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# Lateral retropharyngeal lymph node metastasis from squamous cell carcinoma of the upper gingiva: A case report

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**Abstract.** Lateral retropharyngeal lymph node (LRPLN) is located between the internal carotid artery and the prevertebral muscles. Metastasis to the LRPLN is frequent in nasopharyngeal cancer, but is rare in oral cancer. The prognosis of patients with oral cancer with LRPLN metastasis is usually poor. The present study reported a patient with LRPLN metastasis from squamous cell carcinoma of the upper gingiva, who survived for >7 years. Docetaxel, cisplatin and fluorouracil (TPF) therapy was performed as induction chemotherapy and it was planned to subsequently conduct chemoradiotherapy or surgery. As the tumor only exhibited a transient response to TPF, surgery was selected. Postoperatively, only radiotherapy was performed and a favorable outcome was achieved.

## Introduction

The lateral retropharyngeal lymph node (LRPLN) is located between the internal carotid artery and the prevertebral muscles. The LRPLN is most often seen anterior to the arch of C1, but is sometimes found at the level of the soft palate. The uppermost part of the LRPLN anterior to the atlas is known as the lymph node of Rouvière (1). Lateral retropharyngeal lymph node (LRPLN) metastasis from oral squamous cell carcinoma (OSCC) is rare and the prognosis is extremely poor (2-5). We report an unusual patient with LRPLN metastasis from squamous cell carcinoma of the upper gingiva and no progression for more than 7 years. Docetaxel, cisplatin and fluorouracil (TPF) therapy (6,7) was performed as induction chemotherapy and it was planned to subsequently conduct chemoradiotherapy or surgery. As the tumor only exhibited a transient response to TPF, surgery was selected. Postoperatively, only radiotherapy was performed and a favorable outcome was achieved.

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*Key words:* lateral retropharyngeal lymph node, metastasis, oral cancer, induction chemotherapy

## Case report

A 56-year-old Japanese woman visited the outpatient clinic of the Department of Oral Surgery at Tokai University Hospital in 2009. She had a gingival ulcer near the right maxillary second molar. This molar had been extracted at another clinic 2 months previously, but healing of the socket was poor. A mobile lymph node measuring 1.5 cm was palpable in the right cervical region (Fig. 1). Her medical history included fatty liver with hepatic impairment and her performance status (ECOG) was Grade 0. A panoramic X-ray revealed bone destruction with an uneven margin of the right maxillary molar socket. Contrast CT scans showed a tumor with heterogeneous enhancement that spread from the right maxillary region through the maxillary sinus, and bone destruction with an uneven margin was observed. Enlarged lymph nodes with rim enhancement were seen in the right submandibular, superior internal jugular vein, and LRPLN regions (Fig. 2). PET/CT also demonstrated abnormal accumulation at the same sites. The SUVmax of the primary tumor was 17.2. Biopsy revealed squamous cell carcinoma and the diagnosis was upper gingival carcinoma T4aN2bM0: Stage IV A (Fig. 3).

Laboratory tests gave the following results: WBC $8.6x10^3/\mu l$ (Seg+Stab 73.5%, lymphocytes 20.4%, monocytes 5.1%, eosinophils 0.8%, basophils 0.2%), RBC $3.93x10^6/\mu l$, Hb 12.7 g/dl, Ht 37.3%, Plt $32.3x10^4/\mu l$, AST 34 U/l, ALT 40 U/l, LDH 202 U/l, ALP 244 U/l, γ-GTP 62 U/l, BUN 13 mg/dl, Cre 0.6 mg/dl, TP 8.1 g/dl, Glu 103 mg/dl, TG 84 mg/dl, T-CHO 193 mg/dl, Na 141 mEq/l, K 4.1 mEq/l, Cl 107 mEq/l, and T-bil 0.4 mg/dl. Mild hepatic impairment was observed.

