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Case Report

Complete response of glottic cancer to intra-arterial infusion chemotherapy combined with radiotherapy: A report of 4 cases ^{☆,☆☆}

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ABSTRACT

Surgical resection is recommended for advanced-stage, resectable glottic cancer. However, total laryngectomy results in the loss of vocal function and reduces patients' quality of life. At our institution, patients with cT3N0M0 stage III resectable glottic cancer who wish to preserve their larynx are treated with super-selective cisplatin infusion with concomitant radiotherapy (RADPLAT) to improve local control over systemic chemotherapy. Herein, we present 4 patients with glottic cancer who underwent biweekly intra-arterial infusion chemotherapy combined with radiation therapy 3 times. For intra-arterial infusion chemotherapy, 100 mg cis-diaminodichloroplatinum was infused into the superior thyroid artery, including the superior laryngeal artery branch. Thereafter, intensity-modulated radiation therapy was administered at doses of 70 Gy in 35 fractions for 3 patients and 66 Gy in 33 fractions for 1 patient. These patients showed complete response after chemoradiotherapy with no recurrence or metastases during the follow-up period to date (mean follow-up period: 56 months, range: 39–76 months).

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Introduction

Glottic cancer is a laryngeal cancer that involves the vocal cords, anterior commissure, or posterior commissure [1]. Risk factors for glottic cancer include smoking, excessive alcohol consumption, dietary factors, radiation, and individual predisposition [2]. The typical initial symptom is hoarseness, and most histopathologic types of glottic cancer are squamous cell carcinomas (SCC).

Recommended treatment strategies for glottic cancer differ according to the tumor stage. For example, larynx preservation is recommended for patients with early-stage cancer, either by radiotherapy or larynx preservation surgery, with similar survival outcomes [3]. In contrast, total laryngectomy is recommended as standard therapy for patients with T4 stage cancer with invasion into the soft tissue over the thyroid cartilage [4,5]. However, there are several standard therapies for T3 cases including chemoradiotherapy (CRT), larynx preservation surgery with chemotherapy, and laryngectomy with chemotherapy [4]. Because total laryngectomy results in the loss of vocal function and dramatically reduces the patients' quality of life, CRT is the treatment of choice for patients who wish to preserve vocal function.

Typically, systemic chemotherapy is administered during CRT. In contrast, compared to systemic chemotherapy, intra-arterial infusion chemotherapy (IAIC) [6–8] enables drug delivery to the tumor feeding artery with high concentration and is thought to improve local control. Robbins et al. [9] named the therapy combining radiation and cisplatin IAIC as super-selective cisplatin infusion with concomitant radiotherapy (RADPLAT).

Our institution treats patients with cT3N0M0 stage III (classified using Union for International Cancer Control TNM Classification of Malignant Tumours 8th edition) glottic cancer who wish to preserve their larynx using RADPLAT to improve local control. Herein, we present 4 consecutive cases of glottic cancer with complete response after RADPLAT between 2016 and 2019.

Case presentation

Four patients with cT3N0M0 stage III glottic cancer underwent IAIC and radiotherapy between 2016 and 2019. These patients showed complete response after radiation chemotherapy with no recurrence or metastases during follow-up to date (mean follow-up period: 56 months, range: 39–76 months). Detailed data of all cases are summarized in Table 1.

Case 1

A 62-year-old male presented with a chief complaint of worsening hoarseness. The patient had no significant past medical history but was a current smoker. Endoscopic imaging revealed a right vocal-cord tumor (Fig. 1A). The patient underwent a tumor biopsy, and histopathology revealed that the tumor was an SCC. Positron emission tomography/computed tomography (PET/CT) (Figs. 2A–C) showed no lymph node or

distant metastases, and magnetic resonance imaging (MRI) showed involvement of the paraglottic space (Figs. 2D and E). Therefore, the tumor was diagnosed as a cT3N0M0 stage III right glottic cancer. The patient desired larynx preservation and was treated with radiation and IAIC.

