Quality indicators in head and neck oncology

de Ridder, M.

Publication date
2017
Document Version
Other version
License
Other

CHAPTER 8

Salivary gland pleomorphic adenoma in The Netherlands: an observational nationwide study on primary tumor incidence and recurrence rate.

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Oral oncology. 2017; 66: 93-99

ABSTRACT

Introduction

Whereas salivary gland pleomorphic adenoma (SGPA) is the most common type of salivary gland tumor, little is known about its epidemiology, as national cancer registries do not register this disease.

Objectives

Our aim was to look at SGPA incidence trends, and to establish recurrence rates and associated factors, as well as rates of secondary malignant transformation in the Netherlands.

Materials and Methods

After retrieving SGPA data from the Dutch pathology registry PALGA for the years 1992, 1997, 2002, 2007, and 2012, we calculated figures for incidence, epidemiology, recurrence, and secondary malignant transformation, and performed multivariate analysis to discover the risk factors for recurrence.

Results

We counted 3 506 cases of SGPA, and calculated an overall European standardized rate of 4.2-4.9 per 100 000 person-years. Our figures showed a female preponderance (1:1.43) with an annual 1% rise in female incidence (95% confidence interval [CI]: 0.2-1.8) and a bimodal age distribution in women ($p<0.0001$). The overall 20-year recurrence rate was 6.7%, and median time to first recurrence was 7 years. Positive and uncertain resection margins and younger age at diagnosis were risk factors for recurrence, with odds ratios (ORs) of 4.62 (95%CI 2.84-7.51), 4.08 (95%CI 2.24-7.43), and 0.42 (95%CI 0.29- 0.63), respectively. Tumor locations in minor salivary glands had lower odds of recurrence than tumor sites in the parotids (OR 0.24; 95% CI: 0.07-0.77; $p<0.016$). Malignant transformation occurred in 0.15% of SGPAs (3.2% of recurrences).

Conclusion

This first nationwide study clearly showed sex differences in SGPA epidemiology, possibly suggesting some underlying hormonal mechanism. Long-term recurrence risks were low, and secondary malignant transformation risks were very low.

INTRODUCTION

Most salivary gland tumors are benign, with only 14% malignant lesions[1,2]. The most common type is salivary gland pleomorphic adenoma (SGPA), which accounts for no less than 70% of benign epithelial tumors. These well-circumscribed tumors with ductal and myoepithelial elements affect both major and minor salivary glands, though most occur in the parotids. They seem to develop more often in women and diagnosis is mostly at middle age (40-59)[2,3]. The standard of treatment is nerve-conserving, superficial parotidectomy (or extracapsular dissection in well-trained hands), which shows a 5% recurrence rate, whereas enucleation shows recurrence rates of up to 45%[4,5]. Favorable results in retrospective series suggest that postoperative radiotherapy may be helpful after incomplete resection or tumor spill, or in multiple or multinodular recurrences[4,6,7].

In 1.8-6.2% of cases, SGPA transforms into carcinoma ex pleomorphic adenoma[8,9]. These cases make up 7.7-11.6% of all malignant salivary gland tumors[8,10]. In recurrent SGPA, de novo malignant transformation is reported in 0-23%[4]. As common a tumor as SGPA may be, its epidemiology has long remained uncertain for lack of national registration practices [9,11,12]. Some research focused on benign salivary gland tumors in general or subgroups of SGPA[2,13–16]. Others looked at regional incidence of SGPA or national incidence of parotid SGPA[1,9], but national incidence of all-location SGPA and trends over time were not investigated. Of course, without any national data, no rates can be calculated for all-location SGPA incidence, recurrence, and secondary malignant transformation while ruling out referral bias. We, therefore, decided to turn to PALGA, the Dutch nationwide registry of pathology reports. This registry is not restricted to any specific type of finding or disease, thus making a suitable database for studying SGPA epidemiology features, including trends over time.

OBJECTIVES

Our primary aim was to accurately establish SGPA incidence rates and trends over time, as well as any age and sex differences. We further aimed to establish recurrence rates and risks of secondary malignant transformation and to explore risk factors. This knowledge will help physicians to measure treatment results and express population-based prognoses.

