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Research Article

Magnetic Resonance Diffusion-Weighted Imaging to Evaluate the Clinical Efficacy of CalliSpheres Drug-Loaded Microspheres in the Treatment of Advanced Bladder Cancer

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The MR diffusion-weighted imaging technique was used to evaluate the efficacy and safety of CalliSpheres drug-loaded microspheres for transarterial chemoembolization in the treatment of advanced bladder cancer. 35 patients with advanced bladder cancer were treated with CalliSpheres DLMS for transarterial chemoembolization. Imaging techniques such as magnetic resonance (MR) diffusion-weighted imaging were used to evaluate the therapeutic effect. The changes in serum tumor markers, immune function indexes, and oxidative stress indexes in patients before and after treatment were compared, and the quality of life of patients and the incidence of adverse reactions during follow-up were also evaluated. The results showed that the overall response rate (ORR) was 74.29% and that the disease control rate (DCR) was 97.14%. Compared with that before treatment, the ADC value of the tumor in patients with advanced bladder cancer detected by MR diffusion-weighted imaging technology was significantly increased after treatment and the maximum tumor diameter was significantly decreased ($P < 0.05$). Compared with those before treatment, the levels of serum tumor markers (CA199, CA724, and CA125) in advanced bladder cancer patients after treatment decreased ($P < 0.05$). The levels of T-lymphocyte subsets (CD3+ and CD4+) decreased, and CD8+ levels increased ($P < 0.05$). The levels of superoxide dismutase decreased ($P > 0.05$). At the same time, the subscale evaluation of function, symptoms, quality of life, adverse reactions, and economics of patients with advanced bladder cancer on the QLQ-C30 scale improved after treatment, and the incidence rate and recurrence rate during the follow-up period were 8.57% and 11.43%, respectively. It showed that CalliSpheres DLMS had a good clinical effect and high safety in the treatment of advanced bladder cancer and was a safe and feasible treatment method. The use of MR diffusion-weighted imaging technology could achieve quantitative evaluation of clinical efficacy of advanced bladder cancer.

1. Introduction

Bladder cancer is a very common urological malignant tumor in clinical practice, and most patients are accompanied by symptoms such as painless or intermittent urinary frequency, urgency, and hematuria. In recent years, there has been a trend of increasing incidence rates [1]. According to the degree of tumor invasion, bladder cancer can be divided into muscle-invasive bladder cancer and non-muscle-invasive bladder cancer. Among them, muscle-invasive bladder cancer has a high degree of malignancy and a high risk of metastasis and recurrence after treatment [2]. Radical cystectomy is a common method for clinical surgical treatment of muscle-invasive bladder cancer. However, surgical treatment brings great trauma to patients, and the postoperative complication rate and the recurrence rate are high, which can easily affect the bladder function of patients and then easily lead to a poor prognosis of patients [3]. Therefore, transcatheter internal iliac artery infusion chemotherapy has become one of the important methods for the treatment of bladder cancer. When bladder cancer patients cannot undergo radical cystectomy, transcatheter internal iliac artery infusion chemotherapy can significantly improve the patients' quality of life and prolong survival [4].

The traditional embolic agent (Lipiodol) is not easy to enter the blood-supplying artery of the tumor, which affects the therapeutic effect of transarterial chemoembolization. Drug-loaded microsphere (DLMS)-transarterial chemoembolization is a new type of drug-loaded embolization system. It can prolong the action time of the drug by injecting high doses of chemotherapy drugs into the tumor and reduce adverse reactions caused by chemotherapy drugs entering systemic blood circulation [5]. Compared with traditional transarterial chemoembolization, DLMS-transarterial chemoembolization has been demonstrated to have lower treatment toxicity and a lower incidence of postoperative adverse events [6, 7]. CalliSpheres DLMS is a novel drug-loaded embolization system made in China. At present, studies have confirmed that CalliSpheres DLMS can significantly improve the clinical symptoms of patients with lung cancer and help in its treatment, and it has good safety [8]. However, there are relatively few studies on the application of CalliSpheres DLMS for transarterial chemoembolization in bladder cancer.

