

RISK FACTORS FOR RECCURENCE OF PLEOMORPHIC ADENOMA AND POSTOPERATIVE FACIAL NERVE MORBIDITY

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Abstract

Pleomorphic adenoma (PA) is the most frequent tumor of the salivary glands. It is characterized by a tendency to recur, which is determined by the biological characteristics of the tumor as well as the mode of its treatment. Fine needle aspiration cytology (FNAC) is widely used but its sensitivity is controversial up till now. MRI provides information on the exact localization and extent of the lesion, also in the deep lobe and the parapharyngeal space. MRI allows detecting perineural spread, bone invasion and meningeal infiltration. CT should be used for further staging if MRI is not available or contraindicated.

Recurrence of the tumor is associated with a high risk of postoperative facial palsy, risk of subsequent recurrence and an increased risk of malignant transformation. Among the factors, the most important are: incomplete excision, intraoperative capsule rupture, myxoid subtype, presence of the satellite nodules and the experience of the surgeon.

The aims of the study were evaluation and correlations of histological properties of tumor (it's size, location, subtype), mode of treatment and rate of recurrence, to compare the incidence of postoperative facial morbidity related to these variables, by using clinical- neurophysiological assessment of facial nerve function post-operatively.

This study includes retrospective combined with prospective and descriptive clinical study cases of overall 77 patients with confirmed PA, treated in our clinic in a period from 2016 to 2020. The values of the size and the subtype of the tumor were obtained from the pathohistological findings after the surgery, comparing with preoperative assessment of CT or MRI values. Clinical assessment was based on House-Brackmann scale (H-B), postoperatively and the neurophysiological diagnostic measurement which included surface mimetic muscle electromyography (S-EMG), comparing the affected side with the non-affected one. Multivariable logistic regression analyses and descriptive inferential with binary logistic regression were conducted to identify risk factors for the recurrence, postoperative facial nerve dysfunction, tumor size, location and it's subtype. A statistically significant relationship was found between the appearance of facial paresis and tumor location in the superficial lobe, size and myxoid subtype. Neurophysiological studies detected clinically silent facial nerve neuropathy of mandibular marginal branch in postoperative period. S- EMG, allows for the evaluation of face muscles reinnervation and facial nerve regeneration. The commonest complications after parotidectomy are temporary or permanent facial palsy and Frey's syndrome. Tumor location in the parotid superficial lobe upper area, size and myxoid subtype are risk factors that can worsen facial paresis. The knowledge of these complications is relevant for patient's counseling and to achieve better long-term outcomes.

Keywords: pleomorphic adenoma, risk factors, recurrence, facial nerve palsy, facial nerve neurophysiology.

1. Introduction

Pleomorphic adenoma, also known as benign mixed tumor, is the most common salivary gland tumor. The term mixed tumor was first used by Broca in 1866, the first microscopic description of the term was published by Minissen in 1874 [Fotte *et al.* 1953], on behalf of Willis, from 1948 the term pleomorphic adenoma is in use, emphasizing the origin of the tumor - the cells of two epithelial layers, considering the term mixed tumor to be inadequate. Histological examination of the majority (80%) of parotid tumors shows a benign character, while about 20% are malignant with different histological variants [Eneroth *et al.* 1971, Bradley *et al.* 2013]. Pleomorphic adenoma microscopically contains two components: epithelial and mesenchymal. It has been shown to originate from salivary gland epithelial cells and myoepithelial cells [Sikorowa *et al.* 1989]. Myoepithelial cells are derived from totipotent stem cells, and this explains the morphological diversity of

pleomorphic adenoma, which is characterized by biphasic growth of epithelial or myoepithelial cells [Lee P.S. *et al.* 2000].

Based on the amount of stromal component, according to the classification of Seifert *et al.* [Seifert G. *et al.* 1976], pleomorphic adenoma is divided into three subtypes:

1. Cellular subtype with stromal content of 20-30%,
2. Classic subtype with stromal part 30-50% and
3. Myxoid subtype with stromal content up to 80%

Microscopically it is encased in a translucent capsule, sometimes thin and opaque, which is easily separated from the tumor mass. The capsule usually envelops the entire tumor, but may be incomplete, in some places thin and interrupted by tumor expansion or satellite nodules.