Three courses of the induction chemotherapy were conducted with docetaxel (Taxotere, Sanofi-Aventis), cisplatin (CDDP), and fluorouracil (TPF) therapy (docetaxel at 60 $mg/m^2$, CDDP at 60 $mg/m^2$, and fluorouracil at 600 $mg/m^2$) (6,7). At the end of the first course, CT demonstrated reduction in the size of the primary lesion and lymph nodes. However, repeat CT after 3 courses showed re-enlargement of metastatic lymph nodes, although the primary tumor was unchanged. There was only one adverse event of Grade 3 or higher during chemotherapy, which was leukopenia.

Thus, the primary tumor and LRPLN responded to the first course, but regrowth of the LRPLN was observed after 3 courses (Fig. 4). Similarly, the right submandibular lymph node initially decreased in size, but then showed regrowth. Therefore, she was judged to have progressive disease and it was decided to perform surgery. After induction of general anesthesia, surgery was started with tracheotomy followed by bilateral modified radical neck dissection. A midline lower lip incision was made and the mandibular swing approach was employed. The right maxilla was resected. From the dorsal region of the submandibular gland, fatty tissue was removed from the parapharyngeal space and it was explored in the cranial direction until the base of the skull was observed. The fascia of the superior constrictor muscle was detached. The internal carotid artery and vagus nerve were exposed, and were pulled aside using vascular tapes. Then the internal carotid artery, vagus nerve, and sympathetic nerves were dissected up to the base of the skull and fatty tissue was removed from the prevertebral fascia to complete dissection of the retropharyngeal space (Figs. 5 and 6). Postoperatively, only radiotherapy was administered (60 Gy). At 7 years after surgery, there has been no sign of relapse or metastasis. The patient has no difficulty with eating, swallowing, or speaking, and she returned to work postoperatively.

Histopathological examination of resected specimens from the primary lesion indicated that the sites where tumor cells presumably had been present were replaced by fibrous tissue showing mild edema. Inflammatory cells (mainly lymphocytes) were observed at these sites, but no tumor cells were seen. Some LRPLN sections showed fibrosis and cyst formation within the structure of the lymph node, but proliferation of cancer cells was also observed and part of the capsule was involved. Tumor cells with enlarged, densely stained nuclei were observed, suggesting changes induced by chemotherapy (Fig. 7).

The present study was approved by the Institutional Review Board for Clinical Research of Tokai University (Kanagawa, Japan). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

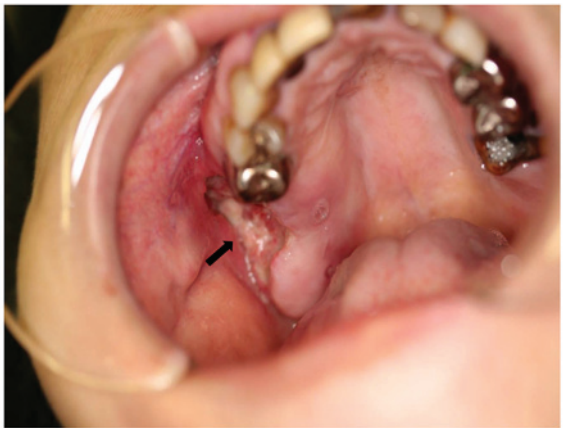

Figure 1. Oral findings at the initial examination: There is an ulcer adjacent to the right upper molar region.

