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Clinical outcomes and management of facial nerve in patients with parotid gland cancer and pretreatment facial weakness

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ABSTRACT

Objectives: In parotid gland cancer (PGC), it is not clear whether facial weakness always reflects tumor invasion of the facial nerve (FN) requiring nerve resection. The aims of this study were to evaluate oncological and functional outcomes in patients with PGC and pre-treatment facial weakness, and to analyze local tumor invasion of the FN.

Materials and methods: The clinical outcomes of patients (n = 45) with PGC and pretreatment facial weakness were retrospectively analyzed. Patients had undergone 1 of 4 types of treatments: complete tumor resection, FN sacrifice with or without FN reconstruction, tumor resection with FN preservation and primary non-surgical treatments. Pathologic specimens in patients with nerve resection patients (n = 26) were reviewed to identify FN invasion by the tumor.

Results: Patients with PGC and facial weakness had poor clinical outcomes (44.0%, 3Y progression-free survival), and 86.7% of tumors were high-grade. In these subjects, regional or distant metastasis was an independent prognostic factor for survival. Recovery from facial weakness was suboptimal in patients with FN graft. In cases with nerve resection, 26.9% had intra-neural tumor invasion, 42.3% had perineural invasion, and 30.8% had no neural invasion in the FN.

Conclusion: Facial weakness did not always indicate tumor invasion of the FN in PGC. Thus, the decision regarding FN resection can reasonably be further based on intraoperative findings. In cases with incomplete facial weakness and safe separation of the FN from the tumor, FN preservation offers the best functional outcomes, without compromising oncological outcomes.

Introduction

Primary cancers arising from the parotid gland account for 14–25% of all parotid lesions and 3–6% of all head and neck malignancies [1]. Parotid gland tumors are usually detected as a painless palpable mass, although they may also present with facial numbness, facial pain or facial motor weakness (up to 20%) [2–5]. Along with tumor grade and stage, facial nerve palsy before treatment has been reported as strongly predictive for shorter survival [2,6–8]. In addition, facial nerve function in parotid gland cancers is correlated with larger tumor size and higher tumor grade [9].

The cause of facial nerve palsy from parotid gland cancers has been attributed to direct infiltration of cancer cells into the nerve rather than to extrinsic compression or other causes of nerve dysfunction [10]. When patients with parotid gland cancer presented with facial weakness before operation, a large number of tumors were found to have pathological nerve invasion [10]. Facial weakness in patients with parotid malignancy is an indicator for nerve resection and/or reconstruction during surgery [5,11–13].

However, it is not clear whether facial weakness always reflects tumor invasion of the facial nerve requiring nerve resection, particularly in incomplete facial paresis [4,10]. Even with improved local control, nerve resection can result in acute deterioration of quality of life in patients with parotid gland cancer and incomplete facial palsy [9,11,14,15]. Thus, the purpose of the present study was to comprehensively evaluate the clinical outcomes of patients with parotid gland

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cancer and pre-treatment facial weakness. The specific aims were to evaluate the (i) oncological and (ii) functional outcomes in patients with parotid gland cancers and pre-treatment facial weakness, and (iii) to investigate the pathologic evidence of local tumor invasion to the nerve in the cases with nerve resection.

A prospective clinical study to evaluate these questions is nearly impossible, due to the rarity of parotid cancer with facial weakness. Instead, we conducted a retrospective study including patients in a 20 year study period. Because of study limitations, it was difficult to draw a solid conclusion from out study. However, this study will create discussion about facial nerve management in patients with parotid gland cancer and facial weakness.

Materials and methods

Study patients

All patients diagnosed with salivary gland cancer were enrolled into our salivary gland cancer registry. All registered patients with a diagnosis of malignant parotid gland cancer (n = 333) were identified, and the clinical data of 45 patients with facial weakness at presentation, who had been treated between 1998 and 2017 were extracted. The protocol of this retrospective study was approved by the Institutional Review Board before data collection.

Because the parotid mass with facial weakness highly suggested the parotid gland malignancy, all patients had pre-operative cytology (or core needle biopsy) diagnosis, radiological work-ups for parotid lesions and neck, and a screening test for systemic metastasis.