MATERIALS AND METHODS

Database

Set up in 1991, the PALGA registry automatically receives anonymized pathology reports from all Dutch laboratories, which include age, sex, date, and diagnosis. Excerpts are available for research purposes.

Patient selection

We searched the PALGA registry for codes of pleomorphic adenoma or mixed tumor and manually checked all excerpts thus created for SGPA. Then, we included all patients who had a first histology diagnosis in 1992, 1997, 2002, 2007, or 2012. We excluded 442 patients (11%) for reasons mentioned in Additional Table A. Likewise, we analyzed histology and cytology data about recurrences up to September 1, 2013, defining recurrence as a secondary tumor occurring in the same tumor site at a minimum of six months post surgery.

Incidence

We calculated SGPA incidence in the Netherlands from mid-year population size figures provided by Statistics Netherlands (CBS)[17], and worked out the male to female incidence ratio by looking at average male and female incidence data. To cancel out changes in age structure of the Dutch population over time, we computed European standardized incidence rates (ESRs), basing our calculations on the "2013 reference population"[18,19].

Patient, tumor, and treatment characteristics

To further analyze our primary tumor data, we scored for sex, age at diagnosis, salivary gland of origin, side of the body, surgical procedure, and margin status. In case of ambiguity, we checked with the author pathologists to decide on interpretation. Recurrence rates and malignant transformation: Focusing on patients with at least five years of follow-up, we calculated first-recurrence rates at 5, 10, and 15 years, as well as median time to first and subsequent recurrences. We excluded primary carcinomas ex pleomorphic adenoma from our database, and counted secondary carcinomas ex pleomorphic adenoma (SGPAs that recurred as malignant tumors) both as malignant transformations and as recurrences. Carcinomas in situ ex pleomorphic adenoma were not considered malignant transformations.

Risk factors for recurrence

In determining risk factors, we looked at sex, age, tumor site, and margin status. As the type of surgery was not always specified, and reporting practices varied, we decided to exclude this factor from our observations.

Statistical analysis

We analyzed our data with SPSS (version 21.0; SPSS Inc., Chicago, III) and R[20,21], taking a p-value of <0.05 to be statistically significant for all purposes. Using linear regression and the natural log rhythm of ESR, we computed annual percent changes (APCs) by sex and overall, and we applied finite mixture models to investigate distribution patterns for age at diagnosis[22]. With the Kaplan-Meier method, we calculated times to recurrence, and we identified potential predictors of recurrence using multivariate logistic regression analysis. In addition to our analysis of complete cases, we performed missing data analysis and multiple-imputation analysis, imputing missing data by letting the R MICE package generate five imputed datasets and comparing the pooled results to our analysis of complete cases.

RESULTS

Incidence

After data cleaning, 3 504 unique patients remained of a total of 3 948 diagnosed with pleomorphic adenoma (Table 1). Two developed a second primary SGPA at a different anatomical site. Overall crude incidence varied from 3.9 to 4.7 per 100 000 person-years (Tables 2a and 2b). ESR ranged between 4.2 and 4.9 per 100 000 person-years. After stratifying for sex, we found a statistically significant annual rise of ESR in women (APC= 1.0% per year; 95% CI: 0.2-1.8), but not in men (APC= 0% per year; 95% CI:-1.0 to 0.9) (Figure 1).

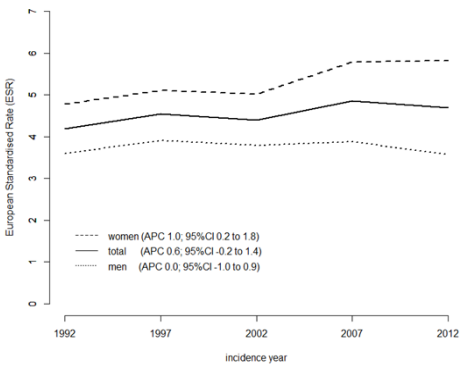

Figure 1. European Standardized Rate (ESR) in the five investigated years, with interpolation in the periods in between. The annual percent change (APC), calculated from the five years, shows an increase in female SGPA incidence.

