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ORIGINAL ARTICLE

Efficacy of low-temperature plasma ablation combined with low-dose cisplatin chemotherapy in laryngeal carcinoma patients and its influence on tumor markers

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Summary

Purpose: *We aimed to explore the efficacy of low-temperature plasma ablation (LTPA) combined with low-dose cisplatin chemotherapy in laryngeal carcinoma patients and its influence on tumor markers.*

Methods: *A total of 86 patients with laryngeal carcinoma were selected and divided into control group (n=43, treated with routine chemotherapy) and observation group (n=43, treated with LTPA combined with low-dose cisplatin chemotherapy) according to different treatment methods. The efficacy, immune function, adverse reactions and tumor marker levels were assessed in both groups, and the survival rate of patients was compared between the two groups.*

Results: *The objective response rate and disease control rate in the observation group were significantly higher than those in the control group (p<0.05). After treatment, the observation group had higher levels of cluster of differentiation (CD)3$^+$, CD4$^+$ and CD4$^+$/CD8$^+$ than the control group, and a lower level of CD8$^+$ than the control group (p<0.05). At 4, 8 and 16 weeks after treatment, the levels of serum carcinoembryonic antigen (CEA), carbohydrate antigen 19.9 (CA19.9) and CA125 declined significantly in both groups compared with those before treatment, more obviously in the observation group (p<0.05). Moreover, the incidence rate of postoperative complications in the observation group was evidently lower than that in the control group (p<0.05). According to the 5-year follow-up, the 5-year survival rate in the observation group was significantly higher than that in the control group (p<0.05).*

Conclusions: *LTPA combined with low-dose cisplatin chemotherapy has better efficacy in laryngeal carcinoma patients, and it can improve the patient's immune function with less toxic and side effects, which is worthy of clinical popularization and application.*

Key words: *low-temperature plasma ablation, low-dose cisplatin chemotherapy, laryngeal carcinoma, tumor markers*

Introduction

The larynx is an important organ for phonation, breathing and swallowing. Laryngeal carcinoma is a kind of common malignant tumor [1]. Clinically, early laryngeal carcinoma is mainly treated with surgical resection, while middle-advanced laryngeal carcinoma is treated with chemotherapy and radiotherapy [2]. Due to the special structure and functional characteristics of the larynx, surgical resection will cause serious damage to the phonation function. Therefore, many patients are only willing to receive chemoradiotherapy, but this has great side effects, and the patient's compliance is poor, thus achieving unsatisfactory therapeutic effects [3]. Low-temperature plasma ablation (LTPA) is a minimally-invasive surgical treatment method, which not only retains the patient's laryngeal

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structure and normal phonation function to the greatest extent, but it also obtains significant efficacy, and greatly prolongs the patient's survival [4]. Carcinoembryonic antigen (CEA), carbohydrate antigen 19.9 (CA19.9) and CA125 are used as tumor markers, and they are of great value in the diagnosis and therapeutic evaluation of malignant tumors [5, 6]. In the present study, laryngeal carcinoma patients were treated with LTPA combined with low-dose cisplatin chemotherapy, and the efficacy and changes in tumor markers were assessed, hoping to provide a scientific basis for the treatment of laryngeal carcinoma

Methods

General data

This study was approved by the Ethics Committee of Daqing Oilfield General Hospital. Signed written informed consents were obtained from all participants before the study entry. A total of 86 laryngeal carcinoma patients treated in our hospital from July 2013 to June 2014 were selected. Inclusion criteria: 1) patients meeting the diagnostic criteria for laryngeal carcinoma and definitely diagnosed via CT or MRI [7], 2) those with an estimated survival time >3 months, and 3) those who signed the informed consent. Exclusion criteria: 1) patients with coagulation disorders, or 2) those with obnubilation or communication disorders. The patients enrolled were divided into control group (n=43) and observation group (n=43) using a random number table, and the general data had no statistically significant differences between the two groups (p>0.05) (Table 1).

