







ORIGINAL RESEARCH

Effects of percutaneous injection laryngoplasty on voice and swallowing problems in cancer-related unilateral vocal cord paralysis

Min-Gu Kang MD^{1,2}  | Han Gil Seo MD, PhD¹  | Eun-Jae Chung MD, PhD³  |
Hyun Haeng Lee MD³  | Seo Jung Yun OT, MS¹  | Bhumsuk Keam MD, PhD⁵  |
Tae Min Kim MD, PhD⁴  | Seong Keun Kwon MD, PhD^{2,6,7}  |
Byung-Mo Oh MD, PhD^{1,8,9,10,11} 

¹Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul, Republic of Korea

²Department of Physical Medicine and Rehabilitation, Dong-A University College of Medicine, Busan, Republic of Korea

³Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, Seoul, Republic of Korea

⁴Department of Rehabilitation Medicine, Konkuk University Hospital, Seoul, Republic of Korea

⁵Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

⁶Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea

⁷Cancer Research Institute, Seoul National University, Seoul, Republic of Korea

⁸Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

⁹Institute on Aging, Seoul National University, Seoul, Republic of Korea

¹⁰National Traffic Injury Rehabilitation Hospital, Yangpyeong, Republic of Korea

¹¹Neuroscience Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

Correspondence

Seong Keun Kwon, MD, PhD, Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, Seoul National University of College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.
Email: otolarynx@snuh.org

Byung-Mo Oh, MD, PhD, Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.
Email: moya1@snu.ac.kr

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Abstract

Background: Unilateral vocal cord paralysis may result from nerve compression by tumors or direct nerve injuries during tumor resections, which can cause dysphonia or dysphagia, and reduced quality of life.

Objectives: This prospective, single-group study aimed to investigate the effect of percutaneous injection laryngoplasty on voice and swallowing function in patients with cancer-related unilateral vocal cord paralysis.

Methods: Patients underwent percutaneous injection laryngoplasty with hyaluronic acid under local anesthesia. Stroboscopy and videofluoroscopic swallowing study were conducted to evaluate the voice- and swallowing-related outcome measures, respectively. The participants were evaluated before injection laryngoplasty, as well as after two weeks and three months.

Results: Injection laryngoplasty significantly improved the glottal gap, vocal fold position, Maximum Phonation Time, and Voice Handicap Index-10. Post-hoc analysis

Seong Keun Kwon and Byung-Mo Oh contributed equally to this work.

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using Bonferroni correction showed that the improvements occurred within two post-treatment weeks and remained at three post-treatment months. In the subgroup analysis, the patients who underwent injection laryngoplasty within 8 weeks from onset showed significantly higher improvements in the videofluoroscopic dysphagia scale and swallowing function than the patients who received the procedure after 8 weeks or more.

Conclusion: Percutaneous injection laryngoplasty improves glottal closure and voice in patients with cancer-related unilateral vocal cord paralysis. Early injection laryngoplasty may lead to greater benefits on swallowing function.

Level of Evidence: 4.

KEYWORDS

deglutition disorders, dysphonia, laryngoplasty, neoplasms, vocal cord paralysis

1 | INTRODUCTION

Unilateral vocal cord paralysis in patients with cancer can cause dysphonia or aspiration, which lead to a reduced quality of life.¹ This paralysis can result from vagus nerve or recurrent laryngeal nerve compromise caused by tumor infiltration or compression.² Further, iatrogenic injury can often induce unilateral vocal cord paralysis, which could involve intubation, transection, traction, and thermal injury.³

Unilateral vocal cord paralysis can be treated using medialization thyroplasty, injection laryngoplasty under general anesthesia, and office-based percutaneous injection laryngoplasty.⁴ General anesthesia in patients with cancer may pose additional risk to patients with impaired lung capacity or cancer- or treatment-related blood clotting disorders. Office-based injection laryngoplasty has a temporary effect compared to thyroplasty, but has similar efficacy and is more economical.⁵ Moreover, invasive thyroplasty can be avoided if nerve recovery occurs for several months while the therapeutic effect remains in patients who have undergone injection laryngoplasty. Therefore, office-based percutaneous injection laryngoplasty may be the optimal treatment method for new onset unilateral vocal cord paralysis in patients with cancer.

Although there have been studies on the efficacy of percutaneous injection laryngoplasty in voice outcomes, its effect on other laryngeal functions, especially dysphagia, in patients with cancer-related unilateral vocal cord paralysis remains unclear.⁶ This study aimed to investigate the efficacy of percutaneous injection laryngoplasty for voice and swallowing function in patients with cancer-related vocal cord paralysis.

