SALIVARY GLAND CARCINOMA IN CHILDREN AND ADOLESCENTS
STANDARD CLINICAL PRACTICE RECOMMENDATIONS

Publication reference:
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TITLE: SALIVARY GLAND CARCINOMA IN CHILDREN AND ADOLESCENTS

Document version: 6 (June 2021)

This document has been developed by the Partner Project:
PARTN-ER aims to create a European Registry dedicated to children and adolescents with very rare tumors (VRT) linking existing national registries and to provide a registry for those countries not already having a registry for VRT in place. The European Registry will be an essential part of the activity of the VRT subnetwork part of the ERN PaedCan. The possibility to link the registry with a virtual consultation system and the elaboration of diagnostic/treatment recommendations will create a platform that can be easily accessed by EU Health care providers. The increasing expertise in VRT based on the data collected in the European registry will increase the capacity to provide international consultation and define standard of treatment recommendations. This will ultimately result in improved patients’ care and reduce currently existing inequalities in cancer outcome across EU member states.

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1. BACKGROUND AND RATIONALE

1.1 Summary

Pediatric very rare tumors (VRT) constitute an extremely heterogeneous group of neoplasms. Some of them are typical of pediatric age, while other more commonly arise during adulthood and only rarely develop in children. Using the definition any solid malignancy or borderline tumor characterized by an annual incidence < 2/million children <18 years old the European Cooperative Study group for Pediatric Rare Tumors (EXPeRT) has initially identified a number of pediatric VRT1. Due to the low number of patients, it is very difficult – or even impossible - to conduct clinical trials on them, and this makes it hard to arrive to evidence-based treatment guidelines. Consequently, the treatment of patient with VRT is often individualized.

Background:

Salivary gland carcinomas (SGC) are rare pediatric tumors, with an annual incidence of 0.8 cases per 1 million children and adolescent2, accounting for less than 10% of pediatric head and neck cancers3. SGC in children are often diagnosed during adolescence with a median age at diagnosis around 15 years (between 10 to 16 years depending on series)2. Most children present with a palpable poorly symptomatic mass in the salivary gland region, slowly growing, after an average time to presentation of about 12-24 months3. Distant metastases, mainly to the lungs, but also described in liver or bones, are extremely rare at presentation4. Given the rarity of these tumors in the pediatric population, no standardized recommendations for the diagnosis and therapeutic management of pediatric SGC are available, and pediatric oncologists and surgeons generally follow adult guidelines, mainly consisting in complete surgical resection with adequate margins3,5. If the role of adjuvant radiotherapy (RT) is not well established yet, it can be considered for high-risk SGC given favorable results in adults but taking into consideration the potential long-term morbidities in young children. The place for chemotherapy in the management of SGC is highly controversial even in adults and is limited to the setting of unresectable or recurrent tumors. The prognosis in primary SGC in children and adolescents/young adults (AYA) is favorable, approaching 95% of overall survival at 5 years2,6,7. Poor outcomes from salvage therapy strongly support the need of adequate initial treatment with aggressive approach especially in the setting of high-risk tumors.

Objective:

To establish internationally harmonized consensus recommendations for the diagnosis and treatment of children and adolescents with SGC (WP6 – “Standard of care recommendations for children with VRT”). This constitutes one of the deliverables of PARTN-ER project (ERN-PAEDCAn Partner Paediatric Rare Tumours Network – European Registry), an EU funded project.
1.2 Background

Salivary gland neoplasms represent a rare and heterogeneous group of tumors whose incidence – all histologic types and grades combined – varies from 0.4 to 13/100,000 person in the general population\(^8\). Malignant salivary gland tumors are quite rare even in adults, since close to 80% of cases are benign, and represent less than 1% of all malignancies\(^8\). In the pediatric population, salivary gland cancers are even rarer with an annual incidence not exceeding 0.8/1,000,000 in 0 to 19 year olds for malignant epithelial salivary gland tumors (i.e., SGC, which is the most common histologic type)\(^2\), accounting for less than 10% of all pediatric head and neck cancers\(^3\). The distribution between low- and high-grades tumors differs from adults with a 50-70% probability of malignancy among epithelial salivary gland tumors\(^9\) – \(^11\).

Pediatric SGC are often diagnosed during the second decade of life with a median age at diagnosis around 15 years (between 11 to 16 years depending on series)\(^2,7,9,12,13\). They are extremely rare before the age of 10, but are more likely to be high-grade and associated with a poorer prognosis\(^10\). Demographics data report a slight female predominance considering all SGC in children and adolescents (58% of female patients versus 43% in adults according to Sultan et al.), and this finding is even more marked for acinic cell carcinoma (ACC) with a sex-ratio F/M of 2.3 versus 1.07 for mucoepidermoid carcinoma (MEC) as reported by Morse et al.\(^2,14\).

The main common site of occurrence, all benign and malignant tumors combined, is the parotid gland (involved in 80% of cases), followed by the minor salivary glands (MSG) of the oral cavity and the submandibular glands, and rarely the sublingual glands\(^2\) – \(^4,7\).

The 4\(^{th}\) edition of the World Health Organization (WHO) classification describes over 30 histologic subtypes of salivary gland tumors, including over 20 subtypes of malignant epithelial tumors (carcinomas) in adults (Table 2)\(^15\) – \(^17\). Unlike adults, the histologic spectrum of SGC is smaller in children and adolescents and shows disparities in terms of biological behavior\(^2\). MEC represents one-half of all pediatric SGC, followed by ACC (25-35%). Histologically, both of these histotypes represent low-grade tumors. More rarely, adenocarcinoma and adenoid cystic carcinoma (AdCC) may be found, which are both associated with a more aggressive course. Other subtypes such as myoepithelial carcinoma, undifferentiated carcinoma, or carcinoma ex pleomorphic adenoma have also rarely been described\(^3\).

Familial clustering of SGC have been described and suggest that the etiology of SGC may be related to multiple susceptibility genes and/or environmental factors\(^18\) – \(^22\). Nevertheless, no genetic predisposing syndrome has been reported to date, even if some intrafamilial associations have been outlined, such as parental colorectal cancer\(^23\), Hodgkin lymphoma or brain tumor in siblings\(^24\). Contrary to most other head and neck cancers in adults, SGC are not linked to tobacco or alcohol consumption\(^6,25\). Various environmental exposures have been investigated, such as asbestos, nickel compounds, silica dust, rubber manufacturing and woodworking materials\(^26\). In a recent French epidemiological study, significantly increased risk for SGC was observed for some occupations (waiter, charworker, electrical and electronic equipment assembler, plumber, electric arc welder, sheet-metal worker, building painter, and material handling equipment operator)\(^25\). Yet, to date, only radiation exposure has clearly been
shown to increase the risk of developing SGC. Personal history of cancer and its treatment (RT and/or chemotherapy) have also been reported as potential risk factors. Finally, some studies have suggested the role of some viral infections (Epstein-Barr Virus, Human Papilloma Virus, Cytomegalovirus) in the development of SGC.

Most children with SGC present with a palpable asymptomatic mass in the salivary gland, slowly growing. Less commonly, other symptoms may include recent pain with no infectious or inflammatory symptoms, regional lymph node involvement, and, even more rarely, facial nerve palsy, nasal obstruction, vision impairment or trismus. Skin tethering and/or ulceration are more likely present with malignant tumors. Distant metastases are rare at presentation and are mainly located to the lungs, then liver and bones.

The overall prognosis in primary SGC in children and AYA is good, with a 10-year overall survival (OS) of more than 90%. According to Sultan’s review, the 10-year overall survival for children/AYA reached 94%, compared to 46% for adults. However, locoregional recurrence and distant metastases are not rare, and survival of patients experiencing recurrence varies considerably depending on histologic type and tumor grade. The poor outcomes observed after salvage therapy strongly support the need for adequate initial treatment with an aggressive approach, especially in the setting of high-risk tumors. However, overtreatment of low-risk tumors must be avoided due to the potential risk of late side effects. Nevertheless, the prognostic stratification of pediatric patients with SGC still constitutes a major challenge due to the rarity of these tumors, the difficulties of accurate histologic grading and the overlap between and within histologic subtypes. For example, several grading systems have been proposed for MEC, such as the Armed Forces Institute of Pathology (AFIP), the Brandwein system, and other systems, with significant discrepancies between systems in terms of grading criteria, which may lead to discordant or suboptimal treatment decisions due to potential under- or over-grading.

