Effect of voice rehabilitation training on the patients with laryngeal cancer after radiotherapy

Mei-jia Zhang, MM\textsuperscript{a}, Ji-wei Mu, MM\textsuperscript{a}, Xiang-ru Chen, MM\textsuperscript{b}, Xin Zhang, MM\textsuperscript{b}, Chong Feng, MB\textsuperscript{c,}\textsuperscript{*}

Abstract
This retrospective study examined the effect of voice rehabilitation training (VRT) for patients with laryngeal cancer (LC) after radiotherapy.

Eighty-three eligible patients with LC were included. Forty-three patients were assigned to a treatment group, and underwent VRT, while the other 40 subjects were assigned to a control group, and were on waiting list. Primary outcome was measured by the Grade, Roughness, Breathiness, Asthenia, and Strain (GRBAS) scale. Secondary outcome was measured by Patient Perception Measures. All outcomes were measured before and 3 months after VRT intervention.

Patients in the treatment group did not show better outcomes, measured by GRBAS scale (Grade, $P=0.78$; Roughness, $P=0.61$; Breathiness, $P=0.83$; Asthenia, $P=0.89$; and Strain, $P=0.41$), and Patient Perception Measures (Vocal quality, $P=0.17$; Acceptability, $P=0.35$; Hoarseness, $P=0.23$; Vocal fatigue, $P=0.39$; and Ashamed, $P=0.51$), compared with patients in the control group.

The results of this study did not exert better outcomes in patients received VRT than those at waiting list.

Abbreviations: GRBAS = Grade, Roughness, Breathiness, Asthenia, and Strain, LC = laryngeal cancer, VRT = voice rehabilitation training.

Keywords: effect, laryngeal cancer, voice rehabilitation training

1. Introduction
Laryngeal cancer (LC) is one of the most common cancers in head and neck\textsuperscript{[1,2]} It is also the second most common cancer of respiratory tract, following the lung cancer\textsuperscript{[3,4]} Such condition can not only affect the quality of life for patients with LC, but also bring huge financial burden for both families and society\textsuperscript{[5]} Previous study reported that almost 80% of the patients diagnosed with LC are men, and most of them are between 50 and 85 years old\textsuperscript{[6]} The prognosis for LC mainly depends on the localization and size of tumors, as well as the possible presence of metastases\textsuperscript{[7]} It has been reported that there were 156,877 new cases and 83,376 deaths of LC in the world in 2012, with the rates of incidence in 2.1/100,000 and mortality in 1.1/100,000, respectively\textsuperscript{[5]} In China, it is reported that about 12.76% LC cases, and 14.65% deaths according to the report of World Health Organization\textsuperscript{[8,9]} Several treatments are utilized to treat LC\textsuperscript{[10–12]} mainly including nonoperative and operative treatments. Of those, nonoperative therapy often used to keep organ preservation and a decrease in the use of primary surgery in patients with LC\textsuperscript{[11]} This kind of therapy often includes concurrent chemoradiation\textsuperscript{[13–15]} The other treatment for such condition is primary surgery\textsuperscript{[14,16]} However, nonoperative treatment is more likely to preserve the organ for patients than the primary surgery\textsuperscript{[14]} Thus, clinical evidence is still more likely to recommend the nonoperative intervention for treating LC.

No matter what kinds of treatments the patients received, they all affect the voice quality after the treatment\textsuperscript{[17–21]} Thus, it is very important to improve voice quality after the intervention\textsuperscript{[17–21]} Several studies have reported that voice rehabilitation training (VRT) may benefit to improve voice quality for patients after LC treatment in other countries\textsuperscript{[6,17–21]} However, no data of VRT for patients after LC are available among Chinese population. Thus, in this retrospective study, we first investigated the effect of VRT in Chinese patients with VRT.

2. Methods/design
2.1. Design
This retrospective study was approved by the Ethical Committees of First Affiliated Hospital of Jiamusi University, Second Affiliated Hospital of Mudanjiang Medical University, and Hongqi Affiliated Hospital of Mudanjiang Medical University. All patient cases were collected between October 2016 and September 2017 from the above hospitals. All patients provided the written informed consent.