The patient underwent 3 biweekly IAIC sessions combined with radiation therapy. Intensity-modulated radiation therapy (IMRT) was administered for whole-neck irradiation comprising 40 Gy in 20 fractions, followed by local boost radiotherapy comprising 26 Gy in 13 fractions. Granisetron hydrochloride (3 mg) diluted in 100 mL saline solution was infused as premedication before IAIC to prevent nausea and vomiting. Figure 3 shows an image of the right superior thyroid artery (STA), including the superior laryngeal artery (SLA) branch, which is the main feeder of the glottis, using an angiography and sliding CT scanner system with interventional radiology features (IVR-CT). This artery was identified as the feeding artery because tumor staining was observed on the IVR-CT image. Therefore, cis-diaminodichloroplatinum (CDDP) 100 mg was infused into the right STA as IAIC. Systemic sodium thiosulfate neutralization was performed during and after CDDP infusion. Hydrocortisone sodium succinate was infused into the same feeding artery after CDDP infusion to prevent mucosal and skin disorders. Systemic heparinization was performed during the catheterization procedure to prevent cerebral infarction. Additionally, hydration was administered before and after IAIC to prevent renal failure.

According to the Common Terminology Criteria of Adverse Events version 4.0, grade 2 radiation dermatitis and grade 1 leukopenia were observed after therapy completion. The patient achieved a complete response to therapy and has had no recurrence or metastasis after radiation chemotherapy to date (76 months). A follow-up endoscopic image is shown in Figure 1B.

Case 2

A 71-year-old male presented with a chief complaint of worsening hoarseness. Endoscopic imaging revealed a right vocal-cord tumor (Fig. 1C). The patient had a history of chronic obstructive pulmonary disease, gastritis, hyperuricemia, cholelithiasis, asthma, and postoperative bladder cancer. Tumor biopsy and histopathology revealed that the tumor was an SCC. PET/CT showed no lymph node or distant metastases, and MRI revealed the involvement of the inner cortex of the thyroid cartilage. Therefore, the tumor was diagnosed as a cT3N0M0 stage III right glottic cancer.

The patient underwent 3 biweekly IAIC sessions with radiation therapy. IMRT was administered for whole-neck irradiation comprising 46 Gy in 23 fractions, followed by local boost radiotherapy comprising 24 Gy in 12 fractions. For IAIC, CDDP 100 mg was infused into the right STA, including the SLA branch. Angiography and IVR-CT images are shown in Figure 4. Systemic heparinization, hydrocortisone sodium succinate infusion, and premedication were administered as described in Case 1. Grade 2 radiation dermatitis, grade 2 pharyngitis, and grade 1 leukopenia were observed after therapy completion. The patient achieved a complete response to therapy but was diagnosed with primary lung cancer during follow-up, and a lobectomy was performed. To date, no recur-