Like other pediatric very rare tumors, SGCs in children and adolescents often present diagnostic and therapeutic challenges for pathologists, surgeons and pediatric oncologists. Since specific pediatric standardized guidelines are lacking, management decisions are often made at a case-by-case level, based on guidelines validated for adult patients. However, several disparities have been reported between children and adults with regard to the histologic spectrum and clinical behavior of SGCs. The therapeutic management of children and adolescents with cancer must also pay special attention to potential long-term sequelae. Based on adult guidelines, complete surgical resection with adequate margins and attempt to preserve nerve structures, constitutes the mainstay of treatment. However, indications for adjuvant therapies in children, including concomitant or second-look cervical lymph node dissection and adjuvant radiotherapy (RT), have yet to be defined, taking into account pediatric specificities and potential long-term morbidities. In addition, the abovementioned difficulties in stratifying patients prevent identification of those patients likely to benefit from adjuvant therapy. Neck dissection is not systematically necessary considering the rarity of lymph node metastasis and is only performed in case of clinical and/or radiological lymph node enlargement, or in a second-look strategy in the case of high-grade or advanced tumors as nodal metastases occur in up to 50% of cases in these situations. Based on favorable results in adults, adjuvant RT may be considered for highly selected cases.
cases such as high-grade histotypes (especially AdCC and other high-grade tumors with perineural invasion, extraglandular extension and vascular invasion) and advanced tumors with or without lymph node involvement, but taking into account pediatric specificities and potential long-term morbidities in children (such as growth defect and risk of secondary malignancies)\textsuperscript{2,3,5,6,42,43}. The role of chemotherapy is even more controversial, even in adults, and is now usually limited to palliative therapy for recurrent and/or metastatic disease not amenable to further surgery or radiation\textsuperscript{3,45}. Clinical trials investigating the efficacy of systemic therapy in SGC are very scarce in adults, and data about chemotherapy even rarer in children\textsuperscript{14,36}. Based on a few number of small studies and case reports in adults, chemotherapy agents considered to be potentially effective include cisplatin, 5-fluorouracil, vinorelbine, paclitaxel, cyclophosphamide or doxorubicin\textsuperscript{47–55}. Finally, recent research into the underlying molecular disorders in malignant SGC has suggested several potential therapeutic targets, but exclusively based on preliminary data. Targeted therapies should therefore only be delivered in the context of a prospective trial.

We present here the internationally harmonized consensus recommendations for the diagnosis and treatment of children and adolescents with SGCs established by the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) in the framework of the EU-funded PARTN-ER project (Paediatric Rare Tumours Network - European Registry).
2. METHODOLOGY

According to the Consensus Conference Standard Operating Procedure methodology, the levels of evidence can be classified from Level I to V and the grades of recommendation A to E (Table 1)\textsuperscript{56}.

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity</td>
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<tr>
<td>II</td>
<td>Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
</tr>
<tr>
<td>III</td>
<td>Prospective cohort studies</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective cohort studies or case–control studies</td>
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<tr>
<td>V</td>
<td>Studies without control group, case reports, expert opinions</td>
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<th>Grades of recommendation</th>
<th>Description</th>
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<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
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<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
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<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
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Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Disease Society of America-United States Public Health Service Grading System)

EXPeRT/PARTN-ER members recognized that due to the rarity of this tumor, no evidence of Level I to II exists. Therefore, recommendations for VRTs are developed based on the evidence collected from some published prospective studies (Level III), but more frequently retrospective series (Level IV), case reports (Level V) and personal expertise (Level V). In addition, the “strength” of recommendations will be categorized by additional grading (Grade A to E).

To identify tumors that need shared recommendations, PARTN-ER members designed the following procedure:

- Identification of the tumor of interest on the base of its relevance, and previous PARTN-ER experience, (i.e., data analysis and publication). Tumors should be classified as VRT (i.e. < 2/100000/inhabitants/y),
not already analyzed in previous Expo-r-Net project (pleuropneumoblastoma, pancreatoblastoma, thymic tumors, rare sarcomas), not included in specific international protocols and frequent enough to be of interest\(^1\).

- Designation of two main coordinators for each VRT on the basis of their experience (data analysis, publications, personal experience).

Coordinates have to:

- Analyze the medical literature and select the relevant papers.
- Propose a series of recommendations in a form of a first draft of recommendations.
- Identify the main diagnostic and therapeutic problems for the designated VRT. The first drafts will be shared and discussed, along with the relevant publications, into a selected expert group of PARTN-ER members and annotated.
- A mature version of recommendations will be produced, taking into account proposals from the group of selected PARTN-ER members.
- The annotated draft will be then proposed to external experts identified by the coordinators based on a recognized experience on the tumor (pediatricians, medical oncologist, radiation oncologist, surgeon...).
- The final version will be validated by the whole PARTN-ER group. In case of remaining disagreements, a vote will be done, during a physical consensus meeting, to agree on in a final consensus.
- Validated version will be submitted to publication in an open-source peer review journal.

The final document including recommendations will be available on PARTN-ER website.

\textbf{NB:} These guidelines may change over time according to new data available. Local clinicians remain responsible for the care of his patient. The EXPeRT/PARTN-ER members are not responsible for results or complications related to their use. If necessary, medical discussions are possible with EXPeRT members of these groups via the expert website: \url{https://vrt.cineca.it}
3.1 Diagnostic Criteria

As the majority of SGC usually present as a slowly growing asymptomatic mass, diagnosis is often delayed by up to 12-24 months. Nevertheless, metastases at diagnosis (mainly to the lungs, followed by the liver and bone) remain rare. Contrary to adults, salivary gland tumors are more often malignant in children (10-25% versus 50%) and a possible or likely malignant diagnosis should therefore be considered in the presence of any non-inflammatory salivary gland mass (parotid gland in 3/4 of cases, then minor salivary gland and submandibular gland, rarely sublingual gland), in order to avoid diagnostic and therapeutic mismanagement. Less frequently, recent pain or swelling without infectious or inflammatory symptoms, regional lymph node involvement, and rarely facial nerve palsy can be observed. Skin tethering and/or ulceration are more likely associated with malignant tumors. Symptoms of more advanced minor salivary gland tumors are due to their localization and may include nasal obstruction, congestion, vision impairment or trismus.

Appropriate clinical and imaging studies at diagnosis are useful to assess disease stage, extent of locoregional and metastatic spread, and eliminate some differential diagnoses. Histology is mandatory for the diagnosis of SGC, since cytology, although useful in the diagnostic management and planning of the surgical procedure, is frequently insufficient for definitive histopathological diagnosis.

Discussion by a Multidisciplinary Team (MDT) is highly recommended early in the assessment process, and before any invasive procedure (including biopsy).

3.1.1 Imaging

3.1.1.1 Primary tumor and its loco-regional tumor extension:

- **Full clinical evaluation** including cervical lymph node and neurological examination [Level V; Grade A] is necessary in addition to imaging studies.

- **Cervical ultrasound** is a useful, easily accessible, well-tolerated, non-invasive and non-irradiating imaging method, which can provide valuable information about tumor characteristics (solid/cystic component, size, location and local extent). Doppler studies can also eliminate differential diagnoses such as hemangioma. Ultrasound can also be used to guide preoperative fine-needle aspiration (FNA) or core-needle biopsy (CNB) [Level V; Grade A].

- **Head and neck** magnetic resonance imaging (MRI), including functional analyses, is necessary in the presence of a suspected neoplasm to confirm the precise tumor site and its locoregional extent, especially to deep tissues or nerves. MRI also provides valuable information about lymph node and/or bone involvement, and may help to determine the probable nature of the lesion on diffusion-weighted and dynamic contrast-enhanced sequences [Level V; Grade A]. When MRI is not feasible, computed tomography (CT) can be performed, but with lower accuracy.
3.1.1.2 Distant metastasis

- **Chest CT scan** is recommended for malignant tumors, especially high-grade tumors, since lungs represent the main site of dissemination\(^5\) [Level V; Grade B]. Chest X-ray may be sufficient for low-grade tumors [Level V; Grade C].

- The place of **fluorodeoxyglucose (FDG) positron emission topography (PET)/CT** in pediatric SGC remains unclear. Based on adult studies, FDG PET/CT is not sufficiently accurate to discriminate benign from malignant lesions because of the overlap of FDG avidity in both conditions\(^61,62\). However, it appears to be superior to standard imaging (head and neck CT or MRI, and chest X-ray/CT) for the detection of lymph node and distant metastases and could therefore be helpful for staging assessment\(^61,63-67\) [Level III; Grade D]. Several studies support the value of metabolic-derived parameters of FDG PET/CT (such as metabolic tumor volume, and primary tumor and/or positive nodes SUVmax) as prognostic parameters for event-free survival (EFS) and OS in adults\(^64,68-70\). False negative cases were yet reported in patients with AdCC. Preliminary data indicate the added diagnostic value of prostate-specific membrane antigen (PSMA) PET/CT in these patients\(^71\). However, there are no studies to support the systematic use of FDG or PSMA PET/CT in pediatric SGC, and these examinations should therefore be limited to clinical trials [Level V; Grade D].

