Evaluation of therapeutic effects of ^{125}I particles brachytherapy for recurrent bladder cancer

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Abstract. The aim of the present study was to evaluate the clinical value of ^{125}I particles implantation in the treatment of recurrent bladder cancer. The study is a retrospective analysis of 32 patients with recurrent bladder cancer treated between May 2010 and January 2010. Of these, 16 cases (chemotherapy group) received conventional chemotherapy. A total of 16 patients (^{125}I group) received radiotherapy with ^{125}I particles, followed by conventional chemotherapy. By guidance of B ultrasound, ^{125}I radioactive particles were implanted. All 32 patients were relieved after treatment, and the tumors were significantly reduced after 2 months. However, the tumors in the ^{125}I group were significantly smaller than those in the chemotherapy group ($P<0.05$). The patients were followed-up for 1 year and no recurrence was found. Additionally, no complications occurred. Compared with the chemotherapy group, the tumor volume of the ^{125}I group was significantly reduced ($P<0.05$). The disease-free survival and 5-year survival rates of the patients in the follow-up showed that the disease-free survival and 5-year survival rates of the patients in ^{125}I group were significantly improved compared to those in the chemotherapy group. Therefore, the results have shown that ^{125}I radioactive particles in the treatment of bladder cancer improve the symptoms of patients with bladder cancer in the short term, and continuously kill residual tumor and prevent recurrence.

Introduction

^{125}I particles are capable of releasing X-ray and gamma-rays in the process of decay, through *in vivo* implantation for continuous internal radiation therapy. These particles have the ability to inhibit tumor cell proliferation and induce apoptosis. ^{125}I has a low dose rate, high relative biological effect, appropriate radius of killing, and is used widely in the treatment of a variety of malignant tumors, showing obvious advantages in the local control and survival rate of patients (1,2). With the rapid development of molecular biology, modern advanced biology techniques have been used to study the mechanism of tumorigenesis and prognosis, and the treatment of malignant tumors with ^{125}I particles is no exception. Through a lot of basic research, the molecular mechanism of ^{125}I particles in radiotherapy for malignant tumor has achieved certain results in the induction of tumor cell apoptosis and cell cycle arrest, intracellular signal transduction and inhibition of tumor angiogenesis. In patients with recurrent bladder cancer, the efficacy of the general chemotherapy regimen is limited (3). In this study, we implanted ^{125}I radioactive particles into the tumor, and observed the clinical efficacy of this treatment modality during recurrent bladder cancer.

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Materials and methods

General. A total of 16 patients with recurrent bladder cancer treated with ^{125}I, there were 13 males and 3 females, aged 47-69 years , and the average was 59.2±3.28 years. Of the 16 cases, 10 cases were diagnosed as transitional cell carcinoma, 1 case was squamous cell carcinoma, and 5 cases were hamartoma. All 16 patients had hematuria, urinary frequency and urgency symptoms, and 1 patient had dysuria. In the chemotherapy group, there were 14 males and 2 females, aged 43-65 years, with an average age of 58.3±2.33 years. Of these, 8 cases were transitional cell carcinoma, 4 cases were squamous cell carcinoma, and 4 cases were hamartoma. All 16 patients had hematuria, urinary frequency and urgency symptoms. There was no significant difference in age between the two groups. There was no significant difference in pathological types and the number of complications by the Chi-square test ($P>0.05$) (Table I).

The present study has been approved by the Ethics Committee of The First Affiliated Hospital of Xiamen University (Fujian, China). Informed consents were signed by the patients and/or guardians.

Instruments. The instruments used for the study were: 3D-stereotactic radiotherapy planning system for tumor tissue (TPS, jointly designed and developed by the China Institute of Atomic Energy and Beijing Bo Intel System Engineering Co., Ltd., Beijing, China). Plant equipments included planting needles, planting guns, templates and B ultrasonic. The radio-

Table I. Comparison of general clinical data.

Variables	No. of cases	Sex (male/female)	Age (years)	Transitional cell carcinoma	Squamous cell carcinoma	Hamartoma
^{125}I group	16	13/3	59.2±3.28	10	1	5
Chemotherapy group	16	14/2	58.3±2.33	8	4	4
T/χ^2 value	-	0.43	0.22	0.83		
P-value	-	0.59	0.78	0.18		

Table II. Tumor location and number of implanted particles.

