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Salivary gland carcinomas in children and adolescents: A retrospective analysis of the European Cooperative Study Group for Pediatric Rare Tumours (EXPeRT)

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ABSTRACT

Background: Salivary gland carcinomas (SGCs) are exceedingly rare in children, with a reported annual incidence of 0.8–1.4/1000,000 under 20 years of age. Evidence regarding optimal treatment of pediatric SGCs is limited, and for a long time, no guidelines have been available. Here, we report on an international retrospective series of SGCs in children and adolescents collected by several national rare tumor study groups cooperating in the European Cooperative Study Group of Pediatric Rare Tumors (EXPeRT)

Patients and methods: Patients diagnosed between 2000 and 2014 were included. Data were reviewed by the respective national rare tumor working groups and reported on a harmonized data sheet to EXPeRT for central analysis.

Results: Overall, 121 patients were identified, including 103 patients with parotid tumors, 12 with submandibular tumors and six tumors in minor glands. In 11 patients, SGCs were secondary cancers. Mucoepidermoid carcinoma was the most frequent diagnosis (n = 65), followed by acinic cell carcinoma (n = 39), adenocystic carcinoma (n = 7), sialoblastoma (n = 3) and other carcinomas (n = 7). All patients underwent tumor resection (R0: 66%, R1: 34%). Neck dissection was performed in 47 patients, revealing nodal metastases in 13. Twenty-four patients underwent irradiation, and 11 patients received adjuvant chemotherapy. During a median follow-up of 25 (6–140 months), 14 relapses were observed (7 local, 5 with nodal and 2 with distant metastases). Five patients died of disease. Higher histological tumor grade was associated with advanced local tumor stage and risk of recurrence.

Conclusions: SGCs in children and adolescents mostly present as localized tumors with low malignant potential. In approximately 10% of patients, regional lymph node metastases present at diagnosis. After complete resection, prognosis is favorable. Surgery is the mainstay of treatment; adjuvant local or cervical irradiation should be reserved to those rare patients with nodal metastases or less favorable biology such as adenocystic carcinoma.

1. Introduction

Salivary gland carcinomas (SGCs) are rare neoplasms in adults, but are exceedingly infrequent in children, with a reported annual incidence of 0.8–1.4 per million population under 20 years old [1]. SGCs share with other very rare tumours (VRTs) of pediatric age not only their low incidence, but also that they have always been “orphan” diseases, meaning that few clinical and biological details have been available and for long, no specific protocols have been developed to support paediatric oncologists and surgeons in defining the best treatment approach. The European landscape for pediatric VRTs, however, has changed in the last two decades, with the establishment of various national cooperative programs [2–6] and thereafter their joining forces in the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) [7–9]. EXPeRT has already published retrospective series of several VRTs, pooling national cohorts to obtain series large enough to subsequently provide a frame for reaching consensus on treatment recommendations [10].

Due to the relative paucity of data available in the literature on SGCs in the pediatric age, the clinical management of children with these tumours is a real challenge for surgeons and pediatric oncologists, and diagnostic and treatment recommendations are generally extrapolated from those for adults [11–13] [14–17]. However, whether tumor biology and clinical course are the same in pediatric compared to adult SGCs is still unclear. In some of the above-mentioned studies, an atypical distribution of tumor sites e.g. with a high proportion of palatine tumors of the minor glands may indicate a selection bias [13], and in others, the cohort also included young adults or patients with benign tumors such as pleomorphic adenoma [13,15] [18]. Moreover, concerns regarding treatment-related late effects (in particular related to radiotherapy in survivors) may influence the treatment approach in different age groups.

This article reports the clinical features of a series of children and adolescents with SGCs, collected by different national groups in the framework of EXPeRT.

2. Methods

Inclusion criteria for the study were the following: a) patient’s age between 0 and 17 years; b) histologically confirmed diagnosis of SGC, c) diagnosis between 2000 and 2014. Exclusion criteria were tumors of benign malignancy including (pleomorphic) adenoma.

