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Management of retropharyngeal lymph node metastasis in oral cancer

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ABSTRACT

Objectives: Retropharyngeal lymph node (RPLN) metastasis is extremely rare, and prognosis is significantly poor in oral cancer. We retrospectively examined the management of RPLN metastases in oral cancer.

Materials and methods: A total of 1247 patients with oral cancer were treated at our department from January 2002 and December 2016. Among these patients, 374 (30%) had histologically positive lymph node metastases. Of these, 15 patients (1.2%) were diagnosed with RPLN metastases. We evaluated the diagnostic period, size, recurrence pattern, laterality, treatment, and therapeutic outcomes. The Kaplan–Meier method was used to determine overall survival (OS) among the RPLN metastasis group, cervical lymph node (CLN) metastases group, and treatment methods group for RPLN metastases.

Results: One patient had RPLN involvement at the initial treatment, and RPLN involvement in other patients was found subsequently. The mean duration in confirming RPLN metastases was 228 days (range, 50–867 days). Surgical therapy was performed in 5 patients, chemoradiotherapy in 7 patients, and best supported care (BSC) in 3 patients. The cumulative 5-year OS rate for the RPLN metastasis group (n = 15) was 38.1%, compared with the rate of 71.3% for the CLN group (n = 359). Regarding the therapeutic approach for RPLN metastases, OS rates were 80.0% (n = 5) in the surgical therapy group, 28.6% (n = 7) in the chemoradiotherapy group, and 0% (n = 3) in the BSC group.

Conclusion: Early detection and surgical treatment of RPLN metastases are associated with increased survival rate in oral cancer.

Introduction

Cervical lymph node (CLN) status is one of the most important prognostic factors in head and neck cancer. Retropharyngeal lymph node (RPLN) metastasis most often develops in pharyngeal and thyroid cancer; however, it is extremely rare in oral cancer.

RPLNs are located within the retropharyngeal space. The pharyngeal constrictor muscles bound this space anteriorly, prevertebral fascia posteriorly, carotid sheath laterally, and skull base superiorly, and inferiorly the space continues to the level of C3 vertebra at its caudal extent [1]. The lymph node can be divided into medial and lateral RPLN, and generally lateral RPLN is known as the Rouvière lymph node.

RPLNs are not routinely excised in neck dissection, and metastases to the lymph nodes are frequent in secondary and recurrent cases of oral cancer. Due to the low metastatic rate, most previous studies were case presentations [2–6] and reported that the prognosis of RPLN metastasis in oral cancer is significantly poor. Despite advances in diagnostic technology and therapeutic techniques, there is no unified management of diagnosis and therapy for RPLN metastases.

This study was conducted to examine the management of RPLN metastases in oral cancer.

Materials and methods

Between January 2002 and December 2016, a total of 1247 patients with oral cancer were treated at the Department of Oral and Maxillofacial Surgery of the Tokyo Medical and Dental University

Abbreviations: BSC, best supportive care; CLN, cervical lymph node; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; OS, overall survival; RPLN, retropharyngeal lymph node

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(Tokyo, Japan). Among these patients, 374 (30%) had histologic lymph node metastases. The median follow-up period was 48 months (range, 1–180 months). Of these, 15 patients (1.2%) were diagnosed with RPLN metastases. Clinicopathological information was obtained from medical charts, including age, sex, primary subsite, histology, TNM classification (Union for International Cancer Control 7th edition), and first treatment. As for RPLN metastases, we evaluated the diagnostic period, lymph node size, recurrence pattern, laterality, treatment, and therapeutic outcomes. Overall survival (OS) was defined as the time from the date of the initial visit to our department until death from any cause or last follow-up date. We calculated the survival rate in the RPLN and CLN metastasis groups. As for the RPLN metastasis group, the OS rate was calculated in the therapeutic methods, surgical therapy, chemoradiotherapy, and best supportive care (BSC) groups. Survival curves were estimated according to the Kaplan–Meier method, and these differences were examined using the log-rank test. A P-value < 0.05 was considered statistically significant. The analyses were performed using PASW Statistics version 25 (SPSS Inc., Chicago, IL, USA).

