RESEARCH ARTICLE

Efficacy of Permanent Iodine-125 Seed Implants and Gemcitabine Chemotherapy in Patients with Platinum-Resistant Recurrent Ovarian Carcinoma

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Abstract

Background: The aim of this study was to explore the efficacy and adverse reactions of CT-guided radioactive 125I-seed implantation treatment combined with chemotherapy for platinum-resistant recurrent ovarian carcinoma. Materials and Methods: From September 2010 to December 2012, 23 patients with platinum-resistant recurrent ovarian carcinoma were enrolled. All the patients refused, could not bear, or were not suitable for surgery. They all had no more than 3 lesions, which were detected and could also be measured by CT. All were clarified as single-lesion or multiple-lesion groups. A total of 41 lesions underwent implantation of from 8 to 106 125I seeds (median=43). Multi-plane implanting was adopted and 125I-seeds of (0.4-0.7)mCi were placed at intervals of (0.5-1.0) cm. After implantation treatment, all patients underwent 4 cycles of chemotherapy with gemcitabine 800 mg/m2 (days 1, 8 and 15). Results: The outcome was evaluated with CT 3 weeks and every 3 months after implantation treatment. After 6 months, the volume of 32 out of 41 lesions (78.0%) was reduced at least 30%, within which 9 lesions completely disappeared(22.0%). Complete response was observed in 7 cases (30.4%), with a partial response in 4 cases (17.4%),4 cases stable(17.4%)and 8 cases showing progression (34.8%). The total clinical remission rate was 47.8% (11/23). The clinical remission rate was 77.8% (7/9) in the single-lesion group and 28.6% (4/14) in the multiple-lesion group with a significant difference between the two(P=0.036). The common side effects observed were mild gastrointestinal reactions. Conclusions: 125I-seed implantation combined with chemotherapy applies an effective way in the treatment of platinum-resistant recurrent ovarian epithelial carcinoma with the advantages of high local control rates, good short-term effects, little trauma and less side effects.

Keywords: Ovarian neoplasms - brachytherapy - antineoplastic combined chemotherapy protocols

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Introduction

Seventy percent of patients with epithelial ovarian cancer in advanced stage ultimately suffer disease recurrence, and the 5 years' survival rate is generally below 30% (Scarabelli et al., 2001). The treatment of recurrent ovarian cancer is a difficult problem all the time. Paclitaxel combined with platinum is considered to be the first-line chemotherapy for ovarian carcinoma; and platinum resistant ovarian cancer was defined as recurrence within 6 months after the application of platinum drugs. The patients who are sensitive with platinum in the first treatment recurrent and then treated with platinum are often resistance in the final. Once ovarian cancer is resistance to platinum drugs, the treatment is poor. How to improve the treatment of these patients is a thorny problem for gynecologist. CT-guidedradioactive ^{125}I-seed implantation treatment has been applied in liver cancer, non-small cell lung cancer and other tumors which has been proven some advantages of less trauma, high local control rate, less impact on the surrounding normal organs (Nag et al., 2006; Trombetta et al., 2008; Liebling et al., 2013; Nam et al., 2013), and there are rarely reports for applications of ovarian cancer. From 2010 September to 2012 December, we observed the curative effect and the poisonous side effect for 23 patients of platinum -resistant recurrent epithelial ovarian cancer with CT-guided radioactive ^{125}I-seed implantation treatment in our hospital, which aim to explore its clinical application value.

Materials and Methods

Clinical data

From September 2010 to December 2012, 23 patients with platinum-resistant recurrent ovarian carcinoma which have been treated with CT-guided radioactive ^{125}I-seed implantation were enrolled. All 23 patients who matched

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(or met) the following requirements were included in this retrospective study:1) All the patients refused, could not bear, or were not suitable for operation. 2) They have been received cytoreductive surgery for epithelial ovarian cancer once at least. 3) All the patients who received 6 months of chemotherapy with platinum based on the first treatment of CP, CAP or TP chemotherapy have recurrent. 4) The recurrent lesions can be measured with CT or PET-CT examination. 5) Patients treated with gemcitabine chemotherapy were not included in this study. 6) KPS score ≥ 70, liver and kidney function is normal. This study was approved by the Institutional Review Board of Shandong cancer Hospital & Institute, Jinan, China. and informed consent for brachytherapy from all patients was taken.