Treatment modalities

The patients had undergone one of four types of treatments: complete tumor resection (parotidectomy) and facial nerve sacrifice without nerve reconstruction (n = 15), complete tumor resection, facial nerve sacrifice with nerve graft (sural nerve graft) (n = 11), complete surgery with facial nerve preservation (n = 5) and primary non-surgical treatments (n = 12). Surgical records of the two remaining patients were unclear regarding facial nerve management during surgery; thus these patients were excluded from the subgroup analysis (Fig. 1).

Primary surgery for parotid gland cancers in cases without systemic metastasis is the standard of care in our institute. Decisions regarding facial nerve management were made by the responsible surgeon. Along with resection of primary tumors, appropriate dissection of regional lymph nodes was performed to include infra-parotid lymph nodes, levels Ib, IIa, IIb, and III in elective neck dissection and ipsilateral comprehensive lymph node dissection of levels I to V in therapeutic neck dissection. In cases of adenoid cystic carcinomas, elective neck dissection was omitted. High risk features on pathology report according to the National Comprehensive Cancer Network (NCCN) guideline indicated a need for post-operative adjuvant radiation (n = 21) or chemoradiation (n = 7) [16]. Decisions on the adjuvant treatment modalities were made based on physician preference.

Patients with systemic spread at diagnosis (n = 5), performance status not allowing surgery and general anesthesia, and those reluctant to undergo surgery (n = 7) were subject to initial non-surgical management (palliative chemotherapy in 5 patients, primary radiation in 4 patients, and concurrent chemoradiation in 3 patients).

Oncological and functional outcomes

The median follow-up duration for all cases was 20 months [range: –178 months], and most disease recurrence or progression (75.0%, 21 of 28 recurrences) occurred within 1 year post-treatment. The final oncological status was divided into no evidence of disease, alive with disease (loco-regional or distant disease), and death of disease (there was no death from other causes).

Facial weakness at presentation was scored with the House-Brackmann grading system for facial paralysis [17]. For statistical purposes, grading scores were simply stratified into two categories; incomplete (House-Brackmann grades 1–4) and complete facial weakness (grades 5–6). In incomplete facial weakness, the dysfunctional subsites (forehead, eye and lip) were also reviewed. The functional outcomes of facial expression were evaluated at 6 to 12 months after completing treatment. In cases with continuous treatments (palliative chemotherapy), the facial expression status at last follow-up was recorded.

Pathology review and analysis of tumor invasion into the facial nerve

The 409 pathology slides (15–16 sections per each primary tumor) of patients who underwent facial nerve resection during surgery (n = 26) were independently reviewed by two pathologists (HB and JHC). First, facial nerve bundles were identified on pathology sections. The anatomical locations of tumors relative to the facial nerve were analyzed using multiple slide sections per tumor, and the closest distance between them was determined. The degree of local tumor invasion of the facial nerve was classified into three categories; intra-neural invasion, peri-neural invasion, and no tumor invasion. Equivocal cases were discussed jointly, and allocated into one category.

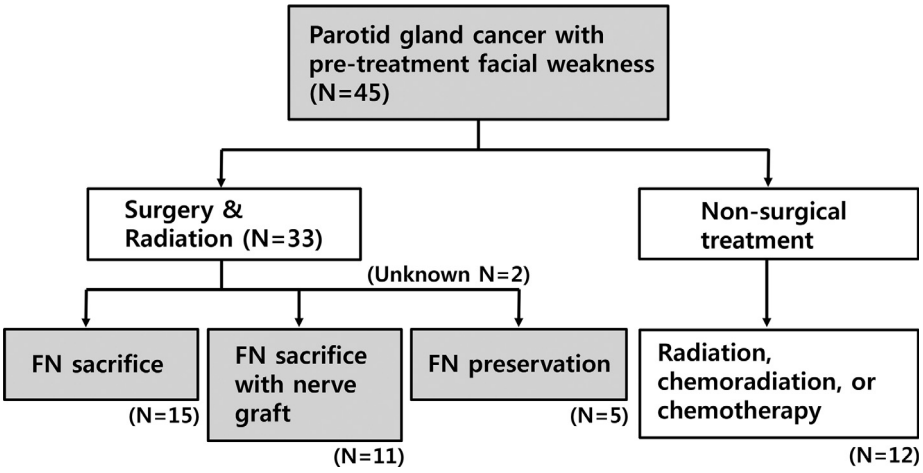


Fig. 1. Treatments for parotid gland cancer in patients with pre-treatment facial weakness in our series.

