- to intermediate-signaling intensity on T2-weighted images, ill-defined borders, and invasion into surrounding structures such as the skin or parapharyngeal space; these findings along with aggressive clinical features such as palpable nodes or facial paralysis may lead clinicians to suspect SDC [41, 42]. PET/CT usually shows SDC to be a highly metabolic tumor and can be quite useful for detecting regional and distant metastases [43].

Treatment

Treatment is variable across studies, but most cases of SDC are treated with complete surgical resection of the primary site (i.e., superficial or total parotidectomy) and neck dissection followed by adjuvant therapy [2, 19, 35], similar to other high grade primary salivary gland malignancies. Facial nerve resection is often required (40–73%) to achieve oncologically sound resection of the primary site [5, 7, 9, 10, 18].

Since the risk of occult nodal disease in SDC is 24% (36% for high grade SDC and 8% for low grade SDC) [36], elective neck dissection is recommended for patients with SDC even in the absence of clinical nodal involvement. The only exception may be in patients with low grade SDC, who have a lower risk of occult nodal disease and seem to have a better prognosis [24, 36, 44]. For those reasons, most reports of SDC in the literature include treatment with neck dissection (57–96%) [2, 4–6, 10–12, 14, 16, 18, 32, 34, 45] at the time of initial surgery.

Given the rarity of SDC, specific indications for adjuvant therapy (radiation or chemoradiation) have not been prospectively evaluated. Nevertheless, adjuvant radiation is performed in most series, which is reasonable given the aggressive clinical course of SDC. The role of systemic cytotoxic chemotherapy in the adjuvant setting is unclear, although it can be an option in patients with recurrent or distant metastatic disease [7, 38].

OUTCOMES: SURVIVAL AND PROGNOSTIC FACTORS

Clinical outcomes of SDC across published studies are shown in Table 1. The weighted average of local and regional failure was 20% and 17%, respectively (see Figure 1a). Distant failure is relatively common (47%; see Figure 1a) in patients with SDC and is often

associated with eventual patient demise, as median survival after distant metastasis is 13 months [12]. The most common sites of distant disease are lung and bone, but liver and brain metastases have also been reported [2, 4, 6, 7, 11, 14, 16, 22, 35, 45].

Five-year overall survival (OS) in patients being treated for SDC ranges from 12–55%; the weighted average of five-year disease free survival (DFS) and OS across studies was 46% and 35%, respectively (see Table 1 and Figure 1b) [2, 5, 9, 31, 32, 40, 45–47]. Most clinical outcomes studies of SDC present data from a single institution; however, Jayaprakash et al. [19] reported results from an analysis of 228 patients using the Surveillance, Epidemiology, and End Results (SEER) database. They reported a 10 year OS of 42%, although most deaths occurred within the first five years after diagnosis. Median overall survival was 79 months [19]. Even for early T stage SDC, patients have an overall poor prognosis (49% five-year DFS and OS) [48].

Statistically significant prognostic features are described in Table 2. Given that many studies are limited by sample size, statistical analyses were not performed in many studies or were limited in their power. In the SEER database analysis, the authors found that increasing age, late stage, and N+ disease were associated with OS in multivariable analysis [19]. Similarly, a recent NCDB analysis showed that increasing age, male sex, and Stage IV disease were significant predictors of worse OS in a multivariable Cox regression model [38].

Certain pathologic features (PNI, LVI, extraparenchymal extension, positive surgical margins, and extracapsular spread (ECS)) and facial nerve resection were shown to be associated with survival in single institution studies, although findings were often inconsistent (see Table 2). Unfortunately, these factors were not available for analysis in the SEER or NCDB analyses [19, 38]. Therefore, the relationship between these factors and survival could not be assessed and were not used for adjustment in the multivariable analysis in these larger database studies. A study utilizing three merged Danish nationwide registries of 34 SDC patients included pathologic data and found that advanced stage, positive surgical margins, and LVI were associated with OS; however, multivariable analysis could not be performed due to sample size [2].

Similar to the effect of tumor grade in other parotid malignancies, high grade SDC of the parotid gland is associated with higher risk of nodal metastasis, occult nodal metastasis, and worse OS [36]. Although most patients with SDC have high grade pathology (79%) [36], reports of low grade SDC suggest much better survival (100%), although sample size is limited in these studies [24, 44].

