

ORIGINAL**Risk factors of first bite syndrome after surgical resection of parapharyngeal space tumors**

Koji Abe^{1,2}, Atsuhiko Uno³, Koichi Tamura⁴, Ryo Kanamura¹, Hiroki Ohnishi¹, Yuhki Ishitani¹, Eiji Kondo¹, Takahiro Azuma¹, Go Sato¹, Yoshiaki Kitamura¹, and Noriaki Takeda¹

¹Department of Otolaryngology-Head and Neck Surgery, Tokushima University Hospital, Tokushima, Japan, ²Department of Otolaryngology, Japanese Red Cross Tokushima Hospital, Tokushima, Japan, ³Department of Otolaryngology-Head and Neck Surgery, Osaka General Medical Center, Osaka, Japan, ⁴Department of Otolaryngology, Tokushima Municipal Hospital, Tokushima, Japan

Abstract : **Objective :** First bite syndrome is a complication of surgical resection of parapharyngeal space tumors and the development of cramping pain in the parotid region with the first bite of a meal. The present study aimed to identify the potential risk factors for the development of first bite syndrome. **Methods :** We retrospectively reviewed 30 consecutive patients with parapharyngeal space tumors who had been surgically treated between August 2003 and December 2015 at our department. **Results :** The tumor site (prestyloid or retrostyloid) and surgical approach (transcervical-parotid, transparotid, or transcervical) were not correlated with the development of first bite syndrome. Ligation and mobilization of the external carotid artery was significantly correlated with the development of first bite syndrome. Moreover, patients with complete resection of the parotid gland did not experience first bite syndrome. **Discussion :** The present findings suggest that concomitant surgical settings of 1) sympathetic denervation of the parotid gland with ligation of the external carotid artery or injury of the sympathetic nerve plexus around the external carotid artery during its mobilization, and 2) residual parotid gland tissue are risk factors for the development of first bite syndrome after surgical resection of parapharyngeal space tumors. *J. Med. Invest.* 70: 150-153, February, 2023

Keywords : First bite syndrome, complication, parapharyngeal space tumor, external carotid artery, parotid gland

INTRODUCTION

Parapharyngeal space tumors arising within the parapharyngeal space are rare and represent approximately 0.5% of all head and neck tumors (1, 2). The parapharyngeal space is the central space of the deep face and includes the internal carotid artery, internal jugular vein, parotid gland and masseter muscle. Complications are commonly associated with the surgical resection of parapharyngeal space tumors, because of their deep location, complex anatomy, and the regional structures. The complications are 1) bleeding and cerebrovascular diseases caused by damage to blood vessels such as the internal carotid artery, external carotid artery, and internal carotid vein, 2) VII, IX, X, XI, and XII cranial nerve palsy due to nerve damage, and 3) Horner's syndrome due to cervical sympathetic nerve damage (3).

Recently, first bite syndrome has been widely recognized as a complication of the surgical resection of parapharyngeal space tumors (4), after the term of first bite syndrome was initially reported by Haubrich in 1986 (5). First bite syndrome develops several days postoperatively in patients who undergo surgical resection of parapharyngeal space tumors. Patients experience severe sharp or cramping pain in the parotid region during the first bite of each meal. The most intense pain is experienced during the first meal of the day, and the pain increases when ingesting foods that stimulate saliva secretion, such as sour food. However, the pain improves as patients continue to bite, and only recurs at the start of the next meal (6). The pain intensity and

frequency of first bite syndrome is gradually relieved approximately 1 year postoperatively (7, 8).

In the present case series, 30 consecutive patients with parapharyngeal space tumors who had been surgically treated at our department were enrolled. First bite syndrome developed in 6 patients postoperatively. The present study aimed to identify the potential risk factors for the development of first bite syndrome, based on our experiences.

PATIENTS AND METHODS*Patients*

We retrospectively analyzed the hospital charts of 30 consecutive patients with parapharyngeal space tumors who had been surgically treated between August 2003 and December 2015 at the Department of Otolaryngology-Head and Neck Surgery of Tokushima University Hospital (sex: males 15, females 15, age: 21-80 years, mean: 53.2 years). This study was approved by the Committee for Medical Ethics of Tokushima University Hospital (#4061).