No.	Age	Tumor location	Tumor size (cm^3)	No. of particles
1	58	Right anterior wall of bladder	21.2	40
2	57	Right posterior wall of bladder	9.2	20
3	54	Right anterior wall of bladder	9.8	20
4	59	Right anterior wall of bladder	4.8	9
5	53	Left posterior wall of bladder	10.2	20
6	50	Left posterior wall of bladder	11.3	20
7	49	Posterior wall and right wall of bladder	20.3	40
8	63	Right anterior wall of bladder	12.5	20
9	52	Right posterior wall of bladder	3.8	9
10	53	Right anterior wall of bladder	4.4	9
11	54	Posterior wall and right wall of bladder	5.4	9
12	59	Posterior wall and right wall of bladder	5.7	9
13	61	Right wall of bladder	7.8	10
14	60	Left and right posterior wall of bladder	9.8	20
15	58	Right posterior wall of bladder	9.6	20
16	69	Posterior wall and right wall of bladder	3.5	9

active ^{125}I particle source was obtained from the American SynQor Inc. (Boxborough, MA, USA), and the activity of each particle was 0.40-0.50 mCi, with a half-life of 60.1 days; gamma-ray energy of 27,35 kEV; and tissue penetration distance of 1.7 cm.

Methods. To determine the range of tumor surface markers measured by B ultrasound, combined with the TPS planning system, the grid was drawn using the pitch 1.0 cm square matrix. Each intersection of the grid served as the access channel. After local routine disinfection, an ultrasonic probe navigation frame was fixed to the edge of the tumor. From this point, the needle was taken up to 1 cm from the edge of the tumor, the first particle was planted, and the needle was withdrawn 1 cm. The second particle was planted, up to 1 cm from the edge of the tumor, the last particle of the channel was planted, and the replacement of the channel continued to grow. A postoperative indwelling catheter was left, with regular bladder irrigation, antibiotics were taken to prevent infection, and hemostasis and other symptomatic treatments were taken. Tumor sites and the number of implants of ^{125}I group are presented in Table II.

Chemotherapy regimen. Both groups of patients were treated with internal iliac artery chemotherapy for the first time within 2 weeks after surgery, and the second internal iliac artery chemotherapy was performed within 1 month after surgery in the two groups. The chemotherapeutic drugs Pharmorubcin 30 mg/m^2 (surface area) was taken each time. The Seldinger technique was used to puncture one side of the femoral artery, and internal iliac artery angiography was taken on both sides to observe the blood supply of the bladder. The catheter was placed into the internal iliac artery of the affected side, and 2/3 of the drug was injected. Then the catheter was placed into the contralateral internal iliac artery, and the remaining 1/3 of the drug was injected. Following chemotherapy, hydration, alkalization and hepatoprotective treatments were taken.

Curative effect judgment. According to the improvement of clinical symptoms, the changes of tumor size by the re-examination of B-ultrasound or CT and CT review after 17 months, the curative effect was evaluated.

Statistical analysis. The collected data were processed using SPSS 15.0 statistical software (SPSS, Inc., Chicago, IL, USA). Measurement data were presented as mean ± SD. An independent sample t-test was used for comparison between groups. Countable data were expressed by case number or constituent ratio, and tested using the Chi-square test. The log-rank test

Table III. Changes of tumor volume before and after treatment.

Variables	Number of cases	Before treatment	After treatment	T-value	P-value
^{125}I group	16	9.33±5.27	3.44±1.23	2.18	0.02
Chemotherapy group	16	9.21±1.23	6.57±2.17	3.28	0.012
T-value	-	0.27	3.49	-	-
P-value	-	0.79	0.003	-	-