MUTATIONAL LANDSCAPE OF SDC

Recent studies using a variety of techniques including immunohistochemistry (IHC), in situ hybridization, and targeted and whole-exome sequencing have identified genomic alterations common to SDC tumors (summarized in Figure 2), many of which may be actionable targets for this challenging disease. The overall expression pattern seems to be remarkably similar to that of apocrine breast carcinoma [49]. Whole exome sequencing of 16 SDC specimens revealed a low to moderate mutational burden compared to other solid tumors, with a

relatively low rate of copy number alterations and unique fusion genes noted in about a third of the tumors [49]. This sequencing study corroborated several common alterations noted in other studies, the most common of which was mutation of *TP53* [49]. A targeted sequencing study of 30 SDC specimens also showed *TP53* mutation to be the most common alteration [50].

The most widely studied genomic alteration in SDC is copy number gain of *ErbB2*, also known as *HER-2/neu*. *ErbB2* overexpression is also noted in a large proportion of ductal breast carcinoma and associated with a negative prognosis [28]. *ErbB2* expression has been evaluated in dozens of SDC studies by immunohistochemistry and fluorescence in situ hybridization (FISH) (Table 3). The percentage of SDC tumors positive for *ErbB2* varies widely across studies due to different evaluation and scoring methods, with only a subset of studies using ASCO guidelines for *ErbB2* scoring [28]. While proportions of SDC that are positive for *ErbB2* by IHC are often quite high, those showing increased expression by FISH or chromogenic in situ hybridization are much lower [23]. The significance of *ErbB2* expression in SDC remains unclear. While some studies show that it correlates with advanced-stage disease and poor survival, other studies show no prognostic significance (Table 3). As mentioned above, many of these studies were not sufficiently powered to detect prognostic effects of *ErbB2* and other tumor characteristics.

Another growth factor commonly overexpressed in SDC is epidermal growth factor receptor (EGFR). High expression of EGFR has been found in a large proportion of tested SDC specimens; the prognostic significance of EGFR in SDC is unclear, with one study showing EGFR status to be an independent predictor of disease-free survival [33] but most studies showing no obvious effect on prognosis [15, 33, 40, 51].

The majority of SDCs also express androgen receptors (ARs). Williams and colleagues found that 179 of 183 tumors from a multi-institutional study demonstrated AR expression [22]. The authors concluded that AR-negative SDC must be extremely rare, and that some specimens diagnosed as SDC without AR positivity may be misclassified. Androgen receptor expression appears to be more common in SDCs from men than in SDCs from women [40, 52]. Studies investigating the prognostic significance of AR positivity have shown mixed results [6, 18, 33, 49, 52]. Genetic alterations in androgen receptors noted in SDC specimens include mutations and extra gene copies, but not gene amplification as seen in prostate cancer [49, 52, 53]. Androgen receptor splice variants missing exons needed for receptor activation, in particular the AR-V7 splice variant, are expressed in a significant number of SDC specimens; these AR splice variants encode a truncated AR protein that has only the transactivating N-terminal domain without the C-terminal ligand binding domain, which results in constitutive activation of AR [52, 53]. Presence of AR-V7 in circulating tumor cells has been associated with resistance to androgen deprivation therapy in prostate cancers [54], but it is unclear whether presence of AR-V7 in tumor tissue in SDC would be associated with outcome or therapeutic resistance. Importantly, SDC tumors often express other prostate cancer markers including prostatic acid phosphatase and prostate specific antigen, which can make the diagnosis challenging when dealing with a metastatic tumor of unknown primary site [55]. Some SDC tumors also have mutations in *FOXA1*, which may impair androgen receptor signaling and has been linked to resistance to androgen deprivation

therapy in prostate cancer [49]. The role of androgen receptor signaling in salivary gland cancers has been extensively reviewed elsewhere [53].

Expression of other hormones and their receptors may also be important. Scattered expression of both estrogen and progesterone receptors has been reported [56]. In one series of 84 SDCs, estrogen receptor beta (ER β) was expressed in nearly half of the tumors, and ER β downregulation correlated with recurrence and poor survival [40]. Other patient series have shown estrogen receptor expression to be uncommon in SDC [16].