Histopathological examination of the resected parapharyngeal space tumors showed salivary gland origin tumors in 21 patients, nerve origin tumors in 8 patients and blood vessel origin tumors in 1 patient (Table 1). Among parapharyngeal space tumors originating from the salivary gland, pleomorphic adenoma was the most frequent in 14 patients, while malignant tumors included acinic cell carcinoma in 2 and adenoid cystic carcinoma in 1. Among parapharyngeal space tumors originating from the nerve, schwannoma was the most frequent in 6 patients, which originated from the vagal nerve in 2 patients, the sympathetic nerve in 2, the trigeminal nerve in 1, and the hypoglossal nerve in 1.

Received for publication December 1, 2022; accepted December 9, 2022.

Address correspondence and reprint requests to Noriaki Takeda, M.D., Ph.D., Department of Otolaryngology, University of Tokushima School of Medicine, 3-18-15 Kuramoto, Tokushima 770-8503, Japan and Fax: +81-88-633-7170. E-mail: takeda@tokushima-u.ac.jp

Table 1. Patients characteristics, tumor site and histopathology

Age (years)	21-80 (mean : 53.2)
Sex	
Male	15
Female	15
Tumor site	
PS	22
RS	8
Salivary gland origin	21
Pleomorphic adenoma	14
Basal cell adenoma	2
Warthin's tumor	2
Acinic cell carcinoma	2
Adenoid cystic carcinoma	1
Nerve origin	8
Schwannoma	6
Paraganglioma	1
Neurofibroma	1
Blood vessel origin	1
Cavernous hemangioma	1

PS : prestyloid, RS : retrostyloid

Surgery

The parapharyngeal space comprises 2 compartments, the prestyloid (PS) and retrostyloid (RS) compartments, which are separated by the styloid process. In the present study, parapharyngeal space tumors were located in the PS in 22 patients and the RS in 8. The transcervical-parotid approach was used to resect parapharyngeal space tumors located in the PS in 7 patients ; the transparotid approach was used to resect parapharyngeal space tumors located in the PS in 4 patients ; and the transcervical approach was used to resect parapharyngeal space tumors located in the PS in 11 patients and in RS in 8. Median mandibulotomy were added to the transcervical approach in 2 patients for each resection of adenoid cystic carcinoma and schwannoma. No patients underwent cervical sympathectomy.

Statistical analysis

Statistical analysis was performed using chi-squared analysis and $p < 0.05$ was considered significant.

RESULTS

Postoperative complications after surgical resection of parapharyngeal space tumors were observed in 22 (73%) of the 30 patients (Table 2) : facial nerve palsy in 16 patients, hypoglossal nerve palsy in 6, vagal nerve palsy in 6, Horner's syndrome in 4, and Frey syndrome in 3. First bite syndrome developed in 6 patients. Permanent complications were observed in 6 patients : facial nerve palsy in 1, hypoglossal nerve palsy in 5 (3 showed it preoperatively), vagal nerve palsy in 4, Horner's syndrome in 4 (2 showed it preoperatively), and Frey syndrome in 2. First bite syndrome gradually improved 1 year after onset in all 6 patients.

The risk factors for the development of first bite syndrome are shown in Table 3. The tumor site (PS or RS) and surgical approach (transcervical-parotid, transparotid, or transcervical) were not correlated with the development of first bite syndrome. Ligation and mobilization of the external carotid artery was significantly correlated with the development of first bite syndrome. First bite syndrome developed in all 3 patients who underwent ligation of the external carotid artery. Among 13 patients who underwent mobilization of the external carotid artery, first bite syndrome developed in 3. Fourteen patients without surgical manipulation of the external carotid artery did not experience first bite syndrome. Moreover, 5 patients with complete resection of the parotid gland did not complain of first bite syndrome, while 6 of 25 patients with residual parotid gland tissue suffered from first bite syndrome.

