



# Correlation of Histopathological Sub Typing and Adverse Morphological Features of Pleomorphic Adenoma of the Parotid Gland

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## Abstract

**Background and Aim:** The aim of this study is to assess the histopathological sub typing of the pleomorphic adenoma of the parotid gland which were treated with superficial parotidectomy and analyze the relationship with the adverse morphologic characteristics.

**Materials and Methods:** Demographic features and Hematoxylin and Eosin stained histologic slides of 71 patients that were treated with superficial parotidectomy for pleomorphic adenoma of the parotid gland were reviewed retrospectively. Histological subtypes, capsular characteristics as; capsular penetration, capsular integrity, satellite tumors, the presence or absence of pseudopodia and size of the tumors were evaluated.

**Results:** In total of 71 patients, 54 patients whose features met the inclusion criteria were included into the study. Both the stroma-rich and classic types were observed significantly as more common histological subtypes ( $p=0.016$ ). There was no statistically significant relationship between any histological subtype and capsular characteristics and any histological subtype and tumor size ( $p=0.474$ ). We only found a significant association between satellite nodules and tumor size that were larger than 4 centimeter ( $p=0.017$ ).

**Conclusion:** There was no significant association between any histological subtypes, capsular features and tumor size but only satellite nodules were often observed when tumor was larger than 2 centimeters.

**Keywords:** Parotid gland; Pleomorphic adenoma; Histopathology; Recurrence

## Introduction

Parotid tumors occurred rarely and represent 1% to 3% of all head and neck tumors, with an incidence of nearly 1500 cases each year in the United States [1]. Pleomorphic Adenoma (PA) is the most common salivary gland tumor and accounts for more than 50% of the benign tumors of salivary gland [1,2]. It is mostly seen in parotid gland (80%) but affecting minor salivary glands like hard palate [2,3]. PA presents frequently with a painless mass, smaller than 4 cm, locating superficial lobe, a predilection for females, unilateral and with a peak ages between 30 and 50's [1,3,4].

PA has a complex histology, consisting different morphological features and may play challenges for diagnosis. PA exhibits epithelial and myoepithelial cells which are formed in various patterns, compromising different types of stromal formations [1,3-6]. Evaluation of a parotid mass should be done to rule out malignancy and should include a fine-needle aspiration biopsy and imaging studies as indicated. Accurate preoperative diagnosis is critical for surgical planning and appropriate management in adequate tumor removal and preventing complications [1]. In the early 20<sup>th</sup> century,

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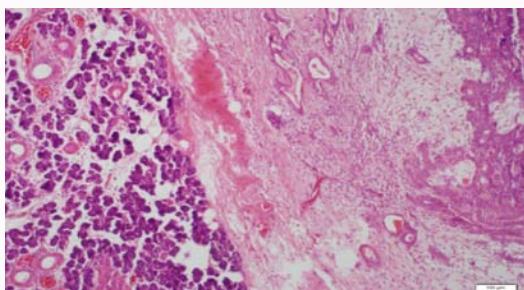
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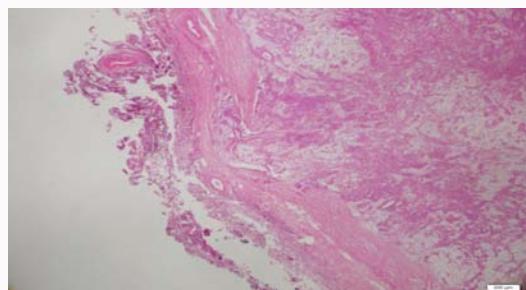
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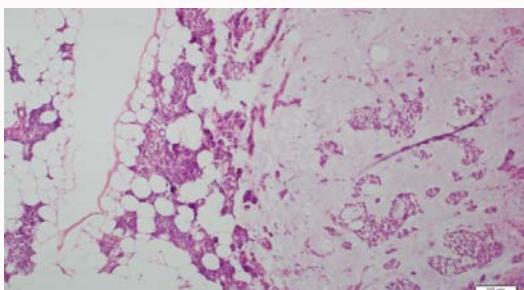
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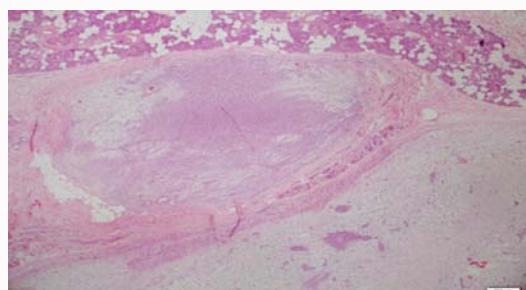
**Figure 1A:** PA with incomplete capsule. Stroma-rich (myxoid) subtype merging with fat tissue (Hematoxylin-Eosin Stain, X100).