Table 1. Population characteristics primary SGPA and 1st recurrence

		Primary [n (%)]			1st Recurrence [n(%)]
		Overall (n=3 506)	Male (n=1 421)	Female (n=2 085)	Overall (n=125)
Patients					
Age	Mean (range)	49 (8-94)	48 (9-92)	50 (8-94)	39 (8-89)
Age group	0-19	112 (3)	54 (4)	58 (3)	12 (10)
	20-39	959 (27)	393 (28)	566 (27)	60 (48)
	40-59	1417 (40)	600 (42)	817 (39)	33 (26)
	60-79	919 (26)	343 (24)	576 (28)	18 (14)
	≥ 80	99 (3)	31 (2)	68 (3)	2 (2)
Location	Parotid gland	2733 (78)	1112 (78)	1621 (78)	110 (88)
	Superficial lobe	2603 (74)	1066 (75)	1537 (74)	102 (82)
	Deep lobe	130 (4)	46 (3)	84 (4)	8 (6)
	Submandibular gland	310 (9)	93 (7)	217 (10)	9 (7)
	Sublingual gland	6 (<1)	4 (<1)	2 (<1)	0
	Minor salivary glands	377 (11)	187 (13)	190 (9)	6 (5)
	Unknown	38 (1)	13 (<1)	25 (1)	6 (5)
	Missing	42 (1)	12 (<1)	30 (1)	0
Side	Left	1 423 (41)	571 (40)	852 (41)	64 (51)
	Right	1 399 (40)	560 (39)	839 (40)	53 (42)
	Unknown	684 (19)	290 (20)	394 (19)	8 (6)
Treatment					
Procedure	Local excision	297 (8)			
	Partial parotidectomy	1 214 (35)			
	Total parotidectomy / Submandib. gl.resection	227 (6)			
	Subtotal parotidectomy	67 (2)			
	Excision deep lobe parotid	103 (3)			
	Biopsy	114 (3)			
	Unknown type of excision	1 449 (41)			
	Missing	35 (1)			
	Negative	2 028 (58)			
Resection margins	Positive	491 (14)			
	Uncertain	261 (7)			
	Unknown	726 (21)			

Patient, tumor, and treatment characteristics

Primary SGPAs occurred more often in women (59.5%) than in men (40.5%) (Table 1), showing a female to male ratio of 1.43:1. The mean age at primary diagnosis was 48.0 in men, and 49.6 in women. Seventy-eight patients (2%) were under 18 when diagnosed. Around 40% of cases occurred in the age group of 40-59. In women, a bimodal age distribution was found, with peaks around the ages of 38 and 64 ($p<0.0001$). Age in men showed a normal distribution (Figure 2). The most common tumor site by far was the parotid gland (78%), followed by the minor salivary glands (11%) and the submandibular glands (9%). Only six SGPAs occurred in sublingual glands (<1%). Submandibular SGPA was more common in women than in men, whereas for minor-gland SGPA, this was the other way around (Table 1). In patients under 18, the minor and submandibular glands were affected more often than in adults (Additional Table B). Surgery had comprised partial parotidectomy in 35% of cases, local excision in 8%, and complete gland removal in 6%. In 41%, the excerpts did not specify the type of excision performed, and in 1%, there was no mention of type of procedure at all. Margin status was negative in 58%, positive in 14%,
uncertain in 7%, and unknown in 21%.

Recurrence rates, characteristics, and malignant transformation

The disease recurred in 125 (4.6%) of the 2 719 patients who had at least five years of follow-up. Twenty (16%) also had a second recurrence, and two (10%) had a third. In 4 patients (0.15%), the disease recurred as carcinoma ex pleomorphic adenoma, which means that 3.2% of all recurrences (4/125) showed malignant transformation. First-recurrence rates were 2.3% at five years, 4.0% at 10 years, 5.6% at 15 years, and 6.7% at 20 years of follow-up, with a 7 years' median time to first recurrence (range 0.6-20.7, 95% CI 5.9-8.1) (Figure 3). Second-recurrence rates were 12% at five years and 14% at ten years of follow-up. The median time to second recurrence was 2 years (95% CI: 0.9-3.1). Sex distribution patterns were similar in both recurrences and primary tumors (58% females versus 42% males).
The mean age at primary diagnosis was 40 in patients who later developed recurrent disease and 49.3 in patients who did not develop recurrent disease. This 10-year age difference appeared in both sexes.

