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ORIGINAL ARTICLE

Research on the efficacy of laryngendoscopic low-temperature plasma ablation on early glottic cancer

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Summary

Purpose: *To evaluate the efficacy and safety of self-retaining laryngendoscope-assisted low-temperature plasma ablation (LTPA) in the treatment of patients with early glottic cancer.*

Methods: *The clinical data of 84 patients with early glottic cancer treated in our department from May 2013 to May 2016 were collected. All patients were divided into the Plasma group (n=42, treated with the laryngendoscopic LTPA) and the Laryngofissure group (n=42, treated with traditional laryngofissure). The operation conditions, pain and cough visual analogue scale (VAS) scores, postoperative complications, mucosal recovery and voice recovery indexes were compared between the two groups, the postoperative recurrence rate was recorded, and the patients were followed up for tumor recurrence and survival.*

Results: *In the Plasma group, the operation time was significantly shorter than that in the Laryngofissure group, the amount of intraoperative bleeding was significantly less than that in the Laryngofissure group (p<0.001), and the postoperative hospitalization time was also significantly shorter than that in the Laryngofissure group. The postoperative pain and cough VAS scores in the Plasma group were obviously lower than those in the Laryngofissure group. The proportion of smooth vocal mucosa after operation in the Plasma group was evidently higher than that in the Laryngofissure group. In Plasma group, the voice parameters Jitter, Shimmer and harmonic to noise ratio (HNR) were all remarkably superior to those in the Laryngofissure group. The overall survival (OS) and progression-free survival (PFS) had no statistically significant differences between the two groups according to the log-rank test.*

Conclusions: *Self-retaining laryngendoscope-assisted LTPA has definite efficacy in the treatment of early glottic cancer, after which the recurrence rate and survival rate are similar to those after open laryngofissure, but LTPA is characterized by short operation time, less postoperative bleeding, quick recovery of patients and better voice recovery.*

Key words: *early glottic cancer, low-temperature plasma ablation, laryngofissure, efficacy*

Introduction

Due to smoking and environmental pollution, there are nearly 180,000 new cases of laryngeal cancer around the world every year, and the morbidity rate of laryngeal cancer is about 26.4/100,000 in China, of which 90% are males [1,2]. Primary laryngeal cancer dominates, in which glottic cancer accounts for about 60%, mainly manifested as cough, hoarseness, etc. Aphonia can occur in severe cases of hoarseness, and with the development of tumor in the late stage, secondary dyspnea, dysexpectoration, difficulty in swallowing and radiating earache will occur, ultimately leading to massive hemorrhage, malignant lesions and aspiration pneumonia [3,4]. Clinical studies have confirmed that the early diagnosis and treatment of glottic cancer can generally preserve the laryngeal phonic function, reduce the postoperative complications, and improve the survival rate of patients [5].

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Radiotherapy, open surgery and transoral microsurgery are three kinds of conventional therapies for early laryngeal cancer. Laryngofissure is a classical surgery for the treatment of early glottic cancer, but it is less tolerable in patients due to its larger trauma [6]. In recent years, self-retaining laryngendoscope-assisted low-temperature plasma ablation (LTPA) applied in the treatment of early laryngeal cancer can not only eliminate the blind zone and radically excise the laryngeal lesions, but also preserve the laryngeal function as far as possible and avoid the adverse reactions in open surgery and radiotherapy, and its minimally-invasive, convenient and efficient characteristics have been recognized by doctors and patients, making it a beneficial complement to the therapeutic regimen of early laryngeal cancer [7,8]. In the present study, the efficacy and safety were compared between laryngendoscopic LTPA and traditional laryngofissure in the treatment of early glottic cancer, which is expected to provide a more scientific basis for the development of rational therapeutic regimens.

Methods

General data

A total of 84 patients with early glottic cancer treated in our hospital from May 2013 to May 2016 were studied, including 68 males and 16 females aged 32-71 years old, and they were all diagnosed *via* preoperative or intraoperative pathological examination. Exclusion criteria: patients with cervical lymph node metastasis or distant metastasis found *via* preoperative routine examination, electronic laryngoscopy and neck enhanced CT, those with a history of radiotherapy or chemotherapy before operation, those with severe abnormality of blood biochemical indexes, severe systemic diseases or a history of other cancers. In terms of the tumor-node-metastasis (TNM) stage, there were Seven cases in Tis stage, 63 cases in T1a stage, and 14 cases in T1b stage. Seven cases had low differentiation, 20 cases had moderate differentiation, and 57 cases had high differentiation. Among the 84 patients, 42 cases were treated with self-retaining laryngendoscope-assisted LTPA, while 42 cases were treated with traditional laryngofissure (Table 1). No statistically significant differences were found in age, gender, course of disease, history of smoking and drinking, T stage and grade of tumor differentiation between the two groups ($p>0.05$), and they were comparable. All patients enrolled adhered to the *Declaration of Helsinki*, and signed the informed consent form. This study was approved by the Ethics Committee of General Hospital of Xinjiang Military Command.