Conventional MRI technology can evaluate the treatment effect through the morphological changes in the tumor, but it cannot distinguish the internal state of the tumor tissue during the treatment process, which is not conducive to the optimization of the treatment method. MR diffusion-weighted imaging technology is a kind of noninvasive functional examination method, which can assist in the diagnosis of diseases and the detection of curative effects through the changes in the diffusion movement of water molecules in tumor tissue. Therefore, this work selected patients with advanced bladder cancer who could not be treated with radical bladder cancer as research objects. First, the clinical effect of CalliSpheres drug-loaded microsphere-transarterial chemoembolization on patients was analyzed by MR diffusion-weighted imaging technology. Then, the effects of the immune function, oxidative stress level, quality of life, and incidence of adverse reactions were also detected. It aimed to provide reference for the popularization and application of CalliSpheres drug-loaded microsphere-transarterial chemoembolization.

2. Materials and Methods

2.1. Research Objects. 35 patients diagnosed with advanced bladder cancer in hospital from May 2019 to December 2021 were selected as the research subjects, including 21 males and 14 females. The age ranged from 48 to 75 years, with an average of 59.5 ± 4.9 years, the disease duration was 3–5 years, with an average of 3.6 ± 0.7 years, and 18 cases were in T3 stage and 17 cases were in T4 stage. This study was approved by the ethics committee of hospital, and all patients gave informed consent.

Inclusion criteria were as follows: those who were unable or unwilling to undergo surgical treatment; those who were staged as T3 or T4 according to the TNM staging standard developed by the International Union Against Cancer [9]; those with obvious clinical symptoms, such as repeated hematuria, dysuria, and bladder irritation; and those who received transarterial chemoembolization for the first time.

Exclusion criteria were as follows: those with a history of surgical treatment such as radical cystectomy; those with liver or kidney insufficiency and coagulation dysfunction; patients with secondary active infection and hypersensitivity to contrast agents; and those with the Karnofsky score less than 70 and expected survival less than 3 months.

2.2. Treatment Methods. The right or left femoral artery was selected as the puncture vessel, and after laying a sterile drape, 2% lidocaine was used for local anesthesia; the modified Seldinger technique was used to puncture the femoral artery. A 5 F catheter sheath was placed, and the guide wire was introduced into the Cobra catheter. After internal iliac arteriography, the blood supply artery to the bladder tumor was searched and the location, number, size, and staining of the tumor were confirmed. 50–100 mg of oxaliplatin was injected into the blood vessel of the bladder tumor. Then, 20–40 mg of pirarubicin was mixed with CalliSpheres drug-loaded microspheres and mixed with the contrast agent 10 min later. The prepared CalliSpheres drug-loaded microspheres were embolized slowly at the blood supply artery of the bladder tumor, and the chemical embolism treatment was performed. The contralateral target vessel was selected using the looping technique, and chemoembolization was performed using the same method. For patients with difficulty in the arterial supply of bladder tumors, internal iliac transarterial chemoembolization should be performed, and the superior gluteal artery should be avoided during embolization. After treatment, hydration and diuresis should be given, and anti-infective treatment should be carried out according to the actual situation of the patient. The evaluation of the embolization effect of CalliSpheres DLMS using contrast imaging technology should be carried out. If the drug-loaded microspheres cannot reach the end point of embolization, drug-loaded microspheres can be mixed with the appropriate blank microspheres of equal specification before embolization treatment.

2.3. MR Diffusion-Weighted Imaging. 50 minutes before the MR diffusion-weighted imaging scan was performed, the patient was instructed to drink 500–1,000 ml of water without urinating, so that the patient's bladder could be filled. Cross-sectional MR diffusion-weighted imaging scans were performed with PHILIPS Achieva 3.0T MR, 4-channel torso coils were selected, and respiratory gating was not used. MR diffusion-weighted imaging scans used a spin-echo-echo planar imaging sequence. The parameters were set as follows: repetition time = 1,000 ms, echo time- = minimum, number of excitations = 8, matrix = 125×125, field of view = 40×40 cm^2, slice thickness = 5 mm, and slice spacing = 1 mm. The diffusion sensitive gradient factor in the scanning process, that is, the b value, was taken as 1,500 s/mm^2. At the same time, the array spatial sensitivity encoding technique (APSET) was collected, the acceleration factor R value was set to 2, and MRI examinations before and after interventional treatment were performed. The MRI images obtained by scanning were transmitted to the workstation, the images were read by 2 professional radiologists, and the

region of interest at the lesion was manually delineated. Irregular margins of the lesions were delineated into hyperintense lesions, and the mean tumor ADC values were calculated.