**Figure 2:** Cellular subtype PA with Finger like tumor herniation of the capsule (Hematoxylin-Eosin Stain, X100).



**Figure 1B:** PA with incomplete capsule. Classic subtype merging with salivary gland tissue (Hematoxylin-Eosin Stain, X100).



**Figure 3:** Classic subtype PA with pseudopodium in contact with the main tumor capsule (Hematoxylin-Eosin Stain, X100).

intracapsular enucleation primarily sought to avoid damage to the facial nerve while performing a subtotal removal of the tumor capsule with a recurrence rate of 45% [7,8]. There are currently different preferred surgical management options of parotid PA such as extra capsular dissection, partial superficial parotidectomy, or complete superficial parotidectomy due to a reduction in tumor recurrence rates as low as 2% [6-8].

Facial nerve close dissection is performed along the tumor which means a limited extra capsular dissection ought to require. Performing a subtotal removal or spreading the tumor cells while excision of the tumor is the main reasons of the recurrence. In addition, incomplete surrounding tumor capsule, pseudopodia, microsatellites, thickness of the capsule and epithelial and stromal component rates of the tumor are the main previously reported histopathological recurrence reasons [3-6]. There is still a controversy if the histopathological features have a role on the recurrences are due to histopathological features or the only the reason to cause the recurrences is incomplete removal of the tumor [3-5]. There are few studies that reported to the detail histopathological features and their association between histopathological features of the PA of the parotid gland in detail and tumor recurrence [5-7].

The aim of the present study is to assess the histopathological subtypes of the PA of the parotid gland which were treated with superficial parotidectomy and analyze the relationship with adverse morphologic characteristics.

## Materials and Methods

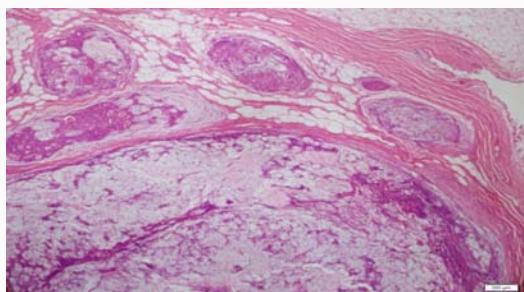
### Patients

This study was conducted retrospectively in patients who underwent superficial parotidectomy because of PA of the parotid gland between 2005 to 2015 at the Department of Otorhinolaryngology, Gulhane Military Medical Academy (GATA), Haydarpasa Training

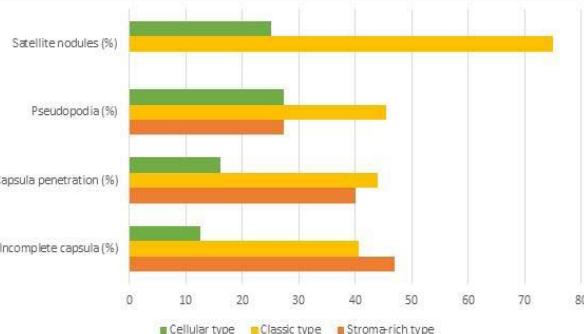
Hospital in Istanbul, Turkey. The study was approved by the GATA Haydarpasa Training Hospital Ethics Committee (Approval No.: 08/01/2015/2015-6) and was conducted according to the Declaration of Helsinki Principles. The study involved 71 patients with PA of the parotid gland for whom paraffin embedded pathology blocks and retrospective clinical data could be gathered. Patients who had undergone previous parotid gland surgery and total parotidectomy and recurrent PA were excluded. We performed a retrospective analysis of the clinical data to analyze gender, age, anatomical location, follow-up period and recurrence status.