Treatment methods

Plasma group: After satisfactory general anesthesia in supine position, the self-retaining laryngoscope was inserted orally, and ablation and hemostasis were performed using the plasma radiometer (Coblator II, USA) and laryngeal plasma cutter (JXHZ G33E42, Beijing, China) under monitoring of Storz 0° or 30° high-definition endoscope. The power of ablation of plasma system was routinely adjusted to Gear 7, and the power of electric coagulation hemostasis was adjusted to Gear 3. The operation and time of ablation and hemostasis were controlled using the foot switch. The range and depth of tumor resection were as follows: T1: According to the tumor site, the tumor was lifted up towards the midline using the nipper, and then the tumor and part of the vocal cords were excised at about 3 mm outside the tumor base using the plasma cutter. T2: The ventricular band and laryngeal ventricle on the affected side were excised till the laminae of thyroid cartilage, and the entire vocal cords were excised downward along the

Table 1. Demographics and general clinical data of all studied patients

Parameters	*Plasma group (n=42) n (%)*	*Laryngofissure group (n=42) n (%)*	*p value*
Gender (Male/Female)	36/6	32/10	0.405
Age (years)	54.93±9.82	56.04±9.58	0.601
Course of the disease (months)	3.5±1.7	3.8±2.1	0.474
Smoking	34 (81.0)	37 (88.1)	0.548
Alcohol	23 (54.8)	29 (69.0)	0.261
TNM staging			0.752
Tis	3 (7.1)	4 (9.5)	
T1a	33 (78.6)	30 (71.4)	
T1b	6 (14.3)	8 (19.1)	
Histologic grade of differentiation			0.501
High	31 (73.8)	26 (61.9)	
Moderate	8 (19.0)	12 (28.6)	
Poor	3 (7.2)	4 (9.5)	

TNM: Tumor, lymph node, metastasis

perichondrium, including the anterior commissure. Part of the arytenoid cartilage on the affected side and the contralateral anterior vocal cords were excised if necessary. During operation, the plasma cutter was used for excision at 3 mm outside the tumor edge, rather than entering the tumor, so that the whole tumor could be excised. After that, the tissues at the incisional edge in each direction were taken and sent for frozen pathology. If tumor cells were found, further excision should be done. Then the tissues at the incisional edge were taken and sent for frozen pathology again, until tumor cells were negative. After thorough hemostasis, chlorotetracycline eye ointment was applied on the wound. After resuscitation, the catheter was withdrawn without tracheotomy and nasal feeding. After the operation, the patients were given aerosol inhalation and antibiotic therapy for 3-5 days, and were forbidden from speaking for 1 week.

Laryngofissure group: After satisfactory general anesthesia in supine position, a 2.5 cm-long longitudinal incision was made at the midline of the anterior neck, the skin and subcutaneous tissues were cut open, and the band muscles of the anterior neck were separated without hurting the isthmus of the thyroid gland. After the trachea was fully exposed, the second or third tracheal ring was incised, and a tracheal cannula (about 0.7 mm) was placed, fixed at the posterior neck and connected to a ventilator. A vertical midline incision was made on the neck, upward to the thyroid cartilage notch and downward to the superior margin of the cricoid cartilage, to fully expose the thyroid cartilage, and part of the laminae of the thyroid cartilage was excised. The outer membrane was peeled off using sharp knife at the superior thyroid cartilage notch, and a curved incision was made into the laryngeal ventricle through the anterior commissure to check the tumor infiltration. Then, the lesion tissues were completely removed, and the excision range was expanded till about 5 mm away from the edge of normal tissues. After thorough hemostasis, the surgical cavity was cleaned, the outer membrane of the thyroid cartilage and the residual mucosa in the laryngeal ventricle were taken to repair and seal the laryngeal cavity, and the anterior cervical muscle group, subcutaneous tissues and skin were sutured layer by layer, followed by pressure dressing of the incision.

