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Parotid pleomorphic adenomas: Factors influencing surgical techniques, morbidity, and long-term outcome relative to the new ESGS classification in a retrospective study

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ABSTRACT

Purpose: To assess long-term results after treatment of parotid pleomorphic adenomas (PPAs) with different surgical techniques, standardized according to the European Salivary Gland Society (ESGS) classification system.
Methods: We analyzed ESGS categories, occurrence of facial nerve paresis (FNP), Frey's syndrome, histopathology, and recurrences. Surgical modalities were compared, differentiating techniques with and without facial nerve dissection. A strict protocol ensured a postoperative follow-up-period of more than 7 years.
Results: 205 patients were included. A complete follow-up was possible in 138 patients, 77 of whom underwent extracapsular dissection (ED) and 61 of whom had other surgical modalities (OSMs). ESGS categories correlated with the extent of surgery, significantly with the risk for FNP and Frey's syndrome, but not with recurrences. Recurrences did not differ significantly between ED and OSMs, whereas the risks for FNP ($p < 0.001$ each) and Frey's syndrome ($p = 0.000$) were significantly higher after OSMs in comparison with ED. Young women with a stroma-rich (myxoid) tumor subtype appear to have the greatest risk for recurrences.
Conclusion: ED is the treatment of choice for PPAs, if possible, resulting in similar recurrence rates but significantly fewer comorbidities in comparison with more extensive surgery. After the treatment of PPAs, a long-term follow-up is needed, including imaging.

1. Introduction

Parotid pleomorphic adenoma (PPA) is the most common type of benign salivary gland neoplasm and comprises about 45–60% of all salivary gland tumors (Woods et al., 1975; Eveson and Cawson, 1985; Spiro, 1986; Mantsopoulos et al., 2015). This entity tends to recur after incomplete surgical removal and can become malignant if left untreated, and especially after recurrence (Chilla et al., 1986; Zbaren et al., 2013; Andreasen et al., 2016). During the early twentieth century, a fear of postoperative facial nerve palsy led to the development of the 'intracapsular dissection' or 'tumor enucleation' technique, but recurrence rates of up to 20–45% (Patey and Thackray, 1958; van Niekerk et al., 1987; Sungur et al., 2002; Maxwell et al., 2004; Wittekindt et al., 2007; Albergotti et al., 2012; Witt et al., 2015) led to rejection of this procedure. The surgical extent for these tumors is still a matter of debate, with the aim being to minimize risks, complications, and side effects (Johnson et al., 2007; Colella et al., 2015; Mantsopoulos et al., 2015; Mehta and Nathan, 2015) and to take into account the specific pathological features of PPAs (Witt, 2002; Ghosh et al., 2003; Zbaren et al., 2013).

Different surgical techniques are available: complete parotidectomy (CP), lateral or superficial parotidectomy (LP), and partial superficial parotidectomy (PSP). These techniques involve dissection of the facial nerve to a varying extent, including the main trunk. In contrast, extracapsular dissection (ED) involves careful

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dissection of the tumor with a cuff of healthy tissue adjacent to it, without dissecting the facial nerve (Witt, 2002; McGurk et al., 2003; Klintworth et al., 2010; George and McGurk, 2011).

The most extensive meta-analysis to date was published in 2015, addressing the surgical treatment of PPAs, including the outcomes of data analysis. The authors concluded that systematic reports on the localization and dimensions of the tumors, capsular properties, and follow-up data are scarce. They stated that the ESGS classification should be included in future publications. The aim of our study was therefore the systematic analysis and comparison of these factors, standardized according to the European Salivary Gland Society (ESGS) categories (Quer et al., 2016, 2017), to make future data comparable, and to identify the most suitable treatment options for PPAs. The study evaluated tumor size and location, different surgical strategies, postoperative facial nerve function, Frey's syndrome, control rates and recurrences, and histopathology. The data were analyzed after a mean follow-up-period of more than 7 years, including imaging of every patient, assessed exclusively in the department in which they were first treated.