2.4. Efficacy Evaluation and Observation Indicators. The treatment effect of solid tumors was evaluated as follows: The evaluation of the treatment effect of patients with solid tumors was carried out 4 weeks after embolization. Imaging techniques were used to measure the maximum tumor diameter, and treatment effects were classified into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). It was considered that the imaging technology examination showed that the tumor completely disappeared as CR, that the tumor diameter was reduced by 30% or more after treatment as PR, that the tumor diameter decreased by −20%–30% after treatment as SD, and that the tumor diameter increased by 20% or more after treatment was considered as PD. The overall response rate (ORR) = (CR + PR)/total number ∗ 100%. The disease control rate (DCR) = (CR + PR + SD)/total number ∗ 100%.

Fasting venous blood was collected from patients before treatment and 15 days after treatment, serum was extracted, and the levels of tumor markers were detected. An automatic electrochemiluminescence immunoassay was used to detect the content of tumor markers of carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), carbohydrate antigen 724 (CA724), and carbohydrate antigen 125 (CA125) in serum.

Before treatment and 15 days after treatment, the patient's venous blood was collected and the serum was extracted. An automatic cell analyzer was used to detect the levels of T-lymphocyte subsets (CD3+, CD4+, and CD8+) in the serum, and CD4+/CD8+ was calculated at the same time.

Before and 15 days after treatment, venous blood was collected and serum was extracted from patients. The xanthine oxidase method was used to detect the oxidative stress index superoxide dismutase (SOD) level in serum.

The quality of life of patients was assessed using the Quality of Life Core Questionnaire containing 30 items (QLQ-C30) [10] prepared by the European Organization for Cancer Research and Treatment. The five functional subscales on the QLQ-C30 scale were the physical function, role function, cognitive function, emotional function, and social function. The 3 symptom subscales were fatigue, pain, and nausea; there was 1 overall quality of life subscale; 5 adverse reactions were dyspnea, insomnia, loss of appetite, constipation, and diarrhea; and 1 economic item was an economic impact. The higher the score of the functional scale and the overall quality of the life scale on the QLQ-C30 scale and the lower the score of the symptom and adverse reactions scale, the better the patient's quality of life.

A follow-up period of 36 months was selected after treatment, with the patient's death or the study period as the termination date. The incidence of adverse reactions such as hematuria, urinary incontinence, and bladder perforation during the follow-up period of the patients was counted.

2.5. Statistical Processing. Statistical analysis of the data was performed using SPSS 19.0 software. Enumeration data were expressed as frequencies (percentages), and differences between groups were compared using the chi-square test. Enumeration data were expressed as a mean ± standard deviation, and differences between groups were compared using the independent samples t-test. $P < 0.05$ meant that the difference was statistically significant.

3. Results

3.1. Clinical Outcomes of CalliSpheres DLMS in Patients with Advanced Bladder Cancer. The clinical effect of CalliSpheres DLMS in the treatment of advanced bladder cancer was analyzed, and the results are shown in Figure 1. After CalliSpheres DLMS treatment of 35 advanced bladder cancer patients, the clinical treatment effect was evaluated as CR in 4 patients (11.43%), PR in 22 patients (62.86%), SD in 8 patients (22.86%), and PD in 1 patient (2.86%). After calculation of ORR and DCR, 26 cases (74.29%) had ORR and 34 cases (97.14%) had DCR.

3.2. Imaging Evaluation of CalliSpheres DLMS in Patients with Advanced Bladder Cancer. Quantitative evaluation of the effect of advanced bladder cancer before and after CalliSpheres DLMS treatment using conventional MRI, MR diffusion-weighted imaging, and CT imaging was performed. Evaluation indicators included ADC and the maximum tumor diameter, and the results are shown in Figure 2. The ADC value and the maximum diameter of the bladder tumor before treatment were $1.19 \pm 0.10 \times 10^{-3}$ mm^2/s and 5.82 ± 1.33 cm, respectively, and the quantitative indexes after treatment were $1.42 \pm 0.11 \times 10^{-3}$ mm^2/s and 1.71 ± 0.46 cm, respectively. After treatment, the ADC value of the tumor in advanced bladder cancer patients was significantly higher than that before treatment, while the maximum tumor diameter was significantly smaller than that before treatment, and the difference was statistically significant ($P < 0.05$).