### Histopathological examination

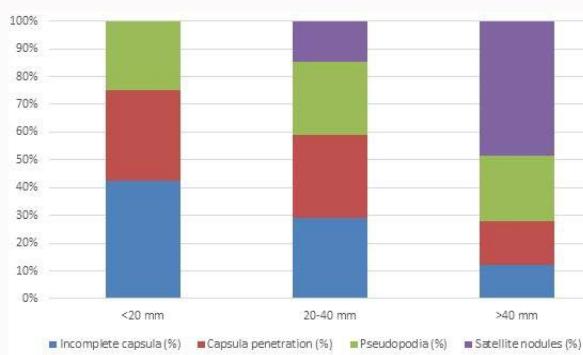
All patients were undergone partial or total superficial parotidectomy under general anesthesia. Superficial parotidectomy terms, excision of parenchyma part of the gland lies lateral to the facial nerve. Surgical specimens were fixed in 10% formalin after parotidectomy. Tumor size was classified as smaller than 2 cm, from 2 cm to 4 cm, as and larger than 4 cm by direct measurement of the tumor in the parotidectomy specimen. According to gross examination procedure of parotidectomy specimen, before dissecting the specimens for histopathological processing the surface of the parotid gland was inked with a specific color marking ink to mark the surgical margin. We used Biomark 5 Color Tissue Marking Dye Kit (Atom Scientific, UK) to orient specimens unambiguously. The inked specimens were dipped into 90% alcohol solution for 30s to mordant the ink to the surface, thus minimizing smearing during dissection. The parotid lobe with the tumor was then cut into whole-organ sections every 2 mm or 4 mm thickness according to the tumor size. At each level, at least 1 section was processed for microscopic examination. The mean number of section was 6.2 (range, 3 to 20 sections). Hematoxylin and eosin stained sections of formalin fixed paraffin-embedded parotidectomy specimens of the 54 patient were analyzed for histopathological evaluation. Sections were reviewed under Olympus BX53 (Olympus, Tokyo, Japan) light microscope at



**Figure 4:** Classic subtype PA with cellular satellite nodule (Hematoxylin-Eosin Stain, X100).



**Figure 5:** The association between histopathological subtype and capsular features of PA.



**Figure 6:** The association between size of the tumor and capsular features of PA.

40X, 100X and 400X magnification by two pathologists.

Tumors were classified according to Seifert et al., [9] into 3 histological subtypes: the stroma-rich subtype with a stroma content of 80%; the classic subtype with a stroma content of 30% to 50%; and the cellular subtype with stroma content of 20% to 30% or less. Each case was examined for capsular integrity, capsular penetration, and the presence or absence of pseudopodia, satellite tumors and surgical margin status.

We considered the surgical margins to be negative when we did not observe tumor in the inking outer surface of the specimen under microscopic examination.

#### Nomenclature of capsular characteristics

Capsular characteristics were described as follows: "Incomplete capsule" designates a focal absence of encapsulation of the PA showing tumor tissue merging with salivary gland tissue (Figure

1A,B). "Capsule penetration" indicates infiltration of the fibrous capsule by tumor tissue without separation of the infiltrating tumor tissue from the main tumor mass by fibrous fibers (Figure 2). The term of pseudopodium is used for a tumor nodule extruded through the incomplete capsule but continued with the main tumor capsule or in contact with it (Figure 3). Satellite nodules are distinct tumor nodules in the vicinity of the main tumor lump with no connection with the main tumor (Figure 4).

#### Statistical analysis

Data were analyzed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL, USA). Associations between the type of affected salivary gland and histopathological features, and between the capsular characteristics and histological subtypes were verified by Pearson's Chi-square or Fisher exact test. A significance level of 5% was adopted for all tests.

#### Results

##### Patients

Seventeen test samples were found to have inadequate histopathological staining for examination and were, therefore, excluded from the study and in total, 54 patients with a primary PA of the parotid gland who met the criteria of the study were included. There were 35 men and 19 women in the study group and their mean age was 36.39 years (range, 15 years to 75 years). All tumors were in the superficial lobe and were treated by superficial parotidectomy with facial nerve preservation. The masses located on the left side in 23 patients and on the right side in 31 patients. Demographic data of the patients are provided in Table 1.

