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Partial Superficial Parotidectomy Versus Extracapsular Anatomical Dissection for the Treatment of Benign Parotid Tumors

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Abstract

Objectives. Superficial benign parotid tumors are a common neoplasm of the salivary glands. Different surgical procedures have been applied for partial superficial parotidectomy (PSP) and extracapsular dissection (ECD), which are the two predominant surgical techniques. Our study aimed to evaluate PSP versus ECD for benign parotid tumors, in relation to post-operative complications and recurrence rates. **Materials and Methods.** 266 patients who underwent parotidectomies of benign superficial parotid tumors were evaluated retrospectively. The first group (PSP group) was composed of 143 patients who underwent PSP, and the second group (ECD group) was composed of 123 patients who underwent ECD. **Results.** In the ECD group the rate of patients presenting with total postoperative permanent facial nerve paralysis, House-Brackmann grade III, was 0.8%, whereas in the PSP group it was 1.4%. Frey's syndrome was only reported in the PSP group. Salivary fistula occurred in both groups at similar rates. Sensation dysfunction due to greater auricular nerve division occurred in 72% patients in the PSP group and 10.6% in the ECD group. No statistical difference regarding recurrence rates was found between the two groups. **Conclusions.** Both ECD and PSP procedures are safe surgical options for superficial parotidectomy in the treatment of benign tumors, with similar recurrence rates and post-surgical complications, apart from sensation abnormalities due to more extensive auricular nerve division.

Key Words: Extracapsular • Parotidectomy • Superficial • Complication • Facial Nerve.

Introduction

The development of salivary glands starts between 6 and 8 weeks of intrauterine life, with a common embryogenesis as their development origins stem from the growth of oral epithelium into the underlying mesenchyme. The parotid gland is encapsulated after the submandibular and sublingual glands, although is the first gland to develop (1).

This salivary gland is divided into superficial and deep lobes, with a border consisting of the facial nerve, which is not visible on preoperative imaging examination. Consequently, the retromandibular vein comprises a landmark for ultrasound, separating the deep and superficial lobes of this salivary gland, since it is usually situated superiorly to the trunk of the facial nerve. Although the extracranial part of the facial nerve may in some cases be visualized on high-resolution Magnetic Resonance Imaging (MRI), the retromandibular vein is commonly the anatomic landmark between the two lobes on preoperative Computerized Tomography (CT) scans and MRI examinations of parotid neoplasms (2).

Parotidectomy is basically an anatomical dissection, especially when the facial nerve needs to be identified. The landmarks most often used for facial nerve identification are the tympanomastoid suture, the mastoid process, the tragal pointer, the stylomastoid foramen, the posterior belly of the digastric, and in some cases the peripheral branches of the facial nerve. Both procedures, partial superficial parotidectomy and extracapsular parotidectomy, are performed when a benign tumor is situated externally to the facial nerve.

Parotid tumors constitute 3% of head and neck tumors (3, 4). The majority of them are benign, and the most common histological type is a pleomorphic adenoma, which accounts for approximately 70% of all benign parotid tumors (3, 5). Pleomorphic adenomas tend to recur more often, therefore total resection is of paramount importance (3, 4, 6). Different surgical techniques have been used to treat benign superficial parotid tumors over the past century (7). In the early 20th century, intracapsular removal was reported as the most popular surgical procedure, due to the low rates of facial nerve damage despite the subtotal removal of the tumor capsule (7). However, with this technique, recurrence rates were as high as 45%. Therefore, more radical techniques were needed (7). About 50 years later, superficial parotidectomy replaced enucleation, consisting of the removal of the entire tumor, along with the surrounding superficial lobe of the parotid gland (5). Some years later, superficial parotidectomy became the most popular procedure due to the reduction in tumor recurrence rates (2%), despite the increased rates of Frey's syndrome, loss of facial sensation and, of course, facial nerve paralysis (7). Extracapsular removal has been performed for the last 25 years as a surgical procedure for which identification of the facial nerve is not needed and only the tumor is removed, including its capsule, without any normal glandular tissue (7).