## Discussion

The LRPLN is located between the internal carotid artery and the prevertebral muscles. The LRPLN is most often seen anterior to the arch of C1, but is sometimes found at the level of the soft palate. The uppermost part of the LRPLN anterior to the atlas is known as the lymph node of Rouvière (1). The incidence of LRPLN metastasis is reported to be 29.1-88.6% in patients with nasopharyngeal cancer, 16-50% in those with oropharyngeal cancer, and 6-20% in those with hypopharyngeal cancer (1). The incidence is reported to be 0.6-1.4% in patients with OSCC (3,5), while it is 6.9-16% in patients with maxillary cancer and upper gingival cancer (4,8). Thus, compared with oral cancer at other sites, the incidence of LRPLN metastasis is high among patients with upper gingival cancer. At our institution, LRPLN metastasis was detected in 3 out of 57 patients with upper gingival cancer (5.2%) between 2003 and 2013. Umeda *et al* (4) discussed the route of LRPLN metastasis in patients with upper gingival cancer and they concluded that, similar to oral cancer at other sites, it occurs via the submandibular nodes and superior internal jugular nodes in upper gingival cancer (4). Lymph channels inside the maxilla also enter both of these lymph nodes. Furthermore, there may be a route unique to maxillary cancer that reaches the LRPLN from tumors adjacent to the anterior and posterior teeth, although it is more developed for the posterior teeth, which means that tumors growing posteriorly tend to metastasize to the LRPLN. Moreover, metastasis to the superior internal jugular lymph nodes could subsequently result in retrograde metastasis to the LRPLN. Therefore, it is considered that LRPLN metastasis from upper gingival cancer may be different to metastasis from other oral cancers.

In many reports about LRPLN metastasis from upper gingival cancer (2-5), it is stated that metastasis to this node occurred following resection of the primary tumor or secondary lymph node metastases and it is common for there to be multiple metastases to other lymph nodes (9). Accordingly, it seems that retrograde metastasis may often occur in patients with secondary lymph node metastasis.

For treatment of LRPLN metastasis, surgery is often considered in patients with hypopharyngeal cancer (10,11). Elective neck dissection and adjuvant radiotherapy are recommended. LRPLN metastasis tends to progress rapidly to involve the carotid sheath. Accordingly, the prognosis is usually quite poor when LRPLN metastasis is detected (2-4). Because there are not so many patients with oral cancer, including upper gingival cancer, evaluation of treatment outcomes has rarely been conducted.

When a patient first presents with a tumor and LRPLN metastasis, curative treatment is attempted with chemoradiotherapy (CRT), radiotherapy alone, neo-adjuvant chemotherapy + surgery, or CRT + surgery + adjuvant CRT (5). Alternatively, chemotherapy is given alone as palliative therapy. Patients with secondary metastasis are often treated by radiotherapy alone or chemotherapy alone (5). LRPLN metastasis can only be detected by CT or MRI and many tumors are already non-resectable when detected, which means that radiotherapy or chemotherapy must be chosen.

On the other hand, there is a small group of patients in whom surgery is effective (3,4). Upper gingival cancer that grows posteriorly with metastasis in the deep cervical area is considered a high-risk tumor for LRPLN metastasis. Dissection of the parapharyngeal space and retropharyngeal space should be conducted and resection of the entire lesion

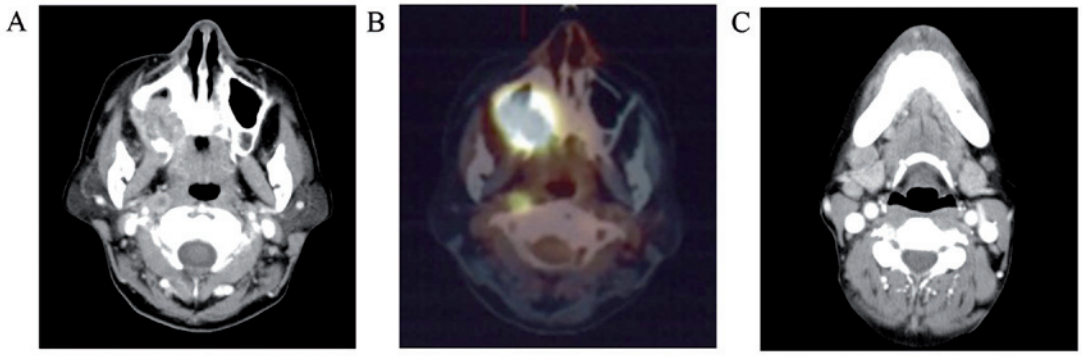


Figure 2. (A) Contrast CT (initial scan): The posterior part of the right maxilla is destroyed by tumor. The right LRPLN is enlarged and shows rim enhancement. (B) PET-CT finding: There is abnormal accumulation in the posterior part of the right maxilla and in the right LRPLN. (C) Contrast CT (initial scan): Metastasis to the right submandibular lymph nodes is observed. LRPLN, lateral retropharyngeal lymph node.

