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Clinical study of a $^{125}$I particle-integrated esophageal covered stent and hyperbaric oxygen in the treatment of advanced esophageal cancer

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ABSTRACT

Objective: this study aimed to investigate the clinical efficacy and feasibility of the treatment of advanced esophageal cancer with a combination of a $^{125}$I particle-integrated esophageal covered stent and hyperbaric oxygen.
**Methods:** forty-five patients with advanced esophageal cancer were enrolled and were randomly divided into two groups: a treatment group and a control group. Patients in the treatment group were treated with a $^{125}$I particle-integrated esophageal covered stent and hyperbaric oxygen, while patients in the control group were treated with a $^{125}$I particle-integrated esophageal covered stent. The clinical effects and long-term survival time of the two groups were observed.

**Results:** in the treatment group, the complete remission (CR) rate and partial remission (PR) rate of local lesions were 19.2 % and 61.5 %, respectively, and the total effective rate was 80.7 %. In the control group, the CR rate and PR rate of local lesions were 10.5 % and 52.6 %, respectively, and the total effective rate was 63.1 %. The total effective rate was higher in the treatment group than in the control group, which was statistically significant ($p < 0.05$).

**Conclusion:** the combination of a $^{125}$I particle-integrated esophageal covered stent and hyperbaric oxygen shows a good short- and long-term efficacy in the treatment of advanced esophageal cancer.

**Keywords:** $^{125}$I radioactive seeds. Coated stent. Hyperbaric oxygen. Squamous cell carcinomas.

**INTRODUCTION**

Esophageal cancer is predominantly caused by malignant hyperplasia of the glandular epithelium or esophageal squamous epithelium. It is one of the most common types of malignant tumor in China and most cases are squamous cell carcinoma. As living standards have improved, the incidence of esophageal cancer has gradually increased (1-3). Almost all patients with advanced esophageal cancer are faced with dysphagia, difficulty eating, nutritional disorders, reduced opportunities for surgery or no indication for surgery and poor quality of life (4,5). Inserting an esophageal stent immediately relieves the esophageal stricture and enables normal eating to be resumed, thus improving quality of life. Esophageal stent placement for the treatment of esophageal stricture in advanced esophageal cancer has the advantage of involving a simple operation that produces little trauma, few complications and immediate relief of the
stricture. Thus, the technique is widely used in clinical practice (6,7). However, the treatment is palliative and does not treat the tumor itself. Radiotherapy with short-distance irradiation of radioactive particles has the advantages of being accurate to the target, using low doses and producing few adverse reactions.

In recent years, the use of $^{125}$I particle-integrated esophageal covered stents in the treatment of advanced esophageal cancer has increased, though the clinical efficacy of the treatment is yet to be confirmed (8,9). Therefore, this study aimed to investigate the clinical efficacy and feasibility of the treatment of advanced esophageal cancer with a combination of a $^{125}$I particle-integrated esophageal covered stent and hyperbaric oxygen, to provide a reliable theoretical basis for the treatment of advanced esophageal cancer.

**PATIENTS AND METHODS**

**Subjects**

In this study, 45 patients with advanced esophageal cancer were enrolled and the study subjects were randomly divided into two groups: a treatment group and a control group. Patients in the treatment group were treated with a $^{125}$I particle-integrated esophageal covered stent and hyperbaric oxygen, while patients in the control group were treated with a $^{125}$I particle-integrated esophageal covered stent alone. The clinical effects and long-term survival time of the two groups of patients were analyzed. Prior to undergoing the operation, all patients were examined by endoscopy, biopsy, barium meal, and computed tomography (CT) to observe the length and degree of stenosis and diffusion around the lesion. The patients also underwent a blood routine test, coagulation test and liver and kidney function test before stent placement. The present study met the requirements of the Declaration of Helsinki of the World Medical Association and was approved by the Ethics Committee of our hospital. All patients provided signed informed consent.

**Inclusion and exclusion criteria**

Inclusion criteria were as follows: a) confirmation of advanced esophageal cancer by pathology or cytology; b) clinical stages of the tumors of III-IV; c) presence of valuable
lesions, as confirmed by CT or magnetic resonance imaging (MRI); d) no radiotherapy or chemotherapy performed within three months of the study start date; e) Karnofsky performance score (KPS) of ≥ 70; f) estimated survival time > 3 months; and g) signed informed consent provided by the patients.

Exclusion criteria were: a) poor compliance; b) KPS < 70; c) heart function of grade II or above; d) esophageal or tracheal fistula; e) mediastinal infection and abscess; f) presence of contraindications of hyperbaric oxygen, such as pyogenic infection, active bleeding, or open contusion of chest wall; and g) incomplete case data.

