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MAJOR SALIVARY GLAND TUMORS: SINGLE INSTITUTION EXPERIENCE

Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

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Abstract

Introduction: The study analyses the occurrence and treatment outcomes of tumors of the major salivary glands in our patients.

Material and methods: Between 2019 and March 2023, a total of 182 salivary gland surgeries were conducted at our clinic. Of these, 111 were on females aged 18 to 76 years, and 71 on males aged 18 to 82 years. Diagnosis comprised a medical history, otolaryngological physical examination, ultrasonography (USG), fine-needle aspiration (FNA) biopsy of tumor, laboratory tests (CBC, CRP), and contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI).

Results: Predominantly (176 patients), benign tumors and neoplasms were found in the parotid salivary gland. Histopathology most commonly revealed pleomorphic adenoma (PA, 74 cases) and Warthin's tumor (WT, 70 cases). Other benign tumors and neoplasms made up only 18% of cases. Malignant neoplasms were only identified in the parotid salivary gland in 3.3% of cases; these were diagnosed as epithelial-myoepithelial carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, mucoepidermoid carcinoma, and ductal carcinoma.

Conclusions: In our dataset, most patients with tumors of the major salivary glands were operated on at ages above 60 years. A low incidence of malignant tumors and a high incidence of WT of the large salivary glands were observed. The main postoperative complication was facial nerve paresis in 7.6% of cases.

Keywords: tumor occurrence • treatment outcomes • major salivary glands

GŁÓWNE NOWOTWORY GRUCZOŁÓW ŚLINOWYCH: DOŚWIADCZENIA JEDNEJ INSTYTUCJI

Streszczenie

Wprowadzenie: Celem pracy była analiza występowania i wyników leczenia guzów dużych gruczołów ślinowych oparta na materiale własnym.

Materiał i metody: W okresie od 2019 do marca 2023 w Klinice przeprowadzono 182 operacje gruczołów ślinowych, w tym 111 u kobiet, w wieku od 18 do 76 lat, a 71 u mężczyzn, w wieku od 18 do 82 lat. Diagnostyka dużych gruczołów ślinowych obejmowała: wywiad, badanie przedmiotowe otolaryngologiczne, badanie ultrasonograficzne (USG) oraz biopsję aspiracyjną cienkoigłową (BACC) (guza), badania laboratoryjne (morfologia, CRP) oraz badanie tomografii komputerowej z kontrastem (TK) lub rezonansu magnetycznego (MRI) w celu dokładnej oceny zmian w gruczołach ślinowych.

Wyniki: Wśród operowanych zmian nowotwory łagodne i guzy występowały jedynie w śliniance przyusznej u 176 chorych, z czego w badaniu histopatologicznym najczęściej stwierdzono: gruczolaka wielopostaciowego (PA) – w 74 przypadkach i guza Warthina (WT) – w 70 przypadkach. Pozostałe guzy i nowotwory łagodne stanowiły zaledwie 18,18% i zaobserwowano je w pojedynczych przypadkach, w tym: gruczolaka kwasochłonnego, torbiel limfocytowo-nabłonkową, gruczolaka mioepitelialnego, torbiel zastoinową, gruczolaka kanalikowego, torbiel z cechami metaplazji płaskonabłonkowej, zmianę limfoepitelialną, chłoniaka, gruczolaka limfatycznego i naczyniaka limfatycznego. Nowotwory złośliwe stwierdzono jedynie w śliniance przyusznej w 3,29% i histopatologicznie rozpoznano następujące nowotwory złośliwe: rak nabłonkowo-mioepitelialnokomórkowy, rak gruczołowo-torbielowaty, rak zrazikowo-komórkowy, rak śluzowo-naskórkowy, rak przewodowy.

Wnioski: W analizowanym materiale chorzy z guzami dużych gruczołów ślinowych najczęściej operowani byli w wieku 61–70 lat oraz powyżej 70 lat. Obserwowano niską częstość występowania nowotworów złośliwych oraz wysoką częstość występowania WT dużych gruczolów ślinowych. Głównym powikłaniem pooperacyjnym był niedowład nerwu twarzowego (7,60%).