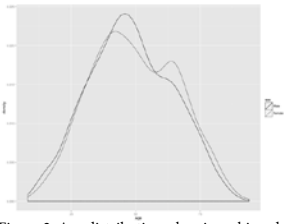

Figure 2. Age distribution, showing a bimodal curve in women.

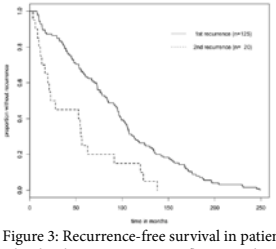

Figure 3: Recurrence-free survival in patients who develop a recurrence, reflecting a decrease in median time to recurrence: 7 years to 1s recurrence and 2 years between 1st and 2nd.

Table 2a. Number of SGPAs in the cohort in relation to the Dutch population

	SGPAs (n)			Dutch population (n)		
	M	F	Total	M	F	Total
1992	253	343	596	7 480 422	7 648 728	15 129 150
1997	280	384	664	7 696 803	7 870 304	15 567 107
2002	288	401	689	7 971 967	8 133 318	16 105 285
2007	304	466	770	8 088 514	8 269 478	16 357 992
2012	296	491	787	8 282 871	8 447 477	16 730 348
Total	1 421	2 085	3 506			

Abbreviations: SGPA salivary gland pleomorphic adenoma; M male; F female

Risk factors for recurrence

Margin status, age at diagnosis, and tumor location all turned out to be associated with risk of recurrence (Table 3). As to margin status, the odds ratios in complete cases (n=1 663) were 4.62 for positive resection margins (95% CI 2.84-7.51), and 4.08 for uncertain margins (95% CI 2.24-7.43), when compared to clear margins. For young age at diagnosis, the odds ratio was 0.42% (per IQR [25y]; 95% CI 0.29-0.63). Primary tumor location showed an odds ratio of 0.24 for minor salivary gland disease when compared to parotid disease (95% CI 0.07-0.77). Risk factors for
malignant transformation of recurrent SGPA could not be determined, due to the low event rate (0.15%).

Table 2b. Incidence of SGPAs in the Dutch population

	Crude incidence (per 100 000 per year)			ESR (per 100 000 per year)		
	M	F	Total	M	F	Total
1992	3.38	4.48	3.94	3.60	4.78	4.19
1997	3.64	4.88	4.27	3.91	5.11	4.54
2002	3.61	4.93	4.28	3.78	5.02	4.39
2007	3.76	5.64	4.71	3.88	5.79	4.85
2012	3.57	5.81	4.70	3.57	5.81	4.69

Abbreviations: ESR European Standardized Rate; SGPA Salivary Gland Pleomorphic Adenoma; M Male; F Female

Missing data and imputation

Type of surgery performed and margin status were not mentioned in 42% and 21% of excerpts, respectively. There were 1 663 complete cases. Missing data on resection margins showed a significant association with recurrence (OR 1.5; 95% CI 1.00-2.23; p = 0.04). Taking this association into account, our analysis of imputed data with multiple-imputation models revealed the same risk factors as our analysis of complete data (Table 3).

Table 3. Multivariate analysis of factors possibly associated with recurrence

Complete-case analysis				
	β-Coefficient	SE (of β)	OR (95% CI)	p-value
Resection margins				
Negative	Reference			
Positive	1.53	0.25	4.62 (2.84 to 7.51)	<0.001
Uncertain	1.41	0.31	4.08 (2.24 to 7.43)	<0.001
Female	-0.15	0.23	1.16 (0.75 to 1.81)	0.501
Age *	-0.86	0.18	0.42 (0.29 to 0.63)	<0.001
Location				
Parotid gland	Reference			
Submandibular gland	-1.02	0.60	0.36 (0.11 to 1.16)	0.087
Minor gland	-1.44	0.60	0.24 (0.07 to 0.77)	0.016
Deep lobe of parotid gland	0.13	0.45	1.13 (0.47 to 2.73)	0.778
Imputed analysis				
	β-Estimate	SE	OR (95% CI)	p-value
Resection margins				
Negative	Reference			
Positive	1.47	0.24	4.35 (2.75 to 6.96)	<0.001
Uncertain	1.38	0.29	3.98 (2.23 to 7.10)	<0.001
Female	-0.07	0.19	0.93 (0.63 to 1.35)	0.711
Age	-0.04	0.01	0.96 (0.95 to 0.97)	<0.001
Location				
Parotid gland	Reference			
Submandibular gland	-0.34	0.38	0.71 (0.34 to 1.51)	0.374
Minor gland	-0.86	0.38	0.42 (0.20 to 0.89)	0.024
Deep lobe of parotid gland	0.24	0.39	1.28 (0.59 to 2.75)	0.535