3.1.2 Histopathology and molecular pathology

When SGC is suspected – based on clinical and radiological findings – **histology** must be obtained [Level V; Grade A]. **Cytology**, although useful in the diagnostic management and planning of the surgical procedure, is frequently insufficient for definitive histopathological diagnosis. However, cytology may be helpful to distinguish SGC from other non-neoplastic lesions and from benign or malignant non-epithelial tumors arising in the region of the salivary glands during childhood, such as lymphomas and sarcomas. In adults, several studies support the role of FNA cytology in the diagnostic work-up of salivary gland lesions but with disparities in between studies [Level III; Grade A-B for adults]. If accuracy to distinguish neoplastic from non-neoplastic lesions by means of a rapid and well-tolerated procedure is well established, the sensitivity of cytology to distinguish between malignant and benign neoplasms is more controversial (ranging from 60 to more than 90%)\(^72-78\). In a recent meta-analysis of 63 studies comprising more than 5000 FNA, Liu et al. reported an overall sensitivity and specificity of 78% and 87.7% respectively for parotid mass\(^76\). Similar results have been reported for submandibular FNA\(^72,79\). **Ultrasound-guided FNA** is preferred to palpation-guided FNA, in order to ensure a correct targeting of puncture and obtain a more representative sampling in the case of heterogeneous tumor, thus allowing a greater diagnostic accuracy\(^79-81\). Yet, if FNA presents numerous advantages (including ease and accessibility of the procedure, no need of general nor local anesthesia, good tolerance, and low economic cost), caution is mandatory to avoid the many potential pitfalls related to low-grade SGC on cytology, with misdiagnosis of malignant lesions in some cases. Thus, therapeutic management should be planned taking into account both clinical, radiological and FNA findings\(^82-85\). Data on the diagnostic
role of FNA in children are very scarce. Tolerance and compliance with the procedure can be difficult for young children\(^3\), and poor concordance has been reported between preoperative cytology and postoperative histology for neoplasms, as reported by Rebours et al. in 2017 (only 20% of concordance among 15 cases of FNA in pediatric patients, 6 of them echo-guided – misdiagnosis in 60%, and inconclusive cytology in 20% of cases)\(^36\). Nevertheless, FNA can provide useful initial information to eliminate differential diagnoses such as infection, other non-neoplastic lesions or non-epithelial tumors, especially in the presence of atypical clinical and radiological signs. Cytology can therefore be considered in the diagnostic work-up of pediatric salivary gland lesions, but should not by itself influence the surgical approach in the case of clinical or radiological suspicion of neoplasm\(^86\) [Level IV; Grade B].

Preoperative CNB may provide an adequate tissue sample with preserved histologic architecture, and may therefore increase the diagnostic accuracy compared to FNA\(^84,87–89\). The CNB procedure can be less well tolerated by young children, requiring general anesthesia, and complications including hematoma, facial nerve injury in case of parotid lesions and potential tumor spillage depending on anatomic site and needle size and type, although rarely reported (7 hematomas/1315 CNB in Kim’s meta-analysis, and only 1 case of cell seeding of a parotid gland/1803 CNB according to Shahs’ review in 1979), may limit its use\(^84\). Once again, only limited data are available concerning the role of salivary gland CNB in children. However, this procedure can be useful in unresectable tumors, before performing mutilating surgery or when the diagnosis remains doubtful after the first cytologic examination\(^3,36\) [Level IV; Grade B].

When justified by the high level of clinical and/or radiological suspicion, histologic diagnosis can be performed at the time of primary surgery\(^3,5,37\) [Level IV; Grade A]. Intraoperative frozen section histologic examination is helpful to ensure clear margins. Caution is nevertheless required in low-grade tumors, for which reliable intraoperative assessment of surgical margins may be difficult. As for example, discordances with definitive diagnosis have been noticed in one-half of cases, with major discordances (benign versus malignant) in 21% and minor discordances (differences in histology subtypes) in 16% of cases in Rebours review\(^36\).

Review of histology slides by an experienced head and neck pathologist with additional experience in pediatric tumors is required, even more because of the challenge caused by the great histomorphologic overlap between and within benign and malignant tumors in this location. In institutions with less experience in the classification of salivary gland neoplasms, external expert pathology consultation should be considered\(^90,91\) [Level IV; Grade A]. Given that the majority of low-grade SGC are defined by recurrent gene fusions, molecular testing may be helpful to confirm the diagnosis in morphologically ambiguous tumors and on limited or crushed biopsy material [Level IV; Grade B]. For example, detection of the MECT-MAML2 translocation using various molecular methods (Fluorescence In Situ Hybridization, Reverse Transcription Polymerase Chain Reaction, Next-Generation Sequencing, etc.) may confirm the diagnosis of MEC\(^92\). Similarly, testing for ETV6-NTRK6 fusion transcript in secretory carcinoma can be useful to confirm the diagnosis, particularly in unusual variants and tumors with high-grade transformation, at the same time providing a valuable treatment option for disseminated,
unresectable or recurrent aggressive tumors with NTRK inhibitors\textsuperscript{93,94} [Level III; Grade B]. More recently, ETV6-RET fusion has also been reported in secretory carcinoma\textsuperscript{95,96}.

The 4\textsuperscript{th} edition of the WHO classification describes over 20 histotypes of malignant epithelial salivary gland tumors (carcinomas) in adults (\textit{Table 2})\textsuperscript{15–17}. Unlike adults, the histologic spectrum of SGC is smaller in children and AYA and shows disparities in terms of biological behavior\textsuperscript{2}.

<table>
<thead>
<tr>
<th>Malignant tumors</th>
<th>ICD-O coding</th>
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<tbody>
<tr>
<td>Acinic cell carcinoma</td>
<td>8550/3</td>
</tr>
<tr>
<td>Secretory carcinoma</td>
<td>8502/3</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>8430/3</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>8200/3</td>
</tr>
<tr>
<td>Polymorphous adenocarcinoma</td>
<td>8525/3</td>
</tr>
<tr>
<td>Epithelial–myoepithelial carcinoma</td>
<td>8562/3</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>8310/3</td>
</tr>
<tr>
<td>Basal cell adenocarcinoma</td>
<td>8147/3</td>
</tr>
<tr>
<td>Sebaceous adenocarcinoma</td>
<td>8410/3</td>
</tr>
<tr>
<td>Intraductal carcinoma</td>
<td>8500/2</td>
</tr>
<tr>
<td>Cystadenocarcinoma</td>
<td>8440/3</td>
</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
<td>8140/3</td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td>8500/3</td>
</tr>
<tr>
<td>Myoepithelial carcinoma</td>
<td>8982/3</td>
</tr>
<tr>
<td>Carcinoma ex pleomorphic adenoma</td>
<td>8941/3</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>8980/3</td>
</tr>
<tr>
<td>Poorly differentiated carcinoma</td>
<td></td>
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<tr>
<td>Neuroendocrine and non-neuroendocrine undifferentiated carcinoma</td>
<td>8020/3</td>
</tr>
<tr>
<td>Large cell neuroendocrine carcinoma</td>
<td>8013/3</td>
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<tr>
<td>Small cell neuroendocrine carcinoma</td>
<td>8041/3</td>
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<tr>
<td>Lymphoepithelial carcinoma</td>
<td>8082/3</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
</tr>
<tr>
<td>Oncocytic carcinoma</td>
<td>8290/3</td>
</tr>
</tbody>
</table>

**Borderline tumor**

- Sialoblastoma                                         | 8974/1       |

**Benign tumors**

- Pleomorphic adenoma                                  | 8940/0       |
- Myoepithelioma                                        | 8982/0       |
- Basal cell adenoma                                    | 8147/0       |
- Warthin tumor                                          | 8561/0       |
- Oncocytoma                                            | 8290/0       |
- Lymphadenoma                                          | 8563/0       |
- Cystadenoma                                           | 8440/0       |
- Sialadenoma papilliferum                              | 8406/0       |
- Ductal papilloma                                      | 8503/0       |
- Sebaceous adenoma                                     | 8410/0       |
- Canalicular adenoma and other ductal adenomas         | 8149/0       |

**Other epithelial lesions**

- Sclerosing polycystic adenosis                        |              |
- Nodular oncocytic hyperplasia                         |              |
- Lymphoepithelial lesions                              |              |
- Intercalated duct hyperplasia                         |              |

**Soft tissue lesions**

- Hemangioma                                            | 9120/0       |
- Lipoma/sialolipoma                                    | 8850/0       |
- Nodular fasciitis                                     | 8828/0       |

**Hematolymphoid tumors**

- Extranodal marginal zone lymphoma of MALT             | 9699/3       |

\textit{Table 2. WHO Classification of Salivary Gland Tumors (2017)}

\textit{ICD-O: International Classification of Diseases for Oncology, third edition}
3.1.2.1 Mucoepidermoid carcinoma