Statistical analysis

The results were mainly presented with descriptive statistical methods (number and %), because there was a small number of study patients. Survival analyses were conducted to identify potential risk factors for poor outcomes. The primary endpoints were progression-free survival and overall survival. Progression-free and overall survival durations were calculated as the time elapsed from the first day of treatments until the time of disease progression or any deaths, respectively. Cases without events by the last clinical follow-up were censored.

Clinico-pathological variables, degree of facial weakness and treatment modalities were included in the analysis. For progression-free survival, adenoid cystic carcinoma pathology was classified as high-grade tumors, because these tumors are usually locally infiltrative. Adenoid cystic carcinoma pathology was separated from other high-grade and non-high-grade tumors in the analysis of overall survival, because it grows slowly and most patients with these tumors have long survival, even with advanced tumor stage.

From univariable analysis, the significant variables were chosen to construct a multivariable Cox proportional hazard model for survival. Multicollinearity among variables was tested by calculating variance inflation factor. The possible association between variables (tumor grade vs. metastasis, presence of distant metastasis vs. initial non-surgical treatment) was also statistically tested. Statistical analyses were executed using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA). All tests were two-sided and $P < 0.05$ indicated statistical significance.

Results

Subject characteristics

Among 45 enrolled patients, adenoid cystic carcinoma and salivary duct carcinoma (high-grade) were the most frequent pathologies, causing facial weakness (Table 1). Of note, high-grade tumors including adenoid cystic carcinoma represented 86.7% of all cases. Regarding tumor size, 77.8% of tumors were more than 4 cm in maximal diameter. We performed neck dissection in 22 patients: elective lymph node dissection in 11 and therapeutic lymph node dissection in 11. However, neck dissection was not indicated in 23 patients (patients with adenoid cystic carcinoma pathology or non-surgical management). As a result, cases diagnosed as N0 were 53.3% and N(+) were 46.6% (Table 1). Five patients with systemic metastasis had undergone palliative treatment alone. Overall, most parotid gland cancers causing facial weakness were advanced tumor stage and high-grade tumors.

Complete facial paralysis (House-Brackmann grades 5–6) was observed in 40% of patients at presentation. Incomplete facial weakness (House-Brackmann grades 2–4) or paralysis on specific face subsites was observed in 60% of patients.

All patients without systemic disease (M0) were subjected to curative treatment, including primary surgery with adjuvant treatment (n = 33) and primary radiation (or chemoradiation) (n = 7).

Oncological outcomes and survival analysis

Overall and progression-free survival rates among all patients were 67.2% and 44.0% at 3 years, 40.1% and 38.5% at 5 years, respectively (Fig. 2). Because of the limited number of patients, oncological outcomes are only presented in the descriptive manner (Table 2). As expected, the group with initial non-surgical treatment showed the worst survival outcomes. The two groups who underwent surgery and facial nerve sacrifice with or without nerve graft had similar oncological outcomes (Supplementary Fig. S1). The group with surgery and facial nerve preservation showed the best outcomes. This was probably due to low tumor burden (no lymph node metastasis) at diagnosis.

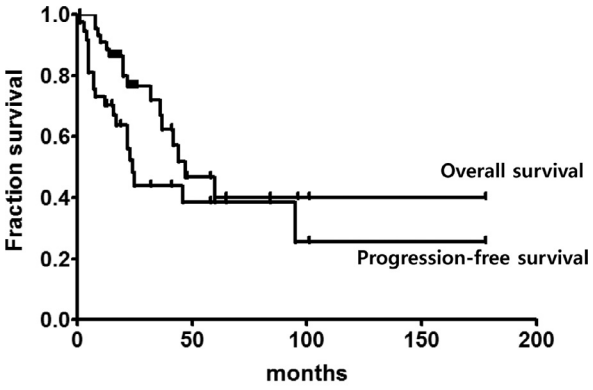
Table 1
Characteristics of patients with parotid gland cancer and pretreatment facial weakness (n = 45).