The follow-up varied from 20 months to 166 months (average 73 months). One patient developed a recurrence after 54 months. The case was a classic subtype of PA with 40 mm in size. It showed incomplete capsule, capsular penetration, satellite nodules and pseudopodia. Surgical margin was negative.

##### Histopathological examination

In terms of histological type, 23 of the 54 (42.6%) patients were stroma-rich type, 23 of the 54 (42.6%) were classic type and 8 of the 54 were cellular type (14.8%). Both the stroma-rich and classic types were observed significantly more common histological subtypes ( $p:0.016$ ). The association between histopathological subtype and capsular features of PA were summarized on Table 2 and Figure 5. Incomplete capsule was presented 32 (59.3%) of the cases and capsular penetration by tumor was presented nearly half of the patients (25 cases with a rate of 46.3%). However, pseudopod and satellite nodule were seen in 11 (20.4%) and 4 (7.4%) patients, respectively. Incomplete capsule was observed in 15 of the 23 stroma-rich tumors (65.21%), 13 of the 23 classic type tumors (56.5%) and 4 of the 8 cellular type tumors (50%). There was no statistically significant relationship between histological type and incomplete capsule ( $p:0.71$ ). Capsular penetration was observed in 10 of the 23 stroma-rich tumors (43.47%), 11 of the 23 classic type tumors (47.8%) and 4 of the 8 cellular type tumors (50%). There was no statistically significant relationship between histological type and capsular penetration ( $p:0.93$ ). Pseudopodia was revealed in 3 of the 23 stroma-rich tumors (13.04%), 5 of the 23 classic type tumors (21.7%) and 3 of the 8 cellular type tumors (37.5%). There was no statistically significant relationship between histological type and pseudopodia ( $p:0.33$ ). A satellite nodule was not seen in none of 23 stroma-rich tumors. However, 3 of the 23 classic type tumors (13.04%) and 1 of the 8 cellular type tumors (12.5%) had satellite

**Table 1:** Demographic and Histological features of the patients with PA of the parotid gland.

Characteristics	Number (%)
Gender	
Male	35 (64.8%)
Female	19 (35.2%)
Age	
Mean	36.39
Range	15 to 75
Size	
Mean	31.61 mm
<20 mm	16 (29.6%)
20-40 mm	27 (50%)
>40 mm	11 (20.4%)
Side	
Left	23 (42.6%)
Right	31 (57.4%)
Follow-up duration, month	
Mean	73
Range	20 to 166
Pathology slide	
Mean	6.2
Range	3 to 20
Histological subtype	p:0.016
Stroma-rich	23 (42.6%)
Classic	23 (42.6%)
Cellular	8 (14.8%)
Capsular features	
Incomplete capsula	32 (59.3%)
Capsula penetration	25 (46.3%)
Pseudopodia	11 (20.4%)
Satellite nodule	4 (7.4%)

nodules. There was no statistically significant relationship between histological type and satellite nodules (p:0.12). Only 3 patients had positive tumor margins among 54 patients and all three patients had classic subtype histology. Classic subtype had the highest rate of capsule penetration (44%), pseudopodia (45.45%) and satellite nodules (75%) but incomplete capsule (46.88%) was common only in stroma-rich group.

Table 3 showed the size of the tumors in relation to histological subtype. The half of the 54 tumors was measured between 21 mm and 40 mm, 16 of 54 were smaller than 20 mm and 11 of 54 were larger

than 40 mm. In terms of the size of the tumors, the tumor size that were measured smaller than 20 mm; 9 of the 16 were stroma-rich tumors (56.2%), 5 of the 16 were classic type tumors (31.2%) and 2 of the 16 were cellular type tumors (12.5%). The tumor size that were measured between 21 mm to 40 mm; 11 of the 27 were stroma-rich tumors (40.7%), 11 of the 27 were classic type tumors (40.7%) and 5 of the 27 were cellular type tumors (18.5%). The tumor size that were measured larger than 40 mm; 3 of the 11 were stroma-rich tumors (27.3%), 7 of the 11 were classic type tumors (63.6%) and 1 of the 11 was cellular type tumors (9.1%). There was no statistically significant relationship between histological type and tumor size (p:0.474).

