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Efficacy of computed tomography-guided implantation of ^{125}I seeds in the treatment of refractory malignant tumors accompanied with cancer pain and its influence on tumor markers in the serum

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Abstract. – OBJECTIVE: This study intended to explore the efficacy of computed tomography (CT)-guided implantation of iodine-125 (^{125}I) seeds in the treatment of refractory malignant tumors with cancer pain and its influence on tumor markers in the serum.

PATIENTS AND METHODS: 76 patients with refractory malignant tumors accompanied by cancer pain that received treatments in LongHua Hospital Shanghai University of Traditional Chinese Medicine from September 2013 to August 2014 were selected. They were divided into control group and observation group using a random number table (38 patients in each group). Patients in the control group received simple chemotherapy, while those in the observation group undergone CT-guided implantation of ^{125}I seeds in combination with chemotherapy. Recent efficacy and 1-3-year survival rate were compared between the two groups of patients. The degree of pain relief after treatment was also compared between the two groups of patients. Electrochemiluminescence method was used to detect the concentrations of carcinoembryonic antigen (CEA), sugar chain antigen 199 (CA 199), sugar chain antigen 125 (CA 125), neuron-specific enolase (NSE) and cytokeratin-19-fragment (CYFRA21-1) in the two groups of patients before treatment, and 3 days, 7 days and 30 days after treatment.

RESULTS: Recent disease control rate of the patients in the observation group was higher than that of the patients in the control group ($p<0.05$). The 1-3-year survival rate after surgery in the observation group was significantly higher than that in the control group ($p<0.05$). The total efficiency of pain control in the observation group was significantly higher than that in the control group ($p<0.05$). The levels of tumor markers in the two groups of patients were significantly decreased after treatment, while the reduction in the observation group was more evident than that in the control group ($p<0.05$).

CONCLUSIONS: Our results showed that CT-guided implantation of ^{125}I seeds is effective for the treatment of patients with refractory malignant tumors accompanied by cancer pain. It can reduce the levels of tumor markers, improve the survival rate and prolong the survival time of the patients.

Key Words:
CT-guided, Implantation of ^{125}I seeds, Refractory malignant tumors, Cancer pain, Tumor markers.

Introduction

Malignant tumors are a serious threat to human health and they are one of the main causes of human death[1]. Cancer pain is the most common symptom of patients with malignant tumors. About a quarter of patients experience pain in the early stage of the disease and more than half of patients are accompanied with different degrees of cancer pain in the middle or advanced stage, which seriously affects the patients' quality of life[2]. Refractory malignant tumors accompanied by cancer pain have always been difficulties of clinical treatment. Physicians usually help patients relieve pain by giving a large dose of opioids, which has a poor effect and great side effects; thus, the patients have extremely poor tolerance and taking the side effects of conventional chemotherapy into consideration as well[3]. Implantation of ^{125}I seeds is a kind of in-vivo chemotherapy, which not only has advantages such as low-dose continuous irradia-

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tion, accurate targeting and killing the tumor cells in a short distance, but also has a certain inhibitory effect on cancer pain. It is an important adjunctive treatment method for refractory malignant tumors[4,5]. Carcinoembryonic antigen (CEA), sugar chain antigen 199 (CA 199), sugar chain antigen 125 (CA 125), neuron-specific enolase (NSE) and cytokeratin-19-fragment (CYFRA21-1) are generally taken as tumor markers clinically for diagnosis of malignant tumors and efficacy evaluation[6]. In this study, computed tomography (CT)-guided implantation of ^{125}I seeds was conducted in the patients with refractory malignant tumors accompanied with cancer pain to analyze its efficacy and its influence on tumor markers in the serum.

Patients and Methods

Patients

76 patients with refractory malignant tumors accompanied by cancer pain who received treatments in LongHua Hospital Shanghai University of Traditional Chinese Medicine from September 2013 to August 2014 were selected. They were divided into a control group receiving simple chemotherapy and an observation group receiving CT-guided implantation of ^{125}I seeds in combination with chemotherapy by using a random number table (38 patients in each group). Inclusion criteria: (1) patients that were diagnosed with refractory malignant tumors via imaging and pathological examinations; (2) patients accompanied with cancer pain with the estimated lifetime >3 months; (3) patients that signed the informed consent form. Exclusion criteria: (1) patients with continuous symptoms excluding cancer pain; (2) patients with severe coagulation disorders. The comparisons of general data between the two groups of patients had no statistical significance (p>0.05) (Table I). The study was approved by the Ethics Committee of LongHua Hospital Shanghai University of Traditional Chinese Medicine.