A total of 23 patients (age range 38-82 years; median age 54 years) which have one lesion (n=9), two lesions (n=10), three lesions (n=4) had histologically verified serous adenocarcinoma (n=14), mucous adenocarcinoma (n=3), and endometrioid adenocarcinoma (n=6). Recurrent lesions location: vaginal stump and rectum nest (8 sites), liver (6 sites), intestine around (15 sites), hepatic subcapsular region (12 sites). The diameter of the tumor range from 1. 8cm to11. 2cm (median=4. 5cm). Furthermore, the tumors were classified into stage II (n=6), III (n=14), IV (n=3) according to the first surgical pathologic data (Table 1). The patients were divided into 2 groups according to the number of lesions: single lesion group (n=9) and multi- lesions group (n=14).

Materials and equipments

1) ^{125}I seeds were provided by Seeds Biological Pharmacy (Tianjin) Ltd. Tianjin China. 2) Prowess Panther version 4. 72 TPS were provided by Prowess Inc. USA.

Methods and chemotherapy

All patients received ^{125}I seeds brachytherapy combined with gemcitabine chemotherapy. At first the patients were performed with a helical CT scanner with slice thickness from 3mm to 5mm. Images were transferred to computers, then radiologists Conducted 3D image reconstruction through TPS, contoured general tumor volume (GTV) and planning target volume (PTV) next. The planning target volume (PTV) included the CTV plus a 0. 5–1. 0cm expanded margin for daily set-up variation and respiratory movement. The prescription dose (prescribed dose, PD) is set to 100 cGy ~ 130cGy and 90% of planning target Volume should reach the prescription dose (V100 ≥ 90%). Adjacent viscera (organs at risk, OAR) allows less than 10% volume reached the prescribed dose (V100<10%). Matched peripheral dose matching (MPD) should include planning target volume (PTV). According to the plan; we calculated the required particle number, the particle spatial distribution and the dose distribution. At the same time, according to the position of patients, we determined needles' number, depth, angle and the azimuth, designing to come to conformal radiotherapy for target region. The radiologists were responsible for planning and the clinicians who responsible for auditing the planning can make comments on the target delineation and dose around other important organs.

A 12-hour fast was performed and Polyethylene Glycol Electrolyte Powder or clysis was used for patients for whom the puncture through intestine is inevitable. The patients take suitable prone position or supine position in the operation. In addition, the patients can shifted premier position to the lithotomy position when clinicians and radiologists implant through vagina and vaginal stump. We may use analgesics during the punctural process when necessary. The Seed activity was 0. 4 mCi -0. 7 mCi and was implanted in multiple slices with an interval of 0. 5-1. 0cm. When the needlepoint reached the destination, without blood reflux, the implantation can be performed. With strict implementation plan, clinicians should reduce the duration of implantation and avoid repeated puncture through vital organs of liver and intestinal tract as much as possible. All the patients undertook CT scan after the first ^{125}I-seed implantation treatment, making sure that the target area were covered by ^{125}I-seed according to the plan, Otherwise performed feasible implantation when necessary. 8-106 ^{125}I-seeds (median =43) were implanted into Each focus, performing by 2-3 times when the ^{125}I-seeds are too much. Postoperative patients may be given nutritional support treatment and antibiotics to prevent infection, hemostasis.

In one week after initial ^{125}I-seed implantation treatment, the patients received single chemotherapy of gemcitabine (gemcitabine 1000 mg/m^2, 1, 8, 15 days) for 4 cycles.

