Cancer Treatment Reviews 80 (2019) 101906

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Tumour Review

# Advances and challenges in precision medicine in salivary gland cancer

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ARTICLE INFO

*Keywords:*
Salivary gland neoplasms [mesh]
Molecular targeted therapy [mesh]
Antineoplastic agents [mesh]
Genetics [mesh]
Adenoid cystic carcinoma [mesh]
Salivary duct carcinoma

ABSTRACT

Salivary gland cancer (SGC) is a rare malignancy consisting of 22 subtypes with different genetic, histological and clinical characteristics. This rarity and heterogeneity makes systemic treatment of recurrent or metastatic (R/M) disease challenging. Use of chemotherapy is scarcely studied and chemotherapy at best has moderate effects. New therapeutic strategies are therefore warranted, but advances made in SGC are lagging behind on advances made in more common cancers. By unraveling tumor characteristics of SGC, such as genetic alterations and protein expression profiles, therapeutic strategies tailored to the patient's tumor can be rationalized. This genomic profiling and mapping of immunohistochemical expression profiles is essential in the search for a suitable treatment approach. Thereby, it alleviates the paucity in systemic treatment options and can significantly alter the prognosis of patients with R/M SGC. This review aims to give a comprehensive overview of known genetic alterations and expression profiles amenable for targeted therapy in every histological subtype of SGC. We discuss the remaining knowledge gaps and the implications of these targets for future studies and personalized treatments, thereby aiding clinicians faced with this rare and heterogeneous type of cancer.

## Introduction

Salivary gland cancer (SGC) is a distinct but heterogeneous group of malignancies comprising approximately 6.5% of cases within head and neck cancer [1]. This makes it a rare cancer, with an estimated age-standardized annual incidence of less than 2/100.000 in most countries [2]. The most recent World Health Organization classification of Head and Neck Tumours distinguishes 22 histopathological subtypes of SGC, which makes each subtype even rarer [3]. Recognition of, and differentiation between these different subtypes is notoriously difficult and different subtypes exhibit different clinical features adding up to the complexity of the disease [4]. For localized and resectable disease, surgical resection with or without postoperative radiotherapy is the cornerstone of treatment [5]. In case of local recurrent or metastatic (R/M) disease, systemic treatment is challenging, but urgent given the prognosis of this disease stage. Lumped for all types of SGC with distant metastases (71% of the patients presenting with recurrent disease) the median overall survival is 15 months with overall survival rates at 1, 3 and 5 years of 54.5%, 28.4% and 14.8%, respectively [6]. This however, varies widely between different subtypes. For example, in adenoid cystic carcinoma (AdCC) median overall survival of several years in distant metastatic disease has been reported [7,8]. This contrasts with salivary duct carcinoma (SDC), an aggressive subtype of SGC, in which median overall survival for R/M disease receiving best supportive care is only 5 months [9]..

The clinicopathological diversity of the disease justifies therapy tailored to the specific SGC subtype, highlighting the importance of adequate pathological examination (e.g. subtype, stage, growth pattern), preferably performed by a salivary gland expert pathologist. However, rarity of SGC and its extensive heterogeneity hinders large-scale patient accrual in prospective trials and difficulties in correct histopathological subtyping of SGC endanger homogeneity of cohorts. Therefore, performance of clinical trials in SGC is challenging. This is reflected in the limited amount of studies performed on classic chemotherapeutic agents in SGC.

In R/M AdCC, chemotherapy at best has moderate effects, objective responses in patients treated with single-agent chemotherapy (several agents) were only observed in 18 of 141 (13%) patients enrolled in clinical trials [7]. Of these, single-agent vinorelbine or mitoxantrone can be recommended based on response rates and toxicity profiles. For combination chemotherapy, cisplatin with an anthracycline is most frequently used in AdCC, with

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https://doi.org/10.1016/j.ctrv.2019.101906
Received 19 June 2019; Received in revised form 11 September 2019; Accepted 7 October 2019

cyclophosphamide + doxorubicin + cisplatin (CAP) as most common combination [7,10]. Evidence is even scarcer for other subtypes. For R/M SDC, retrospective analyses of 18 patients treated with carboplatin in combination with paclitaxel revealed 7 responses (median progression free survival (PFS) 6.5 months (95% confidence interval (CI) 3.6–9.3)) [10,11]. In R/M mucoepidermoid carcinoma (MEC), responses on cisplatin alone or in combination with other agents (e.g. CAP, or cisplatin + gemcitabine) and paclitaxel as monotherapy were observed in small patient cohorts (3 responses on paclitaxel monotherapy in 14 patients in the largest MEC cohort). CAP, paclitaxel monotherapy and gemcitabine or vinorelbine in combination with cisplatin has led to responses in adenocarcinoma not otherwise specified (NOS) [10]. Overall, use of chemotherapy in R/M SGC is poorly studied and is unable to drastically change outcomes in most R/M SGC.

Survival rates and limited benefit of chemotherapy emphasize that there is an unmet need for new therapeutic strategies for patients with R/M SGC. The paucity of treatment options may be reduced by mapping tumor characteristics and unraveling genetic aberrations in search for possible targets for systemic therapies. By doing so, salivary gland cancer patients could also share in the benefits of the therapeutic advances made in more common malignancies, especially since the body of evidence for presence of such targets in different histological subtypes is increasing.

In this review, we give a comprehensive overview of the known genetic mutations, amplifications, and protein expression profiles possibly amenable for targeted therapy in every histological subtype of SGC. Subsequently, we discuss the remaining knowledge gaps and the implications of these targets for future studies and personalized treatments, thereby aiding the clinician faced with this rare and heterogeneous cancer.