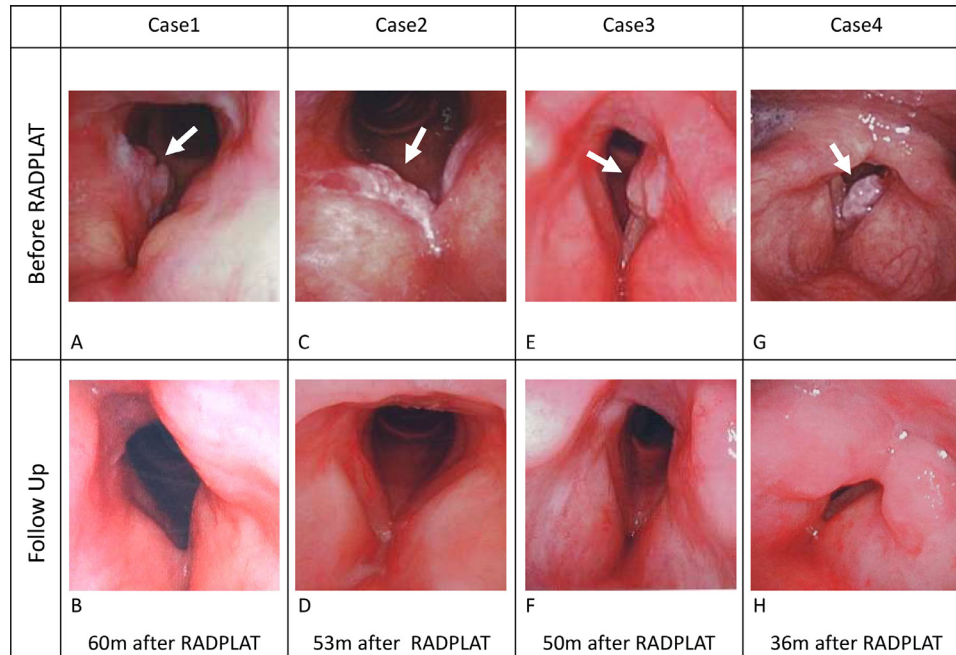


Fig. 1 – Endoscopic images obtained before and after radiotherapy and concomitant intra-arterial cisplatin therapy. The glottic tumors disappeared in all cases, and complete responses to treatment were achieved. Case 1 (A) before RADPLAT, and (B) follow up. Case 2 (C) before RADPLAT, and (D) follow up. Case 3 (E) before RADPLAT, and (F) follow up. Case 4 (G) before RADPLAT, and (H) follow up.

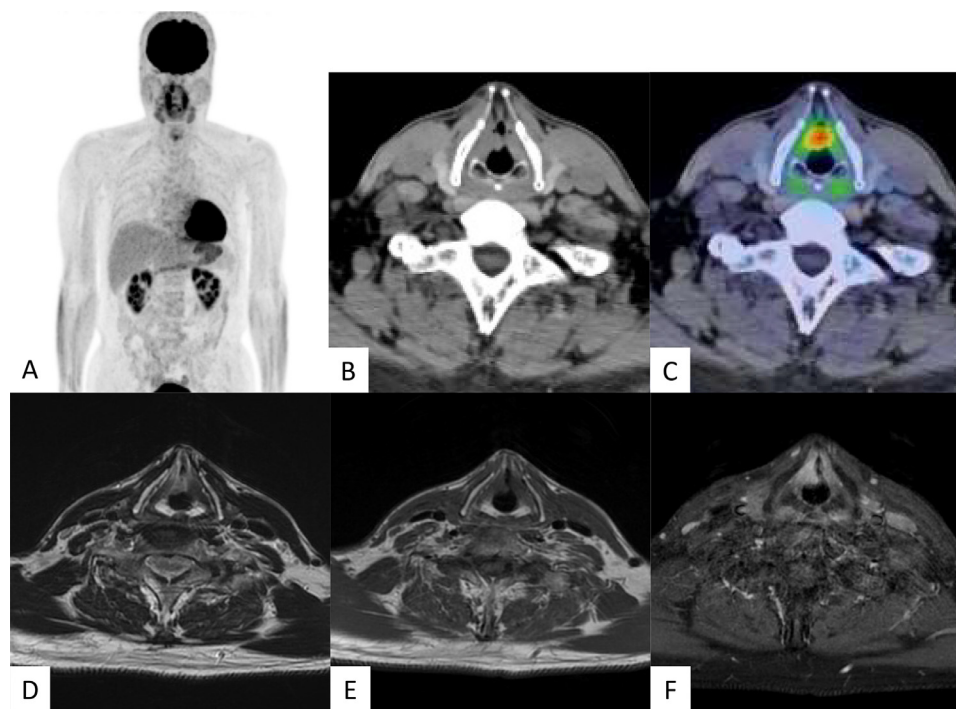


Fig. 2 – Diagnostic images of a 62-year-old male with T3N0M0 stage III right glottic cancer (case 1). (A) Maximum intensity projection positron emission tomography (PET); (B, C) axial computed tomography and fused positron emission tomography/computed tomography images showing intense fluorodeoxyglucose uptake in the right glottic tumor (maximum standardized uptake value, 5.9); (D) T2-weighted image; (E) T1-weighted image; (F) gadolinium-enhanced fat-suppressed T1-weighted images showing involvement of the paraglottic space.