2. Materials and methods

This retrospective study was conducted at the Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen-Nuremberg, Germany, and was approved by the university's ethical review committee. The records for all patients treated for PPAs between 2005 and 2009 were evaluated, ensuring a postoperative follow-up period of at least 5 years as of 2014. Patients with insufficient data —(ultrasonography not performed or carried out elsewhere during the follow-up, follow-up examinations declined, loss of contact, death before the completion of the follow-up period), histopathological findings other than PPAs, or with surgical revision after primary operations carried out elsewhere were excluded from the study.

Preoperatively, all patients received a clinical examination, ultrasonography of the parotid gland, and magnetic resonance imaging in cases where the tumor was not completely visible on ultrasound. Facial nerve function was assessed using electromyography and clinically, using the House-Brackmann grading system (House and Brackmann, 1985).

Postoperatively, patients were only included in the study cohort if both their primary treatment and all follow-up examinations were carried out in our department. Each follow-up visit included a clinical examination, a facial nerve assessment using the House-Brackmann grading system, and imaging. Clinical signs of Frey's syndrome (auriculotemporal nerve syndrome) were recorded using standardized questions on whether any redness or sweating in the parotid region appeared during stimulation of salivation. Every patient received ultrasound examinations. In cases of uncertainty ($n = 4$), MR imaging was also carried out. The mean follow-up period was 7.7 years (±1.5 years; minimum 5.0 years, maximum 11.7 years). All included patients ($n = 138$) were seen regularly every 6–12 months, if possible, or at least once after 5 years to ensure the quality of the follow-up for that period.

A complete follow-up-period (FUP) of at least 5 years was possible in 138 of the 205 patients ($n_{TOTAL} = 138$ or 67.3%; mean $FUP_{TOTAL} = 7.9$ years) to analyze the development of Frey's syndrome and recurrences. For better comparability, two groups were created. The first included patients with extracapsular dissection (ED; $n_{ED} = 77$; FUP_{ED} range = 5.0–11.7 years; mean $FUP_{ED} = 7.6$ years); the second included those treated with other surgical modalities (OSMs; $n_{OSM} = 61$; FUP_{OSM} range = 5.2–11.5 years; mean $FUP_{OSM} = 8.2$ years). Complete data for the 5-year follow-up were not available in 67 patients (32.7%). In 60 cases, ultrasonography could not be performed or was carried out elsewhere, the examination was declined, or contact was lost. Seven patients died of causes unrelated to PPA.

Surgical techniques were classified according to the surgical report, amount of parenchyma removed, and extent of facial nerve dissection. ED was defined as removal of the tumor, including a 2–4-mm margin of adjacent healthy tissue around its capsule, without exposure of the main trunk of the facial nerve (McGurk et al., 1996; Iro et al., 2013; Mantsopoulos et al., 2015). Facial nerve neuromonitoring was performed during surgery in all cases.

Using ultrasound or further imaging, tumor sizes were measured in three dimensions, and ESGS level locations were assessed. Surgical reports described the tumor's location relative to the facial nerve. With these data, each tumor was categorized according to the ESGS classification system (Quer et al., 2017).

Facial nerve paresis (FNP) was defined as any House-Brackmann index grade other than I, as temporary if it resolved within the first year after surgery, or as permanent if it lasted for at least 1 year. FNP was evaluated for patients with a follow-up period of at least 1 year ($n = 168/205$ patients; 82.0%).

For histopathological analysis, PPAs were classified as one of three subtypes, depending on the proportion of stroma cells, as proposed by Seifert et al. (1976), and taking into account specific aspects as described previously (Mantsopoulos et al., 2018).

Statistical analysis was performed using the χ^2 test using SPSS Statistics (Version 22, IBM Corporation, Armonk, NY, USA). p-values < 0.05 were considered significant.

3. Results

3.1. Epidemiology

From 2005 to 2009, 205 patients were treated for PPAs in our department (75 men, 130 women; male:female ratio 1:1.73; mean age 48.0 ± 16.2 years; range 18–85 years). The data show female predominance, with the highest incidence in the fifth decade of life.