## Mucoepidermoid carcinoma

Mucoepidermoid carcinoma (MEC) is the most common histological subtype of SGC and comprises approximately 30% of SGCs arising in the minor salivary glands, and 26–47% of SGCs arising in the major salivary glands [3,12–14]. Compared to other histological subtypes, MEC has a rather good prognosis with 75.2% (95% CI 73.8–76.7%) overall survival at 5 years, although survival highly depends on pathological grade and stage. For high grade disease (26%), 5-year overall survival drops down to 48.5% (95% CI 45.4–51.9%) and to 39.4% (95% CI 34.3–45.2%) in case of N2 stage [15]. Distant metastases are more prevalent in high grade disease, but remain rare: 3.2% of the high grade cases at presentation in a large retrospective database study [16]. Overall, risk of distant metastasis was found to be 16% at 10 years [4].

In 38–82% of MECs (all grades) gene fusions involving *MAML2* are observed (Table 1) [17]. This *MAML2* gene fuses with *CRCT1* as a result of a t(11;19)(q21;p13) translocation in most cases, and in a smaller amount of cases with *CRTC3* as a result of a t(11;15)(q21;q26) translocation [3,18,19]. This *MAML2* gene rearrangement is highly specific and could therefore serve as a diagnostic tool in atypical histopathological cases [17,20]. *MAML2* gene rearrangement has also been proposed as a favorable prognostic marker, although current insights dispute this [17,21–23]. Downstream, the *CRTC1-MAML2* gene fusion causes upregulation of the epidermal growth factor receptor (EGFR) ligand amphiregulin (AREG), thereby supporting tumor growth [24]. This upregulation could serve as potential key for systemic therapy with EGFR-inhibitors. On immunohistochemistry (IHC) EGFR is overexpressed in 46% of the cases (Table 2) [25]. In several case reports (with a total of 5 patients, also including MECs arising in the lungs) responses on EGFR-inhibitors (cetuximab, gefitinib or erlotinib), alone or in combination with radiotherapy or chemotherapy, were observed in MEC. For EGFR-inhibitor monotherapy in 3 reported cases partial responses were seen with gefitinib and erlotinib and one complete response was observed with gefitinib. [26–30]. Of note, *EGFR* gene mutation or amplification status was assessed and some responding patients were negative. However, fusion gene analysis for *CRTC1-MAML2* was not performed, which might explain the responses despite absence of *EGFR* gene mutation or *EGFR* amplification. Three phase II studies on gefitinib, cetuximab and lapatinib included patients with several subtypes of SGC. In these studies, response rates were not reported separately for the subsets of patients with MEC (in total N = 6) and only in the study on lapatinib prior assessment of expression of therapeutic targets on immunohistochemistry (either EGFR or HER2) was required for inclusion [26,31,32]. All identified clinical studies (including case reports) on EGFR-inhibitors in MEC are listed in Table 3.

In conclusion, evidence of clinical benefit of an EGFR-inhibitor in MEC patients is anecdotal and requires further studying. Especially in patients with the highly specific *CRCT1-MAML2* gene rearrangement EGFR therapy is attractive based on preclinical work, as this gene fusions is pivotal in tumor survival through AREG-EGFR signaling [24].

## Adenoid cystic carcinoma

Adenoid cystic carcinoma (AdCC) represents approximately a quarter of all SGCs, and is the most common histological subtype observed in patients with distant metastatic disease (60%) [10,33]. Of patients with AdCC of the head and neck region, approximately 42% will develop distant metastases, predominantly located in the lungs and in most cases occurring within 5 years after diagnosis, although development of distant metastasis after many years is possible. Median survival in case of distant metastatic disease ranges between 14 and 36 months, although longer duration of survival is reported, especially in case metastases are only located in the lungs (median between 25 and 54 months). For prognosis, growth pattern (worse prognosis for solid compared to cribriform or tubular) and molecular tumor profile are important factors (e.g. shorter overall survival in case of *NOTCH1* mutations) [8,34].

A major pitfall in studying AdCC is the often rather indolent growth of AdCC, also in metastatic disease. High percentages of stable disease reported in studies may rather be due to the natural growth pattern than treatment effect, especially if progressive disease is not an inclusion criterion. Besides this, dedifferentiation and solid growth pattern are of prognostic importance but difficult to recognize, adding up to heterogeneity of studied groups.

High percentages (up to 90%) of AdCC have shown KIT overexpression on IHC. Targeting c-KIT with imatinib seemed promising, but failed to show results in the vast majority of cases (Table 3). Response rate on dasatinib (which among others targets c-KIT) in KIT positive AdCC patients was also disappointing with 2.5% partial responses (PR), although evidence of progressive disease was an inclusion criterion and 50% of the patients reached stable diseases (SD) with a median PFS of 4.8 months (95%-CI 1.8–6.9) [7,10,35]. Positivity for epidermal growth factor receptor (EGFR) is also frequently observed on IHC in AdCC (24–85%, different scoring systems), providing a potential target for anti-EGFR therapy [25,36]. This has been studied with single-agent cetuximab, gefitinib and lapatinib (see also MEC) [31,32,37]. Of these three, the study on lapatinib included only AdCC patients with disease progression and confirmed EGFR expression. No responses were observed, but 79% reached SD (47% ≥6 months) (Table 3) [37]. Approximately 76% of AdCCs are immunohistochemically positive for vascular endothelial growth factor (VEGF), which could be targeted with VEGF-inhibitors [38]. Trials using these agents in AdCC patients have been performed, with very limited results [10]. However, an overall response rate of 15.6% (75% SD) with a median PFS of 17.5 months in AdCC patients with progressive disease treated with the multi-tyrosine kinase inhibitor lenvatinib has been reported recently [39].