Evaluation methods

All patients underwent helical CT scan three weeks after and every three months after implantation treatment. And we evaluated the effect after 6 months by CT with 5mm slice thickness according to the evaluation criteria in solid tumors (RECIST) (Sohaib, 2012). Complete remission (CR)was defined as the complete disappearance of all clinically detectable tumors and short size of all the pathologic lymph nodes must be reduced to below 10 mm for at least 4 weeks. A partial response (PR) required at least a 30% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions and there are no new lesions for at least 4 weeks. Progressive disease (PD) required either a 20% increase in measurable lesions or the appearance of any new measurable or non-measurable lesions for at least 4 weeks. Patients who did not meet the definitions of response or progression were classified as stable disease (SD). CR+PR were collectively referred to as Clinical remission. The Common Terminology Criteria for Adverse Events Version 4. 0 was used to score the patient toxicity (Chen et al., 2012).

Follow-up

The follow-up evaluations were performed by the letters or telephones, combining with regular outpatient follow-up review.

Statistical methods

All statistical analyses were performed using the SPSS 18. 0 software package. The exact probability test

was used to process the data. $P < 0.05$ was considered significant.

Results

Follow-up results

The median follow-up for the surviving patients was 20months (range 7to 34 months) as of July 31, 2013. One patient in 18 month after implantation has been out of touch with us. The follow-up rate is 95. 7%.

Short-term curative effects

A total of 23 patients (41 sites) who confirmed as single lesion group (9 cases), double-lesion group (10 cases), triple-lesions group (4 cases), underwent implantation and each site has been implanted 8-106 ^{125}I-seeds (the median=43). All the operations were successful. Twenty-three patients experienced an objective response (CR in 9 sites, PR in 23, PD in 4, and SD in 5) after 6 months, as for the patients are outlined in Table 2. New lesions were found in 6 patients, including 1 case with single lesion, 2 cases with double lesions, 3 cases with three lesions, were detected to have new lesions located in the pelvic floor, paracolic sulci, the dome of the diaphragm, liver and lung parenchyma.

In this context, we hypothesized that the recurrence of epithelial ovarian cancer limited to two or three regions was referred to as multifocal group. The statistical significance of the difference of clinical remission rate of single lesion group and multi-focal-lesion group was assessed using Fisher's exact test with a significance level of 5%. According to our calculations, clinical remission rate of single lesion group (77. 8%)was higher than multifocal group (28. 6%), and the difference was statistically significant (P=0. 036). Among the 8 PD patients, 6 patients had new lesions and 2 patients died of intestinal obstruction caused by abdominal and pelvic multiple masses or hydrothorax and ascites unmanageable respectively.

Adverse reactions

Most of the side effects were mild gastrointestinal reactions such as: nausea, anorexia, abdominal pain, common diarrhea and/or tenesmus. Some patients suffer from fever, dizziness, headache or ^{125}I-seed migration. Another parts of patients had gastrointestinal reaction of nausea, abdominal pain, accompanied by hyperactive bowel sounds near the implant site and vomiting in 2-3days later which remitted after symptomatic treatment. 4 cases of ^{125}I-seeds migration occurred after implantation, 3 in the abdominal cavity, the other in lung, pneumothorax or hemopneumothorax did not occur. Besides, implanting with repeated puncture through the intestinal tract can cause high fever after 1-2 days. In our study, no severe radiation effects, for example intestinal fistula and urinary fistula, were observed.

Table 1. Patients' Characteristics

Features	Isolated recurrence group	Multiple recurrence group
Age (year)		
≤50y	2	4
>50y	7	10
KPS score		
70~80	1	3
≥80	8	11
Initial Surgical stage		
II	3	3
III	4	10
IV	2	1
Histological type		
Serous adenocarcinoma	5	9
Mucinous adenocarcinoma	2	1
Endometrioid adenocarcinoma	2	4
Pathological grading		
Poorly differentiated	3	5
moderately differentiated	2	5
Well differentiated	4	4
Previous courses of chemotherapy		
≥6~<12	6	8
≥12	3	6
Previous surgery		
Only once cytoreductive surgery	7	10
≥2	2	4
Recrudescent-interval(months between latest treatment and relapse		
≤3	3	5
>3~<6	6	9
Diameter of recurrent tumor		
≤4	4	8
>4	5	6

Table 2. Therapeutic Evaluation for Patients

	CR	PR	SD	PD
Isolated recurrence group	5	2	1	1
Multiple recurrence group	2	2	3	7
total	7	4	4	8