Table 1 – Tumor staging and treatment courses in patients with glottis cancer underwent IAIC and radiation therapy between 2016 and 2019 in our institution.

Case number	1	2	3	4
Age	62 y	71 y	69 y	66 y
Sex	Male	Male	Male	Male
Affected side	Right vocal code	Right vocal code	Left vocal code	Left vocal code
Stage	cT3N0M0 Stage III	cT3N0M0 Stage III	cT3N0M0 Stage III	cT3N0M0 Stage III
Infusion artery	Right superior thyroid artery	Right superior thyroid artery	Left and right superior thyroid artery	Left superior thyroid artery
Total CDDP dose	300 mg (100 mg×3)	300 mg (100 mg×3)	300 mg (100 mg×3)	300 mg (100 mg×3)
Systemic sodium thiosulfate infusion	24 g	26 g	26 g	24 g
Dose and fraction				
Whole neck:	40 Gy in 20 fractions	46 Gy in 23 fractions	46 Gy in 23 fractions	46 Gy in 23 fractions
Local boost:	26 Gy in 23 fractions	24 Gy in 12 fractions	24 Gy in 12 fractions	24 Gy in 12 fractions
Side Effect	Radiation dermatitis (Grade2) Leukopenia (Grade1)	Radiation dermatitis (Grade2) Pharyngitis (Grade2) Leukopenia (Grade1)	Radiation dermatitis (Grade2) Pharyngitis (Grade2) Leukopenia (Grade1)	Radiation dermatitis (Grade2) Pharyngitis (Grade2) Leukopenia (Grade2)
Recurrence-free survival time	76 months	57 months	50 months	39 months

CDDP, cis-Diamino-dichloro-platinum; IAIC, intra-arterial infusion chemotherapy; WBC, white blood cell.

The 8th edition of Union for International Cancer Control (UICC) staging system was used for TNM classification and staging.

The Common Terminology Criteria of Adverse Events version 4.0 (CTCAE v4) was used for estimate grade of side effects.

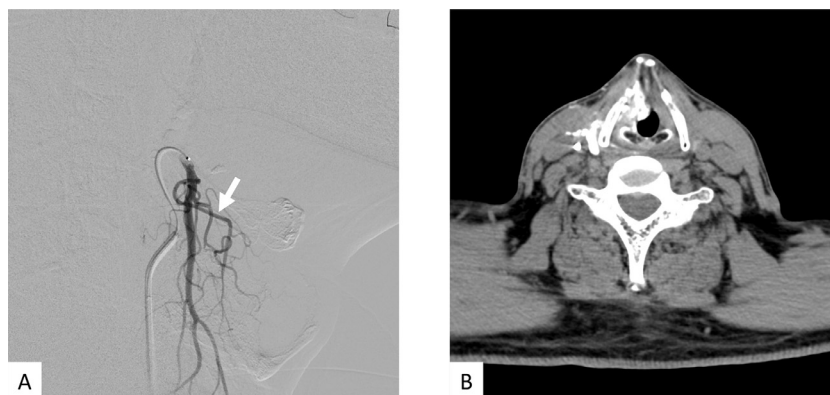


Fig. 3 – Angiography and IVR-CT images of a 62-year-old male with T3N0M0 stage III right glottic cancer (case 1). (A) Lateral angiography of the right superior thyroid artery (STA), including the superior laryngeal artery branch (arrow); (B) image of the right STA using a sliding computed tomography scanner system with interventional radiology features. The entire glottic tumor was enhanced.

rence or metastasis of glottic cancer has occurred after the therapy (57 months). A follow-up endoscopic image is shown in [Figure 1D](#).