In the genomic landscape of AdCC, which has an overall low somatic mutation rate, a large proportion of AdCC patients harbor gene splits in the *MYB, MYBL1* or *NFIB* genes (88%). In approximately half of

**Table 1**
Prevalence of common genetic alterations (> 10%) in different histological subtypes of salivary gland cancer.

| Subtype | Altered genes | Prevalence | Potential therapeutic target | Reference |
|---|---|---|---|---|
| Mucoepidermoid carcinoma | *CRTC1-MAML2, CRTC3-MAML2* rearrangements | 38–82% | EGFR | Luk et al. [17] |
| Adenoid cystic carcinoma | *MYB, MYBL1, NFIB* rearrangements (of which *MYB-NFIB* fusions) | 88% (49–57%) | IGFR1R, INSR, MET, EGFR | Fujii et al. [40], Ho et al. [41] |
| | *NOTCH1* mutation | 14% | NOTCH1 | Ferarrotto et al. [34] |
| | Mutations in genes of PI3K-pathway | 30% | PI3K-pathway | Ho et al. [41] |
| Polymorphous adenocarcinoma | *PRKD1* p.E710D | 50–73% | Unknown | Piscuoglio et al. [63] Weinreb et al. [64] |
| Adenocarcinoma NOS | *PIK3CA* | 20% | PI3K-pathway | Wang et al. [69] |
| | *CDKN2A* | 17% | | |
| | *CDKN2B* | 12% | | |
| | *HRAS* | 14% | | |
| Salivary duct carcinoma | *TP53* | 53–68% | PI3K-pathway | Shimura et al. [81], Schmitt et al. [73] |
| | *PIK3CA* | 18–26% | | |
| | *HRAS* | 16% | | |
| Carcinoma ex pleomorphic adenoma | *HMGA2* or *PLAG1* rearrangements | 86% | Unknown | Katabi et al. [87] |
| Secretory carcinoma | *ETV6-NTRK3* gene fusion | ~100% | TRK | Boon et al. [91] |
| Clear cell carcinoma | *EWSR1* rearrangements (most often *EWSR1-ATF1* fusion) | 82–87% | Unknown | Antonescu et al. [99] Shah et al. [100] |
| Intraductal carcinoma | *RET* rearrangements | 47% | Unknown | Skalova et al. [101] Weinreb et al. [102] |
| Myoepithelial carcinoma | *EWSR1* rearrangements | 39%[1] | Unknown | Skalova et al. [103] |
| Epithelial-myoepithelial carcinoma | *MYB* rearrangements | 18% | IGFR1R, INSR, MET, EGFR | Bishop et al. [104] |
| | *HRAS* | Up to 33% | | Chiosea et al. [105] |
| | *KRAS* | 18% | | Fonseca et al. [106] |

[1] Percentage of EWSR1 rearrangements in myoepithelial carcinoma with prominent clear cell component.

the cases (48–57%) a *MYB-NFIB* gene fusion is observed whereas a *MYBL1-NFIB* fusion is less prevalent [40,41]. These gene fusions lead to overexpression of the *MYB/MYBL1* gene and are likely oncogenic drivers [42]. In vitro testing of AdCC cells with *MYB-NFIB* translocation showed activation of IGF1R, INSR, MET and EGFR, which could be synergistically targeted with linsitinib (IGF1R inhibitor), crizotinib (ALK and MET inhibitor) and gefitinib (EGFR inhibitor) to decrease cell proliferation. Inhibition of IGFR1R also seems pivotal in downregulation of *MYB-NFIB* [43]. Possible new treatment strategies could therefore consist of a combination of these multiple targeted agents or specifically aiming at downregulation of *MYB-NFIB* in AdCC tumors harboring this gene fusion (e.g. with linsitinib, since IGF1R inhibition can downregulate *MYB-NFIB*). Regarding the latter, tumor growth was not inhibited by linsitinib alone in an in vivo AdCC tumor model [43,44]. Monoclonal antibodies targeting IGF1R (e.g. figitumumab) are currently not registered. Regarding figitumumab, one AdCC case with a minor response upon figitumumab (initially combined with dacomitinib, a pan-human EGFR inhibitor) is described, although it was not described whether this patient had a *MYB-NFIB* gene fusion [45]. The combination of figitumumab with dacomitinib showed also significant growth inhibition in 4 out of 6 AdCC xenograft avatar mice (3 out of 6 for figitumumab monotherapy). The simultaneously reported phase I

**Table 2**
Frequently overexpressed targets on immunohistochemistry in different SGC.

| subtype | Overexpression on IHC | Prevalence (%) | Possible therapy | Reference |
|---|---|---|---|---|
| Mucoepidermoid carcinoma | EGFR | 46% | Cetuximab, Gefitinib, Lapatinib | Cros et al. [25] |
| Adenoid cystic carcinoma | c-KIT | 65–90% | Imatinib, Dasatinib | Alfieri et al. [10] |
| | EGFR | 24–85% | Cetuximab, Gefitinib, Lapatinib | Vered et al. [36], Cros et al. [25] |
| | VEGF | 76% (moderate and high staining) | Anti-VEGF | Zhang et al. [38] |
| | NICD | 49–98% | Brontictuzumab, Crenigacestat | Ferraroto et al. [34], Sajed et al. [47] |
| Salivary duct carcinoma | AR | 78–96% | ADT | Boon et al. [74], Takase et al. [75] |
| | HER2 | 29–46% | Trastuzumab, pertuzumab | Boon et al. [74], Schmitt et al., [73] Takase et al. [75] |
| | EGFR | 53% | Cetuximab, Gefitinib, Lapatinib | Schmitt et al. [73] |
| Epithelial-myoepithelial carcinoma | FGFR1 | 86% | FGFR1 inhibitors | Fonseca et al. [106] |
| | c-KIT | 69–83% | Imatinib, Dasatinib | Seethela et al. [107], Cros et al. [25] |

1. Due to the heterogeneous character of the carcinoma component of CXPA, CXPA is not included in this table (see full text).
Abbreviations: EGFR = epidermal growth factor recepetor, VEGF = vascular endothelial growth factor, NICD = NOTCH intracellular domain, PSMA = prostate specific membrane antigen, AR = androgen receptor, HER2 = human epidermal growth factor receptor 2, FGFR1 = FGFR2 = fibroblast growth factor receptor 1.

