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ORIGINAL ARTICLE

Application of esophageal irradiation stents coated with ^{125}I particles in advanced esophageal cancer

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Summary

Purpose: *The current study was designed to investigate the primary efficacy of esophageal irradiation stents coated with ^{125}I particles in the treatment of elderly patients with advanced esophageal cancer.*

Methods: *Forty-three elderly patients with advanced esophageal cancer were treated with esophageal stents in the First Affiliated Hospital of Xinxiang Medical University between September 2009 and December 2010. Patients were randomly divided into group A (N=18), treated with irradiation stents, and group B (N=25), treated with ordinary stents. There were no significant intergroup differences in age, lesion length, degree of stenosis, or cancer stage. The stent implantation success rate, relief of dysphagia and complication rate, and survival were assessed.*

Results: *The stent implantation success and short-term dysphagia relief rates were 100.0% in both groups. The mean survival time was 9.8 months and 4.8 months in groups A and B, respectively ($p<0.01$). However, no significant difference in pain (5/18) or esophageal restenosis (7/25) was found (both $p>0.05$).*

Conclusion: *Dysphagia was relieved and survival was prolonged in advanced esophageal cancer cases treated with ^{125}I particle-coated esophageal stents. This method may be superior to the traditional stents method.*

Key words: *esophageal cancer, esophageal stent, radioactive ^{125}I particle, treatment*

Introduction

Esophageal carcinoma is a common malignant gastrointestinal tumor characterized by progressive dysphagia and China is one of the countries with the highest incidence [1]. Most elderly patients with advanced esophageal cancer are inoperable because of their older age, weaker condition, and greater number of comorbidities. Although radiotherapy is the best therapy for advanced esophageal cancer due to its satisfactory efficacy, it can be difficult to deliver in elderly patients, because it often leads to serious complications. Other therapies also have advantages and disadvantages. For example, esophageal stent placement can relieve dysphagia and improve patients' quality of life but cannot treat tumors, while esophageal brachytherapy can work directly on tumors, but it may cause local edema which aggravates the obstruction [2]. In recent years, ^{125}I as a low-energy radioactive particle has been widely used for the treatment of solid tumors and has achieved satisfactory results [3,4]. Moreover, by combining the two therapies mentioned above, the placement of bare esophageal stents coated with ^{125}I is beneficial [5]. Herein we report the

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results of the use of self-expandable Ni-Ti alloy esophageal stents coated with ^{125}I to treat elderly patients with advanced esophageal cancer in our hospital.

Methods

Clinical data

Forty-three patients (29 men and 14 women; mean age 70.4±3.2 years, range 59-82) with advanced esophageal carcinoma were referred to our hospital for stenting between October 2009 and December 2010. This study was conducted in accordance with the declaration of Helsinki and after approval from the Ethics Committee of Xinxiang Medical University. Written informed consent was obtained from all participants. All patients had esophageal squamous cell carcinoma confirmed by a barium study and an endoscopic biopsy, while gross morphology showed mass or infiltration type but not ulcerative type. Clinical disease stage was III or IV and grade of dysphagia 3 to 4 (mean 3.4). All patients were unfit for or refused surgery and had not received either chemotherapy or radiotherapy. All patients were randomly assigned into two groups: group A included those who would receive esophageal stents loaded with ^{125}I seeds (N=18; 12 tumors were localized within the proximal and middle portions and 6 were localized in the distal third of the esophagus; lesion length, 3.0-9.7 cm, mean 7.6), while group B included those who would receive a conventional stent (N=25; 16 tumors were localized in the proximal and middle portions and 9 were localized in the distal third of esophagus; lesion length, 3.2-10.0 cm, mean 7.5). There were no significant intergroup differences in lesion site, lesion length, grade of dysphagia, or disease stage or grade.

Grading of dysphagia

Dysphagia was graded according to Stooler standard: grade 0, patients had the ability to eat a normal food; grade 1, patients had the ability to eat some solid foods; grade 2, patients had the ability to eat semisolid foods only; grade 3, patients had the ability to swallow liquids only; and grade 4, patients had complete obstruction.

Pre-stenting preparation

Routine bloodwork, coagulation time, liver and kidney function, routine stool and fecal occult blood, immunologic tests (like complement C3), and electrocardiography were carried out before stenting, while esophagography, gastroscopy and computed tomography (CT) were performed to confirm the lesion site, morphology, and length as well as stent type [6]. Group A patients received covered esophageal stents coated with ^{125}I seeds (Nanjing MicroInvasive Medical, Nanjing, China), while those in group B received ordinary covered Ni-Ti alloy esophageal stents (Nanjing Micro-Invasive Medical, China). The stents' lengths were 60-120 mm and the diameters 18-20 mm. The ^{125}I seeds (Shanghai Syncor Medical, Shanghai, China) had a half-life of 60.1 days, x-ray energy of 27.4-31.4 KeV, and mean gamma ray energy 35.5 KeV. The initial dose rate was 7.7 cGy/h, while the effective irradiating distance was 1.7-2.0 cm. The radioactivity was 0.40-0.70 mCi. The dose and location of the ^{125}I seeds were determined according to the treatment plan system on the basis of tumor morphology, while the seeds were loaded into the stents by the interventional radiologists.