Studies using targeted or whole exome sequencing have shown alterations in several other signaling pathways (Figure 2). One of the most frequently altered pathways is the PI3K/AKT/mTOR pathway, with many SDC specimens showing mutations and copy number variations in *PIK3CA*, *PTEN*, *RICTOR*, *AKT1*, *AKT3*, and/or *PIK3R1* [57–60]. As with other tumor types, *TP53* mutations, *HRAS/NRAS* mutations and alterations in cyclin D1/CDK pathways are also found with relative frequency in SDC [4, 50, 57, 59, 61, 62]. A few studies have demonstrated loss of p16 expression [3, 4, 18]. Combinations of alterations in more than one of these pathways is also relatively common in SDC [50, 57, 61]. Other less common gene expression patterns and genomic alterations have been found in small numbers of studies including few tumors, and their significance is unclear [3, 27, 31, 50, 61, 63–67].

Interesting differences have been noted in the genomic patterns of de novo SDC versus SDC ex pleomorphic adenoma (PA). Chiosea and colleagues [27] found that all de novo carcinomas and some SDC ex-PA had intact *PLAG1* and *HMGA2* genes, both associated with PA, whereas subsets of tumors showed evidence of both SDC and PA with alterations in *PLAG1* or *HMGA2*. In a study of 44 SDCs, Bahrami and colleagues found that a small proportion of de novo SDCs did have alterations in *PLAG1* or *HMGA2*, though most were negative [66]. Interestingly, Chiosea et al. found that de novo SDC versus SDC ex-PA had markedly different alterations in other cancer-related genes; for example, *TP53* mutations and *ErbB2/HER-2* copy number gain are more common in SDC ex-PA [27], whereas de novo SDCs were more likely to have combined *HRAS* and *PIK3CA* mutations. These studies demonstrate that there are different genomic alterations driving carcinogenesis of de novo SDC versus the transformation into SDC from pleomorphic adenoma.

SYSTEMIC THERAPIES FOR SDC

Cytotoxic chemotherapy has no known benefit in the treatment of SDC, though it is often used with adjuvant radiation or offered as palliative therapy in patients with recurrent or metastatic disease [7, 38]. Cyclophosphamide, doxorubicin, and cisplatin (CAP) has been traditionally used for recurrent or metastatic salivary gland cancers regardless of histology based on retrospective or small phase 2 studies, and SDC had shown better response rates compared to adenoid cystic carcinoma or mucoepidermoid carcinoma [68]. It is clear that effective systemic therapies are needed for patients who recur after surgery and adjuvant radiation. ErbB2/HER-2 targeting therapy and androgen deprivation therapy have shown some activity in small case series and trials of SDC, and new information on the biology of SDC may lead to other targeted therapies for this treatment-refractory disease.

ErbB2/HER-2 Targeting Therapy

Trastuzumab, an inhibitor of ErbB2/HER-2, has proven quite effective in cases of ErbB2-positive breast cancer, and preliminary studies have shown some promising responses in SDC. The combination of trastuzumab with taxanes, a frequent regimen in breast cancer, has been utilized in several patients with SDC. Of two patients with recurrent/metastatic, ErbB2-positive SDC treated with paclitaxel and trastuzumab, one patient had a complete response with no recurrence after 7 months of trastuzumab maintenance therapy, and the other patient had a partial response followed by stable disease for 21 months on trastuzumab maintenance [69]. Another series of three patients with ErbB2-positive, metastatic SDC showed partial responses after trastuzumab and paclitaxel or docetaxel in all three patients [70]. Another patient with ErbB2-positive disease was treated with carboplatin, paclitaxel and trastuzumab concurrently with adjuvant radiation following parotidectomy and neck dissection; despite this, the patient developed recurrent and progressive disease [71]. Of three more patients treated with carboplatin, paclitaxel and trastuzumab for recurrent/metastatic disease, one died from disease and the other two had prolonged responses, with one patient showing no evidence of disease for three years [39]. Several other single-case reports have been published, summarized by Keller et al. [13], showing complete and/or prolonged responses in patients with ErbB2-positive recurrent or metastatic SDC.

A series of 13 patients treated with this regimen, 8 in the adjuvant setting and 5 in the recurrent/metastatic setting, showed that 62% of patients had no evidence of disease at two years following adjuvant therapy, and all 5 patients treated for recurrent disease responded [17]. The median duration of response in recurrent/metastatic disease was 18 months, and one patient had no evidence of disease at 52 months [17]. In a retrospective review of 13 patients treated with trastuzumab with or without platinum-taxane chemotherapy, 11 of whom had recurrent or metastatic disease, five of the patients with recurrent disease had stable disease or a partial response; however only 10 of these 13 patients had tumors overexpressing ErbB2 [72].