Data were extracted from the databases of the cooperating national paediatric working groups from France (48 patients), Germany (33 patients), Italy (17 patients), Poland (18 patients), and United Kingdom (5 patients). Eighteen patients from the French and seventeen patients from the Italian series have already been presented before [11,19,20], and a patient with sialoblastoma has been presented as a case report [21]. All patients, or their guardians, gave their informed consent for data collection within the national rare tumour group and analysis. This study was approved by the institutional and national research ethics boards.

The histological diagnosis was established by the local pathologists and centrally reviewed by the respective national reference panel. Histological diagnoses (histotype and grade) were categorized according to the 2005 World Health Organization (WHO) Classification of Head and Neck Tumors, and the 2008 Armed Forces Institute of Pathology (AFIP) Atlas of Tumor Pathology - Tumors of the Salivary Glands. Disease stage was defined according to the tumor-node-metastases (TNM) staging system of the Union for International Cancer Control (UICC) (8th ed.).

Due to the absence of specific pediatric guidelines, care was based on national VRT groups’ recommendations, which however, had not yet been harmonized during the time period described here. Moreover, some patients have been treated based on local tumor board decisions, and national groups have been contacted only after surgery. After preoperative assessment, wide tumor removal with salivary gland resection was recommended. In case of parotid primary, partial or total parotidectomy (depending on the size and anatomical tumor extension) was the mainstay of therapy with the aim to achieve free margins. The referral to a center for surgery with expert pediatric or ENT surgeons professionally dedicated to the management of SGC was strongly recommended. Tumor resection with simultaneous monitoring of the facial nerve was recommended.

Cervical lymph node dissection was recommended in cases of clinically or radiologically detectable nodal involvement. Postoperative radiotherapy was suggested in selected cases with various unfavourable features, such as incomplete resection not amenable to a second complete surgery, locally advanced disease, aggressive histological features such as a high grade of malignancy, adenoid cystic carcinoma (AdCC) and/or perineural invasion, or in case of multiple levels of cervical lymph node involvement. In addition, radiotherapy was recommended

in case of relapse, and in case of unclear margins in high-grade tumors. Adjuvant chemotherapy was recommended for patients with sialoblastoma; however, some patients with epithelial SGC have received adjuvant radiochemotherapy based on decisions by local tumor boards.

For data pooling and analysis, a uniform EXPeRT data-form has been used, which includes epidemiological, anamnestic, diagnostic and pathologic data. The prospectively reported clinical data of the national groups have been pseudonymized and transferred from the national data base to the EXPeRT data sheet by the national coordinators. Prior to data transferal, clinical, pathological and therapeutic data have been re-validated by the national coordinators, and follow-up data have been updated upon this analysis. After verification, anonymised data were transferred into a database and analysed with the IBM SPSS programme, version 29. Categorical data were compared using chi-square tests and numerical data with Mann-Withney U test. If suitable, survival analysis was done according to Kaplan-Meier, and differences between subgroups were evaluated with the log-rank test.

3. Results

3.1. Clinical and pathological data

In total, 121 patients were identified. Median age at diagnosis was 12 years and 5 months, ranging from one month to 17.9 years. Fifty-two male and 69 female patients were included. Of note, 11 patients (10 with mucoepidermoid carcinoma [MEC] and one with acinic cell carcinoma (ACC)) had a previous cancer history including Hodgkin lymphoma (n = 3), acute lymphoblastic leukemia (n = 2), acute myeloid leukemia, Non-Hodgkins Lymphoma, neuroblastoma, osteosarcoma, soft tissue sarcoma and Ewing sarcoma (n = 1, each). No patient had a history of previous radiotherapy to the head/neck region.

The most frequent organ of origin was the parotid gland in 103 patients, followed by the submandibular gland (12 patients), minor palatinal glands (5 patients) and lacrimary gland (1 patient). Median tumor size at diagnosis was 2 cm in maximum diameter, ranging from 0.5 cm to 6.7 cm (Table 1**).** Tumors arising in the parotid gland were larger than tumors at other sites (Table 1; p = 0.036).