Stent placement

The same technique was used to place the irradiation and conventional stents. Pre-dilation with a bougie or balloon was performed prior to placement when necessary. The group A patients were tested under fluoroscopy in different positions after deployment of the stents loaded with ^{125}I to confirm that the seeds had not migrated or dropped in the process.

Post-stenting management

Hemostasis and symptomatic supportive treatment were applied after the stent placement, while antibiotics were used when necessary. A solution of 250 mL of glucose or normal saline, 25 mL of 2% lidocaine, and chymotrypsin 20000 U were given orally, and the patients drank 10-20 mL each time. A normal diet was started per the esophageal condition, stent position and expansion, and whether irradiation seed migration occurred, observed by esophagography and chest CT in the second or third day after stenting. In the first week post-stenting, other examinations including routine bloodwork, routine stool and fecal occult blood, liver and kidney function, and immunological testing were reexamined to confirm whether complications such as esophageal perforation and hemorrhage had occurred.

Follow-up

Examinations including routine bloodwork, routine stool and fecal occult blood, liver and kidney function, immunological testing, esophagography, and chest CT were performed in the first, second, fourth, and sixth months after the stent implantation and every 6 months thereafter.

Statistics

The patient data were analyzed using the SPSS 13.0 software. Survival was estimated by the Kaplan-Meier method and the intergroup differences were compared using the log-rank test. X^2 test was used to assess intergroup complications. Statistical significance was determined by two-sided p values <0.05.

Results

General condition

All stents were implanted disposably with a 100% success rate. None of the radioactive seeds migrated during stenting. Dysphagia was obviously relieved in the two groups immediately after the stent placement and all dysphagia scores decreased to grade 0-1 by 1-2 months after stenting. The mental status and body weight of all patients also improved. Most tumors in group A decreased in size at postoperative months 1, 2, and 4 as evidenced on CT.

Complications

1) *Stent migration:* No stents migrated in either group. 2) *Hemorrhage:* There were cases of pre-stenting occult bleeding in both groups; however, no patient showed signs of post-stenting gastrointestinal hemorrhage such as black stool or hematemesis, whereas all fecal occult blood tests were positive. 3) *Other problems:* No obvious gastrointestinal reactions or digestive tract perforations occurred in either group. 4) *Pain:* Most patients in the two groups with lesions located in the proximal segment or with serious stenosis felt tolerable pain after the stent insertion that subsided within 2 weeks. A few patients (3 in group A, 4 in group B) suffered from severe pain lasting for 1-2 months that was relieved only after the use of narcotic analgesics such as morphine or meperidine. 5) *Esophageal restenosis:* A few patients (2 in group A, 3 in group B) had severe esophageal restenosis 4 months after stenting. The restenosis was often located in the proximal and/or distal stent ends. Three cases of restenosis demonstrated hyperplasia on endoscopic examinations, and the stenosis was relieved by inserting another stent. However, one patient in each group, who did not receive further treatment died after 2-3 months. 6) *Complication related to irradiation:* No patients in group A developed radiation pneumonitis, myelosuppression, or immunosuppression. Reexaminations by CT during 2-6 months of follow-up confirmed that 10 tumors in group A decreased in size vs 0 cases in group B, 6 tumors had no obvious change in group A vs 7 in group B, and 2 tumors increased in size in group A vs 18 in group B. There was no significant intergroup difference in complication rates of pain, stent migration, or esophageal restenosis (27.8% in group A, 28.0% in group B; $p>0.05$).

Survival

Mean overall survival in group A was 9.8±4.3 months (5 survivors; 2 patients died of esophageal obstruction, one of massive gastrointestinal hemorrhage, and 8 of systemic failure, severe underlying diseases, or cancer distant metastasis). In contrast, the mean overall survival in group B was 4.8±3.9 months (7 survivors; 3 patients died of esophageal obstruction, 2 of massive gastrointestinal hemorrhage, and 13 of systemic failure, respiratory diseases, or distant cancer metastasis). The intergroup differences in survival were significant ($p<0.01$). Moreover, we speculate that the mean survival of group A might be even longer because 2 patients in group A did not die of tumor-related reasons. Comparisons of survival curves of A and B groups by log-rank test showed significantly better survival of group A patients ($x^2=10.704$, $p=0.001$) (Figure 1).