Methods

Treatment

Patients in the control group received simple chemotherapy. They adopted standard chemotherapy regimen with Gemcitabine [manufacturer: Qilu Pharmaceutical (Hainan) Co., Ltd.; approval number: GYZZ H20113286]. The drug was given in a dose of 1,000 mg/m^2 weekly by intravenous drip within 30 minutes. If the patients suffered from severe toxic or side effects during treatment with chemotherapy, the dose needed to be reduced to 800 mg/m^2 for three consecutive weeks followed by one-week rest as a treatment course.

Patients in the observation group received CT-guided implantation of ^{125}I seeds in addition to the treatment adopted in the control group. The radioactive ^{125}I seeds used in the treatment were provided by Isotope Research Institute of Beijing Atomic Energy Research Institute. Activity of the seeds: 0.5-0.7 mCi. CT scan was performed on the corresponding surface area of the lesion according to the position of the tumor determined by preoperative CT scan. The positioning function of CT scan was used to draw the puncture point on the patient's body surface. Real-time CT scan results were used to adjust the depth, direction, and angle of the needle tip until the deepest site of the tumor lesion was reached. ^{125}I seeds were implanted with an implanting gun at an interval of 0.5 cm. After implantation, gelatin sponge and hemostatic gauze were applied on the puncturing points.

Detection of tumor markers

3-5 mL of venous blood was collected from the two groups of patients before treatment, and 3 days, 7 days and 30 days after treatment. The concentrations of CEA, CA199, CA125, NSE and

Table I. Comparisons of general data between the two groups of patients.

Item	Control group (n=38)	Observation group (n=38)	t/χ^2	p-value
Sex (male/female)	20/18	22/16	0.053	0.818
Age (years old)	40-70	40-75		
Average age (years old)	56.78±6.43	56.32±6.57	0.308	0.759
Tumor types (n, %)				
Pancreatic cancer	13 (34.21)	12 (31.58)	0.244	0.885
Lung cancer	14 (36.84)	13 (34.21)		
Liver cancer	11 (28.95)	13 (34.21)		

CYFRA21-1 were detected by electrochemiluminescence strictly as per package inserts of relevant kits (manufactured by Roche Corporation, Indianapolis, IN, USA).

Evaluation Criteria

After one-month treatment, the efficacy in the patients was evaluated as per response evaluation criteria in solid tumors. Judgment criteria: complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). (1) CR: All the lesions disappeared, which was maintained for not less than 4 weeks. (2) PR: The maximum diameter of the tumor was shrunk by not less than 50%, which was maintained for not less than 4 weeks. (3) SD: non-CR or PR. (4) PD: The sum of the diameter of the target lesion was relatively increased by not less than 20%, and new lesions were observed. Disease control rate (DCR) = (CR+PR+SD) / total cases[7]. A follow-up visit was conducted for 3 years to observe the survival rate of the patients.

After one-month treatment, visual analogue scale (VAS) was adopted to evaluate the pain-control degree of the patients. The range of the score was 0-10 points (0 points referred to painless; 10 points referred to unbearable severe pain). Judgment criteria: (1) Grade I: VAS score was 0-2 points, which referred that the patient was free from pain or suffered from mild pain that was hard to be perceived. (2) Grade II: VAS score was 3-5 points, which indicated that the patient suffered from tolerable pain. (3) Grade III: The score was 6-8 points, which indicated that the patient suffered from pain which influenced on normal activities. (4) Grade IV: The score was not less than 8 points, which meant that the patient suffered from intolerable pain[8].

3-5 mL of venous blood was collected from the patients before treatment, and at 3 days, 7 days and 30 days after treatment to detect concentrations of tumor markers including CEA, CA199, CA125, NSE and CYFRA21-1.

Statistical Analysis

The data were processed by Statistical Product and Service Solutions (SPSS) 19.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA). Measurement data were expressed as mean ± standard deviation ($\bar{\chi} \pm s$). The *t*-test was adopted for the comparison between groups, and repeated measures analysis of variance was used for the comparison within a group. Enumeration data were expressed as rate, and compared by χ^2-test. Rank-sum test was adopted for comparison of efficacy. $p<0.05$ suggested that the difference was statistically significant.

Results

The comparison of efficacy between the two groups of patients showed that DCR of patients in the observation group (92.11%) was significantly higher than that of patients in the control group (65.79%). The difference had statistical significance ($p<0.05$) (Table II).