**MEC** represents the most common primary salivary gland cancer in children and AYA (45-50%). The major salivary glands, especially the parotid gland, are the most common sites of occurrence. MEC is composed of mucous, intermediate, and epidermoid cells, in various proportions. It is usually low-grade in children. Several grading systems have been proposed to better stratify patients and guide the treatment management (see Table 3 for description of main grading systems). If all grading scales now include 3 levels of grade (low-, intermediate-, and high-grade), variability in definition criteria for each level instigates inconsistency between these different systems. Among the most popular grading systems, two are quantitative “point-based” systems, with great reproducibility reported by literature. Firstly described, the quantitative AFIP (Armed Forces Institute of Pathology) grading system proposed by Auclair et al. in 1992 includes five items: intracystic component < 20%, neural invasion, necrosis, mitoses ≥ 4/10 HPF, and anaplasia (Table 3). Taking into account that some patients with low-grade MEC according to the AFIP scale developed metastases or disease-related mortality, Brandwein et al. published a modified grading system with additional features of aggressive MEC (lymphovascular invasion, aggressive pattern of invasion, bony invasion). Thus, as confirmed by a recent comparative study, the Brandwein system tends to assign a higher percentage of high-grade and thus maybe “up-grading” tumors, contrary to the AFIP system which is more inclined to “down-grading”. These differences are amplified in regard of intermediate-grade tumors, which seem to preferentially cluster with high-grade tumors according to the AFIP system, while they tend to follow low-grade tumors behavior with the Brandwein system. If this limitation does not appear in non-quantitative grading systems such as the Healey scale, the cutoff between each grade may be more ambiguous and thus less reproducible than with others. Recent studies argue for a binary grading system such as a “Brandwein high versus low-plus-intermediate” (since intermediate-grade did not differ from low-grade tumors in term of survival) scale to better reflect the prognostic behavior in MEC, but further studies are needed to validate such new scales. To conclude, it is recommended to define grading of MEC to guide the treatment management using a standard scheme – rather than a “personal’ approach – such as the **AFIP** or **Brandwein** system, taking into account the specificity of each all the more for intermediate grade tumors (i.e., “up-grading” tendency of Brandwein contrary to “down-grading” tendency of AFIP) [Level IV; Grade A].
Table 3. Comparison of mucoepidermoid carcinoma histologic grading systems, Cipriani et al.\textsuperscript{40}

A recurrent translocation $t(11;19)(q21p13)$ – although reported in some acute leukemias – has been detected in a high proportion of MEC cases\textsuperscript{40,106,107}. It has been demonstrated that the resultant $\text{MECT1-MAML2}$ fusion transcript leads to the activation of the Notch target gene $\text{HES1}$ and can thus play a role in the oncogenic process\textsuperscript{108}. This translocation has also been described in some cases of Warthin tumors, but including cases of morphologically ambiguous cases of Warthin tumors which were reclassified as highly suspect of MEC, suggesting that these tumor samples of “Warthin tumor” exhibiting the $\text{MECT1-MAML2}$ chimeric gene should be regarded with caution in order not to misdiagnose Warthin-like MEC\textsuperscript{109–111}. Apart from Warthin tumors, MAML2 rearrangement has not been demonstrated in any other salivary gland tumor. Thus, the detection of the MECT2-MAML2 translocation using different molecular methods (Fluorescence In Situ Hybridization, Reverse Transcription Polymerase Chain Reaction, Next-Generation Sequencing, etc.) may represent a useful diagnostic tool in morphologically ambiguous MEC\textsuperscript{92} [Level IV; Grade B].
3.1.2.2 Acinic cell carcinoma

**ACC** is the second most common histotype of pediatric SGC, accounting for 25-35% of cases\(^2,3\). ACC may present various architectural patterns (solid, microcystic, papillary-cystic, follicular) and cellular components, which can make its diagnosis difficult. Like MEC, ACC is main located in the parotid gland (more than 80% of cases), and carries mostly low-grade features\(^112\). In adults, this histotype is associated with a good overall prognosis, despite its tendency for late recurrences in about one-third of cases\(^113,114\). Some cases may have an aggressive evolution, especially in the case of high-grade transformation\(^115\).

3.1.2.3 Adenoid cystic carcinoma

**AdCC** may involve the parotid, submandibular and minor salivary glands. It is composed of epithelial and myoepithelial cells, variably arranged in tubular, cribriform and solid patterns. Perineural invasion constitutes a hallmark of this entity, and a high rate of locoregional invasion is frequently reported, with infiltration of adjacent soft tissues\(^3\). This tumor is characterized by a t(6;9)(q22-23;p23-24) translocation (MYB-NFIB), frequently associated with additional mutations involving MYB\(^116\). AdCC is known to be associated with a relatively poor survival with a high risk of locoregional and distant recurrences, all the more for the solid pattern\(^117,118\). This high-risk histotype requires more aggressive therapy; nevertheless, AdCC is rarely reported in the pediatric cohort.

3.1.2.4 Others

Finally, (ex-mammary analogue) secretory carcinoma, adenocarcinoma NOS, myoepithelial carcinoma, undifferentiated carcinoma, squamous cell carcinoma and carcinoma ex pleomorphic adenoma have also rarely been described in children\(^3,119\).

**Non-epithelial malignant neoplasms** are rare in this location. They mainly include\(^5\):

- Lymphomas,
- Sarcomas, including rhabdomyosarcoma, malignant peripheral nerve sheath tumor, fibrosarcoma, malignant fibrous histiocytoma, angiosarcoma, Ewing family tumor, and synovial sarcoma,
- Neuroblastoma.

**Other rare low-grade or aggressive malignant epithelial tumors** to be excluded are:

- Sialoblastoma in infants and young children\(^120\),
- NUT carcinoma,
- Metastases from other primary cancers (which develop preferentially in the parotid glands and are most often of squamous cell origin) – extremely rare in children.
3.1.3 Additional assessments

- Before RT, **detailed dental assessment** including clinical evaluation, dental panoramic radiography ± dental scan is necessary\(^\text{121}\) [Level V; Grade A].

- In the rare situations where chemotherapy is considered, a **laboratory work-up** (full blood count, liver and renal function) and **specific evaluations** depending on chemotherapeutic agents (e.g., audiometry, echocardiography) are required, in order to limit side effects [Level V; Grade A].

- **Fertility preservation options** are not necessary before surgery and/or locoregional RT [Level V; Grade A] but could be considered before chemotherapy but taking into account that chemotherapy is mostly considered in situations of poor prognosis.

4. TREATMENT DETAILS

General considerations:

- **MDT consultation** is mandatory at diagnosis and during therapy [Level IV; Grade A].

- **Collaboration with an adult head and neck tumor expert network** is highly recommended [Level V; Grade A].

- Patients/families should be invited to participate in a **prospective clinical trial** when available, with **data collection** in national or international databases [Level IV; Grade B].

- **Surgery** designed to achieve complete resection with adequate margins constitutes the cornerstone of treatment [Level III; Grade A].

- The indications for **cervical lymph node dissection, adjuvant RT** and/or rarely **chemotherapy** have yet to be defined and should be discussed by the MDT [Level IV; Grade B].

- The **poor outcomes observed after salvage therapy** in the case of high-grade tumors strongly support the need for adequate initial treatment with an aggressive approach. However, overtreatment of low-risk tumors must be avoided due to the potential risk of late side effects.

- Most **long-term effects** after the treatment of SGC are related to the initial disease extension and thus the extent of surgery required to achieve complete resection, and RT when performed. Long-term follow-up is recommended [Level V; Grade A].

- Treatment guidelines should be identical for all SGC, both primary and secondary tumors. However, treatment decisions must take into account potential long-term sequelae after treatment of the primary tumor [Level V; Grade A].
4.1 Treatment

4.1.1 Surgery

Complete surgery is the mainstay of treatment, regardless of the tumor type and location\textsuperscript{3–5,37,45,57,122–124} \textit{[Level III; Grade A]} and represents a major prognostic factor\textsuperscript{10,125–129}. Excision biopsy or tumor enucleation should be avoided due to the risk of tumor seeding \textit{[Level III; Grade E]}. In the case of close or positive margins, additional surgery designed to ensure microscopically complete resection should be considered, whenever possible without mutilation \textit{[Level V; Grade B]}. Given the rarity of the disease, and the high risk of postoperative facial nerve injury for parotid tumors, referral to a specialized head and neck surgical oncology center is highly recommended\textsuperscript{2,37} \textit{[Level IV; Grade A]}.

4.1.1.1 Primary tumor

\textbf{Parotid tumors:}

Total parotidectomy with complete tumor resection and facial nerve preservation is the treatment of choice for malignant parotid tumors whenever feasible \textit{[Level IV; Grade A]}. Partial superficial parotidectomy (i.e., resection of the latero-facial portion of the gland) can be considered for tumors arising in the superficial lobe, depending on the intraoperative findings (it may be difficult to achieve clear margins with this procedure in most cases)\textsuperscript{2,3,5,37,43,130,131} \textit{[Level IV; Grade B]}. Transient (16 to 50% of cases) or permanent (10 to 30% of cases) postoperative facial nerve injury is one of the main risks of parotid surgery, particularly in children, in whom the smaller caliber of the facial nerve branches makes its dissection difficult, requiring extra-care and dedicated surgical tools to avoid excessive traction\textsuperscript{2,4}. The risk of persistent facial nerve paralysis is higher in case of total parotidectomy. Intraoperative electrophysiologic facial nerve monitoring is highly recommended\textsuperscript{6} \textit{[Level IV; Grade A]}. Facial nerve preservation should be attempted in the absence of macroscopic facial nerve involvement or close margins, making complete resection impossible\textsuperscript{43,130} \textit{[Level IV; Grade A]}. In other cases, intraoperative nerve reconstruction (free graft, vascularized free flap…), whenever feasible, otherwise secondary nerve transplant should be considered\textsuperscript{2,5,37} \textit{[Level IV; Grade A]}. In addition to facial nerve paralysis, Frey syndrome (up to 50% of occurrence), scar complications, sialocele, bleeding, hematoma or fistula have also been reported\textsuperscript{4,5}. Apart from above, first bite syndrome is a rare but burdensome complication of deep lobe parotid and parapharyngeal space dissections\textsuperscript{132}.