3.3. Changes in Serum Tumor Markers in Advanced Bladder Cancer Patients Treated with CalliSpheres DLMS. The differences in the levels of serum tumor markers (CEA, CA199, CA724, and CA125) in advanced bladder cancer patients before and after CalliSpheres DLMS treatment were detected, and the results are shown in Figure 3. Before treatment, the serum levels of CEA, CA199, CA724, and CA125 were 41.25 ± 5.36 ng/mL, 122.58 ± 7.54 U/mL, 89.37 ± 8.97 U/mL, and 71.22 ± 8.05 U/mL, respectively. The levels of each index after treatment were 15.61 ± 4.75 ng/mL, 38.93 ± 6.12 U/mL, 21.60 ± 5.63 U/mL, and 30.95 ± 6.61 U/

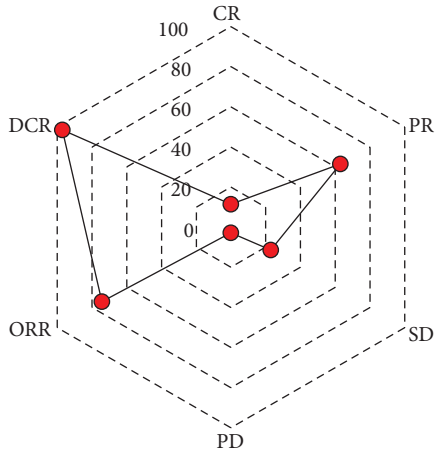

Figure 1: Evaluation of the clinical treatment effect of advanced bladder cancer patients. CR, complete remission; PR, partial remission; SD, stable disease; PD, disease progression; ORR, overall response rate; DCR, disease control rate.

mL, respectively. The serum levels of various tumor markers in advanced bladder cancer patients after treatment were significantly lower than those before treatment, and the difference was statistically significant ($P < 0.05$).

3.4. Changes in the Immune Function in Advanced Bladder Cancer Patients Treated with CalliSpheres DLMS. The differences between the levels of serum T-lymphocyte subsets (CD3+, CD4+, and CD8+) and the CD4+/CD8+ ratio in advanced bladder cancer patients before and after CalliSpheres DLMS treatment were detected, and the results are shown in Figure 4. Before treatment, serum CD3+, CD4+, and CD8+ levels and the CD4+/CD8+ ratio indexes were $64.58 \pm 5.91\%$, $44.75 \pm 4.42\%$, and $23.94 \pm 2.16\%$ and 1.82 ± 0.41, respectively, while those after treatment were $58.11 \pm 4.32\%$, $34.66 \pm 5.10\%$, and $25.72 \pm 2.05\%$ and 1.53 ± 0.39, respectively. After treatment, the levels of CD3+, CD4+, and CD4+/CD8+ in serum of advanced bladder cancer patients were significantly lower than those before treatment, while the level of CD8+ was significantly higher than that before treatment, and the difference was statistically significant ($P < 0.05$).

3.5. Changes in Oxidative Stress Levels in Advanced Bladder Cancer Patients Treated with CalliSpheres DLMS. The differences in serum levels of oxidative stress index SOD in advanced bladder cancer patients before and after CalliSpheres DLMS treatment were detected, and the results are shown in Figure 5. Before treatment, the serum SOD level was 136.53 ± 15.51 U/mL, while that after treatment was 109.22 ± 11.74 U/mL. After treatment, the levels of SOD in serum of advanced bladder cancer patients were slightly lower than those before treatment, but the difference was not statistically significant ($P > 0.05$).

3.6. Evaluation of Quality of Life in Advanced Bladder Cancer Patients Treated with CalliSpheres DLMS. The QLQ-C30 was used to evaluate the quality of life of advanced bladder cancer patients before and after CalliSpheres DLMS treatment. The results are shown in Figure 6. It was found that the five item scores and QOL scores on the functional subscale of advanced bladder cancer patients after treatment were significantly higher than those before treatment, and the difference was statistically significant ($P < 0.05$). After treatment, the scores of 3 items on the symptom subscale, the score of 5 items in on adverse reaction subscale, and the Econ score of patients with advanced bladder cancer after treatment were significantly lower than those before treatment, and the differences were statistically significant ($P < 0.05$).