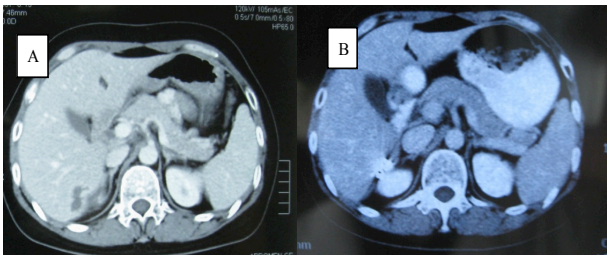

Figure 1. (A) 46-Year-Old Patient, CT Scan of the Recurrent Lesion in the Hepatic Subcapsular Zone. (B) CT Scan Six Months After Implantation (with MPD=130Gy) Shows That the Lesion Almostly Disappear

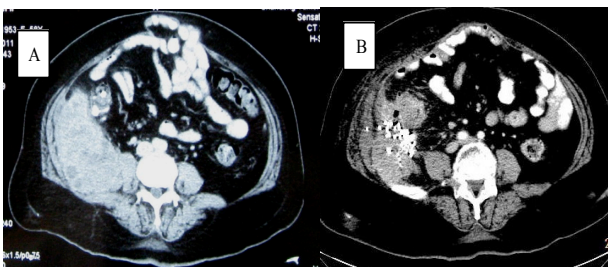

Figure 2. (A) 58-Year-Old Patient, the Recurrent Lesion, Located in Right Iliac Fossa, is Considered Impossible to be Resected. (B) Six Months After Implantation, the Lesion Partial Remission

Discussion

CT-guided radioactive ^{125}I-seed implantation treatment has been applied in liver cancer, non-small cell lung cancer and other tumors which have been proven to have some advantages of fewer traumas, high local control rate, less impact on the surrounding normal organs, and there are rarely reports for applications in ovarian cancer. (Nurwidya et al., 2012; Ding et al., 2013; Kesarwala et al., 2013) Hockel reported 48 patients with gynecological malignant metastatic tumor in pelvic wall with no serious toxicity after implantation, and the local control rate was 68% (Hockel et al., 1996). Mart í nez-Monge have reported that 4years' local control rate was 82. 5% for 183 patients with malignant tumor, including 23 cases of gynecologic malignant tumors (Martinez-Monge and Cambeiro, 2005). After implantation, gamma radiation can effectively guarantee the effect by precise radiotherapy. At the same time, gamma-ray who have advantages of attenuation fast and low dose rate can be defended easily, avoiding severe injury to important organs nearby (Rogers et al., 1997; Peng et al., 2014). In our study, 23patients (41 lesions) had objective response (CR in 9 lesions, PR in 23 lesions) after implantation and lesions remission rate is78. 0%. It shows that radioactive ^{125}I-seed implantation treatment for local lesion of ovarian cancer have better control rate and prognosis.

Once ovarian cancer resistant to Platinum, changing the treatment into second-line chemotherapy is useless. Even if using the relatively sensitive drug, such as gemcitabine, doxorubicin, tunicamycin and ifosfamide, the clinical remission rate is only about 10%-20% (Hiss et al., 2007; Chumworathayi, 2013; Pitakkarnkul et al., 2013; Su et al., 2013). Because this group of patients have treated with multiple cycles of chemotherapy, causing hematological and non hematological toxicity accumulation, we chosed only single gemcitabine combined with ^{125}I-seed implantation treatment as the therapy for patients. According to reports in the literature, Gemcitabine is active in OC (15% to 28% RR) and has a good toxicity profile, which suggest possible combinations with other active treatment (Lund et al., 1994; Shapiro et al., 1996). Ultimately, the total clinical remission rate was 47. 8 % (single lesion group was 77. 8%, multifocal lesions group was 28. 6%), higher than single gemcitabine chemotherapy. Thus it can be seen implantation combining with chemotherapy is better than simple chemotherapy for the treatment of ovarian cancer. The next step, we can further clarify the effect of implantation combined with chemotherapy, comparing with simple chemotherapy for recurrent ovarian carcinoma in the same period.