3.2. Tumor sizes and surgical modalities

Of the 205 surgically treated patients, 117 patients received ED, 19 had a partial superficial parotidectomy (PSP), 24 had a lateral parotidectomy (LP), and 45 had a complete parotidectomy (CP).

Tumor sizes were classified into groups (Table 1), the most common size being 2.0–2.99 cm. Smaller tumors (<3 cm) were mostly removed using ED, while more extensive surgical approaches were necessary for larger tumors. For tumor sizes of around 3 cm, the numbers in the two surgical modality groups were equal. However, large masses (>4 cm) in the inferior part of the gland could occasionally be removed with ED.

Table 1
Size of parotid pleomorphic adenomas and number of patients, treated either with extracapsular dissection (ED) or various other surgical modalities (OSMs).

Tumor size	Surgical technique and number of patients (%)		
	ED	OSM	Total
<1.0 cm	3 (100%)	0 (0%)	3 (1.5%)
1.0–1.99 cm	53 (81.5%)	12 (18.5%)	65 (31.7%)
2.0–2.99 cm	38 (49.4%)	39 (50.6%)	77 (37.6%)
3.0–3.99 cm	17 (42.5%)	23 (57.5%)	40 (19.5%)
4.0–4.99 cm	5 (55.6%)	4 (44.4%)	9 (4.4%)
≥5 cm	1 (9.1%)	10 (90.9%)	11 (5.4%)
Total	117 (57.1%)	88 (42.9%)	205 (100%)

3.3. ESGS categories and surgical modalities

Fig. 1 shows the ESGS categories, depending on the tumor size and gland levels (I–V) involved (Quer et al., 2017), along with the different surgical modalities used to remove the tumor. Most tumors in the study cohort were in ESGS categories I (39%) and II (34.6%); 12.2% were in category III and 14.1% in category IV.

Tumors in lower categories were mostly removed using ED (ESGS I, 77.5%; II, 54.9%), while there was a trend toward more extensive surgery in higher categories (ESGS III, 64%; IV, 75.9%). However, ED was also possible in category III and IV tumors (36.0% and 24.1%, respectively). Tumors in category IV were mainly treated with CP (51.7%). These data show that both tumor size and location are decisive for specific surgical approaches.

3.4. Facial nerve paresis (FNP)

The probability of FNP increased with ESGS category (Fig. 2A), with the risk of temporary paresis rising significantly from 4.3% to 31.6% ($p < 0.003$; not indicated). The risk of permanent FNP did not differ significantly between ESGS categories II, III, and IV (*, $p = 0.234$); however, it did between ESGS category I and non-ESGS category I (**, $p = 0.044$).

ED resulted in significantly lower rates of FNP after the operation, both temporary (2.8%, $p = 0.000$) and permanent (0.0%, ***, $p = 0.001$), when compared with other surgical modalities (OSMs; Fig. 2B). After ED, there were no cases of permanent FNP; all were temporary (poorest result: House-Brackmann grade IV), compared with a mean permanent FNP rate of 8.5% after OSMs (poorest result: House-Brackmann grade VI).

3.5. Frey's syndrome

The incidence of Frey's syndrome rose significantly with ESGS category (*, $p = 0.024$; Fig. 3A). In parallel, ED resulted in significantly lower rates of Frey's syndrome, and the risk increased significantly with the extent of parenchymal resection (**, $p = 0.000$; Fig. 3B).

3.6. Recurrence of parotid pleomorphic adenomas

During the entire follow-up period ($FUP_{TOTAL} = 7.9$ years) for 138 patients, 132 (95.7%) showed no signs of recurrence, either in clinical nor ultrasound examinations.

Six patients were diagnosed with a potential recurrence (6/138, 4.3%; Table 2). All suspicious recurrent masses were found on ultrasound and did not cause symptoms. At the time of writing, surgical revision had been performed in four of these patients, and recurrent PPA was diagnosed (4/138, 2.9%). The remaining two patients asked for regular control examinations and were referred to as having suspected recurrences (2/138, 1.4%).