Moreover, surgical techniques were implemented to dissect the facial nerve trunk and branches anatomically from the gland, to ensure the nerve's preservation, as well as to perform complete superficial gland removal. Recurrence rates were remarkably low, about 0-5% (5). Complete superficial parotidectomy was associated with a higher risk of facial nerve palsy, Frey's syndrome, neuroma, seroma, hematoma and loss of facial sensation (5, 7-10). Consequently, partial superficial parotidectomy (PSP) has replaced total superficial parotidectomy, since the entire tumor is removed, along with about 1-2cm of normal parotid tissue, and the severity of complications is minimized as less parotid tissue is resected (5). In recent years, surgical techniques for benign parotid tumors have been developed in the anatomical direction of less invasive procedures (11). Experienced salivary gland surgeons have taken this approach one step further by performing extracapsular dissection (ECD). An important aspect of ECD is that no dissection of the main trunk of the facial nerve is attempted. ECD is a surgical technique with reduced incidence of facial nerve paralysis, Frey's syndrome, recurrence rates and shorter operation time (12).

The main objective of this review is to evaluate both PSP and ECD procedures for superficial benign parotid tumors regarding post-surgical complications, as well as to address the most appropriate technique by evaluating these outcomes, as mentioned in the current literature.

Patients and Methods

In our study we included patients with benign tumors of the superficial parotid gland, treated with partial superficial parotidectomy (PSP) or extracapsular dissection (ECD) between 2000 and 2020 at the ENT clinic of "Metaxa" Memorial Anticancer Hospital in Piraeus, Greece. Preoperative assessment included U/S (ultrasound), and in many cases Computer/Tomography or Magnetic Resonance Imaging scans. In all patients FNA (fine needle aspiration) had been performed in order to ensure the benignity of the tumors. Since the facial nerve travels into the parotid gland all patients included in the study had normal facial nerve function preoperatively on the House-Brackmann Scale (the House-Brackmann scale is a nerve grading system for clinical evaluation of nerve function from I: normal to V: No facial motion, introduced by Los Angeles ENTs Dr. John W. House and Dr. Derald E. Brackmann in 1985). All tumors extracted in this study were additionally confirmed as benign by histological reports following the surgical procedures. This study includes patients who were naïve regarding parotidectomy, with only one lesion detected, and without spillage or rupture of the removed tumor during the operation. Both surgical procedures were performed by experienced surgeons.

Surgical Techniques

Partial Superficial Parotidectomy

A lazy-S incision is performed and a superficial cervicofacial flap is raised to the anterior border of the parotid mass or the parotid gland. Identification is undertaken of the great auricular nerve and skeletonisation of the anterior border of the sternocleidomastoid muscle, as well as of the posterior part of the digastric muscle and the cartilage of the external auditory canal, up to the pointer and mastoid tip. Identification is made of the common branch of the facial nerve and dissection undertaken of the tumor, controlling nerve function using nerve stimulation. After partial superficial parotidectomy, hemostasis, installation of high-vacuum drainage and non-resorbable sutures for the skin take place.

Extracapsular Dissection

The identical incision and superficial cervicofacial flap are made. Skeletonisation of the anterior border of the sternocleidomastoid muscle follows. Finally, the tumor is dissected, with preservation of the tumor capsule, after identification of the great auricular nerve. Facial nerve identification is not required during this surgical technique. Hemostasis is ensured while high-vacuum drainage and non-resorbable sutures for the skin are inserted.

Nerve stimulation is used in both surgical procedures for all patients. The results of the PSP and ECD procedures were compared in terms of recurrence rates and postoperative complications. A total of 143 patients (PSP group) underwent partial superficial parotidectomy (PSP) of a benign parotid tumor as the primary intervention. Sixty-three (44%) of them were female, while 80 (56%) were male (Table 1). The youngest patient was 19 years old and the oldest 86 years old (mean age: 52.5 years old) (Table 1). A total of 123 patients (ECD group) underwent extracapsular dissection (ECD) of a benign parotid tumor as the primary intervention. The 123 patients consisted of 98 (79.7%) females and 25 (20.3%) males aged between 22 and 91 years (mean age: 54.65 years old) (Table 1).