Observation indexes

During operation, the operation time, amount of bleeding and hospitalization time were recorded. The incidence of complications such as wound infection, dysphagia, difficulty in swallowing and pharyngeal fistula was also recorded. After discharge, the patients were followed up by telephone or clinic visits to know whether there was discomfort in eating and breathing. After operation, electronic laryngoscopy was performed regularly to observe the range of surgical excision and recovery of wound mucosa. Within 3 days after operation, the pain and cough scores were assessed based on the visual analogue scale (VAS), as follows: A 10 cm-long horizontal line was drawn, 0 cm at one end (no pain or cough) and 10 cm at the other end (severe pain or cough), and 1-9 cm in the middle indicated mild to severe condition.

Voice analysis: The patient's voice was analyzed using the Praat software under the ambient noise of less than 40 dB. The patient made the sound for more than 4 s with the mouth at 20 cm away from the microphone. Then, 3 s of stable voice was taken to analyze and record the fundamental frequency (F_0), Jitter, Shimmer and harmonic to noise ratio (HNR).

The patient's survival was recorded *via* follow-up until May 2019. Electronic laryngoscopy was performed every month within 1 year after discharge, and then systematic examination was performed once every 3 months to evaluate the recovery of patient's laryngeal function, presence or absence of recurrence and survival condition.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Measurement data were expressed as mean ± standard deviation, and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. $P<0.05$ suggested statistically significant difference. The survival curves were plotted using the Kaplan-Meier method, and log-rank test was used to compare survival between the two groups. $P<0.05$ suggested statistically significant difference.

Results

Comparison of perioperative indexes

In the Plasma group, the operation time was significantly shorter than that in the Laryngofissure group (13.59±6.43 min *vs.* 98.28±10.87 min, p<0.001), the amount of intraoperative bleeding was significantly less than that in the Laryngofissure group (9.39±9.64 mL *vs.* 95.41±28.16 mL, p<0.001), and the postoperative hospitalization time was also significantly shorter than that in the Laryngofissure group (6.9±0.9 d *vs.* 11.7±2.3 d, p<0.001). The postoperative pain and cough VAS scores in the Plasma group were obviously lower than those in the Laryngofissure group (2.62±1.12 points *vs.* 4.70±1.41 points, p<0.001, 3.51±0.80 points *vs.* 5.83±1.30 points, p<0.001). All patients underwent successful operation, no tumor cells were found at the incisal edge during operation, and the whole tumors were excised at one time, without massive hemorrhage after operation. The proportion of smooth vocal mucosa after operation in the Plasma group (90.5%, 38/42) was evidently higher than that in the Laryngofissure group (76.2%, 32/42), showing a statistically significant difference (p=0.047). Besides, the postoperative complications in both groups mainly included wound infection, cough, difficulty in swallowing, dyspnea and pharyngeal fistula (Table 2), and their incidence rates in the Laryngofissure group were

lower than those in the Plasma group, but without statistically significant differences (p>0.05). During the postoperative follow-up, obvious and persistent hyperplasia of granulation tissues occurred at the wound of the laryngeal cavity in a total of 16 patients generally at 3 months after operation, including 7 cases in the Plasma group and 9 cases in the Laryngofissure group, and the granulation gradually subsided after 3-6 months. The incidence of hyperplasia of granulation tissues had no statistically significant difference between the two groups (p=0.132).

Comparison of voice recovery between the two groups

There were no statistically significant differences in the voice parameters between the two groups before operation (p>0.05). At 1 year after operation, the voice tended to be stable in all patients, and Jitter, Shimmer and HNR were superior to those before operation in both groups (p<0.05), while F_0 had no statistically significant difference compared with that before operation (p>0.05). Besides, in the Plasma group, the voice parameters Jitter, Shimmer and HNR at 1 year after operation were all remarkably better than those in the Laryngofissure group (p=0.018, p=0.007, p=0.009) (Table 3).

Follow-up results of patient's survival

All patients were followed up for 12-50 months, and they were regularly examined *via* electronic laryngoscopy in the clinic. If white surface membrane or unsmooth neoplasms were found, aerosol inhalation of budesonide was performed for 1-2 weeks. If not improved, tissues were taken for biopsy, and reoperation was conducted if laryngeal cancer was confirmed. In the Plasma group, there were 3 deaths within 3 years, including 1 case due

Table 2. Comparison of perioperative data and complications of the studied patients in two different groups