**Therapeutic methods**

In the $^{125}$I particle-integrated esophageal covered stent group (control group), the covered stent was selected before surgery, according to the length of the lesion. The $^{125}$I particles were arranged in a quincunx shape and fixed on the periphery of the irradiated stent according to the growth characteristics of the lesion and the information provided by the Treatment Planning System. During the operation, patients were placed under local anesthesia in a lateral position with a bite block and were implanted with a guidewire and catheter through the oral cavity for angiography. Ten milliliters of the contrast agent meglumine diatrizoate sodium diatrizoate was injected into the upper and lower parts of the lesion, and the length of the lesion and the degree of stenosis were displayed and marked. A new hard and long guidewire was used to replace the old guidewire, the catheter was removed and the selected $^{125}$I particle-integrated esophageal covered stent and pusher were pushed along the hard guidewire to the lesion site. The proximal positioning method was used to confirm the positioning accuracy and the stent was released. The upper and lower edges of the stent were placed beyond the lesion by at least 20 mm.

Patients in the $^{125}$I particle-integrated esophageal covered stent combined with hyperbaric oxygen (treatment group) were treated with hyperbaric oxygen following placement of the $^{125}$I particle-integrated esophageal covered stent. The hyperbaric oxygen pressure was increased to 0.2 MPa (2ATA) and the pressurization time was 20-30 minutes. The pressure was held for 70 minutes and then was slowly released over the course of 30-40 minutes. During the period of stable pressure maintenance, the patients
inhaled pure oxygen twice for 30 minutes, and the air in the tank was aspirated intermittently for ten minutes. This procedure was performed once a day, ten times as a course of treatment for a total of three courses.

**Evaluation criterion of curative effect**

Prior to treatment, the lesions were examined with CT or MRI. One week after the treatment, a further CT or MRI examination was performed and the curative effect was evaluated according to the evaluation standard of solid tumor effect revised by the World Health Organization (WHO) in June 1999 as follows:

- **CR**: all target lesions disappeared;
- **PR**: the sum of the maximum diameter of all target lesions reduced by at least 30 %;
- **Progressive disease (PD)**: the sum of the maximum diameter of all target lesions increased by at least 20 %, or new lesions appeared in the course of treatment;
- **Stable disease**: the lesions neither reduced to PR level nor increased to PD level.

Effective rate = the number of cases of CR + the number of cases of PR/the number of cases × 100 %.

The patients were also observed for complications during this period. The functional status of the patients was evaluated one and two weeks after treatment. The Karnofsky performance score (KPS) scoring system (10) was used. The lowest score was 0 points and the highest was 100 points; the higher the score, the better the general condition of the patient.

**Statistical analysis**

Statistical analysis was performed using SPSS 17.0 software. Measurement data were expressed as the mean ± standard deviation (x ± SD). Count data were expressed as a percentage (%). The normally distributed mean of two samples was compared using a t-test and the non-normally distributed mean of two samples between groups was compared using a non-parametric test. Count data were compared using a Chi-squared test. p < 0.05 was considered as statistically significant.
RESULTS

General data
A total of 45 patients with esophageal cancer were included in the present study. Among these patients, 25 were male and 20 were female. The patients’ age ranged from 54 to 74 years old, with an average age of 63 years. The key clinical manifestation was severe dysphagia; most patients could only drink a small amount of water, milk or other liquids. A recurrence of esophageal cancer was found in five patients following surgery. The lesions of the esophageal stenosis were 4-10 cm in length, and all were esophageal pericyclic lesions with different degrees of stenosis. All 45 patients were treated with a $^{125}$I particle-integrated esophageal covered stent and all technical operations were successful. The stent placement was released in place and the process of release was smooth. No falling-off of particles was observed during the release process. After stent placement, a contrast agent was taken orally for the purposes of angiography and the results revealed stent patency.

KPS score
There was no significant change in the KPS scores after treatment between the two groups at one and two weeks following treatment. The functional state and quality of life did not change significantly and the differences between the two groups were not statistically significant ($p > 0.05$) (Table 1).

CR rate of local lesions
In the treatment group, the CR rate and PR rate of local lesions were 19.2 % and 61.5 %, respectively, and the total effective rate was 80.7 %. In the control group, the CR rate and PR rate of local lesions were 10.5 % and 52.6 %, respectively, and the total effective rate was 63.1 %. The total effective rate was higher in the treatment group than in the control group, and the difference was statistically significant ($p < 0.05$) (Table 2).

Adverse reactions in the two groups after treatment
The dysphagia symptom in all patients was immediately improved. Reexamination on the third and seventh day after treatment revealed that the stent was completely
expanded in 12 patients, the particles had not fallen off and no stent displacement was found. Twenty-one patients had varying degrees of retrosternal pain and discomfort after stent placement. The pain and discomfort were alleviated by painkillers. No serious gastrointestinal reaction was found after the operation. No significant change in routine blood tests before and after the operation and during follow-up was found.