3.7. Safety Evaluation of CalliSpheres DLMS in Advanced Bladder Cancer Patients. The safety of CalliSpheres DLMS in the treatment of advanced bladder cancer was analyzed, and the results are shown in Figure 7. After CalliSpheres DLMS treatment of 35 advanced bladder cancer patients, 2 patients (5.71%) developed hematuria, 2 patients (5.71%) developed urethral stricture, 1 patient (2.86%) developed urinary incontinence, no patients developed bladder perforation (0.00%), and 4 cases (11.43%) with recurrence.

4. Discussion

Bladder cancer is a type of urological malignancy that occurs on the bladder mucosa with a high incidence rate and mortality. Transarterial chemoembolization has been used in the treatment of advanced bladder cancer patients with excellent therapeutic effects [11]. However, problems such as gene mutation and drug resistance prevent patients from benefiting from targeted therapy in the long term. Therefore, finding a more effective treatment method is of great significance for improving the prognosis of patients and their quality of life and prolonging the survival period. The inner diameter of drug-loaded microspheres is the key to affecting the efficacy of transarterial chemoembolization. Currently, the diameter of drug-loaded microspheres used in clinical treatment of liver metastases is 100–300 μm [12]. CalliSpheres DLMS is a new type of drug-loaded microsphere system, and its volume will be significantly reduced after drug loading. After 20 days of interventional therapy, with the gradual release of chemotherapy drugs, the volume of CalliSpheres DLMS will gradually recover, so it can effectively block the blood vessels supplying tumors and prolong the recanalization time of the blood vessels supplying tumors [13, 14].

In this work, CalliSpheres DLMS-transarterial chemoembolization was used for the treatment of advanced bladder cancer patients and imaging techniques such as MR were used to evaluate the therapeutic effect. It was found that the ADC value of the tumor increased significantly after treatment, while the maximum diameter of the tumor decreased significantly. MR diffusion-weighted imaging is a noninvasive functional examination method that can reflect the diffusion of water molecules in tissues. Since the diffusion of water molecules is affected by the microstructure of cells, it can be used in disease diagnosis and therapeutic

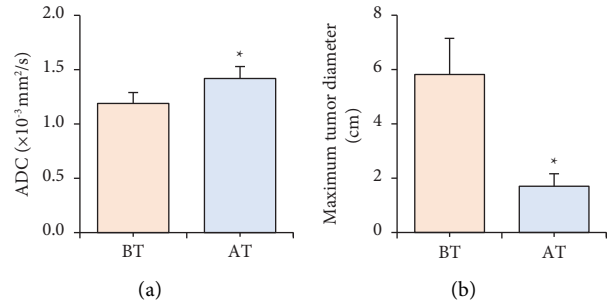

Figure 2: Comparison of MR quantitative parameters in advanced bladder cancer patients before and after treatment. (a) The ADC value of the tumor and (b) the maximum diameter of the tumor. BT: before treatment and AT: after treatment. *Compared with that before treatment, $P < 0.05$.

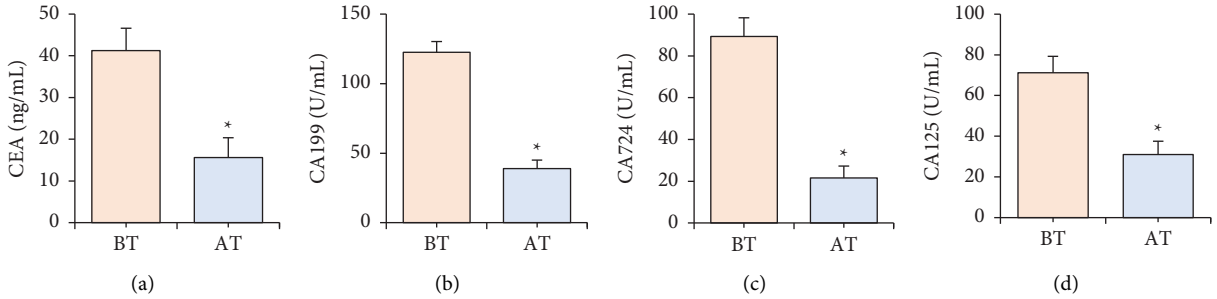

Figure 3: Comparison of serum tumor markers in advanced bladder cancer patients before and after treatment. (a–d) The comparison of CEA, CA199, CA724, and CA125, respectively. BT: before treatment and AT: after treatment. *Compared with that before treatment, $P < 0.05$.