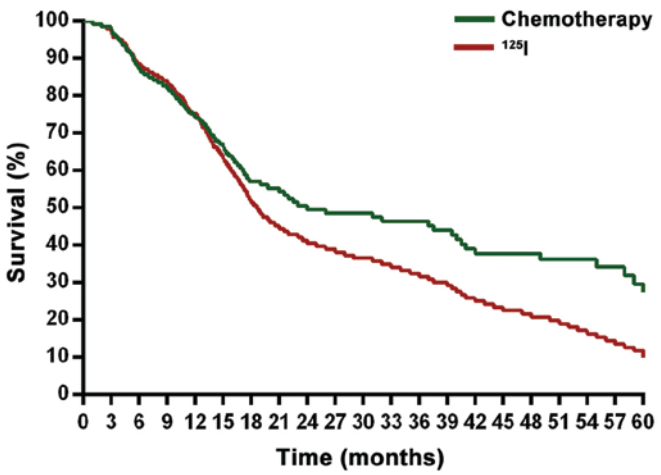

Figure 1. Survival curve. After follow-up, the survival rate of 5 years of the ^{125}I group was significantly lower than that of the chemotherapy group, and the difference was statistically significant between the two groups (Z=12.22, P<0.05).

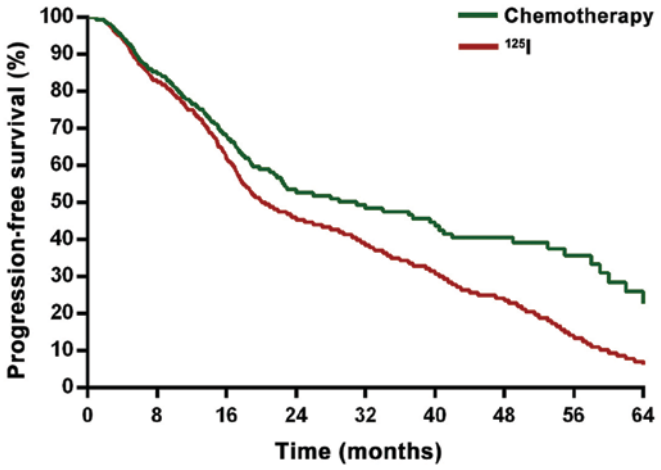

Figure 2. Progression-free survival. After 5 years of follow-up, compared with the chemotherapy group, the progression-free survival was significantly prolonged in the ^{125}I group, and the difference was statistically significant (Z=12.22, P<0.05).

and COX multivariate analysis were used to analyze the prognosis of the patients. A P<0.05 was considered to indicate a statistically significant analysis.

Results

Changes of tumor volume before and after treatment. We analyzed the tumor volume of the two groups before and after treatment by CT. The results showed that the tumor volume of the two groups of patients after treatment was significantly reduced. The tumor volume of ^{125}I was 9.33±5.27 before treatment, while it reduced to 3.44±1.23 after treatment. The tumor volume of patient in chemotherapy group was 9.21±1.23 before treatment and 6.57±2.17 after treatment. However, compared with the chemotherapy group, the tumor volume of the ^{125}I group was significantly reduced (P<0.05) (Table III).

Comparison of survival prognosis. Concerning the survival prognosis of the two groups, we found that compared with the chemotherapy group, the ^{125}I group had a significantly higher survival rate of five years (P<0.05). Disease-free survival was significantly prolonged (P<0.05). The difference was statistically significant (P<0.05) (Figs. 1 and 2).

Discussion

Bladder cancer is one of the most common malignant tumors in the urinary system. The key to treatment is to control the recurrence and metastasis of the local tumor through multidisciplinary efforts (4-6). For nearly half a century, the academic community has made noteworthy progress in the comprehensive treatment of surgery, radiotherapy and chemotherapy. However, the recurrence rate within a few years after tumor resection is 50-80% and invasive evolution accounts for 50-80% in recurrent cases (7). Although radical cystectomy is widely accepted, there is currently no evidence that surgery is more effective than radiotherapy. Furthermore, radiotherapy may retain the bladder, especially in improving the quality of life of patients as it has greater advantages (8). Although there are certain effects of external radiotherapy, the loss of normal tissue is serious and the quality of life is also reduced. Moreover, it has side effects and high equipment costs.