These smaller series, and larger trials in breast cancer, have prompted interest in larger clinical trials exploring trastuzumab combined with taxanes for SDC. In a recently presented study, 48 patients with ErbB2-positive, recurrent/metastatic salivary gland carcinomas, most of which were SDC, were treated with trastuzumab and docetaxel in a phase II, single-arm trial [73]. The overall response rate was high at 76%, with median progression free survival of 9.8 months; grade 3–4 toxicities were seen in 94% of patients. Though these series and trials demonstrate frequent responses, which may be complete and/or prolonged, some patients with ErbB2-positive tumors fail to respond to trastuzumab and taxanes. Dual Erb2 blockade therapy with combination of a trastuzumab based regimen either with pertuzumab [74] or lapatinib [75] has shown to have survival benefit in breast cancer patients.

Preliminary results from a basket trial with trastuzumab and pertuzumab in Erb2 activated salivary gland cancers have shown objective responses in 5 out of 7 patients which warrants further investigation [76]. Given most benefits reported with Erb2 targeting therapy is from combination with cytotoxic chemotherapy, dual Erb2 blockade may yield an option of non-chemotherapy containing regimens. Chiosea and colleagues point out that responses to trastuzumab may be limited in patients whose tumors have ErbB2 overexpression with

PIK3CA mutation or *PTEN* loss, which has been noted in breast cancer [50]. Therefore, testing SDC tumors for ErbB2 alone may not be sufficient information to determine which patients will benefit from trastuzumab therapy. Furthermore, many patients have tumors that are not strongly positive for ErbB2. In breast cancers and gastric cancers, level of Erb2 measured by quantitative proteomic assay was shown to correlate with response to Erb2 targeting therapy [77, 78]. Further investigations are needed to clarify whether Erb2 level can serve as a predictive biomarker. Moreover, additional therapies are greatly needed for patients with ErbB2-negative tumors or ErbB2-positive tumors that are not responsive to trastuzumab.

Androgen Deprivation Therapy

As described above, the vast majority of SDC tumors express androgen receptors, and androgen blockade/deprivation therapy has been used in some cases of SDC. Preclinical studies of SDC cell lines have shown that androgens can enhance cell growth, and proliferation of SDC cells is mitigated by inhibition or knockdown of androgen receptors [52, 79]. Similar to trastuzumab, several single-case reports, summarized in prior reviews [13, 53], have shown complete and/or prolonged responses in patients with recurrent/metastatic SDC treated with androgen receptor inhibitors such as bicalutamide or enzalutamide. AR inhibitors are often used in combination with GnRH/LHRH agonists (triptorelin or goserelin), which inhibit the production of androgens (Figure 2). In one retrospective series, 7 of 8 patients with recurrent/metastatic SDC had either a response or stable disease after treatment with androgen deprivation; two of these patients had a complete response [80]. Another series of 10 patients with recurrent/metastatic disease showed stable disease or a partial response in half of the patients, with the other half of the patients demonstrating disease progression despite bicalutamide and often second- or third-line androgen deprivation regimens [81]. In a larger series of 31 patients with recurrent SDC, 45% of patients demonstrated some benefit, with 4 patients showing a partial response and 10 patients showing stable disease [82]. Similar to trastuzumab, androgen receptor inhibitors can work dramatically well in some patients, but biomarkers are needed to determine which patients are likely to benefit.

Immune checkpoint inhibitors

Immunotherapy has dramatically changed the treatment of previously refractory solid tumors in recent years, with FDA approval of several different immune checkpoint blocking drugs for virtually every solid cancer type, including head and neck squamous cell carcinoma. However, in order for immune checkpoint drugs to be effective for a given tumor, there must be an underlying immune response. This requires the tumor to have mutations that are recognized as foreign by the immune system, and tumors with higher numbers of genomic alterations tend to respond better to immunotherapy [83]. A recent study of whole exome sequencing on 16 fresh SDC specimens showed an average mutational burden of 1.7 mutations per megabase [49]. While this mutational burden is higher than that of other salivary tumors such as adenoid cystic carcinoma [49], it is far lower than that of other cancer types that respond well to immunotherapy, such as colorectal cancer, lung cancer or melanoma [83]. However, a recent study demonstrated that the immune checkpoint ligand programmed death ligand 1 (PD-L1) was expressed in nearly half