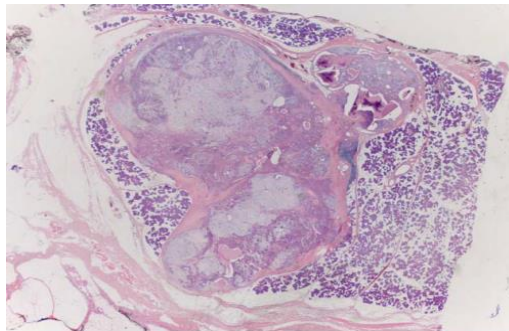


Figure 1. Histological structure and clearly visible pseudopodia in primary PA

Pleomorphic adenoma has a tendency to recur which is related to its biological features as well as the method of surgical treatment. An important role is played by the structure of the tumor capsule, which may have focal defects of encapsulation and through these sites the tumor forms ring-shaped extensions that can penetrate into the surrounding glandular tissue. Inadequate surgical procedure, such as tumor enucleation, is a proven cause of local recurrence.

It is very important to understand the different philosophy behind superficial parotidectomy and extracapsular dissection. Parotidectomy is a dissecting surgery of the facial nerve, ie. surgery primarily follows the plane of the peripheral facial plexus, while extracapsular dissection follows the boundaries of the tumor without exposing the facial nerve. Relapse may occur one year after surgery or much later, as reported in a study [Wierzbicka *et al.* 2012]. Relapse is associated with a marked higher risk of facial nerve paresis (reoperation may increase the risk of facial nerve injury by approximately 70%) and a lack of radicality in reoperation, in a significantly more difficult operation.

RISK FACTORS OF RECURRENCE

Incomplete extirpation and intraoperative rupture of the tumor capsule - the most common cause of recurrence of pleomorphic adenoma is incomplete removal of the tumor. The capsule can be easily damaged, especially when enucleation is performed instead of parotidectomy. Reduced operative field and lack of preoperative imaging preparations are significant risk factors for recurrence due to the possibility of tumor fragments lagging in the operative field [Stennert E *et al.* 2001].

Capsule hernias - much more common in the cellular subtype (42%) cases, while in the myxoid subtype found in 8% of cases.

Tumor extension (pseudopodia) - noted in an average of 40% of this type of salivary tumors. Tumor extension may be an important risk factor for recurrence of pleomorphic adenoma after tumor enucleation.

Satellite nodules - it is difficult to distinguish a satellite nodule from a tumor extension (pseudopodia). Satellite nodules were found in 13% of cases, and together with tumor extension in 48% of cases.

Tumor dispersion during surgery - Tumor rupture during parotid surgery is the main problem when dealing with pleomorphic adenoma. Adenomas may be irregularly shaped, with a dissected surface, especially at sites of contact with the facial nerve.

Myxoid subtype - recurrence of pleomorphic adenoma was most commonly recorded in cases of tumor myxoid subtype, characterized by the presence of capsule ruptures, tumor extension, and focally thin capsule. When there are frequent focal defects of the capsule, the tumor tissue fuses with the glandular parenchyma. Because almost all pleomorphic adenomas are characterized by a large number of thin capsule fragments, any surgical procedure near the periphery of the tumor carries a risk of capsule damage and the possibility of tumor scattering.

Operator experience - the incidence of recurrences of pleomorphic adenoma in long-term follow-up studies is about 2%. Controversial is McGurk's study, which found recurrences equally in both cases, both after extracapsular excision and after superficial parotidectomy. According to these authors, the risk of recurrence is higher when the procedure is performed by less experienced surgeons and does not recommend extracapsular excision as a routine procedure [10].

Tumor size - a correlation between the diameter of the tumor and its recurrence has been confirmed. The average non-recurrent tumor size was 30 mm compared with 43 mm for recurrent tumors. However, large tumors were not always significantly correlated with recurrence rate [15,16].