**Table 3**
Studies performed on targeted therapy in different histological subtypes of SGC.

| Subtype | Study type | Target | Drug(s) | N | Response | Prior target identification[1] | Reference |
|---|---|---|---|---|---|---|---|
| Mucoepidermoid carcinoma | Case reports | EGFR | Cetuximab, gefitinib, erlotinib[2] | 5 × 1 | PR 40%, CR 40%, PR/PD 20% | Variable | Grisanti et al., Han et al., Lee et al., Li et al., Milanovic et al. [26–30] |
| | Phase II | EGFR | Cetuximab | 2 | n.a.[3] | No | Locati et al. [32] |
| | Phase II | EGFR | Gefitinib | 2 | n.a.[3] | No | Jakob et al. [31] |
| | Phase II | EGFR/ERBB2 | Lapatinib | 2 | n.a.[3] | Yes | Agulnik et al. [37] |
| Adenoid cystic carcinoma[4] | Phase II[5] | c-KIT | Imatinib | 71 (6 trials) | RR 2.8%, SD 48% | Variable | Laurie et al. [7] |
| | Phase II | c-KIT | Dasatinib | 40 | 2.5% PR, 50% SD | Yes | Wong et al. [35] |
| | Phase II[6] | EGFR | Cetuximab | 23 | SD 87% | No | Locati et al. [32] |
| | Phase II[6] | EGFR | Gefitinib | 18 | PR/CR 0% | No | Jakob et al. [31] |
| | Phase II | EGFR/ERBB2 | Lapatinib | 21 | SD 79% | Yes | Agulnik et al. [37] |
| | Phase II | VEGF<br>KIT<br>FGFR2 | Lenvatinib | 33 | PR 15.6%, SD 75% | No | Tchekmedyian et al. [39] |
| | Phase I[6] | NOTCH1 | Brontictuzumab | 12 | PR 17%, SD 25% | Yes | Ferrarotto et al. [49] |
| | Phase I expansion[6] | NOTCH1 | Crenigacestat | 22 | Unconfirmed PR 5%, SD 68% | No | Even et al. [50] |
| Salivary duct carcinoma[7] | Phase II[8] | AR | Leuprorelin acetate + bicalutamide | 36 | PR + CR 41.7%, SD 44.4% | Yes | Fushimi et al. [68] |
| | Phase II | HER2 | Trastuzumab + docetaxel | 57 | CR 14%, PR 56%, SD 25%, PD 5% | Yes | Takahashi et al. [77] |
| | Phase II | HER2 | Trastuzumab-emtansine | 10[9] | OR 90% | Yes | Li et al. [79] |
| Secretory carcinoma | Phase II | TRK | Larotrectinib | 12 | n.a.[3] | Yes | Drilon et al. [96] |
| | Case reports | TRK | Entrectinib<br>Repotrectinib | 2x1 | PR | Yes | Drilon et al. [97],<br>Drilon et al. [98] |
| Poorly differentiated carcinoma | Phase II | Various | Sorafenib | 1 | PR | No | Locati et al. [71] |

Abbreviations: N = number, EGFR = epidermal growth factor receptor, VEGF = vascular endothelial growth factor, FGFR2 = fibroblast growth factor receptor 2, HER2 = human epidermal growth factor receptor 2, TRK = tropomyosin receptor kinase, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease.

[1] This column lists whether the targeted agent was only administered to patients with the known genetic aberration, upregulation or protein overexpression at which was aimed.

[2] Cetuximab was combined with either chemotherapy or radiotherapy.

[3] Proportion of responding patients with the specific histological subtype not specified.

[4] Not all studies/case reports are included in this table. See also the review by Alfieri et al. [10].

[5] One trial combined imatinib with cisplatin.

[6] Evidence of disease progression not required.

[7] Not all studies/case reports are included in this table. See also the review by Schmitt et al. [73].

[8] Only 34 of 36 included patients were SDC, 2 adenocarcinoma NOS.

[9] 10 patients with HER2 positive SGC, presumably most patients were SDC.

trial on this combination also included patients with AdCC, but results were not reported separately [46].

An activating *NOTCH1* mutation is found in approximately 14% of AdCC patients. In tumors with this activating *NOTCH1* mutations IHC for NOTCH1 intracellular domain (NICD) is positive. However, in *NOTCH1* wild-type tumors, activation of the NOTCH-pathway has also been observed, indicated by 49% NICD positivity on IHC in these wild-type tumors [34]. Some authors even found 98% NICD1 positivity in all AdCC patients [47]. Possibly the *MYB-NFIB* gene fusion described above could also lead to activation of the NOTCH-pathway in absence of an activating *NOTCH1* mutation [48]. This NOTCH-pathway can be targeted with NOTCH1-inhibitors, which have been scarcely studied for AdCC. Treatment with the NOTCH1-inhibitor brontictuzumab led to PR in 2 out of 12 and SD in 3 out of 12 AdCC patients enrolled in a phase 1 trial [49]. In an expansion of a phase I study on crenigacestat, another NOTCH-inhibitor, a cohort of 22 AdCC patients (64% NICD positive on IHC, mutation status not given) were enrolled and received the recommended phase 2 dose. One patient had an unconfirmed PR and SD was observed in 68% (evidence of disease progression not required for inclusion); median PFS was 5.3 months (95%-CI 2.4-not ended) [50]. Of note, *NOTCH1* wild-type tumors with activation of the NOTCH-pathway on IHC failed to show tumor growth inhibition in a xenografted mouse model upon exposure on a NOTCH1-inhibitor (brontictuzumab) [34]. Currently, one phase 2 trial on the NOTCH-inhibitor AL101 in AdCC patients with a known *NOTCH* mutation is recruiting (NCT03691207) and another phase I/IIA trial on the NOTCH-inhibitor CB-103 is also including AdCC patients (*NOTCH* mutation confirmation not required, NCT03422679).