of 31 SDC specimens, suggesting that anti-PD-1/PD-L1 or other checkpoint inhibitors may have some anti-tumor activity in this disease [84]. Pembrolizumab, an anti-PD1 antibody, showed 11.5% response rate and 46.2% stable disease rate in a small expansion cohort of 26 advanced salivary gland cancer patients – 2 out of 3 responders had SDC [85]. Immune checkpoint inhibitor based combinations such as pembrolizumab plus vorinostat and ipilimumab plus nivolumab are under active investigation. It would be interesting to randomize patients with recurrent or metastatic SDC to receive targeted therapy such as trastuzumab or androgen deprivation plus a checkpoint inhibitor or placebo.

Clinical Trials for SDC

Several clinical trials are recruiting patients with recurrent or metastatic salivary gland malignancies, including SDC. Multiple trials are recruiting patients with androgen receptor-positive salivary gland cancers for treatment with the anti-androgen agents enzalutamide (NCT02749903), abiraterone acetate (NCT02867852) and bicalutamide plus triptorelin (NCT01969578). Another trial is recruiting patients with salivary malignancies for treatment with axitinib, a VEGF receptor inhibitor (NCT02857712). Multiple clinical trials of checkpoint inhibitors, including nivolumab plus ipilimumab (NCT02834013), pembrolizumab and vorinostat (NCT02538510) and single agent pembrolizumab (NCT02628067, KEYNOTE-158) are open to patients with recurrent/metastatic salivary cancers and actively recruiting. A basket trial which assigns advanced salivary gland cancer patients to EGFR, ErbB2/HER-2, FGFR, C-Kit, NOTCH, MEK or PI3K inhibitors or AR targeting therapy based on genomic profiling is underway in Canada (NCT02069730). ErbB2 positive SDC patients can enroll in basket trials with Erb2 targeting therapy arms such as NCI-MATCH (NCT02465060) or My Pathway trial (NCT02091141). The genomic alterations involved suggest that antagonists of Wee1, mTOR and MEK may also warrant investigation. Due to the rarity of this disease, clinical trials solely for SDC may be logistically difficult due to limited accrual.

CONCLUSION

Salivary duct carcinoma is a rare, aggressive malignancy that often presents at advanced stage. Though studies over the past decade have vastly improved our understanding of the biology and pathogenesis of SDC, patients with this disease have a high rate of recurrence and distant metastasis despite surgery and adjuvant radiation. Systemic treatment with trastuzumab, androgen deprivation, and other targeted therapies deserve further study, and biomarkers are needed to predict which patients might respond. Though SDC may be only moderately immunogenic based on its average mutational burden, immunotherapy combined with targeted therapy may be a promising avenue for this disease.

Acknowledgments

Supported in part by NIDCD intramural project ZIA-DC-DC000090. The authors would like to thank Carter Van Waes for critical review of the manuscript and Ethan Tyler from the NIH Medical Arts Branch for assistance with Figure 2.

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HIGHLIGHTS

- Salivary duct carcinoma (SDC) is a rare and aggressive salivary malignancy that often presents at advanced stage and has a high rate of relapse.
- Several recent studies have identified common mutations in SDC, which may impact prognosis and may be actionable targets for therapy.
- ErbB2/HER-2 targeting therapy, androgen deprivation, and immunotherapy deserve further study as possible systemic treatments for this rare disease.

Figure 1. Weight average of survival (A) and sites of failure (B) in SDC. DFS: disease free survival; OS: overall survival.

Figure 2.

Common genomic alterations and signaling pathways involved in SDC. Percentages for each alteration were obtained by totaling the number of positive cases (by IHC or sequencing for ErbB2, EGFR, AR) divided by total cases found in the literature [3, 4, 6, 7, 15, 18, 22, 28, 33, 39, 40, 44, 49–53, 55, 57–64, 67, 86–91]. Percentages representing expression are best estimates, as positivity was defined heterogeneously among studies.

Table 1

Survival and patterns of failure in SDC across studies. Only studies with at least 10 patients were included in the above table.