2 | METHODS

2.1 | Study design

This single-group study was conducted between April 2015 and December 2018 in accordance with the Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. The study protocol was approved by the institutional review board at

Seoul National University Hospital (IRB No. 1412-065-632). All study participants provided written informed consent before participation.

2.2 | Participants

This study enrolled patients with a diagnosis of cancer-related vocal cord paralysis. The inclusion criteria were: (1) age \geq 18 years; (2) having hoarseness or dysphagia symptoms that newly developed during cancer diagnosis or management; and (3) having unilateral vocal cord paralysis confirmed by laryngoscopy. The exclusion criteria were (1) suspected cancer invasion into the vocal fold; (2) allergy to barium sulfate; (3) having previously undergone laryngoplasty; and (4) having other diseases related

TABLE 1 Clinical characteristics of the participants (n = 15)

| Characteristics | Value |
|-------------------------------------|-----------------|
| Age (in years) | 67.0 \pm 9.63 |
| Sex | |
| Male | 10 (66.7%) |
| Female | 5 (33.3%) |
| Primary lesion | |
| Lung cancer | 9 (60.0%) |
| Breast cancer | 2 (13.3%) |
| Colon cancer | 1 (6.7%) |
| Bladder cancer | 1 (6.7%) |
| Diffuse large B-cell lymphoma | 1 (6.7%) |
| Thyroid cancer | 1 (6.7%) |
| Cause of vocal cord paralysis | |
| Lymph node compression of the nerve | 13 (86.7%) |
| Direct cancer involvement | 1 (6.7%) |
| Post-surgical injury | 1 (6.7%) |
| Vocal cord paralysis side | |
| Left | 11 (73.3%) |
| Right | 4 (26.7%) |

Note: Variables are presented as a number (%) or a mean \pm SD.

to laryngeal dysfunction, including stroke, motor neuron disease, or Parkinson's disease. We enrolled 15 patients with cancer-related unilateral vocal cord paralysis (Table 1). All the participants underwent assessment at two post-treatment weeks; among them, nine participants completed the assessments at the three-month follow-up.

2.3 | Videofluoroscopic swallowing study

Swallowing evaluation was performed through videofluoroscopy according to the modified Logemann protocol.^{7,8} The participants were seated upright on a chair; further, nasogastric tubes, if present, were removed before evaluation. The test diets included 2 mL and 5 mL of diluted barium (35% w/v), pudding, curd-type yogurt, semi-blended diet, and boiled rice. A 24-mm diameter coin was taped on the patient's chin as a reference for length measurements. The images were recorded at 30 frames per second. VFSS analysis was conducted by two physiatrists with >2 years' experience in VFSS interpretation who were blinded to the study design and purpose. Based on the VFSS findings and clinical information regarding each patient, a study report was made through a consensus among the physiatrists. Moreover, the study reports included the scores of the videofluoroscopic dysphagia scale (VDS), penetration-aspiration scale (PAS), and Association Speech-Language-Hearing Association National Outcome Measurement System (ASHA NOMS) swallowing scale.

2.4 | Laryngeal electromyography

To identify the neurogenic cause of laryngeal dysfunction and the severity of nerve injury, we performed pre-treatment laryngeal

electromyography.⁹ Patients who refused laryngeal electromyography or were at a high risk of bleeding (platelet < 50 000 or INR > 3.0) or infection (absolute neutrophil count < 500) were not tested but were not excluded from the study. The result of the electromyography was used to help with patient counseling.

Thyroarytenoid and cricothyroid muscles on the paralyzed side were examined using a 37-mm needle electrode during rest, slight contraction, and forceful contraction (Nicolet Synergy, Natus Medical, Inc., San Carlos, California). Each patient was in a supine with the neck extended by using a pillow. Thyroarytenoid muscle is approached by inserting a needle electrode into the mid-point of anterior neck just superior to the cricoid cartilage to pierce the cricothyroid membrane. The needle electrode is directed approximately 45° superiorly and 20° laterally. Cricothyroid muscle is approached by needle insertion 3-5 mm lateral from the midline at the superior border of the cricoid cartilage. The needle is directed approximately 45° superiorly and 30-45° laterally.