Different mutations in genes encoding the PI3K-pathway have also been identified in AdCC (each distinct mutation in less than 8% of AdCCs, but 30% of AdCC harbor a gene mutation important in the pathway), which might entail therapeutic options to patients bearing such mutations [41]. Regarding precision medicine in AdCC, currently, one trial is recruiting besides the abovementioned trials on NOTCH-inhibitors. This trial uses cabozantinib (tyrosine kinase inhibitor targeting VEGFR2 and c-MET) in SGC patients with c-MET positive disease on IHC (NCT03729297).

Besides these targeted drugs, the transmembrane glycoprotein prostate-specific membrane antigen (PSMA) could also serve as key in treating AdCC patients, as PSMA is often expressed in AdCC. Radiolabelled PSMA-ligands, such as $^{68}$gallium-PSMA-HBED-CC have been used in combination with positron emission tomography/computed tomography (PET/CT) as diagnostic tool in AdCC, with moderate to high radioligand uptake in all AdCC patients [51,52]. These patients may benefit from therapy with PSMA-ligands labeled with $^{177}$lutetium, in analogy with prostate cancer therapy [53].

In conclusion, exploring possible drug targetable mutations could be a feasible strategy to select a targeted therapy in AdCC treatment

(Tables 1 and 2). Although phase 2 evidence is lacking, preclinical data indicates that strategies targeting IGF1R alone or in combination with MET or EGFR inhibition could be fruitful in patients with *MYB-NFIB* gene fusions (approximately 48–57% of the cases). The use of notch-inhibitors in patients with an activation of the NOTCH-pathway (activating *NOTCH1*-mutation in 14%, NICD on IHC 49–98%) seems a promising strategy (Table 3), as well as $^{177}$Lutetium-PSMA therapy. Confirmation in trial setting however is warranted.

## Acinic cell carcinoma

Acinic cell carcinoma (approximately 10% of all SGC) most commonly arises in the major salivary glands (90.9%). Most patients present in an early stage (78.2%) and metastatic disease at presentation is very rare (< 1%) [33,54]. Distant metastasis occur in 19% of the cases [55]. Prognosis of patients is generally good, with even a 20-year disease specific survival of 64.3% for patients with stage IV disease, which includes, but is not restricted to distant metastatic disease [54]. Noteworthy is that these numbers stem from a large retrospective database study from 1973 to 2009, while in 2010 (mammary analogue) secretory carcinoma ((MA)SC), which was formerly frequently classified as acinic cell carcinoma, has been described as a separate entity with an excellent prognosis (see below). Therefore these numbers and other data going back further than 2010 may be biased [19,56].

It has been demonstrated that a subset of 4% of acinic cell carcinomas possesses aberrations in the *MSANTD3* gene, of which the majority is a fusion with *HTN3* resulting in the *HTN3-MSANTD3* fusion gene. However, the role of this gene fusion in oncogenesis is unknown. It has not been described in other tumors and *MSANTD3* overexpression does not seem to enhance cell proliferation [57,58]. Therefore, it remains speculative whether the proteins encoded by this fusion gene are valuable targets for systemic therapy, and currently no drug of such kind is available nor is being developed. In case systemic therapy is required for acinic cell carcinoma, no targeted therapy is available. However, we do advice *NTRK* gene fusion analysis in acinic cell carcinoma patients, because secretory carcinoma is often misclassified as acinic cell carcinoma and tumors with *NTRK* fusion genes respond extremely well to targeted therapy (see below). *NTRK* gene fusion analysis should be performed, as immunohistochemistry for pan-TRK is unreliable in SGC [59].

## Polymorphous adenocarcinoma

Polymorphous adenocarcinoma (PAC) is an entity in which the histopathological landscape has been redesigned in the most recent version of the WHO classification of head and neck tumors [19]. PAC consists mostly of tumors formerly described as polymorphous low-grade adenocarcinoma (PLGA) and it controversially also contains the far less prevalent cribriform adenocarcinoma of the minor salivary gland (CAMSG). Between PAC and CAMSG, there might be differences in clinical behavior [60]. PAC (PLGA/CAMSG) is the second most common intraoral SGC and in most cases arises from the minor salivary glands. Prognosis of PAC, both PLGA and CAMSG, is generally good. For PLGA, 5 and 10 year disease specific survival are 98.6% and 96.4%, respectively, and distant metastases are rare, with only 4.3% at presentation [60–62]. The highly specific hotspot mutation *PRKD1* p.E710D, which is likely to be activating, is found in 50–73% of PLGA [63,64]. *PRKD1* abnormalities have also been found in the majority of CAMSG [65]. This specific *PRKD1* p.E710D mutation is not found in other cancers and therapy targeting this activating mutation does not yet exist [64]. In the rare occasion systemic therapy is required to counter progression in patients with PAC, the genomic landscape does not yet reveal promising targeted therapy options.

