Salivary gland cancer: ESMO-EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TEXT

SECTION 1. DIAGNOSTIC IMAGING

The algorithm for evaluating a suspected major salivary gland mass varies according to the specific clinical setting. In all clinical settings, where the mass is superficial, ultrasound should be used as the first imaging step. Ultrasound is effective in assessing the actual glandular origin,[1] but its use is limited when dealing with a solid lesion; neither the signal pattern nor the shape is adequate for differentiating benign from malignant neoplasms. The pooled sensitivity of ultrasound in this setting is 66%, with a specificity of 92%.[2]

When a mass cannot be completely delineated by ultrasound, and in all clinical settings suggesting a malignancy, magnetic resonance imaging (MRI) is the preferred imaging modality. The sensitivity and specificity of computed tomography (CT) and [^{18}F]2-fluoro-2-deoxy-D-glucose–positron emission tomography–CT (FDG–PET–CT) for predicting malignant tumours are lower than MRI[3,4] and MRI has greater tissue discrimination. It is important for MRI to combine different pulse sequences: standard T2 and T1 weighting with diffusion weighting with apparent diffusion coefficient map and dynamic analysis post paramagnetic contrast agent administration are recommended. This 'multiparametric approach' has a pooled sensitivity of 80% and specificity of 90%.[2] The use of contrast-enhanced CT (CE-CT) is mostly limited to patients in whom MRI is contraindicated (e.g. those with a cardiac pacemaker, claustrophobia, ferrometallic prostheses or foreign bodies) or in addition to MRI when there is a suspicion of bone invasion.

Multiparametric MRI is indicated to demonstrate glandular or extraglandular spread.[5] While the invasion of cortical bony structures can be more easily identified by CE-CT, the permeative invasion of an adenoid cystic carcinoma (AdCC) into spongiotic/diploic bones (skull base, mandible) may be missed by CT, particularly when it presents as replacement of medullary fat bone marrow in the absence of

gross cortical erosions. Such findings are better detected with a non-contrast T1 weighted MRI sequence.[6] Post-contrast high-resolution MRI is the modality of choice to detect perineural spread. According to the site of origin of the neoplasm, the facial nerve (parotid gland) and the maxillary and mandibular branches of the trigeminal nerve (minor salivary glands of the palate, submandibular and sublingual glands) should be scrutinised by MRI. The cavernous sinus, Meckel's caves and geniculate ganglion, which are ‘intra-cranial terminal stations’, should be included in the field of view of the MRI study. The sensitivity of MRI for perineural spread has been reported to be greater than CT (92.6% versus 87.9%, respectively)[7]; however, incomplete mapping of all involved nerves lowers MRI sensitivity to 20%-37%.

Regardless of the imaging technique used (MRI or CT), the study should be extended to include the ipsilateral and contralateral neck levels or integrated with ultrasound examination of neck lymph nodes. Several recent reports underline that FDG–PET–CT is not inferior to CT and MRI, and in some studies has been shown to be more sensitive in detecting nodal involvement in salivary gland cancer (SGC).[3,8,9]

Distant metastases at presentation are infrequent. In staging SGC, chest CT is recommended in cT3-4 N0 and all stages of AdCC. FDG–PET–CT is recommended for treatment planning in lymph node-positive or high-grade SGC.[3] The following SGCs may be considered high grade: SGCs graded as high according to criteria [e.g. high-grade mucoepidermoid carcinoma (MEC), high-grade acinic cell carcinoma (AcCC)]; all high-grade transformed tumour types [e.g. AdCC, AcCC, secretory carcinoma, epithelial-myoepithelial carcinoma, myoepithelial carcinoma, MEC, polymorphous adenocarcinoma (PAC), clear cell carcinoma[10]]; all AdCC, basal cell adenocarcinoma, adenocarcinoma not otherwise specified (NOS), salivary duct carcinoma, myoepithelial carcinoma, epithelial-myoepithelial carcinoma, carcinoma ex pleomorphic adenoma (CxPA) including subtypes such as salivary duct ex pleomorphic adenoma and myoepithelial ex pleomorphic adenoma), sebaceous adenocarcinoma, carcinosarcoma, poorly differentiated carcinoma (including undifferentiated, small and large cell neuroendocrine carcinoma) and lymphoepithelial carcinoma.

Bone is the second most common site for distant metastases in SGC, after lung.[11] Although the sensitivity of FDG–PET is comparable to that of morphologic imaging techniques, its specificity has been reported to be significantly higher.[12]