Characteristics		Number (%)
Age (years) (mean ± SD)		56.0 ± 14.8 [range 15–87]
Gender (M:F)		30:15 (66.7:33.3)
Pathologic diagnosis		
	Adenoid cystic carcinoma	13 (28.9)
	Salivary duct carcinoma	11 (24.4)
	Adenocarcinoma, NOS	7 (15.6)
	Mucoepidermoid carcinoma	6 (13.3)
	Carcinoma ex pleomorphic adenoma (Carcinoma components)	4 (8.9)
	Salivary duct carcinoma	2 (4.4)
	Adenocarcinoma, NOS	2 (4.4)
	Others[1]	4 (8.9)
Tumor grade	High-grade[2]	39 (86.7)
	Intermediate-grade	1 (2.2)
	Low-grade	5 (11.1)
T classification[3]	T1	2 (4.4)
	T2	8 (17.8)
	T3	5 (11.1)
	T4	30 (66.7)
N classification[3]	N0	24 (53.3)
	N1	2 (4.4)
	N2	18 (40.0)
	N3	1 (2.2)
M classification	M0	40 (88.9)
	M1	5 (11.1)
Functional status of FN		
	Complete FN weakness[4]	18 (40.0)
	Incomplete FN weakness[5]	27 (60.0)
	Incomplete eye closure	5 (11.1)
	Lip deviation	11 (24.4)
	Mild dysfunction	11 (24.4)
Treatment		
	Surgery ± adjuvant RT or CCRT	33 (73.3)
	FN sacrificed	26 (57.8)
	FN preserved	5 (11.1)
	Unknown	2 (4.4)
	Non-surgical treatment[6]	12 (26.7)

Adenocarcinoma, NOS: Not otherwise specified.
FN: facial nerve, RT: radiation treatment, CCRT: concurrent chemo-radiation.
[1] Other pathologies: Myoepithelial carcinoma, oncocytic carcinoma, carcinosarcoma, neuroendocrine carcinoma.
[2] High-grade tumors included adenoid cystic carcinomas because of locally infiltrative characteristics of adenoid cystic carcinomas.
[3] T and N classification: pT and pN in cases with surgery, cT and cN in cases with non-surgical management.
[4] House-Brackmann grades 5–6.
[5] House-Brackmann grade ≤ 4.
[6] Radiation, concurrent chemo-radiation, or chemotherapy alone.

To confirm the major prognostic factors in these patients, survival analyses were conducted based on known clinico-pathological factors (Table 3). Interestingly, tumor size and tumor grade were not significant prognosticators for survival. Metastasis (lymph node or distant sites) was a significant risk factor for worse survival, in consistent with a previous report [18].

There may be interaction between variables in multivariable analysis; the potential association and independency was evaluated in two ways. First, variance inflation factors of each variable showed values ranging from 1 to 2, suggesting that the multicollinearity among variables was not significant (Supplementary Table S1). Second, correlation analysis between some variables was conducted to show that initial systemic disease status was significantly associated with non-surgical treatment. As a result, treatment modality variable was omitted from multivariable analysis. We did not identify any potential interaction



	Overall survival	Progression-free survival
Median survival	47 months	24 months
3-year survival	67.2%	44.0%
5-year survival	40.1%	38.5%

Fig. 2. Overall and progression-free survival in all patients with pre-treatment facial weakness (n = 45).

between tumor grade and lymph node metastasis, which might be due to the limited number of patients. Thus, this point should be re-evaluated in a larger cohort.

Functional outcomes of facial weakness

Next, the functional outcomes of facial expression were assessed according to treatment modality. Post-treatment facial function was evaluated at 6–12 months after completing treatment (Supplementary Fig. S2). Facial function in nerve-resected patients was stationary or decreased, compared to the initial facial paralysis grades. In some patients, nerve graft was conducted by skilled surgeons, who had more than 5 years of experience in microsurgery. Even with a facial nerve graft, improved facial nerve function was not observed in our series.