Słowa kluczowe: występowanie nowotworów • wyniki leczenia • duże gruczoły ślinowe

Introduction

Salivary gland tumors are divided into benign and malignant, and according to the WHO classification from 2022 [1] can be further divided into non-cancerous epithelial lesions, benign epithelial tumors, malignant epithelial tumors, and mesenchymal tumors specific to the salivary glands. According to the WHO, the most common salivary gland cancer is mucoepidermoid carcinoma, followed by adenoid cystic carcinoma.

Pathologies of the salivary glands include non-neoplastic lesions, which include inflammations of various etiologies, cysts, developmental abnormalities, and salivary parenchymal lesions in the course of systemic diseases. The other group are neoplastic lesions, among which a distinction is made between benign and malignant tumors. The overall incidence of salivary gland tumors varies worldwide from approximately 0.4 to 13.5 cases per 100,000 individuals. Tumors originating from the salivary glands are relatively rare and account for approximately 3–4% of all head and neck cancers [2].

According to the Polish National Cancer Registry, in recent years head and neck cancers have accounted for 5.5–6.2% of all malignant tumors, which translates into about 5,500 to 6,000 new cases a year [3]. In 2015, a total of 347 new cases of malignancies of the major salivary glands were registered, and 181 men and 52 women died from salivary gland cancer [3].

Almost half of minor salivary glands tumors are benign. This discrepancy in the literature results from a variation in the center where the research was conducted. In oncological surgery centers, malignant tumors of the small salivary glands predominate, while in pathology centers benign tumors of the small salivary glands are most common.

In 2015, the crude incidence of malignant tumors of the major salivary glands in Poland was 0.3/100,000 (1.0 for parotid gland) for men and 0.2/100,000 for women (0.8 for parotid gland). In men and women respectively, there were 58 vs 46 new cases of malignant neoplasms of other and unspecified major salivary glands (and 181 vs 166 cases of malignant neoplasms of the parotid gland).

Salivary gland tumors are a heterogeneous group of tumors due to the complex embryogenesis of the salivary glands. The most common benign tumors are adenomas, i.e. pleomorphic adenoma (PA) and Warthin's tumor (WT); less common are cystic lymphadenoma, lymphangioma, and hemangioma (cystic hygroma) [4].

Malignant tumors account for approximately 25–30% of salivary gland tumors and include adenocarcinoma, acinic cell carcinoma, adenoid cystic carcinoma, carcinoma ex PA, and malignant lymphomas (MALT type, B-cell tumor, and also metastases of other malignancies) [4].

The incidence of malignancy depends on the type and location of the salivary gland. In the parotid gland, malignant neoplasms account for approximately 30%, in the submandibular gland, 50%, and in the sublingual gland, 90%. In the minor salivary glands, however, malignant neoplasms most commonly affect the tongue, floor of the mouth, retromolar area, and lower lip. In contrast, benign tumors are more common in the upper lip and buccal mucosa. Tumors in the area of the palate are 50% malignant [5].

The main risk factors for salivary gland cancer are exposure to radiation and dust, as well as addiction to nicotine (specifically associated with WT) [4]. Early diagnosis and introduction of appropriate therapy are of paramount importance and, in the case of malignant lesions, in the long-time prognosis [2].

In the case of neoplastic lesions, the first symptom is usually a tumor in the salivary gland area. It is usually non-painful and solid, with varying degrees of mobility in relation to the surrounding substrate. Symptoms suggestive of a malignant tumor are facial nerve palsy, skin infiltration, soreness, or concomitant enlargement of lymph nodes in the neck [2,6,7].

This study analyses the incidence and treatment outcomes of major salivary gland tumors in our clinic.

Material and methods

Between 2019 and March 2023, 182 salivary gland surgeries were performed in the Clinical Department of Otolaryngology, Head and Neck Surgery at the 4th Military Teaching Hospital and Polyclinic in Wrocław, comprising 111 women (61%) aged 18 to 76 years (mean age 67.0 years), and 71 men (39%) aged 18 to 82 years (mean age 63.0 years).

The diagnoses were based on a medical history, otolaryngological physical examination, ultrasonography (USG), fine-needle aspiration (FNA) biopsy, laboratory tests (CBC, CRP), and contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) from which a detailed evaluation of the salivary glands, and location of lesions and lymph nodes was made.