Postoperative facial nerve morbidity - one of the most important complications that accompany surgery on parotid gland tumors is the high risk of facial nerve palsy. Several methods have been developed to assess the extent of facial nerve function in order to objectively document its function and monitor recovery. The most commonly used methods for assessing facial nerve function and morbidity are the House-Brackmann facial nerve grading system (HBFNGS) and the Sunnybrook Facial Grading System (SFGS). These methods are a widely valid tool that classifies the degree of clinical paresis from grade I (no paresis) to grade VI (total paresis).

2. Material and method

Risk factors that lead to recurrence of pleomorphic adenoma are analyzed with special emphasis on size, location, surgical technique and histological subtype. The postoperative morbidity of the facial nerve was also analyzed, ie the impact of the mentioned variables on the facial nerve and with the help of the surface EMG we evaluated the condition of the nerve by measuring the neuroconduction of its branches on the operated side in relation to the healthy side of the face. The study included 77 patients who were operatively treated at the clinic for maxillofacial surgery - Skopje, from the period 2016 to 2020, with a verified pathohistological finding for pleomorphic adenoma. The preoperative examinations performed during the planning of the surgery were analyzed with special reference to the aspiration biopsy, CT and MRI. Surgical treatment is divided into three types: enucleation, extracapsular dissection, and superficial parotidectomy with preservation of the facial nerve.

Pathohistological analysis was performed postoperatively to determine the patho-histological subtypes that are susceptible to recurrence. Neurophysiological evaluation with EMG of the conduction of the facial nerve in relation to the unoperated side was performed. The S-EMG measuring point was on the forehead, around the eye and around the mouth, where muscle movement was significant. The electrodes were placed in the middle of the m.frontalis, m.orbicularis oculi and m.orbicularis oris, and the test time was 20 minutes. Statistical data processing was performed in statistical program Statistica 8.0 and SPSS Statistics 23.0. Association and differences were tested using the Pearson Chi-Square and Fisher's Exact Test / Monte Carlo Sig. (2-sided). All risk factors that may lead to relapse during surgical treatment of pleomorphic adenoma with the predicted variables have been analyzed.

3. Results

According to the results obtained from a total of 77 patients, 53 (68.8%) were women and 24 (31.2%) men. The age of the patients varies in the range 46.87-12.29 years, the minimum age is 22 years and the maximum age is 70 years. The size of the tumor varies in the range 33.05-14.52 mm, the minimum size is 5 mm and the maximum size is 80 mm. Out of a total of 77 patients, in 70 (90.9%) patients the tumor was in the superficial lobe and in 7 (9.1%) patients the tumor was located in the deep lobe. Regarding the surgical treatment of patients, out of a total of 77 patients, in 30 (39.0%) patients enucleation was performed, in 20 (26.0%) extracapsular dissection was performed while in 27 (35.1%) patients performed is a superficial parotidectomy. According to the histological subtype of pleomorphic adenoma, 9 (11.7%) patients had a cellular subtype, 45 (58.4%) patients had a classical subtype, and 23 (29.9%) patients confirmed a myxoid subtype. Regarding recurrence as a variable, out of a total of 77 patients, 49 (63.6%) had no recurrence and 28 (36.4%) patients had recurrence (Table 1).

Table 1. Rate of recurrence after removal of PA

		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	Yes	49	63,6	63,6	63,6
	No	28	36,4	36,4	100,0
	Total	77	100,0	100,0	

The following analysis was performed on the difference in tumor size with respect to recurrence in operated patients with pleomorphic adenoma. It was found that the obtained $Z = -2.31$ and $p < 0.05$ ($p = 0.02$) tumor size in patients who had relapse ($x = 37.93$ mm) was significantly larger than the tumor size in patients who had no recurrence ($x = 30.27$ mm).

Table 2. Size of Tumor and Recurrence / Crosstabulation

Variable	Rank Sum	Rank Sum	U	Z	p level	Valid N	Valid N
	No recurrence	Recurrence				No recurrence	Recurrence
Size of Tumor	1693,00	1310,00	468,00	-2,31	0,02	49	28

The results shown in Table 3 refer to the crosstabulation between the site position of the pleomorphic adenoma in the parotid gland and the recurrence. In the analysis of 70 patients in whom the pleomorphic adenoma was in the superficial lobe, 43 (61.4%) had no recurrence and 27 (38.6%) had recurrence. Out of a total of 7 patients in whom the pleomorphic adenoma was localized in the deep lobe, 6 (85.7%) had no recurrence, and only 1 patient (14.3%) had recurrence. For Fisher's Exact Test / Monte Carlo Exact Sig. (2-sided) / $p > 0.05$ ($p = 0.412$) there is no significant difference when it comes to recurrence relative to the site position of the pleomorphic adenoma.