SECTION 2. HISTOLOGICAL SUBTYPES

MEC

MEC is the most common SGC[13] and consists of three cell types: (i) mucinous cells, which are often large and goblet-like and frequently line cystic spaces; (ii) epidermoid cells that are nonkeratinising and may even look frankly squamous; (iii) intermediate cells which are more basal or cuboidal. In addition to clinical stage, tumour grade is a prognostic factor that may guide treatment decisions. MEC is classified into three histological grades (low, intermediate and high) based on evaluation of necrosis, mitoses, atypical nuclei and relative size of the cystic component.[14] Translocations *t(11;19)* and *t(11;15)*, leading to the *CRTC1-MAML2* and *CRTC3-MAML2* fusions, respectively, are present in 40%-80% and 5% of MECs, respectively.[15] Some studies indicate that fusion-positive MECs are diagnosed at an earlier stage with a lower grade and a better prognosis than fusion-negative tumours,[16] while others have not demonstrated a prognostic role for the translocation.[17] *MAML2* rearrangements have been detected in up to 75% of low-grade and intermediate-grade MECs, but fewer than 50% of high-grade MECs seem to be fusion positive. Among high-grade MECs, fusion-negative tumours behave much more aggressively than fusion-positive tumours. It has been proposed that *CRTC1-MAML2* fusion-negative high-grade carcinomas with MEC-like morphological features and scanty mucin content actually represent a heterogenous group of other high-grade carcinomas, in line with their more aggressive behaviour.[16] Compared with other histological subtypes, MEC presenting as local/locoregional disease has a good prognosis, with a 5-year survival rate of 75.2% [95% confidence interval (CI) 73.8% to 76.7%]. For high-grade disease (26%), the 5-year survival rate drops to 48.5% (95% CI 45.4% to 51.9%).[18]

AdCC

AdCC is a relentlessly growing tumour, composed of epithelial and myoepithelial cells that form various growth patterns (tubular, cribriform and solid), and is associated with *MYB-NFIB* and *MYBL1-NFIB* fusions. Despite bland histopathological features, AdCC is aggressive and characterised in most cases by

perineural and intraneural invasion and distant spread that may develop over years and decades. Mutations in the *NOTCH* gene family are present in around 14% of patients with AdCC at presentation (especially in patients with solid histology), are increasingly present in recurrent or metastatic disease (40%) and are associated with poor outcome.[19,20] Relapsed and disseminated tumours are generally incurable, and overall prognosis is poor, with 15- or 20-year survival rates of 23%-40%.[21]

AcCC

AcCC exhibits serous acinar and lacks mucinous differentiation. It is characterised by solid, microcystic, follicular, less commonly papillary-cystic architectures, often with a prominent lymphoid stroma. Neoplastic cells are heterogeneous with the most common cell type being the serous acinar cell which features periodic acid-Schiff (PAS)-positive, diastase-resistant basophilic cytoplasmic zymogen granules, with variable intercalated duct-type, nonspecific glandular, vacuolated and rarely clear cells. High-grade tumours exhibit, in addition to conventional areas, a component of high-grade adenocarcinoma (with variable cribriform, solid, trabecular growth patterns) or poorly-differentiated/undifferentiated carcinoma. The majority of AcCC cases harbour a *t(4;9)(q13;q31)* rearrangement that places the active enhancer regions of the *SCPP* gene cluster upstream of the *NR4A3/NOR-1* gene, resulting in upregulation of NR4A3 via enhancer hijacking.[22] Nuclear staining for NR4A3/NOR-1 or NR4A2/Nurr1 has been identified in 98% and 2% of cases, respectively.[22,23] The prognosis of patients presenting with local/locoregional AcCC is generally good, with a 20-year disease-specific survival (DSS) rate of 64.3% for patients with stage IV disease.[24] Notably, this value is derived from a large retrospective database study from 1973-2009; however, in 2010 mammary analogue secretory carcinoma, which was formerly frequently classified as AcCC, was defined as a separate entity with excellent prognosis (see below). Therefore, data going back further than 2010 may be biased.[25]

PAC and cribriform adenocarcinoma of salivary gland

PAC and cribriform adenocarcinoma of salivary gland (CASG) are related entities with partly differing clinicopathological and genomic profiles; they are the subject of

an ongoing taxonomical debate.[26,27] Classical variant PACs, originally called polymorphous (low-grade) adenocarcinomas, are characterised by hotspot point E710D mutations in the *PRKD1* gene,[28] whereas CASGs are characterised by translocations involving the *PRKD1-3* genes.[29] In the 2017 WHO Classification of Head and Neck Tumours, cribriform adenocarcinoma of (minor) salivary gland origin is a subcategory of PAC,[30] but for the purpose of reporting, differentiating between these entities may be helpful given the noticeably different behavioural profiles,[26,27] with CASGs being more frequently extrapalatal, commonly at the base of the tongue, with a propensity for nodal metastasis. The prognosis of patients with PAC is generally good, with 5- and 10-year DSS rates of 98.6% and 96.4%, respectively.[31]

Intraductal carcinoma

Intraductal carcinoma is a rare, low-grade SGC with histomorphological features reminiscent of atypical ductal hyperplasia or ductal carcinoma *in situ* of the breast. The tumour is, in typical cases, characterised by intraductal and intracystic proliferation of luminal ductal cells exhibiting solid, cribriform and papillary patterns. Notably, recurrent *NCOA4-RET* and *TRIM27-RET* fusion transcripts have been observed in intraductal carcinomas.[32,33] As these genetic aberrations are recurrent, they serve as powerful diagnostic tools in SGC diagnosis, and therefore also in refinement of SGC classification.

