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ORIGINAL ARTICLE

Postoperative efficacy of low-temperature plasma radiofrequency ablation in elderly patients with laryngeal carcinoma and its influences on tumor markers and COX-2 and VEGF expressions in laryngeal carcinoma tissues

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Summary

Purpose: *To observe the postoperative efficacy of low-temperature plasma radiofrequency ablation in treating elderly patients with laryngeal carcinoma and its influence on the tumor markers, cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF) expressions in laryngeal carcinoma tissues.*

Methods: *A total of 50 elderly laryngeal carcinoma patients undergoing low-temperature plasma radiofrequency ablation in our hospital from January 2015 to January 2018 were enrolled as observation group, and another 50 elderly laryngeal carcinoma patients receiving conventional surgical treatment were enrolled as control group. At the end of the treatment course, the efficacy and postoperative complications in the patients were observed, the operation time and pain visual analogue scale (VAS) and mucosal recovery scores were recorded.*

Results: *The efficacy in the study group was obviously higher than in the control group ($p<0.05$), and the cases of postoperative complications declined evidently in the study group ($p<0.05$). Moreover, the study group exhibited distinctly shorter operation time and lower VAS pain and mucosal recovery scores than the control group ($p<0.05$). The levels of the tumor markers CA125, CEA and CA19.9 and the expression levels of COX-2 and VEGF in laryngeal carcinoma tissues were substantially lowered in the study group ($p<0.05$).*

Conclusions: *Low-temperature plasma radiofrequency ablation has better efficacy in treating elderly laryngeal carcinoma patients, with few postoperative complications, and decreased expression levels of postoperative tumor markers as well as COX-2 and VEGF in laryngeal carcinoma tissues, and it offers better overall, therefore it is worth trying it in clinical practice. and notable application value.*

Key words: *low-temperature plasma radiofrequency ablation, laryngeal carcinoma in the elderly, efficacy, tumor markers, COX-2, VEGF*

Introduction

Laryngeal carcinoma is the second most common malignancy in the head and neck, and about 3,600 people die of this disease every year, accounting for approximately 3% of newly diagnosed cases of malignant tumors worldwide annually. Squamous cell carcinoma represents 90% of malignant laryngeal tumors, and laryngeal carcinoma and its treatment tend to cause laryngeal function impairment, resulting in obvious problems in communication, breathing and swallowing. The choice of treatment depends on disease site and stage [1]. Five-year survival rate ranges from 36% to 83%, and patients often experience notable complications related to disease treatments, including different degrees of hoarseness or aphonia, dysphagia, dry mouth, aspiration and neck masses. Prior to

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confirming the diagnosis of disease, endoscopy is performed for the suspected laryngeal carcinoma patients, so as to directly observe tumors [2]. Although endoscopy is the most efficient method to evaluate the mucosal range of tumors and activity of spinal cord, submucosal extent and adjacent structures need to be pinpointed through cross-sectional imaging which certainly provides important information on lymph node metastasis, systemic metastasis, synchronous tumors and recurrent disease [3]. Accurate staging is vital for selecting the most suitable therapeutic schemes and predicating prognosis. The efficacy in the treatment of laryngeal carcinoma varies greatly among surgery, radiotherapy and chemotherapy. Any factors that cause inaccurate staging will affect the ability of neck surgeons to choose the most appropriate treatment approach and influence the final therapeutic effect. Additionally, such factors are obstacles for clinicians to provide advice for the patients and guide them to choose the optimal treatment method [4,5]. Currently, low-temperature plasma radiofrequency ablation has been widely applied to the treatment of cancers for its merits, including exact efficacy, small invasiveness, favorable repeatability, high safety and short hospital stay. Back et al [6] reported that compared with conventional tonsillectomy, low-temperature radiofrequency ablation exhibits shorter operation time and less intraoperative bleeding. Low-temperature sublingual radiofrequency ablation is considered as an acceptable way to treat supine position-related obstructive sleep apnea [7]. The advantages of low-temperature radiofrequency ablation in treating laryngeal cyst include clear surgical field, little bleeding, short operation time and low recurrence rate [8]. Liu et al [9,10] found that during the treatment of 14 cases of basilingual cyst with low-temperature radiofrequency ablation, the operative time was 5-10 min, with intraoperative bleeding volume of 1-5 mL. All these studies demonstrate that low-temperature radiofrequency ablation has favorable efficacy in treating various cancers.