Study	Sample size ^a	Median duration of follow-up, months	DFS	OS ^b	Site(s) of failure
Lewis et al, 1996 [16]	n=26			Mean: 36 months	Local: 35% Distant: 62%
Guzzo et al, 1997 [9]	n=26	36 (mean)		2 year: 42% 5 year: 12%	Local: 12% Regional: 27% Distant: 46%
Hosal et al, 2003 [10]	n=15	34 (mean)		43%	Local: 21% Distant: 43%
Jaehne et al, 2005 [4]	n=50	96		Average: ^c 56 months	Local: 48% Regional: 8% Distant: 48%
Williams et al, 2007 [40]	n=59	30		2 year: 62% 5 year: 20%	
Roh et al, 2008 [47]	n=21			5 year: 44%	
Ko et al, 2010 [64]	n=30	37	3 year: 39%	3 year: 47%	Local: 40% Regional: 27% Distant: 50%
Kim et al, 2012 [5]	n=35	43	5 year: 47%	5 year: 55%	Local: 16% Regional: 26% Distant: 38%
Piao et al, 2012 [31]	n=35			5 year: 14%	
Salovaara et al, 2012 [45]	n=25		2 year: 79% 5 year: 56%	2 year: 66% 5 year: 41%	Locoregional: 12% Distant: 24%
Shinoto et al, 2013 [32]	n=25		5 year: 45%	5 year: 47%	Local: 28% Regional: 16% Distant: 32%
Jayaprakash et al, 2014 [19]	SEER database; n=228			10 year: 42% Median: 79 months	
Kim et al, 2014 [14]	n=15	38		4 year: 93%	Local: 13% Distant: 47%
Ku et al, 2014 [61]	n=48	48		Median: 76 months	Locoregional: 17%
Roh et al, 2014 [46]	n=56	71		5 year: 42% Median: 48 months	Local: 13% Regional: 16% Distant: 63%
Han et al, 2014 [15]	n=28	63	3 year: 38%	3 year: 78%	Locoregional: 29% Distant: 50%

Study	Sample size ^a	Median duration of follow-up, months	DFS	OS ^b	Site(s) of failure
Huang et al. 2015 [18]	n=11			2 year: 75%	
Masubuchi et al. 2015 [33]	n=32	22	2 year: 51%	2 year: 73%	
Nakashima et al. 2015 [34]	n=26	26	3 year: 54%	3 year: 48%	
Breinholt et al. 2016 [2]	Danish national database: n=34	29		2 year: 58% 5 year: 52% 10 year: 27%	Locoregional: 42% Distant: 52%
Gilbert et al. 2016 [7]	n=75	55	Median: 32 months	Median: 37 months	
Johnston et al. 2016 [11]	n=54	68		5 year: 43%	Local: 17% Regional: 18% Distant: 52%
Luk et al. 2016 [6]	n=23	26	5 year: 36%		
Mifsud et al. 2016 [12]	n=17	37	3 year: 63% Median: 49 months		Distant: 65%
Otsuka et al. 2016 [35] and Kawatika et al. 2017 [37]	Multi-institutional; n=141	36	3 year: 38%	3 year: 71%	Local: 9% Regional: 13% Distant: 39%

^a All studies were single institution studies, unless otherwise specified

^b If a time point is not specified, then survival at last follow-up is displayed.

^c It was not specified in the study whether the average was mean or median.

Abbreviations: DFS: disease free survival; OS: overall survival; SDC: salivary duct carcinoma; SEER: Surveillance, Epidemiology, and End Result

Table 2

Prognostic factors for overall survival in SDC across studies. Factors associated with worse survival are shown in the table. All results are from univariate analysis, unless otherwise specified.