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Tokyo Medical and Dental University, Faculty of Dentistry (No. D2015-600).

Results

Patient characteristics and initial treatment

Fifteen patients consisting of 9 men and 6 women with a mean age of 65.7 years (range, 43–78 years) were included in the study (Table 1). The oral subsites of tumor development and ratio were the tongue in 3/649 (0.5%), lower gingiva in 6/222 (2.7%), upper gingiva in 3/137 (2.1%), and buccal mucosa in 3/138 (2.2%). Pathological diagnoses were squamous cell carcinoma in 14 patients and mucoepidermoid carcinoma in 1 patient (case 11). All patients had lateral RPLN metastases. There were no medial RPLN metastases.

Tumor clinical stages were stage II in 5 patients, stage III in 2 patients, stage IVA in 7 patients, and stage IVB in 1 patient. One patient had RPLN involvement at the initial treatment and oropharyngeal involvement of buccal mucosal carcinoma (case 5).

Initial treatment for primary cancer consisted of surgery in 14 patients and CyberKnife therapy in one patient (case 3). Eleven of 14 patients, except for a patient who had metastasis at the initial treatment, underwent neck dissection as initial treatment. Of these, 9 patients underwent therapeutic neck dissection, and 2 patients underwent elective neck dissection (case 1, 8). The other 3 patients (case 3, 6, 10) developed RPLN metastases simultaneously with subsequent CLN metastases. Of 15 patients, 14 had metastases at level I and/or II of CLNs (data not shown). The remaining patient (case 1) had RPLN metastasis without CLN metastasis.

RPLN metastases

The mean duration in confirming RPLN metastases in 14 patients, except for a patient who had metastasis at the initial treatment, was 228 days (range, 50–867 days). RPLN metastases were confirmed in 12 patients (85.7%) within 1 year and 13 patients (92.9%) within 2 years. RPLN metastasis was confirmed in a patient (case 13) within 867 days after recurrence in the primary site and cervix.

The modalities used to detect RPLN metastasis were CT in 9 patients, PET-CT in 3 patients, MRI in 1 patient, and clinical symptom observation in 2 patients (case 10, 13). Lateral oropharyngeal swelling was the clinical symptom that was observed in both patients. The mean size of the lymph node was 1.5 cm (range, 0.7–4.2 cm).

RPLN laterality was ipsilateral to the primary tumor in 13 patients and contralateral in 2 patients (case 9, 12).

The pattern of recurrence and treatment for RPLN metastases are shown in Table 1. Surgical therapy was performed in 5 patients,

Table 1
Characteristics of patients with LRPLN metastasis in this study.

