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ORIGINAL ARTICLE

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INFLUENCE OF THE PATIENT'S SEX AND AGE, VOLUMES OF THE SALIVARY GLAND AND PLEOMORPHIC ADENOMA ON THE TUMOR HISTOLOGICAL VARIANTS

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ABSTRACT

Aim: The purpose of the study was to identify the influence of the patient's sex and age, the volumes of the salivary gland and pleomorphic adenoma on the histological variants of the tumor.

Materials and Methods: The study included 21 women and 9 men with pleomorphic adenomas of the salivary gland. In 15 cases, a mesenchymal variant of pleomorphic adenoma was identified, in 5 cases – an epithelial variant, in 10 cases – a mixed variant. The average age of the patients was 39.7±2.9 years. Patients with pleomorphic adenomas underwent magnetic resonance imaging using a Siemens MAGNETOM Aera 1.5T device (Germany), during which three projections of the tumor and salivary gland were measured (antero-posterior, lateral, vertical) with subsequent calculation of their volumes, and then the ratios of these volumes. Classification trees were used to determine whether patients belonged to one of three variants of pleomorphic adenoma. The CART (Classification And Regression Tree) algorithm was used as a branching option. Stopping branching was carried out using the FACT (Fact-style direct stopping) method until each terminal (final) node of the tree does not contain incorrectly classified observations or when their number becomes less than a given proportion of the total group size (less than 5%). Determination of the structure and relationships between the tumor variants and such indicators as gender, age and radiological indicators (volume of the tumor, volume of the salivary gland, ratio of tumor volume to salivary gland volume) was carried out using correspondence analysis.

Results: Epithelial variant of pleomorphic adenoma is more typical for women, and the mixed and mesenchymal variant is more common for patients of both sexes. The epithelial variant can develop in patients of any age, while the mixed variant occurs mainly in patients older than 41 years, and the mesenchymal variant – mainly in patients younger than 41 years. The ratio of the volume of the tumor to the volume of the salivary gland will be predominantly >0.17 in the epithelial variant of pleomorphic adenoma, predominantly ≤0.17 in the mesenchymal variant, and can take any value in the mixed variant.

Conclusions: The authors conducted a study in order to identify the influence of sex, age of the patient, and the ratio of the volume of pleomorphic adenoma to the volume of the salivary gland on the histological variant of the tumor. The revealed data will be useful in the treatment and diagnostic process in patients with pleomorphic adenoma of the salivary gland.

KEY WORDS: sex, age, patient, salivary gland volume, pleomorphic adenoma volume, pleomorphic adenoma histological variants.

INTRODUCTION

Salivary gland tumors widely heterogeneous group that comprise about 3% of all head and neck tumors the annual incidence of which varies worldwide and ranges from 1.0 to 6.5 cases per 100,000 population [1-3]. They are the most complex due to broad histological spectrum resulting from a multiple tumor cell differentiation, cellular arrangements and extracellular matrix synthesis produced by certain tumor cells [4].

Benign tumors of salivary gland are more common when compared to malignant [5]. Pleomorphic adenoma is the most common salivary glands benign tumor, comprising 50-70% of all cases [5-6].

Pleomorphic adenoma was first termed by Willis. Its name comes from the architectural pleomorphism that may be seen with a light microscope [7]. Histological variants of pleomorphic adenoma, their immunohistochemical and morphometric characteristics have been described in our previous studies, as well as by many scientists [8-10].

Literature data regarding the age and gender characteristics of pleomorphic adenomas are contradictory [11]. Pleomorphic adenoma occurs in all ages but is most common in the third

to sixth decades of life. The average age of presentation is approximately 45 years with a female-to-male ratio of 2:1 [2].

Tumor size is an important pathological and clinical variable for benign and malignant salivary gland tumors [12]. Literature data regarding the relationship between the histological variants of pleomorphic adenoma and its size are controversial. Some scientists have not identified such a relationship [12], while other scientists describe it for some histological tumor variants [13].

AIM

The purpose of the study was to identify the influence of the patient's sex and age, the volumes of the salivary gland and pleomorphic adenoma on the histological variants of the tumor.