All four patients with a verified recurrence were female (Table 2, patients 1–4). Their primary tumors were diagnosed at age 26.0 ± 5.5. The recurrent tumors were diagnosed with ultrasound around 58 ± 18 months (range 12–72 months) after the primary operation. Two patients were initially treated with ED, and two with PSP.

Verified recurrences were observed in ESGS categories I, II, and III. The dominant histopathological subtype at primary surgery was stroma-rich (myxoid), and recurrent tumors appeared to be predominantly multilocular, with all of them showing the stroma-rich (myxoid) subtype in cases of recurrence. Histopathology detected no pseudopodia or satellite nodules in three patients at primary surgery. In comparison, in one of 74 recurrence-free patients treated with ED, the primary tumor was found to have attached satellite nodules embedded in a rim of healthy tissue, which were completely removed in the primary operation. This patient was still recurrence free at the time of writing.

In all verified recurrences, however, a 'bare area' was present in which the tumor's capsule was not covered with a cuff of healthy tissue. In two patients, the tumor capsule was not fully intact in that area.

Regarding suspected but not histopathologically confirmed recurrences, one patient was female and initially treated with ED; the other was male and initially treated with LP. Both patients were older than those with verified recurrences, and the primary tumors were larger when discovered. The mean time to suspected recurrence was 20.5 ± 0.7 months.

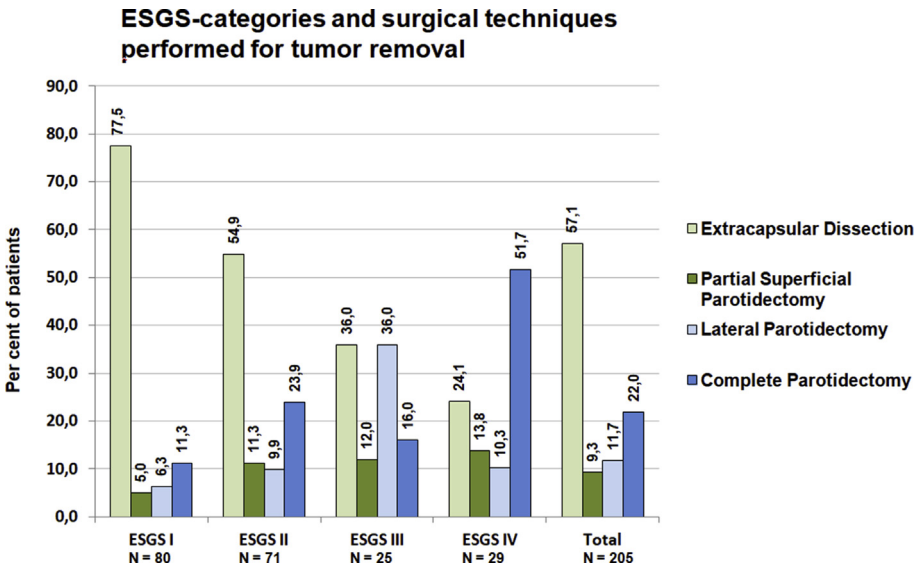

Fig. 1. European Salivary Gland Society (ESGS) categories and surgical treatment modalities used for the removal of parotid pleomorphic adenomas. The higher the ESGS category, the lower was the chance of removing the tumor with an extracapsular dissection, because extensive procedures with facial nerve dissection were more often necessary.

