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Salivary gland pleomorphic adenoma in the Netherlands: A nationwide observational study of primary tumor incidence, malignant transformation, recurrence, and risk factors for recurrence

M.H. Valstar [a,b,*,1], M. de Ridder [a,c,1], E.C. van den Broek [d], M.M. Stuiver [e], B.A.C. van Dijk [f,g], M.L.F. van Velthuysen [h], A.J.M. Balm [a,b], L.E. Smeele [a,b]

[a] Department of Head and Neck Oncology and Surgery, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[b] Department of Oral and Maxillofacial Surgery, Academic Medical Centre, University of Amsterdam, The Netherlands
[c] Department of Radiotherapy, Academic Medical Centre, University of Amsterdam, The Netherlands
[d] The Nationwide Network and Registry of Histo - and Cytopathology in the Netherlands (PALGA), Houten, The Netherlands
[e] Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands
[f] Department of Research, Comprehensive Cancer Organisation (IKNL) The Netherlands, Utrecht, The Netherlands
[g] Department of Epidemiology, University of Groningen, University Medical Centre, Groningen, The Netherlands
[h] Department of Pathology Erasmus Medical Centre, Rotterdam, The Netherlands

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ABSTRACT

Introduction: Whereas salivary gland pleomorphic adenoma (SGPA) is the most common type of salivary gland tumor, little is known about its epidemiology because national cancer registries do not register this disease.
Objectives: To establish SGPA incidence trends, rates of secondary malignant transformation and recurrence and associated factors in the Netherlands.
Materials and methods: Data on incidence, epidemiology, secondary malignant transformation and recurrence were retrieved from the Dutch pathology registry (PALGA) for the years 1992, 1997, 2002, 2007, and 2012. Multivariate analysis was performed to discover the risk factors for recurrence.
Results: 3506 cases of SGPA were recorded implying 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 the minor salivary glands had lower odds of recurrence than tumors in the parotid (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 malignancy found in roughly 14% of lesions [1,2]. The most common tumor type is salivary gland pleomorphic adenoma (SGPA), which accounts for more than 70% of benign epithelial tumors. These well-circumscribed tumors with ductal and myoepithelial elements are found in both the major and minor salivary glands with most

* Corresponding author at: Department of Head and Neck Oncology and Surgery, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands.
E-mail address: m.valstar@nki.nl (M.H. Valstar).
[1] Both authors contributed equally.

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occurring in the parotid gland. They are more common in women and age at diagnosis is mostly between 40 and 59 years old [2,3].

The standard of treatment is nerve-conserving, superficial parotidectomy (or extracapsular dissection in well trained hands). Recurrence is reported in 0–3% of patients [4,5]. Historically, enucleation was performed but this was associated with unacceptably high recurrence rates of up to 45% [6,7]. Results of postoperative radiotherapy for recurrent SGPA, show better local control (up to 94% after 20 years follow-up) than surgery only, in retrospective series [6,8,9].

In 1.8–6.2% of cases, SGPA transforms into carcinoma ex pleomorphic adenoma [4,10]. These cases make up 7.7–11.6% of all malignant salivary gland tumors [10,11]. In recurrent SGPA, de novo malignant transformation is reported in 0–23% [6].

As common a tumor as SGPA may be, its epidemiology has long remained uncertain for lack of national registration [4,12,13]. The literature reports research focused on benign salivary gland tumors in general or subgroups of SGPA [2,14–17]. Others have looked at regional incidence of SGPA or national incidence of parotid SGPA [1,4], but to our knowledge, national incidence of all-location SGPA and trends over time have not been investigated.

Of course, without any national data, no rates can be calculated for all-location SGPA incidence, recurrence, and secondary malignant transformation without a strong possibility of referral bias. We, therefore, decided to use the Dutch nationwide registry of pathology reports (PALGA). 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 for 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) [18], 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" [19,20].

Patient, tumor, and treatment characteristics

To further analyze our primary tumor data, we recorded 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 pathologist to decide on interpretation.

Recurrence rates and malignant transformation

In the subgroup of 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

We investigated 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 for our study.

Statistical analysis

We analyzed our data with SPSS (version 21.0; SPSS Inc., Chicago, III) and R [21,22], 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 [23]. With the Kaplan-Meier method, we calculated times to recurrence and identified potential predictors for 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, 3504 unique patients remained of a total of 3948 diagnosed with pleomorphic adenoma (Table 1). Two patients 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) (Fig. 1).

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

Table 1
Population characteristics primary SGPA and 1st recurrence.