As for the cases with facial nerve preservation (n = 5), the pathological diagnoses were 3 salivary duct carcinoma, one carcinoma ex pleomorphic adenoma (carcinoma component = high-grade adenocarcinoma NOS) and one low-grade mucoepidermoid carcinomas. Even with high-grade pathology, it was possible to safely separate the facial nerve from the tumors during surgery without disruption of tumor. As expected, cases with facial nerve preservation during surgery had the best functional outcomes in terms of the facial expression (Supplementary Fig. S3). The functional improvements (House-Brackmann grades 3–1 and grade 5–3) were observe in most of patients, except one (House-Brackmann grades 3–4), at post-treatment 6–12 months.

Pathological analysis of local tumor invasion into the facial nerve

We also investigated whether pretreatment facial weakness suggests local tumor invasion of the facial nerve. To explore this, the pathology specimens of resected facial nerves were assessed (n = 26). To trace the whole resected facial nerve, multiple slide sections were reviewed for each tumor (15–16 sections), and the area between the facial nerve and tumor was scrutinized. Approximately ⅔ of tumors showed peri-neural or intra-neural tumor invasion of the facial nerve, and ⅓ of tumors did not have local tumor invasion of the facial nerve (Fig. 3). These findings suggest that the facial nerve can be preserved safely in ⅓ of patients even with pretreatment facial weakness.

To further investigate the possible correlation between various tumor factors and pathological nerve invasion, we conducted an additional correlation analysis in the patients with facial nerve resection (n = 26). In summary, we did not find any correlations between pathological facial nerve invasion and tumor-grade, T and N status (Supplementary Table S2). Thus, it seems hard to predict pathological facial nerve invasion, just by tumor factors (tumor grade, T or N status). Rather, intraoperative findings may be important for the decision regarding FN resection.

Discussion

Although parotid gland cancer with facial weakness is a serious clinical situation, clinical outcomes and treatment decisions regarding optimal surgical management are infrequently studied because of the rare incidence of parotid gland cancer with facial weakness. In our study, we tried to refine the surgical guidelines for facial nerve management in patients with parotid gland cancer and pre-treatment facial weakness. Our results challenge the prevailing concept that pretreatment facial weakness with parotid gland cancer is a surgical indicator for facial nerve resection [5,13,19]. Although our study was limited by a small number of patients, it will provoke further discussion about this unsolved clinical problem.

The reported incidence of facial weakness in parotid gland cancers at presentation ranged from 13.6% to 34.7% of patients and was 13.5%

Table 2
Oncological outcomes at final follow-up according to subgroups (n = 43).

Groups	TNM status at diagnosis[1]	Oncological outcomes (No.)[2,3]	Time to recurrence (months) (mean, range)	Follow-up in cases without recurrence or deaths (months) (mean, range)
Surgery, FN sacrificed with nerve graft (n = 11)	T2:T3:T4 = 1:2:8 N0:N2:N3 = 5:5:1 M0 = 11	NED: 6 (54.5%) DOD: 4 AWD: 1	7.0 [1–16]	28.0 [15–101]
Surgery, FN sacrificed without nerve graft (n = 15)	T1:T2:T3:T4 = 2:2:3:8 N0:N1:N2 = 6:1:8 M0 = 15	NED: 8 (53.3%) DOD: 6 AWD: 1	25.8 [0–95]	57.2 [13–178]
Surgery, FN saved (n = 5)	T2:T4 = 3:2 N0 = 5 M0 = 5	NED: 4 (80.0%) AWD: 1	4.0	47.0 [15–84]
Non-surgical management (n = 12)	T2:T4 = 2:10 N0:N1:N2 = 7:1:4 M0:M1 = 7:5	NED: 1 (8.3%) DOD: 5 AWD: 6	7.1 [0–25]	16

FN: facial nerve.
[1] Tumor-Node-Metastasis staging according to 7th AJCC staging system: pTNM in cases with surgery, cTNM in cases with non-surgical management.
[2] NED: no evidence of disease, DOD: death of disease, AWD: alive with disease.
[3] See Supplementary Fig. S1.