For 97 patients with complete staging data, local tumor stage was T1 in 46 patients, T2 in 39 patients, T3 in 9 patients and T4 in 3 patients. In 13 patients locoregional lymph node metastases were described, and no patient had distant metastases (Tables 1 and 2).

More than half of the tumors were histologically classified as MEC (n = 65), followed by ACC (n = 39) and AdCC (n = 7). Rare histological diagnoses included sialoblastoma (n = 3), basal cell carcinoma (n = 2), breast analogous carcinoma (n = 2), secretory carcinoma not otherwise specified (n = 2) and sebaceous carcinoma (n = 1), with equal distribution by site (Table 3). Histological grading was documented in 78 patients: grade 1 in 52 patients, grade 2 in 20 patients, and grade 3 in 6 patients (sialoblastoma was excluded from this categorization).

Among 66 patients with complete data, there was a significant association between histological grade and advanced local tumor stage (p < 0.01), but not with regional lymph node metastases.

3.2. Treatment

All patients underwent tumor resection at diagnosis; in two patients, incisional biopsy was documented before. Among 103 parotid primaries, surgery consisted of a total parotidectomy (84 cases), partial parotidectomy (10 cases), wide surgery (9 cases) without further specification. In 10 patients, postoperative facial injury was documented. For 18 minor salivary gland tumors, resection was reported as complete excision of the tumor bearing gland.

Overall, the resection has been categorized as complete (R0) in 73 cases, microscopically incomplete (R1, 37 cases; 110 patients with complete data for review of surgical report). Resection status was not associated with the organ of origin. There was no statistically significant correlation between completeness of resection and tumor size (p = 0.074). However, all five tumors with a maximum diameter of 4 cm or more were incompletely resected. Incomplete resection was reported in 4/6 grade 3, 5/21 grade 2 and 17/50 grade 1 tumors, respectively (p = 0.15). There was no statistical correlation between grade of differentiation, tumor size and the risk of facial nerve injury.

In 47 patients, unilateral cervical lymph node dissection on the levels IIa and IIB, often III, was performed, and in 13 of them, lymph node metastases were detected (pN1).

As part of the first-line therapy, adjuvant radiotherapy was delivered to 24 patients, at a median dose of 60 Gray (Gy), range 40–65 Gy. Six patients received irradiation for stage T3 or T4 MEC (n = 4 =), basal cell carcinoma or carcinoma NOS (n = 1 each); four of these patients were R1 status. Thirteen patients were irradiated after incomplete resection, and seven patients because of histologically verified lymph node metastases (three tumors were also incompletely resected). In addition, three patients received irradiation despite being stage T1 or T2, N0 and R0 status; these included one grade 3 MEC and two AdCCs.

Eleven patients received cisplatin-based adjuvant chemotherapy due to high-risk features (e.g. incomplete resection of grade 3 tumors) including a concomitant radio-chemotherapy for 6 of them. In addition, three patients with sialoblastoma were treated with adjuvant chemotherapy (Table 3).

Table 1
Study population characteristics (n = 121).

	Number
Age (median)	12 years, 5 months (1 Month – 17.9 years)
Sex	69 female, 52 male
Site	Parotid gland 103
	Submandibular gland 12
	Minor palatinal gland 5
	Lacrimary gland 1
Tumor Size (median, Range)	2 (0.5–6.7) cm
Stage	T1 46
	T2 38
	T3 9
	T4 3
	N0 83
	N1 13
	M0 96
	M1 0
	Tx Nx MX 25
Histology	Mucoepidermoid Carcinoma 65
	Acinic Cell Carcinoma 39
	Adenocystic Carcinoma 7
	Sialoblastoma 3
	Other histotypes 7

Table 2
Distribution of histological groups and tumor stage (97 patients with complete TNM staging data).