Salivary duct carcinoma

Salivary duct carcinoma is a high-grade adenocarcinoma with morphological and molecular features similar to invasive ductal carcinoma of the breast, including androgen receptor expression in 90% of cases and human epidermal growth factor receptor 2 (*HER2)* gene amplification in 30% of cases. Additional common molecular alterations in salivary duct carcinoma include mutations in *TP53, PIK3CA* and *HRAS*, and loss or mutation of *PTEN.*[34,35] The majority of salivary duct carcinomas (74%) have alterations in either the mitogen-activated protein kinase (MAPK) pathway (*BRAF, HRAS* and *NF1*) or in *HER2/neu*, indicating that MAPK pathway activation and *HER2* amplification are the major oncogenic drivers in salivary duct carcinoma.[36] Gene fusions involving the *PLAG1* and *HMGA2* oncogenes are specific for benign

pleomorphic adenomas and they have also been described in salivary duct carcinoma arising in pleomorphic adenoma.[36] Reported 3-, 5- and 10-year survival rates in patients with salivary duct carcinoma are 70.5% (95% CI 61.4% to 77.8%), 43% (95% CI 33% to 52%) and 26% (95% CI 15% to 37%), respectively.[37]

Adenocarcinoma NOS

The diagnosis of adenocarcinoma NOS is reducing due to advances in molecular diagnostics. Androgen receptor expression is observed in some cases of adenocarcinoma NOS, and *HER2* gene amplification can also occur. Fifteen-year survival rates for low-, intermediate- and high-grade adenocarcinoma NOS have been reported as 54%, 31% and 3%, respectively.[38]

CxPA

CxPA is subclassified by histological type and extent of invasion. Noninvasive CxPAs (intracapsular) are completely confined within the capsule of the original pleomorphic adenoma, lacking penetration of the capsule. Intracapsular CxPA has a very low reported rate of recurrence and regional metastasis.[39] Minimally invasive CxPAs (<4-6 mm extension beyond the pleomorphic adenoma border) are prognostically favourable.[40] Widely invasive carcinomas extend beyond 6 mm. Prior to diagnosing a noninvasive CxPA, sectioning of the entire lesion for histological evaluation is recommended in order to exclude the presence of invasive growth. Prognosis parallels the degree of invasion, with noninvasive and minimally invasive cancers having a better prognosis than invasive CxPAs,[41] even if intracapsular/minimally invasive CxPAs can also recur and cause death. There is a trend toward worse disease-free survival and DSS in patients with myoepithelial carcinoma.[42]

Secretory carcinoma

Secretory carcinoma, formerly known as mammary analogue secretory carcinoma,[43] shows morphological, genetic and immunohistochemical similarities to breast secretory carcinoma.[44] One of the main differential diagnoses is AcCC, which

typically contains a basophilic cytoplasm with PAS-positive zymogen granules and a more diverse cytological profile compared with secretory carcinoma. The presence of a chromosomal translocation, *t(12;15)*, between the *ETV6* gene on chromosome 12 with *NTRK3* on chromosome 15, generates the fusion product *ETV6-NTRK3.*[43] A small subset of secretory carcinomas show alternative fusions, such as *ETV6-RET*[45], *ETV6-MET*[46] and *VIM-RET*.[47] Importantly, *ETV6-NTRK3* and *ETV6-RET* fusions may serve as a target for therapy. Secretory carcinoma behaves relatively indolently and has an estimated 5- and 10-year survival rate of 95%. Recurrent or metastatic disease is rare and mainly occurs in high-grade transformation tumours.[48]

SECTION 3. HISTOLOGICAL DIAGNOSIS

Histological tumour grade

The histological (microscopic) grading of SGCs has been shown to be an independent prognostic factor and plays a role in optimising therapy, with high-grade tumours requiring intensified treatment strategies (see **Figures 2, 3 and 4**). Further, there is often a positive correlation between histological grade and clinical stage.[41] Nevertheless, most SGC types have an intrinsic biological behaviour and attempted application of a universal grading scheme is not recommended.[41] By assigning a histological type, the tumour grade itself is often implied. As such, a generic grading scheme is no longer recommended for SGCs.[49]

Carcinoma types for which grading systems exist and are relevant are incorporated into histological type. The major diagnostic categories amenable to grading include AdCC, MEC, PAC and adenocarcinoma NOS.[40,41]

High-grade transformation has evolved into an important concept of tumour progression in SGCs. Historically designated as ‘dedifferentiation’, it describes progression of a typically monomorphic, low-grade carcinoma into a pleomorphic, high-grade carcinoma.[50] The importance of this phenomenon is that tumours demonstrating high-grade transformation show an aggressive clinical course that deviates drastically from the usual behaviour for a given tumour type, thus alerting the treating team to the potential need for more aggressive treatment. Tumours for which this phenomenon is well characterised include AcCC, AdCC, epithelial-myoepithelial carcinoma, secretory carcinoma[51] and many others.[50]