The comparison of survival condition between the two groups of patients showed that the 1-3-year survival rate in the observation group was significantly higher than that in the control group ($p<0.05$) (Table III).

Table II. Comparison of recent efficacy between the two groups of patients (n, %).

Group	No.	CR	PR	SD	PD
Observation group	38	14 (36.84)	13 (34.21)	8 (21.05)	3 (7.89)
Control group	38	6 (15.79)	8 (21.05)	11 (28.95)	13 (34.21)

Note: Rank-sum test was adopted for comparison of efficacy between the two groups of patients, which showed that $z=3.168$ and $p=0.013$.

Table III. Comparison of follow-up visit condition between the two groups of patients.

Group	No.	One-year survival rate (n, %)	Two-year survival rate (n, %)	Three-year survival rate (n, %)
Observation group	38	36 (94.74)	31 (81.58)	25 (65.79)
Control group	38	28 (73.68)	22 (57.89)	15 (39.47)
χ^2		4.849	3.990	4.275
p		0.027	0.046	0.039

Comparison of pain between the two groups of patients showed that one treatment course later, PCR of patients in the observation group was significantly higher than that of patients in the control group (p<0.05) (Table IV).

Comparisons of tumor markers between the two groups of patients before and after treatment showed that CEA, CA199, CA125, NSE and CYFRA21-1 were decreased significantly in the two groups, while the reduction in the observation group was more evident than that in the control group (p<0.05) (Tables V-IX).

Table IV. Comparison of pain rate between the two groups of patients.

Group	No.	Grade I pain	Grade II pain	Grade III pain	Grade IV pain
Observation group	38	29 (76.32)	9 (23.68)	0 (0.00)	0 (0.00)
Control group	38	13 (34.21)	11 (28.95)	8 (21.05)	6 (15.79)
χ^2			20.294		
p			0.001		

Table V. Comparisons of CEA between the two groups of patients before and after treatment (ng/mL).

Group	No.	Before treatment	3 days after treatment	7 days after treatment	30 days after treatment	f	p
Observation group	38	3.26±1.12	2.92±0.53	2.67±0.42	2.36±0.37	26.347	<0.001
Control group	38	3.27±1.18	3.21±0.62	2.95±0.57	2.75±0.43	17.736	<0.001
t		0.038	2.192	2.438	4.238		
p		0.970	0.031	0.017	<0.001		

Table VI. Comparisons of CA199 between the two groups of patients before and after treatments (U/mL).

Group	No.	Before treatment	3 days after treatment	7 days after treatment	30 days after treatment	f	p
Observation group	38	14.65±2.14	11.36±1.63	10.13±1.12	8.13±1.02	21.325	<0.001
Control group	38	14.76±2.23	13.43±1.75	12.26±1.47	10.76±1.17	16.812	<0.001
t		0.219	5.336	7.105	10.445		
p		0.827	<0.001	<0.001	<0.001		

Table VII. Comparisons of CA125 between the two groups of patients before and after treatments (U/mL).

Group	No.	Before treatment	3 days after treatment	7 days after treatment	30 days after treatment	f	p
Observation group	38	13.65±2.15	10.36±1.16	9.03±1.07	7.03±1.08	21.482	<0.001
Control group	38	13.76±2.24	12.73±1.26	11.26±1.26	9.47±1.13	14.957	<0.001
t		0.218	8.530	8.316	9.623		
p		0.828	<0.001	<0.001	<0.001		

Table VIII. Comparisons of NSE between the two groups of patients before and after treatment (ng/mL).

Group	No.	Before treatment	3 days after treatment	7 days after treatment	30 days after treatment	f	p
Observation group	38	17.94±2.14	15.28±1.23	12.03±1.12	10.03±1.07	31.423	<0.001
Control group	38	17.86±2.23	16.83±1.75	15.36±1.57	13.46±1.32	16.825	<0.001
t		0.160	4.467	10.644	12.443		
p		0.873	<0.001	<0.001	<0.001		

Table IX. Comparisons of CYFRA21-1 between the two groups of patients before and after treatment (ng/mL).