Table 2. Complications after surgical resection of parapharyngeal space tumors

	Total (permanent)
Facial nerve palsy	16 (1)
Hypoglossal nerve palsy*	6 (5)
Vagal nerve palsy	6 (4)
Horner's syndrome**	4 (4)
Frey syndrome	3 (2)
First bite syndrome	6
No complications	8

*Preoperative hypoglossal nerve palsy in 3 patients

**Preoperative Horner's syndrome in 2 patients

Table 3. Risk factors for the development of first bite syndrome

	Total	FBS		p
		6	24	
Tumor site				
prestyloid (PS)	22	3	19	
retrostyloid (RS)	8	3	5	n.s.
Surgical approach				
transcervical-parotid	7	2	5	n.s.
transparotid	4	1	3	
transcervical	19	3	16	
External carotid artery				
ligation	3	3	0	p=0.0135
mobilization	13	3	10	
preservation	14	0	14	
Parotid gland				
remaining	25	6	19	
no	5	0	5	n.s.

n.s. : not significant

DISCUSSION

Previously, it was reported that the most frequent complication associated with parapharyngeal space surgery is cranial nerve palsy (2). The present findings that facial, hypoglossal and vagal nerves are frequently affected were consistent with the previous studies. First bite syndrome is another common complication after surgery involving the parapharyngeal space (6, 7). In the present study, 6 of 30 (20%) patients who were treated with surgical resection of parapharyngeal space tumors suffered from first bite syndrome postoperatively. Previously, Kawashima *et al.* reported that among 29 patients with parapharyngeal space tumors, first bite syndrome developed postoperatively in 9 (31%) (8) and Linkov, *et al.* reported it in 22.4% of patients who underwent parapharyngeal space surgery (9). Recently, Avingçal *et al.* reported first bite syndrome in 16 (30%) of 53 patients who underwent surgery in the upper neck region, including that of the parapharyngeal space (10). Thus, first bite syndrome is not a minor complication of parapharyngeal space surgery.

In the present study, perioperative ligation and mobilization of the external carotid artery were correlated with postoperative first bite syndrome in patients with parapharyngeal space tumors. In 1998, Netterville *et al.* suggested that first bite syndrome is secondary to resection or injury to the cervical sympathetic trunk (4). Thereafter, Chiu *et al.* in 2002 suggested that first bite syndrome develops secondarily to ligation of the external carotid artery with its accompanying sympathetic nerve plexus (7). In 2008, Kawashima *et al.* reported first bite syndrome in patients who underwent ligation of the external carotid artery and/or ablation of the sympathetic nerve chain (8). In 2017,

Avingçal *et al.* reported that first bite syndrome developed after upper cervical surgery in 57% of patients who underwent ligation of the external carotid artery, but in 12.5% of patients in whom the external carotid artery was preserved. They also reported that among patients in whom the external carotid artery was preserved, first bite syndrome developed in 43% of the patients in whom sympathetic nerve chain was sacrificed, but in 4% of the patients in whom the sympathetic chain was preserved (10). In 2012, Linkov *et al.* identified parapharyngeal space surgery and sympathetic nerve chain sacrifice as risk factors of first bite syndrome (9). Taken together with previous reports, our findings suggest that perioperative ligation of the external carotid artery and injury of the sympathetic nerve plexus around the external carotid artery during its mobilization are risk factors for the development of first bite syndrome after surgical resection of parapharyngeal space tumors.

Moreover, in the present study, patients who had undergone complete resection of the parotid gland did not complain of first bite syndrome. Linkov *et al.* also reported that few patients who underwent total parotidectomy suffered from first bite syndrome (9).

Based on the autonomic innervation of the parotid gland (Fig. 1), concomitant surgical settings of 1) sympathetic denervation of the parotid gland with resection or injury of the cervical sympathetic trunk, ligation of the external carotid artery, and injury of the sympathetic nerve plexus around the external carotid artery during its mobilization, and 2) residual parotid gland tissue are risk factors for the development of first bite syndrome after surgical dissection of parapharyngeal space tumors.