MATERIALS AND METHODS

The study included 21 women and 9 men with pleomorphic adenomas of the salivary gland. In 15 cases, a mesenchymal variant of pleomorphic adenoma was identified, in 5 cases – an epithelial variant, in 10 cases – a mixed variant. The average age of the patients was 39.7±2.9 years. Patients with pleomorphic adenomas underwent magnetic resonance imaging using a Siemens MAGNETOM Aera 1.5T device (Germany), during which three projections of the tumor and salivary gland were measured (antero-posterior, lateral, vertical) with subsequent calculation of their volumes, and then the ratios of these volumes. The average value of the salivary gland volume was 35041.91±11802 mm^3, the pleomorphic adenoma volume was 6141.86±4887.23 mm^3, and the ratio of tumor volume to salivary gland volume was 0.24±0.27.

Classification trees were used to determine whether patients belonged to one of three variants of pleomorphic adenoma [14]. The purpose of constructing a classification tree is to predict whether an object belongs to a particular class (tumor variant). The classification tree is a hierarchical structure with decision nodes and decisive selection rules. The CART (Classification And Regression Tree) algorithm was used as a branching option.

CART is an algorithm for constructing a classification tree that searches through all possible options for one-dimensional branching and selects the best one. Stopping branching was carried out using the FACT (Fact-style direct stopping) method until each terminal (final) node of the tree does not contain incorrectly classified observations or when their number becomes less than a given proportion of the total group size (less than 5%).

Determination of the structure and relationships between the tumor variants and such indicators as gender, age and radiological indicators (volume of the tumor, volume of the salivary gland, ratio of tumor volume to salivary gland volume) was carried out using correspondence analysis [15].

RESULTS

In this study, two qualitative indicators (gender, tumor type) and four quantitative indicators (age, tumor volume, salivary gland volume, ratio of tumor volume to salivary gland volume) were used for analysis.

For this analysis, the classification tree method [14] was used because it is a nonparametric method, which allows the use of data measured at any scale and under any distribution law. Another advantage of this method is the possibility of graphical presentation of results and ease of interpretation, which allows us to clearly explain why a particular object belongs to a particular class. In this case, it is possible to rank the indicators according to the degree of importance when determining the classified variants of pleomorphic adenomas.

It was applied a complete search of trees with one-dimensional branching using the CART algorithm to solve the classification (analysis) problem. Branching was stopped using a direct stopping algorithm according to FACT method with the established proportion of unclassified observations being less than 5%. Five-fold cross-validation was performed to assess quality.

Classification tree is built on the principle of a hierarchical structure, which consists of decision-making nodes. The decision nodes contain selection criteria. At each branching step, a rule generated at a node divides the set of patients into two parts. The left side of the node is the group where the condition is met; the right side is the group where the condition is not met. The number above the rectangles shows the number of patients included in it. Inside the rectangle is a qualitative diagram in three colors of the relationship between the variants of pleomorphic adenoma that are present at the input.

The resulting model (classification tree) (fig. 1) showed an optimal decision tree with 11 terminal vertices (red rectangles) and 10 branches. At the same time, the classification accuracy was 97% (29 out of 30 cases), the cost of cross-validation was 82.6%, which are very good indicators of the quality of the model.

Thus, we can conclude that indicators such as age and gender turned out to be significant parameters for classification and are associated with the type of pleomorphic adenoma. At the same time, it remains unclear how they are connected. It would be possible to use two-entry contingency tables and Pearson's χ^2 test to establish such relationship for qualitative indicators gender and tumor type. Unfortunately, the obtained values of χ^2 test had no significant differences ($p>0.05$). Therefore, multivariate analysis of contingency tables was used for several indicators (gender, age, ratio of tumor volume to salivary gland volume). This analysis is called corresponding analysis [15], but it requires converting all indicators into dichotomous ones. Figure 2-3 shows the principle of converting numerical indicators into dichotomous ones. After sorting the indicator by tumor type and indicator value, a line graph was constructed and a threshold value of the indicator was selected, which corresponded to the maximum average value of the χ^2 test between tumor types. The original quantitative indicator was transformed into a dichotomous one with the following values: 1 – less than the threshold value, 2 – more.