The first follow up visit was within a week after surgery. The second follow up was scheduled six months after the operation. Further follow up examinations were also scheduled one and two years after surgery. All the post-surgical complications mentioned were reported within the follow up period.

Characteristics	ECD* N (%)	PSP ⁺ N (%)	Total N (%)
Age			
<20	-	2 (1.4)	2 (0.75)
21-40	30 (24.4)	40 (28)	70 (26.3)
41-60	43 (35)	50 (35)	93 (35)
61-80	38 (30.9)	36 (25.1)	74 (27.8)
>80	12 (9.7)	15 (10.5)	27 (0.15)
All ages (N; Mean±SD)	123 (54.65±18.05)	143 (52.5±18.71)	266 (53.5±18.41)
Sex			
Men	25 (20.3)	80 (56)	105 (39.5)
Women	98 (79.7)	63 (44)	161 (60.5)

Table 1. Baseline Characteristics

*Extracapsular dissection; *Partial superficial parotidectomy.

Statistical Analysis

Statistical analysis was performed using the SPSS 25.0 statistical software package (SPSS Inc., Chicago, Illinois, USA). Categorical variables were presented as the number and percentages of the corresponding population. Pearson's chi-square test was used to compare categorical variables between groups. A P-value <0.05 was considered a statistically significant difference.

Results

In the PSP group, the most common histological type was pleomorphic adenoma (81/143; 56.6%), followed by Warthin's tumor (46/143; 32.2%) and 16 other benign lesions (16/143; 11.2%), including cysts (8/143; 5.6%), intraparotid lymph nodes (7/143; 4.9%) and oncocytoma (1/143; 0.7%) (Table 2).

Postoperatively, in (7/143; 4.9%) cases of permanent facial nerve weakness occurred (not completely resolved over a period of 6 months to 1 year). Five of these patients (5/143; 3.5%) exhibited weakness of only a marginal branch of the facial nerve (House-Brackmann grade II), whereas two patients (2/143; 1.4%) suffered from total paresis (House-Brackmann grade III) (Table 3).

Facial nerve weakness was diagnosed using clinical signs (lip and eyelid movement), and electromyographic examination. Facial nerve weakness immediately after the operation was not measured. Two patients (2/143, 1.4%) developed Frey's

Benign tumors	ECD* N (%)	PSP [†] N (%)	Total N (%)
Warthin's	42 (34.1)	46 (32.2)	88 (33.1)
Pleomorphic adenoma	55 (44.8	81 (56.6)	136 (51.1)
Cysts	13 (10.7)	8 (5.6)	21 (7.9)
Lymph nodes	6 (4.9)	7 (4.9)	13 (4.9)
Oncocytoma	3 (2.4)	1 (0.7)	4 (1.5)
Hemangioma	3 (2.4)	0 (0)	3 (1.1)
Kimura disease	1 (0.8)	0 (0)	1 (0.4)

*Extracapsular dissection; *Partial superficial parotidectomy.

syndrome, four patients (4/143; 2.8%) reported salivary fistula, six patients (6/143; 4.2%) seroma, and eight patients (8/143, 5.6%) hematoma. 103/143 patients (72%) reported referred hypoesthesia due to division of the great auricular nerve (Table 3). Local relapse was diagnosed in three patients (3/143; 2%). All three patients (3/143; 2%) with local relapse visited the clinic (one patient during the follow up period and two patients after several years) (Table 3).

In the ECD group the distribution of histological types was pleomorphic adenomas (55/123; 44.8%), Warthin's tumors (42/123; 34.1%) and 26 other benign lesions (26/123; 21.1%) including cysts (13/123; 10.7%), intraparotid lymph nodes (6/123; 4.9%), oncocytoma (3/123; 2.4%), hemangioma (3/123; 2.4%) and kimura disease (1/123; 0.8%) (Table 2).