Case	Age/sex	Primary subsite (Histology)	TN classification	Stage	Initial treatment		RPLN metastases					Outcome
					Primary	Neck dissection	Time of diagnosis (Pattern of recurrence)	Period (days)	Size (cm)	Laterality	Treatment	
1	60/F	LG(SCC)	T2N0	II	S	Elective	Subsequent(RPNL)	185	1.2	Ipsi	S + CR	NED
2	68/M	LG(SCC)	T4aN2b	IVa	S	Therapeutic	Subsequent(RPNL)	101	0.7	Ipsi	S + C	NED
3	76/M	LG(SCC)	T2N0	II	Cyberknife	No	Subsequent(P + N + RPLN)	50	0.8	Ipsi	S + R	NED
4	70/M	LG(SCC)	T2N2b	IVa	S	Therapeutic	Subsequent(RPNL)	281	1.0	Ipsi	S + CR	NED
5	76/M	BM(SCC)	T2N2b	IVa	S	Therapeutic	Initial	–	1.5	Ipsi	S + R	DOD(N,M)
6	62/F	UG(SCC)	T2N0	II	S	No	Subsequent(N + RPLN)	115	1.6	Ipsi	CR	NED
7	61/M	LG(SCC)	T2N1	III	S	Therapeutic	Subsequent(RPNL)	320	3.0	Ipsi	CR	NED
8	52/M	BM(SCC)	T2N0	II	S	Elective	Subsequent(N + RPLN)	272	1.4	Ipsi	CR	DOD(N + RPLN)
9	62/M	UG(SCC)	T4aN2c	IVa	S	Therapeutic	Subsequent(P + N + RPLN)	147	1.7	Contra	CR	DOD(P + RPLN)
10	50/F	TON(SCC)	T2N0	II	S	No	Subsequent(P + N + RPLN)	488	1.4	Ipsi	CR	DOD(P,N + RPLN)
11	43/M	LG(MEC)	T4aN2b	IVa	S	Therapeutic	Subsequent(P + N + RPLN)	104	1.2	Ipsi	CR	DOD(P,N + RPLN)
12	75/F	UG(SCC)	T4bN2b	IVb	S	Therapeutic	Subsequent(N + RPLN)	78	0.7	Contra	CR	DOD(N,M + RPLN)
13	78/F	TON(SCC)	T2N1	III	S	Therapeutic	Subsequent(RPLN)	867	4.2	Ipsi	BSC	DOD(P,N + RPLN)
14	75/F	BM(SCC)	T3N2b	IVa	S	Therapeutic	Subsequent(P + N + RPLN)	113	1.1	Ipsi	BSC	DOD(P,N + RPLN)
15	78/M	TON(SCC)	T3N2b	IVa	S	Therapeutic	Subsequent(N + RPLN)	77	1.1	Ipsi	BSC	DOD(N,M + RPLN)

M, male; F, female; BM, buccal mucosa; LG, lower gingiva; TON, tongue; UP, upper gingiva; SCC, squamous cell carcinoma; MEC, mucoepidermoid carcinoma.
RPLN, retropharyngeal lymph node; S, surgery; Ipsi, ipsilateral; Contra, contralateral; C, chemotherapy; R, radiotherapy; CR, chemoradiotherapy; P, primary recurrence.
N, neck recurrence; BSC, best supportive care; NED, no evidence of disease; DOD, die of disease.

chemoradiotherapy in 7 patients, and BSC in 3 patients. Among 5 patients with RPLN metastases but without simultaneous CLN metastases, 3 patients (case 1, 2, 4) underwent surgical therapy, 1 patient (case 7) with enlarging metastatic lesion underwent chemoradiotherapy, and 1 patient (case 13) with decreased performance status underwent BSC. The mean sizes of the lymph nodes were 1.0 cm (range, 0.7–1.5 cm) in the surgical treatment group, 1.5 cm (range, 0.7–3.0 cm) in the chemoradiotherapy group, and 2.1 cm (range, 1.1–4.2 cm) in the BSC group.

In the surgical therapy group (5 patients), 3 patients underwent lymph node excision by the cervical approach, and 2 patients (case 3, 5) underwent neck dissection combined with RPLN excision. No severe postoperative complications were observed in all patients. Histopathological examination showed positive metastatic lymph node in all patients. These patients received postoperative adjuvant therapy: 2 patients received radiotherapy (50 Gy) (case 3, 5), and 2 patients received chemoradiotherapy (one patient was administered with 2 cycles of cisplatin and received 50 Gy [case 4], and the other with S-1 and 50 Gy [case 1]). Case 2 received S-1 every other week for 1 year.

Chemoradiotherapy was performed on seven patients. The chemotherapy regimens and radiation doses were diverse because of the general status of patients, and the decline of renal function and re-irradiation: two cycles of cisplatin and fluorouracil + radiotherapy (66 Gy) (case 6), a cycle of cisplatin and fluorouracil + radiotherapy (40 Gy) (case 7), 2 cycles of cisplatin and fluorouracil + radiotherapy (30 Gy) (case 8), two cycles of cisplatin and fluorouracil + radiotherapy (40 Gy) (case 9), 2 cycles of cisplatin and fluorouracil + radiotherapy (52 Gy) (case 10), S-1 + radiotherapy (50 Gy) (case 11), and 2 cycles of cisplatin and S-1 + radiotherapy (20 Gy) (case 12). Two patients had a complete response (case 6, 7), 3 patients had a partial response and regrowth of the RPLN later (case 8, 9, 12), and 2 patients had progressive disease (case 10, 11) (Supplementary Table 1).