		Primary (%)			1st Recurrence (%)
		Overall (n = 3506)	Male (n = 1421)	Female (n = 2085)	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	1423 (41)	571 (40)	852 (41)	64 (51)
	Right	1399 (40)	560 (39)	839 (40)	53 (42)
	Unknown	684 (19)	290 (20)	394 (19)	8 (6)
Treatment					
Procedure	Local excision	297 (8)			
	Partial parotidectomy	1214 (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	1449 (41)			
	Missing	35 (1)			
Clear margins	Negative	2028 (58)			
	Positive	491 (14)			
	Uncertain	261 (7)			
	Unknown	726 (21)			

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	1421	2085	3506			

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

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.

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 (Fig. 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, but minor-gland SGPA was more common in men than women (Table 1). In patients under 18, the minor and submandibular glands were affected more often than in adults (Additional Table B).

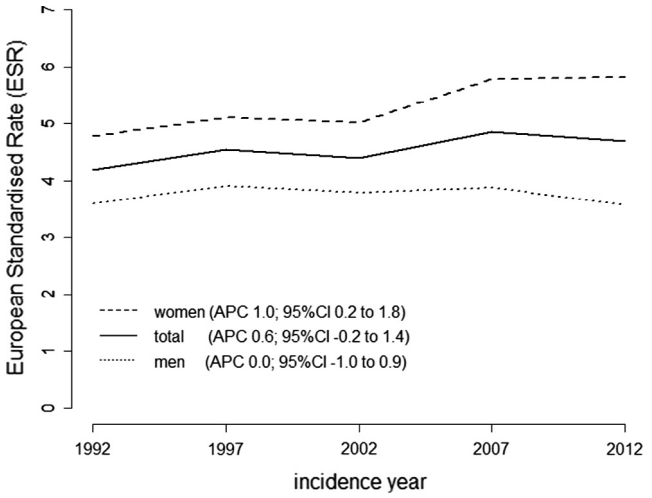

Fig. 1. European Standardized Rate (ESR) in the five investigated years, with interpolation in the periods in between. The annual percent change (APC), calculated from the five years, shows an increase in female SGPA incidence.

Surgical technique was reported as partial parotidectomy (35%), local excision (8%) and complete gland removal (6%). In 41% of cases the excerpts did not specify the surgical technique and in 1%, there was no mention of type of procedure at all. Histological margins were negative in 58%, positive in 14%, uncertain in 7%, and not reported in 21%.

Recurrence rates, characteristics, and malignant transformation

The disease recurred in 125 (4.6%) of the 2719 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) (Fig. 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.

Risk factors for recurrence

Margin status, age at diagnosis, and tumor location were all associated with risk of recurrence (Table 3). In patients with a reported margin status (complete cases, n = 1663), positive resection margins had an odds ratio for recurrence of 4.62 (95% CI 2.84–7.51), and 4.08 for uncertain margins (95% CI 2.24–7.43) 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%).

Missing data and imputation

Type of surgery performed and margin status were not mentioned in 42% and 21% of excerpts, respectively. There were 1663 patients with complete information. 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