Nine patients (9/123, 7.3%) exhibited facial nerve weakness immediately after the operation. Most cases of the cases of paresis (8/9; 88.9%) were House-Brackmann grade II and only one (1/9; 11.1%) House-Brackmann grade III. 7/9 of those patients (7/123; 5.7%) had total restoration of facial nerve functionality over a period of 14 days to 6 months (House-Brackmann grade I). 2/9 patients with post-operative facial nerve paresis (2/123; 1.6%) had permanent facial nerve paresis that persisted for a period of 6 months, and was therefore considered as permanent impairment of facial nerve function (Table 3). One of these patients presented weakness of only the marginal branch of the facial nerve (House-Brackmann

Table 3. Post-Surgical Complications

Complications	PSP* N (%)	ECD [†] N (%)	P [‡]
Facial nerve paralysis	7 (4.9)	2 (1.6)	0.141
Frey's syndrome	2 (1.4)	0 (0)	0.188
Fistula	4 (2.8)	3 (2.4)	0.856
Seroma	6 (4.2)	8 (6.5)	0.401
Hematoma	8 (5.6)	4 (3.3)	0.391
Great Auricular nerve division	103 (72)	13 (10.6)	<0.0001
Local Relapse	3 (2)	1 (0.8)	0.391

*Partial superficial parotidectomy; *Extracapsular dissection

grade II paresis), and one patient presented with House-Brackmann grade III paralysis. Patients with post-operative facial nerve dysfunction underwent further investigation in the form of clinical and electromyographic examination at regular intervals (2 weeks, 3 months, 6 months and 1 year after surgery).

With the ECD method of parotidectomy, thirteen patients (13/123; 10.6%) reported disturbance of sensation, eight (8/123; 6.5%) developed seroma, four (4/123; 3.3%) hematoma, fistula in three cases (3/123; 2.4%) and local relapse in one (1/123; 0.8%), with a follow up interval of two years (Table 3).

No statistical significance was reported between the two surgical procedures relating to post-operative complications in terms of relapse (P=0.391), hematoma (P=0.391), seroma (P=0.401), salivary fistula (P=0.856) and Frey's syndrome (P=0.188), or facial nerve permanent weakness (P=0.141) (Table 3). A statistically significant difference was observed between the two surgical procedures in hypoesthesia due to great auricular nerve division (P<0.0001) (Table 3).

Discussion

In our study, in the PSP group there was a higher rate of reported sensation abnormalities since the greater auricular nerve was divided, while in the ECD group there was a significantly lower percentage of this postoperative complication. Additionally, the rate of complications in terms of permanent facial nerve weakness in the main trunk or peripheral branch (not completely resolved over a period of 6 months to 1 year) was higher in the PSP group than the ECD group. In the PSP group all facial nerve paralysis was permanent, while in the ECD group 22.2% was permanent. However, in our study no statistically significant difference was found in terms of permanent facial nerve disorders between the two different surgical approaches. In PSP facial nerve function is at higher risk since, apart from the peripheral branches, its main trunk must be dissected (13).

Frey's syndrome is a complication of parotidectomy as a result of the regeneration of the postganglionic parasympathetic nerve fibers in relation to the severed postganglionic sympathetic fibers. In our study, this syndrome seems to occur at low rates with the PSP method and it was not observed in ECD procedures. Salivary fistulas, as well as hematoma, also occur at higher rates, but without statistical significance in PSP, as a greater amount of parotid parenchyma is removed.

According to the current literature, ECD is a safe surgical approach, offering early post-operative recovery and better preservation of salivary function (14). As already reported earlier, the long-term outcomes of the ECD technique could be related to the less radical nature of this surgical technique (12). As reported in the literature, ECD has fewer postoperative complications than PSP (15, 16). A meta-analysis by Martin et al. (2020) reported that ECD shows a lower rate of facial nerve paralysis, Frey's syndrome and recurrence (12). In our study, within 2 years of follow up, the percentage of patients with local recurrence requiring re-operation in the PSP group was similar to the ECD group.