This retrospective study included 83 eligible patients with LC after treatment. Of these patients, 43 were assigned to a treatment group, and underwent VRT intervention. The other 40 patients were assigned to a control group, and were at waiting list during the period of the VRT intervention in this study. All outcomes data were analyzed before and 3 months after the treatment.
2.2. Patients

Patients with LC after nonoperative treatments were included in this study. All included patients were diagnosed as LC of Tis to T4 type. Additionally, all of them were more than 18-years old at the time of receiving treatments. However, patients were excluded if they received primary surgery for LC and VRT intervention before this study, incomplete data, and severe cognitive problems that affect the effect of VRT intervention, as well as the outcome assessment.

2.3. Treatment schedule

2.3.1. Radiotherapy treatment. All patients in both groups received radiotherapy at 2 to 2.4 Gy fractions, once daily, for a total of 62 to 68 Gy. Patients underwent radiotherapy to lymph nodes if they had T2 to T4 tumors. Additionally, patients also received chemotherapy if they had tumors of T3 and T4.

2.3.2. Voice rehabilitation training. All patients in the treatment group received VRT according to the previous published study.[6] All VRT was instructed by 2 specific experts 1 month after the completion of the radiotherapy treatment. The training content consisted of 10 sessions of VRT, 30 minutes each session, twice weekly for a total of 5 weeks. All the training schedules included relaxation, respiration, posture, and phonation exercises. The patients in the control group were at waiting list during the training period of patients in the treatment group.

2.3.3. Outcome measurements. Primary outcome was measured by the Grade, Roughness, Breathiness, Asthenia, and Strain (GRBAS) scale.[24] This tool includes 5 items. Each item is a 4-point scale, ranging from 0, normal, to 3, severely impaired.

Secondary outcome was measured by the scale of Patient Perception Measures.23,25,26 This scale consists of 3 subscales, including vocal quality, acceptability, hoarseness, vocal fatigue, and ashamed.23,24 Each subscale varies from 0, never/not at all, to 3, always/a lot. All outcomes were measured before and 3 months after VRT intervention.

2.3.4. Statistical analysis. All values of characteristics, outcomes data were analyzed using SPSS Statistics 17.0 (IBM Corp, Armonk, NY). Fisher exact test was applied for dichotomous variables; Mann–Whitney U test was performed for continuous data; χ2 and Mantel–Haenszel χ2 test was used for nonordered and ordered categorical data, respectively. P < .05 was regarded as the statistical significance.

3. Results

The characteristics of 83 eligible patients with LC after radiotherapy were included in this retrospective study (Table 1). No significant differences of all characteristics were detected between 2 groups. All these characteristics were summarized in Table 1, which includes age, gender, race, performance status, tumor location, tumor category, previous treatment information, and GRBAS scale and Patient Perception Measures before the VRT intervention.

Three months after VRT intervention, patients in the treatment group did not demonstrate more promising outcomes in GRBAS scale (Grade, P = .78; Roughness, P = .61; Breathiness, P = .83; Asthenia, P = .89; and Strain, P = .41; Table 2), and Patient Perception Measures (Vocal quality, P = .17; Acceptability, P = .35; Hoarseness, P = .23; Vocal fatigue, P = .39; and Ashamed, P = .51; Table 3), compared to patients in the control group.

Table 1: Characteristics of all included patients before the VRT.