The hypothesized pathogenesis of first bite syndrome is that

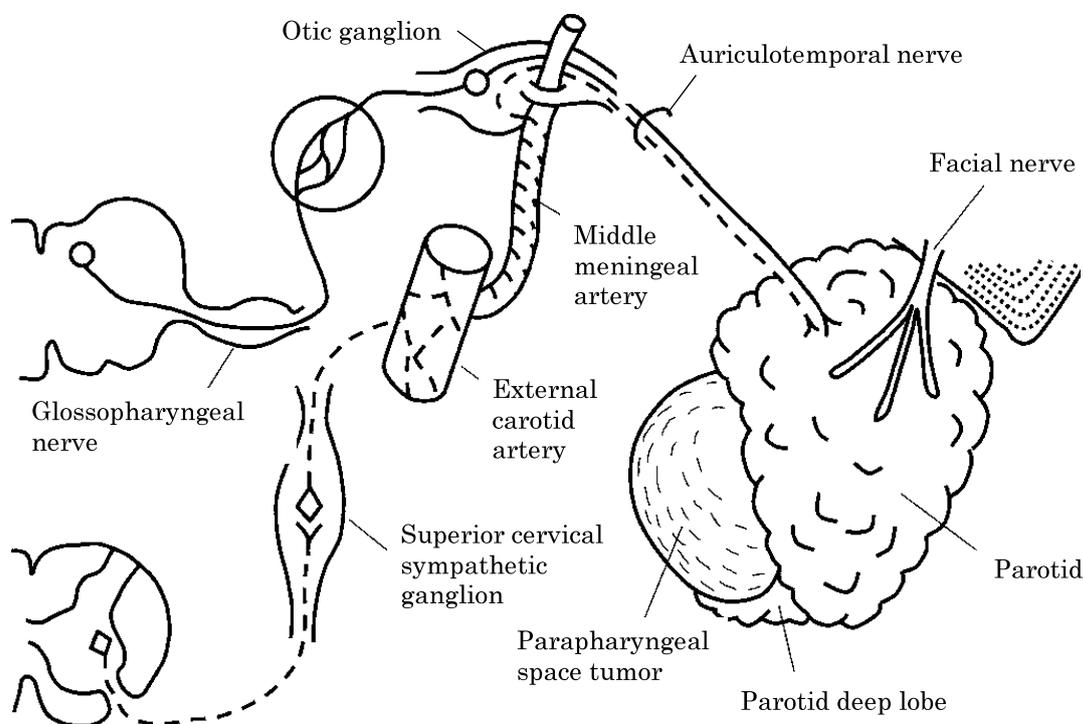


Figure 1. Sympathetic and parasympathetic innervation to the parotid gland
Concomitant surgical settings of 1) sympathetic denervation of the parotid gland with resection or injury of the cervical sympathetic trunk, ligation of the external carotid artery, and injury of the sympathetic nerve plexus around the external carotid artery during its mobilization, and 2) residual parotid gland tissue are risk factors for the development of first bite syndrome after surgical dissection of parapharyngeal space tumors.
Dashed line : sympathetic nerve, and solid line : parasympathetic nerve
Reprinted from Fig. 3 in Ref. 11 with permission

resection of the sympathetic nerve innervating the parotid gland during surgical resection of parapharyngeal space tumors induces denervation hypersensitivity of the myoepithelial cells of the parotid glands toward parasympathetic stimulation, resulting in severe pain from myoepithelial cells spasm associated with an initial oral intake (4, 6, 7). The hypothesis is often cited, but has not been experimentally proven and cannot explain why the most intense pain is associated with the first bite of the day's first meal and improves with subsequent bites.

Previously, we proposed another hypothesis of the pathogenesis of first bite syndrome (11). In the normal salivary gland, parasympathetic impulses mainly stimulate salivary secretion, whereas sympathetic impulses produce synergistic effects of salivary secretion. Both parasympathetic and sympathetic impulses induce myoepithelial cells contraction (12). In an experimental study of rat parotid gland, sympathectomy increased the concentration of salivary amylase and protein in response to initial parasympathetic stimulation. However, during subsequent parasympathetic stimulation, the total amylase output became equal to the normal output, suggesting a gradual decrease in the viscosity of saliva (13). These experimental findings suggested that sympathectomized parotid gland initially secretes the most viscous saliva containing high concentrations of amylase and protein, and subsequently secretes less viscous saliva. Accordingly, we hypothesized the following: denervation of the sympathetic nerve innervating the parotid gland during surgical resection of parapharyngeal space tumors induces the initial secretion of very viscous saliva in response to parasympathetic stimulation at the first bite of the day's first meal and that the viscous saliva blocks the ductal salivary flow like a salivary stone, resulting in salivary colic pain due to a sudden increase in intraluminal pressure within residual parotid gland. During subsequent bites, pain improves in accordance of the decrease on saliva viscosity.