	T1/T2	T3/T4	N0	N1	M0	M1
MEC	49 (89.1%)	6 (10.9%)	50 (86.2%)	8 (13.8%)	57 (100%)	0
ACC	27 (94.5%)	1 (5.5%)	23 (85.2%)	3 (14.8%)	33 (100%)	0
AdCC	5 (100%)	0	5 (100%)	0	7 (100%)	0
SIAL	0	2 (100%)	2 (100%)	0	3 (100%)	0
Other	4 (57.1%)	3 (42.9%)	4 (66.6%)	2 (33.3%)	7 (100%)	0
Sum	85 (87.6%)	12 (12.4%)	84 (86.6%)	13 (13.4)	107 (100%)	

MEC, mucoepidermoid carcinoma; ACC, acinic cell carcinoma; AdCC, adenocystic carcinoma; SIAL, sialoblastoma

Table 3
Distribution of anatomical sites and histological groups among 121 patients with salivary gland carcinomas.

	Parotid	Submandibular	Other	Sum	Median age years (range)
MEC	52	8	5	**65**	12.0 (1–17.8)
ACC	37	2	0	**39**	13.4 (0.4–17.9)
AdCC	5	1	1	**7**	16 (12.1–17.3)
SIAL	3	0	0	**3**	0.8 (0.0–5.2)
Other	6	1	0	**7**	10.1 (6.4–16)
Sum	**103**	**12**	**6**	**121**	12.4 (0–17.9)
Median age years(range)	12.7 (0–17.9)	12.8(0.4–12.4)	9.9 (5.8–12.7)	12.4 (0–17.9)	-

MEC, mucoepidermoid carcinoma; ACC, acinic cell carcinoma; AdCC, adenocystic carcinoma; SIAL, sialoblastoma

3.3. Outcome

During follow-up, 14 relapses were observed after a median interval of 12 (range, 1–46) months. Among these, seven were exclusive local relapses, two patients had combined local/nodal relapses, one with combined local/distant metastatic relapse (grade 3 MEC with a history of previous osteosarcoma), three with isolated nodal relapse, and one patient with isolated lung relapse **(**Table 4**).**

In the group of 74 patients without cervical lymph node dissection, one patient with adenocystic carcinoma developed a nodal relapse. After first-line neck dissection, 5/47 patients developed a nodal relapse; these patients had not previously undergone cervical radiotherapy at first-line treatment. Among all these, there were two ACCs and one MEC (grade 2), AdCC and sebaceous carcinoma, respectively.

Relapses were treated with lymph-node dissection and cervical radiotherapy. After a median follow-up of 25 months (range, 6–140), overall, five patients died from disease progression. One patient with sebaceous carcinoma developed multiple local, regional and distant (lungs, bones) relapses and died of the tumor more than 10 years after initial diagnosis despite several lines of therapy including repeated surgical resections and proton beam therapy. One patient with MEC, grade 3 developed a metastatic relapse to the lungs and died after 17 months. Another patient with MEC, grade 3 initially presented at stage T4 and developed a local relapse and died at 12 months follow-up. A third patient with a huge MEC, grade 3 and a previous history of osteosarcoma died after local relapse. Finally, a patient with sialoblastoma died as a result of metastatic relapse. Overall, at the end of follow-up, 89 patients are alive in first complete remission (CR), 11 in second CR, and five died from disease resulting in a 10-year overall survival of 0.96 ± 0.22.

For the analysis of prognostic factors on event free survival, 103 patients with complete clinical, pathological and follow-up of at least 6 months were included, with a total 11 relapses of any type. Among the histological groups, the rate of relapses was the highest among the few sialoblastoma (2/3 patients), compared to all other histological groups (12/100 patients; $p = 0.023$, Table 5).

Histological grading ($p = 0.009$) and initial tumor stage ($p = 0.001$) correlated with the rate of recurrence (Table 5). Lymph node metastases were not significantly associated with the rate of recurrence; however, 7 of 12 patients with initial nodal metastases underwent cervical irradiation, compared to 2 of 68 patients without lymph node metastases.

Incomplete resection was significantly associated with recurrence. Among 31 patients with incomplete resection, 8 recurrences were observed, while after complete resection (R0), three recurrences were reported among 62 patients ($p = 0.003$), even though the rate of irradiated patients was twice as high as after complete resection (13/31 patients vs. 11/62 patients; Tables 4, 5). All patients with ultimately fatal course, initially underwent incomplete resection (Table 4).