Abbreviations: OR odds ratio; SE standard error; CI confidence interval. a b and OR for 1 interquartile range (25 years) of change.

DISCUSSION

Our investigations of a large cohort of 3 506 patients with extended periods of follow-up have shed new light on SGPA incidence, recurrence, and secondary malignant transformation. Novel findings were a rising female incidence, a bimodal age distribution in women, and an overall 20-year recurrence risk of 6.7%. Positive or uncertain margins and younger age at diagnosis showed an increased overall risk of recurrence, whereas primary tumor locations in minor salivary glands showed lower recurrence.

Incidence

Direct comparisons with previous research on SGPA incidence are hard to make. In the past 50 years, crude incidence figures between 1.5 and 7.2 per 100 000 person-years[1,2,9,13–16] (Additional Table C) have been reported. However, most authors had not categorized tumors by anatomical site, and only one paper discussed national figures, which related solely to parotid SGPAs and did not standardize for age[9]. Interestingly, SGPA ESR in 2012 was 4.7 per 100 000 person-years, whereas salivary-gland cancer ESR in 2010 was 0.74[23]. These figures indicate that any salivary gland lump is 6.5 times more likely to be SGPA than carcinoma.
The 1% annual increase of SGPA ESR in women was a remarkable finding, as was the female preponderance of SGPA. Possibly, women are more aware of their appearance than men and more willing to seek medical attention for any lumps they find[24–26]. On the other hand, there may also be an influence of gonadal hormones, as in breast cancer, since SGPA is known to express estrogen and progesterone receptors[27,28]. Salivary gland neoplasms have been associated with breast cancer before[29]. One risk factor for breast cancer is advanced maternal age at first childbirth[30–32]. In the Netherlands, this age rose from 28.0 to 29.4 in the period we investigated[17]. A link with the increase we found in female SGPA incidence is not inconceivable.

Patient, tumor, and treatment characteristics

The bimodal age distribution in female SGPA incidence remains unexplained. Further research is needed to explore any hormone influences. According to literature, salivary gland tumors affect the parotid, submandibular, and minor glands in a ratio of 10:1:1[1,33]. The ratio we found was 12:1:2, possibly because of an absence of selection bias in our data.
In our cohort, submandibular SGPAs were more common in women than in men, whereas minor salivary gland SGPAs were more common in men than in women. Since we found no previous mention of any sex differences in SGPA location, further research is needed to confirm and explain this finding. As the PALGA database focuses on pathology, information on the type of surgery performed was often missing (42%). Recently, new insights about the benefits of standardized structured pathology reporting[34] have led to improved reporting practices for high-incidence cancers in Dutch laboratories.
Hopefully, this systematic approach will be adopted for other diseases, too, including for SGPA. Resection margins had not been recorded in 21% of cases. In a posthoc analysis, these cases turned out to have a 1.5-fold higher likelihood of recurrence, even after adjustment for gender, age, topography, and type of treatment. There may be several reasons why margin data are often missing. First, SGPAs are usually removed without complete margins of normal salivary gland tissue, for instance when they are close to the facial nerve.

Second, covering (pseudo) capsules may be very thin, and multinodular growth patterns make it hard to determine whether any nodules have been left behind. Third, SGPAs are benign, so there is little priority in describing their margins, unless the pathology order holds a specific request to do so, along with sufficient clinical information.