Cyclooxygenase (COX) isoenzyme COX-2 catalyzes arachidonic acid to synthesize prostaglandins (PGs), and it is regarded as an inducible subtype that is mainly detected in inflammatory sites and collaborates with growth factors, tumor promoters, hormones and bacterial endotoxins to participate in the production of prostaglandin E2 (PGE2) [11]. The experimental research on humans and mice suggested that as the early event of ultraviolet-induced skin cancer, the increase in COX-2 expression results in increased local PGE2 expression [12]. COX-2 overexpression has been corroborated in male actinic keratosis and squamous cell carcinoma [13]. Moreover, the activities of COX-2 receptors have been proven to be able to stimulate the growth of tumors [14], in which COX receptors can serve as interesting potential concentrated therapeutic targets to inhibit the inflammation around the ablation site [15]. It has been confirmed that vascular endothelial growth factor (VEGF) can regulate hypertrophic remodeling of growth plate cartilage, cancer and vascular invasion [16]. Serum carbohydrate antigen (CA) 19.9 is used to act as a tumor marker applied to the diagnosis of pancreatic cancer, whereas it is often employed to observe the efficacy in treating laryngeal carcinoma and ovarian cancer in recent years. Serum carcinoembryonic antigen (CEA) is a widely distributed tumor marker, and CA125 is highly expressed in cancer tissues. The test of the above three tumor markers in laryngeal carcinoma has an indicative implication [17,18].

The present study enrolled elderly laryngeal carcinoma patients undergoing low-temperature plasma radiofrequency ablation and those receiving conventional surgical treatment as the subjects to observe the efficacy and postoperative complications in them, record the operation time and visual analogue scale (VAS) pain and mucosal recovery scores, determine the levels of the tumor markers and detect the expressions of COX-2 and VEGF in laryngeal carcinoma tissues in the two groups using immunohistochemistry and quantitative polymerase chain reaction (qPCR), hoping to verify the postoperative efficacy of low-temperature plasma radiofrequency ablation in treating elderly laryngeal carcinoma patients, postoperative complications and overall effect and provide a theoretical basis and experimental foundation for the development and progression of laryngeal carcinoma in the elderly.

Methods

General information

A total of 50 elderly patients treated with low-temperature plasma radiofrequency ablation in our hospital from January 2015 to January 2018 comprised the study group, and another 50 patients undergoing conventional surgery comprised the control group. The subsequent study was performed after signed informed consent was obtained from the patients. There were 58 males and 42 females, aged 60-85 years old (mean 64±11), with weight of 43-80 kg (mean 56±10).

Inclusion criteria: 1) patients definitely diagnosed with laryngeal carcinoma through ultrasonography and CT scan; 2) those who had no other severe complications before surgery; 3) those with clinical manifestations such as hoarseness and laryngalgia; 4) those who were first pathologically diagnosed with laryngeal carcinoma; 5) those with good physical status; 6) those who had no anesthesia contraindications; 7) those who were toler-

ant to surgery; and 8) those who did not undergo low-temperature plasma radiofrequency ablation previously.

Exclusion criteria: 1) patients with nervous system diseases; 2) those with severe cardiovascular or cerebrovascular diseases, such as coronary heart disease or heart valve disease; or 3) those suffering from severe secondary infection complicated with severe abnormalities in liver or kidney functions. The clinical research scheme, including all the detection items in experiments, was approved by the Ethics Committee of our hospital. There was no statistically significant difference in the general clinical information between the two groups of patients.