4. Discussion

This series constitutes a large prospectively collected and retrospectively analysed series of SGCs in children and adolescents. It has become possible through the foundation of national working groups for VRTs in children and their collaboration at an international level. Looking at the overall data, it first becomes obvious that the different national structures have an impact on the different national registration rates. Compared to other countries and considering population size, France has registered most SGC patients. This may be explained by the fact that this group has already published on SGCs rather early and may thus have increased its visibility in the field [19,21–23]. Moreover, a strong clinical network has been established in Isle de France, including ENT specialists and pediatric oncologists, resulting in a continuously high registration rate of SGC [17]. In this context, if under-reporting could by assumed for some countries with lower numbers of reported cases, a selection bias could be possible. Here, we would hypothesize that more complicated cases, especially those with incompletely resected patients have been reported to specialized pediatric oncology, while completely resected low-grade tumors have exclusively been treated in surgical centers, without involvement of pediatric oncology. This bias

Table 4
Treatment and outcome data stratified by histology and resection status (99 patients with complete data).

	Resection	N	Radiotherapy	Chemotherapy	NED	REL	Local REL	Nodal REL	Distant REL	DOD
MEC (n = 58)	**R0**	38	5	2	37	1	0	1	0	0
	R1	20	9	3	16	4	4*	0	1*	3
ACC (n = 27)	**R0**	21	3	9	20	1	1*	0	1*	0
	R1	6	2	1	4	2	1	1	0	0
AdCC (n = 6)	**R0**	3	2	1	3	0	0	0	0	0
	R1	3	1	1	2	1	1	0	0	0
SIAL (n = 2)	**R0**	1	0	1	0	1	1	0	0	0
	R1	1	0	0	1	0	0	0	0	1
Other (n = 6)	**R0**	2	1	1	2	0	0	0	0	0
	R1	4	1	0	3	1	1*	1*	0	1
All histotypes (n = 99)	**R0**	**65**	**11**	**14**	**62**	**3**	**2***	**1**	**1***	**0**
	R1	**34**	**13**	**5**	**26**	**8**	**7***	**2***	**1***	**5**
Sum	**R0 +R1**	**99**	**24**	**19**	**88**	**11**	**9**	**3**	**2**	**5**

MEC, mucoepidermoid carcinoma; ACC, acinic cell carcinoma; AdCC, adenocystic carcinoma; SIAL, sialoblastoma, NED, no evidence of disease (at minimum > 6 months follow-up) REL, relapse; DOD, death of disease

* Combined local and nodal or local and distant relapse, respectively

Table 5
Univariate analysis of prognostic factors on event free survival (103 patients with follow-up > 6 months).

		Total	NED	REL	Significance
Organ of origin	Parotid	87	75	12	
	Others	16	14	2	n.s.
Histology	MEC	57	52	5	
	ACC	32	28	4	
	AdCC	5	3	2	
	SIAL	3	1	2	
	Other	6	5	1	p = 0.023
Grading	Grade 1	42	41	1	
	Grade 2	19	17	2	
	Grade 3	5	3	2	p = 0.009
Local Stage	T1/T2	70	68	2	
	T3/T4	11	6	5	p = 0.001
Nodal stage	N0	68	64	4	
	N1	12	10	2	n.s.
Resection status	R0	62	59	3	
	R1	31	23	8	p = 0.003

n.s., non significant

could potentially explain the comparably high proportion of incomplete resections in our series. In addition, most patients in this series have not been resected under the suspected diagnosis of SGC, considering the extreme rarity of this diagnosis in this age group, which may also contribute to the number of incomplete resections.

In fact, due to the different structures between the national groups, profound data harmonization was required prior to data analysis. In the future, this issue may be overcome with the establishment of a European database for VRTs in children and adolescents within the EC funded PARTNER project, thus providing better data quality in the EXPeRT-observational study [24].