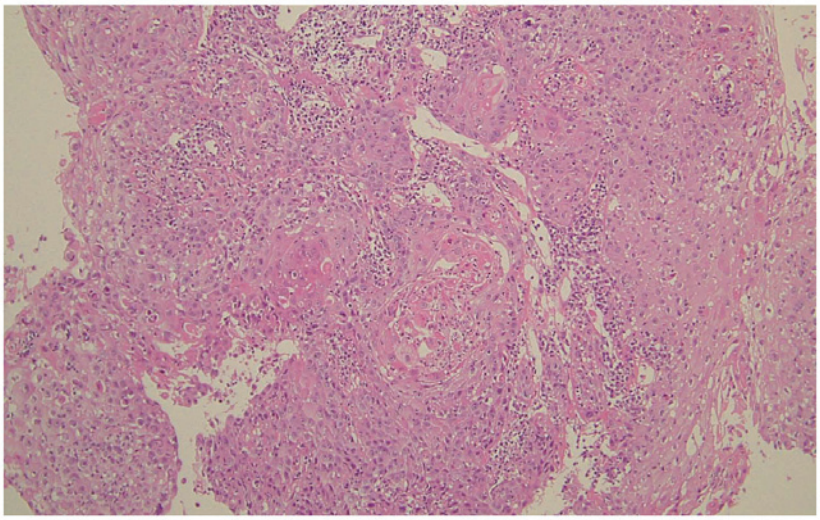

Figure 3. Biopsy specimen (H&E staining). Well-differentiated squamous cell carcinoma. Magnification, x100. H&E, haematoxylin and eosin.

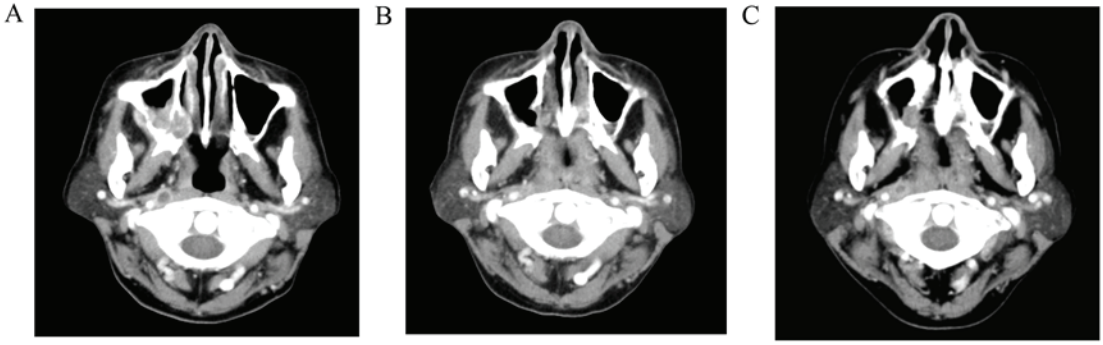


Figure 4. Contrast CT (before and after chemotherapy). (A) At the initial examination, (B) after 1 course of chemotherapy, there was a reduction in tumor size and (C) After 3 courses of chemotherapy, there was tumor regrowth.

together with the primary tumor should be considered (4,12). There have been no reports of a favorable outcome with current standard therapy or CRT according to the National Comprehensive Cancer Network (NCCN) strategy, in which surgery is followed by high-dose CDDP (100 mg/m$^2$ on days 1, 22, and 43) (13). When LRPLN metastasis occurs, it may be debatable whether resection with a sufficient margin is feasible.