Table 3
Survival analyses and risk factors for worse outcomes (n = 45).

Univariable analysis									
Variables	Categories	Progression-free survival				Overall survival			
		Hazard ratio	95% Confidence interval		*P* value	Hazard ratio	95% Confidence interval		*P* value
Age	Continuous	1.023	0.995	1.052	0.112	1.039	1.000	1.080	0.052
Gender	M vs. F	1.420	0.620	3.253	0.407	1.182	0.407	3.432	0.759
Tumor size	d ≥ 4 cm vs. < 4 cm	1.106	0.448	2.733	0.827	0.867	0.278	2.701	0.806
Tumor grade	High-grade vs. non-high-grade	11.154	0.643	193.408	0.098	5.945	0.308	114.776	0.238
	ACC vs. non-high-grade					2.207	0.098	49.650	0.618
Facial weakness	Complete vs. incomplete	1.817	0.860	3.839	0.118	1.872	0.699	5.014	0.212
LN metastasis	N(+) vs. N0	1.964	0.919	4.196	0.081	5.731	1.803	18.221	0.003
Distant metastasis	M1 vs. M0	3.303	1.234	8.843	0.017	4.588	1.549	13.594	0.006
Treatment	Non-surgery vs. primary surgery	3.675	1.675	8.062	0.001	3.129	1.093	8.957	0.034
Multivariable analysis[1]									
Age	Continuous					1.010	0.967	1.055	0.644
LN metastasis	N(+) vs. N0	1.685	0.767	3.699	0.196	4.934	1.413	17.233	0.012
Distant metastasis	M1 vs. M0	2.895	1.064	7.879	0.037	3.896	1.287	11.797	0.016

ACC: adenoid cystic carcinomas.
LN: Lymph node.
[1] Please see Supplementary Table S1. Evaluation of multi-collinearity among variables.

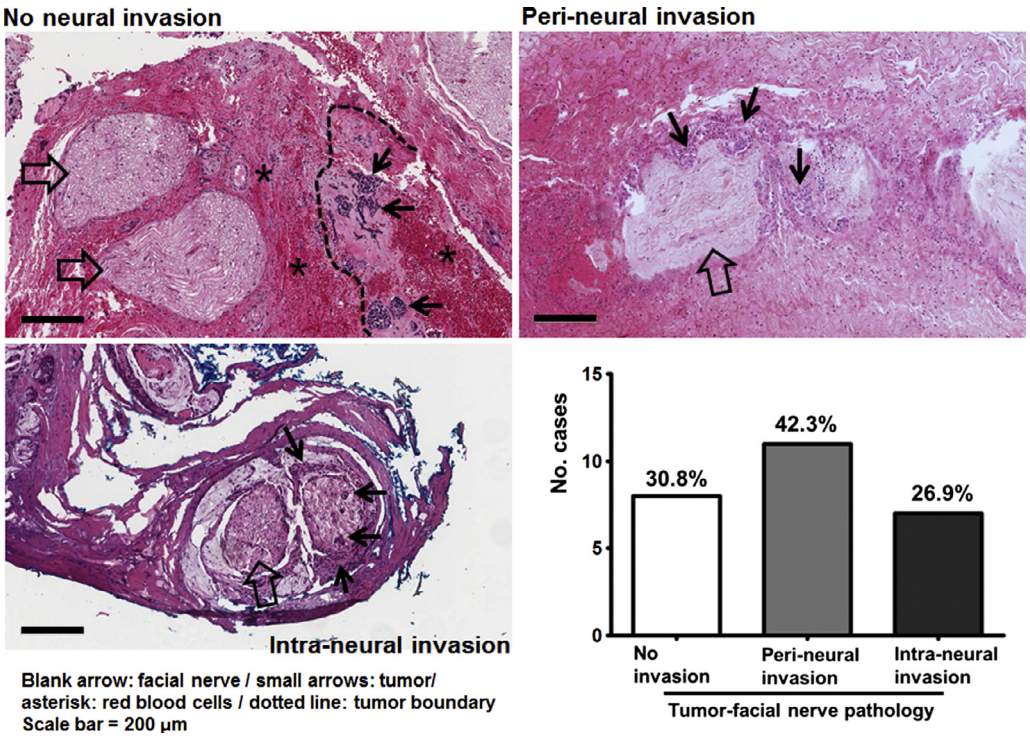


Fig. 3. Pathological analysis of facial nerve invasion by tumors (n = 26, facial nerve-resected patients).