The outcomes of 15 patients were disease-free survival in 6 patients and death in 9 patients. In 6 disease-free survivors, 4 underwent surgical therapy for RPLN metastasis (Table 1).

There was a significant difference in the cumulative 5-year OS rate between the RPLN metastasis group (38.1% [n = 15]) and CLN metastasis group (71.3% [n = 359]) ($p = 0.037$) (Fig. 1). The therapeutic approach rates for RPLN metastases were 80.0% (n = 5) in the surgical therapy group, 28.6% (n = 7) in the chemoradiotherapy group, and 0% (n = 3) in the BSC group (Fig. 2).

Discussion

In this study, RPLN metastases had poorer prognosis (38.1%) than general CLN metastases (71.3%), but our results suggest that early

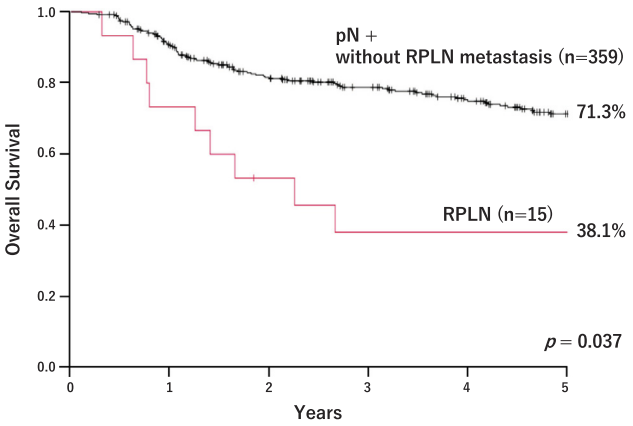

Fig. 1. Kaplan–Meier estimates of overall survival (OS) among patients with lymph node metastasis according to the presence or absence of lateral retropharyngeal node metastasis.

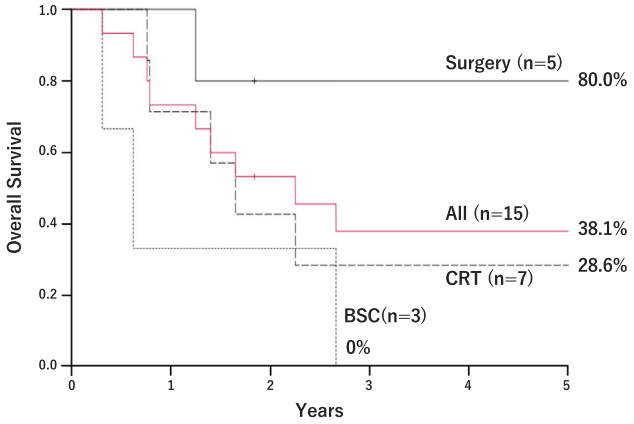

Fig. 2. Kaplan–Meier estimates of overall survival (OS) among patients according to treatment for lateral retropharyngeal node metastasis.

detection of resectable stage and surgical excision (80%) may help improve the prognosis of RPLN metastasis in oral cancer. The frequency of RPLN metastases in pharyngeal cancer was reported to be 64–75% in the nasopharynx [7–9], 10–16% in the oropharynx [10–12], and 16–20% in the hypopharynx [13–15]. In contrast, the frequency of RPLN metastases in oral cancer was reported to be < 1% [4,16]. In our study, the frequency was 1.2% (15/1247). Regarding the mechanism of RPLN metastasis in oral cancer, Nishida et al. [4] proposed two factors. One is reverse lymphatic flow from the superior internal jugular nodes to the RPLN. The other is direct lymphatic flow from the oral mucosa to the RPLN. The distribution of CLN metastases in this study was similar to that in general oral cancer, except for RPLN metastases. Thus, the mechanism governing reverse lymphatic flow from CLNs to the RPLN remains unclear. The afferent vessels of the RPLN originate from the posterior nasal cavity and hard and soft palates [17]. Therefore, metastasis to the RPLN in upper gingival cancer invading the posterior site is possible, besides lower gingival and buccal mucosal cancer progressing to the retromolar trigone and soft palate. In this study, 11 of 15 patients showed this progression in the primary site.