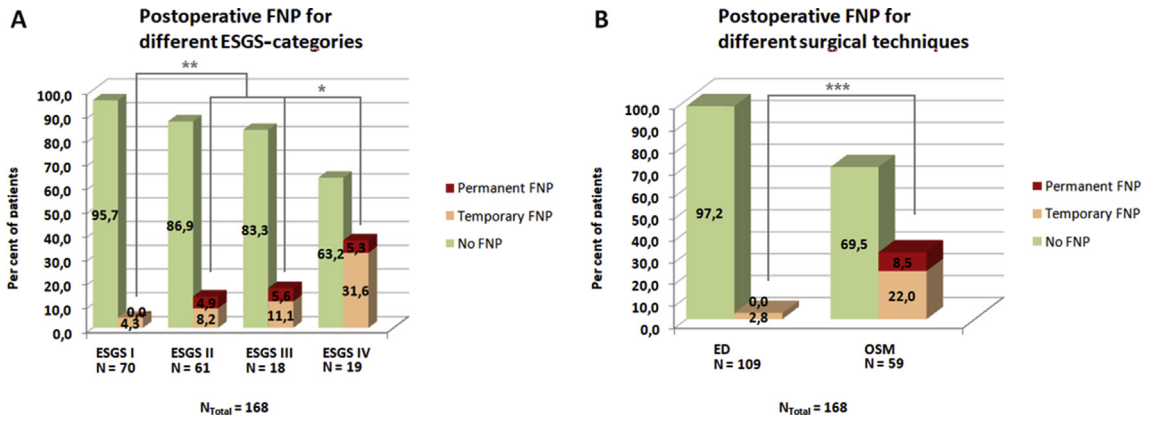

Fig. 2. Incidence of facial nerve paresis (FNP) after surgery; primary operation in all cases. None of the patients showed any limitation of facial nerve function before surgical treatment. N = number of patients. **A** Incidence of FNP relative to the tumor's European Salivary Gland Society (ESGS) category. The risk for a temporary FNP increased significantly with ESGS category ($p = 0.003$; not indicated). The incidence of a permanent FNP did not differ significantly between ESGS categories II, III, and IV (*; $p = 0.234$); however, it did differ between ESGS category I and non-ESGS category I (**; $p = 0.044$). **B** Incidence of FNP after different surgical techniques, differentiating modalities in which the facial nerve was not dissected (extracapsular dissection, ED) and modalities in which the facial nerve was dissected (other surgical modalities, OSM). The risk for both temporary (not indicated; $p = 0.000$) and permanent paresis (***; $p = 0.001$) increased significantly after dissection of the facial nerve.

Taking the 138 cases together, four patients (2.9%) had histopathologically proven recurrences and two (1.4%) had suspected recurrences. After ED, 2.6% of the patients were diagnosed with definite recurrences (2/77) and 1.3% with suspected recurrences (1/77). After OSMs, 3.3% (2/61) of the patients were diagnosed with definite recurrences (both after PSP) and another 1.6% (1/61) with suspected recurrences (after LP). No significant differences between the surgical techniques were observable (ED vs OSMs, $p = 0.81$; ED vs LP, $p = 0.49$; ED vs CP: $p = 0.37$), except between ED and PSP ($p = 0.04$, Table 3).

4. Discussion

Several studies in PPAs have been conducted to analyze results, risk factors for recurrence, and rates of recurrence after different surgical procedures (McEvedy and Ross, 1976; Laccourreye et al., 1994; Albergotti et al., 2012; Barzan and Pin, 2012; Iro et al., 2013; Foresta et al., 2014; Xie et al., 2015). As recurrences usually appear years after the primary operation (Silvoniemi et al., 2010; Valstar et al., 2017), a minimum follow-up-period of at least 5 years and a mean follow-up-period of 7.9 years were ensured in our study. Completion of the strict follow-up-protocol was possible in 138 of 205 patients (67.3%).

Ultrasound as the imaging method of choice proved useful for determining tumor size and location, and thus for categorizing tumors according to the ESGS classification system (Quer et al., 2017), and also for control examinations. All recurrences were detected with ultrasound, not with a clinical examination, and did not cause symptoms — a finding that suggests that imaging during follow-up is essential for detecting potential recurrences at an early stage. Furthermore, the mean duration between the primary operation and the detection of the recurrence was 54 ± 18 months, confirming that all PPA patients should be examined on a regular basis, even many years after treatment.