Recurrence rates and malignant transformation

Whereas the 4.6% first-recurrence rate we found in patients with at least five years of follow-up (2,719) replicates previous findings[4], our 12% secondrecurrence rate at five years is lower than the 14% stated in most papers (Additional Table D). However, some caution is needed here, as populations and follow-up periods vary between cohorts, and none of the figures have taken any clinical or mortality data into account. For this present research project, we excluded malignant transformations of primary SGPA. In earlier research, however, we found 34 cases of salivary gland carcinoma ex pleomorphic adenoma in the same period of investigation[23]. Four occurred in recurrent SGPA and were added to our database, leaving 30 cases to account for a 1.1% risk of de novo malignant transformation of primary SGPA (30 in 2,749). This is a similar percentage as the 1.8% that was reported in parotid pleomorphic adenoma in Denmark[9].

This is a similar percentage as the 1.8% that was reported in parotid pleomorphic adenoma in Denmark[9]. Earlier publications reported a mean 6.2% risk, but their figures relate to single-center data and may reflect a referral bias[8,35]. The 0.15% secondary malignant transformation rate we found (carcinoma ex pleomorphic adenoma in recurrent SGPA in our SGPA cohort; 3.2% of all recurrences) is in the low range of earlier findings[4]. These numbers are also lower than the Danish 0.35% and 12.6% respectively. To some extent, the differences may be explained by different inclusion criteria, but more importantly, we ruled out referral bias by compiling a nationwide cohort, rather than using single-center data. Our results confirm that on a population level, complete surgical removal of SGPA can be difficult, leading to a 4.6% first-recurrence rate and a 16% second-recurrence rate (median times to recurrence 7 and 2 years, respectively). Recurrences are often multinodular (around 50), with a mean number of 25 nodules found in the primary resection bed[36]. These figures provide a strong argument for MRI follow-up after all first recurrences, to avoid a need for more extensive surgery at some later point in time.

Risk factors for recurrence

We found margin status to be the primary risk factor for recurrence. However, our margin data were based on microscopy, whereas in practice, margin status is often determined macroscopically by the surgeon. In many resections, sufficient argins cannot be taken because of adjacent facial nerve branches, and the pathologist will only have a very thin capsule to examine.

This problem may raise doubt as to the reliability of microscopy data for multivariate analysis. Still, if margins are positive or uncertain, it is highly plausible to expect higher recurrence, since positive microscopic margins are accepted as a primary cause for tumors to recur, as are rupture and spillage[4,37].

A second recurrence risk factor we found was age. Mean age at primary SGPA diagnosis was 49 in patients who did not develop a recurrence later on, and 40 in patients who did. Although there may be an age bias here (higher age suggesting shorter survival, with death as a competing event), our findings are in line with literature[33,38–40]. Some researchers have explained the age difference by suggesting that surgeons tend to take a less radical approach and make smaller incisions in younger patients, for esthetic reasons[36]. Our multivariate analysis, however, did not show any correlation between age and margin status. Wittekindt et al. observed a further age difference.

In their study population, mean age at primary diagnosis turned out to be lower in single-recurrence patients than in multiple-recurrence patients (30.2 versus 40.3)[36]. Possibly, tumor biology is somehow different in younger patients, because of hormonal aspects, genetic background, or some other factor as yet unknown.

A third risk factor for recurrence in our cohort was tumor location, which to our knowledge is a novel finding. SGPA in minor salivary glands was found to recur less frequently than SGPA in larger glands. Lumps in the minor glands are possibly more likely to be noted at an earlier stage. Moreover, complete excision of these lumps is easier to achieve, although margin status may be hard to assess for lack of capsule formation[41]. Female gender was not found to be a recurrence risk factor, which is in line with Maran et al[42] in smaller series, but in contrast to other publications[36,43,44].

Limitations

There are some limitations to our study. First, there is a slight information bias. Given the suboptimal diagnostic accuracy of cytology (84%-99%)[45], we included histology-confirmed SGPA, only. With only 98 cytology diagnoses, however, and no data on nonpathology-proven recurrences, the 4.6% recurrence rate we found may be something of an underestimate, although hardly a gross one. A second limitation is the lack of radiotherapy data. Literature suggests there is a (small) role for radiotherapy in the adjuvant treatment of recurrent SGPA[6,46,47]. Third, since we retrieved all our information from nonstandardized pathology reports, there may be an interpretation bias concerning the description of margins by pathologists and the information supplied by surgeons.