2.5 | Percutaneous injection laryngoplasty

The participants underwent percutaneous injection laryngoplasty under local anesthesia in the outpatient clinic. A fiberoptic endoscope (VE-1530, Pentax Precision Instrument Co., Orangeburg, New York) was inserted via the nostril. While observing the vocal fold through the fiberoptic endoscope, a 25-gauge, 1.5-in. needle was percutaneously inserted through the cricothyroid membrane. After confirming that the needle was located in the vocal cord, hyaluronic acid (Restylane Perlane, Galderma, Lausanne, Switzerland) was injected. The amount of injected material was determined according to the size of glottic chink on stroboscopic findings, and

TABLE 2 Clinical characteristics, electromyographic findings and injection volumes of the participants

| No. | Sex | Age | Primary lesion | Paralyzed side | Cause of paralysis | Fib | PSW | IP | Injection volume (cc) |
|-----|-----|-----|----------------|----------------|------------------------|------|------|---------------------|-----------------------|
| 1 | M | 68 | Bladder cancer | Left | Lymph node compression | 3+ | None | No activity | 1.0 |
| 2 | M | 70 | SCLC | Left | Lymph node compression | None | None | No activity | 1.0 |
| 3 | M | 76 | NSCLC | Left | Lymph node compression | None | None | No activity | 1.0 |
| 4 | M | 52 | NSCLC | Right | Lymph node compression | None | None | Single ^a | 0.8 |
| 5 | M | 67 | NSCLC | Left | Lymph node compression | None | None | No activity | 0.8 |
| 6 | M | 64 | DLBCL | Right | Lymph node compression | NT | NT | NT | 0.8 |
| 7 | M | 59 | NSCLC | Right | Cancer involvement | None | None | No activity | 0.8 |
| 8 | M | 73 | Thyroid cancer | Left | Post-surgical injury | None | None | Single ^a | 1.0 |
| 9 | F | 58 | Breast cancer | Right | Lymph node compression | NT | NT | NT | 0.8 |
| 10 | M | 63 | Colon cancer | Left | Lymph node compression | NT | NT | NT | 1.0 |
| 11 | F | 68 | NSCLC | Left | Lymph node compression | NT | NT | NT | 1.0 |
| 12 | M | 89 | NSCLC | Left | Lymph node compression | 2+ | None | No activity | 1.0 |
| 13 | F | 78 | Breast cancer | Left | Lymph node compression | 2+ | None | Reduced | 0.5 |
| 14 | F | 54 | SCLC | Left | Lymph node compression | 1+ | 1+ | Reduced | 1.0 |
| 15 | F | 66 | NSCLC | Left | Lymph node compression | NT | NT | NT | 1.0 |

Abbreviations: DLBCL, diffuse large B-cell lymphoma; Fib, fibrillation potential; IP, interference pattern; NSCLC, non-small cell lung cancer; NT, not tested; PSW, positive sharp wave; SCLC, small cell lung cancer.

^aThe single unit pattern is used to describe a single motor unit action potential firing at a rapid rate during maximum voluntary effort.

the average injection amount was 0.9 mL. Any adverse events that occurred were documented.

2.6 | Outcome measurements

The participants were assessed before injection laryngoplasty, as well as at two post-treatment weeks and three post-treatment months. Swallowing-related outcome measures included the VDS, PAS, ASHA NOMS swallowing scale, and M.D. Anderson Dysphagia Inventory (MDADI). Voice-related outcome measures included the Maximum Phonation Time (MPT), and Voice Handicap Index-10 (VHI-10). Stroboscopy was used to assess the glottal gap and vocal fold location.

2.7 | Swallowing outcome measures

The VDS is a validated tool for determining dysphagia severity in various etiologies.¹⁰ The total VDS score ranges from 0 to 100, with the score being negatively correlated with swallowing function.¹¹ The PAS is an 8-point assessment scale for determining the severity of penetration and aspiration based on the airway invasion depth.¹² Scores of 2-5 and ≥ 6 are indicative of penetration and aspiration, respectively. The ASHA NOMS swallowing scale is a multi-dimensional tool for measuring the supervision required and the current diet level.¹³ Here, the swallowing functional level is evaluated based on a 1-7 score range. The MDADI is a self-administered questionnaire for assessing the dysphagia impact on the quality of life in patients with head and neck cancer.^{14,15} The total score ranges from 20 to 100 with a higher score reflecting a better quality of life.