Treatment methods

Study group: The glottis was fully exposed using Unitec low-temperature plasma operation system and a self-retaining laryngoscope, and the patients were subjected to endotracheal intubation and general anesthesia in supine position. Then the tumor was raised using fiber clamps, ablated with a low-temperature plasma cutter with the extent expanded to 3-5 mm away from the edge of the lesion and close to the vocal cord, and the vocal ligament was protected. Following excision of masses, local tissues were taken from the safety margin for rapid pathological examination, and the cancer cells at the safety margin should be negative, or the excision extent was further expanded. With the trachea not fully cut open, conventional anti-infection was performed postoperatively combined with voice rest for 2 weeks.

Control group: The patients underwent tracheotomy under local anesthesia, and then they received general anesthesia in supine position. After a T-shaped incision was made at the median neck, subcutaneous tissues were successively separated, and both epiglottic edges were cut open and stripped away from the thyroid gorge. Subsequently, the thyroid cartilage plate was cut open to expose the pharyngolaryngeal cavity and confirm the tumor position and infiltration. Finally, the tumor was excised using an electric knife and cauterized at 0.5 cm beyond the excision margin, and the throat wound was fixed, repaired and sutured. The postoperative treatment was the same as that in the study group.

Evaluation of postoperative efficacy

The efficacy in the two groups of patients was observed and compared after operation according to the international efficacy judgment criteria: complete disappearance of patients' clinical symptoms is defined as cure, mitigation of patients' clinical symptoms as effective, and no obvious improvement in patients' clinical symptoms or aggravation as ineffective.

Operation time, VAS pain and mucosal recovery scores

The operation time was recorded in the two groups, and the pain of patients was scored based on VAS, with the pain gradually aggravated from 0 to 10 points. Moreover, mucosal recovery was evaluated according to the following criteria: 1 point: wound pseudomembranes are detached within 7 d after operation and the mucosa is smooth; 2 points: wound pseudomembranes are detached 8-14 d after operation; 3 points: wound pseudomembranes are detached 15-21 d after operation; 4 points: wound pseudomembranes are detached 22-28 d after operation; and 5 points: wound pseudomembranes are detached over 28 d after operation. The above results were recorded in detail and analyzed.

Observation of postoperative complications

The postoperative complications in the two groups of patients were observed and recorded. The incidence of complications such as incision infection and pharyngeal leakage was recorded when the patients were hospitalized, and after discharge, whether the patients had eating and breathing discomforts were confirmed by phone call or outpatient follow-up. Finally, the results recorded in detail were analyzed.

Determination of levels of tumor markers CA125, CEA and CA19.9

The levels of the tumor markers CA125, CEA and CA19.9 were determined using chemiluminescence immunoassay. Specifically, they were measured using Cobas 2000 automatic immunoassay analyzer according to the set running program and the instructions of the kit, and the value of each marker was recorded in detail. Finally, the degree of the changes in these tumor markers was calculated and analyzed.

Immunohistochemistry

After being removed intraoperatively, the tissues surrounding laryngeal carcinoma were soaked in formalin for 7 d and then flushed using running water overnight, dehydrated in gradient alcohol, immersed and embedded in paraffin and sectioned, followed by de-paraffinization and hydration using ethanol. Subsequently, the sections were subjected to antigen retrieval, cooled naturally and washed with phosphate buffer saline (PBS) (pH=7.4) for 5 min×3 times. The resulting sections were blocked in 3% bovine serum albumin (BSA) at room temperature for 30 min, and incubated with primary antibodies at 4°C overnight and with the horseradish peroxidase (HRP)-labeled secondary antibodies for 1 h, followed by diaminobenzidine (DAB) color development and counter-staining with hematoxylin for about 3 min. Afterwards, the sections were dehydrated, transparentized in absolute alcohol I and II and xylene, respectively, each for 5 min, and sealed in neutral resin. Finally, they were photographed and observed under a microscope.