## Adenocarcinoma, not otherwise specified (NOS)

By its very nature adenocarcinoma NOS is a residual group of malignancies that cannot be classified into one of the other subtypes. The reported proportion of SGC constituted by adenocarcinoma NOS ranges between 4.3 and 17.8%, although arguably these numbers overestimate the real prevalence due to misclassification [33,66]. It is unknown whether recently made diagnostic advances such as molecular characterization (see Table 1) would lead to reduction of this rest group, as recent series on adenocarcinomas NOS are lacking. This impedes interpretation of results on expression profiles. However, it is reasonable to perform at least IHC for androgen receptor (AR) and fluorescence in situ hybridization (FISH) for human epidermal growth factor receptor 2 (HER2) in all poorly differentiated adenocarcinomas as AR positive cases should probably be regarded and treated as salivary duct carcinoma. The proportion of AR and HER2 positivity in adenocarcinoma NOS has been reported to be as high as 21% for both targets, which might thus be an overestimation. Nevertheless, androgen deprivation therapy or therapy with anti-HER2 agents is reasonable in AR or HER2 positive patients (also see salivary duct carcinoma) [67]. Indeed patients classified as adenocarcinoma NOS have been included in trials investigating ADT in SGC patients, however results of this small subset were not reported separately [68]. A wide spectrum of genomic alterations has been described in adenocarcinoma NOS. These include genomic alterations in the PI3K-pathway (36.5%), cyclin dependant kinases (34.6%) and *RAS* family (17.3%) [69]. Evidence of use of these targets in systemic treatment in adenocarcinoma is virtually absent, although responses in adenocarcinoma NOS have been described after treatment with trastuzumab in a HER2-positive tumor and after treatment with sorafenib in another case [70,71].

## Salivary duct carcinoma

Salivary duct carcinoma (SDC) is an aggressive subtype of SGC, representing 4–10% of all SGC [33,72,73]. Overall survival at 3, 5 and 10-years is poor: 70.5% [95%-CI 61.4–77.8%], 43% [95%-CI 33–52%] and 26% [95%-CI 15–37%], respectively [72,74]. Of the patients with SDC treated with curative intent, 54% will develop locoregional recurrences and/or distant metastases. In patients with distant metastases, spread to lungs (54%) and bones (46%) was seen most, but a high percentage of brain metastasis was also observed (18%) [74]. Given this dismal prognosis and high prevalence of distant metastasis, systemic therapy is often required.

AR and HER2 (encoded by *ERBB2*) are frequently expressed in SDC, respectively in 78–96% and 29–46% of the cases. Besides this, EGFR is also commonly expressed (approximately 53% of the cases) [73–75]. Targeting AR and/or HER2 is promising and are the best studied therapies in SDC patients. A prospective phase 2 trial evaluating the effect of combined androgen blockade (CAB) with leuprorelin acetate and bicalutamide in 36 SGC patients (of which 34 were SDC patients), showed PR or CR in 41.7% [95%-CI 25.5–59.2%] and SD in 44.4% [95%-CI 27.9–61.9] [68]. Especially given the low rate of observed grade 3 or 4 toxicity, CAB plays an important role in palliative treatment of AR positive SDC patients. Besides its role in palliative treatment, androgen deprivation therapy (ADT) may also be beneficial in the adjuvant setting. Based on retrospective data, adjuvant ADT results in significantly improved 3-year disease free survival (DFS) in patients with stage 4a AR-positive SDC (48.2% [95%-CI 14.0–82.4%] versus 27.7% [95%-CI 18.5–36.9%] in the control group who did not receive adjuvant ADT). Differences in overall survival were just below and above significance level, depending on whether or not correction for confounders was performed [76].

A recent review summarizes evidence gathered on HER2-targeted therapy [73]. In short, trastuzumab in combination with taxane based chemotherapy is the best studied combination, with an overall response rate of trastuzumab-docetaxel of 70.2% [95%-CI 56.6–81.6%] in 57

SDC patients, and a median overall survival of 39.7 months [95%-CI not reached] [77]. This combination could potentially be amplified with addition of another agent targeting HER2 (e.g. pertuzumab, lapatinib) or after progressive disease replacing trastuzumab with the antibody-drug conjugate trastuzumab-emtansine [73,78]. A recent oral presentation at the American Society of Clinical Oncology (ASCO) emphasized the potential of trastuzumab-emtansine in *HER2*-amplified SGC, as 9 out of 10 patients (0–3 lines of prior treatment, median of 2) responded on this treatment. Presumably most of these patients were SDC patients. Median PFS was not reached after a median follow-up of 12 months [79]. In analogy with the positive results achieved in HER2 positive breast cancer by adding pertuzumab to docetaxel/trastuzumab and the cases reported on this combination in SDC, this triple combination deserves pursuit in clinical studies in SDC. Targeting HER2 in SDC patients with HER2 overexpression is thus promising. In patients co-expressing HER2 and AR it is yet unclear whether therapy targeting AR or HER2 is the best approach. However, in case of extensive or rapidly progressive disease, HER2 targeting therapy in combination with taxane-based chemotherapy is the reasonable choice over ADT.

Besides AR and HER2, a wide spectrum of mutations, is observed in lower frequencies in SDC, which altogether forms a genetic landschape highly similar to apocrine breast cancer [80]. This includes mutations in *TP53* (53–68%), *PIK3CA* (18–26%), *HRAS* (16–23%), *BRAF* (4%) and *AKT1* (1.5%) [73,80,81]. Reports of use of these targets in clinical practice are scarce. Two SDC patients responded to treatment with temsirolimus (mTOR-inhibitor, part of PI3K-pathway) combined with bevacizumab; in one patient loss of *PTEN* and therefore an aberration in the PI3K-pathway was demonstrated [82]. Dabrafenib (BRAF-inhibitor) combined with trametinib (MEK-inhibitor) could be beneficial in patients harboring a *BRAF* p.V600E mutation, as was indicated by a case report using this combination [83]. Although only observed in a minority of SDC patients, when identified these mutations could serve as aim for targeted therapy.

In analogy with the observation of high uptake of radiolabeled PSMA-ligands in AdCC, this is also seen to a lesser extent in SDC: 4 out of 10 patients with SDC showed moderate to high ligand uptake [52]. $^{177}$Lutetium-PSMA therapy could also be a novel beneficial strategy for those SDC patients with high ligand uptake, e.g. for patients not responding to or progressive on ADT and/or HER2 therapy. Finally, a phase 2 trial on cabozantinib in immunohistochemical c-MET positive SDC is ongoing (NCT03729297).