Parameters	*Plasma group (n=42)*	*Laryngofissure group (n=42)*	*p value*
Operation time (min)	13.59±6.43	98.28±10.87	0.001
Blood loss (ml)	9.39±9.64	95.41±28.16	0.001
Hospital stay after surgery (days)	6.9±0.9	11.7±2.3	0.001
Pain VAS score	2.62±1.12	4.70±1.41	0.001
Cough VAS score	3.51±0.80	5.83±1.30	0.001
Complications, n (%)			
Incision infection	0 (0)	3 (7.1)	0.078
Hemoptysis	1 (2.4)	4 (9.5)	0.167
Dysphagia	1 (2.4)	4 (9.5)	0.167
Dyspnea	2 (4.8)	6 (14.3)	0.137
Pharyngeal fistula	0 (0)	2 (4.8)	0.152
Granulation tissue hyperplasia	4 (9.5)	9 (21.4)	0.132

VAS: visual analog scale

Table 3. Comparison of voice parameters before and after surgery of patients in the two studied groups

Parameters	*Plasma group (n=42)*	*Laryngofissure group (n=42)*	*p value*
F0 (Hz), mean±SD			
Pretreatment	143.53±15.56	139.79±14.47	0.257
Posttreatment	144.64±16.17	140.46±18.91	0.279
Jitter, mean±SD			
Pretreatment	1.25±0.27	1.22±0.29	0.625
Posttreatment	1.03±0.18	0.93±0.20	0.018
Shimmer, mean±SD			
Pretreatment	6.13±1.35	6.06±1.14	0.798
Posttreatment	4.62±1.66	5.53±1.36	0.007
HNR (dB), mean±SD			
Pretreatment	14.59±3.87	14.89±3.03	0.694
Posttreatment	18.83±3.63	16.68±3.77	0.009

HNR: Harmonic to noise ratio

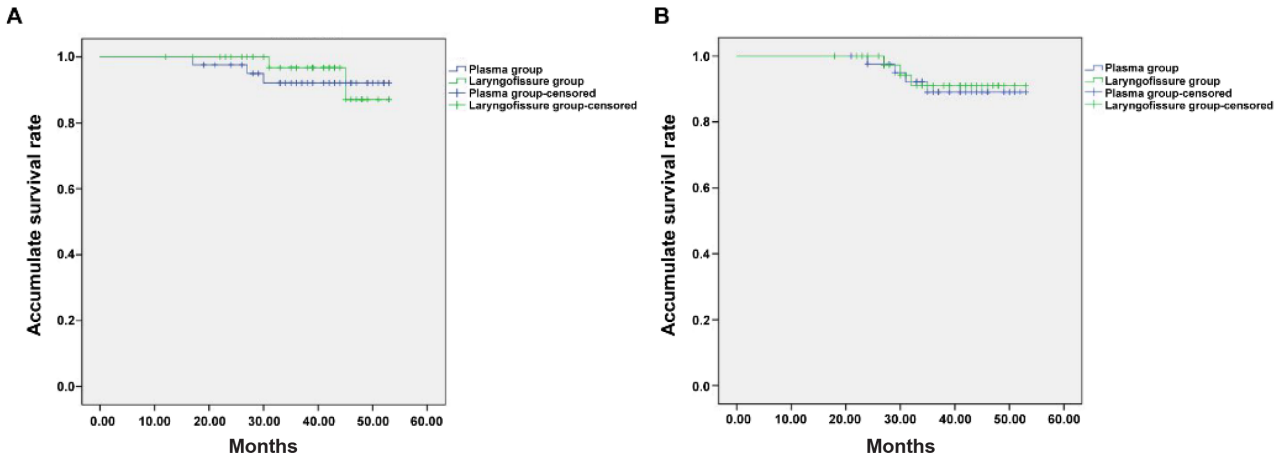

Figure 1. Kaplan-Meier survival curves of the studied patients. The difference of overall survival rate **(A)** and progression-free survival rate **(B)** of patients in the Plasma group and the Laryngofissure group had no statistical significance (p=0.703, p=0.814).

to cerebral infarction, 1 case due to myocardial infarction and 1 case due to traffic accident, with 3-year overall survival (OS) 92.9%. In the Laryngofissure group, there were 2 deaths within 3 years, including 1 case due to rupture of aneurysm and 1 case due to unknown cause, with 3-year OS 95.2%. In the Plasma group, local recurrence occurred in 4 cases at 24, 29, 31 and 35 months after treatment, and the 3-year progression-free survival (PFS) was 90.5%. In the Laryngofissure group, local recurrence occurred in 3 cases at 27, 30 and 32 months after treatment, with 3-year PFS 92.9%. The Kaplan-Meier survival curves of patients are shown in Figure 1. According to the log-rank test, OS and PFS had no statistically significant differences between the two groups (p=0.703, p=0.814).