Limitations of the Study

The limitations of our study are the short follow up interval since it has been reported that at least 10 years is necessary to assess the recurrence rate reliably (17). As far as local recurrence concerns, it depends on the integrity of the tumor capsule (6). However, as reported in our study, surgical procedures were excluded in which the intraoperative rupture of the pleomorphic adenoma capsule occurred, with potential tumor spillage into the surgical field (ruptures occurred in approximately 5% of cases). Recurrence, especially of pleomorphic adenoma, is related to surgery and directly linked to tumor spillage or/and capsular exposure, as well as to tumor factors, such as histological subtype, incomplete capsule and pseudopodia (18). It is important to mention that the ECD procedure is not considered as an appropriate treatment for malignant tumors (3, 8, 13). A small malignant tumor (<3 cm) could masquerade as a benign one. In such cases, a CT scan or MRI and FNAC should be performed pre-operatively. It is reported that in

some cases FNAC might not be diagnostic regarding an underling malignancy since it may fail to target a small diameter tumor (8, 13). This study is a retrospective non-randomized study. It is important to underline that tumor size and the location of tumors were not considered as a selection factor for the ECD or PSP surgical techniques. Another limitation of this retrospective study is considered to be the lack of data regarding retrograde facial nerve dissection. According to the current literature, antegrade and retrograde facial nerve dissection did not demonstrate any significant advantage regarding surgical outcomes (19). Therefore, there is still insufficient evidence regarding which dissection approach produces the best results in the treatment of parotid tumors (19).

Conclusion

The recommendation of extracapsular anatomical dissection or partial superficial parotidectomy as the gold standard for treatment of superficial benign tumors of the parotid gland cannot be entirely supported by the literature. Our study aimed to evaluate both procedures in terms of post-operative complications, and concluded that both procedures are safe options, with a significant difference regarding a higher rate of sensation abnormalities due to the division of the great auricular nerve during partial superficial parotidectomy. This statistically significant difference had as a result the change of the surgical technique used in our Institution and therefore extracapsular anatomical dissection is the preferred choice for Warthin's tumors due to the lower rate of great auricular nerve division, in combination with the extremely low recurrent rate of this benign tumor.

What Is Already Known on This Topic:

Benign parotid tumours of the parotid gland present as an asymptomatic mass in the pre-auricular region. The surgical techniques used most often are extracapsular parotidectomy and partial superficial parotidectomy. Many studies have been published describing both surgical procedures without directly comparing them. There is currently no gold standard for benign parotid tumors situated externally to the facial nerve, and it remains unclear which surgical technique is the most appropriate choice.

What This Study Adds:

Both surgical excisions are valuable and safe options for the treatment of benign parotid tumors. The results of this publication tend to suggest that extracapsular parotidectomy is the more appropriate method, with a statistically significantly lower rate of sensation abnormalities caused by the division of the great auricular nerve. Therefore, surgical practice in our Institution has been changed and ECD is the preferred technique for Warthin's tumors. However, according to the literature, ECD cannot be nominated as the gold standard due to various limitations.

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Conflict of Interest: The authors declare that they have no conflict of interest.

References

- Sangeetha Priya P, Anitha N, Rajesh E, Masthan KMK. Embryology and development of salivary gland. European Journal of Molecular & Clinical Medicine. 2020;7(10):764-70.
- Bialek EJ, Jakubowski W, Zajkowski P, Szopinski KT, Osmolski A. US of the major salivary glands: anatomy and spatial relationships, pathologic conditions, and pitfalls. Radiographics. 2006;26(3):745-63. doi: 10.1148/ rg.263055024.
- Piekarski J, Nejc D, Szymczak W, Wronski K, Jeziorski A. Results of extracapsular dissection of pleomorphic adenoma of parotid gland. J Oral Maxillofac Surg. 2004;62(10):1198-202. doi: 10.1016/j.joms.2004.01.025.
- Smith SL, Komisar A. Limited parotidectomy: the role of extracapsular dissection in parotid gland neoplasms. Laryngoscope. 2007;117(7):1163-7. doi: 10.1097/ MLG.0b013e31806009fe.
- Klintworth N, Zenk J, Koch M, Iro H. Postoperative complications after extracapsular dissection of benign parotid lesions with particular reference to facial nerve function. Laryngoscope. 2010;120(3):484-90. doi: 10.1002/ lary.20801.
- Fukushima M, Miyaguchi M, Kitahara T. Extracapsular dissection: minimally invasive surgery applied to patients with parotid pleomorphic adenoma. Acta Otolaryngol. 2011;131(6):653-9. doi: 10.3109/00016489.2010.543148.
- Kato MG, Erkul E, Nguyen SA, Day TA, Hornig JD, Lentsch EJ, et al. Extracapsular Dissection vs Superficial Parotidectomy of Benign Parotid Lesions: Surgical Outcomes and Cost-effectiveness Analysis. JAMA Otolaryngol Head Neck Surg. 2017;143(11):1092-7. doi: 10.1001/ jamaoto.2017.1618.