We also compared the association between capsular features and size of the tumors. Although there was a significant association between tumor size that were larger than 4 cm and satellite nodules (p:0.017), there was no statistical significance between size of the tumor and incomplete capsule, capsular penetration, pseudopodia (p:0.92, p:0.66, p:0.3 respectively) (Figure 6).

## Discussion

Even PA's are the most common parotid gland neoplasm, no common thought has been reached on the best surgical technique due to concerns on recurrences and its distinct histopathological features [4,7,8,10,11]. Capsular variations, pseudopodia and satellite nodules are well known characteristics of the PA and capsular incompleteness can be vary related to the thickness and tumor penetrance [3,10,12]. The recurrence of the PA of the parotid gland and its surgery is a challenging problem and myxoid subtype, satellite nodules, larger size and tumor spillage are the more suspected characteristics of the recurrence [5,6,10,13]. The Dutch national database reported a recurrence rate of 2.9% after a follow-up for 15 years [14]. There have been few articles published that examined and assessed association between detailed capsular features and the histopathological subtypes and size of the PA of the parotid gland [3,5,6,10]. In our study, we aimed to report histopathological features and its association with each of the features of our PA cases of the parotid gland that only treated with superficial parotidectomy.

PA has epithelial and stromal components that display a diversity of three different subtypes, defined by Seifert et al. [9]. The rates of the subtypes vary in different studies. In three previous studies that only assessed the histopathological features of PA's of the parotid gland, reported different frequency rates of the subtypes [5,6,15]. Stennert reported the most frequent subtype as myxoid (51%) and the less frequent as classical (14%) type [15]. In contrast to previous study, the other two studies reported a high frequency rate for classical subtype [5,6]. The different variation rates for PA's in different locations of the head and neck was also reported in three studies [9,16,17]. In our study, 23 of the 54 (42.6%) patients were stroma-rich type, 23 of the 54 (42.6%) were classic type and 8 of the 54 were cellular type (14.8%). Both the stroma-rich and classic types were

**Table 2:** The association between Histological Subtype and Capsular features of PA.

		Incomplete capsula (n)		Capsula penetration (n)		Pseudopodia (n)		Satellite nodules (n)	
		-	+	-	+	-	+	-	+
Histological subtype	Stoma-rich	8	15	13	10	20	3	23	0
	Classic	10	13	12	11	18	5	20	3
	Cellular	4	4	4	4	5	3	7	1
p		0.71		0.93		0.33		0.12	

n: number of tumors

**Table 3:** The association between Histological Subtype and size of PA.

Histological subtype	<2 cm (%)	2 cm to 4 cm (%)	>4 cm (%)	p
Stoma-rich	56.2	40.7	27.3	0.47
Classic	31.2	40.7	63.6	
Cellular	12.5	18.5	9.1	

observed significantly more common histological subtypes ( $p:0.016$ ) in our study. In consistent with the Zbaren et al. [5] and Park et al. [6] studies, cellular type was the less frequent type in our study. Distribution of the subtypes varies in different studies and this may be related non-uniform definition and interpretation difference of the different pathologist. Even there is no uniform distribution rates of the subtypes, it has been well reported that most of the recurrences of the PA were myxoid subtypes [9,10,15,18]. In our study, one patient developed a recurrence with classic subtype so it is inappropriate to make a comment on association between subtypes and recurrence in our study.

PA has generally a capsule that covers the tumor with a layer of fibrous tissue and there has been a debate on recurrence etiology related to the incomplete capsule and capsule penetration of the tumor [9,10]. Stroma rich tumors have thinner capsule than hypercellular types [3-5,10]. The absence of the capsule and/or very thin capsule are found to be nearly 20% to 70% [10,15]. In our study, 59.3% (32 of the 54) of the patients have incomplete capsule and 46.3% (25 of the 54) of the patients have capsule penetration and these results are consistent with the previously published study [10]. Naeim et al. [16] showed that 69% of the stroma rich type, 30% of the classic type and 18% of the cellular type PA of the all salivary glands had incomplete capsule. Stennert et al. [15] found a distinct focal absence of encapsulation in 71% of the PA of the parotid gland of stroma-rich type. In two studies that assessed only PA of the parotid glands, reported a higher but not a statistically significant association between incomplete capsule and stroma-rich subtype of the tumors [5,6]. In our study, we also did not find a statistically significant association between subtypes and incomplete capsule ( $p:0.71$ ). Capsule penetration has to be found 47.8% of the major salivary glands, 26% of the parotid gland of the PA in two studies and it was mostly seen in classic subtype without a significant association between other subtypes [3,5]. Our results are consistent with both studies in terms of capsule penetration rates and higher capsule penetration in classic subtype (11 of 25 patients). Even it looks like a higher incidence of coexistence of incomplete capsule and recurrence in very limited studies, studies did not find a significant correlation between incomplete capsule and recurrences [6,18,19].