Brachytherapy was performed by implanting radioactive sources into the hollow organs (intracavitary radiotherapy) or directly implanted in the tumor tissue (interstitial brachytherapy). A short range of treatment ranging from approximately 5 mm to 5 cm characterizes it. Additionally, the radiation dose is mainly concentrated in a small part of the tumor tissue and surrounding normal tissue (9). High-dose irradiation can be obtained in the treatment of brachytherapy and the surrounding normal tissues may be well protected (10). Brachytherapy is one of main treatments of bladder cancer and prostate cancer (11). The physical half-life of the radioactive element ^{125}I particles is 59.6 days, with the energy of 27.4-31.5 Kev X-rays and 35.5 Kev gamma-rays (12). When the ^{125}I particles were implanted into the tumor focus and the

lymphatic system, the particles were scattered with low energy X-rays and gamma-rays. Tumor proliferation was significantly reduced by continuous irradiation (13). At the same time, continuous low energy irradiation inhibits tumor mitosis, with the tumor cell concentration in the G2 phase, resulting in tumor cell killing by radiation effect to the maximum, to effectively inhibit tumor cell proliferation and cytothesis, in order to achieve the purpose of cure (14). Furthermore, ^{125}I particles are not involved in metabolism, and cause little damage to the patients and medical staff (15). In particular, according to the intraoperative situation, targeted at a certain location, tumor cells are directly killed at different stages of the cell cycle (16). However, conventional external irradiation is short-time high-intensity fractionated irradiation, which could kill the M cells. This is often terminated because the patient could not tolerate the radiation reaction (17). Interstitial implantation of radioactive ^{125}I particles brachytherapy is a minimally invasive treatment technology developed in previous years, showing a good therapeutic effect in the clinical practice of treating multiple cancers with high efficiency and few side effects (18).

Brachytherapy is primarily used for the treatment of bladder and prostate cancer (19). However, to the best of our knowledge, there is no report on the application of ^{125}I particles implantation in the treatment of bladder cancer (20). Our results have shown that ^{125}I particles were implanted into the lesion or in the tissue for the treatment of bladder cancer, and the local recurrence rate was low. At the same time, the unresectable cancer tissue or the remaining tissue was directly radiated (21). Our study found that tumor volume measurement and statistical analysis in the CT of the two groups of patients before and after treatment were significantly reduced as compared with prior to treatment. However, compared with the chemotherapy group, the tumor volume of ^{125}I group was significantly reduced. Following a comparison of the survival prognosis of the two groups, we found that compared with the chemotherapy group, the ^{125}I group had a significantly higher survival rate of 5 years ($P<0.05$). Disease-free survival was significantly prolonged ($P<0.05$). The results showed that ^{125}I particle radiation therapy has good clinical efficacy in clinical life therapy and survival prognosis of recurrent bladder cancer patients.

^{125}I particle implantation-assisted radiotherapy for the treatment of bladder cancer is optimal compared to *in vitro* irradiation treatment, and especially applicable to patients for whom surgery is not possible. ^{125}I particles are capable of killing the tumor cells directly, and are not affected by the oxygen content in tumor cells (22,23). Owing to the accurate localization, the local effective dose is large, but the radiation distance is small, the radiation damage is slight, and there is no obvious adverse effect on the surrounding tissue. Therefore, the side effects are small and have no significant influence on the quality of life (24). We believe that the treatment of bladder cancer by ^{125}I particles brachytherapy is more advantageous than that of *in vitro* irradiation. It has the following advantages (25-29): i) The radioactive source is small, the half-life is short (only 60 days), the energy is low, and the killing radius is not more than 2 cm; ii) the operation is simple, the ^{125}I particle source may be implanted into the tissue under direct vision, the accuracy of the treatment is improved, and the range of the surgical injury is reduced; iii) the accuracy rate of the cancer tissue is high, and the continuous emission of pure gamma-ray can effectively hit the mitotic phase of the cancer cell. The continuous low-dose irradiation inhibits the mitosis of the tumor cells, and the curative effect is good; and iv) it may effectively improve the dose distribution ratio of tumor and normal tissue.

In conclusion, we believe that ^{125}I radioactive particles in the treatment of bladder cancer may not only improve the symptoms of patients with bladder cancer in the short term, rapidly reduce the tumor, but also continuously kill residual tumor and prevent recurrence of the tumor.

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