Multidimensional two-entry frequency table was used for three dichotomous predictors (sex, age, ratio of tumor

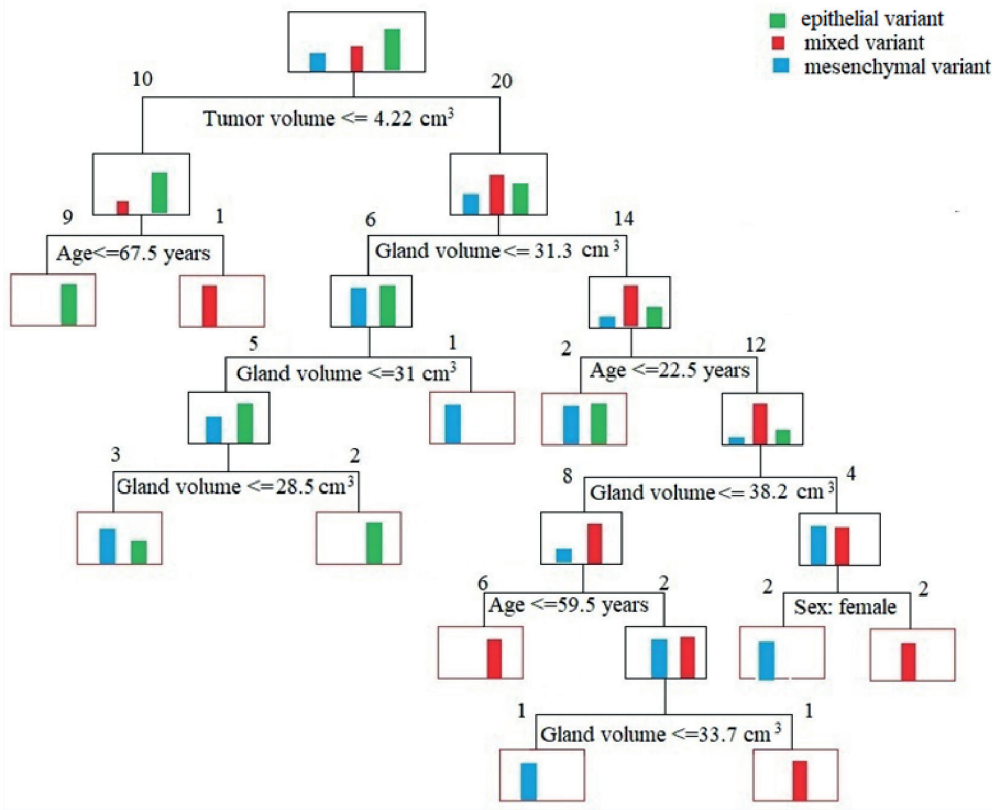

Fig. 1. Classification tree

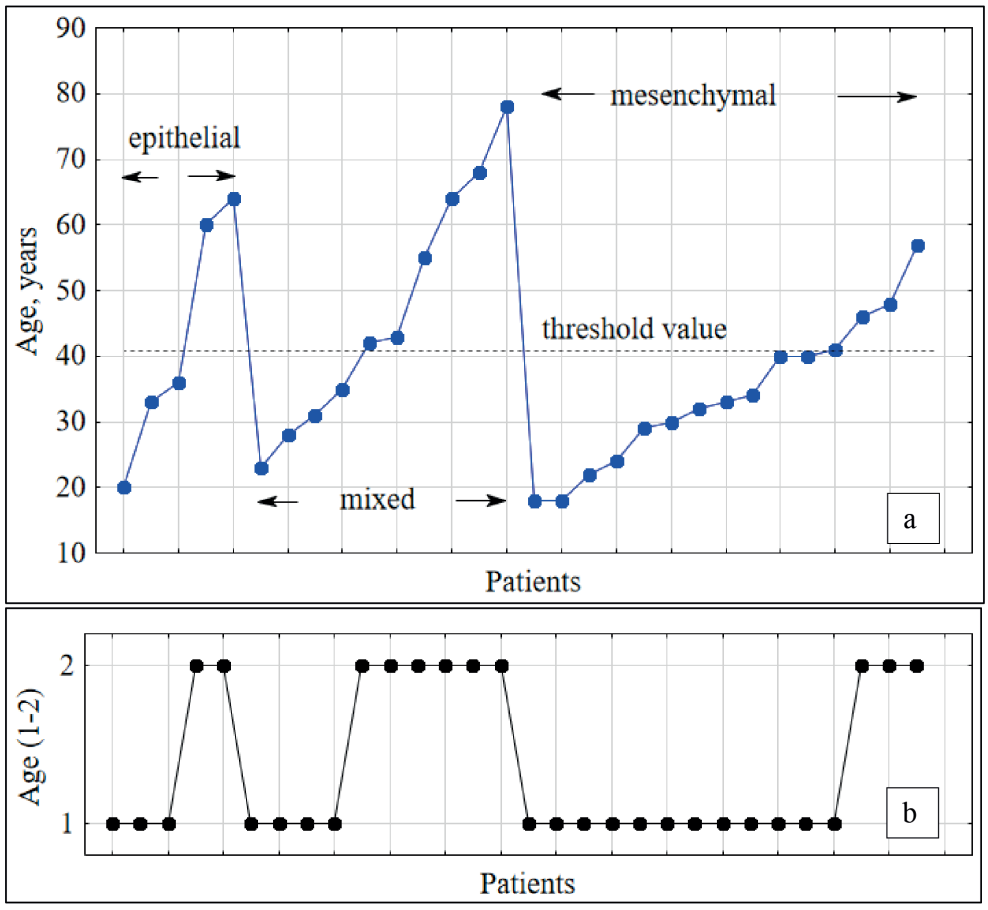