Case 3

A 69-year-old male presented with a chief complaint of hoarseness and difficulty swallowing. The patient had no significant past medical history. PET/CT showed no lymph node or distant metastases, and MRI showed tumor extension to the subglottis. Endoscopic examination revealed a tumor in the left vocal cord that caused fixation of the vocal cord ([Fig. 1E](#)).

Therefore, the tumor was diagnosed as a cT3N0M0 stage III left glottic cancer.

The patient underwent biweekly IAIC combined with radiation therapy 3 times, as described in Case 2. For IAIC, CDDP 100 mg was infused into both the right and left STA, including the SLA branch, due to the narrow feeding area of the left STA and feeding from the contralateral side. Angiography and IVR-CT images are shown in [Figure 5](#). Grade 2 radiation dermatitis, grade 2 pharyngitis, and grade 1 leukopenia were observed after therapy completion. The patient achieved a complete response and has had no recurrence or metastases to date (50 months). A follow-up endoscopic image is shown in [Figure 1F](#).

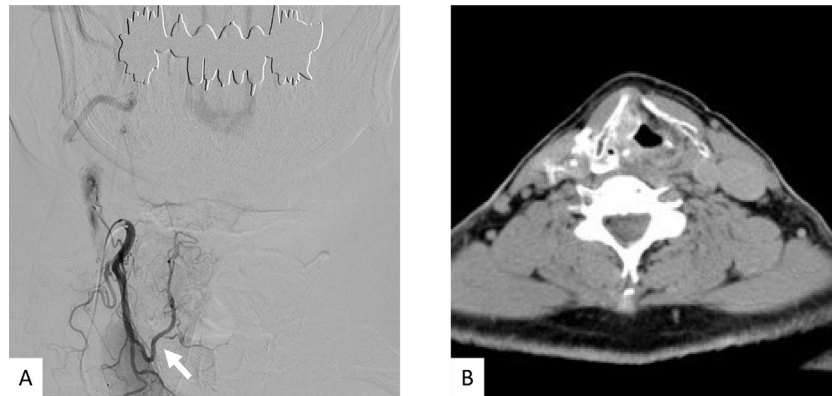


Fig. 4 – Angiography and IVR-CT images of a 71-year-old male with T3N0M0 stage III right glottic cancer (case 2). (A) Frontal angiography of the right superior thyroid artery (STA), including the superior laryngeal artery branch (arrow); (B) image of the right STA using a sliding computed tomography scanner system with interventional radiology features. The entire glottic tumor was enhanced.