Depending on the anatomical position of the lymph node, when clinical symptoms such as cervical pain and headache are present, the metastatic lymph nodes are often quite large. Moreover, it is difficult to evaluate RPLN by ultrasonic examination, which can be used to evaluate the CLN conveniently. Therefore, early detection of RPLN metastasis requires imaging evaluation.

In the comparison of diagnosis between CT and MRI, MRI proved to be better in identifying RPLN metastasis than CT [18,19]. In contrast, Tseng et al. [16] showed the utility of the evaluation of RPLN metastases by FDG PET-CT in oral squamous cell carcinoma. As a diagnostic criterion for metastasis determination, King et al. [20] reported that the diagnostic criteria for RPLN metastases were set to 5 mm for the short axis in the evaluation of lymph node metastases by MRI in nasopharyngeal carcinoma. We typically use CT for diagnostic imaging during the patient follow-up because this modality is excellent for evaluating jawbone and soft tissue recurrence, and screening the cervical lymph node and the lung at the same time. We conducted periodic CT or PET, and if RPLN metastasis was suspected, MRI was performed to confirm the abnormal lymph node. However, it may be possible to detect metastatic RPLN much earlier by taking an MRI at the same time as CT, considering that the accurate diagnostic rate of CT is lower than that of MRI [18,19]. In this study, the minimum size of the metastatic RPLN was 7 mm, and it was impossible to confirm an abnormal RPLN with size < 5 mm. Earlier detection and more accurate diagnosis by advancement in imaging techniques, such as quantification of images, are expected in the future.

The frequency of imaging examination is also as important as the diagnostic modality. In this study, 85.7% of RPLN metastases were

recognized within 1 year, and 92.9% within 2 years. Other studies confirmed the presence of metastases within 1 year after the initial treatment [2–5]. For these reasons, it may be possible to detect RPLN metastases at an early stage by conducting an imaging examination at least once every 6 months after the initial treatment for 2 years. Especially, short-term examination can be recommended in patients with histologic lymph node metastasis, since almost all patients with RPLN metastasis also had CLN metastasis.

The therapeutic approaches for RPLN metastases are divided into radiotherapy with or without chemotherapy and surgical therapy.

Regarding radiotherapy for RPLN metastases, Pollard et al. [21] reported that conformal local field reirradiation in patients with RPLN metastases provided excellent local control. In contrast, radiotherapy sometimes results in treatment resistance. Nishida et al. [4] reported in a case presentation that they performed postoperative radiotherapy in RPLN metastasis followed by surgical treatment and confirmed viable cancer cell pathologically in RPLN removal. This result suggested that treatment might be difficult by radiotherapy alone for RPLN metastases. In terms of molecular biology, studies on resistance or susceptibility to radiotherapy have been increasing recently [22,23]. Henceforth, treatment strategies such as stratifying patients by biomarkers before radiotherapy are expected.

Surgical therapy is more likely to provide better therapeutic outcome compared to radiotherapy. As an approach to the parapharyngeal space including the retropharyngeal space, Som et al. [24] summarize the four methods: peroral, cervical, transparotid-cervical, and cervical-transpharyngeal. We performed a cervical approach to remove metastatic lymph nodes, and as much as possible, postoperative adjuvant therapy was conducted. A cervical approach with mandibulotomy may secure the visual field in large metastases. Postoperative complications of surgical therapy include injury to the internal carotid artery and Horner's syndrome, recurrent laryngeal nerve paralysis, and velopharyngeal dysfunction, induced by damage to the sympathetic nerve, vagus nerve, and pharyngeal nerve plexus, respectively. In this study, no patient developed postoperative complication, although it was impossible to assess velopharyngeal dysfunction because of soft palate excision for primary tumor treatment in some cases.