The primary treatment was surgical resection of the salivary gland tumor under general endotracheal anesthesia. For benign, encapsulated tumors (e.g. WT), treatment involved removal of the tumor itself (so-called enucleation, local excision of the tumor, extracapsular dissection of the tumor) or removal of the tumor with part of the gland (so-called tissue margin). In some cases, partial parotidectomy, i.e. removal of the superficial lobe while sparing facial

Table 1. Number of patients, by gender and year, who underwent surgery

Year of surgery	Women		Men		Total	
	n	%	*n*	%	*n*	%
2019	34	18.7	20	11.0	54	29.7
2020	25	13.7	16	8.8	41	22.5
2021	22	12.1	13	7.1	35	19.2
2022	25	13.7	18	9.9	43	23.6
2023	5	2.8	4	2.2	9	4.9
Total	111	61.0	71	39.0	182	100.0

nerve function, was performed. There was no monitoring of the facial nerve during surgery.

Since the study was descriptive and not experimental, it did not require Bioethics Committee consent. Permission was obtained from the Commandant of the 4th Military Teaching Hospital in Wrocław to use the medical records for research purposes.

All statistical calculations were performed using Statistica version 14 (Tibco Software Inc., Palo Alto, CA, USA). The results of the study were statistically analysed and a Shapiro–Wilk test was used to assess the normality of age distribution, a Mann–Whitney *U*-test to compare the age difference between men and women, and contingency tables and chi-square tests for homogeneity and independence of distributions. Logistic regression was used to assess risk factors for postoperative complications. Results were considered statistically significant when p was < 0.05.

Results

The average age of the patients who underwent surgery was 61.0 ± 14.5 years (median = 65). Women were older than men by an average of four years (67 vs 63 years) but this difference was not statistically significant ($p = 0.153$).

Patients with tumors of the major salivary glands were most often above 60 years: 37 women (20.3%) and 18 men (9.9%) were aged 61–70 years, and 34 women (18.7%) and 19 men (10.4%) were aged over 70 years. There were few cases in the youngest age group: 2 women and 5 men aged 18–30 years.

The distribution of the ages of the women and men who underwent surgery differed significantly from a normal distribution (Shapiro–Wilk test). A chi-square homogeneity test revealed that there was no significant difference between the age distributions of women and men ($p = 0.422$).

Table 1 shows that between 2019 and 2023, a total of 182 patients underwent surgeries for tumors of major salivary glands. In each year there was no statistically significant difference between men and women in the percentage of surgeries ($p = 0.983$). Over the period 2019–2022, there was a negative trend in the number of operated patients, but the linear correlation coefficient ($r = -0.635$) was not significantly different from zero ($p = 0.365$).

Table 2 shows that, of the operated lesions, benign neoplasms and tumors were found only in the parotid gland in 176 patients (96.7%), with the most frequent histopathological findings of PA in 74 cases (42.0%), including 51 women (30.0%) and 23 men (13.1%), and WT in 70 cases (39.8%), including 41 women (23.3%) and 29 men (16.5%). Other benign tumors and neoplasms accounted for only 18.2% and were observed as cases of oncocytoma, lymphoepithelial cyst, myoepithelioma, retention cyst, tubular adenoma, cyst with features of squamous metaplasia, lymphoepithelial lesion, lymphoma, lymphoid adenoma, and lymphangioma.

Benign tumors and neoplasms occurred on the left side in 93 cases (52.8%), including women in 56 cases (31.8%) and men in 37 cases (21.0%), compared to 83 cases (47.2%) of the right, including 51 women (29.0%) and 32 men (18.2%).

The difference in the percentage of tumors located on the right and left side was not significant ($p = 0.337$). Among the 111 women who underwent surgery, tumors and benign neoplasms were diagnosed in 107 (96.4%), and among the 71 men who underwent surgery, tumors and benign neoplasms were diagnosed in 69 (97.2%). The difference in the percentage of benign tumors was not significant ($p = 0.768$).

Malignant tumors were only found in the parotid gland in 6 cases (3.29%). Histopathologically, the following malignancies were diagnosed: epithelial-myoepithelial carcinoma (pT3N0MO), adenoid cystic carcinoma (T2N0M0), acinic cell carcinoma (T2N0M0), mucoepidermoid carcinoma (T2N0M0), and ductal carcinoma (G2 pTxN2b). None of the genders or sides of the body were privileged in terms of diagnosis ($p > 0.05$).