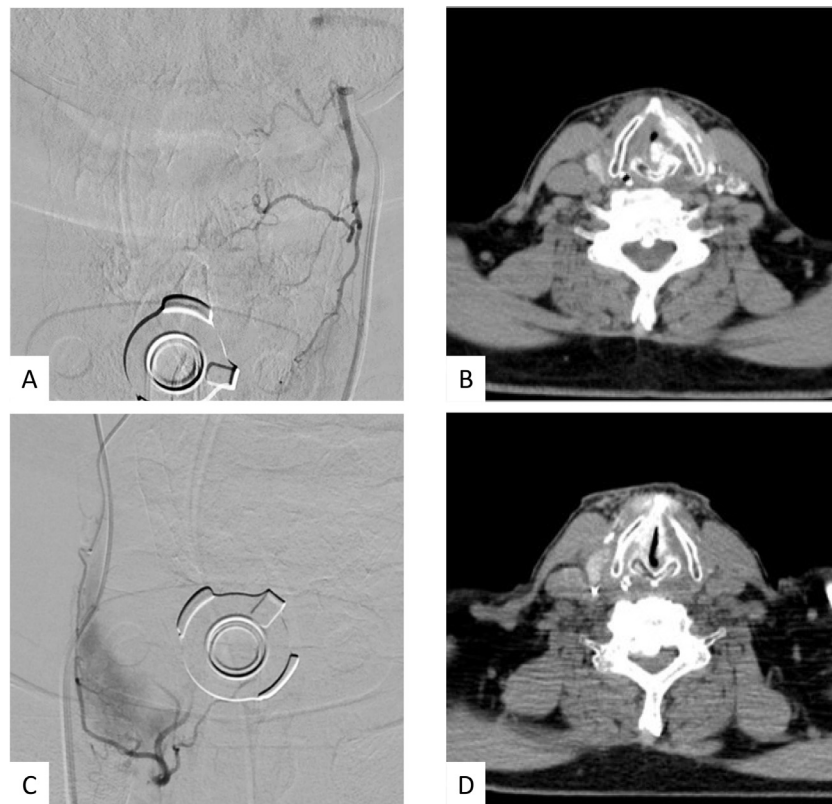


Fig. 5 – Angiography and IVR-CT images of a 69-year-old male with T3N0M0 stage III left glottic cancer (case 3). (A) Frontal angiography of the left superior thyroid artery (STA), including the superior laryngeal artery (SLA) branch; (B) image of the left STA using a sliding computed tomography scanner system with interventional radiology features (IVR-CT). Part of the left glottis shows an unenhanced area; (C) frontal angiography of the right STA, including the SLA branch; (D) IVR-CT image of the right STA. Part of the left glottis shows an enhanced area.

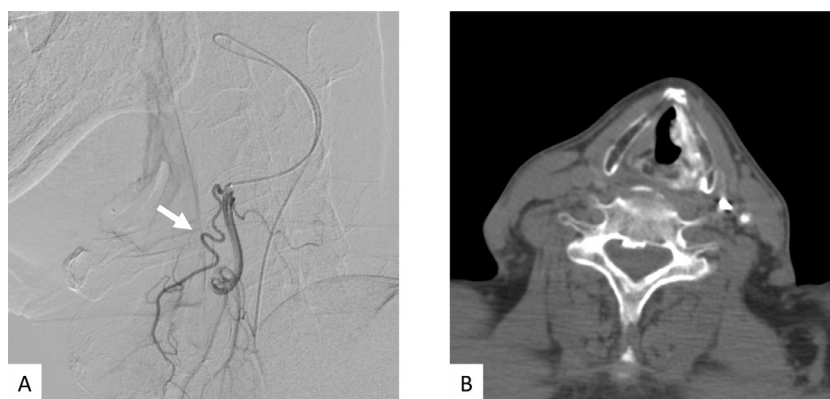


Fig. 6 – Angiography and IVR-CT images of a 66-year-old male with T3N0M0 stage III left glottic cancer (case 4). (A) Lateral angiography of the left superior thyroid artery (STA), including the superior laryngeal artery branch (arrow); (B) image of the left STA using a sliding computed tomography scanner system with interventional radiology features. The entire left glottic tumor was enhanced.

Case 4

A 66-year-old male presented with a chief complaint of hoarseness, and endoscopic imaging revealed a right vocal-cord tumor (Fig. 1C). The patient had a history of high blood pressure and disc herniation. Left glottic tumor biopsy and histopathology showed that the tumor was an SCC. CT and MRI revealed that the tumor had invaded the paraglottic space. No lymph node or distant metastasis was observed on PET/CT. Therefore, the tumor was diagnosed as a cT3N0M0 stage III left glottic cancer.

The patient underwent biweekly IAIC with radiation therapy 3 times, as described in Case 2. CDDP 100 mg was infused into the left STA, including the SLA branch as IAIC. Angiography and IVR-CT images are shown in Figure 6. Grade 2 dermatitis, grade 2 pharyngitis, and grade 2 leukopenia were observed after therapy completion. The patient achieved a complete response and has had no recurrence or metastases to date (39 months). A follow-up endoscopic image is shown in Figure 1H.