Table 3. Site of Tumor and Recurrence / Crosstabulation

			Recurrence		Total
			No	Yes	
Site of Tumor	Superfital lobe	Count	43	27	70
		%	61,4%	38,6%	100,0%
	Deep lobe	Count	6	1	7
		%	85,7%	14,3%	100,0%
Total		Count	49	28	77
		%	63,6%	36,4%	100,0%

The results shown in Table 4 refer to the crosstabulation between surgical treatment and relapse. Of the 30 enucleated patients, 6 (20.0%) had no recurrence and 24 (80.0%) had recurrence. Of the 20 patients who underwent extracapsular dissection, 19 (95.0%) had no recurrence and 1 (5.0%) had recurrence. Of the 27 patients who underwent superficial parotidectomy, 24 (88.9%) had no recurrence and 3 (11.1%) had recurrence. For Fisher's Exact Test = 41,579 / Monte Carlo Exact Sig.(2-sided)/ $p < 0,001$ ($p = 0,000$ / 0,000), there is statistically significant difference when is considered recurrence compared to the operative technique of PA, i.e. it is obvious that in our study the patients with extracapsular dissection had the least recurrence, with the lowest recurrence rate (only 5%), while 11% of patients with superficial parotidectomy had recurrences.

Table 4. Operative mode and Recurrence / Crosstabulation

			Recurrence		Total
			No	Yes	
Operative mode	Enucleation	Count	6	24	30
		%	20,0%	80,0%	100,0%
	Extracapsular Dissection	Count	19	1	20
		%	95,0%	5,0%	100,0%
	Superfital parotidectomy	Count	24	3	27
		%	88,9%	11,1%	100,0%
Total	Count	49	28	77	
	%	63,6%	36,4%	100,0%	

In Table 5, the results show the cross-tabulation between histological subtype of the tumor and recurrence. Out of 9 patients diagnosed with cellular subtype, 6 patients (66.7%) had no recurrence and 3 patients (33.3%) had recurrence. Of the 45 patients diagnosed with the classical subtype, 36 (80.0%) had no recurrence and 9 (20.0%) had recurrence. Of the 23 patients diagnosed with myxoid subtype, 7 (30.4%) had no recurrence and 16 (69.6%) had recurrence. For Fisher's Exact Test = 15,789 / Monte Carlo Exact Sig. (2-sided) / $p < 0.001$ ($p = 0.000$ / 0.000 - 0.000) there is a significant difference when it comes to recurrence in relation to the histological subtype of pleomorphic adenoma.

Table 5. Histological subtype and Recurrence / Crosstabulation

			Recurrence		Total
			No	Yes	
Histological Subtype	Celular subtype	Count	6	3	9
		%	66,7%	33,3%	100,0%
	Classic subtype	Count	36	9	45
		%	80,0%	20,0%	100,0%
	Myxoid subtype	Count	7	16	23
		%	30,4%	69,6%	100,0%
Total		Count	49	28	77
		%	63,6%	36,4%	100,0%

The results of postoperative facial nerve morbidity determined according to the House-Brackmann Scale for facial motor function are shown in Table 6.

Table 6. House-Brackmann scale

		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	HB I	62	80,5	80,5	80,5
	HB II	13	16,9	16,9	97,4
	HB III	2	2,6	2,6	100,0
	Total	77	100,0	100,0	

Out of a total of 77 patients, 62 (80.5%) had an orderly finding, ie HB scale I, 13 (16.9%) had an HB scale II (slight weakness on close inspection with slight smile asymmetry), while 2 (2, 6%) patients had had HB scale grade III (obvious non-deforming weakness with complete closure of the eyes).