Perineural invasion

Perineural invasion is diagnostically useful because it establishes a malignant categorisation. The value of perineural invasion as a prognosticator varies depending on tumour type.[52] Involvement of a specifically named nerve (e.g. facial nerve) is incorporated into staging and is assigned a more advanced stage.[49] It is well known that AdCC can extend along nerves beyond the tumour margins; however, studies on perineural invasion in AdCC have provided conflicting results with regard to whether it is a risk factor for local recurrence.[53] A thorough documentation, to include the extent of perineural invasion, histological pattern of perineural and intraneural invasion, localisation and size of involved nerves, should be considered and may be prognostically relevant.[54]

Lymphovascular invasion

Lymphovascular invasion is nearly always diagnostic for SGC (metastasising pleomorphic adenoma being the obvious exception). Existing data are limited but support its prognostic value, although this varies by tumour type and study.[55]

Extent of invasion

Macroscopic extraparenchymal extension is the parameter required to upstage a tumour to T3 and is thus more important than microscopic extraparenchymal extension. Bone, skin and facial nerve involvement are parameters that define stage T4a.[49]

Margin status

Complete surgical excision to include cancer-free margins is the primary treatment for SGCs, because retrospective studies have shown an increased risk for recurrence and decreased survival with close or positive surgical margins.[55,56] Unlike mucosal sites, there are no data to indicate a specified critical margin distance that yields a prognostic difference. Occasionally, SGCs may show encapsulation similar

to that of pleomorphic adenoma. In superficial parotid gland lesions, a tumour that rests on the facial nerve with its capsule may thus be resected conservatively (i.e. dissecting the tumour capsule from the nerve) in order to spare and minimise injury to the facial nerve. Thus, it is not uncommon for such tumour margins to be judged 'close' with the tumour capsule forming the deep margin. It is not clear whether this scenario indicates an increased risk of local recurrence. There are limited data on the use of extracapsular dissection (a tissue sparing technique recently developed for benign tumours) in SGCs that suggest a favourable outcome even with close margins, but this is likely influenced by selection bias, since most carcinomas treated by extracapsular dissection are slow growing and low-grade tumours that were not diagnosed as malignant preoperatively.[55,57]

Frozen section

Intra-operative frozen sections can be indicated to evaluate margins of resection, perineural invasion and lymph nodes, but only if the result is expected to alter management at the time of surgery.[58] Frozen section analysis has high specificity (99%) and sensitivity (98.5%).[59]

SECTION 4. POST-OPERATIVE RADIOTHERAPY

In a matched pair analysis of patients treated for major SGC, post-operative radiotherapy (RT) improved local control from 17% to 51%.[60] This analysis, however, was based on data collected several decades ago and the treatment groups covered different time periods: surgery alone from 1939-1965; combined treatment from 1966-1982.

In another study of 8580 patients with major SGC, four subgroups were analysed: early stage (T1-2) versus late stage (T3-4) and presence or absence of adverse features (AdCC, intermediate to high grade, positive margins and pN+).[61] After propensity score matched analysis, post-operative RT improved overall survival (OS) in case of adverse features, but not in early stage without adverse features.

Survival was analysed in 2017 patients with minor SGC (70% oral cavity, 15% nasal cavity).[62] The patients were divided into three subgroups with decreasing OS rates,

based on a propensity score matched analysis. Post-operative RT resulted in a 24% survival benefit in patients with advanced T/N category, AdCC, high-grade disease and nasopharynx location. A web-based tool for predicting survival impact of adjuvant RT was developed; however, important data such as surgical margins and perineural and vasoinvasion were lacking.[62]

One of the largest and most detailed retrospective cohort studies is the Dutch Head and Neck Cooperative study, which included 565 patients with SGC, excluding minor SGC of the nasal cavity.[63,64] The reported relative risk for surgery alone, compared with combined treatment, was 9.7 for local recurrence and 2.3 for regional recurrence. The UK National Multidisciplinary Guidelines for the Management of Salivary Gland Tumours are mainly based on this study.[65] Post-operative RT is particularly effective if there are close (<5 mm) or microscopic positive resection margins, enhancing local control from around 50% to 80%-95% in T3-T4 tumours,[66] from 54% to 86% in pathologically confirmed bone invasion and from 60% to 88% in perineural invasion.[64] Grading was not evaluated in this study. Post-operative RT was an independent prognostic factor for patients with pN+ neck involvement, improving regional control from 62% to 86%. For completely resected T1 or T2 tumours with no bone or perineural invasion, surgery alone can result in a >90% 10-year local control rate and adjuvant RT is not indicated.[67]

Several cohort studies in patients with AdCC have reported improved outcomes with the addition of RT to surgery.[68,69] In a cohort of 101 patients with M0 AdCC, post-operative RT improved the 5-year local control rate and disease-free survival compared with surgery alone (81.0% versus 53.4%, $P = 0.0003$ and 71.3% versus 50.0%, $P = 0.0052$, respectively).[70] In a series of 140 patients, besides T4 stage and nerve invasion, omission of RT was an independent negative prognostic factor for local control; however, this was only observed in patients treated with >60 Gy.[68] In case of specifically named perineural invasion (e.g. facial nerve), a radiation field including the extension of the nerve to the base may prevent recurrences.[71]

In a cohort of 87 cases with SGC of the parotid gland ($n = 70$) or submandibular gland ($n = 17$), post-operative RT was an independent prognostic factor for local control, in addition to facial paresis.[70] In another study of patients with parotid gland cancer, 56 patients treated with surgery alone were compared with 91 patients

treated with combined therapy.[72] In multivariate analysis, post-operative RT improved local control, but not OS.