Discussion

This paper reports 4 cases of cT3N0M0 stage III resectable glottic cancer treated with RADPLAT. All patients reported herein had complete responses, no local recurrence, no metastases, and successful preservation of laryngeal function during the follow-up period to date (mean follow-up period: 56 months, range: 39–76 months). Hence, RADPLAT may be associated with good prognoses.

RADPLAT combines radiation with IAIC. The original method was developed by Robbins et al. in 1997 [9]. IAIC enables high-dose intra-arterial local cisplatin chemotherapy regimens using systemic sodium thiosulfate neutralization [10]. Therefore, IAIC has reduced side effects, can improve lo-

cal control, and can outperform systemic chemotherapy combined with radiation (conventional CRT).

Nevertheless, a randomized trial in the Netherlands focused on unresectable oropharyngeal, oral cavity, and hypopharyngeal SCCs reported that RADPLAT did not outperform conventional CRT in terms of the 3-year local control and overall survival (OS) outcomes [11]. However, their report had several limitations. First, the outcome of IAIC depends on the availability of a super-selective IAIC medication; however, the uniformity of the procedure has not been discussed. Second, differences in lymphatic development may make some head and neck regions less likely to respond to IAIC than others. For example, supraglottic carcinomas are more likely to metastasize to the lymph nodes compared to glottic cancers. Therefore, the head and neck regions should be studied separately. Third, >80% of patients in the randomized trial had lymph node metastases; thus, the cancer stage may have been more advanced than that of cancers that responded to RADPLAT. Therefore, this randomized trial cannot be used to determine whether RADPLAT is ineffective for treating all head and neck cancers.

Some studies on glottic cancer have reported that RADPLAT may result in good prognoses. For example, Yoshizaki et al. [12] reported that 87.5% of 16 patients with glottic cancer who underwent RADPLAT therapy and were followed up for ≥ 3 years survived. Additionally, local control was achieved in 67.5% of the cases. Furthermore, Ono et al. [13] focused on 33 patients with T3N0M0 glottic cancer who underwent RADPLAT therapy and reported 3-year OS and local control rates of 87.9% and 87.8%, respectively. Considering these studies and the present cases, RADPLAT may be a beneficial therapy for glottic cancer. Meanwhile, a retrospective study of 2622 patients with T3N0M0 glottic cancer showed no significant differences in the 5-year OS between surgery alone, surgery with radiation therapy, surgery with conventional CRT, and conventional CRT alone; the 5-year OS was approximately 53% across all treatment types [14]. Thus, there may be no difference in outcome between therapies for T3N0M0 glottic cancer. Cur-

rently, no study has compared treatment outcomes between RADPLAT and the above therapies. Therefore, further studies are needed to evaluate whether RADPLAT outperforms these therapies.

Some studies on other head and neck cancer regions have shown favorable outcomes using RADPLAT. Homma et al. [15] reported that the 5-year OS rates of patients with maxillary sinus SCC who underwent RADPLAT therapy were 80%, 66.8%, and 57.1% for patients with T2-3, T4a, and T4b, respectively. In their study, Ebara et al. [16] reported 3- and 5-year OS rates of 59.2% and 55.0%, respectively, in patients with stage III to IVB disease. In addition to maxillary sinus cancer, other head and neck cancer studies have shown that RADPLAT enables good prognoses. For example, good prognoses have been reported for hypopharyngeal [17], oropharyngeal [18], nasal cavity [19], and oral cavity [20] cancer. Further studies are needed to determine which head and neck region and cancer stages in the region RADPLAT can effectively treat.