\textbf{Submandibular tumors:}

Regional dissection of the submandibular triangle bounded by the mandible superiorly, the anterior belly of the digastric muscle anteroinferiorly, and the posterior belly of the digastric muscle posteroinferiorly, is recommended \textit{[Level IV; Grade A]}. Dissection should include the submandibular gland and surrounding lymph nodes and any locally invaded tissues\textsuperscript{3,5}. Postoperative complications include transient or permanent marginal mandibular nerve weakness, ranula, postoperative fluid collection, and cellulitis\textsuperscript{133}.
Minor salivary glands/sublingual tumors:

MSG or sublingual tumors are rare, but mostly malignant. Wide excision with tumor-free surgical margins and an attempt to preserve function is required [Level IV; Grade A]. Surgery modalities depend on the type, location and extent of the tumor. Clear margins can be difficult to achieve in some MSG tumors. Surgery for sublingual tumors may include partial or total en bloc resection of the floor of the mouth mucosa, according to the tumor size and extensions.

4.1.1.2 Regional lymph nodes

There is no consensus in the literature regarding systematic lymph node dissection, especially in the low-grade SGC predominantly observed in pediatric patients. In view of the rarity of lymph node involvement in children (10% versus 30% in adults according to the comparative SEER analysis by Sultan et al. and the recent meta-analysis of Zamani et al.) and considering potential long-term postoperative complications, systematic neck dissection remains controversial for pediatric SGC. According to Zamani et al., only one-third of children with a diagnosis of SGC underwent neck dissection and less than 10% of neck dissected children had positive lymph nodes; these findings are confirmed in the retrospective series of Rebours et al. Thus, several studies have proposed to reserve upfront systematic elective neck dissection to cases with clinically or radiologically suspected lymph node involvement [Level IV; Grade B]. Second-look prophylactic lymphadenectomy can be considered and discussed by the MDT for high-grade and/or advanced tumors, as lymph node involvement has mainly been reported in these situations. Neck dissection should be ipsilateral to the primary tumor, except for midline tumors that require bilateral dissection [Level IV; Grade B].

4.1.2 Radiotherapy

The role of adjuvant RT in pediatric SGC remains unclear. The level of evidence is mostly based on retrospective series of adult patients, in which adjuvant RT was shown to improve local control, EFS and OS compared to surgery alone. As for example, Terhaard et al. have reported in a large retrospective study with 498 patients (112 patients with surgery alone vs. 398 patients with surgery and adjuvant RT) that patients who received postoperative RT had higher local control rates (5- and 10-years actuarial local control rate of respectively 94% and 91% vs. 84% and 76%, p=0.0005), all the more for patients with high-risk tumors such as T3-T4 tumors (84% vs. 18%, p<0.001), close resection margins (95% vs. 55%, p=0.003), incomplete resection (82% vs. 44%, p<0.05), bone invasion (86% vs. 54%, p=0.04), and perineural invasion (88% vs. 60%, p=0.01). Regional control rate was also significantly improved with adjuvant RT for patients with pN+ tumors (86% vs. 62%, p=0.03). However, considering the subgroup of patients with early stage tumors (T1-T2) with complete resection, the impact of postoperative RT on survival is more debatable and was not found to be correlated with higher local control rate in the Terhaard's study. According to the French Network of Rare Head and Neck Tumors...
Salivary gland carcinoma

(REFCOR) guidelines, adjuvant RT in adults should be reserved for high-grade tumors, incomplete surgical resections, advanced stages and/or lymph node invasion\(^{139}\) [Level IV; Grade A for adults].

Due to the rarity of pediatric SGC, mostly corresponding to low-grade tumors, only limited data are available concerning the role of RT. The potential benefit of RT was highlighted in a recent retrospective multicentric study published by Morse et al. enrolling 588 patients. Surgery alone was performed in 351 patients (60%), whereas adjuvant RT was added for 145 patients (25%), the remaining patients received surgery, RT and chemotherapy. Controlling for patient and tumor characteristics, adjuvant RT was associated with improved OS (HR=0.15; IC95% [0.02-0.92]; \(p=0.041\)), even in the subset of patients with high-grade tumors (HR=0.12; IC95% [0.02-0.64]; \(p=0.014\))\(^{14}\). However, there is a high risk of post-radiation complications in this young population, including long-term morbidity, which should be considered in view of the long-life expectancy of these patients. Late side effects of head and neck RT in children can be extensive and include\(^3,5,6\):

- Acute side effects, that may persist for a long time: pain, mucositis, xerostomia, dysgeusia, odynophagia, alopecia, fatigue, hematological side effect (low blood counts).

- Late side effects, which may arise after a long delay from treatment completion: musculoskeletal growth retardation, dental development defect, osteoradionecrosis and fractures, trismus, functional damages including hearing loss and vision impairment, delayed intellectual development, hypothyroidism, and second cancer.

Indications for adjuvant RT in the treatment of pediatric SGC must therefore be carefully considered case-by-case level by the MDT [Level V; Grade A]. According to the comparative population-based study published by Sultan et al., children and AYA received RT less frequently than their adults’ counterparts (27% vs. 51%, \(p<0.001\))\(^2\). This may reflect the lower incidence of high-risk tumors in children compared to adults, and the special attention made to limit long-term morbidity in the pediatric population. Several other retrospective series of pediatric SGC have reported similar average frequency of adjuvant RT, but with various findings depending on the study due to the lack of consensus about its indication and the various periods involved\(^4\).

4.1.2.1 Primary tumor

Based on adult recommendations, weighted by the abovementioned pediatric specificities, adjuvant RT should only be considered for highly selected cases such as high-grade histotypes (especially AdCC and other high-grade tumors with perineural invasion, extraglandular extension and vascular invasion) and advanced (T3-T4) tumors with or without lymph node involvement [Level IV; Grade B].

Indications for RT for low- or intermediate-grades should take into account other factors of poor prognosis, but RT is generally not recommended [Level IV; Grade D]. There is no consensus about treatment modalities. As a general principle, careful treatment planning is necessary and the use of three-dimensional conformal RT, which may improve the therapeutic index and limit the irradiated volume compared to intensity modulated radiotherapy (IMRT) is highly recommended, especially for
lateralized tumors [Level V; Grade A]. Because of the relative radioresistance of SGC (depending on tumor type), a high dose to the tumor bed is generally recommended, i.e. 60 Gy[6,36,37,42,140], in line with general adult recommendations[45,139] [Level IV; Grade B]. Few data are available concerning the potential benefit of proton beam therapy for SGC[141], but the available data suggest satisfactory acute toxicity and dosimetric profile (with a lower rate of low-dose bath of healthy tissues), including for children[140]. Proton beam therapy could be of interest and should be more thoroughly investigated to evaluate the long-term benefit in terms of late effects, which remain very common and severe [Level IV; Grade C]. Finally, in an alternative approach, Mao et al. treated 24 children with high-risk parotid MEC with post-operative $^{125}$I seed brachytherapy (radioactivity of 18.5-33.3 MBq per seed and prescription dose between 60-120 Gy) with promising results in terms of survival and side effects profile[142]. However, these preliminary results from a small retrospective cohort would require to be confirmed in further prospective clinical trials [Level IV; Grade C].

4.1.2.2 Regional lymph nodes

Very few studies have reported data concerning the indications and modalities of adjuvant nodal RT, and no consensus has been reached for either adults or children. Based on adult practices and a few retrospective multicenter pediatric studies, adjuvant nodal RT should be reserved for high-grade tumors when complete neck dissection is not deemed feasible or in the presence of several positive nodes or extracapsular spread [Level IV; Grade B]. Adjuvant nodal RT could be proposed on a case-by-case basis for non-high-grade pN+ tumors with extracapsular spread or more than 3 involved nodes[42] [Level IV; Grade B]. A similar dose to that delivered to the tumor bed can be proposed, i.e. 60 Gy [Level IV; Grade B]. Nodal irradiation area should be ipsilateral to the primary tumor, except for midline tumors, which require bilateral treatment [Level IV; Grade B].