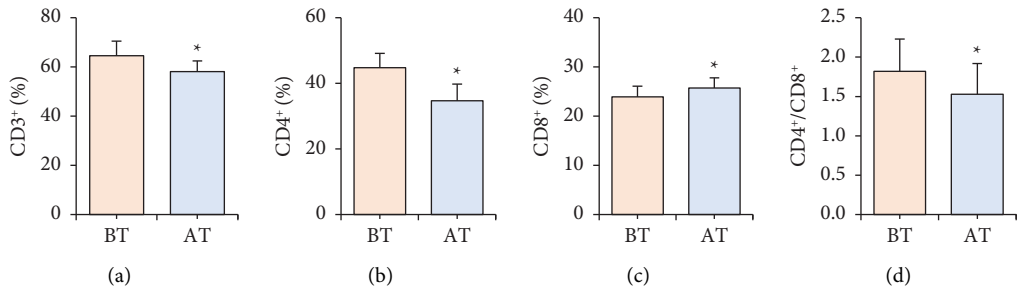

Figure 4: Comparison of serum T-lymphocyte subset levels in advanced bladder cancer patients before and after treatment. (a–d) The comparison of CD3+, CD4+, CD8+, and CD4+/CD8+, respectively; BT: before treatment and AT: after treatment. *Compared with that before treatment, $P < 0.05$.

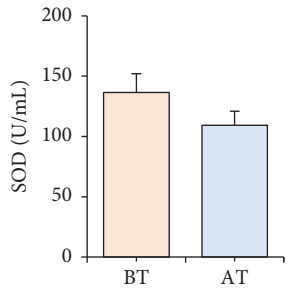

Figure 5: Comparison of serum levels of oxidative stress indexes in advanced bladder cancer patients before and after treatment. BT: before treatment and AT: after treatment.

efficacy monitoring [15]. MR diffusion-weighted imaging and changes in the ADC value can be used to evaluate the dynamic evaluation of the treatment effect of malignant tumors. The decrease in the ADC value in malignant tumors is related to the high density and volume of cells [16]. This work found that the ADC value of tumors in advanced bladder cancer patients was significantly increased after CalliSpheres DLMS-transarterial chemoembolization. It indicated that the bladder cancer cell membrane was destroyed after interventional therapy, that the tumor volume and tumor cell density decreased after cell necrosis, and that the increase in the intercellular space provided space for the diffusion of water molecules. An increase in the ADC

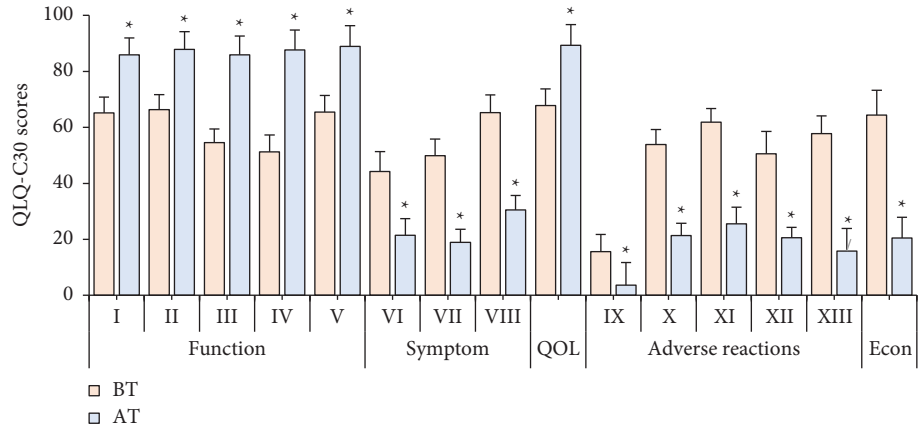

Figure 6: Comparison of QLQ-C30 scores in advanced bladder cancer patients before and after treatment. I–XIII refer to physical function, role function, cognitive function, emotional function, social function, fatigue, pain, malignant vomiting, dyspnea, insomnia, anorexia, constipation, and diarrhea, respectively; QOL, quality of life; Econ, economy; BT, before treatment; AT, after treatment. *Compared with that before treatment, $P < 0.05$.