Table 3 shows that, of the surgical methods used, the most frequent were: tumor enucleation in 102 cases (56.0%) and partial parotidectomy in 62 cases (34.1%); other methods were less frequent, including tumor removal with a margin of healthy tissue in 12 cases (6.6%) and total parotidectomy in 6 cases (3.3%). In the case of a malignant tumor, the lymph nodes of the neck were also removed (level I/II).

The frequency of surgery performed on patients with salivary gland tumors did not depend on the surgical method, side of the body, or gender ($p = 0.664$)

Table 2. Number of patients by tumor location, histopathological diagnosis, side of body, and gender

Histopathological diagnosis	Parotid gland				Total	
	Women		Men		*n*	%
	R	L	R	L		
Pleomorphic adenoma (PA)	24	27	11	12	74	42.0
Warthin's tumor (WT)	20	21	14	15	70	39.8
Oncocytoma	–	–	–	1	1	0.6
Lymphoepithelial cyst	1	1	1	1	4	2.3
Myoepithelioma	1	1	–	–	2	1.1
Retention cyst	1	3	0	3	7	4.0
Tubular adenoma	1	1	1	0	3	1.7
Cyst with signs of squamous metaplasia	–	–	–	1	1	0.6
Lymphoepithelial lesion	–	1	–	–	1	0.6
Lymphoma	–	1	1	1	3	1.7
Lymphadenoma	2	–	4	2	8	4.5
Lymphangioma	1	–	–	1	2	1.1
Total	51	56	32	37	176	100.0

Table 3. Number of salivary gland tumors by location, surgical method, side of body, and gender

Surgical method	Parotid gland				Total	
	Women		Men		*n*	%
	R	L	R	L		
Tumor enucleation	24	36	18	24	102	56.0
Tumor removal with a margin of healthy tissue	5	1	4	2	12	6.6
Total parotidectomy	3	1	–	2	6	3.3
Partial parotidectomy	22	19	10	11	62	34.1
Total	54	57	32	39	182	100.0

Table 4. Results of logistic regression of occurrence of complications

Risk factor for postoperative complications	Regression analysis				
	univariate		multivariate		
	b	*p*	beta	*p*	*OR* (95% CI)
Male gender	0.533	0.085	0.500	0.129	1.65 (0.86–3.14)
Days of hospital stay	0.314	0.018	0.301	**0.029**	1.35 (1.03–1.77)
Left side of body	0.846	0.006	0.784	**0.014**	2.19 (1.18–4.08)
Total parotidectomy	0.530	0.082	0.174	0.610	1.19 (0.61–2.33)
Tumor removal with a margin of healthy tissue	–1.216	0.077	–0.821	0.284	0.44 (0.10–1.99)
Parotid fistula	–1.895	0.084	–2.227	**0.048**	0.10 (0.01–0.98)

Legend: *b,* regression coefficient; *p,* significance; beta, multivariate regression coefficient; OR, odds ratio; 95% CI, odds ratio confidence interval. Risk factors significant at $p < 0.05$ are in bold. The logistic model for estimating the probability of a complication takes the form: Logit $P\,(complication = 1/X) = -1.67 + 0.30$ * days of hospital stay + 0.78 * left side – 2.23 * retention cyst.

The following postoperative complications were found: facial nerve paresis in 12 cases (7.6%), postoperative hematoma in 8 cases (4.4%), complete facial nerve palsy in 2 cases (1.1%), and tumor recurrence in 1 case (0.55%). The incidence of postoperative complications did not depend on gender ($p = 0.398$) or side of the body ($p = 0.294$). Logistic regression was used to assess the effect of the analyzed variables on the likelihood of surgical complications, and the results are shown in **Table 4**. In univariate analysis, factors contributing to surgical complications (stimulants) were the number of days of hospital stay and tumor location on the left side of the body. In the multivariate analysis, the number of days of hospital stay and the left side of the body were again the stimulants and, further, a retention cyst proved to be a destimulant. The odds of a postoperative complication in the group of patients with a tumor on the left side are more than twice as high compared to a tumor on the right side (OR = 2.19). The odds of a complication in patients staying one day longer in hospital are 1.35 times higher (OR = 1.35). The presence of a parotid fistula reduces the odds of a complication 10-fold (OR = 0.10; 1/OR = 10).