In a study of patients with SGC, 10-year locoregional control was significantly improved in patients who received surgery plus RT versus RT alone for stage I-III and stage IV disease (89% versus 71% and 60% versus 20%, respectively).[73] Although the RT group included a higher number of patients with minor SGC, T4 tumours and AdCC, the significant difference remained in multivariate analysis.

SECTION 5. PARTICLE THERAPY

Photon treatment

In some small retrospective studies of patients with predominantly T4 disease treated with primary curative photon treatment, 5-year locoregional control rates of up to 50% have been reported; however, after 10 years, these rates may drop to 30%.[64,73,74] A radiation dose of >66 Gy (2 Gy fractions) is advised (preferably 70 Gy).[64,74]

Particle treatment

Particle therapy regimens vary widely, ranging from normofractionated protons[75,76] to mixed beam[77] and hypofractionated carbon ions (C12).[78,79] Fractionation regimens have never been prospectively compared, hence the choice of fractionation remains at the discretion of the treating institution. Particle RT with biologically effective doses >70 Gy yields promising local control rates, especially in advanced tumours, with mostly mild acute and late toxicity. Depending on the proportion of very advanced cases (T4), reported local control rates are ~60%-70% at 5 years.[78,80]

Experience with C12-only regimens indicates a consistently mild toxicity profile. A pooled analysis of 289 patients with AdCC across four Japanese particle centres reported a local control rate of 88% at 2 years (median follow-up 30 months).[79] Longer-term follow-up of 69 patients with AdCC in China reported a 5-year local control rate of 73%.[78] Subgroup analysis of patients with T4 tumours in the C12 cohorts showed no significant difference in either local control or OS between subtotal resection and definitive RT without prior surgery, suggesting that subtotal

and/or potentially mutilating surgery can be avoided on the condition that high-dose RT can be applied.

In one study, a combination of photons and passive scattered protons up to 75.9 Gy following partial or complete resection in 50% of cases was evaluated in 23 patients.[75] Late toxicity was very high (grade 3 late neurological toxicity in 10 out of 23 patients), potentially due to passive scanning technique. In another study, 35 patients were treated with scanned protons for AdCC; 26 post-operatively (70 Gy in 35 fractions) and 9 as primary therapy (75.6 Gy in 35 fractions).[76] The 2-year local control and progression-free survival rates were 92% and 74%, respectively. Nevertheless, the reported median follow-up of 2.5 years was short and should ideally exceed 5 years, which would also allow for the detection of late toxicity. Similar to the C12 cohorts, resection did not impact OS in high-dose proton therapy, albeit at lower overall case numbers.[76]

Studies comparing photon treatment with particle therapy

One randomised study compared photon treatment with neutron therapy.[81] The study had to be stopped because of a difference in 2-year locoregional control after inclusion of only 32 patients. The 10-year locoregional control probability was 17% after photon therapy and 56% after neutron therapy; however, survival was equal and late morbidity was higher with neutron therapy.

In a retrospective (not case controlled) study of 75 patients with unresectable or recurrent AdCC, photon treatment was compared with neutrons and demonstrated 5-year local control rates of 32% and 75%, respectively.[82] Survival rates were equal, and grade 3/4 late toxicity was higher for neutrons (4% versus 19%, respectively).

In one prospective study, intensity-modulated RT (IMRT) photon therapy (*n* = 37) was compared with IMRT with a C12 boost (*n* = 58) for unresectable or partially resected AdCC. The choice of treatment was based on the availability of C12. Although the study was not randomised, 5-year locoregional control and OS rates were higher with a C12 boost than without (60% versus 40% and 77% versus 59%, respectively).[77] Acute and late toxicity were comparable.

There are no prospective studies directly comparing photons with protons.

SECTION 6. FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

All decisions around follow-up monitoring and its frequency should be made between the patient and the treating clinical team. Decisions should take into consideration tumour histology, tumour aggressiveness and the wishes of the patient.

In patients with AdCC, frequent and prolonged follow-up is recommended since relapse and distant metastases might occur several years after diagnosis. Locoregional imaging (preferably head and neck MRI with contrast imaging) is suggested every 3-4 months for the first 2 years, every 6 months from the third to the fifth year and then on an annual basis thereafter. A chest CT at least annually should also be considered.[83]

For patients with other types of SGC with no evidence of disease activity, regular scans 1-2 times per year are suggested for the first 1-2 years, before moving to less frequent scans. Patients with residual/recurrent or metastatic disease should be scanned more regularly (i.e. 2-4 times per year), but when a low growth rate is present, the imaging frequency can be decreased. MRI scans are the best imaging tool for locoregional recurrent disease. There is no consensus on the value of FDG–PET–CT in follow-up, surveillance and assessing local recurrence compared with conventional imaging.[84] Chest CT can be carried out at each imaging timepoint and annually, and a CT of the abdomen is advised annually. In some SGCs, metastatic disease can occur after >5-10 years; therefore, in addition to regular imaging, patients should be informed about the risk of recurrent or metastatic disease and the symptoms to look out for.