Treatment methods

In the control group, routine intravenous chemotherapy was performed: Paclitaxel (135 mg/m^2) and cisplatin (100 mg/m^2) were intravenously infused. At 12 h before chemotherapy, 2000 mL of 5% glucose solution was intravenously infused. During chemotherapy, 3000 mL of 0.9% sodium chloride solution was diluted and intravenously infused. At 30 min before administration of paclitaxel, 10 mg of dexamethasone were intravenously injected, 20 mg of diphenhydramine were intramuscularly injected, and 40 mg of cimetidine were also intravenously injected. In the observation group, LTPA combined with low-dose cisplatin chemotherapy was administered: The patients were fasted before operation. Teeth cushion was placed in the oral cavity to protect the premanillary teeth, the lesions were exposed using the corresponding model of laryngoscope, and the clear surgical field was ensured. The tumor was monitored using the endoscope and display system, and the operation was performed using the low-temperature bipolar radiofrequency ablation system (Arthrocare, Andover, MA, USA). Gear 7 was set as the ablation function, and Gear 3 as the hemostasis function. Frozen sections were quickly prepared first for pathological examination. Then, the operation was terminated if negative pathological results were obtained. On the contrary, the whole tumor was resected along 5 mm at the tumor edge if positive results were obtained, and routine antibiotic therapy was given after operation.

Detection of related indexes

At 16 weeks after treatment, 5 mL of fasting venous blood were drawn from patients in both groups, and the serum was separated and extracted. Then the levels of T lymphocyte subsets cluster of differentiation (CD)3$^+$, CD4$^+$, CD8$^+$ and CD4$^+$/CD8$^+$ were detected using a flow cytometer (BD, Franklin Lakes, NJ, USA). Before treatment and at 4, 8 and 16 weeks after treatment, 5 mL of fasting venous blood were collected in both groups, and the serum samples were taken to determine the levels of tumor markers CEA, CA19.9 and CA125 via electrochemiluminescence.

Evaluation criteria for efficacy

The evaluation criteria for efficacy are as follows [8]: complete response (CR): all lesions disappear for ≥4 weeks, partial response (PR): the maximum diameter of tumor declines by ≥50% for ≥4 weeks, stable disease (SD): non-CR and non-PR, and progressive disease (PD): the sum of diameter of target lesions increases by ≥20%, and there new lesions appeared.

Statistics

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing. Measurement data were expressed as mean ± standard deviation, and t-est was performed. Enumeration data were expressed as rate, and x^2 test was performed. P<0.05 suggested statistically significant difference.

Table 1. Comparison of baseline data between the two groups

Item	*Control group (n=43)*	*Observation group (n=43)*	*t/ x²*	*p*
Gender (male/female)	24/19	21/22	0.420	0.517
Age (years)	48-78	46-75		
Mean age (years)	58.74±7.43	58.23±7.56	0.193	0.847
BMI (kg/m^2)	23.08±1.46	23.12±1.48	0.455	0.650
Tumor stage, n (%)				
I-II	23 (53.48)	21 (48.37)	0.186	0.666
III-IV	20 (46.52)	22 (51.63)	0.186	0.666

Results

Comparison of efficacy between the two groups

At 16 weeks after treatment, the objective response rate and disease control rate in the observation group (74.42%, 91.70%) were significantly higher than those in the control group (39.53%, 67.44%), and the differences were statistically significant (p<0.05) (Table 2).

Comparison of T lymphocyte subsets between the two groups

After treatment, the observation group had higher levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ than the control group, and a lower level of $CD8^+$ than the control group (p<0.05) (Table 3).

Adverse reactions in both groups

The total incidence rate of adverse reactions in the observation group was obviously lower than that in the control group (p<0.05) (Table 4).

Changes in levels of serum tumor markers before and after treatment

At 4, 8 and 16 weeks after treatment, the levels of serum CEA, CA19.9 and CA125 declined significantly in both groups, more obviously in the observation group (p<0.05) (Tables 5-7).