RADPLAT for glottic cancer is associated with the risk of complications specific to the glottic area. First, there is a risk of inducing the cough reflex and laryngeal pain during CDDP injection. Moreover, the cough reflex may raise catheter movement and swerve vascular selection because of stimulation from a large and fast CDDP flow into the superior laryngeal artery. Second, there is a risk of airway obstruction due to laryngeal edema, which occurs soon after IAIC, in our experience. The effects of IAIC in addition to radiation-induced inflammation may cause the laryngeal edema to rapidly worsen. In particular, bilateral superior thyroid artery infusion is a high-risk factor because it causes a wide range of laryngeal inflammation. Third, there is the risk of laryngeal necrosis, which may be caused by the addition of impairment from IAIC to radiation damage, with inflammation more likely to occur than systemic chemotherapy. However, there has been no evidence of solutions to prevent these complications.

Nonetheless, we believe that CDDP dose, distribution, and speed are important to prevent these complications. Therefore, we consider the following factors during IAIC. First, catheter position in the superior thyroid artery should be adjusted such that large amount of CDDP infusion is not directed to the superior laryngeal artery. Additionally, for the confirmation of drug distribution, it is important to perform angiography with contrast-media infusion at the same speed as CDDP infusion. Second, CDDP should be infused at a speed that does not produce a cough reflex (eg, 12 cc/min or slower), and this infusion stopped or the speed modified if the patient feels discomfort. It is also important to frequently check for changes in catheter position due to swallowing and cough during infusion. Third, the dose should be low (eg, 20 mg or less) for superselective infusion into the superior laryngeal artery. Fourth, when infusing CDDP into bilateral superior thyroid arteries, tracheostomy should be considered in advance. Fifth, to reduce the risk of necrosis, the total CDDP dose should not exceed 100 mg/body and a sufficient dose (eg, 50 mg or more) of hydrocortisone sodium succinate should be infused to prevent severe inflammation. Further research is needed on suitable procedures to prevent RADPLAT complications in glottic cancer.

In general, RADPLAT for head and neck cancer has a risk of complications. First, there are risks associated with catheter

procedures, such as syndromic and nonsyndromic ischemic brain changes associated with angiography [21], vascular injury, and hematoma at the puncture site. Systemic heparinization, careful catheter placement, and sufficient compression hemostasis at the puncture site are required to prevent these complications. Second, radiotherapy has associated risks, such as tissue necrosis [22], mucosal and skin disorders. Third, chemotherapy has side effects, for example, renal impairment, nausea, and vomiting. It is important to reduce the radiation dose to normal tissues and ensure adequate hydration, skin and oral care, and antiemetic drug administration to prevent these complications. A randomized study in the Netherlands showed that the risk of renal impairment with RADPLAT was lower than that with systemic chemotherapy; however, there were more neurological side effects [11]. A risk-benefit analysis of RADPLAT is eagerly anticipated based on the results of ongoing studies, such as the Japan clinical oncology group (JCOG) 1212 trial [23] and Japan interventional radiology in oncology study group (JIVROSG) 0808 trial.

Conclusions

RADPLAT for T3N0M0 glottic cancer may be beneficial in preserving vocal function and has the potential to improve outcomes. Further investigations on RADPLAT are required.

Patient consent

Informed consent was obtained from the patient for the publication of this case report.

CRedit authorship contribution statement

Ryo Yamakuni: Conceptualization, Writing – original draft, Writing – review & editing. **Hirofumi Sekino:** Data curation, Writing – review & editing. **Masakazu Ikeda:** Data curation, Writing – review & editing. **Yoshiki Endo:** Writing – review & editing. **Masamitsu Ikeda:** Data curation, Writing – review & editing. **Shiro Ishii:** Supervision, Writing – review & editing. **Kenji Fukushima:** Supervision, Writing – review & editing. **Shigeyuki Muro:** Supervision, Writing – review & editing. **Yoshiyuki Suzuki:** Writing – review & editing. **Hiroshi Ito:** Supervision, Project administration, Writing – review & editing.

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