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Original Article

CO_2 laser combined with low-temperature plasma radiofrequency ablation promotes recovery of swallowing function in elderly patients with early glottic carcinoma

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Abstract: Objective: This study was designed to determine the effect of CO_2 laser combined with low-temperature plasma radiofrequency ablation (LPRA) on swallowing function and prognosis in elderly patients with early glottic laryngeal cancer (GLC). Methods: The clinical data of 115 elderly patients with early GLC treated in General Hospital of Daqing Oil Field from May 2013 to September 2015 were retrospectively analyzed. These patients were assigned to a research group or control group according to different therapeutic regimen. Totally 56 cases treated with CO_2 laser resection were assigned to the control group, and 59 cases treated with CO_2 laser combined with LPRA were assigned to the research group. The hospital stay, postoperative pain, mucosal recovery score, postoperative complications, swallowing function, vocal function, and 5-year recurrence rate were compared between the two groups. Independent risk factors for 5-year recurrence in patients were analyzed by multivariate logistic regression. Results: The research group was significantly superior to the control group in terms of hospital stay, postoperative pain, and mucosal recovery score ($P<0.05$), and the postoperative complication rate was not significantly different between the two groups ($P>0.05$). After treatment, the research group showed better swallowing function and vocal function than the control group, and the 5-year recurrence rate of the two groups was similar ($P=0.288$). Multivariate logistic regression analysis identified higher age, lower differentiation, and presence of a cumulative anterior commissure as independent risk factors for recurrence. Conclusion: CO_2 laser combined with LPRA can provide relatively high clinical efficacy for early GLC in the elderly, after which patients' swallowing function and vocal function recover quickly, but the long-term benefit of adding LPRA is not evident.

Keywords: CO_2 laser, low-temperature plasma radiofrequency ablation, early glottic laryngeal cancer, swallowing function

Introduction

Laryngeal cancer is one of the frequent tumours in the department of otorhinolaryngology, and is 1%~5% of all malignant tumours. Its total incidence is approximately 2.04/100,000, and is higher in men [1, 2]. Laryngeal cancer is primarily seen in the elderly, and they usually have unfavourable prognosis and suffer a slow recovery after treatment [3]. Laryngeal cancer can be classified into glottic cancer, supraglottic cancer, and subglottic cancer according to the location of the lesion, among which glottic laryngeal cancer (GLC) is the most common, accounting for approximately 60% of laryngeal cancers [4].

Early GLC does not invade adjacent cartilage scaffold and muscle, and has no cervical lymph node and distant metastasis. The lesion may be confined to unilateral vocal cords, or invade the anterior commissure, contralateral vocal cords, upward supraglottic area, or inferior glottic area, with normal or limited vocal cord activity [5, 6]. Early GLC has obvious clinical symptoms, so it can be easily found, and has rare lymph node metastasis. Its cure rate is high when treated with radiotherapy, open surgery,

laser, and low-temperature plasma radiofrequency ablation (LPRA), but the efficacy decreases greatly when the tumour involves the anterior commissure [7, 8].

At present surgery is the most effective method for the treatment of laryngeal cancer. Traditional laryngectomy causes great trauma to the body and will bring complications, and causes symptoms such as aspiration, choking on food, and dyspnea [9]. Vocal cord tumour resection with CO_2 laser requires no larynx cracking, and causes small surgical trauma while preserving the shape of the larynx, which can preserve the laryngeal function to the maximum extent [10]. As a straight beam, the laser beam is unable to reach every lesion area, so the surgical effect is not favourable for patients with laryngeal cancer invading the anterior commissure and subglottis [11]. Low-temperature plasma ablation uses the energy of low-temperature plasma radiofrequency to resect the tissue at a lower temperature, thus avoiding damage to the tissue, greatly alleviating pain, and shortening the recovery period [12]. However, because of the limited operation due to a narrow throat, it is difficult to ensure a safety margin in low-temperature plasma ablation, and low-temperature plasma ablation cannot cut as accurately as CO_2 laser. Although many studies have confirmed the effectiveness of these two minimally invasive operations, there is still controversy about their efficacy, and there is still little research on the joint application of both therapeutic regimens [13]. Therefore, this study verified the therapeutic effect of CO_2 laser combined with low-temperature plasma radiofrequency ablation (LPRA) on elderly patients with early glottic carcinoma, and evaluated the effect on the 5-year recurrence rate.