Table 2. Comparison of efficacy between the two groups

Group	*n*	*CR* *n (%)*	*PR* *n (%)*	*SD* *n (%)*	*PD* *n (%)*
Observation group	43	18 (41.86)	14 (32.56)	7 (16.28)	4 (9.30)
Control group	43	8 (18.60)	9 (20.93)	12 (27.91)	14 (32.56)

Rank sum test is performed for efficacy in both groups (Z=2.514, p=0.004)

Table 3. Comparison of T lymphocyte subsets between the two groups

Group	*n*	*$CD3^+$*	*$CD4^+$*	*$CD8^+$*	*$CD4^+/CD8^+$*
Observation group	43	69.87±3.78	45.75±3.38	23.13±3.25	1.89±0.38
Control group	43	62.72±3.63	36.58±3.42	29.45±3.17	1.32±0.37
t		12.576	18.172	9.316	5.337
p		<0.001	<0.001	<0.001	<0.001

Table 4. Comparison of adverse reactions between the two groups

Group	*n*	*Gastrointestinal reactions* *n (%)*	*Hepatic dysfunction* *n (%)*	*Thrombocytopenia* *n (%)*	*Neutropenia* *n (%)*	*Total incidence rate* *n (%)*
Observation group	43	3 (6.98)	0 (0.00)	2 (4.65)	2 (4.65)	7 (16.28)
Control group	43	5 (11.63)	3 (6.98)	4 (9.30)	4 (9.30)	16 (37.21)
x^2						6.708
p						0.007

Table 5. Comparison of CEA level between the two groups before and after treatment (ng/mL)

Group	*n*	*Before treatment*	*4 weeks after treatment*	*8 weeks after treatment*	*16 weeks after treatment*
Observation group	43	3.82±1.13	2.92±0.61*	2.73±0.74*	2.16±0.67*
Control group	43	3.89±1.18	3.16±0.78*	3.08±0.67*	3.02±0.53*
t		0.074	12.053	11.106	10.152
p		0.813	<0.001	<0.001	<0.001

*p<0.05 vs. before treatment

Table 6. Comparison of CA199 level between the two groups before and after treatment (U/mL)

Group	*n*	*Before treatment*	*4 weeks after treatment*	*8 weeks after treatment*	*16 weeks after treatment*
Observation group	43	14.89±2.23	9.53±1.25*	8.63±1.54*	7.08±1.07*
Control group	43	14.36±2.28	11.04±2.16	10.89±2.13	10.47±2.18
t		0.025	7.046	11.548	13.671
p		0.859	<0.001	<0.001	<0.001

*p<0.05 vs. before treatment

Table 7. Comparison of CA125 level between the two groups before and after treatment (U/mL)

Group	*n*	*Before treatment*	*4 weeks after treatment*	*8 weeks after treatment*	*16 weeks after treatment*
Observation group	43	13.52±1.23	9.98±1.05*	8.84±0.84*	6.82±0.72*
Control group	43	13.73±1.47	11.39±1.24	10.22±1.05	9.98±0.87
t		0.025	9.457	14.415	11.316
p		0.857	<0.001	<0.001	<0.001

*p<0.05 vs. before treatment

Table 8. Comparison of 5-year follow-up conditions between the two groups

Group	*n*	*5-year survival n (%)*	*Mean survival time (months)*
Observation group	43	39 (90.70)	62.78±6.23
Control group	43	34 (79.07)	51.43±6.32
x^2/t		5.348	21.826
p		0.027	<0.001

Survival conditions in both groups

The mean survival time in the observation group was longer than that in the control group, and the 5-year survival rate in the observation group was also remarkably higher than that in the control group (p<0.05) (Table 8).