In summary, SDC has many targets amenable for systemic therapy (Tables 1 and 2). Elaborate mapping of tumor characteristics regarding receptor expression, genomics and pathway alterations are the keys to alter the dismal prognosis of patients with locally advanced or metastatic SDC.

## Carcinoma ex pleomorphic adenoma

Carcinoma ex pleomorphic adenoma (CXPA) is not a stand-alone diagnosis and the most recent version of the WHO highlights the importance of describing the subtype of the carcinoma component of CXPA; most often this is adenocarcinoma NOS, AdCC, MEC or SDC (and many other subtypes or a mixture have been described less frequently) [3,19,84,85]. Of all malignant SGC 5–15% is reported to be CXPA. Broad ranges of 5-year survival (25–75%) and several factors influencing survival have been reported [84,86]. In the genomic landscape of CXPA, gene fusions of *HMGA2* and more often *PLAG1* with several partner genes are frequently found: up to 86% of CXPA shows rearrangements in either one of these genes [85,87]. Although of diagnostic importance, the role of these gene fusions in CXPA and therefore their possible utility as aim for targeted therapy is unknown [85]. CXPA's heterogeneity is also resembled in the wide spectrum of overexpressed growth factors and receptors that have been described. These include FGF(R)-2, TGFβ-1, TGFα, HGF-A, c-MET, IGFR-1, EGFR and HER2, providing possible valuable entry points for systemic therapy [84]. For instance, responses to trastuzumab based chemotherapy and trastuzumab-emtansine were described in HER2 positive CXPA [88,89]. The possible targets for systemic therapy of other histological subtypes of SGC described in this review highlight the importance of adequate description of the carcinoma component of CXPA as this might reveal promising approaches for treatment.

## Secretory carcinoma

Secretory carcinoma (SC), previously named mammary analogue secretory carcinoma (MASC), is a relatively new entity that was first described in the salivary glands in 2010 [19,90]. In retrospect, most cases of what is now called secretory carcinoma were initially classified as acinic cell carcinoma and also as polymorphous adenocarcinoma or adenocarcinoma NOS [91]. SC is rare, is most often found in the parotid gland (58–68%) and behaves relatively indolent with a good prognosis. R/M disease is rare (estimated 5 and 10 years survival 95%) [91,92]. The genetic hallmark of SC is a *ETV6-NTRK3* gene fusion as a result of a t(12;15)(p13;q25) translocation, although other gene fusions with *ETV6* have been described (for instance *ETV6-MET* and *ETV6-RET*) [93,94]. *NTRK* gene fusions are known oncogenic drivers and have been described in other tumor types [95]. This *ETV6-NTRK3* gene fusion therefore provides a promising target for systemic therapy, and the body of evidence for efficacy of TRK-inhibitors (e.g. larotrectinib, entrectinib, repotrectinib, LOXO-195) in patients with *NTRK* gene fusions is expanding [95]. A recent phase II trial evaluating the efficacy of larotrectinib in *NTRK* fusion positive patients included 12 patients with (MA)SC and reported a response rate of 75%; median progression free survival was not reached after median follow-up of 9.9 months [96]. Responses in patients with MASC have also been observed for entrectinib and repotrectinib [97,98]. A phase I/II trial evaluating LOXO-195 in second line is currently recruiting, and is open for inclusion of *NTRK* fusion positive SGC patients previously treated with a TRK-inhibitor and showing progressive disease, unresponsiveness or intolerance (NCT03215511). Whether *NTRK* gene fusions are present in other subtypes of SGC is currently unknown, but treatment with TRK-inhibitors is a very promising treatment option for patients with advanced SC (Table 3).

## Miscellaneous

Several of the SGC histological subtypes are extremely rare, in general not defined by certain genetic alterations nor do seldom require systemic treatment due to low metastasis or recurrence rate (clear cell carcinoma, basal cell adenocarcinoma, intraductal carcinoma, myoepithelial carcinoma, epithelial myoepithelial carcinoma, sebaceous adenocarcinoma, poorly differentiated carcinoma, lymphoepithelial carcinoma, oncocytic carcinoma, squamous cell carcinoma and sialoblastoma). These are discussed in appendix A (supplementary materials) in lesser detail and are listed in Tables 1–3, if applicable.

## Practical guidelines for SGC patients requiring systemic therapy

Pivotal in choosing the right systemic therapy is an adequate pathological diagnosis to determine the exact subtype. Since SGC is rare and there are many types of salivary gland neoplasms with overlap in histomorphological features, pathological review by an expert salivary gland pathologist is recommended. Further work-up depends on the subtype, as is summarized in Fig. 1. For some subtypes little or no clinical evidence is available to make hard recommendations for additional immunohistochemical staining or molecular evaluation to identify therapeutic targets. For these subtypes we advocate immunohistochemical staining for AR and evaluation of HER2 expression, preferably by immunohistochemical staining and FISH. Besides this, regular use of a next generation sequencing panel which includes frequently affected genes in other cancers which are currently targetable