Reconstruction of the facial nerve is best done at the moment of the ablative surgery.[58] Prosthetic rehabilitation, such as implant-retained epitheses, prostheses and obturators, with or without soft-tissue and/or bone reconstruction, should be incorporated into the primary surgical plan.[58]

Quality of life is underexamined in patients with SGC, who often experience relationship, social, work and psychological problems. Quality of life is of paramount importance, and open and honest communication with clinicians from the start of treatment allows patients to make informed, subjective decisions. Patient-clinician team trust is key.

Late toxicities and long-term effects of treatment include shoulder pain, telegesis, xerostomia, neck immobility, problems with speech and eating, progressive deafness and jaw stiffness. A good multidisciplinary recovery programme is needed for every patient with SGC.

Clinicians should direct patients to relevant patient organisations so they can access support and information. Studies to better understand SGC are urgently needed. Collaboration between patients and clinicians assists research by ensuring studies are appropriate for patients and by increasing awareness of the studies and therefore patient participation.

Supplementary Table S1. WHO classification of malignant tumours of the salivary glands[40] [a]

	ICD-O code[b]
Malignant tumours	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Acinic cell carcinoma	8550/3
Polymorphous adenocarcinoma	8525/3
Clear cell carcinoma	8310/3
Basal cell adenocarcinoma	8147/3
Intraductal carcinoma	8500/2
Adenocarcinoma NOS	8140/3
Salivary duct carcinoma	8500/3
Myoepithelial carcinoma	8982/3
Epithelial-myoepithelial carcinoma	8562/3
Carcinoma ex pleomorphic adenoma	8941/3
Secretory carcinoma	8502/3
Sebaceous adenocarcinoma	8410/3
Carcinosarcoma	8980/3
Poorly differentiated carcinoma	
Undifferentiated carcinoma	8020/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Lymphoepithelial carcinoma	8082/3

	ICD-O code[b]
Squamous cell carcinoma	8070/3
Oncocytic cell carcinoma	8290/3
Uncertain malignant potential	
Sialoblastoma	8974/1

ICD-O, International Classification of Diseases for Oncology; NOS, not otherwise specified.

[a] Reproduced from El Naggar et al.[40] with permission.

[b] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline or uncertain behaviour; /2 for carcinoma *in situ* and grade III intraepithelial neoplasia; and /3 for malignant tumours.

Supplementary Table S2. The Milan system for reporting salivary gland cytopathology: Implied ROM and recommended clinical management[85] [a]

Diagnostic category	ROM (%)[b]	Management
I. Non-diagnostic	25	Clinical and radiological correlation/repeat FNA cytology
II. Non-neoplastic	10	Clinical follow-up and radiological correlation
III. Atypia of undetermined significance	20	Repeat FNA cytology or surgery
IV. Neoplasm		
A. Neoplasm: benign	<5	Surgery or clinical follow-up[c]
B. Neoplasm: SUMP	35	Surgery[d]
V. Suspicious for malignancy	60	Surgery[d]
VI. Malignant	90	Surgery[d,e]

FNA, fine-needle aspiration; ROM, risk of malignancy; SUMP, salivary gland neoplasm of uncertain malignant potential.

[a] Reproduced from Faquin and Rossi[85] with permission.

[b] The following ranges for risk of malignancy for diagnostic categories have been cited in the literature: non-diagnostic 0%-67%; non-neoplastic 0%-20%; atypia of undetermined significance 10%-35%; neoplasm: benign 0%-13%; SUMP 0%-100%; suspicious for malignancy 0%-100%; and malignant 57%-100%.[86-91]

[c] A subset of patients may be followed clinically.

[d] Intra-operative consultation may be helpful to determine the extent of surgery.

[e] Extent of surgery depends upon type and grade of malignant tumour.

Supplementary Table S3. Biomarkers and molecular targets for precision medicines and corresponding ESCAT scores

Biomarker or genomic alteration	Method of detection	Drug match	ESCAT score[a,b]
Androgen receptor in salivary duct carcinoma or adenocarcinoma	IHC	Androgen receptor blocker + gonadotropin-releasing hormone agonist[92]	II-B[92]
HER2 in salivary duct carcinoma or adenocarcinoma	IHC for HER2 protein expression (3+) or FISH for *HER2* gene amplification	Anti-HER2 antibodies (e.g. trastuzumab)[93]	II-B[93]
NTRK fusion in secretory carcinoma	NGS or WGS	TRK inhibitors (e.g. entrectinib, larotrectinib)[94-96]	I-C[94-96]

ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry, NGS, next generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase; WGS, whole genome sequencing.

[a] ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.