- McGurk M, Thomas BL, Renehan AG. Extracapsular dissection for clinically benign parotid lumps: reduced morbidity without oncological compromise. Br J Cancer. 2003;89(9):1610-3. doi: 10.1038/sj.bjc.6601281.
- Roh JL. Extracapsular dissection of benign parotid tumors using a retroauricular hairline incision approach. Am J Surg. 2009;197(5):e53-6. doi: 10.1016/j.amjsurg.2008.06.040.
- Uyar Y, Cağlak F, Keleş B, Yıldırım G, Saltürk Z. Extracapsular dissection versus superficial parotidectomy in pleomorphic adenomas of the parotid gland. Kulak Burun Bogaz Ihtis Derg. 2011;21(2):76-9. doi: 10.5606/kbbihtisas.2011.003.
- Psychogios G, Bohr C, Constantinidis J, Canis M, Vander Poorten V, Plzak J, et al. Review of surgical techniques and guide for decision making in the treatment of benign parotid tumors. Eur Arch Otorhinolaryngol. 2021;278(1):15-29. doi: 10.1007/s00405-020-06250-x. Erratum in: Eur Arch Otorhinolaryngol. 2020 Aug 29.
- Martin H, Jayasinghe J, Lowe T. Superficial parotidectomy versus extracapsular dissection: literature review and search for a gold standard technique. Int J Oral Maxillofac Surg. 2020;49(2):192-9. doi: 10.1016/j.ijom.2019.06.006.
- Shehata EA. Extra-capsular dissection for benign parotid tumours. Int J Oral Maxillofac Surg. 2010;39(2):140-4. doi: 10.1016/j.ijom.2009.11.006.
- 14. Park SJ, Han S, Lee HJ, Ahn SH, Jeong WJ. Preservation of Salivary Function Following Extracapsular Dissection

for Tumors of the Parotid Gland. J Oral Maxillofac Surg. 2018;76(9):2004-10. doi: 10.1016/j.joms.2018.03.033.

- 15. Jia ZY, Zhang XY, Jiang CB, Zhao YZ, Zhang R, Fan XH, et al. Extracapsular dissection versus superficial parotidectomy for treatment of parotid benign tumors: evidence based medicine analysis [in Chinese]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2017;31(11):863-9. doi: 10.13201/j.issn.1001-1781.2017.11.011.
- Ozturk K, Ozturk A, Turhal G, Kaya I, Akyildiz S, Uluoz U. Comparative outcomes of extracapsular dissection and superficial parotidectomy. Acta Otolaryngol. 2019;139(12):1128-32. doi: 10.1080/00016489.2019.1669821.
- 17. Zbären P, Stauffer E. Pleomorphic adenoma of the parotid gland: histopathologic analysis of the capsular characteristics of 218 tumors. Head Neck. 2007;29(8):751-7. doi: 10.1002/hed.20569.
- Mantsopoulos K, Iro H. Tumour spillage of the pleomorphic adenoma of the parotid gland: A proposal for intraoperative measures. Oral Oncol. 2021;112:104986. doi: 10.1016/j.oraloncology.2020.104986.
- Mashrah MA, Al-Dhohrah TA, Al-Zubeiry FA, Yan L, Al-Hamed FS, Zhao X, et al. Antegrade versus retrograde facial nerve dissection in benign parotid surgery: Is there a difference in postoperative outcomes? A meta-analysis. PLoS One. 2018;13(10):e0206028. doi: 10.1371/journal.pone.0206028. Erratum in: PLoS One. 2020;15(11):e0242299.