This study retrospectively analyzed the clinical data of 115 elderly patients with early GLC treated in General Hospital of Daqing Oil Field and found that CO_2 laser combined with LPRA was effective in the treatment of early GLC in the elderly, and could preserve the swallowing function.

Methods

Patient information

The clinical data of 115 elderly patients with early GLC treated in General Hospital of Daqing Oil Field from May 2013 to September 2015 were retrospectively analyzed. These patients were assigned to a research group or control group based on different therapeutic regimen. Totally 56 cases treated with CO_2 laser resection were assigned to the control group (50 males and 6 females; mean age: (69.43±4.74) years), and 59 cases treated with CO_2 laser combined with LPRA were assigned to the research group (49 males and 10 females; mean age: (68.08±5.50) years). This study was performed with permission from the Medical Ethics Committee of General Hospital of Daqing Oil Field.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients whose lesion was confirmed to be in the glottic area through electronic laryngoscope, and confirmed with pathological biopsy [14], (2) patients with no suspected lymph nodes according to observation by CT, (3) ultrasound and MRI before operation, or with suspected lymph nodes but no lymph node metastasis in pathology of cervical lymph nodes after operation, (4) patients whose TNM stage was Tis, T1a, T1b or partial T2, (5) patients ≥60 years old, (6) patients whose pathological type was squamous cell carcinoma, (7) patients (including families) who knew and agreed to the treatment regimen, (8) patients with detailed clinical data.

Exclusion criteria: (1) Patients comorbid with malignant tumour, (2) patients with a history of preoperative radiotherapy or chemotherapy, (3) patients with other diseases affecting swallowing function, (4) patients who were in a poor mental state and unable to cooperate with treatment, (5) and patients who can't tolerate the operation.

Therapeutic regimen

The control group received CO_2 laser resection. Specifically, the patient was fasted from solids and liquids for 12 h, and then let to lie in a supine position, followed by endotracheal intubation combined anesthesia. The laryngoscope was put into the patient to fully expose the glottis, which was connected to CO_2 laser (Shanghai Jiading Optoelectronic instrument Co., Ltd., China, JC40), and connected with the microscope through the coupler. Then, the modulated pulse cutting mode was selected, and the laser output power was set to 2-5 W. Saline gauze was placed under the glottis, and the

tumour was removed about 2-3 mm along the edge of the tumour; if the anterior commissure was involved, the cartilage plate at the anterior commissure was treated at the same time.

On the basis of treatment to the control group, the research group was additionally treated with LPRA (Chengdu Mechan Electronic Technology Co., Ltd, China, MC-GZ130). After CO_2 laser surgery, the saline gauze was taken out, and the low-temperature plasma surgery system, nasal endoscope and its imaging system were connected. The nasal endoscope from different angles was used to fully expose the possible residual tumours at the lateral and lower vocal cords, especially at the anterior commissure. The low temperature plasma ablation power was adjusted to 6-7 gear and the hemostatic power was adjusted to 3-4 gear. When necessary, the front end was bent into different angles according to the lesion site by the laryngeal plasma cutter to fully remove the lesion. During cutting, positioning should be accurate to avoid accidental injury to normal laryngeal mucosa. After the operation, both groups were given routine anti-inflammatory, aerosol inhalation, and silence.

Follow-up mode

The patients were reexamined every month during half a year after operation, every 3 months during the period from half a year to one year, and then followed up every six months. A 5-year follow-up was made to all patients by telephone communication and reexamination.