Detection of related gene expression via quantitative real-time polymerase chain reaction (qRT-PCR)

The specific steps were as follows: (1) Under low-temperature conditions, 150 mg of sterile tissues around laryngeal carcinoma were taken carefully, weighed accurately, added with RIPA lysis buffer and homogenized, and total RNA was extracted. After that, the purity and concentration of the RNAs were determined eligible; (2) the messenger RNA (mRNA) was reversely transcribed into complementary deoxyribonucleic acids (cDNAs) with the amplification system (20 μL) comprising 2 μL of cDNAs, 10 μL of qPCR mix, 2 μL of primers and 6 μL of

ddH_2O for 40 cycles, and stored in a refrigerator at -80°C; (3) Subsequently, PCR amplification was performed under the following conditions: pre-denaturation at 95°C for 2 min and reaction at 94°C for 20 s, 60°C for 20 s and 72°C for 30 s for 40 cycles. The primer sequences of the target genes and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were designed based on the sequences from the GenBank, and the expression levels of the target genes were measured *via* qRT-PCR. The specific primer sequences are shown in Table 1. The relative expression levels of related genes in the tissues around laryngeal carcinoma in each group were calculated using $2^{-\Delta\Delta Ct}$.

Table 1. RT-PCR primer sequences

Target gene	*Primer sequence (5'-3')*
GAPDH	F: TGACTTCAACAGCGACACCCA
	R: CACCCTGTTGCTGTAGCCAAA
COX-2	F: GTCTGATGATGTATGCCACAATCTG
	R: GATGCCAGTGATAGAGGGTGTTAAA
VEGF	F: CAGTTACGGTCTGTGTCCAGTGTAG
	R: CGACACACATGGAGGTTTAAAGAAG

Statistics

The raw experimental data recorded were processed by SPSS 20.0 (SPSS, Chicago, IL, USA) analysis software, and subjected to multiple comparisons. The experimental results obtained were expressed as mean ± standard deviation (± SD), and $p<0.05$ indicated statistically significant differences. GraphPad Prism 7.0 (La Jolla, CA, USA) was employed to plot histograms. The survival curves were plotted using the Kaplan-Meier method and log-rank test was performed to evaluated statistical differences in survival between groups.

Results

Observed clinical efficacy of patients

As shown in Table 2, in terms of postoperative clinical efficacy, the total effective rate was 94% in the study group and 70% in the control group, and the difference was statistically significant ($p<0.05$), suggesting that the clinical effect of the treatment with low-temperature plasma radiofrequency ablation is favorable.

Table 2. Clinical effect observed

Group	*Cure* *n*	*Effective* *n*	*Ineffective* *n*	*Total effective rate* *n*
Control group	15	20	15	70
Study group	33	14	3	94*

According to the comparison of the postoperative clinical efficacy, there is a statistically significant difference in the total clinical effective rate between study group and control group (94% *vs.* 70%) ($p<0.05$). *$p<0.05$ *vs.* control group.

Table 3. Operation time, VAS pain and mucosal recovery scores (mean±SD)

Group	*Operation time (min)*	*VAS score*	*Mucosal recovery score*
Control group	65±5.5	4±0.5	3.9±0.9
Study group	13±4.5*	2±0.8*	1.9±0.5*

The study group exhibits markedly shorter operation time, lower VAS pain and mucosal recovery scores than the control group. *$p<0.05$ *vs.* control group.

Table 4. Postoperative complications

Group	*Infection*	*Swallowing disorder*	*Breathing disorder*	*Laryngeal leakage*
Control group	3	4	3	2
Study group	0*	1*	1*	0*

There are 12 cases of postoperative complications in the control group and only 2 cases in the study group, and the difference is statistically significant. *$p<0.05$ *vs.* control group.

Table 5. Levels of tumor markers CA125, CEA and CA19.9

Group	*CA125 (U/mL)*	*CA199 (U/mL)*	*CEA (ng/mL)*
Control group	51.9±1.2	78.4±2.0	31.5±1.4
Study group	31.6±2.4*	24.8±2.5*	10.5±1.1*

The levels of CA125, CEA and CA19.9 in the study group are obviously lower than those in the control group. *$p<0.05$ *vs.* control group.