in our series [2,4,5,9,10,12]. Facial nerve paralysis at diagnosis is a significant prognostic factor in patients with parotid gland cancers [2,7,10]. In line with previous reports, our data demonstrated that most parotid gland cancers causing facial weakness have high-grade pathology, including adenoid cystic carcinoma. As expected, our patients showed around 40% survivals at 5 years.

In the literature, two papers indicated that facial nerve sacrifice to obtain clear surgical margins improved local control and long-term prognosis in adenoid cystic carcinomas [14,15]. However, there have been no reports in other types of parotid gland cancers with facial weakness. These other tumors are probably high-grade and have more aggressive clinical courses than adenoid cystic carcinomas. Our results raised questions about the clinical efficacy of facial nerve reconstruction with facial nerve resection. Facial nerve graft requires recovery time of 6–12 months to allow nerve regeneration [20,21]. However, half of patients experienced disease recurrence, resulting in the salvage or other type of treatments. With lymph node metastasis, patients did not have enough time for facial nerve regeneration. Thus, we cautiously suggest that static techniques [22] for facial reanimation are better than nerve regeneration techniques for these patients.

Another thing to note was that facial weakness in parotid gland cancers did not always indicate local tumor invasion of the facial nerve, particularly with incomplete facial paralysis. In this study, no tumor invasion was identified in 30% of nerve-resected surgical specimens. Indirect causes, such as extrinsic compression, ischemia or local inflammation, might cause dysfunction of the facial nerve [23,24]. Thus, decisions regarding facial nerve resection should be further based on intraoperative findings with/without radiological clues [25,26]. In our

specimens, we did not observe increased deposit of inflammatory cells around the facial nerve, in cases without neural invasion by tumors. Instead, many red blood cells were found in the anatomical interface between the nerve and tumors (Fig. 3, upper left panel). Thus, our findings suggest a shearing force (extrinsic/ mechanical factor causing hemorrhage) between the tumors and the facial nerve may be the main cause of facial weakness in these cases, rather than inflammatory reaction. However, this point should be re-evaluated with large number of samples.

When preserving the facial nerve during surgery in these patients, surgical procedures should be performed on oncological safety. In our cases (n = 5), the facial nerve was clearly separated from the tumor without violation or spillage of gross tumors (Supplementary Fig. S3). However, the surgical safety margin was not enough for these patients even without cancer cells at the resection margin. Our experience showed comparable oncological outcomes with better facial function in patients with preserved facial nerves. However, the long-term oncological outcomes should be further validated with a large number of patients.

In conclusion, a large portion (86.7%) of parotid gland cancers with facial weakness was high-grade tumors. Patients had poor clinical outcomes (44.0% in 3Y progression-free survival) and approximately half of patients suffered recurrence. Recovery of facial weakness was suboptimal in patients with facial nerve graft, due to short disease-free intervals, that did not allow enough time for facial nerve recovery. Thus, static techniques for facial reanimation may be more desirable for these patients. In cases with incomplete facial weakness and safe separation of nerve from tumors, facial nerve preservation offered the best functional outcomes, without compromising oncological outcomes.

Author's contribution

Conceptualization: WP, HSJ.
Data curation: WP, JP, SIP, HK.
Formal analysis: WP, JP, HB, JC, HSJ, HW, MP.
Methodology: JC, MP, HSJ.
Funding acquisition, Project administration and Supervision: HSJ.
Writing - original draft: WP, JP, HSJ.
Writing - review & editing: All authors.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Declarations

Ethics approval and consent to participate.

The study protocol was approved by the Institutional Review Board of Samsung Medical Center. The data used in this study was de-identified.

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The above funders had no further role in the study design, in collection, analysis and interpretation of data, in writing of the manuscript, or in the decision to submit this manuscript for publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.01.003.

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