[b] II-B, alteration–drug match is associated with antitumour activity with evidence from prospective clinical trials showing that the alteration–drug match in a specific tumour type results in increased responsiveness when treated with a matched drug, however, no data are currently available on survival end points; I-C, alteration–drug match is associated with improved outcome with

evidence from clinical trials across tumour types or basket clinical trials showing clinical benefit associated with the alteration–drug match, with similar benefit observed across tumour types.[97]

Supplementary Table S4. Key molecular alterations in selected SGCs

Tumour type	Chromosomal alteration	Gene fusion/ rearrangement	Prevalence (%)
Secretory carcinoma[43,45]	*t(12;15)(p13;q25)* *t(12;10)*	*ETV6-NTRK3* *ETV6-RET*	95 4.5
Mucoepidermoid carcinoma[15]	*t(11;19)(q21;p13)* *t(11;15)(q21;q26)*	*CRTC1-MAML2* *CRTC3-MAML2*	40-80 5
Acinic cell carcinoma[22]	*t(4;9)(q13;q31)*	*NR4A3/NOR-1*	Majority
Adenoid cystic carcinoma[15]	*t(6;9)(q22-23;p23-24)* *t(8;9)*	*MYB-NFIB* *MYBL1-NFIB*	25-80 10-20
Polymorphous adenocarcinoma, classical variant[28]	*14q12*	Hotspot activating *PRKD1* somatic point mutation (E710D)	20
Polymorphous adenocarcinoma, cribriform variant[29]	*t(1;14)(p36.11;q12)* *t(X;14)(p11.4;q12)*	*ARID1A-PRKD1* *DDX3X-PRKD1* *PRKD2* and *PRKD3* rearrangements	24 13 16
Salivary duct carcinoma[34-36]	*17q21.1* *3q26.32*	*HER2* amplification *PIK3CA, NRAS, HRAS,* etc mutation	30 20
Myoepithelial carcinoma[98]		*CHCHD27-PLAG1* *PLAG1-CTNNB1* *PLAG1-LIFR* Other *PLAG1* rearrangements	

Epithelial-myoepithelial carcinoma[99,100]		*HRAS* mutation, codon 61 *PIK3CA* and/or *AKT1*	82.7 20.7 6.5
Intraductal carcinoma[32,33]	*inv(10)(q11.21q11.22)*	*NCOA4-RET* *TRIM27-RET*	
Hyalinising clear cell carcinoma[101,102]	*t(12;22)(q13;q12)*	*EWSR1-ATF1* *EWSR1-CREM*	80-90 5
Pleomorphic adenoma[36]	*t(3;8)(p21;q12)* *t(5; 8)(p11;q12)*	*PLAG1-CTNNB1* *PLAG1-LIFR* Other *PLAG1* rearrangements *HMGA2* rearrangements	

SGC, salivary gland cancer.

Supplementary Table S5. Pathological TNM staging of major SGC according to the UICC 8th Edition[103] [a]

Primary tumour (T)		Regional lymph nodes (N)		Distant metastasis (M)	
pTX	Primary tumour cannot be assessed	pNX	Regional lymph nodes cannot be assessed	pM0	No distant metastasis
pT0	No evidence of primary tumour	pN0	No regional lymph node metastasis	pM1	Distant metastasis
pT1	Tumour ≤2 cm in greatest dimension without extraparenchymal extension[b]	pN1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension without extranodal extension		
pT2	Tumour >2 cm but ≤4 cm in greatest dimension without extraparenchymal extension[b]	pN2a	Metastasis in a single ipsilateral lymph node, <3 cm in greatest dimension with extranodal extension, or >3 cm but ≤6 cm in greatest dimension without extranodal extension		
pT3	Tumour >4 cm and/or tumour with extraparenchymal extension[b]	pN2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension, without extranodal extension		
pT4a	Tumour invades skin, mandible, ear canal and/or facial nerve	pN2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in		

			greatest dimension, without extranodal extension		
pT4b	Tumour invades base of skull, and/or pterygoid plates and/or encases carotid artery	pN3a	Metastasis in a lymph node, >6 cm in greatest dimension without extranodal extension		
		pN3b	Metastasis in a lymph node, >3 cm in greatest dimension with extranodal extension, or multiple ipsilateral, or any contralateral, or bilateral node(s) with extranodal extension		

TNM, tumour–node–metastasis; UICC, Union for International Cancer Control; SGC, salivary gland cancer.

[a] Reproduced from Brierley et al.[103] with permission.

[b] Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues or nerve, except those listed under T4a and T4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

Supplementary Table S6. Studies evaluating targeted therapy in different histological subtypes of SGC (angiogenesis inhibitors are excluded)[104 a]

Subtype	Study type	Target	Drug(s)	N	Response	Prior target identification[b]
Mucoepidermoid carcinoma	Case reports[105-109]	EGFR	Cetuximab, gefitinib, erlotinib[c]	5 x 1	PR 40%, CR 40%, PR/PD 20%	Variable
	Phase II[110]	EGFR	Cetuximab	2	n.a.[d]	No
	Phase II[111]	EGFR	Gefitinib	2	n.a.[d]	No
	Phase II[112]	EGFR/ ERBB2	Lapatinib	2	n.a.[d]	Yes
Adenoid cystic carcinoma[e]	Phase II[113 f]	c-KIT	Imatinib	71 (6 trials)	RR 2.8%, SD 48%	Variable
	Phase II[114]	c-KIT	Dasatinib	40	PR 2.5%, SD 50%	Yes
	Phase II[110 g]	EGFR	Cetuximab	23	SD 87%	No
	Phase II[111 g]	EGFR	Gefitinib	18	PR/CR 0%	No
	Phase II[112]	EGFR/ ERBB2	Lapatinib	21	SD 79%	Yes