Fig. 2 (a, b). Determining the threshold value for age in order to convert it to the dichotomous indicator.

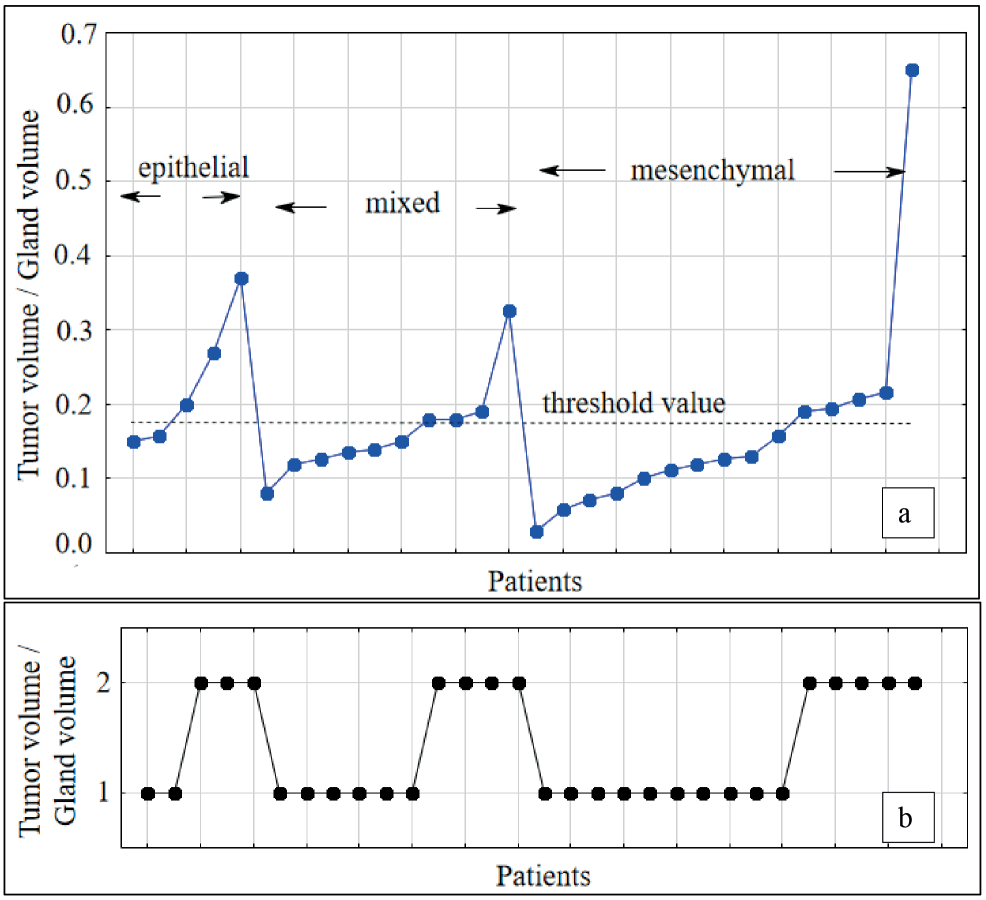

Fig. 3 (a, b). Determining the threshold value for the ratio of tumor volume to gland volume in order to convert it to the dichotomous indicator