The surgical resection technique depended on tumor size and location. Regarding size alone, it seems that the majority of tumors up to 3 cm can be treated with ED, while for larger masses a more extensive surgical approach should be considered. After ED, the risks for temporary and permanent FNP (Fig. 2B) and for Frey's syndrome (Fig. 3B) were significantly lower in comparison with procedures in which the facial nerve was dissected ($p = 0.000$, 0.001, and 0.000, respectively). These results confirm data in the literature that indicate a rise in morbidity relative to the extent of surgically removed gland parenchyma (McGurk et al., 2003; Colella et al., 2015).

To the best of our knowledge, this is the first study to evaluate the treatment and outcomes for parotid gland tumors using the

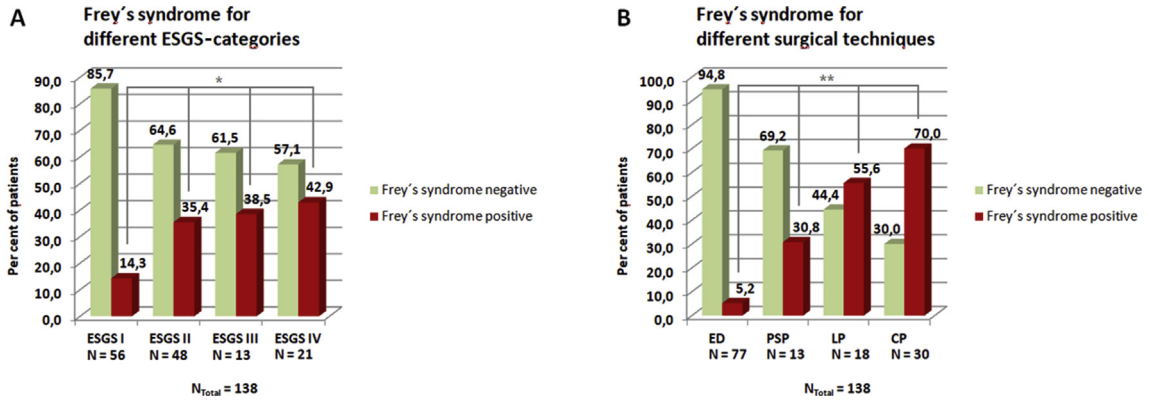

Fig. 3. Incidence of Frey's syndrome after surgery; primary operation in all cases. N = number of patients. **A** Incidence of Frey's syndrome (auriculotemporal nerve syndrome) for tumors with different European Salivary Gland Society (ESGS) categories. The higher the ESGS category, the greater the risk for the development of Frey's syndrome (*; $p = 0.024$). **B** Incidence of Frey's syndrome after different surgical techniques. The risk increases significantly with the amount of parenchyma removal (**; $p = 0.000$).

Table 2
Details of verified recurrences during the follow-up period after different surgical approaches for pleomorphic adenomas of the parotid gland.

Patient No.	Verified recurrences				
	1	2	3	4	Mean
Gender	F	F	F	F	
Age at primary operation (years)	27	20	33	24	26.0 ± 5.5
Surgical modality at primary operation	ED	ED	PSP	PSP	
Size of primary tumor (longest axis)	Two nodes, both < 10 mm	14 mm	35 mm	25 mm	18.4 ± 11.4 mm
ESGS category of primary tumor	I	II	III	II	
Histopathological subtype at primary operation	Stroma-rich (myxoid)	Stroma-rich (myxoid)	Stroma-rich (myxoid)	Mixed type	
Age at revision operation (years)	34	23, 29[a]	39	29	31 ± 6
Surgical modality at revision operation	ED	CP; revision of parotid space[a]	ED	CP	
Number of recurrent tumors	3	Multilocular	Multilocular	Multilocular	
Histopathological subtype at revision operation	As primary	As primary	As primary	Stroma-rich (myxoid)	
'Bare area' at the capsule?	Yes	Yes	Yes	Yes	
Capsule intact at primary operation?	Yes	No	Yes	No	
Presence of satellite nodules at primary operation	No	No	No	No	
Presence of pseudopodia at primary operation/ removed?	Yes/Yes	No/–	No/–	No/–	
Time from primary operation to diagnosis of recurrence (months)	72	12	65	41	54 ± 18
Follow-up time for recurrence (months)	2	56	1	19	38 ± 26
Present state	Suspicion of 2nd recurrence	Suspicion of 2nd recurrence	Suspicion of 2nd recurrence	Suspicion of 2nd recurrence	