Outcome measures

Primary outcome measures: (1) The hospitalization time, postoperative pain, and wound recovery were compared between the two groups. At 24 h after surgery, each patient's pain degree was scored by visual analogue scale (VAS). 0 points: Feeling no pain; 1 point: feeling pain if pay attention to it; 2 points: Feeling pain but sometimes ignoring it; 3 points: Feeling nonnegligible pain that does not disrupt rest and sleep; 4 points: Feeling unbearable pain that disrupts rest and sleep; 5 points: Feeling unbearable pain that requires painkillers [15]. Each patient received examination by laryngoscope every week within 1 month after operation, and mucosal recovery score was used to evaluate the recovery of wound mucosa according to the following criteria: 1 point: The pseudomembrane of the wound fell off within 1 week and the mucosa was smooth; 2 points: The pseudomembrane of the wound fell off within 2 weeks; 3 points: The pseudomembrane of the wound fell off within 3 weeks; 4 points: The pseudomembrane of the wound fell off within 4 weeks; 4 points: The pseudomembrane of the wound fell off past 4 weeks [16]. (2) Comparison of swallowing function. The swallowing function of the two groups was evaluated at the third month after operation. The swallowing function was classified into four grades: grade 0: the patient had no choking cough when eating liquid food; grade 1: the patient had choking cough when eating liquid food, but had no choking when eating pasty food; grade 2: the patient had choking when eating pasty food; grade 3: the patient was unable to eat food through mouth. The ratio of the numbers of patients at grade 0 or grade 1 to the total number of patents was overall good [17].

Secondary outcome measures: (1) Voice recovery index: The German XION noise acoustic software was used for voice acoustic analysis before and 3 months after operation. During the test, the subject was let to set in a quiet examination room with environmental noise <45 dB A. The distance between the microphone and the mouth was 30 cm, and the subject was asked to produce vowel sounds continuously for more than 3 s. The fundamental frequency perturbation (jitter), amplitude perturbation (shimmer), and harmonic noise ratio (HNR) were recorded. Lower jitter and shimmer levels and a higher HNR mean better voice recovery [18]. (2) The postoperative complications of the two groups were evaluated, such as subjective pharynx pain, subjective strong pain, local mild adhesion, dyspnea, and granulation hyperplasia. (3) The recurrence status of two groups within 5 years after operation was counted.

Statistical analyses

This study adopted SPSS23.0 (SPSS Co., Ltd., Chicago, USA) for statistical analyses of all collected data, and GraphPad Prism 7 (Graphpad Software Co., Ltd., San Diego, USA) for visualization of data into figures. Counted data (%) were analysed by the chi-square test, and presented as χ^2, and measured data (Mean ± SD) were normally distributed, and their inter-group comparison was conducted using the indepen-

Table 1. Baseline data

	Research group (n=59)	Control group (n=56)	X^2/t	P
Gender			0.932	0.334
Male	49 (83.05)	50 (89.29)		
Female	10 (16.95)	6 (10.71)		
Age (years)	68.08±5.50	69.43±4.74	1.407	0.162
Differentiation			0.222	0.895
High differentiation	47 (79.66)	44 (78.57)		
Moderate differentiation	8 (13.56)	9 (16.07)		
Low differentiation	4 (6.78)	3 (5.36)		
Disease staging			0.729	0.695
Tis period	22 (37.29)	23 (41.07)		
T1a period	18 (30.51)	19 (33.93)		
T1b period	19 (32.20)	14 (25.00)		
History of smoking			0.132	0.716
Yes	48 (81.36)	47 (83.93)		
No	11 (18.64)	9 (16.07)		
History of drinking			0.387	0.534
Yes	24 (40.68)	26 (46.43)		
No	35 (59.32)	30 (53.57)		
Cumulative anterior commissure			0.154	0.694
Yes	10 (16.95)	9 (14.29)		
No	49 (83.05)	47 (85.71)		
Cumulative vocal cord process			0.498	0.480
Yes	5 (8.47)	7 (12.50)		
No	54 (91.53)	49 (87.50)		

dent-samples T test. The K-M curve was adopted to analyse the recurrence within 5 years after operation, and the log rank test was adopted for analysis. Independent risk factors for recurrence in patients were analyzed by multivariate logistic regression. P<0.05 suggests a significant difference.