Pseudopodia in PA of the parotid gland were found 40% by Zbaren et al., [5], 53.6% by Park et al., [6], and 28% by Stennert et al., [15]. In our study, we found pseudopodia in 11 of the 54 (20.4%) cases and our results are lower than previous studies. Nevertheless, in our study and all three studies above have not found a statistically significant correlation between pseudopodia and subtypes [5,6,15]. Pseudopodia were common in classic subtype in Zbaren et al., [5] and in our study. Henriksson et al., [6] reported the pseudopodia as a risk factor for local recurrence in PA of all salivary gland but Park et al., [13] did not find a significant association between pseudopodia and recurrences in PA of the parotid glands.

Satellite nodules extend to a distance from tumor between 5 mm to 8.5 mm in two studies and it is hard to argue if it is a multifocal tumor [20,21]. Satellite nodules were found 13% in Zbaren et al., [5]

and 14.5% in Park et al., [6] studies and both studies did not find a significant relation between satellite nodules and subtypes. In our study, even we found a lesser rate of satellite nodule (7.5%), we also did not find a significant correlation between satellite nodules and subtype ( $p:0.12$ ). Recurrent PA had higher prevalence (60%) of satellite nodules than non-recurrent tumors (10%) in Park et al., [6] study.

Tumor size is an important pathological and clinical variable for benign and malign salivary gland tumors. Incomplete capsule was mostly observed in tumors larger than 4 cm in three different studies but it was not significant [5,17,21]. In contrast with above studies, Park et al., [6] observed incomplete capsule in tumors smaller than 2 cm but it was also not significant. Li et al., [5] and Zbaren et al., [6] found a significant association between satellite nodules and tumors larger than 4 cm in size, additionally Park et al., [21] found a weak but not significant relation ( $p:0.095$ ). In our study, we found a statistically significant association between satellite nodules and tumors larger than 4 cm ( $p:0.017$ ) and incomplete capsule was mostly seen in tumors <2 cm and >4 cm but insignificant ( $p:0.92$ ). Tumor size and subtype association was not assessed in previous studies. Our study is the first study that evaluated relation between tumor size and any histological subtype and we did not find a significant association ( $p:0.474$ ).

Recurrence surgery is often performed at different centers and by another surgeon other than primary surgeon because of occurring of recurrence of PA in 2 years to 15 years and relatively young patients [10]. Despite of the lack of prospective studies and long follow-up period of patients, there is still controversy of main reason of recurrences whether related to histopathological features or not. Dulguerov et al., [10] reported a systemic review and stated that stroma-rich subtypes, larger PA seem to recur more frequently. They also stated that tumor spillage and positive margins have more recurrence relationship [10]. Park et al., [6] showed a positive significant association between positive margins and tumor spillage with recurrence in multivariate analysis. Recurrence was related with the tumor size in two different studies (larger than 43 mm, 25 mm, respectively) [22,23]. However, Park et al., [6] and Henriksson et al., [13] could not find an association between tumor size and recurrence. In our study, we had only one recurrence and this patient had incomplete capsule, pseudopodia and satellite nodule but it was a classic subtype with 40 mm in size. However, we agreed to avoid commandment on recurrence reasons in our series due to very low rate of recurrence (1.85%) and short follow up period (73 months).

## Conclusion

Both stroma-rich and classic subtypes were common in our study and this study did not find an association between histological subtypes and capsular features. Our study is the first study that evaluated tumor size and histological subtype and did not find a significant relation. Satellite nodule and tumor that was larger than 4 cm has close relationship. Surgical factors are seemed to be more related than histopathological features for recurrence of PA in parotid glands.

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