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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

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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

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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