Results

Baseline data

According to comparison of baseline data, the two groups were similar in gender, age, differentiation degree, disease stage, smoking history, drinking history, cumulative anterior commissure, and cumulative vocal cord process (P>0.05, **Table 1**).

Comparison of hospital stay, postoperative pain, and mucosal recovery score

According to comparison, the hospital stay, VAS score at 24 h after operation, and mucosal recovery score of the research group were all greatly lower than those of the control group (P<0.05, **Table 2**).

Comparison of improvement in swallowing function

Comparison of swallowing function between the two groups revealed a higher total overall good rate in the research group than in the control group (P<0.05, **Table 3**).

Comparison of voice function

According to comparison of voice functions between the two groups, before therapy, the two groups were similar in levels of jitter, himmer, and HNR (P>0.05); after therapy, the voice function of both groups was improved greatly, and the research group showed lower levels of jitter and himmer than the control group (P<0.05) and showed a higher HNR level than the control group (P<0.05, **Figure 1**).

Table 2. Comparison of hospital stay, postoperative pain, and mucosal recovery scores

	Hospitalization time (d)	VAS score at 24 h after operation	Mucosal recovery score
Research group (n=59)	6.49±1.32	1.05±0.63	2.02±0.82
Control group (n=56)	7.84±1.51	2.27±1.09	2.70±1.09
t	5.111	7.395	3.793
P	<0.001	<0.001	<0.001

VAS: Visual Analogue Scale.

Table 3. Swallowing function

	Grade 0	Grade 1	Grade 2	Grade 3	Overall
Research group (n=59)	38 (64.41)	12 (20.34)	8 (13.56)	1 (1.69)	50 (84.79)
Control group (n=56)	25 (44.64)	13 (23.21)	14 (25.00)	4 (7.14)	38 (67.86)
X^2			4.561		
P			0.033		

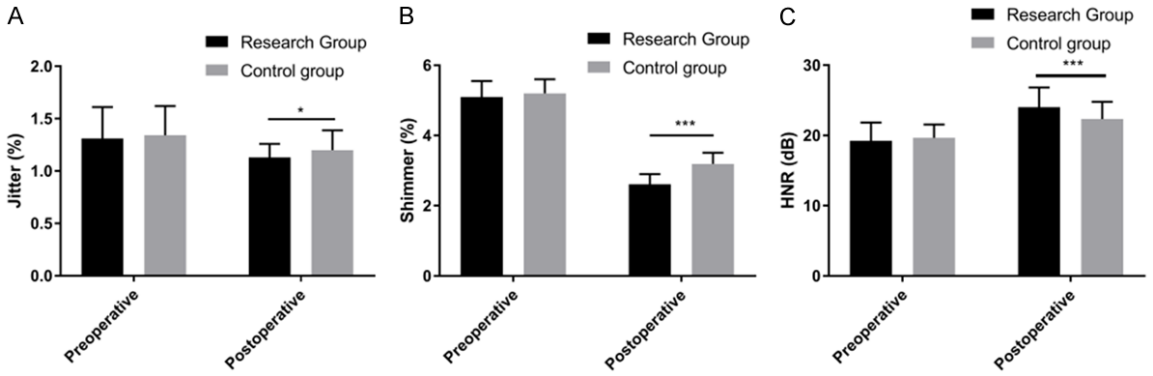

Figure 1. Comparison of voice function between the two groups. A. After therapy, the research group showed a lower jitter level than the control group (P<0.05). B. After therapy, the research group showed a lower himmer level than the control group (P<0.05). C. After therapy, the research group showed a higher HNR level than the control group (P<0.05). HNR: harmonic noise ratio. *P<0.05. ***P<0.001.