Patients with facial nerve paresis received galantamine injections (2.5–5 mg) for 14 days, vitamins B12, B6, and B1 (Milgamma N) 2 ml for 5 days; and physiotherapy. Patients were hospitalised for an average of about 4 days.

Discussion

An analysis of the gender structure in salivary gland pathologies in the available literature reveals some discrepancies. Most studies describe a prevalence of benign salivary gland neoplasms among women [8–10], although some authors report a male predominance [4,11]. The difference may be related to ethnic and geographical factors. Patients with malignant neoplasms are predominantly male in most publications. A similar relationship has also been observed in a Danish analysis based on 1,601 cases of malignant neoplasms: women accounted for 52% ($n = 832$) of surgically treated patients, while men accounted for 48% ($n = 769$) [6].

As far as histopathological diagnosis is concerned, the available literature records findings similar to those here. The predominant histopathological diagnosis among surgically treated salivary gland lesions was benign neoplasms, and among these, PA and WT [8,12–15]. In our work, PA was present in 42.5% and and WT in 39.8% of cases.

Analysis of the variation in the location of lesions in the major salivary glands showed that the majority of cases requiring surgical treatment involved the parotid gland, which was the most common location for both non-neoplastic lesions and neoplasms [4,8,9].

In one Mexican study ($n = 164$), there were different proportions of salivary gland pathology, but these were from an oral pathology center. Their study was dominated by indications for surgery due to pathology of the minor salivary glands, which accounted for 68.9% [8].

A study in northern Greece on 207 patients by Poutoglidis et al. [16] found that benign neoplasms accounted for 87.9% of cases. The most common neoplasm was WT, with a prevalence of 46.8%; the second most common was PA (31.9%). A higher incidence of parotid gland tumors was found in men ($p = 0.025$) and smokers ($p = 0.001$).

Jaremek-Ochniak et al. [17] reported 407 salivary gland neoplasms in their analysed dataset (over 11 years), of which malignant neoplasms accounted for 17.4%. The most common were adenoid cystic carcinoma (28.2%), mucoepidermoid carcinoma (12.7%), and serous cell carcinoma (9.9%). Lymphomas also represented a large group (1.5%). The predominant benign neoplasms were PA (54.1%) and WT (36%). Tumors of the salivary glands most commonly affected the parotid gland (92%).

In the literature, among the multiple histopathological types of salivary gland malignancies, one can observe that several diagnoses predominate. Among those investigated by Mengi et al. [11], the most common malignancies were mucoepidermoid carcinoma with 26 cases (24.3%), acinic cell carcinoma (9.3%), and adenoid cystic carcinoma (8.4%).

In the dataset analysed at the Medical University of Santa Catarina, Brazil, as well as among the Danish population, mucoepidermoid carcinoma predominated [6].

In Poland, the most common histopathological diagnoses were adenoid cystic carcinoma, adenocarcinoma, squamous cell carcinoma, and mucoepidermoid carcinoma [4,7].

Sowa et al. [18] assessed the effect of systemic oxidative stress in patients with selected benign and malignant parotid tumors. Patients with all parotid gland tumors included in the study had elevated plasma lipofuscin (LPS) levels. Furthermore, Cu/Zn-SOD activity in patients with WT was significantly lower than in the control group, the pleomorphic adenoma group, and the mucoepidermoid carcinoma group.

The surgical treatment of most conditions is determined by current surgical standards. There is also a widely accepted classification of salivary gland surgery developed by the European Salivary Gland Society (ESGS) [19]. The operative report of the ESGS indicates the level of removal of glandular parenchyma marked I to V and the non-glandular structures removed. Wong and Shetty [19] proposed an additional subdivision of levels I and II for the parotid glands and to divide them into levels Ia, Ib, IIa, and IIb based on facial nerve branches. The proposed sublevels make it possible to improve the description of key structures and thus increase the reliability of the operational protocol. Such meticulous reporting aims to optimise the management of complications and the planning of re-operations, emphasising the importance of an unambiguous classification system and a comprehensive surgical protocol.