Group	No.	Before treatment	3 days after treatment	7 days after treatment	30 days after treatment	*f*	*p*
Observation group	38	2.78±0.62	2.51±0.37	2.23±0.36	2.02±0.26	16.062	<0.001
Control group	38	2.76±0.61	2.69±0.41	2.54±0.36	2.38±0.27	9.624	<0.001
t		0.142	2.009	3.753	5.920		
p		0.887	0.048	<0.001	<0.001		

Discussion

Patients with malignant tumors, especially those in the middle or advanced stage are usually accompanied by cancer pain. Moderate or severe cancer pain will exert a great impact on the patients' quality of life, which is reflected in the patients' interpersonal communication, sleep quality, depression, anxiety and other aspects[9]. Cancer pain is usually caused by multiple parts. The mechanism of cancer pain is diversified, and malignant tumor can lead to changes in the microenvironment of the body, in which the sensory receptor can be activated not only by the altered chemical constituents, but also by the extrusion and traction of the tumors[10]. With the transformation of medical model from a single biomedical model to a biological-physiological-social medical model, the treatment of malignant tumors not only focuses on the shrinking of the tumors, but also begins to emphasize the patients' quality of life. Therefore, how to control the patient's cancer pain is of great importance on the premise that the efficacy is ensured.

At the beginning of last century, radioactive seeds began to be used for the treatment of malignant tumors clinically[11]. In recent years, with the continuous development of radiobiology and physics, the implantation of radioactive seeds[12] has been increasingly applied to treat solid tumors. Common radionuclide sources include ^{137}Cs, ^{125}I, ^{192}Ir and so on. The results of this study showed that DCR of patients in the observation group (92.11%) was significantly higher than that of patients in the control group (65.79%) (p<0.05), which may be because ^{125}I seeds are attenuated by capturing electrons, meanwhile they can release characteristic electrons and photons, and emit X-rays and γ-rays. The half-value layer is 2 cm, which is convenient for shielding and protection, and will not change with the movement of the irradiation site in the target area. The irradiation dose can be controlled within the established target area to kill the tumor cells, which will not cause damage to the surrounding normal tissue cells. In addition, the half-life period of ^{125}I seeds is relatively long (60.1 days), and the irradiation time is also comparatively long, which can exert impacts on target lesions sustainably[13], thus efficacy is obvious. Therefore, the survival time of patients in the observation group is prolonged and 1-3-year survival rate of patients in the observation group is higher than that of patients in the control group (p<0.05).

Pain is the most common physiological and psychological symptom in clinic, which is usually divided into neuropathic pain and nociceptive pain[14]. Patients with refractory malignant tumors accompanied with cancer pain usually suffer from the two types of pain simultaneously, and the pain will be more and more obvious as drug dose increases, tumor grows and side effects of drugs occur continuously[15]. This study showed that the total efficiency of pain control in the observation group was significantly higher than that in the control group (p<0.05). The reason of the results may be that ^{125}I seeds can provide continuous superimposed radiation, which is easier to make the tumors shrunk than simple chemotherapy, thus alleviating the pain caused by the extrusion and traction of the tumors on the peripheral nerves. Meanwhile, ^{125}I seeds can reduce the release of various pain-inducing factors by killing tumor cells effectively, and resist the permeation of pain-inducing factors through irradiation to cause vascular thrombosis in the mass or beside the tumor, thus relieving the effect[13].

Tumor markers are substances that are secreted or shed from tumor cells, which usually enter into blood circulation in the human body and are detected in the patient's serum at a relatively low dose. These tumor markers include NSE, CYFRA21-1, CA199, CA125, CEA and so on. They can be detected to diagnose tumors, provide guidance for treatment, judge prognosis of the

patients and so on[16,17]. CEA is one of the most widely used tumor markers in clinical practice. It is an antigen in tumor tissues and can be detected in the serum of various cancer patients[18]. NSE is an enzyme in neurons and neuroendocrine cells, which cannot only be used as a marker for tumor diagnosis, but also provide a sensitive judgment on the prognosis of patients[19,20]. CYFRA21-1 refers to two fragments of cytokeratin 19 in the cytoplasm of tumor cells. CA199 and CA125 are frequently used for the diagnosis of liver or gallbladder cancer [21]. The results of this study showed that CEA, CA19, CA125, NSE, and CYFRA21-1 in the two groups of patients were reduced significantly compared with those before treatment, and the reduction in the observation group was more definite than that in the control group ($p<0.05$), which was strongly correlated with the more uniform dose distribution in the implantation of ^{125}I seeds and the continuous irradiation which is effective for inhibiting and killing the tumor cells[13].

Conclusions

In the treatment of patients with refractory malignant tumors accompanied with cancer pain, the CT-guided implantation of ^{125}I seeds can effectively shrink the tumors, prolong survival time, relieve cancer pain and reduce the level of tumor markers for the patients. It has a wide application range, which is worthy of being popularized for clinical application.

Conflict of Interest

The authors have no conflicts of interest to declare.

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