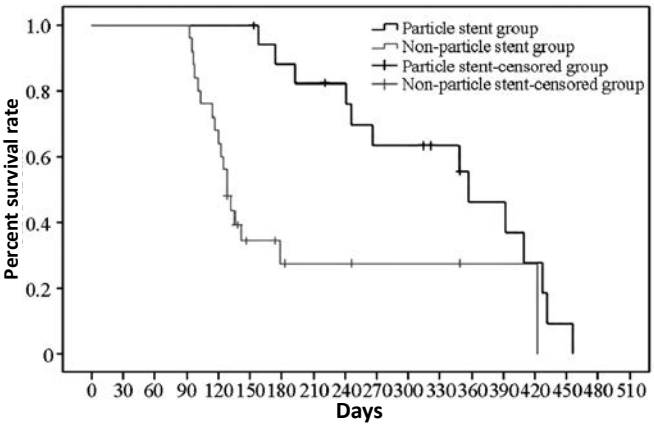

Figure 1. Comparison of survival curves of A and B groups by log-rank test showed significantly better survival of group A patients ($x^2=10.704$, $p=0.001$).

Discussion

Esophageal carcinoma is a common malignant gastrointestinal tumor whose traditional therapies include surgery, systemic chemotherapy and radiotherapy. Most elderly patients with advanced esophageal cancer are not only inoperable, but they cannot tolerate the side effects of chemotherapy due to their older age, weaker condition, and greater number of comorbidities. Therefore, reasonable use of radiotherapy becomes the main treatment method to treat such individuals. Although radiotherapy has been constantly optimized, the long-term survival was not significantly improved and the complication rate remained high at 14.9%. In addition, any kind of complications after long-term radiotherapy, including tracheoesophageal fistula, radiation pneumonitis, esophageal stenosis and esophageal ul-

cer, can cause serious consequences or even death [7]. In recent years, intraluminal brachytherapy has been developed gradually and confirmed to be effective, reducing the complication rates because of the lower irradiation dose than extracorporeal radiotherapy [8,9].

The ^{125}I seeds described here can release low-energy gamma rays with an energy of 27-35 KeV, half-life of 60.4 days, and penetrating distance of 1.7 cm. Interstitial brachytherapy has the following advantages [10,11]: 1) It can improve the irradiation distribution ratio between tumors and normal tissues; 2) The continuous irradiation can inhibit tumor hyperplasia; 3) Mitosis of cancer cells can be restrained by prolonged low-dose irradiation; 4) It can reduce the number of hypoxic cells that resist radiation; 5) This treatment has fewer side effects; 6) The procedure is more simple and accepted; 7) Brachytherapy is safe for patients and others in contact with them. Studies have confirmed that radiotherapy with ^{125}I seeds used to treat solid tumors because showed a better local control rate, lower complication rate, and higher survival rate [12,13].

Conventional esophageal stent placement can immediately relieve dysphagia and other symptoms of esophageal obstruction and improve patients' general conditions and quality of life, but it cannot treat cancer, and, although its short-term efficiency has been verified, its positive impact is not ideal in the mid- and long-term. Survival with this therapy to treat advanced esophageal cancer is reportedly 3.5-5 months [14]. In our study, the mean survival in group B with conventional stents was 4.8 months, which coincided with the literature reports. Su et al. [15] reported that the survival time of 18 patients who were treated with stents loaded with ^{125}I was 10.5 months, while Zhu et al. [16] reported 8.3 months in 30 cases. In our study, the mean survival time of the irradiation group was 9.8 months; furthermore, we speculate that the survival might be longer because of the 5 survivors. We infer that the reason for the longer survival in the ^{125}I stent group is that the continuous low-dose irradiation from the ^{125}I seeds can inhibit tumor growth, retard restenosis speed, delay dysphagia progression, improve quality of life, and prolong survival. Even so, a few tumors continued growing. Guo et al. [17] reported this phenomenon and stated that it may be related to seed dose. We think that another important reason could be that the tumors were deeper into the tissue and the penetrating irradiation could not reach them. Furthermore, complications were similar between the irradiation and conventional stents and could be relieved by revelant treatment as reported by McGrath et al. [18].

In conclusion, the application of esophageal stents loaded with ^{125}I seeds is feasible, secure and more effective for treating elderly patients with advanced esophageal cancer, and its beneficial effect was demonstrated to last by the follow-up results. Therefore, we believe that this treatment should have an extensive application. The limitations of our study (limited number of patients and short follow-up time) call for multicenter long-term comparative studies.

Conflict of interests

The authors declare no confict of interests.

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