CP, complete parotidectomy; ED, extracapsular dissection; ESGS, European Salivary Gland Society (classification); PA, pleomorphic adenoma; PSP, partial superficial parotidectomy.
[a] Histopathological examination of the first revision (CP) did not show any recurrence of the PPA. The second revision of the parotid space revealed a recurrence of the PPA.

Table 3
Overview of recurrence rates of PPAs, comparing different surgical modalities.

	N	Definite recurrence, *N* (%)	Suspected recurrence, *N* (%)
Extracapsular dissection (ED)	77	2 (2.6%)	1 (1.3%)
Other surgical modalities (OSM), grouped together	61	2 (3.3%)	1 (1.6%)
Partial superficial parotidectomy (PSP)	13	2 (15.4%)	0
Lateral parotidectomy (LP)	18	0	1 (5.6%)
Complete parotidectomy (CP)	30	0	0
Significance of recurrences:			
p-value: ED vs OSM grouped		0.81	0.86
p-value: ED vs PSP		0.04	
p-value: ED vs LP		0.49	
p-value: ED vs CP		0.37	
Total	138	4 (2.9%)	2 (1.4%)

ESGS classification system (Quer et al., 2017), in relation to size *and* location. Before therapy, this system is of help in estimating the required extent and duration of the surgical procedure. Moreover, it enables patients to be counseled properly. We found that PPAs in ESGS categories I and II are the most common, followed by categories IV and III.

The higher the ESGS category, the lower the chance of removing the mass with ED, and the greater the need to dissect the facial nerve (Fig. 1). This is also reflected by the fact that more than half the tumors in ESGS category IV required CP. The higher the ESGS category, the higher the risk for developing a temporary FNP ($p = 0.003$) and Frey's syndrome ($p = 0.024$): the risk for temporary and permanent FNP rose stepwise from 4.3% to 31.6% and from 0% to a peak of 5.6%, respectively (Fig. 2A), and the risk for Frey's syndrome rose gradually from 14.3% to 42.9% (Fig. 3A). The risk for permanent FNP increased significantly when the tumor could not be classified as category I ($p = 0.044$), with no significant differences between categories II, III, and IV ($p = 0.234$). In addition to their surgical and scientific importance, these data can be used as a basis to inform the patient in detail about the expected invasiveness of the operation and the risk of these adverse effects preoperatively.

Although the different ESGS categories provide a basis for better comparability of different surgical techniques and outcomes, they showed some limitations: tumors located in the inferior part of the gland, larger than 3 cm, and extending inferiorly or laterally may not automatically involve two levels of the gland — they cannot be classified as either ESGS category I or III. However, in these cases limited surgery may be a viable treatment option (Sesenna et al., 2013; Mantsopoulos et al., 2017).

We found a recurrence rate of 2.9%, without any significant differences between ED and OSMs ($p = 0.81$), except for ED vs PSP ($p = 0.04$; Table 3). Although this rate is lower than that reported in other studies (Andreasen et al., 2016; Valstar et al., 2017), the follow-up periods in the latter were longer. In comparison, Silvoniemi reported recurrence rates of nearly 4% in 230 patients who were exclusively treated with LP or CP due to PPA (Silvoniemi et al., 2010). Our data do not show a significantly higher incidence of recurrence after ED compared with OSMs, in which the main trunk of the facial nerve is dissected. Similar or higher recurrence rates after LP in comparison with ED have also been reported in two meta-analyses (Albergotti et al., 2012; Foresta et al., 2014). However, no definite recurrences after LP or CP were noted in our study cohort, although one recurrence after LP is now suspected. In

summary, ED showed recurrence rates that were lower in comparison with PSP, and no higher in comparison with LP or CP, but the frequency of adverse effects and morbidity was greater after OSMs, supporting previous reports and the demand for minimal invasive surgery when possible.