| Characteristics | Treatment group (n = 43) | Control group (n = 40) | P value |
|-----------------|--------------------------|------------------------|---------|
| Age, y          | 63.8 (10.1)              | 64.5 (9.8)             | .91     |
| Gender          |                          |                        |         |
| Male            | 34 (78.9)                | 32 (80.0)              | .29     |
| Female          | 9 (20.9)                 | 8 (20.0)               | .29     |
| Race (Han ethnicity) | 43 (100.0)       | 40 (100.0)             | 1.00    |
| Performance status |                         |                        |         |
| 0               | 19 (44.2)                | 15 (37.5)              | .43     |
| 1               | 24 (55.8)                | 25 (62.5)              | .43     |
| Location        |                          |                        |         |
| Glottic         | 30 (69.8)                | 29 (72.5)              | .80     |
| Supraglottic    | 13 (30.2)                | 11 (27.5)              | .80     |
| T category      |                          |                        |         |
| Tis             | 1 (2.3)                  | 0 (0)                  | .64     |
| T1              | 33 (76.7)                | 30 (75.0)              | .64     |
| T2              | 6 (14.0)                 | 8 (20.0)               | .40     |
| T3              | 2 (4.7)                  | 1 (2.5)                | .42     |
| T4              | 1 (2.3)                  | 1 (2.5)                | .49     |
| Chemotherapy    |                          |                        |         |
| Cisplatin       | 24 (55.8)                | 19 (47.5)              | .45     |
| Fluorouracil    | 10 (23.3)                | 8 (20.0)               | .72     |
| Captopitabine   | 6 (14.0)                 | 5 (12.5)               | .85     |
| Carboptinlatin  | 8 (18.6)                 | 11 (27.5)              | .34     |
| Paclitaxel      | 4 (9.3)                  | 4 (10.0)               | .91     |
| Gemcitabine     | 3 (7.0)                  | 2 (5.0)                | .71     |
| GRBAS scale     |                          |                        |         |
| Grade           | 1.73 (0.63)              | 1.78 (0.67)            | .73     |
| Roughness       | 1.24 (0.58)              | 1.30 (0.62)            | .65     |
| Breathiness     | 1.08 (0.79)              | 1.07 (0.77)            | .95     |
| Asthenia        | 0.10 (0.21)              | 0.11 (0.23)            | .84     |
| Strain          | 1.15 (0.67)              | 1.17 (0.70)            | .89     |
| PPM scale       |                          |                        |         |
| Vocal quality   | 1.62 (0.74)              | 1.70 (0.80)            | .64     |
| Acceptability   | 1.19 (0.69)              | 1.10 (0.71)            | .56     |
| Hoarseness      | 1.88 (0.62)              | 1.91 (0.79)            | .87     |
| Vocal fatigue   | 1.43 (0.67)              | 1.49 (0.63)            | .67     |
| Ashamed         | 0.56 (0.71)              | 0.52 (0.68)            | .84     |

Data are present as mean±standard deviation or number (%).

4. Discussion

Previous studies have reported that radiotherapy can impair vocal quality in patients with LC, who have received radiotherapy treatment.27,28 Furthermore, such kind of therapy can significantly affect the rough quality and hoarseness.27,28 Fortunately, the other studies provided the evidence that this impaired vocal condition can be prevented by VRT.29 Some published studies have reported that VRT may either help patients to improve their functional outcomes and quality of their life, or benefit them to enhance their psychological well-being/distress issues, especially for those patients who experience probable anxiety or depression.30,31

This is the first retrospective study investigating the impact of VRT in patients with LC after radiotherapy among Chinese population. Results of this study did not show positive benefit for Chinese patients with LC after radiotherapy by using VRT intervention. The results of our study are inconsistent with the previous study.

The results of this retrospective study found that patients in the treatment group did not achieve better outcomes, measured by
Ashamed /C0 Vocal fatigue /C0 Hoarseness

Secondary outcome measurement at 3-mo follow-up (change from baseline).

| GRBAS scale | Treatment group (n = 43) | Control group (n = 40) | Difference | P value |
|-------------|--------------------------|------------------------|------------|---------|
| Grade       | 0.12 (0.03, 0.21)        | 0.07 (0.02, 0.15)      | 0.05 (0.01, 0.09) | .78     |
| Roughness   | 0.07 (0.04, 0.12)        | 0.01 (–0.03, 0.05)     | 0.06 (0.02, 0.11) | .61     |
| Breathiness | 0.05 (0.01, 0.09)        | 0.02 (0.01, 0.04)      | 0.03 (0.01, 0.05) | .83     |
| Astenia     | 0.03 (–0.01, 0.06)       | 0.01 (–0.03, 0.05)     | 0.02 (–0.01, 0.05) | .89     |
| Strain      | 0.11 (0.05, 0.19)        | 0.03 (0.01, 0.07)      | 0.09 (0.05, 0.14) | .41     |

Data are present as mean±standard deviation.
GRBAS = Grade, Roughness, Breathiness, Astenia, Strain.