Nevertheless, despite the above-mentioned obstacles, this series contributes some important data to the field. First, it becomes evident that SGCs are not as rare as it would have been expected from data of national childhood cancer registries [4]. Second, the group of SGCs is heterogeneous. Nevertheless, all histological entities – apart from sialoblastoma – can be categorized as mostly well differentiated tumors with low malignant potential, with few lymph node metastases and no distant metastases at diagnosis. This is in line with other reports that compared to their adult counterparts, SGCs in the pediatric age appear to have a less aggressive biology [1,18,25]. This observation also indicates that in these cases, especially in low-grade tumors, an extensive staging for distant metastases is not required.

Nevertheless, especially high-grade tumors have been associated with higher tumor stage and adverse outcome (Table 2). Moreover, due to the proximity to the facial nerve, incomplete resection was seen more often in high-grade compared to well differentiated tumors. Both factors contribute to impaired outcome in these tumors.

Although our study is not prospective clinical trial, and despite above-mentioned limitations, it brings us to the most important conclusion and recommendations for clinical management. The first step is to increase awareness of rare SGCs in childhood and adolescents and to include them in the differential diagnoses of tumor lesions at these sites. This is of extreme importance as for all these tumors, resection represents the first therapeutic step and may be sufficient as the sole therapy if complete resection is achieved, with the exception of histologic entities such as AdCC with a higher biological risk of local recurrence [26]. To allow for optimal surgery, appropriate imaging including MRI is essential. Surgery of parotid tumors should include facial nerve monitoring, as facial nerve injury with complete facial palsy was seen in 10 patients. Surgery should aim for wide complete resection, because incomplete resection has been associated with a significant higher rate of local or locoregional relapse.

Adjuvant or neoadjuvant chemotherapy should be used in defined situations only and apart from rare exceptions plays no role in the treatment. Here, the eight SGC patients (sialoblastoma excluded), who have been treated with chemotherapy, illustrate the uncertainty regarding treatment strategies in times without consultation networks and standard recommendations for SGC and other VRTs in the pediatric age [10,27]. In contrast, chemotherapy is certainly indicated in sialoblastoma; for this embryonal tumor chemotherapy regimen as for other embryonal tumors have been applied [28,29] [21]. Adjuvant radiotherapy should be considered in selected cases, primarily in high-grade tumors with lymph node metastases and for AdCC. The latter typically shows perineural invasion, and recurrences may be seen in one third to up to half of the patients in pediatric and adult series [26,30].

Yet, it should be noted that the risk of locoregional relapse especially after R1 resection of MEC may be significant. In our series, 8 of 31 patients with incomplete resection suffered a recurrence, compared to 3 among 62 patients with complete resection (p = 0.003). Two of eight recurrences in incompletely resected tumors developed despite adjuvant radiotherapy; both were grade 3 MECs. However, in case of locoregional relapse of low-grade tumors, there may still be a good chance of cure after second resection and adjuvant radiotherapy, when applied in the relapse situation. With this strategy, long-term toxicity of therapy, especially after radiotherapy, can be avoided for many patients without affecting long-term prognosis. To achieve this aim, close collaboration with the ENT surgical specialists, ideally in multidisciplinary tumor boards is essential, so that a stringent treatment plan can be followed right from the start.

Last, we observed a significant proportion of approximatively 10% of patients with SGCs arising after a history of childhood cancer. Therefore, SGCs should be included in the list of potential secondary cancers after childhood cancer, not only after irradiation. Unfortunately, we cannot provide data on genetic cancer predisposition in these children, but this point should be taken into focus [31]. In these children, due to the therapeutic burden they have already undergone, complete surgical therapy is essential, and in case of diagnostic uncertainty, a fine-needle biopsy can be taken prior to surgery [32].

In summary, SGCs during childhood and adolescents are not as rare as previously expected but represent 4% of all pediatric head and neck cancers during childhood [33]. They should be considered as differential diagnosis at tumors at these sites. Complete surgical resection constitutes the central therapeutic step and should therefore be laid into experienced hands. Further decisions regarding adjuvant therapies should be made within the network of national and international working groups specialized in pediatric VRTs.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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