2.8 | Voice outcome measures

The MPT is the maximum time that a patient can sustain a vowel sound phonation.¹⁶ It is indicative of glottal closure, which is an essential mechanism for airway protection during swallowing. The VHI-10 is a validated short form of the VHI, a self-assessment tool for measuring the voice-related quality of life.¹⁷ Each item is scored on a 0-4 Likert scale with the total score ranging from 0 to 40.¹⁸ The score is positively correlated with the impact of dysphonia on the quality of life.

2.9 | Statistical analyses

Outcome measures were compared across multiple time points using Friedman rank sum test. Outcome measures showing significance in the Friedman test were included in a post-hoc analysis with Bonferroni correction. The missing values were imputed using the last observation carried forward method. All statistical analyses were performed using R software version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a *P*-value $< .05$.

3 | RESULTS

3.1 | Electromyographic findings

Ten patients agreed to laryngeal electromyography before injection laryngoplasty. In all participants, needle electromyography of the cricothyroid muscles did not reveal abnormal findings. However, needle electromyography of the thyroarytenoid muscles revealed incomplete interference patterns and abnormal spontaneous activities in

TABLE 3 Comparison of pre- and post-treatment stroboscopic findings and speech function

| | T1 | T2 | T3 | χ^2 | <i>P</i> [†] | <i>P</i> [‡] | | |
|---------------------|------------------|-------------------|------------------|----------|-----------------------|-----------------------|---------|-----------|
| | | | | | | T1-T2 | T2-T3 | T1-T3 |
| Glottal gap | | | | 20.18 | $< .01^*$ | $< .01^*$ | $> .99$ | $< .01^*$ |
| No gap | 1 (7.7%) | 11 (73.3%) | 12 (80.0%) | | | | | |
| Gap | 14 (93.3%) | 4 (26.7%) | 3 (20.0%) | | | | | |
| Vocal fold position | | | | 25.72 | $< .01^*$ | $< .01^*$ | .35 | $< .01^*$ |
| Midline | 0 (0.0%) | 10 (66.6%) | 12 (80.0%) | | | | | |
| Paramedian | 6 (40.0%) | 4 (26.7%) | 2 (13.3%) | | | | | |
| Intermediate | 3 (20.0%) | 1 (6.7%) | 1 (6.7%) | | | | | |
| Lateral | 6 (40.0%) | 0 (0.0%) | 0 (0.0%) | | | | | |
| MPT | 4.33 \pm 3.44 | 9.00 \pm 4.00 | 8.73 \pm 4.68 | 17.26 | $< .01^*$ | $< .01^*$ | .62 | $< .01^*$ |
| VHI-10 | 24.87 \pm 9.04 | 16.60 \pm 10.37 | 12.20 \pm 9.35 | 13.50 | $< .01^*$ | $< .01^*$ | .04 | $< .01^*$ |

Note: Variables are presented as a number (%) or mean \pm SD.

Abbreviations: T1, before injection laryngoplasty; T2, two weeks after injection laryngoplasty; T3, three-month follow-up; MPT, maximum phonation time; VHI-10, voice handicap index-10.

**P* $< .05$, [†]Friedman rank sum test.

[‡]*P* $< .016$, [‡]Wilcoxon signed rank test with Bonferroni correction.

10 and 4 participants, respectively (Table 2). Electromyographic findings indicated that all the participants showed recurrent laryngeal neuropathy of varying severities.

3.2 | Changes in stroboscopic findings and voice

Table 3 shows changes in stroboscopic findings and voice. The Friedman test revealed significant post-treatment improvements in the glottal gap, vocal fold position, MPT, and VHI-10 (all $P < .01$). Post-hoc analysis using Bonferroni correction revealed that the improvements occurred within two post-treatment weeks and remained at three post-treatment months (T1 to T2, all $P < .01$; T1 to T3, all $P < .01$).

3.3 | Changes in swallowing function

Table 4 demonstrates post-treatment changes in swallowing function. Friedman test revealed no significant change in swallowing

parameters. For subgroup analysis, the participants were allocated to subgroups based on the delay in treatment (Table 5). The delayed group comprised of individuals who underwent injection laryngoplasty after 8 post-onset weeks. Time of symptom onset was defined as the time when participants first noticed any symptom related to vocal cord paralysis. Eight weeks was selected as a cut-off because it was the median value of the delay in the procedure. Compared with the delayed group, the non-delayed group revealed significantly higher improvements in the VDS (T1 to T2, $P < .01$, T1 to T3, $P = .02$) and ASHA NOMS scores (T1 to T2, $P = .04$).