If the facial nerve dysfunction is evaluated after the operation as a consequence of a pleomorphic adenoma, then the results of our analysis show that the majority of patients operated on in our clinic (80%) are without facial nerve affection after surgery. Out of a total of 77 patients, 62 (80.5%) did not have facial nerve dysfunction and 15 (19.5%) patients had facial nerve dysfunction (Table 7), indicating the fact that at our clinic the success of parotid surgery is very large with 80% of patients without facial nerve affection after surgery.

Table 7. Postoperative disfunction of facial nerve

		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	No	62	80,5	80,5	80,5
	Yes	15	19,5	19,5	100,0
	Total	77	100,0	100,0	

4. Discussion

The topography of the facial nerve within the parotid glandular tissue and the risk of postoperative facial paresis make the operation on parotid tumors a major challenge. Functional preservation of the facial nerve is one of the most essential surgical steps in parotidectomy [Popovski V. 1998]. To safely identify and preserve the facial nerve, many surgical approaches have been suggested during parotidectomy [Popovski V. 2007]. In addition, preoperative imaging diagnostic evaluation, intraoperative facial nerve monitoring, and the use of a magnifying glass and microscope have been postulated as a routine algorithm in parotid surgery [Ward CM. 1975]. According to previous studies, between 14 and 64% of temporary facial nerve outbursts have been reported, and prolonged or permanent facial nerve paresis is found to be between 0.5-9% after initial parotidectomy [Guntinas-Lichius O. et al. 2006]. However, much higher rates of paresis have been reported in revisional surgery [McGregor A.D. et al. 1988], in extensive surgery (total parotidectomy) [Kim MB. et al 2007], and in tumors located deeper than the facial nerve branches [Domenick NA. et al. 2011]. Preoperative CT scans are known to have modest diagnostic accuracy for facial nerve localization and have diagnostic limitations compared to direct facial nerve visualization with advanced magnetic resonance imaging (MRI) techniques [Popovski V. 1998]. Facial motor paralysis is the most severe complication, which seriously affects the patient's quality of life postoperatively. Reported incidence ranges from 14.0 to 23.1% relative to temporary paresis [Witt R. 2002, Guntinas-Lichius O. et al. 2006]. So far, there are many studies that have analyzed the risk factors for paralysis / paresis after a parotidectomy. Among the variables, age, malignancy, revisional surgery, tumor size, time of surgery, and scope of surgery are risk factors for postoperative facial paralysis [Witt R. 2002, Grosheva M. et al. 2019].

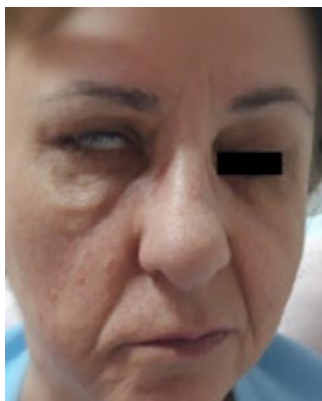


Figure 1. Patient with paresis of right facial nerve



Figure 2. Postop. S-shape Blair incision

In the study [Hokyung J. et al. 2019], the functional status of the facial nerve in the affected side was assessed using the House-Brackmann assessment system, focusing on three locations: the forehead, eye, and lip. Facial paresis at one or more sites, 6 to 12 months after parotidectomy, was defined as permanent facial paralysis. Based on this system, incomplete (grade 4 or less), temporary paresis was observed in 51 patients, ie complete paralysis was observed in 22 patients. Regarding the localization of facial expression, deviation of the lips was the most affected place, both in temporary and permanent facial paralysis.

The standard surgical treatment for PA is superficial parotidectomy [Kim MB. et al. 2007], which is associated with recurrence rates below 2-3% [Grosheva M. et al. 2008]. In contrast, in previous studies, recurrence rates after enucleation were as high as 40% [Kim SH. et al. 2007]. Despite this progress, the exact reasons for the

recurrence of PA remain unclear. The widely held hypothesis is subtotal removal of the tumor due to inappropriate surgery, while the characteristics of the tumor capsule or other histological aspects are rarely examined. In a study conducted by Dulguerov et al. [Dulguerov P. et al. 2017], the clinical pathological and surgical features of pleomorphic adenoma were examined and the same authors try to answer the question: why does pleomorphic adenoma recur. They hypothesize that the various causes of PA recurrence can be grouped into pathologically related (capsule thickness or capsule deficiency, pseudopodia, satellite nodules, multicenterism), and surgical-related factors (tumor rupture, tumor contents, insufficient of resection due to nerve branches, inappropriate excision).