CONCLUSION

Nationwide pathology data regarding SGPA in the Netherlands in the period 1992-2012 reflect some remarkable incidence trends: female incidence was on the rise, there was a bimodal age distribution in women, and women were affected more often than men. These findings may suggest some underlying hormonal mechanism. Overall figures for this period showed an ESR ranging between 4.2 and 4.9 per 100,000 person-years, a 4.6% first-recurrence rate after at least five years of follow-up, and a 6.7% recurrence rate at 20 years of follow-up. Malignant transformation had occurred in 1.1% of primary, and 0.15% of secondary SGPAs at 5 years of follow-up (3.2% of all recurrences). Risk factors for recurrence were positive or uncertain surgical margins, younger age at primary diagnosis, and primary tumor location, with lower odds for minor-gland primaries to recur, when compared to parotid SGPAs. Where margin data were missing, the odds of recurrence were higher, which emphasizes the need for improved, possibly standardized reporting in a joint effort by both surgeons and pathologists alike.

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SUPPLEMENTAL MATERIAL

Additional Table A. Excluded patients	
Exclusion criterion	n
Cytological diagnosis	98
Malignancy	62
Revision of earlier diagnosis	21
Non salivary gland	178
Recurrence/residual disease	63
Expertise for foreign patient	8
Missing data on diagnosis	6
Primary not in inclusion period	6
Total	442

Additional Table A. Excluded patients					
	Age groups [n (%)]				
Localisation	0-19	20-39	40-59	60-79	≥ 80
Parotid gland	67 (60)	759 (80)	1,139 (80)	694 (76)	74 (75)
Superficial lobe	63 (56)	735 (77)	1,075 (76)	662 (72)	68 (69)
Deep lobe	4 (4)	24 (3)	64 (5)	32 (3)	6 (6)
Submandibular gland	21 (19)	78 (8)	113 (8)	92 (10)	6 (6)
Sublingual gland	1 (1)	1 (<1)	3 (0)	1 (0)	0
Minor glands	19 (17)	100(10)	130 (9)	190 (12)	19 (19)
Unknown salivary gland	1 (1)	12 (1)	13 (1)	12 (1)	0
Unknown localization	3 (3)	9 (1)	19 (1)	11 (1)	0
Total	112	959	1,417	919	99

Additional Table C. Reported incidence numbers of benign SG tumors and SGPA									
Author, year (country)	Period	Tumor	n	Parotid	SM	Minor	SL	Incidence	SR
Gunn (U.K.)1	1978-1982	SGPA	232	232	0	0	0	1.5	NR
Pinkston (U.S.A.)2	1968-1989	Benign SG	209	181	28	NR	0	3.05	NR
Przewozny (Poland)3	1991-2000	Benign SG	354	354	0	0	0	1.35	1.6
Mortensen (Denmark)4	1984-2003	Benign SG	621	571	73	NR	0	6.6	NR
Bradley (U.K.)5	1988-2007	SGPA	651	538	67	46	0	6.3-7.3	NR
Moeller (Germany)6	2005	Surg. SGPA	81	71	10	0	0	3.05	NR
Andreasen (Denmark)7	1985-2010	SGPA	5497	5497	0	0	0	4.29	NR
Abbreviations: SG salivary gland; SGPA salivary gland pleomorphic adenoma; SM submandibular gland; SL sublingual gland; SR standardized ratio; NR not reported									

Additional Table D. Reported rate of SGPA re-recurrence			
Author	n	Follow up (year)	Re-recurrence rate
Phillips, 1995[8]	126	Mean 14,5	32.5%
Glas, 2001[9]	52	Median 9	15%
Zbären, 2005[10]	33	Mean 9	18%
Wittekindt, 2007[11]	108	Total 22	16, 42, 75% (1, 5, 15 year)
Redaelli de Zinis, 2008[12]	33	Median 10.5	14, 31, 43, 57% (5, 10, 15, 20 year)
Makeieff, 2010[13]	62	Median 9	9.7%
Riad, 2011[14]	18	Mean 5	11%

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