Table 1. 9×9 dimensional Burt matrix

	Gender: female	Gender: male	Age: ≤41 years	Age: >41 years	Type: epithelial	Type: mixed	Type: mesen-chymal	Tumor/ gland volume: ≤0.17	Tumor/ gland volume: >0,17	Total
Gender: female	21	0	15	6	5	6	10	12	9	84
Gender: male	0	9	4	5	0	4	5	6	3	36
Age: ≤41 years	15	4	19	0	3	4	12	10	9	76
Age: >41 years	6	5	0	11	2	6	3	8	3	44
Type: epithelial	5	0	3	2	5	0	0	2	3	20
Type: mixed	6	4	4	6	0	10	0	6	4	40
Type: mesenchymal	10	5	12	3	0	0	15	10	5	60
Tumor/gland volume: ≤0.17	12	6	10	8	2	6	10	18	0	72
Tumor/gland volume: >0,17	9	3	9	3	3	4	5	0	12	48
Total	84	36	76	44	20	40	60	72	48	750

volume to gland volume) and three tumor types, which was transformed into a 9×9 dimensional Burt matrix for correspondence analysis (Table 1).

Using multidimensional correspondence analysis, the contents of the Burt matrix can be represented as points that correspond to the rows and columns of a table in a lower dimensional space. In the case of the initial nine-dimensional space, it was enough to consider only 4 dimensions with a cumulative contribution to inertia of at least 91.14%. Table 2 shows the coordinates of the original 9 points in four-dimensional space.

Figure 4 shows a graph of one of its two-dimensional projections of the considered 9 indicators, which are specified by the coordinates indicated in Table 2. It should be noted

Table 2. Coordinates of indicators in 4-dimensional space

Indicators	Coordinates			
	Dimension 1	Dimension 2	Dimension 3	Dimension 4
Gender: female	-0.431	0.186	-0.265	-0.326
Gender: male	1.01	-0.435	0.617	0.761
Age: ≤41 years	-0.556	-0.328	0.17	-0.16
Age: >41 years	0.96	0.566	-0.293	0.277
Type: epithelial	-0.958	1.459	-0.715	1.061
Type: mixed	0.855	0.573	0.397	-0.839
Type: mesenchymal	-0.251	-0.868	-0.026	0.206
Tumor/gland volume: ≤0.17	0.353	-0.314	-0.632	-0.091
Tumor/gland volume: >0,17	-0.529	0.472	0.948	0.136

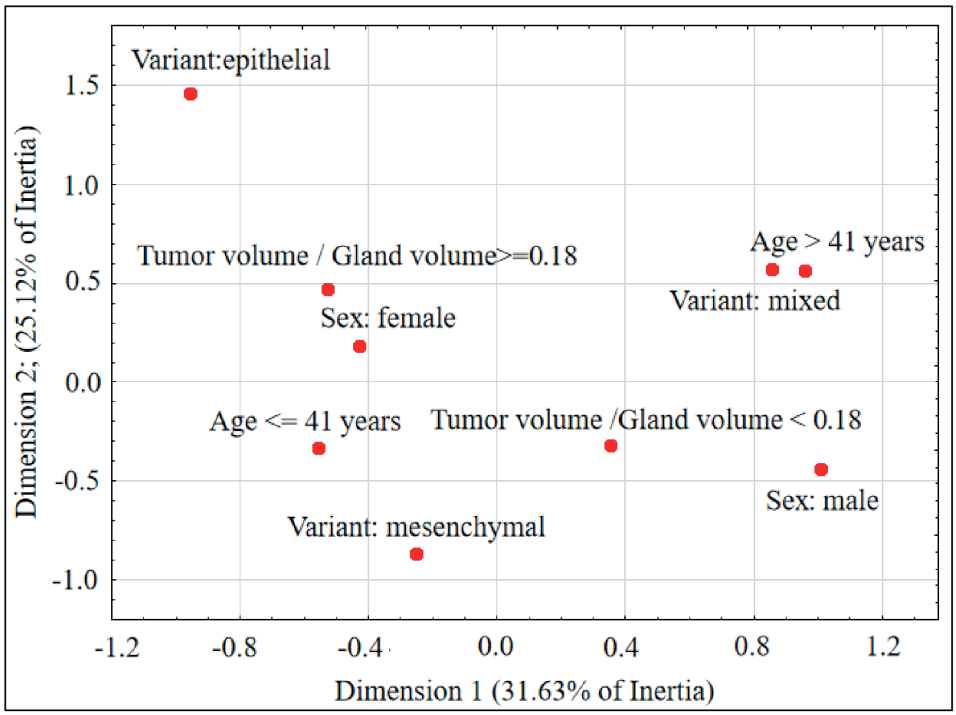

Fig. 4. Map-projection of the relationships between three types of tumor and three indicators: gender, age, ratio of tumor volume to gland volume

that the distances between 9 indicators shown on figure 4 only illustrate their relative positions. Euclidean metric was used in accordance with the coordinates of table 2 to calculate real distances. They are shown in Table 3.