Postoperative complications of the two groups

According to comparison of postoperative complications between the two groups, the groups were not significantly different in the total complication rate after surgery (P>0.05, **Table 4**).

Comparison of prognosis

The research group showed a 5-year recurrence rate of 15.25% with 9 cases of recurrence within 5 years, and the control group showed a 5-year recurrence rate of 23.21% with 13 cases of recurrence within 5 years. According to analysis based on K-M curve, the two groups were similar in the 5-year recurrence rate (P>0.05, **Figure 2**).

Univariate analysis of 5-year recurrence

Patients were regrouped according to their 5-year relapse status, and significant differences between the relapse and no relapse groups were found in age, differentiation, cumulative anterior commissure, and cumulative somatic core process (P>0.05, **Table 5**).

Multivariate analysis of recurrence

We compared the indicators that differed by univariate analysis with multivariate logistic regression analysis and found that higher age, lower differentiation, and presence of a cumulative anterior commissure were independent risk factors for recurrence (**Table 6**).

Table 4. Complications

	Research group (n=59)	Control group (n=56)	X^2	P
Sore throat	3 (5.08)	4 (7.14)		
Dyspnea	3 (5.08)	1 (1.79)		
Granulation hyperplasia	2 (3.39)	1 (1.79)		
Total complications	8 (13.56)	6 (10.71)	0.218	0.641

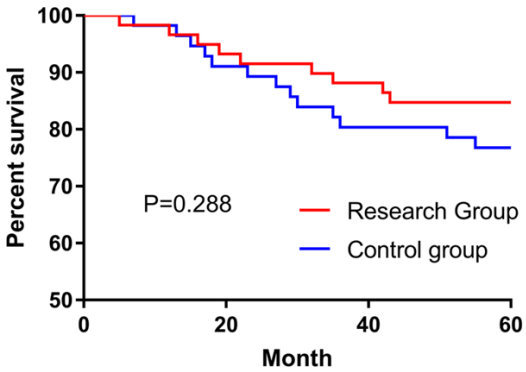

Figure 2. Comparison of 5-year recurrence between the two groups. The two groups were not greatly different in the 5-year recurrence rate (P=0.288).

Discussion

The larynx is an important vocal and respiratory organ in the body, which is of great significance to people's social life. If this part becomes cancerous, patients may suffer symptoms such as cough and hoarseness, but the clinical symptoms are not typical, so most patients pay attention to it only during physical examination [19, 20]. GLC is a common type of laryngeal cancer. Currently, many treatments are available for it, including open surgery, radiotherapy, CO_2 laser and LPRA. The first two treatments cause high trauma and many side effects, which limit their clinical application [21, 22]. Therefore, it is of great significance to actively explore a more reasonable, safe and effective treatment for GLC. CO_2 laser gasifies the lesional tissue through a high-energy thermal effect generated by laser beam, which does not easily damage the nearby and deep tissue. High-power microscope during the operation can improve the definition and help remove the diseased tissue more thoroughly [23]. Low-temperature radiofrequency ablation can cut laryngeal lesions from different angles by bending the cutter head, and the clearance range of lesions is wide. This operation only works on the surface layer of tissues. During the working period, the temperature of the plasma cutter head is 40-70°C, which is low-temperature decomposition. Therefore, the trauma is less, which is conducive to the postoperative recovery [24].

In the present study, after therapy, the hospital stay, VAS score and mucosal recovery score of the research group were all lower than those of the control group, and the research group showed a lower total complication rate than the control group. The results suggest that CO_2 laser combined with LPRA can alleviate postoperative pain, speed up postoperative recovery, and reduce postoperative complications. The reasons are as follows: the high heat energy generated by CO_2 laser will burn the nearby tissues, and then carbonize, causing foreign body reaction, affecting granulation tissue formation, which easily leads to scar hyperplasia on the wound and slows down the recovery of vocal cord viscosity. Combination with LPRA can avoid thermal damage to the tissues near the lesion, and promote wound recovery, with less thermal damage to the surrounding tissues, less postoperative pain, and fewer complications. Tang et al. [25] also mentioned that the combination with LPRA can achieve a higher therapeutic effect. However, Zhang et al. [26] have pointed out that because of the relatively low thermal efficiency of low-temperature plasma radiofrequency ablation, there are some limitations in hemostasis during the operation, and it is sometimes necessary to use a high-frequency electrotome to stop bleeding in the case of arterial bleeding, which is a drawback.