In the present study, first bite syndrome gradually improved 1 year after onset. It was reported that in 11 of 16 patients with first bite syndrome, symptoms spontaneously improved in 2 years (10). In experimental studies of rat parotid gland, chronic sympathectomy reduced salivary secretion and caused a patchy acinar degranulation in response to parasympathetic stimulation (13, 14). Therefore, it is possible that the spontaneous resolution of first bite syndrome is due to progressive deterioration of sympathectomized parotid gland function.

CONCLUSION

We reviewed 30 consecutive patients who had undergone surgical resection of parapharyngeal space tumors, and first bite syndrome developed in 6 patients postoperatively. Concomitant surgical settings of 1) sympathetic denervation of the parotid gland with ligation of the external carotid artery or injury of the sympathetic nerve plexus around the external carotid artery during its mobilization, and 2) residual parotid gland tissue are risk factors for the development of first bite syndrome after parapharyngeal space surgery. During surgical resection of parapharyngeal space tumors, surgeons should be careful to preserve the sympathetic nerve plexus supplying the parotid

gland around the external carotid artery as much as possible to prevent first bite syndrome.

CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

REFERENCES

1. Batsakis JG, Sneige N : Parapharyngeal and retropharyngeal space diseases. *Ann Otol Rhinol Laryngol* 98 : 320-321, 1989
2. López F, Suárez C, Vander Poorten V, Mäkitie A, Nixon IJ, Strojan P, Hanna EY, Rodrigo JP, de Bree R, Quer M, Takes RP, Bradford CR, Shaha AR, Sanabria A, Rinaldo A, Ferlito A : Contemporary management of primary parapharyngeal space tumors. *Head Neck* 41 : 522-535, 2019
3. Bulut OC, Giger R, Alwagdani A, Aldabal N, Stenzinger A, Heimgartner S, Nisa L, Borner U : Primary neoplasms of the parapharyngeal space : diagnostic and therapeutic pearls and pitfalls. *Eur Arch Otorhinolaryngol* 278 : 4933-4941, 2021
4. Netterville JL, Jackson CG, Miller FR, Wanamaker JR, Glasscock ME : Vagal paraganglioma : a review of 46 patients treated during a 20-year period. *Arch Otolaryngol Head Neck Surg* 124 : 1133-1140, 1998
5. Haubrich WS : The first bite syndrome. *Henry Ford Hosp Med J* 34 : 275-278, 1986
6. Steel SJ, Robertson CE : First bite syndrome : what neurologists need to know. *Curr Pain Headache Rep* 25 : 31, 2021
7. Chiu AG, Cohen JI, Burningham AR, Andersen PE, Davidson BJ : First bite syndrome : a complication of surgery involving the parapharyngeal space. *Head Neck* 24 : 996-999, 2002
8. Kawashima Y, Sumi T, Sugimoto T, Kishimoto S : First-bite syndrome : a review of 29 patients with parapharyngeal space tumor. *Auris Nasus Larynx* 35 : 109-113, 2008
9. Linkov G, Morris LG, Shah JP, Kraus DH : First bite syndrome : incidence, risk factors, treatment, and outcomes. *Laryngoscope* 122 : 1773-1778, 2012
10. Avinçsal MÖ, Hiroshima Y, Shinomiya H, Shinomiya H, Otsuki N, Nibu KI : First bite syndrome : a 11-year experience. *Auris Nasus Larynx* 44 : 302-305, 2017
11. Nakagawa H, Tamura K, Abe K, Miyazaki K, Akizuki H, Takeda N : First bite syndrome after dissection of parapharyngeal tumor. *Pract Otol (Kyoto)* 98 : 751-757, 2006
12. Garrett JR : The proper role of nerves in salivary secretion : a review. *J Dent Res* 66 : 387-397, 1987
13. Ekström J, Garrett JR, Månsson B, Tobin G : The effects of atropine and chronic sympathectomy on maximal parasympathetic stimulation of parotid saliva in rats. *J Physiol* 403 : 105-116, 1988
14. Garrett JR, Harrop TJ, Thulin A : secretion of parotid acinar granules in rats during reflex stimulation after chronic sympathectomy. *Q J Exp Physiol* 70 : 461-467, 1985