4.1.3 Systemic therapy

The role of chemotherapy in the management of SGC remains highly controversial and, for most children with SGC, there is no evidence in support of adjuvant chemotherapy. Very few studies have investigated the efficacy of systemic therapy in adults[45,54,143], and most of them concerned AdCC. Chemotherapy is generally reserved for the palliative treatment of recurrent and/or metastatic disease not amenable to further surgery or RT[3,5,45,54] [Level V; Grade C]. No consensus has been reached about the optimal chemotherapy regimens. Based on adult studies, the chemotherapeutic agents considered to be potentially effective in SGC, regardless of the histotype, include: cisplatin, 5-fluorouracil, doxorubicin, and cyclophosphamide[45]. Further data are needed on the safety and efficacy of chemotherapy in pediatric SGC, and situations where this therapeutic option could be discussed should remain rare, limited to unresectable and/or metastatic diseases (which are exceptional in children). In addition, particular attention must be paid to the choice of therapeutic regimen, with the aim of limiting side effects, especially in a palliative situation. As far as possible, these treatments should therefore be delivered in the context of prospective clinical trials [Level V; Grade B]. Similarly, recent research into
the underlying molecular disorders in malignant SGC has suggested several potential therapeutic targets, but data are too preliminary and targeted therapies should only be delivered in the setting of a prospective trial [Level V; Grade B].

In 2006, Laurie et al. performed a systematic review regarding systemic therapy (chemotherapy and targeted agents) used in the palliative management of main histotypes encountered in advanced adult SGC cases54. More recently, Wang et al. reviewed different aspects of SGC treatment in adults, including potential chemotherapy and targeted strategies published45.

- **Adenoid cystic carcinoma:**

Most of published data concern AdCC, including phase II prospective trials in adults, due to the aggressiveness of this tumor. Apart Laurie’s and Wang’s articles, the recent review of Cherifi et al. provided an overview of systemic therapy investigated in locally recurrent or metastatic AdCC143.

Considering chemotherapy, mitoxantrone, vinorelbine and epirubicin have been associated with objective responses or stabilization in a single-agent regimen. Cisplatin-anthracycline-based regimens ± cyclophosphamide (“CAP” regimen) have been proposed with potential benefit, but additional toxicity. Cisplatin and vinorelbine combination therapy has also been associated with 44% of objective response rate, with a median response duration of 15 months for complete responses and 7.5 months for partial responses. Paclitaxel is not recommended in AdCC, because of lack of efficacy53.

Considering targeted therapies, several agents have been investigated, based on potential molecular profiles of AdCC. As c-kit is expressed in up to 90% of AdCC, c-KIT inhibitors such as imatinib or dasatinib have been proposed, but with disparate results, no significant objective response rate (<5%) and a short response duration. Some partial responses have been reported with the combination of imatinib and cisplatin. In the same way, EGFR inhibitors such as cetuximab, gefitinib or lapatinib have been evaluated because of high rates of EGFR overexpression in AdCC (> 80% of cases), but with disappointing results for most of them as a single agent. Combinations of chemotherapy + EGFR inhibitor have been proposed for patients with metastatic AdCC (cisplatin-5FU-cetuximab) or locally advanced (cisplatin-cetuximab + radiotherapy) with around 40% of objective response. Other targeted therapies have been investigated, including proteasome inhibitor (bortezomib), HDAC inhibitor (vorinostat), multi-kinase inhibitors (sorafenib, sunitinib, axitinib, lenvatinib, or pazopanib144…), mTOR inhibitors (such as everolimus), Notch 1 inhibitor (brontictuzumab), but with only few stable diseases or transient partial responses.

- **Mucoepidermoid carcinoma**

Although MEC represents the most common histotype of SGC, there are currently no studies of systemic therapy specific to this histotype, given the rarity of high-risk MEC even in adults (most of these tumors harboring low-grade with low metastatic potential and are therefore treated with exclusive surgery). Considering chemotherapy, contrary to AdCC, paclitaxel has been reported with potential activity, as well as cisplatin-based regimens.
- **Adenocarcinoma, NOS**

Again, no specific study investigating systemic therapies in this specific subtype is available. Based on published studies enrolling different histiotypes of SGC, paclitaxel, vinorelbine, and CAP or variants have demonstrated antitumor activity. EGFR inhibitors could have some activity, as well as Her-2 inhibitors and anti-androgen therapies for patients with high-grade adenocarcinoma NOS and salivary duct carcinoma. Nevertheless, these entities are extremely rare in the pediatric cohort.

- **Secretory carcinoma**

In (ex-mammary analogue) secretory carcinoma which harbors a t(12;15)(p13;q25) translocation forming the ETV6-NTRK6 transcript, long-lasting objective responses have been reported with NTRK inhibitors, such as larotrectinib or entrectinib, in several phases 1 and 2 trials [Level III; Grade B].

Finally, several trials investigating immune-based therapies, such as pembrolizumab, nivolumab and ipilimumab, are still ongoing [Level V; Grade C].

### 4.2 General strategy

#### 4.2.1 Localized and resectable SGC

First-line surgery, whenever possible, is highly recommended [Level III; Grade A].

Upfront neck dissection should be performed in the presence of clinical or radiological suspicion of lymph node involvement [Level IV; Grade B]. Second-look prophylactic dissection should be considered in the case of high-risk tumors (high-grade tumors and/or with perineural spread and/or lymphovascular involvement and/or advanced stages) [Level IV; Grade B].

Adjuvant RT of the tumor bed should be discussed, depending on tumor stage, histotype, grade and completeness of resection. It should be considered for AdCC and other high-grade histotypes (with perineural invasion, extraglandular extension and vascular invasion) and advanced (T3-T4) tumors regardless of node status [Level IV; Grade B]. RT is generally not required for completely resected localized low-grade tumors and should be avoided in the absence of other factors of poor prognosis [Level IV; Grade D]. Its indication in other cases (i.e., advanced non-high-grade tumors or non-advanced high-grade tumors) should be assessed by the MDT, taking into account the benefits and potential side effects [Level IV; Grade C]. Adjuvant nodal RT should be performed in the case of high-grade tumors without complete neck exploration or associated with several positive nodes or extracapsular spread. It may be considered for low- or intermediate-grade tumors with extensive lymph node involvement (i.e., extracapsular spread or more than 3 involved nodes) [Level IV; Grade B].

There is no place for chemotherapy in the treatment of resectable localized SGC, even in the presence of lymph node involvement at diagnosis [Level IV; Grade D].
4.2.2 Unresectable and/or metastatic SGC at diagnosis

Due to the rarity of this situation, no consensus has been reached concerning the management of patients with unresectable locally advanced and/or metastatic SGC at diagnosis. As a general principle, an up-front multi-agent chemotherapy strategy could be considered, but the optimal regimen has not yet been defined [Level V; Grade C]. Targeted therapy or immunotherapy may be proposed but should only be delivered in the setting of prospective clinical trials, and when a distinct molecular target has been clearly identified in the individual tumor [Level V; Grade C].

In the rare cases of localized and unresectable tumor, delayed surgery after tumor reduction should be proposed as soon as possible [Level V; Grade B].

Depending on the tumor response to systemic therapy and its feasibility, delayed surgery of the primary tumor and metastases could be considered for metastatic diseases [Level V; Grade C]. RT of the primary tumor and/or metastases, alone or in combination with chemotherapy as already reported in unresectable AdCC by Haddad et al.\(^{145}\), may also be considered [Level V; Grade C].

4.2.3 Recurrent SGC

Survival of patients with recurrent SGC varies considerably, depending on tumor histotype and grade, and the extent of recurrence.

In the case of low- or intermediate-grade tumor at diagnosis, another biopsy is recommended before treatment to confirm the diagnosis, especially in the case of late recurrence [Level V; Grade A]. Review of the histology of the primary tumor by an expert pathologist (at the time of biopsy of the recurrence) may also be useful in cases with atypical features [Level V; Grade A]. Wherever possible, surgery should be proposed, together with neck dissection in the presence of suspected lymph node extension [Level V; Grade A]. Adjuvant RT could be considered for intermediate/high-grade tumors, disseminated (including lymph node extension) and/or early recurrence, taking into account potential previous radiation fields [Level V; Grade B].

In the case of unresectable locoregional recurrence, preoperative systemic therapy may be considered, but the optimal regimen has not been defined [Level V; Grade C]. Preoperative RT could be an option in some cases [Level V; Grade C].

The prognosis is more uncertain in the case of metastatic relapse. Systemic therapy (chemotherapy, targeted therapy, immunotherapy) and/or palliative RT may be considered case-by-case [Level V; Grade C]. Whenever possible, enrolment in prospective clinical trials is recommended [Level V; Grade B].

4.3 Assessments

Patients should undergo a clinical and imaging evaluation every 3 months for 2 years, then every 4 to 6 months for 3 years (depending on the level of risk of the disease).
Imaging studies could be head and neck ultrasound and/or MRI (the type of imaging evaluation should be discussed with the radiology team depending on the tumor location and previous radiologic findings).

For high-risk tumors, chest X-ray could be performed every 6 months for 5 years.

In the rare cases of metastatic disease, imaging evaluation should include the assessment of known metastatic sites (as for example: chest CT scan for pulmonary metastases).

Other imaging studies should be considered depending on clinical evaluation.