Discussion

Glottic cancer is a common primary laryngeal cancer. The principle of treatment of patients with early glottic cancer is to radically excise the lesions and preserve the laryngeal function to the greatest extent, thus reducing the impact on living quality of patients [9,10]. According to the latest guidance of the National Comprehensive Cancer Network (NCCN2017.V2), it is recommended that Tis-stage glottic cancer be treated with endoscopic surgery, and T1 and T2-stage glottic cancer be treated with open partial laryngectomy, radiotherapy or endoscopic surgery based on the actual situation, without priority option [11]. Laryngofissure, a common surgical treatment, has certain efficacy, but the trachea needs cutting open, with relatively large trauma and more postoperative complications.

In recent years, a variety of minimally invasive therapies have been adopted in the treatment of early glottic cancer. At present, CO_2 laser has been widely used, and it obtains a better curative effect [12]. It is reported in the literature that in the treatment of T1-stage glottic cancer with transoral laser microsurgery, the 5-year local control rate is 83-95%, the 5-year laryngeal salvage rate is 94-98%, the 5-year disease-related survival rate is 97-100%, and the 5-year OS is 70-95%, showing no obvious differences compared with open surgery [13]. However, the high-temperature laser cutting will easily cause irreversible burns in the airway, and the anterior segment of vocal cords cannot be excised due to the inability of the straight line to turn [14]. LTPA is a new minimally invasive technique developed in recent years, and its EIC7070 cutter head is flexible and can be curved in a large range during self-retaining laryngendoscope-assisted or self-retaining laryngendoscope+nasal endoscope-assisted laryngeal surgery. Moreover, the lesions can be excised at different sites through different angles, without the risk of burning and ablating the perichondrium [15]. The principle of LTPA is that the thin plasma layer is formed through saline medium between plasma electrode and tissue, and the ions in the layer are accelerated by the electric field and transfer the energy to tissues to open the molecular bonds under low temperature, so that the target tissues are decomposed into simple carbohydrates and oxides, thereby cutting and ablating lesion tissues under low temperature [16]. LTPA mainly works on the surface of tissues without damaging the deep tissues, so it is characterized by small surgical trauma and quick postoperative recovery. Besides, the surface tissue temperature is 40-70°C during working of the plasma cutter for low-temperature molecular decomposition, so the damage to the surrounding tissues is minimized [17].

In this study, it was found that compared with traditional laryngofissure, LTPA had significantly shortened operation time (13.59 min on average), less intraoperative bleeding (9.39 mL on average) and a significantly lower incidence rate of postoperative bleeding (0 case). After LTPA, the patient's reaction was mild, the recovery time was short and all patients could take care of themselves immediately, with postoperative hospitalization time of 6.9 days on average. In addition, the tracheotomy and laryngofissure were avoided, so the incidence of postoperative pain and cough was obviously reduced, and all patients could speak and eat normally on the same day after operation. After LTPA, the voice recovery was better and there was no increase in the complications. According to the log-rank test, OS and PFS had no statistically significant differences between the Plasma and the Laryngofissure group (p=0.703, p=0.814).

However, LTPA also has its deficiencies: The cutter head is large, because it combines both washing and absorbing functions, and the endoscope and microscopic instruments will interfere with each other during operation, so high surgical skills are required. The excision is not accurate enough, it is difficult to determine the safety boundary during operation, and linear cutting like laser cannot be realized. After operation, the wound is large with rough surface, and hyperplasia of granulation tissues occurs easily, affecting the postoperative voice function [18,19]. In addition, it was found in this study that the voice recovery in the Plasma group at 6 months after operation was obviously superior to that in the Laryngofissure group ($p<0.05$), consistent with the literature reports, suggesting that protecting the laryngeal cartilage support from damage is beneficial to the postoperative voice recovery [20,21].

There are still many shortcomings in this study. For example, the sample size was small, and the evaluation criteria and follow-up content were not comprehensive enough. In the future, further large-sample multi-center randomized controlled trials are needed to verify the conclusions drawn in this study, which is expected to provide a stronger basis for selecting the therapeutic regimen for such patients.

Conclusions

Self-retaining laryngendoscope-assisted LTPA has definite efficacy in the treatment of early glottic cancer, after which the recurrence rate and survival rate are similar to those after open laryngofissure, but LTPA is characterized by short operation time, less postoperative bleeding, quick recovery of patients and better voice recovery.

Conflict of interests

The authors declare no conflict of interests.

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