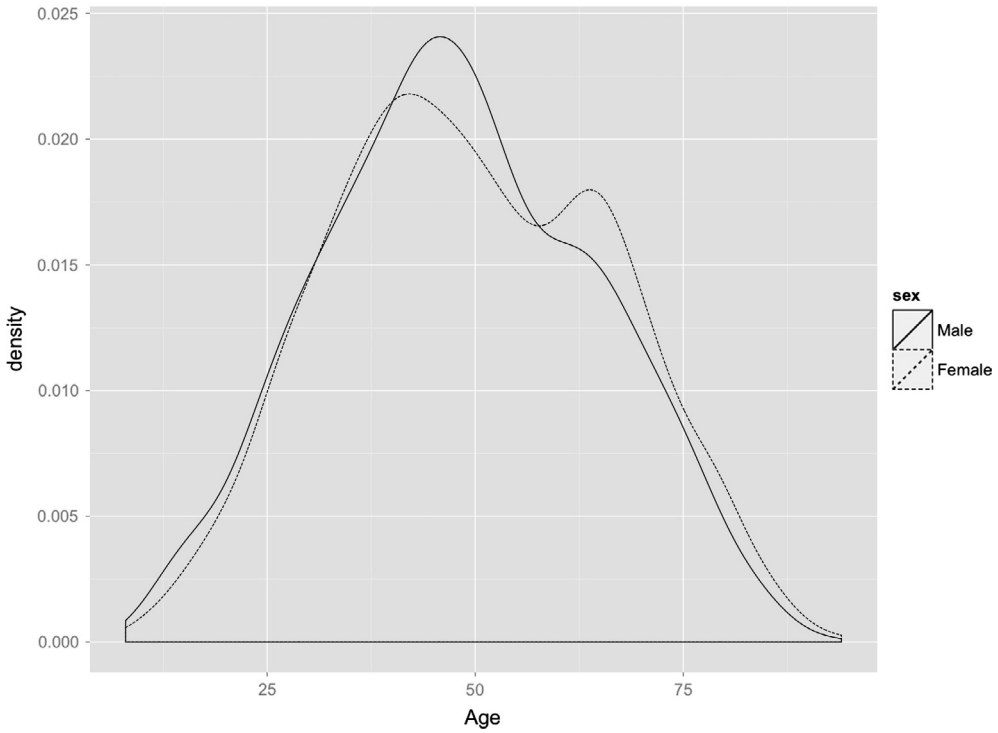

Fig. 2. Age distribution, showing a bimodal curve in women.

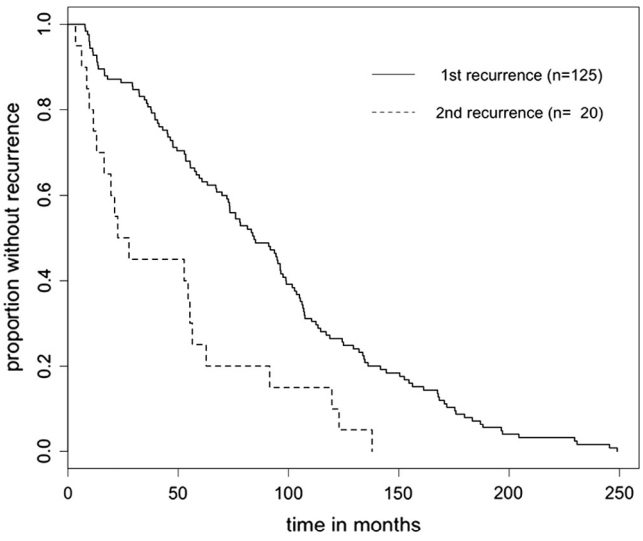

Fig. 3. Recurrence-free survival in patients who develop a recurrence, reflecting a decrease in median time to recurrence: 7 years to 1 s recurrence and 2 years between 1st and 2nd.

models revealed the same risk factors as our analysis of complete data (Table 3).

Discussion

We report a large cohort of 3506 patients with extended periods of follow-up and investigated 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 [1,2,4,14–17] (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 [4].

Interestingly, SGPA ESR in 2012 was 4.7 per 100,000 person-years, whereas salivary-gland cancer ESR in 2010 was 0.74 [24]. 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 [25–27]. 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 [28,29]. Salivary gland neoplasms have been associated with breast cancer before [30]. One risk factor for breast cancer is advanced maternal age at first childbirth [31–33]. In the Netherlands, this age rose from 28.0 to 29.4 in the period we investigated [18]. 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.

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

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

According to the literature, salivary gland tumors affect the parotid, submandibular, and minor glands in a ratio of 10:1:1 [1,34]. 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 [35] 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, location 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 (n = 2719) replicates previous findings [6], our 12% second-recurrence 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, diagnosed as carcinoma ex pleomorphic adenoma at first presentation without a history of SGPA. In earlier research, however, we found 34 cases of salivary gland carcinoma ex pleomorphic adenoma in the same period of investigation [24]. 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 2749). This is a similar percentage as the 1.7% that could be calculated from the population in Denmark [4]. Earlier publications reported a mean 6.2% risk, but their figures relate to single-centre data and may reflect a referral bias [10,36].

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 lower range of earlier findings [6]. These numbers are also lower than in Denmark, reported at 0.35% and 12.6% respectively. To some extent, the differences may be explained by different inclusion criteria, but more importantly, compared to smaller studies, we ruled out referral bias by compiling a nationwide cohort, rather than using single-centre data.

Our results confirm that at 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, with a mean number of 26 nodules (range 1–266) found in the primary resection bed [37]. 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 margins 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 [6,5].

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 [34,38–40]. 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 [37]. 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) [37]. 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 [37,43,44].

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, because literature suggests there is a role for radiotherapy in the adjuvant treatment of recurrent SGPA.

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.

Conflict of interest

None declared.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.oraloncology.2017.01.004.

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