In the present case, induction chemotherapy was provided and it was planned to subsequently conduct CRT or surgery (cetuximab was not available in Japan in 2009). However, surgery was selected as the tumor only transiently responded to TPF therapy. Since TPF therapy had been conducted prior to surgery, postoperative radiotherapy was performed alone to improve tolerability and a favorable outcome was achieved. It is debatable whether our patient should be judged as resectable

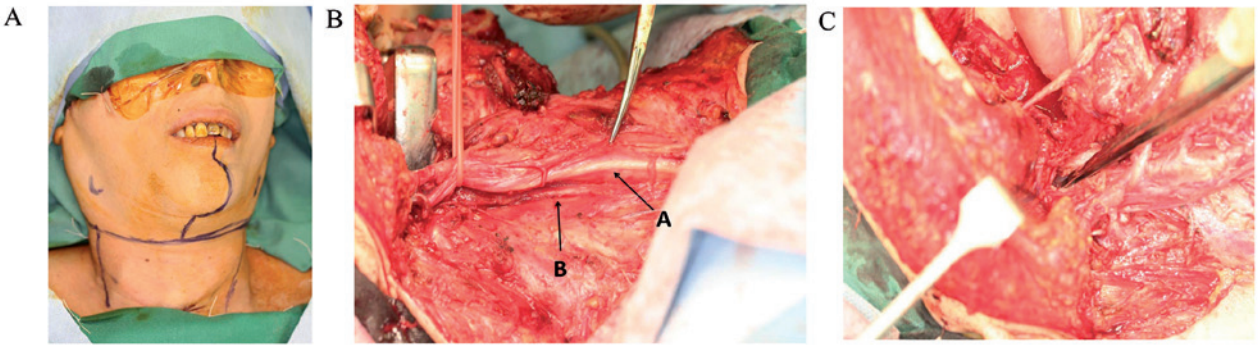


Figure 5. Surgical findings. (A) Intraoperative photograph (skin resection line). Partial resection of the right maxilla, bilateral modified radical neck dissection, right LRPLN dissection and reconstruction with a free skin flap were conducted. (B) Intraoperative photograph (right neck). The carotid sheath (common carotid artery and vagus nerve) (arrow A) and sympathetic nerves (arrow B) are demonstrated. (C) Intraoperative photograph (right neck). LRPLN metastasis is seen (at the forceps tip). LRPLN, lateral retropharyngeal lymph node.

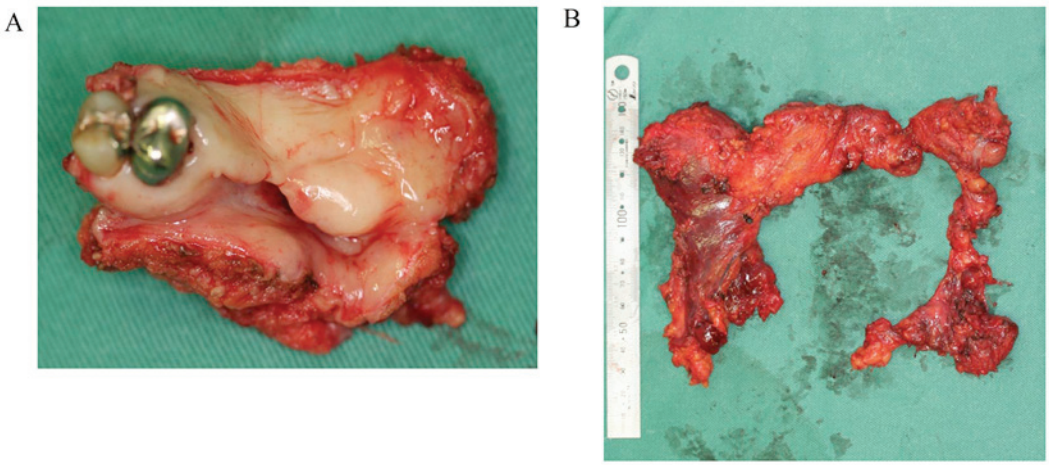


Figure 6. Resected specimens. (A) Resected maxillary tissue. (B) Dissected neck tissue.