Capsular rupture, pathological subtype, differentiation, thickness and type of capsule tissue, size (not noted as an independent parameter in our study cohort), and adhesion to the facial nerve have been reported to be major risk factors for recurrence (Albergotti et al., 2012; Foresta et al., 2014; Triantafyllou et al., 2015; Xie et al., 2015; Witt, 2016). In our study, recurrences were diagnosed after primary tumor sizes of 8–35 mm and in ESGS-categories I, II, and III, although these parameters may not influence the risk of recurrence. Interestingly, all patients with recurrences were young women, which is consistent with recent reports (Valstar et al., 2017), predominantly with a stroma-rich (myxoid) histopathological subtype in the primary and in all of the recurrent tumors. This is supported by the observation that tumors with this subtype have especially thin or even absent capsules (Paris et al., 2004; Zbaren and Stauffer, 2007). All primary tumors in cases of recurrence were in contact with the (peripheral) facial nerve, and consequently a 'bare area' was present in that region of the tumor; a capsule rupture was found in two of the four cases.

Many decision-making algorithms are based on the assumption that recurrence rates are lower when more gland parenchyma is removed. Our data indicate that the risk of recurrence may not be significantly influenced by the amount of parenchyma left over after the tumor is adequately removed. If the facial nerve abuts the tumor, a 'bare area' is left behind, with a greater risk of capsule rupture, although this risk is present with every surgical maneuver, regardless of the extent of surgery. In this context, more extensive surgical approaches than ED may not guarantee additional benefits in terms of avoiding recurrences.

According to our data and previous reports, ED should therefore be considered a viable treatment option in patients with PPAs in the lower ESGS categories, with no contact with the main trunk of the facial nerve. Clinical investigation, imaging, and ESGS classification should be used in preoperative decision making in terms of which surgical approach is suitable, with the most important factors here being location and size of tumor. The final decision on which surgical maneuver has to be performed can only be made during the operation. If the main trunk of the facial nerve has to be exposed, extracapsular dissection is, by definition, not reasonable and a more extensive approach needs to be performed, with an increased risk of adverse effects and morbidity.

One major limitation of this investigation was that we presented results from a single-centre retrospective and not from a prospective, multi-centre study. A randomized study with matched patients would be desirable, but difficult to plan and to conduct. First, patients who present to salivary gland centers ask for minimal invasive surgery whenever possible. Second, a randomization of patients would be refused by any ethical review committee, because more extensive surgery seems to result in higher rates of adverse effects, without any additional benefit as far as we know. Third, given that randomization is not an option, the required data would have to be acquired 'by chance' in order to create comparable or matched groups, which may take a very long time and high patient numbers. Fourth, the target of creating comparable groups may include a biased distribution of patients when randomization is not possible — which is no option if minimal invasive therapy is a promising treatment alternative. Even a prospective, multi-centre study may struggle to meet these criteria.

5. Conclusions

Every patient should receive imaging before surgery, and ultrasound appears to be the most appropriate option. When ultrasound is inconclusive or not available, magnetic resonance imaging is indicated. Taking its size and location into account, the tumor can be categorized in accordance with the ESGS system to estimate the necessary extent of the subsequent operation, to guide patient counseling, and to allow further analysis of data and the ability to compare them.

All PPA patients should receive regular, long-term follow-up examinations, including imaging, and we regard ultrasound in the hands of an experienced examiner as the method of choice.

ED appears to be the technique of choice when possible, because it shows the lowest risk of comorbidities, with a recurrence risk comparable with that for more invasive surgical approaches. In cases in which the criteria for ED cannot be met, a more extensive surgical approach has to be chosen.

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2019.06.009.

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