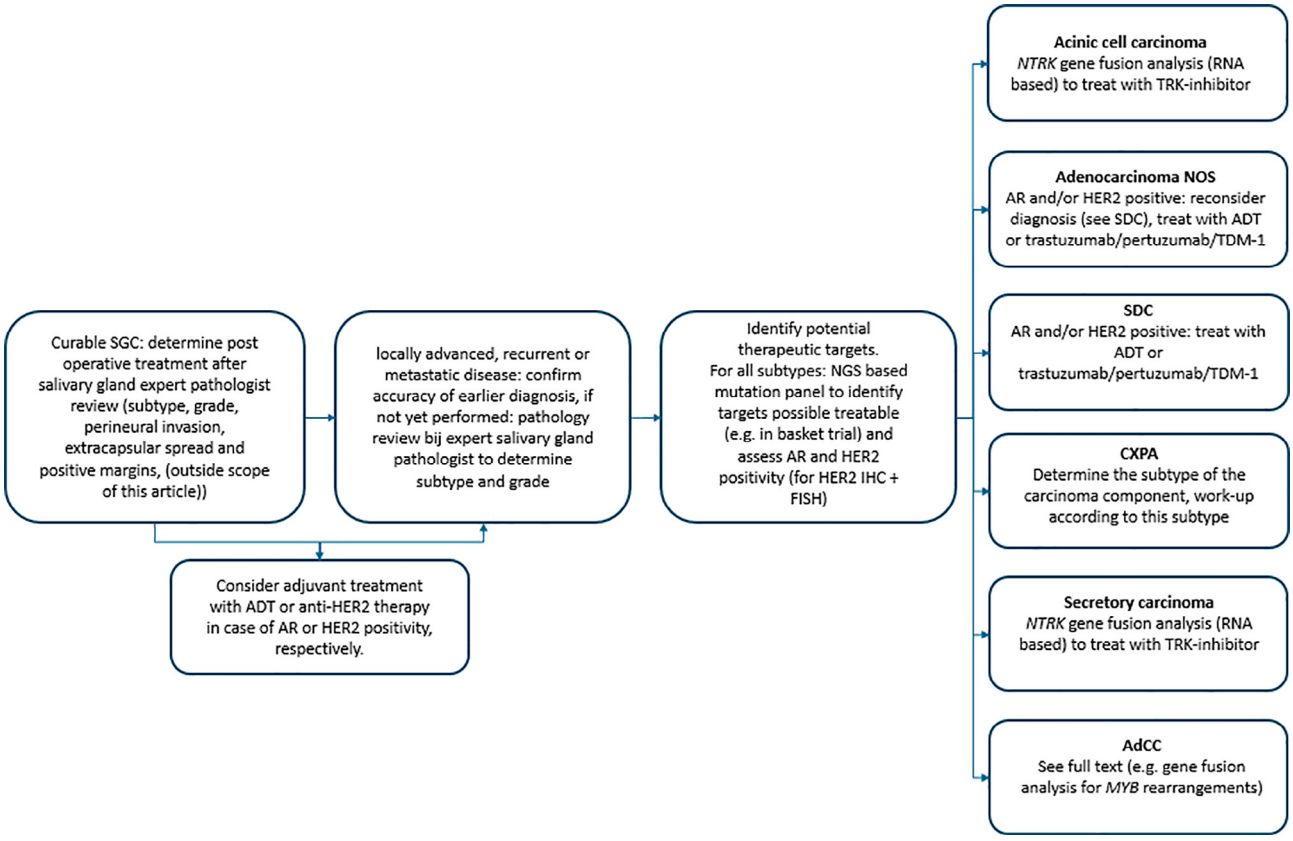


**Fig. 1.** Flow chart of work up for patients with SGC requiring systemic therapy to rationalize targeted therapy options. See full text for more elaborate description of targets (possibly) amenable for systemic therapy sorted by subtype. Abbreviations: SGC = salivary gland cancer, NGS = next-generation sequencing, AR = androgen receptor, HER2 = human epidermal growth factor receptor 2, ICH = immunohistochemistry, FISH = fluorescence in situ hybridization, NOS = not otherwise specified, SDC = salivary duct carcinoma, ADT = androgen deprivation therapy, TDM-1 = trastuzumab-emtansine, CXPA = carcinoma ex pleomorphic adenoma, AdCC = adenoid cystic carcinoma.

with anticancer drugs (e.g. *PIK3CA, BRAF, NRAS, MET)* is recommended. Regarding the different gene fusions, which are often not present in commercially available panels, it is important to test specifically for *NTRK* gene fusions, as this has great implications for individual patients. Other gene fusions are of diagnostic and potentially (in the future) of therapeutic value. To guide treatment decisions, these gene fusions are therefore currently of less importance than *NTRK* gene fusions.

## Conclusion and future perspective

Several different subtypes of SGC have characteristics targetable with systemic treatment. Thereby advances made in modern oncology can also be beneficial for patients with this rare and heterogeneous malignancy, although studies on precision medicine for patients with R/M SGC are scarce. Especially in AdCC and SDC, the histological subtypes of SGC with the largest burden of R/M disease, promising therapeutic strategies are available. Our review highlights the importance of pathological review by and expert pathologist and tumor specific diagnostic testing, especially as many SGC harbor gene fusions, which are notoriously hard to detect. Immunohistochemical expression profiles and unraveling of the genomic profile can reveal excellent keys for targeted therapy in most subtypes. In the future, in both studies and clinical practice, mapping of SGC tumor characteristics will therefore be an invaluable tool to optimize treatment by tailoring it to a patient's tumor.

## Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Author's contribution

Conception and design of the manuscript: CvH, GL, WvB; literature search, data extraction and drafting of the first version of the manuscript: GL; editing and revision of the manuscript: WvB, MJLL, AvE, CvH, GL. All authors are responsible for the final content and approve the final version of the manuscript.

## Declaration of Competing Interest

GL, WvB, AvE: nothing to declare. MJJL is member of advisory boards of Astra Zeneca, Bayer, Roche, Merck, Janssen Pharmaceuticals, and obtained research sponsoring of Bristol-Myers Squibb, AstraZeneca and Illumina. CvH received consultant fees for participation in advisory boards of Bayer, Bristol-Myers Squibb, Ipsen, MSD and Regeneron and received research grants from Astra Zeneca, Bristol-Myers Squibb, MSD, Merck, Ipsen, Novartis and Sanofi.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2019.101906.

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