In the present study, surgery involved tumor enucleation in 56.0% and partial parotidectomy in 34.1%, while other methods were used less frequently (tumor removal with a margin of healthy tissue in 6.6% and total parotidectomy in 3.3%).

In a study by Poutoglidis et al. [16], the majority of patients were treated using extracapsular dissection (60.4%) or partial superficial parotidectomy (22.6%). In 12 cases (5.7%), there was a recurrence of the lesion.

Combination therapy, i.e. surgery (total parotidectomy with facial nerve resection) and postoperative radiotherapy, is also used to treat malignant neoplasms.

Tumor recurrence depends on factors such as the size of the primary tumor, the presence of satellite tumors, incomplete tumor resection, or capsular rupture [19–21]. The decision to reoperate should take these factors into account, and be based on a physical examination, ultrasound, computed tomography, and/or magnetic resonance imaging. Data from the primary surgery should shed light on the likelihood of tumor spread, and patients to be identified who need to be followed up regularly [20,22]. Knowledge of all these factors reduces the risk of intra- and postoperative complications associated with reoperation. For example, if there is contact of the tumor with the trunk or branches of the facial nerve, or its close proximity to the trunk or branches, then before reoperation it is important to consider whether the nerve was previously dissected and exposed; if so, it may take a long time during the reoperation to localise the nerve within the fibrous tissue and preserve it [20].

If a tumor recurs, there are often difficulties in choosing the most appropriate treatment because there can be inconsistent expectations regarding observations in the surgical field, multifocal tumor spread, and scarring. Therefore, complete and accurate reporting of intraoperative observations should be performed during both primary and revision parotid gland surgery, following both the ESGS guidelines and those prepared in the operative report scheme proposed by Piwowarczyk et al. [23].

The standard treatment for pleomorphic adenoma (PA) of the parotid gland is radical surgical management. Radiotherapy (RT) as a primary treatment is controversial and not widely used. However, RT may be considered as an adjuvant therapy in some selected cases.

Piwowarczyk et al. [23] discussed the indications for RT in patients with parotid gland PA, based on the currently available published studies and their own experience. They recommended personalised treatment for each patient, based on the decision of a multidisciplinary panel of specialists. Adjuvant RT should be considered in cases of suboptimal resection of primary PA (close margins, intraoperative capsular disruption or tumor disintegration, risk of recurrence based on clinical factors and histological features) and in cases of recurrent PA. Recommended doses and techniques of radiation therapy were determined, depending on the clinical stage of the primary or recurrent tumor.

Although several reports in the literature document the surgical techniques and oncological outcomes obtained after parotidectomy, only a few describe the complications of parotid surgery and their management. Several complications have been reported after parotid gland surgery, which can be divided into intraoperative and postoperative (early and late). The most common complications after parotidectomy include temporary or permanent facial nerve palsy and Frey's syndrome [24]. The present study found the following postoperative complications: facial nerve paresis in 7.6%, postoperative hematoma in 4.4%, complete facial nerve palsy in 1.1%, and tumor recurrence in 0.6%.

In a study by Poutoglidis et al. [16], the most common complications were facial nerve damage, Frey's syndrome, and postoperative haematomas.

Benign salivary gland tumors have an excellent prognosis after complete surgical resection, and there is no need for adjuvant radiotherapy. In early-stage low-grade cancers, such as adenocarcinoma, mucoepidermoid carcinoma, or acinar cell carcinoma, postoperative radiotherapy (PORT) is not indicated if adequate margins are achieved [25]. However, for patients with high-risk factors, such as high-grade lesions at an advanced stage (T3 and more), positive surgical margins, perineural, vascular or lymphatic infiltration, lymph node involvement (especially extracapsular extension, ECE+), and skin and nerve infiltration, almost always PORT is beneficial for all adenomatous carcinomas [25].

Conclusions

In the analysed dataset, patients with tumors of major salivary glands were most frequently operated on beyond the age of 60 years. A low incidence of malignant tumors and a high incidence of WT of the large salivary glands were observed. The main postoperative complication was facial nerve paresis in 7.6% of cases.

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