### 4.4 Summary of known adverse events associated with treatment recommendation

Main known adverse events associated with treatment recommendation are detailed in previous chapters.

They include:

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Main side effects</th>
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<tbody>
<tr>
<td>Total or partial parotidectomy</td>
<td>Transient or permanent facial nerve paralysis, Frey syndrome, scar complications, sialoceles, bleeding, hematoma, fistula, first bite syndrome</td>
</tr>
<tr>
<td>Surgery of submandibular tumor</td>
<td>Transient or permanent marginal mandibular nerve weakness, ranula, postoperative fluid collection, cellulitis</td>
</tr>
<tr>
<td>Surgery of MSG or sublingual tumor</td>
<td></td>
</tr>
</tbody>
</table>
| Radiotherapy                           | - Acute side effects, that may persist for a long time: pain, mucositis, xerostomia, dysgeusia, odynophagia, alopecia, fatigue, hematological side effect (low blood counts).  
- Late side effects, which may arise after a long delay from treatment completion: musculoskeletal growth retardation, dental development defect, osteoradionecrosis and fractures, trismus, functional damages including hearing loss and vision impairment, delayed intellectual development, hypothyroidism, and second cancer. |
| Systemic therapy                       | Depending on the pharmacologic agent delivered                                                                                                                                 |

Table 4. Summary of known adverse events
4.5 Supportive treatment

After surgery, general supportive post-operative treatment (i.e., scar nursing, analgesic therapy…) are recommended [Level V; Grade A].

In the case where RT is considered, early nutritional status evaluation +/- supportive care if needed are recommended, taking into account the risk of mucositis [Level V; Grade A]. Other supportive treatment may be necessary depending on the potential acute side effects (analgesic therapy, skin care…) [Level V; Grade A].

In the rare situations where chemotherapy is discussed, central venous access insertion may be considered before chemotherapy administration, depending on the chemotherapeutic agents [Level V; Grade B].

4.6 Genetic considerations

Several studies have noticed previous history of primary cancer before the diagnosis of SGC, mainly MEC²⁸,²⁹,³⁶,³⁷,⁴². A recent report from the Childhood Cancer Survivor Study (CCSS) has indeed collected 23 cases of second salivary gland cancer from among 14135 childhood cancer survivors at a mean age of 24.8 years (i.e., 15 years after primary malignancy). Considering the pediatric age, Thariat et al. have reported in a multicentric French study 13 patients with history of various cancer – mainly hematological malignancies – among 38 pediatric patients with SGC (34%)⁴². However, this relatively high proportion of SGC occurring as second cancer has mainly been associated with previous RT and its dose or chemotherapy and its mutagenic potential, more than a genetic predisposition¹⁴⁶,¹⁴⁷. If the role for a genetic predisposition can be questioned for patients who did not previously received head and neck RT, there are no defined genetic predisposing syndromes that have been reported to date.

In this context, there is no specific need of genetic counselling for pediatric SGC, but this option may be discussed and should thus be proposed on an individual basis depending on family history and preferences, even more for patients with a history of cancer [Level IV; Grade B].

4.7 Patient Follow Up

Due to the possibility of frequent long-term toxicities in survivors after RT or invasive surgery, a strict follow-up more than 5 years is highly recommended. Surveillance should focus on both the risk of recurrence (locoregional and/or metastatic), which may occur even after several years, and potential long-term side effects, including surgical complications and radiation-related effects depending on the dose and volume of irradiation (dental and facial development defects with functional and esthetic sequelae, hearing loss, vision impairment, fibrosis, xerostomia, hypothyroidism, etc.)³⁵ [Level IV; Grade A].
Special attention must be paid to potential radiation-induced second cancers or benign tumors, although no significant risk has yet been reported after RT for SGC, and in view of the rarity of these tumors in children \(^4\) [Level IV; Grade A].

5. **REFERENCE LIST**


18. Albeck H, Bentzen J, Ockelmann HH, Nielsen NH, Bretlau P, Hansen HS. Familial clusters of
Salivary gland carcinoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
<th>Journal</th>
<th>Year</th>
<th>DOI</th>
</tr>
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Salivary gland carcinoma

Standard Clinical Practice document

7330.2007.0008


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Salivary gland carcinoma

2017;64(1):57-63. doi:10.1002/pbc.26217


### APPENDIX 1 – TUMOR STAGING

The use of the 8th edition of American Joint Committee on Cancer staging system is recommended[^148] [Level IV; Grade A].

#### Primary Tumor

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension without extraparenchymal extension*</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 4 cm and/or tumor with extraparenchymal extension*</td>
</tr>
</tbody>
</table>
| T4   | T4a: Tumor invades skin, mandible, ear canal and/or facial nerve  
|     | T4b: Tumor invades base of skull, pterygoid plates and/or encases carotid artery |

#### Regional Lymph Nodes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
</tbody>
</table>
| N2   | N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension  
|     | N2b: Metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension  
|     | N2c: Metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension |
| N3   | Metastasis in a lymph node more than 6 cm in greatest dimension |

#### Distant Metastasis

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

#### Stage

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>II</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>T3 N0 M0, or T1-3 N1 M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T1-3 N2 M0, or T4a N0-2 M0</td>
</tr>
<tr>
<td>IVB</td>
<td>T4b Any N M0, or Any T N3 M0</td>
</tr>
<tr>
<td>IVC</td>
<td>Any T Any N M1</td>
</tr>
</tbody>
</table>

Note 1: * 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.

Note 2: AJCC 8th edition introduces the use of extranodal extension (ENE) in pN categorization. It must be clearly defined as tumor present within the confines of the lymph node and extending through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction. Any node with ENE is considered as pN3b.
SGC, salivary gland carcinoma; FNA, fine needle aspiration; CNB, core needle biopsy; MTD, multidisciplinary team discussion; MSG, minor salivary glands; HG, high-grade; R0, microscopically complete resection; R1, microscopically incomplete resection; R2, macroscopically incomplete resection; ν, whatever; w/o, without; ENE, extranodal extension.
APPENDIX 3 – SUMMARY BOXES

**DIAGNOSTIC WORK-UP**

**Diagnosis** of SGC is often delayed due to slow tumor growth.

The main symptom is a single, **non-inflammatory mass in the salivary glands**.

Less commonly, other symptoms may include recent pain or swelling with no infectious or inflammatory symptoms, skin tethering or ulceration, regional lymph node involvement, and, even more rarely, facial nerve palsy, nasal obstruction, congestion, vision impairment or trismus.

**Initial tumor assessment** should include:

- **Full clinical examination** including evaluation of cervical lymph nodes and neurological examination [Level V; Grade A]

- **Head and neck ultrasound** [Level V; Grade A]

- **Head and neck MRI** (or **CT scan** when MRI is not available) when malignancy is suspected [Level V; Grade A]

- **Ultrasound-guided FNA** to eliminate common differential diagnoses and to guide surgery [Level IV; Grade B], particularly in the case of atypical clinical and radiological signs, but a diagnosis of malignancy must be interpreted with caution

- **Preoperative CNB** can be useful in the case of an unresectable tumor or before mutilating surgery or when the diagnosis remains doubtful despite cytology [Level IV; Grade B]

- **Chest CT scan** in the case of high-grade malignant tumor [Level V; Grade A]; chest X-ray may be sufficient in the case of low-grade tumor [Level V; Grade C]

- The place of **FDG (or PSMA for adenoid cystic carcinoma) PET/CT** has yet to be defined and should therefore be limited to clinical trials at the present time [Level V; Grade D]

**Pretreatment investigations** should include:

- Before radiotherapy: **dental assessment** including clinical evaluation and dental panoramic radiography ± dental scan [Level V; Grade A]

- Before chemotherapy: **laboratory work-up** (full blood count, liver and renal function) and **specific evaluations** depending on chemotherapeutic agents (audiometry, echocardiography) [Level V; Grade A]

- **Fertility preservation** could be considered before chemotherapy [Level V; Grade A]

**Staging** should follow the **8th edition of AJCC staging system** [Level IV; Grade A].
### HISTOLOGIC DIAGNOSIS

**Histology** is mandatory for the diagnosis of SGC; cytology is not sufficient for the definitive histopathologic diagnosis [Level V; Grade A].

**Revision** of histology slides by a pathologist experienced in salivary gland tumors is highly recommended [Level IV; Grade A].

**Molecular testing** is a powerful diagnostic tool for the diagnosis of SGC in certain morphologically ambiguous tumors and in the case of limited biopsy material [Level IV; Grade B].

**Main histotypes:**

- **Mucoepidermoid carcinoma** (45-50%), mainly located in the major salivary glands, especially the parotid gland, usually low-grade and variably or predominantly cystic.

  Grading should be defined according to a standard system, such as the AFIP system or Brandwein system, taking into account the specificity of each system (i.e., “upgrading” tendency of the Brandwein system, in contrast with the “downgrading” tendency of the AFIP system) [Level IV; Grade A]. The current WHO classification should be taken into account.

  Molecular studies are recommended to detect the presence of MAML2 rearrangement [Level IV; Grade B].