In the choice of surgical treatment for RPLN metastases, various factors are involved. In our study, the mean size of the metastatic RPLN in the surgical therapy group was 1.0 cm, which was smaller than those of other groups. This finding can be one of the criteria in choosing surgical therapy. Moreover, we need to carefully consider the extent of invasion, experience of the operator, control of the primary tumor and cervix, and patient status in selecting surgical therapy.

Recently, transoral robotic surgery has been reported as a surgical approach [25,26]. The advantage of this approach is minimal invasiveness. Goepfert et al. [26] suggested that this approach may be especially useful in a previously operated or irradiated patient. Thus, it is expected that the number of facilities that excise metastatic RPLN using such an approach will increase.

Our retrospective study had some limitations, notably a very small cohort. In addition, the surgery group had a smaller metastatic lymph node size than the chemoradiotherapy group, and some chemoradiotherapy cases couldn't be treated with radical radiation dose, so we cannot rule out the possibility that chemoradiotherapy is successful for small RPLN metastases from this study. Nevertheless, this study show that surgical treatment can be an effective means for controlling RPLN metastases. Other larger cohort studies comparing surgery group with definitive chemoradiotherapy group should be performed to verify our results in the future.

Therefore, all subsites of oral cancer have the possibility of developing RPLN metastasis, and we are establishing early detection using imaging diagnosis. We believe that better control is possible by surgical treatment and subsequent adjuvant therapy. We will continue to consider many cases in the future, and it is expected that the best management for RPLN metastases in oral cancer will be established.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.104471.

References

[1] Coskun HH, Ferlito A, Medina JE, Robbins KT, Rodrigo JP, Strojan P, et al. Retropharyngeal lymph node metastases in head and neck malignancies. Head Neck 2011;33:1520–9.

[2] Kimura Y, Hanazawa T, Sano T, Okano T. Lateral retropharyngeal node metastasis from carcinoma of the upper gingiva and maxillary sinus. AJNR Am J Neuroradiol 1998;19:1221–4.

[3] Umeda M, Minamikawa T, Yokoo S, Komori T. Metastasis of maxillary carcinoma to the parapharyngeal space: rationale and technique for concomitant en bloc parapharyngeal dissection. J Oral Maxillofac Surg 2002;60:408–13. discussion 13–4.

[4] Nishida M, Yasuda S, Murakami K, Yamamura I, Nagata Y, Iizuka T. Retropharyngeal lymph node metastases from oral cancer: a report of 2 patients. J Oral Maxillofac Surg 2005;63:410–2.

[5] Umeda M, Shigeta T, Takahashi H, Kataoka T, Oguni A, Minamikawa T, et al. Metastasis to the lateral retropharyngeal lymph node from squamous cell carcinoma of the oral cavity: report of three cases. Int J Oral Maxillofac Surg 2009;38:1004–8.

[6] Yamazaki H, Sasaki M, Aoyama KI, Suzuki T, Denda Y, Uchibori M, et al. Lateral retropharyngeal lymph node metastasis from squamous cell carcinoma of the upper gingiva: a case report. Mol Clin Oncol 2018;8:68–72.

[7] Wang XS, Hu CS, Ying HM, Zhou ZR, Ding JH, Feng Y. Patterns of retropharyngeal node metastasis in nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2009;73:194–201.

[8] Wang XS, Yan C, Hu CS, Ying HM, He XY, Zhou ZR, et al. Study of the medial group retropharyngeal node metastasis from nasopharyngeal carcinoma based on 3100 newly diagnosed cases. Oral Oncol 2014;50:1109–13.

[9] Tang LL, Guo R, Zhou G, Sun Y, Liu LZ, Lin AH, et al. Prognostic value and staging classification of retropharyngeal lymph node metastasis in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. PLoS One 2014;9:e108375.

[10] Dirix P, Nuyts S, Bussels B, Hermans R, Van den Bogaert W. Prognostic influence of retropharyngeal lymph node metastasis in squamous cell carcinoma of the oropharynx. Int J Radiat Oncol Biol Phys 2006;65:739–44.