Study	Significant Clinical/Pathologic Predictors of OS	Significant Molecular Predictors of OS
Guzzo et al, 1997 [9]	N+	
Jaehne et al, 2005 [4]		Her-2/neu overexpression, p53 expression
Williams et al, 2007 [40]	Stage IV, N2–3, positive surgical margins, PNI	Hormone receptor negativity (ER β -/AR-)
Roh et al, 2008 [47]	Univariate: Extraparenchymal extension, PNI, LVI, positive surgical margins Multivariable: PNI, LVI	
Ko et al, 2010 [64]	Univariate: T3–4, N+, extraparenchymal extension, positive surgical margins, PNI Multivariable: N+	
Williams et al, 2010 [51]		Chromosome 7 polysomy
Kim et al, 2012 [5]	Univariate: T3–4, PNI, LVI Multivariable: PNI, LVI	
Piao et al, 2012 [31]		CD147 expression, MMP9 expression
Shinoto et al, 2013 [32]	Age $\geq$ 60, LVI	
Jayaprakash et al, 2014 [19]	Univariate: Increasing age, high tumor grade, late stage, N+, tumor size >3 cm Multivariable: Increasing age, late stage, N+	
Roh et al, 2014 [46]	Univariate: Stage III–IV, T3–4, N+, PNI Multivariable: N+	
Han et al, 2014 [15]	Univariate: PNI, LVI Multivariable: PNI, LVI	
Breinholt et al, 2016 [2]	Stage III–IV, positive surgical margins, LVI	
Gilbert et al, 2016 [7]	Univariate: Increasing T stage, facial nerve sacrifice, ECS Multivariable: Increasing age, N2–3	
Johnston et al, 2016 [11]	Univariate: T3–4, N2b–c, ECS, LVI Multivariable: T3–4, ECS	
Otsuka et al, 2016 [35]	Univariate: Age $\geq$ 65, N+, subjective rapid tumor growth Multivariable: Age $\geq$ 65, N+	
Xiao et al, 2016 [36]	N+, high tumor grade	
Kawakita et al, 2017 [86]		Univariate: mGPS $\geq$ 1; CRP $\geq$ 0.39 mg/dL, NLR $\geq$ 2.5, PLR $\geq$ 186.2 Multivariate: mGPS $\geq$ 1; CRP $\geq$ 0.39 mg/dL, NLR $\geq$ 2.5
Osborn et al, 2017 [38]	Multivariable: Increasing age, male sex, Stage IV	

Abbreviations: AR: androgen receptor; CRP: C-reactive protein; ECS: extracapsular spread; ER β : estrogen receptor- β ; LVI: lymphovascular invasion; mGPS: modified Glasgow Prognostic Score (score of systemic inflammatory response); MMP: matrix metalloproteinase; NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PLR: platelet-to-lymphocyte ratio; PNI: perineural invasion; SDC: salivary duct carcinoma.

Table 3

Studies of ErbB2/HER-2 overexpression and prognostic significance in SDC. CISH, colorimetric in situ hybridization; DISH, dual-color in situ hybridization; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry.

Study	# of Tumors Tested	Evaluation Method	% of Tumors ErbB2 (+)	Prognostic Significance?
Al-Qahtani et al., 2016 [86]	7	IHC	28.6%	Unknown
Brandwein-Gensler et al., 2004 [44]	9	IHC	0%	Unknown
Chiosea et al., 2015 [50]	30	FISH	30%	Unknown
Cornolti et al., 2007 [87]	13	IHC, FISH	77% by IHC 62% by FISH	Unknown
DiPalma et al., 2012 [88]	42	IHC, FISH	17% by IHC and FISH	Unknown
Etges et al., 2003 [3]	5	IHC	80%	Unknown
Gilbert et al., 2016 [7]	37	IHC	62%	No
Glisson et al., 2004 [89]	12	IHC	83%	Unknown
Han et al., 2015 [15]	25	IHC	28% +++ 12% ++ 24% +	No
Hellquist et al., 1994 [56]	9	IHC	56% +++ 33% ++ 11% +	Unknown
Huang et al., 2015 [18]	11	IHC	82%	Unknown
Jaehne et al., 2005 [4]	50	IHC	20.6%	Yes
Johnson et al., 2008 [90]	12	IHC, CISH	33%	Unknown
Ko et al., 2010 [64]	27	IHC	33%	Unknown
Kondo et al., 2014 [28]	13	IHC, DISH	54% by IHC 39% by DISH	Unknown
Ku et al., 2014 [61]	37	Nanostring, FISH	100% by nanostring 78% by FISH	No
Lee et al., 2014 [91]	2	IHC	50%	Unknown
Luk et al., 2016 [6]	23	FISH	30% +++ 9% ++	Unknown
Masabuchi et al., 2015 [33]	32	IHC	44%	No
Nabili et al., 2007 [39]	7	IHC, FISH	100% by IHC 43% by FISH	Unknown
Nardi et al., 2013 [60]	30	FISH	30%	Unknown
Williams et al., 2007 [40]	84	IHC	25%	Yes
Williams et al., 2010 [51]	66	IHC, FISH	25.8% by IHC 12.1% by FISH	Unknown