- **Acinic cell carcinoma** (25-35%), almost exclusively located in the parotid gland, usually low-grade.

- **Adenoid cystic carcinoma** (rarely), located in the parotid, submandibular or minor salivary glands, considered to be an aggressive tumor. Perineural invasion constitutes a hallmark of this entity, associated with a high rate of locoregional invasion. Molecular studies may detect the presence of MYB rearrangement [Level IV; Grade B].

**Main non-epithelial malignant neoplasms to be excluded:**

- Sarcomas (rhabdomyosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma, Ewing family of tumors)

- Lymphomas

**Other rare low-grade or aggressive malignant epithelial tumors to be excluded:**

- Sialoblastoma in infants and young children

- NUT carcinoma

- Metastases from other primary cancers
**SURGERY**

*Surgery* designed to achieve microscopically complete resection with adequate margins constitutes the cornerstone of treatment. *First-line tumor resection with perioperative histologic analysis* is generally recommended [Level III; Grade A].

*Primary tumor:*

- **Parotid tumor:**
  Total parotidectomy with complete tumor resection and facial nerve preservation (in the absence of facial nerve involvement or close margins, making a complete resection impossible) is the treatment of choice [Level IV; Grade A].

  In the case of tumor arising in the superficial lobe, *partial superficial parotidectomy* can be considered [Level IV; Grade B].

  *Intraoperative electrophysiologic facial nerve monitoring* is highly recommended [Level IV; Grade A].

  When facial nerve preservation is not feasible, *intraoperative nerve reconstruction or secondary nerve transplant* should be considered [Level IV; Grade A].

- **Submandibular tumor:**
  Regional dissection of the submandibular triangle is recommended [Level IV; Grade A].

- **Minor salivary gland/sublingual tumor:**
  Wide resection with adequate margins and attempt to preserve function is recommended [Level IV; Grade A].

*Regional lymph nodes:*

*Upfront systematic elective neck dissection* should be reserved to cases with clinically or radiologically suspected lymph node involvement [Level IV; Grade B].

*Second-look prophylactic lymphadenectomy* may be considered and discussed by the MDT in the case of high-grade and/or advanced stage tumors [Level IV; Grade B]. Cervical lymph node dissection could also be associated with primary tumor resection when preoperative biopsy shows typical high-grade tumor [Level V; Grade B].

Cervical dissection should be **ipsilateral to the primary tumor**, except in the case of midline tumors, which require **bilateral** dissection [Level IV; Grade B].
RADIOTHERAPY

Indications of adjuvant radiotherapy must be discussed and weighed up on a case-by-case basis by the MDT, taking into account the patient’s age and potential side effects [Level V; Grade A].

Irradiation of the tumor bed should be discussed in the case of high-grade tumors (especially adenoid cystic carcinoma and other high-grade tumors with perineural invasion, extraglandular extension and vascular invasion) and advanced (T3-T4) tumors with or without lymph node involvement [Level IV; Grade B].

Radiotherapy for low- or intermediate-grade tumors could be considered in the presence of other factors of poor prognosis but is generally not recommended [Level IV; Grade D].

As a general principle, careful treatment planning is necessary and the use of three-dimensional conformal radiotherapy is highly recommended [Level V; Grade A].

Proton beam therapy could be useful to ensure better sparing of critical organs, but further data are needed to evaluate the benefit of this modality [Level IV; Grade C].

There is no consensus on the optimal dose and volume of radiotherapy; because of the relative radioresistance of SGC (depending on tumor type), a high dose to the tumor bed, i.e. 60 Gy, is generally recommended [Level IV; Grade B].

Adjuvant nodal radiotherapy should be considered for high-grade tumors when complete neck dissection is not deemed feasible or in the presence of several positive nodes or extracapsular spread. It may also be discussed case-by-case for non-high-grade pN+ tumors with extracapsular spread or more than 3 involved nodes [Level IV; Grade B].
SYSTEMIC THERAPY

The place of chemotherapy in the management of SGC remains highly controversial and is generally reserved for palliative treatment of recurrent and/or metastatic disease not amenable to further surgery or radiotherapy [Level V; Grade C].

No chemotherapy is needed for localized tumor or with nodal extension at diagnosis in children [Level IV; Grade D].

Chemotherapeutic agents considered to be potentially effective in SGC include cisplatin, 5-fluorouracil, doxorubicin, cyclophosphamide and vinorelbine, but no consensus has been reached concerning the optimal regimen [Level IV; Grade C].

Several targeted therapies, and more recently immunotherapies, are currently under investigation, but data are still insufficient to support the routine use of these modalities. Endocrine or Her-2 inhibitor therapy can be considered in adults in the presence of androgen receptors and/or Her-2 expression in the tumor biopsy, but no data are available in children. NTRK inhibitors are a valuable option for disseminated, unresectable or recurrent secretory salivary carcinoma with ETV6-NTRK3 fusion transcript [Level III; Grade B].

Whenever possible, patients with locally advanced or recurrent or metastatic disease should be managed in the setting of a prospective clinical trial [Level V; Grade B].
### GENERAL STRATEGY

**Localized and resectable SGC**

First-line surgery, whenever possible, is highly recommended [Level III; Grade A].

Adjuvant radiotherapy of the tumor bed should be discussed depending on tumor stage, histologic grade and completeness of resection. It should be considered for adenoid cystic carcinoma and other high-grade tumors (perineural invasion, extraglandular extension, vascular invasion) and advanced tumors (T3-T4) regardless of node status [Level IV; Grade B].

Radiotherapy is generally not required for completely resected localized non-high-grade tumors [Level IV; Grade D].

Adjuvant nodal radiotherapy should be performed for high-grade tumors without complete neck exploration or associated with several positive nodes or extracapsular spread. It should be discussed for non-high-grade tumors with extensive lymph node involvement (i.e., extracapsular spread or more than 3 involved nodes) [Level IV; Grade B].

There is no place for chemotherapy in the treatment of resectable localized SGC, even in the presence of lymph node involvement at diagnosis [Level IV; Grade D].

**Unresectable and/or metastatic SGC at diagnosis**

First-line systemic therapy is recommended [Level V; Grade C].

Targeted therapy or immunotherapy may be proposed in the setting of prospective clinical trials [Level V; Grade C].

Delayed surgery of the primary tumor and metastases may be proposed depending on tumor response [Level V; Grade B for localized tumors, C for metastatic diseases].

Radiotherapy of the primary tumor and/or metastases may be considered [Level V; Grade C].

**Recurrent SGC**

The prognosis of recurrent SGC depends on the histotype and tumor grade, and the extent of recurrence.

Another pretreatment histologic examination of a CNB is recommended for low/intermediate-grade tumors, particularly in the case of a long interval since the primary diagnosis [Level V; Grade A].

Second analysis of the primary tumor by an expert pathologist (concurrent to the recurrence biopsy) may be useful in case of atypical evolution [Level V; Grade A].

Whenever possible, surgery should be proposed, together with lymph node dissection in the presence of possible lymph node extension [Level V; Grade A].

Adjuvant radiotherapy should be considered for intermediate/high-grade tumors, disseminated and/or early recurrence, taking into account potential previous radiation fields [Level V; Grade B].
In the case of unresectable locoregional recurrence, neoadjuvant systemic therapy or radiotherapy may be discussed \([\text{Level V}; \text{Grade B and C}]\).

In the case of metastatic disease, systemic therapy (chemotherapy, targeted therapy, immunotherapy) and/or palliative radiotherapy may be proposed, in the setting of prospective clinical trials \([\text{Level V}; \text{Grade B}]\).

**GENETIC CONSIDERATIONS AND FOLLOW-UP**

*Genetic counseling* for patients with SGC is not mandatory but may be considered on a case-by-case basis \([\text{Level IV}; \text{Grade B}]\).

It should be systematically proposed to patients with a history of cancer, although no genetic predisposing syndromes have been reported to date \([\text{Level IV}; \text{Grade B}]\).

*Long-term follow-up* is highly recommended, both for **locoregional and metastatic recurrence** (including late recurrences) and **treatment-related late effects** i.e., facial palsy and Frey syndrome after surgery, radiation-induced head and neck sequelae (xerostomia, dental and facial development defect, hearing loss, vision impairment…) and potential second malignancies \([\text{Level IV}; \text{Grade A}]\).
APPENDIX 4 – MAIN OPEN QUESTIONS REMAINING

- Place of FDG PET/CT within initial assessment.
- Place of FNA and CNB within initial assessment, taking into account specific age-related technical challenges in children.
- Best prognostic stratification of patients according to the pathology, molecular profile and/or clinical features.
- Optimal surgical modalities, including indications for cervical node dissection.
- Role, indications and modalities of adjuvant RT, and the place for proton therapy in the treatment of SGC.
- Role of chemotherapy in case of unresectable, metastatic and/or relapsed tumors.
- Optimal global therapeutic strategy for high-risk tumors (unresectable, metastatic, relapsed SGC).
- Role of new targeted drugs for patients with SGC.