There were significant differences in clinical remission between patients with single lesion (positive for clinical remission in 7of 9 patients) and multifocal lesions (positive for clinical remission in 4 of 14 patients). The local control rate was 77. 8% (7/9) for single-lesion group and 78. 1% (25/32) for mutile-lesions group, with no significant difference between them (P=0. 340). But, during follow-up, new lesions was observed in 1 patient for single lesion group while 4 patients for mutile-lesions group. This suggested that the curative effect may decrease with increasing number of lesions. The reason may lie in the properties of ovarian cancer of metastasizing to abdominal cavity readily. Multiple lesions indicated the existence of small lesions and higher incidence of dissemination, eventually leading to treatment failure. So we suggest that patients who have limited recurrent lesions (<3) can be chosen for ^{125}I-seed brachytherapy. For the same reason, we recommend that the relatively sensitive second-line chemotherapeutics can be used concomitantly for patients to control the growth of metastatic lesions. It also conforms to the advantage of ^{125}I seeds brachytherapy: deliver high dose to the tumor with a minimal damage to normal brain tissue (Schwarz et al., 2012).

The common sites of recurrent ovarian carcinoma are vaginal stump, colon, liver capsule and adjacent liver parenchyma, which adjoin important organs and are almost impossible to complete resection. Through a ccurate implantation of ^{125}I-seed, we can achieve satisfactory tumor conformal radiotherapy, and avoid serious adverse effect on the surrounding organs. As shown in Figure 1, it is difficult to exposure and resects the tumors which were located in the right hepatic lobe. After 6 months of implantation of ^{125}I-seed, lesions were completely relieved from the results of CT follow-up. In Figure 2, a tumor near the colon infringed on iliopsoas, leading to persistent low back pain, then surgical resection was attempted but the tumor cannot be removed easily, after be treated by seed implantation, pain in patients was significantly relieved and the tumor remitted after 6 months. The patients with recurrent ovarian cancer often subject to repeated surgical resection and treatment, resulting in poor quality of life. The vast majority of patients can tolerate of ^{125}I-seed implantation treatment because it has little trauma and risks as a palliative therapy. So the ^{125}I-seed implantation treatment with high local control effect and small side effect was especially suitable for patients with advanced ovarian cancer who cannot tolerate operation, and significantly improved the life quality of the patients.

We suggest that the gynecological tumor implantation should be carried out through the cooperation of gynecologists and radiologists. During the procedure, the following points should be noted: 1) Approaches, such as percutaneous, transhepatic, intestinal and vaginal methods, can be chosen. 2) When the implantation goes through important organs, try to avoid repeated puncture. 3)According to preoperative CT with the TPS system, we make detailed plan, then guide implantation by CT in the operation, and verify after operation using CT. 4)the implanted seeds are more than 1cm from portal, vascular and intestinal tissues.

The side effect was mild gastrointestinal reactions only. We can hear hyperactive bowel sounds near the implant site by auscultation, considering as the reaction of the intestinal tract caused by radiation stimulation. Abdominal pain, diarrhea and tenesmus can be improved after symptomatic treatment. Some patients with nausea and vomiting can be treated with short-term nutritional support. In this study, we observed that the degree and duration of gastrointestinal tract reaction was related to implantation sites and the number of ^{125}I-seed. So that

for the patients who had multiple lesions and should be implanted abundant ^{125}I-seed, the seeds can be implanted at intervals of 1 ~ 2 weeks in order to reducing the gastrointestinal reaction. Two patients had no obvious symptoms when the ^{125}I-seed disseminated to intestinal clearance with abdominal tumor regression. During the follow-up period, we did not observed serious side effects of intestinal fistula or urinary fistula. Thus it can be seen the toxicity of implantation for recurrent ovarian carcinoma was relatively small.

In summary, radioactive ^{125}I-seed implantation treatment combined with chemotherapy for curative intent in ovarian cancer patients with limited recurrence could achieve a better local control rate without severe toxicity, and is a promising treatment that can significantly improve the quality of life of patients in advanced stage. We proposed to give priority to implantation for patients with single recurrent lesion. At least, because the follow-up period is short, curative effect and complications of this therapy need further evaluations.

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