4 | DISCUSSION

This study observed that percutaneous injection laryngoplasty significantly improved the glottal closure and vocal fold position in patients with cancer-related unilateral vocal cord paralysis. Additionally, there was a significant post-treatment improvement in the voice and voice-related quality of life. The effects remained at three post-treatment

| | T1 | T2 | T3 | χ^2 | P^a |
|-----------|---------------|---------------|---------------|----------|-------|
| VDS | 16.87 ± 17.19 | 16.37 ± 16.16 | 14.63 ± 16.95 | 2.28 | .32 |
| PAS | 3.27 ± 3.08 | 3.20 ± 2.68 | 2.87 ± 2.77 | 2.08 | .35 |
| ASHA-NOMS | 6.47 ± 0.83 | 6.33 ± 0.62 | 6.47 ± 0.64 | 1.60 | .45 |
| MDADI | 76.80 ± 13.27 | 75.53 ± 18.50 | 72.40 ± 17.52 | 0.18 | .91 |

TABLE 4 Comparison of pre- and post-treatment swallowing function

Note: Variables are presented as mean ± SD.

Abbreviations: T1, before injection laryngoplasty; T2, two weeks after injection laryngoplasty; T3, three-month follow-up; VDS, Videofluoroscopic Dysphagia Scale; PAS, Penetration Aspiration Scale; ASHA-NOMS, American Speech-Language-Hearing Association National Outcome Measurement System swallowing scale; MDADI, MD Anderson Dysphagia Inventory.

^aFriedman rank sum test.

TABLE 5 Subgroup analysis of swallowing function between the delay and non-delay group

| | T1 | T2 | T3 | χ^2 | P^a | $\Delta T2-T1$ | P^b | $\Delta T3-T1$ | P^b |
|-----------|---------------|---------------|---------------|----------|-------|----------------|-------|----------------|-------|
| VDS | | | | | | | | | |
| Delay(+) | 13.14 ± 9.23 | 22.21 ± 9.96 | 18.57 ± 12.81 | 7.91 | .02* | +69.02% | <.01* | +41.30% | .02* |
| Delay(-) | 20.13 ± 22.19 | 11.25 ± 19.32 | 11.19 ± 20.12 | 2.10 | .35 | -44.10% | | -44.41% | |
| PAS | | | | | | | | | |
| Delay(+) | 2.86 ± 2.91 | 3.14 ± 2.34 | 2.57 ± 2.44 | 2.47 | .29 | +10.00% | .16 | -10.00% | .54 |
| Delay(-) | 3.63 ± 3.38 | 3.25 ± 3.11 | 3.13 ± 3.18 | 0.67 | .72 | -10.34% | | -13.79% | |
| ASHA NOMS | | | | | | | | | |
| Delay(+) | 6.71 ± 0.49 | 6.29 ± 0.49 | 6.43 ± 0.53 | 4.67 | .10 | -6.38% | .04* | -4.26% | .06 |
| Delay(-) | 6.25 ± 1.04 | 6.38 ± 0.74 | 6.50 ± 0.76 | 3.00 | .22 | +2.00% | | +4.00% | |
| MDADI | | | | | | | | | |
| Delay(+) | 73.00 ± 9.56 | 73.86 ± 7.40 | 75.29 ± 9.41 | 1.24 | .54 | +1.17% | .31 | +3.13% | .05 |
| Delay(-) | 80.13 ± 15.71 | 77.00 ± 25.15 | 69.88 ± 22.86 | 1.83 | .40 | -3.90% | | -12.79% | |

Note: Variables are presented as mean ± SD.

Abbreviations: T1, before injection laryngoplasty; T2, two weeks after injection laryngoplasty; T3, three-month follow-up; VDS, Videofluoroscopic Dysphagia Scale; PAS, Penetration Aspiration Scale; ASHA-NOMS, American Speech-Language-Hearing Association National Outcome Measurement System swallowing scale; MDADI, MD Anderson Dysphagia Inventory; Delay (+), participants undergoing injection laryngoplasty after 8 weeks of onset.

^aFriedman rank sum test.

^bWilcoxon rank sum test.

* $p < 0.05$.

months. Although there was no post-treatment significant difference in swallowing-related outcomes, patients who underwent injection laryngoplasty within 8 weeks from onset showed significantly greater improvements than the patients who received the procedure after 8 weeks or more.