Operation time, VAS pain and mucosal recovery scores

The operation time, VAS pain and mucosal recovery scores of patients in the two groups are shown in Table 3. It was found that the study group exhibited substantially shorter operation time, lower VAS pain and mucosal recovery scores than the control group ($p<0.05$), implying that the patients treated with low-temperature plasma radiofrequency ablation recover well.

Postoperative complications

According to the observation results (Table 4), there were 12 cases of postoperative complications in the control group and only 2 cases in the study group, and the difference was statistically significant ($p<0.05$), suggesting that the treatment with low-temperature plasma radiofrequency ablation has obvious effects, with fewer adverse reactions and postoperative complications.

Levels of tumor markers CA125, CEA and CA19.9

The levels of CA125, CEA and CA19.9 in the study group were obviously lower than those in the control group ($p<0.05$) (Table 5).

Immunohistochemistry results

As shown in Figure 1, the positive expression levels of COX-2 and VEGF in laryngeal carcinoma tissues declined significantly in the study group ($p<0.05$).

Gene detection results

The gene expression levels of COX-2 and VEGF in laryngeal carcinoma tissues were substantially lowered in the study group ($p<0.05$) (Figure 2).

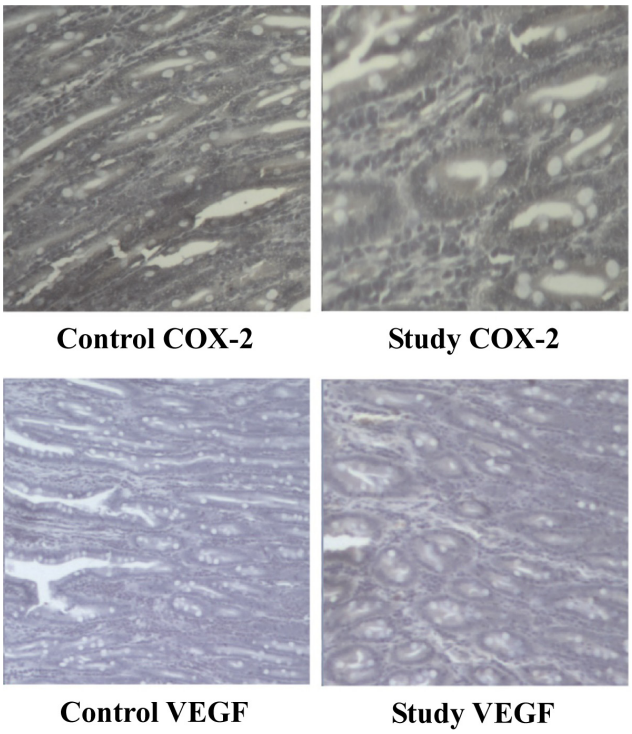

Figure 1. Immunohistochemistry results. The positive expression levels of COX-2 (×20) and VEGF (×20) in laryngeal carcinoma tissues are notably lowered in the study group ($p<0.05$).

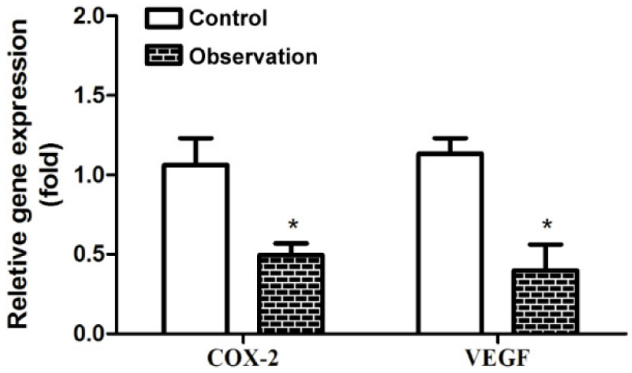

Figure 2. Gene detection results. The gene expression levels of COX-2 and VEGF in laryngeal carcinoma tissues are remarkably decreased in the study group. *$p<0.05$ *vs.* control group.