[11] Baxter M, Chan JY, Mydlarz WK, Labruzzo SV, Kiess A, Ha PK, et al. Retropharyngeal lymph node involvement in human papillomavirus-associated oropharyngeal squamous cell carcinoma. Laryngoscope 2015;125:2503–8.

[12] Gunn GB, Debnam JM, Fuller CD, Morrison WH, Frank SJ, Beadle BM, et al. The impact of radiographic retropharyngeal adenopathy in oropharyngeal cancer. Cancer 2013;119:3162–9.

[13] Amatsu M, Mohri M, Kinishi M. Significance of retropharyngeal node dissection at radical surgery for carcinoma of the hypopharynx and cervical esophagus. Laryngoscope 2001;111:1099–103.

[14] Teshima M, Otsuki N, Shinomiya H, Morita N, Furukawa T, Morimoto K, et al. Impact of retropharyngeal lymph node dissection in the surgical treatment of hypopharyngeal cancer. Head Neck 2019;41:1738–44.

[15] Wu Z, Deng XY, Zeng RF, Su Y, Gu MF, Zhang Y, et al. Analysis of risk factors for retropharyngeal lymph node metastasis in carcinoma of the hypopharynx. Head Neck 2013;35:1274–7.

[16] Tseng JR, Ho TY, Lin CY, Lee LY, Wang HM, Liao CT, et al. Clinical outcomes of patients with oral cavity squamous cell carcinoma and retropharyngeal lymph node metastasis identified by FDG PET/CT. PLoS ONE 2013;8:e79766.

[17] Haagensen CD. The lymphatics in cancer. Philadelphia: Saunders; 1972.

[18] Liao XB, Mao YP, Liu LZ, Tang LL, Sun Y, Wang Y, et al. How does magnetic resonance imaging influence staging according to AJCC staging system for nasopharyngeal carcinoma compared with computed tomography? Int J Radiat Oncol Biol Phys 2008;72:1368–77.

[19] Kato H, Kanematsu M, Watanabe H, Mizuta K, Aoki M. Metastatic retropharyngeal lymph nodes: comparison of CT and MR imaging for diagnostic accuracy. Eur J Radiol 2014;83:1157–62.

[20] King AD, Ahuja AT, Leung SF, Lam WW, Teo P, Chan YL, et al. Neck node metastases from nasopharyngeal carcinoma: MR imaging of patterns of disease. Head Neck 2000;22:275–81.

[21] Pollard C, Nguyen TP, Ng SP, Frank SJ, Garden AS, Gunn GB, et al. Clinical outcomes after local field conformal reirradiation of patients with retropharyngeal nodal metastasis. Head Neck 2017;39:2079–87.

[22] Moeller BJ, Yordy JS, Williams MD, Giri U, Raju U, Molkentine DP, et al. DNA repair biomarker profiling of head and neck cancer: Ku80 expression predicts locoregional failure and death following radiotherapy. Clin Cancer Res 2011;17:2035–43.

[23] You GR, Cheng AJ, Lee LY, Huang YC, Liu H, Chen YJ, et al. Prognostic signature associated with radioresistance in head and neck cancer via transcriptomic and bioinformatic analyses. BMC Cancer 2019;19:64.

[24] Som PM, Biller HF, Lawson W. Tumors of the parapharyngeal space: preoperative

evaluation, diagnosis and surgical approaches. Ann Otol Rhinol Laryngol Suppl 1981;90:3–15.
[25] Byeon HK, Duvvuri U, Kim WS, Park YM, Hong HJ, Koh YW, et al. Transoral robotic retropharyngeal lymph node dissection with or without lateral oropharyngectomy. J Craniofac Surg 2013;24:1156–61.
[26] Goepfert RP, Liu C, Ryan WR. Trans-oral robotic surgery and surgeon-performed trans-oral ultrasound for intraoperative location and excision of an isolated retropharyngeal lymph node metastasis of papillary thyroid carcinoma. Am J Otolaryngol 2015;36:710–4.