Discussion

Laryngeal carcinoma is a clinically common head-neck malignant tumor, which accounts for 1-5% of systemic tumors, and its morbidity rate in males is significantly higher than in females, with a mortality rate of about 2.4/100,000 in males and 0.3/100,000 in females [9,10]. The early manifestations of laryngeal carcinoma are foreign body sensation, hoarseness, bloody sputum and dyspnea, and there are many predisposing factors, including excessive smoking and drinking, environmental pollution, harmful chemical gas inhalation, viral infection, radioactive radiation and abnormalities of sex hormones [11]. Currently, the therapeutic methods of laryngeal carcinoma include surgery, radiotherapy, chemotherapy and biotherapy, which can prolong the survival of patients. How to realize effective treatment on the basis of retaining the phonation function as much as possible has always been the emphasis in clinical research.

LTPA is a minimally-invasive treatment method, in which the bipolar radiofrequency energy is generated to quickly dehydrate cells under low temperature, thereby obtaining a good ablation effect. At the same time, it can also exert a hemostatic effect and effectively ensure the clear surgical field, thus precisely cutting the lesions and achieving a better therapeutic effect [12]. As a commonly used chemotherapy drug in clinic, cisplatin possesses a significant anticancer effect, and it can remarkably inhibit the growth of malignant tumors [13]. Chemotherapy is an important anti-tumor treatment, especially for patients with middle-advanced cancer. However, the long-term chemotherapy has considerable toxic and side effects, thus affecting the effect of the whole treatment [14]. In this study, it was found that at 16 weeks after treatment, the observation group had a better efficacy and a lower incidence rate of adverse reactions than the control group (p<0.05). This is because the tumor can be

cut off in LTPA under low temperature, there are no smog and charring during operation, without causing heat loss to other normal tissues, and the wound healing is quick after operation. During operation, the operating angle can be adjusted easily, and the tissues at the hidden site can be ablated more thoroughly, achieving a better therapeutic effect. Moreover, low-dose cisplatin can interfere in the division and proliferation of tumor cells, create a better opportunity of LTPA for patients, increase the ablation rate, reduce the spread of tumor cells during operation, and lower the risk of postoperative complications. In addition, it can reduce the toxic and side effects in patients, improve the tolerance and benefit the prognosis.

There are often immune imbalance and immune dysfunction in patients with malignant tumors [15]. $CD3^+$ can reflect the levels of all T lymphocytes, while $CD4^+$ can play a positive regulatory role in body immunity [16,17]. $CD8^+$ is able to kill and destroy cells, and inhibit $CD4^+$, aggravating the immune dysfunction of patients [18]. In this study, the results showed that after treatment, the observation group had higher levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ than the control group, and a lower level of $CD8^+$ than the control group ($p<0.05$). This is because LTPA is a kind of minimally-invasive treatment that causes small trauma and milder stress response in patients, without leading to obvious immunosuppression. Besides, LTPA combined with low-dose cisplatin can reduce the tumor burden, regulate the body's immune balance, improve the damaged balance state, inhibit the proliferation of $CD8^+$ T cells, enhance the secretion of $CD3^+$ and $CD4^+$, and improve the systemic conditions of patients.

Tumor markers are substances secreted or shed by tumor cells, and they can be detected in the serum of patients, providing a basis for tumor diagnosis and treatment [19,20]. In this study, at 4, 8 and 16 weeks after treatment, the levels of serum CEA, CA19.9 and CA125 declined significantly in both groups, more obviously in the observation group ($p<0.05$). The reason is that LTPA can kill tumor cells to the greatest extent and lead to significant changes in tumor markers due to its accurate positioning. Besides, LTPA combined with low-dose cisplatin can inhibit the proliferation of tumor cells and postoperative recurrence and metastasis, thereby prolonging the survival of patients.

Conclusions

In conclusion, LTPA combined with low-dose cisplatin has significant efficacy in laryngeal carcinoma patients, and it can effectively reduce the levels of tumor markers and improve the patient immune function, which is worthy of clinical popularization and application.

Conflict of interests

The authors declare no conflict of interests.

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