Moreover, in this study, the research group had better swallowing function than the control group after surgery, which might be bound up with the fact that CO_2 laser combined with LPRA causes a smaller wound volume, lighter body injury and is more conducive to postoperative recovery. In some studies, both radiotherapy and surgery can contribute to good quality of life, while some studies show that laser surgery

Table 5. Single factor analysis table

	Recurrence group (n=22)	No recurrence group (n=93)	X^2/t	P
Gender			1.765	0.184
Male	17 (77.27)	82 (88.19)		
Female	5 (22.73)	11 (11.83)		
Age (years)	72.18±4.76	67.92±4.94	3.662	<0.001
Differentiation			11.487	0.003
High differentiation	12 (54.54)	79 (84.95)		
Moderate differentiation	6 (27.27)	11 (11.83)		
Low differentiation	4 (18.18)	3 (3.23)		
Disease staging			0.789	0.674
Tis period	7 (31.82)	38 (40.86)		
T1a period	8 (36.36)	29 (31.18)		
T1b period	7 (31.82)	26 (27.96)		
History of smoking			0.529	0.467
Yes	19 (86.36)	66 (79.52)		
No	3 (13.64)	17 (20.48)		
History of drinking			0.471	0.493
Yes	11 (50.00)	39 (41.94)		
No	11 (50.00)	54 (58.06)		
Cumulative anterior commissure			7.766	0.005
Yes	8 (36.36)	11 (11.83)		
No	14 (63.64)	82 (88.17)		
Cumulative vocal cord process			8.253	0.004
Yes	6 (27.27)	6 (6.45)		
No	16 (72.73)	87 (93.55)		

Table 6. Multivariate analysis table

	B	S.E,	Wals	Sig.	Exp (B)	95% C.I. for EXP(B)	
						lower limit	upper limit
Age	0.153	0.057	7.24	0.007	1.166	1.043	1.303
Differentiation	-0.948	0.424	5.002	0.025	0.387	0.169	0.889
Cumulative anterior commissure	1.297	0.619	4.396	0.036	3.658	1.088	12.293

could contribute to good quality of life [27]. Acoustic index is a crucial index to evaluate the postoperative recovery of patients with laryngeal cancer. In this study, after therapy, the fundamental frequency, fundamental jitter and shimmer in the research group were all lower than those in the control group, and the HNR in the research group was higher than that in the control group, indicating that the combined operation could improve the patient's voice. The reason is that the combination of two surgical methods can remove the residual tumour tissue in the body to the greatest extent, while preserving the laryngeal function of the patient, thus improving the acoustic indexes. Finally, we followed up the two groups for 5 years, and found no significant difference in the 5-year recurrence rate between them, which indicated that both treatment schemes had a good prognosis. Independent risk factors for 5-year relapse in patients were analyzed by multiple logistic regression. Multivariate logistic regression analysis identified higher age, lower differentiation, and presence of a cumulative anterior commissure as independent risk factors for recurrence. Attention should therefore be paid to high-risk patients in whom these risk factors are present.

This study has some limitations. First, the subjects enrolled into this study were mainly elderly and early stage patients, and the most suit-

able treatment regimen for laryngeal cancer patients with more severe disease progression needs further exploration. Second, we hope to explore the indicators of predictive value for patients' prognosis in future research. To sum up, CO_2 laser combined with LPRA can provide relatively high clinical efficacy for early GLC in the elderly, after which patients' swallowing function and vocal function recover quickly, but the long-term prognosis of single treatment and combined treatment have little difference.

Disclosure of conflict of interest

None.

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