This study has following limitations. First, the sample size in this study is quite small, which may affect the results of this study. Then, data collection and analysis were based on the current available data in this retrospective study. Thus, we only analyzed 2 outcome measurements according to the current available data. To be honest, more comprehensive outcomes should be included in this study, such as anxiety, depression, and general quality of life. Therefore, future studies should avoid these limitations to further investigate the effect of VRT among the same population.

5. Conclusion

The results of this study found that VRT may not benefit for patients with LC after radiotherapy.

Author contributions

Conceptualization: Chong Feng, Mei-jia Zhang, Ji-wei Mu, Xiang-ru Chen, Xin Zhang.
Data curation: Chong Feng, Mei-jia Zhang, Xiang-ru Chen, Xin Zhang.
Resources: Chong Feng.
Supervision: Chong Feng, Mei-jia Zhang, Xiang-ru Chen.
Visualization: Chong Feng, Mei-jia Zhang, Ji-wei Mu, Xin Zhang.
Writing – original draft: Chong Feng, Mei-jia Zhang, Ji-wei Mu, Xiang-ru Chen, Xin Zhang.
Writing – review & editing: Chong Feng, Mei-jia Zhang, Ji-wei Mu, Xiang-ru Chen, Xin Zhang.
Investigation: Mei-jia Zhang, Xiang-ru Chen.
Validation: Mei-jia Zhang, Ji-wei Mu, Xin Zhang.
Formal analysis: Ji-wei Mu.
Methodology: Ji-wei Mu.
Software: Ji-wei Mu.