	Phase I[115] [g]	NOTCH1	Brontictuzumab	12	PR 17%, SD 25%	Yes
	Phase I expansion[116] [g]	NOTCH1	Crenigacestat	22	Unconfirmed PR 5%, SD 68%	No
Salivary duct carcinoma[h]	Phase II[92] [i]	Androgen receptor	Leuprorelin acetate + bicalutamide	36	CR 11.1%, PR 30.6%, SD 44.4%	Yes
	Phase II[93]	HER2	Trastuzumab + docetaxel	57	CR 14%, PR 56%, SD 25%, PD 5%	Yes
	Phase II[117]	HER2	Trastuzumab-emtansine	10[j]	OR 90%	Yes
Secretory carcinoma	Phase II[94]	TRK	Larotrectinib	12	n.a.[d]	Yes
	Case reports[95,96]	TRK	Entrectinib Repotrectinib	2x1	PR	Yes
All SGC	Phase II[118]	HRAS	Tipifarnib	13	PR 8%, SD 58%	Yes

ChT, chemotherapy; CR, complete response; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; n.a., not available; NOS, not otherwise specified; OR, overall response; PD, progressive disease; PR, partial response; RR, response rate; RT, radiotherapy; SD, stable disease; SGC, salivary gland cancer; TRK, tropomyosin receptor kinase.

[a] Reproduced from Lassche et al.[104] with permission from Elsevier.

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

[c] Cetuximab was combined with either ChT or RT.

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

[e] Not all studies/case reports are included in this table. See also the review by Alfieri et al.[119]

[f] One trial combined imatinib with cisplatin.

[g] Evidence of disease progression not required.

[h] Not all studies/case reports are included in this table. See also the review by Schmitt et al.[120]

[i] Only 34 of 36 included patients had salivary duct carcinoma; two had adenocarcinoma NOS.

[j] Ten patients with HER2-positive SGC; presumably most patients had salivary duct carcinoma.

Supplementary Table S7. Studies[a] evaluating angiogenesis inhibitors in SGC, with a focus on adenoid cystic carcinoma

Drug	Subtype	Study type	N	Response rate (%)	Median PFS (months)	Median OS (months)
Axitinib[121]	Adenoid cystic carcinoma	Phase II	33	9.1	5.7	n.a.
Axitinib[122]	Adenoid cystic carcinoma	Phase II	26	8	5.5	26.2
Axitinib[123]	Adenoid cystic carcinoma	Randomised phase II	60 [30 started axitinib (A); 30 observation arm (O)]	A: 0%; O: 0%	A: 10.8; O: 2.8	A: not reached; O: 27.2
Lenvatinib[124]	Adenoid cystic carcinoma	Phase II	32	15.6	17.5	n.a.
Lenvatinib[125]	Adenoid cystic carcinoma	Phase II	28	11.5	9.1	27
Sorafenib[126]	Adenoid cystic carcinoma	Phase II	23	11	11.3	19.6
Sorafenib[127]	All	Phase II	37 (19 adenoid cystic carcinoma)	16	5.9	23.5
Sunitinib[128]	Adenoid cystic carcinoma	Phase II	14	0	7.2	18.7

n.a., not available; OS, overall survival; PFS, progression-free survival; SGC, salivary gland cancer.

[a] Only studies that have been published in a peer-reviewed publication are included.

Supplementary Table S8. ESMO-MCBS table for new therapies/indications in SGC

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[a]
Secretory carcinoma							
Entrectinib	Adult and paediatric patients 12 years of age and older with solid tumours expressing an *NTRK* gene fusion, who have disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have not received a prior NTRK inhibitor, and	STARTRK-1; STARTRK-2; ALKA-372-001[129] Phase I/II NCT02097810 NCT02568267 EudraCT 2012-000148-88	Single arm	ORR: 57% Median DoR: 10.4 months Median PFS: 11.2 months			3 (Form 3)

	who have no satisfactory treatment options						
Larotrectinib	Adult and paediatric patients with solid tumours that display an *NTRK* gene fusion, who have disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options	Studies of larotrectinib in patients with *NTRK* fusion-positive tumours (including SCOUT and NAVIGATE)[94,130] Phase I/II NCT02122913 NCT02637687 NCT02576431	Single arm	ORR: 79% Median DoR: 35.2 months Median PFS: 28.3 months			3 (Form 3)

CI, confidence interval; DoR, duration of response; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; HR, hazard ratio; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; PFS, progression-free survival; QoL, quality of life; SGC, salivary gland cancer.

[a] ESMO-MCBS v1.1[131] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

Supplementary Table S9. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a] Reprinted by permission of Oxford University Press on behalf of the Infectious Diseases Society of America.[132,133]

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