Discussion

The past three decades have seen huge changes in the treatment of laryngeal carcinoma. Since the survival rate remains relatively constant, attention starts to be paid to the improvement in the preservation and function of organs. Great advances have been achieved in the laryngeal preservation techniques as radiotherapy, concurrent chemotherapy and endoscopy are widely applied to the treatment of laryngeal carcinoma. The above therapeutic schemes have been reported to achieve favorable local control and survival rates, with almost the whole organs preserved [19]. The evolution of the choice between surgical and non-surgical treatments emphasizes the importance of precise cancer stage for the consultation and treatment option of patients, and low-temperature plasma radiofrequency ablation has been extensively employed to the treatment of cancers since it has such advantages as exact efficacy, small invasiveness, favorable repeatability, high safety and short hospital stay. A series of postoperative indicators of laryngeal carcinoma were compared between low-temperature radiofrequency ablation and conventional surgery in this study to corroborate the good efficacy of low-temperature plasma radiofrequency ablation, and it was found that the total clinical effective rate was 94% in the study group and 70% in the control group, with a statistically significant difference, illustrating the favorable

clinical effect of the treatment with low-temperature plasma radiofrequency ablation. According to the results of postoperative complications, there were 12 cases of postoperative complications in the control group and only 2 cases in the study group, and the difference was statistically significant, suggesting that the treatment with low-temperature plasma radiofrequency ablation has an obvious effect and contributes to fewer adverse reactions and postoperative complications. Additionally, it was found that the study group exhibited substantially shortened operation time, reduced VAS pain and mucosal recovery scores compared with the control group, implying that the treatment with low-temperature plasma radiofrequency ablation enables good recovery. Similar to previous studies [20,21], the above study results suggest that low-temperature plasma radiofrequency ablation is worth applying for its better efficacy.

Laryngeal papillomatosis is a rare disease, but it is a potential life-threatening condition that is accompanied by considerable dysfunction, especially airway obstruction and dysphonia. As laryngeal papillomatosis often recurs after treatment, repeated operations are required, which tend to result in laryngeal scars and high expressions of tumor markers in patients as well. For example, serum CA19.9, a tumor marker, is often used to indicate the efficacy of treatment in laryngeal carcinoma in recent years, and serum CEA is a widely distributed tumor marker. Besides, CA125 is highly expressed in cancer tissues [22]. According to the findings in this study, the levels of these three tumor markers in the study group were obviously lower than in the control group. COX-2 has been proven in many studies to play a vital role in the development of tumors and inhibiting its action may benefit the management of tumors [23]. Specific blocking methods, such as siRNA, are also extensively employed to resist the promoting effect of COX-2 on the development of cancer [24]. The immunohistochemistry results in this study revealed that the positive expression levels of COX-2 and VEGF in laryngeal carcinoma tissues declined notably in the study group, and, according to the gene detection results their gene expression levels in laryngeal carcinoma tissues were substantially lowered in the study group. The above findings are similar to those in the previous study [25]. Based on the above experimental results, low-temperature plasma radiofrequency ablation has better efficacy in treating elderly laryngeal carcinoma patients, with few postoperative complications and declining expression levels of postoperative tumor markers and COX-2 and VEGF in laryngeal carcinoma tissues, and it is worth popularization for its better overall effect and notable application value.

Conclusions

In summary, the present study corroborated through a series of experiments that low-temperature plasma radiofrequency ablation can remarkably improve the pathological conditions in the elderly patients with laryngeal carcinoma and reduce the expression of tumor-specific substances, thus achieving a preferable overall effect which can be further verified through subsequent animal experiments. In addition, this study provides a theoretical basis for the prevention and treatment of laryngeal carcinoma and a novel idea for further research.

Conflict of interests

The authors declare no conflict of interests.

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