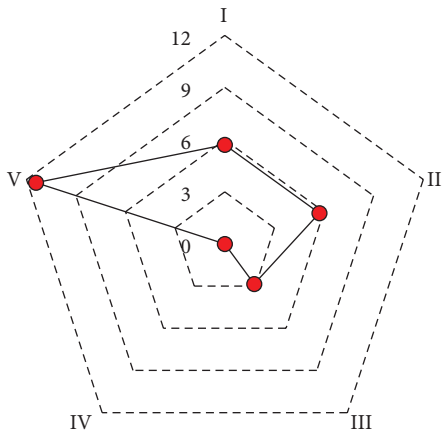

Figure 7: Evaluation of the incidence of adverse reactions in advanced bladder cancer patients. I: hematuria; II: urethral stricture; III: urinary incontinence; IV: bladder perforation; V: recurrence.

value was associated with a reduction in tumor volume [17], which is consistent with the findings of this work. In addition, it was found in this work that the serum levels of tumor markers [18, 19] (CEA, CA199, CA724, and CA12) in advanced bladder cancer patients after CalliSpheres DLMS-transarterial chemoembolization were significantly decreased, that the ORR was 74.29%, and that the DCR was 97.14%. CEA, CA199, CA724, and CA125 are common tumor markers, which are often used in disease diagnosis and treatment evaluation. It indicated that CalliSpheres DLMS-transarterial chemoembolization has a good clinical effect in the treatment of advanced bladder cancer.

Abnormal immune function can induce the occurrence and development of tumors. Immune dysfunction is not conducive to the recovery of the patient's body function and also increases the risk of postoperative recurrence and metastasis in tumor patients [20]. T lymphocytes mediate cellular immunity, and studies have confirmed that the levels of T-lymphocyte subsets in patients with bladder cancer are significantly disrupted [21]. This work found that the levels of serum T-lymphocyte subsets in advanced bladder cancer patients were altered after CalliSpheres DLMS-transarterial chemoembolization. This suggests that CalliSpheres DLMS-transarterial chemoembolization directly infuses chemotherapeutic drugs into target organs and prolongs the drug release time, which helps rapidly kill tumor cells, thereby reducing the impact of tumor infiltration on the immune function of patients. In addition to immune function, oxidative stress is also involved in tumor progression and can also reflect the traumatic stress of patients receiving treatment [22]. SOD can capture and scavenge free radicals in the body [23, 24]. This work found that serum SOD was significantly decreased in advanced bladder cancer patients after CalliSpheres DLMS-transarterial chemoembolization. This suggests that a certain degree of oxidative stress appears in advanced bladder cancer patients after CalliSpheres DLMS-transarterial chemoembolization, but the level of oxidative stress is relatively stable. Yang et al. [25] confirmed that the oxidative stress state can aggravate the expression of inflammatory factors, which in turn promotes the infiltration of tumor cells. This work found that the incidence of adverse reactions such as hematuria, urethral stricture, and urinary incontinence in patients with advanced bladder cancer after CalliSpheres DLMS-transarterial chemoembolization was relatively low, and the incidence and recurrence rates were also relatively low.

5. Conclusion

CalliSpheres DLMS-transarterial chemoembolization is effective for advanced bladder cancer with higher ORR. It can reduce the level of tumor markers in patients, reduce the oxidative stress response caused by surgery, and have a low impact on the immune function of patients, which can help improve the prognosis of patients. Using MR diffusion-weighted imaging technology, it was found that the ADC value of patients with advanced bladder cancer was

significantly reduced after CalliSpheres drug-loadedmicrosphere-transinternal iliac artery chemoembolization. However, this work only compared and analyzed the index changes in advanced bladder cancer before and after CalliSpheres DLMS-transarterial chemoembolization. No randomized controlled trials have been designed to evaluate the efficacy and safety of CalliSpheres DLMS-transarterial chemoembolization. In future studies, more samples need to be included to compare the efficacy and safety of CalliSpheres DLMS-transarterial chemoembolization and traditional transarterial chemoembolization in the treatment of advanced bladder cancer. In conclusion, the results of this work can provide reference for the clinical application of CalliSpheres DLMS-transarterial chemoembolization and improve the prognosis of patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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