References

[1] Britt CJ, Gourin CG. Contemporary management of advanced laryngeal cancer. Laryngoscope Investig Otolaryngol 2017;2:307–9.
[2] Salvador-Coloma C, Cohen E. Multidisciplinary care of laryngeal cancer. J Oncol Pract 2016;12:717–24.
[3] Han DM. Laryngeal Cancer-Treatment and Rehabilitation. People’s Medical Publishing House, Beijing.2003.
[4] van Dijk BA, Kazim-Kos HE, Coebergh JW, et al. Progress against laryngeal cancer in The Netherlands between 1989 and 2010. Int J Cancer 2014;134:674–81.
[5] Du L, Li H, Zhu C, et al. Incidence and mortality of laryngeal cancer in China, 2013. Chin J Cancer Res 2015;27:52–8.
[6] Tuomi L, Björkner E, Finizia C. Voice outcome in patients treated for laryngeal cancer: efficacy of voice rehabilitation. J Voice 2014;28:62–8.
[7] Ding S, Huang J, Huang Z, et al. Variation in prognosis of early laryngeal carcinoma after different types of cordectomy with transoral laser microsurgery. Acta Otolaryngol 2018;138:51–5.
[8] WHO, International Agency for Research on Cancer. GLOBOCAN 2012 (cancer incidence and mortality worldwide in 2012). Available at: http://globocan.iarc.fr/ (accessed April, 2018).
[9] Fu Y, Chen SW, Chen SQ, et al. A preoperative nutritional index for predicting cancer-specific and overall survival in Chinese patients with laryngeal cancer: a retrospective study. Medicine (Baltimore) 2016;95:e2962.
[10] Wick CC, Rezaee RP, Wang T, et al. Use of concurrent chemoradiation in advanced-staged (T4) laryngeal cancer. Am J Otolarangyol 2017;38:72–6.
[11] Sanabria A, Chaves ALF, Kowalski LP, et al. Organ preservation with chemoradiation in advanced laryngeal cancer: the problem of generalizing results from randomized controlled trials. Auris Nasus Larynx 2017;44:18–25.
[12] Fu X, Zhou Q, Zhang X. Efficacy comparison between total laryngectomy and nonsurgical organ-preservation modalities in treatment of advanced stage laryngeal cancer: a meta-analysis. Medicine (Baltimore) 2016;95:e3142.
[13] Aydil U, Akmansu M, Gumusoy O, et al. Comparison of three different concurrent chemoradiation regimens for treatment of laryngeal cancer. Eur Arch Otorhinolaryngol 2016;273:2795–803.
[14] Timme DW, Jonnalagadda S, Patel R, et al. Treatment selection for T3/ T4a laryngeal cancer: chemoradiation versus primary surgery. Ann Otol Rhinol Laryngol 2015;134:845–51.
[15] Lambert L, Forin B, Soulières D, et al. Organ preservation with concurrent chemoradiation for advanced laryngeal cancer: are we succeeding? Int J Radiat Oncol Biol Phys 2010;76:398–402.
[16] Harris RN, Bhuskute AA, Rao S, et al. Primary surgery for advanced-stage laryngeal cancer: a stage and subsite-specific survival analysis. Head Neck 2016;38:1380–6.
[17] Bergström L, Ward EC, Finizia C. Voice rehabilitation after laryngeal cancer: associated effects on psychological well-being. Support Care Cancer 2017;25:2683–90.
[18] Bergström L, Ward EC, Finizia C. Voice rehabilitation for laryngeal cancer patients: functional outcomes and patient perceptions. Laryngoscope 2016;126:2029–35.
[19] Karlsson T, Johansson M, Andrèll P, et al. Effects of voice rehabilitation on health-related quality of life, communication and voice in laryngeal cancer patients treated with radiotherapy: a randomised controlled trial. Acta Oncol 2015;54:1017–24.
[20] Tuomi L, Andrèll P, Finizia C. Effects of voice rehabilitation after radiation therapy for laryngeal cancer: a randomized controlled study. Int J Radiat Oncol Biol Phys 2014;89:964–72.
[21] Luo J, Wu J, Lv K, et al. Analysis of postsurgical health-related quality of life and quality of voice of patients with laryngeal carcinoma. Medicine (Baltimore) 2016;95:e2363.
[22] Karlsson T, Tuomi L, Andrèll P, et al. Effects of voice rehabilitation after radiotherapy for laryngeal cancer: a longitudinal study. Logoped Phoniatr Vocol 2017;42:167–77.
[23] Finizia C, Bergman B, Lindström J. A cross-sectional validation study of self-evaluation of communication experiences after laryngeal cancer—a questionnaire for use in the voice rehabilitation of laryngeal cancer patients. Acta Oncol 1999;38:573–80.
[24] Hirano M. Clinical Examination of Voice. Springer, London, UK:1981.
[25] Finizia C, Hammerlid E, Westin T, et al. Quality of life and voice in patients with laryngeal carcinoma: a post treatment comparison of laryngectomy (salvage surgery) versus radiotherapy. Laryngoscope 1998;108:1566–73.
[26] Finizia C, Lindstrom J, Dotson H. Intelligibility and perceptual ratings after treatment for laryngeal cancer: laryngectomy versus radiotherapy. Laryngoscope 1998;108:138–43.
[27] Hocevar-Boltezar I, Zargi M, Strojan P. Risk factors for voice quality after radiotherapy for early glottic cancer. Radiother Oncol 2009;93:524–9.
[28] Szucs M, Kuhnt T, Punce C, et al. Subjective voice quality, communicative ability and swallowing after definitive radio(chemo) therapy, laryngectomy plus radio(chemo)therapy, or organ conservation surgery plus radio(chemo)therapy for laryngeal and hypopharyngeal cancer. J Radiat Res 2014;56:559–68.
[29] Bibby JR, Cotton SM, Perry A, et al. Voice outcomes after radiotherapy treatment for early glottic cancer: assessment using multidimensional tools. Head Neck 2008;30:600–10.
[30] Stupsiskienė N, Vartkus S, Grebliauskaite M, et al. Quality of life and voice in patients treated for early laryngeal cancer. Medicina (Kaunas) 2008;44:288–95.
[31] Johansson M, Ryden A, Finizia C. Mental adjustment to cancer and its relation to anxiety, depression, HRQL and survival in patients with laryngeal cancer. A longitudinal study. BMC Cancer 2011;11:283.