Distances between points can be considered as a measure of the relationship between indicators, i.e. the closer the points are to each other, the more connected they are and the more likely the events they represent are to co-occur. Therefore, the inverse distances between points can be interpreted as the probabilities of their joint occurrence. Taking into account that tumor type-dependent indicators are dichotomous and the probability normalization condition, we can write the probabilities of indicators for the three types of adenoma (Table 4).

Thus, the data in table 4 indicate that the epithelial variant of pleomorphic adenoma is more typical for women, and the mixed and mesenchymal variant is more common for patients of both sexes. The epithelial variant can develop in patients of any age, while the mixed variant occurs mainly in patients older than 41 years, and the mesenchymal variant – mainly in patients younger than 41 years. The ratio of the volume of the tumor to the volume of the salivary gland will be predominantly >0.17 in the epithelial variant of pleomorphic adenoma, predominantly ≤0.17 in the mesenchymal variant, and can take any value in the mixed variant.

DISCUSSION

The authors conducted a study in order to identify the influence of sex, age of the patient, and the ratio of the volume of pleomorphic adenoma to the volume of the salivary gland on the histological variant of the tumor.

Table 3. Euclidean distances between adenoma types and indicators

Indicators	Gender: female	Gender: male	Age: ≤41 years	Age: >41 years	Tumor/ gland volume: ≤0.17	Tumor/ gland volume: >0.17
Type: epithelial	1.377	2.729	1.832	2.295	2.489	1.077
Type: mixed	1.343	1.019	1.673	0.105	1.02	1.387
Type: mesenchymal	1.07	1.33	0.62	1.877	0.819	1.368

Table 4. Probability of indicators for different types of adenoma

Indicators	Gender: female	Gender: male	Age: ≤41 years	Age: >41 years	Tumor/ gland volume: ≤0.17	Tumor/ gland volume: >0.17
Type: epithelial	66.5%	33.5%	55.6%	44.4%	30.0%	70.0%
Type: mixed	43.0%	57.0%	5.9%	94.1%	57.6%	42.4%
Type: mesenchymal	55.4%	44.6%	75.2%	24.8%	62.6%	37.4%

Research carried out by many scientists, including our earlier analysis of archival material, revealed that pleomorphic adenoma most often develops in women [16, 17]. This study showed that the epithelial variant of pleomorphic adenoma is more typical for women, whereas the mixed and mesenchymal variant is more common for patients of both sexes.

Pleomorphic adenoma of the salivary gland, according to the literature, can develop at any age, including children, but with predominance in the third to sixth decades of life [2]. Our research showed that the epithelial variant of pleomorphic adenoma can develop in patients of any age, while the mixed variant occurs mainly in patients older than 41 years, and the mesenchymal variant – mainly in patients younger than 41 years.

Many scientists in their studies did not analyze the size of salivary gland, the size of pleomorphic adenoma in various types of tumor. In a few studies, tumor size and histological variant were analyzed, and the results obtained were contradictory. Chau and Radden reported that stroma-poor (epithelial variant) pleomorphic adenoma were larger than stroma-rich (mesenchymal variant) ones, and suggested that cellular variant may grow at a faster rate. Cesinaro et al., Alves FA et al. observed that stroma-rich pleomorphic adenoma were significantly larger than other variant [13]. Erkul E et al. did find a significant association between tumor size and its histological subtype [12]. In this study, we noted that the ratio of the volume of the tumor to the volume of the salivary gland will be predominantly >0.17 in the epithelial variant of pleomorphic adenoma, predominantly ≤0.17 in the mesenchymal variant, and can take any value in the mixed variant.

CONCLUSIONS

The epithelial variant of pleomorphic adenoma is more typical for women, but the mixed and mesenchymal variant is more common for patients of both sexes. The epithelial variant can develop in patients of any age, while the mixed variant occurs mainly in patients older than 41 years, and the mesenchymal variant – mainly in patients younger than 41 years. The ratio of the volume of the tumor to the volume of the salivary gland will be predominantly >0.17 in the epithelial variant of pleomorphic adenoma, predominantly ≤0.17 in the mesenchymal variant, and can take any value in the mixed variant.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.