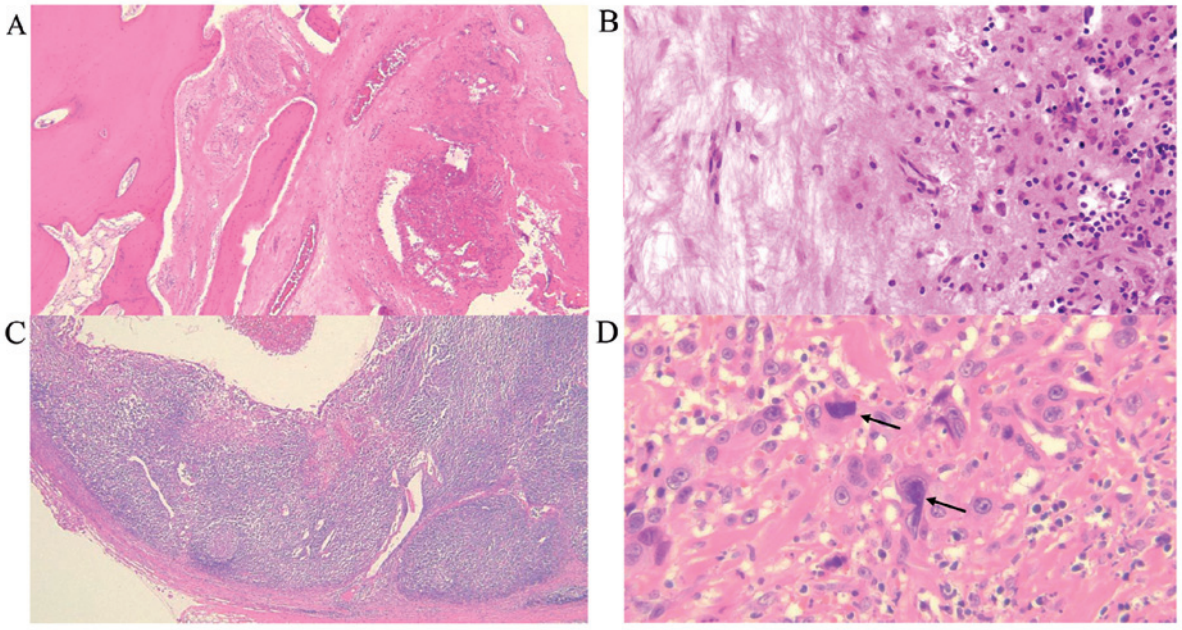


Figure 7. Histopathological findings (H&E staining). (A) A section of the primary tumor (magnification, x40) shows fibrosis between bone tissues where the tumor may have been present. (B) Primary tumor (magnification, x200). Inflammatory cells (mainly lymphocytes) were observed at these sites, but no tumor cells were seen. (C) LRPLN (magnification, x40). Although fibrosis and cysts are present within the lymph node, proliferation of cancer cells is also observed. Part of the capsule is involved by the tumor. (D) LRPLN (magnification, x400). Tumor cells with enlarged, densely stained nuclei were observed, suggesting changes induced by chemotherapy (arrow). H&E, haematoxylin and eosin; LRPLN, lateral retropharyngeal lymph node.

or non-resectable. Induction chemotherapy was reported to be ineffective for resectable OSCC (14,15). Standard therapy for non-resectable OSCC is CRT with high-dose CDDP (13), while induction chemotherapy with TPF therapy is also regarded as standard therapy in Europe (16). Among the regimens for induction chemotherapy, TPF therapy is considered to be the standard (17). On the other hand, a prospective Phase III study and a meta-analysis both failed to show an additive effect of induction chemotherapy (18-20), so re-appraisal of TPF therapy may be needed.

In conclusion, further discussion about whether treatment of LRPLN metastasis was appropriate in the present case seems to be warranted. Since LRPLN metastasis is rare among patients with oral cancer, a multicenter study will be needed to accumulate more cases.

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