The presence of an incomplete or empty capsule as a source of relapse has already been discussed by Stennert et al. [Stennert E. et al. 2004], were probably the first to associate incompleteness encapsulation with the pathological subtype of PA: 69% of myxoid PA had incomplete capsules versus 30% of the classical subtype and 18% of the cellular subtype. Pseudopodia are nodules of the tumor that separate from the edges and are separated by fibrous tissue from the main tumor mass, but still localized within the main capsule of the tumor. They have been cited as a reason for PA recurrence by Patey and Thackray. They were found in 28% of PAs in Stennert samples [Stennert E. et al. 2004], in 40% of PAs from Zbären and Stauffer, and in 54% of Park et al. [Park GC. et al. 2012]. Satellite nodules are separate nodules of the tumor near the main tumor mass, but separated from it by glandular or adipose tissue without any direct connection. Orita et al. [Orita Y. et al. 2010] assessed the distance between the main tumor and the satellite nodules and found a maximum of 5.0 and 8.5 mm, respectively. Park et al. [Park GC. et al. 2012] found an increased incidence of satellite nodules in patients with recurrent PA: 60% vs. 10% in non-recurrent PA. Tumor size can be thought of as pathologically related, operatively related, or a patient-related variable. The association between tumor size and capsular integrity was investigated by Li et al.: larger tumors (> 4 cm) were more likely to show incomplete capsules, although the difference was not significant. Similar findings are described by Webb and Eveson [26]. However, a significant correlation has been confirmed between tumor size and satellite nodules, with larger PAs showing more frequent satellite nodules [Riad M.A. et al. 2011, Popovski V. 1998, Park GC. et al. 2012]. A tumor rupture is described as an injury to the tumor capsule during surgery and is usually accompanied by scattering of the tumor tissue contents in the surgical field. Park et al. [Park GC. et al. 2012] concluded that the risk of recurrence was more than 14-fold (4 vs. 30%) if the tumor had ruptured during surgery. A high incidence of recurrence with tumor rupture was also reported [Grosheva M. et al. 2008], although the difference was not significant.

Facial nerve dysfunction assessment tools include clinical assessment scales, such as the Haus-Brackmann Scale, the Janagihara System, and the Sunnybrook System, which assess paralysis through an appraiser using visual examination of the patient's appearance [Kim MB. et al. 2007] and electrophysical tests such as Nerve Excitability Test (NET), Nerve Conduction Study (NCS), Electromyography (EMG) [Grosheva M. et al. 2008]. The Nerve Conduction Study is widely used to determine the status and prognosis of peripheral nerve disorders, and is a widely used method for assessing facial nerve palsy. It is also used to diagnose and assess disease by assessing the functional status of nerves by means of potential neural activity [Kim MB. et al. 2007]. In superficial EMG there is no pain induction, the method is simpler than conventional EMG, which facilitates repetition of measurement and monitoring because sEMG is a non-invasive method that attaches electrodes to the surface of the skin [Kim SH. et al. 2007]. This suggests that s-EMG measurements can be used as an objective tool for assessing facial paralysis.

5. Conclusion

- Based on the obtained data, their subsequent analysis and the presented results related to the risk factors for recurrence of pleomorphic adenoma and postoperative facial nerve morbidity, we can conclude that PA and relapses are more common in the female population.
- Tumor size significantly affected PA recurrence rate while tumor location did not affect recurrence rate in our study. There is a significant difference when it comes to recurrence in terms of the type of surgical treatment of PA with the highest recurrence rate after operative enucleation. In terms of histological subtype, the myxoid subtype of PA showed the highest recurrence rate.
- Regarding the assessment of facial nerve dysfunction after surgery as a consequence of pleomorphic adenoma, then the results of our analysis show that the majority of patients operated at our clinic are without facial nerve infection, indicating the fact that the success of the parotid surgery is generally very large, with over 80% of patients without facial nerve affection after surgery.

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