DISCUSSION

Radiotherapy is an important method for treating malignant tumors. However, the therapeutic effect of radiotherapy on some advanced tumors is unsatisfactory. This is because the cell type of the tumor tissue affects the sensitivity to radiation and influences tumor cell hypoxia, reducing the therapeutic effect of radiotherapy on tumor cells (10-13). More than a third of the hypoxic cell groups in human tumor tissues show strong resistance to radiation. Even if 1% of these cells are hypoxic, the radiation dose must be increased to achieve therapeutic efficacy because conventional radiation doses are unable to kill these cells. This is far beyond the radiation tolerance of normal tissues. A large number of studies have confirmed that the presence hypoxic cell groups is one of the main causes of tumor recurrence and metastasis after radiotherapy. The present study sought to increase the oxygen content of tumors using hyperbaric oxygen to improve the degree of hypoxia and enhance radiosensitization.

Basal and clinical trials have shown that hyperbaric oxygen can inhibit the growth and metastasis of many tumor cells and improve the sensitivity to radiotherapy, which is one of the main methods for treating late radiation injury (14-16). Hyperbaric oxygen can increase the partial pressure of blood oxygen saturation, increase the amount of oxygen dissolved in the blood, expand the dispersion distance of oxygen, improve the oxygenation of hypoxic cells and subsequently enhance the sensitivity to radiotherapy. Therefore, hyperbaric oxygen can improve the killing effect of radiotherapy on malignant tumors. Hyperbaric oxygen combined with radiotherapy has achieved good results in the treatment of some tumors (17-20).

The present study also showed that patients’ food intake improved significantly after implantation of a $^{125}$I particle-integrated esophageal coated stent. Furthermore, in combination with hyperbaric oxygen treatment, patients’ tumor control was better than
that of particle-integrated esophageal covered stent treatment alone and the
difference was statistically significant. As a combination therapy, 26 patients were
treated with a $^{125}$I particle-integrated esophageal covered stent and hyperbaric oxygen.
Of these patients, 23 improved their food intake and reexamination with CT one and
three months after operation showed good tumor control and the quality of life was
significantly improved. The treatment effect was significantly better than that of the
control group ($p < 0.05$) and the difference was statistically significant.
In summary, treatment of advanced esophageal cancer with a combination of a $^{125}$I
particle-integrated esophageal covered stent and hyperbaric oxygen can improve the
local control rate of advanced esophageal cancer, reduce distant metastasis, improve
patients’ intake and improve their quality of life. It is an innovative, safe and effective
treatment.
This study had the following limitations. First, although this study was a randomized
controlled trial, it was not blinded. Therefore, there is a certain risk of bias. Secondly,
this study was a single-center clinical trial and the sample size was small. As a result,
进一步, multi-center clinical trials with larger sample sizes are needed. Finally, the
clinical follow-up time of this study was short and further long-term clinical follow-ups
are needed.

CONCLUSION
The combination of a $^{125}$I particle-integrated esophageal covered stent and hyperbaric
oxygen shows good short- and long-term efficacy in the treatment of advanced
esophageal cancer.

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collection, analysis, and interpretation of data, and in writing the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
This study was conducted with the approval from the Ethics Committee of Guangdong TCM-Integrated Hospital (2019-040). This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

**AVAILABILITY OF DATA AND MATERIALS**
We declare that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

**REFERENCES**
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Table 1. KPS scores between the two groups at different time periods after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Before treatment</th>
<th>One week after treatment</th>
<th>Two weeks after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group (n = 26)</td>
<td>90.05 ± 9.23</td>
<td>89.85 ± 8.63*†</td>
<td>91.62 ± 8.17*†</td>
</tr>
<tr>
<td>Control group (n = 19)</td>
<td>91.12 ± 8.65</td>
<td>91.05 ± 9.03*†</td>
<td>89.65 ± 9.33*†</td>
</tr>
</tbody>
</table>

*Comparing with pre-treatment; p > 0.05. †Comparing between two groups; p > 0.05.
Table 2. Comparison of clinical efficacy between the two groups after treatment (n [%])

<table>
<thead>
<tr>
<th>Group</th>
<th>The number of cases</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
<th>CR + PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>26</td>
<td>5 (19.2)*</td>
<td>16 (61.5)*</td>
<td>3 (11.5)</td>
<td>2 (7.7)</td>
<td>21 (80.7)*</td>
</tr>
<tr>
<td>Control group</td>
<td>19</td>
<td>2 (10.5)</td>
<td>10 (52.6)</td>
<td>4 (21.1)</td>
<td>3 (15.7)</td>
<td>12 (63.1)</td>
</tr>
</tbody>
</table>

*Compared with control group, p < 0.05.