Phonation begins with vocal fold adduction.¹⁹ Intact abduction and adduction movement of the vocal folds are critical for producing and controlling the voice.²⁰ Patients with glottal insufficiency have breathy voices due to airflow leakage.²¹ Therefore, reducing the glottal gap is a treatment target for improving voice quality in patients with vocal cord paralysis. Medialization thyroplasty and injection laryngoplasty are widely accepted for vocal fold medialization.²² Recently, percutaneous injection laryngoplasty is preferred for its cost-effectiveness; moreover, there have been studies on various injection materials.²³ Additionally, this study showed that hyaluronic acid injection resulted in voice improvement by medializing vocal folds without serious adverse events.

Hyaluronic acid is an extracellular matrix component also present in the lamina propria of the vocal fold.^{24,25} Injected hyaluronic acid remains for up to 6 months before reabsorption and recruits fibroblasts, which yield new connective tissue and lead to endogenous soft tissue augmentation.²⁶ The negligible immunogenicity and implant rejection of hyaluronic acid have made it an ideal skin filler candidate.²⁷ Consequently, hyaluronic acid is widely used as a dermal filler for cosmetic procedures and vocal fold augmentation.²⁸

Glottal closure results in a physical barrier against aspiration during swallowing.²⁹ Unilateral vocal cord paralysis affects glottal closure and increases the aspiration risk.³⁰ Injection laryngoplasty decreases the aspiration risk by increasing the bulk of the paralyzed vocal fold and reducing the glottal gap.^{31,32} However, in this study, it was failed to show significant differences in swallowing outcomes after injection laryngoplasty. There are some possible explanations for the lack of difference. First, this could be attributed to the ceiling effect, which might have been stemmed from the mild aspiration severity among the participants. In this study, only 5 out of 15 (33%) patients showed aspiration. Second, PAS only reflects the presence or absence of aspiration, not the quantity of aspiration. Injection laryngoplasty reduces the glottal gap and may decrease the amount of aspiration. However, PAS cannot indicate a reduction in the risk of aspiration due to a decrease in aspiration volume. Third, injection laryngoplasty cannot improve the sensory abnormalities of larynx. Laryngeal sensation is essential for safe swallowing.³³ Structural changes alone may not be sufficient to indicate a significant improvement in swallowing function. Lastly, it could be also attributed to the varying timing of injection laryngoplasty. The delayed procedure may not have led to improvement in swallowing function. In the subgroup analysis, compared with the delayed group, the non-delayed group showed a significantly superior therapeutic effect in dysphagia severity over time.

A previous retrospective study suggested that injection laryngoplasty improved Eating Assessment Tool-10 and Functional Oral Intake Scale scores in cancer patients with unilateral vocal fold paralysis.³¹ The advantage of our study is that it was a prospective

study which compared objective swallowing parameters from VFSS in detail, including VDS, PAS, and ASHA NOMS. Moreover, the subgroup analysis in the present study stressed that the need for early injection laryngoplasty.

This study has several limitations. First, this study did not enroll a control group. Second, this study has a relatively small sample size. Third, the participants' dysphagia was too mild to demonstrate the treatment efficacy on swallowing function due to the ceiling effect. Fourth, the loss to follow-up at three months was 40%. This may be the cause of the insignificant differences between T2 and T3. Finally, there were variances in the timing of injection laryngoplasty. Further research on patients with severe dysphagia undergoing early injection laryngoplasty might confirm its efficacy on dysphagia following cancer-related unilateral vocal cord paralysis.

5 | CONCLUSION

Our findings suggest that percutaneous injection laryngoplasty using hyaluronic acid can improve glottal closure and voice in patients with cancer-related vocal cord paralysis. In addition, patients with swallowing dysfunction may benefit from early procedure.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ORCID

Min-Gu Kang  <https://orcid.org/0000-0002-0680-9607>

Han Gil Seo  <https://orcid.org/0000-0001-6904-7542>

Eun-Jae Chung  <https://orcid.org/0000-0003-3918-7717>

Hyun Haeng Lee  <https://orcid.org/0000-0001-6666-6284>

Seo Jung Yun  <https://orcid.org/0000-0002-2142-0472>

Bhumsuk Keam  <https://orcid.org/0000-0001-8196-4247>

Tae Min Kim  <https://orcid.org/0000-0001-6145-4426>

Seong Keun Kwon  <https://orcid.org/0000-0001-9218-7666>

Byung-Mo Oh  <https://orcid.org/0000-0001-9353-7541>

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